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Symposium on Clinical Neurology: New Approaches to Old Problems

Multiple Sclerosis

A Critical Update

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The past several years have seen an enormous proliferation of the literature of multiple sclerosis, reflecting intensive research activity in numerous areas. Much of it has recently been reviewed in great detail elsewhere[35] and can only be summarized here. Virology, immunology, epidemiology, genetics, neurophysiology, and radiology have all contributed new information. Unfortunately much of it has been contradictory and controversial. The results of some of the newer diagnostic techniques are forcing a re-examination of long held ideas regarding the natural history of the disease and its pathogenesis.

Two major hypotheses regarding etiology and pathogenesis continue to dominate research in multiple sclerosis: the search for a single, specific causative viral agent with prolonged latency, and the discovery of an altered immunologic status, based upon the animal model of experimental allergic encephalomyelitis. In spite of very large amounts of time and money spent on these endeavors, knowledge of the etiology and the exact pathogenesis of the disease still eludes us. No reliable laboratory test for the diagnosis or for the measurement of the activity of the disease has become available.

Because of these factors, therapeutic regimens, many of which reflect a rather naive understanding of the natural history and pathology of multiple sclerosis have been proposed in support of a particular hypothesis, ranging from the reasonable to the outlandish.[41]

ETIOLOGY AND PATHOGENESIS

Virology and Immunology

The search for a single, specific slow viral infection continues unabated. The reports by Carp et al.[6] and by Henle et al.[20] of an agent

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associated with multiple sclerosis have been refuted by others.[8, 25] Burks[3] claims to have recovered a corona virus from the brains of 2 patients with multiple sclerosis and Mitchell et al.[28] have reported isolating from the bone marrow of 4 patients with multiple sclerosis a filterable agent which causes a cytopathic effect in cell cultures, an effect which can be passed to further cultures. Both of these reports await confirmation. The large numbers of papers dealing with immunologic studies in multiple sclerosis are characterized by the extraordinary inconsistency of their results and have led to little useful information. There is an almost obsessive preoccupation with measles as the culprit in spite of the publications of many studies which fail to establish a reasonable association of this agent with multiple sclerosis. Fuccillo et al.[16] studied 108 patients with multiple sclerosis who had an increase in serum measles antibodies but found no evidence of altered cellular immunity to measles, cytomegalovirus, herpes virus I and II or vaccinia. Raine et al.[38] investigated active demyelinating central nervous system lesions in acute and chronic multiple sclerosis using peroxidase-conjugated antimeasles antibody but found no evidence of measles antigen. Symington and Mackay[45] studied lymphocyte reactivity to measles, parainfluenza and vaccinia virus in 12 patients with early multiple sclerosis and failed to demonstrate any difference in activity from a control group. They suggest that the deficient cellular response to measles virus and possibly to other common viruses is a consequence of the disease itself and not a causal factor.

Abnormalities of cell-mediated immunity have been reported in patients with multiple sclerosis. Several studies have suggested that patients with multiple sclerosis manifest a broad-based depression of cell-mediated immunity, while other studies do not. Evidence of increased cell-mediated immunity to neural antigens in patients with multiple sclerosis has also been observed by some groups but not by others based upon various *in vitro* correlates of cell-mediated immunity including antigen-induced lymphocyte transformation or proliferation, macrophage migration inhibition, direct leukocyte migration inhibition and inhibition of macrophage migration in electrical fields.[35] Lisak et al.[23] found hyporesponsiveness of leukocytes to myelin basic protein, central nervous system extract, crude measles antigen, purified measles nuclear core, and other viral antigens, but failed to show a difference in the pattern of reactivity in a small group of patients with active multiple sclerosis compared with normal subjects, regardless of the stage of clinical disease. They concluded that this hyporesponsiveness found to measles and other viruses in studies of large groups of patients with multiple sclerosis using the buffy coat migration techniques as well as the increased serum and cerebrospinal fluid antibodies to several of the viruses may represent a broad-based deficit in immunologic control and feedback mechanisms, and does not imply a particular viral etiology of multiple sclerosis.

