OCULAR MANIFESTATIONS OF MULTIPLE SCLEROSIS AND RELATIONSHIP TO RETROBULBAR NEURITIS

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ABOUT 1830, an English layman, Augustus D'Esté, illegitimate grandson of George III of England, began the writing of a record of his personal experiences (1) through an illness that began in 1822 and ended finally in death in December 1848, in his 54th year. He wrote an accurate and vivid account of a disease now considered common, disseminated or multiple sclerosis, the first perhaps ever written, for a description of the condition did not appear in a textbook until twenty years after his death, and it was not until 1836 that, independently, Sir Robert Carswell in London and Cruveilhier in Paris recorded cases correlating the pathological and clinical conditions. It was not until 1865 that Charcot and Bouchard clearly defined the ailment, as distinct from other spinal paraplegias.

INTRODUCTION

The purpose of this study is to make statistical analysis of the cases of multiple sclerosis, optic and retrobulbar neuritis, seen at the University of Michigan Hospital between July 1, 1934, and April 1, 1948, in order to gain as accurately as possible a broad view of the ocular aspects of multiple sclerosis, of the relationship between multiple sclerosis and optic neuritis, and of the causes and characteristics of optic and retrobulbar neuritis.

No attempt will be made to compile an exhaustive monograph on these two diseases. Reviews of the symptomatology, diagnosis, pathology, course and treatment of the conditions are almost redundant. No effort will be made to assess the value of treatments. The principal object of this study is to obtain and evaluate data on these two diseases, and, in so doing, to establish some new figures and to check or confirm previously published statistics.

MATERIAL AND METHOD

Records of all patients at the University of Michigan Hospital from July 1, 1934, to April 1, 1948, in which a positive or presumptive diagnosis of multiple sclerosis, optic neuritis, or retrobulbar neuritis was found were reviewed.

Records of 822 patients with multiple sclerosis were used; 348 were rejected. Thus a total of 1,170 charts with this diagnosis were reviewed. Rejections were for the following causes:

1. Diagnosis uncertain	162
2. Diagnosis in error	68
3. Insufficient data for study	67
4. Psychoneurosis, and presence of multiple sclerosis uncertain	34
5. Evidence or history of syphilis	13
6. Diffuse encephalomyelitis	3
7. Necrotizing myelitis, autopsy	1
Total	348

The records of 322 patients with optic and retrobulbar neuritis were used and 155 rejected; that is, a total of 477 charts were reviewed with these diagnoses. Rejections were for the following reasons:

1. Diagnosis in error	82
2. Neuritis secondary to retinitis, uveitis, etc.	24
3. Insufficient data or diagnosis uncertain	24
4. Condition inactive; diagnosis uncertain	22
5. Secondary to trauma direct to nerve or globe	3
Total	155

Separate codes were prepared for the multiple sclerosis series and for the optic neuritis group. Nineteen factors concerned with symptomatology and findings in multiple sclerosis, quite apart from the ocular aspects of the disease, were coded for the first 200 charts only, and thereafter omitted. Every chart used was checked and coded with careful attention to accuracy. However, the desired degree of accuracy was impossible on many points, such as symptoms in the past history of a patient. Some patients were

followed for only a short time, others for years, a variation from chart to chart that greatly influences study of the course and progress of the disease, as well as the incidence of specific symptoms and findings. Punch cards were prepared from the code cards, and run through standard IBM sorting and recording machines. The punch card system allows an almost limitless study and analysis of an enormous amount of detailed material.

To shorten the main portion of the paper, an appendix is added tabulating the basic information, while the body of the paper deals with the major findings, and a comparison with those of previous writers.

ANALYSIS OF 822 CASES OF MULTIPLE SCLEROSIS

Age of patients when first registered ranged from 4 to 66 years inclusive, with an average of 33.74 years. Judging from the histories, the age at the onset of the first symptoms of multiple sclerosis ranged from 4 to 56 years inclusive, with an average of 28.94 years. Onset in 91.2 percent was between the ages of 15-43 inclusive. All writers agree that the disease is rare under 10 years and after 50; the peak of frequency comes around 30, and the majority of cases start between 20 and 40 years. The two instances of onset under the age of 10 in this series were a female with a period of ataxia at four years, then a recurrence with many evidences of multiple sclerosis at the age of 18; and a female who had repeated attacks of numbness of half her body at the age of 8, ataxia at 24, blurred vision at 27, with diagnosis of multiple sclerosis made at that time, and tic douloureux at 41. There is some question of the diagnosis at the age of 4 in the first case.

Carter (8) found in a series of 711 multiple sclerosis cases, that 10 percent began at an age under 17 years. In this series the figure is 6.4 percent. Carter quotes figures of four other writers who gave a range from 6.2–20 percent for onset under 20 years. In this series the corresponding figure is 16.4 percent. At the other end of life, Friedman (9) emphasizes that multiple sclerosis is not a disease of youth only, especially if one includes the surprisingly high number of older patients in whom multiple sclerosis can be found at autopsy. In 310 cases he found the onset to have been after the age of 40 in 13 percent, and quotes Wilson's figure of 17 percent.

He noted that the diagnosis of multiple sclerosis is difficult if the onset is after 40. That figure in this series is 10.4 percent. Von Haesslin (10) found only 4 percent starting after the age of 50; this series had only 1.2 percent.

Many writers note that multiple sclerosis is more frequent in females than males, but do not agree on the proportion. Marburg (11) said there were two females to every male, while on the other hand Drake (12) found three males to two females. In this series there were 52.4 percent females to 47.6 percent males. On the contrary, the series of 141 cases of Sachs and Friedman quoted by the National Multiple Sclerosis Society (13) had only 45.4 percent females.

The incidence and geography of multiple sclerosis is interesting, and is of importance in the broad study of the disease. The present series is of value in this connection only in so far as the Great Lakes region is concerned. As would be expected, 79.3 percent of the patients came from that area; 7.4 percent came from the northeast section of the United States, and 5.6 percent originated in the countries of northern Europe; 1.5 percent came from the Mediterranean area, and the rest from other parts of the United States. The disease is said to be common in Europe, the Baltic area, and in the United States in the northeast and the Great Lakes region, while it is rare in the southern United States and in the Orient (6), though its rarity in the South is denied by Shield (14). Shield believes that in the United States the disease is found in direct ratio to the number of neurologists in an area; its apparent rarity in the Orient is attributed by some to the lack of data. Its incidence is given as 6 or 7 per 10,000 population (6). This world geographic variation in frequency has been stressed by Shield in a thought-provoking analysis suggesting that the demyelinating diseases are related to diet deficiencies through the routine use of artificial manures in farming.

During the period of study there were 14,171 new patient registrations for the Department of Neurology at the University of Michigan Hospital and a total of 79,738 outpatient visits. To new registrations, the 902 multiple sclerosis patients are in a ratio of 6.37 percent. Marburg (11) found a ratio of only 3.04 percent multiple sclerosis in 5,000 neurologic patients.

The Department of Ophthalmology during the period had 10,967 new registrations and a total of 174,181 outpatient visits. The 395 cases of optic neuritis were in a ratio of 3.6 percent to the new registrations.

New registrations for the hospital as a whole during this period were 405,125, of which 0.22 percent were diagnosed multiple sclerosis and 0.1 percent optic neuritis.

It has been shown that multiple sclerosis runs the same course and incidence in the black race as the white. In this series only 1.6 percent were of the black race.

It has been said that multiple sclerosis is especially frequent or severe among Jews (11). In this series only 2.9 percent were Hebrews, 25.8 percent Catholics, and 67.8 percent Protestants.

Characteristically, multiple sclerosis comes in attacks, or a series of relapses. The periods between may be of almost any duration, but in this series, in 200 cases, the duration of the first attack, before remission, was less than 6 months in 43.5 percent and less than a year in 50.5 percent. However, in 41 percent no remission was known as far as the patient was followed (which often was not long). In any study of the course of multiple sclerosis the data must be affected by the length of time that the patient is under medical observation. In this series, 62.4 percent were followed less than 6 months, and 25.1 percent for more than two years, of these 4.4 percent being for more than 10 years. Another cause for variations in statistics lies in the comparative readiness with which different neurologists make a positive diagnosis. Often the diagnosis of multiple sclerosis cannot be proven, and must at the moment be considered only as a possibility. To compare different series accurately, would require reconsideration of all diagnoses and agreement on what is required for a positive diagnosis. In this series, a diagnosis of multiple sclerosis was considered to be certain or proven in 55.1 percent, strongly suspected in 31.3 percent, and likely though not certain in 12 percent.

