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MULTIPLE SCLEROSIS

A PLEA FOR A FRESH OUTLOOK*

BY

DOUGLAS McALPINE, M.D., F.R.C.P.

From the Institute of Clinical Research, Middlesex Hospital

Despite its importance the subject of multiple sclerosis tends to be obscured by an aura of defeatism and even apathy for which there appear to be four main causes: (1) the apparent lack of progress in discovering the cause; (2) the generally accepted view that diagnosis is seldom possible in the early stages and cannot be made unless certain signs are present; (3) the belief that, variable though the course may be, sooner or later increasing disability is inevitable, leading to premature death; and (4) the lack of any therapeutic measure which can be relied upon to influence the disease.

I propose to deal with these points in some detail.

Aetiology—The Allergic Theory

Until quite recently the belief that multiple sclerosis was due to a single cause has dominated thought on this problem. This is well exemplified by the infective theory, which postulates that multiple sclerosis may be caused by a particular form of bacterium or virus. The negative results of earlier experimental work, particularly on the virus theory, are not entirely trustworthy because of limitations in technique. However, Lumsden (1955) has described a tissue-culture method for the detection of virus in plaques. His failure to confirm the presence of virus in a small series of plaques should not discourage others from repeating his experiments. It should be recalled that Dawson (1916), as a result of intensive histological study, concluded that multiple sclerosis might be caused by a soluble toxin conveyed to the nervous tissues, probably by the blood stream. It may well be that this concept, if viewed broadly and translated into terms of immuno-chemistry, may yet prove to be near the truth.

The so-called allergic theory, to which increasing attention has been paid in recent years, carries with it the implication of a multifactorial causation. The idea that a hypersensitivity reaction to an infection might cause disease of the nervous system was probably first put forward by Glanzmann (1927) in connexion with the neurological complications of chicken-pox, smallpox, and vaccination. In 1932 van Bogaert postulated that a similar mechanism might be at work in multiple sclerosis. In 1942 Pette further developed the theory of neuro-allergy when considering the acute forms of demyelinating disease. Ferraro (1944), on the basis of histological studies, suggested neuro-allergy as a common basis in all the demyelinating diseases, including multiple sclerosis. Clinical support for this viewpoint came from studies of the natural history of the disease (McAlpine, 1946; McAlpine and Compston, 1952). The possibility that multiple sclerosis may be due to an antigen–antibody reaction within the nervous system is at present based on deduction from a number of widely different observations.

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Familial Tendency

In England (Pratt, Compston, and McAlpine, 1951) and Northern Ireland (Millar and Allison, 1954) the familial incidence lies between 6 and 7%. In Northern Scotland, Sutherland (1956) obtained the high figure of 11%. Siblings are more frequently attacked than other relatives. Examples of the disease in three generations are exceedingly rare. Studies by Thums (1951) in twins has shown that the disease does not necessarily occur in identical twins. These facts suggest that, when present, the genetic influence is usually weak and must be reinforced by constitutional and environmental factors before the nervous system is attacked, and, furthermore, that the disease may develop in the absence of any obvious genetic influence.

Occurrence of Allergy in Multiple-sclerosis Subjects

In a study of 250 cases of multiple sclerosis and of 250 controls from a hospital population we did not find any difference in the incidence of allergy in the two groups, but just before and after the onset of symptoms of multiple sclerosis a history of some form of allergy was obtained in 9% of this series as compared with 2.5% of the control series (McAlpine and Compston, 1952). In multiple-sclerosis patients the occasional reaction in the nervous system to organic arsenical preparations and to vaccines suggests a similar mechanism.

Precipitating Factors

Although the first symptom of the disease may appear in an apparently healthy individual without any recent incidents in the general health that can be related to the onset, more usually one of the following closely precedes it:

Fatigue.—Long recognized as a factor which may precipitate or aggravate the disease, excessive tiredness, with or without physical or mental cause, is not unusual in the history of these patients. Just as signs of paralysis may be hastened in the laboratory animal, previously injected with brain emulsion, by causing it to run about the cage, so in multiple sclerosis physical exertion may bring the disease to light or cause a relapse.

Infection.—Roughly 10% of patients give a history of an infection, usually in the form of a "cold" or "sore throat" or an attack of influenza preceding the onset. The Table illustrates this point. "Whenever I get a cold, it goes to my legs" is an expression sometimes used by these patients; it illustrates the part which an intercurrent infection may play in causing either a temporary exacerbation of symptoms or a true relapse.

