8 Choroid Plexus–Cerebrospinal Fluid Circulatory Dynamics: Impact on Brain Growth, Metabolism, and Repair

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Contents

1. STRUCTURAL AND FUNCTIONAL COMPONENTS OF THE CEREBROSPINAL FLUID

Cerebrospinal fluid (CSF) has a major impact on the fluid environment of neurons. Choroid plexus (CP) tissue in the four ventricles generates 70% to 80% of actively secreted CSF that derives from the carotid and vertebral systems. Upon flowing from choroidal origins to distal sites, CSF contacts other membranes that encompass the hemispheres: the ependyma of the ventricles and the pia/arachnoid of the subarachnoid space (SAS). Consequently, the composition of flowing CSF and adjacent brain interstitium is progressively modified by bidirectional exchanges of water, ions, and proteins (1, 2).

The CSF, then, is a dynamic system working in parallel with cerebral capillary transporters to optimize the neuronal environment. Disrupted transport at the blood-CSF interface (choroid plexuses mainly) and blood-brain barrier (BBB) compromises cerebral function. Although long known that stable brain fluid volume and composition vitally depend on CP function, it is now more evident that the streaming CSF dynamically interacts with the brain. Accordingly, less efficient exchange of solutes between CSF and the brain, as in aging and disease (3), impairs neuronal activity.

As part of the proximal CSF system, CP is viewed as a "port of entry" for many substances fluxing into the central nervous system (CNS). The unique array of transporters in the choroid epithelial basolateral

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(plasma-facing) membrane, compared with the counterpart luminal membrane of brain endothelium, affords opportunities for selectively translocating agents into the CSF-brain domain (4). That is, upon transport from blood to CSF, a substance readily accesses neurons because little resistance to diffusion is offered by permeable gap junctions between CSF-bordering cells. Consequently, the CP-CSF nexus is an "industrious gateway" for supplying numerous endogenous and exogenous agents to the CNS (5, 6).

2. DIVERSE ROLES OF CSF IN EFFECTING BRAIN WELL-BEING

As an active secretion into the ventricles by CP epithelium, the CSF helps to establish a specialized extracellular environment for neurons. Anatomically, the relationship of CP-CSF to brain and spinal cord is depicted in Fig. 1. Suspended in the ventricles, the CPs generate an avascular, nonlymphatic fluid that acts like a "third circulation." Continual formation and drainage of CSF allows this unique circulatory system to perform diverse metabolic and signaling functions (7). Several physical and biochemical attributes of CSF are summarized in Table 1.

2.1. Buoyancy Effect of Suspension Fluid

CSF is 99% water. The buoyancy of CSF protects the brain against the shearing forces of acceleration and deceleration. The relative specific gravity of CSF (~1.007) versus that of nervous tissue (~1.040) enables the 1400 g human brain to weigh about 45 g when suspended in CSF. Consequently, this >30-fold reduction in effective weight minimizes injury by reducing brain momentum in response to stresses/strains inflicted on the head. Angular acceleration, as in severe trauma, may override the normally buoyant effect of CSF. This can tear or herniate cerebral tissues.

2.2. Intracranial Volume Adjustor

By compensatory mechanisms, CSF volume is increased or decreased to stabilize intracranial pressure (ICP). Rapidly reduced CSF volume, resulting from enhanced CSF absorption, is the response to elevated ICP. On the other hand when ICP falls, the CSF volume increases by the slowing of absorption. The ability of CSF volume to adjust freely to altered ICP is the basis for the Monro-Kellie doctrine. This long-established physiologic principle recognizes that the brain, together with CSF and blood, are encased in a rigid chamber. Because tissue and fluid contents

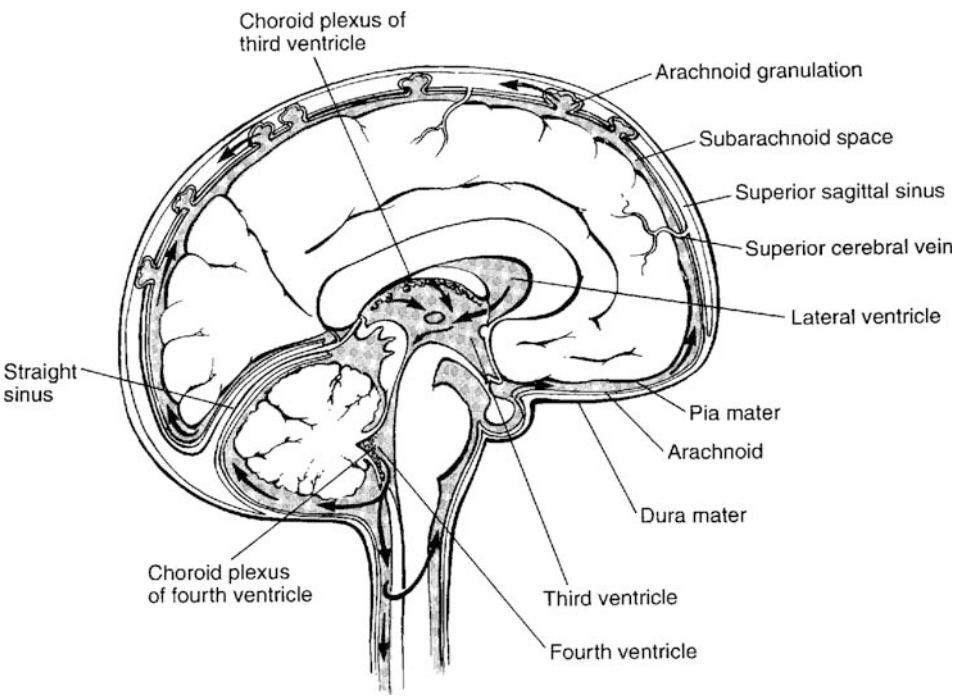

Fig. 1. CSF is formed and secreted by choroid plexus (CP) in the lateral, third, and fourth ventricles. The great vascularity of the plexus imparts a reddish cast to these tissues. In adult humans, the total weight of CPs in the four ventricles is about 2 to 3 g. Choroidal tissue is not present in SAS surrounding the brain hemispheres and spinal cord.

Table 1
Roles of CSF in Serving the Brain

CSF functions	*Examples*
Buoyancy effect	Because the brain weight is effectively reduced by more than 95%, shearing and tearing forces on neural tissue are greatly minimized.
Intracranial volume adjustment	CSF volume can be adjusted, increasing or decreasing acutely in response to blood volume changes or chronically in response to tissue atrophy or tumor growth.
Micronutrient transport	Nucleosides, pyrimidines, vitamin C, and other nutrients are transported by the choroid plexus to CSF and eventually to brain cells.
Protein and peptide supply	Macromolecules like transthyretin, insulin-like growth factor, and thyroxine are transported by the choroid plexus into CSF for carriage to target cells in the brain.
Source of osmolytes for brain volume regulation	In acute hypernatremia, there is bulk flow of CSF with osmolytes, from ventricles to surrounding tissue. This promotes water retention by shrunken brain, i.e., to restore volume.
Buffer reservoir	When brain interstitial fluid concentration of H^+, K^+, and glucose are altered, the ventricular fluid can help to buffer the extracellular fluid changes.
Sink or drainage action	Anion metabolites or neurotransmitters, protein products of catabolism or tissue breakdown, and xenobiotic substances are cleaned from the CNS by active transporters in the choroid plexus or by bulk CSF drainage pathways to venous blood and the lymphatics.
Immune system mediation	Cells adjacent to ventricles have antigen-presenting capabilities. Some CSF protein drains into cervical lymphatics, with the potential for inducing antibody reactions.
Information transfer	Neurotransmitter agents like amino acids and peptides may be transported by CSF over distances to bind receptors in the parasynaptic mode.
Drug delivery	Some drugs do not readily cross the blood-brain barrier but can be transported into the CSF by endogenous proteins in the choroid plexus epithelial membranes.

are practically incompressible, a change in volume of any constituent must be balanced by an equal and opposite effect in another component(s). Except for pathologic changes in brain bulk, the most common displacements of CSF occur in response to acutely altered blood volume (e.g., secondary to CO_2-induced vasodilation or constriction of the cerebrovascular bed).

2.3. Micronutrient Supply System for Neuronal Networks

Secretory mechanisms in choroid epithelial cells transport many water-soluble substances (e.g., micronutrients) into CSF for eventual carriage to brain target cells. These substances are needed in nano- to micromolar concentrations over extended periods. Micronutrients transported into CSF include vitamin C, folates (4), deoxyribonucleosides (8), vitamin B_6 (9), and certain trace elements. Active transport pump-like carriers in the CP epithelium pull these micronutrients across the blood-facing membrane of the plexus. Such substances are subsequently transported from choroidal cytoplasm to CSF by facilitated diffusion in the apical membrane. Thereafter by bulk flow and passive diffusion, these micronutrients are widely distributed across the ventricular ependyma, and more distally in the subarachnoid system across the pia/glial lining. Ascorbate, or vitamin C, is a prototype micronutrient actively secreted across CP but not cerebral capillaries (4). Accordingly, the CP-CSF nexus is the major "gateway" for nourishing the brain.

2.4. Distributor of Centrally Synthesized Peptides, Growth Factors, and Proteins

CSF is a dynamic distribution pathway for communication and integration of peptide signals *within* the CNS. CP is important in the CSF conveyance and/or reception of such peptidergic "signals." Membrane receptors in CP for arginine vasopressin (AVP), atrial natriuretic peptide (ANP), and angiotensin II indicate that centrally released peptides secreted into CSF modulate choroidal blood flow and secretion (10–12). CP synthesizes many growth

factors (13), including insulin-like growth factor II (IGF-II). After secretion into CSF, IGF-II accesses the parenchyma to exert metabolic and trophic effects. Transthyretin (TTR), the main protein secreted by CP, mediates thyroid hormone T_4 transport from blood to CP to CSF (14). Synthesized early in ontogeny and phylogeny, TTR has multiple effects in higher vertebrates. In aging, less TTR is synthesized by CP (15). This deficiency leads to beta-amyloid fibrils and plaque formation in brain (16). Thus CP-CSF convects an array of macromolecules essential to brain development, metabolism and health.

2.5. Source of Osmolytes for Brain and Cord

CSF has a relatively high concentration of NaCl (i.e., 15% to 20% greater than serum). Under certain conditions, the Na and Cl in CSF serve as inorganic osmolytes to restore brain volume decreased by water loss to blood. In acute hypernatremia, the brain shrinks because there is net water movement from CNS to hypertonic plasma. This initial compensation of CSF movement (with its inorganic ions) from ventricles to brain (17) precedes the osmotic adjustment several days later of a parenchymal increase in organic osmolytes such as inositol and taurine.

2.6. Buffering Reservoir: Biochemical and Biophysical

Chemical and physical buffering occurs in CSF. Minimally incremented ion concentrations in brain interstitial fluid (ISF) result from ventricular buffering of ions received from the interstices. Seizures and ischemia, respectively, promote ISF retention of K and acids. Ion buildup in ISF promotes diffusion down concentration gradients into CSF. Thus, the large-cavity CSF reservoir is a "buffer medium" to accommodate brain "spillovers." By volume dilution, and active transport by plexus to remove K from CSF or neutralize H by secretion of HCO_3 (18), there is minimal fluctuation of extracellular ions. CSF [K] is buffered by the Na-K pump and NaK2Cl transporters (19) in the apical membrane of CP epithelium.

Physical buffering also occurs in CSF (i.e., the dampening of vascular pulsations transmitted to the ventricles by brisk choroidal hemodynamics). Functioning like a "shock absorber," the CSF attenuates its own pulsatile motion that if, not appropriately buffered, injures the delicate nervous tissue contiguous with the ventriculo-subarachnoid spaces. Thus, CP vascular pulsations can dilate the ventricles upon increased impedance to the flow of CSF pulsations through the SAS. Such ventriculomegaly is the outcome of redistributed CSF pulses from the subarachnoid compartment back to the ventricles and the capillary-venous circulation (20). Some forms of communicating hydrocephalus may thereby result from pulse redistribution within the cranial cavity. Accordingly, the physical aspect of CSF dynamics, including impedance to flow, importantly determines the configuration and volume of large-cavity CSF.

2.7. Excretor of Catabolites, Proteins, and Toxins

In addition to supplying substances for brain anabolism and maintenance, the CSF also removes and excretes various catabolites from neurons and glia. There is a drain from brain ISF into CSF of the organic anions 5-OH indoleacetic acid (5-HIAA) and homovanillic acid (HVA) (i.e., metabolites of serotonin and dopamine). Once in CSF, these organic anions are actively reabsorbed by CP into blood or cleared convectively by bulk flow of CSF into venous blood. Such removal or "sink action" is exerted on numerous organic anions and cations as well as proteins and peptides. Iodide ion, especially toxic to brain, is avidly transported from CSF by CP.

Some antibiotics and other useful agents are efficiently cleared from CSF by CP, thereby reducing CSF concentrations to subtherapeutic levels. Organic solute transporters (21), such as P-glycoprotein (Pgp or MDR1), the low-density lipophilic receptor related protein (LRP-1), and the multidrug-resistant protein 1 (MRP1) in the plasma membranes of CP (and endothelium of cerebral capillaries), actively transport many drugs out of the CNS. Pharmacologic manipulation of the Pgp, LRP-1, and MRP transporters is a significant challenge to pharmaceutical drug designing.