Principal additional diagnoses were listed, to determine the relative frequency of association with multiple sclerosis. In 47.3 percent there was no additional diagnosis. Retrobulbar neuritis was diagnosed in 11.1 percent; optic atrophy in 13.2 percent; and neurogenic or atonic bladder in 12.3 percent. Palsy or paresis of

the 6th cranial nerve occurred in 6.5 percent, of the 3rd nerve in 6 percent, and psychoneurosis in 4.3 percent. Trigeminal neuralgia occurred in 1.4 percent; sinusitis in only 1 percent; and dental root infection in 1.7 percent. No other general diagnosis was made for more than 6 cases of the 822.

For indication of the occurrence of multiple sclerosis in a relative of the patient, 200 charts were checked. Among 175 patients who answered this question, there was evidence in only one that a parent had multiple sclerosis, and in four that a sibling had it. Although Marburg (11) found three families with more than one person having the disease, and one instance where the disease occurred in three generations, Thums (15) found in 14 pairs of identical twins no instance in which the second twin had the disease, although in each, one of the pair suffered from it. It is generally agreed that multiple sclerosis is not hereditary nor familial in its incidence.

We come now to a consideration of the visual symptoms, a subjective factor as expressed by the patient, which may indicate the onset, or a visual complication, of multiple sclerosis. Usually the symptoms of blurring of vision were rather typical of an attack of retrobulbar neuritis, but based only on the patient's story in many cases. Other causes of blurring could not always be ruled out. In this series of 822, in 53.5 percent, blurring was denied, or had never occurred up to the last hospital visit. It had occurred as the first symptom of multiple sclerosis in one eye in 6.9 percent and bilaterally in an additional 6 percent, or a total of 12.9 percent of patients. Blurred vision was the first ocular symptom of the disease in one eye in 9 percent and bilaterally in 12.9 percent, a total of 21.9 percent. It occurred later, or at an unknown time, in 11.6 percent. Thus in this series, 46.5 percent of patients had blurred vision at some time or other, up to the time they were last examined. The relationship of retrobulbar neuritis and multiple sclerosis will be considered later. Sarbo (16) found 30 percent of his series had blurred vision.

Double vision is a more definite and outstanding symptom, a complaint more dependable as a possible sign of multiple sclerosis than is blurred vision, unless the latter is rather severe. Of this series 68.9 percent denied diplopia, but in 4.7 percent it was the

first symptom of all, and in 14.7 percent it was the first ocular symptom. In 11.1 percent it occurred later in the course of the disease, a total frequency of the complaint of 30.6 percent. Sarbo (16) found it in 26.4 percent of 350 multiple sclerosis patients.

The average patient with a field defect complains only of reduced vision, but some are aware of a peripheral or central absence of normal vision. Of this present group, 95.4 percent had not been aware of a field defect. Only 5 patients (0.6 percent) stated that a unilateral field defect was the first symptom noted; it was the first ocular symptom in 0.7 percent and occurred later in an additional 3.3 percent.

Ocular pain was an uncommon complaint, occurring in only 1.6 percent at some time. Photophobia was rare, occurring only in 3 cases (0.4 percent), and never as an early symptom. It will be shown later that in retrobulbar neuritis the complaint of photophobia is more frequent, though still uncommon, while the symptom of ocular pain is present in 21.7 percent.

The time interval between onset of symptoms in the first and in the second eye could be determined with accuracy in only a few cases. The period was less than 3 months in 10 cases, and between 6 months and 5 years in 11.

As a background for the series, the first 200 charts were checked for some frequent nonocular symptoms and findings. These results are listed in detail in the Statistical Summary, below. Weakness of the extremities, with or without ataxia, was an almost universal complaint. Only 21 percent noted weakness of muscles of the head, chiefly those of speech; 70 percent numbness or paresthesias; while only 8 percent had girdle sensations. Some variety of urinary gastrointestinal or sphincter dysfunction was a complaint of 64.5 percent; 22 percent had suffered from dizziness at some time, about 20 percent with headaches, and 28 percent had a variety of nonocular pains.

The ocular findings are tabulated in the Statistical Summary. Only the general results will be considered here, together with their relation to previously reported statistics.

Visual acuity, at its worst in so far as could be determined, and corrected if so recorded, was about equal in the two eyes, but somewhat less in the right eye. Thirty-six patients, or 13.6 per-

cent, had vision of 20/200 or worse in each eye when acuity was tested near the peak of its loss (265 patients). After remission, it improved considerably, as expected. For example, whereas at the worst, nearly 10 percent had vision less than 20/200, later only 1.3 percent were left with this degree of blindness. However, even after remission, 2 patients had only "counts fingers" or worse in each eye, three had 20/200 in each eye, and one had 20/200 in one eye and 20/400 in the other. This is practical blindness, though many authors report they have never seen a case of permanent complete bilateral blindness from multiple sclerosis.

Visual field determinations were made in 586 cases, and 67.2 percent were normal. Fewer would have been normal had it been possible to test the patient at the interval of his worst vision, but on the contrary many multiple sclerosis victims never have involvement of the optic nerves. Fifteen percent showed a central scotoma and 10 percent concentric contraction. Observers generally report a great variety of field changes to be found in multiple sclerosis, explained by the fact that the causative lesion may be situated almost anywhere in the brain and optic nerves. Frequent and bizarre changes in the defect are rather characteristic, especially for the peripheral changes. Sarbo (16) found 12.2 percent with central scotoma and 41 percent with concentric contraction.

Most writers state that nystagmus is present in multiple sclerosis at some time in 70 percent of patients. But at the University Hospital no nystagmus was found in 38.9 percent and in another 15.8 percent only nystagmoid jerks. Neurologists are quicker to note and diagnose nystagmus than are ophthalmologists, and the former are perhaps more ready to say nystagmus is present while the latter would consider it only a normal jerk of fatigue on extreme excursion. The ataxic nystagmus of Wilson and Harris (17) was not noted in any case. Once nystagmus was found it was permanent so far as known in 81.8 percent, but disappeared or was absent at a later examination in 17.6 percent, as recorded in 296 cases.

Diplopia may be the first symptom of multiple sclerosis. Duke-Elder (18) states that frequently these diplopias are without demonstrable objective muscular palsy. In this series 30.6 percent noted diplopia at some time, but actual ocular palsies were found

in only 12.3 percent in the right eye, and in 9.4 percent in the left. Obviously the palsies were either too slight to uncover objectively, or had cleared before the patient was examined. At the time of examination 84.6 percent showed no muscle palsies in either eye. Of those that did reveal palsy in one or both eyes, 62.4 percent had alone or in combination a 6th nerve palsy, or external rectus weakness, which confirms the frequent assertion that external rectus palsy is the most frequent. In 8.8 percent a bilateral 6th nerve paresis was present. Of the patients with ocular palsies, in 59.2 percent only one eye was involved, in the rest, both eyes. Duke-Elder (18) says palsies of the extraocular muscles occur in 25-35 percent of cases of multiple sclerosis, but they are seldom permanent. Holden (19) gives a figure of 20 percent. Wilbrand and Saenger found ptosis in 15 percent, and Walsh (20) apparently supports this figure, but this series showed it in only 1.9 percent. Duke-Elder notes that ptosis is rare.

All writers seem to agree that pupillary changes are infrequent and not very significant. At the University of Michigan Hospital 12.1 percent were found to have anisocoria, but 87.2 percent were normal.

Horner's syndrome was not noted in any case.

