Ultrastructural Basis of the Vasculopathy In and Around Brain Tuberculomas

Possible Significance of Altered Basement Membrane

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The fine structure of small blood vessels in and around ten brain tuberculomas was examined. In the peripheral reactive zone of the tuberculomas, examination of 1-μ-thick survey sections established the chronic inflammatory process and the vasculitis characterized by infiltration of the vasomurium (vessel wall) by large and small mononuclear cells. This reaction was typical of chronic epithelioid cell granuloma. Electron microscopic examination of the reactive zone confirmed the vascular proliferation and vasculitis, the venule being the most frequently involved type of blood vessel. It showed the infiltrating cells to lie amidst osmiophilic, concentrically proliferated basement membrane laminae, which formed the greater part of the thickened vessel wall, generally surrounding the endothelial cells directly, the pericytes having disappeared. This appearance, together with the results of Gomori's reticulin stain on paraffin sections, suggested that the altered basement membrane material was reticulin. The possibility is discussed that the altered basement membrane material could be antigenic and that it might be responsible for perpetuating the necrotic vascular and perivascular reaction in tuberculous meningitis and tuberculomas. The above change in the basement membrane was not encountered in the blood vessels of the surrounding edematous brain. The endothelial cells and tight junctions were relatively well-preserved. Intact arterioles could be recognized even in severely edematous brain tissue. At both sites the fine structure of the blood vessels was typical of that expected in the central nervous system. Fenestrated vessels were not seen. The perivascular astrocytic end-feet were destroyed in the reactive zone and either distended or ruptured in the overtly edematous brain tissue also. In the central caseous part of the tuberculoma, there were few blood vessels, and they were in a state of advanced necrosis, but ghost outlines of proliferated basement membrane could be seen. (Am J Pathol 89:35–50, 1977)

A VERY RECENT REVIEW of 20 years' collection of intracranial space-occupying lesions (ICSOL) at our Unit, revealed about 17% of them to be brain tuberculomas, considering patients of all ages, and about 41% on considering ICSOL in children under 15 years of age.[1] The high incidence of other forms of neurotuberculosis, notably tuberculous meningitis which is often associated with brain tuberculoma, is given elsewhere.[2]

There is a virtual absence of ultrastructural studies on any aspect of

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neurotuberculosis. While there is one report on the ultrastructure of tuberculosis in lymph nodes and of sarcoidosis,[3] to the best of our knowledge there is no report on electron microscopic changes in any form of neurotuberculosis. We have recently reported preliminary observations on the ultrastructure of reactive cells in brain tuberculoma, with special emphasis on the evolution of the epithelioid cell.[4] Similarly, while published literature abounds on the light microscopic changes in blood vessels in tuberculous meningitis, as reviewed earlier,[5-7] there is no report on the ultrastructure of small blood vessels in any form of neurotuberculosis or even tuberculosis elsewhere.[3] It might be recalled that the main change described in blood vessels is an infiltration of the vessel wall (vasculitis), involving arteries, veins, and capillaries, by small and large mononuclear cells, terminating with vascular necrosis or partial or total vascular occlusion with fibrosis, especially of arteries.[6-7] An identical histologic reaction is seen in blood vessels in the reactive zones of tuberculomas of brain.

In a brief report on the fine structure of small blood vessels in brain tuberculomas,[8] the vasculitis characterizing this change was described. Subsequently, however, changes in the basement membrane of the blood vessels, in their endothelial cells and tight junctions, and in the perivascular astrocytic processes, have impressed us. In this communication, these changes as observed in the blood vessels of both the reactive zone of tuberculomas and the surrounding edematous brain tissue will be described and the possible immunologic significance of altered basement membrane discussed.

Material and Methods

The material presented here was drawn from ten brain tuberculomas—eight cerebellar and two cerebral—removed surgically from patients varying in age from 2 years to 20 years. Average age was 10 years; 6 patients were boys and 4 were girls. The duration of symptoms of the space-occupying process varied from 1 month to 18 months.

The specimen for electron microscopy was collected personally by one of us (UPD) at the operation table. The neurosurgeon was requested to give, where possible, separate specimens from the central necrotic part, the peripheral reactive zone of the tuberculoma, and the surrounding edematous brain tissue. The latter was available separately in 7 of the 10 cases. He was also urged to remove biopsy specimens prior to application of heat coagulation to that area. The specimen was collected in chilled 4% glutaraldehyde in Millonig's phosphate buffer and allowed to fix for about 2 to 4 hours. Standard procedure was carried out for obtaining semithin and ultrathin sections: the essential steps were postfixation in osmium tetroxide, dehydration in ethanol, treatment with propylene dioxide, embedding in Araldite, examination of about 1-μ-thick survey sections with toluidine blue staining, and treatment of silver-gray ultrathin sections with uranyl acetate and lead citrate.

Light microscopic examination and photography was carried out on semithin sections to determine the nature of cell reaction and to select portions for ultrathin sections. The latter were examined at 60 or 80 kV on a Philips EM200 electron microscope at the Tata Institute of Fundamental Research. Electron micrographs obtained on plates were printed and studied in our department.

