MULTIPLE SCLEROSIS IN SOUTH AFRICA*

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Multiple sclerosis (MS) has been known for more than 30 years to have a geographical distribution.[1] In North America the condition is rare in the Southern States, but relatively common in the north.[2] In Europe, similarly, the disease is most prevalent in the north between latitudes 40° and 60°, and is rare in Mediterranean countries.[3] In Israel[4] MS has been found to be commoner in immigrants from North-East Europe than in Israel-born subjects or immigrants from North Africa. In South Africa MS is of special interest, not because of its prevalence, but because of its rarity.

Dean,[5] after extensive research into MS in South Africa, reported that in 1948 there were only 27 in whom the diagnosis of MS could be accepted as probable; of this total, only 10 were South African-born, and the balance were immigrants from Europe. In a later study, extending from 1958 to 1966, the same author[6] reported 158 South African-born Whites out of a total of 281 with the probable diagnosis of MS on his prevalence day (Census day, 1960). Of the total of 281, the mean period from onset to diagnosis was 8 years and from diagnosis to prevalence day 6 years. This indicates that the majority of the cases were of relatively recent onset, and seems to confirm my observations—based on 20 years of neurological practice in Johannesburg—that, from being very rare, MS is becoming relatively common in this country.

The figures in Table I represent patients seen at my consulting rooms only and do not include those seen in hospitals or at private homes. More than 98% of all patients were referred by other doctors, but during 1967 there were 3 MS cases who consulted me direct without being referred by a colleague but at the suggestion of another MS patient. I regard the remaining cases as being free of this bias.

STATISTICAL ANALYSIS

It will be seen that during the period 1959 to July 1968, 42 cases of MS, 25 females and 17 males, were seen; between 1959 and 1962 there were only 7 cases, while in 1965 alone there were 7 cases and in 1967 there were 8. In the 4 years 1964 - 1967 there were no less than 26 new cases of MS, all barring 4 being South African-born. These are not large figures but they become interesting when it is recalled that in 1948 there were only 10 known cases of MS in South African-born Whites in the whole of South Africa (Table II).

Assuming that 'new cases *per annum*' are random samples from 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 routing methods, the 95% confidence interval for the value of b is

TABLE I. INCIDENCE OF MS

	Private cases seen		*Cases of multiple sclerosis*			
			South African-born		*Immigrants*	
Year	*Revisits*	*First consultation*	*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 (to July)	652	346	2*	3	1	–

*Indicates South Africans who have travelled abroad.

TABLE II. ANALYSIS OF YEARLY INCIDENCE

Year	*New cases examined*	*Number with MS*	*p = 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 (to July)	346	6	17·24

For the 6 years 1962 - 1967 the observed values of p increase fairly steadily.

*Date received: 28 October 1968.

1·495 ± 1·280. This can be interpreted as meaning that satisfactory statistical evidence exists that b is positive (though not determined very accurately) and hence that p is increasing with time. The partial evidence available for 1968 supports this judgement.

There is no specific diagnostic test for MS; the diagnosis must of necessity be a clinical one and can only be proved at autopsy. Not one of my cases has been proved in this way, but I regard the diagnosis to be probably correct in each of the 42 cases presented, based on the following essential criteria: (*i*) Clinical evidence suggesting lesions in more than one neuroanatomical site; and (*ii*) at least 2 symptomatic episodes at different times in the course of the illness. The average age of my patients was 39·9 years. A few cases were subjected to special investigations such as lumbar puncture, cerebral angiography, air encephalography and electroencephalography, to rule out other neurological conditions. However, in the majority of cases in which the diagnosis seemed reasonably certain on clinical grounds alone, these tests were specifically avoided because of their possible detrimental effect on the course of the disease.

Further evidence of the former great rarity of MS is provided by neuropathologists who, because of the rarity of the condition in South Africa, have been on the lookout for it. During the period 1956-1964, out of a total of 9,886 neurohistological examinations carried out by the Neuropathology Department of the South African Institute for Medical Research, only 3 cases of MS were found.[7] The first case ever diagnosed histologically was in 1957—an immigrant from Britain. The first South African-born subjects to have the diagnosis of MS confirmed at autopsy were two Whites reported by Wright *et al.*[8] as recently as 1965. During the same year another autopsy report came from Cape Town,[9] and to date (1968) there have been two further cases in Whites, one South African-born and the other of uncertain origin. There has also been a case in a South African-born Indian.[10] These cases confirm that the condition we are encountering today in increasing numbers is in fact MS.

DISCUSSION

Clearly, if there is an increasing frequency of MS in South Africa, this may provide new information as to the aetiology of the condition. This recent increase seems to be in favour of an infective agent playing an important part and against such fairly constant factors as mean average temperature, diet or lack of trace elements being fundamental. I believe that this infective agent, new to South Africa, has been introduced partly by immigrants who are coming in increasing numbers to this country mainly from high-risk European areas, and partly by South Africans whom air travel has encouraged to venture abroad in greatly increasing numbers during the last 15 years or so.

