Trauma, Stress, and Multiple Sclerosis

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The possible relationship between physical trauma or psychologic stress and a symptom of nervous system dysfunction that appears or recurs has long puzzled neurologists, psychiatrists and lawyers. Expert opinions have varied from the definite implication of such relationship to the view that neither trauma nor stress causes or even precipitates disease symptoms.

In studying this question, it is important to make the distinction between an etiologic factor and a precipitating one. Prolonged exposure to cold and the resultant chill may be followed by pneumonia, but the causal factor is the pneumococcus; sexual intercourse does not lead to syphilis unless the spirochete is introduced into the system. How emotional factors produce an alteration of normal physiologic mechanisms in a psychosomatic illness such as peptic ulcer disease is unknown. This is also true in multiple sclerosis, where the causal factor is unknown as well.

There is a vast difference between considering an event as some kind of causal factor, or trigger for a pathogenetic mechanism, and considering it a precipitating factor, which brings about a physiologic alteration leading to the appearance of the signs and symptoms of a pre-existing lesion of the nervous system. A specific event, whether it is an accident, a surgical operation, the death or serious illness of a loved one, or an important decision affecting a career or a marriage, represents severe stress in a person's life. Such an event may precipitate an attack of multiple sclerosis (MS). It could call attention to an already existing but previously overlooked symptom. There is some degree of secondary gain, emotional, financial or social, possible for any of us at such a time.

A better understanding of the pathogenic and pathophysiologic mechanisms in cases of MS will help clarify this question.

Pathogenesis

Neither the etiologic agent nor the exact pathogenetic mechanism of formation of the MS plaque is known yet. Whether the disease results from a prolonged slow viral infection or is the result of an alteration of immune mechanisms related to viral infections remains a source of debate.[1]

What seems sure is that the myelin sheath bears the brunt of the pathologic process, which generally spares the axon. As a result, the function of transmitting trains of impulses through the nerve tracts is impaired. In its most benign form, the disease will simply cause swelling but not destruction

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of the myelin sheath; when the edema disappears, complete function is believed to return. The myelin sheath, however, may be destroyed, and a plaque formed. A certain degree of permanent or potentially recurrent dysfunction then persists. When a plaque is formed, an inflammatory cellular reaction within it and in its vicinity always occurs. Depending upon the severity of the process, a glial reaction results in the area of demyelination. This sclerotic plaque is an irreversible lesion. The inflammatory reaction may extend beyond the area of demyelination and thus affect neighboring nerve fibers which have not been involved in the myelinoclastic process. Remyelination may take place, but in those instances where it has been seen, the amount of myelin that is laid down is only a fraction of the thickness of the previously existing sheath. When MS affects a certain part of the white matter, only the central portion of the plaques will demonstrate myelin destruction, while at the periphery simple swelling of the sheath will take place. As the activity of the process diminishes, the peripheral part of the lesion may well recover, leaving only a small area of permanent damage.

It is impossible to determine clinically if neurologic dysfunction is the result of myelin sheath edema or destruction. It is logical to assume that recovery of function which characterizes the remission of MS is due to the resolution of myelin sheath edema.

It is also assumed, although it is unproved, that myelin which has recovered from edema returns to its normal state. It is, however, equally possible that some of its physical and chemical characteristics have been altered to make it more vulnerable to changes of its physiologic environment.

In some instances, when the disease process is particularly severe, axons will be destroyed, and necrosis may even occur.

Pathophysiology

A lesion in the central nervous system, whether it is caused by MS or by some other insult to the nervous system, results in the establishment of a site of selective vulnerability, a *locus resistentiae minoris,* which will become symptomatic when the central nervous system as a whole is subjected to a nonspecific harmful influence. This explains why general physiologic alterations may produce focal signs and symptoms.

