Proceedings of the Indiana Academy of Science
(1997) Volume 106 p. 161-173

SCANNING AND TRANSMISSION ELECTRON MICROSCOPIC STUDY OF THE ARACHNOID VILLI IN SQUIRREL MONKEY IN RELATION TO CEREBROSPINAL FLUID ABSORPTION

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ABSTRACT: The surface features and fine structure of arachnoid villi were examined using scanning (SEM) and transmission electron microscopy (TEM). With SEM, the endothelium of the superior sagittal sinus was seen extending over the surface of the villi as a continuous layer of endothelial cells that exhibited folds and crypts. The bulging luminal surface of the endothelial cells displayed slender processes, short microvilli, and pores of various sizes. Using TEM, the uninterrupted endothelial cells displayed slender interdigitating cytoplasmic processes that were joined by desmosomes. The cytoplasm of the endothelial cells contained numerous micropinocytotic vesicles and giant vacuoles. The giant vacuoles communicated with basal pinocytotic vesicles and surface pores, apparently creating transcellular channels in the endothelium. The endothelial covering separated the subendothelial space from the venous sinus. The cores contained arachnoid cells, fibroblasts, macrophages, and a network of anastomosing channels. The slender, overlapping cytoplasmic processes of the arachnoid cells lined the channels. The villi were devoid of endothelium-lined tubes and blood vessels. The shallow endothelial crypts seen in some villi were closed off from the subendothelial space by desmosomes. The villi were innervated by myelinated axons. The ultrastructural features of the arachnoid villi of the squirrel monkey revealed by this study are consistent with their function of CSF absorption by transcellular bulk flow and streaming through the surface pores into the dural venous sinuses.

KEYWORDS: Arachnoid cells, channels, desmosomes, endothelial cells, giant vacuoles, pores, vesicles.

INTRODUCTION

The arachnoid villi, or granulations, are small, blunt herniations of the arachnoid membrane which project into the cerebral veins and dural sinuses through small deficiencies in the dura mater. The villi play an essential role in the drainage and absorption of cerebrospinal fluid (CSF) into the venous sinuses. However, the mechanism by which CSF is transported across the villi into the venous blood is unclear.

The histology of the arachnoid villi was described by Weed (1914), Welch and Friedman (1960), Turner (1961), Millen and Woolam (1962), Jayatilaka (1965a), and Potts, *et al.* (1972). A number of ultrastructural studies were carried out on the arachnoid villi of various mammals (Jayatilaka, 1965b; Alksne

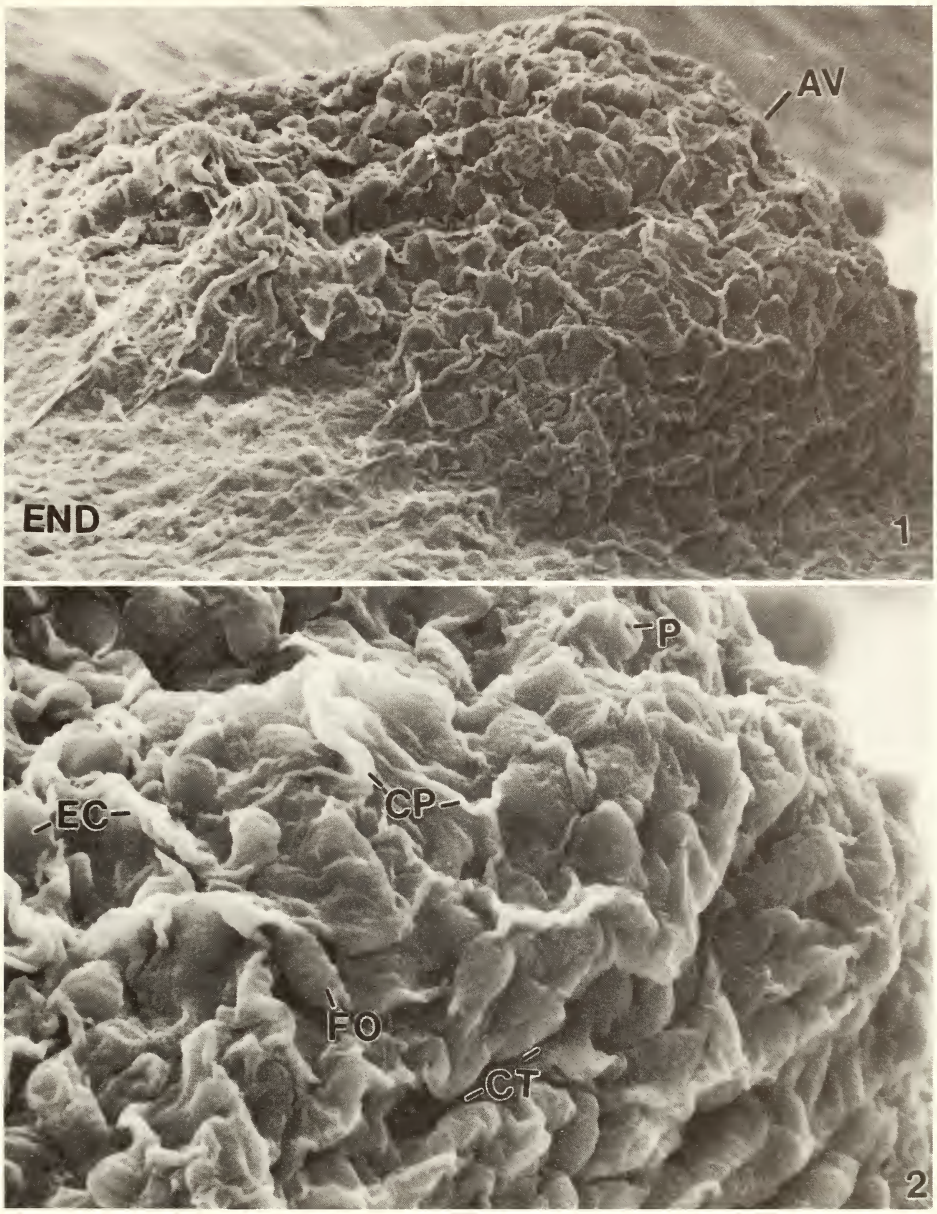
and White, 1965; Shabo and Maxwell, 1968a, b; Alksne and Lovings, 1972a, b; Gomez, *et al.,* 1973; Gomez and Potts, 1974; Gomez, *et al.,* 1974; Peters, *et al.,* 1976; Tripathi, 1973). These studies demonstrated that the arachnoid villi were invested by endothelial cells, that internally the villi were composed of arachnoid tissue and collagen bundles, and that the villi were traversed by a labyrinth of intercellular channels which communicated with the subarachnoid space around the brain. Some investigators asserted that the endothelium of the dural venous sinuses that invested the villi was continuous and joined by tight junctions, supporting Weed's (1923) "closed" system hypothesis which implied that CSF absorption took place across the endothelial covering of the arachnoid villi (Shabo and Maxwell, 1968a, b; Alksne and Lovings, 1972a, b). Other researchers showed that the villus core contained tubular channels lined by endothelium which was continuous with the lining of the dural sinuses, allowing direct flow of CSF from the subarachnoid space into the venous sinuses. Thus, an "open" system was proposed (Welch and Friedman, 1960; Welch and Pollay, 1961; Jayatilaka, 1965a, b; Hayes, *et al.,* 1971; Potts, *et al.,* 1972; Gomez and Potts, 1974; Gomez, *et al.,* 1974). Furthermore, Tripathi (1973) and Tripathi and Tripathi (1974) demonstrated that the giant vacuoles formed within the endothelial lining of monkey arachnoid villi allowed movement of CSF into the venous system by bulk flow.