The fundus findings in multiple sclerosis may be (1) none, or normal; (2) papillitis or papilledema; (3) some degree of atrophy; (4) veinous sheathing as reported by Rucker (21). Temporal pallor of the disc is so common normally, even when compared with the opposite disc, that it should be considered pathologic only when supported by field changes, or when accompanied by loss of capillaries or tissue. Intraocular optic neuritis, or papillitis, or even papilledema, depends on the proximity of the sclerotic plaque to the lamina cribrosa. Since the papillomacular bundle seems most sensitive to toxins or damage, its interruption causes central scotoma, and its atrophy, by obliteration of small capillaries, causes temporal pallor.

Gipner (22) said that temporal pallor was rarely noted at the Mayo Clinic, being definite in only 5.5 percent and suggestive in another 5 percent. He found a generalized pallor in 36.5 percent, but only 7 percent had loss of nerve substance due to atrophy. Sachs and Friedman (13) found temporal atrophy in 32.6 percent.

Sugar (23) found only 36 cases in the literature of papillitis and papilledema in multiple sclerosis, and added two of his own. Benedict (24) said that if optic atrophy is due to multiple sclerosis, it is usually unilateral. Sarbo (16) found temporal pallor in 28.6 percent.

In this series of multiple sclerosis patients, 82 percent of the fundi were normal. Optic atrophy was diagnosed in one eye in 7 percent, and in both eyes in 9 percent. In 1.3 percent papillitis was present in one or both eyes, and one patient (0.1 percent) had bilateral papilledema. Four patients (0.5 percent) showed vascular sheathing, but most of the patients were seen before publication of Rucker's paper (21). Of the multiple sclerosis patients who had also a complicating retrobulbar neuritis, diagnosed by findings or history, 50 percent had normal fundi; 19.8 percent had unilateral optic atrophy and 24.8 percent bilateral; 2.5 percent had unilateral optic neuritis and 1.1 percent bilateral; one patient (0.4 percent) had bilateral papilledema, and 1.4 percent had sheathing.

Retrobulbar neuritis will be considered in detail later. It was diagnosed, or was suspected from the history, in this series, in 30.3 percent of patients. Benedict (25) found it in 25 percent, and Adie in 35–50 percent (26).

Neurological findings were listed for the first 200 patients, as background material for this study. The result is tabulated in the Appendix. In brief summary, 55 percent showed muscular weakness; 79.4 percent had sensory changes; 45 percent had ataxia; only 7 percent had normal major tendon and abdominal reflexes; nearly 60 percent had tremor, and 35 percent had disturbance of speech, emotion, or mind. Oliveras de la Riva and Barraquer Moner (27) emphasize that the Charcot triad is not seen very often, and that the triad noted by Schaltenbrandt (retrobulbar optic neuropathy, abnormal abdominal cutaneous reflexes, and pathological pyramidal signs) is more valuable.

Cerebrospinal fluid changes in multiple sclerosis consist of increase in protein, change in the gold sol curve, and sometimes a minor increase in the cell count. In this series protein was increased in 11.2 percent, the gold sol curve was abnormal in 13.7 percent, and both changes were present in 50.3 percent. Only a quarter of the fluids examined (725) were normal. The figures of Merritt,

quoted by Putnam (6), were: increased protein 24 percent; abnormal curve 71 percent; and entirely normal 17 percent.

Serology of blood was negative in all patients but one, in whom it was 2 + and spinal fluid serology was negative in all cases.

Much has been written on the frequency with which multiple sclerosis manifests itself either in the first place, or later in its course, by ocular symptoms and signs. To determine this frequency at the University of Michigan, charts were coded for the first symptom of the disease (the type of visual symptom that developed first) and the second major symptom. Occasionally, of course, two or three symptoms developed almost simultaneously. In this series, the first complaint of all was ocular in 17.9 percent. The second major symptom was ocular in 15.2 percent. In the entire series, 38.6 percent, so long as they were followed, never had any visual or ocular complaints. In 38.5 percent the first ocular difficulty was blurring of vision, and in 20.7 percent it was diplopia. When ocular complaints were the first evidences of the onset of multiple sclerosis, the complaints consisted of blurred vision in 69 percent, diplopia in 27.6 percent, field defects in 2.8 percent, and ocular pain in 0.7 percent. Taking these same patients whose first manifestation of multiple sclerosis was ocular difficulty, and dividing them by age into those 28 years and under, and those 29 years and over, it was found that the frequency of blurred vision (retrobulbar neuritis) was equal (69 percent) in each group, and diplopia was only slightly more frequent in the older age group, 30 percent vs. 25.6 percent. Walsh (20) and others state that in young people the first symptom is usually retrobulbar neuritis.

In 1930 Adie (26) wrote that nearly half of his multiple sclerosis patients at some time noted loss of vision. In this series the figure is 46.5 percent. Lillie (28) in 1934 stated that a disturbance of vision was the first symptom of multiple sclerosis (500 cases) in 15 percent. In this present series, blurring of vision in one or both eyes was the first symptom of multiple sclerosis in 12.9 percent, very close to Lillie's figure. Lillie stated further that a disturbance of vision occurred as a second or third episode in the disease in 35–40 percent. In the present study, as noted above, 46.5 percent complained of blurring at some time, again very

close to Lillie's figure. Symonds (29) got a history of retrobulbar neuritis in 28 percent, and it was the first symptom in 14.4 percent.

In this series, ocular complaints were the first signs or symptoms in 17.9 percent; they occurred early, but after other neurologic signs, in 24.8 percent; and they developed in the middle or latter part of the disease in 18.6 percent.

Several factors have been accused of precipitating the onset or a relapse of multiple sclerosis. In this series there was no known precipitant in 85 percent. Of the remainder, nearly 5 percent each seemed to be associated with trauma and with pregnancy. Emotional crisis seemed to bring on the disease in 2.1 percent.

In this series, 62 percent had ocular symptoms, and 82.8 percent had abnormal ocular findings, at some time. Only 9 percent, up to the time of the last visit, had neither ocular symptoms nor signs.

OPTIC AND RETROBULBAR NEURITIS: ANALYSIS OF 322 CASES

In the retrobulbar neuritis series, 322 charts were coded. Of these 53 percent were males, and 47 percent females. Carroll (30) found the opposite of this sex ratio. Females seem to develop retrobulbar neuritis at a younger age than males. Comparing the age of onset of first ocular symptoms, females are 14.8 percent more numerous up to the age of 30 years. In every decade above 30, males predominate until the eighth. The arithmetic mean age at the onset of first symptoms of retrobulbar neuritis is 37 years for males and 30.5 years for females. Age range was 4 months to 75 years. Carroll (30) found an average age of 32.7 years. Review of the 7 patients who had onset of optic neuritis or retrobulbar neuritis before the age of 10 shows that one died of neuromyelitis optica at 4 months, and one of tuberculous meningitis at 3 years, autopsy having been performed in each case. Of the other 5 cases, 4 were associated with acute infections, and only one possibly with multiple sclerosis. The ages ranged from 5 through 9.

Geographical distribution and color were similar to the figures in the multiple sclerosis series.

Most of these patients were seen in their first attack, but 11.3 percent gave a history of having had one or more previous attacks. Data as to the duration of these was limited to 27 cases. In 12

the previous attack had lasted less than a week, and in all but 3 it had not lasted over 3 months. These figures are not completely reliable, since they depend on the patient's memory. Data on the duration of the first remission was limited to 44 patients. In 21 it did not exceed 6 months and in 34 it did not exceed a year. At the other extreme, one remission lasted beyond ten years.

Of these 322 patients 72.7 percent were under medical observation less than 6 months. In 84.4 percent the diagnosis of optic or retrobulbar neuritis was considered proved or certain, and in the rest strongly suspected though not proved. No other additional important diagnosis was made in 62 percent. Of this group 16 percent had multiple sclerosis, and 18 percent had optic atrophy; 7.2 percent had neuromyelitis optica, and 3.4 percent had syphilis. Some other diagnoses will be discussed later, and all are listed in the Appendix.

