VASCULAR PATTERN OF LESIONS OF MULTIPLE SCLEROSIS

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PREFACE

This thesis is based upon observations noted in a study of pathologic tissues from 5 cases of clinically and pathologically diagnosed multiple sclerosis. The clincial records and the pathologic reports were kindly furnished by Dr. Ludo van Bogaert and Dr. H. J. Scherer of the Institut Bunge, Antwerp, Belgium. Mrs. R. S. Dow prepared the histologic sections.

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INTRODUCTION

The first pathologic descriptions of the disease which was later to become known as multiple sclerosis (disseminated sclerosis of British authors) were made independently and almost simultaneously by Cruveilhier of France (1835-42) and Carswell of England (1838). Cruveilhier's pathologic descriptions were accompanied by clinical notes. He is thus credited as being the first to record the history with pathologic correlation. Both described the characteristic sclerotic plaques in the spinal cord. Carswell suggested that all primary atrophy of the central nervous system is due to a deficiency of blood supply. According to Putnam there appears to be no recognizable records of cases prior to the reports of Carswell and Cruveilhier.

Charcot [2] states that after these original descriptions the problem "dropped into almost complete oblivion" until its revival by German investigators, especially Rokitansky, Prerichs, Valentine and Rindfleisch, in 1855-65. They called the condition "gray-degeneration of the cord" because of the grayish discoloration of the plaques as compared with the pinkish tint of the surrounding tissue.

Then followed Carcot's great contribution to the symptomatology and pathology of the disease (1868). He described the "three cardinal clinical features" of intention tremor, nystagmus, and scanning speech, and stressed as the three important pathologic features, absence of myelin sheaths,

neuroglial proliferation, and relative peristence of axis cylinders.

In the latter part of the century Marie[3] emphasized the possible role which infectious diseases might have on the etiology of the disease. It was also about this time that Strumpell[4] and Muller[5] suggested that the underlying disturbance was a neuroglial hyperplasia due to an inborn abnormality of the nervous system.

With the aid of new staining methods and more knowledge of glial reactions the sclerotic plaques could be traced to their earlier stages. Neuroglial reactions were relegated to a secondary place and attempts were made to establish multiple sclerosis as an infective, toxic, or degenerative disease.

Dawson[6], in 1915, published an excellent monograph on the histology of multiple sclerosis, in which he included an extensive survey of the literature. He favored the view that a toxin circulating in the blood stream was responsible for the pathologic changes.

There have been many attempts to demonstrate a possible causative organism in and about the plaques of multiple sclerosis. Steiner's[7] claim of demonstration of a spirochete (spirocheta myelophthora) in the diseased tissues has given rise to much investigation and debate.

At the present time the more widely advocated theories as to the nature of the disease process include the primary degenerative theory of Hassin and the venous occlusion theory of Putnam.

There is much diversity of opinion as to the relationship which might exist between multiple sclerosis, the so-called "acute multiple sclerosis", and the acute "disseminated encephalomyelitides" especially those following the exanthemata or vaccination. Hassin[8] believes that disseminated encephalomyelitis, multiple sclerosis (chronic degeneration), and multiple degenerative softening (acute degeneration) to be different clinical entities. Ferraro[9] and Putnam [10,11], on the other hand, believe that the fundamental histopathologic changes are substantially the same and that the structural differences which do occur are a manifestation of the intensity and duration of the disease process.

As there is yet no definite positive knowledge of the cause or nature of the process underlying this disease, and because there is much diversity of opinion regarding the relationship which might exist between the chronic and the various acute demyelinating processes a definition of the disease "multiple sclerosis" must be made in somewhat general terms. It is recognized as a chronic central nervous system disease of unknown etiology, characterized pathologically by a multiplicity of sclerotic foci distributed in any or all parts of the central nervous system, and clinically by symptoms referable to one or more distinct areas of the brain or cord, the symptoms showing a tendency to undergo periods of remission and exacerbation.

Remissions in the symptoms of multiple sclerosis are mentioned in most text books as a characteristic feature. They offer an interesting problem in the clinical-pathological correlation of this disease. Brown and Putnam[18] made a survey of the histories in 133 cases of multiple sclerosis and found 339 instances of improvement in 92 of the 133 cases. In only 41 patients was the disease uninterruptedly progressive or stationary after a single attack. These authors express the opinion that most lesions of multiple sclerosis go through an acute stage after which a variable number of nerve fibers regain the ability to conduct impulses. Destruction of myelin, they believe, does not necessarily mean complete interruption of function. As proof of this they refer to cases of multiple sclerosis in which demyelinization of an entire cross section of the medulla, or of the optic tract does not result in total impairment of function during life.

Pathologically a typical plaque of multiple sclerosis consists of a comparatively acellular circumscribed area of glial fibrosis through which occasional demyelinated nerve fibers may be seen to course. The relative persistence of axons has been stressed by many. In other, more recent foci, the lesion borders are poorly defined, the myelin sheath is seen to be irregularly swollen and fragmented with some of the resultant debris being engulfed by the phagocytic gitter cells. In the literature may be found

numerous contradictory statements pertaining to a possible relation of the cerebrovascular system with these lesions. Despite the dependence of such a correlation by most of the more widely accepted theories of pathogenesis no one has as yet reported a sufficiently large number of lesions studied in serial section to allow a quantitative estimate of the incidence of association between vessels and lesions and the frequency with which the vascular alterations may be found. In an effort to throw more light on this controversial problem, a study of complete serial sections through 60 lesions in 5 cases of multiple sclerosis is reported. Inasmuch as the venous occlusion theory of pathogenesis, supported by Putnam and his collaborators, has been gaining such wide acceptance, emphasis has been placed, in this study, on the presence or absence of evidence of venous thromboses or other vascular change.

REVIEW OF LITERATURE

PATHOLOGY

Charcot[2] was among the first to direct attention to what has often been referred to as the three cardinal points of pathologic change occuring in the disease process of multiple sclerosis. He emphasized proliferation of glia, degeneration of nerve fibers, and blood vessel changes. These changes are more pronounced in circumscribed areas of nervous tissue, hence the name "sclerose en plaques" as suggested by this author. These foci of demyelinization and fibrosis are often regarded as the pathological unit, the morbid process running a fairly well-defined course terminating in the formation of a sclerotic plaque.

Accounts of the morphologic changes as given in many textbooks state that the lesions are entirely devoid of myelin, that they have rounded, clearly defined borders and that they are independent of the architecture of the tissues. Such lesions are commonly found but variant are common elsewhere in the nervous system. In almost any case areas may be observed in which the myelin or its lipoid breakdown products are seen to be phagocytized, these areas usually showing rather marked cellular reaction. In other foci, the phagocytic process has apparently subsided leaving occasional distorted sheaths or none behind. Small areas of myelin destruction tend, in many instances, to be perivascular and round or oval whereas large areas may be rounded or equally often irregular and may fade into the apparently normal surrounding tissue.[10]

The focus of demyelinization is the best known and the most characteristic feature. Scattered throughout the central nervous system and varying in size and form they are more noticeable in the white substance although in some instances the gray matter may be involved by them just as severely as is the white substance[12]. Whether or not the process is limited to focal areas is subject of controversy. Hassin[13,14,15] believes that the foci, plaques, or patches, however, are only the terminal phase of the disease. "The fundamental features of multiple sclerosis are that the changes are not confined to the patches but are diffuse and scattered throughout the entire nervous system". Hassin feels that a much better idea as to the origin of a plaque, its growth and its relationship to the neighboring structures may be gathered from specimens stained with the methods of Marchi-Alzheimer-Mann or of Bielschowsky-Alzheimer[16]. With such procedures the apparently healthy areas (as stained by other methods) show a tumefaction of myelin giving the appearance of a broad swollen band around the well preserved axons. In many places the myelin appears fragmented with the formation of globules and droplets. The changes were said to have been found in all of the thirteen cases studied, outside the patch proper, in areas which with ordinary stains, appeared normal. These myelin changes, "however mild, were always accompanied by marked proliferative phenomena in the glia tissue". The latter occured either as an increase in the amount of glia fibers or as large glia nuclei invested by a "visible, well-

developed membrane and abundantly supplied with cytoplasm".

On gross examination of the brain and spinal cord one finds little nodes, grayish in color and waxy or gelatinous in appearance when cut. These areas which may vary from pin point to several millimeters in diameter are somewhat firm to the touch and their borders tend to be rather sharply demarcated from the surrounding tissues[17]. Upon the bases of these observations the early investigators, including Charcot[2] and Rindfleisch[18], designated the process as "gray degeneration", which name was carried for many years. Other areas whose boundaries are ill-defined and whose color is only slightly less pinkish white than that of the surrounding apparently normal tissue are typical of more recent processes. Lesions, frequently ovoid or circular in shape as viewed on cross section, often seem to coalesce into irregular patches. Plaques are more pronounced in the white matter, but often spread, ignoring junctions between it and gray matter. Further considerations of plaque distribution will be taken up in a later section.

Other gross features may include thickened and opaque membranes over sclerotic patches lying adjacent to the surface[17]. Not infrequently some parts, such as the entire pons and medulla oblongata, appear shrunken and diminished in size.[18]

Changes noted in the myelin:

Among the better known anatomic alterations in multiple sclerosis are those which occur in the myelin sheath of the

nerve fibers. In the sclerotic plaque of long standing the myelin may have almost completely disappeared but it is in the less intense lesions, the more acute lesions, or in the transitional zone of the well developed glial plaques that we find the various stages of myelin alteration. Hassin [13,14,15] has described these changes in detail, and as has been mentioned previously is of the opinion that such alterations are not confined to the sclerosed area. He describes first a "tumefaction" of the myelin sheath, forming a broad swollen band around the apparently well preserved axon. In places thee is a fragmentation of the myelin into globule or drop-like formations. Under magnification with oil immersion the myelin is said to appear reticulated or fenestrated because of the presence of more or less wide meshes. The so-called "Lucken" are thought to be cavities resulting from breakdown of this distended meshwork. Thus we have swelling, fragmentation, and fenestration as part of the early stages.

Marchi stained specimens exhibit numerous small black structureless droplets (Alzholz bodies) scattered along the axon and intermingled with myelin fragments. Hassin further describes myelin fragments made up of concentric layers, and which stain brown or black with osmic acid. These are called "Marchi-globules".

Dawson[6] states that it is common to see a number of fine granule and ball-like formations attached to the outer border of the myelin sheath. "Some of these tiny balls seem to burst, and gradually others re-form till the myelin sheath

projecting into an area is gradually more and more thinned and is finally represented by a series of very delicate globules".

It has long been noted that the fragmented myelin undergoes furthe alteration with the formation of lipoid breakdown products. Charcot[2] held the view that the medullary matter coagulates, then disintegrates and gives origin on the one hand, to "proteine molecules", and, on the other, to corpuscles which at first preserve the appearance of myelin but which, "in consequence of ulterior modifications, soon present all the characters of fatty granulations".

Greenfield and King[20] note that much of the fat is contained within typical well-rounded gitter cells, while much of it lies within phagocytes that have not yet reached the gitter cell stage. Furthermore, a relatively large amount of fat may be seen to be extra-cellular, lying as droplets in the tissue interstices.

In the experience of Dawson[6], the fat granule cells, which are found in such large numbers, could only in rare instances be found to contain large fragments of myelin. "It seemed rather as if a gradual absorption of dissolved substances had taken place, and that these within the cell had become transformed into fine fat-like granules".

The disposal of these lipoid products appears to take two forms[20]. Fat laden cells may pass into the perivascular spaces where they may degenerate, giving up their contents to fresh cells. It is also probable that a certain amount of

free fat might be carried in the tissue currents to the perivascular spaces and there be taken up by phagocytes. To some[20,21] it seems doubtful whether a well-rounded fat laden gitter cell is capable of active migration and it has been suggested that they are passively carried to the perivascular tissue spaces by the tissue currents.

Axis Cylinders in multiple sclerosis:

The relative persistence of the axis cylinders in a sclerotic plaque has long been regarded as an essential feature of multiple sclerosis. Charcot[2] was of the opinion that the axis cylinders were the most stable part of the "nerve-tubes" and even in the central region of the sclerosed patch a certain number of axis cylinders still persisted in the midst of the fibrills. They were said to have no longer retained that comparatively large volume they occasionally possessed in the early phases of the alteration. Many diminished to such a degree that they "might be mistaken, so close is the resemblance, for the fibril filaments of new formation".

Rindfleisch[18] in describing the histologic alterations of "gray-degeneration" states: "The thicker axis cylinders are maintained remarkably long, and may often be demonstrated yet in such parts as according to all appearances have already been degenerated for a very long time".

It is possible that the earlier observers occasionally mistook the longitudinal glia fibrils, which run parallel to the degenerated nerve fibers for the true axis cylinders. They had to rely upon the diffuse stains, yet observations based upon

more modern specific staining technics have supported their conceptions. Leiner[22] states that disintegration of the medullary sheath with comparative intactness of the axis cylinders must be regarded as a specific characteristic of multiple sclerosis. It is quite generally agreed, however, that any persistence of axis cylinders is a relative one.

There have been few quantitative estimations of the proportion of axis cylinders reported. Putnam[10] "casually inspected" thirty-five plaques from eleven subjects. In four there was no definite diminution in the number of axons. Thirteen plaques exhibited an "unmistakable decrease in number", and in eighteen they were absent or only isolated ones present. Thus in his series there was a complete or almost complete loss of nerve fibers in just over 50 per cent. Greenfield and King[20], on the other hand, noted directly opposite results in their series of over 125 plaques representing thirteen cases. "Less than 10 per cent showed what could be called 'severe destruction' (reduction in number to one fifth or one-seventh of the normal density of nerve fibers), the remainder being fairly evenly divided into slight or no loss, and moderate diminution". These authors are of the opinion that the divergencies of results may be explained by the different staining procedures employed. The tissues of Putnam were said to have been stained with aniline blue which Greenfield and King feel is not as satisfactory for axis cylinders as are the ammoniacal silver methods used by them.

