Dermal sensitivity tests in multiple sclerosis

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The hypothesis that allergic factors play a major part in the pathogenesis of multiple sclerosis has been sustained mainly by analogy with experimental allergic encephalomyelitis (Miller and Schapira, 1959). In the experimental condition, however, the animals exhibit a delayed or tuberculin type of dermal hypersensitivity to homologous white matter. This hypersensitivity has not been demonstrated in human demyelinating disease (Stauffer and Waksman, 1954; Broman, Lidvall, Lind, and Meyer, 1960). Furthermore, both clinical studies of the incidence of other allergic disorders and attempts to demonstrate the presence of autoimmune antibodies in patients with multiple sclerosis have been almost uniformly negative (Prigal, 1956; Broman *et al.*, 1960).

If multiple sclerosis were associated with a generalized disturbance of delayed hypersensitivity some abnormality of the tuberculin reaction might be expected. In 1940 Canetti and Lacaze measured Mantoux reactions in many diseases and showed a significant increase in the size of reaction in patients suffering from disease of the nervous system; unfortunately this heterogeneous group included cases of hemiplegia, paraplegia, and Parkinson's disease, as well as patients with multiple sclerosis. In studies of white-matter sensitivity Stauffer and Waksman (1954) also administered intradermal tuberculin to multiple sclerotic patients and obtained apparently normal reactions, but these observations were uncontrolled. Smith, Hughes, and Hunter (1961) found the incidence of negative Mantoux reactions unexpectedly high in female patients with multiple sclerosis, and encountered difficulty in converting Mantoux-negative patients with Vole vaccine; they speculated that 'in multiple sclerosis there is a disorder of the delayed type of hypersensitivity'. This thesis of partial anergy was further supported by the study of Field, Green, and Miller (1961) showing a diminished reaction to TO antigen in response to booster inoculation of T.A.B. in patients with multiple sclerosis. Evidence has, therefore, been put forward suggesting both allergy and anergy in patients with multiple sclerosis, and these conflicting views are based partially on the results of

tuberculin tests, the prototype of delayed hypersensitivity reactions.

This study was performed to determine quantitative and qualitative tuberculin sensitivity in patients with multiple sclerosis and in a control group. Furthermore, other antigens giving delayed hypersensitivity responses were included in order to determine whether any difference demonstrated was peculiar to tuberculin or whether there was any general change in the delayed hypersensitivity reaction.

MATERIALS AND METHODS

PATIENTS The study comprised 80 subjects, 40 with chronic multiple sclerosis and 40 controls. All patients with a diagnosis of multiple sclerosis had signs or symptoms of multiple central nervous system lesions; their disease was longstanding (15 months to 35 years in duration) but none was bedridden or malnourished. The 40 controls included seven spouses of patients with multiple sclerosis and 33 ambulatory patients from the neurological and medical wards who volunteered for the study.

Patients with suspected tuberculosis or with a history of previous Mantoux testing or B.C.G. vaccination were excluded. Weight loss, cachexia, malignancy, collagen-vascular disease, rheumatoid arthritis, pregnancy, and circulatory disturbances of the arms have been reported to alter the tuberculin reaction (Pepys, 1955; Canetti and Lacaze, 1940): patients or controls with complaints suggesting any of these disorders were not tested. Patients currently or previously known to have been treated with hormones or antihistamines were similarly rejected.

Since age, sex, social status, environment, allergy, and past exposure to disease may influence tuberculin sensitivity these factors were compared (Table I). Social status was determined by occupational histories of the patients, their spouses, and their parents, using the General Registry Office classifications of occupations (1960). A higher social status of patients with multiple sclerosis compared with that of the general population of northern England has been reported by Miller, Ridley, and Schapira (1960), and this difference is reflected in this study. An even greater difference in social class was noted in the parents of patients, since 53% of the parents

TABLE I
COMPARISON OF 40 MULTIPLE SCLEROTIC
AND 40 CONTROL PATIENTS

	Multiple Sclerosis	Controls
Number of patients	40	40
Sex		
Male	17	19
Female	23	21
Age		
Range	26-63	19-60
Median	42	41
Mean	42.8	42.1
Social Status		
Class I	1	1
Class II	7	5
Class III	24	20
Class IV	6	10
Class V	1	4
Geographic Distribution		
Resident of urban North-east	37	29
Childhood in urban North-east	33	27
Immunological History		
Known exposure to tuberculosis	6	8
History of parotitis	17	16
History of allergy	7	4
Family history of allergy	12	7

of multiple sclerotic patients were in class III and 50% of the parents of control patients were in class IV. All patients were resident in northern England and over three-quarters in each group had spent their entire lives in Newcastle or the surrounding urban areas. Thus the multiple sclerotic patients and controls were comparable in all relevant respects except for an anticipated slight difference in social status.

