Multiple sclerosis

THE FACTS

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1978

OXFORD
OXFORD UNIVERSITY PRESS
NEW YORK TORONTO

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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 Salpêtrière 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 Salpêtrière, '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 This name has gradually been replaced by that popular in America, multiple sclerosis or MS.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 changes, 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

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 frequently affected than men, the usual ratio being three women to two men.

There are two common methods of expressing the frequency with which a 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 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 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 science of genetics in man is a good deal less predictable than

the results of artificially breeding varieties of peas, but nevertheless in many diseases, of which the best known are probably muscular dystrophy, haemophilia, and Huntington's chorea, the distinctive pattern of inheritance, recessive or dominant, can be detected and advice based on these findings can usefully be given to patients and their relatives. This is not so in MS and the findings from the study of identical twins indicate that the disease is certainly not transmitted by any form of direct inheritance. Identical twins, by definition have identical genes, and if one of these causes a disease both twins would be affected. Even in the most strongly genetically determined diseases the results are never quite 100 per cent, no doubt because factors in the environment also exert an influence. In MS when one identical twin is affected the chance of the other twin having MS is no higher than in non-identical twins, or indeed brothers and sisters.

There is nothing that can be done about an increased risk in parents or in brothers and sisters, and practical advice must obviously be restricted to the question of possible transmission to children. In fact MS in parent and child is a good deal less common that MS in brothers and sisters. There have been recent claims that it is possible to detect by means of blood tests those relatives, in particular children of known cases of MS, who are likely to develop the disease. This work is described in Chapter 7. If substantiated this will be a most important contribution, but as the tests have only recently been described it will probably be another 30 years before it will be possible to say whether the observations and conclusions are correct. If children apparently identified in this way as being vulnerable to MS are treated in the way described in a later chapter with the intention of preventing the development of the disease, it will be virtually impossible to be sure whether or not MS was actually prevented in anyone. There is at present no evidence that 'abnormal' results in these tests indicate susceptibility to MS or that treatment can prevent the disease appearing.

There may be other good reasons, medical or social, for a patient with MS not to have a family or not to have a large

family, but the risk of inheritance should not influence the decision.

Two separate studies in Great Britain have shown that MS is relatively more common in those of higher social and economic standing. Such figures are not easy to interpret but the National Health Service has ensured that these apparent differences cannot be due to better facilities for diagnosis being available for the comparatively wealthy. On a less scientific and entirely subjective plane many experienced neurologists have wondered whether there is not a type of person and personality particularly prone to MS. So often it seems to be the healthy, good-looking, stoical, and hardworking who are affected, people 'who put up with things better than one thinks one would oneself', as it has been expressed. This opinion may be quite erroneous but is one that has been strongly impressed on me over the years.

In conclusion, therefore, for practical purposes, MS does not occur in children or begin after the age of 55. It is commoner in women than in men, and in those with a higher standard of living. To be born and bred in the tropics is virtually to avoid all risk of MS. There is an increased risk of contracting the disease in relatives of those with MS but this is not due to direct inheritance.

3

Early symptoms

BEFORE describing the common modes of onset I must refer to a matter of great importance that caused me to have serious doubts on the wisdom of writing a book explaining MS to the general public. Following every surge of publicity I am asked to see a number of patients, usually young women, who are convinced that they have MS. This is because certain of the early symptoms of the disease that they may have heard described on radio or television have a superficial resemblance to banal every day experiences. To lie on an arm or to sit awkwardly with legs crossed at the knee for too long causes temporary numbness, pins and needles, and even weakness, as everyone is aware. Many people do not have perfect balance between the movements of the two eyes so that, particularly when tired, vision may become double for a moment as the eyes drift apart, clearing at once after blinking or rubbing the eyes. Normally these and other fleeting 'symptoms' are forgotten or rightly ignored as of no importance. After perhaps listening to a friend describe how MS began with numbness or double vision followed by complete recovery it is natural to have misgivings about the commonplace events I have described, even if only in moments of anxiety or depression. Persistent fear, however, results in other more persistent sensations; tingling induced by continuously breathing too rapidly, feelings of dizziness or uncertainty, and doubts about whether knocking over the milk jug was normal clumsiness or something worse. In fact these sensations, by no means imaginary but certainly not in any way sinister, can nearly always be distinguished from the early symptoms of MS by any doctor with extensive experience of the disease. To brood unnecessarily and in secret is the worst possible way of coping. Fears are much more easily dispelled if dealt with quickly.

