

# **Reassessing Cerebrospinal Fluid (CSF) Hydrodynamics**

## **A Literature Review Presenting a Novel Hypothesis for CSF Physiology**

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### **Abstract**

The traditional model of cerebrospinal fluid (CSF) hydrodynamics is being increasingly challenged in view of recent scientific evidences. The established model presumes that CSF is primarily produced in the choroid plexuses (CP), then flows from the ventricles to the subarachnoid spaces, and is mainly reabsorbed into arachnoid villi (AV). This model is seemingly based on faulty research and misinterpretations. This literature review presents numerous evidence for a new hypothesis of CSF physiology, namely, CSF is produced and reabsorbed throughout the entire CSF-Interstitial fluid (IF) functional unit. IF and CSF are mainly formed and reabsorbed across the walls of CNS blood capillaries. CP, AV and lymphatics become minor sites for CSF hydrodynamics. The lymphatics may play a more significant role in CSF absorption when CSF-IF pressure increases. The consequences of this complete reformulation of CSF hydrodynamics may influence applications in research, publications, including osteopathic manual treatments.

### **Keywords**

Arachnoid; Cerebrospinal fluid; Cerebrospinal fluid hydrodynamics; Cerebrospinal fluid physiology; Choroid plexus; Classical hypothesis of cerebrospinal fluid physiology; Osteopathy; Osteopathy in the cranial field;

## **List of abbreviations**

- AV: arachnoid villi  
AVG: arachnoid villi granulations  
CM: cisterna magna  
CNS: central nervous system  
CP: choroid plexus(es)  
CSF: cerebrospinal fluid  
IF: interstitial fluid  
SAS: subarachnoid space

- **Introduction**

This article describes some of the new concepts and hypotheses concerning cerebrospinal fluid (CSF) hydrodynamics. In the traditional hypothesis it is commonly accepted that the CSF is mainly secreted from the choroid plexuses (CP) of the brain ventricles, then flows inside the ventricular cavities to reach the subarachnoid spaces, and then is mainly reabsorbed into venous sinuses across arachnoid villi. A large number of publications from experiments showed there is little convincing “*in vivo*” evidence to support the classical model.<sup>1-23</sup> This traditional model is being increasingly challenged, in view of recent scientific evidence.

- **Cerebrospinal fluid secretion: traditional and non-traditional hypotheses**

- ***Choroid plexuses and ventricular ependyma***

### **The classical model**

Research on cerebrospinal fluid started almost a century ago.<sup>24-26</sup> The classical model describes a continuous production of CSF from the plasma of the CP vasculature. This view was established by the experiments of Dandy in 1919 who performed unilateral choroid plexectomy in a dog and completed bilateral obstruction of the foramen of Monro.<sup>27-29</sup> The blockage produced a dilation in the ventricle still containing a choroid plexus but not in the one without. Therefore he concluded that the CSF is formed from the choroid plexuses. Further, the dilatation of the ventricle implied that CSF absorption does not occur inside the brain ventricle and the “circulation of CSF” is obstructed if the two foramina of Monro are blocked. These interpretations formed the basis of the traditional hypothesis. It is important to note that this experiment was performed on a single dog and it was never reproduced.<sup>30-32</sup> As a consequence of Dandy’s experiment, surgical choroid plexectomy for hydrocephalus was promoted.<sup>27-29</sup>

Choroid plexuses (CP) are villous structures covered by a single layer of epithelial cells. Scientists worldwide agree with the traditional hypothesis that CSF is produced mainly by the choroid plexuses. There are 2 steps in this process:

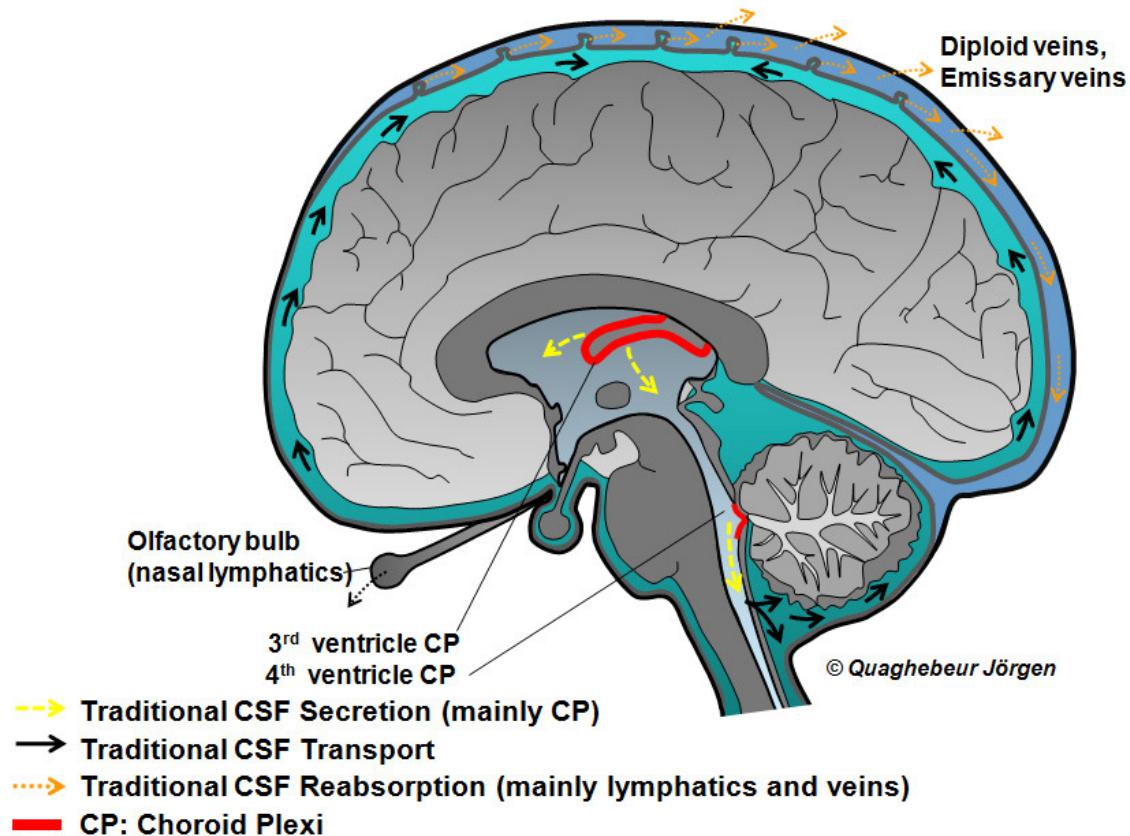


Figure 1: The Traditional Model of Cerebrospinal Fluid (CSF) Hydrodynamics.

A- First, a passive filtration of plasma occurs across fenestrated choroidal capillary endothelium to the basolateral surface of the CP epithelial cells. This phase is facilitated by hydrostatic pressure.<sup>33</sup>

B- Then, an active secretion occurs across a single layer of CP epithelium that is released from the apical side into the ventricular cavity.<sup>34, 35</sup> In this model, hydrostatic or oncotic pressures should not significantly influence active CSF formation. Some authors also describe the ventricular ependyma itself as another source of CSF production.<sup>34, 36-39</sup>

### Data conflicting with the classical model

Dandy's choroid plexectomy for hydrocephalus has been abandoned since results are unsatisfactory. Orešković and Klarica reexamined the CSF formation rate, including the ventriculocisternal perfusion established by Heisey et al., a method still regarded as the most precise one.<sup>11, 40</sup> They showed that the classical ventriculocisternal perfusion method is neither precise nor dependable for measuring CSF formation rate.<sup>7</sup> Contradictory to conventional knowledge Milhorat removed the

choroid plexuses from both lateral ventricles in a human subject and in monkeys and found no significant changes in the volume of CSF secretion nor in CSF composition.<sup>32, 41-44</sup> Even after a total choroid plexectomy the CSF is secreted at the rate of approximately 1 liter per day.<sup>45</sup>

Orešković, Klarica, et al. reproduced many experiments addressing CSF physiology taking great care not to replicate previous experimental errors. The results hold in question our traditional models of CSF.

They inserted a cannula with stopcock, (modified from Flexner and Winters) for the occlusion and drainage in cats aqueduct of Sylvius<sup>4, 46, 47</sup> and observed a fluctuation of aqueduct of Sylvius CSF.<sup>4, 14-16, 18</sup> For 120-190 minutes following aqueductal occlusion they monitored the ventricular size and CSF pressure in cats' ventricles and cisterna magna.

In this experiment an increased ventricular volume and pressure, and the presence of a clear transmantle pressure should be observed, according to the classical model. The transmantle pressure is the difference between the pressure inside the brain ventricles (i.e. lateral ventricles or aqueduct of Sylvius) and the pressure in the subarachnoid spaces (i.e. cisterna magna).

