

## Inflammatory Vasculitis in Multiple Sclerosis

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### SUMMARY

Fifty-two plaque or lesion areas were examined from 25 cases of multiple sclerosis. Twenty-four of these showed acute features, whereas the rest were more chronic in nature. The acute lesions showed lymphocytic infiltration (79%), fibrinous exudation (63%), lymphocytic meningitis (50%) and venulitis (58%). Of the chronic lesions, there were only 21% with lymphocytic infiltration, 11% with fibrinous exudates, none with meningitis, 29% with organising endovenulitis, 36% with fibrosed vein walls. The finding of a fibrinous inflammatory exudate in the acute lesion is a new observation in multiple sclerosis. Likewise, the observation of an inflammatory infiltrate confined to the vein wall (and often present at a distance from the plaque) has not been previously recorded in the disease. The chronic lesion, by contrast, showed relatively little fibrin, but there was considerable reparative thickening of the walls of the involved veins. The evidence provides new humoral and cellular evidence of an inflammatory process in multiple sclerosis which precedes or is not directly associated with the demyelinating process.

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**Key words:** *Exudate – Fibrin – Inflammation – Lymphocyte – Macrophage – Meningitis – Multiple sclerosis – Thrombosis – Vasculitis – Venulitis*

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### INTRODUCTION

The involvement of venules in multiple sclerosis, particularly in the form of a periphlebitis or inflammatory infiltration around venules, has been intermittently

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recognised for many years (Dawson 1916; Birley and Dudgeon 1921; Symonds 1924; Greenfield and King 1936; Adams and Richardson 1961, and others). The proximity of the plaque to the ventricular system and the frequent presence of a vein or venule at the centre of the lesion has led many investigators to speculate about the possibility of a causative agent, such as an enzyme or immuno-agent, that diffuses from the CSF or blood into the brain (see Marburg 1906, 1935; Lumsden 1970). Fog (1964) in a serial section study showed that plaques wrap themselves around small veins over considerable distances, and it would seem that the plaque arises around such vessels. However, it is still not clear whether the plaque arises from just one vein or by coalescence of lesions arising around several veins (Adams 1975).

Over the last decade it has been shown and confirmed, from the pathological study of over 250 cases, that the inflammatory infiltrate around venules and small veins is a feature that is characteristic of the acute stage of the disease rather than the chronic (Adams 1975, 1977; Guseo and Jellinger 1975; Tanaka et al. 1975). From a limited series of cases, Prineas (1975) considered that the infiltrates were more marked in chronic cases, but this view does not seem to have been pursued further.

These infiltrates are often seen in normal or merely oedematous areas of brain at a distance from an actual plaque (Adams 1975, 1977). Perivenular infiltrates away from plaques are usually lymphocytic, whereas those within plaques contain a greater admixture of macrophages, suggesting that the latter are a response concerned with phagocytosis, organisation and repair (Lumsden 1970; Adams 1975; Tanaka et al. 1975). By contrast, the mainly lymphocytic infiltrate is associated with active lesions or is located away from and at a distance from the plaque (Adams 1977). These features have led to the suggestion that the perivascular inflammatory process is the primary pathogenic event in multiple sclerosis and that the demyelinating process is a secondary event caused by the action of inflammatory lysosomal enzymes on the protein framework of the myelin lamellar structure (Adams 1972) or a secondary immune (possibly macrophage-mediated) attack on the myelin sheath (Lumsden 1970). It should be noted that, because these inflammatory features are only prominent in active lesions, they will not be seen in all examples of the disease. It is only with large series of cases (such as those cited above) that the true frequency of inflammatory lesions can be perceived.

Thrombosis of small veins and venules has also been held to be a causative factor in multiple sclerosis (Putnam 1937). However, although Dow and Bergland (1942) observed some such venous thromboses in plaques, they could not regard them as causal. Zimmerman and Netsky (1950) found no thromboses that appeared to antedate the plaque, while experimental cerebral venous thrombosis produces a necrotic rather than a demyelinating lesion. There remains, nevertheless, the tantalising record of increased platelet stickiness in multiple sclerosis (Wright et al. 1965), which has never been very satisfactorily explained. These platelet changes are not associated with a clear-cut increase in the incidence of either coronary or venous thrombosis (Allen 1981; Adams 1983). Plaques sometimes show small haemorrhages (see Walton and Kaufmann 1984), often around vessels, and areas of haemosiderin deposition are seen, suggestive of past haemorrhage. Possibly such haemorrhage may have resulted from previous inflammatory or other damage to the vessel wall.

Hitherto, the perivenular changes (including periphlebitis retinae) have diverted attention away from the vein wall itself. Apart from hyalinisation of vein walls (Lumsden 1970; Allen 1981; Adams 1983), no other changes have been reported within the vein wall, and the occurrence of a vasculitis has not hitherto been commented upon. The new features presented in this paper are that a fibrinous exudate and other humoral inflammatory factors are present in and around venules both in the active lesion and in grossly normal white matter. In addition, this paper reports for the first time on venous intramural cellular infiltration both in active plaques and in grossly normal white matter. Reparative changes and collagenous thickening of the cerebral vein wall are also described in the chronic inactive lesion.

Collectively, these new observations on the active plaque and grossly normal white matter in multiple sclerosis suggest that an exudative inflammatory vascular disorder, in addition to the lymphocytic infiltrates previously reported, are characteristic features of the early pre-demyelinating and active stage of the disease.