2.8. Mediator of Immune Responses Within the CNS

The CP-CSF system mediates immunologic communication between brain and periphery. The plexus epithelium presents antigen to, and stimulates proliferation of, peripheral helper T lymphocytes. Moreover, CSF proteins drain by bulk flow along the SAS that envelops optic and olfactory nerves. Because such drainage eventually passes through cervical lymph, there is a potential for CSF antigenic material to elicit nodal antibody reactions. Such immunologic responses to proteins draining from CSF affect interactions between central and immune systems in

diseases (e.g., multiple sclerosis or allergic encephalitis) in which certain CSF proteins display antigenicity. Leukocyte trafficking across CP is problematic in controlling brain autoimmune diseases (22).

2.9. Neuroendocrine Conduit for Neurotransmitter and Hormonal Signals

Transmitters are moved by CSF over considerable distances to bind receptors in the parasynaptic mode. Neurotransmitters escaping the microenvironment of local synapses can be distributed by bulk flow between ISF and ventricular cavities. Arterial pulsations propel the extracellular fluid containing "informational molecules" along perivascular and subependymal pathways. Mismatches between receptors and ligands, seen by light microscopy, imply parasynaptic transmission. Gamma-aminobutyric acid exemplifies a "mismatched" transmitter acting at a distance between brain and ventricles. In this manner, CSF bulk flow along circumscribed routes mediates parasynaptic transmission. Such CSF convection is known as volume transmission (1).

Peripherally derived hormones are also "ferried" along CSF pathways to integrate signaling between distant regions. Prolactin in plasma uses the CP-CSF nexus to carry its "hormone signal" to central targets. Receptors in CP are regulated by plasma prolactin, which changes in pregnancy and lactation (23). Receptor-mediated transport of prolactin from blood to CSF conveys specific neuroendocrine information by bulk flow to the third ventricle–hypothalamus region where ependymal tanycytes likely transport prolactin to the hypothalamic-hypophysial axis. Consequently, there is the appropriate increase or decrease in synthesis/release of prolactin into plasma for feedback regulation of prolactin-sensitive cells in reproductive organs. In this way, CP serves as a "relay station" to coordinate prolactin transfer between peripheral and central neuroendocrine regions.

2.10. Alternate Drug Delivery Route to Circumvent the Blood-Brain Barrier

In treating brain cancer and other neural disorders, it is difficult to get water-soluble drugs to CNS targets. A novel approach promotes drug passage across the blood-CSF interface by using therapeutic agents transportable by CP endogenous protein carriers (6). An example is the anti-AIDS agent azidothymidine (AZT), with affinity for the nucleoside transporter in CP (24). Accessing the CSF, AZT then penetrates the ependyma interfacing the ventricular CSF with brain ISF. Agents transported within the CP-CSF-ependymal nexus (24, 25) reach tumors or stem cells (8) along ventricular borders. Combinatorial strategies involving bacteriophage can identify novel peptides with affinity for CP epithelium. This holds promise for manipulating the blood-CSF gateway (6, 24, 25).

3. PIVOTAL MODULATORY FUNCTIONS OF THE CSF IN FETAL BRAIN DEVELOPMENT

Embryologically, the ventricular system begins when neural groove closure forms a tube. The earliest fluid in the neural tube precedes CP appearance and so is not true CSF. Ciliary action within fetal ventricles mixes the fluid and promotes diffusional exchange across the tube wall. Early fetal brain fluid is retained in the ventricles because it cannot escape into the SAS.

The major ventricular components appear at early stages (Fig. 2, top). Lateral ventricles are spherical and close to the midline at 2 months. During the second trimester, a portion of the lateral first and second ventricles expands laterally as cerebral hemispheres enlarge. Posterior and inferior expansion of the brain forces the cortex into a "C" shape. Consequently, the underlying lateral ventricles, caudate nucleus, and hippocampal formation are also molded into a "C" shape. At birth, the shape of the ventricular system resembles that in adulthood (Fig. 2, right).

CP tissue first appears in human ventricles during the second month of intrauterine life. There are several stages of choroidal differentiation. By the third gestational month, the plexuses nearly fill the lateral ventricles. Thus fetal CP, relative to brain, is proportionately larger than in adults and fills more ventricular space. This intimates that the CP-CSF ventricular fluid prominently provides nutrients to fetal neural tissue with its low capillary density and blood flow.

Germinal matrix in the ependymal wall supplies progenitor cells for fetal brain. Stem cells give rise to neurons in the cell layer under the ependyma. FGF-2 and TGF-β promote division and differentiation of these primitive cells. Growth factors are supplied by the synthesizing CP and ependyma to the subventricular zone (SVZ). Regulated transport of growth

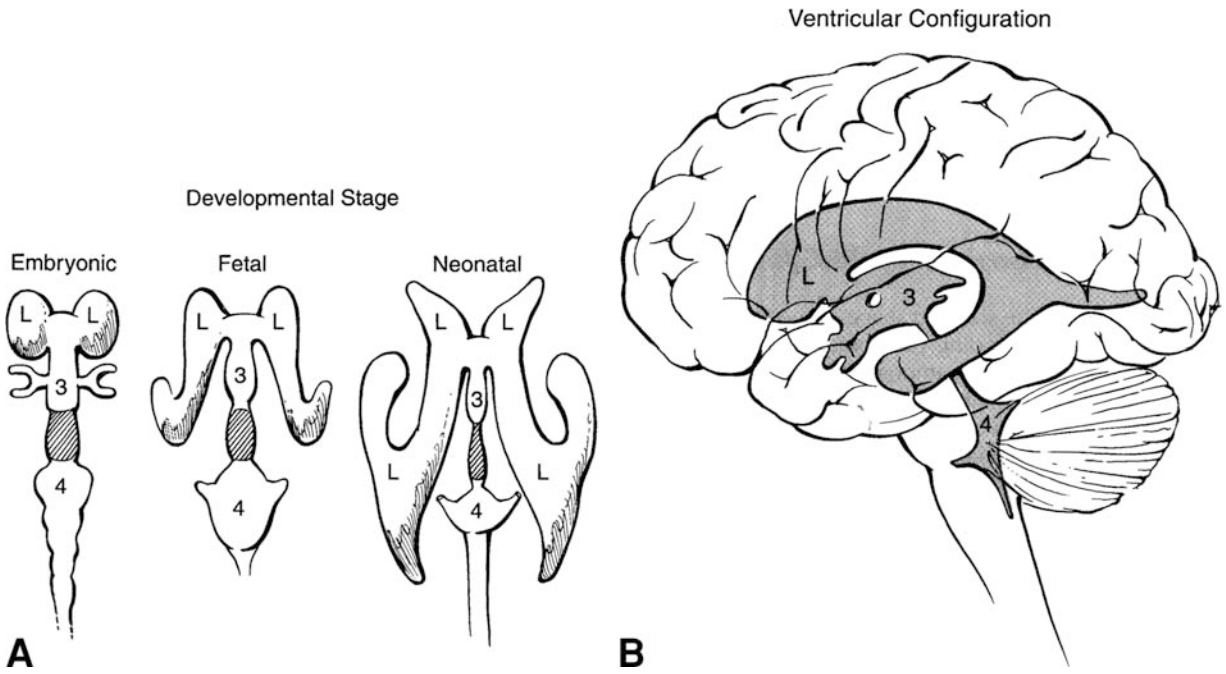

Fig. 2. (A) Shape of the ventricular system at early stages of development. Even by the second month of the first trimester, all of the major components of the ventricles are present. In the 5-month fetus, the first and second ventricles grow laterally as cerebral hemispheres enlarge. By birth, the general configuration of the ventricular system is similar to that of adults. **(B)** Physical configuration of the cerebroventricular system of mammalian brain: Right and left lateral ventricles are located in the medial portion of their respective hemispheres. The third ventricle, which is smaller and in the midline, is physically contiguous with the anterior horns of the lateral ventricles above and the fourth ventricle below. The shapes of the four ventricles are discussed in the text, and the interventricular foramina/channels are summarized in Table 2.

factors, hormones, and other proteins from CSF to SVZ importantly modulates stem cell conversion to neurons (8).

4. PHYSICAL DIMENSIONS OF THE ADULT CSF SYSTEM

The size and shape of the CSF system affects the kinetics of drug distribution among CNS regions, the neuroendocrine integration of fluid balance, and extracellular aspects of neurotransmitter/peptide signaling. Interior or proximal cerebroventricular CSF generated by CP percolates down the ventricles to the cisterns. The attenuation of the ventricular system into the narrow sylvian aqueduct gives rises to flow vulnerability. The more exterior or distal SAS lacks tufts of CP but has villi/granulations/pore-like structures to facilitate fluid outflow. SAS is therefore involved more with reabsorption than secretion.

Ventricles are linked by channels or foramina. Ventricular CSF flows from telencephalon to rhombencephalon, finally mixing with subarachnoid fluid at the brain's base. There the CSF flows out of fourth ventricle foramina into cisterns. The cisterna magna results from an arachnoid membrane bridge between cerebellar hemispheres and medulla. Table 2

Table 2
Channels or Narrow Ducts in the CSF

Name of channel	*Location and significance*
Foramina of Monro	Connect each lateral ventricle to the third ventricle; tissue adhesions may block channels.
Cerebral (sylvian) aqueduct	Connects the third ventricle with the fourth ventricle; narrowest passageway in ventricular CSF flow route and therefore the most likely site of obstruction leading to hydrocephalus.
Foramina of Luschka	Two exits located in the lateral recesses of the fourth ventricle permit access to basal cisterns.
Median foramen of Magendie	Midline at the caudal end of the fourth ventricle; direct access to the cisterna magna.

summarizes channels and pathways that connect the large cavities of CSF.

4.1. Configuration

4.1.1. Ventricular Cavities

In higher vertebrates, the cerebroventricular system has four interconnecting cavities (Fig. 2, right), each containing CP. The two lateral ventricles, more or less symmetrical with each other, are the most prominent in size. CP lies as a narrow band of tissue on the floor of each lateral ventricle. A thin layer, the septum pellucidum, separates the lateral ventricles in the lower medial portion of the hemispheres. Thus the lateral ventricles are not physically contiguous but communicate with the third ventricle via the interventricular foramina of Monro.

Each lateral ventricle has a main body and three horn-shaped recesses. The most rostral lateral ventricle is the *anterior horn*. It angles downward into the frontal lobe and curves around the anterior portion of caudate nucleus. The *inferior horn* bends around the posterior thalamus, extends backward and then laterally downward in the temporal lobe. The *posterior horn* runs laterally and juts backward into the occipital lobe. At the *trigone*, the body divides into inferior and posterior horns.

The third ventricle, lying beneath the lateral ventricle bodies, houses the smallest choroid tissue. A thin cleft in the midline, it is located between two thalami. The third ventricle receives CSF from lateral ventricles and then passes the fluid into the sylvian aqueduct. Anatomically, the irregularly shaped third ventricle has four prolongations or recesses (Fig. 2, right). The front, lower part of this ventricle has adjacent *optic* and *infundibular* recesses. The back, upper part of the third ventricle has recesses named *pineal* and *supra-pineal* because of proximity to pineal gland.

The fourth ventricle occupies the most caudal part of the cerebroventricles. Lying well below the lateral and third ventricles, it is bounded by pons, medulla oblongata, and cerebellum. The rhombus-shaped fourth ventricle has a roof and floor. The roof is V-shaped with thin laminae of white matter between the cerebellar peduncles. A median opening at the caudal end of the roof, the foramen of Magendie, is significant hydrodynamically because CSF flows through this aperture into SAS. Part of the fourth ventricle roof is occupied by CP. The fourth ventricular plexus is T-shaped, with the vertical portion in the midline.

The floor of the fourth ventricle is divided into symmetrical halves by the *median sulcus*. Running perpendicular to this sulcus are delicate strands of transverse fibers, the *striae medullares* of the fourth ventricle. Other neuroanatomic features of the floor are the *medial eminence* and the *sulcus limitans*. The *medial eminence* is a longitudinal elevation that flanks both sides of the median sulcus. The *sulcus limitans* lies lateral to this *eminence*.

In the spinal cord, the analogue to the ventricular system is the central canal. This canal ends within the *filum terminale*. Imaging of normal human adult flow patterns reveals that CSF in the fourth ventricle is not normally contiguous with the central canal.

4.1.2. Subarachnoid Space

The SAS lies between the arachnoid membrane externally and the *pia mater* internally. In adults the SAS provides a route for CSF flow to absorptive sites of exit. The SAS covers the convexities of the cerebral hemispheres and forms a circumferential sleeve around the spinal cord (Fig. 1). Figure 3 displays representative architecture of the SAS.

Because pia intimately hugs the external contour of nervous tissue, whereas the arachnoid membrane bridges the sulci of brain and cord, relatively large pockets of SAS exist. Spaces at the brain base where the bridged-over gaps are large are called cisterns. One of the largest is the *cisterna magna*, situated between the inferior surface of the cerebellum and medulla. Because of accessibility at the foramen magnum, the cisterna magna is used to conveniently sample animal CSF. *Cisterna ambiens* is a CSF pocket dorsal to midbrain. Lying between the base of the brain and the floor of the cranial cavity are the pontine, chiasmatic, and interpeduncular cisternae.

