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Field study of the early history of multiple sclerosis patients in Omaha

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A FIELD STUDY OF THE EARLY HISTORY OF MULTIPLE SCLEROSIS PATIENTS IN OMAHA

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I. INTRODUCTION

Multiple sclerosis was first recognized and described by Carswell and Cruveilhier in 1830.(41) For many years it was considered a rare and obscure condition. With the work of Charcot and penheim a great deal of clinical knowledge was gained regarding this disease. Awareness of the true prevalence of this disease has been a relatively recent development and is due primarily to the many excellent epidemiologic studies that have been carried out.(8,10,17,18,19,20,21,24,27) Recently multiple sclerosis has been cited as one of the most common organic nervous diseases in many parts of the world.(19-30) With the realization of the importance of this disease many research workers have begun focusing their attention on the mysteries surrounding this disease. Much has been learned about multiple sclerosis but a great deal more remains still to be uncovered.

It is the purpose of this thesis to review carefully the early history of a sampling of patients with multipls sclerosis. It was felt that the period immediately prior to the onset is of great importance and consequently this period was carefully studied. Since it seemed supremely important to study the period immediately prior to the onset, and since there is great difficulty in establishing the time of onset, a strong effort was made to determine the first manifestation. Such factors as the relation of pregnancy, illnesses, and injuries to the onset of multiple sclerosis were carefully

considered. The results obtained in this study were compared with previous studies and the possible significance of the findings is briefly discussed.

II. MATERIAL

The gross material forming the basis of this study consists of 37 patients located in Omaha, Nebraska. These patients were contacted through the local Multiple Sclerosis Society. Records at the society were available for reference. However, the material for this study came primarily from a personal interview with each patient. An attempt was made to get a complete detailed early history from every patient. No attempt was made to confirm or exclude the diagnosis of multiple sclerosis. In every case with the exception of two the diagnosis had been made or confirmed by a neurologist. In over 40 per cent of the cases additional confirmation was secured. No attempt was made to select one particular case over another for study. However, because the majority of the patients were contacted in the afternoon there is a certain element of selection to be considered. It is evident that housewives and those individuals who are not able to work would have a greater chance to be selected for study than gainfully employed effected people who would less likely be available for study in the afternoon.

III. GENERAL CONSIDERATIONS

A. Sex Incidence

In this series of 37 cases there were nineteen females

and eighteen males. As the patients in this sampling were not selected entirely at random and because of the limited number in the sample the sex prevalence ratio in the sample is not a reliable clue to that of affected people in the general population.

The actual relative sex incidence in the population does seem to be of importance. It might well reflect factors of possible etiological significance such as occupational, hormonal or other factors.

When one considers the literature on this subject a marked disparity of results is noted. Most of the older literature (1900-1920) noted a Preponderance of males over females. Wechsler[43] reported a series of 1970 cases from the literature prior to 1922 of which 58 per cent were males. Other reports from this period agree in general with this figure. However, the majority of reports since that time clearly noted a gher proportion of females.[1,4,25,26,30,35] In Germany in 1932 Bing[4] reported on 811 cases of which 60% were females and later Sallstrom[35] in 1942 found 54% females in 1394 cases. In the very detailed report of 810 cases by the Swedish investigator, Muller[30], 56% were females. More recent investigators by Americans are also in agreement. In Kurland's survey of all the cases in the Denner area a total of 90 cases were found. Of this number

72% were females.[20] Mackoy[25] reported in 1953 on 309 cases of which 56% were females. Recently (1958) Alexander reported on 554 cases of which 62% were females.[1]

It is certain that any single report must be interpreted with caution because of the danger that the particular hospital population from which the cases were drawn might be predominately male or female. However, the findings of so many investigators in different areas would tend to lead one to believe that there is a slight preponderance of females over males.

B. Age Onset

As it was felt very strongly that the age of onset is of great importance if one is to consider the period immediately prior to the onset, a great deal of effort was made to determine the exact onset of the first symptoms.

In 1955 a very brief questionnaire was sent to the known multiple sclerosis patients in Omaha. The patients were asked to date the age of onset as accurately as possible. These patients not included in the survey in 1955 were asked this question at the beginning of the interview. The answer to this question is listed in Column I of the following table. However, during the course of taking a complete detailed history an attempt was made to trace back as far as possible the actual onset of this disease. The age of onset and first symptom as de-

termined by careful questioning are listed in Column II of the following table.

TABLE I

Age Onset

Comparison of results obtained by a brief questionnaire as compared to those obtained from careful questioning.

	Column I Listed Onset	Column II First Symptoms
Case I Age 49	Age 31 "Bell's Palsy"	Age 29 Tingling in lower extremities following birth of her first child.
Case 2 Age 35	Age 31 Weakness in legs	Age 31 Weakness in lower extremities manifested by frequent falling when he attempted to run.
Case 3 Age 47	Age 42 Loss of balance	Age 42 Sudden onset of stumbling and falling following an attack of influenza.
Case 4 Age 57	Age 45 Weakness in the legs	Age 42 Patient developed G I upset and constipation and "passed out" on several occasions.
Case 5 Age45	Age 38 Difficulty with balance	Age 16 Patient had an episode during which he walked like a drunk for a short period. Following this he had a slight limp lasting for several months without an apparent cause.
Case 6 Age 32	Age 17 Loss of vision	Age 16 In early teens patient was a very excellent ice skater. She began to fall a lot at the age of 16 and had to quit skating.
Case 7 Age 29	Age 17 Paralysis of toes of left foot	Age 17 Frequent "charley horse's in calf of left leg with paralysis of toes of left foot.

TABLE I (Con't)

Age Onset

	Column I Listed Onset	Column II First Symptoms
Case 8 Age 31	Age 20 Numbness in upper extremities	Age 20 Numbness in upper extremities with inability to control hands.
Case 9 Age 44	Age 27 Tingling	Age 26 About 9 months prior to tingling she had episodes of severe pain radiating down the lateral aspect of thighs.
Case 10 Age 43	Age 32 Difficulty walking due to loss of balance	Age 32 At the age of 32 he had a little difficulty walking which soon developed into a peculiar staggering gait.
Case 11 Age 31	Age 31 Double vision	Age 27 Patient first noticed slight blurring of vision and inability to see in peripheral fields.
Case 12 Age 32	Age 29 Numbness on right side	Age 20 Severe backaches.
Case 13 Age 56	Age 35 Difficulty walking and loss of balance	Age 35 Difficulty walking due to loss of balance.
Case 14 Age 57	Age 33 Double vision	Age 16 Patient states that at about the above age he had periods during which he would stumble and fall frequently.
Case 15 Age 54	Age 31 Loss of balance	Age childhood (7-14) During this period the patient was often told by her mother that she was lazy. If she attempted to do something with hands such as shelling peas in a short time her hands would be so tired she could not continue.
Case 17 Age 34	Age 22 Weakness in right leg	Age 22 Fatigue, dizziness and

