Observations

ON

THE AETIOLOGY AND SYMPTOMATOLOGY
OF DISSEMINATED SCLEROSIS*

BY

W. J. ADIE, M.D., F.R.C.P.

PHYSICIAN, CHARING CROSS HOSPITAL; PHYSICIAN FOR OUT-PATIENTS,
NATIONAL HOSPITAL FOR NERVOUS DISEASES

Those who open discussions such as this are expected to review the past history of their subject, to give an account of the present state of our knowledge, and to indicate the lines along which advances may be made. On this occasion, however, such an introduction may be omitted, as the subject of disseminated sclerosis in all its aspects has recently been discussed by Russell Brain¹ in an admirable review. For the purposes of this contribution two groups of cases have been studied: seventy cases of acute retrobulbar neuritis seen at the Royal London Ophthalmic Hospital and 118 cases of established disseminated sclerosis seen elsewhere. The numbers are small, but their value, compared with that of larger series made up of cases collected from the literature, is increased by the fact that the patients were examined in circumstances allowing for a full investigation on a uniform plan. The results will be discussed in the order adopted by Russell Brain; where comparisons are made with the findings of others his review is the main source of my information.

AETIOLOGICAL FACTORS

The statement attributed to Guillain that disseminated sclerosis is, after syphilis, the most frequent disease of the nervous system, will be affirmed by all neurologists in this country. Indeed, most of them would go further and say that, though syphilis still holds the lead in hospital practice, in private practice disseminated sclerosis is by far the more frequent. Statistics compiled in the United States and in Switzerland show a preponderance in urban dwellers. A study of the occupations of the patients forming this series provides no evidence for the recorded beliefs that agriculturists, woodworkers, ironworkers, or persons whose work brings them in contact with water, are particularly susceptible. Although it is now recognized that many of the reported cases of hereditary and familial disseminated sclerosis were examples of other disorders, it is certain that genuine familial cases do occur. There is one example in this series—two young sisters whose characteristic history and present condition leave little room for doubt about the diagnosis.

It is usually stated that males are more often affected than females in a proportion of 3 to 2; in this series 58 per cent. were females. This agrees with Bing's and Reese's figures (281 cases) for North Switzerland, but is a complete reversal of the proportions given by Wechsler and several others, based on very large numbers of collected cases. Fresh statistics on this point and on other differences in the manifestations of the disease in different countries would provide interesting and, possibly, important information. Much attention has been given to various alleged precipitating factors, but no general agreement has been reached, nor have numerous attempts to isolate a specific organism or to transmit the disease experimentally had any success. Despite much labour, even the pathological nature of the lesions is still in doubt. Of the "cause" of the disease nothing is known. Of its clinical manifestations, however, our knowledge has increased rapidly, and is still increasing. Thirty years ago

the disease was characterized by nystagmus, intention tremor, and scanning speech; now it is one in which all of these signs are commonly absent, but almost any conceivable sign or symptom of interference with the functions of any part of the central nervous system may occur.

ONSET AND EARLY SYMPTOMS

According to Russell Brain the modern tendency has been to emphasize the frequency of an insidious onset. Souques, for example, found that it was insidious or slow in 73 per cent. of the cases. Many of us, if we were asked to express an opinion, would say that the onset was almost always sudden. As so frequently happens when experienced observers seem to differ in discussions, the discrepancy is due to failure of the disputants to define the terms they use. If the onset of the disease is the appearance of the first symptom, then it is always sudden. But if onset refers to the time when the disease has become firmly established, then the onset is almost always slow.

Guillain gave paraesthesiae, transitory ocular troubles, and fatigability of gait as the earliest symptoms. Bohmig gives the following order of frequency for the incidence of the earliest symptoms: disturbances of gait, paraesthesiae, sphincter disturbances, giddiness, diplopia, pain and weakness in the back, disturbances of speech, abnormalities in the upper extremities, and facial weakness. In view of what will be said later about the frequency of acute retrobulbar neuritis as the first manifestation, it is remarkable that amblyopia is not mentioned in this table.

