

Comparative epidemiological studies of multiple sclerosis in South Africa and Japan

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SYNOPSIS Evidence is presented pointing to an increased incidence of multiple sclerosis having taken place in South Africa during the period 1964 to 1970 and in Tokyo, Japan, during the period 1966 to 1972. There is a possibility that these changes in incidence point to the introduction during the years immediately after the second world war, of an infective element—probably from a high-risk area—to Tokyo and South Africa. If this is so, it lends support to the theory of an infective basis for multiple sclerosis and that the suspected infection in prepubertal susceptibles may produce the symptoms of multiple sclerosis years later. Other factors relevant to multiple sclerosis such as environmental changes, improved diagnostic techniques, and susceptibility are discussed.

The aetiology of multiple sclerosis (MS) remains an enigma, despite world-wide efforts to understand its causation. In consequence, whatever treatment we may give for the condition is empirical or, at best, palliative; until we have unravelled its aetiology there is little hope for a cure. In the past decade, epidemiology has proved to be a promising field of research, pointing to such factors playing a part as climatic and meteorological variations, genetics, dietary deficiencies or excess, and standards of hygiene. Almost all studies have been based on the surmise of a constant incidence of MS being present in various geographical situations, so we have come to talk about high and low-risk MS areas. Clearly a *changing* incidence, whether increasing or decreasing would have a special significance, detracting from the importance of such constant factors as latitude, mean temperature and other climatic considerations, trace elements in the soil, etc., and would suggest that some environmental change had taken place. This might be a change in dietary habits, improved hygiene, or possibly the introduction of an infective factor. In 1969 an increasing inci-

dence of MS in Johannesburg and its environs was reported by Bird and Kerrich. Coincidentally, a similar increasing incidence was reported in Tokyo (Satoyoshi *et al.*, 1972). The present paper compares environmental factors in South Africa and Japan, two low-risk areas, and points to changes which may have taken place. The South African study has the added interest of the total absence to date (1974) of a single proved case of MS in a black African, contrasting with the increasing incidence in whites.

SOUTH AFRICAN STUDY METHOD

All the MS patients reported were seen in a private consulting neurological practice in Johannesburg during the years 1959-70 (Tables 1 and 2). They were all referred by colleagues, only two presenting themselves direct with their diagnosis established, because of the author's known interest in MS. These were excluded to avoid any possible bias in the numbers seen. The number of MS patients was related to the total number of 'new' neurological cases seen *per annum*. Throughout the period of the study, every patient was examined by the same neurologist, trained in England and Canada, using the same criteria for diagnosis (McAlpine *et al.*, 1965), in the same practice covering more or less the same population. Only such cases regarded as

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TABLE 1
INCIDENCE OF MULTIPLE SCLEROSIS (SOUTH AFRICA)

Year	Private cases seen		Cases of multiple sclerosis			
	Revisits	First consultation	South African-born		Immigrants	
			Male	Female	Male	Female
1959	Figures not available		—	1	—	—
1960			—	1	—	—
1961			—	1	—	—
1962		981	549	2*	1 (Chinese)	—
1963	1 271	704	—	1	1	2
1964	860	646	2	4**	—	—
1965	1 048	666	2	4*	1	—
1966	994	618	2	2*	1	—
1967	870	562	3	3	—	2
1968	1 057	599	3*	5	1	—
1969	945	703	2	5**	—	1
1970	967	521	1	3	—	—

* South Africans who have travelled abroad. * Indicates including a single such case. ** Indicates including two such cases.

TABLE 2
ANALYSIS OF YEARLY INCIDENCE (SOUTH AFRICA)

Year	New cases examined	Number with MS	$P = \text{number}/1\ 000$ new cases with MS
1962	549	3	5.46
1963	704	4	5.68
1964	646	6	9.29
1965	666	7	10.51
1966	618	5	8.09
1967	562	8	14.24
1968	599	9	15.00
1969	703	8	11.38
1970	521	4	7.69

probable MS seen more than twice in follow-up over a period of not less than three months were included in the study. The large majority of patients have been seen from time to time until the present.

