

MULTIPLE SCLEROSIS

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Preface

MULTIPLE, or disseminated, sclerosis ranks high among organic nervous diseases affecting the white races. In the northerly parts of Great Britain at least one adult in every thirteen hundred is affected by it. Although its symptomatology and morbid anatomy are well known from classical writings we are still ignorant of its causation, and treatment remains largely empirical. Yet progress has been made in recent years and some new facts brought to light.

This volume, largely based on our own experience of the disease, is published in the hope that it will be of value not only to the physician and general practitioner, but may also encourage further work in this difficult field of research. Written in collaboration with a general physician and a pathologist, it has three main objects: first to widen the general conception of the disease; secondly to provide an account of early symptomatology and treatment; and thirdly to review the pathology and the relationship of multiple sclerosis to other demyelinating diseases.

In the "Standard Nomenclature of Diseases and Operations," the "Quarterly Cumulative Index Medicus," and the "Current List of Medical Literature," the term "multiple" is preferred to "disseminated" in referring to this disease. This is the principal reason for our use of the former adjective. (See also Chapter XII, p. 208).

A series of 1,072 cases of multiple sclerosis seen in the Department for Nervous Diseases of the Middlesex Hospital between 1930 and 1952 provided the clinical material for this book. Particular aspects of the disease were studied in smaller groups of patients, for example, the natural history in 250 consecutive cases, clinical features in 666, and so on.

Chapters II, III, IV, and IX, based on a previous study of the natural history of the disease, refer to geographical and familial incidence, precipitating and aggravating factors, and to the course of the disease. In Chapters V to VII early symptoms are described with the help of case reports. The chapter on the cerebrospinal fluid includes our own findings as well as references to recent work in this field, including the results of electrophoresis.

The early diagnosis of multiple sclerosis must still rest on the clinical findings, for no specific test has so far been devised. The more important of these are reviewed, together with differential

déjà les lésions sont très profondes, et partant peu accessibles à l'influence des moyens curatifs."

The first book on multiple sclerosis was published in 1869 by two of Charcot's pupils, Bourneville and Guérard. Before the close of the century invaluable contributions had been made. Oppenheim (1887, 1889) described sensory symptoms; Strümpel (1896) noted the disappearance of abdominal reflexes; and Uhthoff, the ophthalmologist, concerned himself with ocular symptoms and signs.

Notable among studies in pathology was that of Ribbert (1882), the first to suggest that thrombosis secondary to an infection in the blood stream was the primary lesion. Further support to the infective theory came from clinicians. Pierre Marie (1884) emphasised the relationship of multiple sclerosis to infectious diseases, especially enteric fever. He considered that the lesions of multiple sclerosis might be caused by ordinary pathogenic organisms.

In 1873 Moxon, physician at Guy's Hospital, described, for the first time in the United Kingdom, a single case of the disease under the title, "Case of insular sclerosis of the brain and spinal cord." Two years later he published in *Guy's Hospital Reports* an account of eight cases, all well documented.

The intense interest which this disease had aroused in the minds of clinicians and pathologists alike, particularly in Germany and France, is well reflected in the monograph of Eduard Müller of Breslau. Published in 1904 under the title, "Die multiple Sklerose des Gehirns und Rückenmarks," the monograph is remarkable for width of outlook and for the bibliography of more than 1,100 references.

During the first half of the present century interest in multiple sclerosis has fluctuated owing to interruption of its scientific study by two world wars. Notable contributions to the pathology of the disease were made by Siemerling and Raecke (1911) and by Dawson of Edinburgh (1916). The subject was well reviewed by Risien Russell in 1911 and Wohlwill in 1913. Wohlwill and Dawson concluded that the essential cause of the disease was an exogenous toxin. This had an important effect in counteracting Müller's (1904) suggestion that the cause was glial hypertrophy due to a congenital anomaly, although he considered that sometimes an acute infection of the nervous system precipitated the disease.

Between 1913 and 1921 the possibility of an infective cause led a number of workers to attempt the transmission of the disease to animals. Notable amongst these contributions were those of Bullock (1913), Bullock (now Gye) (1921), Marinesco (1919), Kuhn and Steiner (1917), Birley and Dudgeon (1921), and Adams, Blacklock, and McCluskie (1924). The results of these experiments were either negative or inconclusive (see Chapter XIII). Meanwhile the scope of

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CHAPTER VI

Early Symptomatology—continued

RETROBULBAR NEURITIS

FOR reasons still unknown the optic nerves and chiasma are particularly vulnerable in the demyelinating diseases. Early literature on multiple sclerosis shows that loss of vision was recognised as a symptom. Parinaud, in 1884, working in Charcot's clinic at the Salpêtrière, described three forms of amblyopia in multiple sclerosis: (1) Gradual impairment of vision, especially for colour, affecting both eyes; (2) rapid loss, sometimes with temporary blindness of both eyes, but with good recovery; (3) a rare form in which vision was lost unilaterally. (The fact that the order in which he placed the varying forms of visual failure must now be reversed to correspond with their actual incidence is doubtless due to the small number of cases on which his observations were made.) He contrasted the pale disc and relatively good vision of multiple sclerosis with the optic atrophy and blindness of tabes.