As patients often use the expression "numbness" and "dead feelings" to refer to troubles that are purely motor, or say that a limb is weak, useless, or paralysed when the defects are sensory in origin, no attempt has been made here to distinguish between the causes of historical disabilities in the limbs. Where a monosymptomatic onset was clearly remembered the order of frequency of incidence of the first symptom was: transitory ocular troubles (amblyopia, diplopia, etc.), 40 per cent.; transitory or variable motor or sensory disturbances in one or both lower limbs (weakness, unsteadiness, abnormal sensations), 30 per cent.; the same in one or both upper limbs (uselessness, weakness, abnormal sensations), 6 per cent.; the same in homolateral leg and arm, 5 per cent.; severe attacks of vertigo (with or without repeated vomiting), 4 per cent.; numbness of one-half of the face, 3 per cent. The reason for the high incidence of visual troubles in this list will be discussed later. Bias due to special circumstances has been eliminated by the exclusion of all cases referred by ophthalmic surgeons.

All writers emphasize the importance for diagnosis of a history of relapses or remissions. The course was discontinuous in every case in this series. This suggests that a steadily progressive course is rare. Defective memory on the part of the patients or the omission of questions designed to revive it or to elicit a history of one or more of the numerous characteristic early symptoms—perhaps well remembered by the patient, but thought by him to have no bearing on his present troubles—account for most of the alleged steadily progressive cases.

AGE OF ONSET

The following table gives the age of onset (appearance of the first symptom) in decades in 107 cases in which the evidence appeared to be trustworthy.

Age at Onset	11-20	21-30	31-40	41-50	51-60
Percentage of total	10.3	45.8	28.7	15.9	1.1

It will be seen that the age of onset is in the third or fourth decade in 74.5 per cent. of the cases.

* Read in opening a discussion in the Section of Neurology at the Centenary Meeting of the British Medical Association, London, 1932.

The earliest age at onset was 12 years. This patient (a girl), now an advanced case, was taken to an ophthalmologist at the age of 12 with sudden loss of the sight of one eye; the diagnosis was optic neuritis, and vision was restored in a few weeks. Of another female patient, now 30 years old, the mother relates that at the age of 13 the child had to stay away from school for six months because she dragged one leg, and when it recovered the arm went wrong. A careful scrutiny of the notes on nine cases with onset after 45 suggests that some of them should have been excluded from the table. The rule that the first symptom of disseminated sclerosis rarely appears after the age of 45 is still a good one. Disseminated sclerosis in the aged will be discussed by Dr. Ferguson. He will probably find that it is diagnosed too often.

DURATION OF DISEASE AND REMISSIONS

The duration of the disease is said to range from a few months to twenty or thirty years. Of Wechsler's 192 patients only 5 per cent. gave a history of more than five years. Byrom Bramwell found the average duration in thirty-six fatal cases to be seven years and nine months. When the significance of acute retrobulbar neuritis and other characteristic early symptoms is better known a lower figure will be given for the average age at onset and a higher figure for the average duration of the disease. Very long remissions, up to twenty years and more, are not uncommon when acute retrobulbar neuritis is the first symptom, but remissions approaching these in length are not common after other modes of onset. The longest remission in this series, if the history is trustworthy, was thirty-two years. An intelligent woman, now aged 56, with a typical recent history of three years' duration and characteristic physical signs, states that she had "an attack of the same thing" at the age of 21. The legs and one arm went numb; she walked unsteadily and dragged one leg. She recovered completely in three months, and remained well until the age of 53, when the legs became weak again.

SOME UNCOMMON SYMPTOMS

Many writers have published figures giving the frequency of incidence of different symptoms. Russell Brain reproduces four tables in his review. Agreement cannot be expected, for example, on the incidence of mental changes, pallor of the disks, nystagmus, or intention tremor where so much depends on personal interpretation. In one series position loss was found in 65 per cent., in another series in 17 per cent., in another it is not mentioned. No attempt has been made to analyse my cases on these lines, but reference will be made to some of the less common symptoms. Most neurologists have seen convulsive and apoplectiform onsets. One of my patients with Jacksonian attacks in one arm and gross loss of postural sense in the intervals narrowly missed an operation for cerebral tumour.