As MS can affect any part of the CNS the initial symptoms can obviously be extremely varied. The distribution of plaques is not, however, completely haphazard and there are certain sites that are particularly vulnerable. In consequence the majority of the initial symptoms fall into well-defined groups.

As will be recalled the optic nerves are part of the central, rather than the peripheral, nervous system and as such are susceptible to involvement in MS. In approximately 15 per cent of patients the initial symptom is what is known as optic or retrobulbar neuritis. These terms simply mean inflammation of the optic nerve and 'retrobulbar' indicates that this has affected the nerve some way behind the bulb of the eye—the eyeball. The original significance of these two labels was that in optic neuritis it is possible for the examining doctor using an ophthalmoscope actually to see the inflamed optic nerve, whereas in retrobulbar neuritis the inflammation does not reach the retina and the diagnosis can be made only from the symptoms. In a typical attack the vision is noticed to be blurred in one eye. It is not always easy to know how rapidly this comes on as, naturally enough, it is quite difficult to recognize even severe loss of vision in one eye if this does not occur suddenly. Some people notice that there is anything wrong only when they accidentally rub the good eye while keeping the other open and are then startled to find that they cannot see clearly. The eye is somewhat painful, although not red or bloodshot, particularly on looking up or to one side, and vision continues to deteriorate for several days. The effect on eyesight varies from slight dimming of the normal vividness of colour appreciation to complete blindness in the affected eye, but the usual result is severe loss of central vision. This is most disturbing as the act of looking at anything involves turning the eyes so that light from the object looked at falls on the area of the retina in which the light receptor cells are most densely packed. It is the axons carrying impulses from this area that most often lose their myelin sheaths in an attack of retrobulbar neuritis. These fibres do, in fact, make up a large part of the optic nerve where they lie centrally and are

therefore involved in any sizeable plaque within the nerve. Fortunately both eyes are rarely affected simultaneously.

Vision usually continues to decline for about a week but seldom for longer. At about this stage the pain subsides and a week or two later, in nearly every case, vision begins to improve. The expected result is complete recovery over the succeeding weeks with normal visual acuity as measured on the familiar wall charts. Sometimes, even when the lowest line can be read with ease, there may be a persistent awareness that vision is not perfect; colours may remain a little dull or contrasts of light and shade may be less sharp. Occasionally central vision remains more severely affected but even here there will have been great improvement over the initial loss of acuity.

This recovery is a characteristic example of that remarkable phenomenon in MS, the *remission;* a term that means substantial or complete recovery from the effects of an initial attack or subsequent relapse of the disease. It would be difficult to exaggerate the importance to the eventual understanding of MS of the potentiality for complete reversal of often severe disability. The implications will be discussed in later chapters.

There are other much less common causes of optic neuritis in which the nerve can be seen to be inflamed, but an unmistakable attack of retrobulbar neuritis is usually the initial episode of MS, or it may occur later in the course of the disease. The proportion of those presenting with retrobulbar neuritis who eventually develop other symptoms and signs of the disease increases with the length of time the patient is observed. Even with the longest follow up, however, there is always a number of people in whom retrobulbar neuritis remains an isolated event but at present there is no method of distinguishing this group at the onset.

The second most common site from which symptoms are produced during an initial attack is the spinal cord. Within the spinal cord run tracts or bundles of myelinated axons conveying nerve impulses to and from the brain and any of these may be involved in a plaque (Plate 6). Most frequently it is the

tracts conveying impulses concerned with the brain's initiation and control of movement that are first affected. This bundle of axons is sometimes referred to as the pyramidal tract, a name that originates from the days of purely descriptive anatomy and refers to the supposedly pyramidal shape of the tract at a certain point in its long course from the cortex of the cerebral hemisphere to the lower end of the spinal cord. Many of the axons form connections with other neurones within the spinal cord whose axons in turn enter the peripheral nervous system and eventually supply the muscles. The effect of demyelination involving the pyramidal tract is weakness, nearly always of one or both legs.

