PREVALENCE AND FAMILIAL INCIDENCE OF DISSEMINATED SCLEROSIS

A Report
to the Northern Ireland Hospitals Authority
on the Results of a Three-Year Survey

By

R. S. Allison and J. H. D. Millar
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R. S. Allison and J. H. D. Millar

Charcot remarked in 1868: "Even to-day I do not believe that disseminated sclerosis is known in England," and this may have been true, although Moxon described a case in 1873 and others some years later. Williamson (1903) reported a proportion of patients with disseminated sclerosis equivalent to 27 cases for every 1,000 nervous diseases seen at the Manchester Royal Infirmary over a period of 10 years, and from Edinburgh, about the same time, Bramwell (1903) published very similar figures. In America (where, possibly, the original diagnostic criteria proposed by Charcot were adhered to more rigidly) the disease appeared at first to be less prevalent. Thus, according to Davenport (1921), in Boston only one case was found among 1,000 patients attending hospital suffering from nervous diseases and in New York only 2-7 cases per 1,000. Yet it is of interest to note at that time there was at least one dissentient—Van Wart (1905), who claimed that the disease was common in the State of Louisiana, having discovered 44 cases per 1,000 nervous diseases at hospitals in New Orleans. The impression that the disease is rare in North America has, of course, long since been corrected. MacLean, Berkson, Woltman and Schionneman (1950) reported from Rochester, Minnesota, a prevalence rate of 64 cases per 100,000 of the inhabitants. This estimate was based on the finding of 21 patients who had attended the Mayo Clinic between 1910 and 1947 and were resident in the city.

In most reports founded on hospital returns, insufficient allowance is made for the individual character of the hospital concerned. Thus, because of its reputation or the special interest of some member of the staff, or because the facilities for physiotherapy may be better organized, one hospital may attract more cases than another. In most places to-day practitioners are familiar with the early symptoms and signs of the disease. There is still, unfortunately, no curative treatment. Unless a diagnostic problem arises, and this can often be settled through a single out-patient attendance, a patient may never be admitted to hospital. Consequently, statistics relating to prevalence which are based on hospital admissions alone cannot be of great value.

Probably the most extensive survey based on hospital admissions is that of Sällstrom (1942), who collected data relating to patients suffering from disseminated sclerosis from all the chief Swedish hospitals between the years 1925 and 1934. When allowance had been made for duplications, readmissions, etc., there were 2,100 cases which gave a prevalence rate of 34 per 100,000 inhabitants. During the ten-year period over which the survey was conducted, the hospital returns showed a fairly steady increase in admissions of patients suffering from the disease, but when the cases were analysed with regard to the respective years of

onset of the complaint, no significant annual increase in the incidence of new cases of the disease was observed. This is an important point which has been borne out by other observers, notably MacLean and his co-workers (1950) and Limburg (1950).

The only sound method of estimating the prevalence of the disease is by determining the number of patients within an area and assessing this in terms of the population. Switzerland was the first country to adopt this method. Bing and Reese (1926) reported, between 1918-1922, in the north-western region of the country (population 771,564), 281 cases giving a rate of 36 per 100,000 inhabitants. In some cantons the rate was much higher than in others. The lowest rate was 3 per 100,000, but in Basle it was 74 per 100,000—a circumstance which the authors attributed to its proximity to the centre of investigation. Later Ackermann (1931) analysed the data for the rest of the country and computed the prevalence rate for Switzerland as a whole to be 24.5 per 100,000 inhabitants. A total of 126 cases was reported in North Wales (Allison, 1931), an area with a population of approximately 489,270. This gave a rate of about 25 per 100,000, but a number of these cases had to be rejected after they were examined, as they presented insufficient clinical evidence to make the diagnosis acceptable. The final rate was 13 per 100,000. In retrospect we think that this was an underestimate, for later, in one of the few other personally-conducted surveys, Pratt (1951) found 14 cases resident in and around Stamford, Bourne, and Market Deeping, in Lincolnshire (population 41,000), giving a prevalence rate of 34 per 100,000, which is fairly close to the Swiss, Swedish, and American figures. Regional surveys may give a truer picture of the prevalence of the disease than do results based on hospital admissions, but even so they are not devoid of error. They are bound to be influenced by the procedure adopted, particularly by whether the cases notified are personally seen and examined or their acceptance determined by report alone.

Rural and Urban Influences.

At one time it was thought that disseminated sclerosis was much more a disease of the country than of the town, and, that when it occurred in town dwellers, inquiry often showed that they had formerly lived on the land. The significance of this is lessened when the tendency of populations to migrate towards cities in recent years is considered. This idea of a high rural incidence was closely related to another belief—that there was an occupational preponderance among farm-workers, wood-workers, etc. None of the surveys of Bing and Reese, Allison or Sällstrom have shown any significant preponderance of cases among rural dwellers or in any particular occupation. Thus, among 1,306 of the Swedish cases in which the place of residence was known, 392 or 30 per cent. had been living in towns and 914 or 70 per cent. in the country. Of the total population, 33 per cent. were living in towns and 67 per cent. in country districts.

Climate and Soil Influences.

The opinion is often expressed that disseminated sclerosis is a relatively common disease in countries having a cold or temperate climate, whereas it is rare in warmer sub-tropical, or tropical latitudes. This hypothesis may have been derived originally from the apparent varying rates of hospital admissions in different

places, but it has received support also from regional surveys. For example, the difference in prevalence rates found by Bing and Reese, and Ackermann, prompted the belief that the disease was more prevalent in the north of Switzerland than in the rest of the country. Others reported that the disease was rarely seen in the East, in Japan (Miura, 1911), in China (Woods, 1929), in India (Sprawson, 1927), but none of these clinical impressions have been supported by extensive regional surveys. According to Selby (1952), the disease is comparatively rare in Australia, so that when a patient is seen, the inquiry is made whether he comes from England.

Dean (1949) has drawn attention to the rarity of the disease in South Africa and this is affirmed by Elliott (1952) and Bull (1953). Dean searched hospital records in the Union, covering the years 1939 to 1948, and discovered records of only 36 cases : of these, 8 had been in the Groote Schuur Hospital, Capetown; 22 in the Johannesburg General Hospital; and 3 in the Pretoria Hospital (all university teaching hospitals). In addition, 3 other cases were reported from Port Elizabeth and Durban. The white population of South Africa is approximately 2,450,000

Limburg (1950), comparing mortality rates in different countries, concluded :— "The colder the climate, the higher the crude death rates for multiple sclerosis." Thus in England and Wales the overall rate was 2.3 deaths per 100,000 of the population; in Scotland 3.7; in Holland 2.0; in Canada 2.3; and in the U.S.A. 1.1. In countries with a warm climate the figures were :—Italy 0.5; Egypt 0.1; Australia 1.2; Strait Settlements 0.2. When the death rates were examined for each of the Italian provinces he found that, on the whole, the northern rate was higher than the southern, but he makes no comment on the surprising figure obtained for Lucania (one of the most southerly provinces), which appears to have the highest rate of all ! The death rates of the different American states between 1939 and 1945 were compared with the rates in the Canadian provinces. Here again he found that :—"All of the states or provinces with high rates either touch or are north of the fortieth parallel." It should, however, be stressed that international comparisons for specific causes of death are most unreliable; in some countries the number of uncertified deaths is so great as to make calculations based on the certified ones of doubtful value.

British Columbia had the highest mortality in North America, but apparently the comparison of death rates can be misleading, for according to Kurland (1951), in the National Office of Vital Statistics and in the Canadian Bureau, such terms as "cerebral sclerosis" and "general sclerosis" (applying chiefly to deaths due to cerebral arteriosclerosis) have been included in the same category as disseminated sclerosis. Thus, of the 50 deaths which had been reported in British Columbia for 1944, 36 had to be rejected for this reason, the corrected rate being then 1.2 per 100,000 instead of 5.6 as previously supposed. However, Kurland found that when all the results were "terminology corrected" there still appeared to be a higher rate among the Canadian and northern American states than among the southern. To test further the validity of any conclusions that might be drawn from comparison of these death rates, it was decided to carry out regional surveys of

two cities which were fairly comparable as regards medical facilities, hospitals, and language, and yet so situated as to be climatically distinct. New Orleans and Winnipeg were chosen, and reports were collected of all cases in the previous ten years known to have died, to have been in hospital or to have been treated by a doctor privately. Medical students were employed and trained in abstracting hospital and clinical records, and interviewed those doctors who had cases to report. On analysing the results, the number of new cases developing annually in the two centres was fairly constant. However, the prevalence rate for Winnipeg, adjusted to the age distribution of the white population of New Orleans, was 43.9 per 100,000 or 3-4 times the prevalence rate for the white population of New Orleans (12.0 per 100,000). The only weakness in this otherwise admirably planned and careful work is that the survey was limited to the collection of reports—no patients were actually examined. In New Orleans a larger proportion of the cases reported were in older people. Kurland thinks this may have been a chance occurrence since the number of cases was small, or that "New Orleans physicians, being less acquainted with the disease, may not diagnose it until it is further advanced." Alternatively he thought it may indicate that the ætiological factor is less frequent in the southern community.

Other factors than climate have been suggested to account for the apparent disproportion in prevalence between the American states : the greater industrialization of northern regions, Kabat (1950); excessive ploughing of the soil leading to mineral deficiency in colder regions, Russell (1950); and the dietetic habits of the population of colder regions, especially in their tendency to consume more fats (Swank, 1953).

Campbell, Daniel, Porter, Russell, Smith, and Innes (1947) described signs and symptoms resembling disseminated sclerosis in four persons doing research work on swayback. This disease, which is a demyelinating encephalopathy occurring in new-born lambs, was formerly attributed to lead poisoning until it was discovered, Bennets and Chapman (1937), Dunlop and Wells (1938), that feeding pregnant ewes with copper supplements prevented its development in the progeny. Swayback is not due to a deficiency of copper in the soil and grass, but to some factor which interferes with its proper assimilation and promotes a "conditioned deficiency," Shearer, Innes and McDougall (1940). Further, none of the sheep displayed signs of plumbism, although high levels of lead were found in the tissues, as in the grass and soil of the districts where the disease was common. The occurrence (although possibly coincidental as mentioned by the authors) of disseminated sclerosis among workers in swayback led to studies being carried out on copper metabolism in cases of the human disease, but no significant departures from the normal were noted, nor does copper therapy appear to have any effect on its course. There have been reports that disseminated sclerosis is more than usually prevalent in certain areas, e.g., in Northern Ireland, Foster Coates (1930); in Scotland Adams (1927), and Sutherland (1952), but so far there has been only one published report on its focal occurrence, Campbell, Herdan, Tatlow and Whittle (1950). This was in a Berkshire village, where five typical cases and another of

progressive spastic paralysis were found. Five of these had attended the village school at the same period, four had dwelt close to one another, and all had lived the first twenty years of their lives there.

NORTHERN IRELAND SURVEY.

Except for estimates based on hospital attendances and mortality rates, no exact information has been available previously about the mass aspects of the disease in this area. It was for this reason and because it was thought there might be some pattern in the geographic distribution of cases that a survey was undertaken in October, 1948.

Letters were sent to all hospitals and doctors in the province, giving an outline of the proposed survey and requesting information of any patients known to be suffering from the disease and for permission to examine them. As each name and address was received a serial number was assigned to it so as to avoid duplication. The Neurological Department was responsible for the collection of information relating to the cases. The Department of Social and Preventive Medicine undertook the clerical work and the subsequent statistical analysis of the results. Whenever it was possible to do so, old hospital records were consulted and the previous findings incorporated in our notes. Early in 1951, when most of the cases had been seen, a further letter was sent to doctors who had not yet replied, pointing out that, even if they had no cases to notify, it was important in investigating the regional incidence of the disease to have negative as well as positive replies. On 1st October, 1951, approximately three years after the start of the survey, it was decided to close the list, no notifications of cases received after that date being included in our results.

All reported cases were examined personally and a case history sheet was prepared (see Appendix I). Many of the items on these proved to be of consistent value during the course of the survey; others were of less value, but the preliminary planning of the information to be sought saved time by standardizing the method adopted.

Visits to country districts were arranged according to the location of the patients, two doctors usually setting out each week and examining 3-5 cases in the district selected. Frequent conferences were held, at which all cases were reviewed and placed in the appropriate category. It would have been relatively simple to have accepted only those cases in which the signs and symptoms were typical, but this method had obvious disadvantages and, instead, the plan was adopted of classifying the cases according to an arbitrary scheme as follows :—

(1) *Early Disseminated Sclerosis.* Patients who showed few or no physical signs, but had a recent history of remitting symptoms of the kind which are commonly associated with the onset of the disease, e.g., transitory uniocular blindness, double vision and vertigo, "pins and needles," numbness or weakness in one or other of the limbs. For example :—

Case No. 840 : female, born 1910. In January, 1949, following the birth of her only child, she noticed weakness and numbness in the legs, but these symptoms disappeared after 2-3 weeks. In December of the same year, following

a pain over the left eye, she developed "a mist over the eye" which lasted for three months, the sight then fully recovering. In October, 1950, there was recurrence of the numbness and weakness in the legs, again transitory, but succeeded by precipitancy of micturition and numbness in the fingers.

On examination no abnormal physical signs were apparent except reduction of vibration sense in the lower limbs and absence of the abdominal reflexes.

(2) *Probable Disseminated Sclerosis.* This group included only those cases in which there was no reasonable doubt about the diagnosis, e.g., patients who showed some physical disablement, usually a remitting quality in the history, and on examination, physical signs explicable only on the basis of multiple lesions. For example :—

Case No. 150 : male, born 1913. In 1933 he noticed double vision which persisted for two months. In 1939 there was gradually increasing weakness in the right foot until 1941 when there was an episode of further diplopia, vomiting, ataxia and some dysarthria. But these symptoms cleared up within 2-3 months and, except for the weakness in the right leg, he kept well until 1945. Then he was taken suddenly ill with supposed meningitis, all four limbs being weak and the vision disturbed. Again there was some recovery, although he was now practically disabled and remained so. In 1947 there were two epileptiform seizures.

On examination there was no evidence of intellectual deterioration, euphoria or increased emotional lability. The optic discs showed some pallor, but vision was J.2 in either eye and the fields were full. The pupils were normal and external ocular movements full, but coarse horizontal nystagmus was present on looking to either side and upwards, being most pronounced in the abducting eye on lateral gaze. No other abnormalities were found in the cranial nerves. The patient was right-handed. There was intention tremor, more pronounced on the left side than the right, with difficulty in performing rapidly alternating movements, but little or no muscular weakness or sensory loss. Both lower limbs were spastic and paretic, so that he was unable to walk without assistance. Joint sense was diminished in the toes. All the tendon reflexes were much increased and there was a bilateral positive Hoffmann's reflex. The abdominal and cremasteric reflexes were absent, and the plantar responses were extensor.

(3) *Possible Disseminated Sclerosis.* This group comprised cases in which, although the findings suggested the diagnosis, and no other cause had been found, the history was progressive or static and there was insufficient evidence of scattered lesions at different levels in the nervous system. For example :—

Case No. 257 : female, born 1909. In 1931 she had gradually increasing weakness of right leg, and later of both legs. There was a dubious history at the onset of transitory dimness of vision. The family history was negative. There was no disturbance of the sphincters.

On examination the mental state was unaffected and no abnormalities were found on testing the cranial nerves. There were no motor or sensory signs in the upper limbs and no increase of the arm jerks. Abdominal reflexes were absent, and there were bilateral extensor plantar reflexes and exaggerated knee and ankle jerks. She had a spastic paraplegia. Vibration sense was diminished over the shins and there was slight impairment of pin prick but good appreciation of light touch. No root pains or evidence of a zone of hyperalgesia were found. The spine was normal.

(4) *Discarded Cases.* This group included cases in which the results of clinical examination suggested some other disease, such as an hereditary ataxia, a cervical myelopathy, or a spinal cord compression. One patient (Serial No. 286), who had been discharged from the Navy in 1944 on account of recurring weakness in the right leg (diagnosed as disseminated sclerosis), was found to have signs of a high cervical cord compression and a neurofibroma was disclosed at operation.

Prevalence.

Prevalence has been used here to describe the actual number of people found to be suffering from the disease per 100,000 of the population at the time of the investigation.

Over the three-year period of the survey notifications were received of 887 patients. After examination, the number finally accepted was 700, which gave an acceptance rate of 78.92 per cent. There was no great difference between the acceptance rates in the different regions (see Table 1), although, except for Antrim and Fermanagh, it was slightly higher for females than for males. The 700 cases were classified as follows :—

Early	79	cases
Probable	476	,,
Possible	145	,,
	700	,,
Discarded	187	,,
Total	887	,,

A census was taken in Northern Ireland in 1951 when the population was found to be 1,370,709.* Table 2 shows the distribution of the 700 cases with regard to age groups and sex. There were few cases under the age of 20, and the largest age groups were 20-39 and 40-59. There were 310 males and 390 females. Prevalence rates per 100,000 of the population have been calculated from the data afforded by the census.

*Co. Antrim	231,099	Co. Down	241,105
Co. Londonderry	155,520	Co. Tyrone	105,421
Co. Armagh	114,226	Co. Fermanagh	53,040
Belfast Co. Borough	443,670	Londonderry Co. Borough	50,099

Incidence.

By incidence rate we mean the number of new cases which occur each year per 100,000 of the population—it can be regarded as an annual rate of onsets. The incidence rate was found by fixing the date of onset of the first symptoms as nearly as possible. This was often difficult as patients either had forgotten or, more usually, referred the onset to the year in which the symptoms became so pronounced as to cause disability. The information could not have been obtained by correspondence; it was only by personal questioning and checking statements with doctors, hospital records, and relatives that we were able to get any satisfactory answers.

TABLE 1.

Number of persons notified and number accepted (all diagnostic groups) classified by present place of residence.

	Number of persons notified.	Number of persons accepted.	Acceptances as a percentage of notifications.
Males.			
Belfast C.B.	117	91	77.78
Londonderry C.B.	8	7	87.50
Co. Antrim	76	62	81.58
Co. Armagh	32	24	75.00
Co. Down	81	63	77.78
Co. Fermanagh	20	17	85.00
Co. Londonderry	28	16	57.14
Co. Tyrone	41	30	73.16
TOTAL	403	310	76.92
Females.			
Belfast C.B.	158	129	81.65
Londonderry C.B.	12	11	91.67
Co. Antrim	86	67	77.91
Co. Armagh	35	30	85.71
Co. Down	102	81	79.41
Co. Fermanagh	19	14	73.68
Co. Londonderry	26	22	84.62
Co. Tyrone	46	36	78.26
TOTAL	484	390	80.58
Persons.			
Belfast C.B.	275	220	80.00
Londonderry C.B.	20	18	90.00
Co. Antrim	162	129	79.63
Co. Armagh	67	54	80.60
Co. Down	183	144	78.69
Co. Fermanagh	39	31	78.49
Co. Londonderry	54	38	70.37
Co. Tyrone	87	66	75.86
TOTAL	887	700	78.92

To make a proper study of age of onset one should really ascertain all the patients who had onsets at specific ages in a specific calendar period which would involve some scheme of forward recording. What we did with the retrospective data at our disposal was to select a period—1937-1951—and to confine observations to the 411 patients who had onsets within that period. This period was chosen

TABLE 2.