Some of the material from every specimen was embedded in paraffin, and these sections were stained with hematoxylin and eosin for cells and by Gomori's silver nitrate method for reticulin fibers. About half the specimens were also stained for glycol groups by periodic acid–Schiff (PAS), for acid mucopolysaccharides by alcian blue, and for acid-fast bacilli by Fite Faraco's method.

Results

The fine structural changes in the small blood vessels will be described separately for the reactive zone of the tuberculoma and for the surrounding edematous brain.

Vasculopathy in the Reactive Zone of Brain Tuberculomas

In Araldite-embedded, toluidine blue–stained semithin sections through this area, the expected inflammatory cell reaction was seen. This consisted of large and small mononuclear cells such as lymphocytes, plasma cells, epithelioid cells, and overt macrophages (Figure 1). In the midst of these cells, proliferated blood vessels, predominantly venules, were encountered (Figure 1). The wall of these small blood vessels was generally thickened and infiltrated by inflammatory cells. These cells were readily distinguishable from the pale nucleated endothelial cells even at lower magnifications and were very clearly delineated on examination under oil immersion (Figure 1). This also brought to view the pericytes and the outer basement membrane of such vessels. It could be further ascertained that the cells infiltrating the vessel wall were clearly between the inner and outer basement membranes of the vessels (Figure 1). Thus the light microscopic appearance of the vasculitis was clearly revealed. This was further clarified by electron microscopic examination of such blood vessels in the reactive zone of the tuberculomas (see Figure 2 of Dastur and Desai[8]).

The endothelial cell contained organelles such as rough endoplasmic reticulum (RER) and mitochondria in varying proportions (Figures 3–5). The nucleated part of the endothelial cells often appeared to bulge into the lumen of the vessel (Figures 3 and 4), rendering the lumen narrow at that site. Such nuclei tended to be large or nucleolated (Figures 3 and 4). The tight junctions between endothelial cells generally tended to be well preserved (Figure 5), but in the presence of vasculitis a tongue of cytoplasm of the invading macrophage seemed, at times, to attack the endothelial cell (Figure 4, lower arrow).

An arresting change in many of the blood vessels in the inflammatory borderzone of tuberculomas was a peculiar alteration in and proliferation of the basement membrane material. Instead of the usual grayish, ground glass-like appearance of the basement membrane (as in Figure 3), in these

vessels the basement membrane had proliferated into several concentric lamellae which then tended to fragment (Figures 4 and 5). The inflammatory cells were seen either amongst the layers of this altered basement membrane, constituting a true vasculitis (as in Figure 4), or outside the vessel wall, representing perivascular reaction (as in Figure 1). Higher resolutions showed a tendency for this basement membrane material to be fragmented, especially in heavily infiltrated vessels (Figure 4). It was homogenous and structureless (Figure 5) and clearly different from collagen, which was generally not encountered.

In an attempt to ascertain the nature of this altered proliferated basement membrane material, reticulin and PAS staining was carried out on paraffin sections of these tuberculomas. Almost all the blood vessels which showed thickening with hematoxylin and eosin staining showed a rich network of proliferated reticulin fibers throughout the vessel wall (Figure 5). This reticulin was arranged either concentrically (e.g., Figure 2), or as an irregular trellis or network. In any event, this proliferated reticulin formed the framework for the thickened vasomurium. It now appeared very likely that the osmiophilic, concentrically proliferated basement membrane material seen in the electron micrographs was predominantly reticulin. Since this fibrillar material generally gave a positive reaction with PAS, it was possibly glycoprotein. However, this reaction was stronger in the center of some of the giant cells and structureless material in the exudate and within blood vessels. The alcian blue reaction was faintly positive in the walls of normal-looking blood vessels but was negative for the proliferated basement membrane material, indicating that this was not predominantly a mucopolysaccharide. No organisms were seen in either the paraffin sections stained for acid-fast bacilli or in the araldite sections examined at electron microscopy.

A feature of note in most of the blood vessels encountered in the reactive zone was the absence of the astrocytic end-feet normally present (Figures 4 and 5). The newly formed basement membrane laminae helped the vessel to retain its shape and lumen even when, rarely, the endothelial cells had been destroyed. The pericytes had invariably disappeared by this time (Figures 4 and 5).

As one approached the necrotic center of the tuberculoma, the caseous zone, the blood vessels tended to be fewer and the cellular infiltration lesser. In semithin sections the vasomurium was either thin or thick and homogenous, in the latter event consisting more of collagen than of reticulin. Ultrathin sections confirmed the paucity of blood vessels and the necrosis of their wall, especially when located in the center of the caseation. The vessels were, at times, barely identifiable as such, and only the laminae of basement membrane revealed their identity. The endothelial

cells disintegrated, with formation of osmiophilic droplets or finely granular lysosomal material, and distension and degeneration of RER. Macrophages bordering the caseous mass also showed similar changes, and elsewhere we have illustrated the altered mitochondria and the lysosomal activity (Figure 18B of Dastur and Lalitha [9]) at this site.

