PROGNOSIS IN DISSEMINATED SCLEROSIS

BY

MARGARET REINHOLD, M.B., B.Ch.(Witwatersrand)
M.R.C.P.(Lond.)

This investigation was undertaken to discover the average expectation of life of patients suffering from disseminated sclerosis and, in particular, whether any relation exists between the mode and age of onset and the progress and duration of the disease. It was thought that the type of symptom experienced at the very beginning of illness, and the age at which this symptom occurs, might have some bearing on the patient's expectation of life and on the probable extent of his disability in relation to time.

It was hoped to collect information regarding a large number of cases which had occurred in England during the last 50 or 60 years, distributed over a wide area. The aim was to include patients subjected to very varying conditions of environment, occupation, nutrition, and social circumstances. It was intended thus to minimize the effects of additional factors which no doubt influence the prognosis in disseminated sclerosis.

The problem then arose whether such information was at all available. Investigation showed that in the London area (and this probably applies equally to other areas) the fate of patients with disseminated sclerosis is limited to four possibilities, which have changed scarcely at all over the last 60 years. (1) They may remain in their homes, receiving the amount of care and nursing compatible with their incomes, the kindness or otherwise of any existing relatives, and the extent of the local charities, State or otherwise. (2) They may with the greatest difficulty obtain admission to a private hospital or nursing-home, this being reserved for the higher-income group. (3) They may obtain admission to the Putney Home for Incurables; the Streatham Home for Incurables; or a home for incurables belonging to one of the religious communities—Church of England, Catholic, or Jewish. Service men or ex-Service men may go to the Star and Garter Home in Richmond. (4) They may—but this only as a last resort—obtain admission to London County Council Homes for the Chronic Sick—these recently having become State-owned.

Collection of Case Records

It is thus clear that the majority of patients who suffer from disseminated sclerosis remain in their own homes. A certain number of these have attended out-patient departments in various hospitals, and some have at times been admitted to the former voluntary hospitals. They were rarely retained for long periods, and as a rule remained only during an acute episode or phase. Of these, some records were obtainable from the National Hospital for Diseases of the Nervous System. None was available from other voluntary hospitals, although no doubt they do exist.

In the greater number of cases, then—those treated in their own homes—there are no records of the illness. Of the rest, the London County Council has not in the past been able to keep detailed records, and unfortunately could not be of any assistance here. Similarly, no records were available from any private nursing-home or hospital. Thus neither the wealthy nor the destitute sufferers could be included in this series. There remained the somewhat selected cases to be collected from the records of the institutions mentioned above.

Admission to the Putney and Streatham Homes used to be gained by a rather curious system in which the prospective inmate had to collect a number of "votes." The patients were of a particular group of society, usually well-educated persons who had lost their fortunes, or teachers, artists, and professional men and women. In some of these homes the system of admission has recently somewhat changed, but the class of patient remains the same.

Records were also available from the Star and Garter Home for Disabled Sailors, Soldiers, and Airmen, and here the patients were of course from a highly selected section of the population. The religious institutions unfortunately had no records available, although the authorities concerned were very willing to be of assistance. The records of the Jewish Home for Incurables had been destroyed by bombing during the war, and none of the other homes which were approached could supply suitable records.

The cases were finally obtained from the Putney Home for Incurables, the Streatham Home for Incurables, the Royal Midland Home for Incurables, the Star and Garter Home, and the National Hospital for Diseases of the Nervous System. In addition, Professor Cloake, of Birmingham, kindly supplied six cases from his own records.

Investigation showed that the records at the National Hospital concerned cases that were in some way unusual—either because the disease was particularly severe or because it was of especially early or late onset. It was therefore decided to examine these as a separate group.

The cases obtained from the above-mentioned hospitals and institutions did not conform very satisfactorily to the original plan, which was to draw material from widely differing sections of society over a very wide area. It was hoped, however, that the cases would be characteristic enough to yield information that might be generally applicable.