Brain considers that the vestibular and vestibulopyramidal forms described by French authors are rare, and that undue weight has been given by them to vestibular as opposed to cerebellar disturbances as factors in the production of symptoms. However this may be, acute attacks of vertigo are not uncommon, and they should be better known, as their nature is rarely suspected. Since an inquiry for these attacks has formed part of a routine interrogation of patients in whom the presence of disseminated sclerosis was suspected, a history of them has frequently been obtained. Sometimes vertigo is the only symptom; repeated vomiting is not uncommon. Sometimes it is accompanied by pain or numbness in the corresponding side of the face or tongue, or by motor or sensory disturbances in the limbs. An attack of true

vertigo in a young adult free from ear disease should suggest the presence of disseminated sclerosis.

Of the many abnormal sensations that patients describe a few will be chosen for special mention. Numbness on one side of the face that passes off in a few days or weeks is not very uncommon; in several of my cases it was an initial symptom, which preceded the appearance of others by as much as five years. It is well known that trigeminal pain exactly like that of *tic douloureux* may occur. In two cases (Oppenheim, Parker) a plaque was found in the pons at the point of entry of the trigeminal nerve. The neuralgia is not accompanied by objective sensory signs. It can be abolished by alcohol injections (Harris). Russell Brain has seen a case in which "electric shocks" radiated through the body when the patient flexed the cervical spine; he reports two similar cases. One of my patients said: "I get an electric shock when I bend my neck forward." Another said: "When I bend forward I get a tingling down the legs. I can bring it on at any time by bending my neck." Still another made similar complaints; and another complained of pain in the neck and up the back of the head on moving the head quickly, and on swallowing. This minor sign is worthy of attention, as it is an addition to the list of the signs that are common to disseminated sclerosis and spinal tumour. At this point it is perhaps worth mentioning that a patient with a history of retrobulbar neuritis and diplopia, who now presents signs of spastic paraplegia, feels severe pain in the distribution of the first lumbar root when he coughs. Beyond mention of severe loss of vibration sense in the lower limbs in patients with little or no impairment of other forms of sensation, no further reference will be made here to objective sensory disturbances.

For the guidance of those who wish to assess the value of new treatments a valuable contribution to this discussion might be made by one who would describe in some detail the remarkable variations in symptoms and signs that occur spontaneously. It would be seen that complete long-standing functional recovery from the severest manifestations occurs, that all physical signs—including extensor plantar responses—may disappear, and that all the subjective and objective improvements that have been recorded as evidence of the efficacy of special treatment are common in the natural course of the disease.

OCULAR SYMPTOMS

To many the word nystagmus at once suggests disseminated sclerosis. Its incidence in this disease is high, but the figures given by different observers vary greatly for obvious reasons. It is necessary for neurologists to reiterate that nystagmus is not always a sign of disease of the nervous system, that its value for the differential diagnosis of organic nervous diseases is limited, that it is frequently absent in disseminated sclerosis—especially in the early stages—and that it is sometimes present in a curable condition which is sometimes mistaken for disseminated sclerosis—namely, spinal tumour. Paresis of an ocular muscle sufficient to cause diplopia is very common, but a squint or a defect so gross that it can be detected by rough tests is very rare. As a working rule it may be said that a persisting gross ocular palsy in a patient otherwise free from symptoms is not due to disseminated sclerosis. Transient diplopia is a common initial symptom; it may precede all signs and other symptoms by many years. It is surprising how frequently it is forgotten. As a history of genuine diplopia in the past often decides the diagnosis, the leading question should be deferred as long as possible, and care must be exercised before an affirmative statement is accepted, as inquiry often reveals that blurring of print, for example, is what

the patient is referring to. It is advisable to insist on a detailed description of some specific incident. From the statements made a judgement as to credibility can usually be made with certainty.

