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Source / Izvornik: **Progress in Neurobiology, 2011, 94, 238 - 258**

Journal article, Accepted version
Rad u časopisu, Završna verzija rukopisa prihvaćena za objavljivanje (postprint)

https://doi.org/10.1016/j.pneurobio.2011.05.005

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:316287

Development of hydrocephalus and classical hypothesis of cerebrospinal fluid hydrodynamics: facts and illusions

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Keywords: Arachnoid villi, Cerebrospinal fluid, Cerebrospinal fluid hydrodynamics, Cerebrospinal fluid physiology, Choroid plexus, Classical hypothesis of cerebrospinal fluid hydrodynamics, Hydrocephalus

Abbreviations: BV, brain ventricle; CH, communicating hydrocephalus; CNS, central nervous system; CSF, cerebrospinal fluid; CM, cisterna magna; EH, external hydrocephalus; ISF, interstitial fluid; ICP, intracranial pressure; LV, lateral ventricle; SAS, subarachnoid space

Abstract

According to the classical hypothesis of the cerebrospinal fluid (CSF) hydrodynamics, CSF is produced inside the brain ventricles, than it circulates like a slow river toward the cortical subarachnoid space, and finally it is absorbed into the venous sinuses. Some pathological conditions, primarily hydrocephalus, have also been interpreted based on this hypothesis. The development of hydrocephalus is explained as an imbalance between CSF formation and absorption, where more CSF is formed than is absorbed, which results in an abnormal increase in the CSF volume inside the cranial CSF spaces. It is believed that the reason for the imbalance is the obstruction of the CSF pathways between the site of CSF formation and the site of its absorption, which diminishes or prevents CSF outflow from the cranium. In spite of the general acceptance of the classical hypothesis, there are a considerable number of experimental results that do not support such a hypothesis and the generally accepted pathophysiology of hydrocephalus. A recently proposed new working hypothesis suggests that osmotic and hydrostatic forces at the central nervous system microvessels are crucial for the regulation of interstial fluid and CSF volume which constitute a functional unit. Based on that hypothesis, the generally accepted mechanisms of hydrocephalus development are not plausible. Therefore, the recent understanding of the correlation between CSF physiology and the development of hydrocephalus has been thoroughly presented, analyzed and evaluated, and new insights into hydrocephalus etiopathology have been proposed, which are in accordance with the experimental data and the new working hypothesis.

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1. Introduction

Based on current belief and knowledge, only a few physiological and pathological states are so strongly interconnected and affirm each other, as do the classical hypothesis of cerebrospinal fluid (CSF) secretion, circulation and absorption and the development of hydrocephalus. The classical hypothesis of CSF hydrodynamics presents CSF simply and schematically as a slow river which forms inside the brain ventricles, then flows unidirectionally along the CSF system toward the cortical subarachnoid space (SAS), and is then absorbed into the venous sinuses (see later). Nothing has influenced the perception of CSF dynamics and its correlation with the development of hydrocephalus more than Dandy's crucial experiment (1919) on the consequences of choroid plexecotomy in dogs. These findings are still considered relevant and are quoted even today (Rekate, 2009). If the choroid plexus of one lateral ventricle was removed, and if foramina of Monro of both lateral ventricles were obstructed, it was reported that the ventricle containing a choroid plexus would dilate and the ventricle lacking a choroid plexus would collapse. This observation led Dandy to conclude that this is "*the only absolute proof that cerebrospinal fluid is formed from the choroid plexus. At the same time, it is proven that the ependyma lining the ventricles is not concerned in the production of cerebrospinal fluid.*" This experiment still points to a few more facts that are crucial in terms of forming a general hypothesis about CSF hydrodynamics. If the obstructed lateral ventricle containing a choroid plexus dilates, it is obvious that the choroid plexus actively produced (secreted) CSF. It is also obvious that the dilatation of the ventricle is possible only if the CSF absorption does not exist inside the brain ventricle. If CSF is absorbed outside the brain ventricles, it should flow (circulate) to the place of its absorption. If the CSF system is obstructed between the place of CSF secretion and the place of its absorption (foramina of Monro), the brain ventricles should, because of the continuity of CSF secretion by the choroid plexuses (CSF pumps), dilate and produce hydrocephalus. In other words, the classical hypothesis of CSF hydrodynamics was founded, and the development of hydrocephalus was

explained with this experiment. At the same time, the postulated hypothesis offers a very reasonable explanation of hydrocephalus development, and the existence of hydrocephalus proves the authenticity of the classical hypothesis. Since that time, one has confirmed the other, and it is nearly impossible to research and discuss these two subjects separately. Therefore, until today this correlation persists with minor modifications in the same way as it did in Dandy's time.

Can we, after nearly a hundred years, still say that this is scientifically sustainable?

Recently, a new hypothesis regarding CSF hydrodynamics has been proposed (Bulat and Klarica, 2010; Klarica et al., 2009; Orešković and Klarica, 2010). According to this new hypothesis, CSF is not formed mainly by the choroid plexuses, and it does not then circulate to finally be absorbed, but it appears and disappears throughout the entire CSF system, depending on the hydrostatic and osmotic forces between the CSF, interstitial fluid (ISF) and blood capillaries. Osmotic and hydrostatic forces are crucial to the regulation of ISF-CSF volume. In terms of the capacity of fluid exchange, the cerebral capillaries are the dominant location, and the choroid plexuses are a less relevant place for this process. There is a permanent fluid and substance exchange between the CSF system and the surrounding tissue which depends on the (patho)physiological conditions that predominate within those compartments (see Section 4.2. - New working hypothesis). In light of this new hypothesis, it would, of course, be necessary to reevaluate the generally accepted concept regarding hydrocephalus development. Therefore, the primary aim of this review is to attempt to critically evaluate the relationship between the classical CSF hypothesis and the development of hydrocephalus. This review will also make an effort to explain if and how the development of hydrocephalus can be incorporated into the new hypothesis. For the same reason, we will try to avoid any discussion about the epidemiology, pathology, classification, treatment, patient status, symptoms or mortality of hydrocephalus. We will make an exception for cases in which the same

subjects would concern the aforementioned close correlation between the classical hypothesis and the development of hydrocephalus, and/or if they would allow us to further analyze that correlation.

The prevalent and crucial experimental data which support the classical hypothesis and explain the development of hydrocephalus have been observed in experimental animals. One should, of course, be extremely careful when the experimental results are extrapolated from animals to humans in any field, including the field of hydrocephalus development and CSF physiology. However, it is necessary to emphasize that the same principles of CSF hydrodynamics and the development of hydrocephalus in humans are present in other mammals. Furthermore, there are no mammalian species in which this matter is conceived outside the framework of the classical hypothesis. Thus, our analysis has not thoroughly explained the species-specific differences.

2. Classical hypothesis of cerebrospinal fluid hydrodynamics

According to experimental scientific interest and the first modern studies of CSF physiology from nearly a century ago (Cushing, 1914; Dandy, 1919; Dandy and Blackfan, 1914; Weed, 1914), CSF physiology is, after a hundred years of investigating, based on three key premises: 1) the active formation (secretion) of cerebrospinal fluid; 2) the passive absorption of CSF; and 3) the unidirectional flow of cerebrospinal fluid from the place of formation to the place of absorption (Fig. 1). Based on all of the above, CSF is referred to as the third circulation (the other two are blood and lymph) (Cushing, 1914; Luciano and Dombrovski, 2007; Milhorat, 1975; Taketomo and Saito, 1965).

2.1. Cerebrospinal fluid formation

There is an assumption that the main production sites of CSF (70-80%) are the choroid plexuses inside the brain ventricles, which is where the filtration across the endothelial capillary wall and the secretion through the choroidal epithelium occur. The remaining 20-30 per cent of CSF production arises as a bulk flow of the interstitial fluid (the extrachoroidal source), probably produced by the ependyma (Brown et al., 2004; Cserr, 1989; Davson et al., 1987; Johanson et al., 2008; McComb, 1983; Milchorat, 1972; O'Connel, 1970; Pollay, 1975). CSF is formed by the secretory activity of the choroid plexuses inside the brain ventricles. Weed (1917) has shown, in the study on the embryology of the subarachnoid pathways, that the opening of the subarachnoid space (SAS) coincides with the development of the choroid plexuses, and that this space enlarges as the choroid plexuses grow. He proposed that the immature choroid plexus could produce the fluid required to open and maintain the arachnoid pathways, and he suggested that an increase in intraventricular pressure might cause it. The endothelium of the choroid plexus capillaries is fenestrated, and the first stage in CSF formation is the passage of a plasma ultrafiltrate through the endothelium, which is facilitated by hydrostatic pressure. During the second stage of CSF formation, the ultrafiltrate passes through the choroidal epithelium, which is an active metabolic process that transforms the ultrafiltrate into a secretion product (cerebrospinal fluid; Fig. 2). Since this second stage is an active process, the CSF formation rate should not be significantly altered by moderate changes in intracranial pressure (ICP; Davson et al., 1987; Pollay et al., 1987).

2. 2. Cerebrospinal fluid circulation

It is generally accepted that CSF circulates in a to-and-fro movement with a caudal-directed net flow through the brain ventricles to the subarachnoid space, with the exchange of various substances (manifested to a higher or lesser degree) happening along the way between the CSF and interstitial compartments (Davson, 1967; Davson et al., 1987; Johanson et al., 2008; Plum and Siesjö, 1975). The CSF flows unidirectionally from the lateral brain ventricles through the foramina of Monro, then through the third ventricle and the aqueduct of Sylvius into the fourth ventricle, and finally through the foramina of Luschka and Magendie into the subarachnoid space (Fig. 1). Some of the CSF descends along the posterior aspect of the spinal cord and then, right in front of the cord, makes a turn and joins the main body of the CSF flow (DiChiro, 1966). A pulsatile to-and-fro flow with a caudal-directed net flow in the ventral and a cranial-directed net flow in the lateral cervical SAS has been reported within the spinal SAS (Henry-Feugeas et al., 1993; Schroth and Klose, 1992). The existence of a CSF flow in any direction within the spinal SAS brings into question the bulk flow of CSF in spinal SAS. On the other hand, if the CSF does not circulate from the cranium into the lumbar sac, it would not make sense to perform a routine lumbar puncture and CSF analysis on patients, expecting that pathological changes in the brain (encephalitis, meningitis, Alzheimer's disease and so on) should be mirrored in the punctuated lumbar CSF. Therefore, it is assumed that CSF circulates through the spinal SAS, but probably with reduced intensity. It is also believed that net flow of CSF results from the pumping action of the choroid plexuses, and that pulsation of the CSF is generated mainly by the filling and draining of the choroid plexuses (Bering, 1955). Each pulse should set up a pressure gradient throughout the CSF system, which tends to force CSF out of the cerebral ventricles. This way, the choroid plexuses act as an unvalved pulsatile cerebrospinal fluid pump, imparting a to-and-fro motion to the CSF.

2.3. Cerebrospinal fluid absorption

The arachnoid villi inside the dural venous sinuses have generally been thought to be the main site of CSF absorption. Villi and arachnoid granulations (Figs. 1 and 3) have essentially the same structure, and the term granulation is used for villi which are more developed, more complex, and visible to the naked eye. It is believed that CSF is passively absorbed from the cranial subarachnoid space to the cranial venous blood by means of a hydrostatic gradient (Brodbelt and Stoodley, 2007; Weed, 1935). Welch and coworkers described an open tubular system projecting into the lacuna lateralis or directly into the venous sinus (Welch and Friedman, 1960; Welch and Pollay, 1961). The ultrastructural studies of these structures differed in their support of these pressure-sensitive opening pathway hypotheses (Alksne and Lovings, 1972; Gomez et al., 1974; Jayatilaka, 1965). Since Shabo and Maxwell (1968) showed that the observed tubular system was probably a consequence of histological tissue preparation, and that the endothelium of arachnoid villi was, in fact, intact (Shabo and Maxwell, 1968), Tripathi and Tripathi (1974) proposed that there are temporary transmesothelial channels which allow the passage of CSF in bulk flow from the SAS to the venous blood (Tripathi, 1974a; Tripathi, 1974b; Tripathi and Tripathi, 1974). In addition, there is a large amount of literature which suggests that a significant amount of the absorption of CSF occurs from the subarachnoid space to the lymphatic system (Bradbury, 1981; Brierly and Field, 1948; Dandy, 1929; Johnston et al., 2005; Johnston et al., 2004; Koh et al., 2005; Koh et al., 2006; Weed, 1914). Also, despite some other proposed places (choroid plexuses, brain tissue, etc; see later), in physiological conditions the dural sinuses are still the main place of CSF absorption. However, all the proposed sites of this process do not affect the general concept of the classical CSF hypothesis.

According to the above-mentioned data, the CSF physiology conceived this way has been presented as the classical hypothesis of CSF hydrodynamics i.e. CSF is actively produced (secreted) mainly

from the choroid plexuses ("CSF pumps"; Fig. 2) inside the brain ventricles, then it circulates slowly (unidirectionally) from the brain ventricles toward the SAS, to be absorbed passively into the venous sinuses by the arachnoid villi. It should also be added that the total CSF volume is a result of the ongoing relationship between the active CSF formation by "CSF pumps" and the passive CSF absorption (Orešković and Klarica, 2010). This means that in physiological conditions the same CSF volume, which is actively formed within the brain ventricles, must be passively absorbed into the cortical SAS.

3. Hydrocephalus

The origin of the word "hydrocephalus" is Greek. It comes from the words: "hydro", meaning water, and "cephalus", meaning head, and its literal translation is "water in the head" (Fig. 4). Hydrocephalus is not a disease. It is a pathological condition with many variations, but it is always characterized by an increase in the amount of cerebrospinal fluid which is, or has been, under increased intracranial pressure (Matson, 1969). It is assumed to be a result of a discrepancy between CSF production and absorption, with a subsequent accumulation of fluid in the cranial cavity and an enlargement of the brain ventricles. The balance between production and absorption of CSF is critically important. Because CSF is made continuously by "CSF pumps" against ICP (Davson et al., 1987; Pollay et al., 1987), medical conditions that block its normal flow or absorption will result in an over-accumulation of CSF. The resulting pressure of the fluid against the brain tissue is what causes hydrocephalus. Based on the above mentioned, one of the recently proposed definitions of hydrocephalus is: "Hydrocephalus is an active distension of the ventricular system of the brain resulting from the inadequate passage of cerebrospinal fluid from its point of production within the cerebral ventricles to its point of absorption into the systemic circulation." (Rekate, 2008).

3.1. Etiology and classification of hydrocephalus based on the classical hypothesis of CSF hydrodynamics

Based on the classical hypothesis of CSF hydrodynamics, hydrocephalus may develop as a result of an obstruction of the circulating pathways, a reduction in the ability to absorb the CSF, or by an over-production of CSF.

Based on an experimental study on dogs, Dandy (1919) concluded that hydrocephalus is practically always caused by an obstruction that prevents the passage of CSF from its place of formation (in the ventricular system) to its place of absorption (in the cerebral SAS). The location and nature of the obstruction vary considerably. The block may be in the ventricular system or in the subarachnoid space (the cisternae or its branches), or in both. There are three general types of obstructions: 1) congenital malformations, 2) tumors and other space-occupying lesions, and 3) inflammatory sequalae. Depending on the location of the blockade, Dandy (1919) classified hydrocephalus into two types: non-communicating and communicating. This classification has been the accepted system since then and still forms the basis of the reimbursement system used in the United States (Rekate, 2009). Non-communicating hydrocephalus is also known as obstructive.