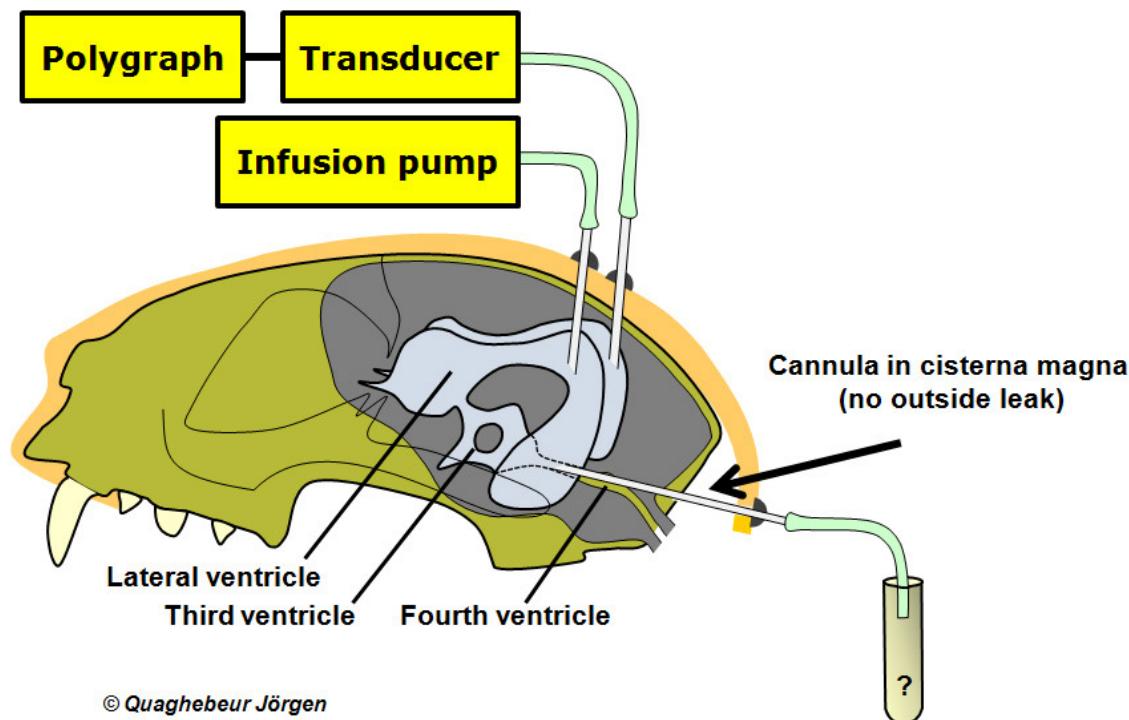


Figure 2: The scheme of the experimental model of Orešković and Klarica to recover CSF from the aqueduct of Sylvius in cats, following aqueductal occlusion. Adapted from Orešković, D., Klarica M., 2010. The formation of cerebrospinal fluid: Nearly a hundred years of interpretations and misinterpretations. *Brain Res. Rev.* 64 (2), 241-262. (Fig. 7 page 11)

However the CSF pressure in the lateral ventricles and cisterna magna of each cat did not differ during 120 min of this experiment. X-ray ventriculography before and two hours after aqueductal occlusion did not confirm ventricular dilatation. In other

words they observed no increase in pressure or dilation of the ventricles with ventriculography, and no transmantle pressure ever developed.<sup>4</sup> These experiments suggested that the CP are not the main location of CSF production.

- ***Capillary Endothelium***

Other experimentation found that the CP are responsible for 60 to 85 percent of the total production of CSF.<sup>35, 48, 49</sup> Some studies have shown that about 15 to 30 percent of CSF is produced from an extrachoroidal origin.<sup>34, 35, 38, 50</sup> Hakim, et al. and Di Chiro suggested that CSF can be formed and reabsorbed everywhere within the CNS.<sup>51-53</sup> The weight of the CP in the lateral, third and fourth ventricles is only two to three grams. Crone and Raichle established that the surface of the brain capillaries is extremely large, 250 cm<sup>2</sup>/g of tissue, which is about 5000 times larger than the surface of the CP.<sup>54, 55</sup> Some experimental models concluded that the CNS capillary endothelium may be an important source of CSF production.<sup>56-59</sup> Research demonstrated that the elevation of intracranial hydrostatic pressure considerably lowers the production of CSF, and vice versa.<sup>10, 13, 46, 60-65</sup> Other experiments showed that the elevation of CSF osmolarity considerably increases the production of CSF, and vice versa.<sup>8</sup> In brain edema, clinicians observe that the injection into the blood stream of an hyperosmolar solution (i.e. mannitol) decreases bulk water flow from brain tissue.<sup>6, 66</sup> These experiments are all contrary to the classical hypothesis from which we expect CSF formation being dependant on active CSF secretion in the CP and passive absorption in the arachnoid villi. According to the experiments of Bulat, Klarica and Orešković, the interstitial fluid (IF), the fluid in the cerebral parenchyma, and CSF, the fluid in the subarachnoid spaces, constitute a functional unit. The volumes of these fluid compartments are mainly regulated by modifications in osmotic and hydrostatic pressure in the capillaries on one side and the IF-CSF unit on the other. They further suggest that the production and reabsorption of CSF mostly takes place within the CNS capillaries.<sup>1, 4, 8, 11, 12</sup>

The fact that the endothelium of CNS capillaries contain Na<sup>+</sup>-H<sup>+</sup> antiporters (for transport of substances across cellular membrane) and the high Na<sup>+</sup>-K<sup>+</sup>-ATPase activity of this endothelium also suggest that brain microvessels play an essential part in CNS fluid volume regulation.<sup>67</sup>

- **Cerebrospinal fluid transport**

The general classical agreement is that the CSF is secreted into the brain ventricles and flows unidirectionally through the ventricular axis (see figure 1). Transchoroidal secretion of water, ions and macromolecules drive CSF down the ventriculo-cisternal axis.<sup>68</sup> Traditionally, secreted CSF flows down the ventricular cavities to the 4<sup>th</sup> ventricle and then out through hindbrain foramina into the cisterna magna and other basal regions of the subarachnoid space.

