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LYMPHSPIRATION

THE BRAIN AND THE LYMPHATIC SYSTEM (I) *

M. Földi

Földiklinik, Hinterzarten, Germany

PART ONE: Anatomical Considerations

It has been generally accepted that there are no lymphatic vessels in the brain. Because "tight junctions" characteristic of brain microvessels sharply limit the egress of plasma protein molecules from entering brain tissue (blood-brain barrier or BBB), there is seemingly no need for a lymphatic drainage system. Such reasoning is misleading, however, because 1) impermeability of cerebral blood capillaries to plasma protein is not absolute (1); 2) the circumventricular organs (area postrema, paraphysis, optical recess) are devoid of a BBB; that is, the blood capillaries are fenestrated or permeable; 3) the cerebrospinal fluid (CSF) contains protein albeit in amounts 1/100 of that of plasma or lymph; 4) under pathological conditions (e.g., meningoencephalitis, hemorrhage, external trauma), copious amounts of plasma protein extravasate into the brain substance and need to be removed both from the brain and the CSF. Although scavenger cells (macrophages and microglia) are responsible for clearance of such protein molecules, an alternative lymph-vascular drainage system should be considered.

In a recent edition of Guyton's *Textbook of Physiology* (2) the following statement appears: *"The blood vessels entering the substance of the brain pass first along the surface of the brain and then penetrate inward, carrying a layer of pia mater, the membrane that covers the brain, with them ... The pia is only loosely adherent to the vessels, so that a space, the* perivascular space *exists between it and each vessel. Perivascular spaces follow both the arteries and the veins into the brain as far as the arterioles and venules but not to the capillaries. (Fig. 1)*

The Lymphatic Function of the Perivascular Spaces. As is true elsewhere in the body, a small amount of protein leaks out of the parenchymal capillaries into the interstitial spaces of the brain; and because no true lymphatics are present in brain tissue, this protein leaves the tissue mainly through the perivascular *spaces but partly also by direct diffusion through the pia mater into the subarachnoid spaces (SAS). On reaching the SAS, the protein flows along with the CSF to be absorbed through the arachnoideal villi into the cerebral veins. Therefore, the* perivascular *spaces, in effect, are a modified lymphatic system for the brain.*

In addition to transporting fluid and proteins, the perivascular *spaces also transport extraneous particulate matter from the brain to the SAS. For instance, whenever infection occurs in the brain, dead white blood cells are carried away through the* perivascular *spaces."*

The above description is based on an article by Weed published in 1914 (3). Patek (4) first questioned this classical view after