Communicating or non-obstructive hydrocephalus (Fig. 5) is caused by impaired CSF absorption as there is no visible CSF-flow obstruction between the ventricles and SAS, and the CSF can flow freely between the ventricles, which remain open. It has been theorized that this is due to the functional impairment of the arachnoid granulations, which are located along the superior sagittal sinus, and are the main site of CSF absorption back into the venous system. Scarring and fibrosis of the subarachnoid space following infectious, inflammatory, or hemorrhagic events can prevent CSF absorption, causing diffuse ventricular dilatation.

Non-communicating or obstructive hydrocephalus (Fig. 6) is caused by a CSF-flow obstruction ultimately preventing CSF from flowing into the SAS. The most frequent places of obstruction are the foramen, or foramina of Monro (dilatation of one or both lateral ventricles); the aqueduct of Sylvius (dilatation of both lateral ventricles, as well as the third one); the fourth ventricle (dilatation of the aqueduct of Sylvius, as well as the third and lateral ventricles), and finally the foramina of Luschka and foramen of Magendie (complete ventricular system). The dilatation of the ventricular system, which is a result of the obstruction of the CSF pathways, should be a consequence of accumulated CSF produced by the choroid plexuses ("CSF pumps") in front of the obstruction, and an increase in CSF pressure. A pressure gradient across the cerebral mantle may be considered a driving force of ventricular dilatation. This transmantle pressure may be defined as the difference between the intraventricular pressure and the pressure inside the subarachnoid spaces of the cerebral convexity (see Section 6 – The transmantle pressure gradient).

The newly proposed classification (Rekate, 2008) is based almost exclusively on the position of the obstruction, which means it assumes all hydrocephalus cases to be of an obstructive nature, with the exception of the overproduction of CSF. Six types were proposed, depending on the site of the obstruction: foramen of Monro; aqueduct of Sylvius; outlets of the fourth ventricle; basal cisterns; arachnoid granulations; venous outflow and overproduction by choroid plexus papilloma. The right classification of hydrocephalus is important because it could improve the focus of the basic research, the development of logical approaches to treatment decisions, the planning of prospective trials, and the development of new technologies to improve the outcomes of this most chronic of medical conditions.

In short, it could be said there is almost no etiology of hydrocephalus which would not closely associate with the classical CSF hypothesis. This primarily involves the active CSF production or

overproduction by “CSF pumps” (choroid plexuses), impaired circulation, inhibited absorption and increased hydrostatic CSF pressure.

4. New insights into cerebrospinal fluid hydrodynamics

4.1. Classical hypothesis and controversial experimental data

A series of obtained experimental results cannot be explained based on the classical hypothesis of CSF hydrodynamics (Bulat and Klarica, 2010; Orešković and Klarica, 2010). The formation of CSF (secretion) was conceived as an active process independent of the CSF pressure (see Section - 2.1. Cerebrospinal fluid formation), however, it has been demonstrated that the rate of CSF formation is a pressure dependent process (Calhoun et al., 1967; Flexner, 1932; Frier et al., 1972; Hochwald and Sahar, 1971; Martins et al., 1977; Orešković et al., 1991; Orešković et al., 2000; Weiss and Wertman, 1978) and it decreases as the CSF pressure is increased, which is opposite to the active nature of CSF secretion by choroid plexuses as “CSF pumps”. It was also shown that CSF formation and absorption are in balance at physiological ICP within the isolated brain ventricles (Orešković et al., 1991). This means that the CSF is not absorbed only into the venous sinuses on the brain surfaces, but that it is also significantly absorbed inside the ventricles (Brightman, 1968; Bulat and Klarica, 2010; Bulat et al., 2008; Cserr, 1971; Hassin, 1924; Hopkins et al., 1977; Naidich et al., 1976; Orešković et al., 1991; Wright, 1972). Furthermore, except for the high spinal CSF absorption in healthy individuals ranging between 0.11 and 0.27 ml/min (Edsbagge et al., 2004), the spinal central canal was additionally proposed as the relevant place of absorption (Dandy, 1929). Namely, when dye (phenolsulphonphtalein) was injected into the spinal canal it was detected in the blood stream in less than two minutes. On the other hand, it took an hour for the dye to reach the cortical subarachnoid space where the pacchionian granulations exist. During that time (before the pacchionian granulations have been reached), nearly 25% of the dye had been excreted

into the urine (Dandy, 1929). Additionally, it is believed that the choroid plexuses are also the place of CSF absorption (Dodge and Fishman, 1970; Foley, 1921). Furthermore, there is a large amount of literature which suggests that significant CSF absorption occurs from the SAS to the lymphatic system (Bradbury, 1981; Brierly and Field, 1948; Dandy, 1929; Johnston et al., 2005; Johnston et al., 2004; Koh et al., 2005; Koh et al., 2006; Weed, 1914). It was also described that CSF has an extrachoroidal origin (Hassin, 1924), and that it is formed, except in the ventricles, within the subarachnoid space (Sato and Bering, 1967; Sato et al., 1971; Sato et al., 1972). These experimental results have been supported by Sato et al. (1994) elaboration, in which the choroid plexuses have been challenged as the main place of CSF formation. Namely, the weight of the choroid plexuses in human beings is estimated to be between 2 and 3 g in total. It is truly amazing to think that an anatomical structure with that total mass can produce 500 ml CSF per day. It can be calculated that the volume of the blood which perfuses the choroid plexuses is approximately 4-5 ml/min/g of the plexus tissue. The choroid plexus is highly vascular, but nevertheless, this amount of blood still seems extraordinarily large. In experiments in which the choroid plexuses (main site of CSF secretion) have been removed, no changes in the volume and composition of the newly formed CSF have been observed (Milhorat, 1969; Milhorat et al., 1976). Furthermore, it has been shown that there is no net formation of CSF in isolated brain ventricles, and that CSF does not circulate along the CSF system, but rather that permanent CSF changes happen within the surrounding tissue, depending on the fluid osmolarity (Bulat et al., 2008; Maraković et al., 2010; Orešković et al., 2001; Orešković et al., 2002; Wald et al., 1976). By monitoring the behavior of different substances in the CSF of some patients, it was also concluded that CSF is formed everywhere and absorbed everywhere inside the CSF cavities (Di Chiro, 1964; 1966). Hakim et al. (1976) presented the brain as a submicroscopic sponge of viscoelastic material, provided by the venous capillaries, extracellular spaces, and other factors. Serving homeostatic functions in the central nervous system,

the exchange of fluid and solute between the CSF and ISF of the brain plays important role in CSF movement.

Recent experimental works have shown that the hypothesis regarding CSF circulation is hardly sustainable/explicable (Bulat and Klarica, 2010; Bulat et al., 2008; Maraković et al., 2010; Orešković and Klarica, 2010; Orešković et al., 2002). Since water constitutes 99% of CSF volume (Bulat and Klarica, 2010), and since, by definition, CSF circulation means the circulation of CSF volume, it is apparent that water should demonstrate the dynamics (bulk flow) of the CSF. But when water was used as a marker of circulation (bulk flow), only fast local absorption into cerebral capillaries via pia mater was obtained, which means that there is no unidirectional net flow of CSF along the CSF spaces. Thus, if the CSF volume (water) does not circulate, then it is obvious that there is no CSF circulation according to classical hypothesis (Bulat and Klarica, 2010; Bulat et al., 2008; Klarica et al., 2009; Orešković et al., 2002). We can reach almost the same conclusions, in relation to CSF circulation, when water is intravenously applied as a marker in humans (Bering, 1952). All of these mentioned results and observations, obtained from different experiments on animals and humans, cannot be explained by the classical hypothesis and therefore call for a new one.

4.2. New working hypothesis

Based on the mentioned results, a new working hypothesis of the CSF hydrodynamics has recently been proposed (Bulat and Klarica, 2010; Bulat et al., 2008; Klarica et al., 2009; Orešković and Klarica, 2010). According to this hypothesis, the interstial fluid (ISF) and CSF bulk (water) constitute a functional unity and are regulated by changes in osmotic and hydrostatic pressure in CNS microvessels. Namely, the continuous turnover of ISF-CSF bulk (water) is created by the filtration of water across arterial capillary walls under hydrostatic pressure and the reabsorption of

water from the interstitium into the venous capillaries and postcapillary venules by osmotic counterpressure. The ISF and CSF are in continuity, and are mixed by to-and-fro fluid pulsations. Since the surface of the choroid plexus is about 5000 times smaller than the surface of cerebral capillaries (Crone, 1963; Raichle, 1983), this and all of the above suggests that the "formation" and "absorption" of CSF mainly take place at the cerebral capillaries (Fig. 7). In the brain, parenchyma capillaries form a dense and interconnected network of vessels (Fig. 7B). This results in fluid filtration and reabsorption which simultaneously occur everywhere between the numerous capillary branches. Thus, arterial capillaries with high hydrostatic pressure can be situated near the vessels with low hydrostatic pressure, as shown in Fig. 7B. During the filtration of water from the arterial capillaries under high hydrostatic pressure, plasma osmolytes are retained since their permeability across the cerebral capillary wall is very poor (reflection coefficient of main electrolytes Na^+ and Cl^- is 0.98, and it is very similar to that of proteins - 0.999), and therefore osmotic counter-pressure is generated, which opposes the water filtration. When such hyperosmolar plasma reaches the venous capillaries and postcapillary venules where the hydrostatic pressure is low, it becomes instrumental in water reabsorption from the ISF, and consequently from the CSF (Bulat and Klarica, 2005; Bulat et al., 2008). Thus, a rapid turnover of water, which constitutes 99% of ISF-CSF volume, continuously takes place between the plasma and ISF-CSF (Bering, 1952; Bulat and Klarica, 2010; Bulat et al., 2008). Therefore, total CSF volume within the CSF system should depend on the fate of the ISF-CSF functional unit. These fluid volume changes depend on physiological and pathophysiological processes which can cause differences in fluid osmolarity between CNS compartments.

4.2.1. Maintenance of cerebrospinal fluid volume

It is generally believed that CSF volume in physiological conditions is a constant value which changes slightly or not at all, and since the maintenance of the total CSF volume is very important for the normal functioning of the CNS, and also for the development of hydrocephalus, it is necessary to consider that issue. It should be stressed that when we think about CSF volume, we should always keep in mind that 99% of CSF is water (Bulat et al., 2008). Therefore, the maintenance of CSF volume is the maintenance of water volume, while CSF hydrodynamics is the hydrodynamics of water. We have suggested that the control of ISF-CSF volume is influenced by hydrostatic and osmotic forces in CNS microvessels (Bulat, 1993; Maraković et al., 2010; Orešković et al., 2000; Orešković et al., 2002; Orešković et al., 1991, Orešković and Klarica, 2010) and that CSF volume will change depending on the prevalence of those forces. Thus, the total volume of CSF is not dependent on CSF secretion inside the brain ventricles and the passive CSF absorption in subarachnoid space, but rather depends on a permanent dynamic change in water volume along the entire CSF system (Fig. 8). And what is the fate of water inside the CNS?

4.2.1.1. Impact of an osmotic force

The net movement of water from the blood into the brain tissue was demonstrated during the development of osmotic brain edema (Go, 1997; Verbalis, 2010). Namely, when the osmolarity of blood is lower than the osmolarity of the brain parenchyma and cerebrospinal fluid (e.g., fast reduction of blood osmolarity in patients with hyperglycemia after the administration of insulin and hypoosmolar solution), an osmotic arrival of fluid from the blood into the brain interstitial tissue and cerebrospinal fluid occurs, which results in a brain edema and increased CSF pressure. On the other hand, hyperosmolar infusion (mannitol) has been used in clinical practice for a long time to reduce intracranial pressure by the osmotic movement of water from the brain tissue. This clearly

indicates that the net movement of water between different CNS compartments, and at the level of a blood-brain barrier (BBB), depends on the osmotic gradient between CNS fluids (blood, ISF, CSF). Furthermore, it has been shown that in the case of a brain ischemia, the ischemic area of the brain parenchyma shows an accumulation of water due to the increase in tissue osmolarity (for twenty mOsm/l above the control values). This level of osmolarity has probably been obtained by the accumulation of osmotically active substances such as glucose, lactate, pyruvate, sodium, potassium and their respective anions (Hossmann, 1985).

It was observed that the accumulation of water in the brain parenchyma due to an increase in tissue osmolarity also occurs in head trauma patients (Katayama et al., 2003; Kawamata et al., 2002). It was shown (Katayama et al., 2003) that samples of necrotic brain tissue taken from the central area of the contusion demonstrated a very high osmolarity. The cerebral contusion induced a rapid increase in tissue osmolality of 90 mOsm/kg, 12 hours posttrauma, and a significant decrease in the specific gravity of the contused tissue reflected water accumulation (Kawamata et al., 2007).

It has also been observed that CSF/water volume depends on the osmolarity force, quite similar to water inside the brain parenchyma. It was shown on cats that an increase in ventricular CSF osmolarity leads to an increase in CSF volume (Marlin et al., 1978; Orešković et al., 2002; Wald et al., 1976). The volume flow rate was inhibited completely with ventricular fluid osmolarity of 127 mOsm/l, and it increased without an apparent limit to more than 70 µl/min with a ventricular CSF osmolarity of 550 mOsm/l (Marlin et al., 1978). It is unquestionable whether osmolarity significantly influences the control of the water/CSF volume. Thus, the increase in CSF osmolarity as compared to the blood and surrounding tissue, enhanced CSF volume, and vice versa. This was confirmed by a very recent investigation (Maraković et al., 2010) in which it was shown that the volume of the CSF depends on both CSF osmolarity and the size of the contact area between the CSF system and the surrounding tissue exposed to hyperosmolar CSF. It means that if a larger contact area had been included, a stronger effect, i.e., larger increase in CSF volume, would be

obtained. The water (ISF/CSF) movement is bidirectional; into the CSF, as well as out of it, and the prevalent direction depends on whether the CSF is hyper or hypoosmolar in correlations to the ISF and blood.

4.2.1.2. Impact of the hydrostatic force

A clear insight into the effects of hydrostatic pressure on the water/CSF volume was shown in the cat experiments in which CSF was collected after a free CSF leakage through the cannula set in cisterna magna, whose collecting end was positioned at different pressure levels. Thus, at hydrostatic physiological pressure (8-10 cm H_2O), the CSF leakage from the CSF system was not obtained over two hours (Orešković et al., 2001; Orešković et al., 2002), whereas at negative hydrostatic pressure (-10 cm H_2O) a steady outflow was obtained (about 16 µl/min) over a period of six hours (Orešković et al., 1995). Therefore, hydrostatic pressure is a significant regulatory mechanism in CSF volume control; when CSF pressure is higher than the pressure that exists at the site of collection, this results in CSF escape. As is well known, the drainage of CSF caused by differences in hydrostatic pressures is a principle according to which many important methods of hydrocephalus treatment, such as an approach via the anterior fontanelle in babies, a surgical burrhole in older children and adults, or an inserted drainage tube (shunt), have been established. Furthermore, such an effect of hydrostatic pressure on the water/CSF volume is an indication of the behavior of ^3H_2O in perfusate during ventriculocisternal perfusion at negative (-10 cm H_2O) and positive (+20 cm H_2O) CSF pressure in cats (Orešković and Bulat, 1993). It was shown that the ^3H_2O concentration was significantly decreased at positive CSF pressure, which would mean that, at higher CSF pressure, the departure of water from the CSF into the brain parenchyma would be larger. This observation is confirmed by a vast number of experiments which explored the effect of hydrostatic pressure on CSF formation using the perfusion method and an equation for the

calculation of CSF formation that was developed by Heisey et al. (1962). Namely, in these studies it was demonstrated that the elevation of hydrostatic pressure significantly lowers the rate of the calculated CSF formation (Calhoun et al., 1967; Flexner, 1932; Frier et al., 1972; Hochwald and Sahar, 1971; Martins et al., 1977; Milhorat and Hammock, 1983; Orešković et al., 2000; Weiss and Wertman, 1978). Since, based on the classical hypothesis of CSF hydrodynamics, it could be expected that CSF volume is regulated by its formation, this observed effect of hydrostatic pressure on CSF formation simultaneously represents the effect on its volume.