Levy et al.[22] have reported that lymphocytes from patients with multiple sclerosis form rosettes around measles-infected cells, thus giving an important boost to the measles theory by claiming 100 per cent

accuracy in diagnosis. Unfortunately, they did not perform similar tests on the siblings of their patients with multiple sclerosis. Offner et al.[31] were the most recent to report that while there were significantly more rosettes formed by lymphocytes from patients with multiple sclerosis, there was considerable overlap between the two groups.

Antel et al.,[1] in a study of the mitogen responsiveness and suppressive cell function in multiple sclerosis, found reduced T-cell responsiveness to mitogens. The number of circulating T-cells was reduced, but the number of B-cells was preserved. They pointed out that these abnormalities may well reflect the genetic endowment of patients with multiple sclerosis, rather than being related to a specific viral infection. In fact, several authors[2, 14, 32] have demonstrated that the high viral titers to measles found in their patients with multiple sclerosis were associated with histocompatibility type rather than with multiple sclerosis.

That some kind of association between measles and multiple sclerosis exists is undeniable, but there is ample evidence to suggest that other viruses play a similar role.[35] That viral infection plays an important role in the pathogenesis of multiple sclerosis appears to be inescapable; that a single, specific viral agent is responsible for the disease appears highly unlikely. In the absence of an animal model of the disease, it is going to be extremely difficult to actually prove that any agent isolated from brain or other tissue in patients with multiple sclerosis is the causative agent. Immunologic studies to date have yet not established if multiple sclerosis is the result of a hyperimmune state or a cellular immunodeficiency although the latter possibility, when coupled with the fragmentary genetic data, appears to be more promising.

Relationship with Experimental Allergic Encephalomyelitis

The lack of an animal experimental model for multiple sclerosis has frustrated investigators for many years. That experimental allergic encephalomyelitis (EAE) may indeed be such a model appears to have received considerable support from the work of Wisniewsky and Keith,[49] who reported having produced a spontaneously remitting and recurrent disease in guinea pigs with histologic lesions which are quite reminiscent of multiple sclerosis. The presence of bizarre, multinucleated glial cells, however, should raise the possibility of a relationship with another demyelinizing condition, progressive multifocal leukoencephalopathy. Furthermore, recurrent episodes of the human equivalent of experimental allergic encephalomyelitis, disseminated vasculomyelinopathy, though rare, are not unknown.[37]

At the present time, in spite of much evidence to the contrary,[35] the experimental allergic encephalomyelitis model is still being pursued with enthusiasm and vigor. Whitaker[47] made an important contribution to the study of this problem when he examined the distribution of myelin basic protein in central nervous system lesions of both multiple sclerosis and experimental allergic encephalomyelitis. Marked diminution of reactivity with anti-myelin basic protein occurred in early lesions of multiple sclerosis and extended far beyond

any identifiable inflammatory elements; in both parenchymal and perivascular areas, lipid laden macrophages in plaques of multiple sclerosis frequently contained myelin basic protein. In experimental allergic encephalomyelitis, however, myelin basic protein was relatively well preserved in the brains of guinea pigs. Normal appearing patterns of myelin basic protein existed adjacent to the perivascular cellular infiltrates and macrophages containing myelin basic protein were rare. Whatever mechanism or mechanisms in multiple sclerosis promote loss of myelin basic protein, the loss is marked once the process is initiated. Reactivity of anti-myelin basic protein with normal white matter in brain tissue from patients with multiple sclerosis could not be distinguished from that of normal brain.

On the other hand, in experimental allergic encephalomyelitis loss of myelin basic protein was co-extensive with the cellular infiltrate, and myelin basic protein was present only immediately adjacent to the outer rim of perivascular cells. Cells containing myelin basic protein were very rare in the lesions of experimental allergic encephalomyelitis, compared to the lesions of multiple sclerosis. Although the initial event for damage and removal of myelin basic protein remains unidentified, there is yet no convincing evidence that the mechanism for loss of myelin basic protein in multiple sclerosis is a direct result of either cell-mediated demyelination or antibody to intact myelin basic protein.