Vasculopathy in the Surrounding Edematous Brain

Inflammatory cells being absent from the brain parenchyma around the tuberculomas, the fine structural changes in the small blood vessels in such areas were similar to those encountered around primary neoplasms of the brain. In general, the vasomurium was better preserved than in the vessels of the reactive zone. The earliest change was a distension of the perivascular astrocytic end-feet, even while the endothelium and the neuropil appeared unremarkable (Figure 3). When the plane of the section allowed full view of the tight junctions, they were often remarkably intact, with the zona adherens and zona occludens (arrows) well defined (Figure 6). Only higher resolutions showed clearly whether the zona occludens part of the junction was truly blocked by osmiophilic material, as in Figure 6 or whether a slight gap had developed here, as in Figure 7. In the latter event, the apposing borders of the two endothelial cells could be defined and the gap of about 50 to 100 Å brought to view (Figure 7, lower arrow).

Figure 6 also shows another feature occasionally detected in endothelial cells of venules and capillaries in this region, viz., very fine myofilaments. A more frequent change noticed in endothelial cells and, to a lesser extent, in pericytes of blood vessels, in the edematous areas was the presence of prominent pinocytotic vesicles, generally along the luminal borders of the cells as in Figure 6. The pericytes often also showed overt phagocytic activity, and in that event they appeared swollen and replete with prominent RER and mitochondria.

In more severely edematous brain tissue, the basement membrane outside both the endothelial cell and the pericyte or the smooth muscle layer was thickened, but with the retention of the normal fuzzy ground glass-like appearance (Figure 7), and without the osmiophilic and proliferated change noticed with basement membrane of blood vessels in the reactive zone. This vessel appears to be an arteriole. The perivascular astrocytic processes were not only distended but tended to rupture (Figure 7) and disappear, and the neuropil tended to be disorganized, with plasmatic material being located outside the blood vessels. Scattered myelinated or unmyelinated axons, synaptic terminals (Figure 7), and cellular organelles were detected in such material.

Discussion

In the absence of detection of acid-fast bacilli in either the paraffin or ultrathin sections of the tuberculomas under report, the evidence for these lesions being tuberculous is derived from other observations. Firstly, the gross appearance of these lesions at operation was typical of tuberculomas, with a yellowish caseous center and a peripheral hyperemic zone of reaction; secondly, in all 10 specimens, the histologic reaction was typical of tuberculomas with the presence of epithelioid cells, giant cells, lymphocytes, and plasma cells in varying proportions, consistent with an "epithelioid granuloma" so well reviewed recently by Adams; [10] thirdly, the only other condition which could produce a similar histopathologic reaction is a fungal granuloma, and no fungal hyphae or spores were seen in any specimen; fourthly, in most of these patients there was evidence of preceding pulmonary tuberculosis with the presence of a febrile illness; finally, all the patients were in the typical age group for neurotuberculosis, viz., between 2 and 20 years.

It may also be recalled that in such chronic solid space-occupying lesions, acid-fast bacilli may be very few and not detected even after examination of several sections.[11] This does not militate against the diagnosis of tuberculosis, for both the primary lesion in the lung and the secondary intracranial lesion (either tuberculous meningitis or tuberculoma), develop as a delayed hypersensitivity reaction.[12] In this type of immunologic reaction, the myobacteria are probably necessary only in the initiation of the tuberculous process, the severe tissue damage being brought about by a strong cell-mediated immune response on the part of the host. This feature becomes most strikingly illustrated in the condition known as tuberculous encephalopathy,[9,13] which has now been reproduced experimentally with the use of various forms of tuberculoprotein and Freund's adjuvant by Wisniewski and Bloom.[14]

Four points of importance appear to emerge from this ultrastructural study of the vasculopathy in and around brain tuberculomas: a) the presence of blood vessels with tight junctions only, the integrity of such junctions, and the disappearance of pericytes and glial end-feet; b) the predominant involvement of venules in the chronic inflammatory process at the border zone of a granulomatous lesion such as the tuberculoma; c) the peculiar concentric proliferation and osmiophilia of basement membrane material of the blood vessels in the reactive zone, with its probable identification as reticulin and possible antigenic role; and d) a relatively better preservation of the vasomurium of blood vessels in the surrounding edematous brain, with a nonspecific change in their basement membrane.

Recently, Hirano has reviewed the literature on the appearance of

fenestrated junctions between endothelial cells of intracranial blood vessels [15] and reported that they occur mostly in intracranial but extracerebral tumors, and rarely in gliomas.[16] In all the sections examined by us from the reactive zone of tuberculomas, where vascular proliferation is an essential component of the inflammatory reaction, and from the surrounding edematous brain tissue, we failed to find any blood vessel with fenestrae between endothelial cells, only tight junctions being encountered. Moreover, such tight junctions of both capillaries and venules were by and large well preserved. When, rarely, a small blood vessel was obviously being destroyed, then there were large gaps between the endothelial cells.[8]

A feature of some importance emerging from the present study is the significant role of venules, which was clearly appreciated in the earlier investigations on inflammation. Movement across the venular wall of both blood cells [17] and plasmatous exudation [18] was well described. Movat and Fernando further showed that pinocytotic vesicles in endothelial cells of venules may attain a larger size and that the pericytes may enlarge and become "activated."[19] They attributed to these cells phagocytic as well as immunologic competence. Gonatas *et al.*,[20] in their ultrastructural investigations of inflammation induced in the rat brain by injection of purified protein derivative (PPD), observed changes identical to those around brain tumors. In the edematous brain around tuberculomas, pinocytotic vesicles were frequently observed in the endothelial cells and pericytes, but in the reactive zone the pericytes were usually destroyed, and the astrocytic end-feet had also disappeared.

