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Interrelationships of the pia mater and the perivascular (Virchow–Robin) spaces in the human cerebrum*

E. T. ZHANG,†‡ C. B. E. INMAN† AND R. O. WELLER†

† *Neuropathology, Southampton University Medical School, UK, and* ‡ *Department of Anatomy, Beijing Medical University, Beijing, China*

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INTRODUCTION

The original concepts regarding the relationships between the perivascular spaces in the brain and the cerebrospinal fluid in the subarachnoid space were strongly supported by the conclusions drawn by Weed (1923) from his physiological studies. Thus it was proposed that a free communication existed between the perivascular spaces and the subarachnoid space. Despite some discrepancies in the interpretation of Weed's results (see Krisch, Leonhardt & Oksche, 1984; Hutchings & Weller, 1986) histological and ultrastructural studies at first seemed to support a free communication between the subarachnoid space and the Virchow–Robin perivascular spaces (Woollam & Millen, 1955; Nelson, Blinzinger & Hager, 1961; Ramsey, 1965; Jones, 1970; Rascol & Izard, 1972).

Doubts about the free connection between these two spaces, however, were raised by the results of tracer experiments in which horseradish peroxidase, Evans blue-labelled albumin or radiolabelled tracers injected into the rat brain were concentrated in the perivascular spaces of the middle cerebral arteries (Bradbury, Cserr & Westrop, 1981; Szentistvanyi, Patlak, Ellis & Cserr, 1984; Cserr, 1988). There was a low recovery of isotope tracer from bulk CSF. These results suggested that interstitial fluid from the brain did not drain directly into the cerebrospinal fluid of the subarachnoid space but followed perivascular pathways along major cerebral vessels in the subarachnoid space.

An anatomical basis for the separation of the subarachnoid space from the perivascular (Virchow–Robin) spaces has now been established in several mammalian species, including man. It has been shown that the pia mater on the surface of the brain and spinal cord is reflected on to the surface of blood vessels in the subarachnoid space, thus separating the perivascular and subpial spaces from the subarachnoid space (Krahn, 1982; Krisch *et al.* 1984; Hutchings & Weller, 1986; Alcolado, Weller, Parrish & Garrod, 1988; Nicholas & Weller, 1988). Nevertheless, the anatomical models suggested for animal and human brain (Krahn, 1982; Hutchings & Weller, 1986; Alcolado *et al.* 1988) still do not correlate exactly with the results of tracer studies in the rat (Bradbury *et al.* 1981; Szentistvanyi *et al.* 1984). There are two major discrepancies: firstly, no direct connection between the perivascular spaces of vessels in the brain and the perivascular spaces of vessels in the subarachnoid space has been established. Thus, with the published models, it is likely that fluid or tracers would be dissipated in the subpial space rather than draining directly into the perivascular

* Reprint requests to Professor R. O. Weller, Department of Pathology (Neuropathology), Level E, South Pathology Block, Southampton General Hospital, Southampton SO9 4XY, UK.

spaces of subarachnoid vessels. Secondly, no distinction has been made between the perivascular spaces of arteries and veins to account for the preferential concentration of tracers in arterial perivascular spaces (Cserr, 1988). In the present paper, we seek to establish a direct anatomical connection between perivascular spaces of arteries in the human cerebrum and perivascular spaces of arteries in the subarachnoid space.

Previous electron microscope studies have shown that, although there are arteries and large veins in the subarachnoid space of both cat and human brains, only arterioles, capillaries and venules are seen in the cerebral cortex (Dahl, Flora & Nelson, 1965; Dahl, 1973, 1986; Roggendorf & Cervós-Navarro, 1977). Arterioles in the brain lack a complete internal elastic lamina but possess a complete coat of smooth muscle cells (Roggendorf & Cervós-Navarro, 1977). Smaller arterial vessels with a discontinuous, one layered sheath of atypical simple smooth muscle cells were identified in the cat brain as metarterioles (Roggendorf & Cervós-Navarro, 1977). No typical smooth muscle cells were seen in the walls of venules in the cat brain (Roggendorf, Cervós-Navarro & Lazaro-Lacalle, 1978). As described by other authors (see Peters, Palay & Webster, 1976), the perivascular spaces of capillaries are obliterated by the fusion of endothelial and glial basement membranes.

Flattened cells forming a thin layer around blood vessels in the brain have usually been described as adventitial cells (Frederickson & Low, 1969; Roggendorf & Cervós-Navarro, 1977). In the present study of vessels in the subarachnoid space, subpial space, cerebral cortex and cerebral white matter, we investigate the ultrastructure of these flattened cells and offer evidence that they are derived from the pia mater. Furthermore, we suggest that they enclose a perivascular space which is continuous from intracerebral arterioles to arteries in the subarachnoid space. One previous problem in identifying cells of pial origin has been the lack of an obvious marker. Ultrastructural and immunocytochemical studies, however, have shown that there are desmosomes, gap junctions and tight junctions in the arachnoid and pia mater of experimental animals (Andres, 1967; Nabeshima, Reese, Landis & Brightman, 1975; Dermietzel, 1975) and man (Rascol & Izard, 1972; Kartenbeck, Schwechheimer, Moll & Franke, 1984; Parrish *et al.* 1986; Alcolado *et al.* 1988). In the present paper we have used the presence of desmosomes and small nexus junctions to identify pial cells around cerebral blood vessels.