Analysis of Material

It was decided to examine the case records between the years 1880 and 1947, using only those in which post-mortem examination confirmed the diagnosis or in which symptomatology during life was so characteristic as to be unmistakable. It was hoped in this way to exclude cases of doubtful pathology, although it was realized that such selection was undesirable from the statistical point of view, as general application of the results was intended.

One of the primary objects of the research, the relation of the age of onset to the prognosis in disseminated sclerosis, could not, however, be achieved. The reason was simple. One of the essential factors—the precise determination of the age at which the disease began—was unobtainable. There was of course no way of verifying the correctness of the recorded time of onset. The difficulties involved in obtaining accuracy regarding the earliest symptoms in this disease are well known. First, the original symptoms may have been of a very vague and fleeting nature; secondly, the patient may have forgotten the episode or may fail to connect it with his present disability. In either case he or his relatives omit to mention it.

It was felt that, except for the cases from the National Hospital, the recorded ages of onset were not reliable enough to be of any value whatever, as the conclusions to be drawn depend entirely upon accuracy in this respect.

The notes made in the homes for incurables have been written by those more concerned with the patients' condition on admission and their subsequent progress than with the details of past history.

It was therefore decided to abandon attempts to relate the age of onset to any aspect of the disease. It was thought that, except in a series in which a most scrupulous watch had been exercised over patients from a very early age, it would not be possible to vouch for the accuracy of any conclusions to be drawn therefrom. It was, however, possible to obtain certain other information from the material.

Duration from Onset to Death.—First, it was decided to investigate the duration of the disease from the onset of disability until death. The "onset of disability" was taken to be the time when symptoms occurred which made the diagnosis of disseminated sclerosis probable or certain. The ages recorded were those at which symptoms caused some permanent disability (however slight), or at which the symptoms, though of a transient nature, were followed so shortly by another episode or series of episodes as to leave little doubt regarding the pathology. The cases were divided into groups according to the age at which "disability" started.

Group I, onset 0–10 years: one case (National Hospital).

Group II, onset 11–20 years: 33 cases (21 from institutions, 12 from the National Hospital).

Group III, onset 21–30 years: 97 cases (79 from institutions, 18 from the National Hospital).

Group IV, onset 31–40 years: 87 cases (75 from institutions, 12 from the National Hospital).

Group V, onset 41–50 years: 55 cases (41 from institutions, 14 from the National Hospital).

Group VI, onset 51–60 years: 12 cases.

Group VII, onset 61–70 years: one case (National Hospital).

Only groups II, III, IV, and V contained enough cases to warrant statistical investigation. In these groups the average duration of life from "onset of disability" until death was estimated.

The cases from the National Hospital were examined separately because of their unusual nature.

The results are shown in Tables I and II.

TABLE I.—Cases from the Institutions

	Group			
	II	III	IV	V
Total duration in years ..	524	1,467	1,258	579
No. of cases ..	21	79	75	41
Average duration in years ..	25	18.6	16.8	14.1
Sum of squares ..	16,024	32,799	24,962	10,275
No. of cases × sum of squares—total squared ..	61,928	439,032	289,586	86,034
Standard deviation ..	12.1	8.4	7.2	7.2
Standard error ..	2.65	0.95	0.83	1.13

TABLE II.—Cases from the National Hospital

	Group			
	II	III	IV	V
Total duration in years ..	118.1	158.1	80.5	70.5
No. of cases ..	12	18	12	14
Average duration in years ..	9.8	8.8	6.7	5.0
Standard deviation ..	15.4	7.6	4.3	4.4
Standard error ..	4.46	1.79	1.25	1.17

These figures do not establish statistically any relation between age of onset and duration of disease.

Classification of Earliest Symptoms.—Secondly, a classification was made of the relative frequency of the various types of symptoms recorded as being the earliest of which the patients were aware. This classification does not pretend to indicate the relative frequency of the various modes of onset of disseminated sclerosis, but merely

tabulates the relative occurrence of overt symptoms in the case records that were available. The age when such symptoms made their appearance was also noted, and the cases were grouped accordingly.