The pathophysiology of MS has been the subject of many excellent studies.[2,3] In contrast to the plasticity of synaptic functions, axonal conduction is stereotyped, normally serving to transmit integrated neuronal output faithfully and rapidly to distant sites. In MS this axonal function breaks down, resulting in a decrease or distortion of information transfer.

The normal impulse is characterized by a safety factor, enabling conduction to occur in the presence of potentially adverse conditions. The safety factor is an action current reserve, which is defined as the ratio of the action current available for propagating an impulse to a minimum amount needed just to maintain conduction. When the nerve fiber is deprived of its myelin sheath, the safety factor is decreased due to the wasteful short-circuiting of action current through the bare internodal region. As the safety factor declines from normal, there is a drop in the conduction velocity, since it takes time for the action current to stimulate the resting

membrane ahead of the advancing impulse. As a result, when the safety factor is decreased to a level that barely permits conduction to occur, the smallest additional insult produces a conduction block even though similar changes would not block the normal nerve. An increase in temperature can lower the conduction safety factor, and, if the latter drops below a critical level, conduction suddenly ceases. Conduction velocity decreases with increasing demyelination, 6.3% of the normal thickness of myelin being the minimum needed to sustain conduction. In a nerve tract which has a demyelinating lesion, loss of clinical function probably depends on what fraction of these fibers is completely blocked, as opposed to simply having impaired conduction with increased latencies. Any factor which serves to alter the number of blocked fibers can be expected to have marked effects on clinical function.

Rasminsky and Sears[4] established that the reduction of conduction velocity in demyelinated fibers is due to an alteration in the passive cable properties of these fibers. They also suggested that a local increase in the amount of extracellular fluid may contribute to conduction abnormalities because of edema. Davis *et al.*[5] concluded that lowering the concentration of calcium may diminish the stabilizing effect that calcium normally has on the damaged fibers. Thus, slowing of conduction, particularly when severe and of unequal degree in different fibers subserving the same function, is likely to interfere with clinical tests which depend upon the delivery of synchronized bursts of impulses at particular sites in the nervous system. Another possibility suggested by the morphologic characteristics of acute MS lesions is that compression of critically demyelinated fibers secondary to edema in regions of tight neural constriction such as the scleral and optic canals may contribute greatly to conduction abnormalities.

One of the major environmental factors responsible for decreasing the safety factor and thus producing symptoms is an elevation of temperature. Rasminsky[6] was able to demonstrate the presence of reversible conduction block in individual fibers with temperature increases within the physiologic range of as little as .5°C. Becker *et al.*[7] produced improvement of vision and pupillary function in patients with MS by the use of oral phosphate administration, which leads to complexing of serum ionized calcium and subsequent lowering of the serum ionized calcium level. This is believed to represent restoration of impulse conduction in some blocked demyelinated optic nerve fibers. In addition, it is possible that an increase in the conduction velocity of slowly conducting diseased fibers contributes to this effect. Experiments have indicated that conduction defects in demyelinated nerve are direct consequences of myelin loss and that the beneficial effect of lowering calcium is expected on the basis of the known effects of calcium on the ionic conductance kinetics of the excitable membrane. Thus, a 60% decrease in calcium concentration can be expected to increase the conduction velocity by 40-50% in a fiber with only 10-20% myelin remaining. In addition, and possibly more important clinically, fibers blocked by demyelination are restored to conduction.

Other possible pathophysiologic mechanisms to explain the appearance of symptoms have been mentioned. Miller[8] suggested that significant local circulatory disturbance may arise in the human spinal cord as a result of the

afferent stimulation excited by a painful injury. In his review of the relationship between trauma and MS, he pointed out that all the injuries sustained by his patients were painful and

> must inevitably have involved the powerful and contingent stimulation of peripheral nerves. It is surely not fanciful to suggest that the activity of the pathological process might be potentiated or the vitality of a diseased area diminished by local circulatory changes produced in this way.

There is, however, no clinical or experimental evidence to indicate that this theory is applicable to MS.