Antibodies to intact myelin basic protein are uncommonly found in serum or cerebrospinal fluid of patients with multiple sclerosis, and cell-bound antibody to intact myelin basic protein has not been detected in lesions of multiple sclerosis. Degradation of myelin basic protein may be brought about by the action of acid proteinase which is increased in plaques of multiple sclerosis. This alone, however, does not account for the differences in distribution of myelin basic protein in experimental allergic encephalomyelitis and multiple sclerosis, because acid proteinase is also increased in the brains of animals with experimental allergic encephalomyelitis. The results of his study suggest differences between multiple sclerosis and acute experimental allergic encephalomyelitis in both the pattern of removal of myelin basic protein during myelinolysis and the subsequent disposal of myelin basic protein.

In another study, Gutstein and Cohen[18] compared the cerebrospinal fluid of sheep with experimental allergic encephalomyelitis and that of patients with multiple sclerosis. In the former they detected antibody to myelin basic protein as well as excess free myelin basic protein. In multiple sclerosis, only free myelin basic protein could be found. They also report that in experimental allergic encephalomyelitis, myelin basic protein antibodies entered cerebrospinal fluid from serum by passive transfer, a mechanism they propose as an explanation for the presence of viral antibodies in the cerebrospinal fluid in multiple sclerosis. They caution that the use of experimental allergic encephalomyelitis as a model for multiple sclerosis should be carefully questioned. On the basis of his review of tissue culture studies of demyelinating disease, Seil[43] stated that the demyelinating factor in mul-

tiple sclerosis is induced by a different antigen than that which induces the antibody in experimental allergic encephalomyelitis and may therefore have a different meaning with regard to pathogenesis. He concluded that result of studies of serum antimyelin factors in experimental allergic encephalomyelitis cannot be extrapolated to multiple sclerosis, and the relevance of serum antimyelin factors to underlying causative mechanisms in multiple sclerosis has not been established.

The problem remains unsolved. However, the suggestion has been made that the initiating mechanisms in multiple sclerosis and in experimental allergic encephalomyelitis may be identical, but that the propagative mechanism underlying multiple sclerosis is lacking in experimental allergic encephalomyelitis; thus, the latter would indeed be useful as a model for initiating a systemic immunologic disturbance which, in some individuals, would result in nonspecific pathologic changes (including alteration of the blood brain barrier); in others it would produce the classical perivascular demyelination, while in still others would trigger a special mechanism that would form plaques of multiple sclerosis. A major obstacle to this hypothesis has been the generally accepted statement that the blood-brain barrier is intact in multiple sclerosis. This concept, already questioned previously[34] has now clearly become untenable in view of the fact that in certain patients with multiple sclerosis, radionuclide brain scans and contrast-enhanced computed tomography reveal significant alterations of the blood-brain barrier. The knowledge that an alteration of the blood-brain barrier indeed occurs in multiple sclerosis at some time and persists for various periods of time, also gives credence to the belief that multiple sclerosis should no longer be considered to be a disease restricted to the nervous system, but rather a systemic illness which manifests itself exclusively by producing lesions in the central nervous system.

Epidemiology and Genetics

Kurtzke[21] has unequivocally stated that multiple sclerosis is a geographically related disease and thus can be thought of as an acquired environmental (exogenous) illness, and that all the epidemiologic information would be most easily explained if multiple sclerosis were an infectious (viral) illness with prolonged latency. In support of this, among other arguments, he alludes to the curious sudden "epidemic" of the disease in the Faroe Islands which would appear to have followed the presence of British troops during World War II. This geographic explanation may be too simplistic since data referring to latitude and longitude can just as well be interpreted as denoting a predisposition among populations of predominantly Germanic (including Anglo-Saxon and Scandinavian origin). The important of environmental factors, confirmed by immigration studies,[35] cannot be denigrated but will have to be correlated with genetic (histocompatibility) studies. Both exogenous (probably infectious) and endogenous (immunogenetic) factors will have to be considered to understand the geographic distribution of multiple sclerosis.

