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COMMENTARY

THE BRAIN AND THE LYMPHATIC SYSTEM REVISITED

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Weller and his associates published in 1998 two important papers (1,2) on brain and fluid dynamics in which they agree with the concept I first put forward with my colleagues in 1968 (3-5), and later in 1976 (6), again in 1978 (7) and most recently rereviewed in *Lymphology* in 1996 (8,9). It is odd, however, that Weller et al fail to mention our contributions and instead cite the previous work of Cserr et al and Bradbury (10,11). To set the record straight, I cite the following starting with an article by Bradbury and Cserr published in 1985 (12).

"Földi and colleagues propose a[n] ... extensive system of interconnecting channels surrounding cerebral vessels of all sizes, including large vessels in the subarachnoid space... These channels, termed collectively "prelymphatics"[1] are held to *drain eventually via the adventitia of the internal carotid arteries and jugular veins into true lymphatics in the neck* [italics added]. These conclusions are based on observations of these perivascular channels following either ligation and/or removal of the cervical lymphatics or injection of Pelikan ink into the cerebral cortex.

Our results support Földi's concept of perivascular channels as pathways of flow ... ; however, they do not indicate an extension of these channels to the extracranial carotids and jugulars. This work ... has been largely ignored by recent workers. *Our analyses of the pathways of flow ... support Földi's concept of perivascular channels as pathways of flow through the subarachnoid space; on the other hand, they do not indicate an extension of these channels to the extracranial carotids and jugulars"* [italics added] (12).

This latter reservation emanates from observations by these workers, "After brain injection of Evans-blue labeled albumin, the coloration in the perivascular space of the

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[1]The term "prelymphatic system" has been coined by Földi et al: "A preformed connective tissue gap system [such pathways are called "paralymphatic" (Ottaviani) and "prelymphatic" (Földi)] realizes the transport mechanism from blood capilaries and tissue cells to the lymphatic system. Since the intra-adventitial gap system of cerebral and cervical blood vessels is switched on just before the system of cervical lymphatics, we are of the opinion that Virchow-Robin spaces belong to the prelymphatic system" (4).

In this paper [Bradbury and Cserr], we have emphasized that "it was not the aim of this study to settle the question whether the outermost layer of the cerebral arteries is adventitia consisting of a connecting tissue proper, or rather a tissue of leptomeningeal origin. The question, whether blood vessels entering the brain lose their original adventitial layer (to be displaced by a leptomeningeal tissue) or not, is a question of primary importance from the point of organo-genesis and embryology, yet it is unimportant for the present question" (12).

Weller and associates write (2) that "there is firm evidence ... for drainage of interstitial fluid from the brain to cervical lymph nodes along periarterial spaces"; and, moreover, they have found *"fluid drainage pathways in the advenatitia"* [italics added] (2).