4.2. Volume of CSF Compartments

Total CSF volume in normal adult humans is about 140 mL. Ventricular system volume is estimated by casting techniques, CAT scans, and radioisotope distribution. By averaging data from several techniques, the mean volume of the ventricular system is close to 30 mL. Thus, the composite volume of the four ventricles is about 2% of the brain volume. Studies find no correlation between ventricular volume (the range of which is 10 to 60 mL) and brain volume.

Most of the total CSF volume of 140 mL is composed of the 110 mL in the SAS of the brain and

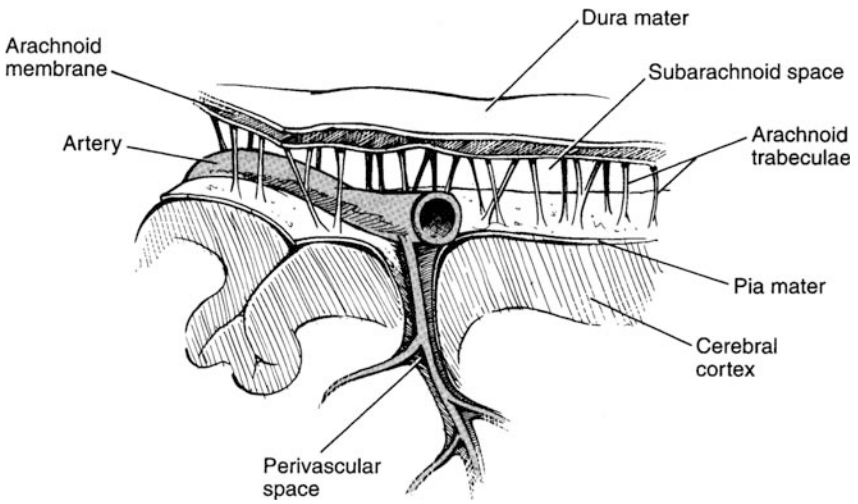

Fig. 3. Meningeal aspects of subarachnoid space: The roof of the SAS is the arachnoid membrane, whereas the floor is the *intima pia* or pia-glia (external limiting membrane of CNS). The ectodermal arachnoid and pia-glia are bridged to each other by arachnoid trabeculae. CSF percolates through SAS. Blood vessels entering and leaving nervous tissue carry arachnoid and pia-glial cuffs. Known as the Virchow-Robin space, these cuffs enable fluid movement between extracellular space and SAS.

spinal cord. CSF surrounding the spinal cord is at least 30 mL. Thus, the largest compartment of CSF is the nearly 80 mL in the SAS and cisterns enveloping the cerebrum, cerebellum, and cord.

CSF is only one of the CNS extracellular fluids (Table 3). Another major type is the ISF that bathes neurons and glia. In practice, CSF and ISF have similar concentrations of many substances. Figure 4 gives the volume relationship between CSF and ISF. An adult brain weighing 1400 g has about 280 mL (or g) of ISF and 140 mL of CSF, for a total of 420 mL of extracellular fluid. This compares with the approximately 800 mL of fluid in the total intracellular compartment of CNS.

Table 3
Extracellular Fluids in the CNS

Fluid	*Location and characteristics*
ECF	Two main types: CSF in the ventricles and SAS, and the ISF that intimately bathes the parenchymal cells of brain (e.g., neurons, glial cells).
Nascent CSF	Secreted across the apical membrane of the choroid plexuses (i.e., lateral, third, and fourth ventricles) into the ventricular space, referred to as nascent or newly formed CSF; active secretion.
Ventricular CSF	Contained in the four cerebral ventricles and aqueduct; consists mainly of nascent CSF with some exchange of content with the ependymal lining and underlying brain tissue as CSF flows down the ventricular axis.
Subarachnoid CSF	Cranial or spinal SAS; mixture of ventricular fluid that has flowed into the SAS and brain fluid that has gained access to the subarachnoid spaces; subarachnoid and ventricular CSF regarded as large-cavity CSF.
Brain ISF	Actively secreted by endothelial cells in walls of capillaries in brain and spinal cord (e.g., blood-brain barrier), modified by the water and solutes that are exchanged with brain neurons and glia; undergoes transependymal exchange with ventricular fluid; chemical composition similar to that of CSF.
Cerebral endothelial secretion	Endothelium in brain capillaries, in conjunction with astrocyte foot processes on the vascular wall, actively secrete ions and solutes from plasma into the interstices of the brain; fluid-secretory capacity of the blood-brain barrier is less than of the choroid plexuses.

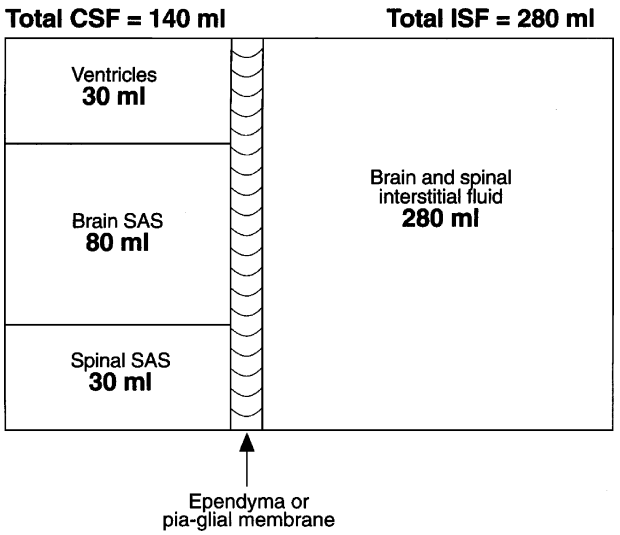

Fig. 4. An analysis of the respective volumes of fluid in CSF and interstitial space of adult humans: Nearly a third of the CNS fluid lies outside cells. A typical 1400 g adult brain contains 140 mL of CSF (10% of its weight) and approximately 280 mL of ISF that bathes neurons and glia. CSF and ISF freely communicate with each other across the permeable interfaces separating them (i.e., the ependyma in the ventricles and pia-glial membrane in SAS).

5. CSF-BORDERING CELLS THAT DEMARCATE THE VENTRICULO-SUBARACHNOID SYSTEM

CSF is contained within and surrounds the brain and cord. CSF bathes the inside and outside surfaces of brain and is separated from the latter by a single-cell layer. In the CNS interior, a thin ependymal lining separates ventricular CSF from underlying nervous tissue. On the exterior, the pia-glial membrane interfaces the subarachnoid CSF with adjacent cortical tissue. A third membranous interface is the choroidal epithelium, a single layer of frond-shaped epithelium that separates ventricular CSF from blood coursing through the vascular plexus. The epithelial parenchyma of CP has an ultrastructure distinct from the ependyma and pia-glial cells (Fig. 5).

5.1. Choroid Plexus Epithelial Cell Polarity: Apical Versus Basolateral Membranes

The epithelium of CP in all four ventricles consists of tightly packed cuboidal cells with finely granular cytoplasm. A distinctive feature of CP epithelium is the *zonula occludens*, or tight junction, at apical regions between adjacent cells. This tight junction occludes the blood-to-CSF passage of hydrophilic molecules and ions. Electrical resistance associated with CP is 100-fold less than that associated with the BBB, renal distal tubule, or urinary bladder.

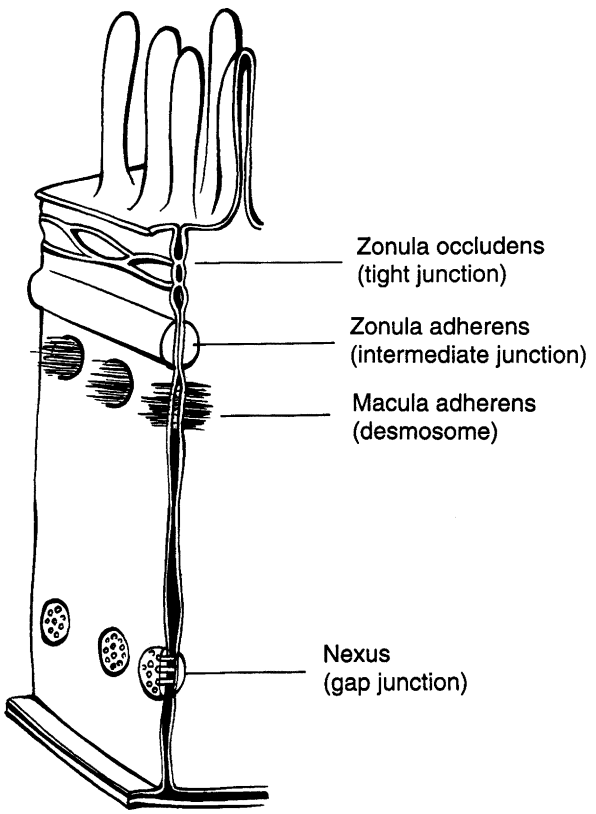

Fig. 5. Ultrastructure of intercellular junctions in CP and ependyma: An integral part of the blood-CSF barrier is *zonulae occludentes*. These tight junctions are near the apical (CSF-facing) borders of CP epithelium where cells abut. Tight junctions are multilayered membranes that completely envelop cells, thus restricting the diffusion of many solutes between plasma and CSF. On the other hand, gap junctions are between cells of the ependymal and pia-glial linings. Gap junctions form incomplete belts around cells, therefore these intercellular junctions are more "leaky" than are tight junction counterparts in CP. Overall, CSF composition resembles brain ISF more than plasma because the ependymal gap junctions permit unrestricted diffusion whereas the tight junctions in CP do not.

Consistent with high-level transport, the typical choroid cell has numerous mitochondria, a rich Golgi apparatus, and extensive microvilli at the CSF face. Basally located are elaborate infoldings and interdigitations as in the proximal tubule. Choroid cell organelle ultrastructure reflects brisk metabolic and transport activity linked with CSF secretion.

5.2. Ependymal Cell Lining: A Specialized Monolayer

Embryologically, the ependyma begins as a layer of spongioblasts lining the neural tube. In late fetal stages, the ependyma becomes multilayered, attaining a thickness of six or seven layers. In neonates, the lining

attenuates to two or three layers. In early postnatal life, ependymal-like tanycytes send long processes from their bases into the neuropil. By adulthood, the tanycytes largely disappear and the ependyma becomes a single layer of cuboidal or columnar cells.

Even within species, the adult ependymal lining is not structurally uniform. Great variations in morphology occur, especially in the third ventricle where ependyma intimately associate with the hypothalamus and subcommissural organ. Emanation of cilia from the apical surface is common. Specialized regions of the ependymal wall contain *tight* junctions between cells. Most ependymal cells, however, have *gap* junction structures intercellularly. Gap junctions do not completely envelop cells. Accordingly, intercellular clefts are permeable to macromolecules. Therefore, the functional hallmark of ependyma is permeability to most ions and molecules. A drug or endogenous substrate in CSF (6) can easily penetrate the ependyma to reach neurons and glia.

5.3. The Pia-Glial Membrane and Other Meningeal Tissue

The thin delicate pial membrane resembles ependyma more than CP. Discontinuous gap junctions between pial cells allow bidirectional exchange of solutes between subarachnoid CSF and subpial space. Large protein markers such as ferritin and horseradish peroxidase move readily across the pia to penetrate subpial tissue. The underlying *glia limitans* however restricts diffusion. On the other hand, Virchow-Robin spaces (perivascular cuffs of pia-glia and arachnoid that envelop major vessels penetrating the brain) promote uptake of materials via bulk flow from SAS to deep brain.

Pia mater along with the arachnoid is designated leptomeningeal tissue. A *thin* connective tissue membrane, the pia hugs the contours of brain and carries blood vessels. Arachnoid, on the other hand, is a *multilayered* avascular membrane between pia and dura maters. Arachnoid is separated from overlying dura by the subdural space and from underlying pia mater by SAS. Dura mater has venous sinuses into which CSF is cleared.

6. CIRCUMVENTRICULAR ORGANS OUTSIDE BLOOD-BRAIN BARRIER

The ventricular wall "houses" several organs with similar structure but distinct interrelated functions (25). These small organs are circumventricular (i.e., surrounding the ventricles). They include area postrema (AP), subfornical organ (SFO), pineal gland (PI), median eminence (ME), organum vasculosum of the lamina terminalis (OVLT), subcommissural organ (SCO), and the neural lobe of pituitary (NLP) (Fig. 6). Neurohypophysis (NH) refers to both ME and NLP. Unlike most CNS regions, circumventricular organs (CVOs) have highly permeable capillaries permitting diffusion of polypeptides into circumscribed, highly specialized regions of brain. Most CVOs readily receive macromolecular chemical "signals" from blood. Such humoral signals integrate neuronal pathways that mediate fluid/electrolyte homeostasis.