TABLE I (Con't)

Age Onset

	Column I	Column II
Case 16	Con't	weakness in right leg noticed within 6 months of pregnancy.
Case 17 Age 45	Age 28 Weakness in left leg	Age 25 Transient paralysis left arm and leg with double vision.
Case 18 Age 44	Age 27 Urgency and frequency	Age 24 In basic training in service patient observed that he had a great deal of difficulty going over the obstacle course. In high school he had been an average athlete.
Case 19 Age 47	Age 22 Numbness in upper extremities	Age 18 Patient states that after she graduated from high school she had episodes during which she noticed that bending her head down caused pain to radiate down arms.
Case 20 Age 59	Age 38 Dizziness and loss of balance	Age 38 Numbness of hands and loss of balance.
Case 21 Age 46	Age 31 Staggering	Age 31 Patient states that she had a nervous breakdown and following this she became unsteady and fell often.
Case 22 Age 44	Age 27 Blurred vision	Age 27 Blurred vision. Also at this time she was told by her husband that she fell a great deal and can remember several incidents during which she fell while crossing the street.
Case 23 Age 26	Age 22 Difficulty with vision	Age 17 Prior to age 17 patient was a good golfer but then he began having difficulty hitting balls and later he had trouble finding balls. This difficulty forced him to give up golf.

TABLE I (Con't)

Age Onset

	Column I	Column II
Case 24 Age 46	Age 46 Difficulty walking due to poor balance	Age 36 Patient had several episodes of mild weakness in right leg.
Case 25 Age 45	Age 26 Dizziness and loss of balance	Age 19 Dizziness and loss of balance.
Case 26 Age 35	Age 26 Loss of balance	Age 24 Slight blurring of vision.
Case 27 Age 33	Age 23 Numbness in right leg	Age 19 Fainting spells and history of falling down stairs on several occasions.
Case 28 Age 35	Age 33 Difficulty walking	Age 33 Staggering gait.
Case 29 Age 60	Age 50 Staggering gait	Age 39 Numbness in all extremities.
Case 30 Age 45	Age 38 Muscle weakness	Age 31 Double vision.
Case 31 Age 49	Age 29 Difficulty with coordination	Age 22 Double vision.
Case 32 Age 54	Age 49 Double vision	Age 49? Patient was unable to talk. History from chart at V. A. Hospital.
Case 33 Age 42	Age 34 Blurring vision	Age 28 At this time patient developed a staggering gait, often fell in the dark and noticed blurring of vision.
Case 34 Age 33	Age 19 Frequent falls and difficulty walking	Onset age 18 Severe fatigue.
Case 35 Age 44	Age 34 Paralysis of lower extremities	Age 30 Temporary loss of vision.

TABLE I (Con't)

Age Onset

	Column I		Column II
Case 36 Age 25	Age 22 Blurred vision	Age 22 of vision.	Nervousness and blurring
Case 37 Age 42	Age 36 Difficulty with balance and frequent falling	Age 23	Blurred vision.

TABLE II

Tabulated

	Column I Listed Age Onset	Column II Age First Vague Suggestion of Disease	Column III Age First Typical Symptom
1.	31	29	29
2.	31	31	31
3.	42	42	42
4.	45	42	45
5.	38	16	16
6.	17	16	16
7.	17	17	17
8.	20	20	20
9.	27	26	27
10.	32	32	32
11.	31	27	27
12.	29	20	29
13.	35	35	35
14.	33	16	33
15.	31	10	31
16.	22	22	22
17.	28	25	25
18.	27	24	24
19.	22	18	22
20.	38	38	38
21.	31	31	31
22.	27	27	27

TABLE II (Con't)

Tabulated

	Column I Listed Age Onset	Column II Age First Vague Suggestion of Disease	Column III Age First Typical Symptom
23.	22	17	17
24.	46	36	36
25.	26	24	24
26.	19	19	19
27.	23	19	23
28.	33	33	33
29.	50	37	37
30.	38	31	31
31.	29	22	22
32.	49	19	19
33.	19	19	19
34.	34	28	28
35.	34	30	30
36.	22	22	22
37.	36	23	23
Mean	30.2 Years	25.7 Years	27.6 Years
Median	31.0 Years	26.0 Years	28.0 Years

We see then that in 25 cases (67.5%) it was possible to trace some vague suggestion of disease preceding the listed age of onset. To be sure in many cases the first manifestation of disease was rather non-specific. Yet, until we understand multiple sclerosis better we cannot completely disregard these first symptoms. In 15 cases (40%) the first symptom was what is generally regarded as a typical early symptom of multiple sclerosis. For the purpose of reviewing the period immediately

prior to the onset we will use the age of onset as that point at which time the first typical symptom occurred.

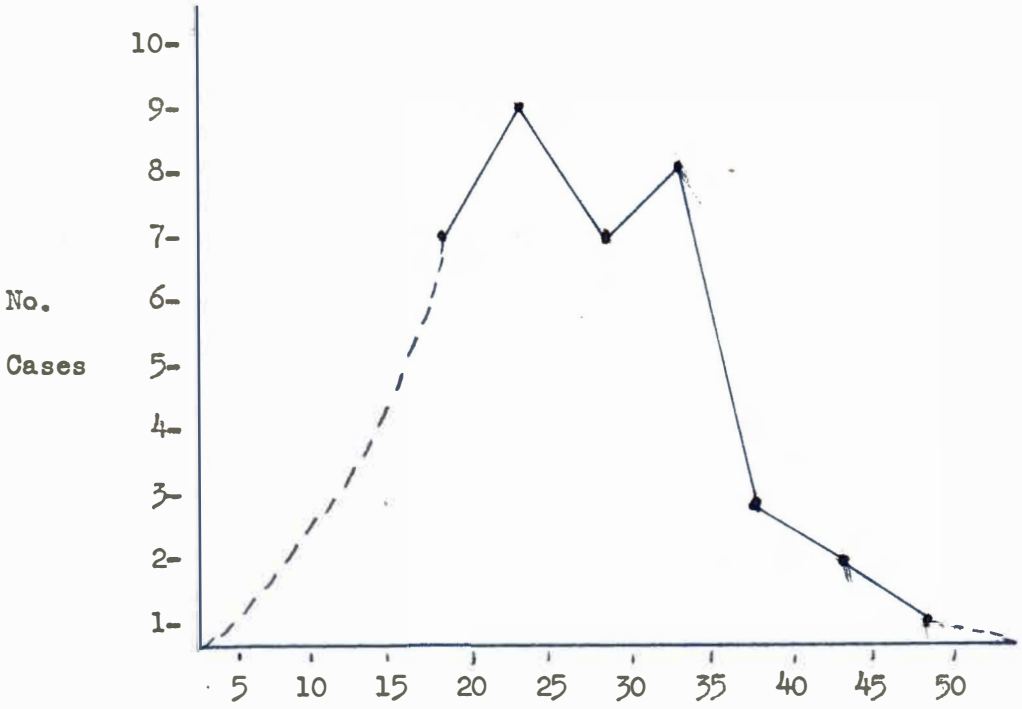
The above chart shows clearly that only with a very carefully taken history can one hope to arrive at anything approximating the actual age of onset.