The relationship of retrobulbar neuritis and multiple sclerosis has been a source of controversy for over fifty years. Traquair (31) said that estimates, by different writers, of the incidence of multiple sclerosis as the cause of retrobulbar neuritis varied from 20 percent to 80 percent. Adie's (26) figure was 34 percent, with another 33 percent suspected. Carroll (30) found 37 percent. Benedict (32) found multiple sclerosis in 68.9 percent of his 225 cases of retrobulbar neuritis. In a German series (33) the frequency was 40 percent. Gifford (34) estimated 50 percent and Koch (32) in a second series, smaller than Benedict's, found 48.3 percent.

As noted by Benedict (35), conclusion that multiple sclerosis is present at the first attack of retrobulbar neuritis may be presumptive and based on insufficient evidence. Decision must be made on history and examination, and resulting data will vary with the completeness of these procedures. As shown by Rychener (36,37) errors in diagnosing the cause of retrobulbar neuritis may be unavoidable, and Woods (38) says: "Until some more accurate method of early diagnosis is developed, such mistakes will continue to be made in the best clinics."

In this series at the University of Michigan Hospital, multiple sclerosis was definitely found to be the cause of the retrobulbar neuritis in 13.5 percent, and possibly in another 17 percent, or a total of only 30.5 percent. Since in this series no sure cause was

found for the neuritis in 43.5 percent, the figures of Adie and Benedict may be correct. Carroll (30) reported the etiology as unknown in 34 percent. A German series (33) reports 31.4 percent, Benedict 1.3 percent, and Koch (32) 3.4 percent, for which no cause was found. Walsh (38) says that in a majority of cases of optic neuritis the etiology is unknown, but adds that idiopathic retrobulbar neuritis is often an abortive multiple sclerosis, and that at some later time the patient may develop further evidences of the disease. R. Lindsay Rea (40) writes that no adequate cause can possibly be found in many cases. Duke-Elder (41) says there is no doubt that multiple sclerosis is the commonest cause of optic neuritis. It appears that the figure derived from any series must depend largely on the thoroughness of one's clinical study of each patient, and one's assurance in assigning a definite cause to every case. Nearly all the patients with retrobulbar neuritis in our series were examined by competent neurologists, and no evidence, or at the most inadequate evidence, was found to justify a diagnosis of multiple sclerosis in 69.5 percent.

The findings in this study seem generally to agree with those of other writers on the incidence of retrobulbar neuritis in multiple sclerosis, and the importance and frequency of ocular signs and symptoms as early manifestations of that disease. But this study does not find that multiple sclerosis is the cause of retrobulbar neuritis in the proportion of cases reported by other writers. Of course, the longer a patient with a retrobulbar neuritis is followed, the better is the chance that he will ultimately develop evidence of multiple sclerosis. This was confirmed by determining the frequency that multiple sclerosis was diagnosed in the retrobulbar neuritis series, in relation to the period in which the patient had been under medical observation. The diagnosis was made in only 11.5 percent when the patient had been followed less than 6 months, 31.7 percent when followed between 6 months and 4 years, and in 36 percent between 4 and 20 years. The older the patient the more likely are evidences of multiple sclerosis to appear, and the more likely a previously presumptive diagnosis is to be confirmed as certain.

In brief summary, the symptoms of these 322 retrobulbar neuritis patients were as follows: Nearly every patient had the symp-

tom of blurred vision, which in this series indicates optic or retrobulbar neuritis. Females more often had the symptom for one eye, males more often for both, while the sexes were equal in the group that complained first of one eye, later of the other. The percentages were:

	One Eye	*Both Eyes*	*One Eye, then Both*
Males	42.9	41.7	15.5
Females	55.0	27.1	17.2

Based on the patient's story, the loss of vision reached its peak in less than 4 days in 40.4 percent, and in from 4 to 20 days in another 30 percent. Most patients were aware only that vision was blurred, but 13.4 percent were cognizant of a central scotoma or defect, and 5.4 percent noted a hemianopic or altitudinal defect; 5 percent of the patients had diplopia; only 1.3 percent had photophobia.

Pain on movement or palpation of the globe in retrobulbar neuritis may be due to swelling of the meninges of the optic nerve. Carroll (30) notes that such pain is an important symptom, occurring in 20 percent of his series, more often on movement than on pressure. Benedict (35) said it occurred in about half of his 90 cases that had both multiple sclerosis and retrobulbar neuritis. In the present series, 21.8 percent had ocular pain; 13.1 percent noted pain on movement of the eyes, and 3.1 percent had pain or tenderness on pressing the eyes. Another 5.3 percent had ocular pain on movements, preceding the blurring of vision.

In most instances, especially where there was only one recording of the visual acuity, it was tested near the height of an attack of retrobulbar neuritis, or at its worst. It may have been worse either before or after the test. Vision at about its worst was thus recorded for 314 patients, and after its improvement, or on remission of the disease, for only 164 patients. The following comparisons can be made:

a) To a slight degree, the left eye averages worse vision than the right, both in remission and in relapse.

b) Grouping all visions of 20/50 and better in either eye, 40.1 percent fell in this category when vision was bad, and 67.7 percent when good, or in remission.

c) Combining all visions of 20/200 and worse in either eye, 51.1 percent fell in this category when vision was in relapse, and 22.3 percent when in remission.

d) Vision of "counts fingers" and worse, including no vision, in relapse, averaged 32.8 percent between the two eyes; in remission this dropped to 13.1 percent.

e) 21 patients, or 6.5 percent of patients with optic and retrobulbar neuritis, had visual acuity of 20/200 or worse in each eye, permanently so far as known. Analysis showed little to indicate why their affliction was so severe. Of these cases 57.1 percent were males. Age range was 6–74 years, with 8 over 50, and 4 of 20 years or under. Four died, and in 9 the cause of the disease was uncertain.

Visual field changes were recorded in 283 cases, and were found to be normal in only 4.2 percent; 64 percent showed a central scotoma in one or both eyes; 3 percent showed a paracentral scotoma. A combined peripheral defect and scotoma was found in one or both eyes in 23.8 percent. Of the patients with visual field changes in Benedict's series (35), half had central scotoma, a quarter centrocecal scotomas, and a quarter other changes.

There were no unusual pupillary changes, and in 81.4 percent the reactions were normal.

The fundi were normal in 64.4 percent. Optic atrophy was diagnosed an average of 8.4 percent, in each eye, and optic neuritis in 19.2 percent; 2.2 percent of all eyes showed optic neuritis followed by atrophy, and 3.2 percent neuroretinitis. This incidence of 21.4 percent neuritis is considerably higher than that of Benedict (24), who stated that blurred discs occur in about 12 percent. It also is higher than Werner's (33) figure of 15 percent. In his series of retrobulbar neuritis, or what he prefers to term "scotomatous neuropathy," the fundi were normal in 85 percent.

The incidence of fundus pathology in the right and left eye was nearly equal. In 22.7 percent there was fundus pathology in each eye, and in 51.6 percent the fundi were normal in each eye. One eye only had an abnormal fundus in 13 percent each, right and left.

On analysis of fundus changes in the 56 patients who had multiple sclerosis also, it was found that 42 (75 percent) had a

normal fundus in each eye; 10.7 percent had pathology in each eye; and the remainder (14.3 percent) had one normal and one abnormal fundus.

Of the 20 cases of neuromyelitis optica, 8 had normal fundi in each eye, 6 had bilateral optic atrophy, 5 bilateral optic neuritis, and one had optic neuritis in one eye only. Only 10 of these patients had visual field determinations; 4 had bilateral central scotomata; 3 had these plus a peripheral defect in each eye; one had the latter change in one eye; one had a paracentral scotoma in one eye; and one had normal fields.

Although Lillie (42) said that only 2 percent of patients with retrobulbar neuritis had permanent visual loss, in this series only 19.2 percent showed no loss; 17.3 percent showed reduced vision in the right eye after the first or early attacks, and 18.5 percent in the left eye; while 43.5 percent showed it in both eyes.

In this retrobulbar neuritis series, out of 308 patients, 4.2 percent showed a positive blood serology, four being one plus, two three plus, and seven four plus. Only 2.7 percent had positive cerebrospinal fluid serology, of 147 patients, three being four plus. Carroll (30) notes that a positive serology does not rule out either multiple sclerosis or tobacco-alcohol amblyopia.