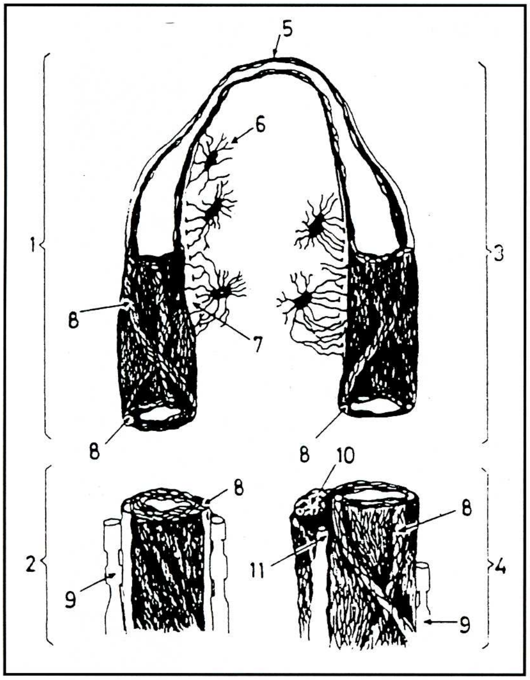

Fig. 1. This figure has been published in the paper "Effect of the Disturbance of Cervical Lymph Drainage (Lymphostatic Encephalopathy) upon the EEG and Cerebral Functions" written by F. Obál, I. Madarász, Ö.T. Zoltán, E. Csanda, and M. Földi, published in Recent Developments of Neurobiology in Hungary 4 (1973), 215-265. It can be seen that it describes the prelymphatic-lymphatic drainage pathways of cerebral interstitial fluid exactly in the same way as Weller (1) (see Fig. 2). 1. Cerebral artery; 2. cervical artery; 3. cerebral vein; 4. cervical vein; 5. cerebral blood capillary; 6. perivascular glia; 7. perivascular space; 8. intra-adventitial (Virchow-Robin) space; 9. lymph vessels; 10. perivascular connective tissue containing lymph vessels; 11. a single layer of connective tissue fibers separating intra-adventitial space from lymph vessel.

intracranial carotid artery stopped abruptly at the point where the artery passed from the bone into the cranial cavity" (13).

Bradbury and Cserr (12) maintain that cerebral interstitial fluid (ISF) extravasates from the "perivascular," intraadventitial channels into the subarachnoidal space and speculate that from the cerebrospinal fluid, ISL can either be *absorbed across the arachnoid villi into blood or be returned indirectly to blood via the lymphatic system.* [italics added] ... The pathway of flow includes passage from the subarachnoid space of the olfactory lobes through the cribriform plate into the submucous space of the nose. From here it is picked up by lymphatics, which finally enter the large retropharyngeal lymph nodes and drain into the jugular lymph trunks" (12).

In sharp contrast to the view of Bradbury and Cserr but in accordance with what we described 17 years earlier (3-5), Weller et al state in 1998 (2), "In the human cerebral cortex, periarterial spaces ... are encompassed on their outer aspects by a layer of pia mater and on the inner aspects by collagen of the arterial adventitia..., periarterial spaces contain perivascular cells which are the resident histiocytes in the drainage pathways; these cells are activated in the dilated perivascular spaces in edematous peritumoral brain in association with the drainage of edema fluid along such pathways ... Such channels are difficult to detect in normal brain as they are collapsed but they are seen in their expanded state when the underlying cortex is edematous[2] or when inflammatory cells have invaded the periarterial channels. With increasing caliber of vessel, periarterial compartments around cerebral arteries contain more and more substantial amount of collagen. *This collagen-rich perivascular compartment can be traced through the base of the skull, alongside the internal carotid artery to the neck, thus forming a potential channel for the drainage of interstitial fluid from the brain to deep cervical lymph nodes in man* [italics added] [Djuanda, Kelsey and Well, in preparation as cited by Weller et al (1)]." Compare *Figs. 1-3.*

[2]Our group had expanded these "prelymphatic" channels by surgically occluding the cervical lymphatics. This effect is the most convincing evidence that these channels constitute a pathway for cerebral interstitial fluid to be absorbed — together with normal and pathologic protein molecules, cells, and tracer-markers by the cervical lymphatics (3-5).