Comparison of age of onset as determined in this series with findings of others.

It is generally being taught most cases of multiple sclerosis begin between the ages of 20 and 40 years. In one of the more recent reports, Mackoy (1953),[25] a series of 309 cases were reviewed. The mean reported in this was 30.2 years and the median 28.9 years. In this series the peak incidence was during the years 21-25 and 26-30. During each of these periods 62 cases out of the 309 were said to have their onset. Only thirteen cases were found to have their beginning before the age of 20. The onset of the earliest reported case was thought to be 4 years. Forty four cases began after the age of 40 years.

Alexander and his group[1] reported in 1958 on 554 cases. In this group the peak age of onset was between the ages of twenty and twenty-five years.

GRAPH I Age Onset this Series



0 - 10 . . . . . 0 Cases

10 - 15 . . . . . 0 Cases

16 - 20 . . . . . 7 Cases

21-- 25 . . . . . 9 Cases

26 - 30 . . . . . 7 Cases

31 - 35 . . . . . 8 Cases

36 - 40 ; . . . . . 3 Cases

41 - 45 . . . . . 2 Cases

46 - 50 . . . . . 1 Case

Mean 27.6

Median 28.0

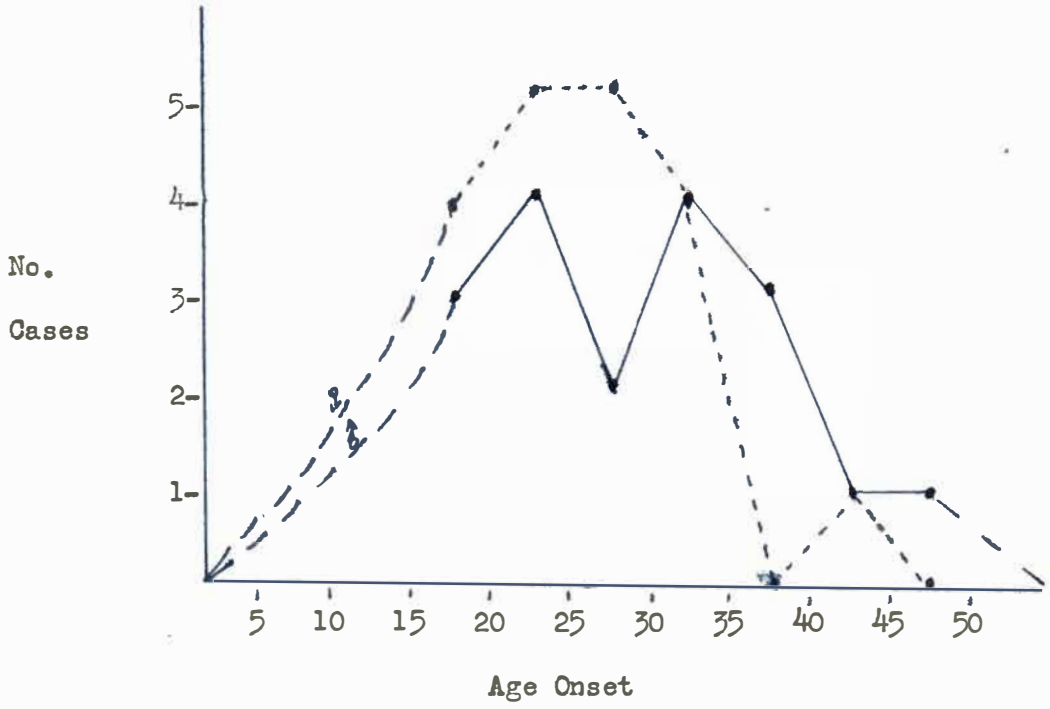
Mode 31.0

Between 20-40 . . . 72.9%

Before Age 20. . . 18.9%

After Age 40. . . 8.1%

GRAPH II Onset Males - - Females



	Males (18)	Females (19)
0 - 10	0	0
11 - 15	0	0
16 - 20	3	4
21 - 25	4	5
26 - 30	2	5
31 - 35	4	4
36 - 40	3	0
41 - 45	1	1
46 - 50	1	0
Mean	29.6	26.2

Many series referable to the age of onset are present in the earlier literature.

TABLE III

Series	Age					
	0-10	10-20	20-30	30-40	40-50	50
Muller[30] 810	3	172	366	189	57	6
Wechsler[43] 194	1	11	65	72	36	9
Klausner[43] 121	4	17	38	36	17	9
Marburg[43] 21	--	4	9	6	1	1
Muller[43] 75	--	12	33	23	6	1
Berger[43] 206	8	49	83	51	10	5
Jeliffe[14] 104	9	8	21	27	20	19
Morauitz[43] 43	1	16	14	10	2	--
Mackoy[25] 310	1	32	124	108	15	2
	27	321	753	522	164	54
1883 Cases	1.4%	17.1%	40%	27.8%	8.7%	2.8%
This series 37	---	18.9%	43.2%	29.8%	8.1%	---

We see then that there is very close agreement between the results found in this survey and that reported in earlier cases. There does seem to be a slightly greater percentage in the younger age groups in this series. This might well reflect the effort made to determine the first symptom of the disease. We have previously pointed out how often the first symptom is forgotten and a later more definite symptom substituted in its place.

We see also that the age of onset in this series seems to be somewhat younger in the females. Papoe(31) recently reported on 171 cases in which it was observed that the age of onset was slightly earlier in females.

C. First Symptoms and Diagnosis

The diagnosis of multiple sclerosis has long been considered a difficult diagnosis to make in its early stages.(15) This is evidenced by the fact that the diagnosis is frequently not made until many years after the initial symptom presents itself. It has been stated(9,28) that an average of five years elapses from onset of first symptoms until diagnosis of the disease is made.

