SPECIAL ARTICLES

THE BIOLOGICAL SIGNIFICANCE OF THE LESIONS OF MULTIPLE SCLEROSIS

IT has long been recognized that the characteristic lesion of multiple sclerosis is the plaque, an area in which myelin is destroyed (though often not entirely absent), axis cylinders are preserved, although often damaged, and there is an overgrowth of glia of variable intensity. Plaques may be of microscopic size, in which case they almost invariably surround a small vein, extending along it like a sleeve, or they may measure several centimeters in diameter. Typical plaques occur in no other disease, although small areas of somewhat similar structure may be encountered, for example, in paresis. The lesion may therefore be considered pathognomic.

Recent observers almost unanimously agree that the lesion is a progressive one. In all cases areas may be found in which the myelin shows evidence of damage but not destruction, and perivascular infiltrations occur which are presumably transitory. More severe lesions are also found in long-standing cases, in which the axis cylinders are destroyed and glial proliferation reaches its extremest degree. In such areas there is a proliferation of capillaries. They are, therefore, mixed scars such as may be seen in the vicinity of old softenings of any origin, and histologically can not be considered in the least specific for multiple sclerosis.

Both the "early" and the typical sclerotic plaques have been produced experimentally in animals. This was first accomplished by means of minute doses of tetanus toxin,[1] but the mechanism of the pathological change remained obscure. One step in the process has recently been elucidated by the demonstration that obstruction of venules in the dog's brain with a bland oil will produce lesions of the type described.[2,3] The obstruction is produced by injecting the oil—usually triolein—between ligatures into the longitudinal sinus in such a way that it is forced against the current of blood into a cortical vein and its tributary venules. The lesions produced are usually limited to the white matter. In early stages, they consist of diffuse proliferation of fixed glial cells and mild myelin damage. The resulting picture is a close imitation of that of post-infectious "encephalitis." At the end of three months, myelin destruction has begun, and after ten months there is a dense isomorphous gliosis in the area of myelin loss, but the axis cylinders remain practically intact.

The experimentally produced lesions have such a perfect resemblance to the pathognomic lesions of multiple sclerosis that it seems scarcely possible to believe that the same histological sequence does not occur in the latter process also. It is hard to imagine any form of spontaneous obstruction in cerebral venules other than thrombosis, and as a matter of fact venous thrombi have been described in post-infectious "encephalomyelitis"[4,5] a disease which bears certain similarities to multiple sclerosis. Thrombi have been reported in cases of multiple sclerosis also, but very rarely. Their scarcity is perhaps not surprising when we consider that a thrombus in a small vessel may become so completely organized as to be unrecognizable within a week. Abnormalities in the coagulability of the blood may regularly be observed in multiple sclerosis.[6]

The sclerotic plaque may perhaps therefore be considered the mildest form of permanent damage produced by a disturbance of blood supply. Complete asphyxia of the cortex for a relatively short time leads to loss of nerve cells, but apparently if the gas exchange is disturbed to a milder degree but over a longer period, the myelin suffers most.[7,8] In areas of severe ischemia all ectodermal structures are destroyed. Loss of myelin in itself does not prevent the transmission of nervous impulses. In multiple sclerosis, a practically complete demyelination of some levels of the brain stem is compatible with life, and almost complete demyelination of the optic nerves is compatible with vision.

A consideration of the various types of lesion seen in multiple sclerosis suggests that it may be a general rule that injury to structures of ectodermal origin alone in the central nervous system leads to gliosis—that is, repair by ectodermal elements—with minimal mesodermal proliferation. To be sure, there is usually some thickening of vessels in typical sclerotic plaques, but no more than might be accounted for by organization of thrombi within, and expansion of adventitia to wall in perivascular infiltrations externally. The isomorphous character of the gliosis is doubtless to be accounted for by the persistence of axis cylinders which support the growing fibrils. Only when ischemia reaches such a degree that the capillaries become necrotic does a sort of granulation tissue make its appearance. Mallory[9] has long since called attention to the almost specific stimulation which fibrin

[1] T. J. Putnam, J. McKenna and J. Evans, *Jour. f. Psychol. u. Neurol.*, 44: 460–467, 1932.

[2] T. J. Putnam, *New Eng. Jour. Med.*, 209: 786–790, 1933.

[3] T. J. Putnam. (To appear in *Arch. Neurol. and Psychiat.*)

[4] H. Spatz, In Handbuch der Geisteskrankheiten. Bd. 11, Spez. T. VII, p. 173.

[5] P. Kreider. Personal communications concerning work to be published shortly.

[6] P. Solomon and B. Simon. Personal communications concerning work to be published shortly.

