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SOME ASPECTS OF THE NATURAL HISTORY OF DISSEMINATED SCLEROSIS[1]

PART I. THE INCIDENCE, COURSE, AND PROGNOSIS

PART II. FACTORS AFFECTING THE ONSET AND COURSE

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PART I. THE INCIDENCE, COURSE, AND PROGNOSIS

A CLINICAL study of disseminated sclerosis was begun in April 1948. Between this date and September 1950 the case reports of 840 patients were examined. These were the records of patients who had attended the Middlesex Hospital since 1930 (651 cases), private patients of one of us (127 cases), a small number of patients seen at the Maida Vale Hospital for Nervous Diseases (20 cases), and 42 patients who had been seen through the courtesy of the Ministry of Pensions. We have been successful in tracing 675 of these cases by means of a letter to the doctor or to the patient, or to both. The following are the categories into which our material falls:

Traced:	Dead	78
	Not interviewed	122
	Reinterviewed and examined: alive	468
	Reinterviewed and examined: subsequently died	7
Untraced		165
		840

Among the group of 475 patients interviewed and examined, 250 form a consecutive series of patients seen for the first time by us between April 1948 and September 1950; 163 were in-patients of the hospital. The groups will be referred to as follows:

Group A. Total series of 840 patients.

Group B. Patients traced, 675.

Group C. Patients seen and re-examined between April 1948 and September 1950, 475.

Group D. 250 patients subjected to special inquiry.

The first part of this paper is largely based upon the 475 patients in Group C, the majority of whom were seen twice a year during the period of study. At the first interview the history was checked and brought up to date, and subsequently fresh developments and any correction or omission in the previous history were noted.

[1] Received August 31, 1951.

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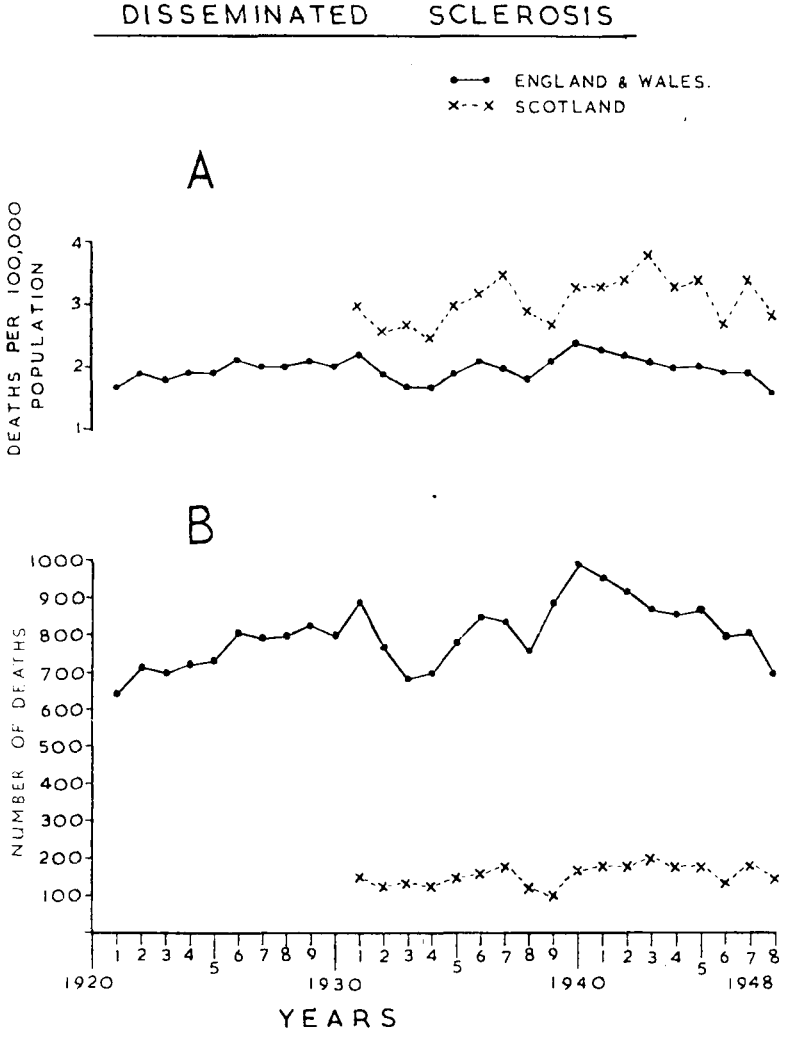
Incidence in the United Kingdom

Only a few limited surveys of the incidence of disseminated sclerosis have been conducted in the United Kingdom. In 1931 Allison reported the results of a survey of part of North Wales, where he found a prevalence-rate of 1 in 8,600



Death-rates (A) and total deaths (B) from disseminated sclerosis in England and Wales and in Scotland.

of the population. Subsequent experience in Northern Ireland (personal communication) has led him to assess the rate as being much higher in that country. Campbell, Herdan, Tatlow, and Whittle (1950) found an incidence of 1 in 5,000 in the population of Cornwall, Berkshire, Buckinghamshire, and Suffolk. A survey of 260 square miles around Stamford (Lincs.) revealed 18 cases in a population of 40,000, an incidence of 1 in 2,280 (Pratt, 1951*a*).

The graph shows the total number of deaths from disseminated sclerosis per year in England and Wales from 1921, when the figures first became available,

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until 1948, and those in Scotland from 1931. The mortality-rate from disseminated sclerosis per 100,000 of the population is also shown. In a later section of this paper we estimate that the average duration of life of patients with disseminated sclerosis is at least 20 years, so that the prevalence-rate of the disease can be calculated approximately by dividing the total number of persons dying from the disease in a 20-year period by the population in the first year of that period. This gives a prevalence-rate in England and Wales of approximately 1 in 2,400 (1929–48) and in Scotland of 1 in 1,570 (1931–50).

Sex Incidence

Allowing for a slight excess of females in the population of the United Kingdom, it has been generally accepted that they are more commonly affected than males. Brain (1947) assessed the sex ratio as three females to two males. Our material does not constitute a pure random sample, as it includes 42 patients seen through the Ministry of Pensions, 39 of whom were men. Of our total of 840 patients 522 were female and 318 male. If the Ministry of Pensions cases are excluded there are 519 female and 279 male patients; the percentage of females is 65 per cent. and of males 35 per cent., compared with 54 per cent. females and 46 per cent. males among other neurological patients attending the hospital. An analysis of the sex incidence of fatal cases recorded in the Registrar-General's Reports indicates that since 1921 there have been 10,222 male deaths (45·7 per cent.) and 12,144 female deaths (54·3 per cent.), giving a sex ratio of 1:1·21, compared with a sex ratio for the whole population of 1:1·08; the difference is significant. In Scotland the sex ratio for patients dying of disseminated sclerosis is the same as that in the general population (1:1·08). It can be concluded, therefore, that in the United Kingdom there is a slight excess of female over male patients.

Course of the Disease

It has long been recognized that the course of disseminated sclerosis may be characterized by relapses or remissions, or by chronic progression either from the onset or after a number of remissions (Charcot, 1872; Marie, 1892). Müller (1949) analysed the course of the disease in 810 cases. The average duration of hospital observation in these cases was 9·3 years, and there was an average of 5·6 years between the onset of the disease and the first registration at hospital. Müller defined an episode or 'bout' as the appearance of a new symptom or the return or exacerbation of a previous one. He classified episodes as remittent or progressive; among the former he included symptoms which receded partially or entirely or which, after a period of progression, became stationary. He regarded as progressive symptoms which, on the whole, became worse from the beginning or which, having been stationary or having regressed for less than one month, then progressed. He was able to classify 3,797 of the 3,932 bouts in his patients. Only 6 per cent. of bouts which progressed for one year eventually became remittent. The risk of a second bout was greatest during the first year, and of a third, fourth, or fifth during the first five years of the disease. The

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disease became progressive in about a quarter of the patients during the first two years, and in about half during the first 10 years of the disease. If the disease started with a remittent bout, and no fresh bouts occurred for five years, there was less risk of the disease subsequently becoming progressive than if further remittent bouts had occurred during that period. The longer the duration of remittent bouts, the greater was the likelihood that the following bouts would be progressive. About one in ten of the patients suffered from progressive disease from the onset. The risk of progressive disease was greater in older than in younger patients; it occurred in four-fifths of the patients at or over the age of 35 years; in one-third of the patients of this age-group the disease was progressive from the onset. Male patients were more prone than female patients to develop progressive bouts. Müller confirmed the view that the risk of progressive disease is greater when pyramidal pathways are initially involved than when the disease affects cranial nerves or sensory pathways. The methods used by Müller in his analysis and the conclusions drawn are of great value, but the difficulty in obtaining details as to the course of the disease by a single interview with a patient or relative, and from hospital notes going back in some instances 25 years, is obvious.

In our analysis of the course of the disease we have used the term 'episode' synonymously with Müller's term 'bout', but have analysed separately remittent episodes, progressive episodes, and episodes which show neither remission nor progression. Even in cases running a chronically progressive course, fresh remittent attacks may occur which affect symptoms other than those that are progressively deteriorating, but more commonly in this type of case the disease spreads almost imperceptibly. We have confined the detailed analysis of the course of the disease to patients in Group C of the material. Among the 475 patients in this group were 61 who gave a poor account of their illness, either from lack of co-operation or from poor memory, and these have been excluded, leaving 414 cases for analysis. These include eight patients whose only symptom was retrobulbar neuritis, but who all showed other signs of the disease in the nervous system.

It is necessary to examine the degree to which our results have been modified by the omission of patients, both traced and untraced, who have not been re-interviewed. It is not likely that the exclusion of untraced cases affects the issue, as in the main these patients were last seen early in the course of their disease, its average duration to the time when they were last seen being 6·6 years, compared with an average duration in the cases analysed of 11·3 years. Furthermore, the reasons why they were untraced are unlikely to have borne any relation to their state of health in the majority of cases. Attempts to trace them were made initially through doctors, and were unsuccessful in 103 instances. Attempts to trace patients directly were made in 62 instances: in 16 of these there was no reply, while in the remaining 46 letters were returned, indicating that the patients had changed their address. The omission of dead patients from the analysis almost certainly modifies the general picture. The omission of 122 patients traced but not reinterviewed probably modifies the results to a

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lesser degree, as only 30 out of this group were unable to be reinterviewed because of the advanced state of their disease; furthermore, the average duration of their disease was 15·9 years. Modifications of results by these omissions will be indicated in the appropriate section. As all patients in Group C have not suffered from the disease for the same length of time, there are decreasing numbers of patients available for analysis in each year after onset of the disease.