Distribution of ascertained patients with disseminated sclerosis classified by age when seen.

(All diagnostic groups combined.)

	Age in Years.				
Males.	15-19	20-39	40-59	60+	Total
Number of Patients	3	124	165	18	310
Rate per 100,000	5	66	112	21	73*
Females.					
Number of Patients	2	150	223	15	390
Rate per 100,000	4	75	138	14	84*
Persons.					
Number of Patients	5	274	388	33	700
Rate per 100,000	5	71	126	17	79*

*Aged 20 and over.

TABLE 3.

Age at onset distribution of patients with disseminated sclerosis with onset in the period 1937-1951.*

(All diagnostic groups combined.)

	Age of Onset.						
Males.	10-19	20-29	30-39	40-49	50-59	60-69	Total
Number of Patients	18	49	69	41	8	1	186
Average annual number of onsets per 100,000 of population	1.04	3.33	5.25	3.65	0.87	0.14	2.56
Females.							
Number of Patients	17	66	84	48	9	1	225
Average annual number of onsets per 100,000 of population	1.01	4.17	5.93	3.91	0.88	0.12	2.91
Persons.							
Number of Patients	35	115	153	89	17	2	411
Average annual number of onsets per 100,000 of population	1.03	3.77	5.60	3.79	0.88	0.13	2.74

*This table includes 25 patients (15 males, 10 females) whose exact place of onset was not known but was somewhere in Northern Ireland.

because we could make a good estimate of the average population at risk. They were distributed according to age at onset, and at each age and sex the number of patients per 100,000 of the average population in the period in the same age and sex group was ascertained. (All of them were living in Northern Ireland.) The rates shown in Table 3 (all diagnostic groups) and Table 4 (probable cases only) give the estimated average annual number of onsets per 100,000 persons in each age and sex group. For example (Table 3) there were 5.25 onsets per 100,000 of the population of men aged 30-39 each year. All these rates are likely to be understatements because patients who had onsets in the period and died before the survey started were omitted. If, however, we assume that such omissions had the same age of onset distribution as the patients examined, then the tables do give some idea of the comparative age risks; for example, the onset is five times more likely to be in middle age than in the "teens." The incidence rates tend to increase up to the age group 30-39 and then to fall again while generally female rates exceed male.

TABLE 4.

Age at onset distribution of cases of probable Disseminated Sclerosis with onset in the period 1937-1951.*

	Age of Onset.						
Males.	10-19	20-29	30-39	40-49	50-59	60-69	Total
Number of Patients	12	32	38	20	2	—	104
Average annual number of onsets per 100,000 of population	0.69	2.18	2.89	1.78	0.22	—	1.43
Females.							
Number of Patients	14	41	54	26	3	—	138
Average annual number of onsets per 100,000 of population	0.83	2.59	3.81	2.12	0.29	—	1.78
Persons.							
Number of Patients	26	73	92	46	5	—	242
Average annual number of onsets per 100,000 of population	0.76	2.39	3.37	1.96	0.26	—	1.61

*This table includes 9 patients (6 males and 3 females) whose exact place of onset was unknown but was somewhere in Northern Ireland.

DEATH RATE.

In the International Code for classifying causes of death (which is used in Northern Ireland as it is in England and Wales) "Disseminated Sclerosis" is listed in section 345 with "Multiple Sclerosis," "Insular Sclerosis," "Combined

Sclerosis" and "Cerebral Sclerosis." So, as in the case of the uncorrected North American statistics, the official death rates are inaccurate owing to the possible inclusion among them of deaths from cerebral arteriosclerosis. Bearing this in mind, average annual death rates during the period 1942-1950 were :—

2.8 per 100,000 of population of Northern Ireland.
1.8 ,, ,, ,, ,, ,, England and Wales.
3.1 ,, ,, ,, ,, ,, Scotland.

Geographical Distribution.

There were 319 patients who had always lived in the same town or country district; the remaining 381 patients had moved from place to place during the course of their lives.

Geographical Distribution by Present Address : Tables 5 and 6 show the distribution of male and female patients according to age and present place of residence. The absolute number of patients is shown in brackets. The unbracketed figures show for each area, age group, and sex the number of patients expressed per 100,000 of the census population of 1951 for the same area, age, and sex groups. Table 5 includes all diagnostic groups of early, probable, and possible cases. Table 6 gives the same information for the probable cases only (476 cases). Thus, for example, in Table 5 there were 12 male patients between the ages of 20-39 living in Co. Armagh. This represents a prevalence rate of 79 per 100,000 of the population of the same age, and sex, in the same area. With regard to geographical differences, it would appear that generally the two county boroughs have relatively fewer patients in both Tables 5 and 6. In Table 5 only Belfast women, aged 20-39, had a higher than average rate, and in Table 6 this was true only for women aged 40-59 in Londonderry County Borough. Apart from this, there appeared to be no consistent geographical pattern.

Geographical Distribution by Place of Onset : As the probable time and place of onset of symptoms was known in many cases, it was possible to correlate them with the populations of the areas at the different times, in the same way as had been done in estimating the incidence rate. Between the years 1937 and 1951 there were. however, 25 cases (9 of them probable cases), in whom the exact place of onset in Northern Ireland was not known. These 25 patients were excluded when considering the geographical distribution of onsets. This could, of course, result in bias, if the omissions came disproportionately from one area, but the number is small Tables 7 and 8 have been calculated from data similar to that shown in Tables 3 and 4 giving the incidence rates, except that the 25 patients referred to have been excluded. Table 7 deals with patients in all the diagnostic groups; Table 8 with probable cases only. The geographical distribution of the onsets is given in the second column of the tables; the expected number of onsets, on the assumption that age specific rates do not vary between the areas, is given in the third column; the fourth column shows the observed number of onsets as a percentage of the expected number. Thus, both in Tables 7 and 8 it appears that Counties Tyrone, Fermanagh, Down, and Antrim have an incidence of onsets

TABLE 5.

Geographical distribution of ascertained patients with Disseminated Sclerosis classified by age when seen and present place of residence.

(All diagnostic groups combined.)

Patients per 100,000 of the population.

	Present Age in Years.				Total
Males.	15-19	20-39	40-59	60 and over	20 and over
Belfast C.B.	11 (2)	56 (34)	100 (49)	26 (6)	67 (89)
Londonderry C.B.	— (–)	64 (4)	66 (3)	— (–)	53 (7)
Co. Antrim	— (–)	68 (22)	155 (38)	14 (2)	87 (62)
Co. Armagh	21 (1)	79 (12)	75 (9)	25 (2)	66 (23)
Co. Down	— (–)	70 (23)	134 (35)	31 (5)	84 (63)
Co. Fermanagh	— (–)	82 (6)	182 (11)	— (–)	94 (17)
Co. Londonderry	— (–)	35 (5)	94 (10)	14 (1)	50 (16)
Co. Tyrone	— (–)	99 (18)	73 (10)	20 (2)	72 (30)
TOTAL	5 (3)	66 (124)	112 (165)	21 (18)	73 (307)
Females.					
Belfast C.B.	11 (2)	78 (53)	115 (67)	21 (7)	80 (127)
Londonderry C.B.	— (–)	51 (4)	122 (7)	— (–)	65 (11)
Co. Antrim	— (–)	69 (24)	156 (42)	6 (1)	84 (67)
Co. Armagh	— (–)	76 (12)	132 (17)	12 (1)	80 (30)
Co. Down	— (–)	72 (25)	174 (50)	30 (6)	97 (81)
Co. Fermanagh	— (–)	93 (6)	151 (8)	— (–)	87 (14)
Co. Londonderry	— (–)	79 (11)	103 (11)	— (–)	68 (22)
Co. Tyrone	— (–)	88 (15)	158 (21)	— (–)	89 (36)
TOTAL	4 (2)	75 (150)	138 (223)	14 (15)	84 (388)
Persons.					
Belfast C.B.	11 (4)	68 (87)	108 (116)	23 (13)	74 (216)
Londonderry C.B.	— (–)	57 (8)	98 (10)	— (—)	60 (18)
Co. Antrim	— (–)	68 (46)	155 (80)	9 (3)	86 (129)
Co. Armagh	11 (1)	77 (24)	104 (26)	18 (3)	73 (53)
Co. Down	— (–)	71 (48)	155 (85)	30 (11)	91 (144)
Co. Fermanagh	— (–)	87 (12)	168 (19)	— (—)	91 (31)
Co. Londonderry	— (–)	56 (16)	98 (21)	7 (1)	59 (38)
Co. Tyrone	— (–)	94 (33)	115 (31)	10 (2)	80 (66)
TOTAL	5 (5)	71 (274)	126 (388)	17 (33)	79 (695)

Figures in brackets show actual number of disseminated sclerosis patients ascertained.

TABLE 6.

Geographical distribution of ascertained patients with probable Disseminated Sclerosis classified by age when seen and present place of residence.

Patients per 100,000 of the population.

	Present Age in Years.				Total
Males.	15-19	20-39	40-59	60 and over	20 and over
Belfast C.B.	— (–)	38 (23)	67 (33)	22 (5)	46 (61)
Londonderry C.B.	— (–)	32 (2)	44 (2)	— (–)	30 (4)
Co. Antrim	— (–)	47 (15)	98 (24)	14 (2)	58 (41)
Co. Armagh	— (–)	40 (6)	50 (6)	25 (2)	40 (14)
Co. Down	— (–)	43 (14)	80 (21)	6 (1)	48 (36)
Co. Fermanagh	— (–)	14 (1)	133 (8)	— (–)	50 (9)
Co. Londonderry	— (–)	35 (5)	47 (5)	14 (1)	34 (11)
Co. Tyrone	— (–)	72 (13)	58 (8)	10 (1)	53 (22)
TOTAL	— (–)	42 (79)	73 (107)	14 (12)	47 (198)
Females.					
Belfast C.B.	6 (1)	51 (35)	77 (45)	21 (7)	55 (87)
Londonderry C.B.	— (–)	38 (3)	105 (6)	— (–)	53 (9)
Co. Antrim	— (–)	54 (19)	119 (32)	6 (1)	66 (52)
Co. Armagh	— (–)	57 (9)	85 (11)	12 (1)	56 (21)
Co. Down	— (–)	43 (15)	129 (37)	15 (3)	66 (55)
Co. Fermanagh	— (–)	46 (3)	113 (6)	— (–)	56 (9)
Co. Londonderry	— (–)	65 (9)	93 (10)	— (–)	59 (19)
Co. Tyrone	— (–)	58 (10)	113 (15)	— (–)	62 (25)
TOTAL	2 (1)	52 (103)	100 (162)	12 (12)	60 (277)
Persons.					
Belfast C.B.	3 (1)	45 (58)	73 (78)	22 (12)	51 (148)
Londonderry C.B.	— (–)	36 (5)	78 (8)	— (–)	43 (13)
Co. Antrim	— (–)	51 (34)	109 (56)	9 (3)	62 (93)
Co. Armagh	— (–)	48 (15)	68 (17)	18 (3)	48 (35)
Co. Down	— (–)	43 (29)	106 (58)	11 (4)	57 (91)
Co Fermanagh	— (–)	29 (4)	124 (14)	— (–)	53 (18)
Co. Londonderry	— (–)	49 (14)	70 (15)	7 (1)	47 (30)
Co. Tyrone	— (–)	65 (23)	85 (23)	5 (1)	57 (47)
TOTAL	1 (1)	47 (182)	87 (269)	13 (24)	54 (475)

Figures in brackets show actual number of probable disseminated sclerosis patients ascertained.

above the average for the whole county, but that the ratios do not differ significantly from 100 per cent. They do, however, show agreement with previous tables.

Sex Distribution.

There is possibly some evidence of a greater prevalence of female over male patients. From Table 5 in the age group 20-39 the female rates are greater in

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Table 7.

Geographical distribution (place of onset) of patients ascertained with Disseminated Sclerosis with onset in the period 1937-51 inclusive.

(All diagnostic groups combined.)

Persons.	Total Age of Onset 10-69. Observed Number	Expected Number	Observed / Expected %
Belfast C.B. - -	125	134.86	92.69
Londonderry C.B. -	9	14.26	63.11
Co. Antrim - -	69	62.67	110.10
Co. Armagh - -	30	31.35	95.69
Co. Down - - -	71	65.66	108.13
Co. Fermanagh - -	20	14.54	137.55
Co. Londonderry - -	22	27.36	80.41
Co. Tyrone - - -	40	35.27	113.41
Total - -	386	385.97	100.0

The expected numbers have been calculated on the hypothesis that the incidence in the above areas is the same as the incidence for the whole country, taking into account the age and sex distribution of the areas.

Table 8.

Geographical distribution (place of onset) of patients ascertained with probable Disseminated Sclerosis with onset in the period 1937-51 inclusive.

Persons.	Total Age of Onset 10-69. Observed Number	Expected Number	Observed / Expected %
Belfast C.B. - -	71	81.48	87.14
Londonderry C.B. -	7	8.69	80.55
Co. Antrim - -	42	37.83	111.02
Co. Armagh - -	17	18.93	89.80
Co. Down - - -	41	39.52	103.74
Co. Fermanagh - -	10	8.72	114.68
Co. Londonderry - -	16	16.56	96.62
Co. Tyrone - - -	29	21.27	136.34
Total - -	233	233.00	100.0

The expected numbers have been calculated on the hypothesis that the incidence in the above areas is the same as the incidence for the whole country, taking into account the age and sex distribution of the areas.

Belfast and Counties Antrim, Down, Fermanagh, and Londonderry; and in the age group 40-59 the female rate is higher everywhere except in County Fermanagh. A very similar pattern is observed where the argument is limited to the probable cases (Table 6), the only exception being in the younger age group 20-39, in County Tyrone.

DISCUSSION.

The data obtained in this survey illustrate some of the difficulties which may arise in reaching even an approximate estimate of the prevalence of a disease like disseminated sclerosis in any given area. It is probable that, in the past, too little attention has been paid to these difficulties, and especially to the criteria used for ascertainment. Figures which are not really comparable have often been used to support the thesis that the disease is more prevalent in one part of the world than another. The most convincing evidence that it is more prevalent in cold and temperate climates than in warmer latitudes is that of Kurland, whose comparison of Winnipeg and New Orleans was based on identical methods of ascertainment. In three of the cases in his series the diagnosis was confirmed by post-mortem examination and in our series also, the necropsy results were available in only three cases. In Serial No. 826, classified as a 'possible' subject, there was no evidence of the disease. In Serial No. 456, a 'probable' case, the appearances were typical. In Serial No. 402 the diagnosis was also confirmed at necropsy, although clinically the features were not distinct, and a 'possible' label had later been changed to one of 'discarded.'

In estimating the prevalence we had the choice of taking into account all the 887 cases for which notifications were received, of considering the 700 accepted cases, or of exercising even stricter criteria and utilizing only the 476 'probable' cases. The prevalence rate proposed is 79 per 100,000, which is the figure obtained for all patients aged 20 and over, and for both 'early' and 'possible' as well as 'probable' groups. The prevalence rates for the age and sex groups is contained in Table 5. Thus, our experience shows that one case may be found in Northern Ireland for every 1,200–1,300 of the adult population. This is probably not an overestimate, for, although no cases were included after the 1st October, 1951, others subsequently came to light in the course of routine clinical work. Some cases too were probably overlooked because on the closing date replies had still not been received from 25 per cent. of the doctors in Northern Ireland.*

The rate of 79 per 100,000 is higher than comparable American, Canadian, English, and Scottish figures and much more so than the Swedish and Swiss estimates, 34 and 24.5 per 100,000 respectively, although allowance must be made for the different modes of ascertainment used and the different age and sex distribution of the populations. Because of the lack of uniformity in this respect it cannot be assumed confidently that the disease is significantly more prevalent here than it is in other parts of the world. The evidence, however, confirms the impression that Northern Ireland is a region having a high rate of prevalence.

*The proportion of the total not replying was about the same for each of the Six Counties. Had there been any gross discrepancy this might have invalidated the conclusions drawn as to the geographic distribution of the cases in the different counties.

The *incidence* rate determined for all the diagnostic and age groups (411 cases) was 2.74 per 100,000, or 2.56 for males and 2.91 for females. When the material was limited to 'probable' cases only (242 cases) it was 1.61, or 1.43 for males and 1.78 for females. These figures, it must be noted, are likely to be underestimates of the true incidence rate, because omitted from the data are patients who had onsets in the period 1937 to 1951, but who died before the survey was carried out, and patients who have had onsets in this period and who have not yet been

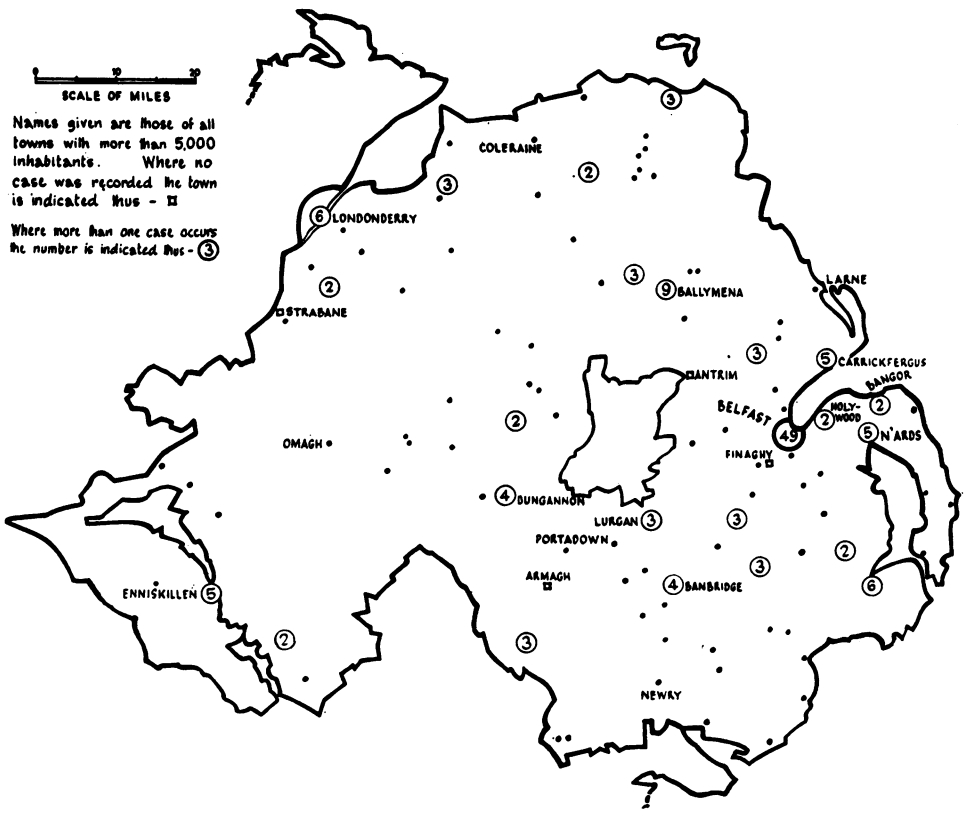

FIG. 1.—"Probable" cases who have lived in the same place all their lives indicated by dots.

recognized as suffering from disseminated sclerosis. The figure of 2.74, however, is not very different from the incidence rate in Winnipeg, 2.23, although it is higher than that quoted for New Orleans, 0.83; but again age and sex differences of the populations may affect the comparison.

