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WHAT IF MULTIPLE SCLEROSIS ISN'T AN IMMUNOLOGICAL OR A VIRAL DISEASE? THE CASE FOR A CIRCULATING TOXIN

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The literature contains studies on many causes of demyelination: Vascular occlusion—exogenous toxins—allergic reactions—and virus diseases. There remains, however, a small group of conditions which seems to have been ignored almost completely in discussions of cerebral demyelination. These consist of brain damage apparently resulting from some toxin liberated within the human body and not obtained from the outside.

A. B. Baker (1)

INTRODUCTION

In discussing the possible etiologies of MS with other investigators, this writer has been impressed by a recurring remark to the effect that: "MS *has to be* an immunological and/or viral disease because what else can it be?" One can only wonder if the younger MS investigators of today ever read the older literature (circa 1900–1950) on the subject. Anything antecedent to the discovery of myelin basic protein must seem hopelessly out of date to them. However, a careful study of that literature will reveal many interesting observations and hypotheses on the pathogenesis of MS. Our predecessors speculated, of course, that MS might be an immunological or a viral disease, but they wisely considered other possi-

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bilities. Three decades of myopic preoccupation with EAE have resulted in limiting our investigations almost exclusively to immunology and virology, although either discipline has yet to offer a credible explanation of the etiology of MS. The purpose of this communication is to plead for wider horizons and, in particular, to reassemble an hypothesis that was considered rather often in the older literature (2–5), namely that the demyelination in MS is caused by a circulating compound of low molecular weight.

THREE POINTS ABOUT THE DEMYELINATION IN MS

A striking feature of the topography of the plaques in MS that is mentioned often in the pathological literature is the regular occurrence of periventricular lesions in chronic cases (6–8). This, together with the perivenular (7) nature of the demyelination, has been taken to indicate, as Gerd Peters (6) phrased it, that there is ". . . a noxious agent exuding from the vascular system. . . ." This seems to be a reasonable assumption: that whatever causes the demyelination in MS arrives at the CNS via its blood supply.

The second point is that one of the most time-honored tenets of neuropathology has been that only CNS myelin is involved in MS and that PNS myelin is unaffected. This is probably incorrect. Peripheral nerve abnormalities have been described frequently (9–14) but were explained away as being due to the poor physical state of the patient rather than to the MS per se. A recent elegant study (15) of sural nerve biopsies from MS patients with little disability showed marked changes in the PNS myelin and, in particular, a generalized reduction of myelin lamellae. This is of the utmost importance, because theories for an autoimmune etiology for MS are based to a large degree on the presumed specificity of the demyelination. We are now justified in assuming that the circulating etiological agent is nonspecific and that it attacks both types of myelin. The reason that PNS abnormalities are seldom seen clinically in MS is probably due to the great capacity of Schwann cells to regenerate peripheral myelin and, therefore, to compensate for injury.

The third point is that, while electron-microscopic studies of MS brains are scanty, there seems to be unanimity of opinion (for refs. see 16) that the demyelination is not of the cell-mediated type that Lampert (17) observed in EAE. If this observation holds, it would seem to eliminate sensitized cells as the cause of the demyelination. The demyelination might then be caused by a virus or a protein (an antibody, enzyme, or toxin). It might be any of these, but it might also be caused by a simple

molecule of low molecular weight. The irony of MS research for the past 30 years has been that it assumed one of the most complex possible etiologies—autoimmunity—without having made the slightest effort to eliminate simpler causes.

KNOWN LOW-MOLECULAR-WEIGHT COMPOUNDS THAT CAUSE DEMYELINATION

Chronic poisoning with sublethal doses of carbon monoxide (18–20) or cyanide (21–24) produces focal demyelination in a small percentage of experimental animals, probably by interfering with the oxidative metabolism of the intrafascicular oligodendrocytes. Lead intoxication (25–27) and triethyltin (28) also result in demyelination as does the administration of a number of solvents (29, 30), detergents (31, 32) and even spinal anesthetics (33, 34). None of these, of course, is a serious candidate for causing the demyelination in MS. The reason for mentioning them is only to make the point that known low-molecular-weight compounds can and do produce demyelination in the CNS.