#### METHODS

Sections from 25 recent cases of multiple sclerosis from the 115 cases in the files of the MRC Multiple Sclerosis Tissue Bank at Guy's Hospital were reviewed, and 52 paraffin blocks with different lesions were cut from this material. Ten cases of cerebral oedema were identified in our recent postmortem records: these patients had died from renal failure (2), astrocytoma (2), cerebral infarction (3), cerebral haemorrhage (1), carcinoma of the breast (1) and spinal angiomatosis (1). Ten random cases without cerebral oedema were also chosen: these comprised visceral carcinoma (3), myocardial infarction (1), leukaemia (2), Down's syndrome (1), hypertension (1), cerebral infarction (1) and congestive cardiomyopathy (1). Fresh paraffin sections were cut from 20 blocks of these control cases. Standard controls for fibrin were also used (placenta and polyarteritis).

The paraffin sections cut from the blocks of multiple sclerosis and control brains were stained with haematoxylin and eosin and with a modified Verhoeff elastic-modified Lendrum MSB-modified Mallory trichrome method (VMT method; Buk 1984). Some sections were also stained with phosphotungstic acid haematoxylin (PTAH), periodic acid Schiff (PAS), and the Lillie-Glenner diazotisation coupling method for tyrosine (see Adams 1967). This last method is a particularly useful method for the combined staining of albumin, globulins and fibrin and its degradation products (FDP).

Standard paraffin sections were stained by immunoperoxidase (Bourne 1984), using the peroxidase-antiperoxidase technique with polyclonal antibody and the direct technique with monoclonal antibody. The following antibodies were used: (a) polyclonal antifibrin antibody (Dako); (b) monoclonal anti-common leukocyte antigen antibody (PD7/26; Warnke et al. 1983). This antibody reacts strongly with all lymphocytes and slightly less strongly with macrophages and polymorphonuclear neutrophils: excellent results can be obtained with formalin-fixed paraffin-embedded tissue; (c) polyclonal antimuramidase (lysozyme) antibody (Dako). This is a marker for macrophages and polymorphonuclear neutrophils; it stains reactive histiocytes more strongly than

unstimulated histiocytes (Mason and Taylor 1975); (d) anticomplement (C3) antibody (Dako).

## RESULTS

Active plaques can be distinguished from inactive plaques by the following criteria (see Lumsden 1970; Adams 1980, 1983): the presence of a shelving edge, glial hyperplasia at the edge, macrophage or microglial activity in relation to myelin breakdown, perivenular lymphocytoid infiltration, oedema and astrocytic activation. By contrast, inactive lesions show an abrupt almost punched-out contour and none or few of the features listed above.

Examination of the sections from the multiple sclerosis cases showed the presence of active or acute lesions in 19 out of the 25 cases examined (Table 1). Of these 19 cases, 5 had only active lesions, while the rest were a mixture of active and quiescent plaques. Six cases showed only inactive plaques. Of 9 periventricular plaques in the material, 7 were quiescent. Of the remaining 2, one was associated with regional lymphocytic meningitis and the other was active and showed marked hypercellularity.

Sixteen out of 24 active lesions, as defined above, showed a greater or lesser degree of fibrinous exudation in relation to veins or venules within or around plaques or in normal white matter. These cases often showed severe oedema around the affected veins or venules (Fig. 1). Such fibrin was present within the vein wall, deposited in the adventitia, laid down as a network of fine strands in the oedematous area around the vein or appeared as a halo of moderate intensity for some distance around the vein or venule. Such fibrin was stained by both dye (VMT, Figs. 1 and 2; PTAH, Fig. 3) and antifibrin (Figs. 4 and 5) methods. However, the fibrin present in haloes was more prominent with the antifibrin than with the dye-staining methods: this was probably due to the more clear-cut contrast obtained with the immunohistochemical method. From the examination of fibrin in a relatively long-standing condition (astrocytoma, see below), it seemed probable (but was not proven) that old fibrin and FDP reacted positively with the antifibrin peroxidase method but stained only blue with MSB-trichrome (VMT method; for discussion, see Lendrum 1963). Both staining and immunohistochemical methods showed occasional thick bands in the vein wall which were intensely stained for fibrin.

The anticomplement (C3) antibody showed a diffuse perivenular reaction in the

TABLE 1

FIBRINOUS EXUDATES, MENINGITIS AND CEREBRAL PHLEBITIS IN ACTIVE PLAQUES OF MULTIPLE SCLEROSIS

No.	Lymphocytic infiltrates	Fibrin MSB	Immunofibrin	Meningitis	Venulitis	Thickened vein wall
24	19 (79%)	15 (63%)	5/10 (50%)	12 (50%)	14 (58%)	0