As regards *geographical distribution*, at one stage in our work the impression was formed that there might be some areas in which the disease was unduly prevalent. Reference to the maps (Figs. 1 and 2) suggests that this might be true, for example, for parts of Counties Antrim and Down; but subsequent statistical

analysis offered no convincing evidence in favour of such. Further, not one instance was encountered of a husband and wife being affected. There were 44 families in which more than one member had the disease (Millar and Allison, 1954), but apart from these instances no obvious points of contact were observed between patients living in the same district.

We were tempted in considering the possible rôle of environment to investigate particularly the distribution of the 319 patients who had a fixed abode, but this

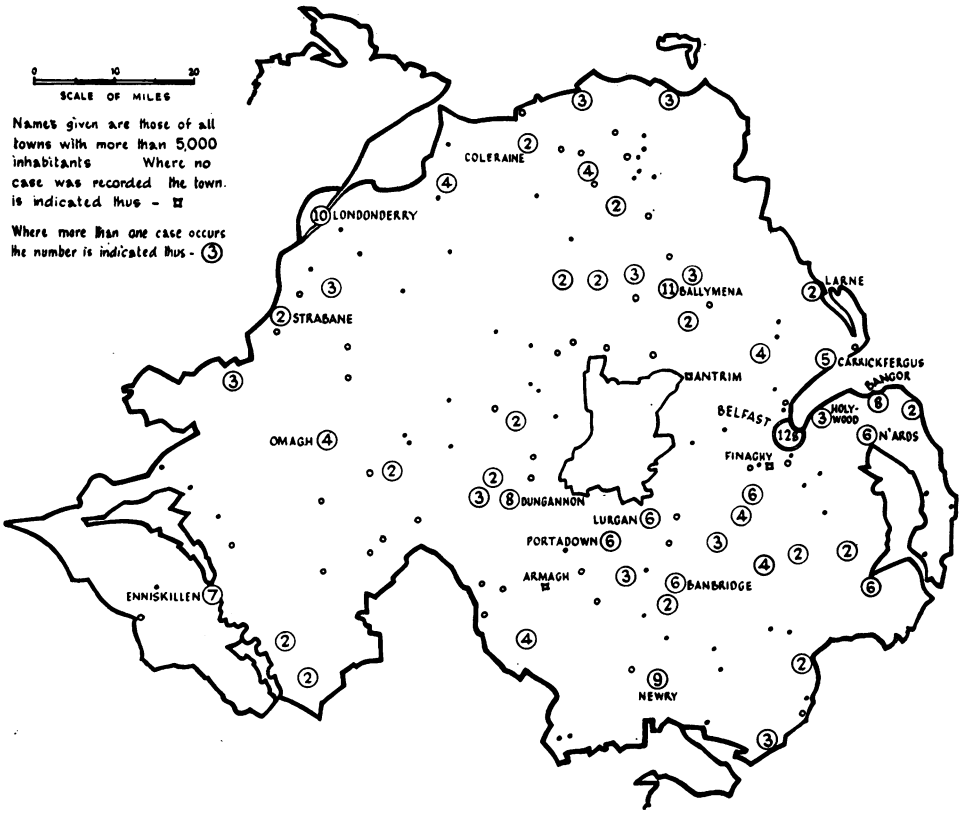

FIG. 2.—All "probable" cases. Distribution by present address : circles are cases who have moved from place to place.

would have been misleading owing to the tendency of the population to move from west to east and to migrate from rural to urban areas. Distributing them according to the present place of residence was also open to criticism, for it overlooked the 381 cases who had moved from one place to another. By this method, however, it is difficult to see any particular geographical pattern (Tables 5 and 6). Figures 1 and 2 are maps of Northern Ireland showing the distribution of probable cases. Figure 1 deals with probable cases who had a fixed abode and Figure 2 with all probable cases.

An alternative method of distributing the cases according to the place of onset is preferable, if it can be accepted as reasonable to discount any errors which may have arisen in deciding the place of onset. From Table 7 (all diagnostic groups) it will be seen that the ratio of observed to expected onsets was highest for County Fermanagh (137.55), and next for County Tyrone, County Antrim, and County Down in that order. Considering only the probable cases (Table 8), the same four counties still show a higher incidence, but this time Tyrone leads (136.34). In no county, however, are the differences very great, and we do not feel justified in drawing any conclusions from them.

Summary.

1. In Northern Ireland, which has a population of 1,370,709, a comparatively high prevalence rate for disseminated sclerosis was found of 79 per 100,000 for all age groups over 20.

2. The incidence rate between 1937 to 1951 was 2.74 per 100,000, but this is probably an underestimate, for allowance must be made for patients who died before the survey began or whose cases have not yet been diagnosed.

3. No evidence was found to suggest that the disease was more prevalent in one district of this region than in another or that there was any tendency to focal distribution of cases.

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APPENDIX.

SPM 22 **FORM D**

DEPARTMENT OF NEUROLOGY, THE ROYAL VICTORIA HOSPITAL
DEPARTMENT OF SOCIAL AND PREVENTIVE MEDICINE, THE QUEEN'S UNIVERSITY

DISSEMINATED SCLEROSIS ENQUIRY

Surname and First Names	Sex	Serial No.

A. MODE OF ONSET OF DISEASE

Date	Age		Duration of Initial Symptoms	Recovery
		Sudden Gradual		Complete Partial Static

Symptoms and Signs suggestive of: Single Multiple Lesions
Minimal Severe

Symptoms and Signs indicating Involvement of:
- Cerebrum
- Optic nerve
- Brain stem
- Cerebellum
- Spinal cord

Symptoms related to:
1. Pregnancy or parturition
2. Trauma
3. Physical or mental shock
4. Surgical operation
5. Intercurrent illness
6. Signs of acute encephalomyelitis

B. COURSE OF ACUTE OR CHRONIC PROGRESSIVE CASES	Age	Year	No. Years from Onset
Onset of Persistent Sphincter Disturbances			
Onset of Mental Changes			
Onset of Severe Disablement			
Date of Death			

Duration of Severe Disablement		Duration of Illness	

Cause of Death as entered on Death Certificate

I(*a*)

I(*b*)

I(*c*)

II

C. RELAPSING AND REMITTING CASES

Relapse	Date of Onset	Age	Sudden or Gradual	Character and Duration of Symptoms	Extent of Recovery	Relation to Pregnancy, Trauma, etc. (Part A, 1-6)
1						
2						
3						
4						
5						
6						
7						

D. FAMILY HISTORY

(*a*) Deformities

(*b*) Mental Disease

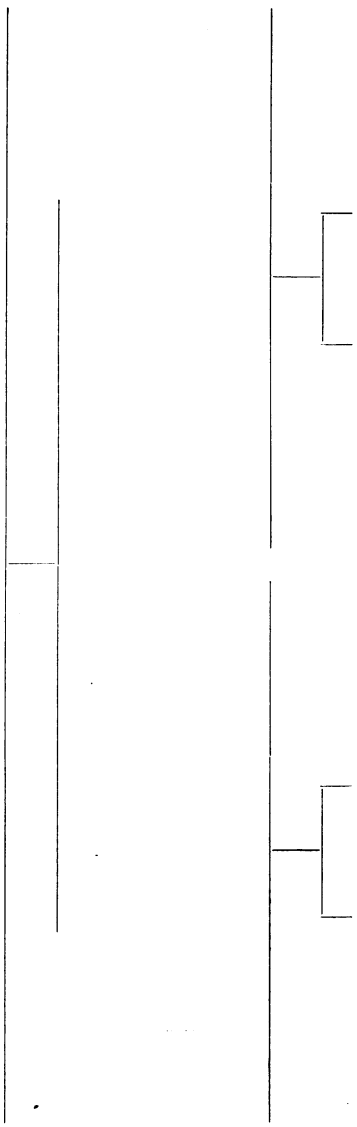
(*c*) Nervous Disease

(*d*) Peptic Ulcer

(*e*) Asthma

(*f*) Migraine

(*g*) Twins



PLACES LIVED AND DATES

E. PERSONAL HISTORY AND GENERAL HEALTH

Childhood

Delivery and Labour	Feeding Artificial Breast	General Condition Delicate baby Average baby Strong baby

Early Food Intolerance or Fads

Bilious Attacks, Cyclical Vomit, Hives, Eczema

Walking	Talking

Bedwetting, Nail Biting, Fears, Nightmares

Car, Train or Bus Sickness

Infectious Diseases

Accidents (Major)	Games, Ability to Run, etc.

Adult life. (Note any other illnesses and especially enquire for allergic disorders, evidence of psychoneurosis, gastric disorders, goitre and tuberculosis.)

F. WOMEN

Date of Menarche	Character and Frequency of Menstruation	Date of Menopause

Dates of birth of Children	1.	2.	3.	4.	5.	6.
	7.	8.	9	10.	11.	12.

FAMILIAL INCIDENCE OF DISSEMINATED SCLEROSIS IN NORTHERN IRELAND

J. H. D. Millar and R. S. Allison

In Northern Ireland we have recently completed a survey of disseminated sclerosis; 700 cases have been traced and examined and in 44 families we have found more than one member affected, giving a familial incidence of 6.58 per cent.; this figure corresponds closely with the incidence in recent surveys from the Middlesex Hospital 6.5 per cent. (Pratt, et al., 1951), and from the Bristol area 6 per cent. (Campbell, 1952).

It is only in the past decade that the familial aspect of the disease has been generally recognized in the English literature, although the subject was much discussed on the Continent. As recently as 1930 Russell Brain, in a review of the literature of disseminated sclerosis, stated: "In striking contrast to diseases attributable to an inherited germinal defect, multiple cases of disseminated sclerosis in one family are extremely rare compared with sporadic cases, and its occurrence in more than two members of a family and in two successive generations is almost unknown. These facts suggest that inherited predisposition plays no part in the ætiology of the disease, and that the occasional occurrence of multiple cases in one family is due either to chance, exposure to a common environment or mutual infection." Curtius (1933) made an extensive study of the 2,778 near and distant relatives of 56 cases of disseminated sclerosis in Bonn and a less extensive study of 346 relatives of a further 50 cases in Heidelberg. In the Bonn series he found 6 definite cases and in the Heidelberg series 4 definite cases of disseminated sclerosis among the relatives. Later, in 1937, with Speer, he described 2 further families with multiple cases. They found one doubtful case in the 212 parents and 4 definite, and 1 doubtful case in the 444 siblings; 4 in 444 is equivalent to 90 per 10,000 and 40 times the incidence in the general population, based on the Swiss surveys (Bing and Reese, 1926; Ackermann, 1931). As a control group, Curtius investigated the 640 relatives of 56 patients with fractures and found no case of disseminated sclerosis. Mackay (1950) reviewed the literature and, after careful consideration of the case reports, accepted 79 families with multiple cases of disseminated sclerosis. He added a further 5 families. He also found that up to and including 1948, autopsy confirmed the diagnosis in 3 patients in one family, in both patients in 4 families, and in one of two patients in 13 families. Pratt, et al. (1951), found 184 families in the literature where more than one member was affected with disseminated sclerosis. In their series of 310 cases the familial incidence was 6.5 per cent. (20 families). The incidence of disseminated sclerosis in the siblings of 168 cases and the parents of 310 cases was significantly higher than that expected on the basis of a random distribution of the disease.

Material.

We have attempted to trace all cases of disseminated sclerosis in Northern Ireland. In addition to many patients who have attended the Neurological Clinic, all general practitioners were asked to notify us of the names of patients suffering from the disease. Seven hundred cases were seen, the majority in their homes. This had the advantage that relatives could supply missing details in the clinical and family histories. Frequently it was possible to obtain details concerning the health of grandparents and distant relatives, and in a relatively compact and self-contained community such as Northern Ireland the news that we had visited a relative increased the likelihood of obtaining a positive family history. In 1947 one of us (Millar, 1949) made a limited survey of the disease and traced 91 cases. There were multiple cases in 3 out of 89 families. Some of these 91 cases are included in this survey and two additional familial cases have been found, now making an incidence of 5 in 89 families. This suggests that the greater the scope

TABLE 1.

Distribution of 700 Cases in the Diagnostic Groups.

Probable	476
Possible	145
Early	79
	700

of the study the greater the chance of finding multiple cases in one family. We cannot, of course, claim to have seen every person suffering from this disease in Northern Ireland, but we think we have seen the majority, for reasons given in the first paper (Allison and Millar, 1954). We have been strict in the criteria of diagnosis and cases were placed in the following three groups (Table 1). The criteria for this grouping are discussed in greater detail elsewhere (Allison and Millar, 1954), but briefly "probable" cases are those which show typical evidence of dissemination of lesions with or without a history of remissions. "Possible" cases are those where the history is progressive or static, but where the findings suggest the diagnosis and no other cause has been found for the clinical picture. "Early" cases are those where the history is suggestive, but where there are few or no neurological signs.

There were 44 families with two or more members affected out of a total of 668 families, giving an incidence of 6.58 per cent. Table 2 shows the relationships. We examined 64 cases in the series and an additional 6 cases not included in the series—70 cases in all. In this total were 56 probable, 11 possible, and 3 early cases. The familial group is again sub-divided into two categories (see Appendices XY for case histories and pedigrees) :—

1. Families in which we had examined two or more members (23 families) or where we had examined one member and the evidence from another centre was sufficiently strong to warrant a firm diagnosis in the other (6 families).

2. Families in which we had examined one member and the evidence concerning the other was less convincing, such as letters from the family doctor, or death certificates (15 families).

In addition, in the Appendix Z we have recorded the incidence of other neurological conditions found in near relatives of our cases. Under the heading

TABLE 2.

RELATIONSHIPS

(including cases dead or not examined).

Grandfather, father and son	1
Father and son	5
Mother and daughter	1
Mother and two daughters	1
Mother and son	1
Mother, son and daughter	1
Brother and sister	13
Brother, sister and her daughter	1
Two brothers and one sister	3
Three brothers	1
Two sisters	8
Two sisters and one brother	1
Uncle and nephew	2
Aunt and niece	2
Cousins (first)	3
Total number of families with more than one member affected	44 (6.58%)

chronic neurological disorders are included 18 persons about whom remarks such as the following were made:—

"Paralysis of the spine many years before death," "both legs affected, can't walk," "similar complaint to mine." This group may well include further cases of disseminated sclerosis. This is one indication that our estimate of the familial incidence in this series is conservative.

DIFFERENTIAL DIAGNOSIS FROM FAMILIAL NEUROLOGICAL DISORDERS.

Hereditary Spastic Ataxias: This group includes Friedreich's Ataxia (1863), and here the absence of the deep tendon reflexes makes confusion unlikely, although 6 cases were notified in this series. However, regarding the other two components of this group, hereditary ataxia and spastic paraplegia, the differential diagnosis may be very difficult if not impossible on clinical grounds. There are, however, certain points which would be in favour of these two conditions as compared with

TABLE 3.

Distribution of Symptoms and Signs in the Three Groups. Expressed in percentages.

Number of Cases	Familial D.S.* 61 cases	Probable D.S. 423 cases	Hereditary Ataxia 18
Remissions	61%	76%	0%
Onset under 20 years	11	20	39
Deformities	—	—	33
Diplopia	30	37	22
Retrobulbar neuritis	28	36	—
Paræsthesiæ	45	65	22
Urinary symptoms	46	66	28
Weakness of legs	96	92	78
Weakness of arms	33	49	6
Ataxia of legs	33	42	67
Ataxia of arms	35	42	60
Nystagmus	58	56	44
Monocular nystagmus	25	9	—
Pale discs with visual impairment	18	27	22
Pale discs without visual impairment	42	34	22
Euphoria	35	38	28
Dementia	17	11	—
Dysarthria	13	25	22
Impaired vibration sense	51	60	28
Impaired postural sense	37	43	28
Other forms of sensory impairment	21	27	11
Titubation	2	4	16
Labyrinthine symptoms	7	17	—

*64 cases seen in the survey less three "early" cases.

disseminated sclerosis. The onset is before the age of 20 and similar in the siblings, although this is not so when the inheritance is due to a dominant gene (Bell, 1939). The progressive history of spastic or ataxic weakness of the lower limbs can also occur in disseminated sclerosis. Carter, et al. (1950), investigated the clinical records of 46 cases of disseminated sclerosis in whom the diagnosis had been confirmed by autopsy. Remissions occurred in 59 per cent. of their series and weakness of the legs remitted in only 26 per cent. Deformities such as scoliosis and pes cavus may not be present in all cases of hereditary ataxia—Carmichael and Bell found no scoliosis in 4 and no pes cavus deformity in 7 out of a total of 40 cases of spastic ataxia in their English material; also 6 of the 40 showed severe mental deterioration; 7 had generally pale discs and 4 temporal pallor, without visual impairment; urinary symptoms occurred in 8 (Bell, 1939). Ophthalmoplegia of varying degrees is a well-known phenomenon in cases of hereditary ataxia. Retrobulbar neuritis, which is usually regarded as strong evidence in favour of disseminated sclerosis, has been reported in 2 members of a family suffering from hereditary spastic paraplegia. Both cases were under the age of 10 and had no other neurological symptoms or signs (Bickerstaff, 1950). Leeuwen and Van Bogaert (1949) found that in certain cases of hereditary ataxia optic atrophy shows the typical picture of "retrobulbar neuritis"; the onset of blindness may be acute and a partial remission may occur, as in Leber's optic atrophy. The condition, however, does not altogether mimic the retrobulbar neuritis of disseminated sclerosis in which the lesion is usually unilateral and remits in a matter of weeks or months, although this did happen in one of Bickerstaff's patients. Nor can the presence of a Lange curve associated with a negative Wassermann in the C.S.F. always be considered as confirmatory evidence in favour of disseminated sclerosis (Aring, 1938). Thus it would be possible to construct from the above facts a case of hereditary ataxia which would be indistinguishable clinically from disseminated sclerosis.