In 309 cases in which the age when the first symptoms appeared was definitely stated in the history the groups are as follows :

	No. of Cases
Group I, under 10 years ..	1* (0.32%)
Group II, 11–20 years ..	34 (11.0%)
Group III, 21–30 years ..	110 (35.5%)
Group IV, 31–40 years ..	92 (29.7%)
Group V, 41–50 years ..	59 (19.0%)
Group VI, 51–60 years ..	12 (3.9%)
Group VII, 61–70 years ..	1* (0.32%)

* Proved by post-mortem examination at the National Hospital.

It may be noted that this distribution closely resembles the figures tabulated by Adie (1932). Adie, however, regarded his figures as indicating true age of onset. In the present series "age of onset" is regarded as indicating the "onset of disability," as described above.

Death in Disseminated Sclerosis

Finally, an attempt was made to investigate the immediate causes of death. According to the records (excepting the National Hospital series) there are two main opinions on this subject, both equally unfounded on fact, necropsy being rarely performed on institution cases.

In many instances death was attributed to disseminated sclerosis alone, without bulbar symptoms necessarily having been present. An overwhelming episode of the disease was apparently considered sufficient reason to account for death. In the remaining cases it was thought necessary to mention as immediate cause of death a concomitant disease such as pyelitis, cystitis, asthenia, septic absorption from bedsores, or bronchopneumonia. These concomitant diseases were, however, beliefs rather than facts, largely unconfirmed post mortem, and cannot be regarded as accurate.

The following figures relating to deaths ascribed to disseminated sclerosis have been taken from the Registrar-General's Statistical Reviews :

Year	Deaths Assigned	Crude Rate per 1,000,000 Population*
1931 ..	755	19
1932 ..	762	19
1933 ..	733	18
1934 ..	697	17
1935 ..	781	19
1936 ..	845	21
1937 ..	836	20
1938 ..	754	18
1939 ..	885	21
1940 ..	984	25
1941 ..	945	24
1942 ..	913	24
1943 ..	848	22
1944 ..	845	22
1945 ..	860	23

* For the years 1931–8 the deaths include non-civilians and the rates are per 1,000,000 population, whereas for the years 1939–45 the deaths are those of civilians only and the rates per 1,000,000 civilian population.

The deaths of non-civilians in the years 1939–45 were 1, 4, 2, 1, 1, 1, and 5 respectively. No rates are available.

Regarding additional causes of death, the only year in which the secondary causes were tabulated was 1925. In that year of 733 deaths assigned to disseminated sclerosis 522 had no secondary cause mentioned. Of the rest, "the more important secondary causes were found to be cerebral haemorrhage, other forms of paralysis, bronchitis, pneumonia, heart diseases, kidney and bladder diseases."

The only cases worthy of mention among the records examined are 51 of those from the National Hospital and the six from Birmingham in which necropsy was performed. A survey of these 57 cases showed that death was ascribed

to disseminated sclerosis, with the following secondary causes :

	No. of Cases
Disease of the urinary system (with subsequent toxic absorption or uraemia)	12 (21.1%)
Disease of the respiratory system (bronchopneumonia, 15; basal pneumonia, 2; pleurisy, 1; pulmonary embolism, 1; empyema, 2; lung abscess, 1; tuberculosis, 4)	26 (45.5%)
Carcinoma	2 (3.5%)
Perforated peptic ulcer	1 (1.8%)
Death during laminectomy	3 (5.3%)
Cerebral haemorrhage	1 (1.8%)
Overdose of a hypnotic	1 (1.8%)
Aplastic anaemia from arsenical treatment	1 (1.8%)
Disseminated sclerosis involving the medulla	2 (3.5%)
No immediate cause (death ascribed to cachexia and septic absorption from bedsores)	8 (14%)

Here again no conclusions are justifiable beyond the fact that diseases of the urinary and respiratory tracts seem to have accounted for the greater proportion of deaths.