Orešković, Klarica, et al. used a cannula that permits the flow of CSF unless a stopcock is turned off to occlude the flow. This way an acute occlusion of the aqueduct of Sylvius in cats was performed.<sup>4, 14-16, 18</sup> They monitored CSF flow in the cats' aqueduct of Sylvius, but did not retrieve any CSF via the cannula in the

aqueduct of Sylvius in more than 3 hours! They observed CSF continually pulsating but no liquid was drained during these experiments! These data added to their suspicion of a faulty classical model and made them ask whether CSF really circulated.<sup>14</sup> The same phenomenon (no outflow of CSF) was noticed in control cats at physiological CSF pressure without aqueductal obstruction.<sup>14</sup> At the same time, when they injected artificial/mock CSF at different rates during a 20-min. period into the lateral ventricles, they found that at 13 µl/min infusion, an important transmantle pressure was recorded. Transmantle pressure is the pressure recorded between ventricle and SAS. However, after the infusion of artificial CSF was ended, CSF pressures returned toward physiological values and transmantle pressure returned to normal. This suggests that the absorption of CSF took place in the isolated ventricles.<sup>4</sup> Clinically, patients with communicating and non-communicating hydrocephalus do not exhibit transmantle pressure gradients either.<sup>69, 70</sup>

Bulat, Orešković, Klarica, et al. did other experiments where they slowly infused cats' lateral ventricles with <sup>3</sup>H-water (Tritium). Since approximately 98.5 percent of CSF and IF bulk volume is water, the movement of water will determine most of CSF-IF physiologic activity. They realized that CSF does not flow along CSF spaces but is very rapidly reabsorbed into neighboring brain capillaries. During slow infusion (1.77 µl/min) of <sup>3</sup>H-water into cats' lateral ventricles under normal CSF pressure, CSF concentrations in the cisterna magna and arterial plasma were identical.<sup>2, 71</sup>

Fenstermacher et al. showed that <sup>3</sup>H-water passes across brain ependyma into caudate nucleus only a few mm, being rapidly eliminated into CNS capillaries (half life of 1.5 min).<sup>72</sup> Retrospectively, in the experiment creating an acute occlusion of a cat's aqueduct of Sylvius, the fact that pressure is not modified in isolated ventricles supports the hypothesis that CSF is quickly reabsorbed transventricularly into periventricular capillaries. In contrast, distribution of substances with larger molecular weight into subarachnoid spaces has a completely different outcome. When a marked macromolecule such as <sup>3</sup>H-inulin was injected into the CSF within the subarachnoid space, it was very slowly eliminated into the bloodstream and distributed multidirectionally because of its long elimination time from subarachnoidal spaces. Renkin and Crone observed the distribution of <sup>3</sup>H-inulin from the CM to the cisterna basalis and lumbar cistern, over a 24-hour period.<sup>54, 73</sup>

These kinds of macromolecules have been used in the past to study CSF physiology, which brought numerous misconceptions about CSF circulation and reabsorption. In these earlier experiments, the injection of macromolecules into the ventricular spaces to define circulation of CSF gave the wrong impression that CSF is transported from lateral ventricles to 3<sup>rd</sup> and 4<sup>th</sup> ventricles and then into the cisterna magna and all the subarachnoid spaces.<sup>20-22, 74</sup> In contrast, injection of <sup>3</sup>H-water in any part of the CSF system, can result in multidirectional water distribution including a "retrograde" path into the lateral ventricles<sup>1</sup>.

These results have been confirmed by Iliff, et al., who demonstrated that tracers injected in ventricular spaces or subarachnoid CSF of mice entered the parenchyma of the brain depending on their molecular size,<sup>75</sup> and get transported in a space between the brain capillaries and astrocyte's feet the 'glymphatic system' (gliovascular clearance system). The CSF circulation appears across all blood vessels in and outside the brain within the CNS.