The altered and proliferated basement membrane with its arrangement into concentric layers, which was such a striking feature of many of the venules in the reactive zone of the brain tuberculomas, does not appear to have been described before, except in a case of chromophobe adenoma of the pituitary.[21] Even here the nature of this peculiar basement membrane material is not suggested. On the basis of our concurrent reticulin and PAS staining on paraffin sections, we deem it highly probable that the substance constituting this type of basement membrane is like reticulin. Its linearity and osmiophilia are consistent with a proteinous or glycoproteinous material, and it was clearly different from collagen on both light and electron microscopy. According to Cervos-Navarro and Matakas [22] "in many organs and tissues the substrate of reticulin is basement membrane."

The possible sources of origin of the proliferated basement membrane must be considered. The plump appearance of many of the endothelial cells and their frequently rich content of rough endoplasmic reticulum

and mitochondria would be consistent with a synthesizing activity. Pierce *et al.*[23] had adduced evidence that the basement membrane at the base of epithelial cells was a secretion of these cells, probably originating in their endoplasmic reticulum, and that such a secretion was antigenically similar to basement membranes at the bases of all epithelial cells. An alternate source of increased basement membrane material could be the pericyte, as suggested by Ashton [24] in the case of retinal blood vessels in diabetes. The disappearance of pericytes from the vessel wall in brain tuberculomas is difficult to explain. Is it possible that the pericytes perished in a final effort to preserve the integrity of the infiltrated vessel wall, by martialling the formation of copious proteinous material—the multiple laminae of a new basement membrane? Ashton [25] has recently contended that the basement membrane precursors in diabetic retinopathy originate from the blood and result in accelerated glycoprotein synthesis. This argument was supported by the frequent observation of damaged endothelium and the leakage of other hematogenous elements. Even intact endothelium and tight junctions, such as were generally found in our material, could permit occasional egress of small molecules from the lumen outwards. It is interesting to recall at this juncture the similar though lesser proliferation of basement membrane material of intraneural blood vessels in tuberculoid leprosy [26,27] which, like most forms of neurotuberculosis, shows severe tissue damage with few or no detectable bacilli (*Mycobacterium leprae* in this case). In both these conditions increased vascular permeability results.

The greatest amount of work on the antigenic capacity of the basement membrane has been on the renal glomerular, i.e. capillary, basement membrane in human and experimental glomerular nephritis.[28] Anti-glomerular basement membrane antibody has been demonstrated, and Dixon [29] has also shown, by electron microscopy, the presence of abnormal material between endothelial cell and basement membrane in such cases. In view of the powerful hypersensitivity reaction prevailing in all forms of neurotuberculosis (earlier part of this Discussion), and the constant occurrence of antibody-producing or immunologically competent cells, viz., plasma cells or lymphocytes and larger epithelioid mononuclear cells, respectively, in and around the walls of the affected blood vessels,[6-9,11] the possibility arises that the vasculitis and vascular necrosis in this disorder result from an antigen–antibody reaction to proteins of the basement membrane material. While tuberculous bacillary protein must be responsible in *initiating* the CMI type of reaction characterizing tuberculous meningitis [9,13,14,30] or the reactive zone of a tuberculoma, in *perpetuating* this reaction other antigens, such as those of the

altered basement membrane we have described, might be responsible. Hence, hitherto unexplored humoral factors (antibodies) might be playing a role along with the more accepted delayed type of hypersensitivity (CMI), in the pathogenesis of tuberculosis of the nervous system at least. In fact, this could be one reason why patients with tuberculous meningitis who receive late treatment with anti-tuberculous drugs fail to respond and show a florid cellular, vascular, and necrotizing reaction [7,11,5,9,8] in the meninges and brain.

The more usual type of homogenous thickening of the basement membrane encountered in the blood vessels of the edematous brain surrounding the tuberculomas was clearly different from the concentrically proliferated basement membrane mentioned above, but comparable to the thickened basement membrane reported in many other conditions. Thus, for example, Long *et al.*[31] reported this change in human cerebral edema, Aleu *et al.*[32] observed it in edema around experimental gliomas, Cervos-Navarro [33] described it in hemangioblastomas and angioblastic meningiomas. Garcia *et al.*[34] reported it in experimental cerebral infarction. The thickened and homogenous basement membrane of the arteriole illustrated in Figure 7 might reflect an edematous change occurring in it, as also suggested by Rubinstein *et al.*,[35] who observed very similar changes in the blood vessels in the rat cerebrum exposed to ultraviolet irradiation. Such diffuse homogenous thickening of the basement membrane might be a nonspecific consequence of anoxia of the brain, as Hills [36] reported in anoxic-ischemic cerebral lesions in the rat. In the present study, even at sites of severe edematous destruction of the neuropil, the necrotizing reaction in the vasomurium had not developed.