In the same year Gnauck found evidence of retrobulbar neuritis in twenty-eight out of fifty cases of multiple sclerosis. He recognised the diagnostic importance of this incident and its frequent initial appearance. Uthtoff, to whom credit is usually given for this observation, did not publish his findings until 1889; out of 100 cases of multiple sclerosis he found forty instances of optic atrophy and five of optic neuritis.

Varying diagnostic criteria for retrobulbar neuritis on the one hand and for multiple sclerosis on the other, and the long interval which may occur between the initial attack of retrobulbar neuritis and the appearance of subsequent manifestations of the disease, seem to account for diverse opinion as to the frequency of an optic nerve lesion in this disease.

Some authorities make a diagnosis of retrobulbar neuritis if there is definite failure of vision lasting at least a few days; others accept as significant a milder impairment amounting to a blurring of vision only. A parallel exists in the interpretation of sensory symptoms in this disease. As it seems reasonable to accept the import of mild and transitory paræsthesiæ, so we are obliged to take notice of the mild fleeting attack of retrobulbar neuritis. Only in this way is it possible to account for temporal pallor in patients who cannot recall any

(c) *Emotional shock.*

(d) *Allergy.*—A history of a recently acquired allergic disorder.

4. Factors temporarily aggravating Symptoms.—A history of short-lived exacerbations of symptoms, particularly blurring of vision and paræsthesiæ brought on by such factors as emotion, exertion, a hot bath, or smoking, should suggest multiple sclerosis, provided the history and findings are compatible with that diagnosis. Such factors appear to affect the patient with multiple sclerosis more readily than those with other types of organic nervous disorder.

The Use of the Term “Multiple Sclerosis (Suspect).”—If a person between the ages of 10 and 50 gives a history suggestive of multiple sclerosis but by no means conclusive, if physical signs are minimal, equivocal, or absent, and if adequate steps, including the examination of the cerebrospinal fluid, exclude other possibilities, a diagnosis of “multiple sclerosis (suspect)” should be made. Under these circumstances the patient should be asked to return for a routine examination at regular intervals and to report at once should fresh symptoms appear.

The provisional diagnosis “multiple sclerosis (suspect)” must not, in the first instance, be made in a case of progressive paraplegia with signs limited to the spinal cord.

RETROBULBAR NEURITIS

Although this condition has such an intimate and characteristic relationship to demyelinating disease in general and to multiple sclerosis in particular, rare causes of rapid loss of vision attended by defects in central vision must not be forgotten. The swelling of the optic disc (papillitis) occasionally met with in multiple sclerosis is usually unilateral, and confusion with papilloedema is unlikely if due importance is attached to the accompanying rapid loss of vision in retrobulbar neuritis. When this is due to severe states of malnutrition, toxic agents (including insecticides: Campbell, 1952), or pernicious anæmia, pain in the eye is as a rule absent, the onset is seldom sudden, and loss of central vision is usually bilateral and progressive. Nevertheless occasionally abrupt failure of vision may occur in these conditions. The cause is not likely to become clear until a full history has been taken and the results of examination of the blood and gastric contents have been made available.

In young persons exudative choroiditis may cause rapid failure of central vision due either to involvement of the macula directly or to spreading oedema; clouding of the vitreous by inflammatory exudate may be a complication. Similarly a central serous retinopathy characterised by oedema without inflammation may cause objects to

strongly suggests that mechanical factors (*i.e.*, stress lines) determine the pathways of extension which undoubtedly seem to conform to some sort of pattern.

Colour and Texture of Plaques.—The oldest plaques are grey, glassy, slightly shrunken, and firm and rubbery to the finger-tip. They are never friable and when cut on the freezing microtome are almost perfectly transparent in the usual 15- μ sections. The most sclerotic plaques present an extraordinary resistance to the scalpel compared with normal tissue, tending to cut, like rubber, with a furrowed surface.

More recent plaques, which are small and spherical or oval with regular contours, are greyish pink; and though the sharply demarcated contours are still discernible no difference between the physical consistency of the plaque and the surrounding tissue can usually be detected. Such plaques are not only difficult to photograph because of their lack of colour distinction but are also easily overlooked since their colour and texture are almost the same as normal white matter; on oblique illumination, however, they can be detected as matt areas. Such lesions measure only a few millimetres in diameter and are usually circular. Sometimes they present a distinct concentric ring structure (Plate 10, B), if examined in a good light, which recalls Baló's concentric sclerosis in miniature. Many cases in a series will show few early lesions of this type, but on the other hand they may be quite numerous.