SOME DEMYELINATION IN HUMANS THAT IS PROBABLY PRODUCED BY CIRCULATING TOXINS

Of much more pertinence than the production of experimental demyelination by such unphysiological compounds as those mentioned above are the diseases of man, other than MS, where there is a distinct possibility that demyelination in the CNS is caused by a circulating toxin. To this writer's knowledge, a compendium of these conditions, such as the one that follows, has not been presented previously in the literature. Hopefully, it will illustrate, among other things, that demyelination in humans, where low-molecular-weight toxins are suspected, is by no means rare.

Marchiafava-Bignami Disease (MB)

Less than one hundred cases (35) of this disease have been reported since it was first described in 1903 (36). MB is characterized by demyelination of the medial zone of the corpus callosum with relative preservation of axons and no significant loss of neurons in the grey matter (37). The highest incidence of MB is in Latins, especially in Italians, and it is predominantly a disease of alcoholics that drink heavily of cheap red

wine. The unusual feature of the disease, other than the restricted focus of demyelination, is the demyelination itself; for the characteristic neuropathological feature in chronic alcoholism is the destruction of neurons (38) rather than of myelin. The rarity of MB in comparison to the number of chronic alcoholics drinking cheap red wine might suggest some unusual genetic susceptibility; however, it has been suggested that MB is not uncommon in Frenchmen but that it is seldom reported (37). At any rate, it is reasonable to hypothesize that there is a component of some varieties of cheap red wine, other than ethyl alcohol, that either directly or by metabolic change in the body can produce demyelination in humans.

Central Pontine Myelinolysis (CPM)

CPM like MB is a noninflammatory demyelination (39). In practically all of the reported cases, the lesion is restricted to the pons; however, there are exceptions (40, 41). There is, as in MS, an almost total loss of oligodendrocytes from the demyelinated region, so that we are uncertain whether the myelin or the oligodendrocytes are affected first. There have been many attempts to implicate some single factor in CPM. Alcoholism (39), liver disease (35), malnutrition (39), hyperosmolarity due to dehydration (41), etc., have all been singled out; but exceptions can be found for each. Adams et al. (39), in their original paper on CPM, concluded: "The etiology is unknown. The nature and location of the disease favor either an exogenous or an endogenous intoxication, or a deficiency of some essential substance." There has been no research on CPM other than case reports. This is partly due to the fact that it is difficult to diagnose antemortem (35). It is unfortunate that so little progress has been made with CPM because an understanding of its etiology will provide important information about the vulnerability of myelin or oligodendrocytes, at least in the pons. Many of the pathological reports (39, 40, 42, 43) seriously consider a toxic etiology for CPM; and if this proves to be the case, its relevance to MS may be exceedingly important.

Concentric Sclerosis

This rare and bizarre primary demyelinating disease is characterized by concentric segments of demyelination interpolated by layers of normal myelin. Balo (44), who first described it, and Hallervorden and Spatz (45) and Davison (46) all regarded it as being caused by some toxin that has a special affinity for myelin. Davison (46) also thought that it is a variant of MS.

Uremia would not seem to offer great promise for studying demyelination, but a few words on the hypothetical uremic toxin are in order. Strangely enough, it seems not to be urea (56). Methyl guanidine (57) and guanidinosuccinic acid (58), both metabolites of arginine, have been proposed as candidates. Merrill and Hampers (59) aptly summarized the status of the research: "Efforts to discover a toxin responsible for the signs and symptoms of uremia have much in common with the attempts to identify the Yeti or Abominable Snowman. Evidence of its presence is clearly visible, but attempts to identify and isolate the factor have yet to be successful."

Liver Disease and Post-Shunt Myelopathy

In the literature on both MB and CPM there are numerous suggestions that the demyelination may be a consequence of liver damage. The implication is that some unidentified toxin, that is either metabolized or detoxified by the normal liver, is allowed to circulate in these diseases.

The question of demyelination in liver disease has been controversial. Baker (1) found patchy areas of demyelination, but in a later study Adams and Foley (60) found the myelin to be normal in their cases. In a still later study, Brown (61) found myelin changes in 85% of the 42 cases of liver disease that he examined. He also cites 10 other studies, including Baker's in which demyelination was noted as a feature of the cerebral pathology of liver disease. It would seem then that some degree of demyelination can accompany liver disease, but its appearance is by no means constant.