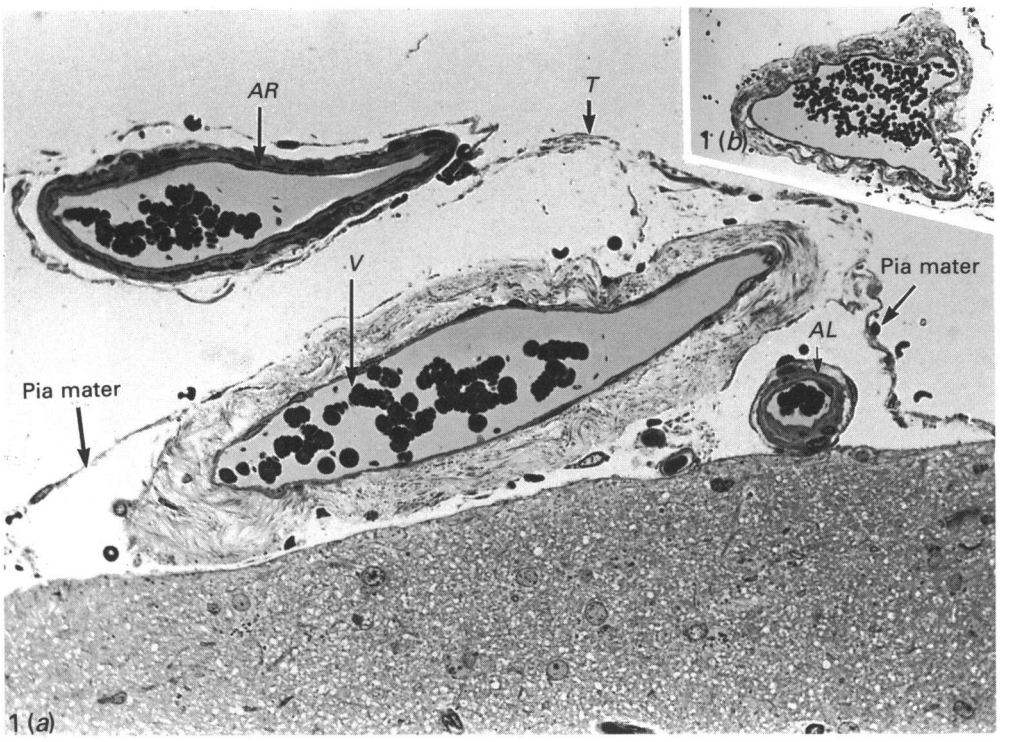
MATERIAL AND METHODS

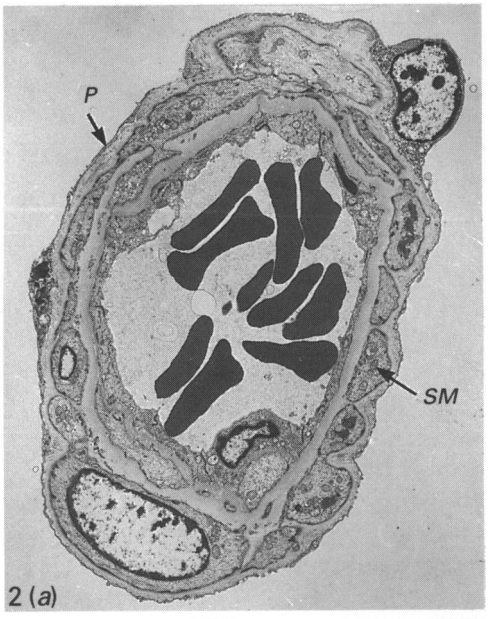
Fresh human cerebral cortex from frontal and temporal lobes was obtained from 6 patients (4 male and 2 female aged between 18 and 53 years) who underwent surgical lobectomy for cerebral tumour. Tissue was taken from areas not directly involved by the tumour. Multiple blocks of cortex and white matter, together with overlying pia

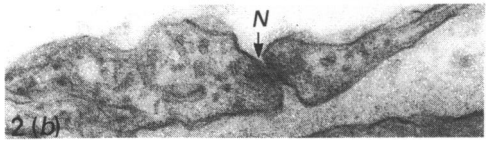
Fig. 1(*a–b*). Blood vessels at the surface of the cerebral cortex. A trabecula (*T*) joins the periarterial sheath of an artery in the subarachnoid space (*AR*) with the pia mater. An arteriole (*AL*) in the subpial space also has a pial sheath. A vein (*V*) in the subpial space and a vein in the subarachnoid space in (*b*) are surrounded by thick layers of collagen. The subpial vein lacks a complete pial sheath. Resin section stained with toluidine blue. (*a*) ×330; (*b*) ×145.

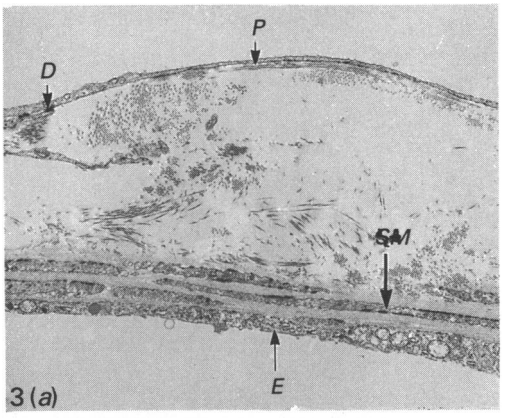
Fig. 2(*a–b*). An arteriole in the subarachnoid space with a single layer of smooth muscle cells (*SM*) in the media. A thin layer of pial cells (*P*) surrounds the vessel. Adjacent pial cells are joined by nexus junctions (*N*) shown at higher magnification in (*b*). Electron micrographs. (*a*) ×2525; (*b*) ×57600.

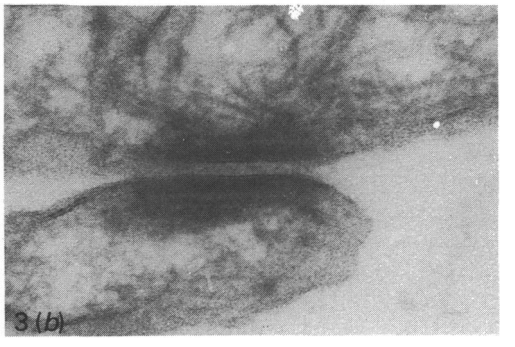
Fig. 3(*a—b*). Vein in the subarachnoid space. The endothelium (*E*) and flattened smooth muscle cells (*SM*) of the vessel wall are separated from the pial sheath (*P*) by a wide perivascular space and collagen bundles. A desmosome (*D*) between the pial cells is seen at higher magnification in (*b*). Electron micrographs. (*a*) ×3800; (*b*) ×96000.


AR
T
V
Pia mater
AL
Pia mater
1 (a)
1 (b)


P
SM
2 (a)


N
2 (b)


P
D
SM
E
3 (a)


3 (b)

and arachnoid mater were fixed for 4 hours in 3% glutaraldehyde in 0·1 M cacodylate buffer (pH 7·4) within 10 minutes of surgical excision. Mirror image blocks were fixed in buffered formalin, embedded in paraffin and sections were examined histologically to exclude involvement by tumour.

Following glutaraldehyde fixation, blocks were washed in cacodylate sucrose buffer, postfixed in 2% osmium tetroxide, stained in 1·5% aqueous uranyl acetate, dehydrated in graded alcohols and Histosol and embedded in Spurr's resin. Resin sections, 0·5–1 μm thick, were stained with toluidine blue and examined by light microscopy. Ultrathin sections were cut from selected areas for transmission electron microscopy, mounted on uncoated copper grids, counterstained with lead citrate and examined in an H7000 Hitachi transmission electron microscope at 60 kV.

