MULTIPLE SCLEROSIS

THE FACTS

W. Bryan Matthews

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OXFORD

OXFORD UNIVERSITY PRESS

NEW YORK TORONTO

Oxford University Press, Walton Street, Oxford OX2 6DP

OXFORD LONDON GLASGOW
NEW YORK TORONTO MELBOURNE WELLINGTON
IBADAN NAIROBI DAR ES SALAAM LUSAKA CAPE TOWN
KUALA LUMPUR SINGAPORE JAKARTA HONG KONG TOKYO
DELHI BOMBAY CALCUTTA MADRAS KARACHI

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ISBN 0 19 261139 9

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Typeset in Northern Ireland
by the Universities Press, Belfast
Printed in Great Britain
by Richard Clay & Co. Ltd., Bungay

Preface

THE primary fact about multiple sclerosis is all too well known: that it is potentially and often actually a disabling disease of previously healthy young adults. Beyond this, hard facts are curiously elusive, even on such basic questions as how common, how serious, and how certain is the diagnosis, let alone on the more controversial matters of cause and treatment. Sources likely to be consulted by those with multiple sclerosis or their relatives are sometimes dogmatic, biased, or simply wrong, erring on the side of pessimism in describing only the effects of serious disease or, when treatment is considered, towards uncritical optimism. There is, indeed, no lack of information but we are learning not to accept anything as factual that has not been independently confirmed. Even allowing for this necessary but belated caution there is an air of expectancy that effective treatment and prevention cannot be long delayed. Facts then, as accurate as we can make them, and the theories that can be drawn from them will provide the answers, although not perhaps without the spice of inspiration.

Some may feel that discussion should be confined to the obscurity of medical and scientific journals but the facts and current theories of multiple sclerosis are matters of legitimate public interest. In the selective and abbreviated form imposed by a book for general reading I have emphasized facts of practical importance to those with multiple sclerosis, their families, and friends. Some of these facts are inescapably unpleasant and I must hope that in explaining them I have caused no one needless distress.

Oxford W. B. M.
October 1977

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1

What is multiple sclerosis?

ALTHOUGH there had been earlier partial descriptions, multiple sclerosis was first identified as a distinctive disease in 1868 by the great French neurologist Charcot, working at the hospital of the Salpétrière in Paris. It may seem strange that a disease that now seems so well-defined should have remained so long unrecognized but methods of examining the patient with organic disease of the nervous system were only then being developed and Charcot's great contribution to medicine was in linking the careful observation of symptoms and signs of disease in life with the pathological findings in the nervous system after death. He called this new disease that he had separated from the many causes of paralysis to be found in the wards of the Salpétrière, 'sclérose en plaques', a phrase that in his original lecture he feared would sound barbarous to his audience. The 'sclérose' or sclerosis of his title means hardening, and refers to the scarring that is the end result of the damage caused to the nervous system by multiple sclerosis. The word is used elsewhere in medicine, notably in arteriosclerosis, or hardening of the arteries, which has nothing to do with multiple sclerosis. Another occasional source of confusion is with the word 'cirrhosis' usually applied to the liver and originally referring to the orange colour sometimes displayed by that organ when diseased. This again has no connection with multiple sclerosis.

The word 'plaque', still very much in use in the study of multiple sclerosis, literally means a tablet, that is to say, something with a flat surface. This is a misconception of the nature of the individual areas of damage to the nervous system—the lesions—and is derived from the appearance of such a lesion cut across and viewed with the naked eye or through a microscope. As can be seen from Plate 7 this

naturally presents a flat surface—the plaque—but this is merely a cross-section of a lesion that may extend a considerable distance through the nervous system. In Great Britain the disease was originally known as disseminated sclerosis, shortened to DS, a name that emphasized an essential feature, that of *scattered* plaques throughout the central nervous system. This name has gradually been replaced by that popular in America, multiple sclerosis or MS. The main reason for the change was the existence of the Multiple Sclerosis Society in America and the importance attached to ensuring that the Society in Great Britain was similarly named. Disseminated and multiple sclerosis are the same disease.

To understand the impact of MS it is necessary to have at least an elementary knowledge of the anatomy of the nervous system and of how it works. The central nervous system (CNS) consists of the brain within the skull, and the spinal cord running down the centre of the backbone. These are not, of course, separate organs but join at the base of the skull. The CNS communicates with the muscles and receives information from sensory organs through the peripheral nervous system that ramifies throughout the body. The distinction is important because the lesions of MS are strictly confined to the CNS. The optic nerves that connect the eyeballs to the brain are also part of the CNS and are frequently affected in MS, but apart from this the plaques occur in the brain and spinal cord only.