Several CVOs bear intimately to the diencephalon. A typical CVO has an ependymal interface and a highly permeable capillary interface. Collectively, the ependymal and capillary surface areas of CVOs are small (i.e., about 1% of the ventricles and brain capillary bed, respectively). Even with diminutive

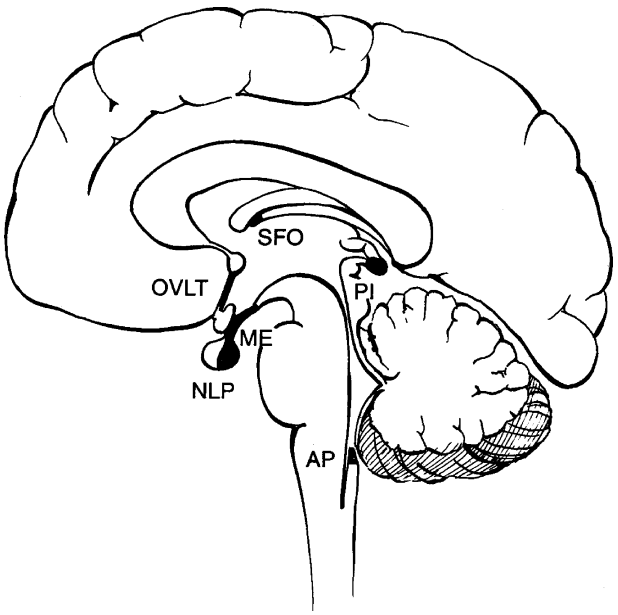

Fig. 6. Sagittal view of anatomic relationships among circumventricular organs (CVOs) located on the brain midline. CVOs are situated at strategic positions on the surface of the cerebroventricular system to perform neuroendocrine functions. The diminutive CVOs are highly vascular and have a variable number of neurons. Generally not protected by a BBB, the CVOs therefore contain central receptors for peripherally circulating factors (e.g., peptides). Neuronal processes extend into large perivascular spaces of CVOs. Each CVO is encompassed by a ring of glia (tanycytes) with tight junctions that isolate the CVO from surrounding brain. Area postrema (AP) and subfornical organ (SFO) attach to CPs, with which they shunt blood. ME, median eminence; PI, pineal gland; OVLT, organum vasculosum of lamina terminalis; NLP, neural lobe of pituitary.

transport interfaces, the CVOs coupled with neuropeptide systems (e.g., angiotensin and AVP) importantly maintain fluid balance in the brain and whole organism (Table 4).

CVOs are categorized three ways. First, the "parenchymal" CVOs (e.g., SFO and AP) have dominant vascular inputs and neuronal outputs (Fig. 7A). Second, the "neurohumoral" CVOs or "gates" (e.g., the ME and OVLT) have substantial neuronal inputs and vascular outputs (Fig. 7B). Third, the "ependymorgans," exemplified by SCO, have an intact BBB but extensive communication with CSF. The major communication of "ependymorgans" seems to be active apical release of solutes into the ventricles and possible absorption of peptides from CSF.

CVOs have structural and functional connectivity. The SFO integrates water balance via angiotensin signaling. SFO communicates with other CVOs. AP is physically contiguous with fourth ventricle CP, the latter resembling a CVO. Lateral ventricle CP blood flow is markedly altered when AP is stimulated (26), suggesting CVO modulation of CSF formation.

Table 4
Functions and Anatomic Associations of Some CVOs

Organ	*Location*	*Projections*	*Functions*
Subfornical organ (SFO)	Attached to anterior dorsal wall of third ventricle, between the interventricular foramina of lateral ventricles.	*Afferent*: Central input is poorly characterized but is probably significant. *Efferent*: Projects into the preoptic area and hypothalamus (e.g., paraventricular and supraoptic nuclei).	Induction of drinking behavior, mediated by angiotensin signals; SFO can modulate fluid homeostasis by many mechanisms through multiple projections to endocrine, autonomic, and behavioral areas of the CNS.
Area postrema (AP)	Lies at caudal extent of fourth ventricle on the dorsal medulla in contact with the nucleus of the solitary tract.	*Afferent*: Input from underlying nucleus of the solitary tract and the dorsal motor nuclei of vagus; hypothalamus also innervates the AP. *Efferent*: Projections to major relay nuclei for ascending visceral sensory information; major projection to the parabrachial nucleus of the pons.	Modulates interoceptive information that reaches it through visceral sensory neurons or humorally by way of its permeable capillaries; directly affects motor outflow of the dorsal motor nucleus; stimulation of a chemotaxic center causes vomiting.
Organum vasculosum of the lamina terminalis (OVLT)	Lies in the anterior ventral extent of the third ventricle along the lamina terminalis.	Connectivity of the OVLT is poorly understood but seems to have a greater afferent input than efferent outflow.	Implicated in water balance because damage to it and surrounding structures affects drinking behavior and vasopressin release.
Median eminence (ME)	Forms the ependymal floor of the third ventricle in the central portion of the tuber cinereum in the hypothalamus.	*Afferent*: ME receives neuronal input from the arcuate nucleus and medial areas of preoptic hypothalamus. *Efferent*: No efferent projections to the brain; portal circulation carries hormones to the anterior pituitary.	Represents the final common pathway for the neural control of hormone production in and secretion from cells of the adenohypophysis (e.g., anterior pituitary).

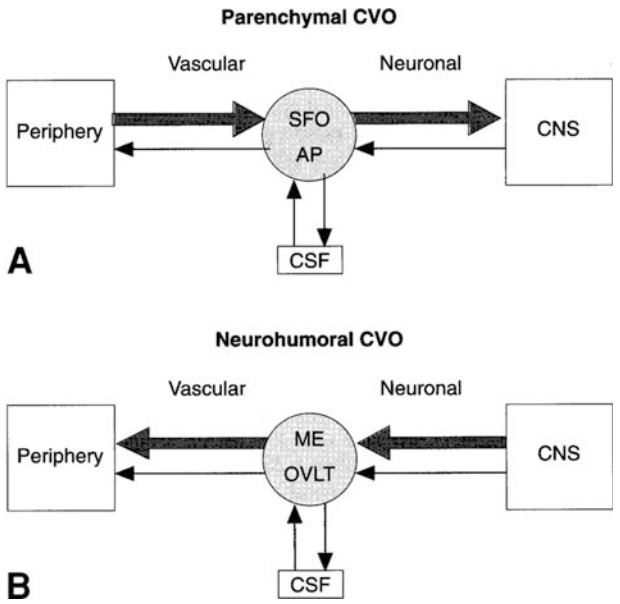

Fig. 7. Schema of the vascular, neuronal, and ependymal components of circumventricular organs (CVOs). **(A)** Subfornical organ (SFO) and area postrema (AP) receive a prominent vascular *input*, whereas **(B)** median eminence (ME) and organum vasculosum of lamina terminalis (OVLT) have a substantial vascular *output*. Neuronal *output* is strongest in SFO and AP, whereas neuronal *input* is substantial in ME and OVLT. On the other hand, SCO has relatively weak vascular and neuronal connectivities but a significant secretory and reabsorptive communication with CSF.

Complex anatomic connections of the CVOs with each other, and with the pituitary and autonomic nervous system, enable these CSF-adjacent organs to modulate neuroendocrine processes that stabilize the *internal milieu*.

7. ELABORATION OF CSF

Fluids are generated at multiple sites in adult CNS. The main source is CP. Extrachoroidal sites of production include a CSF-like secretion by the cerebral capillary wall and the metabolic generation of water by brain glucose oxidation. Because CP is the preponderant production site, representing 75% or greater of the total fluid formed, it is customary to regard true CSF as choroidal in origin.

CSF is not a passive filtration of fluid across membranes at the blood-CSF barrier (BCSFB). It is an *active* secretion by CP epithelium. The high rate of secretion of CSF (i.e., about 0.5 mL min^{-1} g^{-1} CP) depends upon a brisk vascular perfusion of the plexus. Blood flow to CP is about 5 mL min^{-1} g^{-1} (i.e., 10-fold faster than mean cerebral blood flow (CBF)). A ruddy color is imparted to CP by a large content of blood.

CSF is continually replenished. At least thrice daily, the normal volume of 140 mL turns over. NMR studies of humans reveal that CSF production increases at night. The net production of approximately 0.35 mL/min in man results in a 24-hour formation of about 500 mL in adults.

The initial step in CSF secretion is plasma filtration across CP capillaries. Fenestrated endothelium does not impede macromolecule movement across the capillary wall into CP interstitium. Furthermore, the choroidal interstitial space offers minimal restriction to diffusion of ions and substrates for transporters at the epithelial base. Several ion transporters have been identified. Their vectorial properties are schematized in Fig. 8.

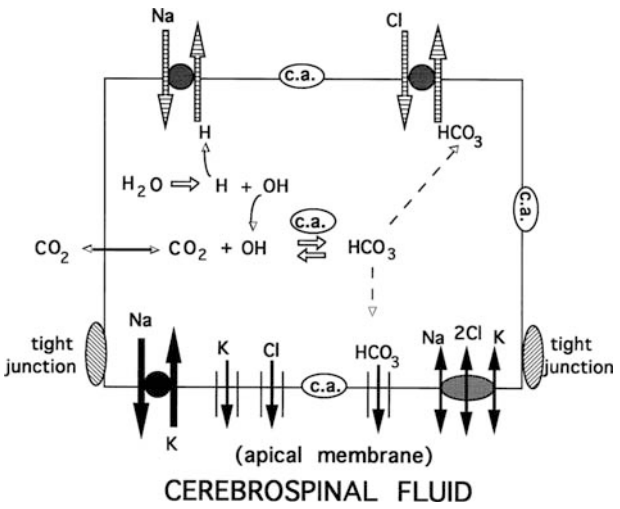

Fig. 8. Schema for ion transport processes in CP that underlie CSF secretion: There is coordinated activity of ion transporters and channels in the apical and basolateral membranes of CP that allow vectorial transport of Na, K, Cl, HCO_3, and water from epithelium to CSF. Membrane active transporters are depicted as *circles* or *oval*. *Arrows* indicate direction of transported ions. Antiporters (exchangers) are *arrows with horizontal lines*. The primary driving force for CSF secretion is Na-K pumping in the apical membrane, which keeps the choroid cell [Na] much lower than extracellular fluid [Na]. As a result, there is an inwardly directed Na gradient that promotes secondary active transport in the basolateral membrane. Na is taken up by epithelium in exchange for cellular H ion, and Cl for HCO_3. K, Cl, and HCO_3 (generated from carbonic anhydrase (c.a.) catalyzed hydration of CO_2) exit the cell via apical channels. Water movement across apical membrane aquaporin 1 channels is intimately associated with active ion transport. Na, K, and Cl are also extruded by a co-transporter (symporter). This unified model is for transport data from amphibians (Zeuthen T, *J. Physiol.* 1991; 444: 168) and mammals (Johanson C and Murphy V, *Am. J. Physiol.* 1990; 258: F1544).

Mammalian CSF is distinctive for a relatively low concentration of protein and certain organic substrates. Total protein concentration in adult CSF is 2 to 3 orders of magnitude lower than that in plasma. Glucose and urea concentrations are held at concentrations 60% to 70% of plasma. Many amino acids in CSF are at 10% to 20% of concentrations in plasma. This is due to transporters that actively remove amino acids from CSF.

The pH of CSF (7.35) is slightly more acidic than that of arterial blood (7.40) because CSF PCO_2 is higher than arterial PCO_2. Osmolality is greater than that of plasma by a few mOsm/L, due to the relatively high concentrations of Na and Cl in CSF. Normally CSF is a crystal-clear, colorless fluid. Coloration is pathologic. Composition of human CSF is remarkably similar to that of other mammals.

7.1. Formation of Cerebrospinal Fluid

The main constituents of CSF are Na, Cl, and HCO_3. Knowledge of ion transport across CP enlightens understanding of CSF production. The apically-located Na-K pump (ATPase) has a pivotal role (Fig. 8). Primary active pumping of Na from choroid cells to CSF keeps intracellular [Na] low (20 to 30 mM) compared with the interstitial [Na] of 140 mM. A substantial inwardly directed transmembrane gradient for Na is the driving force for secondary active transport of Na into the cell by basolateral Na-H exchange. Coordinated activity of basolateral Na uptake and apical Na extrusion (Na pump and NaK2Cl co-transport) ensures continual net flux of Na across CP to CSF. K moves down its electrochemical gradient, from choroid cell to CSF. By way of aquaporin 1 channels, water accompanies the outward flow of CP ions into ventricles.

With respect to anion movement, Cl uptake by CP occurs by secondary active transport. Inward transport of Cl across the blood-facing membrane is driven by exchange with intracellular HCO_3. HCO_3 is amply generated from CO_2 hydration catalyzed by carbonic anhydrase. Cl and HCO_3 move into ventricular CSF via channels and transporters such as NaK2Cl symport (Fig. 8). Net transcellular movement of ions is fueled by ATP (hydrolyzed by ATPase), providing energy to create the Na gradient that drives transporters. Figure 8 recapitulates transporters that form the CSF.

7.2. Composition and Homeostasis of CSF

7.2.1. Nascent Fluid

Newly formed fluid from the apical surface of CP epithelium has a high Na (158 mEq/kg H_2O), Cl (138), and HCO_3 (25) and lower concentrations of K (3.3), Ca (1.7), and Mg (1.5). Because of active transport, CSF Cl concentration is greater than that of plasma. CSF [K] is 1 to 1.5 mEq/kg H_2O less than in plasma. Nascent CSF levels of Ca and Mg, respectively, are held slightly lower and higher than corresponding normal concentrations in plasma. Stability of CSF [K] and [Ca] is essential because small deviations alter CNS excitability. Table 5 relates ionic concentrations in various fluids.