Infection Preceding Onset (From McAlpine, Compston, and Lumsden, 1955)

Author	%	No. of Cases
Bramwell (1917)	14·0	200
Hoesslin (1934)	10·5	109*
Kolb *et al.* (1942)	2·0	199
McAlpine (1946)	5·0	142
Adams *et al.* (1950)	14·0	389†
McAlpine and Compston (1952) ..	10·0	250

* Acute. † Within six months of onset.

Trauma.—Since the end of the last century references may be found in medical literature, especially German, to the relation between trauma and multiple sclerosis. In Hoesslin's study of 516 cases trauma (including operation) precipitated the onset in 11.4% of cases. In our series of 250 cases we obtained a history of trauma, including dental extraction but not surgical operations, in 14% as compared with 5.2% in the control series. In a recent series Abb and Schaltenbrand (1956) estimated a figure of 10%. Hoesslin first suggested that there may be a relationship between the site of the trauma and the level of the lesion in the central nervous system, a finding which we confirmed in certain of our cases and which has a parallel in acute poliomyelitis.

Emotional Stress.—Although statistical evidence that an emotional upset can be regarded as a valid precipitating factor is lacking (Pratt, 1951), in individual cases it can be so regarded. Of its importance during the course of the disease, particularly as a cause of temporary exacerbations of symptoms, there can be no doubt.

Mode of Onset and Course of Disease

An abrupt onset and a natural tendency for symptoms to remit and later recur are features which have long been recognized as likely to provide a clue to the underlying cause of multiple sclerosis. Particularly in the middle-aged, there may be a slow progression of symptoms from the onset (the progressive spinal form of the disease). It would seem likely, as in certain other diseases, notably rheumatoid arthritis, that age may be a factor in modifying the individual's reaction to the morbid process.

Changes in Cerebrospinal Fluid

In roughly 70% of cases the C.S.F. is abnormal at some stage of the disease, as shown by a mild pleocytosis, an increase of protein, or an abnormal Lange colloidal gold curve. It is known that any one of these abnormalities may occur as an isolated finding. At the present stage of our knowledge it is impossible to estimate the significance of these changes in relation to the course of the disease. Recent electrophoretic studies have shown that the gamma-globulin fraction in the C.S.F. is usually increased, while that of the serum is not significantly raised. Furthermore, it is known that a change in the colloidal gold curve is closely linked with the gamma-globulin content of the fluid. Press (1956) has reported the presence of a protein in the C.S.F., component "S," which she isolated from the gamma-globulin fraction; this substance has the effect of inhibiting the colloidal gold reaction. In multiple sclerosis the proportion of component "S" tends to be decreased as compared with the amount in normal C.S.F.

Since antibodies migrate mostly with the gamma-globulin fraction of the serum it is reasonable to suppose that this component of the C.S.F. performs the same function. From the above findings it seems permissible to make two tentative deductions: first, that the changes in the C.S.F. are the result of an immunological reaction, and, secondly, that this reaction may be in the nervous tissues rather than due to an increased selective permeability of the blood/C.S.F. barrier.

Experimental Evidence

The experimental pathologist now has at his command an established technique by which he can produce a demyelinating disease (encephalomyelitis) in animals by injecting them with homologous or heterologous brain tissue. This injection has a greatly increased effect if it is given with an adjuvant, such as heat-killed tubercle bacilli. Neither the injection of an emulsion of other organs nor that of the adjuvant alone produces this effect. Brain antibodies have been demonstrated by complement-fixation tests, but they are not capable of passive transfer. All grades of encephalomyelitis, ranging from acute to chronic, can be produced by varying either the number of injections or the amount of brain tissue injected. When a chronic form is produced in the monkey, cerebellar and pyramidal signs are prominent, partial remissions may occur, and at post-mortem examination plaques of demyelination may be found in the optic nerve and brain stem that, superficially at least, bear a striking similarity to the plaques of multiple sclerosis. The literature on the subject, the reasons for supposing that this reaction may represent an immunological mechanism, and the light which these experiments may throw on the cause of multiple sclerosis have been discussed by Lumsden (1949, 1951, 1956) and by Wolf (1952).