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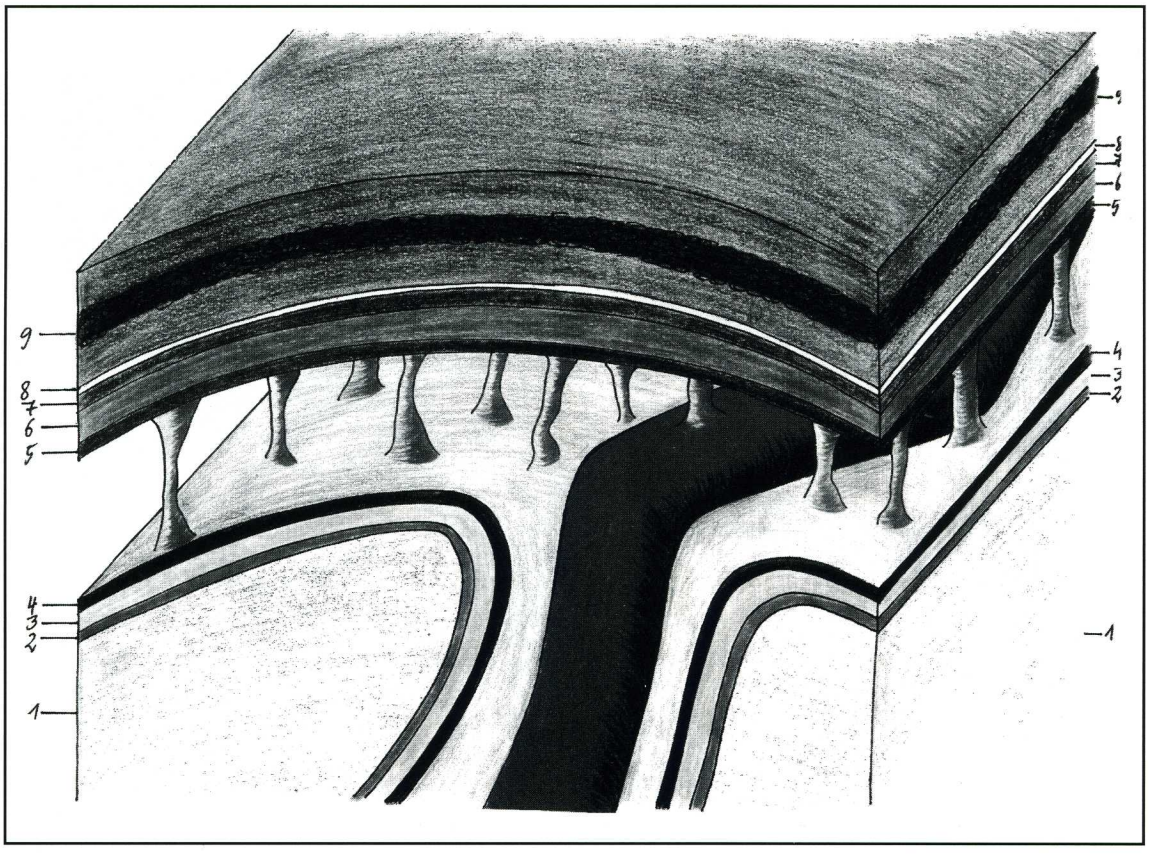

Fig. 1. Classic anatomy in which the subarachnoid space (SAS) accompanies the blood vessels entering/leaving the brain to form the "perivascular" space. 1=brain; 2=membrana limitans gliae; 3=subpial space; 4=pia mater; 5=arachnoid mater; 6=cavum subdurale; 7=dura mater; 8=epidural space; 9=bone.

use of electron microscopy. He described that the pia mater extended along the blood vessels entering and leaving the brain for only a very short distance. Thus, the pia mater did not form the outer layer of the perivascular space; hence the latter was not continuous with the SAS. These findings were confirmed by Hager (5) who also showed that the pia mater did not accompany blood vessels which enter the brain from the SAS. In other words, the perivascular space was not an extension of the SAS or in effect there was no "open neck" of the perivascular space into the surrounding part of the CSF as Bradbury and Cserr (6) surmised in 1985. Hager noted, *"The space around the blood vessel bound internally by the ... basement membrane of the tunica media and externally by the glial basement membrane, is considered the true perivascular space ... it contains constantly adventitial elements"* (5).

A similar description was advanced by Krahn (7) and later by Krisch et al (8). Hutchings and Weller (9) stressed that *"neither the pia mater nor the SAS extends into the brain besides blood vessels"* and that the perivascular space is continuous with the subpial space *(Fig. 2)*. The only region where blood vessels are bathed by CSF is in their intracranial-extracerebral segments. Similar findings were described by Alcolado et al (10). They observed that after subarachnoidal hemorrhage red blood cells did not enter the perivascular space nor did India ink injected