Alterations in the pupils apart from the transient effects of severe acute retrobulbar neuritis are very rare. The presence of grossly defective pupillary reactions should cause doubt about the diagnosis. The Argyll Robertson phenomenon, if it ever occurs, must be extremely rare. Lesions in the optic nerves, chiasma, and tracts are very common; but permanent blindness, or even permanent severe loss of vision, is rare. Visual failure may come on insidiously, and pathological pallor of the disks is often found in patients who make no corresponding complaints. Mild transitory attacks of amblyopia are common. In a proportion of cases that is probably much higher than is recognized at present more severe attacks of amblyopia occur early, in which the symptoms are those of acute retrobulbar neuritis.

ACUTE RETROBULBAR NEURITIS

In the 118 cases analysed here a clear history of a severe attack of acute retrobulbar neuritis was obtained in forty-one. In arriving at this figure no account has been taken of a history of "misty vision" where no decisive details could be given. In order to obtain a true idea of the frequency of acute retrobulbar neuritis in disseminated sclerosis all the cases that were referred for defective vision or were in any sense picked cases were eliminated. There then remained eighty patients who came complaining of extraocular symptoms; twenty-nine of these described an attack of acute retrobulbar neuritis in the past; in twenty of these it was the first symptom, or rather the first symptom the patient could remember; and in every instance it was an early symptom—that is, it always appeared during the stage of the disease characterized by premonitory symptoms and remissions. It seems, therefore, as if an attack of acute retrobulbar neuritis rarely occurs after the disease is firmly established. Further evidence on this point would be welcome.

It is well known that an attack of retrobulbar neuritis may precede other symptoms of disseminated sclerosis by many years. In six cases followed up by Fleischer the intervals varied from four to fourteen years. In my cases the intervals varied from a few weeks or months up to 10, 14, 19, 20, and 24 years. The average interval was 6.8 years. An obvious fallacy here is that patients recall so memorable an event as blindness of an eye more readily than other symptoms. While these notes were being written a patient made a second visit after an interval of eight years. At the first interview she gave a history of transient numbness of one limb followed in six months by blindness of one eye. At the second visit she stated confidently that her first symptom was visual, and held to this statement until she was confronted by the earlier note. As with diplopia, so with retrobulbar neuritis, failure to mention it is common, even when the importance of the general questions regarding past visual troubles is emphasized; and often no account of it is obtained until the leading question is put, when a description of a severe attack is obtained so circumstantial as to leave no room for doubt as to its nature. In three cases the patients themselves had no knowledge of attacks that had occurred in the early teens; information was obtained from the parents. It is because *ad hoc* inquiries were made in every case that the incidence of acute retrobulbar neuritis recorded here is higher than that usually given.

In many cases, as we shall see later, definite physical signs are already present when a patient free from other

subjective symptoms comes to us for failure of vision in one eye. It is certain, however, that retrobulbar neuritis may be not only the first symptom but also the first manifestation of the disease. A man had a definite attack of retrobulbar neuritis at the age of 21. He was perfectly well until the age of 35, when he had transient diplopia; at this time he was examined by a neurologist who told him he could find no signs of organic disease (the history of the earlier visual trouble was not elicited). At the age of 37 he had difficulty in walking, and examination revealed characteristic signs of disseminated sclerosis. Many similar histories might be given. Fleischer's cases already referred to establish the same point.

It was a surprise on going over the notes of my cases to find that simultaneous affection of both eyes was not recorded once, and that distinct acute attacks in sequence within a month are mentioned only once. In three cases several years (in one case fifteen) elapsed between a first and second attack in the same or the other eye. As a point worthy of discussion it is suggested that simultaneous or early consecutive attacks are very rare, and that their occurrence should suggest some other form of inflammation of the optic nerves such as disseminated encephalomyelitis.