ANTIGENS AND METHOD Tuberculin in the form of purified protein derivative (P.P.D.) was furnished by the Ministry of Agriculture and Fisheries Laboratory at Weybridge, mumps virus antigen was donated by Eli Lilly and Co., and *Candida albicans*, streptococcal antigen Fl (containing streptococci of Lancefield groups A, C, and G, *Strep. pneumoniae* and *Strep. salivarius*), and bacterial control antigen were obtained from the Bencard Allergy Division of Beecham Research Laboratories. Intradermal tuberculin was injected simultaneously into comparable sites on the two forearms in two dilutions, one containing 1 unit (0.028 mg.) per 0.1 ml. and one containing 10 units of P.P.D. per 0.1 ml. (0.28 mg.). Mumps, *Candida albicans*, streptococcal, and control antigens were similarly injected intradermally on the volar surfaces of the forearms in 0.1 ml. quantities. Sites of injection were examined in 10 minutes for wheal and flare reactions and at 24 and 48 hours for erythema and induration. Maximum and minimum diameters of areas of erythema and of induration were carefully measured and the average diameter determined.

The same batch of each antigen was used throughout and all questioning, injections, and measurement of reactions were performed by the same person to minimize variation.

RESULTS

IMMEDIATE HYPERSENSITIVITY Wheal and flare reactions were rare, occurring almost exclusively with *Candida albicans* and mumps antigens. These immediate hypersensitivity reactions were manifest against mumps antigen in six and *Candida albicans* antigen in three of the patients with multiple sclerosis, and in three and four respectively of the control patients. The differences are not statistically significant and could well have arisen by chance.

DELAYED HYPERSENSITIVITY To compare the incidence of delayed hypersensitivity reactions in the two groups, a diameter of induration of 0.5 cm. or more at 48 hours was interpreted as positive. Since induration in response to the mumps virus antigen was shallow and poorly defined, a diameter of erythema of 1.0 cm. or more at 48 hours was interpreted as positive for this antigen. These results are

TABLE II
INCIDENCE OF DELAYED
HYPERSENSITIVITY REACTIONS IN 40 MULTIPLE
SCLEROTIC AND 40 CONTROL PATIENTS

Antigen	Number and Percentage of Positive Reactions	
	Multiple Sclerosis	Controls
P.P.D. (tuberculin) 1 unit	23 (58%)	19 (48%)
10 units	31 (78%)	30 (75%)
Mumps virus	30 (75%)	26 (65%)
<i>Candida albicans</i>	12 (30%)	14 (35%)
Streptococcal group Fl	25 (63%)	21 (53%)
Bacterial control	1 (3%)	3 (8%)

shown in Table II, and indicate that the exposure and development of delayed hypersensitivity were similar in the two groups. Smith *et al.* (1961) reported in a large series of patients with multiple sclerosis that a higher percentage of females were Mantoux-negative than males, and state that this would not be expected in the general population. In this series 26% of females with multiple sclerosis were Mantoux-negative compared with only 18% of males; however, this difference was even more marked in the control group where 33% of females were negative compared with 16% of males. These findings suggest only that males in both groups had greater exposure to tuberculosis than females. No such discrepancy was found in reactions to mumps, *Candida albicans*, or streptococcal antigens.

To compare the nature of delayed hypersensitivity reactions any diameter of erythema and induration over 0.2 cm. was included, and at 24 and 48 hours average diameters of erythematous and indurated reactions were compared. These results are shown in

TABLE III

NATURE OF DELAYED HYPERSENSITIVITY REACTIONS IN 40 MULTIPLE SCLEROTIC AND 40 CONTROL PATIENTS

Antigen	Time (hr.)	Reaction Measured	Diameter of Reaction (cm.)			
			Multiple Sclerosis		Controls	
			Range	Mean	Range	Mean
P.P.D., 1 unit	24	Erythema, induration	0.5-4.0	1.65	0.4-3.6	1.54
			0.5-1.7	1.01	0.4-2.4	1.01
	48	Erythema, induration	0.6-6.0	2.41	0.4-6.2	2.47
			0.5-3.5	1.24	0.4-1.8	1.07
P.P.D., 10 units	24	Erythema, induration	0.5-5.0	2.53	0.8-6.5	2.62
			0.5-2.6	1.61	0.4-3.0	1.49
	48	Erythema, induration	1.3-9.0	4.91	0.8-10.5	4.54
			0.6-6.2	2.32	0.5-5.0	1.83
Mumps virus	24	Erythema	1.0-3.3	2.06	0.4-3.5	2.16
	48	Erythema	1.0-4.0	2.46	1.0-5.3	2.57
<i>Candida albicans</i>	24	Erythema, induration	0.4-3.5	1.22	0.3-1.8	1.03
			0.3-1.5	0.72	0.4-1.0	0.68
	48	Erythema, induration	0.3-3.2	1.57	0.4-3.2	1.56
			0.4-1.9	0.86	0.5-2.0	1.04
Streptococcal group F1	24	Erythema, induration	0.4-2.8	1.54	0.4-3.5	1.53
			0.3-2.5	0.64	0.3-1.9	0.79
	48	Erythema, induration	0.4-5.1	2.11	0.5-4.5	2.24
			0.4-1.7	0.64	0.3-1.8	0.78

Table III. There was no statistically significant difference in the size of erythema and induration shown in any of the 18 measurements carried out in each subject ($P < 0.3$). Further, the rate of reaction and the relation of reaction to dosage with P.P.D. were similar in the two groups.

CONCLUSIONS

These observations have failed to show any difference in the dermal delayed hypersensitivity reactions between patients with multiple sclerosis and comparable controls. Previous observations of hyper-reactivity and hyporeactivity to tuberculin have not been confirmed, and the reactions to mumps virus,

Candida albicans, and a mixed streptococcal antigen showed no enhancement or inhibition in patients with multiple sclerosis.

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