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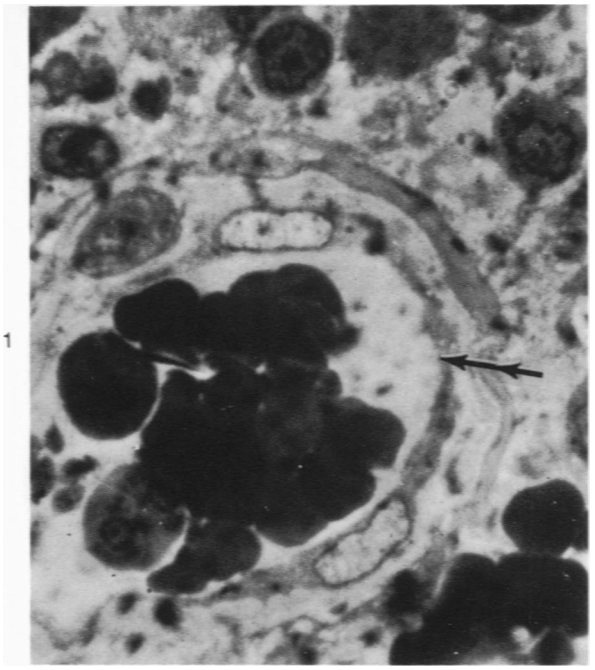
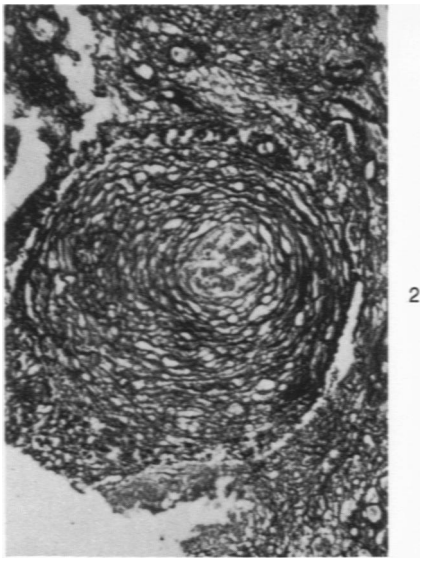
[*Illustrations follow*]