Symmetry.—Despite the apparently haphazard distribution of plaques throughout the cerebrum, brain-stem, and cerebellum, there is undoubtedly some tendency to symmetry. Confluent plaques, or the diffuse types of demyelination in the subependymal zones of the lateral ventricles, are almost invariably bilateral, and are often nearly symmetrical (Plates 3, 4, B), constituting a very characteristic feature of the disease. In one case, from which the photograph in Plate 8, A was made, there was a narrow band of demyelination and sclerosis, interrupted by normal white matter only in a few places, extending round the whole of the lateral ventricles, including the inferior horns, and occupying an approximately equal volume of the white matter on both sides; in addition, however, to this diffuse lesion there were twenty-nine small discrete plaques scattered peripherally in the cerebral white matter mostly just under the cortex. Fourteen of these were in the right hemisphere and fifteen in the left, and of the twenty-nine, four pairs were symmetrical and a further pair were of equal size and identical location but differed somewhat in shape. In another case, showing by way of contrast the state of affairs when plaques are few, there were only eight small plaques in the whole cerebrum, four in each hemisphere, yet there were two pairs of

CHAPTER XIV

The Problem of Ætiology

DURING the past eighty years many theories have been advanced as to the cause of multiple sclerosis. These have been the subject of some excellent reviews in recent years, notably by Brain (1930), and by Reese (1950, 1952).

The main views may be listed, in approximately chronological order:—

1. The original Strümpel-Müller theory of dysplastic glial development.
2. Marburg's theory of a circulating myelinolytic toxin.
- ~~3. The infection theory.~~
4. The vascular theories of venular thrombosis, and of vascular spasm.
5. The allergic theory.
6. Recent biochemical theories.

The experimental evidence—histological, bacteriological, and biochemical—for and against each of the above theories has already been examined in the preceding chapter.

The "theory of dysplastic glial development" is only of historical interest, since it was based on the mistaken concept of a neoplastic glial reaction in multiple sclerosis in ignorance of the normal reactive powers of glial cells. But the rejection of this theory has never precluded the notion that in multiple sclerosis the attack upon the myelin may not be primary but mediated in some way through the specific agency of glial cells, probably, for reasons to be discussed, the oligodendrocytes.

With regard to the other theories, those postulating a toxin in the blood stream and cerebrospinal fluid, or assuming the existence of an infective agent or vascular thrombosis, have now been extensively explored. Though many problems remain to be clarified in each of these fields the bulk of evidence justifies the direction of future research into other more promising channels.

However, the moment we turn to hypotheses invoking allergy or biochemical disorders operating at the cellular level within the central nervous system we are confronted by lack of basic knowledge both of the function of the satellite oligodendroglia and of the metabolism of

myelin. Nevertheless a number of observations have been presented in Chapters XII and XIII which suggest that in all of the primary demyelinating diseases the disorder may be attributed primarily to the oligodendroglia rather than to the neurone itself, while, in the instance of multiple sclerosis, clinical evidence has been adduced (Chapter IV) suggesting that hypersensitisation may be a causal factor in the disease. Therefore it is chiefly in the light of these two hypotheses of disordered oligodendroglial function and allergy that, it seems to us, the so far unexplained facts of the natural history and pathology of the disease should be examined. How far these two hypotheses can be reconciled into a single theory is for the future to decide.

ÆTIOLOGICAL FACTORS IN THE NATURAL HISTORY

Geographical and Racial Distribution.—Multiple sclerosis is predominantly, but not exclusively, a disease of the peoples of Western culture or civilisation. It is more prevalent in the Northern than in the Southern hemisphere.

The incidence may vary in different parts of one country, but contrary to older views evidence that rural populations are more prone to the disease than urban is not conclusive.

Reasons for the anomalies of distribution are not known. The behaviour of the disease has never been observed to be in any wise epidemic; conjugal cases are exceedingly rare; and, as has been discussed fully in Chapter XIII, the bulk of the evidence does not support an infective origin. It has been suggested that the geographical incidence may be due to meteorological factors which, in susceptible individuals, might induce vasomotor alterations, varying from transient to prolonged vasospastic episodes. Such factors operate in Raynaud's disease and may play an important role in rheumatoid arthritis, but in multiple sclerosis it is more probable that they aggravate symptoms and are not strictly ætiological. Again, it has been suggested, following the early writings of Oppenheim, that the geographical factor may be linked with a deficiency of some essential trace element (a position analogous to swayback in sheep) or related to the presence of some toxic mineral element in the water supply dependent on local geological factors.

The apparent rarity of the disease among immigrants to South Africa from Northern Europe or North America, where the disease is relatively common, suggests the influence of climate rather than a genetic factor. On the other hand, the preliminary results of a recent survey of the disease in the Orkney and Shetland Islands suggest that the high prevalence rate in these islands is linked with an exceptionally high familial incidence (Sutherland, personal communication). The