In the end, it is well known that, at the capillaries level, the relationship between hydrostatic and colloid osmotic pressures in both the capillaries and the interstitium is used to explain fluid filtration and reabsorption across the microvascular walls by the Starling colloid osmotic hypothesis. The correction of the Starling hypothesis, which fails to clarify fluid homeostasis when hydrostatic capillary pressure is high (in the feet during orthostasis) and low (in the lungs), or when colloid osmotic plasma pressure is significantly decreased (e.g. genetic analbuminemia), was explained by Bulat and Klarica (2010). Nevertheless, the control of fluid/water volume inside the craniospinal space strictly depends on hydrostatic and osmotic pressures at the CNS tissue capillaries level.

Also, it should not be forgotten that one of the most important mechanisms for maintaining the physiological homeostasis in the CNS is the active transport of substances. Such an active and energy consuming process proceeds in both directions (in and out of the cell), directly impacting the homeostasis (among others, the isoosmolarity of fluids) of the CNS (Strikić et al., 1994; Vladić et al., 2000; Zmajević et al., 2002). Therefore, it is thereby included in the regulation of osmotic balance, and subsequently in the maintenance of CSF volume.

All of the above strongly indicates that the movement of water inside the CNS is influenced by osmotic and hydrostatic forces, and that the CSF exchange between the entire CSF system and the

surrounding tissue fluids (ISF) depends on physiological or pathophysiological processes (trauma, ischemia, inflammation, hydrocephalus, etc.) which can cause changes in fluid osmolarity and hydrostatic pressure in different CNS compartments. In fact, as was suggested by the new working hypothesis, in a manner similar to the way they regulate the volume of extracellular fluid in other parts of the body (Fig. 7, 8).

Based on everything that has been presented so far, we can only wonder: How is it possible to understand and explain the development of hydrocephalus in light of the classical hypothesis and elaborated results?

5. Controversy between hydrocephalus and the classical hypothesis

Let us return to Dandy (1919) and his historical experiment. At this point we will not discuss the scientific foundation of this experiment (which was performed on a single dog) nor the unsuccessful attempts of scientists to reproduce the experimental results (Hassin, 1924; Milhorat, 1969), because these facts are irrelevant in comparison to the huge impact which this experiment has had, until today, on the framework of thinking regarding the interpretation of CSF physiology and the development of hydrocephalus (Orešković and Klarica, 2010). Two things are important; first of all: based on this experiment, the classical hypothesis of CSF hydrodynamics and the development of hydrocephalus had borne each other out, and were once and for all closely connected; and second: a new approach to the treatment of hydrocephalus by choroid plexectomy was established/developed and used in the following decades. Namely, Dandy demonstrated that CSF is formed exclusively from the choroid plexus (see Section 1. – Introduction), and according to the experimental results obtained that way, it seemed logical that the removal of the choroid plexuses (if the CSF pathways are blocked) should result in preventing the development of hydrocephalus, and in the recovery and healing of the patients as well. For many years, this surgical procedure was the most popular form

of hydrocephalus treatment, but because of universally poor results, it has no place in the current treatment of hydrocephalus (Lapras et al., 1988; Milhorat, 1976; see Section 7.1. - Choroid plexectomy). After all of this, we must comment that it is strange that the results obtained from an experiment on a single dog were transferred to people, and were then used to create a treatment for hydrocephalus, which remained in clinical practice for so long. One would expect that such a long and unsuccessful clinical practice would call for a scientific reexamination of the obstructive hydrocephalus entity. Namely, if the source of the active CSF formation was removed (choroid plexuses i.e. "CSF pumps"; which should dilate the brain ventricle by its active CSF formation in front of the obstruction), and still the desired therapeutic effect was not obtained, the real question arises; could the obstruction cause hydrocephalus? So, if active CSF formation does not exist (because there is no choroid plexuses), why would the obstruction lead to the dilatation of the brain ventricles? Although this question seems very logical, it has not led to any serious scientific debate. We believe that the main reason behind not having a debate was the simultaneous existence of many experimental models on different animal species, in which the obstruction of CSF pathways leads to the development of hydrocephalus.

5.1. Experimental models of hydrocephalus

The first known attempt to produce experimental hydrocephalus in animals was by Burr and McCarthy (1900), in which they injected several types of irritating solutions into the lateral ventricles of kittens. They reported inflammation of the ependymal lining of the ventricles, but did not find dilatation. The first successful attempt at producing experimental hydrocephalus was made by Dandy and Blackfan (1913). They were able to induce hydrocephalus by placing a small obstruction (cotton pledget in a capsule) into the aqueduct of Sylvius in a dog. The cerebral ventricles proximal to the occlusion became dilated, while the fourth ventricle did not enlarge.

Since that time, many methods have been devised to make large laboratory animals hydrocephalic in order to study the impaired circulation of CSF and to test therapeutic measures, and much of the basic data have been produced as a result of experimental studies. For this purpose, monkeys, dogs, cats and rabbits have often been used, and the obstruction has been accomplished by introducing foreign substances (irritative agents such as kaolin, Indian ink, Pantopaque, Silastic or siliocone oil, blood, cotton, inflated Foley catheter, etc.) into the CSF space (Bering and Sato, 1963; Dandy, 1919; Edwards, et al., 1984; Hochwald, 1985; Milhorat et al., 1970). However, except for the obstruction of the CSF pathways, in all these models there are additional pathophysiological states. In other words, there is no clear hydrocephalus model, and we can not talk only about obstruction in any of those models. Tissue inflammations would be found, caused by introducing irritating solutions into the CSF system, or an increase in pressure would be put on the surrounding brain tissue which was caused by a foreign body being forced into the narrow spaces inside the CSF system, or both. As such obstructions in the aforementioned models rarely lead to the onset of hydrocephalus, no special attention was paid to the analysis of these additional pathophysiological conditions, or how important (if important at all) their contribution was to the development of hydrocephalus.

According to the new working hypothesis (see Section 4. - New insights into cerebrospinal fluid hydrodynamics), these additional pathophysiological conditions should be of crucial importance. Namely, based on the new hypothesis, CSF volume is determined by the hydrostatic and osmotic pressures inside the blood, ISF and CSF, and we expect that for the development of hydrocephalus, the disruption of this balance is essential.

5.1.1. Hydrocephalus and obstruction

A relatively common finding of a mild degree of aqueductal stenosis in hydrocephalus, despite the clearly unimpaired CSF conduit function, is the most cogent reason for questioning the traditionally accepted relationship between stenosis and hydrocephalus. It is possible that aqueductal narrowing or even closure occurs as a result of hydrocephalus, which could have therefore wrongly been considered in the past as the cause of hydrocephalus, to which it contributes only in the final stages (Williams, 1973). The best clinical evidence of a secondary aqueductal stenosis was given by Foltz and Shurtleff (1966), who found that among 27 patients with communicating hydrocephalus, 12 developed secondary aqueductal stenosis or aqueductal occlusion during chronic venticulo-atrial shunting. Furthermore, in lambs, acute and chronic hydrocephalus was induced without interfering with the CSF circulation or absorption (Di Rocco et al., 1978) by mechanically increasing the amplitude of the CSF intraventricular pulse pressure without modifying the mean CSF pressure. On newborn hamsters and cats, after an intracerebral infection with a virus vaccine, hydrocephalus has been developed without the stenosis of the aqueduct or fibrosis of the subarachnoid space (Davis, 1981). Three weeks after intracerebral inoculation, brains demonstrated severe hydrocephalus with marked dilatation of the lateral ventricles and thinning of the cortical mantle. The third ventricle appeared moderately dilated, but gross enlargement of the fourth ventricle was not noted. The configuration of the aqueduct was similar to the normal one. During the first week a moderate inflammation of the ependyma, choroid plexus and meninges occurred. The choroid plexus became swollen with some necrosis of the choroid cells, and three weeks later it was atrophic. Also, Masters et al., (1977) have shown that the infection by a reovirus type 1 in mice causes hydrocephalus, which develops in proportion to the degree of the inflammatory/fibrotic changes within the cerebrospinal fluid pathways. As the hydrocephalic state progresses, axial herniation and compression of the midbrain result in the appearance of aqueduct stenosis. It was demonstrated that stenosis of the aqueduct is a secondary phenomenon, not causally related to the pathogenesis of

hydrocephalus. Furthermore, it was recently noted (Klarica et al., 2009) by a new experimental model of complete acute aqueductal blockage in cats, that the CSF pressures in isolated brain ventricles were identical to those in control conditions, and that brain ventricles did not dilate during three hours of obstruction. This recent result is very similar to earlier results by Guleke (1930), who found, using a technique of introducing cotton into the aqueduct of Sylvius, that hydrocephalus resulted in only 8 of 38 animals in which the aqueduct had been occluded. Hassin et al. (1937) have also performed the same type of experiment on 15 dogs, and ventricular dilatation resulted in only 3 animals.

In response to the question regarding which came first, the obstruction of the CSF pathways or hydrocephalus, indicative studies were made by producing congenital hydrocephalus using teratogenic methods. Thus, a diet causing hypovitaminosis A in rabbits (Millen and Woolam, 1958) or a pteroylglutamic acid-deficient diet in rats (Monie et al., 1961) suggested that stenosis of the aqueduct of Sylvius was a result of hydrocephalus. Anomalies obtained on rats with a zinc-deficient diet during pregnancy suggest that the occlusion of the aqueduct was the cause of the enlargement of the ventricular system (Adeloye and Warkany, 1976). Additionally, in some animals with deformed but not occluded aqueduct, hydrocephalus was present throughout the ventricular system. It seems possible that some cases of congenital hydrocephalus, which are attributed to aqueductal stenosis, are an example of hydrocephalus with a secondary blockage of the aqueduct. Ventricular dilatation caudal to the obstructed point of the aqueduct was also observed. Other animal experiments on mutant mice were reported by Borit and Sidman (1972). The mice had genetically determined postnatal communicating hydrocephalus, which secondarily produced aqueductal stenosis by compression of the mesencephalon.

Now, when it is shown that in many cases the stenosis of the aqueduct is not the cause of hydrocephalus, but rather a consequence, and that hydrocephalus could develop without the

obstruction, let us return again to the analysis of the experimental models of hydrocephalus. We will analyze experimental models which are very illustrative of the relationship between the development of hydrocephalus and the classical hypothesis of hydrodynamics; kaolin-induced hydrocephalus and communicating hydrocephalus.

5.1.2. Kaolin-induced hydrocephalus

The kaolin-induced hydrocephalus model (Fig. 9) was the first carried out by an injection of kaolin into the cisterna magna by Dixon and Heller (1932). Until today it has remained one of the most reliable models most commonly used on different animals (monkeys, dogs, cats, rabbits, hamsters, rats, mice) for the production of hydrocephalus (Bering and Sato, 1963; reviewed in Del Bigio, 2001; Dohrmann, 1971; Klinge et al., 2009; Lollis et al., 2009; Schurr et al., 1953). Kaolin causes an intense and severe inflammatory response in the meninges, and that results in post-inflammatory fibrosis with obliteration of the cisterna magna, occlusion of the outlets of the fourth ventricle, and subsequently hydrocephalus (Hochwald, 1985). Approximately 20% of treated animals (cats) died within two weeks (Hochwald et al., 1972). In some other experiment situations the results were even worse (Kim et al., 2000), and out of thirty cats treated by kaolin, twenty-five died within three days, and one died at the end of the second week. Only four cats survived and fully recovered by the fourteenth day. The effects of the intracisternal application of kaolin were apparent within 48 hours of the injection. In this interval, the foramina of the fourth ventricle became occluded, and the intraventricular pressure increased as much as 10-fold (Edvison and West, 1971; Hochwald et al., 1972). The animals were lying on their sides in their cages, unable to stand, with spasticity of all extremities. The obstruction of the CSF pathways typically appears to be a combination of the physical deposition of kaolin particles (Fig. 9) and a local fibrotic response in the arachnoid and pial membranes. Some critics have argued that the application of kaolin is not an appropriate induction

method because it could produce a global inflammatory response throughout the brain and cranial cavity. The increased collection of fluid in some inflammation processes as peritonitis, pleuritis, or pericarditis could be so voluminous that it could result in forming from 100 ml to more than a liter. The method of formation and the appearance of that fluid volume inside the pleural, peritoneal and pericardial space could be explained exclusively as a consequence of inflammation. It is important to say that the peritoneal, pleural and pericardial cavities do not have any special way of producing fluid, and also do not have a curve of fluid absorption very different from the subarachnoid space. At the same time, it is believed that pathological CSF accumulation associated with the inflammation is not a sufficient factor, and that impaired CSF circulation and absorption should necessarily exist (see Sections 2. - Classical hypothesis of the cerebrospinal fluid hydrodynamics and 3. - Hydrocephalus). In other words, hydrocephalus may develop only as a result of the obstruction of the circulating pathways or as a result of a reduction in the ability to absorb the cerebrospinal fluid. Is the obstruction of the CSF pathways so important?

As a matter of fact, in some experiments recently done on cats (Lollis et al., 2009), there have been attempts to reduce this global inflammatory response with a reduction of the kaolin dosage and the postoperative administration of a high-dose of corticosteroid therapy with the intention of reducing the morbidity and mortality rates. However, to conclude after such a clinical picture that adhesions and the physical deposition of kaolin causes impaired CSF flow, which will result in the development of hydrocephalus, without taking into consideration and analyzing that maybe inflammation (*per se*) is a sufficient reason for the development of hydrocephalus, is not scientifically correct. The following experimental results introduce additional confusion.

Taketomo and Saito (1965) have induced hydrocephalus by injecting kaolin into the cisterna magna of mongrel dogs. The final state of the CSF pathways blockade was confirmed during autopsy by using a dye injection, and in 65 of 75 dogs the blockade was found to be complete (Fig. 9). Of these

65 completely blocked animals, it is interesting that dilatation of the ventricles was found in 48 dogs. In other words, although the blockade was complete in 17 dogs (24%), hydrocephalus had not developed. So, in 24% of the animals we have permanent CSF production, and simultaneously the complete blockade of the CSF pathways, but without hydrocephalus. How can we explain this phenomenon? The explanation is not possible in accordance with the classical hypothesis. Namely, the active formation of CSF by the choroid plexuses ("CSF pumps") and the inability of CSF absorption due to blockade, should undoubtedly lead to the development of hydrocephalus in front of the blockade. But if this cannot be explained using the classical hypothesis, the explanation might be found by way of the inflammation process. Inflammation may produce different reactions depending on the immune status of each animal. In most animals it could result in an abundant leakage of exudate volume and the development of hydrocephalus. In others, admittedly few and far between, this does not necessarily have to take place.