In considering the relative proportion of the number of

axis cylinders preserved it should be remembered that the plaque area is relatively smaller. Dawson[6] observed that when sclerosis affects the entire transverse section of the cord, the area is frequently little more than one half the normal.

Putnam and Alexander[23] suggest that the appearance of preservation of the axons in certain lesions is frequently an optical illusion. They emphasize that no assumption of complete or relative preservation of axis cylinders should be made from the inspection of pathologic material without comparative counts of axis cylinders and of myelin sheaths.

Numerous changes have been described as occuring in the axis cylinders. Dawson[6] notes that one of the most frequent changes is a slight homogenous swelling, even in old sclerotic areas. There may be spindle-like enlargements which in some instances precede actual disintegration with the formation of "homogenous clumps and granules". It is probable that the fibers which survive the swelling may ultimately be compressed by the dense sclerosis into thin spiral threads. Proliferated glia fibrils may surround the axon in a sheath-like manner. In many instances an apparently normal myelinated nerve fiber can be traced into a sclerotic area where it undergoes loss of myelin and the above described axis cylinder changes only to emerge from the plaque and assume its original appearance. Dawson concludes that the density of the non-myelinated axons is rarely the same as that of normal fibers, but sometimes they are found of normal calibre and numbers.

The question of axis cylinder regeneration will not be

discussed except to mention that numerous German and French investigators have introduced as evidence for possible regeneration such findings as brush-like formations, nerve sprouts, end bulbs, on the end of some axis cylinders, similar to those described in regenerating nerve tissue in the peripheral nerves. Horst, according to Dawson[8], holds the view that the special staining methods, especially as used by Bielschowsky and Strahuder in their study on regeneration, stain certain kinds of glia fibrils so similar to axis cylinders that it is impossible to draw any conclusions.

Changes in Nerve Cells:

It is quite universally accepted that nerve cells offer stout resistence even in the face of advancing sclerosis. Alterations tend to come late and their eventual decay may be due to a trophic 'reaction a distance', to nutritional deficits, or to direct strangling[17]. As Dawson[8] points out the relation of the cell changes to the sclerotic process is difficult to decide. Many of the alterations should probably be referred to the inter-current disease which caused death, or to the exhaustion and anemia which accompanied the nervous affection.

As a rule the ganglion cells are normal[15]. Whatever changes of axonal reaction, neuronophagia, chromatolysis, pigment and fat accumulation they might show, they are insignificant when compared with those of the white substance and may be considered secondary or accidental.

Dawson describes plaques showing almost complete

demyelinization with advanced fibril formation in which the only recognizable changes in the ganglion cells was absence of the processes, a rounding of the cell body, and an increase in the amount of cell pigment. In other areas these same findings were more marked. He describes another common type of change. This is in the form of a gradually advancing atrophy which is proportional to the increasing density of sclerosis. Minute structures of the processes suffered first. Later the chromatophile granules in the cell body became powdery and were dissolved. The nucleus tends to become peripheral, and in some there was disappearance of the nucleus with complete chromatolysis.

Cells in the demyelinated areas of the cortex when involved tend to be much more uniformly so than in the cord[6]. Changes involve not only the demyelinated area but also the adjoining parts of the cortex to some extent. Dawson believes the most characteristic manifestation of the process in the cortex to be a nuclear increase around the ganglion cells. This again is said to be not limited to the demyelinated areas.

Glial fibrosis:

The glial scar is probably the most striking feature of the lesions of multiple sclerosis. Weigert is said[9] to have suggested that in no other disease does such a dense gliosis occur. Many would dispute this concept. Putnam[10] compared some of the densest plaques of multiple sclerosis with areas of intense secondary degeneration about cysts of softening of

arteriosclerotic origin two or more years old and found that the gliosis was at least as heavy in the latter condition as in the former. Further, it was noted that many plaques show only a moderate fibrosis.

The gliosis is often described as being isomorphous, that is, the glia fibers are laid down parallel to the axis-cylinders. Storch, according to Dawson[6], has pointed out that in chronic diseases the newly formed glia fibrils show the same arrangement as the original fibers, whereas in cases of acute destruction of tissue, this regularity does not hold good. To Putnam[10] it seemed that the axons form a scaffold for the new fibers. In some plaques, where the axis cylinders as well as myelin have degenerated, the glia fibers tended to radiate from theblood vessels.

Hassin[14,15] is of the opinion that it is after the damaged tissues have been cleaned up and the area freed of the debris that the destroyed nerve tissue is replaced by gliosis. A typical patch consists of thin neuroglia fibrils emanating from thickly packed oval or rod-like nuclei. In other instances there are many homogenous appearing cytoplasmic glia cells with eccentric chromatin-rich nuclei and masses of thin processes.

When the reaction has ceased the plaques are formed of richly interlacing fibers, whose nuclei and cells are few and far between.

Nature and distribution of the cellular changes:

In 1914, Siemerling and Raecke[24] reviewed the histology of eight cases and concluded that destruction of nervous tissue

was related to changes in and around small vessels. These changes included dilation, congestion, capillary hemorrhages, and perivascular infiltration with lymphocytes and plasma cells. He is of the opinion that the first cell-infiltration of the vessel walls is one of fat granule cells and is therefor associated with resorptive processes. This is then followed by cell proliferation in the adventitia, and finally by a more or less large number of "small round lymphocyte-like cells common to all chronic processes".

Hassin[24,15] favors the view that the perivascular infiltration consists almost entirely of fat-granule cells. "In toluidin blue, thionin, hematoxylin-eosin, Van Gieson and similar stains such infiltrated blood-vessels suggest at first glance an inflammatory condition, as if the infiltration consist of lymphocytes, plasma cells and similar hamatogenous elements. Such an error can easily be corrected by having the specimens stained with osmic acid or scarlet red which will show that the infiltrative cells are fat granule bodies (gitter cells)".

Symonds[25] has very carefully studied a case of multiple sclerosis, clinically as well as histologically, in an effort to see if inflammatory cells were present. Around the vessels there were two kinds of cell infiltrations: 1) in foci which were in the phase of fatty degeration the cells were almost entirely fat laden cells, and 2) in certain areas an occasional venule was seen surrounded by a cuff of densely packed nuclei, apparently those of lymphocytes with an occasional plasma cell.

"This type of perivascular infiltration was indistinguishable from the commonly seen in encephalitis lethargica, but in the present instance the individual vessels affected were comparatively few and far between". Such infiltrated vessels were observed only in the more recent foci or at the periphery of what appeared to the author to be advancing lesion.

Putnam[10], using appropriate stains for lipoids, noted in one specimen from a patient who had had the disease for eighteen years, that "a perivascular collection of round 'castellated nuclei was not microglial. In the infiltration in one plaque even a few polymorphonuclear cells were observed". Putnam is of the opinion that because of a variation from case to case in the relative degree of lymphocytic and glial infiltrations, any attempt to divide the processes into inflammatory and degenerative is unjustified.

It is generally admitted that the majority of the infiltrating cells are phagocytic. Rod cells, a variant of the microglia are occasionally seen and proliferation of astrocytes, diffusely throughout the tissue and in perivascular accumulations are common[10]. Acutely swollen ameboid astrocytes and regressive glial changes may be seen. Meningeal infiltrations are also found.

Relation of plaques to blood vessel distribution and vascular abnormalities in multiple sclerosis:

Observations of vessel proliferation, engorgement, perivascular hemorrhages, obliteration, and thrombi have been reported by many investigators including the earlier ones.

Cruveilhier (1838) compared the areas of sclerosis with the results of embolism[26], Rindfleisch (1863) noted the presence of an engorged vessel in the center of smaller plaques. "If we attentatively consider the smaller and smallest of the gray depots, we are certainly struck with the peculiar phenomenon that in the midst of each of them there is a red point or streak, the transversely or obliquely divided lumen of a vascular branch filled with blood[18]". Charcot (1863) observed that the vessel wall, even of the finest capillaries become much thickened, and in many instances the calibre suffers a notable diminution[2].

Ribbert (1882) is one of the earliest to have devoted particular attention to the presence of thrombi. He described numerous thrombi composed of white cells and fibrin in arteries and gives an illustration[27]. According to Dawson[6], Ribbert related the areas in multiple sclerosis to apprimary disseminated thrombosis, and in all the patches he described a vessel. Many were seen to have run through the whole extent of an area. In two small patches cut in serial sections the vessel lumen contained white blood-cells, partly adherent to the vessel walls and partly filling the vessel as emboli.

Dejerine (1884) thought the configuration and dissemination of the patches to be explained only by relating them to changes in the blood-vessels. In the monograph of Dawson[6] reference is made to Dejerine's observation of a vessel with periarteritis and diminished caliber as the central point of each plaque.

Williamson[28] as 1894 laid emphasis on the presence of arterial and venous thrombi, the frequent central position of vessels, and on the occasional extension of areas of sclerosis corresponding to an area of blood vessel distribution. Falkiewicz[29] and Anton and Wohlwill[30] studied some serial sections and felt that the plaques tended to surround vessels.

Borst[31] (1903), in a histologic examination of five cases of multiple sclerosis, noted fresh thrombi with softenings, and also that the vessels within the areas were hyaline and often obliterated, especially the paracentral vessels.

Dawson[6] writes: "During the course of this investigation (Dawson's histological study), a large number of small isolated areas, both in the brain and spinal cord, have been cut in serial section with the object of tracing the possible presence of thrombosis or of capillary hemorrhages. In a few instances, especially in the lateral vessels of the cord and medulla, there have been found aggregations of white cells and the presence of fibrin which have taken as evidence of intra-vital thrombosis, but nowhere has evidence been present of organization of such thrombi nor of alterations in the vessel walls in relation to them, nor have these always been in relation to sclerotic areas". After studying "several small areas serially, throughout their whole extent" he came to the conclusion that the changes appear within, but do not coincide with, the areas distribution of the arteries.

Taylor[32] in a study of "many hundred specimens" was

unable to show any distinct relationship between vessels and lesions. He opinions that what vessel changes occur in relation of the sclerotic patches are not cause and effect, but rather as parts of a general process. In many cases vessel changes of any sort were not discovered.

Hassin[15] makes a statement to the effect that the patches of sclerosis are not representative of territorial areas in relation to the arterioles, the venules and the perivascular lymph drainage. Mild vascular changes, distended adventitial spaces, hyperplasia and thickening of their walls, were seen in apparently healthy regions, in the intermediate zone and in the patches themselves. Regardless of the condition of the nerve tissues and the degree and extent of the lesions, the vascular changes seemed to be alike.

More recently Putnam[11,33,34,35] has stressed pathologic findings on the venous side of the vascular tree as a primary alteration. In every one of his fourteen cases of multiple sclerosis marked vascular changes were said to have been observed. There was adventitial proliferation, engorgement, tortuosity and proliferation of the veins in the vicinity of the plaques. Clots of fibrin and leukocytes occurred in vessels of various sizes, some of which were being invaded by endothelial cells. Complete occlusion of vessels by fibrous tissue was encountered "with considerable frequency".

Putnam and Adler[36] made plate glass reconstructions of three sclerotic plaques in an effort to study changes in architecture and the spatial relationships of blood vessels.

Small plaques tended to surround engorged veins, which are tortuous and gnarled. Areas of fresh degeneration were found in close relation to venous thrombi. Using a Benzidine stain, there was usually an increase of capillaries in the plaque, but a decrease was also found. Early plaques stand out as hyperemic areas[36,37].

Putnam[38] states that one can observe evidences of vascular occlusion other than thrombi in cases of multiple sclerosis, such as closure of vessels, perivascular accumulation of pigment and "enormous passive dilation - far greater than one ever sees in an active inflammatory area".

To date no one has apparently studied a sufficiently large group of complete sclerotic plaques to determine the occurrence rate of the various types of alterations or of the relation between vascular architecture and plaque areas.

Form, symmetry, and distribution of sclerotic plaques:

Lesions in the spinal cord may vary in size from those of microscopic dimension to those which permeate the whole thickness of the cord, leaving only a few portions free[19]. Wedge shaped lesions, with the base at the periphery are commonly described[3]. Dawson[4] describes other typical spinal cord lesions as follows: small irregular ampulla-like areas with the ampulla-neck at the periphery of the cord; large areas located between the anterior and the posterior roots, occasionally extending to the gray matter; in the lateral columns the areas tend to be round or oval whereas in the posterior columns there is more of a tendency to be of an elongated oval shape; the most frequent gray matter involvement is said to be in the form

of a pericentral gliosis. "In the frontal longitudinal section of an isolated area in the posterior columns, it is possible to recognize how the numerous vertical branches of a vessel system are all involved and not one primary vessel stem". The apparent dependence upon the vessel regions was seen in the small wedge shaped lesions situated at the periphery of the spinal cord, "in which there was always found a condensed or even obliterated vessel radiating from the pia".

Evidence of the sclerotic process is said by Oppenheim[10] to be even more extensive in the pons and medulla oblongata. Here they were seen to occupy up to one-quarter to one-half of the transverse area, or even the whole of it.