Until more is known about the nature of the hypothetical antigen in brain tissue, the significance of experimental encephalomyelitis in relation to multiple sclerosis must remain *sub judice*. However, grounds for the belief that a form of allergy may be operative in both of these diseases have been strengthened by the marked similarity that exists between the type of polyneuritis which can be produced in rabbits by injecting them intradermally with rabbit sciatic nerve or spinal ganglia and the clinical picture of the Guillain–Barré syndrome or acute toxic polyneuritis (Waksman and Adams 1955).

Comment

It is clear that none of the clinical facts which I have briefly mentioned are in any way conclusive with regard to the allergic theory of multiple sclerosis. However, when viewed collectively the occasional familial incidence, the nature of the precipitating factors, the occurrence in some patients of a known form of allergy or a hypersensitivity to drugs, the abrupt onset and fluctuating course, and the change in the C.S.F. are all compatible with this theory.

Until disproved, the allergic theory of multiple sclerosis should be used as a basis for further research, particularly in the direction of determining the nature of the hypothetical antigen or antigens. By analogy with the results of experimental encephalomyelitis it would seem likely that, if an antigen–antibody reaction is concerned in the genesis of multiple sclerosis, part of the antigen is derived from a chemical component of the central nervous system; in other words, multiple sclerosis could in part be explained by autosensitization (Kabat, Wolf, and Bezer, 1947; Wolf, 1952; Lumsden, 1956). In addition to an *intrinsic* component of the antigen it is necessary to postulate an *extrinsic* one. Theoretically this could be a specific chemical agent derived from one or more sources.

The work of Colover (1956) on the chemistry of the tubercle bacillus may point the way to the type of chemical agent that might be expected to serve as the source of extrinsic antigen in multiple sclerosis; he has shown that the residue in the tubercle bacillus, which is active in producing encephalomyelitis, is largely protein in character with

glutamic acid and alanine as predominant amino-acids. From clinical observations, it would seem necessary first to consider as possible sources of allergen the breakdown products of the common pathogens. From the foregoing remarks it is obvious that for the elucidation of this fascinating problem we must rely on the immuno-chemist and experimental pathologist, but there remains a place in research not only for the epidemiologist but also for the clinician who is prepared to view the problem broadly.

Early Diagnosis

A diagnosis of multiple sclerosis is usually not made until at least the fourth or fifth year of the disease. There are two main reasons for this delay. (1) The patient fails to report to his or her general practitioner early symptoms—for example, an episode of tingling or of numbness or of tiredness in a limb. Only by making the public aware of the existence of the disease and its early manifestations could this difficulty be overcome. Until the medical profession adopts a less defeatist attention towards treatment it is doubtful whether such a step is at present justified, although as an indirect result of the activities of lay societies knowledge of the disease is slowly spreading. (2) The fallibility of us all, consultant and general practitioner alike, when confronted with a minor disturbance of function of any part of the body, more especially of the nervous system. Instead of dismissing an apparently trivial complaint regarding vision, sensation, or use of a limb, sometimes with labels as "eye-strain" or "neuritis," we must train ourselves to think of multiple sclerosis as a possible cause, even though on examination of the patient we can find little or no evidence to suggest organic disease.

There are certain features of the clinical picture which individually or collectively may lead to a correct diagnosis.

History.—This is of major importance, since it often raises suspicion of the disease, especially if after careful probing of the past one or more episodes come to light, often trivial and almost forgotten, suggesting a previous lesion in the central nervous system.

Family History.—In a suspected case of multiple sclerosis discreet inquiries should always be made for any neurological disorder in a near relative. Occasionally a positive history of multiple sclerosis in another member, or of paralysis occurring in youth or early middle age, which hospital records may confirm as due to multiple sclerosis, will heighten the suspicion of the same disease in the patient.

Prodromata.—Lassitude, easily induced fatigue, headache, irritability, difficulty in concentrating, and vague pains in the limbs are among the symptoms which may occasionally precede or accompany the onset and which may indicate a constitutional phase of the disease.

Behaviour of Early Symptoms.—Of major importance in diagnosis is the tendency for early symptoms to clear up, entirely or partially. Often, however, this important feature of multiple sclerosis, instead of arousing suspicion, has the opposite effect, and the reassurance given to the patient may seem well founded when perhaps months or even a few years pass by without any recurrence. The word "transitory" as applied to early symptoms is usually interpreted as meaning days or even weeks. However, quite commonly when taking the history one comes across episodes of disturbed vision, giddiness, or of tingling or numbness that lasted only hours or even minutes. Just because these early symptoms may be very short-lived they should not be dismissed as insignificant.