5.1.3. Communicating hydrocephalus

Communicating hydrocephalus (CH) occurs frequently, especially in older adults, and is often associated with persistent neurological deficits. It is postulated that CH is caused by an impairment of CSF absorption, since absorption deficit has been demonstrated by elevated CSF outflow resistance in human hydrocephalus (Fig. 5) and animal models designed to simulate this pathological condition (Gjerris et al., 1989; Johanson et al., 1999; Malm et al., 2004; Sorensen et al., 1989). All portions of the ventricular system exhibit dilatation, and usually the enlargement of the lateral ventricles is proportionally greater than the rest of the ventricular system. The aqueduct of Sylvius is patent and posteriorly expanded, and the CSF (injected tracer into lateral ventricle) moves freely from the ventricular system into the subarachnoid spaces (Fig. 5). The experimental CH has often been induced on different animals by injecting kaolin or silicone into the

subarachnoid space overlaying the cerebral hemispheres (Cosan et al., 2002; Daniel et al., 1995; Li et al., 2008). It has always been assumed that the impediment to CSF absorption occurs at the arachnoid villi and granulations because bulk CSF absorption is believed to arise through these structures (see Section 2.3. - Cerebrospinal fluid absorption), although the location of the absorption deficit has never been established and the function of the arachnoid granulations has become increasingly unclear (Egnor et al., 2002; Koh et al., 2005; Li et al., 2008; Nagra et al., 2008; Papaiconomou et al., 2002; Papaiconomou et al., 2004; Zakharov et al., 2004). Since the way of the CSF bulk absorption through the arachnoid villi is still speculative, and since at normal CSF pressure in experimental animals very little bulk absorption of CSF into the cranial venous system is obtained (McComb et al., 1982; McComb et al., 1984; Papaiconomou et al., 2004; Zakharov et al., 2004), recently the lymphatic pathways have been proposed as the main location of CSF absorption (especially in CH), with a route through the cribriform plate into the extracranial lymphatic system located in the nasal submucosa (Koh et al., 2005; Nagra et al., 2008; Papaiconomou et al., 2002). Therefore, except for the choice of another main location of bulk CSF absorption, nothing substantial has changed in the interpretation of CH development, because CH is still characterized by an impaired CSF flow and bulk absorption in the subarachnoid spaces. But this interpretation did not answer Dandy's and Blackfan's (1914) question which pointed out the fundamental dilemma of CH; how does obstruction of the CSF absorption at the arachnoid villi cause ventricular expansion? Namely, it is postulated that a transmantle pressure gradient (see Section 6. - The transmantle pressure gradient) precedes the ventricular dilatation, but it is not clear how would obstruction of CSF absorption at the arachnoid villi cause a pressure gradient across the mantle. If a pressure gradient happens, it should favor the expansion of the subarachnoid spaces, but not the ventricles. Also, it is absolutely not clear how would the impaired CSF absorption through the cribriform plate lead to a transmantle pressure gradient favoring dilatation of the ventricles, since CSF pressure would probably rise equally in all CSF spaces within the cranium. The

explanation cannot be found in light of the classical hypothesis of CSF hydrodynamics, and therefore, in recently presented research of CH in adult rats with kaolin obstruction, Li et al. (2008) concluded that the obtained experimental results do not support the theory by which mechanical obstruction of CSF absorption causes hydrocephalus. It seems that the development of CH could be a result of the redistribution of CSF pulsation in the cranium (Egnor et al., 2002; Greitz, 1993; Nagra et al., 2008) which significantly differs between the higher ventricular system pulsations and the lower subarachnoid space pulsations.

The observation that the occurrence of CH is not related to the classical hypothesis of CSF hydrodynamics and the obstruction of the arachnoid villi as the main place of CSF absorption, can also be confirmed by earlier experiments that made a deliberate attempt to occlude the superior sagittal sinus in a series of animals (Beck and Russell, 1946). In those experiments, especially on puppies and kittens, the longitudinal sinus was occluded and that operation was not followed by any unequivocal clinical or pathological evidence either of an increased ICP or hydrocephalus. Although the longitudinal sinus, as the main place of CSF absorption, was blocked, hydrocephalus did not develop. It should be stressed that in this experiment surgical treatment was out of the CNS, and no inflammation inside the CSF system was observed.

A special chronic type of communicating hydrocephalus is a normal-pressure hydrocephalus described as a syndrome of ventricular enlargement which occurs in the absence of elevated CSF pressure and is accompanied with gait disturbance, dementia and incontinence (Bergsneider et al., 2005; Hakim and Adams, 1965; Marmarou et al., 2007; Vanneste et al., 1993). Despite the clinical problems indicated in the guidelines for diagnosing and treating such patients, the main interest of this article is to discuss the nature of its development. In the end, the conclusion is that the normal-pressure hydrocephalus still introduces new controversies. Namely, the fundamental question – how does the obstruction of the CSF absorption at the arachnoid villi cause ventricular expansion in CH

in the absence of elevated CSF pressure during hydrocephalus development – is completely inexplicable based on the classical CSF hypothesis.

5.2. External hydrocephalus

Another enigma in the explanation of hydrocephalus ethiopathology is external hydrocephalus (EH). EH is a rare, but well documented condition in which the cerebrospinal fluid is found in excessive amounts between the dura and the brain, with mild or no brain ventricular dilatation (Anderson et al., 1984; Harbeson, 1939; Kumar, 2006; Maytal et al., 1987). Since the fluid continues to accumulate over the surface of the brain, the cerebral hemispheres are pushed toward the base of the skull (Fig. 10). The volume of the brain and the size of the ventricles could then be reduced to a minimum (Dandy, 1969). Various terms have been used to describe these conditions in literature: subarachnoid space enlargement, extra cerebral fluids collection, benign infantile hydrocephalus (Caldarelli et al., 2000), benign external hydrocephalus and the benign expansion of subarachnoid spaces (Swift and McBride, 2000). These different terms have been used arbitrarily to describe similar conditions to define the entity of EH.

In contrast to communicating hydrocephalus, the accumulation of CSF in the cortical subarachnoid space is exactly what one should expect in light of the classical hypothesis, if CSF absorption by the arachnoid villi is prevented. But the most interesting question is how the existence of mild or no distension of brain ventricles could be simultaneously explained. Namely, the total volume of CSF which causes external hydrocephalus should be produced by a "CSF pump" (choroid plexuses; Fig. 10) positioned inside the brain ventricles. If this is so, it is difficult to imagine that the ventricles could stay mildly distended, or not at all, and that newly secreted CSF circulates to the surface of the brain to be accumulated there and thus produce hydrocephalus without any effect on the brain ventricles. Even more, in some cases the volume of the brain and the size of the ventricles are

reduced to a minimum (Dandy, 1969). And although the ventricles were reduced to a minimum, "CSF pumps" inside the ventricles still permanently produced CSF with the same intensity without having any effects on the distension of the brain ventricles. Thus, the source of CSF which has caused such remarkable changes on the surface of the brain did not cause any change at the site of origin (brain ventricles).

6. The transmantle pressure gradient

One of the dogmas relating to hydrocephalus is the existence of a transmantle pressure gradient as a key factor in hydrocephalus development. A pressure gradient across the cerebral mantle may be considered a driving force of ventricular dilatation. This transmantle pressure may be defined as the difference between the intraventricular pressure and the pressure in the subarachnoid spaces of the cerebral convexity. One of the greatest paradoxes within the concept of transmantle pressure gradient is the failure of researchers to consistently measure transmantle pressure gradient in humans and in animal models, especially of the communicating hydrocephalus. It seems that without such a gradient it would be difficult to conceptualize how brain ventricular dilatation occurs. It is equally unclear if the pressure gradient can really be the fundamental mechanism of hydrocephalus development, regardless of whether it is low (Conner et al., 1984; Hakim and Hakim, 1984; Levine, 2008; Penn et al., 2005) or high (Kaczmarek et al., 1997; Nagashima et al., 1987; Smillic et al., 2005). There are, nevertheless, some other authors who believe that a CSF pressure gradient is not possible within the cranium firmly enclosed by bones, mostly because they did not observe such a gradient neither in experiments involving animals (Shapiro et al., 1987) nor in patients with communicating or non-communicating hydrocephalus (Stephensen et al., 2002).

Since the data regarding the gradient-related results in literature are so contradictory, the question arises as to whether a transmantle pressure gradient is necessary for the development of

hydrocephalus, or whether some other factors may play an important role in such a process with the occlusion or stenosis of the CSF pathways. This consideration is supported by the observations that in patients with communicative and non-communicative hydrocephalus, transmantle pressure is absent (Stephensen et al., 2002). All of the evidence supports the idea that the transmantle pressure gradient may not be necessary or instrumental for the development of hydrocephalus, and that some other factors such as an increase in the ventricular CSF pulse pressure without affecting the CSF pressure (Di Rocco et al., 1978), an impairment of systolic-diastolic displacement of the CSF with the development of periventricular ischemia (Miše et al. 1996), changes in the arterial pulsations (Greitz, 2004 and 2007), an increase in ventricular CSF osmolarity without affecting the CSF pressure (Krishnamuthy et al., 2009), and venous compliance (Bateman, 2000 and 2003) may play an important role in the development of that pathological process (see Section 8. – Mechanisms of hydrocephalus development which are not in accordance with the classical hypothesis of CSF hydrodynamics). Based on the abovementioned, it can be said that hydrocephalus may occur with and without a transmantle pressure gradient.

As a matter of fact, the development of a transmantle pressure gradient in the CSF system was recently clearly shown in experiments on cats (Klarica et al., 2009). The gradient can only occur in the case of a total blockade of the CSF pathways between the brain ventricles and subarachnoid space, and with a simultaneous (pathological) increase in CSF volume in front of the blockade. These results eliminate the possibility of the appearance of a pressure gradient, at least in communicating and external hydrocephalus, and call for a revision of the popular theory regarding how CSF accumulates in the CSF system. But these results also offer a potential explanation for the fact that a patient develops acute ventricular dilatation when the aqueduct is completely obstructed by a clot after bleeding into the CSF, as well as why the patient should undergo urgent extraventricular drainage. Namely, as in the mentioned experiments (Klarica et al., 2009), the patients' ventricular system is blocked and the CSF volume in front of the obstruction continuously

increases by a pathological process. This way the ICP increases, a pressure gradient develops and the ventricles should acutely dilate. The pathological CSF volume increase could be due to the bleeding itself, or as a consequence of increased osmolarity caused by aseptic inflammation and/or decomposition of the blood. The pathological process involving increased CSF osmolarity should be the first to appear. Increasing osmolarity leads to water influx from the surrounding tissue, and to an increase in the CSF volume (see Section 4.2.1.1. - Impact of the osmotic force). When the newly formed clot blocks the aqueduct, it leads to a rapid increase in ICP, creating a transmantle pressure gradient and finally an acute enlargement of the brain ventricles. It should be noted that a rapid increase in ICP and enlargement of the brain ventricles could also be obtained by a sudden osmolarity increase in the ventricles' CSF, even when the CSF system is completely open (Klarica et al., 1994; see Section 8. – Mechanisms of hydrocephalus development which are not in accordance with the classical hypothesis of CSF hydrodynamics).

Additionally, it is necessary to say that the role of increased intracranial pressure is not entirely clear, either regarding ventricular enlargement or the symptomatology of hydrocephalus. In some patients, a moderate increase in ICP is accompanied by hydrocephalus and mental changes, while in others, with high ICP, the ventricles and mental functions remain unaltered (Hakim et al., 1976). However, in extremely severe cases, crippling neurological deficits were dramatically reversed by using the shunt treatment, although the enlarged ventricles showed a definite reduction in size (Foltz and Ward, 1956).

All of the results mentioned so far would seem to argue against the theory that the mechanical obstruction of the CSF pathways and impaired CSF absorption are the main causes of hydrocephalus. This implies that hydrocephalus may not fundamentally be a disorder of the CSF bulk flow.

7. Some controversies in the treatment of hydrocephalus

Despite improvements in shunting techniques and the increasing sophistication in investigating hydrocephalus by computerized tomography (CT) and magnetic resonance imaging (MRI), the treatment of hydrocephalus remains quite a challenge and there is still a high complication rate. There are only few conditions in neurological practice more frustrating to manage than hydrocephalus. It is a disturbance whose capricious nature has its origins in the incomplete understanding of the pathophysiology; where diagnostic difficulties abound despite sophisticated aids to investigation; and for which an apparently straight forward operative procedure may have devastatingly disastrous consequences (Punt, 1993). Although these features of hydrocephalus were presented nearly twenty years ago, the picture today is almost the same and continues to be far from satisfactory, indicating that much research is still needed. Regardless of the significance of hydrocephalus treatment, we will more closely analyze only the choroid plexectomy and the shunt treatment, two methods of treatment which have shown some results that are difficult to fit into the classical hypothesis of CSF hydrodynamics.

The treatment of hydrocephalus can be divided into two main groups; medical and surgical treatment. In terms of medical treatment, the methods used are: compressive head wrapping, drug treatment and lumbar puncture; and in the case of surgical treatment: choroid plexectomy, external ventricular drainage and various types of intracranial and extracranial shunts.

7.1. Choroid plexectomy

Choroid plexectomy was introduced by Dandy (1918; 1945) as a mean of decreasing CSF production within the ventricular system. For many years this surgical procedure was the most popular form of treatment for infantile hydrocephalus in the United States. However, over the

decades it became clear that bilateral extirpation and/or cauterization of the choroid plexuses invariably failed to benefit the patients. As was mentioned, because of universally unsatisfactory results, choroid plexectomy was abandoned by neurosurgeons as a treatment for hydrocephalus, so today it is an operation of historic interest only, and has no place in the treatment of hydrocephalus (Lapras et al., 1988; Milhorat, 1976). Despite these discouraging results, the introduction of the endoscopic method renewed an interest in different surgical procedures on the choroid plexuses, especially in the mid 90s (Enchev and Oi, 2008; Pople and Ettles 1995; Wellons et al., 2002). Although the results of the treatments were somewhat better than those using a classic surgical approach, the same problems still persisted. The ventricular size was not significantly reduced by choroid plexus coagulation and only 35% of the patients achieved long-term control without cerebrospinal fluid shunts (Pople and Ettles 1995). In another study (Griffith and Jamjoom, 1990), in 48% of the cases, shunting was required, which was done from one week to thirteen months after the choroid plexus coagulation. And so, even when the plexus is removed, the development of hydrocephalus can still occur. These results show that the role of the choroid plexus in the pathophysiology of hydrocephalus is still unclear; that our knowledge of hydrocephalus pathophysiology is still insufficient; and the results clearly confirm the above mentioned claims about CSF formation related to the choroid plexuses. Anyhow, although each new generation of endoscopes brings a resurgence of interest in this approach, it has never gained anything more than transient acceptance because of its fundamental ineffectiveness.

7.2. Shunt treatment

As it is believed that all forms of hydrocephalus are essentially obstructive in nature, the ideal treatment would be the removal of the obstructive lesion. Since this access to the obstructive lesion is very rarely possible, the most commonly used approach is to bypass the lesion by using a shunt.

That way, CSF, which is permanently produced by “CSF pumps” (choroid plexuses) in front of the lesion, would be delivered to the CSF absorption place instead of causing hydrocephalus. For that reason, the internal part of the shunt should be introduced into the dilated CSF space, and the external part into almost any other body cavity. But the only routes that remain in current use are the ventriculo-peritoneal, ventriculo-atrial, ventriculo-pleural and theco-peritoneal. Today, the shunt therapy, despite all the shunt complications, remains the most effective treatment of hydrocephalus.

This is one of the most interesting topics for neurosurgeons, and although there are many questions that should be answered, we will focus our discussion only on arrested hydrocephalus. In 17–26% of patients with hydrocephalus, arrest of the process apparently occurs after some time, and removal of the shunt system is well tolerated (Hayden et al., 1983; Holtzer and de Lange, 1973; Lorber and Pucholt, 1981). The hydrocephalus is classified as arrested if the ventricular size is no longer increasing and if the CSF pressure is normal. Due to the situation that the arrest persists even if the shunt no longer functions or is removed, the term shunt independent arrest was introduced (Holtzer and de Lange, 1973). Of the 127 children treated with a Holter ventriculocardiac shunt, 27% were no longer shunt dependent; their shunt systems were removed and hydrocephalus remained arrested from 1-12 years (Guidetti et al., 1976; Holtzer and de Lange, 1973). Half of these compensated children had obstructive hydrocephalus.