Kida, *et al.* (1988) reported that the entire luminal surface of human arachnoid villi was invested by endothelial cells. However, other investigators showed that only a small portion of the human arachnoid villus is covered by endothelium, the rest is mainly invested with a layer of arachnoid cells (Upton and Weller, 1985; Yamashima, 1986). Studies by d'Avella, *et al.* (1980, 1983) on human arachnoid villi revealed the presence of giant intracellular vacuoles, pinocytotic vesicles, and large gaps between them in the endothelial cells, supporting both the "closed" and "open" mechanisms of CSF absorption. However, Upton and Weller (1985) did not observe any pores in the endothelium covering human arachnoid villi.

Thus, the mechanism of CSF absorption through the arachnoid villi into the venous sinuses still remains controversial. The aim of the present study is to elucidate the surface features and fine structure of the arachnoid villi in squirrel monkey and to relate them to the mechanism of CSF absorption.

MATERIALS AND METHODS

The squirrel monkey, *Saimiri sciureus*, used in the present study was obtained from the monkey colony maintained at the Yerkes Regional Primate Research Center, Emory University, Atlanta, Georgia. A normal adult squirrel monkey was anesthetized at the Histochemical Laboratory at the Yerkes Primate Research Center using an appropriate dose of sodium nembutal given intraperitoneally and was perfused with 2.5% glutaraldehyde in 0.1M phosphate buffer at pH 7.4 for 30 minutes. After craniotomy, twelve arachnoid villi were excised from the inner wall of the superior sagittal sinus under a dissecting microscope and



Figures 1 and 2. **Figure 1.** A scanning electron micrograph (SEM) of an arachnoid villus (AV) projecting into the lumen of the superior sagittal sinus. Note the continuity of the endothelial lining (END) of the sinus with that of the villus (675X). **Figure 2.** An SEM of the same villus shown in Figure 1 (1,500X). Note the somewhat rounded profiles of the endothelial cells (EC) with cytoplasmic processes (CP), crypts (CT), folds (FO), and pores (P).