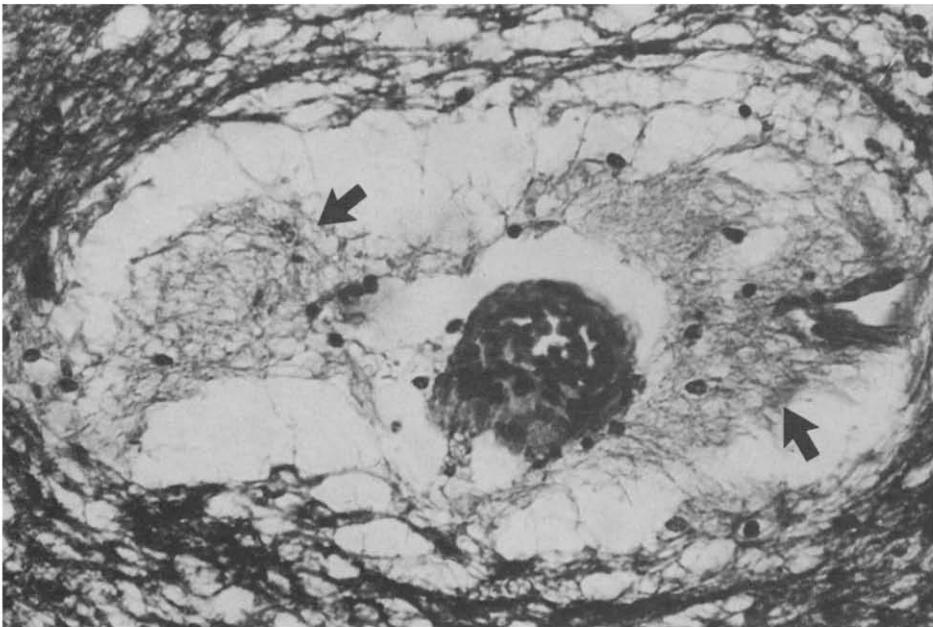
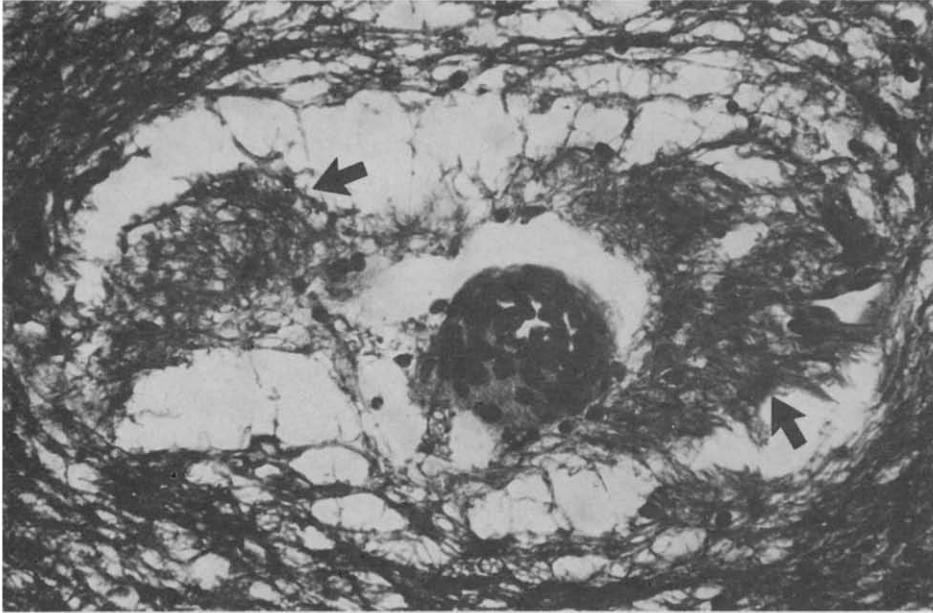


Fig. 1. Above with blue filter: strands of fibrin (stained red, arrows) in oedematous area around a vein wall about 4 cm from an active plaque of multiple sclerosis. Below with red filter: the red fibrin reaction is no longer seen. VMT,  $\times 120$ .

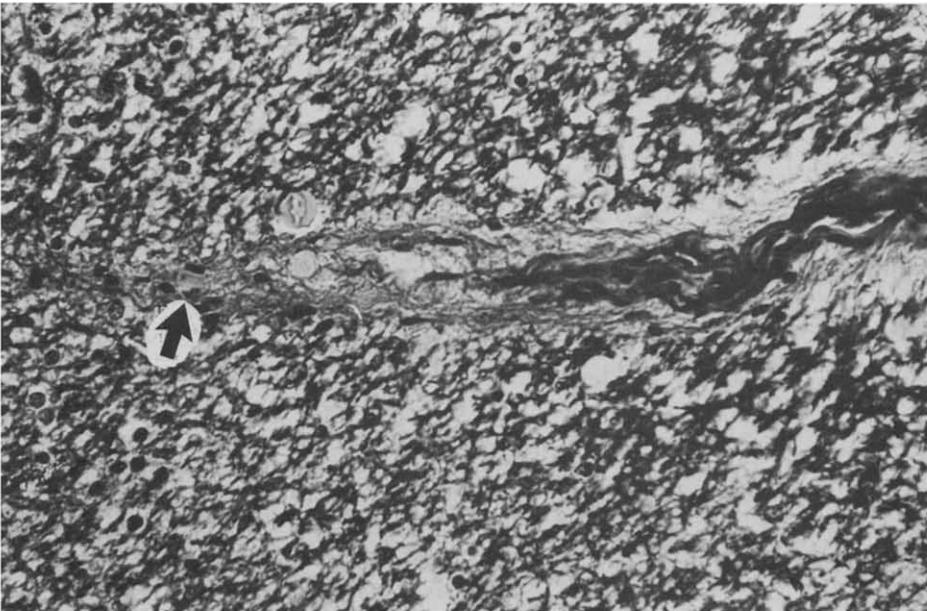
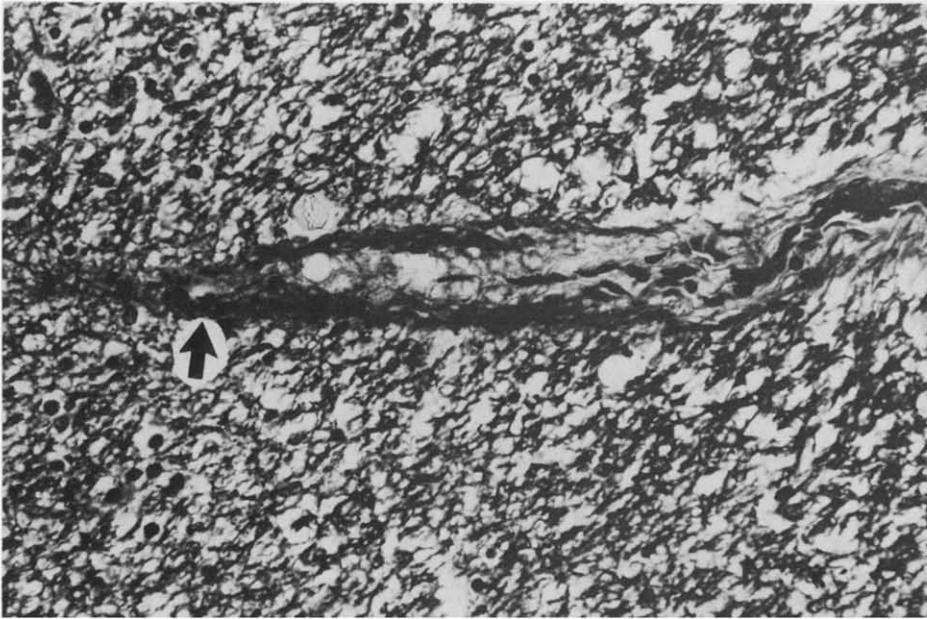