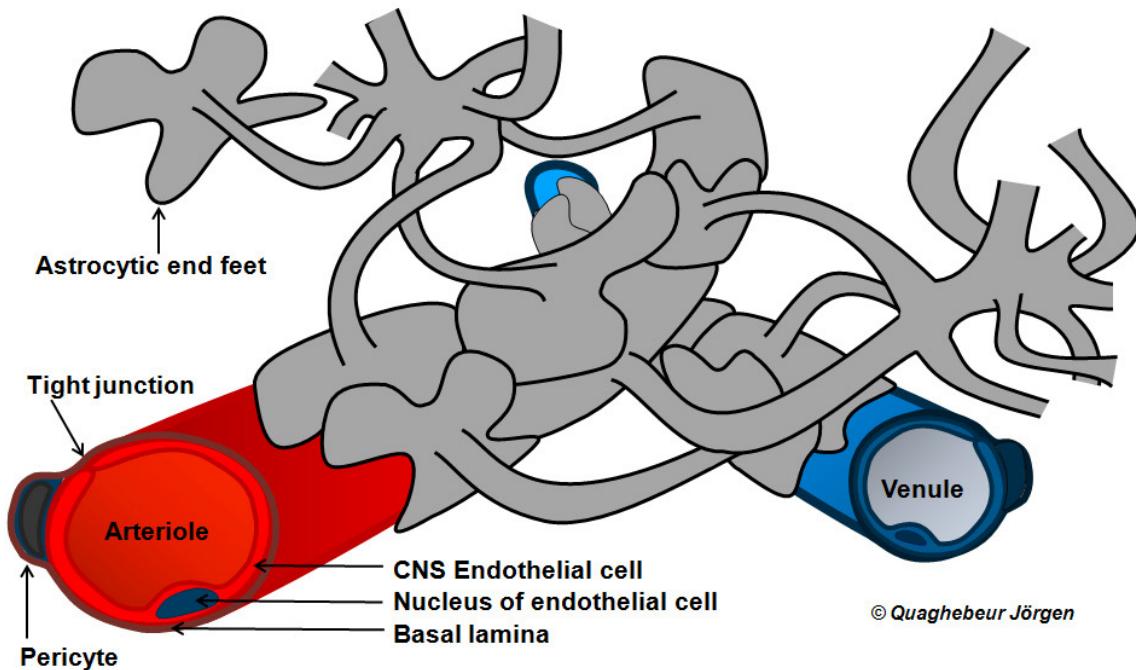


Figure 3: Astrocytic endfeet: they cover approximately 99% of all cerebral capillaries.

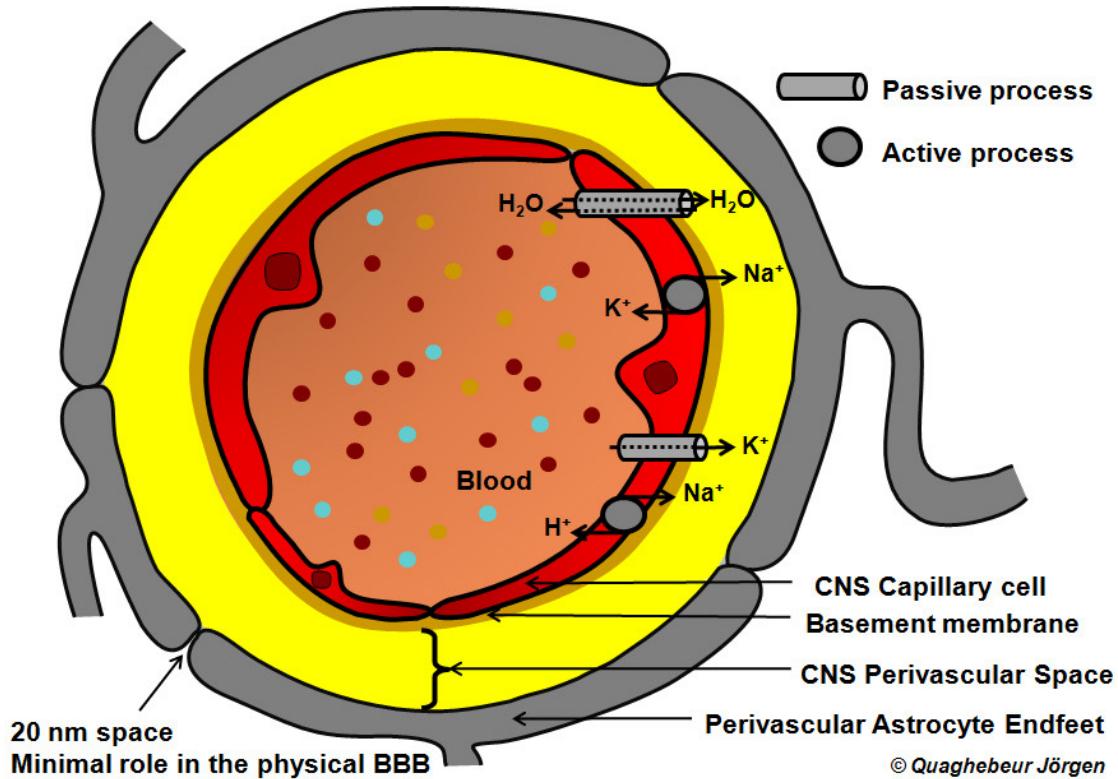


Figure 4: Cross section of a CNS capillary and its perivascular astrocytic endfeet.