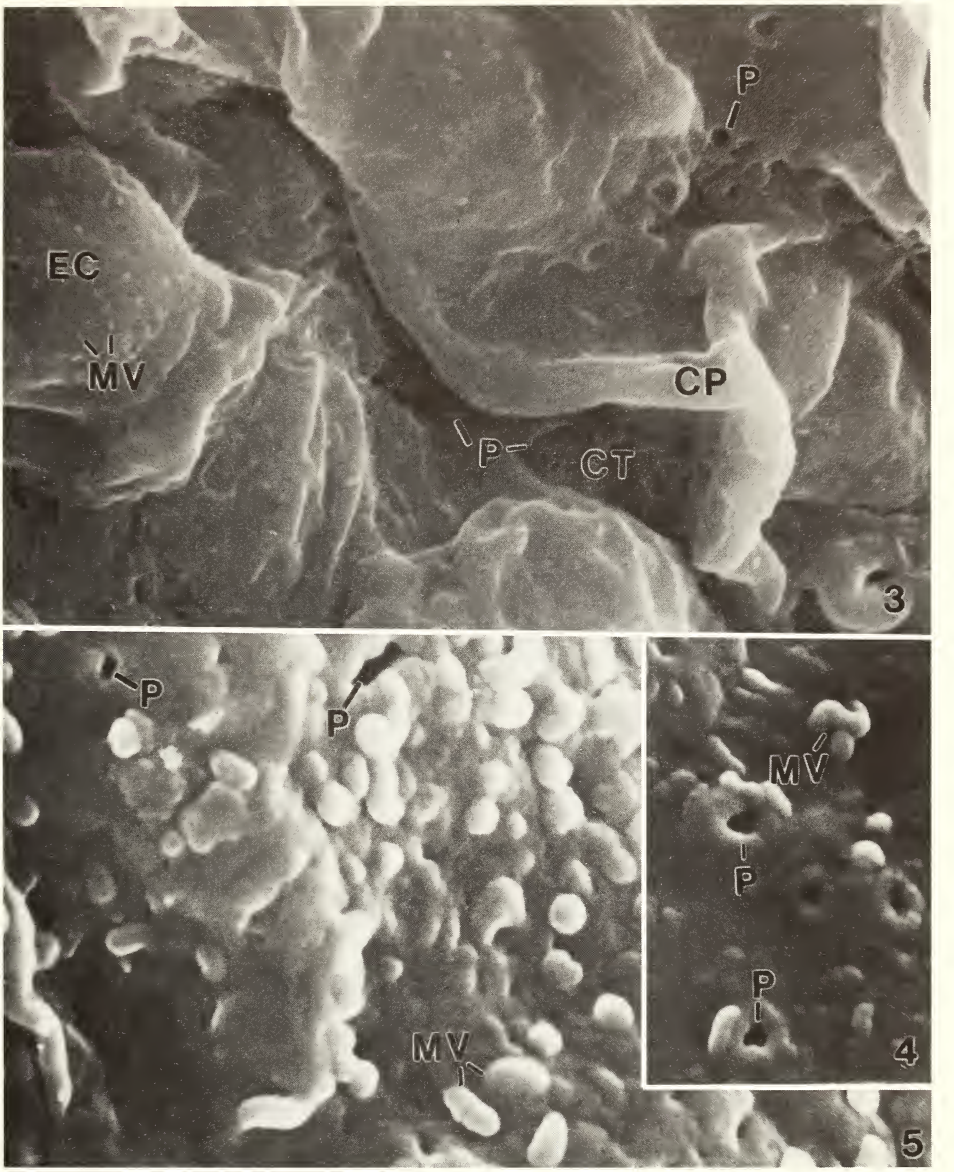
fixed in fresh 2.5% glutaraldehyde in 0.1M phosphate buffer (pH 7.4) for two hours at room temperature. The samples were rinsed in phosphate buffer and post-fixed in 1% osmium tetroxide in the same buffer. The material was dehydrated in an ethanol series, transferred to propylene oxide, and embedded in Epon 812 (Luft, 1961). Polymerization was carried out overnight at 60° C. The sections were cut on a Porter-Blum MT_{-2} ultramicrotome, stained with uranyl acetate and lead citrate, and examined with an RCA-3C and a Hitachi HU-11A transmission electron microscope (TEM). Similarly fixed material was dried using the liquid CO_2 critical point method, coated with gold/palladium, and examined in an ETEC autoscan scanning electron microscope (SEM). Two (2) μm thick sections were cut using glass knives, stained with azure II, and examined under a light microscope (LM).