Evidence of Multiple Lesions.—It is often held that a diagnosis of multiple sclerosis cannot be entertained unless there is evidence of multiple lesions. It is quite true that such evidence—for example, the association of double or blurred vision and of paraesthesiae or weakness in a limb—is extremely helpful. However, a monosymptomatic type of onset is relatively common. In a recent analysis of 309 cases admitted to the Middlesex Hospital over a five-year period, in no less than 63% a history of a single symptom was obtained at the onset: retrobulbar neuritis (21%) headed the list, followed by paraesthesiae (17%), motor weakness (14%), double vision (7%), and vertigo or vomiting (5%) (McAlpine, 1955).

Distribution of Symptoms.—Highly characteristic of multiple sclerosis is the irregular distribution of plaques in the central nervous system; consequently symptoms tend to be asymmetrically distributed. However, it is important to realize that they may occasionally show a remarkable degree of symmetry; for example, an attack of blurred vision in both eyes or paraesthesiae appearing symmetrically in the upper or lower limbs. If this feature of the disease is not recognized, difficulties in diagnosis may arise, especially when symmetrical paraesthesiae are present, thus imitating the distribution seen in acute polyneuritis.

Tendency for Local Spread of Early Plaques.—While it is quite common for a symptom to remain localized, not uncommonly there is a tendency towards spread. For example, a patient may describe how she first noticed a blurring in the centre of the field of vision which rapidly spread to involve the whole field. Or, again, numbness may spread locally; for example, from the little and ring fingers to the remaining fingers and rest of the hand, or widely from the upper limb to the trunk and lower limb on the same side, or in the reverse direction. This type of spread does not occur haphazardly, but is determined by the anatomical arrangement of fibres in the neighbourhood of the plaque. For example, paraesthesiae such as tingling and numbness are usually caused by a plaque in the posterior column, and if they spread widely it is sometimes possible to correlate the mode of spread with the arrangement of the proprioceptive fibres. The rapid manner in which spread may occur in multiple sclerosis is of diagnostic importance.

Physical Signs.—It is still widely held that a diagnosis of multiple sclerosis cannot be made unless certain signs are present, notably nystagmus and an extensor plantar response. It is of course true that the presence of these and other signs, particularly temporal pallor of a disk, are of the utmost value; nevertheless their relative or complete absence should not allay suspicion if the history is suggestive.

Cerebrospinal Fluid Findings.—A mistaken idea that lumbar puncture may be harmful in cases of multiple sclerosis may be one reason why this important diagnostic procedure is not used more often. Replacement of the fluid by 5 ml. of sterile normal saline solution reduces the risk of headache.

Some Remarks on Early Symptoms

Retrobulbar Neuritis

The clinical picture of an acute retrobulbar neuritis and its close association with multiple sclerosis is well known. I wish to draw attention to certain atypical features of this condition, some of which, so far as I can judge, are not well recognized. The first concerns short-lived attacks of blurred vision in both eyes, a history of which may sometimes be obtained in a patient who presents with a frank retrobulbar neuritis or with other evidence of the disease. Frequently, but not invariably, these attacks are brought on by exertion, fatigue, bright light, or reading. Multiple sclerosis is, of course, not the only condition in which temporary attacks of blurred vision occur; it may, for example, be caused by cerebral anoxia, or by posterior fossa tumours (Shephard and Wadia, 1956). In multiple sclerosis this symptom has a significance, not only for early diagnosis, and as a probable explanation of temporal pallor of a disk in the absence of a positive history of a frank attack of retrobulbar neuritis, but also in relation to the physiopathology of the early plaque.