What does it mean from the standpoint of the classical hypothesis? It means that the shunt is not functioning; that the CSF pathways are still blocked; that the place of CSF absorption (subarachnoid space) is out of reach of nascent CSF; that “CSF pumps” produce CSF properly (430-580 ml/day; reviewed in Orešković and Klarica, 2010; Fig. 6); and that after all of this, nothing happens inside the brain ventricles. CSF pressure does not increase, brain ventricles do not dilate any further, and patients have no clinical problems. How can this be explained in light of the classical hypothesis? To be honest, there is no explanation except that the development of hydrocephalus is not related to the hypothesis, especially if we take into account the many

previously described cases of arrested hydrocephalus that remained dormant for years, but subsequently required shunt revision when some other pathological process took place within the cranium (Hayden et al., 1983; Zulch, 1958). This rapid deterioration in patients could be explained the same way as in the case of acute ventricular dilatation caused by aqueduct clot obstruction during bleeding into the ventricular CSF (see Section 6. – The transmantle pressure gradient).

Despite more than 50 years of research on shunts, the long-term results are far from satisfactory and we must acknowledge that a shunt is not a cure for hydrocephalus, but it is only a "patch", an unreliable one at that (Bergsneider et al., 2006). It appears that rather than continuously increasing the cost and complexity of shunts, we need more research to gain a better understanding of the conditions that lead to hydrocephalus.

8. Mechanisms of hydrocephalus development which are not in accordance with the classical hypothesis of CSF hydrodynamics

Today, literature mentions several causes that have lead to the development of hydrocephalus, which are not in line with the classical hypothesis. These are cases when the development of hydrocephalus is not related to secretion, circulation and absorption of CSF, and it is not a consequence of impaired CSF circulation, insufficient CSF absorption by arachnoid villi or CSF oversecretion.

8.1. Experimentally induced hydrocephalus

Bering (1962) suggested that the choroid plexuses were the generators of force for ventricular enlargement in dogs. It was presented that hydrocephalus developed as a result of the choroid plexuses pulsations which generated their pumping force as they filled with blood via an arterial

pulse. This created compression waves in the ventricles, and if the ventricles were blocked, the intraventricular pulse increased correspondingly and this entire force had to be absorbed by the brain. Due to the increased pressure waves, the ventricular walls should dilate. Bering's observations were criticized by Portnoy et al. (1985), who came to the conclusion that the CSF pulse wave seen in hydrocephalic dogs was the result of how the cerebrovascular bed processed the cardiac pulse wave, and was independent of the hydrocephalic process, and there was no evidence that the pulse wave produced hydrocephalus. However, the use of the mechanically induced ventricular pulsations has clearly shown that hydrocephalus can be produced by pulsatile waves. Namely, hydrocephalus was induced in lambs by increasing the amplitude of the CSF intraventricular pressure mechanically (Di Rocco et al., 1978), without modifying the mean CSF pressure and without interfering with CSF circulation or CSF absorption. The fact that the CSF system was completely passable and that CSF absorption was not insufficient, clearly indicates that the high-amplitude intraventricular CSF pulsation is the genesis of ventricular enlargement.

The increase in CSF osmolarity as a reason for the development of hydrocephalus was shown on rats by a chronic (12 days) intraventricular infusion of hyperosmolar substances (Krishnamurthy et al., 2009). The hyperosmolar fluid was infused by a microcatheter connected to an Alzet osmotic minipump inserted through the needle track into the lateral ventricle. Infusion of hyperosmolar solutions resulted in ventricular enlargement as a consequence of the increase in the osmotic load in the ventricles and the water influx into the ventricles to normalize the newly formed osmotic gradient, which finally resulted in hydrocephalus. It is important to note that during the process of hydrocephalus development the CSF system had been fully open, the transmantle pressure gradient was not observed, the compliance changes were not seen, nor was the CSF pressure affected. A very similar effect of hyperosmolarity on dilatation of the brain ventricles was obtained in acute experiments on dogs (Klarica et al., 1994). The acute application of a hyperosmolar solution into the ventricle without any unphysiological change in ICP was performed by using the microvolume

exchange method (Klarica et al., 1994). Five minutes after the application of the hyperosmolar substance into the ventricular CSF, ICP increased twofold, and a slight enlargement of the lateral ventricle was seen on the CT scan. In the same time, the absence of any significant periventricular edema on the CT scan suggested that the increase in CSF osmolarity caused augmentation of the ICP by the osmotic inflow of water volume from the surrounding tissue, which may have led to dilatation of the brain ventricles. If after such a short period of time (5 min) the changes were so indicative, in the case of chronic treatment, the development of hydrocephalus should naturally be expected, as was shown in experiments on rats. In experiments on dogs, as well as on rats, obstruction in CSF circulation or absorption has not been present, so it is obvious that the classical theory of fluid accumulation and development of hydrocephalus calls for a revision, in which osmotic processes should play a very important role (see Section 4.2.1.1. – Impact of the osmotic force).

8.2. Pulsatility hypotheses

Besides experimentally inducing hydrocephalus by pulsation, there has been considerable interest in an effort to present that hydrocephalus may develop as a result of pulsatility, causing ventricular dilatation (Foltz et al., 1990; Madsen et al., 2006). The hydrodynamic concept by Greitz (2004; 2007) stated that communicating hydrocephalus was caused by a decrease in intracranial compliance, increasing the systolic pressure transmission into the brain parenchyma. The increase in systolic pressure in the brain should distend the brain toward the skull and simultaneously compress the periventricular region of the brain against the ventricles, with the final result being the enlargement of the ventricles and the narrowing of the subarachnoid space. The fact that systolic pressure could be involved in the pathogenesis of hydrocephalus was elaborated in experiments on

cats (Miše et al. 1996) in which the importance of systolic craniospinal displacement was suggested as the reason for the hydrocephalus development.

A similar hypothesis was proposed (Egnor et al., 2002) in which the cause of CH was the redistribution of CSF pulsations inside the cranium. The redistribution should be the result of the dissipation of arterial pulsation into the subarachnoid space, and the flow of the stronger arterial pulsations to the choroid plexus and capillary and venous circulation. The pulse pressure gradient between the ventricles and the SAS causes ventricular dilatation at the expense of the SAS. The malabsorption of CSF is not involved as a causative factor in the development of any of the mentioned hydrocephalus cases.

The fact is that in hydrocephalic patients, there was no evidence of transmantle gradient in pulsatile ICP found (Eide and Saehle, 2010), i.e., pulsatile ICP is higher within the CSF of the ventricles than within the SAS. However, it cannot be excluded that the gradients in pulsatile pressure might be present over a certain period of time, until the ventricles have reached a given size.

The hypothesis that chronic ventricular distension and the accompanied hydrocephalus can be explained by the combined effect of a reversal interstitial fluid flow into the parenchyma, and by reduced tissue elasticity, can be included in this discussion (Pena et al., 2002). These changes have been incorporated into a computer simulation of hydrocephalus in which the CSF pressure in the ventricles and SAS were higher than in parenchyma, and the elasticity of gray and white matter was reduced. The simulation revealed a substantial ventricular distension, and as a consequence of the movement of CSF into the tissue, a pressure gradient was established between the CSF spaces and the cerebral mantle, i.e. an intramantle pressure gradient.

8.3. Vasogenic hypotheses

The venous hypothesis of hydrocephalus by Williams (2007) proposes that all instances of hydrocephalus are linked together because of CNS venous insufficiency, as a result of which the pressure level continues to increase. An increase in CNS volume (with space occupying lesions) causes compression of the veins. This may result in increased venous pressure, a reduction in the blood flow out of the CNS, and a reduction of CSF absorption back into the blood circulation. Therefore, any increase in CNS tissue volumes can lead to CSF accumulation and the development of hydrocephalus. It is also believed that a combination of a reversible form of cerebral ischemia and a reduction in venous compliance in the territory drained by the superior sagittal sinus are associated with the development of hydrocephalus (Bateman, 2000 and 2003). Andeweg (1991) has reviewed that an insufficient venous flow from the brain can cause cerebral atrophy and ventricular dilatation. The venous insufficiency was related to an occlusion of the great vein of Galen, and the possible explanation that the ventricles dilate due to atrophy of the periventricular white matter caused by insufficient blood perfusion.

Since the evidence suggests that patients with chronic adult hydrocephalus have increased incidences of vascular disease, it was hypothesised that chronic ventriculomegaly may result in cardiac dysfunction (Luciano and Dombrowski, 2007). Furthermore, it was suggested that a feedback loop exists between hydrocephalus and cardiac disease. Namely, if changes in cardiac function can increase the brain compliance and exacerbate hydrocephalus, which can result in congestive heart failure, then chronic hydrocephalus and chronic cardiac failure may represent a vicious pathophysiologic cycle. This was supported by the observation that hydrocephalus may increase the risk of cardiovascular disease via the compression of the cardioregulatory nuclei near the hypothalamus.

In our discussion, we can include an observation made on mice, that the water-transporting protein aquaporin-4 (AQP4) plays a significant role in the transparenchymal CSF absorption in hydrocephalus (Bloch et al., 2006). It was shown that the deletion of AQP4 accelerates the progression of kaolin induced hydrocephalus by decreasing parenchymal extracellular fluid clearance. Since the water-transporting protein aquaporin-4 enhances CSF absorption it was suggested that maybe this approach could provide a rational basis for the evaluation of AQP4 inductions as a nonsurgical therapy for hydrocephalus.

8.4. Does the obstruction of CSF pathways cause hydrocephalus? (New insights into the pathophysiology of hydrocephalus)

Based on all of the mentioned data, we believe that a blockade of the CSF pathways *per se,* without other active pathological processes, would not cause clinically manifested hydrocephalus. So far, we have presented the facts which suggest that hydrocephalus may develop in a fully open and passable CSF system (see Section 8.1. - Experimentally induced hydrocephalus); that the blockade of the CSF pathways is very often a consequence of the development of hydrocephalus and not its cause (see Section 5.1.1. - Hydrocephalus and obstruction); and that despite an evident occlusion of the CSF pathways, the brain ventricles do not dilate and hydrocephalus does not develop (see Sections 5.1.2. - Kaolin induced hydrocephalus and 7.2. - Shunt treatment).

Therefore, we propose a new concept of hydrocephalus development. Namely, regardless of how hydrocephalus is created and how it is defined, although the definition is still subject to debate (Bergsneider et al., 2006), the fact is that hydrocephalus is an excessive amount of CSF which is accumulated within or outside the brain. As was already mentioned several times, 99% of CSF is water (Bulat et al., 2008), and for this reason it is evident that hydrocephalus is an excessive amount of water. As there are almost no obstacles/barriers for water within the CNS, and as water quickly

and easily crosses from one compartment to another (blood, CSF, ISF, intracellular fluid), the cause of the excessive accumulation should be searched for in pathophysiological conditions leading to the displacement of water into the CSF space, and its accumulation within the CSF area. According to the new working hypothesis, the changes in the ISF-CSF functional unit should be included in the pathophysiology of fluid accumulation inside the CSF system. Thus, we presume that all pathological processes in which an increase of CSF osmolarity or hydrostatic pressure takes place will result in hydrocephalus development without significant obstruction or stenosis of the CSF system (see Sections 4.2.1. - Maintenance of the cerebrospinal fluid volume). It is well known that pulsatile CSF movement in a cranio-caudal direction exists as a consequence of systolic-diastolic oscillations of cranial blood circulation through the vessels. Stenosis or the obstruction of CSF pathways, caused by different pathological processes, in which significant disruption of that physiological CSF to-and-fro movement has occurred, could lead to decreased blood perfusion and/or ischemia of a certain tissue region. These processes should subsequently result in damage to the brain parenchyma and an increase in the CSF space. This concept is very compatible with the new hypothesis of CSF dynamics (Bulat and Klarica, 2010; Orešković and Klarica, 2010) and offers possible explanations for the controversy regarding hydrocephalus development. It should be stressed that pathophysiological processes similar to those included in hydrocephalus etiology should exist in the rest of the body, anywhere that pathological accumulation of water/fluid is present.

In our opinion, a blockade of the CSF pathways is the important preferential factor which could accelerate the development of hydrocephalus and result in noticeable severity. We assume that hydrocephalus develops over a prolonged period, and that it is a chronic rather than an acute process. It may change from chronic into its acute form under certain conditions (ventricular dilatation with high CSF pressure) due to the appearance of a transmantle pressure gradient. As was elaborated, a transmantle pressure gradient can develop only if two conditions coexist at the same

time: completely blocked ventricular CSF pathways, and a pathological process which increases fluid volume inside isolated ventricles (see Section 6. – The transmantle pressure gradient). In the situation in which pathological changes occur along with an interruption of CSF communication in front of the blockade (e.g. bleeding, infection, a tumor, a cysticercous cyst), this should lead to accelerated ventricular dilatation and the occurrence of an acute hydrocephalus phase.

To summarize, although a series of arguments in favor of a new concept have already been presented in this paper, by which the concept of noncommunicating, as well as communicating, external and arrested hydrocephalus development could be explained, it will take a number of clinical analyses on hydrocephalus patients and animal experiments to prove this concept.

9. Facts and illusions regarding classical pathophysiology of hydrocephalus

The fact is that hydrocephalus can occur in a fully open and passable CSF system without impaired CSF circulation and absorption (pp. 26, 27, 41, 42).

The fact is that despite the established blockade of CSF pathways, it was reported that (the development of) hydrocephalus was not obtained (pp. 27, 29, 30, 32).

The fact is that hydrocephalus may occur without an elevation in intracranial pressure (pp. 32, 33, 41, 42).

The fact is that hydrocephalus may occur without a transmantle pressure gradient (pp. 31, 32, 33, 41, 42).

The fact is that a transmantle pressure gradient cannot develop in communicating and external hydrocephalus (open CSF system) (pp. 30, 31, 32, 33, 34, 35, 36).

The fact is that in shunt therapy of obstructive hydrocephalus, there are patients in which the shunt does not work, but there is no worsening of their health conditions or the progression of the hydrocephalus (arrested hydrocephalus) (p. 39).

The illusion is that communicating, external and arrested hydrocephalus can be explained in the context of the classical hypothesis of CSF hydrodynamics (pp. 31, 32, 33, 34, 41).

The illusion is that treatment by choroid plexectomy should eliminate hydrocephalus (pp. 37, 38).

The concept of the classical hypothesis of CSF hydrodynamics is an illusion (Bulat and Klarica, 2010; Orešković and Klarica, 2010), so it is also an illusion that impaired CSF circulation, insufficient CSF absorption by arachnoid villi and CSF oversecretion are the main reasons for the occurrence of hydrocephalus (pp. 26, 27, 28, 29, 30, 31, 32, 33, 35, 36, 39, 41, 42).

10. Concluding remarks

Finally, it can be concluded that hydrocephalus is a pathological state rather than an illness, characterized by an excessive accumulation of CSF within the ventricles and the central canal of the spinal cord, or within the subarachnoid spaces. It is typically characterized by an enlargement of the head, prominence of the forehead, brain atrophy, mental deterioration and convulsions. It may be congenital or acquired, and may have slow or acute development. This pathological state is not the result of some unique etiopathogenesis, but it is rather the result of different pathophysiological processes (inflammations, bleeding, tumors, increased CSF osmolarity, trauma, increased CSF pressure on the surrounding brain tissue, an increase in the ventricular CSF pulse pressure) which sometimes overlap and work together. However, hydrocephalus could sometimes (in experiments) also be provoked by just one of them (increased CSF osmolarity or increased wave pulsation in an intact CSF system).