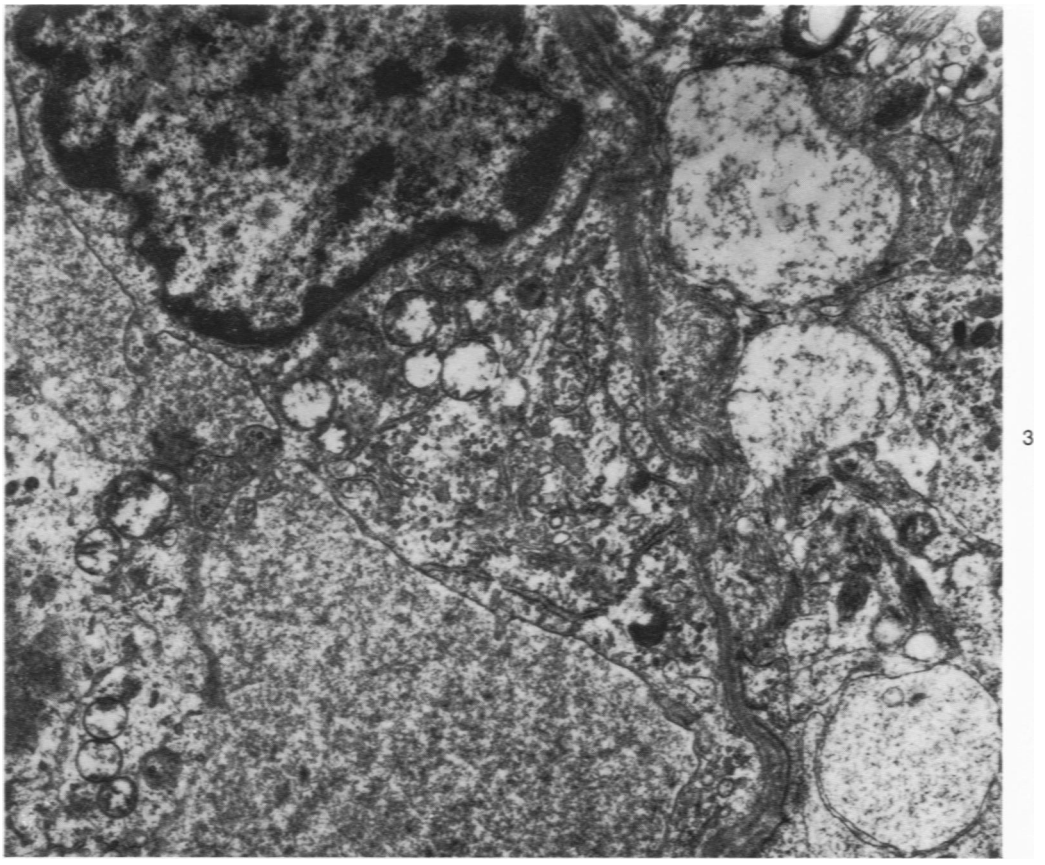


Figure 1—Blood vessel in the reactive zone of a cerebellar tuberculoma showing two endothelial cells continuous with the inner basement membrane of the vessel and a strap-like pericyte outside, continuous with the outer basement membrane (*arrows*). Note the infiltrating cell between the two basement membranes and the inflammatory cells outside, along the upper border of the vessel. (NP/G/657; semithin osmicated araldite section, toluidine blue, ×1400) **Figure 2**—A small blood vessel in the reactive zone of tuberculoma showing dense concentric proliferation of reticulin (NP/G/946; Paraffin section, Gomori's reticulin, ×100). **Figure 3**—A longitudinally cut blood vessel in slightly edematous brain tissue, showing three pale perivascular astrocytic end-feet near normal basement membrane, distended nucleated endothelial cell on the right wall, and three to four platelets bridging the narrowest part of the lumen (NP/G/657; thin araldite section, osmicated and stained with uranyl acetate and lead citrate, ×8500).

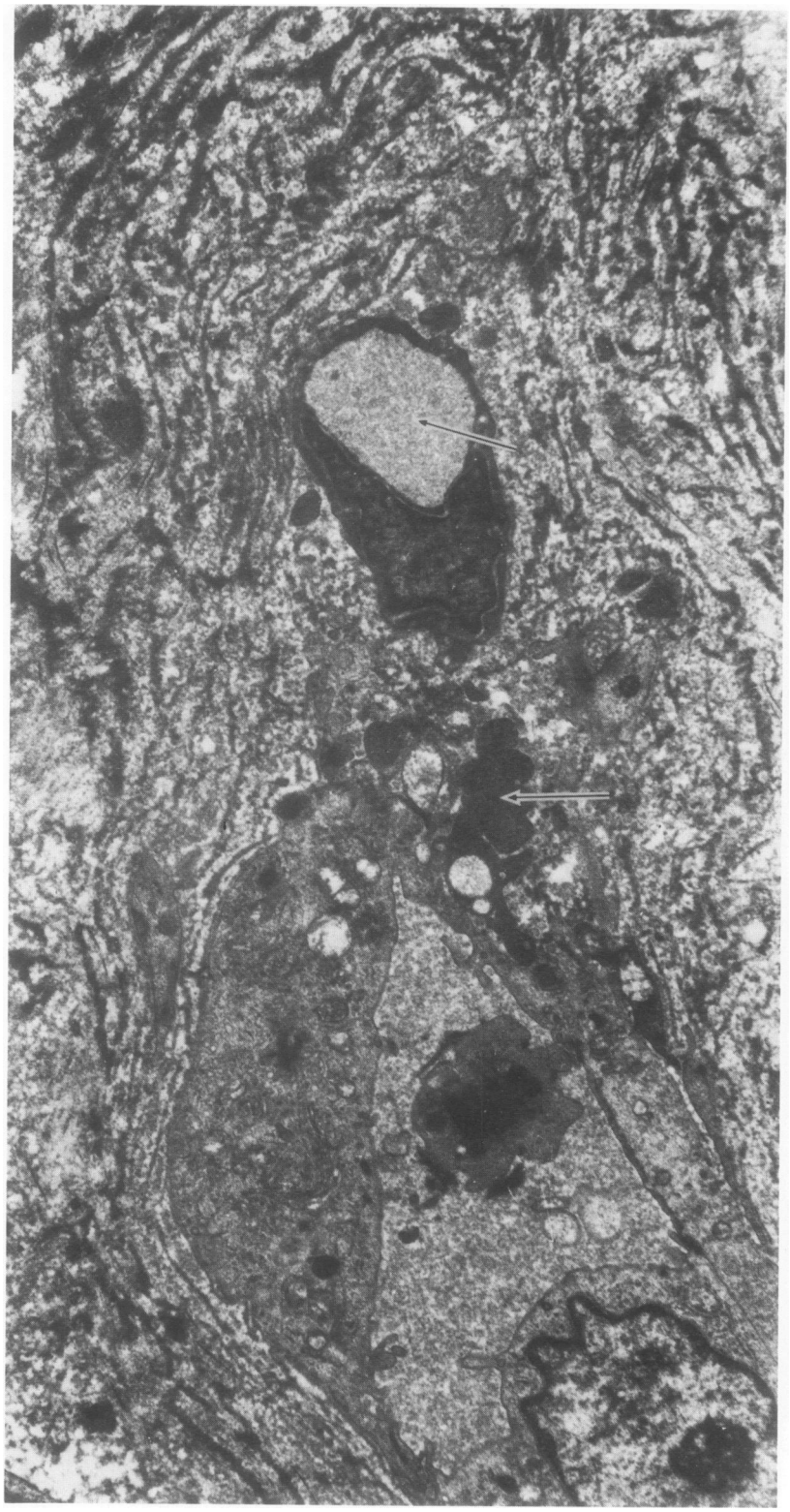
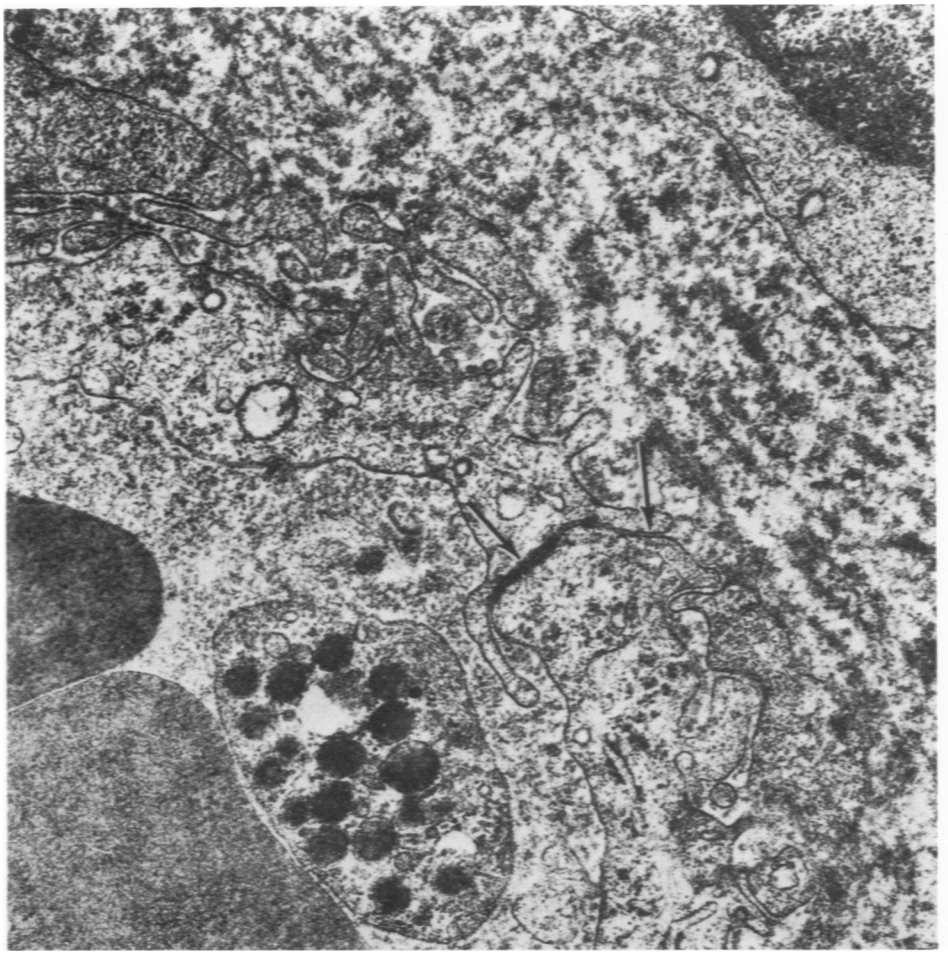