Cerebrospinal fluid changes were recorded in 147 cases, and were normal in 58.5 percent. The others, as in multiple sclerosis, showed either or both an increase in protein or a change in the gold sol curve. Scheid (43) reports that isolated acute retrobulbar neuritis rarely leads to changes in the cerebrospinal fluid. This finding surprised him, since multiple sclerosis so seldom has a normal fluid (20 percent) and yet it so often causes retrobulbar neuritis.

When a patient has some organic condition together with syphilis, one tends to assume that the first is due to the second until proved otherwise. When a patient has optic or retrobulbar neuritis and multiple sclerosis, one tends to assume on the basis of past teaching that the former is due to the latter. However, it is acknowledged even by the staunchest holders of this view that other factors can and do cause retrobulbar neuritis. Faced with such possible causes as foci of infection, metabolic diseases, alcohol, and arteriosclerosis, one wonders which to hold responsible in a

given case. Often a patient is found to have two or more conditions, each of which could cause optic neuritis. In this series, the possible causes were listed and the frequency of occurrence totaled. Even then it was found that no definite cause for the retrobulbar neuritis was shown to be present in 43.5 percent. The percentages of the more frequently occurring possibilities are as follows, others being listed in the Statistical Summary: uveitis or retinitis or both, 5.4; sinusitis, 6.5; multiple sclerosis, 20.2; neuromyelitis optica, 7.2; tuberculosis, 2.2; syphilis, 4.7; a genitourinary infection, 5.2. Percentages of foci were as follows: in the teeth, 17.1; tonsils, 11.5; prostate, 4.1; female pelvis, 1.8; kidney or bladder, 2.3; and in combinations of these, 3.2. Other percentages were arteriosclerosis, 4.2; hypertension, 3.7; tobacco amblyopia, 3.8; ethyl alcohol amblyopia, 4.5; and a combination of the two, 1.3. One patient had arsenic poisoning, one a contusion to the globe, and one a head injury. Excluding Leber's disease, which was found in no case, possible causes of retrobulbar neuritis were grouped under seven headings for coding this series: in 30.5 percent of cases no cause was known or assigned; in 50.5 percent one cause was listed; in 15.3 percent two possible causes were given; in 3.1 percent three; and in 0.6 percent (two patients) four possible causes were noted. Faced with such a choice of possibilities, conclusion as to the etiology of the retrobulbar neuritis must obviously be uncertain.

The possible causes of optic neuritis are very numerous. Duke-Elder (41) and Benedict (25) give classifications, to which Werner (33) would add six more groups. Woods (38) gives a sound and simple classification, but the papers of Benedict (24,25,32,35) give the most detailed list of all possible causes. For data on different recent series one may consult the reports of Benedict and Koch (32), Costen (44), and Carroll (30). The belief that foci of infection, especially sinus infection, are common causes of retrobulbar neuritis, as was generally held twenty years ago, has largely disappeared, in large part as a result of the efforts of Benedict and Lillie. Lillie (45) felt so strongly on this that he stated in 1936 that sinusitis was the last etiologic factor he would consider in a patient with acute retrobulbar neuritis, and Benedict (35) wrote in 1942 that in the preceding ten years not a single patient seen at the

Mayo Clinic with retrobulbar neuritis had also a recent acute sinus disease. But Koch (46), Walsh (39), and Carroll (30) agree that a small percentage of such cases may be caused by sinusitis, and Benedict (24) in 1949 admitted the possibility.

Studies of the course of the disease again vary with the period in which the patient has remained under medical observation. In this series 52.2 percent were seen only once. In the rest there were one or more remissions. Of the total 5.0 percent (16 patients) are known to have died at an age ranging from 4 months to about 56. Six were males and 10 females. Five died of neuromyelitis optica and three of multiple sclerosis; two, of spread of malignancies of the nasopharynx; one, of metastatic breast carcinoma; two, of leukemia; one, postoperatively, of carotid aneurysm. One died from extensive osteomyelitis of the base of the skull and orbit following surgery for pansinusitis, and one 3-year-old child died of tuberculous meningitis.

Treatment was usually by vasodilatation, effected by foreign protein, nitrites, vitamin B, and so on. Surgery was done on 19 percent, to remove teeth, tonsils, and to treat other foci. Of these cases, 2.9 percent were surgery on the sinuses; and 1 percent were craniotomy for brain tumor. Other treatments were for syphilis, prostatitis, hypertension, and radiation for malignancy. The results of treatment were often unknown, since the patient frequently returned to his own physician before these could be ascertained. This was true of 31.9 percent; 55 percent improved.

It was felt that multiple sclerosis could not be diagnosed in 69.5 percent, and was surely present in only 13.5 percent. It was felt that only 6 percent showed evidence of sinus disease, this being certain in 2.3 percent. This last supports Benedict's (24) recent statement that there are few authenticated cases of retrobulbar neuritis due to sinusitis. It neither supports nor disproves the belief that demyelinating diseases cause the majority of cases of retrobulbar neuritis.

SUMMARY

Statistical data is presented on the symptoms and the physical and ocular findings of 822 patients with multiple sclerosis and 322 patients with optic or retrobulbar neuritis. Analysis gives the following major conclusions.

Multiple Sclerosis

1. Age of onset of disease averaged 28.9 years.

2. There was little sex preference.

3. Among neurologic patients, the percentage of incidence was 6.37.

4. Nearly half of the patients complained of blurred vision at some time; this was the first symptom of multiple sclerosis in 12.9 percent, and the first ocular symptom in 21.9 percent.

5. Of the total, 30.4 percent complained of diplopia at some time; 4.7 percent as the first evidence of multiple sclerosis; and 14.7 percent as the first ocular symptom.

6. With visual acuity in relapse due to the disease, 13.6 percent were blind (20/200 or worse); and in remission 1.3 percent remained with loss of this degree.

7. Visual fields were normal in 67.2 percent.

8. Nystagmus was found in only 40 percent.

9. Ocular muscle palsies occurred in 15.4 percent.

10. The fundi were normal in 82 percent; among multiple sclerosis patients with retrobulbar or optic neuritis, 50 percent had normal fundi.

11. Retrobulbar neuritis was diagnosed, or suspected from the history as having occurred, in 30.3 percent.

12. The first complaint of multiple sclerosis was ocular in 17.9 percent, and the second major symptom was ocular in another 15.2 percent. No ocular complaint occurred in 38.6 percent.

13. Among those whose onset of multiple sclerosis was with ocular symptoms, 69 percent had blurred vision and 27.6 percent had diplopia.

14. Retrobulbar neuritis as an initial sign of multiple sclerosis was no more frequent in younger than in older patients.

15. Only 9 percent of patients showed no abnormal ocular signs or symptoms, at some time.

Optic and Retrobulbar Neuritis

16. Females developed retrobulbar neuritis at a younger average age than males, but there was little sex preference in the frequency. Mean age at onset was 30.5 years for females, and 37 years for males.

17. The disease occurred in 3.6 percent of ophthalmic patients.

18. Multiple sclerosis was present with certainty in 13.5 percent and was suspected in another 17 percent, or a total of 30.5 percent, as the cause of the retrobulbar neuritis.

19. Males gave a history of bilateral involvement more frequently than females.

20. Ocular pain occurred in 21.8 percent.

21. Half of all eyes were blind (20/200 or worse) with visual acuity in relapse, 22.3 percent when in remission.

22. Permanent blindness, in each eye, so far as known, occurred in 6.5 percent, from the disease.

23. Visual fields were normal in only 4.2 percent.

24. Fundi were normal in 64.4 percent of eyes, 51.6 percent of patients, and 75 percent of those patients who also had multiple sclerosis.

CONCLUSIONS

Ocular signs and symptoms are present in so large a proportion of patients with multiple sclerosis that ophthalmologists must keep this disease constantly in mind in considering every diagnostic problem. Multiple sclerosis is the most frequent of all the many possible causes of retrobulbar neuritis.

STATISTICAL SUMMARY

MULTIPLE SCLEROSIS: 822 CASES[a]

Age when first registered: Range 4 to 66 years, inclusive, with average of 33.74 years.