The CNS performs a great variety of functions, based essentially on the reception and analysis of information from the outside world and from internal organs, and the initiation and control of the response, whether this be movement, emotion, or some more basic activity, such as sweating or evacuation of the bladder. This crude statement should not be taken to imply that the nervous system acts solely as an automatic machine and there is obviously much that is controversial or unknown, particularly with regard to such functions as consciousness, memory, and reason. All these functions, however, depend on the neurones or nerve cells, of which the nervous system contains some million million (a British billion) linked together in an orderly but literally inconceivably complex manner. Each

neurone consists of a cell body and a variable number of elongated processes, of which the one that is of particular importance in MS is the axon. For it is along the axon, or nerve fibre, that the nervous impulse, generated in the cell body, passes on its way to link with other neurones in the nervous system or, via the peripheral nervous system, to effector organs such as muscles or secretory glands. The impulse, which involves both electrical and chemical charges, travels at different speeds according to the diameter of the axon in cross section, conduction being fastest in the largest fibres. To give an idea of the scale, the diameter of the largest fibres is of the order of one fiftieth of a millimetre. These large axons, and also many of those of smaller diameter, are surrounded by a sheath of a complex chemical containing protein and lipid or fat, and known as myelin. This is laid down in a spiral manner around the length of the axon (Plate 1) but is not continuous, being interrupted every millimetre or so by a short bare segment of axon known as the node. The myelin, although a chemical, is laid down and supported within a living cell. These are much easier to study in the peripheral nervous system and most of the experimental work has been done there. However, it is known that in the CNS it is a particular form of the neuroglial cells that is responsible for the myelin. The neuroglia or glial cells are the other major component of the CNS and are concerned with many supporting activities such as the nutrition of the neurones, and with the healing process. It is the group recognized under the rather formidable title of the oligodendrocytes (cells with few branches) that is responsible for the myelin sheath, each short segment between two nodes being formed and maintained by one oligodendrocyte. The functions of the myelin sheaths are not fully known. The comparison with an insulated electric wire, with the conducting axon in the centre surrounded by insulating myelin is certainly too simple, but it is known that myelin has an important role in accelerating conduction along the axon.

MS is often referred to as a primary demyelinating disease, by which is meant that the initial damage produced by the disease is to the myelin sheaths, leaving the axons intact. It is

in fact difficult to be certain of the exact sequence of events in the formation of an MS plaque because the early stages are not often examined under the microscope. From studies of what seem to be early lesions and comparison with results in experimental animals that are probably relevant, some conclusions can be reached. As will be shown in later chapters some of these facts are important when considering the cause of the disease and the means by which it produces symptoms.

Very early in the formation of a new plaque a cluster of white blood cells, lymphocytes, appear around a small vein in the substance of the nervous system. Some maintain that this change is the earliest that can be detected, while others believe that myelin is damaged first. The lymphocytes spread along the course of the vein and are surrounded by an area in which the myelin sheaths have been destroyed (Plate 2). Opinion is still divided on whether the oligodendrocytes responsible for the formation and maintenance of myelin disappear from the early plaque, as these cells can be difficult to identify. It is not known whether the myelin breaks down because the oligodendrocytes are destroyed or whether the myelin, from whatever cause, is destroyed first. The plaque appears to spread by extension from the edges (Plate 3). The plaque and the surrounding tissues become swollen with excess fluid. The axons remain intact and can be seen running apparently undisturbed through the devastated area (Plates 4 and 5). As time passes the broken-down myelin is removed by scavenger cells and there is an increase in another form of neuroglia, the astrocytes, so called from their star-shaped appearance in stained sections under the microscope, and it is these cells that form the scarring or sclerosis. The lymphocytes disappear from the centre of the plaque but may persist at the edge where the disease process may still be active (Plate 3). In the chronic plaque it is still possible to see axons intact in the now scarred and otherwise burnt out area but at this stage some of the axons finally degenerate and disappear.

The factor most likely to be responsible for the symptoms of MS does therefore seem to be the loss of myelin. There is experimental evidence to show that severe and extensive

demyelination completely blocks conduction through the bared axon. If the loss of myelin is less severe, conduction is slowed and, in particular, the transmission of a rapid series of impulses, of great importance to the normal functioning of the nervous system, becomes severely defective. That the axons remain intact is also potentially of great significance. If, within the CNS, axons are cut or degenerate from disease they may grow again from the end nearest the cell body but the original connections are never re-established. This means that a disease that causes destruction of CNS axons is certain to leave permanent damage and, almost certainly, permanent symptoms. In the peripheral nervous system the chances of recovery are much greater but even there the newly grown axons may not establish their original connections but go to different muscles altogether. Until a late state of MS, however, the axons remain normal in appearance and do not degenerate. This offers the hope that symptoms due to defective conduction in the demyelinated but persisting axons are at least potentially reversible in that they are not the result of irrevocable destruction.