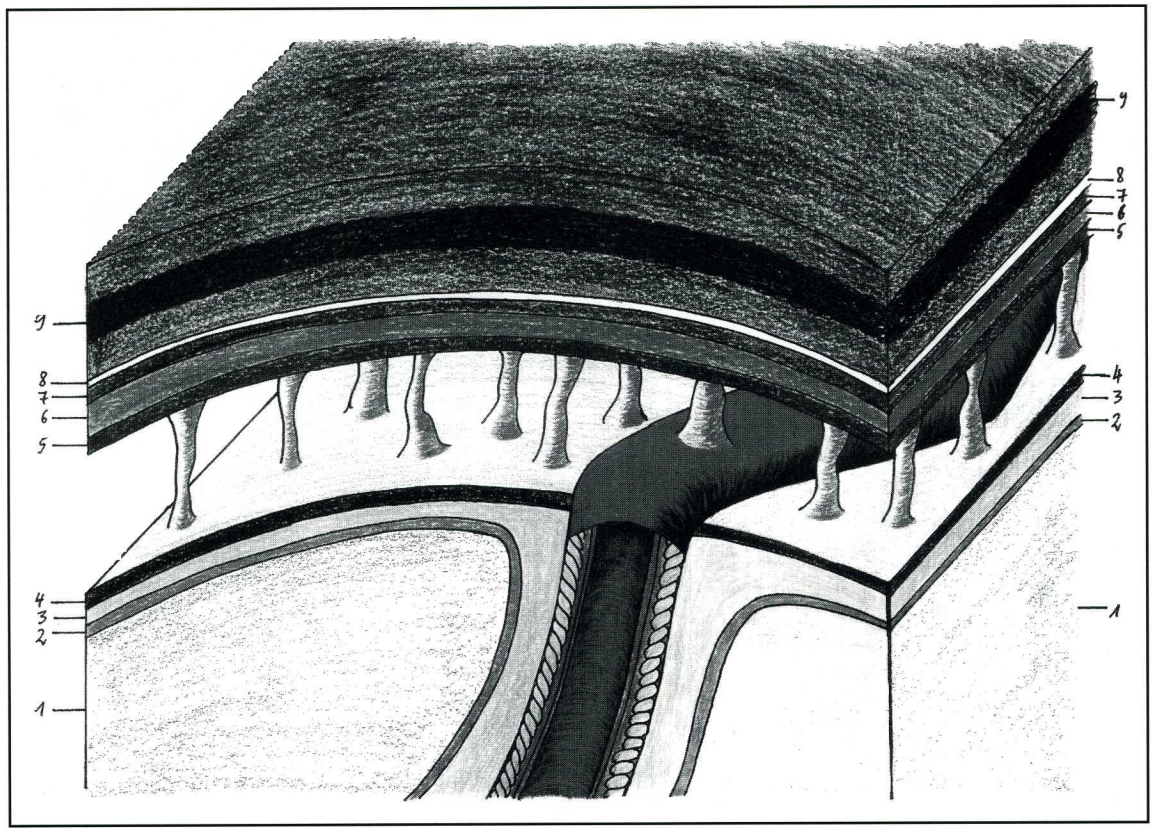

Fig. 2. Modern anatomy in which the subarachnoid space (SAS) does not accompany the blood vessels entering/leaving the brain. Between 2 and 4 lies 3. The bridging spiral structure corresponds to the intraadventitial space.

into the SAS. On the other hand, inflammatory cells were detected in patients with purulent leptomeningitis in the perivascular space and in the contiguous subpial space.

Of pertinent interest are the findings of Zervas et al (11) who showed that the adventitia of the intracranial-extracerebral segments of the blood vessels *"consist(s) of a labyrinthine space occupied by fibroblasts, collagen, ... nerve fibres ... A considerable amount of the adventitia is composed of empty space which is in continuity with the SAS."* This finding was echoed thirteen years earlier by Frederickson and Low (12): *"... The only space associated with the vascular system of the brain is the extension of the tissue space that follows the course of the blood vessels ... The bulk of this space does not differ essentially from the adventitial space of blood vessels elsewhere in the body."* Accordingly, water and macromolecules readily pass from the CSF into the adventitial labyrinthine space and vice-versa.

The Perineurolymphatic Connections Between the SAS and Regional Lymphatics

As far back as 1869, Schwalbe described (13) the appearance of colored markers in the cervical lymph nodes after injection into the SAS and contended that the lymphatic system constituted a major drainage pathway for CSF. Weed, however, in 1914 (3) established the importance of the arachnoid villi as the major site for bulk CSF outflow.

Nonetheless he acknowledged that some of the injected dye migrated into the nasal mucosa, the cranial nerve root sheaths and cervical lymph nodes but he deemed these pathways primarily auxiliary.