Sex: Male, 47.6; Female, 52.4.

Place of longest residence

	Percent		*Percent*
Great Lakes area	79.3	Northern Europe	5.6
N.E. United States	7.4	Mediterranean	1.5
N.W. United States	0.6	Central and S. America	0.4
Central United States	3.4		
Southern United States	1.8		

Race: White, 98.0; Black, 1.6; Other, 0.4.

Religion: Protestant, 67.8; Catholic, 25.8; Hebrew, 2.9; Unknown, 3.5.

[a]All the listings are in percent of cases unless otherwise noted.

Age at onset of first symptoms

(range 4 to 56 years inclusive; average, 28.94 years):

Age in Years	*Percent*	*Age in Years*	*Percent*
1–10	0.2	30–39	34.7
10–19	16.1	40–49	11.3
20–29	36.2	50–56	1.5

Duration of first attack (200 cases)

Age in Years	*Percent*	*Age in Years*	*Percent*
0–6 months	43.5	10–15 years	1.0
7–12 months	7.0	15–20 years	0.5
1–2 years	2.5	over 20 years	0.5
2–4 years	1.5	no remission known	41.0
4–7 years	0.5	unknown	1.5
7–10 years	0.5		

Time patient has been under medical observation

Age in Years	*Percent*	*Age in Years*	*Percent*
0–6 months	62.4	7–10 years	5.2
7–12 months	5.8	10–15 years	2.8
1–2 years	6.4	15–20 years	1.2
2–4 years	8.0	over 20 years	0.4
4–7 years	7.5		

Certainty of diagnosis of multiple sclerosis

	Percent
Certain or proven	56.0
Strongly suspected	31.8
Likely, not certain	12.2

Additional general diagnoses

	Percent		*Percent*
None	47.3	Uveitis	2.6
Optic atrophy	13.2	Dental root infection	1.7
Neurogenic bladder	12.3	Trigeminal neuralgia	1.4
Retrobulbar neuritis	11.1	Sinusitis	1.0
6th nerve palsy	6.5	Pregnancy	1.0
3rd nerve palsy	6.0	Hypertension	1.0
Strabismus	4.4	Amblyopia	1.0
Psychoneurosis and psychosis	4.3		

Did any relative have multiple sclerosis? (200 cases)

			Percent
No	170	Yes, one parent, 1 Yes, one sibling, 4	2.9 of 175
Unknown	25		

Symptoms, visual: Blurred vision

	Percent
Never	53.5
First symptom of all, unilateral	6.9
First symptom of all, bilateral	6.0
First ocular symptom, unilateral	9.0
First ocular symptom, bilateral	12.9
Later in course of disease, unilateral	4.2
Later in course of disease, bilateral	6.4
Time unknown	1.0

Symptoms, visual: Diplopia; Ptosis

	Percent		Percent
Never	68.9	Ptosis alone	0.1
First symptom of all	4.7	Ptosis with diplopia	0.1
First ocular symptom	14.7		
Later in course of disease	11.1		
Time unknown	0.4		

Symptoms, visual: Visual field defect

	Percent
Never	95.4
First symptom of all, unilateral	0.6
First symptom of all, bilateral	0.0
First ocular symptom, unilateral	0.2
First ocular symptom, bilateral	0.5
Later in course of disease, unilateral	1.9
Later in course of disease, bilateral	1.4

Symptoms, visual: Ocular pain

		Percent
Never, not otherwise explained		98.4
First symptom of all	2	
First ocular symptom of all	5	13 or 1.6
Later in course of disease	6	

Symptoms, visual: Photophobia, not otherwise explained

	Percent
Never	99.6
Later in disease	0.4

Symptoms, muscular: Weakness, Ataxia (200 cases)

	Percent		Percent
Never	2.5	Ataxia alone	17.0
Weak arms, 1 or both	1.5	Weak leg and ataxia	34.0
Weak leg, 1 or both	25.5	Weak side and ataxia	6.0
Weak side (hemiparesis)	7.0	General weakness and ataxia	5.5
General weakness	1.0		

Symptoms, muscular: Weakness of cranial muscles (200 cases)

	Percent		Percent
Never	78.5	Difficulty with speech, swallowing, facial weakness	0.5
Facial weakness	3.5	Difficulty with speech, facial weakness	1.0
Difficulty with speech	13.5		
Difficulty with swallowing	1.0		
Difficulty with speech, swallowing	2.0		

Symptoms, sensory: Paresthesia (200 cases)

	Percent		Percent
Never	28.0	Numbness of face or head	0.5
Numbness of extremity	45.0	Numb extremity and astereognosis	0.5
Tingling of extremity	6.0	Numbness extremity and face	1.5
Numbness and tingling	18.5		
Astereognosis	0.0		

Symptoms, sensory: Girdle, Vibration, Position (200 cases)

	Percent		Percent
Never	84.5	Girdle and loss sense vibration	0.0
Girdle sensation	8.0	Girdle and loss sense position	1.0
Loss sense of vibration	0.5	Girdle; loss vibration and position	1.0
Loss sense of position	4.0		
Loss sense vibration and position	1.0		

Symptoms: Urinary and Gastrointestinal (200 cases)

	Percent
Never	35.5
Frequency	5.0
Urgency	16.5
Frequency and urgency	8.0
Constipation	2.0
Urinary symptoms and constipation	11.0
Incontinence, bladder or rectum	22.0

Symptoms: Dizziness, Convulsions, etc. (200 cases)

	Percent		Percent
Never	70.5	Convulsions	1.5
Vertigo	22.0	Fainting	1.5
Vomiting	2.0	Vertigo and Fainting	0.5
Vertigo and Vomiting	2.0	Tremor	0.5

Symptoms: *Headaches, Drowsiness (200 cases)*

	Percent		*Percent*
Never	78.0	Severe	1.0
Occasional	14.0	Drowsiness alone	0.0
Frequent	5.5	Drowsiness and headache	1.5

Symptoms: *Pain other than ocular (200 cases)*

	Percent
None	72.0
Trigeminal neuralgia	2.0
Pain in extremities	14.5
Pain in trunk	9.5
Pain in both extremities and trunk	2.0

Course of the disease: *Remissions (200 cases)*

	Percent
Seen once, no further knowledge	10.5
No remission known	29.0
One remission without known relapse	0.5
One remission, then relapse	12.5
Two relapses	7.0
Three to five relapses	17.0
Six and more relapses	23.0
Unknown	0.5

Findings, Visual Acuity: *Vision at its worst (265 cases)*

	Right Eye	*Left Eye*
20/20 or better	36.6	38.1
20/30	17.0	19.2
20/40	5.3	7.5
20/50	5.3	3.0
20/70	0.4	0.4
20/100	8.7	7.5
20/200	12.8	11.3
20/400	4.5	2.6
less than 20/400	9.0	10.2

Findings, Visual Acuity: *Vision after remission (475 cases)*

	Right Eye	*Left Eye*
20/20 or better	60.1	57.3
20/30	19.5	21.6
20/40	6.1	6.1
20/50	4.2	5.1
20/70	0.2	0.6
20/100	6.3	6.0
20/200	2.3	1.9
20/400	0.0	0.2
less than 20/400	1.3	1.3

Findings, Visual field changes (586 cases)

	Percent
Absent or normal	67.2
Hemianopic or quadrantic defect one eye	0.3
Hemianopic or quadrantic defect both eyes	1.2
Scotoma, central, one eye	8.4
Scotoma, central, both eyes	6.7
Scotoma, paracentral, one eye	1.5
Scotoma, paracentral, both eyes	1.9
Peripheral defect and scotoma, one eye	1.7
Peripheral defect and scotoma, both eyes	0.9
Concentric contraction, one or both eyes	10.4

Findings, Nystagmus

	Percent
Absent	38.9
Nystagmoid jerks only	15.8
Horizontal nystagmus	37.4
Horizontal and vertical nystagmus	3.9
Vertical nystagmus only	0.5
Rotatory nystagmus	2.0
Rotatory and horizontal	1.5