At this juncture it is pertinent to mention two interesting instances in the literature where pathologically there were present both the lesions of Friedreich's ataxia and disseminated sclerosis. In 1922 Mondini published a report of a young woman whose clinical history was typical of Friedreich's ataxia; the autopsy was, unfortunately, limited to examination of the cerebellum and medulla; sections showed symmetrical degeneration of the direct spino-cerebellar tracts and other tracts, also many sclerotic plaques. He was of the opinion that this was a case of Friedreich's ataxia complicated by disseminated sclerosis. More convincing is Brouwer's report in 1933 of two sisters suffering from Friedreich's ataxia. Post-mortem findings in one sister showed, in addition to the findings of Friedreich's ataxia, lesions resembling the plaques of disseminated sclerosis.

There were 18 cases of hereditary spastic ataxia among those notified, and in Table 3 we have compared them on the basis of symptomatology with the familial and probable groups. The number of cases in each of the three groups is so dissimilar that it is not possible to draw any significant conclusions, but the table does illustrate some of the points of differential diagnosis between disseminated sclerosis

and the hereditary ataxias mentioned above; also it shows that the distribution of symptoms in the familial group is similar to that in the probable group. It has not always been possible, however, to make a firm diagnosis, and below are two examples which were excluded from the series :—

Female, Mrs. G., born 1902 : 1914, at the age of 13, numbness and weakness of right hand for a few months; 1918, diplopia on two occasions, each lasting one week; 1920, the vision of the right eye was hazy for two weeks; 1928, dizziness and numbness of the legs and back which cleared up rapidly; 1939, gradually increasing weakness of the right leg and staggering. Since 1944 left leg also affected. Bedridden since 1946. The right foot had been deformed from birth; 1949, examination showed marked right-sided clubfoot deformity; visual acuity R = J.12, L = J.2; pallor of both discs; weakness and hypotonia of arms, especially the right; wasting of the small muscles of the right hand; slight intention tremor left finger-nose test, limited voluntary movements left leg only; legs contracted, left extended, right semi-flexed; extensor plantar responses; all deep tendon reflexes were unobtainable; abdominal reflexes absent; vibration sensation absent throughout; muscle joint sensation absent in toes.

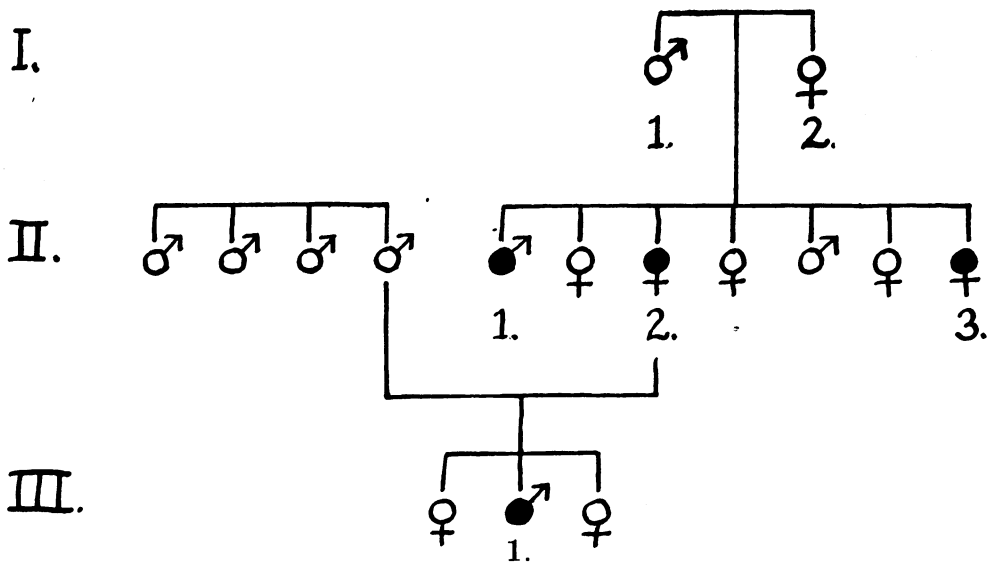
Family History : Mother alive and well, aged 74. Father died of "ulcer" at 35. Mother's cousin in U.S.A. has a neurological condition of 20 years' duration. Sister, Mrs. M. D., as below.

Female, Mrs. M. D., born 1896 : 1928, aged 32, blindness in right eye for a few months which recurred in 1935; 1945, increasing weakness left leg; 1948, admitted to Royal South Hants Hospital, then complained of precipitancy of micturition. On examination—Slight nystagmus to right and left; bitemporal pallor of discs; weakness of both legs, especially the left; generalized hyper-reflexia; absent abdominal reflexes; extensor plantar responses; absent vibration sensation in legs; postural sense diminished left leg.

C.S.F. : Cells 2; protein 50 mgms. per cent.; globulin : faint trace; W.R. : negative; Lange 2344432100.

Later bedridden and paraplegia in flexion developed and she died in April, 1952.

To summarize : Two sisters with history in keeping with disseminated sclerosis. One had a congenital clubfoot deformity and the tendon reflexes were unobtainable, although contractures could account for the absent knee and ankle jerks. For these reasons this family was excluded from the series.



(iii) 1.—*Case J. A., male, born 1911 :* 1934, "useless" right hand for three weeks; 1944, blurred vision for three weeks; 1949, gradually increasing stiffness of legs and hesitancy of micturition with partial remission after two years. Examination 1950: Cranial nerves normal; right hand slightly clumsy; spastic weakness of legs with generalized hyper-reflexia; abdominal reflexes absent on left side; plantar reflexes extensor; vibration sensation absent in legs; position sensation slightly diminished in toes. C.S.F. : White cells 3; protein 55 mgms. per cent.; globulin trace; W.R. : negative; Lange 4432100000.

(ii) 1.—*Case J. C., male, born 1880 :* 1936, in the National Hospital, Queen Square, London, under the care of Dr. Gordon Holmes with a diagnosis of subacute combined degeneration of the spinal cord. Two years' history of aching and stiffness of the legs. Examination at that time showed no abnormality in the cranial nerves; slight inco-ordination in the finger-nose test of both arms; there was spastic weakness of both legs with sustained knee clonus, absent ankle jerks and extensor plantar reflexes; vibration sensation was diminished in the legs. R.B.C. count: 4.84 million; hb. 90 per cent.; colour index 0.93; F.T.M. showed achlorhydria. W.R. : negative. C.S.F. normal.

Patient died in 1950 in the Home and Hospital for Jewish Incurables, where he was considered to be suffering from disseminated sclerosis.

(ii) 2.—*Female, born 1882 :* According to her doctor, she has been suffering from "spastic paralysis" of 15 years' duration, but is able to walk with sticks. No other signs. Mentally normal. No nystagmus. No intention tremor. No dysarthria.

(ii) 3.—*Female, born 1890 :* A progressive illness since the age of 40; now bedridden.

(i) 1 and 2.—*Grandparents :* Polish and first cousins.

Although case J. A. could be diagnosed as disseminated sclerosis, his uncle, J. C., in the early stages of his condition, was diagnosed as subacute combined degeneration of the cord, and it is most unlikely that the condition was disseminated sclerosis in view of the absent ankle jerks. For this reason, this family was discarded from the series.

Other Familial Neurological Diseases.

There are other less common familial neurological disorders which can simulate disseminated sclerosis. Ferguson and Critchley (1929) described a form of hereditary ataxia resembling disseminated sclerosis, the unusual features being limitation of upward gaze, exophthalmos and parkinsonism. In 1907 Holmes described a form of familial degeneration of the cerebellum. In another paper, he reviewed and classified cerebellar disease. He did not consider olivo-ponto-cerebellar atrophy to be hereditary or familial. However, in a more recent paper Critchley and Greenfield (1948) found a few familial cases of olivo-ponto-cerebellar atrophy in the literature, and distinguished this condition from cerebello-olivary degeneration, which was mainly familial, on pathological grounds.

Ferraro (1927) reported a familial form of encephalitis periaxialis diffusa—occurring in two brothers and one sister, who were clinically diagnosed as disseminated sclerosis. In each case the onset of the disease occurred in the third

TABLE 4.

All cases in this table are counted as affected whether "probable," "possible," or "early." The table includes all sibships whether no, or one, parent is affected.

Family Size	No. of Families	Males			Females			Total		
		A	U	T	A	U	T	A	U	T
1	36	19	—	19	17	—	17	36	—	36
2	60	28	29	57	34	29	63	62	58	120
3	70	31	66	97	39	74	113	70	140	210
4	100	47	149	196	56	148	204	103	297	400
5	86	48	181	229	45	156	201	93	337	430
6	97	41	262	303	63	216	279	104	478	582
7	75	40	229	269	40	216	256	80	445	525
8	64	21	238	259	45	208	253	66	446	512
9	42	17	154	171	31	176	207	48	330	378
10	21	8	98	106	14	90	104	22	188	210
11	6	3	32	35	4	27	31	7	59	66
12	6	2	31	33	4	35	39	6	66	72
13	4	1	27	28	3	21	24	4	48	52
14	1	1	4	5	—	9	9	1	13	14
Total	668	307	1500	1807	395	1405	1800	702	2905	3607

A = Affected. U = Unaffected. T = Total.

decade. He discussed the possible relationship of this condition to Pelizæus-Merzbacher disease.

The Problem.

When, in disseminated sclerosis, as in many other conditions, the familial incidence of the condition is definite but low, many problems arise in interpretation. It is clear that the proportion affected in the sibships of the propositus is too low to be interpreted as the expression of a single gene. By the word 'propositus' we mean the index case or case which brought the family to our attention. The minimum proportion to be expected on a single gene hypothesis would be 1 in 4, whereas the actual expression is about 1 in 50 (allowing for the fact that the method of ascertainment was by one affected sib in the sibship). To satisfy any single gene hypothesis it would therefore be necessary to postulate that the gene was only expressed in less than 10 per cent. of the people who had the gene. The

TABLE 5.

All cases in this table are affected whether they are "probable," "possible," or "early." The table excludes sibships where a parent is affected.

Family Size	No. of Families	Males			Females			Total		
		A	U	T	A	U	T	A	U	T
1	36	19	—	19	17	—	17	36	—	36
2	59	27	28	55	34	29	63	61	57	118
3	69	30	64	94	39	74	113	69	138	207
4	96	43	145	188	56	140	196	99	285	384
5	85	47	180	227	44	154	198	91	334	425
6	96	41	257	298	62	216	278	103	473	576
7	74	39	228	267	40	211	251	79	439	518
8	63	20	235	255	45	204	249	65	439	504
9	41	17	151	168	29	172	201	46	323	369
10	21	8	98	106	14	90	104	22	188	210
11	6	3	32	35	4	27	31	7	59	66
12	6	2	31	33	4	35	39	6	66	72
13	4	1	27	28	3	21	24	4	48	52
14	1	1	4	5	—	9	9	1	13	14
Total	657	298	1480	1778	391	1382	1773	689	2862	3551

A = Affected. U = Unaffected. T = Total.

more usual methods of expressing this would be to say that the gene had less than 10 per cent. penetration or that less than 10 per cent. of the susceptible genotypes showed the trait.

It is always tempting to proceed logically at this stage and to say that perhaps two genes are involved, and by juggling with possible combinations of one or two dominant and/or recessive genes to demonstrate that one's own observations fit in with some theoretical hypothesis. For many reasons this is a dangerous exercise. However, proceeding along somewhat different lines from our original observations of undue concentration of cases within sibships, it is more reasonable to argue as follows :—

First, we are going to consider the sibships in which the cases occur, and we want to know whether there is undue concentration of cases in these sibships. There will always be at least one case in each sibship, because each was 'ascertained' by a propositus or index case. Therefore we must allow for this or we should never in any condition arrive at an incidence in sibships so ascertained of less than one divided by the mean sibship size. Or to reduce to absurdity in another way—if all the families consisted of two sibs we should have a minimum of 50 per cent. affected. To be accurate, as, for example, if we were trying to fit our observations to a simple ratio, we should have to make a separate adjustment for each family

TABLE 6.

All cases in this table are regarded as affected as in Tables 4 and 5.

This table includes only sibships where one parent is affected.

Family Size	No. of Families	Males			Females			Total		
		A	U	T	A	U	T	A	U	T
1	—	—	—	—	—	—	—	—	—	—
2	1	1	1	2	—	—	—	1	1	2
3	1	1	2	3	—	—	—	1	2	3
4	4	4	4	8	—	8	8	4	12	16
5	1	1	1	2	1	2	3	2	3	5
6	1	—	5	5	1	—	1	1	5	6
7	1	1	1	2	—	5	5	1	6	7
8	1	1	3	4	—	4	4	1	7	8
9	1	—	3	3	2	4	6	2	7	9
Total	11	9	20	29	4	23	27	13	43	56

A = Affected. U = Unaffected. T = Total.

size. This is hardly worth while. Nevertheless, we have set out the data in tables by family size (a) in order to make it clear that we recognize the point; and (b) so that it may be possible, if desired, to make further calculations (Tables 4-9).

We do not know the frequency of the genotype which is often, but not constantly, expressed as disseminated sclerosis. However, if we presume that the disease is the expression, precipitated by environmental factors of a specific genotype, then we should expect that the same genotype would occur more frequently in the sibs of affected persons than in the general population. If we exclude from our calculations the affected individual by whom we identified the family, all the others have independently the same chance of being affected and the fraction, affected sibs divided by total sibs, will give the incidence in the sibs, which can then be compared with that in the general population.

TABLE 7.

ALL PROBABLE SIBSHIP

i.e., where at least one affected person was regarded as a "probable" case. "Possible" or "early" cases are counted as "unaffected" in this table. It includes all families, whether parent affected or not.

Family Size	No. of Families	Males			Females			Total		
		A	U	T	A	U	T	A	U	T
1	26	15	—	15	11	—	11	26	—	26
2	47	22	24	46	26	22	48	48	46	94
3	43	18	40	58	25	46	71	43	86	129
4	68	28	100	128	40	104	144	68	204	272
5	61	34	126	160	31	114	145	65	240	305
6	59	19	160	179	43	132	175	62	292	354
7	46	22	143	165	25	132	157	47	275	322
8	46	14	170	184	33	151	184	47	321	368
9	33	13	127	140	22	135	157	35	264	297
10	12	4	57	61	9	50	59	13	107	120
11	3	1	16	17	2	14	16	3	30	33
12	4	1	18	19	3	26	29	4	44	48
13	4	1	27	28	3	21	24	4	48	52
14	1	1	4	5	—	9	9	1	13	14
Total	453	193	1012	1205	273	956	1229	466	1968	2434

A = Affected. U = Unaffected. T = Total.

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TABLE 8.

PROBABLE SIBSHIP—excluding those where a parent was affected.
As in Table 7, "possible" or "early" cases are counted as "unaffected" in this table.

Family Size	No. of Families	Males			Females			Total		
		A	U	T	A	U	T	A	U	T
1	26	15	—	15	11	—	11	26	—	26
2	46	21	23	44	26	22	48	47	45	92
3	43	18	40	58	25	46	71	43	86	129
4	66	26	96	122	40	102	142	66	198	264
5	61	34	126	160	31	114	145	65	240	305
6	58	19	155	174	42	132	174	61	287	348
7	46	22	143	165	25	132	157	47	275	322
8	46	14	170	184	33	151	184	47	321	368
9	33	13	127	140	22	135	157	35	262	297
10	12	4	57	61	9	50	59	13	107	120
11	3	1	16	17	2	14	16	3	30	33
12	4	1	18	19	3	26	29	4	44	48
13	4	1	27	28	3	21	24	4	48	52
14	1	1	4	5	—	9	9	1	13	14
Total	449	190	1002	1192	272	954	1226	462	1956	2418

A = Affected. U = Unaffected. T = Total.

The Data used in the Genetic Analysis.

The Sibships of the Propositi.

The genetic analysis considers in all 668 sibships with 702 cases in the sibship of the propositi.

The reasons why the genetic analysis considers 702 affected sibs in the sibship of the propositi while the epidemiological analysis considers 700 cases are as follows :—

1. In the epidemiological analysis are included 20 cases excluded from the genetic analysis for the following reasons :

	No. of Cases
(i) Sibship size not known - - - - -	13
(ii) Cases not in the sibship of the propositus, although they were relations of the propositus - - - -	7
Total - - - - - -	20 cases.

2. In the genetic analysis are included cases where sibs were regarded as affected, but they were either dead or they were not seen by the observers. These totalled 22 cases, i.e., there are in all 2 more (22 minus 20) cases considered in the genetic analysis. Siblings under 15 years, or who did not survive 15 years, are omitted.

TABLE 9.

Probable Sibship—only those with one parent affected are included in this table. As in Table 7, "possible" or "early" cases are counted as "unaffected" in this table.

Family Size	No. of Families	Males			Females			Total		
		A	U	T	A	U	T	A	U	T
1	—	—	—	—	—	—	—	—	—	—
2	1	1	1	2	—	—	—	1	1	2
3	—	—	—	—	—	—	—	—	—	—
4	2	2	4	6	—	2	2	2	6	8
5	—	—	—	—	—	—	—	—	—	—
6	1	—	5	5	1	—	1	1	5	6
Total	4	3	10	13	1	2	3	4	12	16

A = Affected. U = Unaffected. T = Total.

TABLE 10.

SUMMARY.

Clinical Classification	No. of Sibships	Neither Parent Affected					
		Males			Females		
		A	U	T	A	U	T
"Probable" Sibships	449	190	1002	1192	272	954	1226
All Sibships	657	298	1480	1778	391	1382	1773

Clinical Classification	No. of Sibships	One Parent Affected					
		Males			Females		
		A	U	T	A	U	T
"Probable" Sibships	4	3	10	13	1	2	3
All Sibships	11	9	20	29	4	23	27

Clinical Classification	No. of Sibships	Total								
		Males			Females			Total		
		A	U	T	A	U	T	A	U	T
"Probable" Sibships	453	193	1012	1205	273	956	1229	466	1968	2434
All Sibships	668	307	1500	1807	395	1405	1800	702	2905	3607

Probable sibships are those where at least one case which is classed as probable occurs. In this line any "possible" or "early" cases which occur in sibship or parent are counted as unaffected.

All sibships includes every case occurring in the sibship of the propositus : i.e., "probable," "possible," and "early" cases are all counted as affected. Similarly, an affected parent, by that definition, puts the appropriate sibship in the "One parent affected" column.

TABLE 11.

Parental Consanguinity.

	Present Series		Mathers		Curtius (1933)		Bell (1940)		Pratt (1951)	
	No.	Per Cent.	No.	Per Cent.	No.	Per Cent.	No.	Per Cent.	No.	Per Cent.
Number of Families - - -	*558	100.00	670	100.00	106	100.00	632	100.00	134	100.00
No Consanguinity - - -	538	96.42	668	99.70	100	94.34	624	98.73	131	97.76
First Cousin Marriages - -	6	1.08	—	—	3	2.83	6	0.95	2	1.49
Second Cousin Marriages - -	6	1.08	2	0.30						
Paternal Grandparents First Cousins	4	0.72	—	—	3	2.83	2	0.32	1	0.75
Other Relationships - - -	4	0.72	—	—						
Total Incidence of Consanguinity -	20	3.58	2	0.30	6	5.66	8	1.27	3	2.24

*Of the 668 sibships considered, information was available only in respect of 558 sibships.