A great deal of interest has been generated by the reports of Cook et al.[10] and others which purport to establish an association between multiple sclerosis and close contacts with household pets, small dogs in particular. Other investigators have not found such association, and Sylwester and Poser[44] were able to demonstrate a similar statistically significant association between the disease and exposure to cows and/or chickens. Furthermore, they also pointed out that any risk factor associated with exposure to dogs in their study could be ascribed to the fact that individuals who have cows and/or chickens also are more likely to have dogs. The implication of the association with dogs is that canine distemper virus (a relative of measles) may play a role in the etiology of the disease. A study by Nathanson et al.[30] of multiple sclerosis and canine distemper in Iceland conclusively showed that multiple sclerosis has occurred in that country in regions in which distemper has been essentially absent for close to 70 years. Thus, Iceland is a country with a very high prevalence of multiple sclerosis in the virtual absence of distemper. In addition, the almost total elimination of dogs in Reykjavik for at least 50 years has not prevented a high prevalence of multiple sclerosis.

Most of the published studies of potential risk factors exemplify the dangers of playing statistical games with data obtained retrospectively from small numbers of subjects. Such studies are designed to test a particular hypothesis and collect only information which the investigator believes to be relevant. Further confusion is created by failing to distinguish between causative and precipitating events. What is yet to be accomplished is a collaborative effort, involving large numbers of patients with multiple sclerosis and well selected controls, including siblings and coeval non-siblings exposed to similar environmental factors, investigating all possible risk factors.

Histocompatibility studies of patients with multiple sclerosis have opened up perhaps the most important and exciting avenue of research in this disease in many years. The original reports by a number of investigators of a significant increased incidence of the histocompatibility antigens A3, B7, and in particular, DW2 in western European and North American Caucasians strongly suggested that a genetically determined factor may play an important role in the pathogenesis of multiple sclerosis.[35] As more populations were studied, however, it became quite clear that the association with these particular antigens was quite inconsistent (Table 1). An additional important finding relates to the statistically significant decreased incidence of certain histocompatibility antigens which suggests the possible existence of protective genetic factors as well.

The relationship between histocompatibility antigens and the presence of elevated viral antibody titers[2, 14, 32] offers a potentially fruitful area of investigation for the purpose of establishing the pathogenic significance, if any, of the many immunologic alterations that have been reported in multiple sclerosis.

The hope of identifying groups and individuals prone to develop multiple sclerosis on the basis of these promising studies has yet to be

Table 1. *Statistical Significance of Histocompatibility Antigens in Patients with Multiple Sclerosis*

GROUP	I	II	III	IV	V	VI	VII	VIII	IX	X	XI
COUNTRY	USA	USA	USA	CAN	DENM	NORW	GER	AUST	ISRL	IRAN	JAPAN
NO. OF PATIENTS	135	330	56	224	209	46	1000	50	197	35	41
ANTIGEN											
A1	−.025		0		−.05	−.05	−.001	0	0	0	0
A3	0	0	+.005	+.01	+.01	0	+.001	+.01	0	+.001	0
A10	0		0	0	0		0		+.02	−	0
A11	0		0	0	0		0	0	+.04	+.001	0
AW19	−.025		0	0	0		0	0	0	0	0
B7	+.05	0	+.025	+.001	+.001	+.05	+.001	+.005	0	+.005	0
B8	0		+.05	0	0	0	0	0	0	0	+
B12	−.05		0	−.005	−.05	−.05	−.001	0	0	0	−
B18	0			+.005	0	0	0	0	0	0	0
BW15	0		0	0	0	0	−.001	0	0		0
BW17	0			0	−.01	0	0	−.05	0	0	0
BW22	0		0	0	−.05	0	0	0	0	0	0
BW35	+.005			0		0			0	0	0
BW40	−.01			0		0			+.001	0	0
DW2		+.00001			+.000002	+.001		+.0001	0		0