Findings, Did the nystagmus remain? (296 cases)

	Percent
No, it later disappeared	17.6
Yes, no known remission	81.8
One remission, then return	0.7

Findings, Paresis of ocular muscles

	Right	Left
Normal so far as known	87.7	90.6
External rectus alone	4.6	3.7
Internal rectus alone	3.5	2.5
Superior rectus alone / Inferior rectus alone	1.1	0.5
Superior oblique alone	0.0	0.0
3rd nerve branches	1.0	0.4
6th and 3rd nerves	2.2	2.2
3rd and 4th nerves	0.0	0.1

Findings, Ptosis

	Percent
None	98.2
Right eye only	0.25
Left eye only	0.9

Findings, Ptosis—Continued

Right, with 3rd nerve palsy of other branches	0.0
Left, with 3rd nerve palsy of other branches	0.25
Bilateral ptosis, with paresis other 3rd nerve branches	0.5

Findings, Paresis of conjugate movements and of convergence

	Percent
None	93.6
To right alone	0.7
To left alone	1.0
To right and left	1.4
Vertical alone	1.0
To right or left, and vertical	0.1
To right and left and vertical	0.5
Paresis of convergence	0.4
Combination of above	0.25
Disassociation of movements	1.1

Findings, Ophthalmoplegia

	Percent
None	99.5
Internal, right eye	0.1
External, bilateral	0.4

Findings, Pupils

	Percent		*Percent*
Normal	87.2	Argyll Robertson Pupil	0.4
Anisocoria	12.1	Irregular pupils	0.1
Miosis	0.1	Fixed to light and accomm.	0.1

Findings, Fundus

	Percent		*Percent*
Normal	82.0	Papilledema, unilateral	0.0
Optic atrophy, unilateral	7.0	Papilledema, bilateral	0.1
Optic atrophy, bilateral	9.0	Sheathing alone	0.5
Optic neuritis, unilateral	0.9		
Optic neuritis, bilateral	0.4		

Findings, Retrobulbar Neuritis

	Percent
Not present	69.0
Present or suspected, unilateral	8.0
Present or suspected, bilateral	8.0
History suggests previous attack	14.3

Findings, General Muscular Weakness (200 cases)

	Percent
None	45.0
One or both legs	25.0
One or both arms	3.5
One or both sides (hemiparesis)	20.0
Facial muscles alone	4.0
Speech and swallowing alone	0.0
Side or extremity, and face	1.0
Side or extremity, and swallowing	0.5
Face, speech and swallowing	1.0

Findings, Loss of body sensations (200 cases)

	Percent
No loss	20.6
Numbness	6.2
Loss of sense of vibration	24.7
Loss of sense of position	3.6
Combinations of above three	43.3
Transverse myelitis	1.0

Findings, Ataxia, Adiadokokinesis, Paraplegia (200 cases)

	Percent
None	18.5
Ataxia, hand or gait	45.0
Adiadokokinesis	1.0
Above two combined	6.0
Spastic paraplegia	20.5
Spastic paraplegia and adiadokokinesis	4.5
Spastic paraplegia and ataxia	4.0

Findings, Cutaneous and Tendon Reflexes (200 cases)

	Percent
Normal	7.0
Abdominal reduced or absent	8.5
Abdominal and cremasteric reduced	1.5
Babinski present, unilateral	5.5
Babinski present, bilateral	20.0
Babinski present, abdominal absent	57.5

Findings, Oppenheim Reflex (200 cases)

	Percent
Absent or normal	49.0
Present unilateral	8.0
Present bilateral	43.0

Findings, Tremor (200 cases)

	Percent
None	40.4
Intention tremor	44.4
Tremor extremities	11.1
Intention and extremities	3.5
Tremor of head	0.5

Findings, Aphasia; Disturbance of speech and of mind (200 cases)

	Percent
None	64.5
Disturbance of speech, scanning, etc.	14.0
Emotional or mental change	8.5
Disturbance of speech and of mind	5.5
Euphoria	5.5
Mental change and euphoria	0.5
Change in speech and euphoria	0.5
Mental change, dist. of speech, euphoria	1.0

Findings, Laboratory, on Cerebrospinal Fluid (725 cases)

	Percent
Normal	24.4
Increased total protein	11.2
Change in gold sol curve	13.7
Combination of above two	50.3
Increase in cells and protein, change in gold sol curve	0.4

Findings, Serology on Blood

All normal or negative, except one of ++

Findings, Serology of Cerebrospinal Fluid

All normal or negative

What was the first symptom of Multiple Sclerosis?

	Percent
Faulty vision or ocular function	17.9
Muscular weakness, ataxia, etc.	41.9
Muscular weakness of head, speech, swallowing	0.7
Urinary symptoms	2.6
Sensory changes	26.1
Tremor	0.7
Dizziness, fainting	3.8
Pain	5.2
Convulsive seizures	1.1

What was the first ocular symptom in the disease?

	Percent
Never had ocular complaints	38.6
Blurring of vision	38.5
Diplopia	20.7
Visual field defect	1.4
Ocular pain	0.9
Photophobia	0.0

What was the second major symptom of all?

	Percent
Ocular	15.2
Weakness of trunk or extremities; ataxia	38.3
Weakness of muscles of head, speech, swallowing	2.5
Urinary	10.5
Sensory changes	23.6
Tremor	1.8
Dizziness and fainting	2.4
Pain	5.3
Convulsive seizures	0.5

When in the course of the disease did the ocular symptoms occur?

	Percent
Never	38.5
As first symptom of multiple sclerosis	17.9
Early in disease, but not first	24.8
Middle of the disease	15.8
Late in disease	2.8
Occurred, but time unknown	0.4

History of a precipitant of onset of the disease

	Percent
None known	85.5
Trauma	4.8
Infection	1.4
Emotional upset	2.1
Fatigue	0.7
Pregnancy	4.7
Combination of above	0.2
Lumbar puncture or encephalogram	0.0
Exposure to the elements	0.5

OPTIC AND RETROBULBAR NEURITIS: 322 CASES[a]

Age when first registered for ocular treatments

Years	*Males*	*Females*
1–10	1.8	1.3
10–19	10.6	15.9
20–29	18.2	30.5
30–39	25.3	22.5
40–49	18.2	12.6
50–59	14.7	10.6
60–69	8.8	4.6
70–75	2.3	2.0

Sex: Male, 53.0; Female, 47.0.

Place of longest residence

	Percent		*Percent*
Great Lakes area	81.4	Southern United States	2.2
Northeast United States	6.0	Northern Europe	6.0
Northwest United States	0.3	Mediterranean area	0.6
Central United States	3.7		

Color: White, 98.4; Black, 1.6.

Age at onset of first ocular symptoms

Years	*Males*	*Females*
1–10	1.2	3.3
10–19	11.2	15.9
20–29	20.7	29.1
30–39	24.3	22.5
40–49	17.8	11.9
50–59	15.4	10.0
60–69	7.7	4.6
70–75	1.8	2.0

History of previous attack

	Percent
None, or no remission	88.7
1 previous attack, 1 eye	5.3
2 previous attacks, 1 eye	0.6
3 previous attacks, 1 eye	0.9
1 previous attack, both eyes	2.5
2 previous attacks, both eyes	0.6
3 previous attacks, both eyes	1.2

[a]All the listings are in percent of cases unless otherwise noted.