RESULTS

Blood vessels in the subarachnoid and subpial spaces

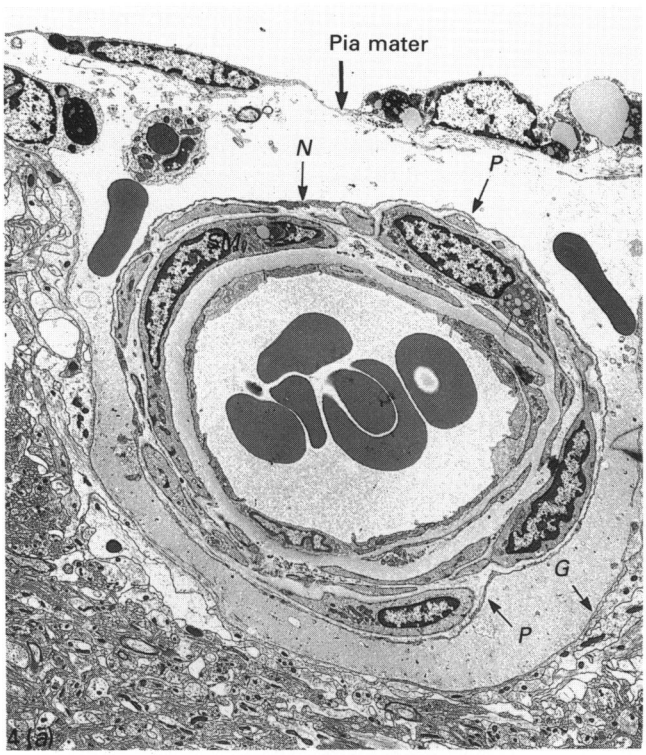
Blood vessels on the surface of the cerebral cortex lie both in the subarachnoid space and in the subpial space (Fig. 1*a*, *b*). An artery in the subarachnoid space (Fig. 1*a*) has a complete internal elastic lamina and a coat of smooth muscle. It is surrounded by a layer of pial cells which is continuous through a trabecula with the pia mater. Electron microscopy (Fig. 2*a*) shows how the thin single-layered covering of pial cells closely invests a subarachnoid arteriole and is separated from the smooth muscle coat of the vessel by a thin layer of collagenous connective tissue. Small pores or gaps are seen in the pial coating but adjacent cells are joined by desmosomes and by small nexus junctions (Fig. 2*b*).

Veins in the subarachnoid space are also coated by a thin pial sheath (Figs. 1*b*, 3) which is separated from the endothelium by a substantial layer of randomly orientated bundles of collagen and flattened cells with surface densities characteristic of smooth muscle cells (Fig. 3*a*). As with the arteries, cells of the venous pial sheath are joined by desmosomes (Fig. 3*b*) and by small nexus junctions.

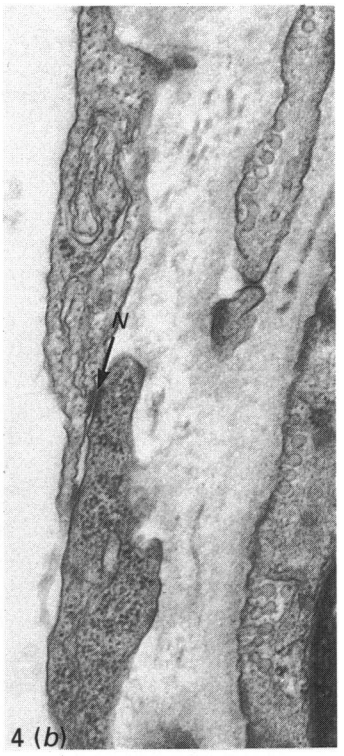
Arterioles within the subpial space (Figs. 1*a*, 4*a*) are smaller than the arteries in the subarachnoid space and they lack a complete internal elastic lamina (Fig. 4*a*). Subpial arterioles, however, are completely invested by a very thin layer of cells which resembles the pia mater. In Figures 1 and 4*a* this sheath of cells is completely separate from the overlying pia mater and from the surface of the cerebral cortex. Individual cells are joined by nexus junctions (Fig. 4*b*) which are often difficult to classify exactly; true desmosomes between the cells in this location were not seen. Occasionally (i.e. on two occasions in the present material), the pial sheath of a small arteriole, or metarteriole (Roggendorf & Cervós-Navarro, 1977), in the subpial space appeared to be subtended from the deep surface of the pia mater itself (Fig. 5). The vessel in Figure 5 has a small lumen surrounded by endothelium and an incomplete layer of smooth muscle cells. Separated from the smooth muscle by bundles of collagen is a thin and focally fenestrated layer of cells which appears to be continuous with the pia mater.

Fig. 4(*a–b*). A 25 μm diameter arteriole in the subpial space. The media, composed of two layers of smooth muscle cells (*SM*), is surrounded by a very thin layer of pial cells (*P*) joined by nexus junctions (*N*) shown at higher power in (*b*). Glia limitans (*G*). Electron micrographs. (*a*) ×2800; (*b*) ×32600.