Fig. 2. Above with blue filter: fibrin (stained red, arrows) around a vein wall in grossly normal white matter in an active case of multiple sclerosis. Below with red filter: the red fibrin reaction is no longer seen. VMT,  $\times 120$ .

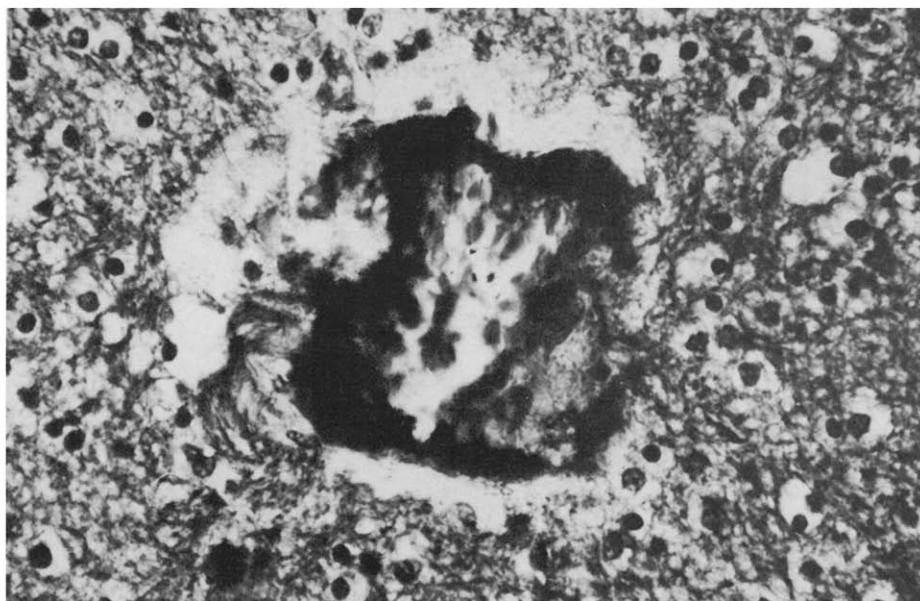


Fig. 3. Fibrin in and around a vein wall in grossly normal white matter in an active case of multiple sclerosis, PTAH,  $\times 300$ .

brain parenchyma, as though it had leaked out from blood vessels around the active lesions studied. In this respect, the distribution of this inflammatory mediator paralleled that of fibrinogen which tended to form haloes around the vessels (see above).

Only 3 out of 28 inactive lesions, stained with the VMT method, gave a positive fibrin reaction (Table 2). A smaller series stained with antifibrin peroxidase showed no cases reacting immunologically that did not stain with VMT or PTAH. Some veins gave a slight diffuse non-specific reaction within the vein wall with the antifibrin peroxidase method. This non-specific reaction was not seen with the VMT and PTAH stains. Blood-clot within the vein lumen reacted strongly and formed an internal control.

The presence of a perivenular cellular infiltrate was not uniformly matched by the occurrence of perivenular exudation. Fibrinous exudates with surrounding oedema but no cellular emigration was frequently seen around veins in areas of otherwise normal white matter at a distance from plaques (Figs. 1 and 2). However, in or around plaques,

TABLE 2

FIBRINOUS EXUDATES, MENINGITIS AND CEREBRAL PHLEBITIS IN CHRONIC PLAQUES OF MULTIPLE SCLEROSIS

No.	Lymphocytic infiltrates	Fibrin MSB	Immunofibrin	Meningitis	Venulitis	Thickened vein wall
28	6 (21%)	3 (11%)	2/9 (22%)	0	8 (29%)	10 (36%)