7.2.2. Mixing of Choroidal Secretion with Brain Interstitial Fluid

CSF is modified as it flows from its origin in the CNS interior to distal SAS on the exterior of brain and cord. Nascent and cisternal CSF are compared in Table 5. Small concentration differences occur because the relatively permeable ependymal and pial linings permit exchange of CSF with brain ISF. The source of ISF is a slow, steady secretion by the cerebral capillary wall (i.e., astrocyte-endothelial

Table 5
Concentrations (mEq/kg H_2O) of Ions in Fluids Derived from Plasma

*Fluid**	Cl^-	Na^+	K^+	Ca^{2+}	Mg^{2+}
Plasma	132	163	4.4	2.62	1.35
Plasma ultrafiltrate†	136	151	3.3	1.83	0.95
Choroid plexus fluid (nascent CSF)	138	158	3.28	1.67	1.47
Cisterna magna fluid	144	158	2.69	1.50	1.33

*Fluids were collected from cats (Ames A, Sakanoue M, Endo S. *J. Neurophysiol.* 1964; 27: 674).
†Plasma ultrafiltrate data, obtained from dialysis experiments, are values expected if the CSF were formed by passive distribution phenomena rather than by an active secretory process in the choroid plexus.

Table 6
Regional Differences in the Concentrations of Proteins at Various CSF Sampling Sites

Protein	*Ventricular (n = 27)*	*Cisternal (n = 33)*	*Lumbar (n = 127)*
Total protein	25.6 ± 1.1	31.6 ± 1.0	42.0 ± 0.5
Albumin	8.3 ± 0.5	12.7 ± 0.7	18.6 ± 0.6
IgG	0.9 ± 0.1	1.4 ± 0.1	2.3 ± 0.1

Values are means ± standard errors, given in units of mg/dL. The data demonstrate a gradient of protein concentration from ventricular to spinal fluid. Protein concentrations in CSF are 2 to 3 orders of magnitude less than that in plasma. Newly secreted CSF has a protein concentration of about 10 mg/dL. A CSF protein content of >500 mg/dL can indicate a lesion that is blocking the SAS.

complex) of a fluid similar to CSF. In addition, the exchange of ions and nonelectrolytes across the external limiting membranes of neurons and glia contributes to ISF composition.

Protein concentrations vary within CSF. There is an approximate twofold difference among regions. Lumbar CSF has about twice the IgG and albumin as ventricular fluid (Table 6). Such differences reflect regional variations in secretory and reabsorptive phenomena at the BCSFB. Still, the comparable compositions of CSF and ISF ensure that, even after mixing, CNS extracellular fluid has a characteristic if not uniform composition. In other words, as CSF flows down the neuraxis and exchanges with brain, the content of protein and ions in cisternal CSF, spinal fluid, and ISF, although altered, still closely resembles the nascent ventricular CSF rather than plasma.

7.2.3. Regional Sampling of CSF and ISF

Sampling CSF or brain ISF sheds light on the neuronal extracellular environment. Experimental and clinical sampling sites include nascent CSF, large-cavity ventricular CSF, cisternal and lumbar fluids, and brain ISF. Nascent CSF exuding from CP is collectable by pipette, but complex surgery is necessary to isolate the plexus. CSF sampled from lateral, third, and fourth ventricles is a mix of nascent CSF and ISF percolating across the ependyma. It can be procured by invasive but limiting stereotactic procedures. Common sampling procedures include removal of subarachnoid CSF from cisterna magna (i.e., animal models) and the lumbar region (i.e., human spinal taps).

Experimental neuroscience has benefited from recent technical advances in microprobe dialysis. A tiny probe is inserted into a discrete region for continuous collection of brain ISF as a dialysate. Microdialysis is fruitful for assessing microregional differences in neurotransmitter concentrations. Microprobes placed in cisterna magna to analyze CSF do not disturb brain or significantly alter CSF volume (27).

Whereas relatively small regional differences in CSF or ISF concentrations exist for inorganic ions, urea, and glucose, fairly large differences in regional concentrations occur for neuropeptides secreted by specific cell groups. A relatively high titer of angiotensin is found in hypothalamic ISF and in nearby third ventricle CSF; the elevated concentration of secreted peptide dissipates with increasing distance from hypothalamus.

7.2.4. Homeostasis of CSF Composition

The hallmark of CSF is stability of solute composition in the face of excesses or deficiencies in plasma. CSF ion homeostasis is critical because small alterations in CSF [K], [H], [Mg], and [Ca] affect respiration, blood pressure, heart rate, muscle tone, and emotional state. CSF composition has been extensively analyzed after acute and chronic perturbations in systemic acid-base parameters and ion concentrations. Analyses of nascent and cisternal CSF samples reveal an impressive ability of CSF to maintain levels of K, Mg, Ca, and HCO_3 ions when challenged with plasma fluctuations. CP plays a major role in ensuring these *minor* changes in CSF ion concentrations. Water-soluble vitamins B and C are maintained during vitamin deficiency (4, 9). Even lipid-soluble vitamin E concentration is regulated in CSF (9).

Two factors undergird the ability of the blood-CSF interface to stabilize ventricular fluid in the face of vascular biochemical oscillations. First, the CP tight junctions act as a structural barrier that thwarts bidirectional diffusion of substances between blood and CSF. Second, many ionic and molecular transporters enable the plexus to regulate solute passage. CSF homeostasis thus involves finely controlled movement of solutes by active transport or facilitated diffusion not directly requiring energy.

In hypovitaminosis C, low levels of ascorbate in plasma are scavenged by an active transporter in the blood-facing membrane of CP (4, 24). Vitamin C concentrated in the cytoplasm moves out of the cell by facilitated diffusion across the CSF-facing membrane. Coordinated transport by these mechanisms at opposite poles of the cell, working in series, enables the CSF to concentrate vitamin C fourfold above that of plasma. Moreover, the basolateral active transporter for ascorbate is one-way into the cell. Therefore, vitamin C is not leached from CSF when the plasma level is severely reduced. Comparable mechanisms for other micronutrients (4, 9), also dependent on plasma substrate concentration and CP carrier affinity, ensure stable CSF concentrations.

7.2.5. Neurohumoral Regulation of CSF Secretion

Neurotransmitters and neuropeptides modulate choroidal secretion of ions, water, and proteins. In CP there is a great density of receptors for norepinephrine (α and β), serotonin (5-HT_{1c}), angiotensin II (AT_1), and vasopressin (V_{1a}). These receptors localize to the vasculature and choroidal epithelium. In cultured CP cells, serotonin stimulates secretion of transthyretin, a quantitatively important protein that transports thyroid T_4 across the blood-CSF interface. There is no evidence, though, for neurohumoral modulation of CP secretion of proteins to adjust CSF viscosity.

In the *in vitro* CP with no blood flow, exogenously applied serotonin, vasopressin, and angiotensin inhibit Cl release from epithelial cells into artificial CSF bath. Because Cl transport from the *in situ* plexus to ventricles is integral to CSF formation, the *in vitro* findings agree with known effects of neurohumoral agents to reduce CSF formation rate. Neuropeptides administered *in vivo* also curtail CSF formation, in part by reducing blood flow to CP (28). Markedly reduced perfusion of CP limits delivery of water and ions to the secreting epithelium.

Sympathetic nervous activity also "tones" the CSF secretion (Fig. 9). The superior cervical ganglia send adrenergic fibers to CP. Upon resecting the sympathetic fibers, there is increased CSF formation. This indicates a baseline inhibitory sympathetic tone. When such "braking action" is released by blocking sympathetic signals, fluid output is enhanced. Denervation findings have been bolstered by pharmacologic analyses establishing that α and β adrenergic agonists inhibit CSF production.

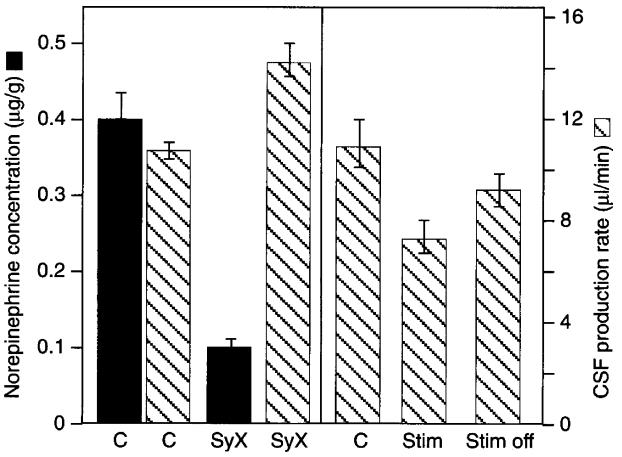

Fig. 9. Regulation of CSF formation by the sympathetic system: The involvement of sympathetic nerves in rabbit CP norepinephrine concentration (*bars with solid black fill*) and CSF production (*bars with diagonal lines*) was demonstrated from denervation (*left*) and electrical stimulation of nerves (*right*). One week after sympathetic denervation (SyX) of CP, there was a substantial decrease in norepinephrine concentration concomitant with significantly increased CSF formation compared with nondenervated controls (C). Electrical stimulation (Stim) of both superior cervical ganglia (which sympathetically innervate CP) significantly reduced CSF production rate. After stopping stimulation (Stim off), there was normalization of CSF formation. Bars are means ± SE. (From Nilsson C et al., Brain Res Rev 1992; 17: 109–138.)

7.2.6. Pharmacologic Manipulation of CSF Formation Rate

The clinical need for selective agents to lower ICP spurs research to find drugs to curtail CSF production. Agents from several classes have been used to assess dose-response phenomena in the CP-CSF. Acetazolamide, an inhibitor of carbonic anhydrase abundantly present in CP, consistently reduces CSF formation rate by 50% to 60%. Acute usage of acetazolamide is therapeutically effective in unloading augmented CSF pressure, but chronic use causes undesirable systemic acidosis. Cardiac glycosides such as ouabain markedly reduce CSF production by inhibiting Na-K-ATPase but have limited therapeutic value because of poor access to CSF and their ability to raise CSF [K]. Amiloride, by inhibiting Na-H exchange in CP decreases CSF formation appreciably if hefty doses (75 to 100 mg/kg) are employed. Other diuretic agents slow down CSF formation but introduce the expected complications consequent to urinary loss of water and electrolytes. More efficacious agents are needed to complement the moderately-effective acetazolamide.

8. INTERACTIVE BLOOD-CSF AND BLOOD-BRAIN INTERFACES IN MILIEU STABILIZATION

The epithelial BCSFB and endothelial BBB concertedly stabilize the fluid composition and volume (Fig. 10). Therefore the neuronal microenvironment depends upon material transfer at the two interfaces. Each barrier has distinctive transport and permeability features. The integrity of *both* barriers is essential for CNS extracellular homeostasis. Disrupted barrier function, individually or in tandem, harms brain parenchyma through altered fluid composition or pressure. Coordinated flow of solutes and water across the blood-CNS interfaces thereby optimizes the neuronal environment.

8.1. Biochemical Composition of Brain ISF

CSF formed by CP and ISF manufactured by capillary walls are not simply plasma ultrafiltrates. Rather, the finely controlled fluids generated across these barriers are active secretions. CSF and endothelial-derived fluid mix (Fig. 11). Bulk flow and diffusion promote mixing, depending upon the direction and magnitude of hydrostatic pressure or solute concentration gradients. Fluid mixing is substantial at ependymal and pial membranes. Solute and water movements between CSF and brain are bidirectional.

With ventricular fluid as the reference, CSF is either a "source" or "sink" for brain (Fig. 12). Brisk secretion by CP furnishes generous amounts of Na, Cl, Ca, vitamins B, C, and E (and other micronutrients), transthyretin, IGF-II, prolactin, leptin, BDNF, and other neurotrophins to ventricular fluid. Collectively, this is a CSF supply "source" for brain. On the other hand, nascent CSF is normally low in protein and catabolites. Consequently, as ventricular fluid sweeps down the neuraxis, it acts as a drain or "sink" to remove harmful proteins and catabolites at higher concentration in ISF (due to metabolism and BBB leaks) than in CSF. Overall, ISF composition is influenced by transependymal fluxes of solutes, the gradients for which are impacted by transport activity at CP and BBB.

8.2. Stability of Brain Volume

Regulation of brain water content, hence volume, is critical for maintaining ICP within tolerable limits. Brain volume is affected by many parameters. Influx of water across the BBB and BCSFB interfaces importantly determines water balance among CNS compartments. Brain volume is stabilized at two levels: (1) interstitial (extracellular) fluid, and (2) neuronal and glial intracellular fluid (ICF).