The onset may be relatively rapid, particularly when influenced by fatigue. For example, the first few miles of a country walk may be accomplished normally, but weakness may make the return journey impossible. More usually, weakness increases over a few days or a week or two, remains unchanged for a further few weeks and then recovers. The degree of weakness in a first attack is seldom severe and often amounts to dragging of one leg, inability to run and some difficulty on stairs.

The sensory tracts within the spinal cord carry nervous impulses derived directly or indirectly from a variety of sensory receptor organs. Sensations of touch, pain, and difference in temperature derived from the skin, and of pain from both the skin and internal organs are familiar enough, but there are other highly important sensory impulses that do not give rise to anything that we are normally aware of as 'sensation' at all. We are aware of the positions of our limbs, trunk, and head in space in a most precise manner without having to think about the matter. Information of which we are completely unconscious is fed into the CNS from minute structures in the muscles, ligaments, and joints sensitive to stretch. This sensory input is essential for the efficient control of movement and for many of the automatic or reflex reactions of the body to change of posture. The symptoms arising from demyelination in the sensory tracts ascending to the brain vary

according to which of the different forms of sensation are affected.

A common mode of onset of MS is with a sensation of numbness in the feet, ascending in the course of a few days to the waist. Numbness implies loss of feeling, although it is often difficult to distinguish from loss of use, but it is seldom severe. A pinprick may still be felt as sharp but somehow distant. The loss of feeling may involve the bladder and bowels so that, although there is no loss of control, the normal sensation of passing water or of the desire to do so is absent. Vaginal sensation may also be absent or unpleasantly distorted. There is no difficulty in walking as neither strength nor the sensory inflow from the muscles and joints is affected. Remission normally occurs after several weeks.

Rather more disabling is an initial attack in which the sense of position, the knowledge of where the limb is in space, is lost. When this occurs it usually affects the upper limb, resulting in a 'useless arm'. The arm is not weak in the least, but loss of sense of position and of all the essential information from the muscles and joints makes any co-ordinated movement impossible.

The spinal cord is also involved in the reflexes that control the function of the bladder and bowel and of sexual function in men. These are often disturbed late in the course of the disease, but also occasionally at the onset, even without any other obvious symptoms. This may present with the sudden complete inability to pass urine—acute retention of urine—for some reason virtually always in young women. There are other causes for this uncomfortable event and MS is certainly not the most common. Impotence is a common symptom in the late stage of MS and may rarely be present in the initial attack but I have never encountered this as an isolated symptom of the disease. The importance of this is that men troubled by sexual impotence, who do not have any other symptoms or signs of organic nervous disease do not have MS.

The other two common modes of onset are due to plaques in what is known as the brain stem (Plate 7). This is a part of

the brain immediately above the spinal cord through which pass all the motor and sensory tracts already mentioned, but which is also crowded with nuclei, or groups of neurones, controlling, among other important functions, the movement of the eyes and the reception of sensory information from the ears. Weakness of one of the six muscles that control the movement of the eyeball causes double vision as the two eyes are no longer always correctly co-ordinated. Double vision as a first symptom of MS is transitory, but always persists for at the very least several days, and therefore does not resemble the momentary double vision of fatigue acting on imperfectly balanced eye muscles that many otherwise normal people experience.

For unknown reasons MS plaques only rarely cause deafness, although the brain stem contains nuclei concerned with hearing. The delicate mechanisms of the ear are not, however, solely concerned with hearing but also with balance, and here again the brain stem is an important relay station for nerve impulses serving this function. Giddiness may therefore be the first symptom of MS. I must hasten to qualify this statement, because giddiness of some form or another is an almost universal experience, usually the result of some passing event; an infection, getting out of a hot bath too quickly or having too much to drink, for example. The giddiness of MS is true vertigo, that is to say, an intensely unpleasant and persistent feeling of rotation of the outside world or of oneself often accompanied by vomiting and inability to walk straight, or indeed to walk at all. There are many other causes for vertigo but a young adult prostrated for a week or more, and without other evident cause may well have MS.