RESULTS

During the period 1959 to January 1970, 53 cases of MS were seen, 33 females and 20 males. In the first three years of this period there were only three cases. In 1965 only, seven cases presented and in 1967 there were eight cases. In the four years 1964–67 there were no less than 26 new cases of MS, all except four being South African-born. In the years 1968, 1969, 1970 there were 21 cases (Tables 1 and 2). The number

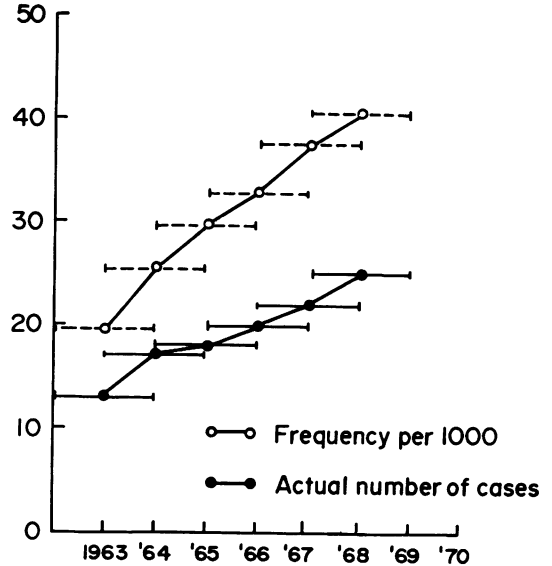


FIG. 1 Three years running total of new multiple sclerosis cases (●) and their frequency per 1 000 new neurological cases (○) during the period 1962–69 (South Africa).

of new MS cases per 1 000 new neurological patients *per annum* has apparently increased since 1964, particularly after 1967. Running totals of new MS in cases in three year epochs and its frequency per 1 000 new neurological patients during the period 1963–68 indicated a gradual increase in yearly incidence (Fig. 1).

Assuming that 'new' cases *per annum* are random samples of some much larger population, the figures suggest the hypothesis that in the population the proportion *p* increases linearly with time according to the formula $p = a + bt$. On fitting this line by routine methods, the 95% confidence interval for the value of *b* is 1.495 ± 1.280 . This can be interpreted as meaning that satisfactory evidence exists that *b* is positive (though not determined very accurately) and hence that *p* is increasing with time (Fig. 2). In actuality, during the first decade of neurological practice, a great paucity of MS cases was recognized, and then during the second decade the same trained observer noted an increasing incidence. This was found to be significant by a statistician and by independent computerized study (Bird and Kerrich, 1969; Bird, 1971).

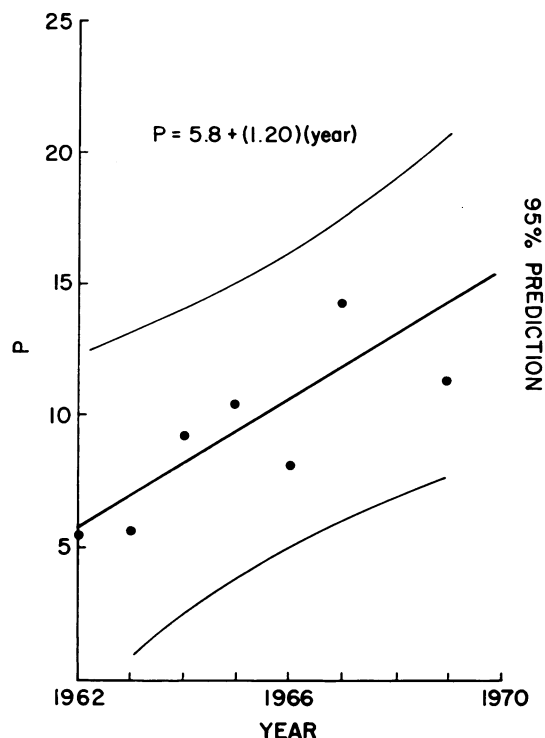


FIG. 2 Computerized study based on numbers of new multiple sclerosis cases per annum per 1 000 new neurological cases during the period 1962-69 indicates the linearly increasing incidence of multiple sclerosis with 95% confidence (South Africa).