In the medulla, pons, cerebral peduncles and cerebellum the same two primary forms which Dawson[6] describes for the cord are said to be present. Subpial areas are frequently wedge-shaped whereas lesions within the substance of the white tissue tend to be round or oval in form. Lesions involving the cranial nuclei, white matter of the cerebellum, the hilum of the dentate nucleus, and nuclei of the roof of the fourth ventricle were common.

The apparent predilection of multiple sclerosis for paraventricular areas is commonly mentioned. The whole of both lateral ventricles may be involved or the process may be limited to a part of one ventricle. Brain[39] states that it is most marked in the horns, especially the posterior horns. The aqueduct of Sylvius and the fourth ventricle may be similarly affected. Dawson[6] noted numerous wedge-shaped areas with the

base directed to the ventricle. From these there were frequently finger-like extensions, in each of which a central vessel could usually be found. He noted also that in the basal ganglia isolated areas were often round but in the optic thalamus, internal capsule and lenticular nucleus areas tended to be large and irregular, probably the result of fusion.

Sclerotic areas which occur in the cerebral cortex have been classified into three divisions[6]: a) lesions which spread from the white matter into the gray; b) lesions wholly within the cortex with a zone of intact nerve fibers forming a fine network superficial to it, and c) plaques which seem to have spread from the surface and extend for a variable distance inwards. In the latter group the areas often have the shape of a modified wedge or of an arch.

Similar forms are said to be found in the cortex of the cerebellum[6,39].

Symmetry of plaque distribution is strongly supported by Dawson[6]. "A remarkable symmetry can be recognized, in their localization - a symmetry which can easily be underestimated when the areas are at different stages of development".

Pathological changes in special situations:

The sclerosing process may involve the visual fibers at many points. The optic radiations may be affected as a result of direct extension from commonly found periventricular sclerosis, there may be primary areas, or the whole intracranial course of both optic nerves may be devoid of myelin[39]. Dawson observed that the optic chiasma, especially the anterior border

is most frequently affected. Velter[40] considers the areas in the optic nerves to be related to the central vessels while in the chiasma and optic tracts they may be either subpial or subependymal in relation to the chiasmatic recess of the third ventricle.

Typical sclerotic areas of multiple sclerosis are generally considered confined to glia bearing parts of the nervous system[39], thus it seems unlikely that manifestations of the disease process would be found in the cranial or spinal nerve roots or in the peripheral nerves. Dawson examined the nerve-roots in one of his cases and found considerable variation in the extent of demyelinization and gliosis. This he attributed to a variability in the extent to which glia might normally be in nerve roots.

Internal hydrocephalus associated with multiple sclerosis has been described. In its production the following factors have been considered: obstruction of the cerebral aqueduct by surrounding sclerosis and ependymitis[41], and possibly atrophy of the cerebral hemispheres[39].

ETIOLOGY

Since the first descriptions of multiple sclerosis as a morbid entity there has been speculation concerning the nature of the etiological factors. Much work has been carried out along experimental and bacteriological lines in an attempt to discover the determining cause. Although many theories have been advanced there is as yet no positive knowledge concerning the nature of the causative process or agent. Some of these various theories will be briefly reviewed and discussed.

Abnormalities of development as etiological factors:

Muller[5], an early advocate of this theory, was of the opinion that there were inborn defects of the central nervous system. Furstner, according to Dawson, speaks of an early invalidity of the nervous system which is unloosed by later factors. Mott[44] suggests that congenital anomalies of development may be present in the sense that "they lay the foundation of the constitutional tendency which renders the individual more susceptible to the injurious influences of later life".

Much interest was taken in the reported discovery of the casual agent of multiple sclerosis by Chevassut[45] in 1930. The agent was thought to be filterable virus (Spherula insularis) which was said to have been obtained and cultured from the cerebrospinal fluid of patients with multiple sclerosis. Carmichael[46] and Weil[47], under carefully controlled conditions, failed to substantiate the presence of

a virus in cultures of cerebrospinal fluid. Stewart[48], Miss Chevassut's laboratory supervisor, failed to duplicate demonstration of a virus even though familiar with Chevassut's technic and using the same laboratory and assistents.

Steiner[7], using a special silver reduction technic, claims to have demonstrated extracellular spirochetes "Spirocheta myelophthora) and intracellular argentaffine particles ("spirochetal debris in glia cells and lymphocytes" -"silver cells") in the nervous tissue of patients with multiple sclerosis. His controls revealed no similar elements. Blackman and Putnam[49] demonstrated the argentophilic particles but suggest that they may be of hematogenous origin and not necessarily of spirochetal or bacterial origin. Hassin and Diamond[50] prefer to call the particles "Silver granules" and are in agreement with Blackman and Putnam in believing that they do not originate from spirochetes.

Toxi-infective agents have long been held to be of primary importance by many observers. According to Dawson[6], Marie early urged the recognition of acute infectious diseases as the actual final cause of multiple sclerosis. Brain[39] states that the strongest advocates of a casual relationship between such diseases as the exanthemata, rheumatic fever, enteric fever, and multiple sclerosis can only claim that such an association occurs in about 25 per cent of cases. Suggestions have been made by Bramwell[51] that the toxic factors might be bacterial endotoxins or exotoxins.

Toxic agents as etiological factors:

It has been suggested that multiple sclerosis is a manifestation of lead intoxication. Cone, Russel, and Harwood[52] obtained a positive test for lead in the cerebrospinal fluid in 6 out of 8 cases of multiple sclerosis tested. Rabinowitch[53], using the same technic, examined the cerebrospinal fluid from 27 cases of the disease and obtained only two positive results. Garvey and Rockwell[54] found all 9 cases of multiple sclerosis in which they tested the cerebrospinal fluid to be negative for lead.

Experimentally the following agents have been shown to produce demyelinization when injected into animals: tetanus toxin[55], carbon monoxide[56], saponin, cobra venom, bilt salts, potassium ferrocyanide[57], and brain extracts[58]. Bramwell[51] suggests the possibility that the offending toxins may be products of deranged metabolism.

Lysolytic ferments as etiological factors:

Marburg is said[57,59] to have been one of the first to suggest that the lesions found in multiple sclerosis might be the result of the action of an enzyme which destroys lecithin. Brickner[59] immersed segments of rat spinal cords in blood plasma from patients with multiple sclerosis. Sections of these cords after twenty-four hours of such immersion showed that this blood had a demyelinating action which was not demonstrable in blood from controls. Weil and Cleveland[60] repeated these experiments using serum rather than whole blood and obtained similar results. Weil and Heilbrunn[61]

demonstrated in the urines of patients with multiple sclerosis a substance which acted destructively upon the myelin sheaths or rat spinal cord. Brickner, Watters, Wexler and Soltz[62] expressed the opinion that the myelinolytic agent present in the blood of diseased patients is a true esterase. Using a different method for determining esterase activity of serum Richards and Wolff[63] found no difference in the behavior of serum from patients with multiple sclerosis (143 determinations from 30 cases) and serum from any other person (102 determinations from 55 individuals).

Intravascular clotting of blood as an etiological factor:

Because of the frequent occurrence of venous thromboses in relation to the more recent plaques of multiple sclerosis Putnam and his collaborators look upon disturbances in the clotting mechanism of blood as a possible determining factor. Simon and Solomon[64] compared the reaction of the clotting time of blood to the intravenous injection of typhoid vaccine and to the subcutaneous administration of epinephrine in twelve patients with multiple sclerosis and in fourteen controls. Although there was individual variation there was a decrease in the clotting time of both groups of subjects but was much more marked in the group of the multiple sclerosis cases. The authors concluded that these results indicated a lability of the clotting time in multiple sclerosis, such as would favor intravascular clotting.

Dattner[65], in contrast to Simon and Solomon, records an increase in clotting time in patients with the disease.

"The considerable increase in the blood clotting time of many of the patients with multiple sclerosis is worthy of consideration as the expression of a metabolic disturbance depending on the liver". He gives no experimental evidence in support of his claim that the clotting time is sometimes lengthened.

Miscellaneous factors which have been considered to be of etiological significance:

Allergy[5 7], cold, psychical shock[6], and trauma have all been mentioned by various authors as possible determining factors in the pathogenesis of sclerotic plaques. Dawson[6] suggests that cold, fatigue, and psychical shock may act as immediate factors by lowering the vitality or the resistance of the individual, or possibly they result in vasomotor changes which would permit the rapid emergence of a toxin circulating in the blood. Dawson refers to Mendel as an advocate of the theory that external trauma results in the transmission of an "impulse" to the cerebrospinal fluid to produce minute capillary hemorrhages and outpourings of lymph into the tissue. These were then thought to lay a foundation of a lowered resistance for toxi-infective agents. In Dawson's investigation he found no evidence for the existence of capillary hemorrhages except those probably pre-agonal ones due to respiratory difficulties.

PATHOGENESIS

In discussing the development of the disease process of multiple sclerosis consideration will be given to two fundamental questions. What is the nature of the process? and what tissues are primarily affected?

Much has been said concerning the probable natum of the disease and out of this discussion many divergent views emerged. According to one of the earlier theories to be advanced the pathological process was thought to be essentially a hypertrophy of the glia arising from a congenital abnormality of the nervous tissue. Strumpell[4], one of the first advocates of this theory of multiple gliosis, believed that the extent of glia proliferation gives the impression of it being a primary process. Muller[5] thought it striking that enormous glia proliferation should be met within a disease in which there is relative integrity of the true nervous tissue. In support of the endogenous or developmental nature of the process he stressed the following: foci tend to be found in those parts of the central nervous system which normally contain much glia; difficulty in finding evidence of primary disease of the blood vessels within the area; and the fact that no known exogenous factors seem to produce in any other organ the development of a process comparable in any way to multiple sclerosis. Muller, recognized, however, that in some cases the glial overgrowth was precipitated by an acute infection of the nervous system while in other cases no such predisposing cause could be found. He thus recognized two

types of glia proliferation, a primary form which he thought to be the result of malformation of the glia and that which is secondary to infection and intoxication. It was Muller's belief that the demyelinization in multiple sclerosis is a degeneration secondary to the glial overgrowth which was thought to exert its effect partly through direct compression of the myelin sheaths and partly as a result of deranged circulation. He felt that blood vessels within the sclerosed area showed changes which were entirely secondary to the sclerotic process. Muller examined material from six cases of multiple sclerosis and is said to have found none of the "undoubted components of inflammation".[6]

Dawson[8] did not agree with Muller's view of two types of glia hyperplasia. "The examination of many hundreds of areas has satisfied me that 'early' areas, so-called areas of fat granule myelitis, can develop into areas of compact gliosis with all the characteristics of those described by Muller as typical of true primary, disseminated sclerosis".

Schmaus[66] is said by Dawson to have suggested that congenital hypoplasia or agenesia (deficient anlage) of the myelin sheaths to be a factor in addition to the presence of glia which was thought to have a special capacity for proliferation.

An alternative to the hypothesis that multiple sclerosis is an endogenous glial hypertrophy implies an alteration of tissue nutrition or the presence of an exogenous factor affecting the nervous system. The possibility of the disease

process being on an inflammatory, degenerative, or vascular basis will be discussed in the section dealing with the origin of the process.

Origin of the disease process: Which tissue element is primarily effected?

As has been previously pointed out, Strumpell, Muller, and Schmaus were of the opinion that abnormally placed glia cells take on a latent vegetative activity and produce multiple gliosis. Dawson[6] summarizes this concept as follows: "The substance of the arguement of those who support this view seems to lie in the acknowledged fact that in many areas the glia proliferation is far in excess of that required as a mere reparative or substitutive process, and that it must therefore be looked upon as a productive primary stimulation". Charcot[2] thought that some exogenous factor stimulates the glia anywhere within its range to a marked glia fibril formation, the atrophy of the nerve elements and vessel wall changes being secondary. He thought the neuroglia to be a reticulated connective tissue the meshes of which contain nerve fibers. In this view the process starts as a "formative irritation" of glia which is comparable to chronic interstitial inflammation in other organs.

Redlich[67] contended that the "noxa" acts directly and primarily upon the nerve fiber before there is any trace of glia proliferation of vasculer wall alteration. The first impulse may be given, for example, by infectious diseases to produce an "acute degenerative decay" of the myelin. He also

suggests the possibility of the original agent causing nutritional alterations in other parts of the central nervous system so that further later stresses or excesses of function might cause the affected parts to perish. The glia reaction was thought to be secondary to the parenchymatous degeneration, but might also be productive, "passing beyond the bounds of a substitution process".

Mott[44] and Marburg[68] emphasize the primary susceptibility of the myelin sheath for some toxic agent and speak of the process as essentially a "lecitholysis". Morr[69] thought the process might be the result of a lipolytic ferment which had a slow, limited and localized action.

Dawson[6] points out that in using Weigert myelin sheath sections numerous small areas may be found in which there is no appreciable change but a demyelinization of the affected tissue. This, he says, is "more apparent than real, for sections stained by Heidenhain's iron-hematoxylin almost invariably show that in such small areas the slightest demyelinization is accompanied by a commencing glia cell proliferation which continues parallel to, or even exceeds in proportion, the destruction of the myelin sheath". Dawson is in agreement with the view that the most constant and uniform change is the absence of the myelin sheath. The glia proliferation, he believes, is called forth by a stimulant action of the "noxa", and secondarily, by degenerative products of the parenchyma.