The main purpose of this communication is to keep alive the discussion that has been proceeding spasmodically for forty years or more on the relation of acute retrobulbar neuritis in general to disseminated sclerosis. Reference to standard textbooks will show that further discussion is necessary. In two textbooks of neurology published during the last six years accurate clinical accounts of acute retrobulbar neuritis or "acute axial neuritis" are followed by a long list of causes, but disseminated sclerosis is not among them, and in the accounts of disseminated sclerosis acute retrobulbar neuritis is not named as one of its symptoms. The condition of informed ophthalmological opinion is given in the statement that

"multiple sclerosis is accepted by all ophthalmic surgeons as a common cause of retrobulbar neuritis, but its incidence is estimated as widely as from about 20 per cent. to about 80 per cent." (Traquair²).

Characteristics of Retrobulbar Neuritis

Estimates will vary so long as those who make them are thinking about different things. At present the name retrobulbar neuritis is used indiscriminately when reference is being made to a number of manifestations—usually distinguishable clinically—of the effects of various unrelated pathological processes, the only common feature being that the signs indicate a lesion of the optic nerves. For our present purpose the term will be reserved for cases characterized by (1) acute onset, (2) unilateral incidence, (3) "central" scotoma, and (4) tendency to recovery. We shall do well to confine our attention to the cases that present these distinguishing features. After agreement has been reached on their nature we may safely begin to consider whether other cases should be included in the same category.

Some pain is almost always present at the onset, at rest, on voluntary movement, or on pressure of the eyeball. Visual failure is rapid rather than sudden, and usually reaches its maximum in a few hours or at most in a day or two. Vision is often reduced to a perception of hand movements or even less. The visual defect is always most intense in the central area of the field, but peripheral parts are frequently affected as well. Recovery usually begins within a week or two, and by the end of six weeks or two months is often considered by the patient to be complete, when examination with a small coloured object may reveal a residual defect. It is often

stated that visible changes at the disk in the acute stage are rare. In seventy cases referred to here definite changes were noted by the surgeon in twenty-one. In most instances the report was: disk blurred, distinctly blurred, pinker and less distinct, cloudy, or slight swelling; in two cases the disk was described as swollen and oedematous, and in three the terms used were papillitis or optic neuritis. The incidence of slight changes is probably higher than these figures indicate, as special attention has not been paid to this point in my records. Certainly the observer should be prepared to meet them frequently. Intense swelling, the typical choked disk, if it occurs at all, is very rare in the unilateral type. It is a common feature in bilateral cases. It is suggested that intense swelling in one or both eyes or bilateral incidence of even mild visible changes with severe visual failure indicates a different aetiology.

Frequency of Retrobulbar Neuritis in Disseminated Sclerosis

Discussion is invited on this point and particularly on the following statements: (1) Disseminated sclerosis is the only known common cause of acute unilateral retrobulbar neuritis as here defined. (2) Apart from certain rare allied acute inflammatory diseases of the nervous system it is the only cause. These statements cannot be proved or disproved; but if they are accepted as approximating to the truth much will be gained. Clear ideas can then be substituted for the muddled mental state that must exist so long as the incidence of disseminated sclerosis as the cause is variously estimated as "from about 20 per cent. to about 80 per cent.," and we may at last begin to hear less of hypothetical sinus disease and dental or tonsillar sepsis as possible causes. Nothing more can be offered here in support of these statements than evidence that disposes at once of the lower estimate (20 per cent.), but is for the rest indirect. Seventy cases of acute retrobulbar neuritis were examined within a week or two of onset. In 31.3 per cent. the patients were already suffering from disseminated sclerosis; in 41.8 per cent. the diagnosis "probably disseminated sclerosis" was made; in the remaining 26.8 per cent. there were no other suspicious symptoms and no definite organic signs.