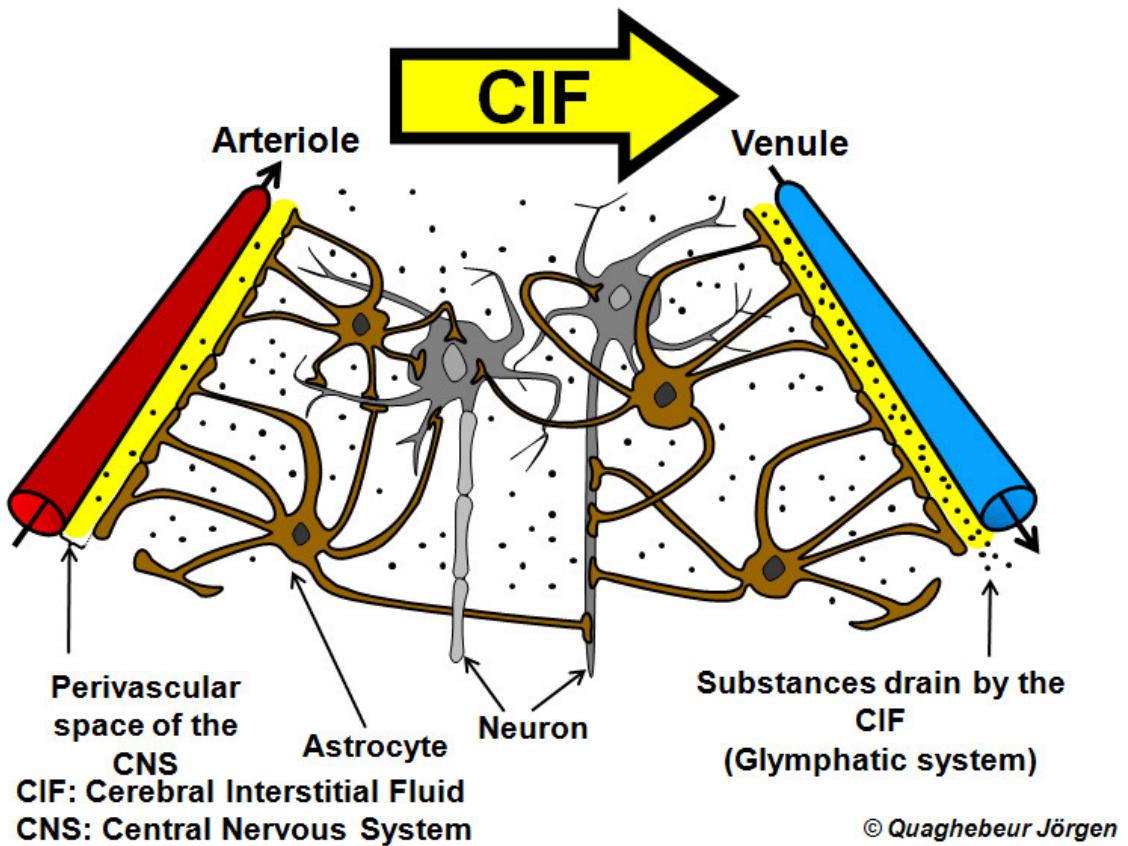


Figure 5: The Glymphatic System (Gliovascular Clearance System) in the CNS: draining from arteriole to venule. Adapted from Iliff, J.J., Wang M., Liao Y., Plogg B.A., Peng W., Gundersen G.A., Benveniste H., Vates G.E., Deane R., Goldman S.A., Nagelhus E.A., Nedergaard M., 2012. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including Amyloid  $\beta$ . Sci. Transl. Med. 4 (147), 147ra111. (Fig. 5, page 7)

- **Cerebrospinal fluid absorption: traditional and non-traditional hypotheses**
  - ***Choroid plexus absorption***

The Choroid Plexi may absorb about 1/10<sup>th</sup> of their own secretion.<sup>76-82</sup> For that reason, the function of these structures has been compared to the proximal renal tubule.

- ***Arachnoid villi: the venous side***

In the 18<sup>th</sup> century Pacchioni described extrusions of the cranial arachnoid membrane that project into the venous sinuses of the dura mater called arachnoid villi. Arachnoid villi are microscopic while arachnoid granulations can be seen with the naked eye. In 1914, Weed showed in a crucial experiment that the arachnoid villi and granulations (AVG) are the major source of CSF absorption.<sup>26</sup> This hypothesis has become firmly established and most investigators still believe reabsorption of CSF is a passive process located mainly in the AVG.<sup>83, 84</sup> The exact means by which CSF transports through the AVG remains controversial, but numerous mechanisms have been suggested. The hypothesis of an open tubular system communicating directly

or indirectly with the AVG has been refuted by Shabo and Maxwell, describing them as the results of histological preparation artefacts.<sup>85</sup> Other described mechanisms include transport via vacuoles, transcellular channels, endothelial cell gaps, and arachnoid cellular phagocytosis or pinocytosis. Recent research seems to show that the AVG, under physiologic conditions are not the locus of most CSF reabsorption, but accessory pathways at best, even though under conditions of elevated CSF pressure AVG may participate modestly in CSF reabsorption.<sup>86</sup> There are a few reasons against the idea that the AVG is a major source of CSF absorption. First of all venous sinuses do not exist in rats until 20 days after birth. The AVG do not appear to exist before birth in sheep as well as in humans. They begin to develop around the time of birth and increase in number with age.<sup>87-90</sup> Furthermore, it is imperative that a mechanism exists to clear CSF in gestation. Extracranial lymphatic vessels play an important role in CSF transport before birth and may represent a better pathway for CSF clearance in the neonate.