The chronic hepatic myelopathy following partial surgical shunts or normal anastomoses around the liver was first described in 1960 (62), and as of 1970 (63) about 30 cases had been described. There is controversy in the reports (62–65) as to whether the demyelination is primary or secondary, and perhaps this is to be expected in light of the great differences in the cases. However, two features have been emphasized in several of the reports, and they are worth repeating. The first is that the myelopathy occurs in chronic cases (63); it usually does not tend to appear immediately. The second point is that the myelopathy tends to appear in those cases where less blood is shunted around the liver, such as in a lienorenal shunt or in spontaneous anastomosis, in contrast to complete shunting as in a portal-caval shunt (63).

A Search for Correlates in These Diseases

There are several points that need to be mentioned: (1) frequency of hepatic damage, (2) origins of the toxins, (3) chronic nature of the toxic

demyelinating process, and (4) semantics of "primary" versus "secondary" demyelination in toxic states.

Hepatic Damage. The constant references to hepatic damage in these demyelinating conditions are impressive. If there is any one organ that is to be implicated in toxic demyelination, it is certainly the liver. Demyelination can be a consequence of liver damage or even of partial liver bypass; the surgical shunt studies clearly indicate that. However, the paucity and rudimentary nature of the existing data discourage much analysis. The effects on the CNS of slowly progressive liver disease or of moderate shunting of intestinal blood around the liver deserve much more attention than has been received.

The Origins of the Toxins. MB disease seems to be confined to alcoholics; CPM is frequently, but by no means entirely, a disease of alcoholics. It seems reasonable to speculate that the hepatic cirrhosis from chronic alcoholism results in the liver being unable to cope with some potential toxin in the alcoholic beverage. These hypothetical toxins, which would be inactivated by the normal liver, are, therefore, able to circulate and produce demyelination. This, of course, in no way explains the restricted focus of the demyelination in each disease. Parenthetically, it might be added that the organic constituents of alcoholic beverages, other than ethyl alcohol, are known as congeners, and many of them have been identified (66). In general, they are other simple primary and secondary alcohols; simple organic acids and their esters; ketones; and aldehydes. With the modern analytical technique of combined gas–liquid chromatography and mass spectrometry, it should be possible to identify most, if not all, of the congeners in a wine or other alcoholic beverage that an MB or CPM patient was drinking regularly and thus get some idea of the toxicological basis of these diseases.

The demyelination consequent to partial liver bypass, as in hepatic myelopathy, indicates that this toxin is presumably in the normal diet or at least a metabolic precursor of it is in the normal diet. It has been considered that for acute hepatic encephalopathy the toxin(s) is formed from dietary constituents by the intestinal flora (67, 68). The production of hepatic coma and encephalopathy (not myelopathy) in dogs by feeding meat after a portal-caval shunt (Eck's fistula) suggests that metabolites of proteins (ammonia, amines, etc.) are involved.

The Chronic Nature of the Toxic Demyelinating Process. These conditions, such as slowly poisoning oneself with cheap wine, phenylketonuria of long duration, the prolonged effects of severe burns, the hepatic myelopathy, etc., are chronic processes. A sudden, severe insult to the nervous system by a toxin tends to produce much more than demyelination, but a slowly progressive insult seems to favor demyelination.

This is a matter of great importance because of the epidemiological studies (69) that tend to indicate that there is a long latency, perhaps a period of years, between the time one "acquires" MS and the onset of clinical signs and symptoms. This has been interpreted as evidence for a slow viral infection being operative in MS (70). Certainly this is a possibility, but it is not the only possibility. Toxic demyelination of humans is a chronic process of months or years, and a long latency is just as compatible with demyelination by a toxin as it is with a slow infection.