Relapses and remissions. Of the patients analysed from Group C, 21 suffered only a single progressive episode of their disease. A further 22 had a progressive

TABLE I

Frequency of Relapse in 393 Patients by Age at Onset

Age at onset (years)	*Number of patients*	*Number of patient-years*	*Number of episodes*	*Average number of episodes per year*
10–14	7	143	46	0·32
15–19	44	615	222	0·36
20–24	85	892	371	0·42
25–29	78	848	340	0·40
30–34	72	706	259	0·37
35–39	58	442	179	0·40
40–44	30	225	98	0·44
45–49	14	97	36	0·37
50–54	4	28	8	0·29
55–59	1	6	2	0·33
Total	393	4002	1561	0·39

symptom from the onset, but other symptoms such as diplopia, paraesthesiae, or a retrobulbar neuritis remitted. Three hundred and ninety-three cases, at some time or other, had episodic features in their course, although many sooner or later became chronically progressive. The histories of these 393 cases cover a total of 4,002 patient-years; they had 1,561 separate episodes of the disease, giving an average incidence of 0·39 attacks per year. Analysis of this material to show the attack-rate per year by age at onset (Table I) does not indicate any significant variations between the age-groups. The average yearly attack-rate for 155 male patients, who had 588 attacks in 1,556 years of disease, was 0·38, and that for 238 female patients, who had 973 attacks in 2,446 years of disease, was 0·40. Table II shows the attack-rate for each year of the disease up to the 30th year. It will be seen that the average attack-rate for each five years of the disease shows a slight fall after the first 10 years. Few cases were followed up for 25 years or more, so that the rate for the group 25–30 is not reliable.

Duration of episodes. We have been able to obtain accurate information as to the duration of episodes only in the cases in Group D. This group contains a high proportion of recent cases; therefore in order that the number should be significant we have limited the analysis to the duration of the first and second episodes. Among these 250 patients were 45 who had only one episode, either remitting, progressive, or stationary, and these are excluded. A further 16 are excluded because they were unable to give accurate enough information of

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either their first or second episode. The remaining 189 had first and second episodes as shown in Table III. There is a slight tendency for second episodes to be longer than first episodes. The second episode was of similar duration in 37 patients, shorter in 62, and longer in 90. It is our impression that later episodes tend to last longer than the first two.

TABLE II

Relapse Rate According to Year after Onset of Disease

Year of disease	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
Number of patients	393	377	347	316	285	265	238	214	196
Number of attacks	485	158	119	105	100	66	79	61	64
Average number of attacks per year	1·23 (0·23)	0·42	0·34	0·33			0·31		

Year of disease	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*19*
Number of patients	175	157	139	126	107	92	77	67	61	55
Number of attacks	52	44	29	35	25	17	15	13	16	13
Average number of attacks in 5-year groups			0·26					0·22		

Year of disease	*20*	*21*	*22*	*23*	*24*	*25*	*26*	*27*	*28*	*29*	*30*
Number of patients	48	43	39	31	25	23	19	16	14	13	13
Number of attacks	11	15	7	3	6	4	3	3	5	2	3
Average number of attacks in 5-year groups			0·22					0·20			

TABLE III

Comparison of Duration of First and Second Episodes in 189 Patients from Group D

	Days							*Weeks*							*Months*										*Non-remitting*
	<1	*1*	*2*	*3*	*4*	*5*	*6*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	
First episode	20	4	2	2	2	–	3	8	17	14	13	3	18	1	12	17	3	3	9	1	–	1	1	–	7	28
				33							86								42							28
Second episode	18	–	–	2	1	–	–	3	11	12	15	2	21	1	17	10	6	1	23	–	1	2	–	–	2	41
				21							82								45							41

Duration of first remission. Table IV shows the interval between the first and second episodes of the disease. Sixty patients are excluded from this Table, as they have had no second episode; twenty-one of these are the 'chronic progressive' cases referred to above, and the remaining 39, although they passed into remission following their initial attack, are mainly cases seen recently. From this Table it is apparent that approximately 35 per cent. of patients having a second attack did so within one year, 54·5 per cent. within two years, and 75 per cent. within five years of the onset of their disease. The first remission may last 15 or more years (19 patients, 5·3 per cent.). The longest remission in our series was 37 years. Cases presenting with retrobulbar neuritis (113) have been analysed separately in order to determine if a longer remission can be expected following this type of onset. Of the 19 patients whose remission lasted 15 years or more, 13 (68·4 per cent.) had commenced their disease with retrobulbar neuritis, whereas only 31·9 per cent. of all patients analysed in this Table did so ($\chi^2 = 12{\cdot}3$, $n = 1$, $P < 0{\cdot}001$).

The chronic progressive stage. The effect of sex, age at onset, duration of the disease, and number of previous remitting episodes upon the incidence of chronic progressive disease has been analysed. Out of a total of 414 patients, 146

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(35·3 per cent.) have so far passed into a chronically progressive stage of their disease. As many of our cases are still early, this figure must underestimate the overall incidence of this type of case. This fact is further emphasized by the higher incidence of such cases in the groups excluded from analysis because of inadequate information. Among the 78 patients who were traced and had died, 48 (61·5 per cent.) were in a chronically progressive stage of the disease when

TABLE IV

Interval between First and Second Episodes (354 Cases)

Cases commencing with retrobulbar neuritis shown separately.

Duration (years)	*With retrobulbar neuritis*	*Without retrobulbar neuritis*	*Total*	*Percentage with retrobulbar neuritis*
1 or less	43	81	124	29·7
2	15	54	69	
3	9	24	33	
4	7	16	23	
5–9	19	49	68	27·9
10–14	7	11	18	38·9
15–19	5	4	9	55·6
20–24	5	2	7	71·4
25–37	3	—	3	100·0
Total	113	241	354	31·9

last seen. The percentage of chronically progressive cases among patients traced but not reinterviewed was 42·6. Further, in both these groups there was a higher incidence of disease chronically progressive from the start—19 cases out of 78 (24·4 per cent.) among the dead and 16 out of 122 (13·1 per cent.) among the living patients. Sex had no bearing on the occurrence of chronic progression. Of our patients with chronic progressive disease 60·3 per cent. were females, while 60·7 per cent. of the remaining 268 who have so far continued a remitting course are also females.

Age at onset in chronic progressive cases. Of the 146 patients running a chronic progressive course, 43 did so from the onset, and 103 after a preliminary relapsing course. Analysis of the age at onset in the 43 cases progressive from the onset (Table V) shows that these cases occurred at all ages from the 20th year onwards,

TABLE V

Age at Onset of 43 Cases Chronically Progressive from First Episode Compared with Age at Onset in Remitting Cases

Age at onset (years)	*10–14*	*15–19*	*20–24*	*25–29*	*30–34*	*35–39*	*40–44*	*45–49*	*50–54*	*55–59*
Remitting cases	7	44	82	75	69	52	26	11	4	1
Chronic progressive cases	..	..	3	6	10	10	7	5	2	..
Total	7	44	85	81	79	62	33	16	6	1
Percentage chronic progressive	..	..	3·5	7·4	12·7	16·1	21·2	31·3	33·3	..

but none under 20 years, although 51 out of the total of 414 cases in Group C (12·3 per cent.) commenced before the age of 20 years. Of these 43 cases nine (20·9 per cent.) commenced in the third decade of life, 20 (46·5 per cent.) in the fourth, 12 (27·9 per cent.) in the fifth, and two (4·7 per cent.) in the sixth.

Duration of disease prior to onset of the chronic progressive stage. Table VI shows the number and percentage of patients who enter the chronic progressive

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stage, and the number and percentage of cases in the chronic progressive stage, for each year or group of years after onset. It is apparent from this Table that, apart from the first year of the disease, there is a fairly constant rate of change from a remitting to a progressive course, and that there is a gradual rise in the total percentage of progressive cases as the disease advances.

TABLE VI

Numbers of Patients Changing from a Remitting to a Chronically Progressive Course, and those in the Chronic Progressive Stage, in each Year or Group of Years of Disease

	Numbers or average numbers of patients			
Year of disease	*Total*	*Following remitting course at beginning of each year*	*Becoming chronically progressive for first time during each year*	*Chronically progressive in each year*
1	414	..	43 at onset +4 = 47 (11·4%)	47 (11·4%)
2	397	351	10	46
3	367	311	12 (3·7%)	56 (15·0%)
4	335	272	13	63
5–9	252·8	187·4	9·0 (2·9%)	65·4 (25·9%)
10–14	144·8	102·4	6·6 (3·9%)	42·4 (29·2%)
15–19	68·6	45·4	2·6 (3·2%)	23·2 (32·0%)
20–24	38·6	23·4	1·2	15·2 (39·4%)
25–29	18·0	10·0	0·4 (4·6%)	8·0 (44·4%)
30–34	7·4	3·0	0·2	4·4 (59·5%)
35–40	2·4	2·0	0·0	0·4 —

TABLE VII

Number of Episodes Before Onset of Chronic Progression (146 Patients)

Number of episode	*Number of patients exposed*	*Patients becoming chronically progressive*	
		Number	*%*
1	414	43	10·4
2	357	37	10·6
3	255	28	11·0
4	170	13	7·6
5	116	12	7·7
6	79	3	
7	46	3	
8	37	3	7·1
9	30	2	
10+	67	2	3·0

Number of previous attacks. Correlation of the onset of the stage of chronic progression with the number of previous episodes of disease, shown in Table VII, indicates that there is a slightly decreased tendency for cases to become chronically progressive at and after the fourth episode ($\chi^2 = 5{\cdot}33$, $n = 1$, $0{\cdot}02 < P < 0{\cdot}05$).

The nature of the disability in chronic progressive cases. In Table VIII symptoms in the chronic progressive group of patients are compared with those in a similar number of patients running a remitting course. The latter group was compiled by taking at random from the remitting group a number of first, second, third, or later episodes comparable to those which, in the chronic progressive group, had initiated a downhill course. The tendency for motor (including cerebellar) symptoms to progress and sensory symptoms to remit will be noted.