Incidence in the Sibs of the Propositi.

In the 668 sibships there were 3,607 sibs, and of these 702 were affected. Ignoring the propositi, there were 34 affected sibs in 2,939 sibs of the propositi at risk, i.e., 1.15 per cent. (Table 4). Where neither parent was affected there were 657 sibships, having in all 3,551 sibs, and of these 689 were affected. Thus, 32 in 2,894 sibs at risk were affected when the propositi are ignored, or 1.11 per cent. (Table 5). Where one parent was affected, in 11 sibships there were 56 sibs, and in all 13 sibs were affected, so that 2 of 45 sibs of the propositi or 4.44 per cent. were affected (Table 6).

TABLE 12.

Sex Distribution in Affected Sibs.

Sib Pairs and Threes.

Sib Sex Groups	No. of Families	M	F	Total
M M	—	—	—	—
M F	13	13	13	26
F F	9	—	18	18
2M F	2	4	2	6
M 2F	1	1	2	3
3M	1	3	—	3
3F	—	—	—	—
	—	—	—	—
Total	26	21	35	56

Similar calculations are made for those sibships where there was at least one probable case (Tables 7-9). There were 13 in 1,981 sibs, or 0.66 per cent., affected. Where neither parent was affected, 13 in 1,969 sibs, or 0.66 per cent., and where one parent was affected there were no sibs affected in 12, or 0 per cent., but in this instance the small number of sibships make it impossible to draw any conclusions. It should be stressed that, in the probable sibships, all possible and early cases were counted as unaffected in these calculations. Tables 4-9 set out the data for family size and the figures are summarized in Table 10. It will be noted that the number of very large families, 10 or over, is small, but there appears to be a trend for the number of multiple cases within sibships to increase between family sizes 2 and 9 where the number of sibships is considerable.

The incidence in the sibs of the propositi, 1.15 per cent., is greater than the prevalence rate in the general population in Northern Ireland when all age and diagnostic groups are included, 0.072 per cent. It is also greater than the highest rate of 0.182 per cent.—that of County Fermanagh in the age group 40-59 years. (Allison and Millar, 1954.) When we confine our attention to the incidence in the probable group, or 0.66 per cent., it is again greater than the prevalence rate of cases in the general population, 0.05 per cent., even 0.124 per cent., the highest rate again in County Fermanagh in the age group 40-59 years. It would therefore be fair to say that the incidence in the sibs of the propositi is somewhere between 5 and 15 times greater than the prevalence rate in the general population. Although

TABLE 13.

Sex linkage information from Consanguinity Data.
Sex of parent of offspring of first-cousin marriages with sex of paternal grandparent.

Serial No.	Sex of Patient	Relationship through Father's Father or Mother
164	F	Mother
251	F	Mother
267	M	Mother
597	M	Father
708	F	Mother
830	F	Mother

these figures are impressive, it is difficult to be sure that they are technically significant, a fact not always taken into account. There are two main difficulties in making a numerical comparison. The first is the size of the sampling error involved, and secondly, the difficulty in making standardizations for age.

Consanguinity.

In 558 of the 668 sibships considered, information about consanguinity of the parents of the propositus was collected (Table 11). The parents of the propositus were full cousins in six instances and second cousins in a further six instances. There was believed to be a common ancestor of parents several generations back, the relationship not being quite clear in four instances. That is, in 16 sibships there was some degree of consanguinity of parents. In addition, in four instances

the parents of the propositus' father were full cousins. Full-cousin consanguinity of parents, therefore, occurred in 6 of 668 sibships, or 0.90 per cent.; if the sibships where no information was available are excluded, 6 of 558 sibships, or 1.08 per cent.

No reasonable control figures are available for comparison as Bell's (1941) figures for England and Wales could not safely be used. Mathers (1952) found that of 670 married adults questioned in casualty department of the Royal Victoria Hospital, Belfast, two were married to a second cousin. It cannot be said that consanguinity is unduly common in the parents of disseminated sclerotic patients, especially when compared with, for instance, the figure 21.7 per cent. found in the parents of patients suffering from the myopathies (Stevenson, 1953). Table 11 also sets out the consanguinity rates in disseminated sclerosis in other papers. There is reasonable agreement.

Sex Incidence and Associations.

The sib pairs and threes in the 26 sibships are shown in Table 12. These figures do not suggest any tendency for one sex to be more affected than the other. The information about the sex of the patient, relevant parent and grandparent, where there was consanguinity, is shown in Table 13. Here the numbers are small, and speculation about partial sex linkage seems too hazardous to warrant discussion, although our findings are similar to those shown in Pratt's Table 6 (Pratt, 1951).

Discussion.

This is the first time that the familial and general population rates of disseminated sclerosis have been ascertained in the same area at the same time. We have also been fortunate in that there has been a census of the population in Northern Ireland in 1951 during our investigation. We feel confident in stating that there is a familial incidence in this disease and can answer Mackay's question in the affirmative—"However, the precise question we wish answered is whether the incidence of familial multiple sclerosis is greater than the incidence of the disease in the general population" (Mackay, 1950). The figures, although conclusive, are small, and the familial factor cannot be the only one; like many other diseases, there are both genetic and environmental factors.

There are no known generally accepted environmental factors, but recently there has been agreement that a familial factor exists (Mackay, 1950; Pratt, et al., 1951). This is at present the only widely accepted factor in the ætiology of the disease. In the Middlesex Hospital series the incidence in the sibs was 0.82 per cent.; in the Curtius and Speer series (1937) 0.9 per cent.; these percentages correspond very closely to the figure in this series which lies between 0.65 per cent. and 1.15 per cent.

In the past a common environment or exposure to the same "toxin" has been used to explain the occurrence of the familial cases; however, if this were true, one would expect a higher incidence in husbands and wives than in the general population. There was no instance of conjugal disseminated sclerosis in this series, and we have found only two instances in the literature (Steiner, 1938). Table 14

shows the environmental factors in our families, where these were known, and in four instances there were no common environmental factors.

No paper on the familial aspects of disseminated sclerosis would be complete without mentioning the literature on twins suffering from this disease. Strangely, we had only one instance of an affected dizygotic twin. Table 15 sets out the number of monozygotic twins affected in the literature. Dizygotic twins are not included, as the genetic risk is no greater than that of siblings. From the table it will be seen that 30.8 per cent. of the sibs at risk were affected. This is strong supporting evidence that there is a genetic factor, and, again, that this cannot

TABLE 14.

ENVIRONMENTAL FACTORS IN THE AFFECTED MEMBERS OF 32 FAMILIES.

The period of common environment ceased after the onset in one member	6
The period of common environment continued after the onset in both members	10
The period of common environment continued after the onset in all three members	2
The period of common environment ceased prior to the onset in all affected members	10
No common environmental factors— Serial Numbers—278, 414, 489, and 339	4

be the only factor. It should be stated, however, that, by modern standards, the evidence that the twins were monozygotic was in some instances lacking.

There are other conditions where genetic factors play a part, of much the same order as in disseminated scleroris. In juvenile rheumatism 5.03 per cent. of the sibs at risk are affected (Stevenson and Cheeseman, 1953). Harris (1951) found 4.3 per cent. of the sibs affected in diabetes mellitus. Also in diabetes mellitus Steinberg, et al. (1952), found 4.7 per cent. incidence in the sibs of the propositi where neither parent was affected; 11.4 per cent. where one parent was affected, and 16 per cent. where both were affected. In psoriasis, the figures were 2.45

per cent. where neither parent was affected and 9.0 per cent. where one parent was affected (Steinberg, et al. (1951). Stamos (1940), in a series of 645 cases of pernicious anæmia, found the familial incidence to be 7.9 per cent.

TABLE 15.

CASES OF DISSEMINATED SCLEROSIS IN MONOZYGOTIC TWINS.

Author	Both affected	One unaffected	Remarks
Legras (1934)	1	–	(a) Onset 19, died 28 (male). (b) Onset 24, died 27 (male).
Kranz (1936)	–	1	Microcephalic observed until 22 years (male).
Jentsch (1937)	1	–	Onsets 19 and 31 (male).
Curtius & Speer (1937)	1	–	Onsets 24 and 48 (male).
Voss (1937)	–	1	Observed until 42.
Isenschmid & Olloz (1939)	1	–	Onsets 24 and 26 (male).
Schaltenbrand (1943)	–	2	
Williams (1946)	1	–	Onset at 30; no details of second twin (female).
Jequier (1949)	1	–	Onsets 30 and 36 (female).
Reese (1950)	1	–	Male.
Pratt (1951)	–	2	(a) Onset 25 (female); observed for two years. (b) Onset 47 (male); observed two years.
Thums (1951)	1	12	
TOTAL	8	18	

This table is a modification of Pratt's Table 3 (Pratt, 1951).

SUMMARY.

In Northern Ireland we have found 44 families with two or more members affected out of a total of 668 families, an incidence of 6.58 per cent.

The incidence of the disease in the sibs of the propositi is 5 to 15 times greater than the prevalence rate in the general population.

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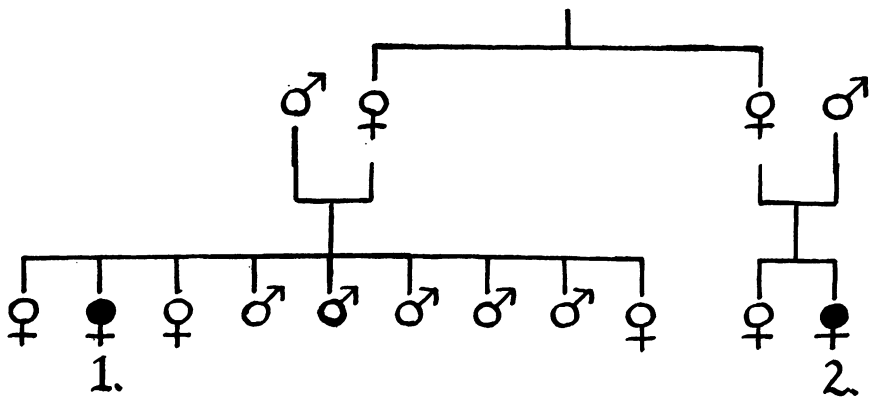
APPENDIX X.

Case histories of families 1-23 inclusive, in which we have examined two or more affected members.

Case histories of families 24-29 inclusive, in which we examined one member, and the evidence from another source was sufficiently strong to warrant a firm diagnosis in the other.

(1)

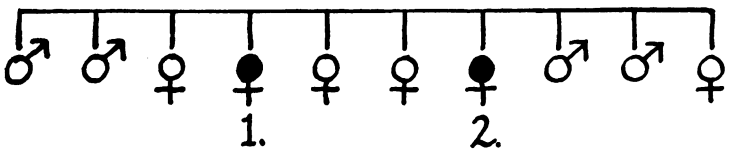


1.—Serial No. 644, female, born 1908: 1942, aged 34, gradually increasing weakness right leg, intermittent attacks of diplopia; 1949, increasing difficulty in starting micturition and weakness of arms. Examination 1951, bilateral pallor of discs, visual acuity normal, spastic weakness of legs, generalised hyperreflexia, absent abdominal reflexes, extensor plantar responses, impaired vibration and muscle joint sensation in legs. (Probable D.S.)

2.—Serial No. 414, female, born 1920: 1946, aged 26, headache, vomiting and generalised paræsthesiæ; examination, small central scotoma right eye, nystagmus to right, ataxic weakness of right arm and legs, astereognosis right hand, impairment of sensation to pain and light touch over trunk and legs, generalised hyperreflexia, absent abdominal reflexes; complete recovery in two months; 1949, sudden paralysis of arms and legs, with retention of urine; complete recovery in one month. Examination, bilateral temporal pallor of discs, good visual acuity, total quadriplegia except slight movements of fingers, flexors of knees and dorsiflexors of feet, generalised hyperreflexia, absent abdominal reflexes, extensor plantar responses; 1952, paræsthesiæ in limbs for two weeks, power normal and plantar reflexes flexor. (Probable D.S.)

Cousins, no common environmental factor.

(2)

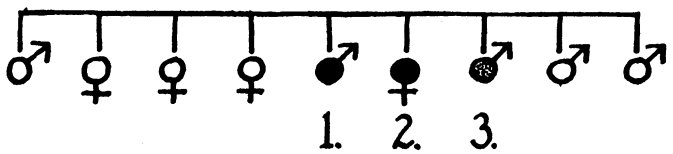


1.—Serial No. 551, female, born 1904: 1951, aged 46, weakness left leg, tendency to drop things out of left hand with slight weakness of left arm, curious paræsthesiæ in head and shoulders; no previous episodes. On examination, slight weakness left arm and leg, rapidly repeated movements not quite normal left hand, hyperreflexia and doubtful extensor response on left side. (Early D.S.)

2.—Serial No. 78, female, born 1913: 1939, aged 26, "useless" right arm, difficulty in appreciating the nature of objects in the hand when the eyes were closed; this symptom lasted four months; 1940, weakness of right leg, which gradually got worse, especially after the birth of her second child with slight precipitancy of micturition. Examination 1948, temporal pallor left disc, V.A. 6/6, 6/6, spastic weakness right leg, generalised hyperreflexia, absent abdominal reflexes, extensor plantar reflexes, vibration diminished right leg; 1950, weakness of legs improved and able to carry on with household duties. (Probable D.S.)

Two sisters, same environment.

(3)



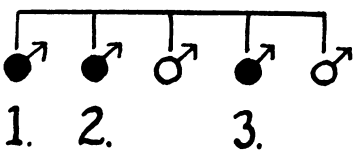
1.—Serial No. 625, male, born 1921 : 1940, aged 19, dragging right leg, progressive and spreading to other leg, temporary cold feeling in legs and slight weakness of hands; 1951, examination, pallor of both discs, V.A.R. J2, V.A.L. J12, very slight intention tremor both arms, legs ataxic and slight weakness right leg, generalised hyperreflexia, extensor plantar responses, vibration sensation absent and muscle joint sensation defective in legs. (Probable D.S.)

2.—Serial No. 313, female, born 1922 : 1943, aged 21, pain and loss of vision left eye, with partial recovery in four months; 1944, diplopia, weakness and paræsthesiæ of legs, with partial recovery; 1950, increasing weakness and ataxia legs. Examination 1951, euphoric, bilateral optic atrophy, with impairment of visual acuity, weakness of left external rectus, horizontal nystagmus on right lateral gaze, intention tremor of arms, weak spastic ataxic legs, generalised hyperreflexia, absent abdominals, extensor plantar responses, impaired vibration and muscle joint sensation in legs. (Probable D.S.)

3.—Case M. McC., male, born 1925, died 1947, diagnosed as disseminated sclerosis.

All three siblings lived at same address.

(4)



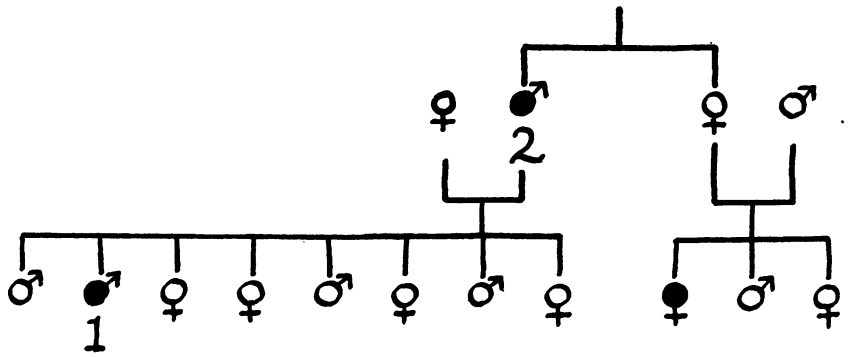
1.—Case J. A. H., male, born 1913: 1944, aged 31, numbness and awkwardness of the right leg for one month, with complete recovery; 1951, rapid onset of numbness and weakness of right leg progressing in a matter of days to ataxia so that he was unable to walk. Examination then showed weak ataxic legs, with extensor plantar reflexes and absent abdominal reflexes. Subjective complete recovery in one month. Examination then showed considerable improvement, the plantar reflexes being doubtfully extensor, vibration sensation absent and muscle joint sensation impaired in the legs. (Probable D.S.)

2.—Serial No. 18, male, born 1915: History not very reliable, but certain facts are available. The illness began 1934-38. He was a patient under Professor Sir W. W. D. Thomson in the Royal Victoria Hospital in 1940, when he complained of girdle pains around his abdomen, vertigo, numbness of the hands and ataxic gait. There was also a note that he had had "poliomyelitis" at the age of 18 months, with a residual weakness of the left leg. Examination 1949, bedridden, dysarthric, nystagmus to right and left, right-sided facial weakness of upper motor neurone type, tongue protruded to right, marked ataxia of upper limbs, with intention tremor, legs paraplegic in flexion, incontinent of urine, no definite sensory changes. Died 1950. (Probable D.S.)

3.—Serial No. 19, male, born 1919: 1942, aged 23, frequency and precipitancy of micturition, no improvement; 1943, gradually increasing failure of vision of both eyes until unable to read small print; 1945, increasing weakness and ataxia of legs. Examination 1950, bilateral optic atrophy, with central scotomata. V.A.R. 6/60. V.A.L. 6/90. Monocular coarse horizontal nystagmus on right lateral gaze, vertical nystagmus on upward gaze and slight rotatory nystagmus in the central neutral position, slight ataxia in arms, ataxia in legs, all modalities of sensation impaired slightly in legs, generalised hyperreflexia, absent abdominal reflexes and extensor plantar responses. (Probable D.S.)

Three brothers—same environment until 1935.

(5)



1.—Serial No. 912, male, born 1925 : 1945, aged 20, gradual onset of frequency and urgency of micturition, no remission; 1946, diplopia for two months; 1951, "useless" right arm and weak right leg for two months, with partial recovery; 1952, gradually increasing weakness left arm and leg. Examination 1952, bitemporal pallor. V.A.R. and L J2, coarse horizontal nystagmus on right lateral gaze, slight intention tremor of arms, dysdiadokokinesia left arm, slight ataxic weakness left leg, left plantar reflex extensor, brisk tendon reflexes, absent abdominal reflexes, impaired vibration sensation in legs. (Probable D.S.)