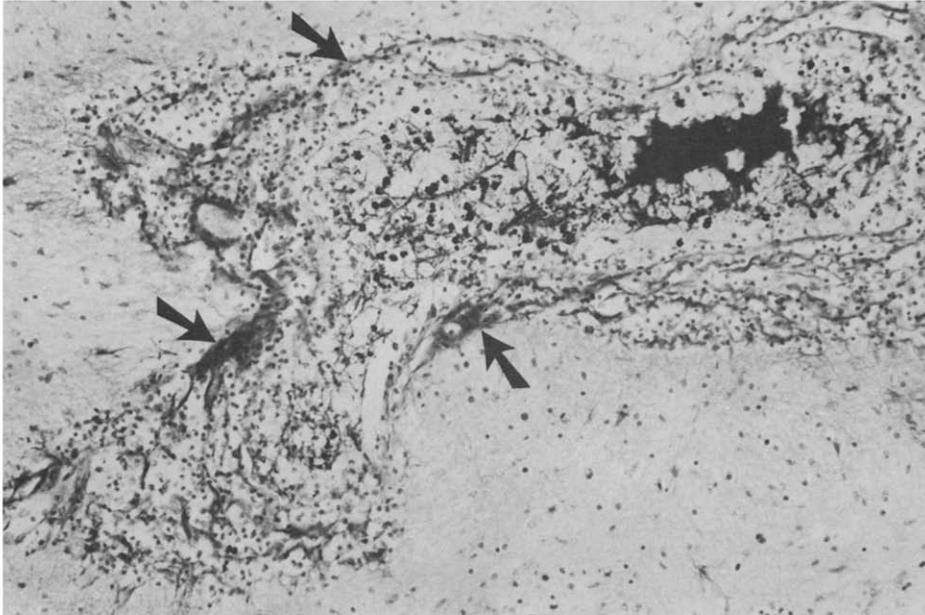


Fig. 4. Fibrin in and around a vein wall, with lymphocytic infiltration, near an active plaque of multiple sclerosis, blue filter, antifibrin peroxidase,  $\times 30$ .

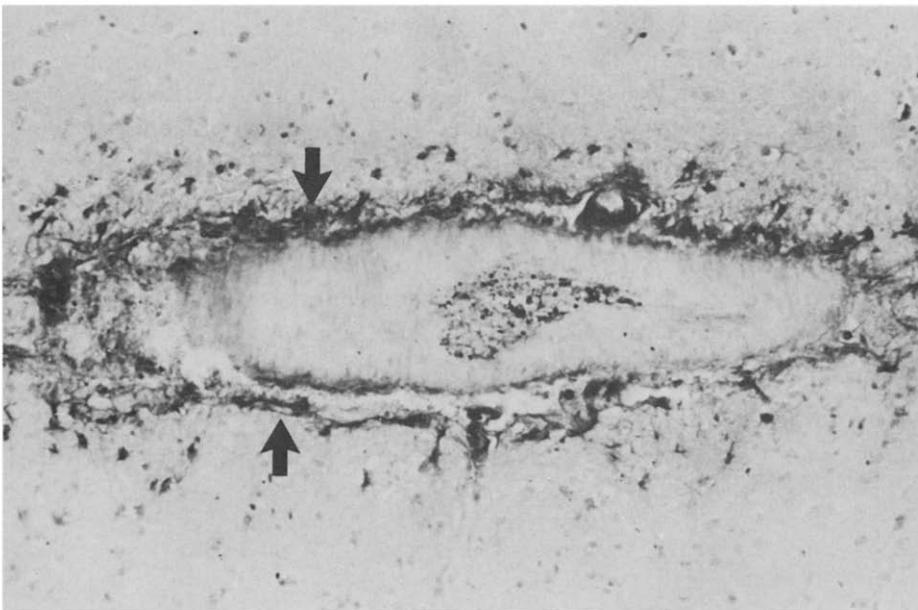


Fig. 5. Fibrin in a vein wall, with little cellular infiltration, about 4 cm from an active plaque of multiple sclerosis, blue-sensitive film, antifibrin peroxidase,  $\times 30$ .

perivenous fibrinous exudates were often accompanied by perivenous lymphocytic infiltration, with or without macrophages (Figs. 4 and 5).

The veins and venules in or at a distance from active lesions frequently showed an inflammatory lymphocytic reaction essentially located only in the vessel wall (Figs. 6 and 7). This was particularly well seen with the common leukocyte antigen method, which on occasions showed lymphocytes confined to the vein wall (Fig. 8), whereas the muramidase method showed that macrophages had entered to a greater depth into the surrounding parenchyma (Fig. 9). An oedematous onion-skin separation of the smooth muscle and collagenous components of the vein wall (Fig. 6) was frequently noted and, in two instances, venular damage seemed to have led to a perivenular haemorrhage.

When confined to the vein wall, these inflammatory changes can be regarded as a local venous vasculitis or cerebral venulitis. In inactive – presumably old – lesions the vein walls were frequently thickened or hyalinized (Fig. 10), which the VMT method revealed to be due to an increase in blue-staining collagen fibres. These thickened cerebral veins sometimes showed areas of organisation and repair, together with focal areas of intimal hyperplasia (Fig. 10). These areas probably represented organising platelet encrustations. Such changes constitute cerebral endovenulitis, if only in modest form. Several cases showed recent fibrin-enriched thrombi within veins, but all of these looked to be more recent than the adjacent plaque. Thus, none of them were tightly attached to the vein wall, nor were they organised, apart from the two encrustations that are mentioned above.