8.2.1. Interstitial Volume

ISF volume is mainly the extracellular water content. It comprises 15% to 20% of brain weight. Water is transported across the relatively impermeable cerebral capillary wall slower than it is convected across

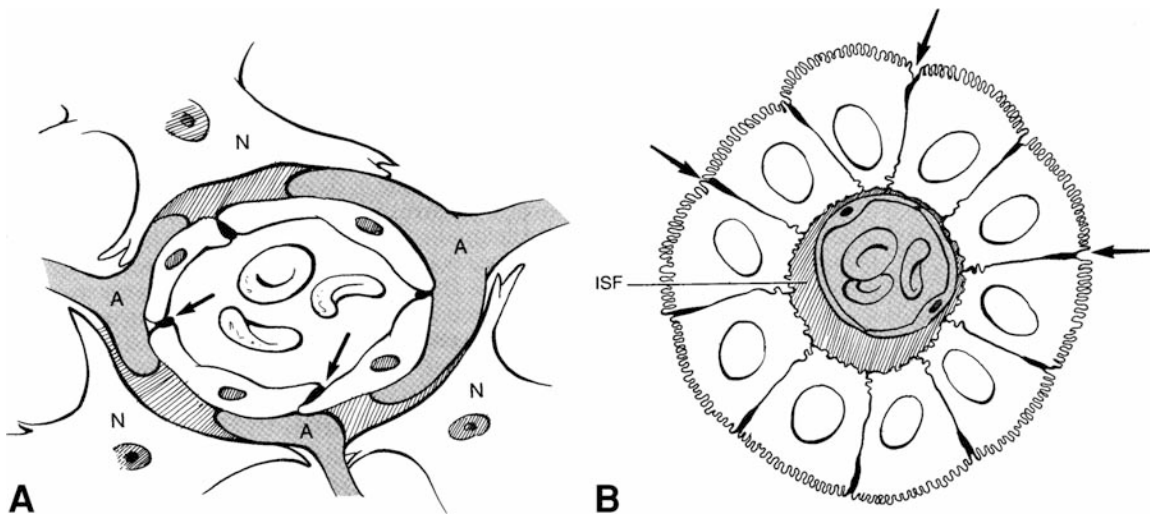

Fig. 10. Parenchymal cells of blood-brain and blood-CSF barriers (**A**) Highly idealized schema for components of BBB. Endothelium of cerebral capillaries lack fenestrations and are tightly joined by *zonulae occludentes* (*arrows*). Astrocyte foot processes (**A**) extensively abut the outside endothelial surface. Darkened area is the interstitial space surrounding the capillary wall. N, neuron. **(B)** Cross section of a choroidal villus. A ring of CP epithelial cells surround the ISF and adjacent vascular core. The basolateral surface has interdigitations, whereas the outer CSF-facing apical membrane presents an extensive microvilli system. *Arrows* point to tight junctions between cells at apical poles.

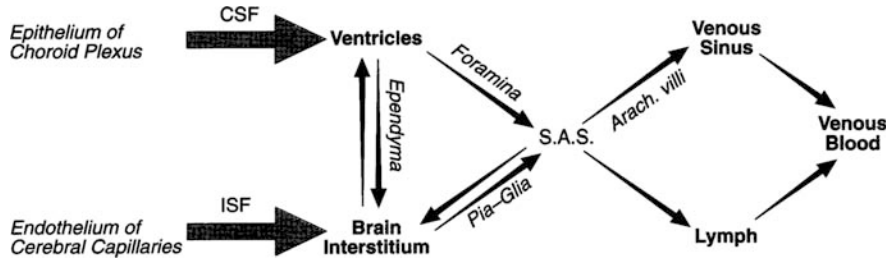

Fig. 11. Schema for fluid formation, exchange, and drainage routes in CNS: CSF is derived from constituents of plasma ultrafiltrate in the plexuses, by active secretion in the choroid epithelia. Plexus-generated fluid percolates down the ventricular system and then into the SAS of cisterna magna. From this great cistern, CSF continues to flow in the SAS overlying the hemispheres and cord. Finally, SAS fluid is reabsorbed into venous blood by a hydrostatic pressure–dependent mechanism in the arachnoid villi within dura mater, and into lymphatics via the cranial and spinal nerves. Simultaneous with CSF formation by CP is the slow production of cerebral ISF by brain endothelia. Once formed, ISF undergoes bulk flow exteriorly across the pia-glial membrane into SAS and interiorly into the ventricles, across the ependyma. Fluid flow is usually unidirectional through the ventricular foramina and arachnoid villi but is potentially bidirectional across the ependyma and pia-glia. For example, in hydrocephalus when CSF pressure is elevated, fluid moves from ventricles into brain tissue. The fluid in SAS is a mixture of CSF and ISF. Subarachnoid fluid drains into blood across arachnoid villi and via lymphatic tissue in the eyes and nose, which receive fluid draining along nerve roots. (Adapted from Audus KL, Raub TJ, eds. *Pharmaceutical Biotechnology*. New York: Plenum Publishing, 1993; 5: 467.)

permeable peripheral capillaries. Low hydraulic conductivity at the BBB is due to the high resistance at interendothelial tight junctions. It is debatable whether Starling's hypothesis, describing the role of passive hydrostatic and osmotic pressure gradients for driving net filtration in many vascular beds, applies to fluid exchange between brain capillaries and surrounding ISF. Normally, the water gaining access to brain by slow permeation across capillaries eventually flows out via CSF. As a result, the pressure and volume of ISF are optimally maintained.

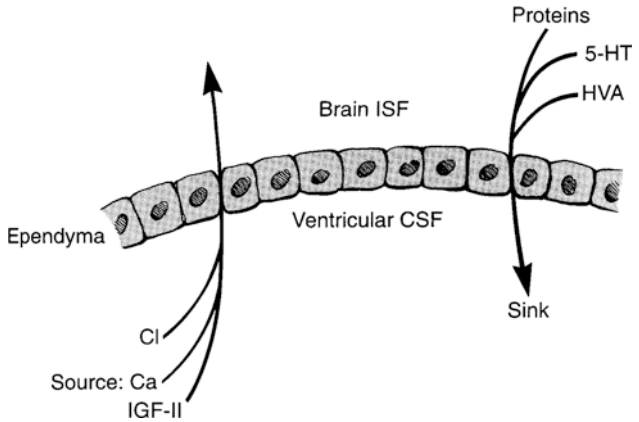

Fig. 12. CSF as a "source" or a "sink" for the brain. Depending upon the prevailing concentration gradient for diffusion across the ependyma, the CSF either supplies or removes solutes. CP secretes ions, proteins, and various micronutrients into ventricles. These transported solutes are derived either from plasma or the CP epithelium, which synthesizes certain proteins. Upon accessing the ventricles, the solutes are distributed by bulk flow of CSF acting as a supplier (or source) of materials for targeted cells in brain. Conversely, CSF acts as a drain or sink for solutes (metabolites of neurotransmitters, protein catabolites, iodide, etc.) that are break-down products of metabolism or leak across barriers from blood. Once in CSF, these potentially harmful materials are actively reabsorbed by CP or cleared from CNS by bulk flow drainage. IGF-II, insulin-like growth factor-II; 5-HT, 5-hydroxytryptamine; HVA, homovanillic acid.

Water is also transported into CNS via CP with CSF formation. Most of the water generated in CNS originates from the four CPs. Once formed, CSF moves by bulk flow along pathways of least resistance (i.e., through the ventricles and SAS rather than through less compliant brain tissue). Consequently, the orderly flow of CSF and ISF along defined pathways keeps extracellular fluid volume and ICP stable.

8.2.2. Intracellular Volume

Brain volume intimately relates to water content. Cellular water content depends upon total osmotically active solutes. Neurons and glia continually exchange ions and organic molecules across external limiting membranes. Co-transporters move Na, K, Cl, inositol, and taurine into and out of cells, depending upon concentration gradients and transporter capacity. Consequently, water follows the net movement of transported solutes. In this manner, cell volume is stabilized even when extracellular tonicity is altered.

As brain tissue swells or shrinks in acute hyponatremia or hypernatremia, the activity of cellular co-transporters is upregulated or downregulated. Consequently, cell volume is rapidly reestablished.

Ischemic or pharmacologic disruption of cellular transporters swells the parenchyma, and thus the brain. Various states that alter the size of CNS intracellular and extracellular compartments are discussed below.

9. FLUID IMBALANCES: EFFECTS ON BRAIN AND CSF VOLUMES

Consideration of relative and absolute volumes of brain and CSF is essential to understand normal and deranged cerebral states. Water imbalance in brain affects the tortuosity (geometry of pathway winding) of extracellular channels. Such altered configuration of the interstitial space impacts excitability phenomena and signal transmission. Moreover, severely contracted ventricular volume (e.g., slit ventricle syndrome) may compromise the CSF sink and source functions. This is how brain and CSF volume changes affect neural activities.

A substantial increase in brain water content (i.e., edema) predisposes to herniation and intracranial hypertension. Edema may be generalized or localized around a tumor or infarct. In severe edema, the flow of nutrients to brain tissue and the orderly removal of unwanted catabolites are disrupted. In localized edema, tissue herniation can involve the cerebellar tonsils through the foramen magnum or the temporal lobe uncus across the tentorium. Edematous states are classified as affecting mainly the interstitium or cells.

9.1. Vasogenic Edema

The most prevalent brain edema, vasogenic, occurs in ischemia zones. Vasogenic edema is caused by increased permeability of the BBB, which allows plasma proteins and ions to leak across the endothelial wall. The resulting increase in ISF volume raises ICP, slows the EEG, and impairs consciousness. White matter is particularly affected. Vasogenic edema, frequent in head trauma and meningitis, is visualized by magnetic resonance imaging (MRI) or computed tomography (CT). Substantially increased brain volume from vasogenic edema occurs at the expense of the ventricles, which, because of CSF displacement, diminish to slits.

9.2. Interstitial Edema

Another distortion of the brain extracellular compartment is interstitial edema. Elevated ICP in obstructive hydrocephalus promotes spreading of ventricular water and Na into adjacent white matter. Axial MRI reveals periventricular edema as a "white rim" around the frontal and occipital horns of the ventricles. Interstitial edema caused by chronic hydrocephalus is relieved by surgically shunting CSF to another body cavity. Hydrocephalus-induced interstitial edema is associated with enlarged ventricles.

9.3. Cytotoxic Edema

Cytotoxic edema is swelling of glia, endothelia, and neurons. As a result of expanded cell volume collectively, there is an attenuated interstitial space. Cell swelling results from drug poisoning, water intoxication, hypoxia from asphyxia, and acute hyponatremia. Under such conditions there is a net shift of water from extracellular space into brain cells. Cytotoxic edema can coexist with other forms of edema in encephalitis and meningitis. Brain swelling in severe cytotoxic edema diminishes the size of the ventricles and basal cisterns. Distorted ventriculo-subarachnoid spaces disrupt the CSF circulation. This alters homeostatic molecular exchanges mediated by CP-CSF.

10. CIRCULATION OF CSF

CSF is referred to as the "third circulation." CSF derives from the anterior and posterior choroidal arteries. Choroidal venous drainage occurs largely by the vein of Galen. There are no lymphatic capillaries in CP or brain. However, the continuous flow of CSF through large spaces acts as a quasi-lymphatic system. Also, ISF percolates along low-resistance circumscribed pathways (e.g., around myelinated fibers) without lymphatic capillaries.

More than being clearance conduits, the CSF circulatory pathways distribute trophins and micronutrients from CP to brain parenchyma. Heading for multiple venous drainage sites, the human CSF flows through ventricles and SAS at about 0.35 mL/min. CSF movement is hampered by "upstream" clogging of CP (by deposits of Ca, immune complexes, and amyloid) and by "downstream" obstruction in the arachnoid (by fibrosis and amyloid). CSF disruption in neurodegeneration such as Alzheimer's disease interferes with the renal-like function of CP-CSF. This exacerbates the primary disease.

10.1. Pressure Gradients

Several driving forces propel CSF. Formation of CSF by CP provides a hydrostatic pressure head of

about 150 mm of water, thereby generating a force for forward movement of newly formed fluid. Pulsation of blood in choroidal vessels promotes CSF circulation. Moreover, cilia beating at the apex of CP epithelium and some ependymal cells imparts additional thrust on ventricular CSF. The higher pressure of CSF relative to that in dural venous sinuses creates a positive gradient of 70 to 80 mm water that clears CSF by bulk flow from SAS to blood.

10.2. Direction of Current Flow

Ventricular fluid moves from lateral ventricles through the foramina of Monro down to the front of the third ventricle. After leaving the posterior third ventricle, CSF flow continues through the sylvian aqueduct eventually to empty into the fourth ventricle. CSF in the fourth ventricle seeps into SAS by three different apertures. Two exits are the bilateral foramina of Luschka at the extreme lateral portions of the fourth ventricle. The other major exit is the foramen of Magendie in the fourth ventricle roof. Here CSF empties into the *cisterna magna* or the *cisterna cerebello-medullaris*.

CSF flows from the base of the brain up over the hemispheric convexities until reaching the arachnoid villi in the walls of the superior sagittal sinus (Fig. 13). Thus CSF flows from the *cisterna pontis* to other cisterns: the *interpeduncularis* and *chiasmatis*, from which it sweeps upward over the hemispheric surfaces. It then progresses anteriorly upward along the longitudinal fissure, over the corpus callosum, along the sylvian fissure, and over the temporal lobes. At the most distal end of the flow route, the cranial subarachnoid CSF finally encounters the arachnoid villi (Fig. 13).

CSF also moves down from the *cisterna magna* to the posterior or dorsal surface of the spinal cord. CSF fills a sleeve of SAS around the spinal cord and even extends below the end of the cord into the region of the second sacral vertebra. Although the spinal subarachnoid CSF is in effect an anatomic "blind pocket," nevertheless there is a slow mixing of spinal and cranial CSF induced by changes in posture.

10.3. Volume Transmission

Volume transmission is simply bulk flow or convection of CSF. Although CSF sloshes "to and fro" (with the cardiac cycle) in transit down the neuraxis, the *net* movement of fluid to distal drainage sites occurs as the result of hydrostatic pressure gradients from CSF to venous blood. Bulk flow distributes materials *much faster* than by diffusion (1). Accordingly, CSF volume transmission enables efficient distribution of many peptides and hormonal signals along the CP-CSF-brain nexus. Moreover, volume transmission allows CSF to be "turned over" relatively rapidly and thereby helps to purify the CNS interior.