The experimental and clinical evidence clearly underlines the fact that environmental factors, both external (heat) and internal (calcium ion concentration), influence the symptomatic manifestations of existing lesions within the central nervous system. The presence of MS plaques results in the loss of part or all of the system's margin of safety. This system will continue to function normally until an event which introduces an alteration in the physiologic state produces dysfunction and thus the emergence of neurologic signs and symptoms. While this mechanism has been most extensively studied in MS, it is not specific for it and can be demonstrated with lesions of the nervous system due to other causes.

Clinicopathologic Correlations

One of the most puzzling features of MS is the inconsistency between the central nervous system pathology and the occurrence of symptoms and signs. Disability in MS is probably due to a functional imbalance set up by demyelination, rather than to the usual concept of lesion pathology.[9]

Postmortem examination invariably reveals from several to many plaques for which clinical manifestations cannot be elucidated. In fact, the single most characteristic lesion of MS, periventricular demyelination, produces no recognizable symptomatology. In some postmortem series,[10] as many as 16% of cases of MS are found to have been asymptomatic. It is possible that symptoms were produced but were so transient that they were not brought to the attention of a physician. However, in some instances,[11] in spite of excellent documentation, the site and size of lesions make it extremely difficult to understand the absence of signs and symptoms.

Thus, on the one hand, a person may have extensive involvement of the nervous system by MS without being aware of it, while on the other hand, he may have a single strategically placed small lesion with devastating effects upon nervous system function. The clinical manifestations of this disease depend upon the appropriate combination of site, possibly size, and external and internal environmental factors leading to altered physiology.

This explains the fact that patients with, for example, a plaque in the medial longitudinal fasciculus may be completely asymptomatic at all times, and may complain of diplopia only when venturing out of their air-conditioned hotel in July, or following a minor car accident on an icy road.

The appearance of a new or first symptom has almost invariably been

interpreted as resulting from the formation of a plaque of demyelination. While this is unquestionably possible, alternative considerations must be kept in mind. The symptom may be the first clinical manifestation of a lesion which has been in existence for some time, but which has been brought to the fore by physiologic factors such as heat, changes in calcium concentration, or other factors including physical trauma and psychological stress. The problem becomes even more complex when considering exacerbations in a patient with known MS. These may represent the formation of new plaques, extension of previously existing plaques or recurrence of previously experienced symptoms due to physiologic alterations. In a review of 105 attacks of MS in 60 patients, Thygesen[12] pointed out that clinical observation suggests that an attack often affects precisely one previously damaged site of the central nervous system, and is a "true copy" of previously remitted symptoms. In fact, he provides statistical evidence to prove that the symptoms of the first attack are apt to occur in the same site in the next attack. In analyzing his cases, he makes a distinction between simple intensification of existing symptoms,. recurrence of previously completely remitted symptoms, and dissemination, i.e., manifestations of entirely new symptoms. In his analysis, entirely new symptoms occurred in only 19% of the total of 105 attacks. This and other studies strongly suggest that exacerbations are more likely to represent physiologic alterations than the production of new plaques, or expansion or reactivation of old ones. They also indicate that what can be called psychologically induced recall phenomena exist. Many patients with MS have admitted upon close questioning that certain symptoms never actually disappear, but that they get accustomed to them so that they are unaware of them until some event brings them to mind.[13]

Diagnostic Procedures

The problem of establishing the existence of asymptomatic lesions in MS has been considerably helped by the utilization of several diagnostic techniques.

(1) The hot bath test: Immersing a patient in a bath of water at a temperature of 104°F. (40°C.) will often result in the reappearance of symptoms which have been present in the past, such as double vision, numbness of an extremity or decrease in visual acuity, as well as of neurologic signs such as nystagmus, cerebellar incoordination or extensor plantar response which were not present during the neurologic examination. More important, the patient may present symptoms which he or she had never complained of previously. Whatever signs or symptoms become apparent as the result of raising body temperature, they always disappear with cooling. No permanent change in neurologic state has ever been produced by this test or by casual exposure to elevated ambient temperature. This test is based upon the known alterations in nerve conductivity through demyelinated areas with a reduced safety factor when body temperature is raised.