Courtice and Simmonds (14) in 1981 corroborated that after radiolabeled albumin was instilled into the SAS, radioactivity was detected in the cervical lymph obtained from the jugular lymph trunk. Yet these authors erroneously concluded as did Weed that lymphatic drainage of protein molecules from the SAS was of minor importance. Four hours after injection of albumin, Courtice and Simmonds detected 5% of the marker in the cervical lymph and concluded that 95% was resorbed via the arachnoid villi, but, in fact only 14% of the radiolabeled albumin was actually detected in the bloodstream. Accordingly, 26% of the radiotracer which had left the SAS had done so via the cervical lymphatics. Potentially, however, the amount of albumin transported by the lymphatics may even have been higher, as an unknown amount of the radiotracer was likely stored in cervical lymph nodes.

In 1963, I suggested (15) that Simmonds (16) misinterpreted other experimental findings. Simmonds observed that after ligation of the jugular lymphatic trunks, the clearance of labeled erythrocytes injected into the SAS was not reduced and concluded that the cervical lymphatics did not play a significant role in the drainage of cellular elements. But bilateral ligation of the main jugular lymphatic trunks alone is insufficient to promote lymph stasis of the head and neck. A truly effective cervical lymphatic blockade requires a radical, extirpative procedure similar to bilateral neck dissections as carried out for the treatment of head and neck cancer.

The anatomical pathways which connect the SAS with the cervical lymphatic system was established by Ivanov (17) who was able to fill the lymphatics of the nasal mucosa with India ink injected into the SAS. Others (18,19) also showed after injection of

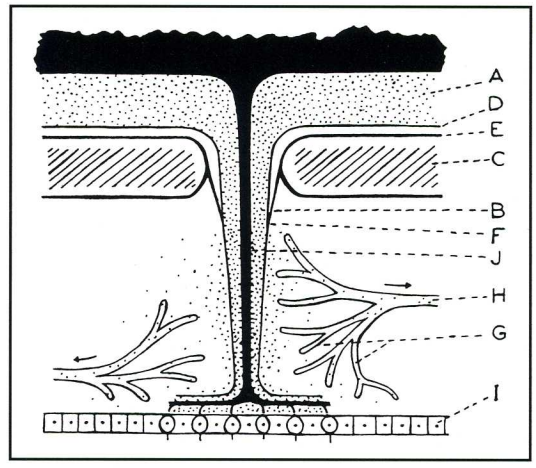

Fig. 3. Schematic diagram of the olfactory pathway for CSF drainage (modified from Brierly and Field; ref. 19). A=subarachnoid space containing India particles ink; B=perineural space. C=cribriform plate; D=arachnoid; E=dura; F=fusion of dura and arachnoid with epineurium; G=lymphatic capillaries; H=lymphatic collecting trunk; I=mucous membrane of nose; J=olfactory nerve bundle.

brominized oil, or thorotrast into the SAS, that these materials could be detected in the nasal region, around the optic nerve and in the cervical lymph nodes. These markers accompanied the periorbital angular vein. As confirmed by Field and Brierly (20,21), the optic nerve, the olfactory bundle, and the spinal nerve roots are apparently covered as is the brain, by an arachnoid sheath, by the pia and the arachnoid mater, carrying with them extensions of the SAS. The pia and the arachnoid fuse, creating a cul-de-sac. Through this leptomeningeal membrane, particles, CSF and macromolecules cross to be reabsorbed by the lymph capillaries situated in the nearby connective tissue. A schematic diagram from their article (Field and Brierly) shows the olfactory bundle covered by the pia, the arachnoid and between these membranes the extensions of the SAS and the lymphatics in the nasal mucosa *(Fig. 3)*. De La Motte (21) has described a similar arrangement with respect to the optic nerve and its sheath. Based on experimental studies in crocodiles, cats and

fowl, von Rautenfeld (personal communication) maintains that the SAS does not extend along the olfactory bundle into the nasal mucosa; that is, the olfactory nerve terminates intracranially and that CSF drains into the endoneurium, then into the perineurium, and finally, gains access to lymphatics of the nasal mucosa.

Grüntzig et al (23,24) instilled radiolabeled colloids into the orbit and documented a lymphatic drainage system. The tracer was found in cervical lymph nodes but the transport time was slow which probably explains why Bradbury and Cserr (6) in acute experiments were unable to detect tracers in the cervical lymph after their injection into the retrobulbar tissues. Arnold also provided evidence that CSF drains via the perilymph across the fenestra rotunda into lymphatics located in the mucosa of the middle ear (25).