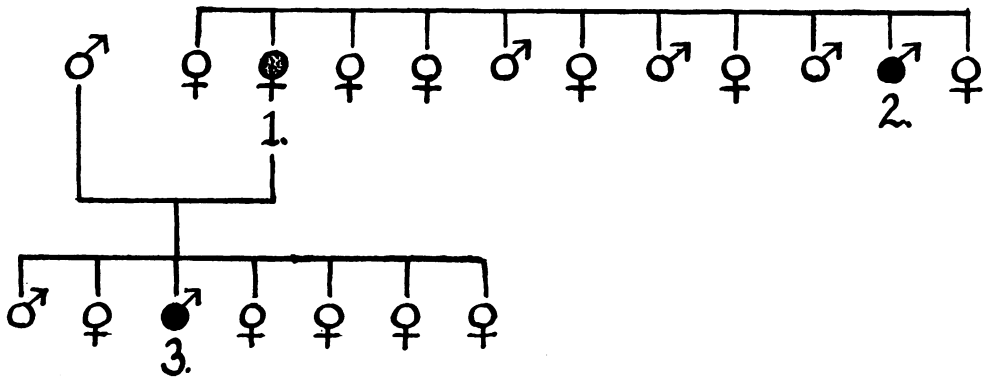
2.—Case J. McN., male, born 1897 : 1940, aged 43, gradually increasing weakness left leg, paræsthesiæ left hand; variable course, but no clear-cut remission; 1948, weakness spread to right leg; 1950, slowness in micturition. Examination 1952, slight pallor left disc, horizontal monocular nystagmus on left lateral gaze, weakness of legs, increased reflexes in legs, absent abdominal reflexes, extensor plantar reflexes. (Possible D.S.)

Father and son, same environment.

The following case, not included in the series, has recently been seen, and is the eldest child of J. McN.'s only sister.

Case Mrs. R., female, born 1930 : 1950, loss of sight right eye for three weeks, with complete recovery. March, 1953, paræsthesiæ in all limbs, vertigo, transient loss of sight right eye, diplopia and weakness of limbs. On examination, nystagmus, generalised weakness, increased tendon reflexes, extensor plantar reflexes, absent abdominal reflexes, impaired postural and vibration sensation in arms. (Probable D.S.)

(6)



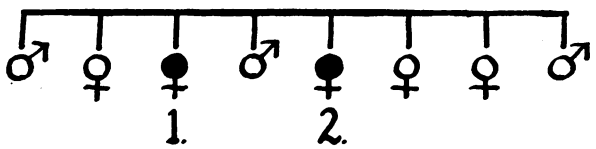
1.—Case, Mrs. McD., female, born 1882, died 1941 : 1926, gradually increasing weakness of legs until, by 1930, unable to walk. (Possible D.S.)

2.—Serial No. 489, male, born 1895 : 1943, aged 48, difficulty in concentrating and lapses of memory; 1946, difficulty walking and retention of urine. Examination 1947, dementia, small contracted unequal pupils, with sluggish reaction to light and convergence, weakness right arm, spastic ataxic legs, with hyperreflexia, absent right abdominal reflexes, extensor plantar responses; 1948, made remarkable spontaneous remission; 1949, Sir Russell Brain diagnosed disseminated sclerosis. April, 1949, slight pain, with loss of vision of right eye, with recovery in one month. On examination, pallor of both discs, jaw jerk increased, intention tremor and slowing of rapidly alternating movements of arms. Abdominals absent. Unsustained patellar and ankle clonus, generalised hyperreflexia, plantar reflexes extensor, loss of sense of passive movement right great toe. (Probable D.S.)

3.—Serial No. 65, male, born 1904: 1924, aged 20, pain right buttock and leg diagnosed as "sciatica" for two years; 1932, sensation like "belt" and paræsthesiæ in legs, two months' duration; 1936, dragged left leg for two months, with partial recovery; 1937, diplopia for one month and since intermittently; 1939, vomiting, followed by gradual weakness both legs lasting two months, with partial recovery; 1946, loss of power of legs for one month, with partial recovery; 1947, feeling "as if walking on wooden legs" for one month, with partial recovery; 1949, increasing weakness of legs. Examination 1949, walking quite well with stick, monocular nystagmus to right and left, temporal pallor left disc, visual acuity normal, slight weakness and spasticity of legs, absent abdominal reflexes, generalised hyperreflexia and extensor plantar responses, impaired muscle joint and vibration sensation in legs. (Probable D.S.)

Nephew and uncle, different environments.

(7)

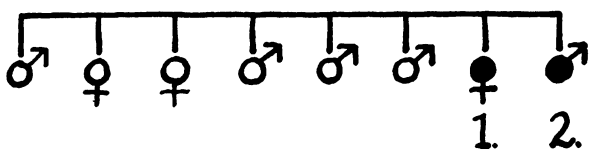


1.—Serial No. 229, female, born 1907 (history not very reliable as memory impaired): 1947, aged 40, "nervous breakdown," weeping, depressed, ataxia, and precipitancy of micturition; complete recovery in four months except for persistence of precipitancy of micturition; 1949, gradual weakness left leg, ataxic gait and clumsy left arm. Examination 1950, dementia, euphoria, monocular nystagmus on right and left lateral gaze, weak handgrips, slight ataxic left arm, two-point discrimination impaired left hand, ataxic weakness of legs, generalised hyperreflexia, absent abdominal reflexes, extensor plantar reflexes, impaired vibration sensation in legs. (Probable D.S.)

2.—Serial No. 830, female, born 1910: History vague and indefinite, but has dragged left leg "for years." Examination 1951, bitemporal pallor of discs, generalised hyperreflexia, left knee and ankle jerks brisker than right, left plantar reflex extensor. (Possible D.S.)

Two sisters, same address until 1932.

(8)

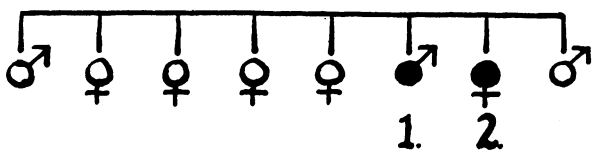


1.—Serial No. 484, female, born 1926 : 1947, aged 21, paræsthesiæ right foot, and twice had fallen because of tripping with the right foot; 1948, "heavy sensation" left arm; all the symptoms cleared up in 1949. Examination 1950, no abnormal neurological signs. (Early D.S.)

2.—Serial No. 485, male, born 1929 : 1944, aged 15, weakness and paræsthesiæ of legs for three months; 1949, gradual onset weakness right leg, with complete recovery in four months. Examination 1950, no abnormal neurological signs except that both knee jerks increased, especially the right. (Early D.S.)

Brother and sister, same address.

(9)

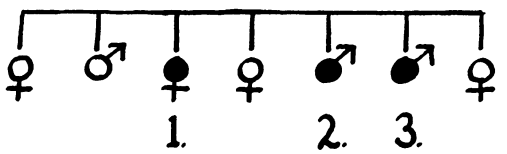


1.—Serial No. 773, male, born 1898: 1935, aged 37, blurred vision for one month; 1939, trailing right leg after a long walk. Examination 1951, pallor both discs, V.A.L. J4, V.A.R. J4, horizontal and slightly rotatory nystagmus to left, bilateral ptosis, slight weakness of arms with slight ataxia, paraplegia in flexion, generalised hyperreflexia, absent abdominal reflexes, extensor plantar reflexes, vibration and position sensation, impaired in legs. (Probable D.S.)

2.—Serial No. 924, female, born 1903: 1942, aged 39, numbness left side of face and tongue for one year; some months later, following lumbar puncture at National Hospital, Queen Square, developed weakness and pains in legs for two years, with complete recovery; 1947, dragging right leg, partial recovery after a few months; 1949, "film" over both eyes for three months. Examination 1951, creamy pallor of both discs, V.A.L. J2, V.A.R. J4, weakness right leg, with slight ataxia, generalised hyperreflexia, absent abdominal reflexes, extensor plantar responses, vibration sensation absent in legs. (Probable D.S.)

Brother and sister at same address until 1934.

(10)



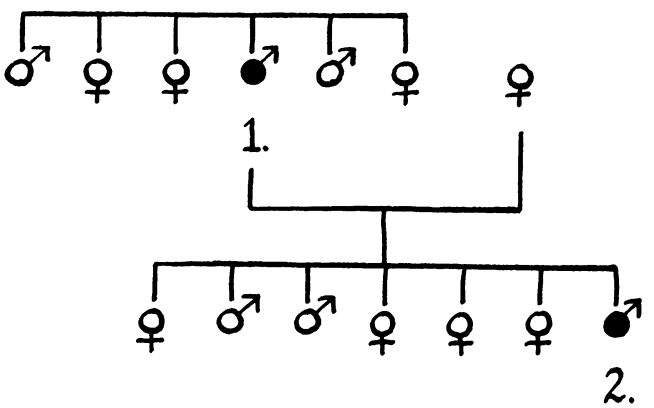
1.—Case M. G., female, born 1899 : No detailed history available. Examination 1949, euphoria, coarse horizontal nystagmus to right and left, generalised hyperreflexia, ataxic gait, extensor plantar reflexes, bilateral ankle clonus. (Possible D.S.)

2.—Serial No. 627, male, born 1905 : 1939, aged 34, legs became weak over a period of three weeks, retention of urine and paræsthesiæ in legs, had to retire to bed, gradual improvement, and in four months could walk again with only slight residual disability. Examination 1949, spastic ataxic paraparesis, generalised hyperreflexia, absent abdominal reflexes, extensor plantar reflexes, light touch and vibration sensation impaired in legs (had been investigated fully in Mater Hospital, Belfast, in 1945, with negative results). (Possible D.S.)

3.—Serial No. 940, male, born 1908 : 1920, aged 12, sudden loss of power both legs for two months, confined to bed with gradual and nearly complete recovery, but right leg tended to drag when he walked far; 1934, onset chronic backache. Examination 1948, no abnormal findings except for nystagmoid jerks on extreme lateral gaze. (Possible D.S.)

Two brothers and one sister, similar environment until 1920.

(11)

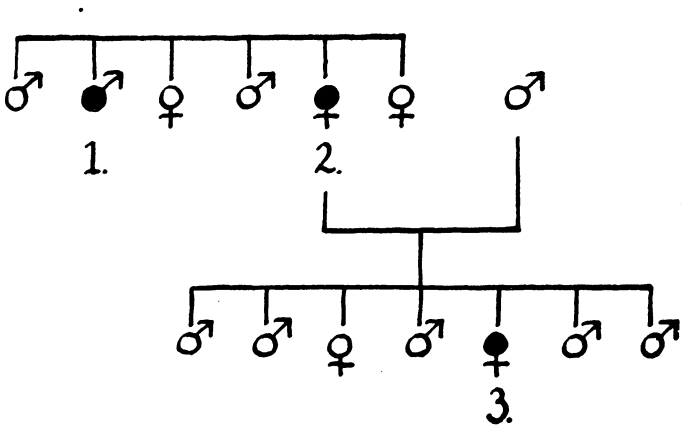


1.—Serial No. 274, male, born 1884 : 1903, aged 19, weakness of all limbs and unsteadiness of gait for eighteen months (recovery may not have been complete); 1930, gradual onset of weakness of limbs and unsteadiness of gait, with partial recovery after three years; 1931-45, diplopia at intervals; 1931, sudden urgency of defæcation. Examination 1950, bilateral optic atrophy, visual acuity two-inch print, nystagmoid jerks to the right, increased knee jerks, doubtful plantar reflexes, vibration sensation absent left leg. (Probable D.S.)

2.—Serial No. 273, male, born 1919 : 1949, aged 30, gradual progressive onset of stiffness in legs and ataxia, followed in two months by intermittent diplopia; 1950, urgency of micturition. Examination 1950, temporal pallor left disc, slight ataxia of arms, weakness and spastic ataxia of legs, increased tendon reflexes, absent abdominal reflexes, extensor plantar responses, knee and ankle clonus. (Possible D.S.)

Father and son, same environment until 1938.

(12)



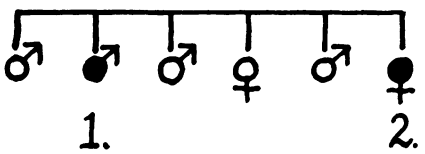
1.—Serial No. 58, male, born 1891 : 1923, aged 32, weakness left leg, no remission; 1925, sudden dimness of vision left eye for one month; 1933, gradual weakess left arm. Examination 1951, pallor left disc, with impaired vision, weak spastic left arm, right arm slightly weak, spastic paraplegia in extension, generalised hyperreflexia, absent abdominal reflexes, extensor plantar responses. (Probable D.S.)

2.—Serial No. 51, female, born 1897 : 1937, aged 40, pains and weakness of legs suddenly, following the birth of second son; the pains disappeared in two months, but the legs gradually became weaker; 1947, bedridden, urgency of micturition and onset of mental deterioration. Examination 1949, pallor of both discs, V.A. 6/9, 6/9, horizontal nystagmus, arms slightly spastic, spastic legs in extension, generalised hyperreflexia, absent abdominal reflexes, extensor plantar responses. Died 1952. (Probable D.S.)

3.—Serial No. 148, female, born 1924 : 1944, aged 20, paræsthesiæ and weak left leg, later paræsthesiæ in fingers, complete remission two months; 1946, loss of vision left eye for one month, paræsthesiæ in fingers and numbness of cheek; 1947, loss of power right leg, which recovered rapidly, but returned later in year; 1948, transient diplopia and incontinence, increasing weakness of legs. Examination 1949, emotional lability, titubation, scanning explosive dysarthria, bilateral pallor both discs. V.A. 6/30, 6/60, nystagmus—fine vertical rotatory in central position and on upward and downward gaze, fast horizontal on lateral gaze, marked tremor on maintaining posture of arms, weak slightly spastic arms, spastic weak legs, generalised hyperreflexia, absent abdominal reflexes and extensor plantar responses Slight wasting of small muscles of both hands. (Probable D.S.)

Brother and sister and her daughter. Brother and sister same environment until 1918.

(13)

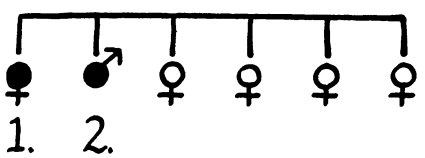


1.—Serial No. 692, male, born 1896: 1949, aged 53, "cold feeling" from below knees and also in left hand for two months; 1950, increasing ataxia of legs, urgency of micturition and occasional dysarthria; 1951, marked improvement in symptoms. Examination 1951, horizontal nystagmus on left lateral gaze, dysarthria, extensor plantar reflexes. No other abnormal neurological signs. (Probable D.S.)

2.—Serial No. 29, female, born 1914: 1933, aged 19, blind left eye for nine months and paræsthesiæ left leg, with complete recovery. Examination 1935, facile manner, central scotoma left visual field, left abdominal reflexes absent and right sluggish; 1946, slight vertigo. Examination 1946, pallor right disc, nystagmus to right, absent abdominal reflexes, increased knee jerks, doubtful plantar responses; 1948 (no symptoms). Examination, no nystagmus otherwise as in 1946; 1951, no symptoms, examination pallor left disc, nystagmus on right lateral and upward gaze, abdominal reflexes absent, tendon reflexes increased in the right arm and both legs, plantar reflexes extensor, muscle joint sensation defective right great toe. (Probable D.S.)

Brother and sister, same environment.

(14)

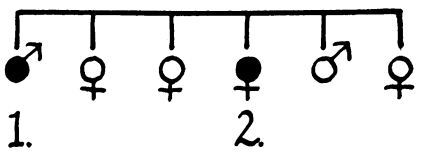


1.—Serial No. 910, female, born 1918 : 1930, aged 12, diplopia for three weeks; 1948, unsteadiness on walking, diplopia and paræsthesiæ in hands. Examination 1948, euphoria, nystagmus to right and left, slight ataxia of arms, ataxic gait, slightly spastic legs, generalised hyperreflexia, extensor plantar reflexes and bilateral ankle clonus, absent abdominal reflexes. (Probable D.S.)

2.—Serial No. 939, male, born 1920 : 1945, aged 25, sudden onset of dysarthria, dyslexia, ataxia and headache (invalided from army with a diagnosis of "acute encephalomyelitis") and when examined in 1947 there were few neurological signs except slight weakness of the handgrips, slightly increased tendon reflexes on the left side, absent abdominal reflexes, extensor plantar reflexes; 1952, pains in the left leg, backache and weakness of left leg for three months. Examination 1952, no abnormal neurological signs except absent abdominal reflexes, increased knee and ankle jerks, plantar reflexes now flexor. (Probable D.S.)

Sister and brother, same address until 1940.

(15)

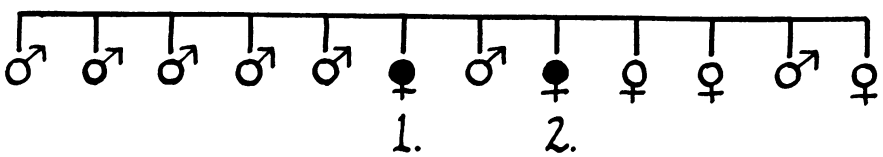


1.—Serial No. 694, male, born 1900: 1938, aged 38, weakness left leg; 1940, both legs weak; 1947, legs weaker, hands weak, precipitancy of micturition, impairment of memory, transient diplopia. Examination 1951, euphoria, horizontal nystagmus to right and left, weak arms, intention tremor right and left, legs weak with slight hypotonia, chairfast, extensor plantar reflexes, absent abdominal reflexes, arm jerks increased, leg jerks not increased, muscle joint and vibration sensation defective in legs. (Probable D.S.)

2.—Serial No. 276, female, born 1907: 1941, aged 34, paræsthesiæ in legs, urgency and incontinence of micturition for three months; 1944, loss of sensation in right arm for two months, followed by loss of sensation left arm for two months; 1945, sudden blindness of left eye, followed by squint and later diplopia for two months, complete recovery except for slight impairment in visual acuity; 1947, gradual onset of numbness of legs and cramps; 1949, sudden blindness left eye for one week. Examination 1950, emotional lability, left-sided temporal pallor. V.A.R. J1, V.A.L. J8, intention tremor right arm, slight weakness right hand grip, weak legs, with spasticity, generalised hyperreflexia, absent abdominal reflexes, extensor plantar responses, impaired vibration and muscle joint sensation in legs. (Probable D.S.)

Brother and sister, same environment until 1916.

(16)

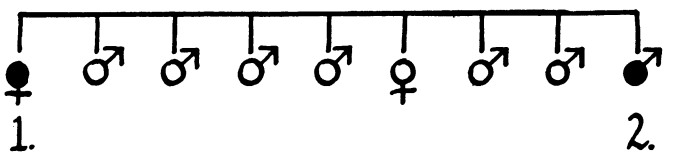


1.—Serial No. 200, female, born 1897: 1923, aged 26, sudden onset blindness both eyes, paræsthesiæ all limbs and weakness of the legs; in six months made an almost complete recovery except for a little residual weakness of the left leg; 1932, vision again impaired, weakness of legs, especially left, and precipitancy of micturition, and again made nearly complete recovery except for some weakness of the legs; 1939, increasing weakness of legs and impairment of memory, marked precipitancy of micturition; 1942, bedridden. Examination 1950, marked euphoria, dementia, bilateral optic atrophy, with visual impairment, pupils react sluggishly to light, marked ataxia in upper limbs, paraplegia in flexion, generalised hyper-reflexia, extensor plantar reflexes, gross impairment of sensation for light touch and vibration in lower limbs. (Probable D.S.)