(2) Color vision testing: The optic nerve is one of the most commonly involved sites in MS. The central fibers, originating in the macular region of the retina, seem to be preferentially involved. Minor degrees of optic or

retrobulbar neuritis need not produce a noticeable decrease in visual acuity but will result in a diminution of color vision. When such alteration affects only one eye, the patient will not notice it, but testing each eye independently will show color blindness, usually of the red-green type, when Ishihara or AO pseudo-isochromatic color plates are used. Color blindness in one eye is distinct evidence of a previous unnoticed involvement of the optic nerve. Such monocular color blindness may also be brought out by the hot bath test.

(3) Evoked response studies: The introduction of visual evoked response studies, using either the flash, or preferably the pattern reversal stimulus, has proved extremely useful in demonstrating the existence in the visual system of totally unsuspected lesions: Feinsod and Hoyt [14] noted abnormalities in 15 MS patients who had never had any indications of visual involvement by history or ophthalmologic examination. Halliday *et al.*,[15] using a checkerboard pattern of light and dark squares reversed at a frequency of two per second, found abnormalities in 86% of patients with normal optic discs and without a history of optic neuropathy. McSherry and O'Brien [16] noted abnormalities of the visual evoked responses in 69% of patients with MS who denied ever having had visual symptoms.

(4) The Kimura blink reflect: This reflex is elicited by stimulating the supraorbital nerve and measures the response in the facial nerve. Kimura demonstrated that 40% of patients with MS who have no clinical signs of brainstem involvement had a measurable delay of the response.[17]

(5) Brainstem auditory evoked responses: The auditory evoked response has also been measured in MS as an indicator of the integrity of brainstem structures. Robinson and Rudge found that it was abnormal in half the patients with MS without detectable brainstem signs or symptoms.[18]

(6) Psychologic testing: It has long been known that psychologic alterations occur in patients with MS. These have been variously described as reactions to the disease, concommitants of the physical disability, or specific manifestations of the illness. Peyser *et al.*,[19] have recently demonstrated that significant cognitive impairment, not recognized clinically, may occur quite early in the course of the disease and is independent of the degree of neurologic dysfunction. In fact, significant cognitive impairment, based upon the Halstead Category Test and the Similarities subtest of the WAIS test, was found to exist in 48% of patients judged to be intellectually and mentally intact by the examining neurologist. It is suggested that this cognitive impairment may well be a manifestation of the otherwise asymptomatic plaques in the subcortical white matter.

(7) Computer assisted tomography (CAT scan): There are several reports of asymptomatic plaques having been demonstrated in the cerebral white matter by means of this technique.[20]

The diagnosis of MS is still based upon purely clinical criteria. No specific, pathognomonic laboratory test exists for this disease, and thus the demonstration of signs and symptoms of multiple lesions remains the basis for this diagnosis.[13] The diagnostic techniques that have just been discussed have been of great value in moving suspected MS patients from the possible into the probable category.

Discussion

For the purpose of this discussion, physical trauma, except as it affects the skull or spine directly, has been assumed to be equivalent to serious emotional trauma in that the shock and pain of the physical injury probably sets into motion the same physiologic mechanisms that are triggered by emotional factors. In regard to direct cranial and spinal trauma, careful consideration must also be given to the possible effects of concussion as well as to contusion. In cases of concussion, it is extremely unlikely that the physiologic changes, or even the microscopic changes which result, could lead to the formation of subcortical plaques or spinal cord lesions. Even in cases of contusion, the scattered nature of the typical MS lesions makes a causal relationship between the two events most unlikely.