Brinker et al has even suggested after several experiments that at least 50% of CSF reabsorption occurs via lymphatics rather than via the arachnoidal villi (26). Leeds et al (27) estimated jugular lymph flow under resting conditions and recorded a notable increase in jugular lymph flow with elevated intracranial pressure after the injection of normal saline into the SAS.

Connections Between the Brain and the Lymphatics

Dubois-Ferriere (28) first described an intraadventitial pathway connecting cerebral blood vessels with the cervical lymphatics after injection of markers into the brain tissue rather than into CSF. Extra precautions were taken to minimize the escape of the injected agents from the brain into the SAS. Thirty years later, Kozma et al examined the anatomical basis of the prelymphatic system in the brain (29) after an injection of thorotrast-India ink mixture into the cortical parietal lobe of cats. When killed 10 hours later, the marker was detected in the basement membrane of cerebral blood capillaries, in the adventitia of intracerebral blood vessels (both in the cortex and in the white matter), in the adventitia of the common carotid artery, in cervical lymphatics, and in cervical lymph nodes. No marker was detected in the SAS. On the other hand, Oehmichen et al (30), studied the drainage pathways of intracerebrally injected carbon, ferritin, gold and erythrocytes and were able to detect these particulates in the CSF and ultimately in the cervical lymph nodes. Casley-Smith et al (31) reported that carbon particles injected into the cerebral cortex of cats and rabbits could be detected in the adventitia of intracerebral arteries including those of the circle of Willis, in the adventitia of the internal carotid artery in the neck, in the vasa vasorum of the cervical lymphatics and in the cervical lymph nodes. The nasal mucosa, however, was only faintly stained.

Similar studies were performed by others (32). Carbon particles injected into the cortex of rats were located in the basement membrane of the cerebral blood capillaries, in the adventitia of cerebellar, basilar and vertebral arteries (both inside and outside the skull), and in cervical lymph nodes. Specifically, carbon particles were not detected in the SAS. Because of limitations using techniques which may create factitious or false passages, our group since 1950 has used an alternative approach, namely to examine the anatomic and pathologic changes after extensive ligation-blockade of regional lymphatics. For example, after blockage of periportal draining hepatic lymphatics there is dilatation of the spaces of Disse, intrahepatic lymph vessels and edema of the hepatic parenchymal cells (33). Another is edema of the arterial wall after surgical ligation of adjacent lymphatics (lymphostatic hemangiopathy) (34,35).

In similar fashion, in order to study the prelymphatic system of the brain, we extensively ligated the cervical lymphatics in rats, rabbits, cats and dogs *(see next article for references)*[Ed.]. We noted lymphostatic hemangiopathy characterized by spaces in the blood vessels of the neck, edema fluid in the adventitia of the intracranial-extracerebral as

well as the intracerebral vessels and those of the neurohypophysis and in the basement membrane of the cerebral blood capillaries. These changes were most noticeable in the blood microvessels of the area postrema, a region with highly permeable fenestrated blood capillaries. Here the basement membrane normally consists of two layers with a gap between them of 0.1-0.5μ. After diffuse cervical lymphatic blockade, these gaps widened 6 to 10 times (i.e., 1 to 3μ). Glial astrocytes with projections in close contact with the membranes of the blood capillaries also became prominently swollen.

Taken together with the findings after injection of markers described earlier, it seems reasonable to conclude that there is a distinct drainage pathway which connects the brain substance with the cervical lymphatics originating with the cerebral interstitial space (CIS), the glial elements and the basement membranes of the intracerebral blood capillaries. These in turn join the intraadventitial channels of the intracerebral blood vessels and from their direct continuations, traverse the SAS to enter and leave the skull to reach the neck where transport occurs into the lymphatic capillaries of the adventitial vasa vasorum. In the blood vessel segments located in the SAS, the intraadventitial prelymphatic channels apparently freely communicate with the CSF. Zervas et al (11) suggest that CSF entering the adventitial layer nourishes the blood vessel wall. It is conceivable that some of the CSF drains through this hemangiolymphatic pathway to gain access into cervical lymphatics. Reversal of flow, i.e., passage of CSF upwards into the intracerebral-intraadventitial networks, seems unphysiologic but rarely may occur if markers are injected under pressure into the SAS. It is also noteworthy that after subcutaneous injection, colloidal radiotracers are detected in tubular spaces located in the adventitia of blood vessels (36) suggesting that the adventitial layer is a universal prelymphatic pathway. The view that the hemangiolymphatic pathway is the principal means by which the brain is connected to the cervical lymphatics is also shared by Krisch et al (8).