Huber[70] accepts the view of a primary parenchymatous

change, that is, that the process is "a simple degenerative decay, not an inflammatory decay". The outstanding present day advocate of this theory is Hassin[13,14,15,71] who bases his opinion upon his observation of degenerative changes in the myelin sheaths outside the plaques, and a denial of the perivascular distribution of the affected tissue. "The patches of sclerosis are not representative of territorial areas in relation to the arterioles, the venules, or the perivascular lymph drainage.[14]

Many observers have considered the blood-vessels or the perivascular spaces to be first involved and the changes have been expressed in a number of ways[6]: 1) a primary thrombosis or thrombosis secondary to irritation of the intimal lining by circulating toxins, 2) a chronic inflammation which may affect the nutrition of the area supplied by the affected vessel, 3) a primary acute vascular change with perivascular cellular infiltration (a true inflammation) which might extend to involve the adjoining tissues, 4) minute capillary hemorrhages from a toxic or mechanical effect on the intimal lining, or 5) vessel change that lead to adhesions and closure of the lymphatic sheath with subsequent stasis.

Rinfleisch[18] was among the first to note the significance of blood vessel changes in the areas of "gray degeneration" and the intimate relation of these areas to the blood-vessels. He believed that malnutrition of the tissues resulted from a chronic irritative condition of the vessel wall. "In these

changes of individual vascular trees I perceive the first link of the anatomical process. The second is a fibrous metamorphosis and hyperplasia of the neuroglia". Rindfleisch thought the growing connective tissue network penetrated into the "space destined for the nerve-tubules, narrows it, and finally brings the nerve-tubules themselves to disintegration". He gave no suggestion as to the nature of the primary cause of vessel alterations.

Ribbert[87] related the areas in multiple sclerosis to a primary disseminated thrombosis. He is said by Dawson to have described a congested vessel in all the patches examined, and in several the vessel was so cut that it was seen to pass through the whole extent of the area. In two small plaques, studied in serial section, he found in the vessel lumen white blood cells "partly adherent to the vessel walls and partly filling the vessel as emboli". Ribbert looked upon these as multiple thrombi and assigned to them an important causative role. He postulated that the exciting cause of the inflammation circulates in the blood stream, and because of its presence a clot is formed at some point in a small blood-vessel. At this point an irritation of the vessel wall results with a perivascular inflammation which extends to involve the surrounding tissue. This in turn was thought to result in a degeneration of nerve fibers and a proliferation of glia. Putnam[72] states that Ribbert suggested that the plaques of multiple sclerosis are dependent on venous thrombosis.

According to Dawson[6], many French writers, particularly

Dejerine and Pierre Marie support the vascular origin of multiple sclerosis. Dejerine[75] is said to have found a peri-arteritis with diminished vessel caliber and "That a vessel, thus changed, was a central point of each plaque". He advanced the possibility that the casual factor might be a microbe or humeral agent of undetermined nature which as a result of circulating in the blood stream modified the nutrition of these vessels in some way. He thought the effect on the surrounding tissue was first seen in the form of glia proliferation, this in turn was said to have caused an "excentric compression of the nerve-tubes" leading to their disappearance.

Marie[3] emphasized the relation of multiple sclerosis to infectious diseases, such as measles, scarlet fever, entric fever and pneumonia. He did not think the process to be due to the organisms responsible for these diseases but rather to a concomitant or symbyotic infection occuring during their course. Dawson refers to Marie's conception by saying that "the etiological influence of the infectious diseases is such that there may result changes of the vessels and the sclerotic areas are therefore due to the localization of infectious vessel disease in the central nervous system".

Williamson[74] noted marked vascular changes such as round cell infiltration, sclerotic or hyaline thickening, occasional central position of vessels, and occasional extension of sclerotic areas corresponding to the area of blood vessel distribution. He describes thrombi in arteries, in the anterior

median vein, and in small vein in the pia mater on the surface of the cord.

Siemerling and Raecke[24] attached considerable importance to the presence of capillary hemorrhages. They looked upon these minute hemorrhages as the first evidence of the inflammatory process, and the cause of the initial fiber degeneration. Dilatation, congestion, and perivascular infiltration with lymphocytes and plasma cells were also found in each of the eight cases examined by them. According to Symonds[25] they noted that such changes were not present in all the foci examined, nor when they did occur were they uniformly distributed throughout the focus.

Dawson studied a "large number" of small isolated areas with the object of tracing the possible presence of thrombosis or of capillary hemorrhages. In a few instances he found aggregations of white cells and the presence of fibrin which he looked upon as indications of thrombi. He did not, however, observe alterations of the vessel walls in relation to these thrombi. He saw no evidence of organization and when thrombi were found they were not always in relation to sclerotic areas. He felt that the absence of histological evidence of changes in the vessel walls associated with thrombosis or hemorrhages is incompatible with a primary vascular lesion. "Keeping in mind the difficulties in recognising small thromboses after actual sclerosis has set in, and also the admitted long time that extravasated blood may remain unchanged in the nervous tissue, it is difficult to account for the origin of

sclerotic areas in such primary changes".

Symonds[25] was of the opinion that changes such as vascular engorgement and perivascular cellular infiltration, although not a constant feature of the lesions of multiple sclerosis, does occur in the acute phases of the disease. In the substance of the brain and brain stem the relation of each small focus to a central blood vessel (venule) seemed to Symonds to be quite constant. In the spinal cord this relation was not established.

Many authors ascribe a primary significance to true inflammatory changes in the blood-vessel walls. The responsible factor might be transmitted directly, by diffusion, to the perivascular tissues causing a reactive inflammation or the agent might be restricted to the vessels giving rise to vessel wall changes which in turn may alter the nutrition of the surrounding tissues. Dawson reasoned that an irritative substance circulating in the blood, in its filtration and diffusion into the tissues, would stimulate the capillary endothelium and cells of the adventitia to proliferate. Thus, the first effect would be on the vessel wall through which it passed. This investigator then studied his material with this in mind but found that a primary proliferation of the capillary endothelium or a primary increase in the nuclear content of the adventitia could be traced only in rare instances. He concluded: "In the event, therefore, of a disease-producing agent, either bacterial or toxic, being carried with the blood or circulating in the lymph sheaths, it must be assumed that this poison leaves

the blood channels in so slight an amount or in such weak concentration that a recognizable injury of the vessel wall does not result. The only part played by the blood-vessels would thus be the bringing of the 'noxa' to the tissues".

Bielschowsky[75] supports the view that the vascular changes are secondary to the resorptive processes and that the "noxa" penetrates the vessel wall but leaves it intact.

Borst, according to Dawson, placed emphasis on disturbance of the lymph circulation as a factor in the formation of sclerotic plaques. He believed the primary lesion to be in the blood-vessel wall. This, in turn, was thought to result in obstruction either by cellular infiltration or by fibrous obliteration of the adventitial lymphatic spaces. The resultant lymphstasis, it was suggested, gave rise to myelin sheath degeneration and a forcing apart of the glial meshes. Later as the lymph congestion subsided the glia would undergo proliferation and to invest the persisting axis cylinders with a more or less dense fibrous network. As to the primary cause which acts on the membrances and vessel walls, Borst concludes must be mere conjecture.

Although some of the earlier investigators supported the "lymph-congestion" theory of pathogenesis little has been said in support of this view by the more recent authors. Dawson thought the chronic inflammation of the vessel-walls with closure of the lymph spaces to be a late change so while he agrees with Borst in that the fundamental basis of the process underlying multiple sclerosis may be a flooding of the tissues

with toxic lymph he disagrees regarding the mechanism by which such change is brought about in the early stages. In late stages Dawson believes the vascular changes with obliterated lymph spaces may contribute "to the production of a vicious circle in which hyperlymphosis plays a part".

Taylor[32] opinions that there is not a distinct relationship between vessels and lesions nor do the blood-vessels show any alteration in the sclerotic areas as contrasted with normal areas. He regards these vessel changes as "insignificant" and to be manifestations of a general process rather than cause and effect. "This", he writes, "does not preclude the theoretical possibility that the agent producing the lesions circulates in the blood and then produces its effects".

In Brain's review[33] of multiple sclerosis he suggests that the blood vessel changes as well as the glial reactions might be in response to the pathogenic agent and to the products of tissue damage.

Putnam and his collaborators have been among the most recent adherents to the view that vascular changes are primary. They emphasize the formation of venous thrombi and reason that the focal areas of demyelinization and gliosis are the ultimate result of a mild and chronic local tissue anoxemia which thus results. Putnam[34] suggests that the sclerotic plaque represents the "mildest form of permanent damage produced by a disturbance of blood supply". Complete asphyxia of the cortex for a relatively short time is said to lead to loss of all ectodermal structures, but if the gas exchange is disturbed to a milder

degree but over a longer period of time Putnam[34] and Ferraro[75] believe the myelin suffers most. As evidence for the apparent early vulnerability of myelin Putnam points out that loss of myelin in itself does not prevent the transmission of nervous impulses and that in some cases of this disease a practically complete demyelinization of some levels of the brain stem is compatible with life, and almost complete demyelination of the optic nerves is compatible with vision.

An effort will be made in this discussion to outline the observations and interpretations of Putnam supporting the theory of venous occlusion as the precipitating factor in the pathogenesis of sclerotic plaques. When Putnam first approached the subject of multiple sclerosis he thought the fundamental questions were whether or not the process of demyelination such as is seen in the acute encephalomyelitides regularly or ever lead to chronic sclerosis and if so, what would be the nature of theacute process?

Attempting to determine a relationship, if any, between the typical plaques of multiple sclerosis and the acute lesions of the encephalomyelopathies especially those following vaccination or measles, he reviewed sections from seventeen cases of multiple sclerosis and three cases of "disseminated encephalomyelitis".[10,26]. He thought that all the histologic characteristics of "encephalomyelitis" may be seen in varying degrees in the more acute plaques of multiple sclerosis. The structural differences, especially the dense glial fibrosis in the latter condition, were explained as due to the intensity

and duration of the disease. In all three cases of "encephalomyelitis" numerous fresh thrombi were observed. Most thrombi were described as masses of agglutinated platelets in which occasionally the beginning of organization could be detected. Of the seventeen cases of multiple sclerosis "definite thrombi" were observed in veins of nine. "The thrombus was not always in direct relation with a plaque". The lesions related to venous thrombi were "invariably" acute and devoid of gliosis[26]. In multiple sclerosis the closure of vessels by fibrous plugs or endothelial cells was said to be more common than by thrombi. It was seen in fourteen cases. "This", he writes, "is not surprising, for a thrombus is necessarily an evanescent structure, while a fibrous cord may persist indefinitely".[26]

In an effort to determine if this vessel closure could be the result of perivascular infiltration he examined material from four cases in which there was "intense" secondary degeneration about old apopletic foci or areas of injury". In no instance did he note any obstruction of the vessel lumen nor did he observe any fibrous cords.

Putnam[38,55,56,77] also attempted to produce demyelinating lesions by the injection of various substances or by exposure to carbon monoxide. Of sixteen animals treated with carbon monoxide to the point of coma, only two showed satisfactory lesions and only two out of eighty dogs injected with tetanus toxin developed central nervous system lesions. In both experiments lesions could be found in which the myelin was destroyed and phagocytized and in which the axis cylinders remained almost intact. Perivascular cellular infiltration

consisted of fat laden cells, lymphocytes, and plasma cells. Putnam believes these lesions closely resemble those of "post-infectious encephalomyelitis".

In looking for a common denominator which might exist between carbon monixide poisoning, tetanus injection, "postinfectious encephalomyelitis", and fresh plaques of multiple sclerosis he noted that when the lesions were perivascular the central vessel could usually be identified as a vein, never an artery. He also noted that thrombi were occasionally found in all the above named conditions. It seemed to him justified to make the tentative hypothesis that the lesions were the result of venous obstruction, probably venous thrombi. To test this hypothesis he injected a bland oil retrogradely into an isolated segment of the superior longitudinal sinus of dogs in an effort to produce obstruction on the venous side of the vascular tree [78]. He describes the early stages of lesions produced in this manner to be similar to those of "nonsuppurative encephalitis". The later stages, up to ten months, of the lesions consist of "plaques of demyelination with practically complete preservation of the axis cylinders and with dense fibrous gliosis confined to the white matter".

Because of the "similarity between such lesions and many of those seen in cases of multiple sclerosis is so striking" he feels that the conclusion appears almost inevitable that venular obstruction is the essential immediate antecedent to the formation of typical sclerotic plaques of multiple sclerosis.

MATERIAL

All 5 of the cases studied were typical examples of multiple sclerosis from a pathologic standpoint. In 4 cases the clinical course was in every way characteristic of the disease. In the case of Geerts a more fulminating course than is usually seen obscured the true nature of the process. A detailed summary of the clinical findings in this case as well as a report of the pathologic observations in all 5 cases follows.

Case 1 (Geerts) -- A woman aged 38 was examined by Dr. L. van Bogaert on December 11, 1934. In 1930 she had fallen in a stairway, after which she had pain in the back. Six months prior to the time of examination she had undergone a definite change of personality. Three weeks before the examination she suffered from severe vertigo and a few days later fell backward. At this time she vomited frequently and complained of severe pain in the back and limbs.

Examination revealed the patient to be prostrated with incessant vomiting. There was flaccid paraplegia, with abolition of tactile, pain and deep sensation up to the level of the twelfth dorsal to the first lumbar segment. The plantar and abdominal reflexes were absent, and the achilles and patellar reflexes were greatly diminished. There was incontinence of the vesical sphincter. The reflexes were equal and active in the upper limbs. There was marked nystagmus. The pupils were miotic and reacted normally to light and in convergence. The eyegrounds were normal. Examination of the spinal fluid showed

20 cells per cubic millimeter, 280 mg. of total protein per hundred cubic centimeters and a strongly positive Pandy reaction. On December 18 stiffness of the neck, complete paralysis of the right arm, weakness of the left arm and difficulty with swallowing were noted. The patient died on December 22nd. Because of the peculiar evolution of the disease during the short period of observation, the diagnosis of multiple sclerosis was not made.