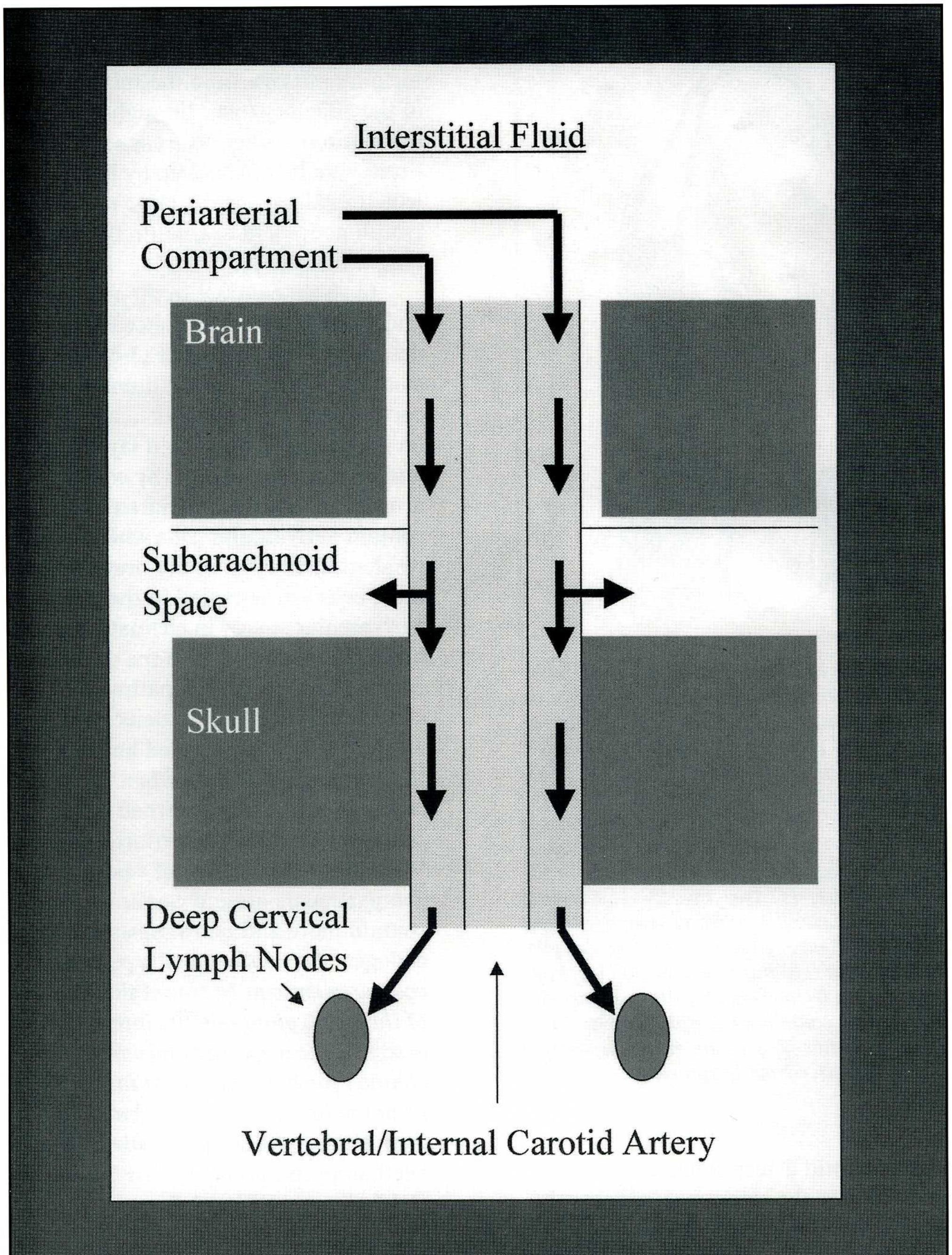

Fig. 2. Redrawn from the paper of Weller (1). The drainage of cerebral interstitial fluid through periarterial/ intraadventitial prelymphatic channels into the vasa lymphatica vasorum of the cervical arteries and from these into the cervical lymphatics. This description corresponds to that of Földi et al in 1968 (3-5). Concerning the functional significance of the Virchow-Robin spaces, it is unimportant whether they are situated around the blood vessels, as Weller describes them or in their adventitia; what only matters is that they function as prelymphatic channels. Because extracranially no "perivascular compartment" exists around the vertebral and the internal carotid arteries, the prelymphatic channels can only be situated in the adventitia!