It is obvious that the development of hydrocephalus is a very complex problem and it is impossible to imagine and conclude that its solution is simple. But what we can conclude is that the interpretation of the development of hydrocephalus using the classical hypothesis of CSF secretion, circulation and absorption, certainly does not offer a viable solution. Thereby, the reason for so much confusion regarding hydrocephalus today is in good part the result of an uncritical insistence on the interpretation of hydrocephalus development in light of the classical CSF hypothesis. Unfortunately, this is also the reason why knowledge about hydrocephalus pathogenesis is still rather insufficient. We can also conclude that the presence of hydrocephalus does not bear out the classical CSF hypothesis, or that the hypothesis could explain the development of hydrocephalus, as was implicated by Dandy's historical experiment (1919). On the contrary, the existence of hydrocephalus is considerable evidence against the classical CSF hypothesis. In other words, if we want to explain the development of hydrocephalus, it would be better to abandon the classical concept of CSF hydrodynamics. The newly suggested CSF hypothesis (Bulat and Klarica, 2010; Klarica et al., 2009; Orešković and Klarica, 2010) is based on the fluid changes in the CNS which follow a pattern similar to the fluid changes in other parts of the body. Hence, the new hypothesis does seem realistic because it provides opportunities for a reasonable explanation of both the clinical and experimental results. In light of the reasons mentioned, it is certainly justified for the researchers to ask themselves if the questions raised so far, regarding the CSF pathophysiology and hydrocephalus, were in fact, the right ones (Bergsnider et al. 2006; Levine, 2008). Therefore, we would suggest that factors such as osmotic and hydrostatic pressures should certainly be included in the contemplations about the hydrocephalus pathophysiology, since those are the factors that crucially regulate the ISF-CSF volume (functional unit). Additionally, if the disturbance of the physiologic to-and-fro CSF movements, created as a consequence of the narrowing of the CSF pathways, leads to the pathologic hydrodynamics of cerebral perfusion, it could initiate hydrocephalus development. From all of this it seems to arise that the development of

hydrocephalus has a slow nature, which can assume an acute form (enhanced development of hydrocephalus) only under certain biophysical conditions (e.g. narrowing, created by the slow shifting of the brain masses; intraventricular bleeding; extensive CNS inflammation).

However, the recognition of hydrocephalus as a brain pathological state should be thoroughly reevaluated with an open mind (and without the historical misconceptions), and this should eventually lead to new therapy and treatment methods. The updating of experimental and clinical work should always be done with this in mind.

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12. Acknowledgements

With all of our heart, we wish to thank our teacher, Prof. *emeritus* Marin Bulat, for introducing us to the complex field of CSF hydrodynamics and for directing us regarding accurate analytical and critical thinking about the scientific work. We also sincerely thank Milan Radoš Ph.D. for drafting the figures presented in this paper. This work has been supported by the Ministry of Science, Education and Sport, Republic of Croatia (Projects: 1. Hydrodynamics of cerebrospinal fluid No. 098-1080231-2328 and 2. Pathophysiology of cerebrospinal fluid and intracranial pressure No. 108-1080231-0023).

Figures legend

Figure 1. Projection of the ventricles and subarachnoid spaces on the left human surface and location scheme of the choroid plexuses, arachnoid granulations and the distribution of CSF in the central nervous system. CSF is represented by the white area, and the arrows point in the direction of CSF circulation and the sites of CSF absorption.

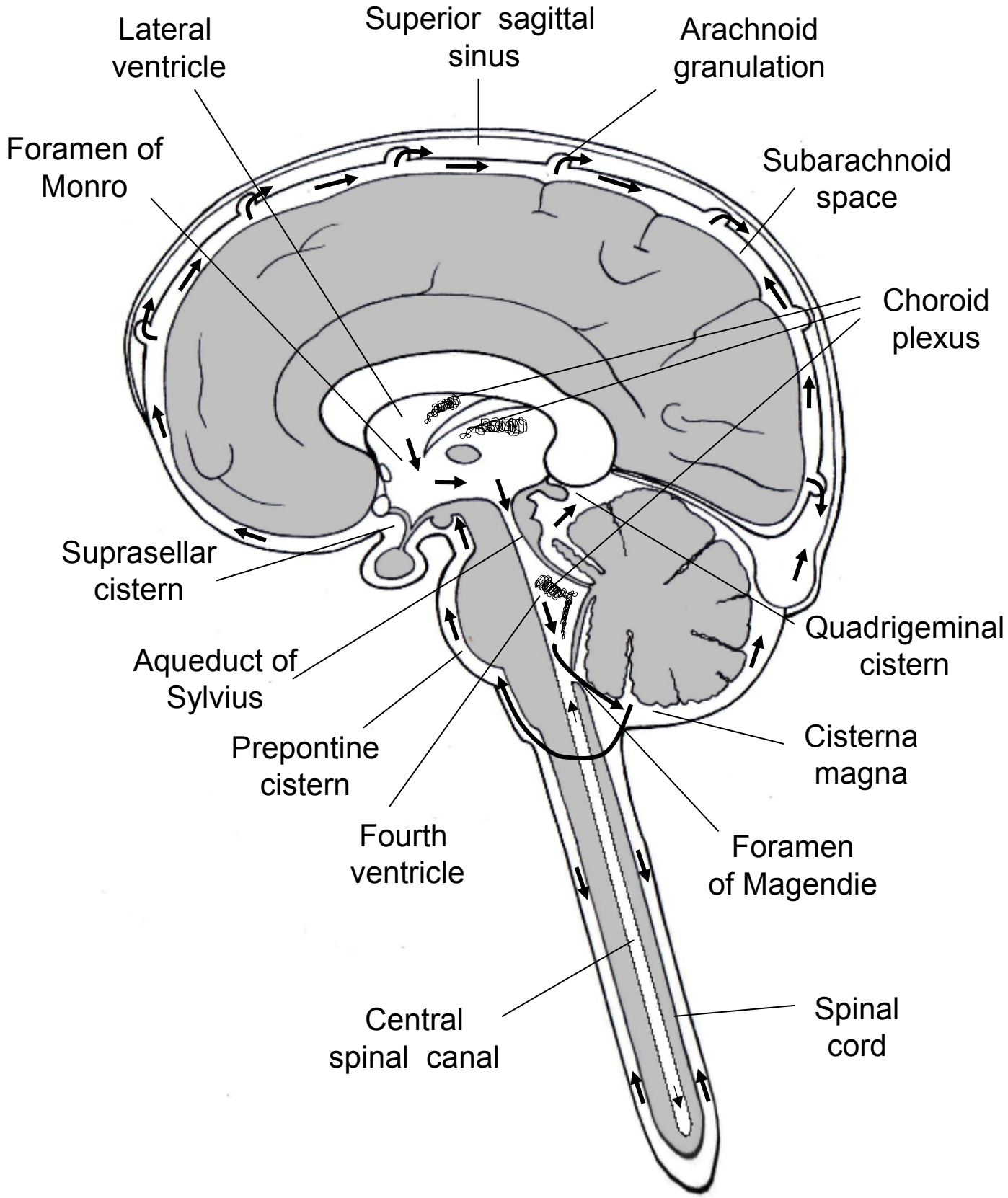

Lateral ventricle
Superior sagittal sinus
Arachnoid granulation
Foramen of Monro
Subarachnoid space
Choroid plexus
Suprasellar cistern
Quadrigeminal cistern
Aqueduct of Sylvius
Prepontine cistern
Cisterna magna
Fourth ventricle
Foramen of Magendie
Central spinal canal
Spinal cord

Figure 2. Structure scheme of the choroid plexus as a physiological CSF pump. Branched structure of the choroid plexus with villi projecting into the brain ventricle. Each plexus consists of a network of capillaries covered by a single layer of cuboidal epithelial cells. The bold arrows represent the direction and active nature (secretion) of CSF formation.

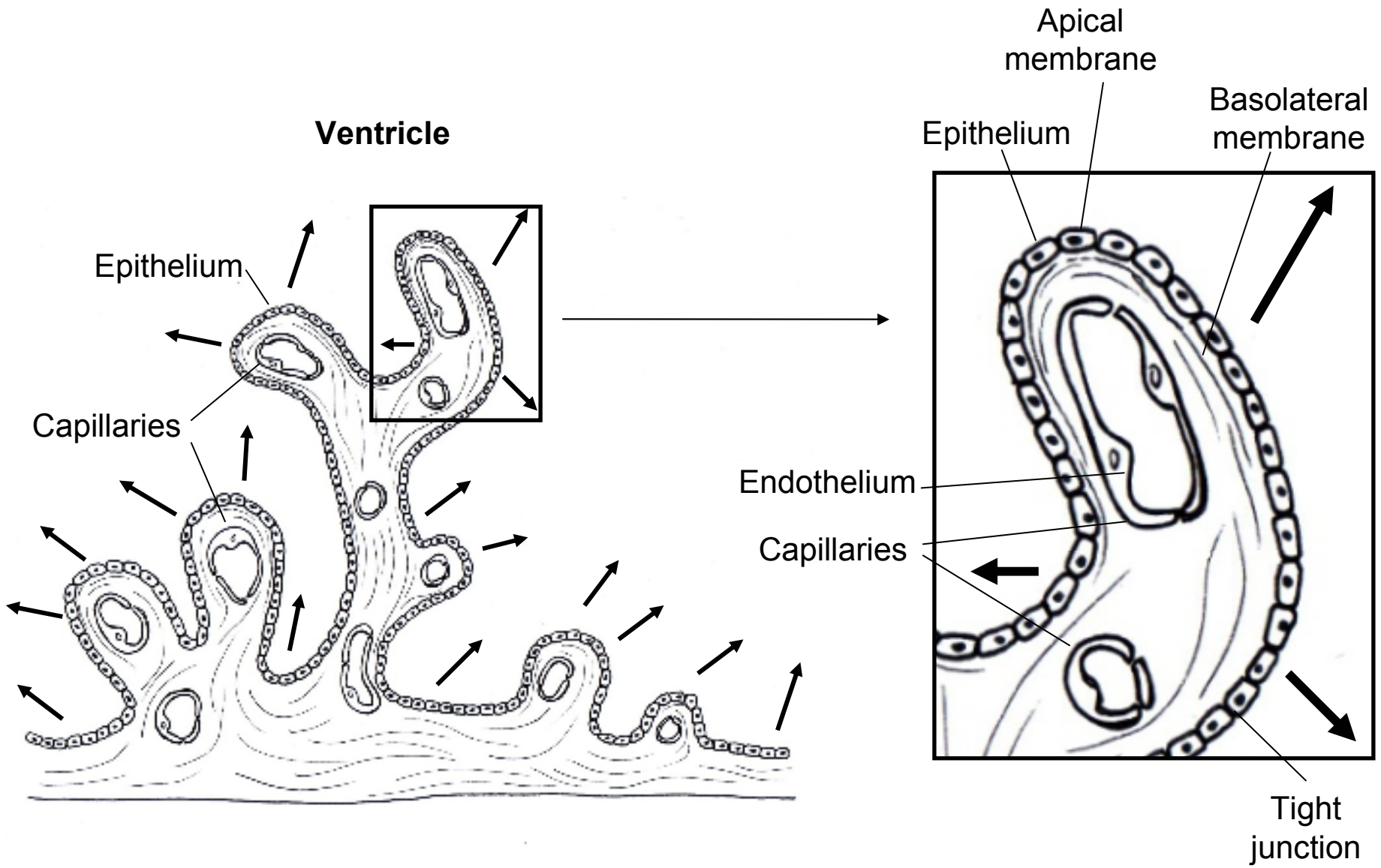

Ventricle
Epithelium
Capillaries
Apical membrane
Basolateral membrane
Epithelium
Endothelium
Capillaries
Tight junction

Figure 3. Scheme of the main site of CSF absorption in relation to the arachnoid granulations and dural sinuses, shown in the coronal plane. The diagram represents the anatomical relationship between the meninges, subarachnoid space, blood and cortical CSF. The bold arrows show passive absorption through the arachnoid granulations from the CSF into the blood.

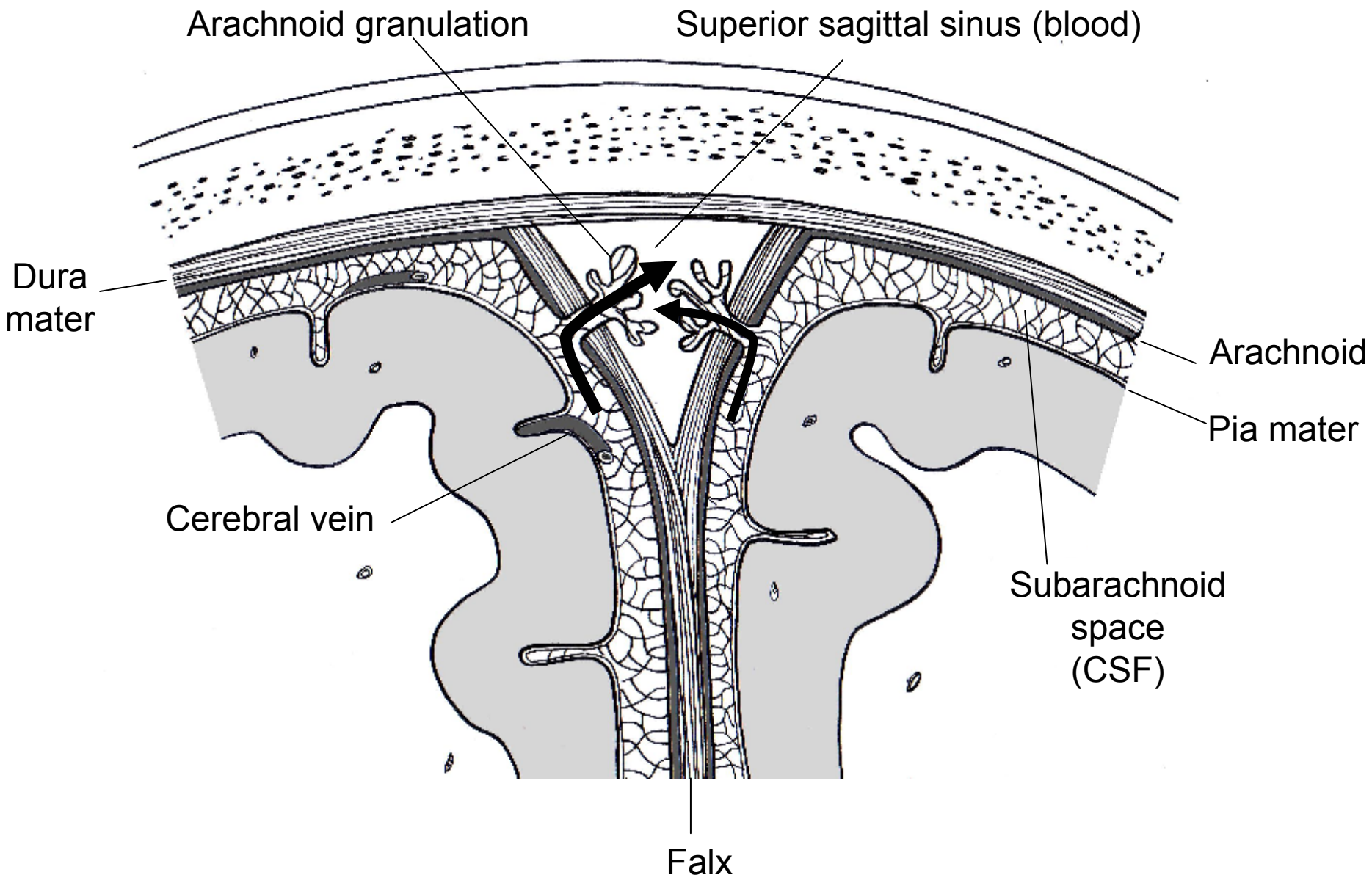

Arachnoid granulation
Superior sagittal sinus (blood)
Dura mater
Arachnoid
Pia mater
Cerebral vein
Subarachnoid space (CSF)
Falx

Figure 4. Schematic representation of marked hydrocephalus with an enormously dilated lateral ventricle, and the third brain ventricles with flattened cortical nervous tissue presented in the left lateral plane. The CSF system is represented by the white area, and the nervous tissue by the gray area.