As we shall see, spontaneous recovery from the early symptoms of MS is the rule but it is not obvious from examination of the plaques how this can come about. In particular, it is not known whether *re*myelination occurs in the CNS. Such reformation of myelin is common in diseases quite distinct from MS that cause extensive demyelination in the *peripheral* nervous system and is there accompanied by recovery from severe paralysis. Some axons within the plaques can be seen to have an abnormally thin covering of myelin, a few turns of the spiral instead of the normal thick sheath, but it is not possible to distinguish between partly destroyed and perhaps partly reformed myelin. Another factor that is almost certainly important both in the production of symptoms and in the initial rapid recovery is the swelling in the plaque. The excess fluid could exert pressure on the bared axons and block conduction, which would be restored when the swelling subsided even in the absence of myelin sheaths.

These then are the plaques. They are 'multiple' in the sense

that certainly by the time the nervous system can be examined there are virtually always many plaques in different stages of development scattered throughout the CNS. It is not known whether the plaques are multiple from the onset of the disease and in many patients the initial symptoms suggest that there is a single lesion. Even in advanced cases plaques do not seem to be scattered entirely at random. They are never completely symmetrical, but do show a strong tendency to develop on both sides at certain apparently vulnerable sites, including the optic nerves and the spinal cord in the neck. The plaques are not only scattered in their anatomical positions but are also scattered in time, so that both the appearance of the CNS and the history of the illness indicate either successive outbreaks or, less commonly, continuous spread, often over 20 years or more.

Apart from some inconstant abnormalities in the blood that will be described in later chapters, there is virtually nothing to suggest that MS is a generalized disease in the sense that tuberculosis, for example, can affect many different organs and systems of the body. MS does not affect the lungs, or heart, or skin, or even the peripheral nervous system where the myelin has a different chemical composition. Whatever the final conclusion about the nature of the disease it is unlikely that symptoms are ever produced except directly or indirectly as the result of damage to the CNS.

This pattern of disease is not totally unfamiliar as there are obvious parallels with many diseases of the skin. Here too there is often no sign of general ill health and the colloquial word 'spots' indicates that the disease is patchy, with most of the skin free from blemish. Certain forms of urticaria, or nettle rash, and some rashes due to sensitivity to drugs bear a close resemblance to some of the features of MS. Particular areas of skin are involved, seemingly at random, while the rest is spared although the noxious agent must be present throughout the body. The rash comes and goes, often with long intervals of freedom, and returns, often without a recognizable reason. Particularly striking is the rash known as a fixed drug eruption. Here, in response to a minute dose of a drug to which the

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patient's skin is sensitive or allergic, large round plaques of inflammation appear haphazardly about the body surface. These persist for a number of weeks, fading gradually, but if a second dose is taken they extend from the edges in a fresh ring. The capacity of the skin for healing exceeds that of the nervous system and no permanent harm ensues, even after repeated attacks, so the comparison must not be pursued too far. However, here is another disease, at first sight quite mysterious, producing multiple, disseminated plaques with intervals of recovery. Even in skin diseases where the course can so easily be followed, the cause may be difficult to uncover but, once found, prevention is completely successful. There are certainly many enigmas in the disease process of MS but these are not the main obstacle to fruitful research as in many diseases effective treatment or prevention has been achieved without reaching the probably unattainable goal of total comprehension.

2

Who gets multiple sclerosis?

THERE are many strange facts concerning the distribution of MS in the world population that must be taken into account in any comprehensive theory of causation of the disease. Before describing these I must emphasize that all figures relating to the prevalence of MS must be approximate. Early cases are often not diagnosed because the symptoms have been slight or fleeting. The figures are also influenced in the opposite direction because, no matter how careful the examination, there are always some patients thought to have MS who are eventually found to have some quite different disease. Investigators are forced to classify their patients in separate categories of diagnostic certainty or doubt, the most usual being possible, probable, and definite cases, and other classifications are now coming into use. Bearing in mind these considerations imposed by difficulties in diagnosis the pattern of who gets MS and who does not can now be discussed.

The symptoms of MS are exceedingly rare in childhood. I have personally seen only two patients in whom the onset was definitely below the age of 10, and this is general experience. There is another form of demyelinating disease, confined to children, called Schilder's disease, and some believe that this is an exceptionally severe form of MS declaring itself in childhood. Even if this is so, MS remains a disease showing itself in adult life, as Schilder's disease is a great rarity. The frequency of onset of MS begins to increase around the age of 17 and reaches a peak in the early 30s. Thereafter the onset becomes increasingly uncommon but new cases, without any past history at all suggestive of earlier attacks, continue to occur into the 60s. Where notes are available, either from the hospital or from the general practitioner, it is astonishing how frequently people forget symptoms sufficiently severe to lead them to seek medical advice, so the age of onset of symptoms must

again be an approximation. It is, however, quite well known that the diagnosis may be made only by finding a few scattered plaques at routine postmortem examination in people who died in their 80s without apparently ever having experienced symptoms that could be attributed to MS. It is young adults and those of middle age who bear the brunt of the disease. In virtually every series reported women are more more frequently affected than men, the usual ratio being three women to two men.