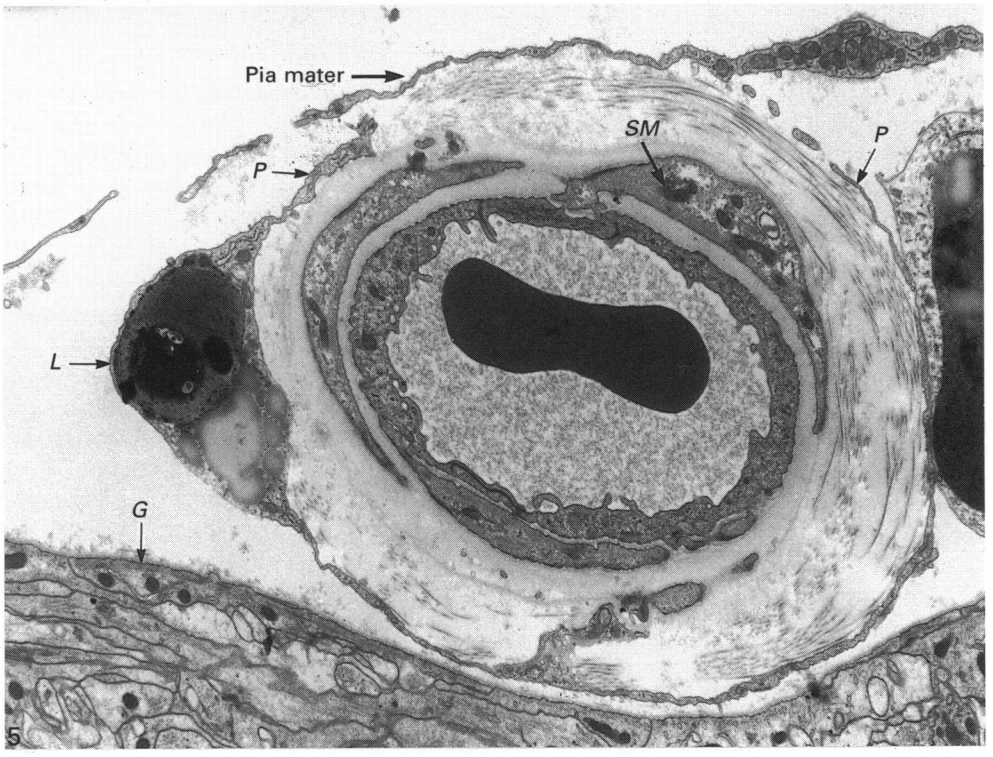
Fig. 5. An 8 μm diameter metarteriole in the subpial space. It is surrounded by a fenestrated layer of flattened cells (*P*) subtended from the deep aspect of the pia mater. This pial sheath is separated from the vessel wall by collagen bundles. Lipofuscin-like material (*L*), glia limitans (*G*), Smooth muscle (*SM*). Electron micrograph. ×9000.



4 (a)



4 (b)



5

Cells comprising this outer sheath are joined by nexus junctions and lack a basement membrane; in both these characteristics they resemble pial cells. Occasional projections from the inner surface of the perivascular sheath of pial cells come into close contact with smooth muscle cells of the vessel wall (Fig. 5). Dense material resembling lipofuscin is seen in the cytoplasm of one of the cells in the sheath.

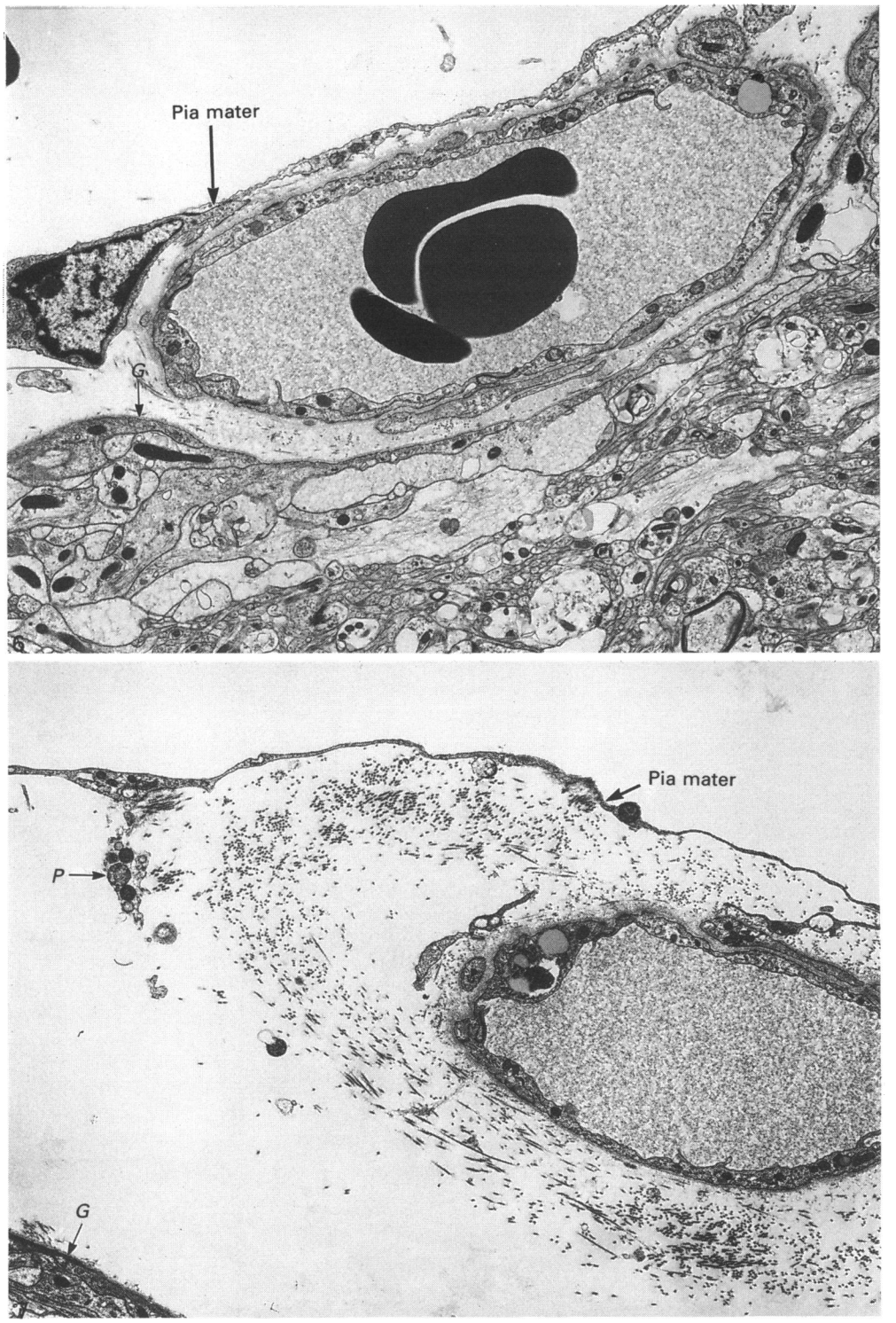
Large veins in the subpial space are frequently surrounded by substantial layers of connective tissue composed of randomly orientated bundles of collagen (Fig. 1*a*). This layer of connective tissue is similar to that seen around veins in the subarachnoid space (Figs. 1*b*, 3*a*) and is more substantial than that around most arteries in the subarachnoid space or around arterioles in the subpial space. In most instances, small veins within the subpial space (Figs. 1*a*, 6) have little connective tissue surrounding them and have no continuous perivascular sheath of pia mater comparable to that of arterioles in the subpial space. In Figure 6 a small venule is separated from the pia mater on the one hand and from the surface of the brain on the other by a few strands of collagen. Apart from the endothelial cells forming the wall of the vessel, there are only occasional small cell processes; they resemble the atypical smooth muscle cells associated with venules in other species (Roggendorf *et al.* 1978). On rare occasions, small venules in the subpial space are coated by a more substantial layer of collagen bundles (Fig. 7). This arrangement of collagen, and the rudimentary spur of cells arising from the deep aspect of the pia mater, suggest that this vessel may be entering a trabecula (see Alcolado *et al.* 1988) to pass into the subarachnoid compartment. The vessel would, under these circumstances, acquire a pial sheath which it would retain during its passage in the subarachnoid space. No example of a vein or venule in the subpial space was observed around which there was anything other than a rudimentary and incomplete pial sheath (Fig. 1*a*).