As already mentioned, MS is commonest in colder climes. Does this suggest the agent concerned may be one of the many which may produce an upper respiratory tract infection? These infections appear to be more prevalent in overcrowded cities of the cooler north than, say, in South Africa. If this were so, an epidemic caused by such an organism would be unremarkable and pass unnoticed. Only in susceptibles would the CNS be involved. If this occurs, the initial onslaught in the CNS may be insignificant, perhaps producing just headache or mild signs of meningism. In the majority of patients this is probably where the illness would end. It is possible that the infective period lasts only 2 or 3 days; in the days of ocean travel, when a journey from England to the Cape took more than 14 days, the chances of the agent being carried to and spread in South Africa would be less than today when air travel has cut the travelling time to little more than 12 hours. Subjects are arriving at the height of their short period of infectivity. Presumably many contract the respiratory infection but only a few susceptibles develop MS.

What makes the increasing incidence of MS in South Africa doubly interesting is that, while this has been taking place among Whites, not a single proved case in a Bantu has been reported. At Baragwanath Hospital with a yearly turnover of more than 10,000 Bantu medical cases admitted, and with a competent staff of neurologists using the same diagnostic criteria as with White patients, until recently the condition was looked upon as being of great rarity. There was one case diagnosed as MS and considered of sufficient interest to publish,[11] but this was proved at autopsy to be another condition.[12] There has been one case of a Bantu with neuromyelitis optica confirmed at autopsy.[13] I have seen 2 cases of retrobulbar neuritis in Bantu which in Whites would have been suggestive of MS; neither has so far developed any further symptoms to substantiate this diagnosis. This disparity of incidence of MS between Whites and Bantu suggests a factor other than that of a pure infection alone playing an important role in the aetiology of MS. This may be a hypersensitivity reaction triggered off by the infection. Auto-immune conditions such as certain types of haemolytic anaemia, rheumatoid arthritis, thyroiditis and myasthenia gravis do occur in the Bantu but are extremely rare.[14] It is known that the tendency to develop auto-immune allergic conditions is transmitted genetically; auto-immunity may be the recognized genetic factor in MS.[15] This may be the explanation of the complete absence of reported cases of MS in the Bantu. He may contract the rare initial infection from abroad and transmit it; but not one up to now has developed MS, because the large majority of the Bantu do not develop hypersensitivity reactions. Although it will only be a matter of time before cases occur, they will always be much rarer than among Whites.

The suggested infective basis of MS is by no means new and has frequently been propounded in the past. Every attempt to isolate the organism or to prove its presence by antibody reactions, however, has failed. This may be because the condition may have two distinct phases: (*i*) infective, occurring at the onset of the illness and producing non-specific symptomatology when the organism could be isolated, and (*ii*) neurological, resulting from the formation of auto-antibodies to myelin, which may occur months or even years after the infective phase. Weir,[16] in a paper on the immunological consequence of cell death, makes this statement: 'It is conceivable that in chronic infective states (bacterial or virus) soluble tissue antigens could induce antibody formation rather than tolerance'. Perhaps in MS the auto-antigen is formed by my proposed infective agent combining with degradation products of myelin. Such a development would be favoured by the action of one of the so-called 'slow viruses' or a long-acting infective agent.

Comparable Slow Infections

Veterinary science has provided us with a parallel biphasic pathological process taking place in animals. This is visna, an ataxic paralytic disease of sheep caused by a virus.[17] Sigurdsson *et al.*[18] described this as a 'slow infection'. During a prolonged premonitory period without obvious clinical symptomatology, the virus concerned can be isolated, leucocytosis occurs and antibodies are produced. This is followed by a secondary phase with the development of neurological signs and a completely different pathological picture. MS may have two similar phases, the first sensitizing and the second and subsequent demyelinating.

Another animal condition which has been compared with MS is scrapie, a chronic neurological disease of sheep, characterized by an exceptionally long incubation period, pruritus and ataxia with pathological changes in the CNS. Field[19] claimed to have produced scrapie in white mice injected with material from a human case of MS, but Dick *et al.*[20] were unable to produce scrapie in sheep injected with human MS material. Be that as it may, scrapie is doubly of interest in South Africa, for, although it has been known in Europe for more than 200 years, it was not identified in South Africa until May 1966.[21] The diagnosis was made among the progeny of Hampshire Down sheep imported from England. The agent of scrapie is extremely small and much more resistant to the action of ionizing and ultraviolet radiation than any known virus. This may be true of the MS agent as well, and may explain the difficulty in isolating it. If the contention made in this paper is correct, viz. that MS, instead of being a rare condition in South Africa, is becoming relatively common through the introduction of some exotic infective agent, the same may be said of scrapie. There is no evidence to show that it is the same infective agent in the two conditions, but the relatively recent appearance of both in this country may be more than coincidence and may be somehow connected.

SUMMARY

Statistical evidence is presented that in South Africans multiple sclerosis, which was extremely rare 20 years ago, is becoming more frequent. During the last 4 or 5 years the incidence has increased significantly in locally-born Whites, suggesting an infective basis. The absence of any proved cases among Bantu points to some factor other than infection alone. This may be explicable on an immunological basis; auto-immune reactions are extremely rare in the Bantu. The suggestion is made that in MS during a chronic infection (slow virus or infective agent) soluble myelin antigens induce antibody formation; biological reactivation of the infective agent stimulates the formation of further antimyelin antibodies which produce the MS relapses.

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