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Degree of recovery from episodes. The previous section has dealt with the occurrence of episodes which not only showed no degree of recovery, but passed into a stage of chronic deterioration. The number of patients so affected was 146, and of the remaining 268 patients some had episodes that showed only a slight degree of recovery or none at all. The frequency of such episodes has been analysed in order to determine whether persistent disability is influenced

TABLE VIII

Symptoms Occurring in Chronic Progressive Episodes Compared with Symptoms in Remitting Episodes

Symptom	*Chronic progressive*	*Remitting*
Motor	97	43
Motor with cerebellar	8	1
Motor and sensory	27	20
Motor with diplopia or retrobulbar neuritis	13	5
Sensory	1	41
Diplopia only	—	6
Vertigo	—	2
Retrobulbar neuritis only	—	21
Retrobulbar neuritis with diplopia or sensory	—	6
Impotence	—	1
Total	146	146

TABLE IX

Number of Attacks showing Failure to Remit, Grouped according to Episodes

Number of episode	*Total number of attacks*	*Number not remitting*	*Percentage not remitting*
1–4	1075	182	16·9
5–9	296	27	9·1
10–14	55	6	10·9
15+	10	—	—

by the duration of the disease or by the number of previous episodes. Table IX shows that out of 1,436 attacks suffered by our patients, 215 (15 per cent.) were not followed by any reasonable degree of remission. The 146 episodes leading to chronic progressive disease are excluded from this Table.

Of the first four episodes, 16·9 per cent. failed to remit, compared with 9·15 per cent. of all others. The difference is significant ($\chi^2 = 12{\cdot}9$, $n = 1$, $P < 0{\cdot}001$). Duration of disease, irrespective of the number of attacks, does not affect this tendency. It appears that the tendency for episodes to pass into remission is lower during the first few attacks, and that thereafter it remains unaltered. There is, of course, an increasing percentage of patients in each year who are in the stage of chronic progression or who suffer from established disability, because of the yearly increment of cases passing from a relapsing and remitting course to a progressive or stationary course.

Prognosis

Degree of disablement. Standards used to assess the degree of disablement have usually been based either upon working capacity or upon degree of mobility. The former criterion is unreliable, as it must depend upon individual

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fortitude, economic needs, and the nature of employment. The degree of mobility is a better standard, although here again the factors already mentioned play a part. Kolb (1950) estimated the degree of disability in 176 of a total of 199 cases followed up for 10 years. Eighty per cent. of the patients were unable to work within five years of the onset of their disease, and no patient was able to work after the 15th year of disease. Thygesen (1947), in a study of 110 patients followed up and re-examined for eight to 15 years, found 25 per cent. able to do some form of work; but in assessing the duration of disease he did not take into account an initial retrobulbar neuritis. Müller (1949) classified his patients as normal, or having slight, moderate, or severe disablement, those in the second group being able to walk out of doors with the help of one stick, those in the third only with two sticks or support, and those in the fourth being either completely disabled or only able to get about with great difficulty inside the house. From the information given it is possible to calculate that at five years approximately 11 per cent. of his patients were slightly disabled, 17·2 per cent. moderately disabled, and 15·8 per cent. completely disabled. At 10 years the figures are 6·7 per cent., 19 per cent., and 29 per cent.; and at 15 years 8 per cent., 18 per cent., and 40 per cent. respectively. Müller studied in detail the factors in his material which appeared to warrant a bad prognosis. Whereas 76 per cent. of episodes affecting the cranial nerves and sensory pathways passed into complete remission, only 30 per cent. of episodes affecting motor pathways did so. The ultimate prognosis was dependent upon the initial symptom of the disease, motor involvement again leading to a higher rate of early disablement than sensory or cranial-nerve involvement. Ninety per cent. of patients became disabled within two years of the onset of a progressive episode. Motor symptoms had a worse prognosis in the older patients than in the younger, and a slightly better prognosis in women than in men.

In seeking to classify the degree of disability of our patients we have discarded a classification based upon working capacity, as among our patients are some who, for example, gave up work on the appearance of trivial disability, and others who persisted working in the face of a complete paraplegia. We have classified our patients according to their degree of mobility. Such a classification has a number of shortcomings, as it does not incorporate disability due to defective vision and impairment of function of the upper limbs, nor does it take account of the difficulties presented by defective bladder-control. Our classification is as follows:

1. *Unrestricted.* Without restriction of activity for normal employment and domestic purposes, but not necessarily symptom-free.
2. *Restricted.* Able to walk unaided for short distances (up to half a mile), and able to get on and off public transport.
3. *Markedly restricted.* Capable of moving out of doors with difficulty for up to a quarter of a mile, usually with the aid of sticks; often unable to use public transport.
4. *Mobile at home.* Able to move with difficulty about the house, with support from furniture; unable to mount stairs.

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5. *Immobile at home.* Confined to a chair or wheelchair, and entirely dependent upon others for moving from room to room.
6. *Bedridden.*

We have classified the disability of our patients according to their standard between active episodes of their disease, since many patients during attacks are immobile or confined to bed. In this analysis we have been able to use only

TABLE X

Degree of Disablement, according to Year of Disease, in 414 Patients

Year of disease	Numbers or average numbers of patients	Percentage in each category									
		Unrestricted		Restricted		Markedly restricted		Mobile at home		Immobile at home	Bedridden
1	414	72·7		24·4		2·9		0·0		0·0	0·0
2	397	67·0		25·4		7·1		0·0		0·5	0·0
3	367	61·3	63·1	27·8	26·8	9·5	8·9	0·3	0·7	0·5	0·5 0·2
4	335	57·6		28·7		12·5		1·2		0·0	0·0
5	304	53·3		28·3		14·8		2·6		0·7	0·3
6	282	50·4		28·4		17·4		2·1		1·4	0·3
7	249	49·0		28·9		16·9		2·8		2·0	0·4
8	224	48·7	47·8	25·4	27·2	19·6	19·1	4·5	3·4	0·5	1·8 1·3 0·7
9	205	46·8		26·3		19·0		5·4		0·9	1·6
10	180	42·2		26·1		24·5		2·8		4·4	0·0
11–15	127·8	44·1		23·9		23·6		4·0		3·8	0·6
16–20	63·6	39·7		28·3		19·5		5·0		7·5	0·0
21–25	33·4	32·3		25·7		24·6		9·0		7·8	0·6

the 414 cases from Group C, because of insufficient detail in the information relating to the other groups. In any group of patients who are seen for the first time at varying intervals after the onset, an unduly favourable impression will be gained both as to degree of disability and the duration of life. The inclusion of the remaining 78 patients in our series who are dead, and of those who though traced were not interviewed, would undoubtedly modify the general picture and indicate a higher proportion of patients in the more disabled groups at each year of disease. Table X indicates the percentage of patients in each category by years of disease. The figures for the years after 25 are based on such small numbers as to be insignificant, and have been omitted.

Prognosis as to life. 'The duration of the disease varies greatly in different cases. The course is slow and chronic; the disease may last for 20 or more years before the fatal termination is reached. In rare cases the disease pursues a rapid course. It is probable that in a few rare and exceptional cases the disease is permanently arrested'; so wrote Byrom Bramwell in 1905. Since that date little accurate information about the duration of life has been added. Three methods have been used: (1) that of 'following forward' from the onset, requiring a study over many years; (2) subtraction of the average age of onset from the average age at death; (3) estimation of the average duration of fatal cases, and comparison of this with the normal duration of life of controls. These last two methods are dependent upon accuracy in establishing the age of onset and the diagnosis at death. For example, Limburg (1950) calculated an average duration of 20 years in Holland, and of 40 years in Canada. The latter is obviously an over-estimate, and was due to the fact that a proportion of the deaths attributed to disseminated sclerosis were in fact due to cerebral sclerosis (Kurland, 1951). In Müller's material (1949; 810 cases) the average duration

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of life in fatal cases was 10·4 years. He estimated that 38 per cent. of patients are dead by the 20th year of the disease, the figure for chronic progressive cases being 50 per cent. He calculated that, if all his living patients immediately died, the average duration of life for the whole group would be 16·4 years, and that, if all his living cases had a normal expectation of life as calculated from life tables, the average duration of life of the whole group would be 33·8 years.

TABLE XI

Duration of Disease in 840 Patients at Death, or to September 1950

Duration of disease in years		*1–4*	*5–9*	*10–14*	*15–19*	*20–24*	*25–29*	*30–34*	*35–39*	*40–50*
475 patients seen between April 1948 and Sept. 1950	Alive	129	139	107	40	30	12	8	3	0
	Dead	1	0	2	1	2	1	0	0	0
191 patients traced in 1948–50 but not seen	Alive	5	25	28	24	15	11	7	1	2
	Dead	7	21	21	10	9	4	1	0	0
165 untraced patients (onset to date of last information)		80	42	21	16	5	1	..	..	..
Patients dead, but date of death unknown (onset to date of last information)		5	1	2	0	0	1	..	..	..

Thus the actual duration of life in his series must lie between these two figures. In 1950 Allison reported the result of a follow-up of 40 unselected patients observed during a survey of North Wales in 1930, and found that 28 had died. The average duration of disease in these 28 patients was approximately 20 years. He calculated that when all the patients had died the average duration would be somewhat greater than 22 years. Forty per cent. of the patients who died had survived for over 20 years from the onset of their disease. Although the numbers followed are small, Allison's calculations are of importance. As a considerable proportion of our patients seen between 1930 and 1939 have not been traced, and as 250 out of the total of 840 have been seen for the first time since 1948, it has not been possible to make an estimate of the duration of life. Table XI gives some information about the duration of the disease in our patients. From the calculations of Müller and Allison it seems probable that the average duration of life in disseminated sclerosis is at least 20 years.