JAPANESE STUDY METHODS

A retrospective study has been made of patients with demyelinating disease, all seen personally by one of us (Satoyoshi) during the last 18 years in hospital practice. All the patients were examined either in the outpatient clinics or the wards of the Department of Medicine in three teaching hospitals: the Toho University Ohmori Hospital (650 beds), the Toho University Ohashi Hospital (300 beds), and the Nihon Kokan Hospitals (300 beds). These are general hospitals serving a fairly fixed community in the southern part of Tokyo. All patients came from the area normally served by the hospital except a few cases referred from distant places with the diagnosis suspected.

Yearly incidence of new MS cases, seasonal incidence, clinical signs and symptoms were studied from adequate records and compared with findings reported by other authors.

RESULTS

A total of 118 patients was seen with demyelinating disease, of whom 111 or 94% suffered from MS. Only two cases (1.7%) were diagnosed as neuromyelitis optica and five (4.2%) as acute disseminated encephalomyelitis. Of 111 cases of MS, the ratio of male to female was equal. The age of patients at onset of MS ranged from 13 to 49 years, the mean being 31.2 years (Table 3). Of the 111 patients with MS, 77 (69.4%) were considered 'definite' cases, 27 (24.3%) were 'probable', and the remaining seven (6.3%) were 'possible'.

ANALYSIS OF YEARLY INCIDENCE During the

TABLE 3
AGE OF ONSET IN 111 CASES WITH MULTIPLE SCLEROSIS
(JAPAN)

Age (yr)	Male	Female	Total cases	Percentage
0-9	0	0	0	0
10-19	6	12	18	16.2
20-29	19	12	31	27.9
30-39	17	20	37	33.3
40-49	13	11	24	21.6
Above 50	0	1	1	0.9
Total	55	56	111	

TABLE 4
ANALYSIS OF YEARLY INCIDENCE (OUTPATIENTS)
OF MULTIPLE SCLEROSIS (JAPAN)

Year	New cases in outpatient clinic	New cases with MS	P = number new cases with MS/1 000
1956	2 379	0	0
1957	3 097	1	0.32
1958	3 057	2	0.65
1959	3 267	3	0.92
1960	4 325	0	0
1961	3 690	0	0
1962	3 813	1	0.26
1963	3 668	0	0
1964	4 017	1	0.25
1965	4 515	0	0
1966	4 230	0	0
1967	4 496	2	0.44
1968	6 520	9	1.38
1969	6 925	18	2.60
1970	7 336	32	4.36
1971	7 612	9	1.18
1972	6 186	20	3.24
1973	2 170	9	4.15

TABLE 5
ANALYSIS OF YEARLY INCIDENCE (INPATIENTS)
OF MULTIPLE SCLEROSIS (JAPAN)

Year	Total number of inpatients	Number of admitted MS cases	P = number new cases with MS/1 000
1956	542	0	0
1957	664	1	1.51
1958	629	2	3.18
1959	644	3	4.66
1960	610	0	0
1961	510	0	0
1962	624	1	1.60
1963	747	0	0
1964	753	1	1.33
1965	915	0	0
1966	841	0	0
1967	963	1	1.04
1968	1 108	9	8.12
1969	1 213	7	5.77
1970	1 166	11	9.43
1971	1 058	6	5.67
1972	1 045	16	15.31
1973	397	9	22.67

TABLE 6
FREQUENCY OF SYMPTOMS AND SIGNS DURING THE
COURSE OF MULTIPLE SCLEROSIS (JAPAN)

Symptoms and signs	Satoyoshi (1974) (%)	Ivers and Goldstein (1963) (%)	Okinaka et al. (1958) (%)
Increased tendon jerks	96	75	82
Impaired vision	59	38	93
Sensory disturbance	55	47	48
Ataxia and intention tremor	52	57	43
Optic atrophy	51		52
Facial weakness	47	2	14
Babinski sign	44	69	
Nystagmus	43	35	
Ocular palsy	40		
Dysarthria	35	19	16
Paralysis of limbs	27	13	68
Psychiatric symptoms	22	2	45
Bladder trouble	16	1	
Dysphagia	11	1	
Seizure	8	2	

period 1956 to 1973, 107 cases of MS were seen in the outpatient clinics of the Toho University Ohmori and Ohashi Hospitals. As shown in Table 4, during the period 1956 to 1960 only five cases of MS were seen. In the following five years only two such patients were examined. During the period 1966 to 1970, however, the same neurologist using the same criteria for diagnosis (McAlpine *et al.*, 1965), saw no less

than 61 new MS cases. The ratio of new MS cases per 1 000 new medical patients *per annum* increased strikingly in the last five years as compared with those in the previous 11 years.