TABLE IV

Case	Age First Symptom	Time Elapsed Until Doctor Consulted	Time Until Diagnosis
1.	29	2 Years	8 Years
2.	31	0	.25
3.	47	.5	1
4.	45	0	4
5.	16	22	22
6.	16	1	7
7.	17	0	10
8.	20	0	1.5
9.	27	0	8
10.	32	1	1
11.	27	5	5
12.	29	0	.25
13.	35	.5	.5
14.	33	5	6
15.	31	.5	2
16.	22	0	4
17.	25	0	8
18.	24	8	11
19.	22	0	22
20.	38	.25	5
21.	31	0	12
22.	27	0	11
23.	17	5	7
24.	36	8	9
25.	24	2	2
26.	19	0	3
27.	23	0	.25
28.	33	.5	1
29.	37	15	15
30.	31	2	8
31.	22	12	13
32.	45	1	1
33.	28	2	3
34.	19	0	.5
35.	30	0	2
36.	22	0	.5
37.	23	16	16

Average time from first symptom until doctor consulted is 2.9 years and the average time until diagnosis is 6.21 years. We see then that the average time from consultation with doctor until diagnosis was made was 3.31 years.

TABLE V

Age Group	Average Time Until Doctor Seen	Average Time Until Diagnosis
10 - 20	4.0 Years	7.33 Years
20 - 30	3.13 Years	7.00 Years
30 - 40	2.63 Years	5.43 Years
40 - 50	.50 Years	2.00 Years

It would seem then from these results that the younger age group tends to delay more in consulting their doctor after the onset of the first symptoms as compared to the older age groups. The total elapsed time from the onset until diagnosis is also slightly greater in the younger age group.

Much of the difficulty in making an early diagnosis is that we have no reliable laboratory aids to assist in establishing the diagnosis. Therefore, the clinical signs and symptoms together with the course of the disease are the principle criteria in diagnosing multiple sclerosis. Some people may feel that an early diagnosis is of no great

practical value because to date we have no treatment of proven value. Yet, it need not be stated that it is only good medical practice to strive for an early diagnosis in all disease states. Aside from this the future may at any time turn up some form of therapy of real value in the very early stages of this disease. All physicians should be aware of the early symptoms of multiple sclerosis.

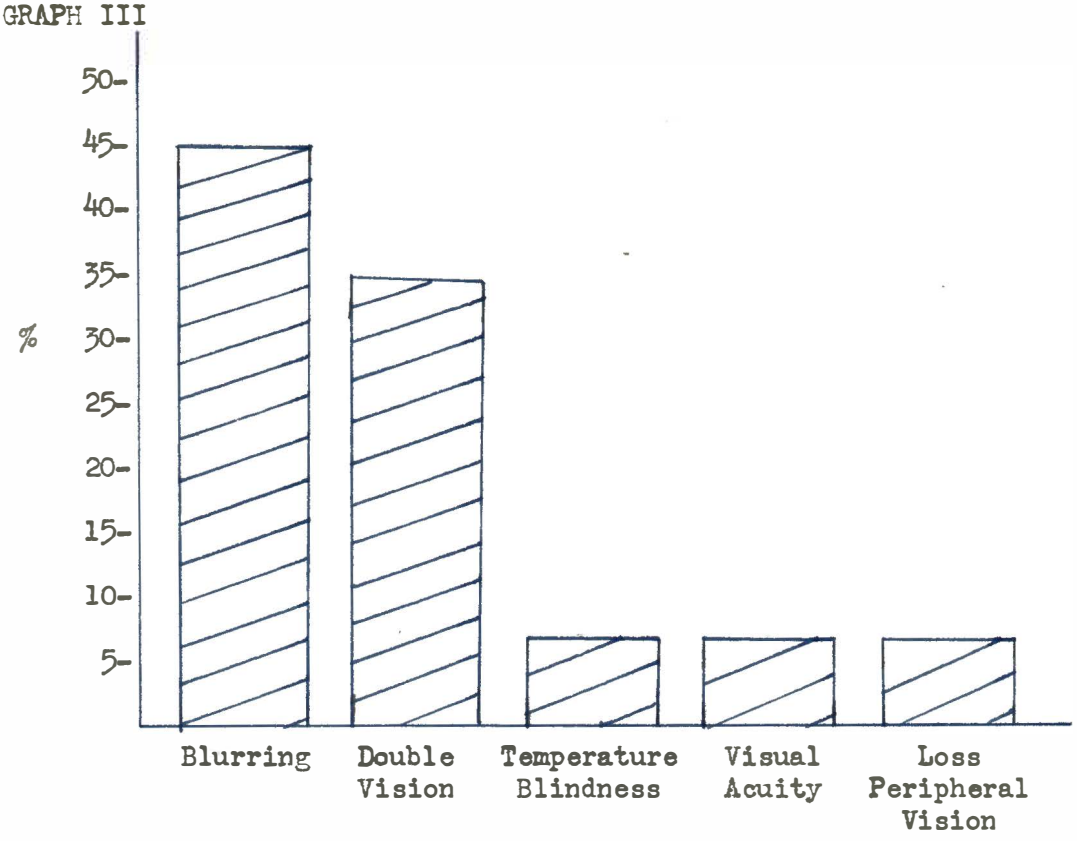
D. Discussion of Symptoms

(1) Visual

There were 13 patients with 14 symptoms in the visual system as the first, or one of the first, symptoms of the disease. One case had both blurring of vision and difficulty with peripheral vision as the first symptoms.

The symptoms occurred as follows: Blurring of vision (6 times) double vision (5 times), temporary blindness (1 time), impairment of visual acuity (1 time) and difficulty with peripheral vision (1 time). Among the patients having visual symptoms, the proportion of the various manifestations is shown in graph III. (In graph VII, the proportion of the various early evidences, as distributed among the entire group of 37 people is shown.)