Duration of previous attack in first involved eye

Duration	*Patients*	*Duration*	*Patients*
Unknown	295	1–3 months	3
Less than 1 day	9	3–6 months	0
1–3 days	1	6–12 months	0
3–7 days	2	1–2 years	3
1–4 weeks	9		

Duration of first remission

Duration	*Patients*
No remission indicated on chart	100
1 remission, no relapse known	34
0–6 months	21
6–12 months	13
1–2 years	2
2–4 years	8
4–7 years	2
7–10 years	1
10–20 years	1
Unknown	140

Time that patient has been under medical observation

	Percent		*Percent*
0–6 months	72.7	4–7 years	5.6
6–12 months	5.6	7–10 years	0.9
1–2 years	7.1	10–20 years	1.2
2–4 years	6.8		

Certainty of the diagnosis of Optic or Retrobulbar Neuritis

	Percent
Certain or proved	84.4
Strongly suspected	14.6
Likely, not certain	0.9

Additional important diagnoses

	Percent		*Percent*
None	62.0	Atonic or neurogenic bladder	2.8
Optic atrophy	18.0	Genitourinary infection	2.8
Multiple sclerosis	16.0	Acute sinusitis	2.5
Dental apical infection	8.1	Glaucoma	1.6
Septic tonsils	6.2	Strabismus	1.6
Neuromyelitis optica	5.9	Chronic alcoholism	1.6
Uveitis	5.0		

Additional important diagnoses—Continued

	Percent		Percent
Retinitis and retinopathy	4.7	Metastatic carcinoma	1.6
Prostatitis	4.0	Acute respiratory infection	1.2
Syphilis	3.4	Otitis media	1.2
Hypertension	3.1	Pelvic inflammatory disease	1.2
Arteriosclerosis	3.1	Palsy ocular muscle	1.2
		Pulmonary tuberculosis, etc.	1.2

Symptoms, Blurred vision (one or both eyes)

	Percent
Not noted as a symptom	0.3
Present in one eye	48.4
Present in two eyes	35.0
First in one eye, later both	16.2

Symptoms, Speed at which blurred vision reached peak (213 cases known)

	Percent
1 day	13.1
2 days	10.8
2–4 days	16.4
4–10 days	22.1
10–20 days	8.0
3–6 weeks	11.7
2–4 months	6.1
4–12 months	7.0
Over one year	4.7

Symptoms, Blurred vision, type of blur, first eye

	Percent
General blur	81.0
Central scotoma or blur	13.4
Hemianopic or altitudinal defect	5.4

Symptoms, Ocular pain; Headache

	Percent
None	64.7
Ocular pain on movement	13.1
Ocular pain on pressure	3.1
Ocular pain preceding blur, on movement	5.3
Ocular pain preceding blur, on pressure	0.3
Headache related to eye	8.1
Headache independent of eye	5.3

Symptoms, Associated ocular

	Percent
None	91.9
Diplopia	5.0
Accommodative difficulties	0.3
Photophobia	1.3
Metamorphopsia	0.9
Ptosis	0.6

Findings, Visual acuity at its worst, or in relapse

	Right eye	*Left eye*
20/20 or better	21.3	24.2
20/30	8.3	6.7
20/40	4.5	4.8
20/50	5.7	4.8
20/70	1.3	0.6
20/100	9.2	6.1
20/200	11.5	9.9
20/400	7.3	8.0
less than 20/400	24.5	27.4
Nil	6.4	7.3

Findings, Visual acuity at its best, or in remission

	Right eye	*Left eye*
20/20 or better	44.5	39.0
20/30	13.4	15.9
20/40	4.9	7.9
20/50	6.1	3.7
20/70	0.6	1.2
20/100	9.1	8.5
20/200	5.5	6.7
20/400	3.0	3.0
less than 20/400	9.8	11.0
Nil	2.4	3.0

Findings, Visual field changes

	Percent
Absent or normal	4.2
Hemianopic defect, 1 eye	2.5
Hemianopic defect, both eyes	2.5
Scotoma, central, 1 eye	29.7
Scotoma, central, both eyes	34.3
Scotoma, paracentral, 1 eye	1.1
Scotoma, paracentral, both eyes	1.9
Peripheral defect and scotoma, 1 eye	16.0
Peripheral defect and scotoma, both eyes	7.8
Combinations of above	0.4

Findings, Pupillary changes

	Percent
None or normal	81.4
Fixed	4.1
Reactions present but limited	6.3
Anisocoria	3.2
Reactions those of a blind eye	5.0

Findings, Fundus

	Right eye	Left eye
Normal	64.3	64.6
Optic atrophy	8.1	9.6
Optic neuritis	19.0	19.3
Papilledema	0.3	0.0
Sheathing alone	0.3	0.0
Optic neuritis followed by atrophy	1.9	2.5
Neuroretinitis	4.3	2.2
Arteriosclerosis	1.9	1.9

Defects residual after first or early attacks

	Percent
None	19.6
Reduced vision right eye	17.3
Reduced vision left eye	18.5
Reduced vision both eyes	43.5
Field defect with normal vision	1.2

Findings, Blood serology

	Percent
All normal except 13, 4 being + 2 being +++ 7 being ++++	4.2

Findings, Serology of cerebrospinal fluid (148 cases)

All normal except 4, or 2.7%, 1 being +, and 3 being ++++

Findings, Cerebrospinal fluid changes

	Percent
Normal	58.5
Increase in total protein	15.0
Increased protein and cells	0.7
Change in gold sol curve	8.2
Increased protein and change in gold sol curve	17.7

Etiology, Local inflammation; tumor

	Percent
None	88.8
Uveitis and retinitis	5.4
Sympathetic ophthalmia	0.0
Meningitis	1.0
Orbital infection	1.6
Arachnoiditis	1.3
Brain tumor	1.3
Malignancy of orbit, skull	0.6

Etiology, General inflammatory and infectious

	Percent
None	65.3
Multiple Sclerosis	20.2
Encephalomyelitis	0.0
Neuromyelitis Optica	7.2
Encephalitis periaxialis	0.0
Herpes Zoster	0.0
(Epidemic) Encephalitis	0.4
Poliomyelitis	0.0
Tuberculosis	2.2
Syphilis	4.7

Etiology, Focal Infection

	Percent
None	58.5
Teeth	17.1
Tonsils	11.5
Prostate	4.1
Female pelvis	1.8
Gall bladder	0.5
Kidney or bladder	2.3
Ear and mastoid	0.9
Two or more of above	3.2

Etiology, Exogenous Toxin

	Percent
None	89.7
Tobacco	3.8
Alcohol, ethyl	4.5
Tobacco and alcohol	1.3
Arsenic	0.6

Etiology, Sinusitis:

	Percent
None	93.5
Maxillary	0.8
Ethmoid	0.8
Sphenoid	0.8
Combination or pan.	4.2

Etiology, Leber's Disease:
None

Etiology, Endogenous Toxins; Infection

	Percent
None	93.6
Influenza	0.4
Measles	0.4
Genitourinary infection	5.2
Typhoid	0.4

Etiology, Metabolic:

	Percent
None	84.6
Diabetes	1.1
Anemia	2.1
Avitaminosis	1.1
Pregnancy	1.1
Arteriosclerosis	4.2
Peripheral vascular disease	0.5
Nephritis	1.1
Hypertension	3.7
Hyperthyroidism	0.5

Course of the disease

	Percent
Seen only during one attack	52.2
One remission	34.4
One remission and relapse	3.4
Two recurrences	3.1
Three to five recurrences	1.2
Death	5.0

Treatment, Vasodilatators

	Percent
None	26.0
Typhoid intravenous	10.9
Oral nitrates	0.6
Intravenous nitrates	11.6
Vitamins and vasodilatators	27.0
Tuberculin	0.6
Other combinations	3.9

Treatment, Surgery

	Percent
None	80.8
On sinuses	2.9
Teeth	8.1
Prostate	0.6
Pelvis	0.3
Tonsils	5.8
On other foci	1.0
On brain tumor	1.0

Treatment, Other

	Percent
None	88.3
Antiluetic	3.9
For hypertension	1.8
Medical, prostatitis	3.2
Irradiation, malignancy	1.4
Penicillin	0.4
Arsenic, Quinine	1.1

Results of Treatment

	Percent
None apparent, or known	31.9
Improved	55.0
No change	3.1
Condition of eyes worse	2.6
Death	7.0

Evidence that the Optic or Retrobulbar Neuritis was due to Multiple Sclerosis or other demyelinating disease

	Percent
None	69.5
Slight, doubtful	4.8
Some, possible	7.4
Considerable, likely	4.8
Quite certain	13.5

Evidence that the Retrobulbar Neuritis was due to accessory sinus disease

	Percent
None	94.0
Slight, doubtful	1.7
Some, possible	1.7
Considerable, likely	0.3
Quite certain	2.3

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