Convection of drugs via CSF importantly affects elimination half-time. Thus, CSF-borne methotrexate, an antitumor agent, has an excretion half-time similar to the CSF renewal rate of about 6 hours. Substantially reduced CSF turnover (as in aging, chronic hydrocephalus, and Alzheimer's disease) compromises volume transmission. Such stagnated CSF flow enhances drug residence time in CNS and leads to pharmacotoxicity.

11. DRAINAGE OF CSF

CSF drainage is of neurosurgical interest because ICP problems attend inadequate fluid clearance from CNS. Normally, CSF drainage keeps pace with formation, and so ICP is stabilized. There are two bulk-flow mechanisms or pathways for CSF leaving the CNS. The lesser is valve-like drainage directly into cranial sinus venous blood. The other *more extensive* pathway is convective clearance via the cranial and spinal nerves into prelymphatic tissue spaces and then lymphatic nodes.

11.1. Arachnoid Villi and Granulations

Concepts about CSF reabsorption are under revision. For many decades, the prevailing view was that the arachnoid villus plays a prominent role in CSF egress to venous blood. Arachnoid villi and the compositely larger granulations increase more or less with mammalian species size. Historically important research by Welch, Davson, Pollay, Gomez, and Butler extensively described the anatomy and *in vitro* function of arachnoid villi; see the overview by Rapoport (29). Recent topographic assessments of human arachnoid granulations on the cortical surface (30) set the stage for functional studies of these granulations in patients with impaired CSF reabsorption.

11.2. Intracranial Arachnoid Villi and Granulations

In the traditional model, CSF returns to blood (passively along hydrostatic pressure gradients) across arachnoid villi into the dural venous sinus. A hydrostatic pressure gradient of at least 30 mm H_2O from CSF to blood enables large proteins and

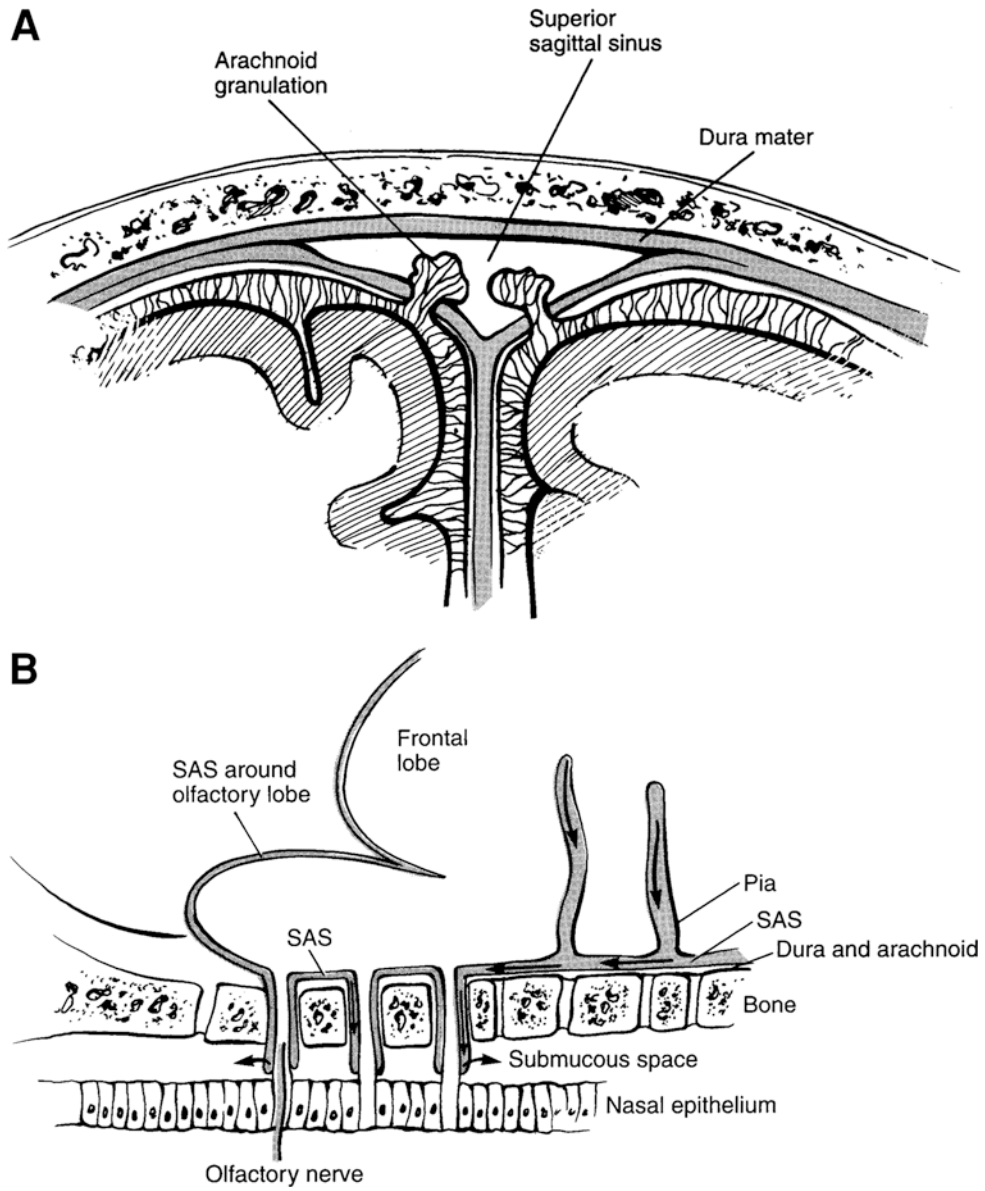

Fig. 13. CSF drainage by bulk flow across arachnoid villi in the dura mater and into lymphatic capillaries of eye and nose. (*Top*) A hydrostatic pressure gradient drives CSF in SAS into the venous sinus via valve-like structures in arachnoid villi. Valves are big enough to allow protein cells in CSF to pass, but normally only unidirectionally, from CSF to blood. Therefore once CSF-borne macromolecules have flowed into the venous sinus, they effectively have been cleared from CNS. Villi increase in size and number with advancing age. (*Bottom*) Another route for CSF drainage is along cranial nerves into submucosa of nose and eye. CSF flows via sleeve-like extensions of the SAS around the nerve, through the cribriform plate, finally to reach nasal submucosa. Lymphatic capillaries drain the submucous spaces and convey fluid to lymph nodes. (From Bradbury M et al., *Am. J. Physiol.* 1981; 240: F335.)

erythrocytes to penetrate the one-way valves that regulate outward CSF flow. At about 120 mm H_2O of CSF pressure, the rate of absorption equals CSF production. Conversely, when venous pressure exceeds ICP, the valves close and prevent blood reflux into SAS.

Vacuoles in the mesothelium of arachnoid villi suggest a dynamic pressure-sensitive vacuolation. Vacuole formation in the valves likely constitute transendothelial channels for CSF flow. Such function may be particularly relevant when ICP is substantially elevated, as in congenital hydrocephalus. However, under normal ICP in most animals modeled, a relatively small proportion of CSF is convected across arachnoid villi.

11.3. Extracranial and Spinal Nerve Outflow Pathways

With respect to the preponderance of CSF drainage, the fluid must first pass through *lymphatic tissue* before reaching venous blood (Fig. 13). The systematic and elegant work of Johnston and colleagues over the past decade provides substantial evidence from several mammals that a large fraction of CSF outflow occurs across the cribriform plate and along the olfactory nerve into submucosal spaces (31). Sleeves of subarachnoid CSF surround the optic and olfactory nerves in particular as well as other cranial and spinal nerves (31–33). A positive-pressure gradient promotes CSF flow along the perineural space that extends into the submucosa of eye and nose. There the lymphatic capillaries reabsorb CSF and convey it to cervical lymph glands. CSF exiting by this route is thus first exposed to the immune system prior to reaching venous blood. Antigenic material (e.g., products of myelin breakdown) in outflowing CSF thereby induces antibody reactions that eventually affect the CNS via altered immune cell transport at the CP and BBB (34).

12. CSF PRESSURE-VOLUME RELATIONSHIPS

The adult skull is incompressible. Therefore ICP rises after a significant increase in any of the major constituents of the intracranial space: brain parenchyma, CSF, and vascular tissue. The CSF constituent is a potential liability as well as asset. A life-threatening increase in ICP results from CSF occlusion. On the other hand, shunting of CSF unloads ICP. CSF pressure is thus useful to evaluate or "titrate" therapeutic responses.

Markedly elevated ICP seriously injures the CNS. Normally, the CSF buffers impact forces and acute changes in vascular pressure. Tumors, infections, neurosurgery, trauma, and diseases, however, can elevate ICP. There are several sites for monitoring ICP and numerous treatment modalities to alleviate intracranial hypertension.

12.1. Normal Ranges of ICP

ICP is commonly assessed in the lumbar region. In patients with normal blood pressure and no pathologic lesions, the SAS pressure of reclining individuals is close to 100 mm H_2O. The typical range for lumbar CSF pressure is 50 to 150 mm H_2O or 4 to 11 mm Hg. CSF production is stable over the normal range of CSF pressure. Formation of CSF, however, may decrease when ICP is substantially elevated as in severe hydrocephalus. Augmented CSF pressure reduces plasma filtration across choroidal capillaries (i.e., the initial step in fluid formation).

12.2. Measurement of ICP

Pressure on the intracranial contents can be probed at various depths under the skull. Probes are placed epidurally as well as in the SAS, brain parenchyma, or lateral ventricle. Figure 14 depicts monitoring sites. The paragon for measuring ICP is the intraventricular catheter connected to a manometer by a fluid-filled tube. To place the catheter, a burr hole is drilled over frontal cortex. Upon dural piercing, the catheter is directed into a lateral ventricle with the tip near the foramen of Monro. ICP assessments are made by ventricular probing with usually few complications (Table 7).

Relatively noninvasive pressure probes can be applied epidurally. Epidural pulsations, an indirect measure of ICP, are monitored by fiberoptic, strain gauge, or pneumatic systems. This approach lacks the accuracy to justify regular usage. Pressure recorded subarachnoidally over the convexities also estimates ICP. The subarachnoid screw or bolt is a hollow tube secured to the calvaria. The device is connected to a fluid-filled system with an external transducer. Intraparenchymal pressure recording guides ventricular cannula placement. Camino fiberoptics are used for intraparenchymal, epidural, and intraventricular monitoring. Infection rates for pressure-measuring systems are $<1\%$ if monitors are placed 4 days or less. Table 7 recapitulates various approaches.

12.3. CSF Pulsations and Pressure Waves

CSF pulsates due to oscillating arterial and venous pressures. Intracranial venous pressure decreases and increases, respectively, during respiratory inspiration and expiration. Altered venous pressure in the respiratory cycle transmits to ICP. Moreover, arterial systolic pulsations, particularly in CP, synchronously elevate the CSF pressure.

Sustained intracranial hypertension causes pathologic "plateau waves." Unstable vasomotor control (e.g., loss of cerebrovascular autoregulation or reduced CBF) can trigger an onset of plateau waves. Clinically significant plateau waveforms may last 5 to 20 min and be associated with an ICP of >1000 mm H_2O. Elevated CSF pressure results from enhanced cerebral blood volume. Plateau waves occur in advanced stages of intracranial hypertension and often indicate CNS damage.

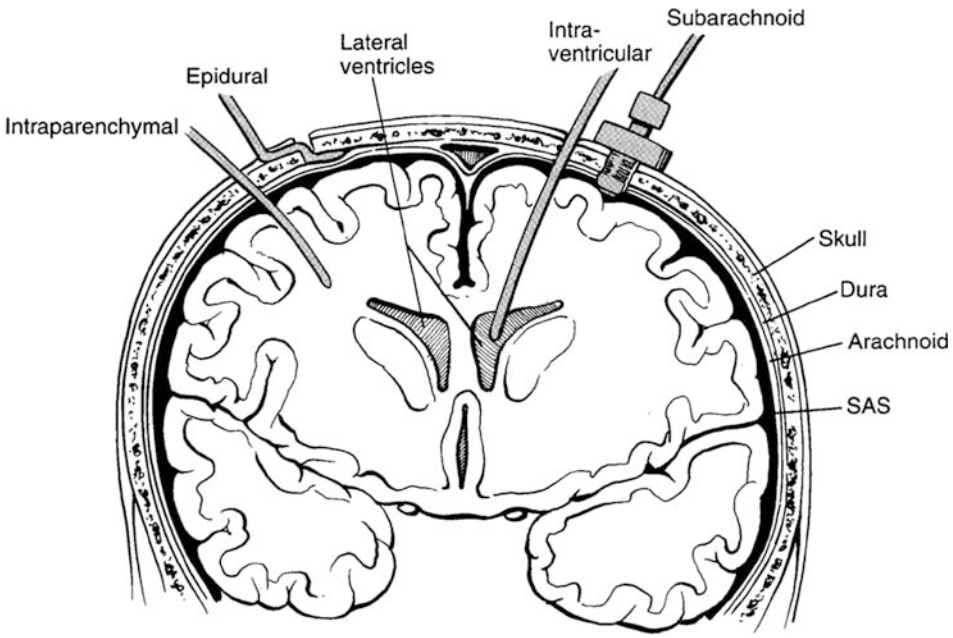

Fig. 14. Various sites for monitoring ICP. The intraventricular catheter is inserted through a burr hole in the frontal lobe, down into a lateral ventricle near the foramen of Monro. Placement of probe in the epidural space carries minimal risk for brain infection because the dura remains intact. The subarachnoid bolt is placed in SAS but often needs saline irrigation to remain patent. Intraparenchymal microtransducers are insertable for 2 to 3 cm into white matter. (From Lyons MK and Meyer FB, *Mayo Clin. Proc*. 1990; 65: 684.)