Direct causes of death. It is rare for patients suffering from disseminated sclerosis to die in general hospitals. The majority die at home or in institutions for the chronic sick, where autopsies are seldom performed. Death directly due to involvement of vital centres in the central nervous system is rare, and is largely confined to patients with acute disease who die within a few months of the onset. Reinhold (1950) reported the secondary cause of death determined at autopsy in 57 cases; 26 patients died of respiratory infection, 12 of urinary infection, eight from 'cachexia and septic absorption from bed sores', two from involvement of medullary centres by the disease, and the remainder from carcinoma, peptic ulcer, cerebral haemorrhage, aplastic anaemia, overdose of a hypnotic, or as a result of surgical exploration. Zimmerman and Netsky (1950) performed autopsies upon 41 patients and found the surprising incidence of coexistent malignant neoplasm in 10. They pointed out that death was usually due to multiple causes, 60 per cent. of their patients having bronchopneumonia, 42 per cent. decubitus ulceration, and 40 per cent. urinary tract infection. Three of their patients showed old or recent myocardial infarction. Among our cases are three examples of death from respiratory failure; one such patient died within

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three months of the onset. One other patient died at home in status epilepticus; Müller (1949) recorded two similar cases. Of the remaining 81 patients in our series who have died, information is limited to 29, of whom 14 died from respiratory infections, three from infection attributed to bed sores, three from intestinal obstruction (in two cases paralytic and in one case organic). The remainder died of rheumatic heart disease (1), cerebral haemorrhage (1), tuberculosis (1), nephritis (1), carcinoma of the oesophagus (1), coronary thrombosis (1), secondary carcinomatosis (1), myocardial disease (1), and accident (1).

PART II. FACTORS AFFECTING THE ONSET AND COURSE

In 1946 one of the authors reported the results, in 142 cases, of a study of factors that might influence the onset and course of disseminated sclerosis (McAlpine, 1946). In April 1948 it was decided to continue this study and extend its scope, in the hope that detailed information about the general health of these patients would throw some light upon the pathogenesis of the disease. A consecutive series of 250 cases (Group D) was chosen for this purpose. Each patient was interviewed by one or other of the authors, and information was obtained in three sections: (1) the whole-life history, (2) the history of health in the three-month period preceding onset, and (3) the history of health in the three-month period preceding each relapse. The period of three months preceding onset and relapses was arbitrarily selected as being a reasonable period during which factors in health might be operative. After establishing the dates of onset and relapse, the patients were questioned in accordance with a schedule which covered many aspects of general health, such as trend of weight, trauma (including operations and dental extractions) infections, allergic disorders, gastro-intestinal and skin diseases, vasomotor abnormalities, rheumatic diseases, history of immunization, emotional disturbances, pregnancy and menstrual history, and tobacco and alcohol consumption. A family history was also obtained from each patient, to include grandparents, aunts and uncles, and cousins where possible. There were, however, many patients who were unable to provide reliable information about their families.

The use of a control population was considered essential. It consisted of 250 random admissions to the Middlesex Hospital, and included patients from almost all departments, selected to give the same sex- and age-distribution at the time of interview as cases in Group D. Information from the control patients was necessarily confined to family history, whole-life history, and history of the three-month period before the onset of their disease. The list of control patients included many who were admitted as a direct result of some disorder which was sought in the history of patients with disseminated sclerosis, and therefore the control population showed an unreal incidence, for example, of rheumatic fever and peptic ulcer. Certain corrections were therefore necessary in making a comparison. There are inherent difficulties in comparing a study group of patients with a control group. The time interval between the onset of illness and the date of inquiry in the latter group is likely to be considerably shorter than in

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the study group. Furthermore, the interest taken in the study group over a period of years may favourably affect the tendency to recall facts in their medical history and their degree of co-operation. Therefore, although statistically significant differences occur between the two groups, it is not always possible to accept their validity with confidence.

Family History

1. Disseminated sclerosis. A previous paper (Pratt, Compston, and McAlpine, 1951) reported the results of an investigation into the familial incidence in 310 cases. An incidence of 6·5 per cent. was found; one in 108 of the sibs was affected, and one in 115 of the parents. An analysis of our own and published familial cases of disseminated sclerosis indicated that a predisposition to develop the disease may be genetically determined. The evidence suggested that this predisposition could be inherited by both a dominant and a recessive mode. Thirty-five (5·2 per cent.) of our 675 traced cases, and 15 (6 per cent.) of the 250 specially studied, were familial.

2. Other diseases. Few investigations into the occurrence of other diseases in the families of patients have been reported. Curtius (1933) investigated the family history of patients with disseminated sclerosis, and concluded that both a specific tendency to develop the disease and a non-specific 'more general neuropathic constitution' were inherited in the same families. He found examples of hereditary tremor, nystagmus, stutter, ocular palsy, and various reflex abnormalities, in the families of 30 of his 106 patients. In the present study we investigated the incidence of allergic diseases, migraine, rheumatic fever, rheumatoid arthritis, chorea, Bright's disease, diabetes, peptic ulcer, tuberculosis, hypertension, and degenerative diseases of the cardiovascular system, in the families of the patients in Group D. Neither relatives nor their medical records could be examined. In both the study group and the control group a large number of affected relatives must have been omitted. Analysis showed that, with the exception of disseminated sclerosis, no disease was more common in the families of the disseminated sclerosis group than in the families of the controls.

Medical History

The incidence of various factors in the health of the 250 patients was compared with the incidence in the control population; the three-month periods before onset and relapse were excluded. Nine patients admitted with rheumatic disease, and 13 with peptic ulcer, accounted for the increased incidence of these diseases among the controls. The incidence of certain fevers in the control group was unaccountably greater than in the study group. A significant increase in the incidence of superficial infections (including whitlows, boils, carbuncles, infected cuts, bites, and burns) was apparent in patients in the study group—193 cases (77·2 per cent.) compared with 134 (53·6 per cent.) in controls ($\chi^2 = 30{\cdot}7$, $n = 1$, $P < 0{\cdot}001$). This difference was accepted with some reserve, as control patients, interviewed only once, had less opportunity to recall minor incidents in their medical history, and were unable to obtain information from

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their parents. The incidence of allergic disorders (including clear-cut examples of asthma, hay fever, urticaria, angioneurotic oedema, food allergy, contact dermatitis, and eczema) was also higher in Group D—68 (27·0 per cent) compared with 41 (16·8 per cent.) in the controls. Six control patients admitted for the treatment of allergic disease were excluded. The significant difference ($\chi^2 = 7{\cdot}7, n = 1, 0{\cdot}01 > P > 0{\cdot}001$) found between the two groups is probably valid, as these disorders, producing rather striking manifestations, are likely to be readily recalled on direct questioning. In 17·6 per cent. of patients the allergic history was positive before the onset of disseminated sclerosis. Reference to the incidence of allergy in the past history of patients with disseminated sclerosis has been made by Baer and Sulzberger (1939), who concluded that the incidence was at the upper limit of normal. Their study concerned only 30 patients, and controls were not used. In a series of 142 cases McAlpine (1946) obtained a history of a previous attack of asthma, hay fever, or urticaria in 6 per cent. of cases. Alexander, Loman, Lesses, and Green (1950) studied the effect of blood transfusion in 50 patients with disseminated sclerosis. Allergic reactions to transfusion, usually urticarial, occurred in 14 per cent. of 298 transfusions in these patients, compared with an incidence of 0·4 per cent. in 1,795 transfusions performed on other patients at the same hospital.

Age at Onset

The determination of the age at onset of disseminated sclerosis is often difficult. In this paper it is taken as the time when symptoms first appeared. In many cases the initial symptom interferes so little with the health of the individual that no attention is paid to it, or with the passage of time it is forgotten. Despite careful history-taking, therefore, it is probable that in a significant proportion of our patients the actual date of onset of the disease was earlier than determined by us. According to published figures, the highest incidence of onset of disseminated sclerosis is during the third decade. The incidence in the third and fourth decades combined lies between 60 and 80 per cent. An appreciable number of cases, 11 per cent. in our series, commence in the second decade. The incidence falls rapidly after the age of 40 years, and only occasionally does the disease occur after the age of 50. Müller (1949) found the age of onset in his 810 cases to be lower than that found by others, with 22 per cent. of cases occurring before the age of 20, and 65·5 per cent. before the age of 30 years. The maximum incidence occurred at 20–21 years. The ages at onset in our series of 840 patients are shown in Table XII. Among the 41 cases occurring below the age of 16 years, there was a higher proportion of female patients (29). In Müller's series, of 46 patients with an onset before the age of 14 years 35 were female. This indicates a special preponderance of female patients in this age-group.

Precipitating Factors

Frequent references have been made in the literature of disseminated sclerosis to the effect of various exogenous factors on both its onset and its course. Charcot

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(1872) referred to the prolonged action of moist cold, injury, and emotional disturbances, but he pointed out that these factors may also be encountered at the beginning of other chronic diseases of the nervous system. Febrile illnesses, injuries, pregnancy, emotional upsets, localized infections, and malnutrition have all been put forward as causative or contributory factors in the genesis of the disease. Von Hoesslin (1934) and McAlpine (1946) made clinical studies of

TABLE XII

Ages at Onset in 840 Patients with Disseminated Sclerosis

Age at onset (years)	*Males*	*Females*	*Total*
10–14	5	7	12
15–19	30	56	86
20–24	52	91	143
25–29	59	95	154
30–34	63	83	146
35–39	44	84	128
40–44	35	59	94
45–49	21	29	50
50–54	7	13	20
55–59	1	5	6
60–64	1	0	1
Total	318	522	840

these factors, but did not use controls. In the following sections of this paper we shall briefly review the literature and present our own findings. Where doubt has existed about the time interval within the three-month period, it has been taken as three months.

Febrile illnesses. In 1884 Pierre Marie drew attention to the occurrence of disseminated sclerosis within a few months of an infectious fever. He also referred to the possible role of fevers of undetermined origin, attended in some instances by gastro-intestinal or pulmonary symptoms. Since Marie's paper infectious fevers and other types of infection have been considered by most writers on the subject of aetiology. The interval between the infection and the onset of symptoms has seldom been mentioned, and furthermore some of the cases recorded would now be classified as acute disseminated encephalomyelitis. Von Hoesslin (1934) found a feverish illness preceding the onset in 18 (16·5 per cent.) out of 109 cases beginning acutely. Kolb, Langworthy, and Cakrtova (1942) found evidence of fever in only four of 199 cases. McAlpine (1946) obtained a history of fever associated with a chill, generalized pains or sore throat, usually described as 'influenza', in eight (5 per cent.) of 142 cases. In no instance did the disease follow one of the infectious fevers.