I US JNSci 34:287,77
II US Tiss Ant 9:54,77
III US JNSci 22:419,74
IV Canada JNSci 32:371,77
V Denmark Transpl Rev 22:148,75
VI Norway JNSci 32:187,77
VII Germany Cit.V
VIII Australia JNSci 32:153,77
IX Israel Tiss Ant 10:291,77
X Iran JNNsPsy 41:699,78
XI Japan Tiss Ant 10:191,77

realized. In an extremely important study, Eldridge et al.[11] investigated seven families with two or more first degree relatives affected with multiple sclerosis and reviewed 28 similar families reported elsewhere. No consistent segregation of HLA type was noted between affected and unaffected individuals in these families. They concluded that there is not a single mapping in the genetic complex which predisposes to multiple sclerosis. In none of the seven families was there a specific haplotype which occurred only in affected members. There seems to be little or no relationship between genes at the HLA-A or B locus or DW status and the course of the disease. No particular relationships between HLA type or DW2 phenotype and measles antibody titer was observed.

Several conclusions can be drawn from the many studies of the HLA system in multiple sclerosis: there may well be a genetic factor, located in the vicinity of some of the loci on the sixth chromosome, but these loci are quite different in various populations. Secondly, a single specific genetic association is unlikely but it is probable that the associations are secondary effects of linkage dysequilibrium, a tendency of certain alleles of linked but different loci to occur in association; what may be genetically determined is an abnormality of antibody production.[9] Identification of an individual's haplotype or genotype even in an affected family has no predictive value whatsoever. It is then the combination of genetic factors and exposure to a variety of viral agents which probably determines the risk of multiple sclerosis.

DIAGNOSTIC METHODS

Cerebrospinal Fluid

Cohen et al.,[7] using a radioimmunoassay of myelin basic protein, reported having found a direct correlation between the levels of myelin basic protein in cerebrospinal fluid and the clinically determined activity of the disease. False-positive results included other conditions characterized by destruction of myelin. They claim, however, that the material is found only very rarely in patients with strokes. A number of authors[1] have confirmed the value of agarose electrophoresis for the demonstration of oligoclonal IgG bands which can be found in over 90 per cent of patients with multiple sclerosis. Unfortunately, the rate of false-positive results can be as high as 40 per cent and thus the test is hardly specific for the disease. The significance of these oligoclonal bands remains obscure. Because of the technical difficulties relating to this procedure, it has not yet gained wide clinical acceptance. The determination of cerebrospinal fluid IgG by radioimmunoassay and other methods remains the mainstay of cerebrospinal fluid diagnosis, although its overall accuracy in the routine clinical laboratory is approximately 50 per cent. Schmidt et al.[40] have once again demonstrated that there is no correlation between the level of cerebrospinal fluid IgG and age, duration of illness, clinical activity, extent of plaques, or

gravity of the illness. Williams et al.[48] and others have now shown that in a significant number of patients there is elevation of the cerebrospinal fluid IgM level, without correlation with the IgG level. At the present time, in terms of attempting to determine the level of activity of the disease, the only reliable indicator is the presence of cerebrospinal fluid leukocytosis.

Clinical Neurophysiology

An increasing number of reports have underlined the value of neurophysiological studies, in particular visual evoked potentials to both flash and pattern reversal stimulation, in confirming the presence of lesions in the optic nerves, and more important, in demonstrating the existence of hitherto unsuspected or asymptomatic lesions in the visual system. Halliday et al.,[19] using a checkerboard pattern of light and dark squares reversed at a frequency of 2 per second, found abnormalities in 86 per cent of patients with normal optic discs and without a history of optic neuropathy. McSherry and O'Brien[27] have developed a technique for demonstrating the presence of unsuspected retrochiasmatic lesions in patients with multiple sclerosis by means of visual evoked responses. Bynke et al.[4] demonstrated that 76 per cent of 25 patients with myelopathy of unknown etiology and without subjective symptoms of central nervous system involvement outside the spinal cord had increased visual evoked potential latencies. Lowitzsch et al.[24] measured the optically and electrically evoked Kimura blink reflexes in 107 patients with multiple sclerosis. All patients with mesencephalic lesions had delayed responses of the optically evoked reflex and 74 per cent of these patients had delayed latency of the components of the electrically evoked blink reflex. In addition, 18 patients without brain stem signs had a delay of the blink reflex.