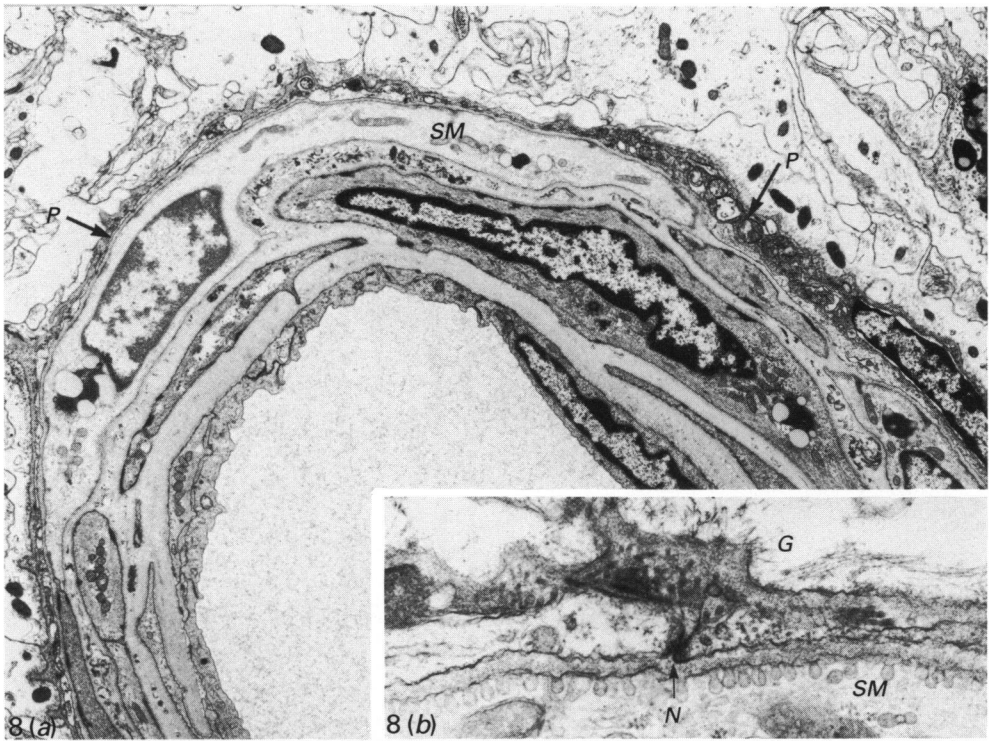
Blood vessels in the cerebral cortex and white matter

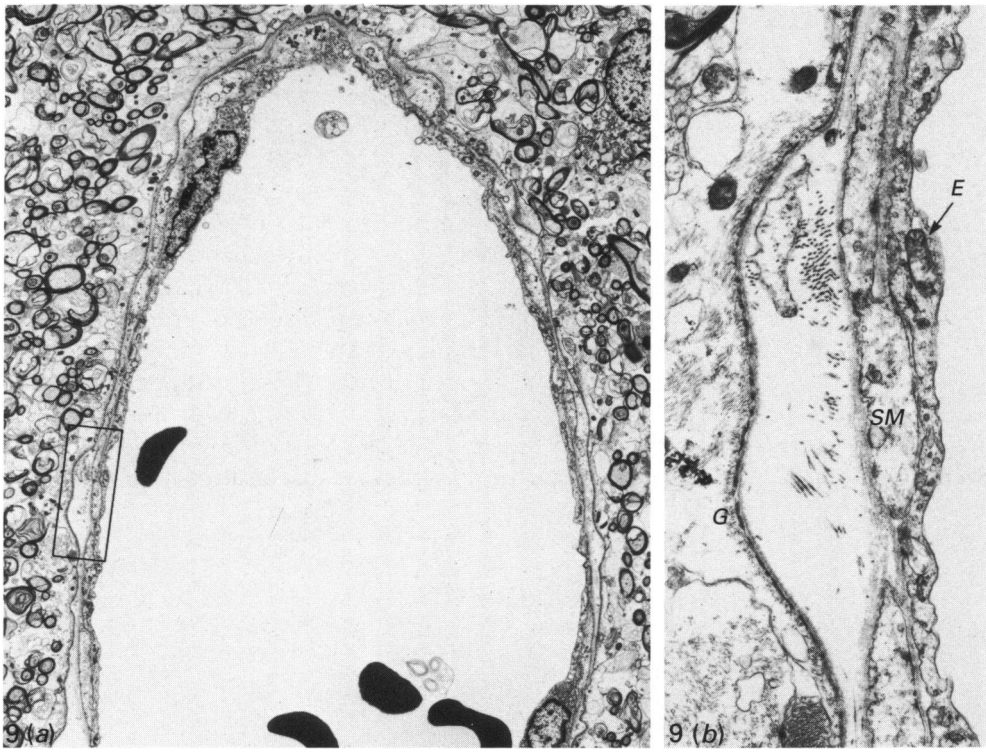
The larger arterioles in the cerebral cortex and white matter are surrounded by two or three layers of smooth muscle cells, but they lack a complete internal elastic lamina (Fig. 8). Completely surrounding such an arteriole is an attenuated layer of flattened cells joined by nexus junctions (Fig. 8*b*). These cells, which resemble pial cells, separate the smooth muscle coat from the surrounding glia limitans (Fig. 8). There is little connective tissue or space between the layer of pial cells and either the glia or the underlying smooth muscle (Fig. 8*b*). The layer of pial cells surrounding vessels of this size is complete with only occasional very small pores of fenestrations. As the number of smooth muscle cells surrounding arterioles decreases, however, the size of the fenestrations in the pial sheath increases. This is particularly apparent as gaps appear in the smooth muscle coating. In general, the pial cells surrounding the smaller arterioles and metarterioles are associated with the smooth muscle cells. As in other species, the perivascular spaces around capillaries are obliterated by fusion of the endothelial and glial basement membranes. No identifiable pia mater cells were seen around capillaries.