At the end of his review of the problem, Miller[8] concluded that the relationship between injury and neurologic illness in such cases may be fortuitous, causal, or that the patients were already suffering from MS without clinical signs, and that trauma converted a silent into an overt disease. He thought the third possibility the most likely one.

Even if physical trauma is to be considered as a precipitating (not a causal) factor, a reasonable time relationship must exist between the injury and the development of symptoms. Edema of myelin can develop in a matter of minutes; thus to ascribe a symptom occurring several days or weeks after the event to involvement of the myelin sheath is completely unreasonable. In McAlpine's series of 250 cases using the unrealistic maximum latency period of three months, trauma could be implicated as a precipitatory event in only 14% of the cases.[21] Furthermore, in the extremely unlikely event that a direct and timely relationship does exist between trauma and the emergence of a symptom of MS, it is impossible to ascribe to the injury the subsequent course of the disease with its remissions and exacerbations, and its multiplicity of signs and symptoms. Based on the available evidence, it is absolutely clear that no mechanism exists by which physical trauma can influence the development of the pathologic lesions of MS.

McAlpine also stated: "In the present state of our knowledge, the possibility of a causal relationship in certain cases between trauma and MS cannot be denied."[21] This is a loose way of using the word "causal"; "precipitating" would have been more exact.

Accidents or episodes of psychologic stress may also be the result of MS. For example, a patient who is unaware of a mild cerebellar gait disturbance, loss of position sense, or incoordination may be more prone to an accident without knowing it. The subtle psychologic and cognitive alterations which occur in the disease may also produce an exaggerated psychologic response to an occurrence or situation which might have been handled quite differently by a well person. The symptoms of MS may not only be transient, lasting no longer than a few minutes, but may also be extremely bizarre. Their true nature therefore may not be recognized. Symptoms are frequently misinterpreted. One of the most common illustrations is that of the MS patient with urinary frequency, urgency and stress incontinence who has been diagnosed and treated for urinary tract infection in spite of the absence of dysuria, until the true nature of his urinary disturbance is discovered. Thus, what was a manifestation of the disease may well have

been passed off as inconsequential or, more frequently, hysterical in nature.

The difficulty in distinguishing early MS from hysteria was stressed by Buzzard [22] as long ago as 1897 in the following words: "In its infancy the name given to MS is hysteria." It must also be remembered that in all the phases of MS, hysterical manifestations complicate the picture.[23] Brain[24] also observed that hysterical symptoms occur more often with MS than with other organic diseases of the nervous system. All diseases of the nervous system manifest themselves in loss of function: "functional" is not the antithesis of "organic" and is not a euphemism for "hysterical." The relationship between emotional trauma, symptomatology ascribed to conversion, and MS raises some extremely important questions in terms of pathophysiology. Mei-Tal *et al.*[25] cite a number of case reports which are relevant. In one, a 40-year-old woman became unable to walk during an air raid. When finally allowed to leave the shelter, she had to be carried out because of her inability to walk. After that time she recovered somewhat but manifested a persistent gait abnormality. A few years later, the diagnosis of MS was made on the grounds of spastic paresis. In another case, a 34-year-old woman saw her three-year-old son being hit by a car. At the time she experienced sudden general body weakness, particularly in the legs, and was unable to move for some minutes. Within a few weeks she started complaining of paresthesiae in her legs and gradual weakness of gait. Several months later she was diagnosed as having MS on the basis of objective findings.

Such case histories are frequent. It is only in retrospect that the initial episode, often ascribed to hysteria, becomes significant as a manifestation of an already existing lesion. MS patients, as well as many other persons suffering from diseases of the nervous system, quite often have what might be called real symptoms upon which are superimposed manifestations which are clearly hysterical in nature. The patient who complains of triplopia or quadriplopia, clearly hysterical complaints, may simply be exaggerating a true diplopia resulting from an internuclear ophthalmoplegia. One patient who had loss of color vision secondary to a well documented optic neuropathy in the right eye subsequently demonstrated a similar loss of color vision in the completely unaffected left eye.