Robinson and Rudge[39] measured the brain stem auditory evoked responses and found them to be abnormal in half their patients with multiple sclerosis without clinically detectable brain stem signs or symptoms. Mastaglia et al.[26] found that 56 per cent of their patients had abnormal somatosensory evoked responses and of these at least 19 (41 per cent) were without clinical sensory symptoms or signs. Furthermore, 48 per cent of 54 patients with multiple sclerosis had abnormal horizontal saccadic eye movement velocity.

The neurophysiologic studies serve the useful purpose of documenting the existence of multiple lesions and confirming or denying the validity of past events and current symptoms. The introduction of these procedures to clinical practice must be considered as one of the most important advances in the diagnosis of multiple sclerosis and has allowed clinicians to move patients from the possible and probable categories into the definite group. In some instances, these tests also provide means of determining if the appearance of new or recurrent symptoms represent a true exacerbation of the disease, a hysterical manifestation or a psychologically induced recall phenomenon.[36] They also at times provide objective evidence of improvement.

Neuroradiology

The technetium 99 radionuclide brain scan can demonstrate only lesions with a diameter of at least 1.5 cm and the yield of the procedure is relatively small. In some instances, some correlation has been obtained between the symptoms and the brain scan, providing objective evidence for exacerbation.[29]

Several papers have also emphasized the value of computed tomography (CT) for both the diagnosis of the disease and the evaluation of its activity. Some of these data, however, must be interpreted with care. Wuthrich et al.[50] examined 60 patients with multiple sclerosis and found that only in 31 were the CT scans normal; atrophy was a common finding but is not specific enough to be of significant value; unequivocal foci were present in 5 and equivocal foci were present in 15 of their cases. Cala et al.[5] examined 100 patients with established or suspected multiple sclerosis with CT scanning. They found areas compatible with demyelinating lesions in the white matter of the cerebral hemisphere and brain stem in 47 per cent. These lesions of the hemisphere were commonly multiple, typically situated in the deep white matter and periventricular regions, and were often asymptomatic. They make the important point that lesions in spinal cord, brain stem, and cerebellum, being usually quite small, can be identified only by study of the computer printout. Computed tomography can be of great value in demonstrating the multiplicity of lesions in patients with possible or probable multiple sclerosis. The test, however, is not as sensitive as clinical neurophysiologic studies and is also considerably more expensive.

Of perhaps even greater theoretical importance are the studies of contrast-enhanced computed tomography. Sears et al.[42] reported a series of four patients in whom lesions were demonstrated by contrast enhancement at the time of clinical exacerbations. Furthermore, they showed that corticosteroid therapy reduced the intensity of enhancement. They believe that the basis for this phenomenon is a transient alteration of vascular permeability, and that corticosteroid therapy reestablishes the integrity of the blood-brain barrier. One of their cases is of particular interest in that the focal enhancement occurred twelve hours prior to the clinical manifestations of an exacerbation.

Both radionuclide studies and contrast-enhanced computed tomography studies re-emphasize the need to consider that a transient alteration of blood-brain barrier permeability may precede the appearance of clinical symptoms. These studies would also suggest that improvement following ACTH or corticosteroid therapy may be related to the same phenomenon. Finally, they put credence in the suggestion made that the best time to look for manifestations of the pathogenetic mechanism of multiple sclerosis is shortly before the onset of clinical symptoms.[34] Careful analysis of several published cases of multiple sclerosis with lesions demonstrated by radionuclide or enhanced CT scanning, presumably showing disease activity, reveals poor, possibly even coincidental clinico-anatomical correlation with concurrent symptomatology. This troubling observation raises difficult questions in regard to the pathogenetic mechanism of the clinical exacerbation. In addition to

the diagnostic procedures already mentioned, examination of the patient for monocular color blindness (usually of the red-green type) with pseudo-isochromatic Ishihara or AO plates can be quite useful, as is the use of the hot bath test (water temperature at 40° C). This latter procedure may bring out signs and symptoms which have previously not been experienced by the patient, or may reproduce symptoms reported by the patient but not objectively confirmed.