Fig. 6. A venule, 12 μm mean diameter in the subpial space, lacks a pial sheath. The vessel is separated from the pia mater and glia limitans (*G*) by a few subpial collagen fibres. Electron micrograph. × 6500.

Fig. 7. Venule (approximately 10 μm diameter) in the subpial space. A thick layer of collagen bundles surrounds the vessel and a small spur of pial cells is seen (*P*). The venule may be at a point at which it leaves the subpial space to enter a leptomeningeal trabecula (see text). Glia limitans (*G*). Electron micrograph. × 6700.


Pia mater
G
Pia mater
P
G


SM
P
P
8 (a)
G
SM
N
8 (b)


9 (a)
E
SM
G
9 (b)

Venules in the cerebral cortex and white matter have relatively large lumina in relation to the thickness of their vessel walls when compared with arterioles and metarterioles. The vessel illustrated in Figure 9(*a*) has a wall composed of flattened endothelial cells and an incomplete layer of atypical smooth muscle cells similar to those seen around venules in the cat brain (Roggendorf *et al.* 1978). A narrow but irregular perivascular space separates the wall of the venule from the basement membrane of the glia limitans and contains small numbers of fine collagen fibres (Fig. 9*b*). Occasional cell processes are seen within the perivascular space but only rarely around venules are these processes joined by nexus junctions or desmosomes. No complete layer of leptomeningeal cells was seen around any venous vessel in the cerebral cortex or superficial white matter.

DISCUSSION

The results of the present study suggest that the pia mater is arranged around cerebral blood vessels in a manner illustrated diagrammatically in Figure 10. With this arrangement there is a perivascular compartment around arterioles in the cerebrum which is bounded externally by a layer of pial cells and is in continuity, along subpial arterioles, with the perivascular spaces of arteries in the subarachnoid space. No comparable sheath was observed around veins (Fig. 10).

The pial sheath around arterioles in the human brain is similar to the layer of adventitial cells described in rat and cat (Frederickson & Low, 1969; Roggendorf & Cervós-Navarro, 1977). In the present study, however, we have equated this layer with the pia mater through the presence of nexus junctions. Desmosomes were rarely seen between pial cells around subpial or intracerebral arterioles, a feature which supports the earlier observations that no desmosomes can be identified around arterioles in the cerebral cortex by immunocytochemistry (Alcolado *et al.* 1988). It was difficult to classify exactly many of the nexus junctions of the intracerebral arteriolar pial sheaths. However, Dermietzel (1975), who emphasised the heterogeneity of the junctional complexes of the pia and arachnoid in the cat, concluded from the results of his freeze fracture study that they were of two basic types: gap junctions and tight junctions.

None of the previous studies in which adventitial cells or pial cells have been described around blood vessels in animal and human brains (Frederickson & Low, 1969; Rascol & Izard, 1972; Roggendorf, & Cervós-Navarro, 1977; Krisch *et al.* 1984) appears to have made the same distinction between the pial coats of arteries and veins as demonstrated in the human brain in the present study. However, a continuous perivascular channel extending from arteries in the brain to arteries in the subarachnoid space on the surface of the brain does correlate with the periarterial drainage of tracers from the brain observed in the rat (Bradbury *et al.* 1981; Szentistvanyi *et al.* 1984). The pial sheath may prevent dispersal of fluid (or tracer)

Fig. 8(*a–b*). Arteriole in the cerebral cortex completely surrounded by layers of smooth muscle cells (*SM*). A single layer of pial cells (*P*) separates the vessel from the brain tissue. Cell processes of the pial sheath are joined by nexus junctions (*N*) shown at higher power in (*b*). Glia limitans (*G*). Electron micrographs. (*a*) × 5600; (*b*) × 32000.

Fig. 9 (*a–b*). Venule in the cerebral white matter showing a relatively large lumen and a thin wall. It lacks a pial sheath. Higher magnification of the outlined area is seen in (*b*); the glia limitans (*G*) is separated from the atypical smooth muscle cells (*SM*) by a perivascular space containing a few collagen fibres and occasional cell processes. Endothelium (*E*). Electron micrographs. (*a*) × 1950; (*b*) × 11300.