Postmortem Examination (Dr. H. J. Scherer). --Anatomic Description of the Brain:

The brain was fixed in solution of formaldehyde U. S. P. and sectioned grossly. The meninges and basal vessels showed no changes. The cut sections revealed a certain hyperemia of the white substance. Inspection revealed plaques, generally round, nicely limited and about the size of a pea. Some of them involved the cortex alone; others were limited to the U fibers and here formed a half-moonshaped lesion along the boundry between the gray and white matter. Almost no lesions occured in the deep white substance. There was predilection of the spots in the brain substance for the area about the lateral ventricles. The plaques were often gray, but more often pink. Similar lesions were observed in the pons, the medulla and the cerebellum.

Anatomic Diagnosis.--The diagnosis was multiple sclerosis, of relatively acute type.

Case 2 (Andre).--The case of this patient, who had been ill

for five years, was a classic instance of multiple sclerosis, fulfilling all the criteria of the disease, and was diagnosed by Dr. L. van Bogaert as one of multiple sclerosis.

Postmortem Examination (Dr. H. J. Scherer).--Anatomic Description of the Brain:

The entire brain and spinal cord were fixed in a solution of formaldehyde. The basilar vessels showed no lesions. The frontal convolutions were slightly atrophic. The meninges presented a slight whitish thickening over the two fronto-parietal convexities. In the sections cut in the frontal plane one found at all levels small gray, discretely limited lesions the area of which was variable but generally smaller than a lentil. The lesions were sparse but were more frequently seen in the frontal sections about the ventricles and immediately under the cortex. Lesions of the same quality, but more extensive, were seen about the occipital horns. In places the gray lesions took on the character of a thin, concentric periventricular ribbon. At the level of the thalamus some tiny lesions were noticed. In the medulla there was a zone of demyelination about the fourth ventricle. The cerebellum was almost completely spared.

Anatomic Diagnosis.--The diagnosis was typical multiple sclerosis.

Case 3 (Sel).--The clinical findings in this case are to be reported elsewhere by Drs. Borremans and van Bogaert. The disease began at the age of 35 years and ran a course of six years. The clinical diagnosis was multiple sclerosis.

Postmortem Examination (Dr. H. J. Scherer).--Anatomic Description of the Brain:

The entire brain was fixed in solution of formaldehyde and sectioned horizontally. Very extensive symmetric periventricular demyelination, especially in the occipital and parietal lobes, and equally small grayish plaques in all parts of the centrum ovale, as well as in the white matter of the cerebellum, were noted. In the temporal lobes the demyelination occured also in the axial part of the white matter. Here only the U fibers seemed intact. There was intense gliosis of the external capsule and the white substance of the insula. The changes were not obvious in the region of the third ventricle. The corpus callosum seemed little shrunken, and the plaques were not frequent. The basilar parts of the pallium showed tiny cystic lesions. There were no changes in the meninges or vessels. The ventricles were not enlarged. The spinal cord and peripheral nerves were not examined.

Anatomic Diagnosis.--The diagnosis was multiple sclerosis, with symmetric diffuse periventricular demyelination.

Case 4 (Depris).--This case was a classic instance of multiple sclerosis, fulfilling all critis of the disease. The onset was at 31 years of age, and the illness ran a course of eight years. The clinical diagnosis by Dr. L. van Bogaert was multiple sclerosis.

Postmortem Exahmination (Dr. H. J. Scherer).--Anatomic Description of the Brain:

The brain was fixed in solution of formaldehyde. The

meninges presented no abnormality. The frontal lobes showed moderate atrophy of their convolutions. The basal vessels were soft and not thickened. Sections of frontal lobes showed the lesions were numerous, especially in the subcortical regions and in the white matter of the convolutions, while the neighborhood of the ventricles showed very few lesions. A large lesion had destroyed the whole region of the right dentate nucleus. Some large lesions were found in the thalamus bilaterally. The ventricles were not enlarged. The spinal cord was badly damaged, and multiple lesions were recognized at various levels.

Anatomic Diagnosis.--The diagnosis was multiple sclerosis.

Case 5 (Urbain).--In this case early mental changes were associated with the onset of the disease, coincident with an acute infection. There was progressive mental deterioration, wih eventual complete disorientation in space and partial disorientation in time. The patient also showed all the classic neurologic signs of multiple sclerosis. The disease ran a course of six years, beginning at the age of 25 years. The clinical diagnosis by Dr. L. van Bogaert was multiple sclerosis.

Postmortem Examination (Dr. H. J. Scherer).--Anatomic Description of the Brain:

The entire brain was fixed in solution of formaldehyde. The meninges and basilar vessels showed no changes. In the frontal sections small gray plaques were present in all parts of the cerebral white matter, being especially pronounced about the ventricles, where they formed a large periventicular stripe.

The cerebellum and medulla were also very rich in lesions.

Anatomic Diagnosis.--The diagnosis was typical multiple sclerosis, with extensive periventicular lesions.

METHOD

Histologic examination of all the cases by the Nissl, Pal-Weigert, Bielschowsky and Holzer technics confirmed in every instance the anatomic diagnosis of multiple sclerosis. For the serial sections a dark Van Gieson stain was found very suitable for showing the outline of the lesions as well as the vascular structures in pyroxylin-embedded material. In some series every section, in most series every other section and in a few series every fifth section was mounted. In all cases it was possible to follow even the smallest vessels from one section to the next. Each section throughout the series for each lesion was enlarged and drawn on translucent paper with the use of an Edinger projection apparatus.

Orthographic projections of the drawings of the individual sections were reconstructed for most of the lesions. In a given transverse section two planes (A and B, fig. 2), perpendicular to each other and to the plane of the section, were passed through an arbitrary point within the lesion. Points of intersection of these planes with the borders of the lesion and the vessel walls were plotted on graph paper for each of the serial transverse sections. If, in a given section, the vessel was not cut by one of the intersecting planes, points corresponding to the position and diameter of the vessel were projected to the intersecting plane and these readings used in reconstructing the lesion and its vessel. This offers a satisfactory method for visualizing, in three plane diagrams,

the course of the vessel as it traverses the lesion plaque. The projection of the vessel when it lay outside the true plane of the diagram was frequently represented by an interrupted line, rather than a solid line, connecting the projection points.

Care was taken to maintain the proper magnification in all diameters of the reconstruction. To obtain alinement of the serial sections at least three relatively fixed structures were chosen. Large vessels in tissues adjacent to the lesion, boundaries between the cortex and the white matter and meningeal surfaces served as fixed points. As each section was enlarged and drawn, the fixed points were alined with those from the enlargement of the preceding section. The orthographic projections of the sectional views thus reconstructed were made at enlargements of 25 or 50, depending on the size of the lesion. A blotting paper model of a part of the basal nuclei in case 5 (Urbain) was made. In some series intermediate sections were stained with the Nissl technic to assist in the identification of cellular elements. A few blocks were stained with the Masson technic, but in our hands the Van Gieson stain was by far the most useful. A preliminary survey of a case of thrombosis of the longitudinal sinus and of postvaccinal encephalomyelitis was made. The lesions, however, were so different from thos of multiple sclerosis as to make comparison unfeasible.

RESULTS

An analysis of the 60 lesions in respect to location, size and shape, both for the whole group and for plaques from the individual cases, is shown in tables 1-3 incl. It will be noted that over half the lesions were from a single case, that of Urbain. It so happened that most of these lesions were from a single series through the brain stem in the mesencephalic and diencephalic regions. In this series an unusually large number of small lesions was found. This accounts in the case of Urbain, for the disproportionately large number of lesions in the group occurring in mixed gray and white matter, as well as in the group under 2 mm. in largest diameter. When all 5 cases were taken together, lesions were studied from the cerebral cortex, the subcortical white matter, the corona radiata, the internal capsule, the basal ganglia and mid-brain, the optic tract, the cerebellum and the spinal cord. As blocks from corresponding regions were not always available in each case, there was some difference in the parts of the brain studied in the various cases. When the location of the lesions was correlated with their shape it was found that the 3 crescentic lesions were all located in the subcortical white matter and the adjacent cortex. Aside from this association of location and shape, there did not seem to be any one part of the nervous system in which the lesions tended to have a particular shape.

Fig. 1. Orthographic projection of an irregularly shaped lesion having no vessel larger than a capillary within its borders.

Fig. 2. Orthographic projection of a cylindric lesion with a vessel passing through it along its long axis.

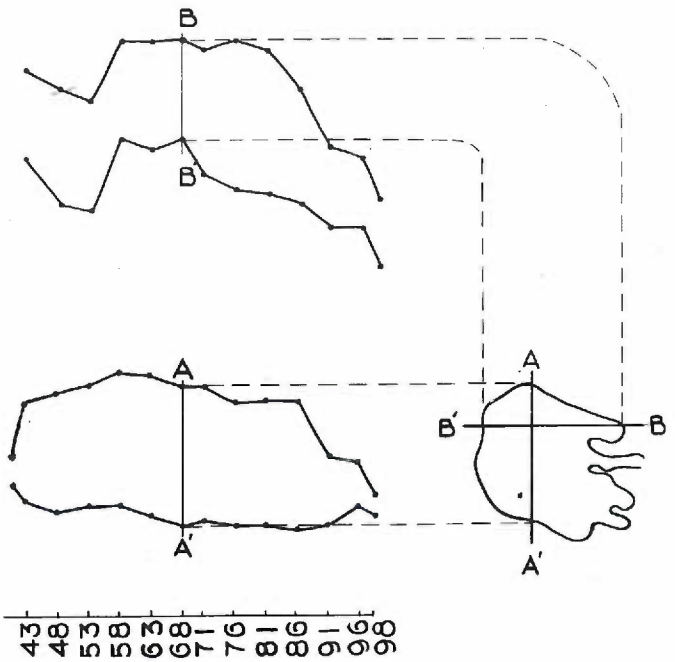
B
B'
A
A'
B'
B
A
A'
43 48 53 58 63 68 71 76 81 86 91 96 98

Fig. 1.

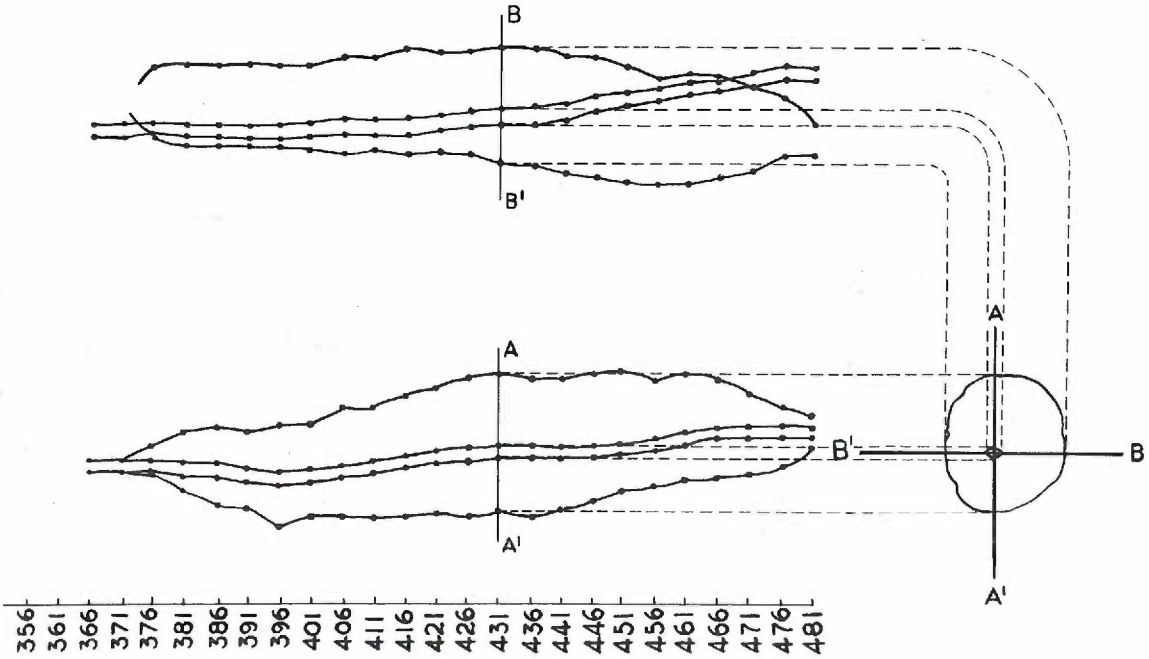
B
B'
A
A'
B'
B
A'
356 361 366 371 376 381 386 391 396 401 406 411 416 421 426 431 436 441 446 451 456 461 466 471 476 481

Fig. 2.