CLINICAL ASPECTS

The classical clinical notion that the course of multiple sclerosis characterized by remissions and exacerbations closely reflects the underlying pathological changes needs closer examination. While it has usually been assumed that new plaques have developed in the patient who suddenly experiences symptoms, physiological, radiological, and pathological studies reveal that asymptomatic lesions may have been present for quite some time. Symptoms and signs of multiple sclerosis may indeed result from the formation of plaques, but it is now clearly understood that they may also result from physiologic alterations (e.g., heat, calcium concentration) affecting previously existing plaques.[35] In addition, other mechanisms must be considered: since symptoms and signs may be the result of swelling rather than destruction of myelin, it is conceivable that when the edema subsides, the myelin does not revert to its normal state, and thus may be more vulnerable to these physiological alterations. Recurrence of edema in the same location is still another possibility, as is enlargement of a previously existing plaque. The occurrence of a new lesion at another level of one of the long tracts may also mimic a previously experienced symptom. Furthermore, while the exact pathogenetic relationship between emotional stress and physical trauma is poorly understood, the association of these events with acute exacerbations or appearance of new symptoms is well documented. It is not farfetched to suggest that some still not understood physiological alteration affects conductivity in a manner similar to changes in temperature or calcium concentration: the phenomenon of such psychologically induced recall needs further study.

Thygesen[46] in his review of 105 attacks of the disease in 60 patients pointed out that a new symptom suggestive of a new plaque occurred in only 19 per cent of these attacks. An attack often affects precisely one previously damaged site of the central nervous system and is a true copy of previously remitted symptoms. It would seem that clinical exacerbations can with equal probability represent either physiologic alterations or evidence of the production of new plaques, or expansion or reactivation of old ones. Many patients with multiple sclerosis have admitted, upon close questioning, that certain symptoms never actually disappear, but they get accustomed to them so that they are ignored until some external event brings them to mind.[36] In other words, this suggests that clinical observation provides only a very incomplete and inaccurate reflection of the progression of the disease in terms of formation of new plaques. Clinical evaluation of degree of activity of the underlying demyelinizing process is totally in-

adequate and particularly burdensome when trying to evaluate the results of therapeutic regimens. Measurements of evoked responses and to a lesser extent radionuclide and contrast-enhanced CT studies will prove to be of considerable help in this regard.

The notorious lack of clinicopathologic correlation in multiple sclerosis is best exemplified by our continued inability to detect lesions in the subcortical white matter such as the classical periventricular plaque. It is well known that even large plaques are found at autopsy in patients who have never had neurologic symptoms.[17, 35] It must also be pointed out that it may be quite wrong to assume that the bilateral Babinski signs and nystagmus found in a patient who presents with numbness of the left arm all occurred simultaneously. Our understanding of the pathophysiological changes which result from the presence of demyelinizing lesions is still too incomplete to allow for the establishment of chronologic relationships between symptoms and their underlying lesions. This problem assumes great importance in not only gauging the overall progression of the disease but also in evaluating the possible relationship existing between external factors such as emotional stress and/or physical trauma and the occurrence of signs and symptoms. That these represent precipitating events is undeniable; that they are responsible for plaque formation is highly unlikely.[36] Finally, the slow progression of symptoms and signs may represent nothing more than the results of the reparative gliosis secondary to the inflammatory reaction to the myelinoclastic process.

Mention should also be made of the value of psychological evaluation. Peyser et al.[33] have demonstrated the presence of unsuspected significant cognitive impairment in 49 per cent of patients judged by the neurologist to be mentally intact. This impairment is unrelated to the severity of overall neurologic involvement but appear to correlate best with a history or presence of involvement of the visual system; the visual involvement, however, is not a factor in the cognitive impairment. These findings suggest that cognitive impairment may represent the clinical manifestations of some of the subcortical white matter plaques which are otherwise asymptomatic. These evaluations also may provide useful guidelines for the physician in the overall management of the patient, including the recognition that psychological characteristics may influence the course of the illness and the occurrence of exacerbations.