The Semantics of "Primary" Versus "Secondary" Demyelination in Toxic States. There is general agreement that Wallerian degeneration following axonal section is a "pure" secondary demyelination. One can only wonder if there is such a thing as a "pure" primary demyelination. As evidence for this, consider the loss of nerve fibers in chronic plaques in MS (71) and the central necrosis of the pons in CPM while the axons are spared at the periphery (72). The controversy as to whether the demyelination in, say, hepatic myelopathy is primary or secondary seems unimportant (for references and discussion, see reference 63). The response of the nervous system is certainly a function of the duration and severity of the insult. With the sudden onset of a complete liver shunt, the insult may be so severe that neuronal death and necrosis are the only possible results. With a partial shunt, the body may be able to compensate to the extent that the encephalopathy is averted; but the protracted, less severe insult results in a myelopathy. Until the factors that produce the damage are identified and until they can be experimentally controlled, our efforts should not be diverted by conflicting statements about primary and secondary demyelination.

IS MS A RELATIVELY RECENT HUMAN DISEASE?

Aleu and Terry (73) wisely observed that alcoholism and malnutrition are ancient scourges but that CPM, which they usually accompany, is a new disease. In a similar vein, Burkitt (74, 75) has proposed that appendicitis, cancer of the colon, and diverticular disease of the colon attained numerical prominence comparatively recently. He attributes this to the profound dietary changes in Europe and North America following the Industrial Revolution when the consumption of meat increased dramatically and when refined flour and refined sugar were introduced and gained immediate acceptance.

There is a curious lack of reference to the obvious symptoms of MS in the medical literature prior to the middle nineteenth century. Charcot,

according to Putnam (76), considered it to be something of a curiosity. There is the fascinating case of Sir Augustus D'Este (77) where, in the early nineteenth century, the best physicians in England were unfamiliar with the now classical symptoms of MS. There is an interesting discussion about the frequency of MS in the minutes for 1902 of the New York Neurological Society (78), and there was general agreement there by a group of nine neurologists that MS was then a rare disease in New York. MS increased dramatically (79), by 140%, in Germany and Switzerland between 1906 and 1940. At the present time, it is increasing in the Orkney Islands (80). It has also recently increased among non-European Jews born in Israel when compared to their parents (81).

It is clearly impossible to prove or disprove from such fragmentary evidence that MS attained numerical prominence in, say, the last 150 years. However, that possibility should be kept in mind, as should the possible relationship of MS to the modern diet of Caucasians.

MS AND DIET

It is beyond the scope of this overview to review the literature on diet and MS. However, two important points are seldom mentioned in that literature.

MS among Blacks. MS is apparently extremely rare among the blacks in Africa (82, 83), but scant attention has been paid to the high incidence of MS among blacks in the United States (84, 85). It may be that blacks in the United States suffer common exposure, along with the whites, to an infectious MS agent that does not exist in Africa. However, blacks in the United States also have high incidences of cancer of the colon (86) and heart disease (87), and both of these are considered to be due, at least in part, to diet. Of all the non-European immigrants to the United States, one would imagine that the blacks most quickly adapted to the whites' diet.

Starvation and MS. Heart disease (88) and MS (89) decreased in occupied Norway in World War II when food was severely restricted, and they returned to normal after the war when an adequate diet was resumed. This is the only recorded instance where the incidence of MS has been manipulated, but it has been virtually ignored.

THE HYPOTHETICAL MS TOXIN

The following is largely speculation. Multiple sclerosis is a genetically determined disorder of the liver in which some component of the wes-

ternized diet is not metabolized. This toxin then circulates in the blood. It penetrates the CNS either because it can traverse the blood–brain barrier or by damaging the barrier and then entering. It is interesting that the demyelination in MS is perivenular because the flow of blood is slowest in the venules, and this may provide an optimal situation for the toxin to escape from the vascular system. The toxin may exert its effect on myelin by purely physical means, such as by being slightly surface active. It is clearly not a generalized cellular toxin because axons, astrocytes, and neurons are refractory to it. The intrafascicular oligodendrocytes die, but whether this is the cause or a result of the demyelination is unknown. At any rate, the demyelination and the death of oligodendrocytes proceed; macrophages and lymphocytes invade the demyelinating areas and an immunological reaction is generated. This immunological reaction has nothing to do with the demyelination except to clean up the debris. In short, we have mistaken the smoke for the fire.

CONCLUSION

If the reader thinks that the search for an etiological agent in MS has been logical, unbiased, and that "no stone has been left unturned," then consider the following: Do we have any evidence as to whether there is or isn't a low-molecular-weight compound in the brains of MS patients that disrupts myelin? The answer is: "no," because no one has ever bothered to look.

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