Figure 4—Part of a blood vessel in the reactive zone of a cerebellar tuberculoma. Note the altered proliferated basement membrane which extends all around the vessel, especially towards the top, and one mononuclear cell infiltrating the thickened vasomurium (*upper arrow*), containing a large finely granular body. Towards the apex of the vessel, the endothelial cell is breaking up and shows dense homogenous osmiophilic material (*lower arrow*) which may be the process of an infiltrating macrophage. In the lower right corner a nucleated endothelial cell is bulging into the lumen. There is a platelet aggregate in the lumen attempting contact with the endothelial cell on the right. Note absence of pericytes or glial end-feet. (NP/G/946; as in Figure 3, × 10,900)



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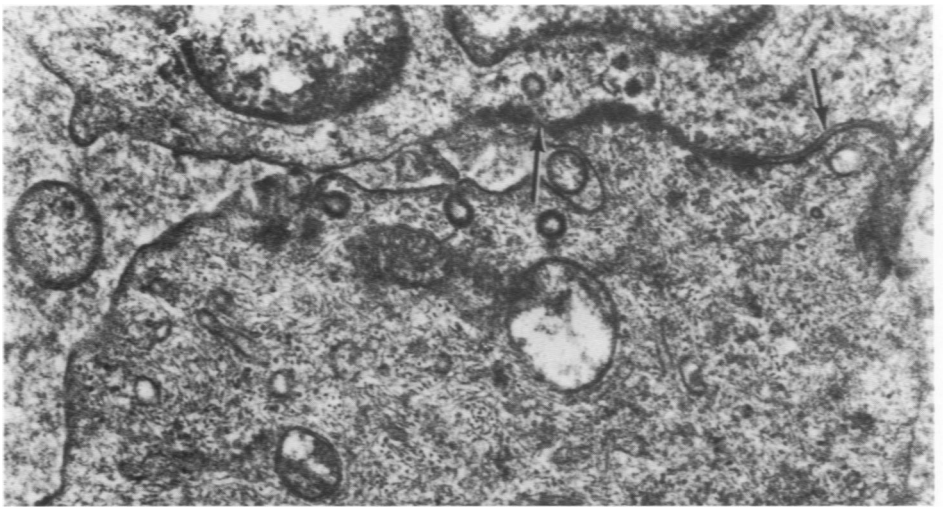