Plaques often form in the cerebellum or in the tracts of nerve fibres leading to or from it to other centres in the nervous system, but more commonly later in the disease than at the onset. The cerebellum is a complex organ of the brain situated at the back of the head, to which information from all the sensory systems is carried, analysed, and used to regulate movement. The effect of interruption of its functions is not to

produce loss of any form of sensation, for the cerebellum is not concerned with consciousness, but loss of control of movement. Strength is retained but smooth action of the limbs becomes impossible and movements are said to be incoordinated or ataxic. At the onset of MS this may show itself as unsteadiness in walking or in clumsiness in the use of one or both hands, without weakness or loss of sensation on testing.

These then are the common modes of onset of the more usual form of MS, that with remissions and relapses. The list could be extended almost indefinitely in conformity with the multitudinous functions of the nervous system, but I am not writing a textbook of neurology. All these modes of onset have features in common. In the first place patients very rarely feel generally unwell. Some authorities have tried to identify even earlier symptoms preceding those clearly indicating organic nervous disease and have written of 'rheumatic' symptoms or headache in particular. I have not been able to identify anything resembling these joint and muscle pains and have only occasionally encountered headache that I thought might be related to the onset of MS. In the great majority of cases the subject is feeling in perfect health at the time of onset and in particular there is no fever, rash, nor other evidence of a generalized disease. A point of particular interest is that the onset can be extraordinarily rapid. A young woman went to her daughter's school sports and entered for the mother's race feeling very fit and, as she said, intending to win. She ran five yards and then her legs became weak and numb so that she fell down. She was helped up and walked with difficulty and recovered completely in the course of the next two months. This later proved to have been the initial symptom of MS.

I have described the onset as affecting a single part of the CNS; optic nerve, spinal cord, or brain stem, and this is often so. The disease is, however, *multiple* sclerosis, and even at the onset there may be symptoms and signs of damage to several areas that could not possibly be due to any form of disease confined to a single circumscribed site. Thus a combination of

double vision and vertigo with loss of feeling below the waist would clearly indicate disease in both the brain stem and the spinal cord and thus provide evidence of multiple plaques.

In approximately 10 per cent of patients with MS the mode of onset differs from that described above in that it is progressive from the beginning. In many of these patients symptoms begin at a relatively late age, beyond the peak age of those in the early 30s. In this group the first symptom is nearly always gradually progressive weakness of one or both legs. There is nothing resembling an acute attack and unfortunately no remission either. In technical terms these patients have 'progressive spastic paraparesis'. 'Progressive' is self-evident. 'Spastic' refers to the type of weakness that results from interruption of the pyramidal tracts. In addition to weakness of the legs there is loss of control over certain essential automatic reflex actions that are normally carried out through the nervous connections in the spinal cord. These can be tested by the doctor's rubber hammer of the comic cartoon, which is used to tap the tendons at the knee and ankle to stretch the muscles and induce a reflex contraction. A knee jerk is, as everyone knows, a normal finding, but when the pyramidal tracts are not functioning normally in MS or in other diseases the knee jerk is much increased. In itself this is of little consequence, but is an indication of abnormally increased reflex activity, so that stretching the muscles in ordinary movement also causes exaggerated reflex contraction. Sometimes a repetitive reflex may be set up, particularly in the calf muscles, resulting in an effect perhaps best described as 'juddering'. This may first show itself when the foot is firmly pressed on the brake pedal of a car. The calf muscles are stretched and contract reflexly, causing a jerk, and this is repeated for as long as pressure is maintained. The technical name for this is *clonus*. The result of these increased reflexes is a stiff 'spastic' leg and the patient scrapes the toe on walking and drags the limb. The abnormality also shows itself in an abnormal reaction to firm stroking of the sole of the foot when the toes normally reflexly curl under, but in a spastic leg they stretch out in the opposite direction.

Many people find this test unpleasant but it is of considerable value in diagnosis. It is virtually impossible to elicit this reflex on oneself and self-examination is to be deprecated. The word 'paraparesis' means weakness of both legs and is a milder form of the more familiar paraplegia used when there is complete paralysis such as may follow injury to the spinal cord.

The symptoms and signs as described above are present alone or in combination at the onset of the disease in perhaps 85 per cent of cases, the remainder having other symptoms more commonly encountered later in the course of the disease, which I will describe in the next chapter.

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