Table 1. Location of Lesions for the Total Group and for the Individual Cases

Individual Case	Total Number of Lesions Studied	Gray Matter	White Matter	Mixed Gray and White Matter
Geerts	2	1	1	0
Andre	2	0	1	1
Sel	5	0	5	0
Depris	19	1	10	8
Urbain	32	1	12	19
Total	60	3	29	28

Table 2. Size of Lesions for the Total Group and for the Individual Cases

Individual Case	Less than 2 Mm.	2 to 3 Mm.	Over 3 Mm.
Geerts	0	1	1
Andre	1	0	1
Sel	2	1	2
Depris	7	6	6
Urbain	25	5	2
Total	35	13	12

Table 3. Shape of Lesions for the Total Group and for the Individual Cases

	Spherical	Ellipsoid	Cylindric	Crescentic	Irregular
Geerts	0	2	0	0	0
Andre	0	1	1	0	0
Sel	0	4	0	0	1
Depris	2	7	7	1	2
Urbain	8	17	3	2	2
Total	10	31	11	3	5

Table 4. Presence or Absence and Type of Vessel in the Total Group of Lesions and in Individual Cases

	Total No. of Lesions Studied	Central Vein Absent	Normal Appearing Vein	Collapsed Central Vein	Distended Vein	Thrombus Formation
Geerts.....	2	1	1	0	0	0
Andre.....	2	1	1	0	0	0
Sel.....	5	2	2	0	1	0
Depris.....	19	5	5	0	4	5
Urbain.....	32	11	11	2	4	4
Total.....	60	20	20	2	9	9

For example, the 11 cylindric lesions were scattered among all possible sites except the cerebellum. As can be seen from table 3, over two thirds of the total number of lesions were definitely elongated, there being 31 ellipsoid and 11 cylindric lesions. Aside from a slightly greater number of cylindric lesions in the case of Dopris than might be expected, the case distribution could be entirely explained on a chance basis.

The relation of the vascular system to the lesions may be seen in table 4. It will be noted that by chance exactly one third, or 20, of the lesions were classified as those with the "central vein absent." In 14 of these no vein whatever could be found. Figures 1 and 3 illustrate such a lesion. The lesion might contain a vessel of capillary size, but neither a vein nor any sign of an old obliterated venous channel could be found. In the remaining 6 lesions in this group multiple small venous channels were seen. They could not be classed as central, but apparently were fortuitously included in the sclerotic plaque. There were 4 lesions with multiple veins which were so oriented as to be considered truly central. The 40 lesions in which a central vein was found were further subdivided into lesions the veins of which were normal, collapsed, distended or thrombosed. It is of interest that in no lesion could it be said that there was a central artery. To be sure, small arteries might be seen in the

larger lesions. The central vessel could in all cases be identified as a vein by tracing it to its union with a large unmistakable venous channel. All veins were traced for considerable distances central and peripheral to the lesion. In 20 lesions the vein appeared to be perfectly normal (fig. 4 and 5), in 2 lesions the vein was collapsed and in 9 it was distended. In the remaining 9 lesions definite occlusions were found which were interpreted as being due to venous thrombosis. These occlusive changes consisted of complete filling of the vascular channel by a plug of mononuclear cells of various types, and in a few instances a segment of the vein was replaced by a cord of fibrous tissue. There was proliferation of the endothelium and occasionally necrosis of the vessel wall. The vessel central to the occlusion was collapsed, and peripherally it was dilated. Immediately distal to the occlusion there was freshly clotted blood, with broken-down blood corpuscles and strands of fibrin. This in turn gave way to a segment of the vessel which was distended and packed with normal-appearing red blood corpuscles. Putnam and his associates have laid considerable stress on the statement of Ehrmann[79] that thrombi in small veins may disappear completely, without leaving a trace. It seems that a statement such as that by Putnam[34] "A thrombus in a small vessel may become so completely organized as to be unrecognizable within a week," is

Fig. 3. Photomicrograph of a section from the lesion shown diagrammatically in figure 1.
A, low magnification, and B, high magnification.

Fig. 3 A

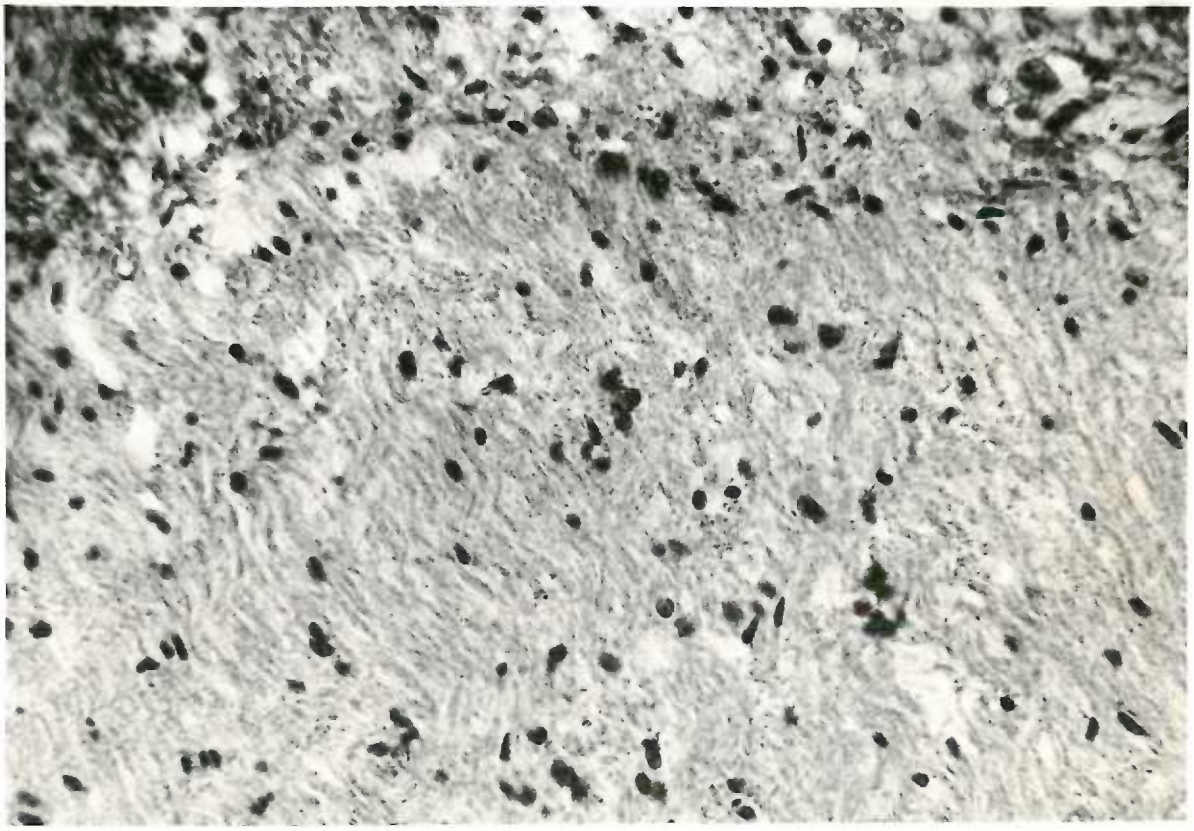

Fig. 3 B

Fig. 4. Photomicrograph of a section from the lesion shown diagrammatically in figure 2.
A, low magnification, and B, high magnification.

Fig. 4 A

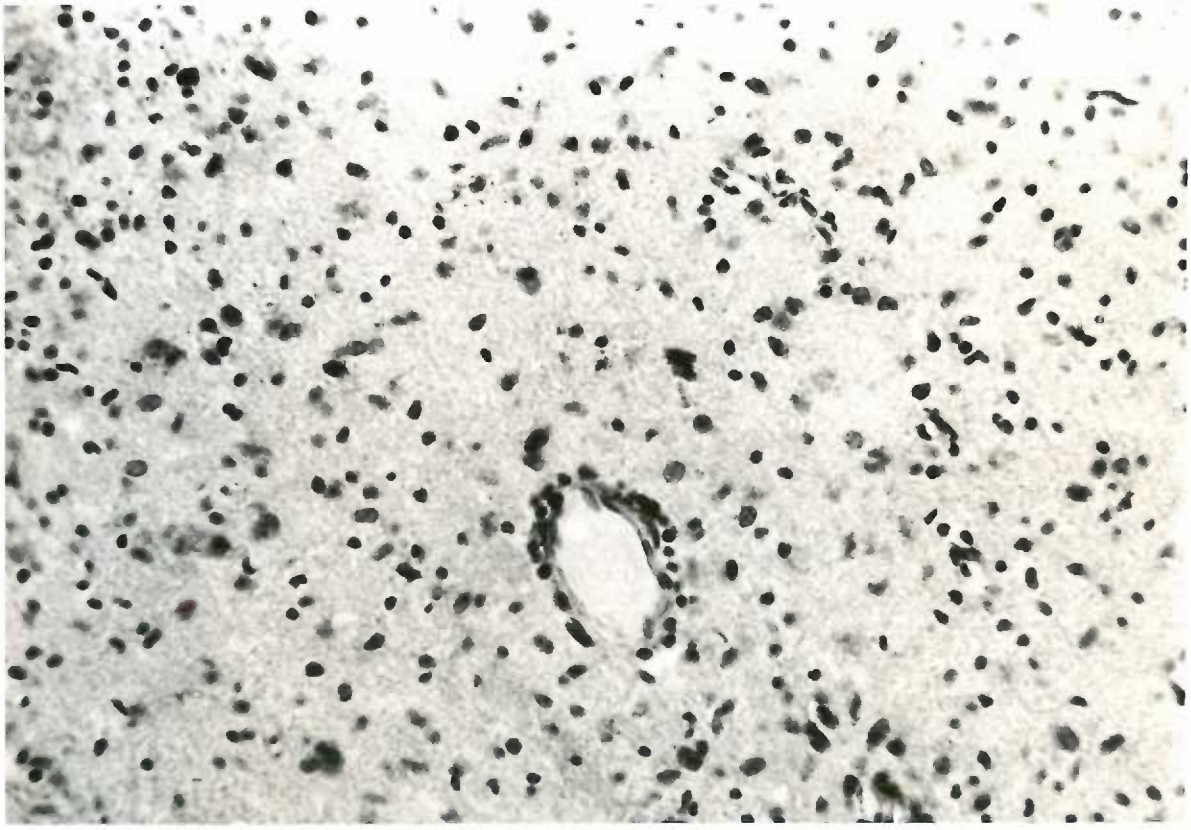

Fig. 4 B

Fig. 5. Photomicrograph of a section from the lesion shown diagrammatically in figure 2. Note venous tributary. A, low magnification, and B, high magnification.

Fig. 5 A

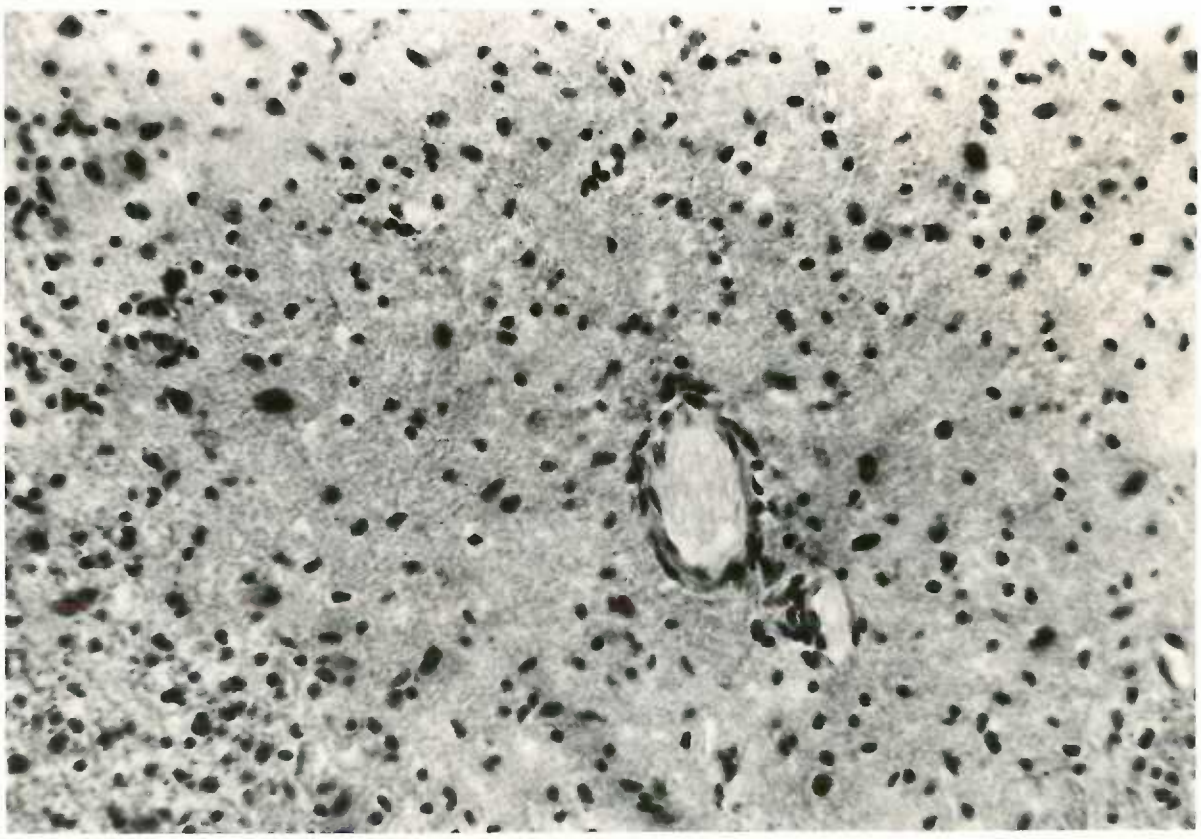

Fig. 5 B

Fig. 6. A lesion with a central vein thrombosed outside the lesion. The diagram was made from the composite tracings through several sections to show the topical relations of vein, thrombus and lesion. A is a high power photomicrograph through the thrombus.