The same tendency was also observed in patients admitted to hospital (Table 5). A total of 67 MS patients were admitted during the last 18 years to the Toho University Hospitals. During the years 1956 to 1967, three or less MS patients were admitted yearly. The incidence of MS to 1 000 inpatients in medical wards was 0 to 4.66 in the former period. However, in the last six years, it ranged from 5.67 to 22.67 with a mean of 10.09. In addition, the ratio of MS to amyotrophic lateral sclerosis was 1 to 1 in the former period and 7 to 1 in the last six years.

SEASONAL INCIDENCE; SIGNS AND SYMPTOMS
Seasonal incidence: the initial attack was most commonly in winter (December to February) (36.5%) and the lowest incidence was in summer (14.9%), though relapses occurred in all seasons with almost equal frequency. As precipitating factors, pregnancy or delivery was noticed in 17.9%. Impaired vision, numbness or paraesthesiae were common initial complaints of these cases. The symptoms observed throughout the clinical course and their frequency are summarized in Table 6. Frequency of these symptoms was similar to the findings of other authors (Okinaka *et al.*, 1955, 1958; Ivers and Goldstein, 1963). The sites of lesions, inferred clinically, were spread all over the central nervous system: 28.1% in cerebrum, 77.1% optic tract, 78.1% in brain stem, 52% in cerebellum, and 92.1% in the spinal cord.

DISCUSSION

In South Africa multiple sclerosis is of special interest, not because of its prevalence, but because of its rarity. Dean (1949), after extensive research, reported only 27 probable MS cases of whom only 10 were South African born whites. In a later study, covering the period 1958-66, the same author reported 158 South African born whites out of 281 probable MS cases. Further evidence of this former great rarity of MS is provided by neuropathological studies. During the period 1956-64, out of a total of 9 886 neuropathological examinations carried out by the

Neuropathology Department of the South African Institute for Medical Research, only three cases of MS were found (annual reports). The first MS case ever diagnosed histologically was in 1957, an immigrant from Britain. The first South African born subjects to have the diagnosis of MS at necropsy were two whites reported by Wright *et al.* as recently as 1965. During the same year, another necropsy report came from Cape Town (Thomson and Ames, 1965). To date, there have been three further cases in whites, two South African born and the other of uncertain origin. There has also been a case in a South African born Indian (Procter and Kauffman, 1970, personal communication).

As indicated in this study, the incidence of MS has been increasing in 4 000 000 whites, though not a single proved MS case has been observed in 16 000 000 South African blacks. One case of neuromyelitis optica in a black patient, proved at necropsy, was reported by Reef and Kauffman (1969, personal communication). Hift and Moodley (1973) reported a possible case of neuromyelitis optica in a Bantu. Neurologists have seen occasional cases of reticulospinal neuritis, even the 'possible' MS case, but not one proved case. At the busy and well-staffed Neurology Department of Baragwaneth Hospital for Africans there is no single case of MS on record. If MS existed in the African community, one would expect to see some at least of the terminal bed-ridden cases which form a tragic part of the MS scene, even if the early, difficult diagnosis were missed.

Japan, located between latitudes 30° and 45°, is regarded as a low prevalence area. Since the first report of Okinaka *et al.* (1955), population studies, attempted in several Japanese cities, indicated a prevalence rate of 2 to 4 per 100 000 population (Okinaka *et al.*, 1958, 1960, 1966). Concerning the neuropathological findings of demyelinating disease in Japan, earlier reports pointed to a predominance of neuromyelitis optica (Okinaka *et al.*, 1958; Shiraki, 1966). During the period 1890 to 1955 a total of 270 demyelinating cases was collected and 64.8% of these cases were diagnosed as having neuromyelitis optica and only 24.4% as MS. During the following decade 1956-65, Tsubaki (1966) collected 328 cases of demyelinating diseases including 104 necropsy cases; 45.1% of these