[7] A. Ferraro, *Arch. Neurol. and Psychiat.*, 29: 1364–1367, 1933.

[8] T. J. Putnam, *loc. cit.*

[9] F. B. Mallory, "Pathologic Histology," Saunders, Philadelphia, 1914.

furnishes to the growth of connective tissue—a stimulation also probably partly to be explained on mechanical grounds.

The question naturally arises, granting the abnormal coagulability of the blood, why thrombi should occur in cerebral venules rather than elsewhere. It is well recognized that venous blood coagulates more readily than arterial, perhaps because of its higher hydrogen-ion concentration, and the oxygen consumption of the brain exceeds that of other organs.[10] Further, the cerebral venules are unusually small, variable in caliber and tortuous[11]—structural factors which impede the flow of blood and so doubtless favor clotting. But perhaps it should be admitted that we have no data in regard to the presence of thrombi in venules in other parts of the body. It is quite possible that they do occur, disappear and, except in the nervous system, leave no trace behind.

The problems of the precise nature of the change in coagulability of the blood, of its cause, and whether it may be influenced by any therapeutic procedure, are still under investigation.

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THE MUCOID PHASE OF STREPTOCOCCUS HEMOLYTICUS

IN a recent communication[1] evidence was presented to show that *Streptococcus hemolyticus* possesses three chief variant phases: (1) M (mucoid); (2) S (smooth); and (3) R (rough). Further evidence was presented to show that these three chief variant phases of *Streptococcus hemolyticus* correspond closely with the three chief variant phases of a wide variety of other bacteria. Three similar variant forms have also been identified for pneumococcus.[2] In the case of the latter bacterial species, however, there exists an unfortunate inconsistency in the terms employed to describe those phases which correspond with the chief phases of other bacteria.

The nature and the significance of the mucoid phase of *Streptococcus hemolyticus* have recently been investigated in this laboratory. It has been shown that the use of Neopeptone rabbit's blood agar plates, to which 0.2 per cent. dextrose has been added, facilitates the development of mucoid colonies. Three hundred and sixty-three strains of *Streptococcus hemolyticus* have been examined on this medium. The strains have been obtained from a wide variety of sources and include 118 freshly isolated cultures. The freshly isolated strains have been grown on Neopeptone media exclusively. The stock strains had been subcultured in a variety of media prior to the present study; they were then subcultured three times on Neopeptone blood-agar plates. The lack of uniformity in the cultural methods previously employed to grow the stock strains may therefore have appreciably affected the nature and appearance of the resulting growth. Under the conditions of the present study, however, the cultures exhibited a considerable degree of stability.

The source and nature of the cultures examined were as follows:

	Mucoid	Smooth
(1) Stock strains	108	137
(2) Freshly isolated strains	64	54
Total	172	191

Particular significance is attached to the origin of the mucoid and smooth variants, especially in the case of freshly isolated cultures. It can be definitely stated that there is a close parallelism between the type of infection and the variant form associated with that infection. Thus, with possibly one exception, all acute and fulminating infections have yielded mucoid organisms, while the smooth variant has almost invariably been associated with milder or more chronic forms of disease. Furthermore, there is suggestive evidence that, as the acuteness of the infectious process subsides, the organisms frequently change from the mucoid to the smooth phase. On the other hand, mucoid organisms have occasionally been encountered in the throats of individuals long after the acute stage of the infection has subsided.

Two main varieties of smooth organisms have also been identified; one of these produces convex, glossy colonies of moderate size; the other forms larger, flatter, faintly granular colonies with a "porridgy" consistency. The former variety is frequently associated with sub-acute or subsiding infections and the latter variety is commonly found in more chronic conditions and in apparently normal throats. The evidence suggests that these two forms constitute different phases of the same organism and that the larger colony represents the initial stage of a transformation to the true R form.

Virulence: Cultures exhibiting a high degree of virulence for white mice are usually, if not always, in the mucoid phase. On the other hand, all mucoid cultures are not necessarily virulent. Smooth cultures are definitely less virulent: in moderate dilutions they may cause the death of animals, but cultures from the peritoneum and heart's blood of such animals usually yield mucoid organisms. In these cases it seems reasonable to assume that there has been a change from the smooth to the mucoid phase within the animal body.

[10] W. Lennox, *Arch. Neurol. and Psychiat.*, 6: 719–724, 1931.

[11] R. Pfeifer. Berlin: Julius Springer, 1930, pp. 220.

[1] M. H. Dawson, *Proc. Soc. Exper. Biol. and Med.*, 1934, 31, 590.

[2] M. H. Dawson, *Proc. Soc. Exper. Biol. and Med.*, 1933, 30, 806; *Jour. Path. and Bact.* (in press).