The results of our study indicate a low incidence of febrile illness preceding the onset of the disease. A history of tonsillitis or quinsy in the three-month period preceding onset of the disease occurred in 10 patients of the disseminated sclerosis group, and in three of the control group. In only two of the cases did tonsillitis occur within four weeks of the onset. The incidence of coryza and 'influenza' in the same period—15 cases in the disseminated sclerosis group and 18 in the control group—was also scattered widely throughout the three-month period preceding onset. In only two patients did the disease commence within three

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months of an attack of an infectious fever. After onset 21 patients suffered from acute tonsillar infection, and six of these patients developed a fresh episode of their disease within three months. Pneumonia occurred in five patients after onset, and bronchitis in eight, without further episodes of the disease. But of 19 patients who have a history of 'influenza' 11 suffered a fresh episode of disease within three months. In five of these patients the relapse developed on the first day of the influenzal attack.

Trauma. Mendel (1897) described four cases of disseminated sclerosis in which the onset of the disease appeared within a year of severe trauma. He considered that trauma might be an aetiological factor if there was direct injury to the skull or spine, if no other cause was obvious, if symptoms were previously absent, and if there was a definite time-relationship between the appearance of the first symptoms of the disease and the accident. Mendel concluded that, in persons in whom there is a predisposition to the disease, trauma may be followed by signs of disseminated sclerosis which might not otherwise have developed. In Hoffmann's (1901) series of 100 cases there was a history of severe trauma in 13 patients, in eight within a year of the onset. Klausner (1901) obtained a history of trauma in 26 out of 126 cases; except in two cases the interval was less than a year. The conclusion reached by the Association of Research into Nervous and Mental Diseases in 1921 was as follows: 'In a small percentage of cases it appears to be excited by trauma, but trauma cannot itself cause it, but may apparently awaken a disease process already potentially existent.' Harris (1933), in a series of 234 cases of disseminated sclerosis, found that in 16 cases symptoms developed shortly after severe injuries to the back or head. In von Hoesslin's study (1934) of 516 cases, trauma (including operations) precipitated the onset in 58 cases (11·4 per cent.). The time interval between the trauma and the onset of symptoms was not given, though he implied that in the majority of cases this was not more than two months, and in some cases considerably less. In 109 cases with an acute onset, trauma appeared to be a precipitating factor in 36 (33 per cent.). Von Hoesslin was the first to suggest that there may be a relationship between the site of the trauma and the level of the lesion in the nervous system. McAlpine (1946) found that trauma, unassociated with sepsis and unrelated to a fall caused by the disease, occurred within a month of the onset in eight out of 142 cases (5 per cent.). Both von Hoesslin and McAlpine concluded that there are cases of disseminated sclerosis in which there can be little doubt of the close relationship between trauma and the appearance of signs of the disease. Kolb, Langworthy, and Cakrtova (1942), in their study of 199 cases in Baltimore City, obtained a history of trauma in four (2 per cent.). Their reasons for rejecting many cases seem inadequate.

In the present series (Group D) a history of trauma during the three months preceding the appearance of the first symptoms of the disease was obtained in 36 cases (14·4 per cent.). Care was taken to exclude cases in which trauma was possibly due to an early symptom of the disease. The site of the injury was correlated with the approximate site of the initial lesion in the central nervous system. Table XIII shows the time-relationship of trauma to onset in all cases,

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and separately in those cases in which the site of injury bore a relationship to the site of the initial symptom. Dental extraction is included in this section. In 22 out of 36 patients there was a correlation between the site of injury and the site of the initial lesion; this was striking in patients who developed symptoms within one week of injury (nine out of 11). In the control series 13 patients received injury within a three-month period of the onset of their disease; an additional eight were admitted to hospital for treatment of the injury itself. The time-relationship in these cases is also shown in Table XIII.

TABLE XIII

Time-Relationship of Injury to Onset of Disease

(a) Injury preceding onset (all cases)

	Weeks								*Days*						
	9–12	*8*	*7*	*6*	*5*	*4*	*3*	*2*	*1*	*6*	*5*	*4*	*3*	*2*	*1*	*<1*
Disseminated sclerosis	9	2	–	1	2	6	1	4	–	–	–	2	1	2	1	5
	36 (14·4%)															
Controls	5	2	–	1	–	1	–	–	–	–	–	–	2	2	–	–
	13 (5·2%)															

(b) Injury preceding onset, related to site of lesion

	Weeks								*Days*						
	9–12	*8*	*7*	*6*	*5*	*4*	*3*	*2*	*1*	*6*	*5*	*4*	*3*	*2*	*1*	*<1*
Disseminated sclerosis	4	1	–	1	1	3	1	2	–	–	–	1	1	2	1	4
	22															

The incidence of trauma in the disseminated sclerosis group is significant ($\chi^2 = 11{\cdot}3$, $n = 1$, $0{\cdot}01 > P > 0{\cdot}001$). To obtain confirmatory information regarding the figure of 55·5 per cent. of injuries related to the site of the initial lesion, the relationship of remote injuries was studied. In 31 patients, out of a total of 146 who suffered injury more than three months before the onset of their disease, the site of their initial lesion was related to the site of injury (21·2 per cent.). Even allowing for the greater likelihood that injury, especially when apparently related to the first symptom, will be recalled in patients suffering from disseminated sclerosis, it seems probable that injury does sometimes precipitate the onset of the disease, and may determine the site of the initial lesion.

Fifty-eight patients suffered 80 traumatic incidents after the onset of their disease, and in 29 of these patients the trauma was followed within three months by a fresh episode of the disease. A number of patients had an episode following trauma on more than one occasion; in all, 34 episodes followed trauma. Cases in which it appeared that trauma was due to a fall caused by disability were excluded. In Part I of this paper we showed that the average number of relapses per year in all patients is 0·39. The average number in three months is therefore approximately 0·1. In 80 three-month periods following trauma there were 34 episodes of the disease, giving a relapse-rate of 0·43. This difference suggests

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that trauma influences the occurrence of relapse, but its validity depends upon the accuracy of the figure for traumatic incidents that were not followed by episodes of the disease. Such incidents are more likely to have been overlooked by patients than those followed by fresh developments. Included among the 80 incidents of trauma were 36 operations. In the three-month periods following these operations nine patients developed fresh lesions, giving a relapse rate of 0·25, which differs significantly from the overall relapse rate.

Superficial infections. Under the heading of superficial infections we have included septic conditions such as boils, abscesses, and infected burns or cuts, on the limbs, trunk or face (including dental sepsis). In the disseminated sclerosis group 27 patients gave a history of some infected lesion in the three-month period preceding onset, compared with seven in the control group. This difference is significant ($\chi^2 = 12{\cdot}4$, $n = 1$, $P < 0{\cdot}001$), but the same reservations as have been made in the case of trauma govern its validity. The time-relationship of sepsis to the onset of the disease, and its relationship, if any, to the site of the initial lesion, are shown in Table XIV. Similar figures for the control group are also shown. The tendency for superficial infections to determine the site of the initial lesion in disseminated sclerosis has previously been noted (McAlpine, 1946).

TABLE XIV

Time-Relationship of Sepsis to Onset of Disease

(a) Superficial sepsis preceding onset (all cases)

	Weeks									*Days*						
	9–12	*8*	*7*	*6*	*5*	*4*	*3*	*2*	*1*	*6*	*5*	*4*	*3*	*2*	*1*	*<1*
Disseminated sclerosis	10	1	–	1	–	6	–	2	–	–	–	–	1	1	–	5
	27 (10·8%)															
Controls	3	–	–	–	–	1	–	2	–	–	–	–	–	1	–	–
	7 (2·8%)															

(b) Superficial sepsis preceding onset, related to site of lesion

	Weeks									*Days*						
	9–12	*8*	*7*	*6*	*5*	*4*	*3*	*2*	*1*	*6*	*5*	*4*	*3*	*2*	*1*	*<1*
Disseminated sclerosis	2	1	–	–	–	2	–	1	–	–	–	–	1	1	–	2
	10															

Sixty-eight patients suffered from 103 superficial infections after the onset of their disease. Twenty-two of these patients suffered fresh episodes of disease within three months on 30 occasions; in 60 patients the infection had no effect upon their disease on 73 occasions. On only seven of the 30 occasions were the sites of sepsis and of neurological manifestations related. The relapse-rate of the three-month period following superficial infection, calculated as for trauma above, is 0·29, compared with the general relapse-rate of approximately 0·1 for that period.

Pregnancy. In textbook accounts of disseminated sclerosis reference is usually made to pregnancy as a factor which may precipitate or influence the course of

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the disease. In this country this view appears to have originated in a single sentence in Gowers' *Textbook of Nervous Diseases* (1893): 'I have known it to begin during pregnancy, remain stationary until the next pregnancy, and then become progressive.' At the end of the last and the beginning of the present century references appeared in the German literature to single cases, or small groups of cases, in which the onset or course of the disease appeared to have been influenced by pregnancy (von Hoesslin, 1904; Beck, 1913; Dimitz, 1928). Beck collected 118 cases from the literature; 40 of these patients had been pregnant, and 16 (40 per cent.) showed evidence of an effect of pregnancy on the onset or course of the disease. In von Hoesslin's series of 516 cases (sex-distribution unstated) pregnancy and childbirth appeared to influence the onset or course of the disease in 30 cases; in seven of these the onset was acute. Von Hoesslin, like other writers, did not mention the number of female patients who were unaffected by pregnancy. Müller (1949) studied the disease in 448 female patients, and dealt specifically with the effect of childbirth upon the onset and course. The illness began in 15 patients during pregnancy or the first three months of the puerperium. In view of the proportion of women in the general population who are pregnant at any one time, Müller did not consider this incidence excessive. To assess the effect of pregnancy upon the course of the disease, he compared the relapse-rate in childbearing women with that in non-childbearing women. There were 133 childbirths amongst 99 women, and including the three-month puerperium there were 24 relapses in 133 pregnancy-years (18 per cent.) compared with 703 relapses in 3,210 patient-years (21·9 per cent.) in all women in the series.