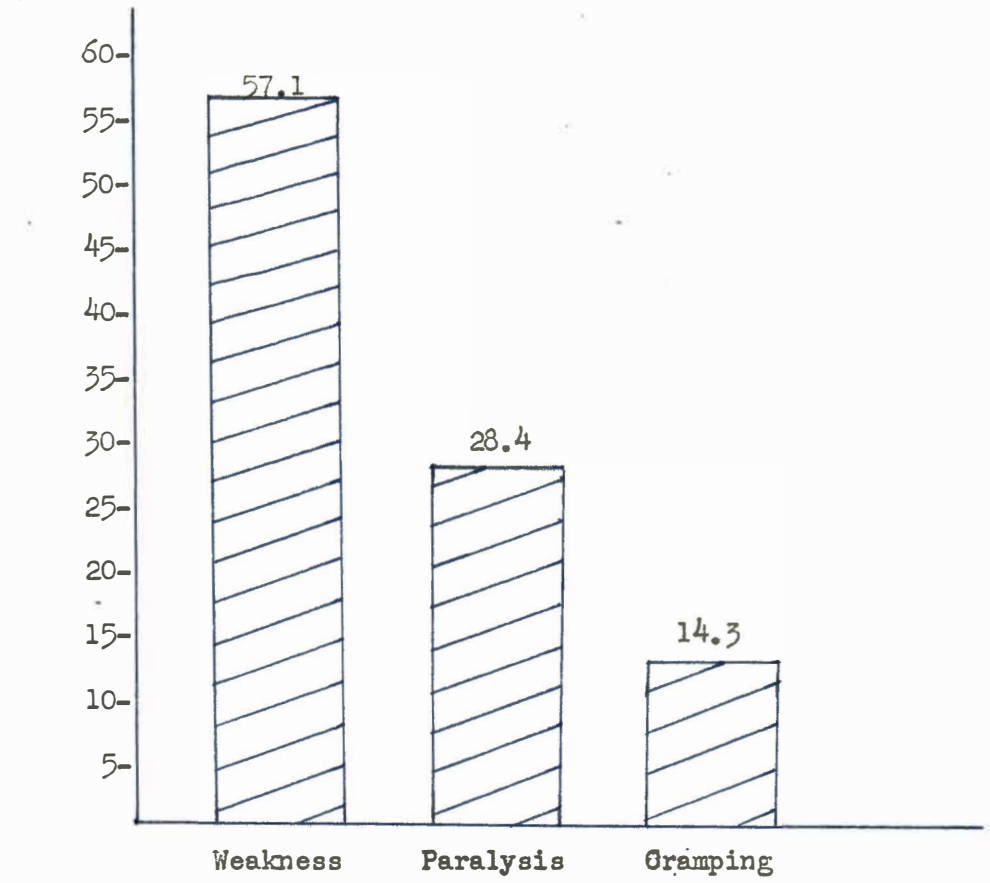
GRAPH III



(2) Motor

There were 6 patients who had 7 motor symptoms as the first or one of the first symptoms. The symptoms occurred as follows: weakness (4 times), paralysis (2 times), and cramping of toes (1 times). Among the patients having motor symptoms, the proportion of the various sensory manifestations is shown in graph IV.

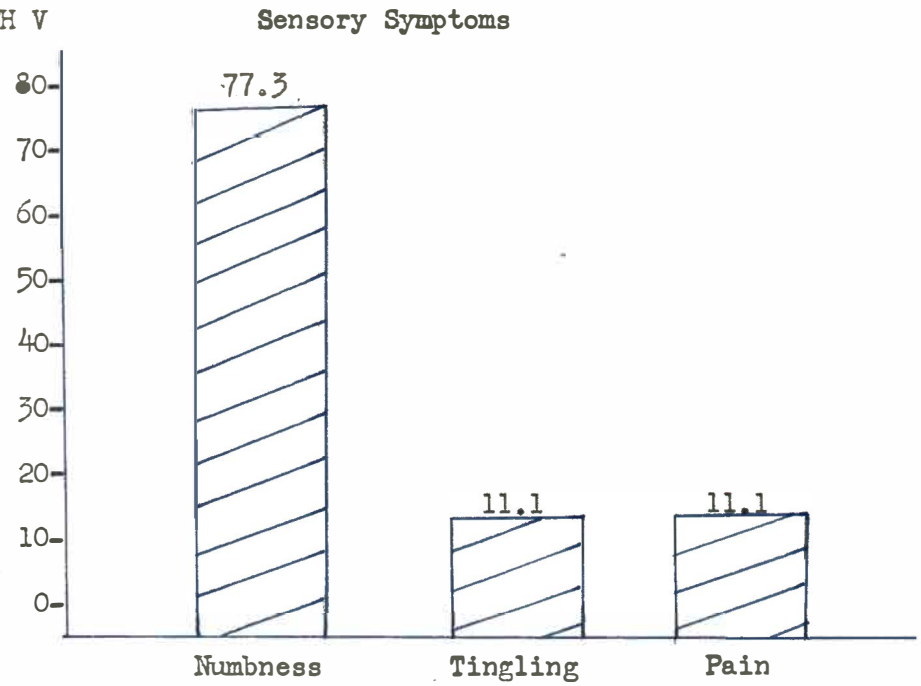
GRAPH IV MOTOR SYMPTOMS



(3) Sensory

There were 9 patients who had 9 sensory symptoms as the first, or one of the first symptoms. These symptoms occurred as follows: numbness (7 times), tingling (1 time), headache (1 time). The proportions of the various sensory symptoms are shown in graph V.

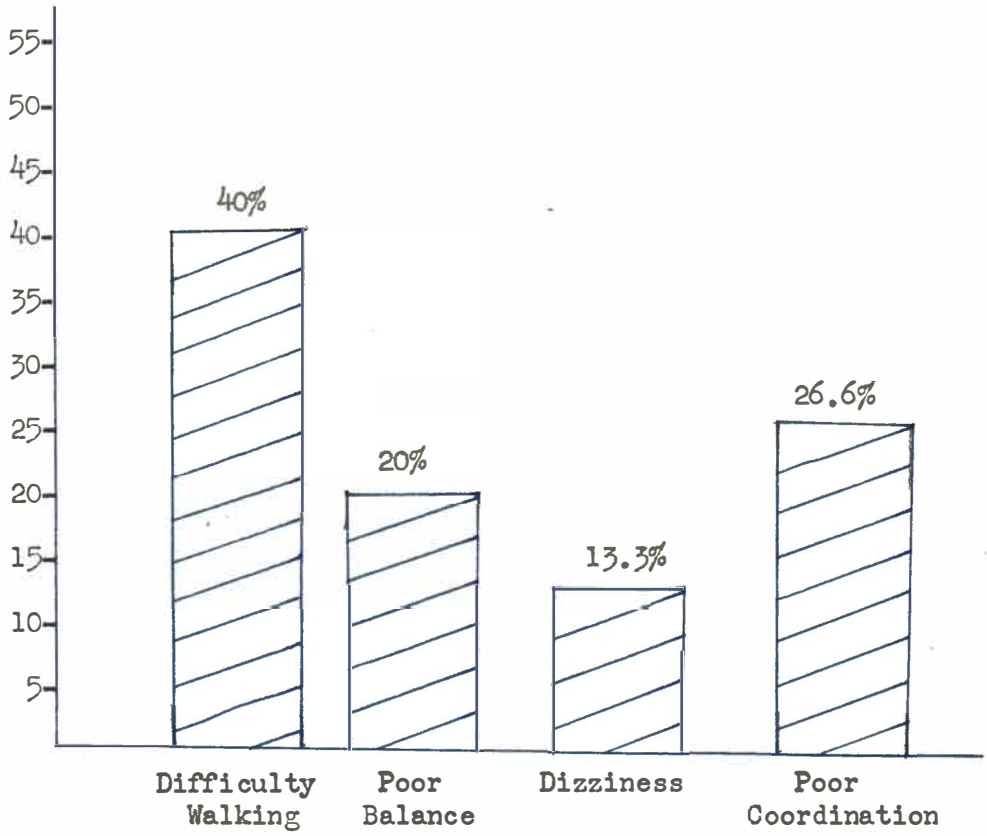
GRAPH V



(4) Coordination

Coordination was affected in some way in 13 patients who had 15 symptoms occurring as the first, or one of the first symptoms of the disease. The symptoms occurred as follows: difficulty walking (staggering) (6 times), poor balance (3 times), dizziness (2 times), and poor coordination (4 times). The proportions of the symptoms affecting coordination are shown in graph VI.