2.—Serial No. 199, female, born 1900: 1918, aged 18, diplopia for one year; 1930, gradual onset of weakness of legs, with partial recovery over five years. Pregnancies 1936 and 1937, without ill effect. However, following third pregnancy 1939, legs became gradually weaker. Examination 1950, bilateral optic atrophy, visual acuity 6/6 R. 6/6 L., slight intention tremor left arm, spastic ataxia paraplegia, with increased knee and ankle jerks, vibration sense absent in legs, Romberg positive, plantar reflexes extensor. (Probable D.S.)

Both sisters lived at home together until 1935.

(17)

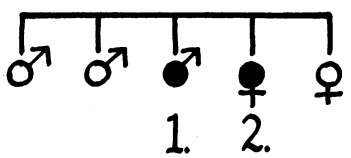


1.—Case H. M., female, born 1890 : 1927, aged 37, weakness of legs; 1930, temporary numbness left arm and dysphagia; 1945, weakness left arm. Examination 1947, bedridden, dysarthric, left arm and legs spastic, with limited voluntary movements, ataxic right arm, astereognosis right hand, impossible to test reflexes as legs were markedly contracted. Died 1948. (Possible D.S.)

2.—Serial No. 61, male, born 1908 : 1933, aged 25, precipitancy and frequency micturition; 1935, retention of urine for few days, which recovered, but returned to precipitancy and frequency; 1936, progressive weakness right leg, accompanied by paræsthesiæ; 1947, transient blurred vision. Examination 1947, slight impairment of memory, slight nystagmus on upward gaze, slight dysarthria, spastic in extension, generalised hyperreflexia, abdominal reflexes absent, extensor plantar reflexes. Vibration sense impaired in legs. (Probable D.S.)

Brother and sister, same environment.

(18)

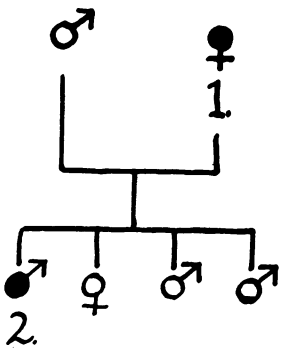


1.—Serial No. 487, male, born 1911 : 1932, aged 21, gradual increasing weakness of legs. Examination 1950, nil abnormal found in cranial nerves and arms, spastic weakness of legs, increased reflexes, ankle clonus, absent abdominal reflexes, extensor plantar reflexes. (Possible D.S.)

2.—Serial No. 486, female, born 1914 : 1939, aged 25, following childbirth, marked impairment of vision for four months; 1949, paræsthesiæ right leg and right foot drop for one year. Examination 1949, temporal pallor right disc, visual acuity normal, weakness right leg especially, dorsiflexors of right foot, right abdominal reflexes absent, impairment of all modalities of sensation up to level of T8. Examination 1950, normal findings except for pallor right disc. (Probable D.S.)

Brother and sister, common environment until sister's marriage in 1937.

(19)

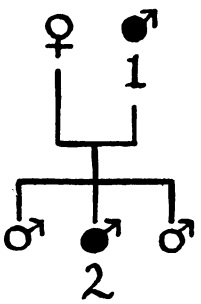


1.—Serial No. 436, female, born 1890 : 1939, aged 49, weakness and unsteadiness of legs. Examination 1949, euphoria, mild dementia, pallor right disc, with good visual acuity, coarse monocular nystagmus to right and left, weak and ataxic left hand, legs slightly weak, especially left leg, spastic ataxic gait, generalised hyperreflexia, absent abdominal reflexes, extensor plantar responses and diminished vibration sensation in legs. (Probable D.S.)

2.—Serial No. 149, male, born 1908 : (History not very reliable.) Paræsthesiæ left hand, bilious attacks, recurring diplopia and unsteadiness on feet. Examination 1949, dementia, facile euphoria, coarse monocular nystagmus to right and left, spastic ataxic legs, generalised hyperreflexia, absent abdominal reflexes, extensor plantar reflexes, difficulty starting micturition. (Probable D.S.)

Mother and son, same environment.

(20)

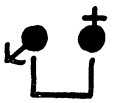


1.—Serial No. 614, male, born 1884: 1942, aged 58, gradual onset of progressive weakness of legs; 1945, slowness in micturition. Examination 1952, horizontal nystagmus to right and left, spastic legs, generalised hyperreflexia, absent abdominal reflexes, extensor plantar reflexes, vibration sensation absent in legs. muscle joint sensation defective in legs. (Investigated fully in hospital in 1945.) (Possible D.S.)

2.—Serial No. 571, male, born 1910: 1945, aged 35, weakness right leg, gradually progressive. Examination 1951, euphoric, weak spastic left arm and leg, left arm jerks increased, leg jerks increased, ankle clonus, left abdominal reflexes absent, extensor plantar reflexes. (Possible D.S.)

Father and son, similar environment.

(21)



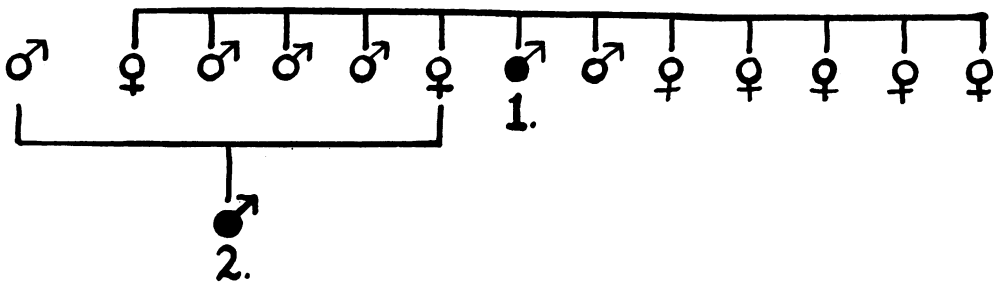
1 2

1.—Serial No. 194, male, born 1916 : 1940, aged 24, numbness right cheek for several days, followed by impairment of vision in right eye and to lesser extent left eye; total recovery in two months. Six months later left leg weak, progressing in a few days to total uselessness lasting for one month; gradual recovery, with slight residual disability; 1942, vision again impaired in both eyes; recovery followed by diplopia lasting two weeks; 1947, difficulty in micturition and defæcation, impotence and increasing weakness of legs. Examination 1949, bilateral optic atrophy, visual acuity R6/18, L6/20, well-marked monocular nystagmus to left and conjugate nystagmus to right. Slight weakness of arms, legs spastic ataxic, with slight weakness, knee and ankle jerks increased, plantar responses extensor, impaired vibration and postural sensation in legs, Romberg's sign positive; 1952, just able to walk. (Probable D.S.)

2.—M. B., female, born 1913 : Examination 1946, bedridden, fatuous euphoria, marked nystagmus and optic atrophy. Duration 9-12 years, diagnosed as disseminated sclerosis.

Brother and sister, same environment.

(22)

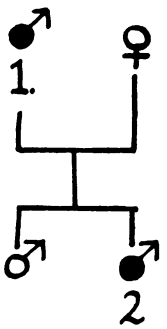


1.—Case T. D., male, born 1896 : 1925, aged 29, sudden paralysis of left arm and leg, left side numb, and diplopia without loss of consciousness. He made a partial recovery, but still has occasional diplopia and stiff legs. Examination 1950, euphoria, fine monocular nystagmus on left lateral gaze, paraplegia in extension, generalised hyperreflexia, absent abdominal reflexes, extensor plantar reflexes. (Possible D.S.)

2.—Serial No. 278, male, born 1925 : 1942, aged 17, loss of feeling and control of the right foot and unsteady gait, lasting two months. Six months later clumsiness and loss of feeling in the right hand; 1944, dimness of vision in the right eye for two months; 1947, numbness of the right leg, followed in a few days by "influenza"; when he got out of bed on the seventh day he found he was very unsteady, right leg weak, and had difficulty with micturition. Examination 1947, pallor right disc, fine lateral nystagmus, generalised hyperreflexia, absent abdominal reflexes, extensor plantar responses and vibration sensation absent in legs. (Probable D.S.)

Uncle (M) and nephew, no common environment.

(23)

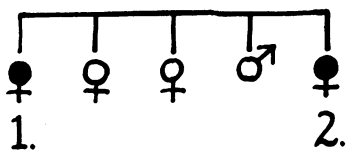


1.—Serial No. 508, male, born 1895: 1935, aged 40, weakness and numbness right arm for one week; 1940, gradual onset weakness left leg and arm especially after exercise, also hesitancy of micturition with "stuttering bladder," both symptoms remain unchanged; 1945, right leg "gave way" and numbness right leg for one week. Examination 1950, euphoria, weakness left arm and leg, hyperreflexia, absent abdominal reflexes, extensor plantar responses, vibration and muscle joint sensation impaired in legs. (Probable D.S.)

2.—Serial No. 256, male, born 1925: 1948, aged 23, paræsthesiæ and weakness right arm and leg for four weeks; 1949, sudden difficulty speaking and weakness of right arm and leg for a few weeks; 1950, sudden weakness of both legs and dysuria for two months. Examination 1950, slight nystagmus on left lateral gaze, marked impairment of all forms of sensation below level of fourth thoracic segment, with weakness of legs, especially left, absent abdominal reflexes and extensor plantar responses (C.S.F. normal pressure, 4 cells, trace globulin, 45 mgms. per cent. protein, Lange 112200000); 1951, sudden weakness and numbness left arm and leg, precipitancy of micturition and occasional incontinence. Partial recovery; 1952, sudden loss of sight right eye, with recovery in three months. (Probable D.S.)

Father and son, same environment.

(24)

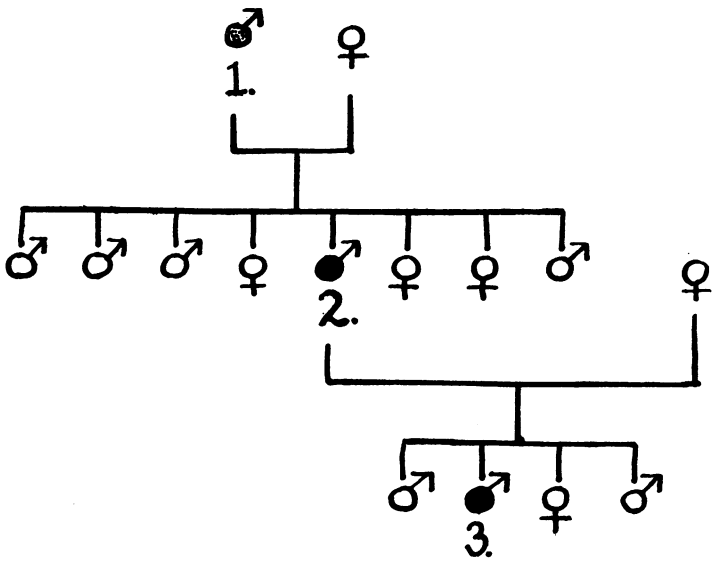


1.—Case J. P., female, born 1903 : 1950, aged 47, Dr. Stulik, Larchmont, New York, reports that this patient has been ill for twelve years; at present she has dysarthria, ataxia, and weakness of all limbs. W.R. negative. "The diagnosis might be multiple sclerosis."

2.—Serial No. 417, female, born 1911 : 1927, aged 16, weakness and ataxia of legs, weakness right hand, diplopia and precipitancy of micturition; after four years nearly complete recovery except for slight weakness right leg; 1946, sudden weakness of legs, with remission for three months, but recurrence and variable but progressive downward course; 1949, blurred vision for two weeks. Examination 1950, temporal pallor left disc, nystagmus on left lateral gaze, intention tremor right arm, legs weak, generalised hyperreflexia, abdominal reflexes absent, plantar responses extensor, vibration sensation diminished in legs; 1951, much improved except for occasional weakness of legs. Examination, mild spastic ataxic gait. (Probable D.S.)

Two sisters lived at home in Ireland together until 1928.

(25)

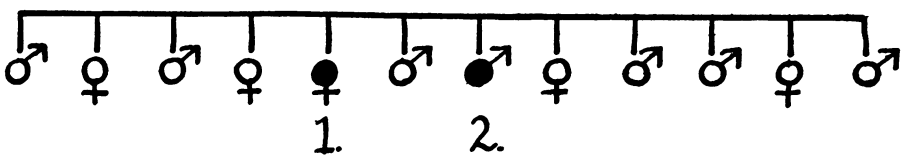


1.—Case G. F., male, died age of 57. Following a fall, he was paralysed for many years before death.

2.—Serial No. 243, male, born 1889: 1935, aged 46, increasing weakness left leg, which spread to the right leg. At times dysarthria, frequency and urgency of micturition. Examination 1950, temporal pallor right disc, slight irregularity of the pupils, slight intention tremor right hand, paraplegia in flexion, impairment of all modalities of sensation in legs, generalised hyperreflexia, absent abdominal reflexes and extensor plantar responses. (Probable D.S.)

3.—D. M. G., male, attended out-patients London Hospital, 1948. Dr. Russell Brain diagnosed disseminated sclerosis. Patient complained that for two years his legs had been weak and his walking unsteady. He also complained of blurred vision and diplopia. There was marked nystagmus to right and left and upwards, slight intention tremor in left arm, the abdominal reflexes diminished, both plantar reflexes were probably extensor, left knee jerk increased, gait spastic ataxic. (Probable D.S.)

(26)

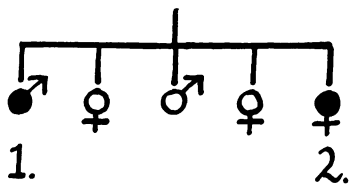


1.—Case E. S., female, born 1903, died 1938: Superintendent of mental hospital stated that this was a "typical case of disseminated sclerosis, with emotional outbursts, dysarthria, spastic paraplegia, and absent abdominal reflexes. The C.S.F. showed a marked lange paretic curve with a negative W.R."

2.—Serial No. 73, male, born 1905: 1933, aged 28, sudden ataxia of legs, weakness right leg and "dimness of vision." Six months later marked precipitancy and urgency of micturition, slight deterioration since. Examination 1947, euphoria, slight deterioration in recent memory, temporal pallor right disc, with slight impairment of vision, nystagmus on lateral gaze, dysarthria, tone increased in arms, intention tremor in all limbs, spastic ataxic legs, with slight weakness, generalised hyperreflexia, absent abdominal reflexes, extensor plantar responses, Romberg positive. (Possible D.S.)

Brother and sister, similar environment.

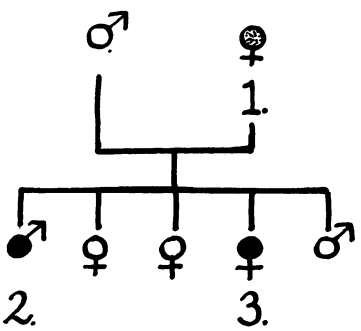
(27)



1.—Case W. B., male, born 1896, seen by Sir Henry Cohen, 1934, in Liverpool, who commented as follows : "History of paræsthesiæ fourteen years ago, following a fall whilst skating, accompanied by a typical 'barber's chair' phenomenon, affecting the lower limbs and trunk to the waist and also the arms; 1932, cramps in legs and right arm associated with increasing weakness and unsteadiness of gait. Examination showed pale discs, slight nystagmus on extreme lateral gaze, slight weakness and spasticity right arm, spastic legs, generalised hyperreflexia, bilateral extensor toe responses, diminished abdominal reflexes, marked diminution of muscle joint and vibration sensation in legs. I fear there can be no doubt that he is suffering from disseminated sclerosis."

2.—Serial No. 304, female, born 1905 : 1928, aged 23, noticed that the thigh muscles were weak after tennis; 1929, "nervous breakdown," couldn't eat, shakiness of legs, paræsthesiæ of head and back for three months; 1931, sudden severe pains in legs, weakness of legs, following influenza, with partial recovery, but had to retire from teaching; 1939, gradually increasing weakness right leg. Examination 1951, right arm paralysed, spastic at shoulder and elbow joints, flaccid at wrist, left arm slight weakness, spastic paraplegia, very limited voluntary movements of legs, chairfast, extensor plantar reflexes, absent abdominal reflexes, Hoffmann reflexes present. All modalities of sensation impaired in legs, postural and vibration sensation impaired in hands. (Probable D.S.)

(28)

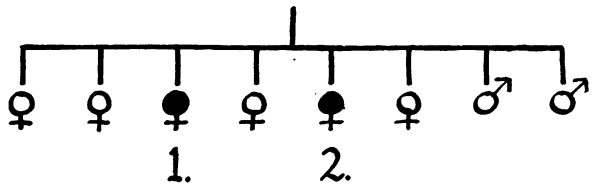


1.—Case M. B., female, born 1874, died 1928 : Ataxic paraplegia for four years prior to death; had been seen by Professor Sir William Thomson on several occasions.

2.—Serial No. 328, male, born 1902 (the following is a brief résumé of a letter from Dr. Fergus Ferguson, Manchester) : 1948, aged 46, paræsthesiæ of legs, increasing weakness of legs; 1950, difficulty in focussing and urgency of micturition. Examination 1950, bilateral pallor of discs, defective movements of eyes to the left, with nystagmoid movements, left plantar reflex indefinitely extensor, right definitely extensor, abdominal reflexes absent, left arm jerks brisker than right, Hoffmann reflexes positive.

3.—Serial No. 115, female, born 1911 : 1929, aged 18, dimness of vision (? both eyes) and severe headaches which lasted three months; 1940, severe pains around lower thorax, lasting two months; 1945, paræsthesiæ of legs and progressive ataxia of legs; 1948, frequency and occasional incontinence of micturition and weakness of hands. Examination 1949, euphoria, pallor left disc, V.A.L. 6/6, V.A.R. 6/6, coarse horizontal nystagmus to left, slight weakness of hands, ataxia of arms and legs, increased knee and ankle jerks, absent abdominal reflexes, extensor plantar reflexes, vibration sensation diminished in legs. (Probable D.S.)

(29)



1.—Case E. O'R., female, born 1906: 1941, aged 35, numbness and stiffness of hands for several months; 1949, sudden onset of weakness, numbness and stiffness of left leg, followed by similar symptoms in right leg, difficulty in micturition and increasing constipation. Examination 1951 (the Presbyterian Hospital, New York), slight generalised spastic weakness of all limbs, with generalised overactive tendon reflexes, Babinski reflex positive, absent abdominal reflexes, slight ataxia of arms, impaired muscle joint and vibration sensation in legs. All investigations, including myelogram negative. (Diagnosed multiple sclerosis.)