There is, however, a notable discrepancy between this view and that held by Bradbury et al and others (37-39). These workers injected radiolabeled albumin into the brain and estimated the subsequent radioactivity in the arteries of the circle of Willis, in the extracranial carotid artery, in the CSF and in the cervical lymph nodes. Radioactivity was highest in the arteries of the circle of Willis, less so in the CSF, and lowest in the extracranial carotid artery. Radioactivity was consistently greater, however, in the lymph nodes on the side of the injection compared to the contralateral lymph nodes. No such lateralization occurred if the radiolabeled albumin was injected into the SAS. According to Bradbury and Cserr, tracers injected into the brain travel within the perivascular spaces and from there into the SAS and finally via the leptomeningeal pathways which are also primarily responsible for the drainage of CSF. But McComb (40) has pointed out that the higher concentration of labeled albumin in the cervical lymph nodes on the same side as the brain injection and the greater concentration of labeled albumin in the cervical lymph nodes after brain injection compared with after injection into the SAS favors a direct prelymphatic pathway from the brain substance to the cervical lymphatics.

If the tracer injected into the brain drains into the SAS, its concentration throughout the CSF should rapidly be equilibrated in part based on physical principles (second law of thermodynamics) and in part due to the fact that in mammals the CSF undergoes a complete turnover every 200 minutes. In other words, CSF is not stagnant and its "streaming" facilitates mixing of the tracer with the CSF, which perhaps explains why the concentration of the radiotracer was lower in the cervical segment of the blood vessels than in those of the circle of Willis. Thus, in the neck, vasa lymphatica vasorum