RESULTS

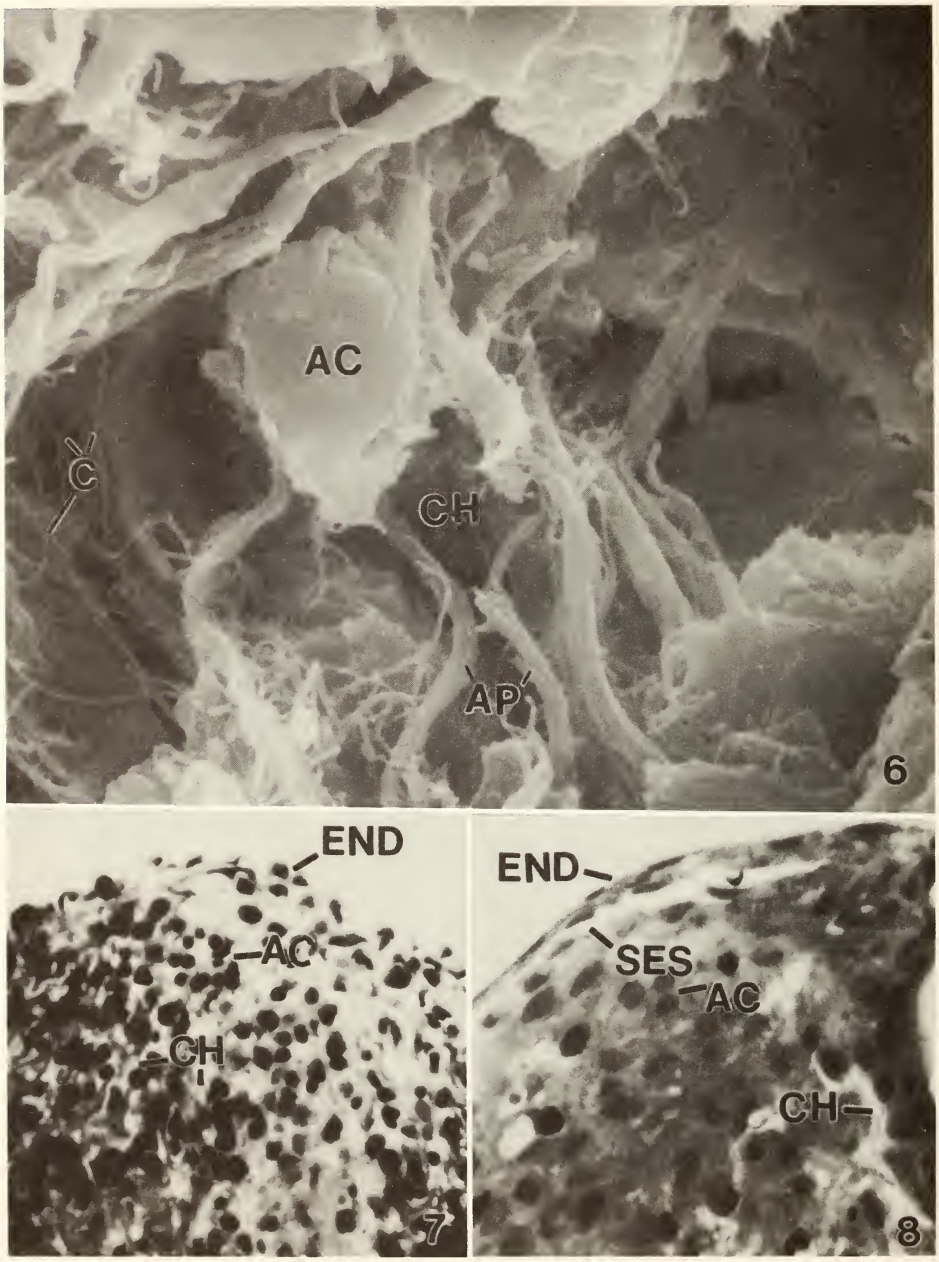
Scanning Electron Microscopy. After opening the dorsal wall of the superior sagittal sinus, many arachnoid villi measuring 125-200 μm in diameter were seen protruding into the sinus lumen. A panoramic view of the inner wall of the sinus revealed that the intact endothelial lining of the superior sagittal sinus extended over the villi to form their endothelial covering (Figure 1). The endothelial covering displayed folds and crypts. The endothelial cells appeared somewhat rounded in contour, possibly due to the presence of underlying giant vacuoles and/or nuclei (Figure 2). The cells had slender cytoplasmic processes and displayed short, club-shaped microvilli on their luminal surface (Figures 3-5). A prominent surface feature of the endothelial cells was the presence of pores measuring about 0.4 μm in diameter with somewhat thickened margins. More pores were found at the attenuated periphery than in the central region of the endothelial cells (Figures 3-5). Longitudinal sections through the middle of the villi revealed that the central core contained arachnoid cells with stout cytoplasmic processes and channels containing collagen bundles (Figure 6).

Light and Transmission Electron Microscopy. In semi-thin sections, the arachnoid villi were composed of a continuous, thin endothelial covering and an underlying core of arachnoid cells and interconnecting channels (Figures 7 and 8). The arachnoid villi were devoid of blood vessels, and they lacked the endothelium-lined tubes which have been reported in the arachnoid villi of other animals (Figures 7 and 8: Jayatilaka, 1965a; Potts, *et al.,* 1972). A pictorial summary of the general organization of the arachnoid villi of the squirrel monkey as revealed by electron microscopy is presented in Figure 9.

Transmission electron micrographs of the arachnoid villi revealed that their continuous endothelial covering was composed of fusiform endothelial cells displaying short microvilli on their luminal surface. The cells were separated from the underlying core by a subendothelial space (Figure 10). The central core of a villus contained loosely packed arachnoid cells, fibroblasts, macrophages, and bundles of collagen. The core was traversed by a network of channels (0.6-1.5 μm in width) that were in continuity with the subendothelial space



Figures 3-5. **Figure 3.** An SEM of the luminal surface of a villus showing endothelial cells (EC) displaying microvilli (MV) and cytoplasmic processes (CP). The pores (P) are seen in the crypt (CT) and at the attenuated periphery of the endothelial cells (6,800X). **Figures 4 and 5.** Scanning micrographs of the luminal surface of endothelial cells showing microvilli (MV) and pores (P) of different sizes. Note the pores with thick margins in Figure 4 (14,000X). Note the club-shaped microvilli in Figure 5 (19,000X).