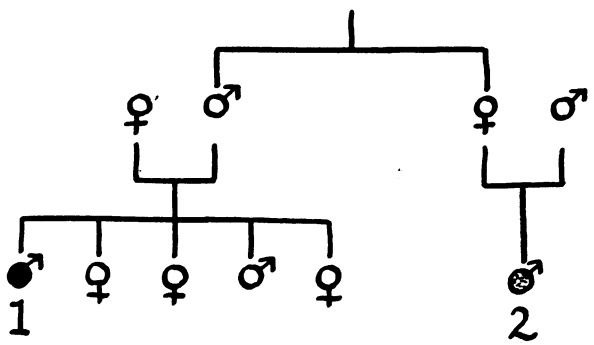
2.—Serial No. 825, female, born 1910: 1950, aged 40, impairment of vision both eyes for six weeks; February, 1951, impairment of vision left eye, followed in two weeks by impairment of vision right eye which lasted two weeks, right leg weak, right hand clumsy; in May, diplopia developed. Examination 1951, euphoria, V.A.L. J14, V.A.R. J8, fundi normal. Complete palsy left VI nerve, horizontal nystagmus on right lateral gaze, slight inco-ordination of arms, spastic ataxic gait, but no weakness, generalised hyperreflexia, absent right abdominal reflexes, extensor plantar reflexes; 1952, much improved, less ataxic and vision normal. (Probable D.S.)

Two sisters, same environment until 1930.

APPENDIX Y.

Case histories of families 30-44 in which we examined one member and the evidence concerning the other was less convincing, such as a letter from the family doctor or a death certificate.

(30)

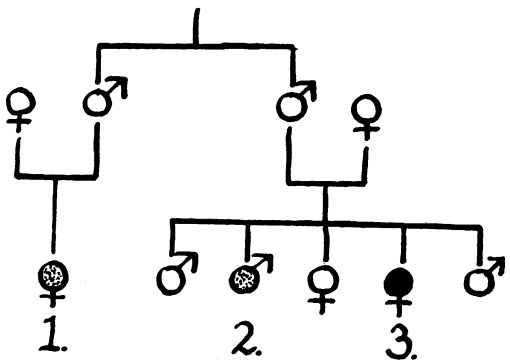


1.—Serial No. 339, male, born 1913 : 1937, aged 24, diplopia for three weeks, unsteadiness of gait for one year; 1940, paræsthesiæ of arms and legs and weakness of legs for one month, with complete recovery; 1949, following influenza, weakness, and ataxia of legs for three weeks, with nearly complete recovery; 1950, following sore throat, weak ataxic legs, with increasing disability. Examination 1950, euphoria, bitemporal pallor, V.A.R. and L. 6/6, coarse horizontal nystagmus of monocular type, vertical nystagmus on upward gaze, intention tremor in both arms, slight spasticity right arm, slight spastic ataxia of legs, generalised hyperreflexia, absent abdominal reflexes, doubtful plantar reflexes, stereognosis slightly impaired in hands, vibration sensation absent in legs (Probable D.S.)

2.—Case Wm. C., male, died 1944, aged 30. Death certificate—disseminated sclerosis.

First cousins, different environment.

(31)



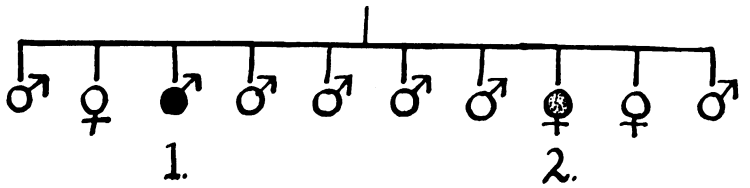
1.—Female, died aged 38; suffered from disseminated sclerosis for four years.

2.—Male, born 1893, died 1939; paralysed for fourteen years; supposed to have suffered from disseminated sclerosis.

3.—Serial No. 219, female, born 1895: 1924, aged 29, dizziness, blurred vision, weakness of back, partial remission (history not satisfactory). Examination 1951, deteriorated, euphoric, V.A.R. J10, lens opacity left eye, pallor right disc, horizontal monocular nystagmus to right and left, rotatory nystagmus on upward gaze, arms slightly weak and spastic, arms ataxic, especially left, legs paraplegic in flexion, no voluntary movements, generalised hyperreflexia, vibration sensation absent, pain, light touch and muscle joint sensation defective in legs. (Probable D.S.)

Brother, sister, and male cousin. All three cases lived in close proximity.

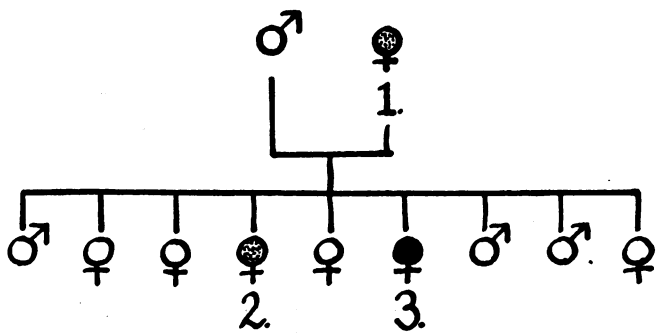
(32)



1.—Serial No. 723, male, born 1887 : 1920, aged 33, progressive weakness and unsteadiness of legs; 1946, attack of tic douloureux, with two relapses in period 1946-1951; 1948, sudden weakness left arm. Examination 1951, pallor left disc, with impairment of vision, coarse monocular nystagmus on right lateral gaze, finer monocular nystagmus on left lateral gaze, left facial weakness, slight spastic weakness left arm, spastic paraplegia of legs, generalised hyperreflexia, absent abdominal reflexes, extensor plantar responses, vibration and muscle joint sensation absent in legs, light touch and pain sensation impaired below knees. (Probable D.S.)

2.—Case M. H., female, born 1899, and died 1946 : Illness started 1941 with "eye trouble and paralysis from the waist down. At the end her speech was affected."

(33)

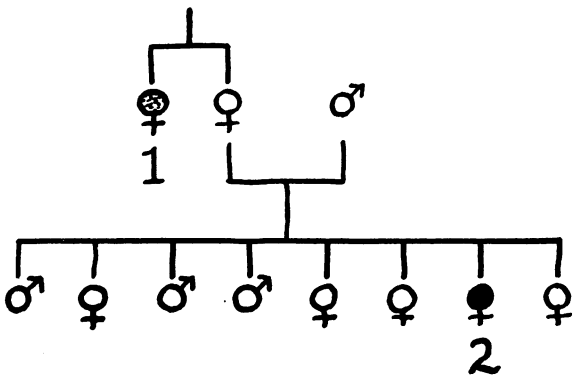


1.—Case M. M., female, died aged 80 : Paraplegic for many years.

2.—Case M. E., female, born 1891, died 1951 : Twenty years' history of weakness of legs.

3.—Serial No. 207, female, born 1897 : 1935, aged 38, retention of urine for four days, followed by difficulty in micturition for three weeks, with full recovery; 1940, gradual onset weakness and stiffness right leg, which progressed. Examination 1951, euphoria, fine nystagmus to right and left, weakness right handgrip, with slight ataxia, spastic paraplegia, generalised hyperreflexia, extensor plantar responses, absent abdominal reflexes. (Probable D.S.)

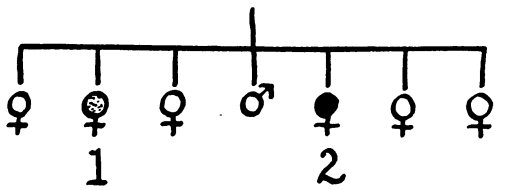
(34)



1.—Case M. W., female, died 1950 : Considered by her own doctor to have been a case of disseminated sclerosis of long standing.

2.—Serial No. 833, female, born 1903 : 1926, aged 23, vomiting and vertigo for three days, followed by ataxia for ten days; 1932, right leg weak, especially after a long walk, with partial recovery in two months; 1939, gradual increasing weakness of both legs; 1951, left arm weak and unsteady, frequency and precipitancy of micturition. Examination 1951, bedridden, euphoric, coarse horizontal nystagmus, left-sided upper motor neurone facial weakness, ataxic arms, spastic paraplegia in flexion, generalised hyperreflexia, absent abdominal reflexes, extensor plantar responses. (Probable D.S.)

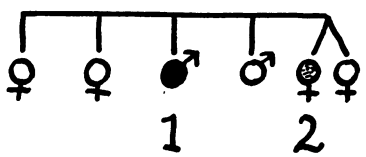
(35)



1.—Case A. A. W., female, died 1942, aged 44 : Death certificate—disseminated sclerosis.

2.—Serial No. 251, female, born 1903 : 1939, aged 36, dragging and weakness right leg, paræsthesiæ right foot, urgency of micturition and increasing ataxia; 1948, difficulty focussing the eyes at intervals. Examination 1950, bilateral optic atrophy, with normal visual acuity, generalised hyperreflexia, absent abdominal reflexes, spastic ataxic weakness of legs, left arm falls away, with pseudo-athetotic movements of fingers, extensor plantar reflexes, impaired muscle joint and vibration sensation in legs and left arm. (Probable D.S.)

(36)

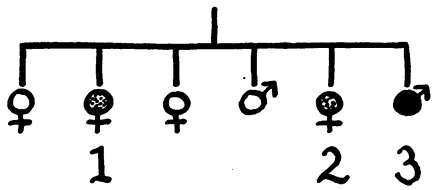


1.—Serial No. 899, male, born 1900 : 1926, aged 26, diplopia for some months; 1928, sudden loss of sight right eye for four months, with complete recovery; 1931, gradual progressive weakness of legs; 1935, bedridden. Examination 1952, obese, euphoric, pallor left disc, V.A.R. J8, V.A.L. J8, marked monocular nystagmus to right and left and slight vertical nystagmus on upward gaze, no voluntary movements right arm, which is spastic at elbow and flail at wrist, slight weakness left arm, paraplegia in flexion, generalised hyperreflexia, vibration sensation impaired in arms, absent in legs, other forms of sensation slightly impaired. (Probable D.S.)

Case 2.—Case E. S., female : Died, aged 35, from disseminated sclerosis; diagnosis confirmed by Sir Thomas Huston. No notes available.

Brother and sister, lived together until brother went to Canada 1927-28 for a number of years.

(37)

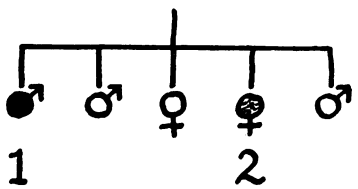


1.—Case A. H., female: Died in New York, approximately 1931, from "spinal paralysis."

2.—Case M. H., female, born 1897: Died 1948; had been diagnosed as disseminated sclerosis. Paralysed for seven years prior to death.

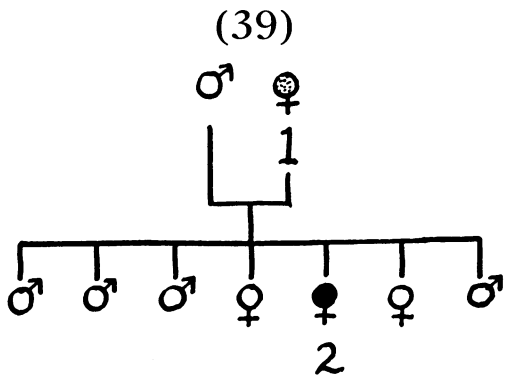
3.—Serial No. 395, male, born 1904 (not a reliable witness, on account of mental deterioration): 1946, aged 42, increasing weakness and stiffness left leg. Examination 1949: euphoric, bitemporal pallor, with slight impairment of vision, horizontal monocular nystagmus on lateral gaze, intention tremor in arms, slight weakness and marked spasticity of legs, generalised hyperreflexia, with patellar and ankle clonus on left side, absent abdominal reflexes, extensor plantar responses, diminished vibration sensation in legs. (Probable D.S.)

(38)



1.—Serial No. 2, male, born 1900 (history unreliable owing to faulty memory and low intelligence); 1946, aged 46, increasing weakness of legs. Examination 1949, dementia, euphoria, pallor of both discs, V.A.R. 6/9, V.A.L. 6/60, concomitant internal strabismus, horizontal nystagmus to right and left, spastic paraparesis, generalised hyperreflexia, extensor plantar reflexes, absent abdominal reflexes. (Probable D.S.)

2.—Case G. L., female, born 1910: 1943, aged 33, paræsthesiæ in hands and feet and "dizziness"; 1950, attended hospital for "rheumatism"; 1951, admitted to hospital and diagnosed as disseminated sclerosis.

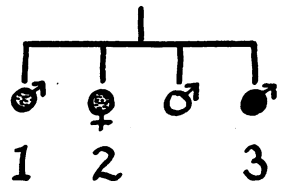


1.—Case E. G., female, born 1879 : 1920, aged 41, numbness of left leg, which trailed when she walked; 1922, right leg similarly affected; 1925, difficulty of micturition. Examination 1926 (Royal Victoria Hospital, Belfast; Professor Sir W. W. D. Thomson), nystagmus, spastic weakness of legs, absent abdominal reflexes, increased knee and ankle jerks. Died 1931, diagnosed as disseminated sclerosis.

2.—Serial No. 584, female, born 1918 : 1944, aged 26, diplopia and ataxia for three days; 1949, weakness of legs, with partial recovery. Examination 1951, slight spastic weakness of legs, generalised hyperreflexia, absent abdominal reflexes; 1952, sudden increased weakness of legs, with rapid recovery in a few weeks. (Probable D.S.)

Mother and daughter, same environment until 1931.

(40)

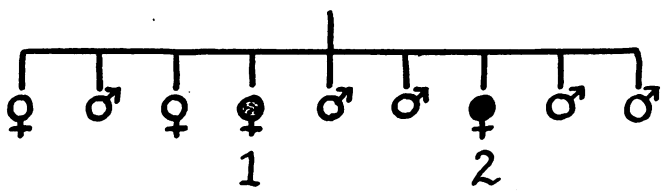


1.—Case W. S., male, born 1874 : Died 1936, paralysed for many years before his death.

2.—Case M. S., female : Died 1943, "paralysed for many years."

3.—Serial No. 586, male, born 1888 : 1935, aged 47, sudden weakness of legs, with pain in back, unable to walk, complete recovery in one month; 1939, blurred vision, especially left eye, for four weeks; 1941, gradual onset of increasing weakness left leg, spreading to right leg. Examination 1951, euphoria, pallor both discs, especially the right, intention tremor right arm, spastic paraplegia, generalised hyperreflexia, absent abdominal reflexes, extensor plantar reflexes, slight impairment of muscle joint and vibration sensation in legs. (Probable D.S.)

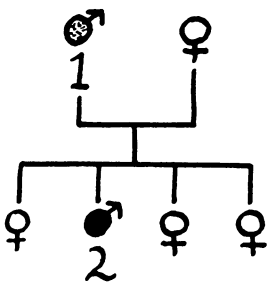
(41)



1.—Case C. B., female, born 1894 : Died 1929; "legs became weaker and weaker." Diagnosed as disseminated sclerosis.

2.—Serial No. 192, female, born 1907 : 1942, aged 35, numbness and weakness right leg for three months; 1946, gradual progressive weakness right leg, spreading to left leg, diplopia and precipitancy of micturition. Examination 1950, monocular nystagmus on right and left lateral gaze, spastic ataxic legs, generalised hyperreflexia, absent abdominal reflexes, extensor plantar reflexes, diminished muscle joint and vibration sensation in legs. (Probable D.S.)

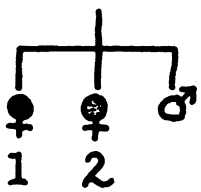
(42)



1.—Case D. H., male: Died, aged 76; "partially paralysed since age of 30, bedridden for the last four years."

2.—Serial No. 297, male, born 1885: 1920, aged 35, recurring paræsthesiæ left leg and also myoclonic jerks left leg; 1941, gradually increasing weakness of legs. Examination 1949, bilateral optic atrophy. V.A.R. and L. J6, slight weakness left arm, with increased reflexes, weakness and spasticity of legs, with increased tendon reflexes, absent abdominal reflexes, extensor plantar reflexes, absent vibration sensation in legs. (Probable D.S.)

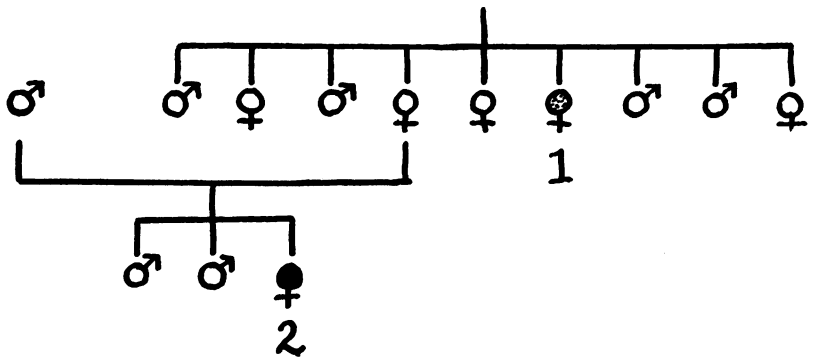
(43)



1.—Serial No. 564, female, born 1902: 1939, aged 37, progressive weakness of legs; 1938, gradual onset of impairment of vision of right eye; 1946, "stiffness" of right hand; 1950, retention of urine, following gynæcological operation. Examination 1951, bilateral optic atrophy, V.A.L. and R. J11, horizontal nystagmus on lateral gaze, monocular to right, intention tremor in arms, slight weakness in arms, spastic paraparesis, generalised hyperreflexia, absent abdominal reflexes, extensor plantar reflexes, vibration sensation absent in legs, muscle joint sensation impaired in toes, slight hypalgesia and hypæsthesia right arm and leg, two-point discrimination impaired right hand. (Probable D.S.)

2.—Case M. C., female, born 1903: Died 1945, diagnosed disseminated sclerosis at Mater Hospital, Belfast (no notes available).

(44)



1.—Case B. McR., female : Dead, diagnosed as disseminated sclerosis; paralysed for fifteen years. Doctor writes—"Bedridden, euphoric, dysarthric, intention tremor of arms. I have no doubt that she suffered from disseminated sclerosis."

2.—Serial No. 388, female, born 1912 : 1949, aged 37, numbness of scalp which lasted three weeks, followed by sudden blindness of right eye, which made a partial recovery; 1950, "dizzy attacks," paræsthesiæ of right leg, followed by paræsthesiæ of left arm, pains in legs, and weakness of ankles, with partial recovery; 1952, increased weakness of legs, with increasing pains in back for three months, with partial recovery. Examination 1952, pallor right disc, with V.A.R. J12, slight weakness of legs, increased knee and ankle jerks, extensor plantar reflexes. (Probable D.S.)

Niece and maternal aunt, same town until 1946.

APPENDIX Z.

Other Neurological Disorders among the Near Relatives.

Chronic neurological disorders without a diagnosis	18
Psychosis	16
Mentally defective	7
Psychoneurosis	5
Parkinson's disease	5
Muscular dystrophy	2
Epilepsy	1
Vascular accidents	1
Subacute combined degeneration of the cord	1
Myasthenia gravis	1

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