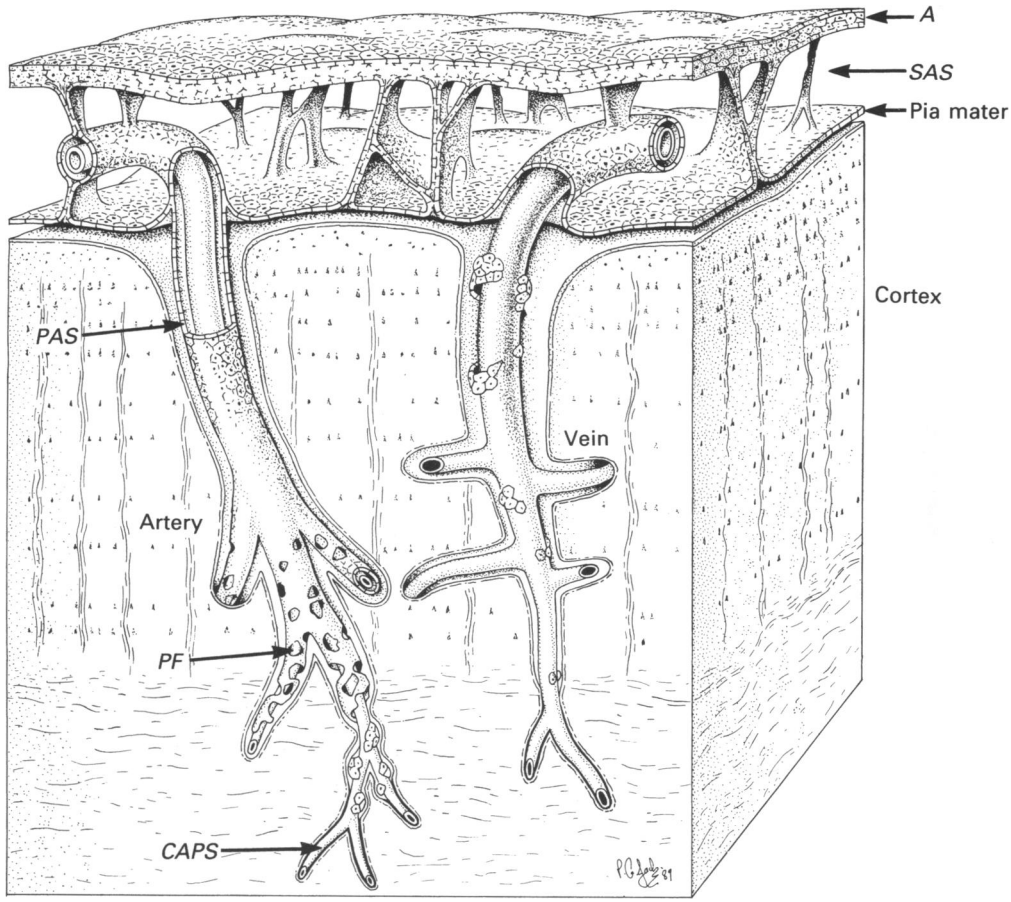


Fig. 10. Diagram demonstrating the relationships of the pia mater and intracerebral blood vessels. Subarachnoid space (*SAS*) separates the arachnoid (*A*) from the pia mater overlying the cerebral cortex. An artery on the left of the picture is coated by a sheath of cells derived from the pia mater; the sheath has been cut away to show that the periarterial spaces (PAS) of the intracerebral and extracerebral arteries are in continuity. The layer of pial cells becomes perforated (*PF*) and incomplete as smooth muscle cells are lost from the smaller branches of the artery. The pial sheath finally disappears as the perivascular spaces are obliterated around capillaries (*CAPS*). Perivascular spaces around the vein (right of picture) are confluent with the subpial space and only small numbers of pial cells are associated with the vessel wall.

into the subpial space; the absence of such a sheath was a defect in earlier models (Krahn, 1982; Hutchings & Weller, 1986; Alcolado *et al.* 1988).

Although a small part of the anatomical pathway for the drainage of interstitial fluid from the brain may have been clarified by the present study, the nature of the complete pathway is still unclear. Following injection into the rat brain, tracers appear in retropharyngeal lymph nodes (Cserr, 1988). Furthermore, obstruction or extirpation of cervical lymphatics interferes with drainage of interstitial fluid from the brain (Földi, Csillik & Zoltán, 1968). From the present and previous studies it seems that fluid and tracers could pass along periarterial spaces in the brain and into the perivascular spaces of major arteries in the subarachnoid space. However, tracers go no further than the entry of the carotid artery into the skull in the rat (Bradbury *et al.* 1981). Furthermore the perivascular space ends at the dura where the vertebral artery enters the skull in man (Alcolado *et al.* 1988). Thus there does not seem to be a direct

drainage pathway along periarterial spaces to extracerebral lymphatics. Krisch *et al.* (1984) suggested that horseradish peroxidase drains along spaces within arachnoid trabeculae but no pathways into dural lymphatics have been demonstrated (Krisch, 1988). Tracers do, however, enter the lymphatics in the nasal mucosa (Cserr, 1988), but the pathways by which the tracers pass from the periarterial spaces to the cribriform plate and nasal mucosa are still unclear.

A further problem remains to be solved in the correlation of the anatomical arrangement of the leptomeninges and their physiological characteristics. In man, little is known about the permeability characteristics of the pia mater or of the pial sheaths surrounding arteries in the brain and in the subarachnoid space. The fenestrated nature of the leptomeningeal sheath around arteries in the subarachnoid space has been emphasised in the rat (Frederickson & Low, 1969) and in the cat (Zervas, Liszczak, Mayberg & Black, 1982). Similar fenestrae were seen in the present study in man. Furthermore, although tight junctions may exist in the pia mater (Dermietzel, 1975) they were not definitely identified in the pia mater or in the perivascular pial sheaths within the brain in the present study. Other authors have commented upon the fragility of the pia mater and the frequency of artefactual tears (Krisch *et al.* 1984; Zervas *et al.* 1982). It seems, therefore, that the pia mater may be fully permeable at least to solutes although it appears to prevent the passage of large particles such as erythrocytes following subarachnoid haemorrhage in man (Hutchings & Weller, 1986). In the cat, perfusion of horseradish peroxidase into the subarachnoid space is quickly followed by the wide distribution of the tracer in perivascular spaces, suggesting that the pia mater is fully permeable to peroxidase (Zervas *et al.* 1982; Rennels *et al.* 1985).

In addition to its role as the outer boundary of periarterial spaces, the pial sheath of cerebral arteries may act as an enzymic barrier. Kaplan, Hartman & Creveling (1982) showed that the pia mater, together with the choroid plexus and ependyma, contains a higher concentration of catechol-O-methyltransferase than other brain cells. They suggested that leptomeningeal cells containing this enzyme may form an enzymic barrier which could protect the central nervous system cells from peripherally produced catecholamines. The anatomical arrangement of the leptomeningeal cells around arteries and arterioles in the human brain and in the subarachnoid space supports this hypothesis. The leptomeningeal sheath is more complete around vessels with a complete coat of smooth muscle cells and becomes highly fenestrated around those arteries in which the smooth muscle cells are reduced in number. With the known noradrenergic innervation of intracerebral vessels (Edvinsson, 1987), the leptomeningeal cells could fulfil the role of a barrier preventing catecholamines entering brain tissue.

SUMMARY

Biopsies of histologically normal adult human cerebral cortex, underlying white matter and overlying leptomeninges were taken from frontal and temporal lobectomy specimens excised during the removal of cerebral tumours. Multiple blocks from 6 patients (aged 18–53 years) were examined by light and transmission electron microscopy. A thin sheath of pia mater cells was found to surround completely arterioles and arteries in the brain, in the subpial space and in the subarachnoid space. Pia mater cells, forming the perivascular sheath, were identified by the presence of desmosomes or small nexus junctions and by continuity with the pia mater itself. The presence of the pial sheath suggests that the perivascular spaces around intracerebral

arteries are in direct continuity with the perivascular spaces around subarachnoid arteries. No similar pial sheath was observed around intracerebral or subpial venules. The role of the periarterial spaces, enclosed by the pial sheath, is discussed in relation to the results of physiological experiments suggesting drainage of interstitial fluid from brain tissue into the perivascular pathways along major cerebral arteries in the subarachnoid space. As arterioles in the brain become smaller and lose their smooth muscle coats, the pial sheath becomes incomplete. The anatomical relationships between the pia mater and blood vessels in the human cerebrum is summarised diagrammatically, and a possible role for pial cells as an enzymic barrier protecting the brain from exogenous catecholamines is discussed.

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REFERENCES

ALCOLADO, R., WELLER, R. O., PARRISH, E. P. & GARROD, D. (1988). The cranial arachnoid and pia mater in man: anatomical and ultrastructural observations. *Neuropathology and Applied Neurobiology* **14**, 1–17.