Figures 6-8. **Figure 6.** An SEM of the interior surface of a villus sectioned through the middle. Note the presence of channels (CH) lined by arachnoid cells (AC) and their stout cell processes (AP) containing collagen (C) fibrils (4,500X). **Figure 7.** Light photomicrograph (LM) of a longitudinal section through an arachnoid villus showing the core containing arachnoid cells (AC) as well as channels (CH) and covered by the endothelium (END) (380X). **Figure 8.** A LM of a longitudinal section through a villus showing its endothelial cap (END) separated by a subendothelial space (SES) from the core containing arachnoid cells (AC) and channels (CH) (600X).

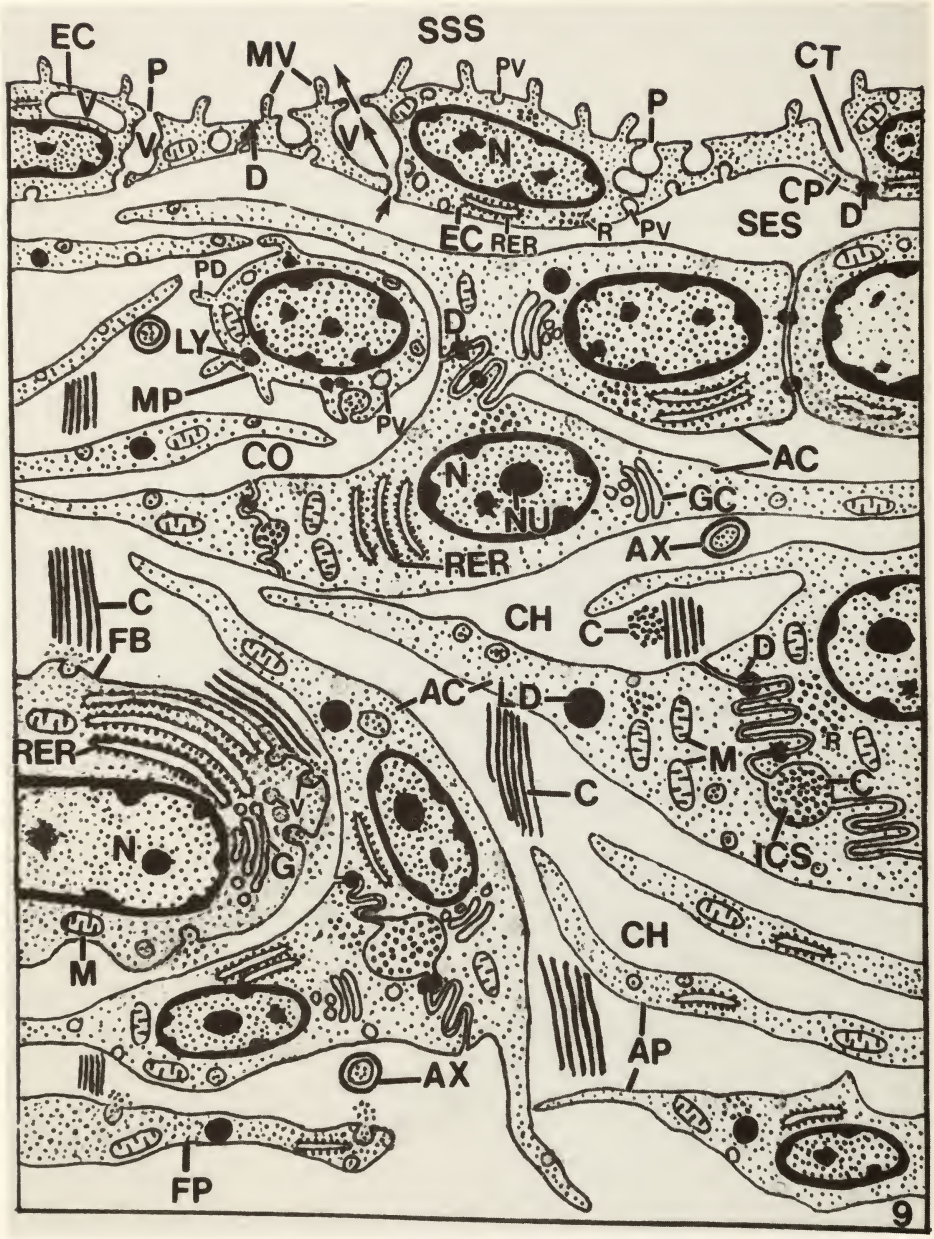
(Figures 9 and 10). In addition, the core contained fine myelinated fibers in close proximity to the arachnoid cells (Figure 10, inset). The slender interdigitating cytoplasmic processes of the endothelial cells were joined by desmosomes (Figure 11, inset). The shallow crypts occasionally seen between the endothelial cells did not open into the subendothelial sinus (Figures 11 and 12). The endothelial cells had flattened nuclei and giant vacuoles (0.4 μm in diameter), rough endoplasmic reticulum, ribosomes, and mitochondria in the cytoplasm. Numerous micropinocytotic vesicles were observed in the basal and apical cytoplasm of the endothelial cells as well as surrounding and fusing with the giant cytoplasmic vacuoles (Figures 9-13). The luminal surface of the endothelial cells displayed pores (0.27 μm in diameter) which opened into the sinus lumen. The pores communicated with the giant cytoplasmic vacuoles and their joint alignment apparently created transcellular channels (Figures 12 and 13). The pores seen in TEM appeared smaller than those seen in SEM.