6

Figure 5—Closer view of a small segment of a venule in the reactive zone showing, from the lumen outwards, a platelet aggregate; parts of two endothelial cells with prominent mitochondria, ribosomes, and rough ER; a fairly preserved tight junction with zona occludens (*left arrow*) and zona adherens (*right arrow*); proliferated fragmented basement membrane material; and part of a mononuclear cell. (The area of proliferated basement membrane of this vessel extended far beyond the field included here and contained many inflammatory cells, but no pericytes or glial end feet.) (NP/G/546; as in Figure 3, × 22,200) **Figure 6**—Closer view of part of a vessel showing endothelial tight junction clearly comprising the zona occludens (*left arrow*) and the zona adherens (*right arrow*). Note also the large endothelial cell replete with myofilaments and the pinocytotic vesicles, mostly along its luminal border, some in the stage of formation and a few near the outer border (*right side*) of the cell. (NP/G/546; as in Figure 3, × 33,600)

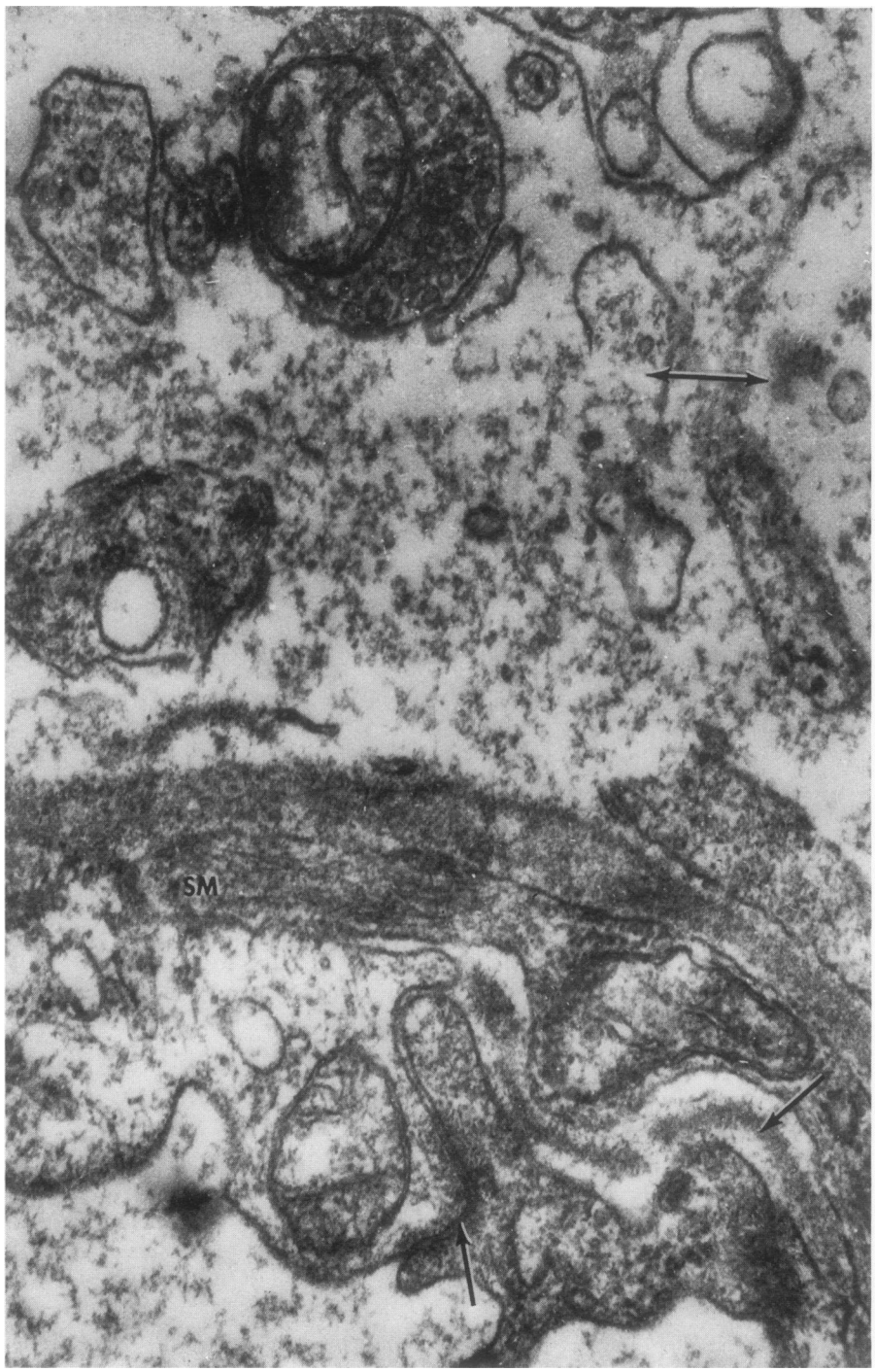

Figure 7—A small blood vessel, probably an arteriole from overtly edematous area around a cerebral tuberculoma, showing thinner basement membrane outside the smooth muscle coat (*SM*) and severely disorganized neuropil. **Note** the distended and ruptured astrocyte processes (*upper arrow*) and one axon terminal bearing synaptic vesicles (**at the** *top*). The endothelial tight junction is fairly preserved but shows slight loosening of the zona occludens (*lower arrow*) on comparison with that in Figure 6. The left endothelial cell (with large mitochondrion) seems to be in direct contact with outer basement membrane at the site of breach in smooth muscle (left of SM). (NP/G/653; as in Figure 3, × 64,300)