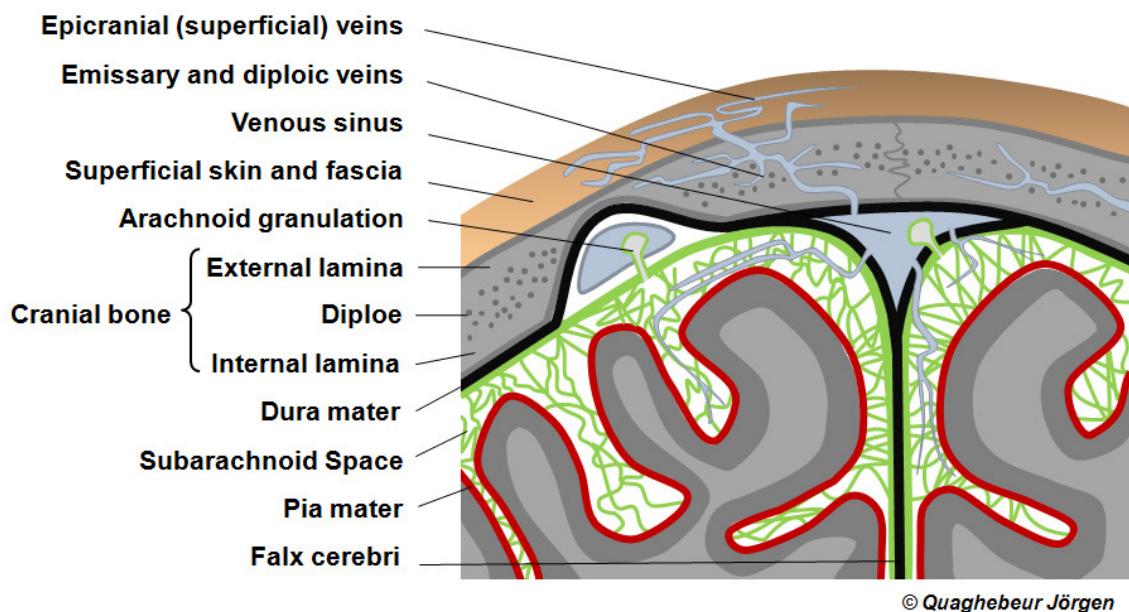


Figure 6: Arachnoid Granulations: CSF Reabsorption, the traditional model.

#### - *The lymphatic side: "perineural pathways"*

To this day no lymphatics have been found in the brain parenchyma, but lymphatic vessels have been noted in the dura mater, the pia mater, the pituitary capsule, the orbit, the nasal mucosa, and the middle ear.<sup>91</sup> Some type of lymphatic-like drainage is necessary to evacuate the small amount of proteins of the central nervous system, which becomes particularly important in cases of edema, haemorrhage or infection.<sup>92, 93</sup> The traditional hypothesis was updated by reviewing a large collection of evidence presenting the lymphatics as the primary site of CSF reabsorption in a previous publication.<sup>90, 94</sup> By injecting Berlin Blue dye into a dog's subarachnoid space in 1869, Schwalbe made the first observation that the lymphatic pathways were the major means to absorb CSF.<sup>80</sup> Later, in 1872, Quincke theorized that the CSF can leave the subarachnoid space through small areas surrounding the nerve roots.<sup>95</sup> In 1875, Key and Retzius were the first to demonstrate the circulation

through the arachnoid granulations into lymphatic vessels in the nasal mucosa, the frontal sinus and along cranial nerves using dye-colored gelatin.<sup>96</sup> More recently this CSF lymphatic absorption hypothesis has been reexamined.<sup>88, 97-99</sup> Boulton et al. demonstrated for example that 48 percent of the protein tracer injected in the lateral ventricles of sheep is transported into extracranial lymphatics.<sup>100, 101</sup> Brinker et al. also showed that at least 50 percent of CSF is reabsorbed through the lymphatics rather than arachnoid villi.<sup>102</sup> Increase in CSF intraventricular pressure will augment the amount of CSF drained by the lymphatics rather than the arachnoid villi.<sup>93, 103-107</sup>