The arachnoid cells were the predominant cells in the core of the villi. They were irregularly shaped and had ovoid nuclei containing clumps of chromatin located both beneath the nuclear membrane and dispersed in the nucleoplasm. The arachnoid cells contained many mitochondria, rough endoplasmic reticulum, and vesicles in their cytoplasm, but Golgi complexes were rare. The arachnoid cells had long, overlapping cytoplasmic processes that were often joined by desmosomes. The cytoplasmic processes lined the channels and often enclosed rounded intercellular spaces filled with collagen bundles (Figures 9, 14, and 15). Similar spaces in the rat arachnoid matter were described as "extracellular tunnels" by Peters, *et al.* (1976).

In addition to the arachnoid cells, fibroblasts and macrophages were also found in the core of the villi. The fibroblasts displayed vesicles fusing with the plasma membrane, apparently releasing their product by exocytosis near the cell surface for assembly into collagen fibrils in the channels and intercellular spaces (Figure 15). The macrophages were globular in shape and exhibited blunt pseudopodia at the surface. They had large, occasionally indented, nuclei, and their cytoplasm contained mitochondria, vesicles, vacuoles, and lysosomes (Figure 16). Endothelium-lined tubes and blood vessels were absent in the arachnoid villi of the squirrel monkey.

DISCUSSION

Most researchers believe that the arachnoid villi/granulations are responsible for transporting cerebrospinal fluid (CSF) from the subarachnoid space into the venous blood (Weed, 1914; d'Avilla, *et al.,* 1983; Takahashi, *et al.,* 1993). In the present study, the arachnoid villi of the squirrel monkey were shown to have a continuous covering of endothelial cells that had many pores on their luminal surface. The pores seen in SEM appeared to be larger in diameter than those seen in TEM. The apparent difference in pore size might be related to the size of the vacuoles with which they communicated. The giant vacuoles in the cytoplasm of the endothelial cells resembled those described in monkey by



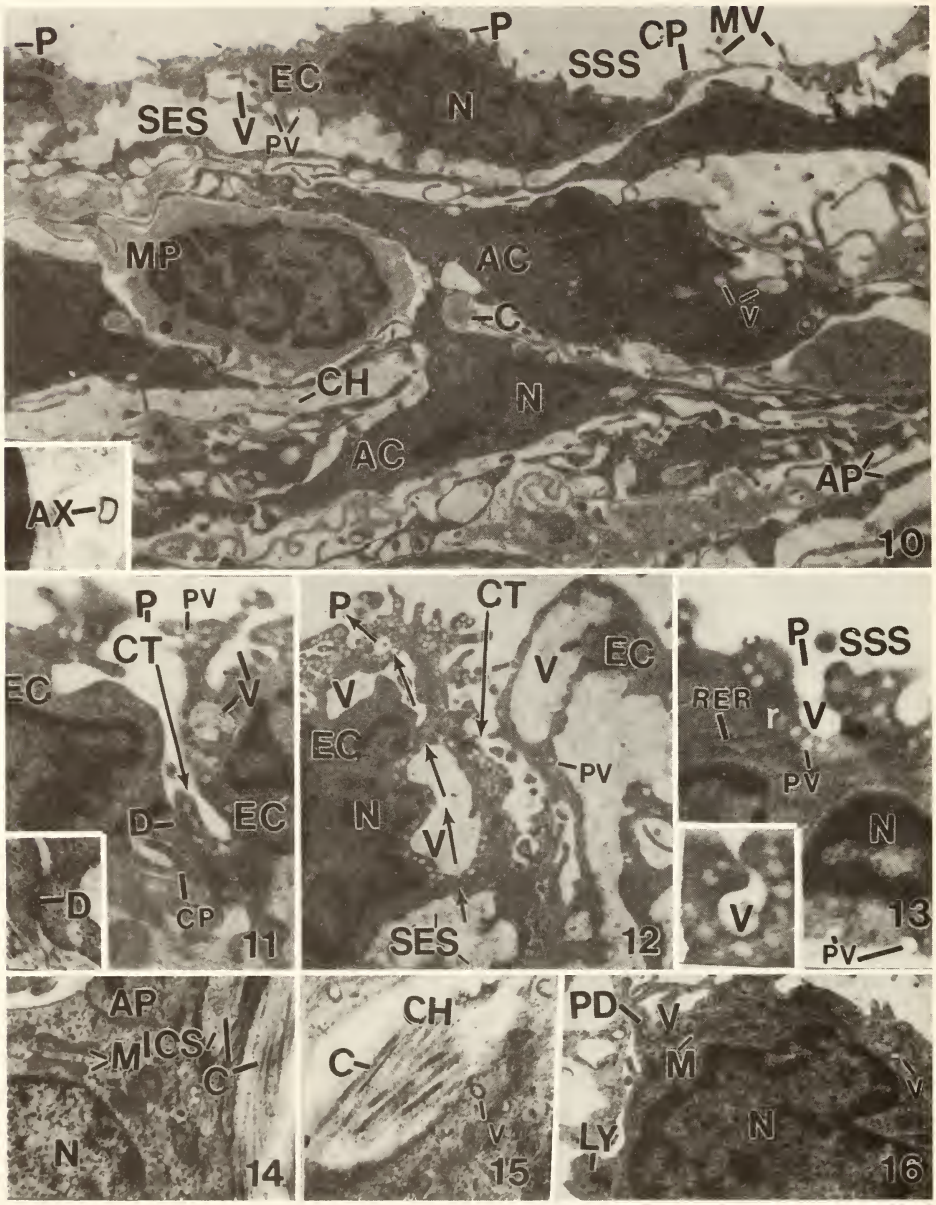
Tripathi (1973) and Takahashi, *et al.* (1993). The presence of micropinocytotic vesicles near and apparently fusing with the giant vacuoles suggests that the vesicles coalesce to form and/or increase the size of the giant vacuoles. The giant vacuoles align and coalesce with the apical pores and basal micropinocytotic vesicles, apparently creating transcellular channels through the endothelial cells. The presence of transcellular channels in the endothelial covering of the arachnoid villi strongly suggests that open intracellular communication occurs between the subarachnoid space and the venous sinus into which the villi project.