It should be borne in mind that the incidence of both disseminated sclerosis and pregnancy is highest during the third decade. Since pregnancy with a puerperium of three months lasts one year, it is reasonable to expect that the onset of disseminated sclerosis and pregnancy will occasionally coincide. If pregnancy were a factor in the genesis of the disease, there should be a larger proportion than normal of childbearing women amongst the sufferers from the disease. This has not been found in our series (Group D, 61; controls, 65). Among our 250 cases in Group D were 146 female patients, of whom 51 were single and 34 were non-childbearing married women. Of the remaining 61 childbearing patients, 42 had a total of 78 pregnancies before the onset of the disease. Only one patient developed the disease during her first pregnancy. Three patients developed disseminated sclerosis during a subsequent pregnancy. Therefore of a total of 82 pregnancies in 43 women, in only four did pregnancy coincide with the onset of the disease. The results of our study are in agreement with the conclusions of Müller (1949) and Tillman (1950) that pregnancy does not affect the onset of the disease.

Of our 43 patients who had pregnancies before or at onset, six had subsequent pregnancies, and fresh manifestations of the disease appeared in four of these patients at the time of pregnancy, in one patient on two occasions. The one patient whose disease commenced during her first pregnancy had a separate manifestation of the disease one month after delivery. After the onset of the

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disease, 18 patients became pregnant for the first time, and in five of these the pregnancy or puerperium coincided with a fresh manifestation. Five of these 18 patients had six subsequent pregnancies which did not affect the course of the disease. Therefore, of a total of 24 women having 33 pregnancies, nine relapsed in association with 11 pregnancies, a yearly relapse-rate of 0·33, which does not differ significantly from the general relapse-rate of 0·39. If pregnancy materially influenced the course of the disease, the prognosis would be worse in childbearing than in non-childbearing women. However, the average number of attacks per year among childbearing patients was 0·42, and among non-childbearing women 0·48. The fact that both the rates are higher than the general relapse-rate of 0·39 is due to the proportion of cases in both groups falling in the first few years of the disease, when the relapse-rate is higher. It is probable that among non-childbearing women there are some who have avoided pregnancy because of the unfavourable course of their disease, and that this fact accounts for the slightly higher attack-rate in the non-childbearing group.

Anxiety and emotional disturbance. It was our impression early in the present study that emotional factors might play a part in the disease. Pratt (1951*b*) studied 100 patients taken at random from our material and 100 control patients from the Department for Nervous Diseases of the Middlesex Hospital, all save three of whom were suffering from organic neurological disease. The two groups were matched approximately as to sex, age, and severity of disease. He found that emotional disturbance or prolonged nervous strain in the month immediately preceding onset occurred in 38 patients with disseminated sclerosis and in 26 controls. The disseminated sclerosis group suffered 229 relapses, of which 58 (25·2 per cent.) were preceded by emotional disturbances. Although no control study was available for comparison with the figure for relapse, it is in approximation to the figure for onset in the control population. Although this analysis does not show an association between emotional disturbance and the onset or relapse of disseminated sclerosis, in certain patients the history has been so striking as to indicate that emotion may sometimes be an operative factor.

Allergy. The incidence of active allergic disease during the three-month period preceding the onset of the disease was 20 (8 per cent.) compared with six (2·5 per cent.) in the control group; a further six control patients were admitted for treatment of an allergic condition. Excluding these, the incidence in the disseminated sclerosis group is significantly high ($\chi^2 = 7{\cdot}6$, $n = 1$, $0{\cdot}01 > P > 0{\cdot}001$). Among these 20 patients were eight who had developed an allergic disorder for the first time during the period of three months preceding onset. Seven patients were exhibiting an allergic disorder on the day the first symptom of disseminated sclerosis developed. One of these seven cases has previously been described (Compston, 1951). Of the 68 patients who suffered from allergic disease, 29 had active manifestations after the onset of their disease, 15 for the first time. The allergic manifestations were active in the three-month period preceding 11 relapses in nine patients. Three patients suffered relapse within three months of developing an allergic manifestation for the first time in their

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lives. In a typical remitting case, on four consecutive occasions fresh episodes of the disease followed a weekly injection of an autogenous vaccine at an interval of approximately 60 hours.

Miscellaneous. Five patients were suffering from migraine at some time during the three months before the onset of their disease; all these patients, however, had suffered from migraine previously. In one patient the disease commenced 14 days after vaccination and inoculation with typhoid-paratyphoid vaccine and antitetanus toxoid. Another patient, who ultimately developed typical disseminated sclerosis, had transient paralysis of both legs within one day of the administration of anti-diphtheritic serum. A third patient developed symptoms within 24 hours of his first typhoid-paratyphoid inoculation. In the disseminated sclerosis group 10 patients complained of joint or muscle pains in the three-month period preceding onset of their disease, compared with three in the control group. In one patient there was frank polyarthritis.

Nutritional factors. Brickner and Brill (1941) studied the dietary intake of 34 patients with disseminated sclerosis. They concluded that the diet was certainly deficient in 17 of their patients, probably deficient in five, and possibly deficient in eight, while in only four could no abnormality of dietary habit be found. Many of the diets were especially deficient in fat. It was their impression that the disease tended to appear during periods of increasing nutrition in previously undernourished patients. Swank (1950) studied changes in the incidence of disseminated sclerosis in Norway, Denmark, and Holland, and correlated them with alterations in the amount of fat available to the population. Periods of greater incidence of disseminated sclerosis coincided with periods of high fat intake. Swank postulated that a high fat intake 'may contribute to a high incidence of the disease by accelerating it in susceptible individuals'. We have been able to study the dietary intake of only 50 patients (41 females, nine males). This has been assessed for us by the Department of Dietetics at the Middlesex Hospital. The method used was inquiry by routine dietary history-taking; it is obvious that such a method gives only approximate results, so that quantitative analysis, although made for our own guidance, will not be reported. Separate assessments were made for dietary habit in the remote past, in the year preceding the first appearance of symptoms, and in similar periods preceding the appearance of relapses. The average dietary intake of patients during each of these three periods did not differ from that recommended for sedentary workers in general. In certain cases dietary intake was deficient, but changes in dietary habit could not be correlated with phases of activity of the disease. Analysis revealed no specific deficiency of protein, fat, carbohydrate, or vitamins, nor was an increased fat intake found amongst our patients during the period preceding the onset of their disease.

Fluctuation in Established Symptoms

The intensity of symptoms may vary from day to day, and even from hour to hour. It is important to differentiate a true relapse from a temporary exacerbation of an established symptom. It will appear from the following account

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that symptoms may be markedly worse, for example, during feverish illness or periods of great anxiety or fatigue. These periods of exacerbation may be as short as a few minutes or as long as a few days. Recovery is always immediate and complete as soon as the adverse exogenous factor has ceased to operate. Although true relapses may appear to be provoked in the same way, they can be distinguished by the fact that either they produce new symptoms or, if they constitute a marked deterioration of old symptoms, this deterioration persists. It would seem that in this disease the functional capacity of the diseased parts of the nervous system is easily upset by any internal or external environmental change, but control studies have not been undertaken to determine whether this is a specific feature of disseminated sclerosis or occurs in other organic neurological disorders. Our impression is that such fluctuations are less common in other neurological disorders. The following is an account of the factors that have operated in this way in our patients.

Exertion and fatigue. Patients frequently state that their symptoms are more marked after exercise or fatigue. They note this tendency particularly in relation to their paresis. Patients with mild paresis find that locomotion may be normal for up to three or four miles, and then suddenly they develop weakness of the affected limb. In severer cases this effect is apparent after two or three hundred yards, and is often severe enough to halt the patient completely. With rest for a period, often as short as five minutes, the patient may set out again, but is halted after a decreasing distance at each attempt. This phenomenon, closely resembling intermittent claudication, was marked in 17 of our patients in Group D, and was less clear-cut in an additional 67. The effect of exertion and fatigue does not operate only upon motor function. On exertion paraesthesiae may be more intense, and blurring of vision or diplopia may be more marked, or may only appear in such circumstances; similarly nystagmus may temporarily become so severe as to cause disturbance of vision.

Febrile illness. Twenty-two patients reported a marked effect of fever upon the intensity of their symptoms, either motor or sensory. Bladder function may be similarly affected. We have been able to note such effects upon in-patients who had an artificially induced pyrexia: 12 out of 50 complained of an increase in the intensity of their symptoms.

Emotional disturbance. Emotional upsets are more often responsible for short temporary exacerbations of symptoms than any other factor. Eighty-two of the 250 patients in Group D gave a history of temporary worsening during moments of stress. Emotion acts very rapidly upon symptoms, and often produces intensification of symptoms within a minute. This may be so severe at times as to render immobile patients who are normally capable of walking. Pratt (1951 *b*) found that this effect was much more common in disseminated sclerosis (18 per cent.) than in his control group (5 per cent.).

Menstruation. A chart was prepared and sent to 90 female patients who were in the menstrual phase of life. Patients were asked to record daily for three months whether their symptoms were unaltered, worse than usual, or improved. Analysis of the material revealed a tendency towards improvement during

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menstruation and during the first half of the menstrual cycle, and towards deterioration during the second half of the cycle. The improvement was so striking in one patient that she requested her doctor to provide her with treatment that would produce perpetual menstrual flow, and another stated that her husband could immediately tell the day of onset of her period by the marked improvement in her walking.

Drugs. Certain of our patients have been given intravenous organic arsenic (neoarsphenamine), and some have shown marked reactions in the nervous system. These reactions have usually been of a slight nature, but in two cases were well-marked. One female patient who developed a severe pyrexial reaction for 24 hours following an injection of neoarsphenamine, and who had had previous attacks of retrobulbar neuritis but was from that point of view symptomless, developed amblyopia for three-quarters of an hour during the reaction, with a pyrexia of 105° F. A male patient suffering from an established but slight hemiplegia due to disseminated sclerosis became completely hemiplegic for about 12 hours after an intravenous injection of neoarsphenamine on four separate occasions. His reaction was not associated with fever. Recovery was complete in both these patients.

Temperature. It is common for symptoms to be intensified by changes in temperature. Warmth was a more potent factor than cold in our patients. The effect of warmth is noticed markedly when taking a hot bath. Among the 250 patients in Group D, 33 experienced intensification of symptoms with heat, and 29 with cold. Guthrie (1951) has recently shown that the effect of external warmth is a peculiar characteristic of disseminated sclerosis, and does not commonly occur in other chronic neurological diseases.