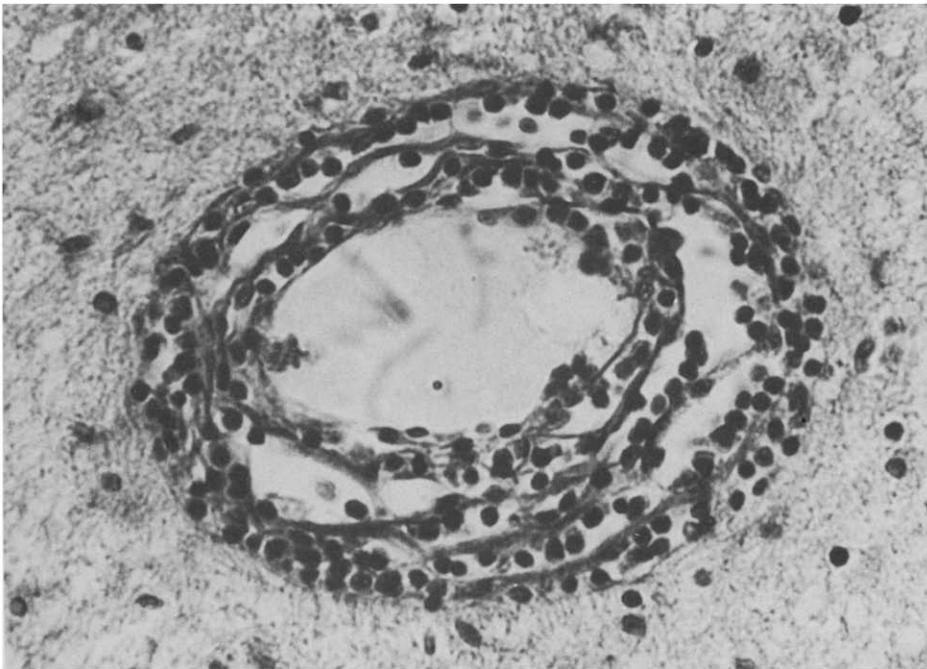
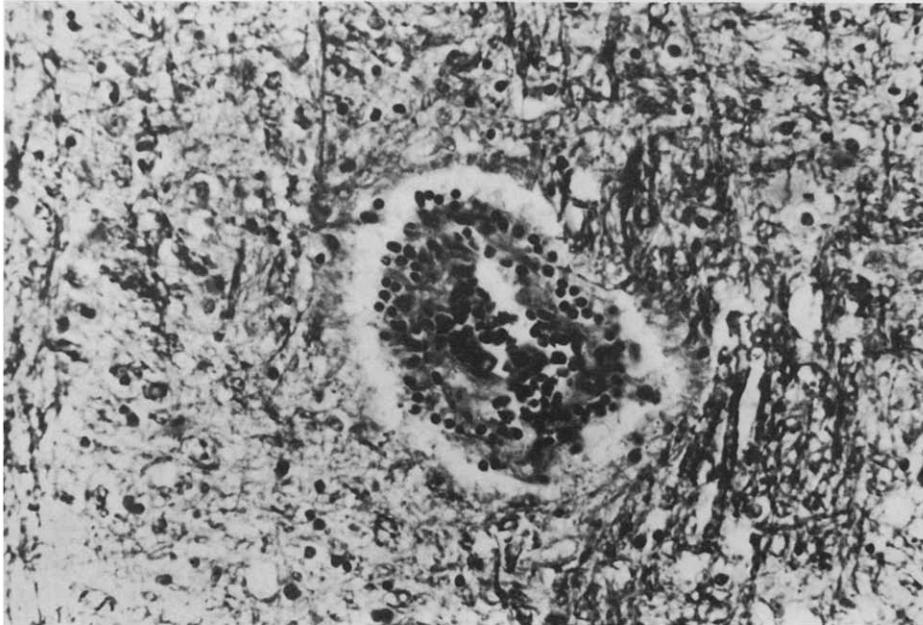
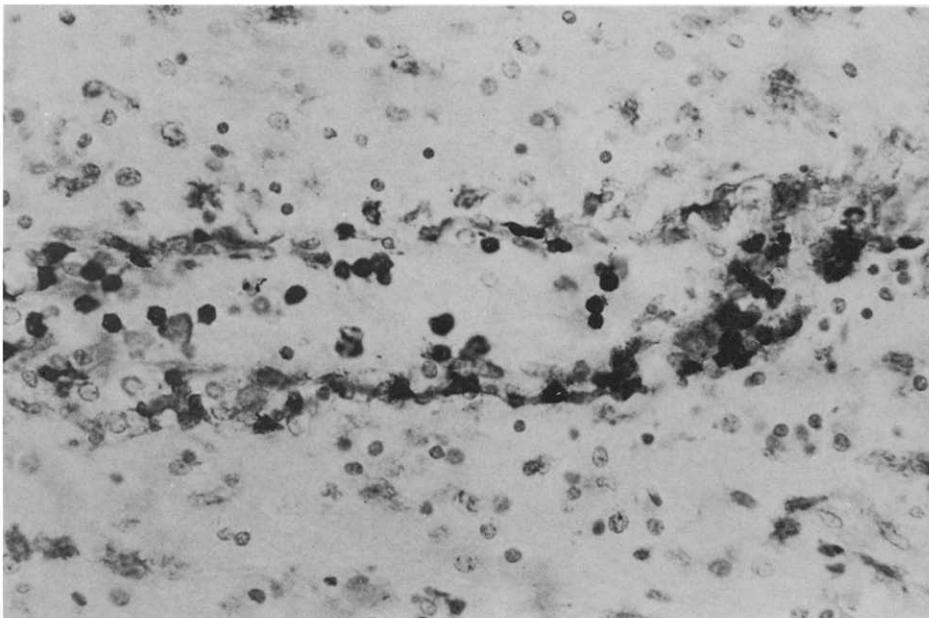


Fig. 6. Lymphocytic infiltration and oedematous onion-skin change in vein wall in normal white matter about 1.5 cm from an active multiple sclerosis plaque, VMT,  $\times 300$ .