Figure 9. A pictorial summary of the basic ultrastructural features of an arachnoid villus of the squirrel monkey. A continuous layer of endothelial cells (EC) bearing microvilli (MV) covers the core of the villus. The fusiform endothelial cells have elongated nuclei (N) and slender cytoplasmic processes (CP) joined by desmosomes (D). The endothelial cells display micropinocytotic vesicles (PV) on both basal and apical surfaces and have giant vacuoles (V) in the cytoplasm which open on the apical surface through pores (P). Shallow crypts (CT) are found between the endothelial cells. The core of the villus contains arachnoid cells (AC) with long cytoplasmic processes (AP), fibroblasts (FB), macrophages (MP) with pseudopodia (PD), bundles of collagen (C), and a network of anastomosing channels (CH). The arachnoid cell processes (AP) are united by desmosomes (D) and enclose rounded intercellular spaces (ICS) containing collagen. The arrows indicate the direction of transcellular outflow of CSF from the subendothelial space (SES) into the lumen of the superior sagittal sinus (SSS). Myelinated axons (AX) are found in association with the arachnoid cells. (FP = fibroblast cell process; GC = Golgi complex; LD = lipid droplet; LY = lysosome; M = mitochondria; R = ribosomes; and RER = rough endoplasmic reticulum.)

A subendothelial space was present which resembled the structure reported in the arachnoid villi of the Macaque monkey (Shabo and Maxwell, 1968a, b). The network of anastomosing extracellar channels in the core of the villi apparently allows CSF to pass from the subarachnoid space into the subendothelial sinus. Alksne and Lovings (1972b) demonstrated in dogs that after injection of blood into the subarachnoid space, intact erythrocytes accumulated and degenerated in the channels but did not pass through the endothelium into the venous sinus. Also, in human arachnoid villi affected by subarachnoid hemorrhage, intact erythrocytes were found in the core channels (Upton and Weller, 1985; Yamashima, 1986). These observations confirm that the core channels are continuous with the subarachnoid space. Thus, the channels function as a pathway for CSF drainage.

The fact that the cytoplasmic processes of the endothelial cells, including those located at the bottom of shallow endothelial crypts, were joined by desmosomes strongly suggests that no intercellular openings exist in the endothelial covering of the arachnoid villi of the squirrel monkey. This conclusion is supported by the observation that the endothelial covering of the dog arachnoid villi remained intact but became thinner with increased intracranial pressure (Alksne and White, 1965).

The endothelium-lined tubes that have been reported in the arachnoid granulations of other mammals (Jayatilaka, 1965a, b; Hayes, *et al.,* 1971; Potts, *et al.,* 1972; Gomez and Potts, 1974; Gomez, *et al.,* 1974) were absent in the arachnoid villi of the squirrel monkey. These endothelium-lined tubes might represent long, narrow endothelial crypts which subdivide the relatively large arachnoid granulations into small arachnoid villi. Based on this view, the large arachnoid granulations merely represent clusters of small arachnoid villi which are the actual functioning units that drain CSF from the subarachnoid space into the venous system. This conclusion is supported by morphological evidence that



the endothelium-lined tubes are found only in the largest arachnoid granulations of calves (Hayes, *et al.*, 1971).