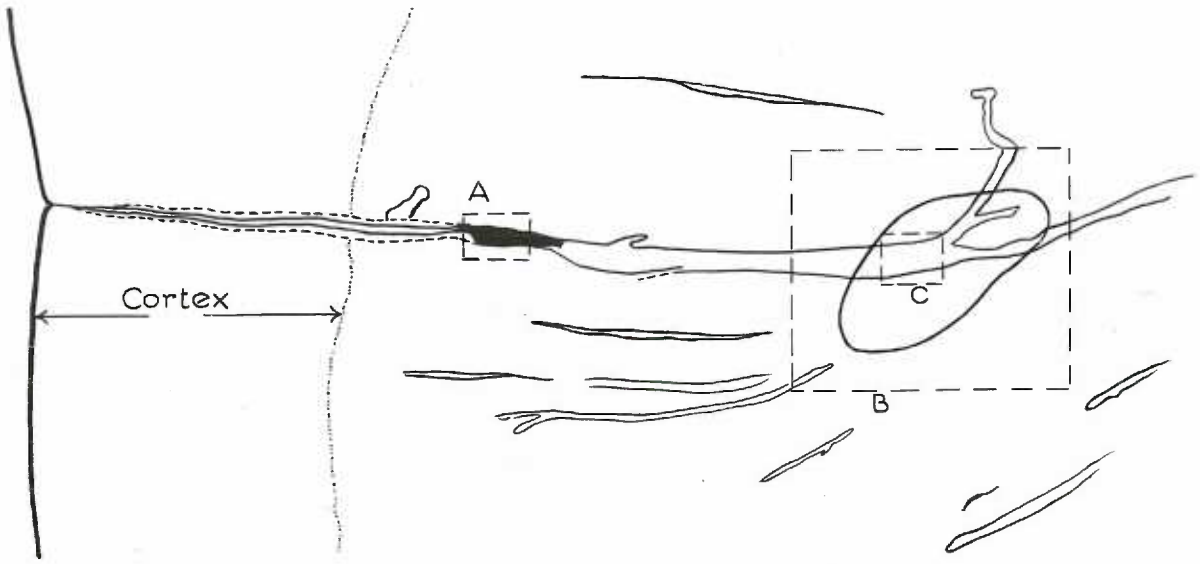

Fig. 6.

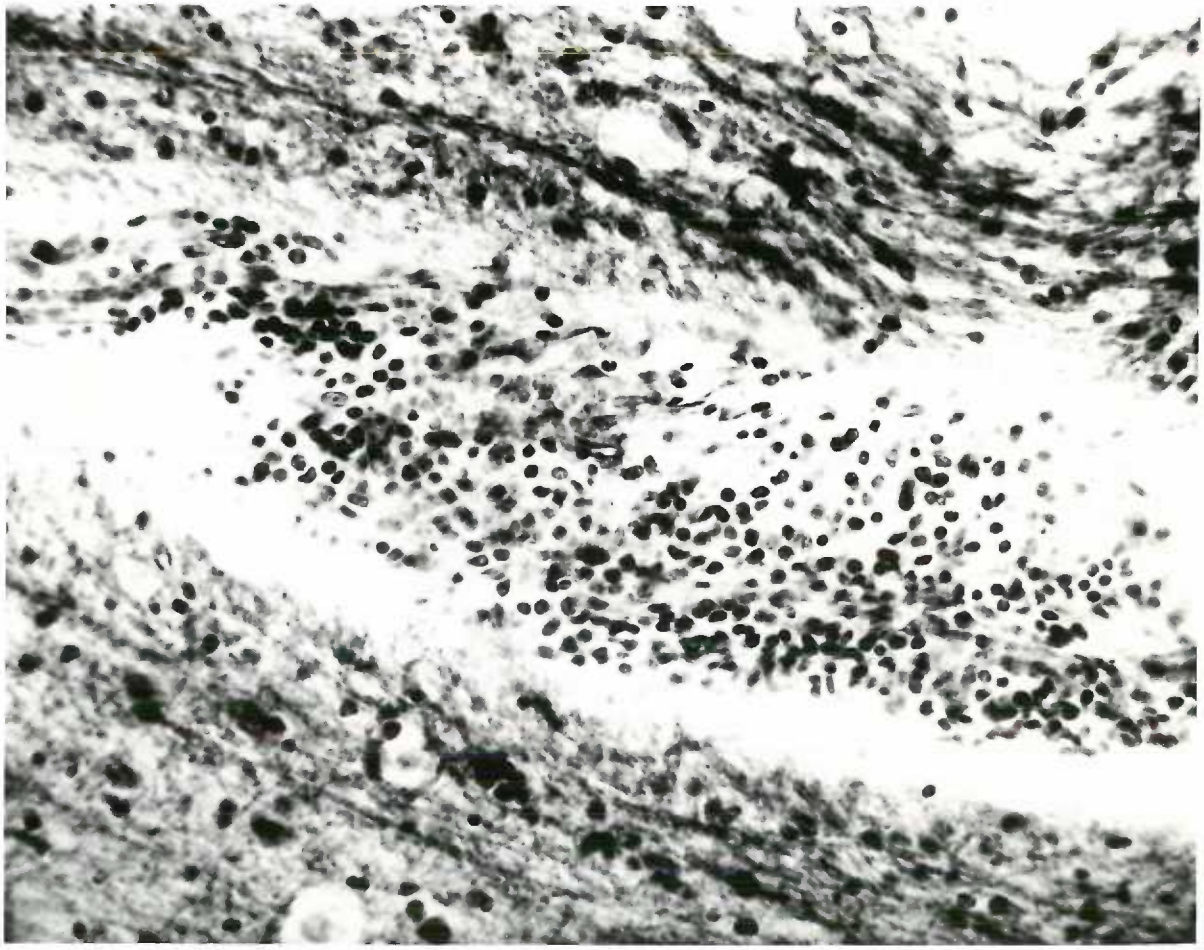

Fig. 6A

Fig. 6 cont.

D shows the lesion proper under low magnification.

C shows the central vein dilated and packed with red blood cells in which one sees occasionally areas of freshly formed fibrin (high magnification).

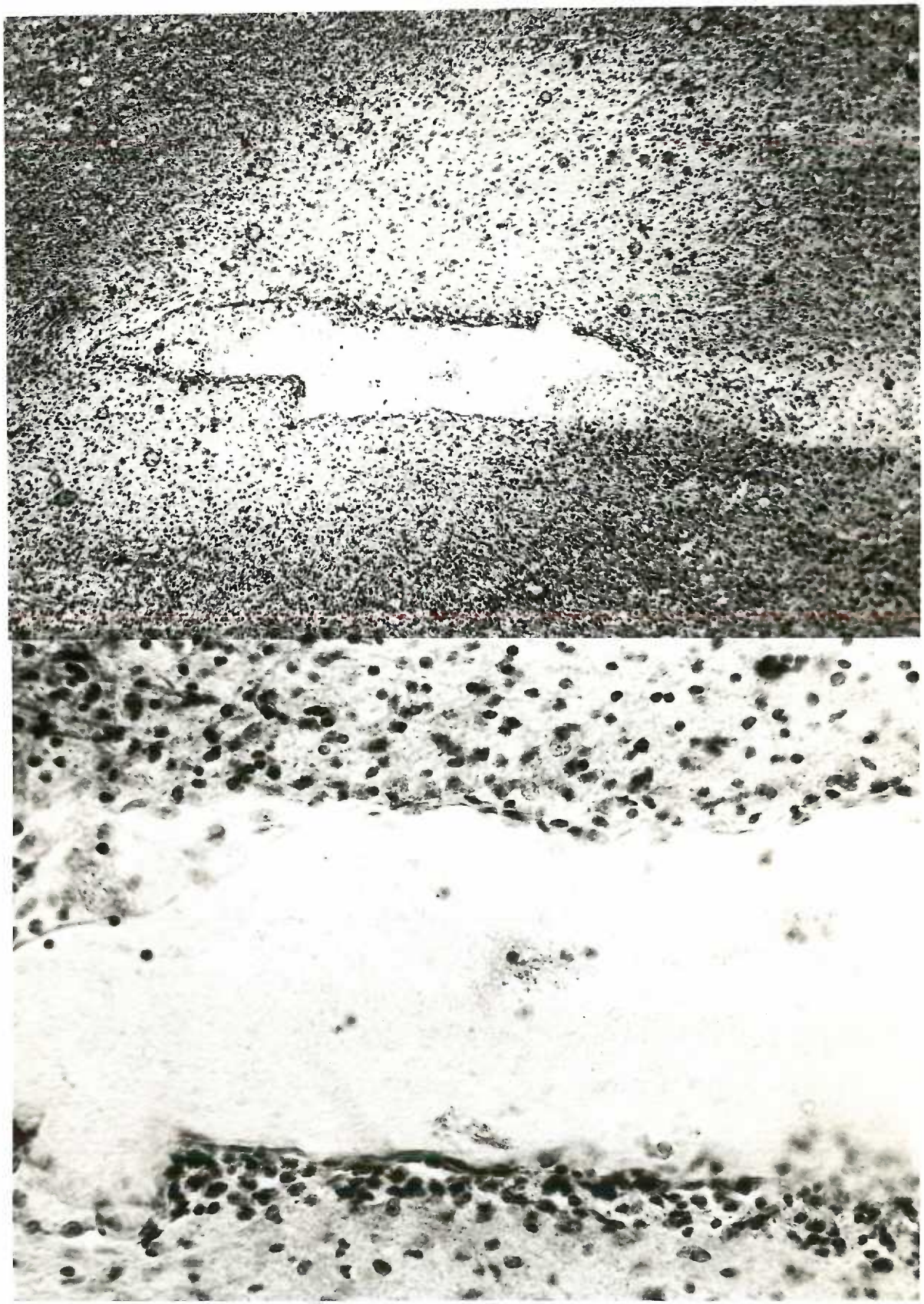

Fig. 6 B
Fig. 6 C

Fig. 7. A large lesion with a thrombosed central vein cut longitudinally. A, low magnification, and B, high magnification.

Fig. 7 A

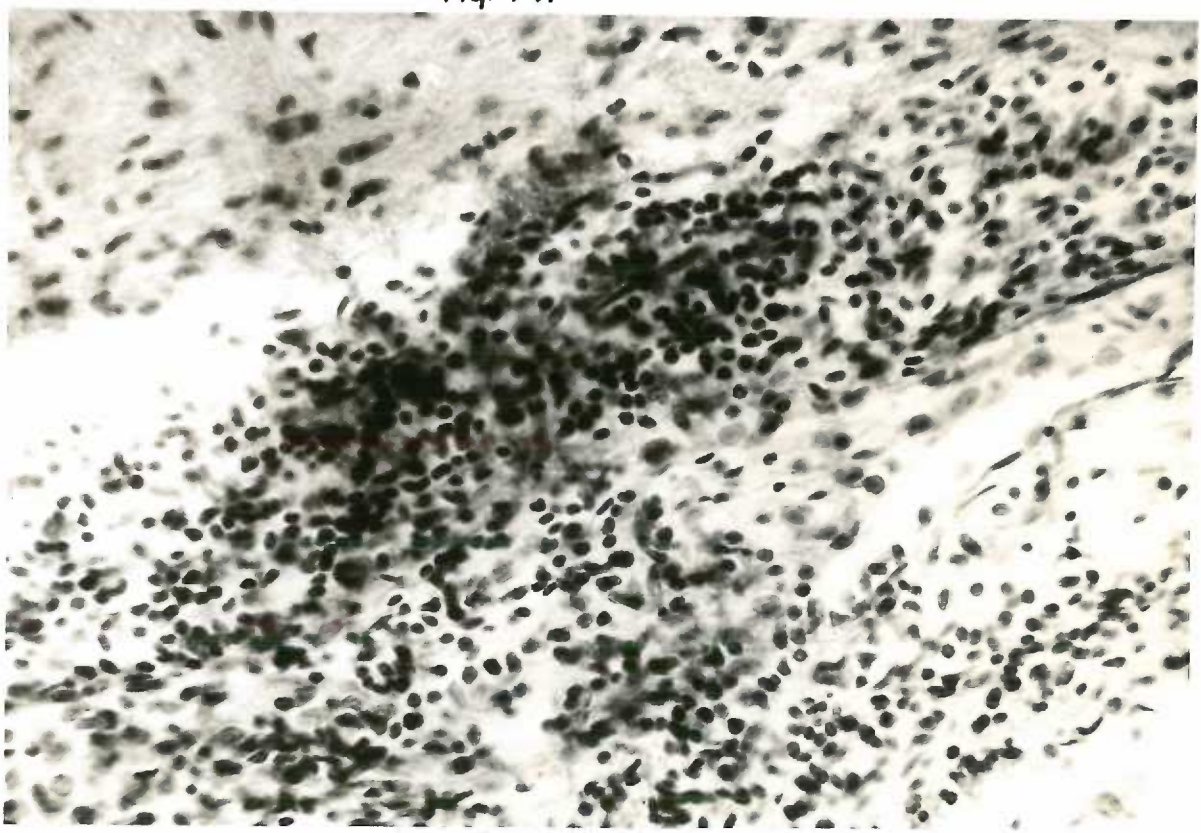

Fig. 7 B

difficult to prove. Speaking again of the ultimate vascular changes resulting from thrombi in small veins, Putnam stated:[26] "The vessel may disintegrate entirely, leaving a collection of fibers and leukocytes behind, or the endothelial obstruction may become gradually transformed into a fibrous plug." It is difficult to tell exactly what Putnam and his collaborators consider to be the fate of the thrombosed veins in multiple sclerosis. It seems likely that these vascular changes would leave a permanent scar in the tissues and that the fibrous cord could be recognized in serial sections as an obliterated vein. The occlusions which were observed have every appearance of being of considerable duration. Of the 9 said to contain a thrombosed vein, in 2 the presence of a thrombus must be admitted to be questionable. In these cases the veins were cut longitudinally and the essential sections happened not to be mounted. The presence of definite distention of the vein distally and a collapsed wall proximally made the existence of an occlusion likely, and and the missing sections probably contained the thrombus. In 3 of the 9 cases the site of the venous occlusion was at a considerable distance from the lesion, the central vein within the lesion showing only dilatation (fig. 6). In 3 lesions the thrombosed part of the vein was partly within the lesion and partly outside it in perfectly normal appearing tissue. In only 3 of the 60 lesions studied

were the thrombi in the central vein wholly within the lesion. Figure 7 shows one of these lesions in a fortunate section cut longitudinally through the vein. So fas as the numbers of individual cases would allow one to say, there seemed to be no difference between the various cases in respect to the frequency of vascular lesions.