There are two common methods of expressing the frequency with which the disease occurs in a given population. The annual incidence is the number of new cases recorded every year in some stated number, often 100 000 of the population. The prevalence is the number of people, again in every 100 000, known to have the disease on a given day. The former figure is obviously the one to use when dealing with acute short-lived diseases like influenza, while the prevalence rate is the more useful for most purposes in a chronic disease like MS. These figures are clearly partly dependent on the standard of medical care, the number of doctors capable of separating MS from other nervous diseases, and the accuracy with which the facts are collected and published. Over many parts of the world, for example, the Soviet Union, China, and South America, figures are scanty or non-existent. In many tropical countries, while no attempts at precision can be made, a fair idea of relative prevalence can be formed. Despite these deficiencies there is an impressive body of evidence from around the world for a striking pattern of distribution. The prevalence of MS varies markedly according to geography, and, with a few notable exceptions, the most obvious factor concerned is distance from the equator.

In tropical countries for which any estimate can be made MS is either extremely rare or does not occur at all in the indigenous population. In India occasional small series of patients have been reported but it is plain that prevalence is low. In contrast, in north-west Europe and in the northern states of the United States of America and in Canada, in the northern hemisphere, and in southern Australia and New Zealand,

prevalence is high, that is to say, above 40 per 100 000. In Great Britain generally the prevalence is about 50 per 100 000 of the population, but even within these islands the figure is higher in northern latitudes. In north-eastern Scotland the prevalence is around 100 per 100 000 and in the Shetlands and Orkneys may reach 300 per 100 000, the highest known prevalence in the world. Intermediate zones, such as the southern states of the United States, northern districts of Australia, and the Mediterranean shores have intermediate prevalence rates of from 20–39 per 100 000. If the effect was simply due to latitude then the prevalence rate in Japan would be expected to resemble that in Great Britain, but MS is comparatively rare in Japan (though the severity is greater) and there are other anomalies showing that simple distance from the equator or some secondary effect of this, such as temperature, cannot be the only factor concerned. MS is, for example, said to be rare in Eskimos.

It is not easy to visualize the meaning of such figures in every day terms. Fifty per 100 000 is 1 per 2000; one person with MS in a large village or in a single doctor's practice. Put like this the prevalence scarcely sounds 'high' but it has been calculated that in Ulster 1 in 1000 people born alive will develop MS. Odds of 1000 : 1 against are astronomical when it comes to backing horses but in densely populated areas still add up to a great many people with MS.

The figures from South Africa suggest that there is a racial effect on prevalence as MS occurs among the white population, although at a low rate, while it appears to be completely absent in the black population. In the United States, however, prevalence rates for white and black people, although still different, are much closer. These figures at first sight suggest that it is not race but geography that determines susceptibility but the relative rarity and increased severity of the disease in Japan remain something of an anomaly. There are also marked differences in prevalence between areas of similar latitude in America and Europe, being much higher in the latter. MS is certainly not confined to those of European stock but there certainly appears to be a relationship between high

prevalence and indigenous or colonizing Europeans, and some authorities have found this more obvious than the relationship to latitude.

There have been many detailed studies of the incidence of MS among restricted populations and particular regard has been paid to any hint that cases have formed 'clusters'. In virtually every study of this kind groups of cases have been found, apparently unrelated by blood or marriage but clustered in some small locality. The statistics used in working out the odds against clusters of a relatively uncommon condition occurring by chance are complex but apparently reliable. For anyone who believes that he has found some promising clues to MS because there are six cases in a small village it is disappointing to find how easily this could be a chance event. In those studies in which chance is statistically unlikely and some common environmental factor is looked for, nothing very convincing is found. In one survey MS is more common in rural areas, in another clusters occur in certain river valleys or on sheep farms but no convincing link between these different findings can be detected. For practical purposes, within a given area there are no consistent indications that any particular occupations or habitats are unduly hazardous with regard to the development of MS.

A matter naturally of great concern to all patients with MS and their families is whether the disease is inherited. As will be seen in Chapter 6 on theories of causation there is evidence suggesting an inbuilt, genetically determined, factor that increases susceptibility. There is also increasing evidence that MS is a good deal more common among the close relatives of those with the disease than in the general population. Some studies have put the risk as high as 15 times greater among first degree relatives, that is to say, parents, brothers and sisters, and children. This figure certainly sounds alarming but in Great Britain would mean that about 7 per 1000 of such relatives would be expected to develop MS, and odds of more than 100 : 1 against are not generally regarded as being too formidable. It is also clear that MS does not behave at all like any of the recognized patterns of inheritable disease. The

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