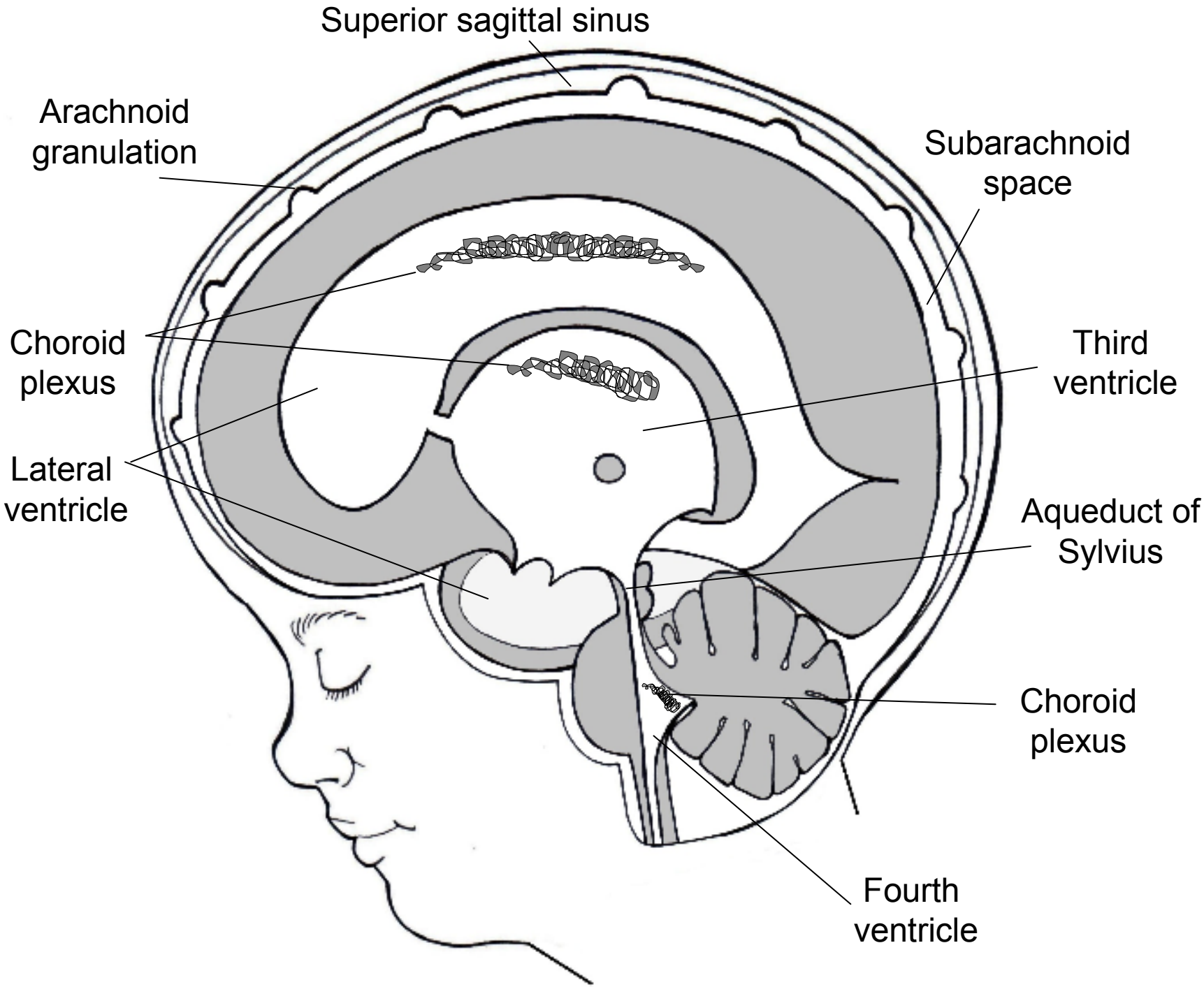

Superior sagittal sinus
Arachnoid granulation
Subarachnoid space
Choroid plexus
Third ventricle
Lateral ventricle
Aqueduct of Sylvius
Choroid plexus
Fourth ventricle

Figure 5. Schematic representation of communicating or non-obstructive hydrocephalus. The insets represent the functions of the arachnoid granulations and choroid plexuses. At the arachnoid granulations, the black square represents a blockade of the CSF drainage pathways, and the bold arrows represent the impossibility of CSF absorption into the superior sagittal sinus. At the choroid plexuses, the black arrows show simultaneously undisturbed active CSF formation (secretion).

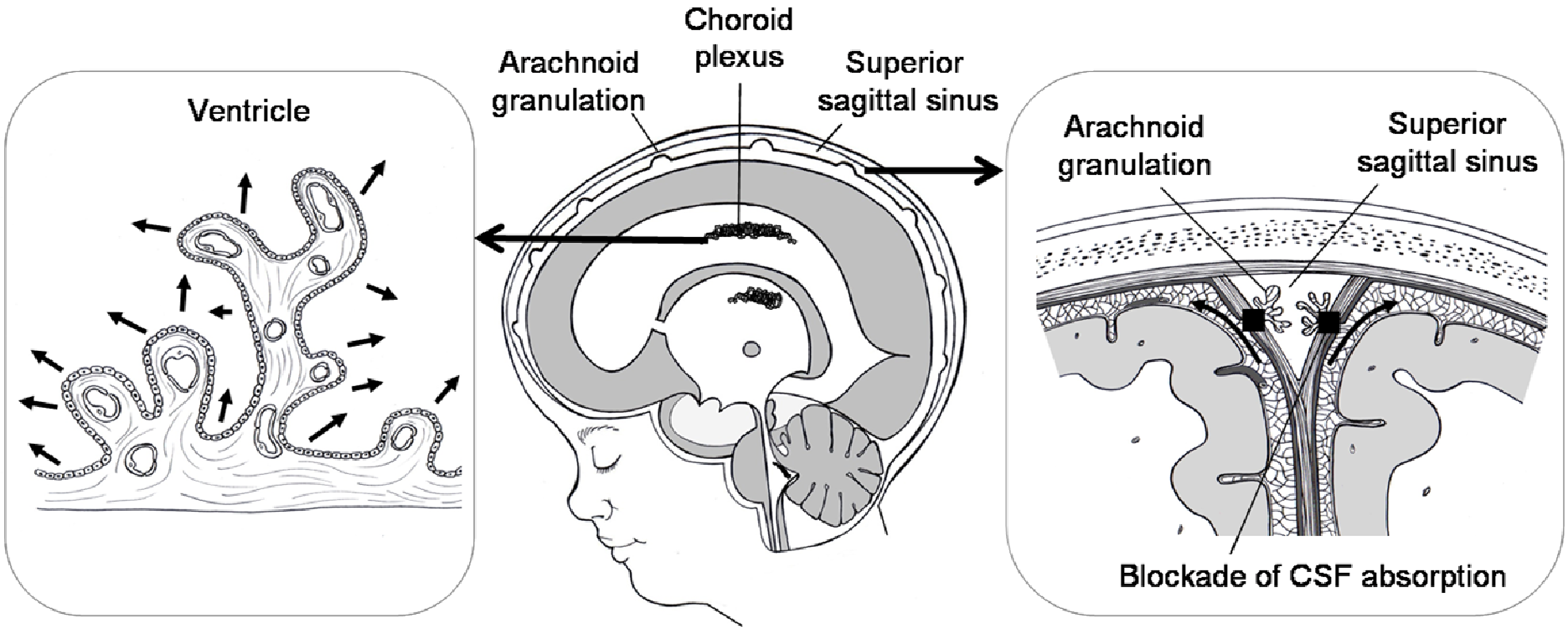

Ventricle
Arachnoid granulation
Choroid plexus
Superior sagittal sinus
Arachnoid granulation
Superior sagittal sinus
Blockade of CSF absorption

Figure 6. Schematic representation of non-communicating or obstructive hydrocephalus. The black square represents the complete blockade of the aqueduct of Sylvius. The insets represent the functions of the arachnoid granulations and choroid plexuses. The bold arrows on the arachnoid granulations represent the undisturbed CSF absorption through the villi arachnoides into the venous blood. The black arrows on the choroid plexuses show simultaneously undisturbed active CSF formation (secretion).

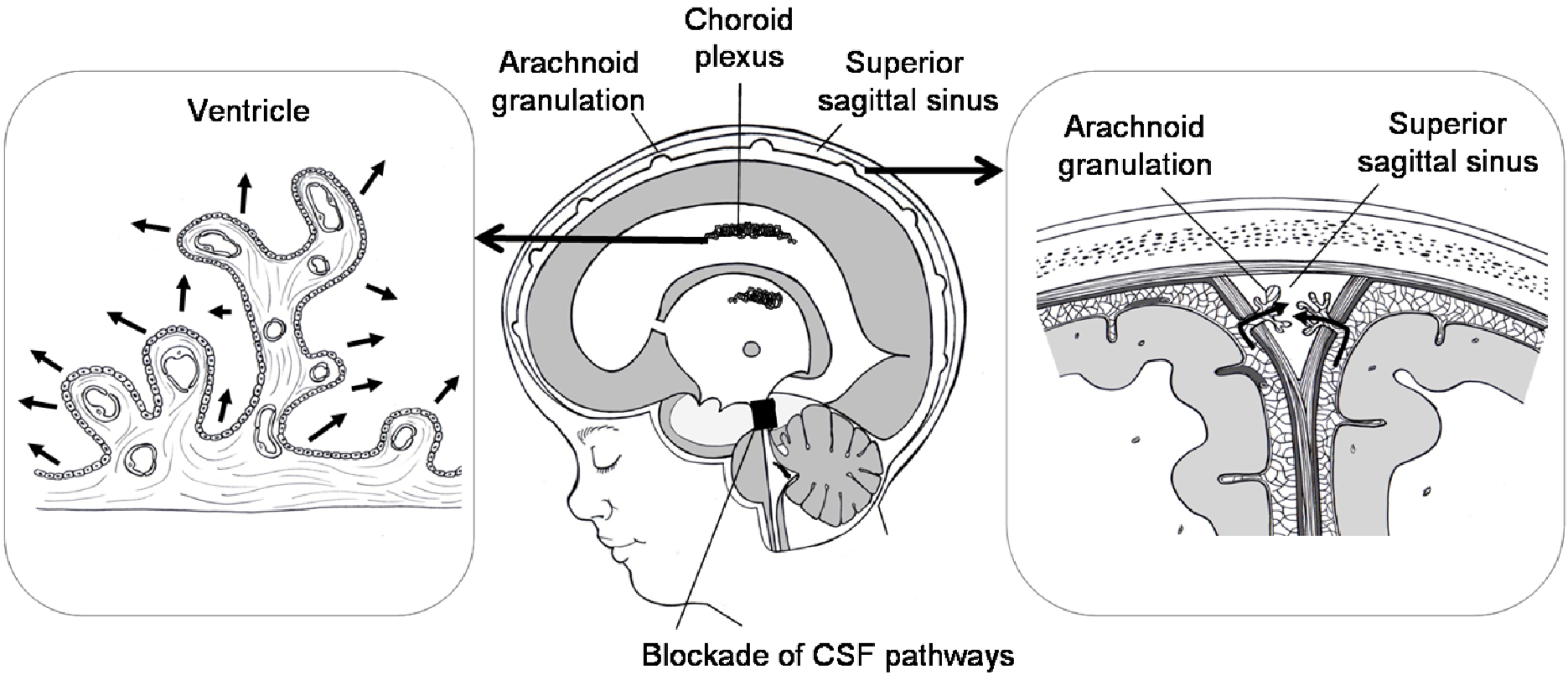

Ventricle
Arachnoid granulation
Choroid plexus
Superior sagittal sinus
Blockade of CSF pathways
Arachnoid granulation
Superior sagittal sinus

Figure 7. Schematic representation of the new working hypothesis of CSF hydrodynamics. The black bold arrows represent the CSF bulk (water) exchange with the surrounding tissue throughout the CSF system.

A. Larger blood vessels enter deep into the brain tissue. The substances with large m.w. can, after being applied into the CSF system, rapidly enter deep into the tissue via perivascular spaces and reach the vast capillary net. Due to the slow elimination from ISF-CSF into the blood, those substances should be widely distributed inside the brain parenchyma and along the CSF system. On the other hand, smaller molecules like water can rapidly reach the capillary net situated under the pia mater after application into the CSF, and then they can be removed from the ISF. Similarly, the molecules of water from the ventricles can rapidly reach the choroid plexus and the capillaries under the ependyma surrounding the ventricles.

B. The contact surface of the capillaries inside the brain is vast (250cm^2/g of the tissue), and it is about 5000 times larger than the surface of the capillaries inside the choroid plexus. Apart from this, the surface of the arachnoid villi and perineural sheaths of the cranial and spinal nerves are not assumed to be greater than 10 cm^2. Filtration of water from the blood to the ISF takes place at the arterial capillaries (high capillary pressure), and absorption is observed at the vessels under low hydrostatic pressure (venous capillaries, postcapillary venules). The rapid turnover of water volume between the cerebral capillaries and ISF-CSF takes place. Due to great differences between the contact surface of the capillaries in the brain tissue and in the choroid plexus, it should be expected that the volume of CSF-ISF is predominantly regulated inside the brain parenchyma. The differences in hydrostatic pressure inside the capillaries are shown by the intensity of the color gray.

C. A scheme of the relationship between a cerebral capillary endothelial cell and the surrounding structures (pericytes, neurons, astrocyte end-feets, basement membrane) which contribute to the blood-brain barrier function.

D. The ways substances pass through the membranes of the cerebral capillaries' endothelial cells. A passive diffusion is highly expressed regarding liposoluble substances, and it is conducted under gradient of concentration. The net transport of water depends on the gradients of hydrostatic (hydrostatic capillary pressure-HPc, and hydrostatic interstitial pressure-HPi) and osmotic (osmotic capillary pressure-Opc, and osmotic interstitial pressure-Opi) pressures. The transport systems enable the entrance of more hydrophilic and larger molecules from the blood to the ISF (influx; the straight arrow at the top of the figure). There are also transport systems which enable the return of molecules from ISF-CSF into the bloodstream (efflux; the straight arrow at the bottom of the figure). The transport of molecules with large m.w. often occurs via endosomes (the formation of the endocytic vesicles; it can also be receptor-dependent). Reproduced with permission from Orešković and Klarica 2010.