The next point concerns field defects. Although usually centrally placed, a scotoma may vary not only in density but also in its position in the visual field. Whatever the site of the original defect, there is a tendency for the scotoma to spread. Retrobulbar neuritis may be painless; on the other hand, pain in or behind the eye, especially on upward or

inward movement, is not uncommon. Of particular interest is the fact that pain in this situation may precede any subjective alteration in vision by a week or even longer. I have seen patients with retrobulbar neuritis who have had one or more attacks of pain in the eye without any visual failure. Pain preceding retrobulbar neuritis may be referred sometimes to the same frontal region or more widely over the whole of the side of the head. Where is the site of the pain in such cases? Ophthalmologists usually localize pain in and around the eye to the attachment of the superior and internal recti in the sheath of the optic nerve. This explanation does not adequately account for the occasional widespread pain met with in retrobulbar neuritis. Obviously this is a subject much in need of study, since if we knew what structures were involved we might have a valuable clue to the site of the early lesion.

Paraesthesiae

When a young or middle-aged patient presents with a disturbance of sensation as a solitary symptom the possibility of disease of the central nervous system does not readily come to mind. However, before explaining such symptoms as tingling, pins-and-needles, numbness, or deadness on the basis of a disturbance of the peripheral nervous system, the distribution, mode of onset, and duration of paraesthesiae should be carefully noted. If they are referred to the periphery of one limb confusion with a mononeuritis may readily occur; if, however, pins-and-needles or numbness is referred to the proximal half of a limb or to the trunk, then a root or cord lesion must be considered. I have already drawn attention to the symmetry sometimes shown by the paraesthesiae of multiple sclerosis and their striking resemblance to those occurring in some forms of polyneuritis (including the opening phase of subacute combined degeneration of the cord). Rapidity of onset and of spread characterize the paraesthesiae of multiple sclerosis. A spreading tingling going on to numbness and clumsiness of the affected part, with diminution or loss of two-point discrimination and vibration and postural senses, are well-recognized features of a plaque in the posterior column. A feeling of warmth or of coldness or dampness in a lower limb or inability to appreciate the warmth of a hot bath, coming on abruptly, should arouse suspicion of a plaque in the contralateral spinothalamic tract. The issue as between a peripheral and a central cause of paraesthesiae may be clarified first by the results of clinical examination and secondly by the clearing up of symptoms. Symmetrical or four-limb paraesthesiae when due to a peripheral neuritis tend to progress, while depression of the deep reflexes is followed by their disappearance.

Pain is not at all uncommon in the opening phase of multiple sclerosis. It is usually described as an ache referred to the back or the upper or lower limbs. Occasionally it may be sharp, though it is not aggravated by coughing or straining. A recent history of pain should not automatically exclude multiple sclerosis as a possible cause of an episode of paraesthesiae.

Motor Weakness

Here again it is the minor degree of disability, disguised as a "tiredness," a "heaviness," or a "stiffness" in one or both limbs, especially after walking, that is often misinterpreted. In some cases pyramidal signs are evident; in others a careful examination is required to bring out fatigability or depression of the abdominal reflexes, a slight inequality in knee- and ankle-jerks, and an equivocal plantar response. When the first plaque or plaques giving rise to symptoms are situated in the optic nerve or the dorsal half of the brain stem or posterior columns, pyramidal signs may be absent.

Sphincter Disturbance

Spincter disturbance is uncommon as an early symptom unless there is evidence of a myelitis due to the disease. Occasionally, however, frequency and urgency of micturition or, rarely, incontinence are presenting symptoms, and I have met with a few cases of this type in which pyramidal signs were indefinite or even absent. If the urologist's report is negative, then the possibility of multiple sclerosis should be considered and lumbar puncture performed.

Progressive Spinal Form of Multiple Sclerosis

In approximately 10% of all cases of multiple sclerosis the onset is insidious and the course progressive. This form is more common in the middle-aged than in the young. Differentiation from other causes of paraplegia in the middle-aged may be extremely difficult. Two conditions are apt to be confused with it: cervical spondylosis and spinal cord compression. Some progressive cases of multiple sclerosis have relapses superimposed on their progression, and this fact may be helpful in diagnosis. More important may be the detection of an extraspinal lesion, either from the history or from the clinical findings. Among the latter, nystagmus, other than purely horizontal, temporal pallor of a disk, dysarthria, or intention tremor in an upper limb should be looked for. A positive Lange colloidal gold curve in the C.S.F. may decide the issue. Lastly, radiological proof of a cervical spondylosis does not necessarily mean that associated cord signs are due to it; multiple sclerosis and cervical spondylosis may coexist. Myelography is necessary to establish this fact, as well as exclude the possibility of spinal-cord tumour.