**Fig. 7.** Lymphocytic infiltration confined to vein wall in normal white matter in an active case of multiple sclerosis, VMT,  $\times 50$ .



**Fig. 8.** Lymphocytic and mononuclear infiltration confined to vein wall about 5 cm from active multiple sclerosis plaque, anti-common leukocyte antigen, peroxidase-antiperoxidase,  $\times 120$ .

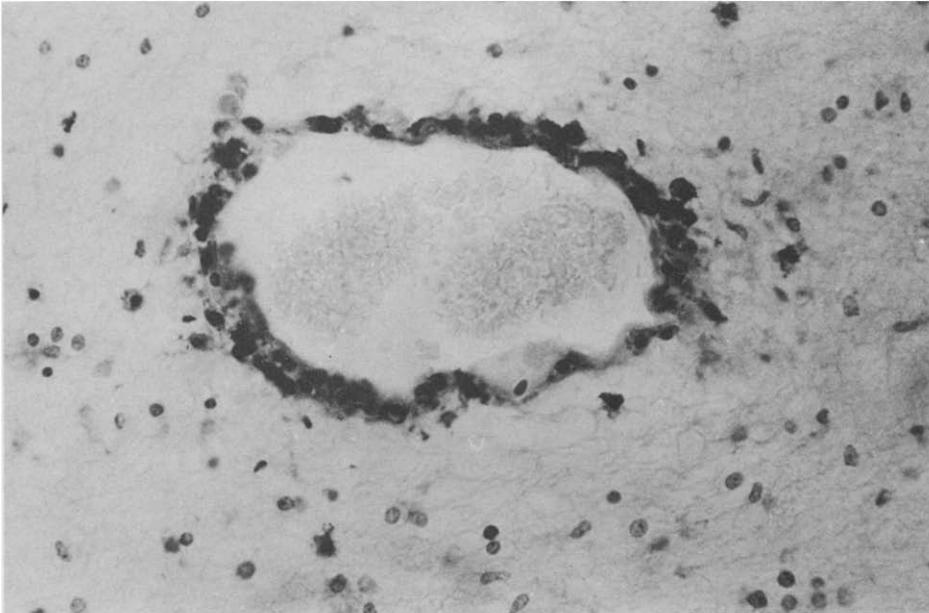


Fig. 9. Mononuclear and macrophage infiltration in and around a vein wall near an active multiple sclerosis plaque, antimuramidase peroxidase,  $\times 120$ .

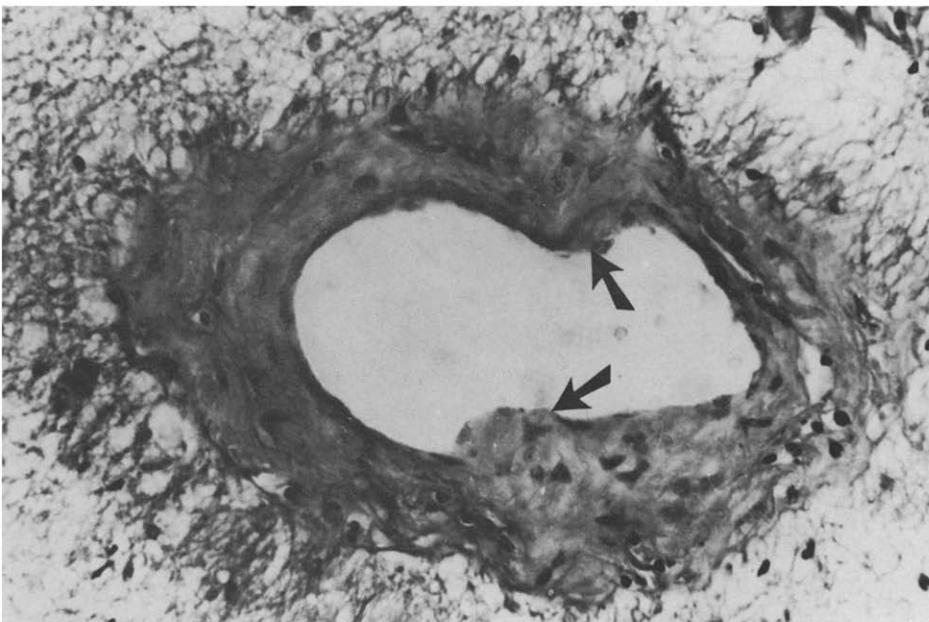


Fig. 10. Collagenous thickening of a vein wall and organizing endothelial encrustations (arrows) in a chronic periventricular plaque, VMT,  $\times 200$ .