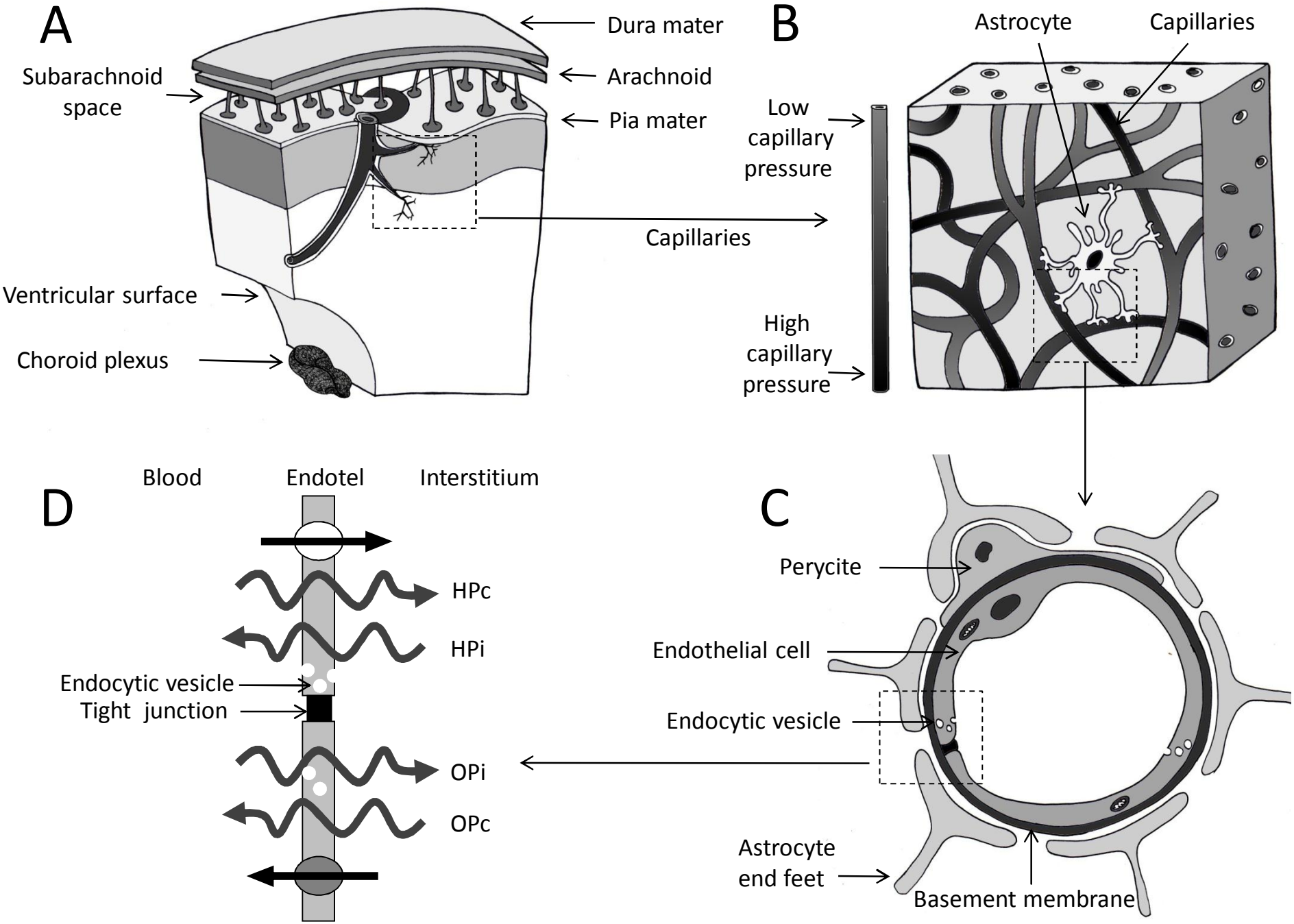

A
Dura mater
Arachnoid
Pia mater
Subarachnoid space
Capillaries
Ventricular surface
Choroid plexus
B
Astrocyte
Capillaries
Low capillary pressure
High capillary pressure
C
Perycite
Endothelial cell
Endocytic vesicle
Astrocyte end feet
Basement membrane
D
Blood
Endotel
Interstitium
HPc
HPi
Endocytic vesicle
Tight junction
OPi
OPc

Figure 8. A scheme of the interrelation between the cerebrospinal fluid (CSF), interstitial fluid (ISF) and cerebral blood vessels, and the exchange of water and substances between the blood and ISF-CSF through the blood-brain barrier.

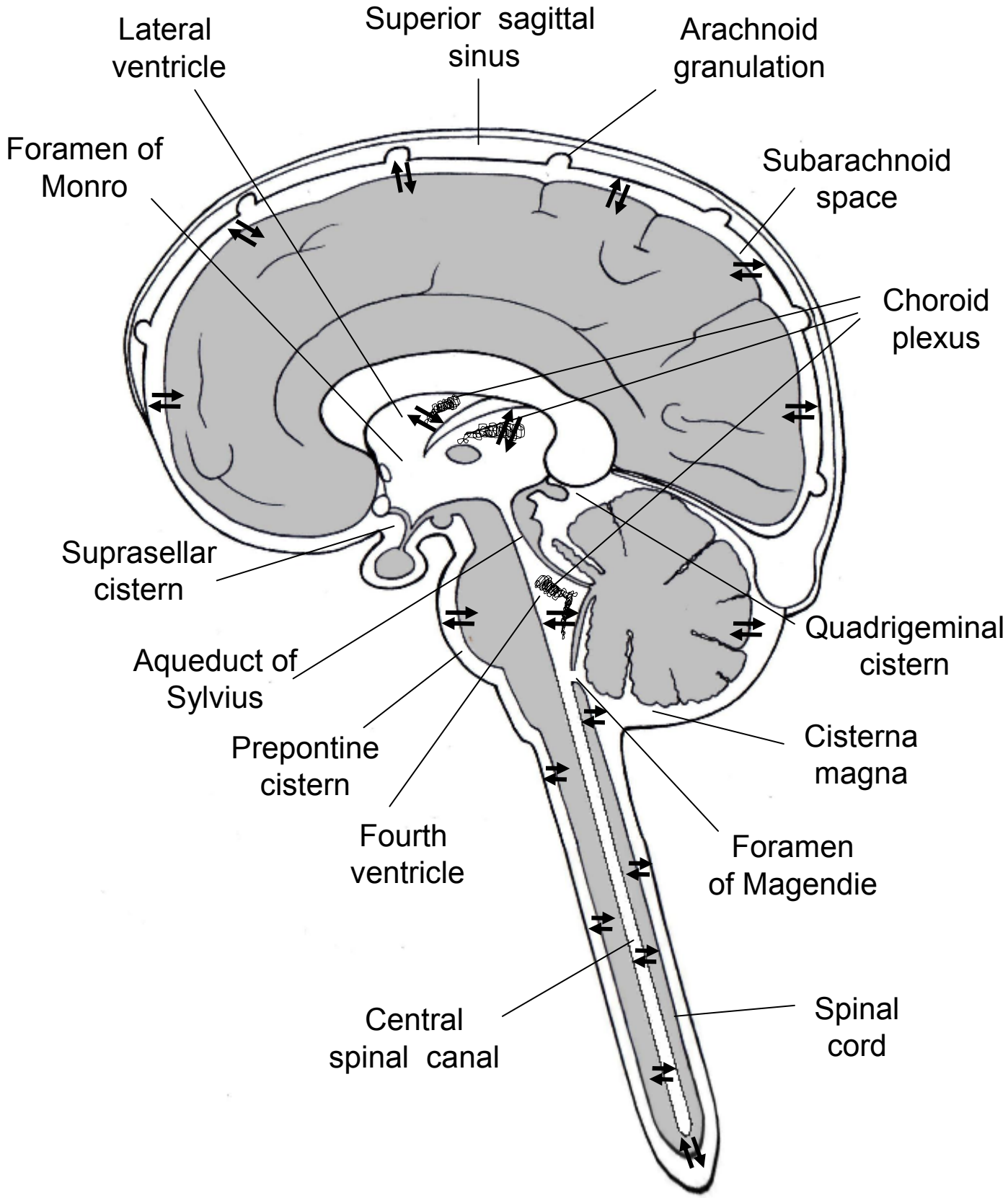

Lateral ventricle
Superior sagittal sinus
Arachnoid granulation
Foramen of Monro
Subarachnoid space
Choroid plexus
Suprasellar cistern
Quadrigeminal cistern
Aqueduct of Sylvius
Prepontine cistern
Cisterna magna
Fourth ventricle
Foramen of Magendie
Central spinal canal
Spinal cord

Figure 9. Schematic representation of kaolin-induced hydrocephalus in a dog. The stars represent the distribution of kaolin inside the CSF spaces after application into the cisterna magna. The insets represent the functions of the arachnoid granulations and choroid plexuses. The bold arrows on the arachnoid granulations represent the undisturbed CSF absorption through the villi arachnoides into the venous blood. The black arrows on the choroid plexuses show simultaneously undisturbed active CSF formation (secretion).

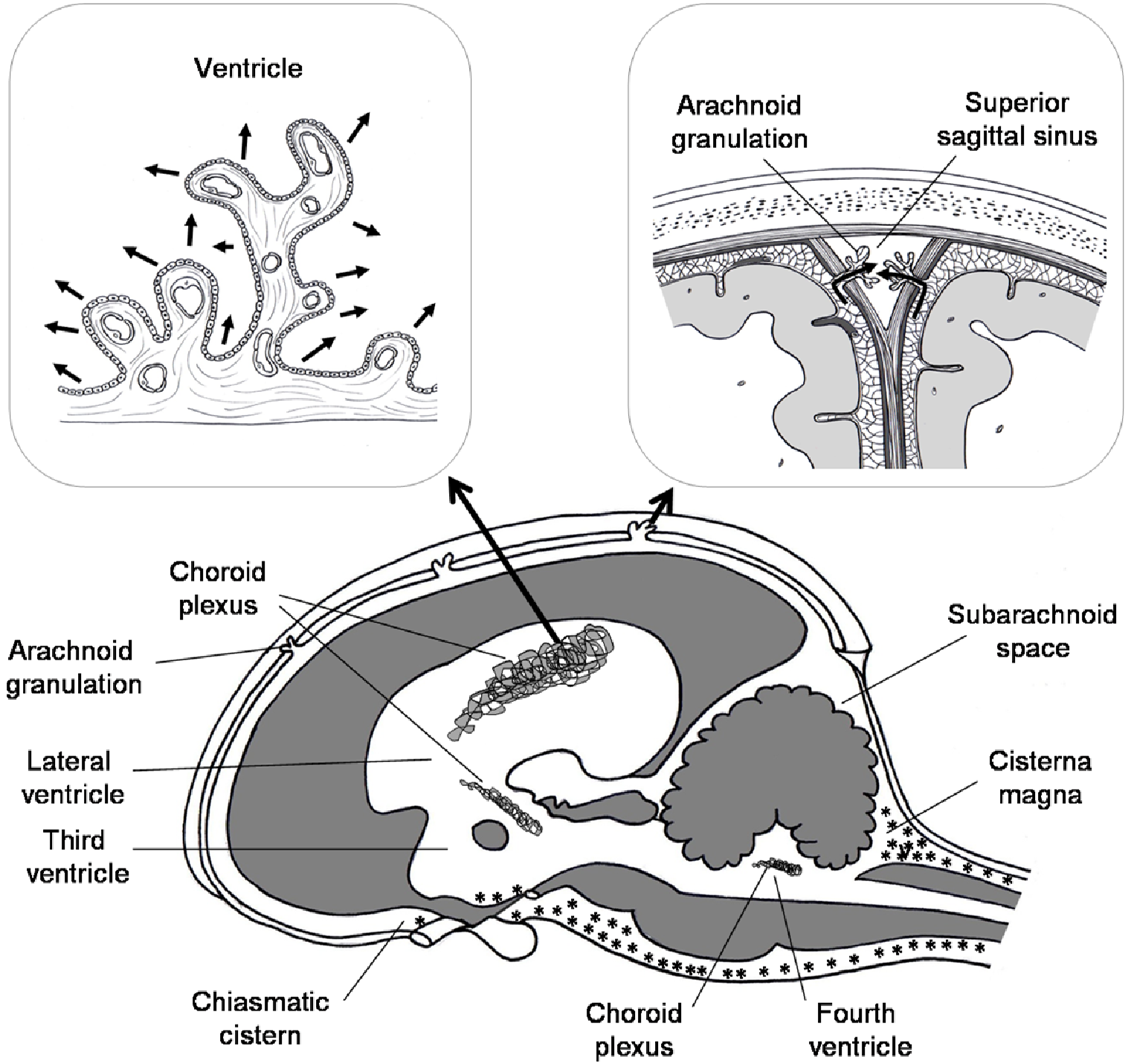
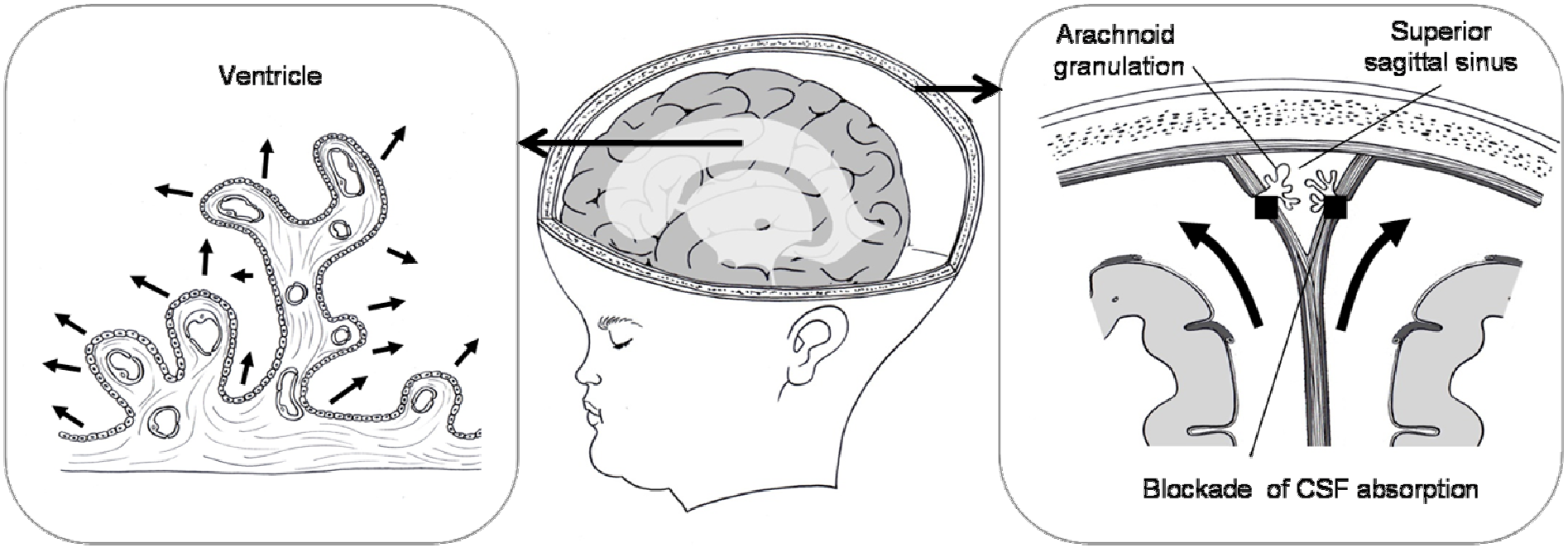

Ventricle
Arachnoid granulation
Superior sagittal sinus
Choroid plexus
Arachnoid granulation
Lateral ventricle
Third ventricle
Subarachnoid space
Cisterna magna
Chiasmatic cistern
Choroid plexus
Fourth ventricle

Figure 10. Schematic representation of external hydrocephalus. The CSF (white area) is located, in enormous volumes, inside the subdural cortical space. The brain (gray area) is pushed toward the base of the skull. The insets represent the functions of the arachnoid granulations and choroid plexuses. At the arachnoid granulations, the black square represents a blockade of the CSF drainage pathways, and the bold arrows represent the impossibility of CSF absorption into the superior sagittal sinus. At the choroid plexuses, the black arrows show simultaneously undisturbed active CSF formation (secretion).


Ventricle
Arachnoid granulation
Superior sagittal sinus
Blockade of CSF absorption