Brain-stem Signs

An early case of multiple sclerosis may present signs which clearly indicate the presence of plaques in both brain stem and spinal cord. However, when signs are confined to the brain stem the diagnosis may not be clear. There are three ways in which multiple sclerosis of the brain stem may present.

(1) *As an Acute or Subacute Encephalitis.*—An abrupt onset of drowsiness, paresis of one or more cranial nerves, especially the third or sixth, with the appearance of motor, sensory, and cerebellar signs in the limbs, may closely simulate a virus encephalitis, particularly that due to poliomyelitis virus, and it is understandable that such cases should sometimes be admitted to infectious-fever hospitals. The absence of fever and neck stiffness, a positive Lange colloidal gold curve in the spinal fluid, a tendency for fresh symptoms to develop in the second or third week of the illness, and the persistence of sensory disturbance are some of the features which would suggest acute multiple sclerosis. Euphoria is occasionally met with in both these types of acute encephalitis, but is relatively more common in multiple sclerosis.

(2) The second group of cases are characterized by focal signs, sometimes suggesting a unilateral lesion, for example, of the pons, but more usually a paresis of a single cranial nerve. *Double vision* occurs at the onset of multiple sclerosis in roughly 15% of cases, in half this percentage as an isolated symptom. The sixth nerve is more commonly affected than the third. Multiple sclerosis is a common cause of a transitory diplopia in a young adult, and here again lumbar puncture may be of the greatest value. *Numbness in the face* may occur either as part of a unilateral pontine picture or as an isolated symptom. If, after extraction of a tooth, numbness persists for a few days it should not be attributed to the effect of a procaine injection. *Bell's palsy* may on rare occasions be the first symptom. Although an absence of pain and of loss of taste with rapid recovery may be noted as unusual features, its possible relationship to multiple sclerosis is usually not considered until later, when the patient presents with undoubted signs of the disease.

(3) *Vertigo* in varying degrees of severity is a relatively common symptom during the course of multiple sclerosis and occasionally it may be the presenting symptom. Vomiting may accompany or precede giddiness. The resemblance to Ménière's syndrome may be close, particularly when a degree of deafness is present. As a rule, however, in multiple sclerosis hearing appears to be normal though audiometry

may show some degree of nerve deafness on one or both sides. Although "epidemic vertigo" and "vestibular neuronitis" are better-recognized causes of an acute vestibular upset with normal hearing, multiple sclerosis should not be forgotten as a possible cause, more especially when nystagmus persists after vertigo has disappeared or other signs are present. *Cerebellar signs* may be prominent at the onset, as shown by dysarthria and a reeling or drunken gait without vertigo; as a rule other evidence of the disease can be found.

Course of the Disease

Most textbook descriptions of multiple sclerosis imply that, although its course is extremely variable, sooner or later a severe degree of disability is inevitable. Although this statement is unfortunately true of the majority of cases, it fails to take into account the possibility of a high resistance to the disease. For example, in the Middlesex Hospital series of 586 cases, 13% of those followed for 15 years showed no disability (McAlpine and Compston, 1952). The preliminary results of a fresh follow-up on which I am at present engaged would appear to confirm the existence of a *benign form* of the disease, characterized in the main by a good recovery from the initial attack and a tendency for relapses to be mild and infrequent or cease altogether. It has long been recognized that after an attack of retrobulbar neuritis the disease may remain quiescent for many years; for this reason such cases are often excluded from a follow-up of this type, and accordingly I have adopted this practice unless on one or more occasions there have been other signs of the disease or changes in the cerebrospinal fluid. However, the emphasis on retrobulbar neuritis in relation to long latency of the disease has tended to obscure the fact that other isolated symptoms such as diplopia or an episode of paraesthesiae may be followed by an equally long latent interval.

Earlier I mentioned certain factors that might influence not only the onset but also the course of the disease. These in order of importance are (1) intercurrent infection, (2) fatigue, (3) emotional upset, and (4) trauma. From work on the effects of pregnancy (Müller, 1949; Tillman, 1950; McAlpine and Compston, 1952) it is clear that its role has in the past been exaggerated. The risk of relapse can be further minimized by discouraging pregnancy until the disease has been stabilized for at least two years, by an extra period of rest after confinement, and by the provision of adequate help in the house so as to reduce fatigue, consequent upon the care of a young baby.