It must also be recognized that MS will produce nonsymptomatic neurologic signs and thus may escape attention. Nystagmus produces no complaints except for the extremely rare oscillopsia; serious cognitive impairment may be completely overlooked or of no clinical significance, depending to a large extent upon the patient's occupation; hyperreflexia of one extremeity or a Babinski sign without significant weakness or spasticity will completely escape the patient's attention. These signs of neurologic dysfunction will in most instances be noticed only when the patient develops symptoms that make him seek medical attention. The presence of these abnormal neurologic signs at the time of the first examination does not necessarily mean that they appeared at the same time as the actual symptoms.

Many papers have been devoted to psychologic studies of patients with MS. It has been suggested that certain psychologic types might be predisposed to the disease, but there is no convincing evidence to support

such a concept. On the other hand, Peyser *et al.*[26] have divided patients with well documented MS into several groups, providing clinically useful guidelines in regard to diagnosis and management. In some of these groups, hysterical manifestation or psychologically induced recall phenomena are more likely to occur than in some of the others. The suggestion by a number of authors that psychologic or physical trauma results in the activation of autonomic phenomena appears less far-fetched today in view of our current knowledge of the effect of psychologic variations upon the transmission of the nerve impulse in individuals with MS.

Weinstein,[27] in his excellent review of the behavioral aspects of MS, makes several important points. Emotional tension can certainly worsen symptoms and impair performance, but this does not make it an etiologic factor. Moreover, many of the stresses that are cited are common to all people, and it is not easy to grade the degree of emotional trauma. With one exception, almost all studies of the effect of emotional stress have been retrospective. In the one controlled study,[28] there was no statistically significant correlation between the onset of the symptoms and their emotional antecedents when patients with MS were compared to subjects with other diseases of the nervous system. Another consideration is that patients may ignore symptoms until some disturbing event creates anxiety and a sense of vulnerability. This is particularly the case with sensory and visual phenomena. There is also the need of a disabled person to find some familiar explanations or reationalizations for his condition. Attributing illness to a family crisis, or to overwork, has the effect of strengthening one's sense of family or occupational identity.

In some ways MS serves as a model for other diseases of the nervous system. Thus the persistence of symptoms and even signs after head and neck trauma for many months, even for years, can be explained by the same mechanisms, in particular the acceptance of the concept of selective vulnerability. It has been well established that symptoms of Parkinsonism, myasthenia gravis, hyperthyroidism and other diseases will often become apparent for the first time after emotional stress or physical trauma. No one has suggested that these events produce a loss of the pigmented cells of the substantia nigra, or alter the postsynaptic membrane of the neuromuscular junction in myasthenia gravis. Thus, there appears to be no logical reason to postulate that the destruction of myelin in MS might follow such nonspecific events.

In spite of the fact that knowledge of the pathogenesis of MS remains incomplete, no evidence supports the hypothesis that physical trauma or psychologic stress plays a role in its causation. Trauma and stress must be considered precipitating factors, not causal ones. That transient symptomatic exacerbations of the disease may follow such events is conceivable. The existence of unsuspected, asymptomatic lesions has now been documented by means of new diagnostic techniques which explain how physiologic alterations produced by physical or emotional trauma may lead to the emergence of temporary symptoms. These physiologic alterations, however, do not influence the pathologic manifestations of the disease in the central nervous system and cannot be implicated in the formation of new plaques, nor in the genesis of permanent neurologic dysfunction.

There remain two questions which must be dealt with on legal grounds alone, since they cannot be resolved medically: would the patient subsequently have shown symptoms of the disease had there been no trauma or stress? or, alternatively, might not the onset of the disease have been postponed for several years? Our experience with MS strongly suggests that the basic course of the disease is not influenced by such precipitating factors.

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