Blood transfusion. Two of our patients have had blood transfusions, one for aplastic anaemia and one for haematemesis; in the former case marked exacerbations of symptoms occurred. Alexander, Loman, Lesses, and Green (1950) reported that 12 per cent. of patients with disseminated sclerosis had 'neural' reactions to transfusion. These comprised temporary paralysis, diplopia, blindness, or increase in established spastic paralysis, the reactions lasting between three and four hours. In some cases the reactions were associated with urticaria.

Discussion

There are two factors in the development of any disease, first the agent initiating the damage to tissue, and secondly the pathological process thereby set in motion. Many hypotheses as to the aetiology of disseminated sclerosis have not distinguished between these two factors. It is probable, as Lumsden (1951) has recently pointed out, that in disseminated sclerosis demyelination is accompanied by cellular biochemical changes, and that these changes are dependent upon enzymic reactions. This does not mean that the primary cause of disseminated sclerosis is an enzymic defect, unless it be that this is of the nature of an inborn error of metabolism. Similarly, theories of a vascular origin are theories of mechanism and not of aetiology. The retention of the term 'sclerosis' as applied to this disease has tended to obscure the fact that primarily

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it is a form of encephalomyelitis, and that gliosis is a secondary process. Lumsden has drawn attention to the intimate relationship existing between the oligodendrocyte and the myelin sheath, and to the significance of the primary changes in these structures. He has put forward the hypothesis that in disseminated sclerosis two processes are at work: (1) a preparatory exogenous factor damaging the white matter, and (2) an endogenous mechanism which liberates a myelinolytic substance related to the myelin sheath or oligodendrocytes. In the present paper we are concerned with the nature of the exogenous factor. Any satisfactory theory regarding the cause of disseminated sclerosis which is based primarily on clinical facts must be consistent with our knowledge of its neuropathology, and at the same time must explain partially or wholly the varied features of its natural history. These include the geographical and focal distribution, the genetical background, the part played by such factors as trauma and infection, and the variations in the mode of onset and progress of the disease.

It was a natural consequence of the discovery of the aetiological role of specific infective agents that such an agent should be sought in disseminated sclerosis. Brain (1930) reviewed the various claims of experimental pathologists in favour of a viable agent, including those of Bullock (1913), Kuhn and Steiner (1917), and Adams, Blacklock, Dunlop, and Scott (1924). Their positive results, and those of a number of others, have not been confirmed. Brain suggested that spontaneous neurological disease in laboratory animals might have been a source of error in such experiments. In 1946 Margulis, Soloviev, and Shubladze claimed the isolation of a virus from two cases of encephalomyelitis; this virus was neutralized by serum from 50 per cent. of patients with disseminated sclerosis, but not by the serum of other neurological controls. These findings await confirmation. The hypothesis of a specific infective agent is compatible with certain features of the disease, but its characteristic relapsing and remitting course is difficult to correlate with the presence of an infective agent in the central nervous system, although latency of infection is exemplified by neurosyphilis, and by experimental herpes simplex encephalitis in rabbits. In the latter condition Good and Campbell (1948) have shown that infection may be latent, and may be reactivated by the administration of histamine or the induction of anaphylactic shock with foreign proteins. But no virus disease in any system, with the exception of herpes labialis, behaves in this manner naturally. It would therefore appear that animal experiments demonstrating an infective agent within the nervous system of patients with disseminated sclerosis lack confirmation. As Lumsden remarks, 'If the real cause is a specific transmissible agent it must be a virus or a chemical substance not yet even listed amongst the known pathogenic agents, and one with some extremely uncommon properties'.

The view that disseminated sclerosis may be due to a form of sensitization or allergy has gained ground in recent years. Ferraro (1944) concluded that unification of the pathology of the demyelinating diseases seemed possible if they were considered as an expression of an allergic reaction in nervous tissue. McAlpine (1946), on clinical grounds, postulated that the disease is determined by an immune reaction to an infection, and that a varying interval may occur between

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the original sensitization of the nervous system and the first appearance of symptoms. In seeking a firmer basis for the theory of a hypersensitivity reaction in disseminated sclerosis, attention has naturally turned to other forms of encephalomyelitis. There is some evidence to suggest that hypersensitivity plays a part in the post-vaccinal and post-exanthematous forms. In 1907 von Pirquet postulated that, since the symptoms of post-vaccinal encephalomyelitis almost invariably arose on the ninth or tenth day, they could be explained on the basis of an allergic response. A similar mechanism has been evoked for the various forms of post-exanthematous encephalomyelitis (Glanzmann, 1927; van Bogaert, 1932; Finley, 1938). But there is no proof that these varieties of encephalomyelitis are ever followed by disseminated sclerosis (Lumsden, 1951; van Bogaert, 1950). The relationship of acute 'spontaneous' disseminated encephalomyelitis to disseminated sclerosis is less clear. McAlpine (1946) reported that three out of five cases diagnosed as acute disseminated encephalomyelitis in 1931 subsequently followed a course typical of disseminated sclerosis. On the other hand van Bogaert (1950), with a larger experience, has recently reported the follow-up of 19 patients seen between 1927 and 1932. Four of these subsequently developed signs of multiple sclerosis, one could not be traced, one died in the acute stage, and two other cases were inconclusive. The remaining 11 patients were completely free from any neurological disease. Van Bogaert considers that acute disseminated encephalomyelitis is a manifestation of an immunizing process in the neural ectoderm, just as a rash indicates the same process in the skin. He points out that a history of recurring focal infections and allergic skin and joint manifestations is not uncommon in the personal or family history of patients who develop encephalomyelitis in the course of atypical general infections. Thus, although the evidence would suggest that acute disseminated encephalomyelitis does not usually develop into disseminated sclerosis, there can be no doubt that occasionally it may do so.

Lumsden (1949) and others have emphasized the fact that the experimental encephalomyelitis of animals does not reproduce the pathological features of disseminated sclerosis, but those of disseminated encephalomyelitis. It has been widely assumed that the development of foci of demyelination, following the injection of brain emulsions in animals, is due to the production of an anti-brain antibody, and the disorder is therefore now commonly called 'allergic' encephalomyelitis; but the evidence that this condition is allergic in origin is inconclusive. Hurst (1940) and others have shown that similar lesions may be produced by various procedures, certain of which cannot involve an immunizing process. Although affected animals develop antibodies, these are not entirely specific, and appear in animals that do not develop brain lesions (Lumsden, Kabat, Wolf, and Bezer, 1950). It has been suggested by Lumsden that their appearance is coincidental, and that there is some other 'encephalitogenic agent' which may be neurotoxic without producing its effects by sensitization. Although the administration of anti-histamine drugs may modify the effect of brain emulsions, Lumsden (1949) considered that the results of his experiments were inconclusive. Nevertheless, the fact that its induction is greatly facilitated

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by the inclusion of dead tubercle bacilli in the emulsion suggests that immunizing processes may be an important factor in the production of experimental encephalomyelitis. Thus, although clinically there is no definite link between the various forms of encephalomyelitis and disseminated sclerosis, with the possible exception of spontaneous encephalomyelitis, there are some grounds for believing that sensitization may be a common factor in their aetiology.

The clinical manifestations of nervous disease that have been attributed to allergy are varied, and range from the effects of serum sickness and anti-rabies vaccine to those that may occasionally occur in individuals allergic to food and other substances. Certain of these effects are transitory, such as migraine, drowsiness, attacks of coma, and convulsions; from them recovery is complete. More rarely there may appear in allergic patients symptoms such as hemiplegia, retrobulbar neuritis, vertigo, diplopia, sensory symptoms, and paresis (Kennedy, 1938, 1950; Pardee, 1938; Winkelman and Moore, 1941). The majority of the reported cases appear to have responded favourably to the elimination of the cause, and have not suffered any permanent disability; others have relapsed in remarkable fashion on exposure to a specific allergen, and in a few instances signs in the central nervous system have persisted. Furthermore, changes in the cerebrospinal fluid similar to those found in disseminated sclerosis have been reported. In fact, were it not for the demonstration in such cases of an allergic manifestation such as hay fever or urticaria, it would be difficult to arrive at any other neurological diagnosis than disseminated sclerosis. On the other hand, cases of disseminated sclerosis may run a typical course for some years without any outward evidence of allergy, only for this to develop later in association with a relapse of their neurological condition. Some of our patients have shown a close time-relationship between cutaneous or mucosal allergy and the appearance of fresh lesions in the central nervous system. It should be stated that, striking as certain of these cases are, it is only possible to obtain such a history in a small minority of cases.

In the present study we have demonstrated an increased incidence of accepted allergic diseases among a group of 250 patients suffering from disseminated sclerosis, as compared with 250 controls. This association may not be fortuitous, but may depend on an inherited or acquired constitutional tendency to develop hypersensitivity in certain tissues. A parallel example is afforded by rheumatic fever. Rittwagen, Romano, and Svigals (1946) found an incidence of 31 per cent. of allergic symptoms in 100 children suffering from rheumatic fever, compared with an incidence of 8 per cent. in a control population. The evidence presented by Alexander and his colleagues (1950) of a raised incidence of allergic reactions to blood transfusions in patients with disseminated sclerosis suggests an inherent tendency for these patients to develop allergic symptoms. It is possible, therefore, that of those individuals who have a general tendency to develop hypersensitivity reactions a few may react only in the central nervous system. This is in accordance with the view of Rich (1947) that constitution determines not only the tendency to develop allergic disease, but also the site of allergic processes.