Treatment

The lack of a realistic approach to the problem of multiple sclerosis is chiefly responsible for the negative attitude towards its treatment. The knowledge that no drug is available that can be relied upon to prevent relapses and thus modify the course of the disease is not a valid reason for neglecting general principles in treatment. In a case of rheumatoid arthritis or of chronic asthma the physician is not content to focus his attention on joint or chest but realizes that success or failure may depend on the extent to which he can improve his patient's physical and mental health.

Likewise in treating an early case of multiple sclerosis our attention should be fixed on the constitutional and environmental background of the patient rather than on the nervous system. If arrest of the disease may occasionally occur spontaneously, this fact should encourage us to do our utmost for the early case. Failing an effective remedy, I suggest that the greatest contribution that we can make towards early treatment is to adopt the same attitude of mind as that taken towards the tuberculous patient. If this were done I feel convinced that, in a worth-while proportion of cases, the disastrous results which we see all too often would be avoided or at least mitigated. Therefore every effort should be made to establish the diagnosis at the earliest possible moment.

Turning to general principles, there are two that should be in the forefront of our minds when confronted by an early case. (1) To ensure the maximum degree of recovery from the initial attack and early relapses. This is best attained by an adequate period of rest in bed during the active phase of the disease, followed by prolonged convalescence, varying from two to six months. (2) To adopt all measures which may reduce the risk of relapses. In practice this means careful attention to general health and mode of life. When the diagnosis of multiple sclerosis is suspected admission to hospital should be arranged, preferably under the care of a neurologist, for a fourfold purpose: (*a*) to confirm the diagnosis from clinical and cerebrospinal fluid findings; (*b*) to ensure proper rest in bed; (*c*) to afford an opportunity of correcting any abnormalities in the general health suggested by the history—in particular, possible foci of infection (for example, sinuses, tonsils, teeth, and urinary tract), and to discuss frankly the cause of any anxiety symptoms; and (*d*) to carry out any therapeutic measure that may increase resistance.

The variety of remedies at present advocated scarcely suggests that any will eventually prove to be of value. They include isoniazid, vasodilators, a low-fat diet (Swank, 1955), Evers's uncooked food diet, and lastly vaccines and serums. Of those preparations used in Great Britain liver and vitamin B_{12} are the most popular; multiple sclerosis is not a deficiency disease, therefore their use does not extend beyond the possible effect on general health. Theoretically a claim could be made out for trace elements, in particular copper and cobalt, but in practice they have not so far proved effective. Judged by reports in the literature, the results from the use of corticotrophin and cortisone have been disappointing. If the allergic origin of the disease be used as a working hypothesis some method of stimulating the defence mechanism of the body would seem worth a further trial. In the meantime we must rely on an old-established remedy —namely, arsenic. I have used this for many years in the form of intravenous neoarsphenamine, four courses yearly, with Fowler's solution in between the courses. Although this treatment, if begun early in the disease and kept up for five years or more, does not necessarily prevent relapses, I believe that in some patients it may modify their frequency and severity and so delay or even prevent the stage of progression. In those patients whose resistance is low a downward course occurs despite this or any other form of treatment. An antihistamine drug is indicated when there is an associated allergic disorder or in those patients who can tolerate arsenic only in the form of Fowler's solution.

Many of those who advocate a particular line of treatment in multiple sclerosis are inclined to quote individual cases in which a cure seems to have been produced. They should bear in mind that in at least one patient in every ten resistance is high and there may be no disability after 15 years. In order to prove the efficacy of any method of treatment it would have to be shown that in a series of cases relapses were prevented, and that disability was negligible in more than 20% of a series of cases followed up for a similar period.

Under what circumstances should a patient with multiple sclerosis be informed of the diagnosis? Neurological opinion, in this country, would, on the whole, appear to be in favour of withholding this knowledge until the disease is well established. However, a positive attitude towards the management of the early case demands the intelligent co-operation of the patient, and therefore in responsible adults an explanation of the nature of their illness is essential. A comparison with the known allergic disorders is useful as it affords an opportunity of referring to relapses, to the circumstances which may lead up to them and which therefore must so far as is possible be avoided, and to the importance of complete rest should a relapse occur. A decision to recommend long-term treatment, for example with arsenic, is usually accepted by the patient if the advice is given with a degree of conviction. If tactfully conducted, this method of approach nearly always leads to a quick

adjustment and a readiness to co-operate to the full during the first crucial years of the disease. Above all, the impression must not be left on the patient's mind that he or she is suffering from a mysterious disease about which nothing is known and for which there is no treatment.