Discussion

An important contribution to the study of the prognosis in disseminated sclerosis has recently been made by Ragnar Müller (1949). He mentions that the literature on this subject "mainly gives casuistic information and reports expressing the respective author's personal opinion, which opinion is not supported by objective facts." Müller conducted a very careful investigation of 810 cases collected from various hospitals in Sweden. He concluded from his results that the prognosis is to a great extent dependent on the type of the initial symptoms, the age at which the patient becomes ill, and also probably, though to a less extent, on sex. He stated :

"When the disease commences with sensory or cranial nervous disorders the prognosis is considerably more favourable than when motility impairments are initial. In the latter case the patients become invalids much earlier. The prognosis is appreciably better when the patients are taken ill at a low than at a high age, in respect to both men and women. This applies even if younger and older persons become ill with symptoms of the same kind. It also seems as if invalidity sets in, on an average, at an earlier age among persons whose illness starts at a high than at a lower age. The prognosis seems to be less good for men than for women. The average lifetime remaining after the incipience of the disease seems to lie between 16 and 34 years.

"From this investigation it cannot be deduced that the changes in the disease picture which are liable to take place in connexion with childbirth are of specially malign character."

Conclusions

It is clear that research regarding the incidence and prognosis of disseminated sclerosis is severely handicapped by inadequacy of the existing case records.

Until accurate notes are available concerning all those suffering from disseminated sclerosis who come under medical supervision (even these being possibly only a small proportion of the total number of patients), no more precise data regarding the onset and prognosis of the disease are likely to become available.

Scrupulous attention to details of early history, as well as the following-up and the long-term observation of patients in all out-patient departments and homes for incurable diseases, is very desirable.

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GYNAECOMASTIA AND TESTICULAR APLASIA

BY

D. FERRIMAN, D.M., M.R.C.P.

Physician, North Middlesex Hospital

A case of gynaecomastia with presumed testicular aplasia is described and the reason for the appearance of gynaecomastia in this condition is considered.

Case Report

The patient, a youth aged 17, was referred to me by a colleague, Dr. M. C. Chapman. He complained of pronounced breast development starting at the age of 14. He had not shaved or experienced emissions or erections. He had evinced no interest in members of either sex, but his hobbies had always been those of a boy. He had not had mumps, or disease of or injury to the testicles.

Examination revealed pronounced gynaecomastia (see photograph). The penis was small and the urethra opened at the base of the glans with a patulous orifice. The scrotum was normal and the testicles were normally developed. A sound could be passed down the urethra into the bladder; the prostate could not be felt (Mr. B. H. Page). Pubic hair of feminine distribution was present. Axillary hair was scanty, and the face was covered with a fine down only. His height was 63½ in. (161 cm.), span 66 in. (168 cm.); head to pubis measured 32 in. (81 cm.), and pubis to ground 31½ in. (80 cm.). His manner was retiring and diffident. Urinary gonadotrophins (Dr. A. M. Hain, of Manchester University) amounted to 30 mouse units in 24 hours. Biopsy of the breast by Mr. Page showed hyperplasia of duct elements and fibrous tissue (Dr. J. F. Heggie). Testicular biopsy was refused. A laparotomy, undertaken because the 24-hour excretion of 17-ketosteroids totalled 40 mg., revealed no enlargement or tumour of the adrenals, or tumour of aberrant adrenal tissue anywhere in the abdomen. Subsequent 17-ketosteroid estimations have been within normal limits and the original estimate is believed to have been erroneous. The only adequate treatment of the gynaecomastia is surgical removal, but this his father declined to allow. Treatment with testosterone propionate has not affected the gynaecomastia, but it has led to a quite marked increase in self-confidence and masculine aggressiveness.