TABLE 3  
FIBRIN IN OEDEMATOUS AND CONTROL BRAINS

Condition	No. of cases	Oedema fluid	Fibrin in oedema fluid	Fibrin in vessel wall	Fibrin in lesion
Cerebral infarct	4	3	0	2	1
Renal failure	2	2	2	0	—
Glioma	2	2	0	0	2
Cerebral haemorrhage	1	1	1	0	1
Spinal angioma	1	1	0	0	—
Carcinoma	4	1	0	1	—
Leukaemia	2	0	0	0	—
Heart failure	2	0	0	0	—
Cardiomyopathy	1	0	0	0	—
Down's syndrome	1	0	0	0	—

Focal lymphocytic meningitis was present in many active cases and, in one case, had seemingly proceeded to thick scarring of the meninges. No other abnormality was present to explain this scarring.

None of the 10 non-oedematous control brains showed any of the features described above. However, the 10 oedematous brains presented a variable picture of fibrin response, but only one case of cerebral embolism and one case of renal failure showed a similar perivenular pattern to that seen in the cases of multiple sclerosis described above. Focal perivascular fibrin was apparent in another case of cerebral infarction and in the other case of renal failure. One astrocytoma showed a diffuse band of fibrin at its edge, but the other two examples were negative in this respect. This band of fibrin reacted with antifibrin peroxidase, but only stained blue with VMT. It was presumably old fibrin (see above).

In none of the oedematous or non-oedematous control brains was there any evidence of perivenular or intramural inflammatory infiltration, or of venulitis.

#### DISCUSSION

The new finding of a fibrin-enriched exudate in or around cerebral veins in an overall 34% of our cases of multiple sclerosis (active and non-active combined) is further evidence of an inflammatory process centred on the vessel wall in this disease process. A fibrinous exudate is characteristic of certain types of inflammation, particularly those where the inflammatory agent is of a physical, chemical, immunological or of a relatively avirulent bacteriological nature. Vascular permeability in inflammation seems to be largely mediated by kinin, leukotriene and complement components, whereas cellular diapedesis and infiltration are separately controlled by other leukotrienes and chemotactic agents (Larsen and Hensen 1983). By contrast, passive oedema of circulatory origin causes a transudate with a relatively low protein content and is not controlled by inflammatory mediators.

The presence of complement (C3) around the affected cerebral veins and venules is another reflection of the leakage of plasma proteins in inflammatory exudates. It is relevant to this question of increased permeability that the incidence of fibrinous exudates in our combined active and chronic cases (34%) is of the same order as that of raised CSF albumin levels (23%) in multiple sclerosis patients (Walsh and Tourtelotte 1983).

It is reported here for the first time that the cerebral venular wall in multiple sclerosis is the site of lymphocytic infiltration that may at first, particularly in grossly normal white matter, be confined to the vessel wall alone. As the inflammatory process proceeds, the cellular infiltrate appears to spread to the perivascular space and even into plaque tissue. Vein walls then undergo focal intimal hyperplasia, intimal organisation and collagenous thickening. Such features suggest a mild expression of subacute or chronic endovenulitis of the cerebral veins. In the absence of other pathology, it is reasonable to assume that the scarring results from the earlier inflammatory changes. We wish particularly to emphasise that lymphocytic infiltration of the vein wall alone frequently occurs in the absence of any surrounding perivenular infiltration, and that such intramural inflammatory changes in the vein wall may be located at a distance from plaques in areas of grossly normal white matter or in oedematous (but otherwise normal) white matter. This particular sequence of events strongly suggests that the inflammatory process may start or be first manifest in the vein or venular wall and argues against it merely being a result of brain damage. It does not, of course, necessarily imply that a component of the wall is primarily involved in an immune or other type of inflammatory process.

The veins of the brain, spinal cord and meninges differ from those in the rest of the body in that they contain much collagen (Maximoff and Bloom 1960), presumably of the structural type III. Inflammation results in the production of coarse collagen fibres (type I), with a less dense molecular construction and larger pore size, which would lead to increased permeability. For example, the scarred capillary loop in diabetic glomerulosclerosis is markedly more permeable than its thickened walls might at first suggest. This could be particularly relevant to the episodes of increased permeability that are encountered in multiple sclerosis (Broman 1964; Engel et al. 1984).

This mural inflammation of the cerebral veins in multiple sclerosis could be the result rather than the cause of fibrin deposition, as illustrated by the later stages of atherosclerosis where encrustations of fibrin and platelets lead to progressive chronic inflammatory thickening of the vessel wall (Duguid 1952). Nevertheless, this is an unlikely explanation for the observations.

The cause of the inflammatory process in the CNS veins in multiple sclerosis is not clear, and it is a truism that all explanations for the pathogenesis of multiple sclerosis are speculative and at best incomplete. The usually modest nature of the venulitis counts against a bacterial or viral attack, unless the agent concerned is relatively benign or incomplete in nature. Likewise, the non-necrotising and modest inflammatory response is too slight and of a too chronic nature for a florid autoimmune reaction. However, the very point could be that the process is slow and subtle, such as is seen in autoimmune atrophic thyroiditis.

The two instances of perivenular haemorrhage reported here and further cases, including haemosiderin deposition, reported in the literature (Walton and Kaufman 1984) suggest that more acute cerebral vascular damage may sometimes occur in multiple sclerosis.

To conclude, the pathogenic mechanisms that cause the cerebral venulitis in multiple sclerosis, reported herein, could be the deposition or penetration into the vein wall of some circulating factor from the blood, a specific lesion of the vein wall or the release of a substance from the damaged brain, such as a lysosomal enzyme or thromboplastin.

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