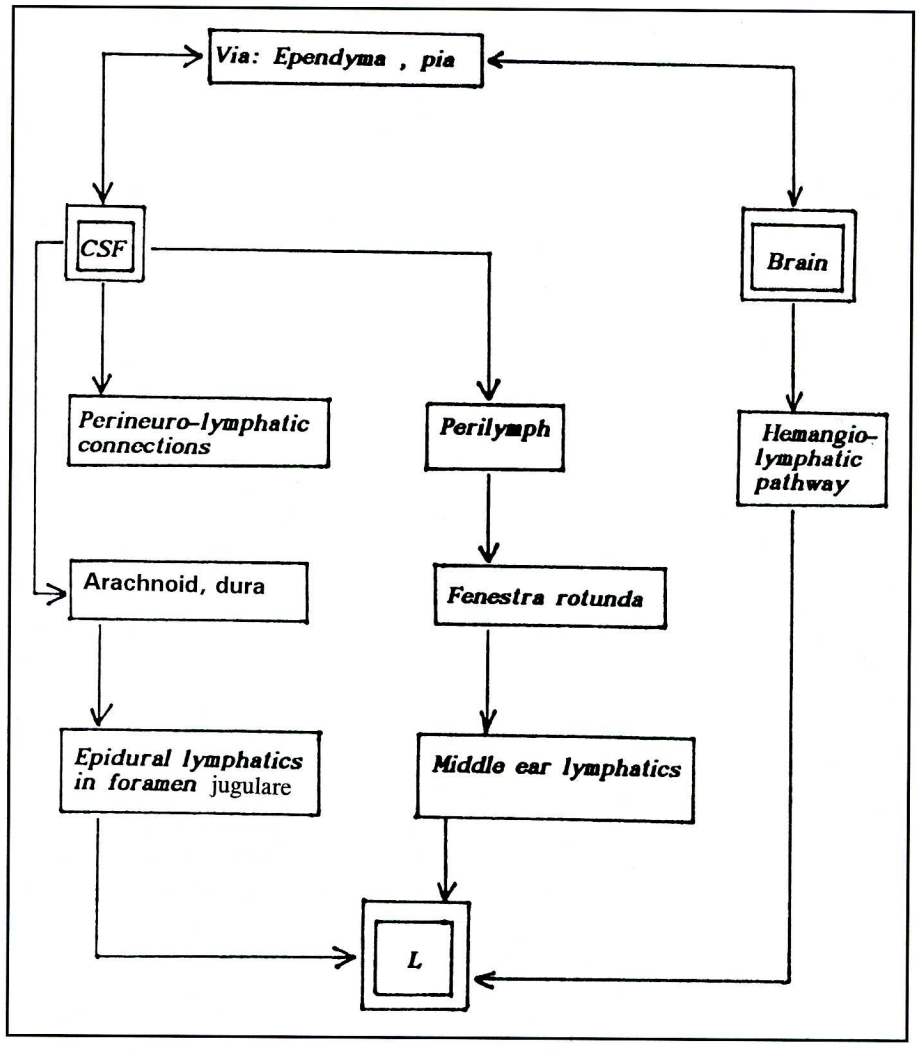

Fig. 4. Schematic diagram demonstrating the connections between the cerebrospinal fluid (CSF), the brain or cerebral interstitial fluid (CIF), and the lymphatics (L).

"suck" the tracer from the perilymphatic intraadventitial channels.

The terms "perivascular" and "intravascular" ("intraadventitital") spaces (channels), are potentially confusing. The Latin term "peri" means "around." If one removes blood vessels from the brain, as Bradbury et al did, ([the arteries] "were dissected from the brain with fine scissors") (41), and estimates the concentration of the tracer in the wall, it is inaccurate to describe the tracer as located in a perivascular space. More properly the space is "intravascular" or "intraadventitial." Another source of potential misunderstanding originates in the "classical" description of Weed to which Guyton and Bradbury and Cserr adhere, whereby blood vessels entering the brain carry with them an extension of the SAS, an anatomical viewpoint which is no longer valid. It also seems prudent to discontinue use of the term Virchow-Robin space (42), a structural concept derived from light microscopy.

As for the hemangiolymphatic, intraadventitial prelymphatic pathways, it is important to stress that this drainage system is devoid of intraluminal valves; hence, retrograde flow may occasionally occur. Grüntzig

et al (24) after unilateral injection of markers into the retrobulbar space detected them not only in the cervical lymph nodes but also in both optic nerves and in the contralateral orbit. It is possible, but improbable, that some materials that leave the intraadventitial prelymphatic space gain access to the subpial space which directly connects with the perineural space where the nerves leave the brain to be reabsorbed into the bloodstream by the leptomeningeal connections.

Under pathologic conditions (e.g., seizures) which disrupt the BBB, protein and cerebral breakdown products of the CIS drain into the intraadventitial prelymphatic pathways (43). After death from poliomyelitis, encephalitis and multiple sclerosis, cerebral debris and exudate can be seen to accumulate in the intraadventitial spaces (44,45).

Whereas this discussion has largely been limited to the cerebral aspects of the central nervous system, connections between the spinal cord and the lymphatic system have also been described (17,46).

The revised drainage pathways of the brain, the CIF, the CSF and that of the blood vessel wall are summarized in *Fig. 4*.

CONCLUSION

Whereas no true lymphatic vessels exist in brain substance, there are lymphatics in the dura mater, the foramen jugulare, the pituitary capsule, the orbit, the nasal mucosa, the middle ear and the adventitia of cervical blood vessels. The principal pathway which connects the brain and the cerebral blood circulation, which contributes even under physiologic conditions some macromolecules and other lymph-like material to the interstitium, and which eventually gains access to the lymphatic system is termed the "hemangiolymphatic" pathway. CSF, on the other hand, is primarily drained by the perineural lymphatic system.

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Prof. Prof. h.c. Michael Földi, M.D.
Földiklinik GmbH & Co. KG
Rößlehofweg 2-6
79856Hinterzarten, GERMANY