### **Drainage through nasal lymphatics**

The historical experiment of Schwalbe using Berlin blue dye, as well as the work of Weed, showed some quantity of the marker passing along the olfactory bulb, olfactory nerve pathways to the nasal mucosa, the nasal lymphatics and then to the cervical lymphatics.<sup>80, 108, 109</sup> Numerous experiments with different species confirmed the existence of the same pathway.<sup>49, 88, 97, 98, 104, 109-122</sup> At relatively low intracranial pressures, carbon particles and labelled proteins follow the olfactory tracts and pass through the cribriform plate (lamina cribrosa) to the nasal mucosa, the retropharyngeal lymph nodes and to the nodes at the base of the neck. This pathway has been confirmed in humans,<sup>59, 88, 118, 123</sup> and nonhuman primates.<sup>124-127</sup> To demonstrate the importance of lymphatic drainage of CSF, Papaiconomou, et al. sealed the cribriform plate extracranially, which significantly impaired CSF transport.<sup>128</sup>

### **Drainage through other perineural pathways**

Lymphatic drainage has been found in most cranial and spinal nerve pathways including optic nerve pathways<sup>49, 106, 112, 121, 129, 130</sup>; auditory nerve pathways<sup>131</sup>; trigeminal nerves, facial nerves and other cranial nerves<sup>132</sup>; as well as lumbar spinal nerves<sup>133, 134</sup>.

### **Direct dural pathway**

Under high pathological pressure, the CSF can also escape from the arachnoid barrier and be reabsorbed by the lymphatics of the dura mater.<sup>135</sup> In addition, McComb et al. infused cats and rabbits with marked CSF under high pressure. He found the tracer in the olfactory bulbs, optic nerves, and deep cervical lymph nodes, but when it was infused at normal CSF pressure, the tracer was not shown in these structures. This suggests that the lymphatic pathway is a secondary path that can become more important under high CSF pressure.<sup>106, 136</sup>

#### *- Transependymal exchange*

According to the classical model the secretion of CSF is mainly an active process in the choroid plexi. There is a filtration across the endothelial capillary wall a secretion through the choroidal epithelium. Since the second phase of CSF formation is an

active process, the CSF formation rate should not be CSF pressure-dependant, it should not be significantly altered by moderate changes in intracranial pressure.

This is contradictory to various studies showing that CSF secretion decreases as CSF pressure increases and vice-versa.<sup>13, 19, 60, 61, 63, 65</sup>

Orešković, et al. showed that at physiological pressure, CSF formation and absorption are in balance within the isolated brain ventricles.<sup>19</sup> This implies that the CSF is not only transported to the subarachnoid spaces to be reabsorbed mainly into the venous sinuses, but that it is also significantly absorbed inside the ventricles themselves.<sup>1, 2, 19, 30, 56, 77-79, 82, 137, 138</sup>

We previously noted that Bulat, Orešković, Klarica, et al. observed that CSF does not flow along CSF spaces but is rapidly reabsorbed transventricularly into periventricular brain capillaries. Under normal CSF pressure, <sup>3</sup>H-water is reabsorbed into periventricular capillaries and is not delivered to subarachnoid spaces, suggesting that CSF bulk water is absorbed into brain ventricles.<sup>2, 71, 139</sup> Iliif also saw the CSF in the SAS getting reabsorbed by cerebral capillaries (paravascular spaces).<sup>75</sup>

There is no net CSF formation under normal conditions. It seems that CSF is produced and is reabsorbed everywhere in the CSF spaces. The volume of CSF depends on the hydrostatic gradients and osmotic forces present between the blood (capillaries) on one side and the interstitial fluid of brain parenchyma and the CSF on the other.

## Conclusion

From more recent research, there is relatively little convincing, *in vivo* evidence to support the traditional model of the production, circulation, and reabsorption of CSF. The traditional model is seemingly based on faulty research and misinterpretations of that research, and this hypothesis is now increasingly being challenged.

Evidence for the new model presented here is strong and is being more widely adopted by investigators around the world.

The CSF is a filtrate and secretion, produced in active and passive processes.

Interstitial fluid (IF) surrounding the subarachnoid space and CSF form a unit of function that is produced by hydrostatic and oncotic exchange across the endothelial walls of arterial capillaries in the CNS.

Essentially, the volume of CSF depends on the hydrostatic pressure and osmotic force within the CNS between the capillaries on one side and the IF and CSF unit on the other. The future will tell us the exact percentage of choroid plexi/cerebral capillary CSF secretion and lymphatic/venous/CP/capillary endothelium CSF reabsorption. It seems these percentage are now shifting in favour of cerebral capillary endothelium.

The consequences of this reformulation of CSF hydrodynamics will affect research and publications in physiology, medicine and surgery, especially related to the treatment of hydrocephalus and other neurological disorder. This model may also be of interest in the practice of osteopathy in the cranial field.

## **Disclosure Statement**

No competing financial interests exist.

## **Author's contribution**

Both authors contributed equally to this work.

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