GRAPH VI



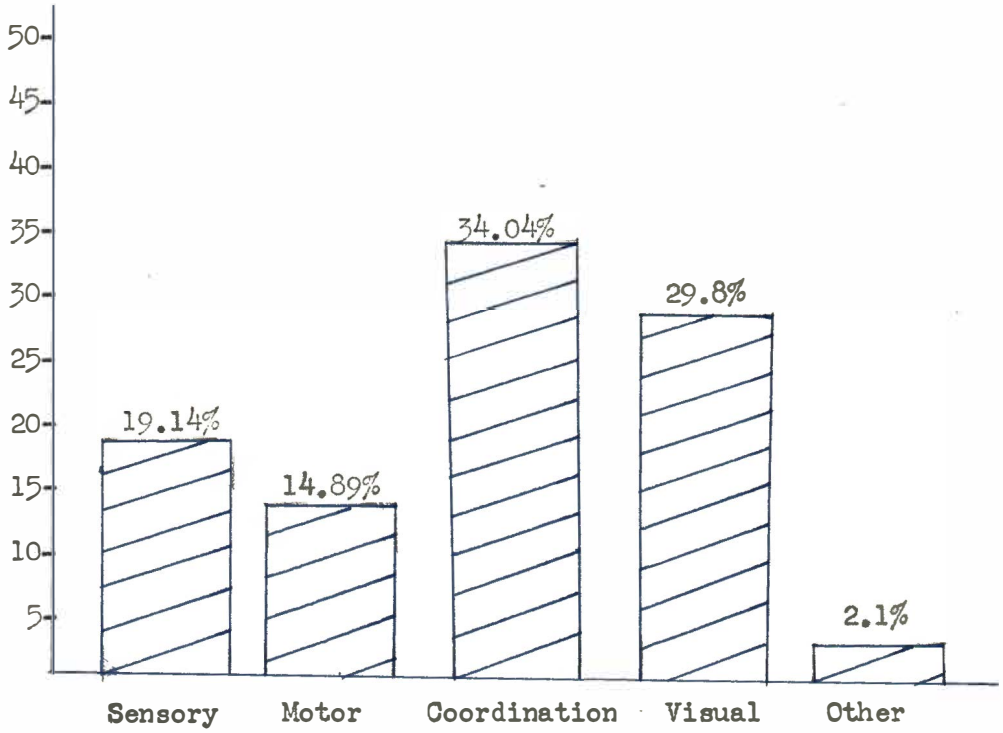
(5) Other

There was one patient who had urgency and frequency as the first symptom.

(6) Summary

There were 37 cases with 47 first symptoms. The symptoms occurred under the following systems as follows: visual (14 times), motor (7 times), coordination (16 times) sensory (9 times) and other (1 time). This is shown in graph VII.

GRAPH VII



In this series of patients there were several cases in which the first symptoms were somewhat vague and not a usual early symptom of multiple sclerosis. These were not used in calculating the age of onset because of their questionable association with multiple sclerosis. However, I feel they should be listed because it is possible that these symptoms were caused by multiple sclerosis.

These symptoms included constipation, sciatics, backache, fatigue, fainting spells, clumsiness and pains radiating down arms.

Comparison with Findings of Others

As the survey is somewhat limited it is important that we compare the results of this paper with those reported recently in the literature. The latest reports concerning the initial symptom are those of Imes[13] 1957 and McAlpine[28] 1955.

In Imes report of 116 initial symptoms he reports as follows: Visual (30 times), motor (29 times), sensory (26 times), coordination (28 times) and other symptoms (3 times). McAlpine reports as follows: Sensory 17%, motor 14%, sensory and motor 13%, micturition 14%, retrobulbar neuritis 20%, diplopia 15%, ataxia 10%, vomiting and vertigo 10%. Alder reports by Muller[30] 1949, Ziegler[44] 1929 and Reese[33] in general agree with the above reports.

In summary then it seems that visual complaints are the most frequent initial complaint followed by motor, sensory and coordination. In our series symptoms relating to coordination were the most frequent in contrast to the abovereports. This may well be explained by the fact that the majority of these patients were seen in the afternoon. Patients with difficulty with coordination are often incapacitated and unable to work.

E. Remission of First Symptom

It has long been known that multiple sclerosis is a disease in which remissions and excerbations are very common. In fact, many people feel that unless there is a history of remissions the diagnosis is questionable.

At this time we will consider the types of remissions of the first symptom in the 37 cases in this series. Four types of remissions were considered. These are described as follows: Complete (the initial symptom cleared completely with no residual). Almost complete (the initial onset seemed to be clear but some slight impairment of function was noted). Partial (first symptoms persisted but decreased markedly in intensity). No remission (only very slight, if any improvement of first symptoms were noted).

TABLE VI

Remission First Symptoms

Complete	15 Cases
Almost Complete	3 Cases
Partial	15 Cases
No Remission (or very slight)	4 Cases

In this series almost 50% had complete remission of first symptom. This is slightly higher then that generally reported by others.(7,36)

TABLE VII

Correlation First Symptom with Type of Remission

First Symptom	Complete (20)	Almost Complete (3)	Partial (20)	Slight Or More (1)
Sensory (8)	3	2	3	0
Coordination(15)	5	0	8	2
Visual (14)	8	0	6	0
Motor (9)	4	1	3	1
Bladder (1)	0	0	0	1

An analysis of the above table we see that in 62.5% of first sensory symptoms there was complete or almost complete remission while in 37.5% there were partial or no remission. In 33.3% of symptoms referrable to coordination there was complete or almost complete remission while in 66.7% there was partial or no remission. In 57% of visual symptoms complete remission was noted while in 43% only partial remission was noted. In 55% of the motor symptoms there was complete or almost complete remission of symptoms while in 45% of the cases only partial or no remission was noted. In the one case in which bladder problems were the initial symptoms no remission was noted.

From this analysis it would seem that there is less

tendency for complete remission in the cases in which coordination difficulties are the first symptoms.