were diagnosed as MS and 28.3% as neuromyelitis optica. Modern workers, however, have shown that Devic's disease is no more prevalent compared with MS in Japan than elsewhere in the world, and are of the opinion that a large proportion of cases formerly diagnosed as Devic's disease would be regarded as MS today (Satoyoshi *et al.*, 1972). The first necropsy typical of MS in a Japanese was carried out in 1966 by Satoyoshi *et al.* By a coincidence, this was one year after the necropsy on a South African MS patient (Wright *et al.*, 1965). Since then, further classical necropsy evidence of MS has been reported from various parts of Japan (Matsuyama and Satoyoshi, 1970; Toyokura and Mannen, 1970; Yonezawa, 1970).

In this report, we have pointed to an increasing incidence of MS in Tokyo, Japan and in South Africa. An increasing incidence has a special significance suggesting that some change has taken place.

1. There may have been the introduction of an infective agent from high-risk areas.
2. There may have been an environmental change.
3. There may have been an increase in susceptibility in a racially resistant group.
4. Or MS is brought to light where it has 'always' existed, by improved diagnostic techniques.

INTRODUCTION OF AN INFECTIVE AGENT There is good evidence pointing to MS having two phases, the first (? infective) preceding the second (neurological) by as long as 20 or more years (Poskanzer *et al.*, 1963; Schapira *et al.*, 1963). If an infective agent has been introduced, why did not the early pioneers to South Africa bring it with them? This may have been because of the rarity of MS 200 years ago (this point is contentious). A more likely explanation is that the condition may have a very short period of infectivity—say, 24 to 36 hours—as is known to be the case with certain viral respiratory diseases. The jet age has cut the travel time from Europe to Africa and the Far East from weeks to hours, so that carriers of respiratory diseases arrive while still infective. Both Tokyo and Johannesburg are terminals of intercontinental air routes. Air travel may have played a key role in the introduction of MS; once introduced, the infec-

tion would spread at the predictable speed of a newly introduced respiratory viral disease, ultimately becoming endemic. Years later, MS would begin to appear, show an increasing incidence for a period, and then maintain a fairly constant incidence related to racial susceptibility and environmental factors. During the last three years there appears to have been a slight falling off in the annual number of new MS cases seen in Johannesburg in the practice of one of us, but observations will have to be continued over a longer period to establish whether this is a significant trend or not.

In the course of the second world war there were massive troop movements from high-risk areas, but these were mostly by ship. Towards the end of the war, however, air transport was more widely used, especially for the repatriation of prisoners-of-war. Not a single case of MS has been reported from 14 583 South African prisoners-of-war in Europe. They may well have been carriers of the suspected infective agent which they transmitted on return. Some of these infected in South Africa would have been prepubertal, and of these only susceptible subjects developed MS 15 to 20 years later. Not a single South African out of a total of well over 50 000 who served in central Europe and Italy during the Second World War receives a military pension for MS. One suspected case of MS in a South African soldier returned from the Middle East, was shown at necropsy to have had inclusion-body encephalitis (Geerling and Bird, 1951).

Japan, never having been colonized, would not have been exposed to the risk of immigrants introducing new disease. Immediately after the second world war, however, occupation forces, mainly from the United States, numbering more than 800 000, were stationed in Japan over a seven year period. At first, they were mainly males, but subsequently women and children came as well. This influx was almost certainly responsible for the introduction of the poliomyelitis epidemic which swept through Japan in 1951. They may equally well have brought in MS, which is manifesting itself only now approximately 20 years later (Alter *et al.*, 1966; Alter and Okihiro, 1971).

ENVIRONMENTAL CHANGES *Standard of hygiene*
It has been suggested that Japan may have a low

prevalence of MS because human excreta is widely used as a fertilizer (Poskanzer, 1968). By western standards, this would be regarded as a 'low standard of hygiene' but it did not protect the Japanese from the epidemic of paralytic poliomyelitis referred to above. This epidemic came about as a result of an introduced virus and was unrelated to standards of hygiene. The same argument may apply with regard to MS and would weigh against standards of hygiene playing much part in the aetiology of MS as the propounders of the 'polio analogy' would have us believe (Poskanzer *et al.*, 1963).