TREATMENT

Nearly all therapeutic regimens have been based upon the belief that multiple sclerosis results from a hyperimmune state and a number of immunosuppressive agents and measures have been utilized. Ellison and Meyers[12] reviewed the use of systemic nonspecific immunosuppressive agents including cyclophosphamide, azathioprine and levamisole: frequency of relapse, rate of progression, and cerebrospinal fluid IgG may be decreased, at least temporarily, in some patients treated with these agents; the few controlled studies of immunosuppressive therapy show less apparent benefit than the uncontrolled

studies but treatment regimens have not been directly comparable. In general, the dosages used and the duration of follow-up have been inadequate. They suggest that routine use of immunosuppressants is not warranted at this time. Further, it raises serious ethical problems. While the short-term after-effects are well documented, patients have not been followed for lengths of time adequate enough to detect increased malignancy or other and unsuspected complications. No laboratory test seems completely predictive of efficacy.

Treatment based upon the concept of multiple sclerosis as an immunodeficiency state, using transfer factor, has proved to be valueless.[15]

Other forms of therapy based upon less convincing rationales and with inconclusive and contradictory results have included linoleic acid, tryptophan, plasmapheresis, human myelin basic protein, hyperbaric oxygen, anti-thymic globulin, total body x-irradiation, and so forth.

In spite of the fact that their use remains extremely controversial, many clinicians continue to administer different corticosteroids or ACTH for the treatment of acute symptoms. The general belief, albeit anecdotal, is that these drugs do indeed shorten the course of the exacerbation and afford relief of symptoms. There appears to be considerable variation in individual patients in their response to either ACTH or corticosteroids. Similarly, some patients will have dramatic response to one corticosteroid while others will respond to another, or to cosyntropin and not to ACTH. The only rationale that can be invoked for their use is as anti-edema and anti-inflammatory agents, and possibly as stabilizers of the capillary membrane. It is possible that myelin edema may respond to ACTH or corticosteroids but myelin destruction does not. In regard to symptomatic treatment, dantrolene and baclofen, the latter in particular,[13] have been of some value in the relief of spasticity and its concomitant symptoms such as flexor spasm, clonus, and resistance to passive movement. Unfortunately, these drugs may cause gastrointestinal disturbances, and interference with ambulation in those patients who need a certain amount of spasticity in order to lock hip and knee joints.

The control of bladder problems such as frequency, urgency, and stress incontinence remains one of the most important aspects of long-term management. The judicious use of propantheline bromide (probanthine) or drugs with a similar parasympatholytic effect, will provide the patient with relief for several hours. External sphincterotomy will make the use of a Texas catheter and leg urinal comfortable for a male patient and will avoid the need for repeated self-catheterization.

In general, patients who can be demonstrated, by hot bath tests or by history, to be sensitive to heat should avoid hot showers or baths and prolonged exposure to the sun. The installation of air conditioning units in the patient's home may maintain him or her in a functional state during hot summer weather.

The placebo effect of any kind of therapeutic regimen, of simple rest at home, or of hospitalization and removal from the stresses and strains of daily life must always be considered, since in some patients exacerbations may represent a psychophysiological phenomenon. It

should also be pointed out that patients may be highly motivated by an enthusiastic investigator using a specific form of treatment, who thus provides the patient with considerable attention and who may unwittingly reinforce this placebo effect. Many of the proposed therapeutic regimens are designed to test a particular etiologic or pathogenetic hypothesis; until we have a better understanding of the pathogenesis of multiple sclerosis, such hypothesis-testing should be entered upon only with extreme care and detailed preparation,[41] and with the full realization that the mechanics of treatment, i.e., the placebo effect, may be more beneficial to the patient than the treatment itself.

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