TABLE VIII

Correlation Age Patient at Onset with Remission

Complete		Almost Complete		Partial		Slight or More	
Case	Age	Case	Age	Case	Age	Case	Age
1	.29	8	.20	2	.31	3	.42
5	.16	21	.37	4	.45	13	.35
6	.16	34	.28	10	.32	23	.19
7	.17			12	.29	24	.36
9	.27			14	.33		
11	.27			15	.31		
16	.22			18	.24		
17	.25			20	.38		
19	.22			25	.24		
21	.31			27	.23		
22	.27			28	.33		
26	.19			32	.49		
30	.31			33	.19		
31	.22			35	.30		
37	.23			36	.22		
Mean Age Onset	23.6		28.3		31.5		32.5

From the results in this series it seems that the younger the age of onset of first symptoms the greater are the changes of a complete remission.

This might lead one to speculate that the actual pathological changes of multiple sclerosis begin quite early. In some an acute episode occurs, possibly due to some precipitating factor such as injury or pregnancy, and makes

the disease manifested. In this early period there is a tendency for complete remissions, while in other cases the pathological changes tend to progress insidiously until when symptoms appear the pathological changes are advanced to the point that complete remissions are not likely.

IV. THE RELATION OF PREGNANCY TO THE ONSET OF MULTIPLE SCLEROSIS

Multiple sclerosis is unquestionably one of the more mysterious diseases of our era. As so very little is actually known about this disease many factors have been incriminated as of possible importance in the etiology of the disease. It has long been held by many investigators that multiple sclerosis may begin with, or be accentuated during pregnancy or in the weeks following the birth of the child. It would of course be of much more then academic interest if we could prove or disprove this association. Many patients in the past have been advised against pregnancy and many therapeutic abortions have been done in the hope that this would prevent or delay an exacerbation of the disease.(22) If there is a definite statistically proven association this might be considered a wise practice. On the other hand if adequate proof is not available to support these claims then the wisdom of these practices might well be questioned. To deprive a family of children may many times in itself be a severe hardship.

In this series there were 19 female patients. Of this

number three had never been married. One had married but because of medical advice regarding the dangers of pregnancy had never had children. There were fifteen patients in this series who among them had had 40 pregnancies. Two of these pregnancies ended in abortions.

TABLE IX

Time Relation of Pregnancies to the Onset of Multiple Sclerosis

Time Period from date of Birth of child to Onset of the Disease

	No.	Percent
1 - 6 Months	6	15.8%
6 -12 Months	2	5.3%
1 - 2 Years	7	17.5%
3 - 5 Years	4	10.0%
5 Years and over	6	15.8%

In 13 pregnancies or 33.3% the onset of first symptoms of disease was present before the pregnancies occurred.

There were six pregnancies that began six months or less before the onset of multiple selerosis. In thee of these cases, the onset of illnes so dramatically followed pregnancy as to appear to be a factor contributing to the disease. In the other three cases the patients did not feel that pregnancy contributed to the onset. As these six cases were so closely associated with multiple sclerosis I feel they should be considered in a little more detail.

TABLE X

Cases Occurring Within Six Months of Childbirth

	Age Onset	Total Pregnancies
Case I	22	2
Case II	27	3
Case III	33	1
Case IV	33	6
Case V	31	6
Case VI	19	6

It would seem to appear on first observation that the onset of multiple sclerosis frequently is associated with pregnancy. In this group 21% of the pregnancies occurred within one year prior to the onset of the first symptom of the disease. Or to put it another way in 31% of all female patients pregnancy occurred within one year of the onset of the disease.

There are several other factors which must be considered before a conclusion can be reached. First, the total number of pregnancies in this group of patients in which pregnancy occurred within six months of delivery. The six patients in this group accounted for 24 pregnancies or 60% of the total number of pregnancies. The remaining 9 patients accounted for only 16 or 40% of the pregnancies. We see then that the pregnancy rate in the group with close association with multiple sclerosis was 4.0%

while in the remainder of the group it was only 1.7%.

We must also keep in mind that the peak age of onset in females as determined by this series is about 26 years. This at an age in which pregnancy is very common. Thus, the statistical chance for a close association of these two factors, without an actual relationship, is quite high. The third factor we must realize, and a very important one, is that in any given limited survey chance alone might well account for what appears to be a significantly high figure. One is on dangerous grounds if he allows himself to draw definite conclusions from any limited series.

When one consults the literature regarding this problem it immediately becomes evident that there is no unanimity of opinion regarding the association of pregnancy and multiple sclerosis. In general most investigators seem to favor the opinion that pregnancy is an important factor in multiple sclerosis.(9,12,32) Some feel so strongly about this that they recommend the interdiction of pregnancy in any women who is known to be suffering from multiple sclerosis and the artificial interruption of gestation when pregnancy has occurred.(15) Yet, there are several authors who stubbornly maintain that no relation has statistically been established.(30)

Most investigators approach the problem by determining the number of women in the material among which the disease developed or was unfavorably affected by childbirth. In the following table

we will list the investigator, the number of patients in his study and the number of cases in which multiple sclerosis was thought to be made worse or brought on by pregnancy.

TABLE XI

Investigator	Cases in Study	No. in Which Close Association Noted	%
1. Deacon[9]	16	3	19%
2. Barker[2]	44	3	7%
3. Henner[30]	95	10	11%
4. Uierhoilig[30]	212	19	9%
5. Von Hoesslin[42]	516	30	6%
6. Beck[3]	40	16	40%
7. Ziegler[44]	340	25	8%
8. Tullman[40]	278	11	11%

When one analysis this series of reports the disparity of the results is obvious. They range from Beck's reported 40% of the cases in which a relationship between pregnancy and multiple sclerosis was felt present, a figure also mentioned by Donney-Brown[11], to the 6% reported by Von Hoesshen.[42] However, most of the larger series seem to place the figure around 10%.

As pointed out by Kurland[19], if we accept for onset and relapse a figure of ten per cent of the female cases, we would have to know how this compared with what might be suspected from

chance alone. The average period of childbearing is from 15 to 45 years or 30 years. If the average women have three pregnancies she would spend about 36 months or 10% of the time on this period in a pregnant or postpartum state. Thus, by chance alone one might easily account for the10% association as determined by many of the above listed series.

Muller(30) approached this problem from a slightly different angle. He determined how many of the women in the material, who gave birth to a child during a certain year of the disease, had a new bout in connection with this birth. He compared this with the proportion of all the women during the same year of illness who had a new bout. In his large series of 810 cases he concluded that the difference between the two groups was no greater then what could be explained as due to chance variations. He, thus, concluded that the changes in the disease - picture, which are liable to take place in connection with childbirth, are of no specially malign character.

It seems then while there are many isolated instances in which there is a seemingly striking association between the onset of multiple sclerosis and pregnancy, this association has not been proven statistically. In fact, analysis of a large number of reports would tend to lead one to conclude that this association might well be due to chance alone. More study is indicated before a definite conclusion is reached. However,

until such times as these studies are carried out, I feel that no one is justified in performing a therapeutic abortion in these cases and I seriously question the wisdom of advising against pregnancy at least from the standpoint of exacerbation of the disease.