Summary

An air of defeatism tends to surround the subject of multiple sclerosis. The reasons for this attitude are examined in some detail.

Aetiology is discussed with especial reference to the allergic theory.

A diagnosis of multiple sclerosis is usually not made until the fourth or fifth year of the disease. The causes of this delay are discussed and early symptomatology is reviewed.

The traditional belief that multiple sclerosis inevitably leads to increasing disability and premature death requires modification in the light of recent studies. A brief reference is made to the concept of varying degrees of resistance and to a benign form of the disease.

A plea is made for a more positive attitude towards treatment. In an early case more attention should be paid to the constitutional and environmental background of the patient. Stress is laid on the importance of rest during active phases of the disease, followed by prolonged convalescence. In responsible adults an explanation of the nature of their illness is essential in order to obtain intelligent co-operation in treatment.

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A new British Standard (2805 : 1957) specifies a range of straight artery (haemostatic) forceps of the Spencer Wells pattern having a screw joint and made of stainless steel. Provision is made for the 5 in., 6 in., 7 in., 8 in., and 9 in. (12.7–22.8 cm.) sizes. The preparation of this Standard was recommended by the Ministry of Health and authorized by the Surgical Instruments and Medical Appliances Industry Standards Committee of the British Standards Institution. British Standard 2805 may be obtained through the Sales Branch of the British Standards Institution, 2, Park Street, London, W.1, price 3s. 6d.

POLYRADICULITIS (LANDRY–GUILLAIN-BARRÉ SYNDROME)

TREATMENT WITH CORTISONE AND CORTICOTROPHIN

BY

R. HUGH JACKSON, *M.C.*, B.M., M.R.C.P.
Senior Registrar

HENRY MILLER, M.D., F.R.C.P.
Physician in Neurology

AND

KURT SCHAPIRA, M.B.
Research Fellow in Neurology

The Royal Victoria Infirmary, Newcastle upon Tyne

The clinical and pathological identity of Landry's ascending paralysis and the Guillain–Barré syndrome (polyradiculoneuritis; acute infectious, toxic, or febrile polyneuritis; or infectious neuronitis, polyneuritis cranialis, etc.) was fully established by the important review of Haymaker and Kernohan (1949). Since then the non-specific nature of the syndrome and its relation to other acute inflammatory diseases of the nervous system, and possibly to allergy, have been noted (Stanton *et al.*, 1953), while the results of treatment with corticotrophin and cortisone have been described by Clarke *et al.* (1954) and others.

In the past three years we have treated five deteriorating cases of this condition with corticotrophin or cortisone, and in this paper we present these cases, review the available literature on the subject, and endeavour to draw some general conclusions.

Case 1

On November 6, 1953, three weeks after a brief attack of acute febrile bronchitis, a 28-year-old docker developed an illness initially regarded as influenzal, characterized by fever, backache, and headache. Twenty-four hours later he developed tingling in the tip and dorsum of the tongue, and, after a similar interval, ascending paraesthesiae and weakness in both lower limbs. By November 9 he could progress round the room only by holding on to the furniture. Weakness of the legs increased further, and on November 13 he noticed paraesthesiae in both hands. His speech became slurred, and food stuck in his throat; there was slight dysuria and some constipation. At this stage he came under medical observation, and over the course of the next few days all deep reflexes disappeared, asymmetrically bilateral facial weakness developed, and loss of superficial sensibility became evident over the whole of both lower limbs, the forearms, and a band round the trunk between nipples and umbilicus. The legs were much weaker than the arms, and when he was admitted to our care on November 18 he was unable to stand. Weakness and muscle tenderness were generalized, but were most marked in the proximal limb muscles. Blood examination, E.S.R., E.C.G., and *x*-ray films of the chest and spine showed nothing abnormal. The only abnormality in the spinal fluid was a protein content of 240 mg. per 100 ml., rising subsequently to [illegible]0 mg.

In view of continuing deterioration, and especially pharyngeal pooling of mucus owing to bulbar weakness, oral administration of cortisone was begun at once. He was initially given 300 mg. daily, but this was reduced gradually to 100 mg. daily by the fifth day, and the smaller amount administered daily for a further five days.