It seemed of interest to see whether thrombosis occurred more frequently in the veins which passed through lesions than in veins selected at random and traced throughout their course in normal-appearing tissue. Tables 5 and 6 show the two sets of veins compared as to the perivascular cellular response, the condition a nd the location of the vein. Twenty-five veins were selected at random for this comparison. They were located in white, in gray and in mixed white and gray matter, just as were the 40 vessels in the lesions. The veins of the two groups had the same diameter and length. It will be seen that the presence or absence of perivascular cells was not restricted to eigher group. However, the two groups were decidedly different in the percentage showing perivascular cellular infiltration. Only 6 out of 25, or 24 per cent, of the group of veins selected at random showed a perivascular collar, while 25 out of 40, or 63 percent, of the group showed this cellular reaction. Even more striking was the presence of thrombi in the two groups. Whereas 9, or 22.5 per cent, of the veins in lesions had occlusions,

Table 5. Comparison as to Location, Perivascular Inflammation and Vascular Changes of Twenty-Five Veins Selected at Random in Apparently Normal Tissue.

	Veins Selected at Random	
	Number	Percentage
Perivascular round cell response		
Negative	19	76
Positive	6	24
Total	25	100
Condition of vessel		
Collapsed	0	0
Distended	3	12
Occluded	0	0
Normal	22	88
Total	25	100
Location		
Gray matter	0	0
White matter	18	72
Mixed gray and white matter	7	28
Total	25	100

Table 6. Comparison as to Location, Perivascular Inflammation and Vascular Changes of Forty Veins About Which Lesion Was Found

	Central Veins of Lesions	
	Number	Percentage
Perivascular round cell response		
Negative	15	37
Positive	25	63
Total	40	100
Condition of vessel		
Collapsed	2	5
Distended	9	22.5
Occluded	9	22.5
Normal	20	50
Total	40	100
Location		
Gray matter	0	0
White matter	22	55
Mixed gray and white matter	18	45
	40	100

Table 7. Correlation Between Presence or Absence and Condition of the Vessel and the Size of the Lesion

	Total Number of Lesions	Size of lesion: Less Than 2 Mm.	2-3 Mm.	Greater Than 3 Mm.
Central vein absent.....	20	14	3	3
Central vein present but no Thrombus.....	31	15	9	7
Central vein present with evidence of thrombosis...	9	6	1	2
Total.....	60	35	13	12

Table 6. Correlation Between Presence or Absence and Condition of the Vessel and Location of the Lesion

	Location of Lesion		
	Gray Matter	White Matter	Mixed Gray and White Matter
Central vein absent.....	3	7	10
Central vein present but no thrombus.....	0	17	14
Central vein present with evidence of thrombosis.....	0	5	4
Total.....	3	29	28

none of the veins selected at random had thrombi. Distended veins were occasionally observed in the first group, but not as frequently as in the veins which passed through lesions. In other words, perivascular cellular reaction and pathologic central veins are more common among veins which pass through lesions than in veins which do not.

It was thought that a case of thrombosis of the longitudinal sinus might be useful for comparison with the lesions of multiple sclerosis. It was not possible to demonstrate any perivenous demyelination which remotely resembled the lesions of multiple sclerosis. This is in accord with observations of Hassin[30]. Tables 7 and 8 show the relation between the size and location of the lesions and the absence or presence of veins. It is evident that the distribution of the lesions does not indicate any particular relation between the presence or condition of the vessel and the size or location of the lesion. One notes in table 9 that, aside from the small group of irregular-shaped lesions in which for some unknown reason there was a disproportionate number without a central vein, there was no correlation between the presence or absence of a central vein and the shape of the lesion. If, however, a central vein was found in an ellipsoid or a cylindric lesion, it was almost certain to be seen extending along the long axis of the lesion.

An example of such a lesion is shown in the orthographic projection of a cylindric lesion (fig. 2). The photomicrograph of the same lesion is shown in figures 4 and 5.

An attempt was made to compare the lesions with each other in respect to the degree of various changes found in the plaque. Among these were the perivascular cellular response about the central vein, the degree of demyelination and the phagocytic cellular reaction. The last two changes might be considered to indicate the age of the lesion. Tables 10, 11, and 12 show this evaluation for the whole group and for the 9 lesions the central veins of which had thrombi. The smaller group was then subdivided into the 3 lesions with the thrombus outside the plaque and the 6 with the thrombus partly or wholly within the plaque. It will be noticed that only in respect to the perivascular response was there any essential difference between the group of thrombotic lesions and the group as a whole. In other words, with respect to the degree of demyelination or the phagocytic cellular reaction, which was taken as an indication of the recent origin of the lesion, the 9 thrombic lesions fell just about where one might expect they would if there was no relation between the recentness of the lesion and the presence of the thrombus. In respect to the perivascular response, however, all 6, or 100 per cent, of the lesions with thrombi within them showed a 2 or 3 plus cellular

Table 9. Correlation Between Presence or Absence of Vein and Shape of Lesion

	Total No. of Lesions	Spher-ical	Ellip-soid	Cylin-dric	Cres-centic	Irreg-ular
Central vein absent.....	20	2	11	3	0	4
Central vein present, not in long axis of lesion.....	40	8	2	0	2	1
Central vein present, in long axis of lesion.....			18	8	1	
Total.....	60	10	31	11	3	5

Table 10. Correlation Between Lesions Showing Non-occluded and Those Showing Thrombosed Veins with Respect to the Intensity of the Perivascular Cellular Reaction About Central Vein.

Degree of Change	Total Number of Lesions	Thrombotic Lesions	
		Thrombus in Lesion	Thrombus Outside Lesion
0	15	0	3
+	14	0	0
++	6	3	0
+++	5	3	0
++++	..	..	..
	40	9	

Table 11. Correlation Between Lesions Showing Non-occluded and Those Showing Thrombosed Veins with Respect to the Degree of Demyelination.

Degree of Change	Total Number of Lesions	Thrombotic Lesions: Thrombus in Lesion	Thrombotic Lesions: Thrombus Outside Lesion
0	..	..	..
+	4	0	0
++	13	1	1
+++	32	3	2
++++	11	2	0
	60	6	

Table 12. Correlation Between Lesions Showing Non-occluded and Those Showing Thrombosed Veins with Respect to the Phagocytic Cellular Response.

Degree of Change	Total Number of Lesions	Thrombotic Lesions	
		Thrombus in Lesion	Thrombus Outside Lesion
0	5	0	0
+	26	3	0
++	17	1	2
+++	12	2	1
++++	..	..	..
Total	60	9	

reaction, whereas among the 40 lesions with central veins, the group with a cellular reaction 2 and 3 plus included only 11 lesions, or 28 per cent. In other words, there does seem to be a positive correlation between the presence of a thrombus in the lesion and a strong perivascular cellular response in the lesion. This correlation might be explained in one of three ways: The thrombus may have caused the more intense cellular reaction; the presence of the cellular infiltration may have resulted in the thrombosis, or the two processes may have shared a common causative agent. The correlation seems too strong to admit pure coincidence. Although one cannot deny the possibility that the presence of the thrombus, with its effects on the vessel, may not be a factor, the fact that almost an equal number of lesions without thrombi were rated as having just as intense a cellular reaction seem strong evidence against this being the only factor. It seems impossible to say which of the other two possibilities is correct. On the basis of the present data either explanation seems equally good.

COMMENT

In respect to the possible dependence of sclerotic plaque formation on vessel distribution or vascular changes, the observations noted in the study of this series of 60 sclerotic plaques of multiple sclerosis suggest that the views of both Putnam and Hassin are at extremes. Hassin believes that the patches of sclerosis are not representative of territorial areas in relation to venules. Although one-third of the lesions had no apparent direct relation to veins it would not seem reasonable to account for the distinct perivenous position of the remaining two-thirds of the plaques merely on a chance basis. Furthermore, in the elongated lesions containing a vein, this vessel almost always traversed the long axis of the plaque and tended to maintain a central position. In some instances, a collar-like area of demyelination and sclerosis was seen to follow, for short distances, tributaries of the central veins. These findings would seem to indicate that there is some causal relationship between lesion areas and distribution of the cerebral venules.

In a consideration of vascular alterations and their possible relation to the pathogenesis of the sclerotic plaques it will be noted that in one-half (30) of the lesions which contained a central vessel no significant changes were noted. The condition of the vessel wall and the content of of the vessel lumen appeared unchanged. In the other one-half

of the perivenous lesions a total of 9 central veins contained thrombi, an equal number were distinctly distended and 2 appeared to be partially collapsed. When compared with the twenty-five veins of like distribution and size, selected at random, changes of the lesion vessels appear even more significant. No evidence of occlusion or collapse of the lumen was observed in this group of veins, nor was the perivascular round cell response as noticeable. It is apparent, then, that in this study the vascular changes as evidenced by thrombosis, distention, partial collapse, or perivascular cellular accumulation are certainly more commonly found and more marked in those veins which are unquestionably related to the sclerotic plaques.

In ascribing a causal relationship between vascular alterations and foci of demyelinization and gliosis one must account for those lesions which contained no significantly large vessel and those perivenous lesions in which no vessel changes could be detected. Also, explanation must be made relative to the site of thrombotic occlusion and extent of demonstrable demyelination. Of the 9 thrombi 3 were totally outside the confines of the sclerotic plaque, 3 were partially within and partially without the boundaries, while only 3 were confined to the sclerotic area. If one might assume, as Putnam has suggested, that thrombi in small veins are only transitory, disappearing without trace

it is conceivable that thrombi might be a causative factor in the pathogenesis of the process. In view of the fact that there seems to be little evidence in support of this assumption and that thrombi may occur in veins which are surrounded by apparently normal tissue it seems unlikely that the occurrence of thrombi is the primary factor in the pathogenesis of the sclerotic plaques of multiple sclerosis.

As was previously mentioned, thrombi, although found in veins which were related to the lesion plaques, were never found in the series of twenty-five veins selected at random. If the thrombus is not the cause of the pathologic process, to what might the occurrence of thrombi in the lesion veins be attributed? There are three alternatives -it might be entirely coincidental; the thrombi and plaques, perhaps, share a common cause; or the thrombi might be a result rather than cause of the process. Regarding the latter alternative it was interesting to note that all lesions with thrombi within them showed a marked perivascular cellular response. This might be interpreted as being an indication of a somewhat intense process with relatively rapid tissue alteration. Whereas extracts of brain tissue are known to be potent agents for production of intravascular clotting, it might be possible that products of the destroyed nervous tissue in the lesions of multiple sclerosis enter the vessel lumen and there exert a coagulating effect to

produce clots and ultimate thromboses. This, however, would not account for the fact that in 3 out of the 9 thrombotic veins the thrombus was completely outside the confines of the lesion.

The observations noted in this study are in accord with the view expressed by Dawson, Symonds and many others who recognised the frequent association of lesions and pathologic vessels but did not assign a causative role to the vascular changes.

SUMMARY AND CONCLUSIONS

Sixty lesions from 5 cases of multiple sclerosis were studied by serial sections and their relation to the vascular system noted. The veins in the lesions were also compared with a group of 25 veins selected at random in the normal-appearing part of the brain in the same cases.

The lesions in the 5 cases studied were found to be uniform so far as the number from each case would allow an opinion. Of the 60 lesions it was found that 30 were without a central vein, that 20 were oriented about a normal-appearing vein and that only 9 were about a vein in which a thrombus could be found. In 2 lesions the vein was collapsed, and in 9 it appeared distended. In 3 of the 9 lesions which had a thrombosed vessel the thrombus was completely outside the lesion; in 3 others the thrombus was partly inside and partly outside the lesion boundaries, and in only 3 was the thrombus confined to the lesion area. The occurrence of a thrombus in 1 of these was questionable, as the actual site of the thrombus was missing and its presence was inferred from the state of the vessel proximally and distally.

No positive correlation was found between the lesions with a thrombus and the peculiarities of size or shape of the lesion, the degree of demyelination or the phagocytic

cellular response. No positive correlation was found between the size or shape of the lesion and the presence or absence of a vein except that for some unexplained reason 4 out of the 5 irregular lesions were without central veins. When a vein was found within an ellipsoid or a cylindric lesion it was almost invariably oriented along the long axis of the lesion. There was a strong positive correlation between the perivascular cellular reaction of the central vein and the presence of a thrombus wholly or partly within the lesion.

The view that the demyelination in this disease is entirely unrelated to the vascular system does not seem likely in the light of the foregoing observations. The view that the vascular changes, particularly thromboses, are an essential part of the pathogenesis of the lesion plaque seems equally unlikely unless one accepts the assumption that venous thrombosis can disappear without trace, and at the same time exist long enough to cause permanent demyelination.

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