Where so much depends on intimate knowledge of the numerous early symptoms and on personal interpretations of physical signs, agreement by different observers on the number of cases that fall into these groups cannot be expected. My own opinion is that conclusive historical or physical evidence of the presence of disseminated sclerosis can be obtained in over 30 per cent. of cases of unilateral retrobulbar neuritis in the acute stage, and that the diagnosis can be made with a close approach to certainty in about 50 per cent. What is the fate of the cases in which the cause is uncertain? The answer could be given if we were able to keep in touch with our patients sufficiently long, but this is hardly possible, because, as we have seen, ten, twenty, or more years may pass before other signs or symptoms appear. Fleischer followed up some of his cases and found that 66 per cent. of them developed disseminated sclerosis. Further than this direct evidence does not take us at present.

Significant indirect evidence is obtained by comparing the age of onset and sex incidence in acute uncomplicated cases and in cases of patients with established disseminated sclerosis who give a history of an acute attack of visual failure in one eye as their first symptom. In the first group in 85.8 per cent. and in the second in 86.9 per cent. the acute attack occurred between the ages 21 and 40; in the majority in both groups, between 21 and 30. The average age of onset in

Traquair's 139 cases of "acute unilateral type" was thirty-two years. Misgivings about the value of these figures arising from a consideration of the proportion of the population living at these ages may be set at rest by a comparison of the sex incidence in the groups just named. The facts may be set forth as follows: acute unilateral retrobulbar neuritis, uncomplicated, 64.7 per cent. females; history of unilateral retrobulbar neuritis as first symptom in patients with disseminated sclerosis, 63.7 per cent. females; all cases of established disseminated sclerosis, 58 per cent. females.

Traquair found that 65 per cent. of his cases of the "acute unilateral type" of retrobulbar neuritis were females. This agreement in age at onset and sex preponderance in females in the two groups is remarkable, and it is suggested that it indicates a common cause. As 65 per cent. of the patients with established disseminated sclerosis who gave a history of acute retrobulbar neuritis at any stage in the course of the disease were females, another conclusion seems to be justified—namely, that females are more susceptible to it than males, and that in them it is more often the first manifestation of the disease. It is to be hoped that the ensuing discussion will lead to some advance in our knowledge of the aetiology of acute retrobulbar neuritis; the subject is one wherein the profession is in great need of guidance.

REFERENCES

- ¹ Brain, W. Russell: *Quart. Journ. Med.*, 1930, xci, 343.
- ² Traquair, H. N.: *Trans. Oph. Soc. United Kingdom*, 1930, 1, 351.

ADAMANTINOMA OF THE TIBIA: AETIOLOGY AND PATHOGENESIS*

BY

B. J. RYRIE, M.B., CH.B.

PROFESSOR OF PATHOLOGY, UNIVERSITY OF CAPE TOWN

(With Special Plate)

Extra-alveolar adamantinomata have been infrequently reported. Those occurring at the base of the skull and in relation to the pituitary gland are well recognized, and their origin is satisfactorily explained on embryological grounds.¹ So far as I know the only other extra-alveolar adamantinomata are the very infrequently described adamantinomata of the tibia. Besides the case to be described I know of only two recorded cases—that of Fischer² and that of Baker and Hawksley.³

These cases of adamantinoma of tibia are so similar as to indicate that we are dealing with a rather clear-cut, if rare, clinical and pathological entity. In each case there is a history of trauma; in each case the trauma is slight so far as surface injury is concerned; in each case this trauma is followed by a tumour after a latent period; in the two recent cases at least there is evidence suggesting that during the latent period some local lesion persisted; in each case the tumour is one of the bone and periosteum and not of the soft parts. The histology of the tumour is the same in all cases, being that of certain types of adamantinoma, basal-celled carcinoma, or rodent ulcer, a structure which possibly justifies the diagnosis of adamantinoma. To this list of similarities one may add the tendency to local recurrence. While the interest of these cases lies partly in their clinical significance and their morphological diagnosis, their chief interest to the pathologist lies in the realm of aetiology and pathogenesis, and in the hope that the study of a rare lesion may throw light on wider problems.

* Paper read in the Section of Pathology at the Centenary Meeting of the British Medical Association, London, 1932.