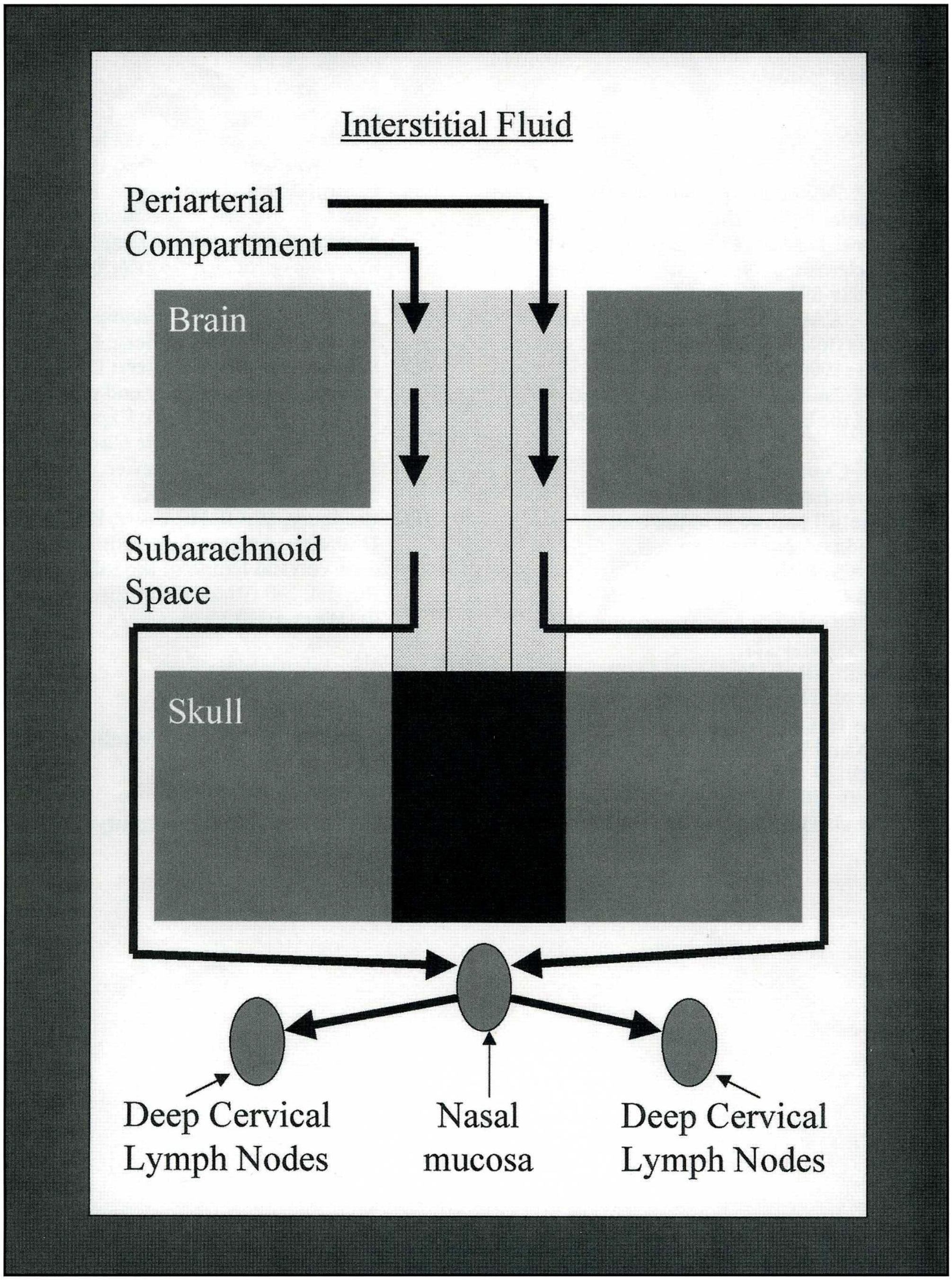

Fig. 3. According to Bradbury and Cserr (12), the cerebral interstitial fluid which trickles into the "perivascular" channels empties into the subarachnoid space to reach the cervical lymph vascular system via the cribriform plate and the submucous space of the nose.

I look forward to seeing how the paper of Djuanda et al deals with the data previously published by our group.

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