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Other facts emerging from our study include the apparent trigger action of trauma, infection, superficial sepsis, and emotion upon the appearance of lesions. The relationship between peripheral trauma and the onset of the disease was sufficiently close in certain of our cases as to suggest a causal relationship, particularly when, as in over 50 per cent. of cases, there was a close correspondence between the site of the trauma and the level of the lesion in the nervous system. Similarly, in certain of our patients there appeared to be a topographical relationship between peripheral sepsis and the manifestations of the disease. Theoretically the effect of trauma or sepsis on the corresponding segments of the spinal cord could be explained by neural, chemical, or vascular mechanisms. Peripheral stimulation is known to produce alterations in blood-supply throughout a stimulated limb, probably through antidromic mechanisms which persist for about 10 minutes after stimulation (Bayliss, 1901). The vasomotor nerve-supply, including that to the intramedullary portions of the spinal cord, is distributed segmentally in the same way as the motor and sensory nerves; it is possible that alterations in blood-supply occur not only throughout the skin and muscle following stimulation, but also in the corresponding segment of the spinal cord, thus possibly altering local antigen-antibody balance. Generalized infections are known to provoke not only a specific antibody response but a general antibody response (the anamnestic response), and it is possible that, whereas trauma and sepsis may produce their effects locally, infections may do so by producing generalized alterations in antigen-antibody balance. Similar factors have been invoked as secondary or conditioning agents, particularly in the group of simple allergic disorders, and in other conditions of more complex aetiology in which hypersensitivity plays an important part. The role of infection, emotional disturbance, and trauma in the precipitation of allergic reactions of the skin and mucous membranes is generally accepted. In rheumatoid arthritis and iritis the operation of similar factors has often been claimed. It has been postulated that the provocation of disease by a wide range of noxious factors is due to a disordered adrenal response. It is difficult to conceive of such a response causing first localization and secondly some of the more immediate reactions which we have encountered in our study.

It is necessary to examine the course of disseminated sclerosis to see whether its natural variations are compatible with a hypothesis of a hypersensitivity origin. Relapse and remission, sudden onset, brief duration, day-to-day variations in intensity, are characteristic features of such allergic conditions as asthma, hay fever, urticaria, and eczema. Other diseases in which hypersensitivity plays a part—rheumatic fever, rheumatoid arthritis, nephritis, and iritis—are also characterized by a relapsing and remitting course. It may not be without significance that the association of rheumatoid arthritis, iritis, or psoriasis with disseminated sclerosis is in our experience not a rarity. The existence of both a remitting and a progressive form of disseminated sclerosis finds a parallel in rheumatic disease. Hypersensitivity has been postulated as a factor in the genesis of all these diseases, but there are admittedly others with a

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varying course in which no such factor has been invoked, such as peptic ulcer and thyrotoxicosis.

The genetical influence which has been shown to operate in certain cases of disseminated sclerosis is compatible with the above hypothesis. A hereditary factor is accepted as part of the natural history of simple allergic states such as asthma (Williams and Williams, 1949), and of the more complex allergic states such as rheumatic fever (Wilson, 1944) and rheumatoid arthritis (Copeman, Savage, Bishop, Dodds, Gottlieb, Glyn, Henly, and Kellie, 1950). It may also exist in animals (Landsteiner and Chase, 1940). Endocrine factors appear to play a small part in the background of disseminated sclerosis. Cases occur almost exclusively during the most active endocrine phase of life from 14 to 50 years, and there is an increased incidence of the disease in female as compared with male subjects at the time of puberty. A similar increased incidence of asthma in female subjects during the development of puberty has recently been demonstrated (Williams and Williams, 1949).

Clinical and pathological evidence suggests that the chronic progressive type of the disease does not differ essentially from the more usual remitting and relapsing form, in that fresh symptoms may occur during life, and lesions of all ages may be found post-mortem. It is not necessary, therefore, to postulate an alternative hypothesis of causation for these progressive cases.

We have discussed in this paper the rapid fluctuations in the intensity of symptoms that occur in disseminated sclerosis, and in particular the influence of certain internal and environmental factors upon them. Pratt (1951*b*) has shown that, at least so far as emotion is concerned, these fluctuations appear to be a peculiar feature of disseminated sclerosis, and do not commonly occur in other neurological diseases. Guthrie (1951) has recently compared the effect of changes in environmental temperature upon patients with disseminated sclerosis with that upon controls suffering from other neurological disorders. He found that rapid change in the intensity of symptoms following heating was peculiar to disseminated sclerosis. The effects upon remote lesions of heating one limb could be abolished by applying a tourniquet to that limb, and he postulated that the lesions are affected either by warmed blood or by some humoral agent released in a warmed limb, and not by reflex nervous influences. The application of Cannon's law of denervation would provide further evidence in favour of a chemical explanation of the rapid fluctuations in symptoms in disseminated sclerosis. In 1939 Cannon stated: 'When in a series of efferent neurones a unit is destroyed an increasing irritability to chemical stimulating agents develops in the isolated structure or structures, the effect being maximal in the part directly denervated.' Since transitory variations of symptoms are uncommon in other organic nervous disorders, there would appear to be some feature of those lesions in disseminated sclerosis in which gliosis is not advanced which renders them highly susceptible to humoral influences. This view of the disease is not incompatible with a general hypothesis of a hypersensitivity origin.

The occasional focal occurrence of the disease must also be considered. Campbell, Herdan, Tatlow, and Whittle (1950) found a relatively high incidence

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of the disease in a Berkshire village, and three patients who had lived in cottages in close proximity to each other in a village in Gloucestershire. Adams in Scotland, and Allison in Northern Ireland (personal communications) have also found evidence of a number of foci of the disease. An abnormally high lead-content in the teeth of patients, and in the soil in the vicinity of the two groups of cases reported by Campbell and his colleagues, suggested that lead might play a part in this disease. Their work awaits confirmation, but many arguments can be put forward against such a view. Since foci tend to occur in small rural communities, it is possible that they may, in part at least, be genetically determined. The explanation of the occurrence of a disease closely resembling disseminated sclerosis in four out of seven workers on swayback in lambs, as reported by Campbell, Daniel, Porter, Russell, Smith, and Innes (1947), may lie not in the immediate environment of these workers, as suggested by the authors, but in other facts, namely, that 'two at least' of the affected persons came from the same locality in Scotland, and one other had a sister similarly affected. It is possible that environmental factors may, in some unknown way, predispose to the development of hypersensitivity states.

A consideration of the changes in the cerebrospinal fluid should help to elucidate the aetiological problem of disseminated sclerosis. The positive colloidal gold curve is dependent upon a relative increase in the quantity of globulin in the fluid. This has been proved electrophoretically and immunochemically by Kabat, Moore, and Landow (1942) and Kabat, Glusman, and Knaub (1948), and confirmed by unpublished work carried out on our patients by Field. The presence of increased quantities of globulin suggests an immune response, and at first sight might indicate the presence of an infective agent in the central nervous system. We have already given reasons for discounting this theory. It is equally possible that globulin is produced in excess as a result of sensitization. When the biological nature of the globulin has been determined, this may provide a further clue to the aetiology of the disease.

In postulating a hypersensitivity origin for disseminated sclerosis no reference has been made to the factor or factors responsible for sensitization. In general 'allergens' are non-specific so far as the clinical manifestations are concerned. Rich (1947) has pointed out that it is the constitution of the host, rather than the nature of the allergen, that determines the clinical picture, and further that although an allergic disorder may be evoked at first by only a single allergen, sensitization may ultimately develop to a wide range of substances. Antigens in general may be either infective agents or non-viable protein-containing substances, or even non-protein-containing substances such as drugs, which produce sensitization by forming an antigenic complex with some body-protein. Theoretically, in disseminated sclerosis there may be a single antigenic substance or more than one such substance capable of provoking reactions in the nervous system in predisposed subjects. On general grounds the latter appears the more likely explanation.

We have marshalled certain facts which suggest that disseminated sclerosis is initiated by an antigen-antibody reaction within the central nervous system

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as a result of previous sensitization. The evidence for this hypothesis is inconclusive, and in particular the crucial demonstration of sensitization in many patients suffering from this disease is lacking. This does not invalidate the hypothesis, as sensitization may be limited to nervous tissue, and may give no evidence of its presence by skin reaction or by serological testing. We believe that the broad facts of the natural history of the disease are more compatible with the hypothesis of an allergic origin than with any other.

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Summary

1. An estimate has been made of the incidence and sex-distribution of disseminated sclerosis in England, Wales, and Scotland.

2. The case reports of 840 patients seen since 1930 have been reviewed. Six hundred and seventy-five patients have been traced, and 475 patients reinterviewed.

3. The course of the disease has been studied in detail in 414 patients.

4. Episodes of the disease have been classified as remittent, progressive, or stationary. The behaviour of episodes has been correlated with age at onset, sex, and the duration of the disease.

5. The amount of disability has been estimated according to the degree of mobility.

6. The prognostic significance of certain symptoms as regards both disablement and life has been indicated, and an attempt made to assess the average duration of life of patients with this disease.

7. The general health of 250 patients with disseminated sclerosis has been studied in detail. A control series of 250 patients was used. Other information relating to 840 patients has been presented. The relevant literature has been reviewed.

8. A hereditary factor is evident in about 6 per cent. of cases.

9. The incidence of allergic disease is significantly increased in the disseminated sclerosis group (27 per cent.) compared with the control group (16·8 per cent.).

10. Of 840 patients, the onset occurred in the third decade in 297 (35·3 per

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cent.), after the age of 40 years in 171 (20·3 per cent.), and between the ages of 10 and 14 years in 12 (1·4 per cent.).

11. Factors which appeared to precipitate the onset or relapse in certain cases include trauma, infection, peripheral sepsis, and less frequently emotional stress. Pregnancy did not appear to be of importance.

12. In a significant proportion of cases in which trauma or peripheral sepsis preceded the onset, the site of injury could be correlated with the site of the lesion in the central nervous system.

13. A distinction is drawn between true relapses and temporary exacerbations of symptoms. The latter are influenced by many factors, including emotion, fatigue, fever, drugs, environmental temperature, and menstruation.

14. The result of a dietetic inquiry in 50 patients was negative.

15. Reasons are given against the view that disseminated sclerosis is due to a specific infective agent within the nervous system.

16. Consideration is given to the theory of hypersensitivity. The relationship of disseminated sclerosis to the various forms of encephalomyelitis and to the known forms of allergy affecting the nervous system is discussed. The occasional genetical and allergic background in patients with disseminated sclerosis, the nature of the precipitating and aggravating factors, the simultaneous activity of the disease and of allergic symptoms in certain cases, the variation in the mode of onset, and the relapsing course of the disease, are all consistent with the theory of a hypersensitivity reaction.

17. It is postulated that more than one antigen may be capable of sensitizing the central nervous system in disseminated sclerosis.

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