ANDRES, K. H. (1967). Über die Feinstruktur der Arachnoida und Dura mater von Mammalia. *Zeitschrift für Zellforschung und mikroskopische Anatomie* **79**, 272–295.

BRADBURY, M. W. B., CSERR, H. F. & WESTROP, R. J. (1981). Drainage of cerebral interstitial fluid into deep cervical lymph of the rabbit. *American Journal of Physiology* **240**, F329–F336.

CSERR, H. F. (1988). Role of secretion and bulk flow of brain interstitial fluid in brain volume regulation. *Annals of the New York Academy of Sciences* **529**, 9–20.

DAHL, E. (1973). The fine structure of intracerebral vessels. *Zeitschrift für Zellforschung und mikroskopische Anatomie* **145**, 577–586.

DAHL, E. (1986). The ultrastructure of cerebral blood vessels in man. *Cephalalgia* **6**, *Suppl.* 4, 45–48.

DAHL, E., FLORA, G. & NELSON, E. (1965). Electron microscopic observations on normal human intracranial arteries. *Neurology (Minneap.)* **15**, 132–140.

DERMIETZEL, R. (1975). Junctions in the central nervous system of the cat. V. The junctional complex of the pia-arachnoid membrane. *Cell and Tissue Research* **164**, 309–329.

EDVINSSON, L. (1987). Innervation of the cerebral circulation. *Annals of the New York Academy of Sciences* **519**, 334–348.

FREDERICKSON, R. G. & LOW, F. N. (1969). Blood vessels and tissue space associated with brain of the rat. *American Journal of Anatomy* **125**, 123–146.

FÖLDI, M., CSILLIK, B. & ZOLTÁN, Ö. T. (1968). Lymphatic drainage of the brain. *Experimentia* **24**, 1283–1287.

HUTCHINGS, M. & WELLER, R. O. (1986). Anatomical relationships of the pia mater to cerebral blood vessels in man. *Journal of Neurosurgery* **65**, 316–325.

JONES, E. G. (1970). On the mode of entry of blood vessels into the cerebral cortex. *Journal of Anatomy* **106**, 507–520.

KAPLAN, G. P., HARTMAN, B. K. & CREVELING, C. R. (1981). Localization of catechol-O-methyltransferase in the leptomeninges, choroid plexus and ciliary epithelium: implications for the separation of central and peripheral catechols. *Brain Research* **204**, 353–360.

KARTENBECK, J., SCHWECHHEIMER, K., MOLL, R. & FRANKE, W. W. (1984). Attachment of vimentin filaments to desmosomal plaques in human meningiomal cells and arachnoidal tissue. *Journal of Cell Biology* **98**, 1072–1081.

KRAHN, V. (1982). The pia mater at the site of the entry of blood vessels into the central nervous system. *Anatomy and Embryology* **164**, 257–263.

KRISCH, B. (1988). Ultrastructure of the meninges at the site of penetration of veins through the dura mater with particular reference to Pacchionian granulations. Investigations in the rat and two species of New World monkeys (*Cebus apella*, *Callitrix jacchus*). *Cell and Tissue Research* **251**, 621–631.

KRISCH, B., LEONHARDT, H. & OKSCHE, A. (1984). Compartments and perivascular arrangement of the meninges covering the cerebral cortex of the rat. *Cell and Tissue Research* **238**, 459–474.

NABESHIMA, S., REESE, T. S., LANDIS, D. M. D. & BRIGHTMAN, M. W. (1975). Junctions in the meninges and marginal glia. *Journal of Comparative Neurology* **164**, 127–170.

NELSON, E., BLINZINGER, K. & HAGER, H. (1961). Electron microscopic observations on subarachnoid and perivascular spaces of the Syrian hamster brain. *Neurology (Minneap.)* **11**, 285–295.

NICHOLAS, D. S. & WELLER, R. O. (1988). The fine anatomy of the human spinal meninges. A light and scanning electron microscopy study. *Journal of Neurosurgery* **69**, 276–282.

PARRISH, E. P., GARROD, D. R., MATTEY, D. L., HAND, L., STEART, P. V. & WELLER, R. O. (1986). Mouse antisera specific for desmosomal adhesion molecules of suprabasal skin cells, meninges and meningioma. *Proceedings of the National Academy of Sciences of the USA* **83**, 2657–2661.

PETERS, A., PALAY, S. L. & WEBSTER, H. DE F. (1976). *The Fine Structure of the Nervous System: The Neurons and Supporting Cells*. Philadelphia: W. B. Saunders.

RAMSEY, H. J. (1965). Fine structure of the surface of the cerebral cortex of human brain. *Journal of Cell Biology* **26**, 323–333.

RASCOL, M. & IZARD, J. (1972). La jonction cortico-piemèrienne et la pénétration des vaisseaux dans le cortex cérébral chez l'homme. *Zeitschrift für Zellforschung und mikroskopische Anatomie* **123**, 337–355.

RENNELS, M. L., GREGORY, T. R., BLAUMANIS, O. R., FUJIMOTO, K. & GRADY, P. A. (1985). Evidence for a 'paravascular' fluid circulation in the mammalian central nervous system, provided by the rapid distribution of tracer protein throughout the brain from the subarachnoid space. *Brain Research* **326**, 47–63.

ROGGENDORF, W. & CERVÓS-NAVARRO, J. (1977). Ultrastructure of arterioles in the cat brain. *Cell and Tissue Research* **178**, 495–515.

ROGGENDORF, W., CERVÓS-NAVARRO, J. & LAZARO-LACALLE, M. (1978). Ultrastructure of venules in the cat brain. *Cell and Tissue Research* **192**, 461–474.

SZENTISTVANYI, I., PATLAK, C. S., ELLIS, R. A. & CSERR, H. F. (1984). Drainage of interstitial fluid from different regions of the rat brain. *American Journal of Physiology* **246**, F835–F844.

WEED, L. H. (1923). The absorption of cerebrospinal fluid into the venous system. *American Journal of Anatomy* **31**, 191–221.

WOOLLAM, D. H. M. & MILLEN, J. W. (1955). The perivascular spaces of the mammalian central nervous system and their relation to the perineuronal and subarachnoid spaces. *Journal of Anatomy* **89**, 193–200.

ZERVAS, N. T., LISZCZAK, T. M., MAYBERG, M. R. & BLACK, P. MCL. (1982). Cerebrospinal fluid may nourish cerebral vessels through pathways in the adventitia that may be analogous to systemic vasa vasorum. *Journal of Neurosurgery* **56**, 475–481.