V. THE RELATION OF OPERATIONS, ILLNESSES AND INJURIES TO MULTIPLE SCLEROSIS

The association of operations, illnesses and injuries to the onset of multiple sclerosis are other interesting clinical observations. In this series of 37 cases we will attempt to consider the time relationships between these events and the onset of multiple sclerosis.

TABLE XII

Time Period	Operations	Injuries	Illnesses
0 - 3 Months	1	0	2
0 - 12 Months	2	2	2
1 - 3 Years	3	1	2
3 - 5 Years	3	0	1
Over 5 Years	17	6	0
After Onset	12	3	0

Operations - - In two cases an operation was performed within one year prior to onset of disease.

Case I - Hemorroidectomy with spinal followed within 2 months by first symptoms.

Case 2 - D & C with general anesthesia.

In one other case a severe exacerbation of disease followed a diagnostic spinal tap. We see then in 5.4% of the cases an operation was performed within one year of the onset. However, in only 2.7% of the cases did the patient associate the onset with the operation.

In only one case did an injury occur within one year prior to onset of multiple sclerosis. In this case the patient fell down stairs and injured his head. He was unconscious for a short period but no fracture was discovered. In one case, exacerbation of disease was related to injury. In this case the patient who had symptoms of the disease for ten years was in a auto accident and injured his head. He was not unconscious. An acute exacerbation occurred within a few weeks and included symptoms of ataxia which had never been noticed before. In 5.4% of cases injury was associated with the onset or exacerbation of the disease.

The problem of illnesses in association with multiple sclerosis is slightly more difficult to assess. However, in two cases the patient felt there was a definite association between the onset and a prior illness. In one case the symptoms developed following a rather severe case of "flu". In the other case the onset of first symptoms occurred within a few

weeks of a case of mumps. In no case did a patient implicate illnesses as causing an exacerbation of disease. In 5.4% of cases illness was associated with the onset of multiple sclerosis.

There is only limited information in the literature regarding the association of operations, injuries and illnesses to multiple sclerosis. McAlpine[28] in a series of 250 cases implicated trauma or dental extractions in 35 cases or 14% as being related to the onset of multiple sclerosis. In 22 cases the site of injury correlated with the part of the body in which the first symptom occurred. He compared this study with a control group in which trauma occurred in 5.2% of the cases. Barker[2], reported on 44 cases. Physical trauma preceded the onset in 11 cases and in three cases occurred within one year. Ziegler[44], reported 22 cases in 350 in which trauma seemed to play a part in the onset of multiple sclerosis. Keschner[15], regards trauma as only those cases in which severe cranial or spinal injury are present. This history was obtained in 4 out of 255 cases. In this same series, 31 major operations were performed. In only one case, a lumbar laminectomy, did exacerbation of the disease occur. Kolb[17], reported on 199 cases. Operation was said to cause an exacerbation in 6 cases.

VI. OTHER FACTORS OF POSSIBLE IMPORTANCE IN ONSET OF MULTIPLE SCLEROSIS

In one case, that occurring in a physician, a severe emotional experience was implicated as being of possible importance in the onset of multiple sclerosis. In this case the patient first noticed numbness in hands following a severe emotional experience associated with the birth of his child. In another case the patient felt that fatigue was an important factor in the onset of this disease. He had been working about 15 hours a day for many months prior to the onset of the disease.

Only two patients could associate severe emotional upsets with exacerbations but 17 felt that emotional upsets made existing symptoms worse. Nine patients felt that fatigue made conditons worse but they could not associate fatigue with the onset of new symptoms.

Emotional upsets are mentioned frequently in the literature as being important in the onset of multiple sclerosis(22). Breckner(6) in fifty cases found 6 followed suddenly after an emotional upset.

VII. OTHER CONSIDERATIONS IN THE EARLY HISTORY

A. Family Incidence

In this series only one patient had a blood relative on whom the diagnosis of multiple sclerosis had been made.

This occurred in a cousin and apparently the diagnosis was made by a neurologist. This cousin was not interviewed. We see then that in this series there was only 2,9% of cases with a positive family history.

Reports in the literature[8,28] generally report a higher famalial incidence then listed above. Pratt and McAlpine[28] report a family incidence of 6-7% in England. Surtherland[28] obtained the high figure of 11% in his series from Northern Scotland. In these series it was observed that siblings were more frequently attacked then other relatives. Weachsler[43] found only one case in 200 with a family history while Curtius[28] in 106 patients reported 9.4% with a family history.

In summary then the facts suggest that, when present, the genetic influence is usually weak and must be reinforced by constitutional and environmental factors before the nervous system is attacked.

B. Rheumatic Fever and Glomerulonephritis Preceding Multiple Sclerosis

As it became evident that multiple sclerosis is far more prevalent in the north[16,23,39] many people began to speculate that perhaps this is an allergic reaction to a previous infection similiar to rheumatic fever[29,34,37,38].

In this series of 37 cases two patients had a prior

history of rheumatic fever and one of glomerulonephritis. That is 5.4% had a prior history of rheumatic fever and 2.7% of glomerulonephritis. This figure is not far from that found in the general population.

VIII. SUMMARY AND CONCLUSIONS

1. The early history of a sampling of 37 cases of multiple sclerosis was reviewed.

2. In this series the mean age of onset was 27.6 years. In 72.9% of cases the onset occurred between the ages of 20 and 40 years.

3. The average length of time from onset of first symptom until the doctor was consulted was 2.9 years and the average time until the diagnosis was made was 6.21 years.

4. First symptoms related to coordination in 34% of cases, to vision in 30% of cases, to sensory system in 19% of cases, to motor system in14% of cases and to other systems in 2% of cases.

5. There was complete or almost complete remission of first symptoms in 18 cases and only very slight or no remission in 4 cases.

6. In this series childbirth preceded onset by one year or less in 31% of the female cases.

7. Injuries and operations each were associated with the

onset of multiple sclerosis in 5.4% of the cases.

8. In one case a blood relative was known to have multiple sclerosis.

9. Two cases had a prior history of rheumatic fever and one case of glomerulonephritis.

Conclusions

In general the onset of multiple sclerosis occurs between 20 and 40 years. The mean age of onset in any given series depends a great deal on the effort made in illiciting the first symptoms. The earlier the onset occurs the more likely a complete remission will occur. When coordination is involved as the first symptom the chances of a complete remission is somewhat lessened.

The relation of pregnancy, injuries, operations and illnesses to the onset of multiple sclerosis is a very difficult factor to determine. In many cases there seems to be a striking association. Yet, careful analysis of the data in this series and in that of others leads me to conclude that the association of these factors to multiple sclerosis has not been statistically proven and in fact may well be due to chance alone. Before a definite conclusion can be reached it is certain that additional work with careful controls must be carried out.

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