In Johannesburg a change was made in the late 1920s from bucket sanitation to water-borne sewage. This applied also to urban blacks. Infant mortality can be regarded as a measure of the standard of hygiene in a community; with improved hygiene, infant mortality in urbanized Africans in and around Johannesburg has fallen to 70/1 000 compared with 140/1 000 in a typical group living under tribal conditions. Despite this improvement in the standards of hygiene, the incidence of MS, even in urbanized blacks, has remained zero. Other infective conditions in general have decreased in the city dwellers. The urbanized group is exposed to the pressure of city life and 'westernized refined' diet with chemical preservatives, colouring matter, and other pollutants. Recent studies have shown that food antibodies—notably to heat-dried cows milk and boiled egg—play a part in the aetiology of myocardial infarction (Ellis, 1974). Other workers have suggested that processed food (presumably in bottle-fed infants) could constitute an almost unlimited source of possible antigens (Davis *et al.*, 1974). This may play a part in the aetiology of MS, determining susceptibility, and explain the so-called 'diseases of civilization'—rheumatoid arthritis, duodenal ulcer, coronary thrombosis, diabetes, hypertension, and gall-stones—diseases rare among Africans living in 'uncontaminated' tribal conditions but becoming more common in the urbanized (Seftal, 1974, personal communication).

From our own observations, there has been little change in the character of the diet of South African whites, except for increase in quantity and quality with improved economic status. Among whites and urbanized blacks, the feeding of infants has swung away from breast feeding,

which predominated 20 years ago, to the use of prepared feeds today. At least 90% of all African infants, however, are still breast-fed today. It is possible that the apparent racial immunity of black Africans to MS is genetically determined and related to breast-feeding during infancy. If MS has an infective basis, the probability is that black Africans have been contracting the disease (? as a respiratory infection) but do not develop the secondary neurological manifestations because of their racial immunity to the process (? hypersensitivity) responsible for its development.

In Japan also, with increased earnings, diet is swinging away from the traditional rice and fish to tinned foods, 'sterilized' preserved food, and refined cereals and sugar. Breast feeding decreased remarkably in the last 10 years in and around Tokyo and where the 'diseases of civilization' are now manifesting. However, the mean age of MS patients in Tokyo is 31 years, suggesting that decreased breast-feeding has played an unimportant part, if any, in the development of MS in Tokyo. Exposure to pollutants such as mercury may conceivably have played a part in the increasing incidence of MS in Tokyo. The constant incidence of MS in Fukuoka (Kuroiwa and Shibasaki, 1973) where these factors are equally operative, refutes this suggestion.

INCREASED AWARENESS OF MS The suggestion has been made that countries like South Africa and Japan are regarded as 'low risk' MS areas simply because of a lack of suitably trained neurologists; it is implied that the incidence of MS has always been constant and that, in the past, the cases were there, but not diagnosed. Reported clinical studies and neuropathological examinations in the past are against these possibilities. If the incidence were due to 'increased awareness' either on our part or on the part of the referring doctors, at least some of the new cases would have been lower down on Kurtzke's disability scale (Kurtzke, 1961). In any long-established MS community there will be a predictable number of each group, from one to 10. If our patients had been referred because of 'increased awareness', then one would expect at least some, probably a predominance, to come from the usually more easily diagnosed lower

group with more obvious disability. However, such cases did not present originally and only now, after years of observation, are becoming confined to a wheelchair or bedridden.

SUSCEPTIBILITY DIFFERENCE Individual susceptibility may play an important role in developing MS. Recent work pointed to HL-A 3 and HL-A 7 histocompatibility antigens being associated with MS (Jersild *et al.*, 1973; Bertrams and Kuwert, 1974). Degos and Dausset (1974) suggested that there is a specific gene for susceptibility to MS. It would seem that this gene might be absent in South African blacks. Comparative studies of this aspect in the various population groups of both countries might lead to a valuable method of demonstrating susceptibility to the MS process. It is conceivable that South African blacks may have a protective factor in their blood which, if it could be isolated, may prove to be a valuable therapeutic agent.

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