This study supports the mechanism of vacuolar transport proposed by Tripathi (1973) and Tripathi and Tripathi (1974). Based on their mechanism, the giant vacuoles formed within the endothelial cells of the villus transport CSF from their basal to their apical side into the lumen of the venous sinus. This form of CSF absorption along with its protein constituents across the endothelial cells depends upon a mechanism of bulk flow which is believed to combine features

Figures 10-16. **Figure 10.** A transmission electron micrograph (TEM) of a transverse section through the villus showing a continuous layer of fusiform endothelial cells (EC) with slender cytoplasmic processes (CP). Note the anastomosing channels (CH) lined by arachnoid cells (AC), the cytoplasmic processes (AP) of the arachnoid cells, and collagen bundles (C) in the core (8,500X). (MV = microvilli; MP = macrophage; N = nucleus; P = pores; PV = micropinocytotic vesicles; SES = subendothelial spaces; SSS = superior sagittal sinus; and V = giant vacuole.) The inset shows an axon (AX) near an arachnoid cell (18,000X). **Figure 11.** An endothelial crypt (CT) between two endothelial cells (EC) is closed off by a desmosome (D) from the subendothelial space (11,500X). (P = pore; PV = micropinocytotic vesicles; and V = vacuoles.) The inset shows a desmosome (D) uniting the endothelial cell processes (37,000X). **Figure 12.** A TEM displaying endothelial cells (EC) containing giant vacuoles (V) and numerous micropinocytotic vesicles (PV). (CT = endothelial crypt; N = nucleus; P = pore; SES = subendothelial space.) The arrows indicate outflow of CSF from the subendothelial space (SES) into the sinus lumen through the pores (9,000X). **Figure 13.** A portion of an endothelial cell showing micropinocytotic vesicles (PV) in the basal and apical cytoplasm. The vesicles are seen surrounding and some opening into giant vacuoles (V) which, in turn, open through pores (P) into the lumen of the superior sagittal sinus (SSS). Note the ribosomes (r) and the rough endoplasmic reticulum (RER) in the cytoplasm (35,000X). (N = nucleus.) The inset shows a giant vacuole (V) opening into the sinus lumen through a narrow pore (51,000X). **Figure 14.** A portion of an arachnoid cell displaying cytoplasmic processes (AP) that enclose an intercellular space (ICS) containing collagen fibrils (C). (M = mitochondria and N = nucleus.) (10,000X). **Figure 15.** A portion of a fibroblast showing a smooth vesicle (v) in contact with the plasma membrane and collagen (C) fibrils in the channel (CH). (22,000X.) **Figure 16.** Part of an active macrophage in the villus core displaying pseudopodia (PD), mitochondria (M), lysosomes (LY), and nucleus (N). (8,300X).

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of both the "closed" and "open" systems (Tripathi and Tripathi, 1974; Kendel, *et al.,* 1991; Fishman, 1992). That bulk flow is a pressure-dependent process is supported by the observation that, with CSF hypotension, the giant vacuoles involved in this process are not formed in the endothelial covering of monkey arachnoid granulations, which also appear smaller in size (Takahashi, *et al.,* 1993). The presence of numerous pinocytotic vesicles at the basal and apical surfaces of the endothelial cells indicated that these cells were also engaged in the passive diffusion of smaller molecules (McComb, 1983).

The central core of the arachnoid villi contained three cell types: arachnoid cells, fibroblasts, and macrophages. The predominant arachnoid cells had long, overlapping cytoplasmic processes often joined by desmosomes which apparently maintained the longitudinal orientation of the core channels to facilitate CSF flow. The fibroblasts displayed ultrastructural features resembling those reported in the arachnoid villi of calves (Hayes, *et al.,* 1971) and humans (Kida, *et al.,* 1988). The fibroblasts apparently synthesize the collagen found in the intercellular spaces and core channels.

The presence of macrophages in the villi indicates that they might be involved in removing and destroying particulate material, such as viruses, bacteria, and dead cells, from the CSF. Furthermore, the macrophages might engulf calcarious material which has been reported to develop in the arachnoid matter with advancing age (Millen and Woolam, 1962). Macrophages have been reported in the subendothelial space of the arachnoid villi of the Macaque monkey (Shabo and Maxwell, 1968b), and their presence has been suggested in human arachnoid granulations (Upton and Weller, 1985).

The present study confirmed the presence of fine, myelinated axons in the arachnoid villi of the squirrel monkey. Innervention of the arachnoid granulations in sheep and monkey had been reported earlier by Jayatilaka (1965b) and von Düring and Andres (1991), respectively. The absence of blood vessels suggests that the nerve fibers reported here are sensory in function.

ACKNOWLEDGMENTS

The author wishes to thank Dr. S.L. Manocha, Yerkes Primate Research Center, Atlanta, Georgia, for providing and anesthetizing the squirrel monkey and for the use of his laboratory facilities. The author also thanks his colleagues Drs. Lee Engstrom and Stuart Walker for their critical reading of the manuscript. Thanks are due to Dr. Larry Ganion for the use of RCA-3C electron microscope. The author is also grateful to Mrs. Beth Verhoestra for technical assistance and to Mrs. Lisa Garrison for her skillful typing of the manuscript. The author is further grateful to the library staff of Ball Memorial Hospital, Muncie, Indiana, for a medline literature search and for obtaining interlibrary loan articles.

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