12.4. Relationship Between ICP and Cerebrovascular Parameters

Markedly elevated ICP thwarts arterial perfusion, causing irreversible damage. Cerebral perfusion pressure, the difference between mean systemic arterial blood pressure and ICP, is critical. When ICP rises to the systolic blood pressure, CBF ceases because the driving force for perfusion becomes negligible. If prolonged, brain death ensues.

Substantially elevated ICP compromises delivery of O_2 and nutrients to the brain. Because of skull rigidity, the fixed volume of the intracranial space does not properly accommodate increased tissue mass (such as space-occupying tumors and blood clots) or edematous fluid secondary to trauma. In such cases, failure to adequately lower the ICP and maintain perfusion can be fatal.

12.5. Management of Elevated ICP

Trauma is a common cause of rising ICP. Cerebral edema or bleeding into CSF markedly elevates ICP. Surgical and nonsurgical means help to alleviate

Table 7
Devices and Locations for Monitoring ICP

Location	*Advantages*	*Disadvantages*
Intraventricular	Reliable measure of ICP; allows CSF drainage; good pressure waveform.	Invasive; risk of infection, need to enter ventricles; can obstruct.
Epidural	Less invasive, dura remains intact; less risk of infection.	No CSF drainage; poor measure of ICP; no waveform.
Subarachnoid	Brain theoretically not penetrated, lower risk of infection; ease of placement.	No CSF drainage; brain tissue easily obstructed; fluid-filled system but waveform usually poor.
Intraparenchymal	Non–fluid-filled system; fairly reliable measure of ICP.	Invasive; risk of infection; no CSF drainage.

CSF, cerebrospinal fluid; ICP, intracranial pressure. (Adapted from Lyons MK, Meyer FB. Cerebrospinal fluid physiology and the management of increased intracranial pressure. *Mayo Clin. Proc*. 1990; 65: 684; and from McComb JG [personal communication].)

intracranial hypertension. Surgical decompression is feasible in patients with hematomas located epidurally, subdurally, or parenchymally. Drainage via ventriculostomy is the prime method of lowering ICP elevated by obstructed CSF drainage.

When surgery is contraindicated, there are postural and pharmacologic strategies to unload ICP. Head elevation above the heart facilitates venous drainage. To minimize edema from injured cerebral vessels, fluid restriction is useful in the patient without *diabetes insipidus*. High levels of blood glucose should be avoided because the hyperglycemia of head injury is detrimental to cerebral function if ischemia is concurrent. Ventilatory support by hyperventilation rapidly lowers ICP in many patients. This benefit results from cerebrovascular constriction to lower blood volume.

Diuretic agents reduce CNS water content, thereby decreasing ICP. Furosemide and acetazolamide curtail the CP output of CSF into the ventricles and also act as renal diuretics to eliminate body fluid. Mannitol is used as an osmotic agent because it slowly permeates the blood-brain and blood-CSF barriers. Consequently, the osmotic gradient set up between blood and brain "pulls" water from nervous tissue. The dehydrating effect of mannitol may be prolonged by concurrently using loop diuretics. Because osmotic agent clearance from blood is faster than CNS, a "rebound" intracranial hypertension occurs if mannitol is not carefully administered.

Corticosteroids and barbiturates have limited use in controlling ICP. High doses of dexamethasone and methylprednisone decrease ICP in some patients with large brain tumors by suppressing edema formation and stabilizing membranes near the tumor. Barbiturates such as pentobarbital are used when conventional modalities fail. Pentobarbital decreases CBF and cellular metabolism, thereby reducing ICP.

12.6. Compression of CSF and the Optic Nerve

Ventricular tumors directly occlude CSF drainage, with a resultant increase in ICP. Tumors distant from the ventricles may not significantly obstruct CSF flow until the mass becomes substantial. Tumor growths in the posterior fossa (e.g., in cerebellum) exert pressure on the fourth ventricle roof, thereby obstructing CSF flow into SAS. Brain tumors compressing the optic nerve cause papilledema by choking the optic disk. Sustained papilledema severely damages the optic nerve and can cause blindness. Papilledema also results from *pseudotumor cerebri* or benign intracranial hypertension. In this disorder, there is augmented CSF production and interstitial edema. Benign intracranial hypertension elevates ICP in young obese women. It can be effectively treated over several weeks.

12.7. Hydrocephalus, Ventriculomegaly, and ICP

Hydrocephalus is enhanced CSF volume, with or without elevated ICP. *Compensatory hydrocephalus* occurs without augmented ICP. Here an expanded CSF volume compensates for cerebral atrophy in primary CNS disease. Another syndrome, *normal pressure hydrocephalus (NPH)*, results from chronically impaired absorption into blood. CSF composition and pressure are variably altered in NPH. Although ventricles enlarge, there may not be size changes in cerebral cortex or SAS. CSF shunting in selected adult NPH patients relieves the triad of unsteady gait, dementia, and urinary incontinence.

Hydrocephalus is either communicating or noncommunicating (obstructive). In *communicating hydrocephalus*, there is an open system between ventricles and SAS. Hydrocephalus can be caused by altered CSF dynamics (production or absorption) or by obstructed flow of CSF through the SAS. In *obstructive hydrocephalus*, something impedes fluid percolation within the ventricles, aqueduct, or fourth ventricle outlets. With blocked CSF flow in developmental abnormalities, inflamed tissue, or tumors, the retained fluid in ventricles elicits a rise in ICP.

Continuously elevated ICP in hydrocephalic states with accumulating CSF causes ventriculomegaly. Enlarged ventricles compress underlying cells and their processes. During early hydrocephalus stages, there is damage to ependyma and periventricular white matter. Two to 3 weeks of severe hydrocephalus can compress the cortical mantle, sometimes to 25% of original thickness. Cytological and cytoarchitectural studies of brain cells in animal models reveal greatly shrunken somata and abundant vacuoles. In severe hypertensive hydrocephalus, there is a diminution of axons and blood vessels. Surgical shunting of CSF to the peritoneum reduces ventriculomegaly and decompresses cortex. With early shunting, much structural and functional damage is reversed. Shunting evidently facilitates removal of substances from ISF, the effect of which needs elucidation.

13. CELLULAR COMPOSITION OF CSF

A distinguishing feature of CSF, especially in relation to blood, is a paucity of cellular elements. CSF usually contains no more than four mononuclear cells

or lymphocytes per cubic millimeter. White cell counts of 5 to 10 per mm^3 can signify pathology. Elevated cell counts in CSF occur after brain injury, central inflammatory processes, or tumor cell invasion. Cytologic examination of CSF is becoming delineative with application of polyclonal and monoclonal antibodies to specify pathology.

13.1. Normal Conditions

The high water content of CSF (> 99%) reflects a low cell count. Normal CSF contains a few small B and T lymphocytes and monocytes. The relatively impermeable CNS barriers prevent significant penetration of blood cells into CSF of healthy humans. An elevated erythrocyte count in CSF can indicate blood contamination of the specimen. Sloughed choroid epithelial, ependymal, or arachnoidal cells in CSF samples are rare.

13.2. Infective States

CSF pleocytosis is common in acute infections of the CNS. In fungal infections, the predominant cell in CSF is the lymphocyte, whereas in bacterial infections it is the neutrophil. In acute bacterial meningitis, >90% of cells in CSF may be neutrophils. With severe infections such as a ruptured abscess, CSF cell counts exceed 20,000 per mm^3.

The appearance of ependymal and choroidal cells in CSF, along with white blood cells, signifies neurologic diseases and infections. However, mumps virus uniquely causes ependymitis. Ependymal destruction leads to aqueductal narrowing and hydrocephalus.

Cellular composition of CSF in AIDS patients is highly variable. In one study of HIV-1, only a small percentage of patients developed lymphocytic pleocytosis in CSF even with fully acquired immunodeficiency. AIDS patients have many opportunistic infections. Therefore, CSF immune cell profiles will be similar to those caused by opportunistic invaders, although response magnitude may be blunted by immunodeficiency.

13.3. Neoplastic Diseases

CSF sampling is used to manage brain tumor patients. Primary neoplasms around the brain stem, cerebellum, and spinal cord can abut CSF pathways and shed tumor cells that appear as sediment in CSF samples. Medulloblastomas arising from the external germinal layer of cerebellum shed many tumor cells into CSF. In contrast, meningiomas shed few malignant cells. Meningiomas are firm arachnoidal elements that do not readily exfoliate cells, thus the low frequency of CSF-positive specimens.

Metastatic neoplasms (carcinomatosis) have a greater propensity to exfoliate cells than do most primary tumors. Thus there is a high yield (20% to 50% positive) from cytologic examination of CSF malignant cells in cerebral metastases. Carcinomas of lung, stomach, and breast commonly metastasize to CSF. The less frequently occurring melanoma usually metastasizes rapidly to brain and CSF and is characterized by pigmentation. Occasionally, the CNS-CSF metastasis is present before the primary peripheral tumor is discovered. Inflammatory cells intersperse with tumor cells in CSF. When exfoliated tumor cells in CSF are sufficiently characteristic, the peripheral origin can sometimes be identified.

Complete treatment of leukemia depends on CSF cytologic analysis. Because chemotherapeutic agents do not readily penetrate the BCSFB and BBB, malignant cells inside CNS can remain after treatment. Because surviving tumor cells in the SAS are a reservoir contributing to systemic relapses, it is essential to pinpoint even a few leukemic cells in CSF. Flow cytometry combined with monoclonal antibody staining detects small numbers of specific malignant cells. Such CSF examination is important in leukemia management to decide upon radiation or intrathecal treatment.

14. CLINICAL USAGE OF CSF

Many neurologic disorders present with altered CSF chemistry. As brain metabolism is altered by disease or trauma, many cellular metabolites released into ISF gain access to CSF. Thus, CSF biochemical profiles often change during illness or injury. Such modified CSF composition often mirrors perturbed neurochemistry. Therefore, clinicians use CSF findings to guide diagnoses and management. Limitations to this approach need to be recognized. Nevertheless, if CSF samples are appropriately interpreted, the biochemical and cellular information is diagnostically valuable.

Lumbar SAS is a convenient region for sampling CSF, after the potential value and risks of tapping have been considered. Although CT obviates some punctures (e.g., suspected subarachnoid hemorrhage), there are many indications to procure CSF samples.

14.1. Diagnostic and Prognostic Benefits

Lumbar punctures are done mainly for diagnoses. CSF analyses can strengthen the diagnoses of

neurosyphilis, multiple sclerosis, and many inflammatory diseases involving meninges. Inexplicable seizures should also prompt the analysis of CSF biochemistry. In myelography, the CSF removed at the initial procedural stage should be characterized as a baseline for future comparisons. Access to CSF by way of a lumbar tap also permits measurement of pressure in clinical assessments of intracranial hypertension.

14.2. Intrathecal/Intraventricular Administration of Drugs

Drugs that cross the BBB and BCSFB too slowly for therapeutic usefulness can be administered intraventricularly (by lateral ventriculostomy) or intrathecally (by infusion into spinal SAS); see Fig. 15. Drug injection into human nervous tissue is usually not feasible. However, agents infused into CSF gain access to the permeable ependymal and pial linings where diffusion into brain occurs.

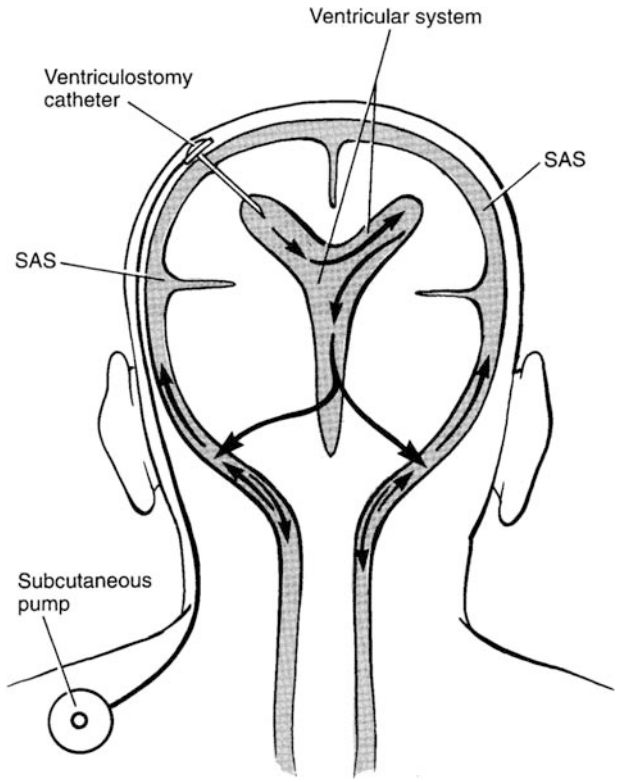

Fig. 15. CSF infusions of drugs through a totally implanted system for constant intraventricular drug infusion. Components of the system include a subcutaneously implanted Infusaid pump, Silastic catheter, and ventriculostomy reservoir and catheter. The amount of drug for refill is calculated as the product of dose rate times pump capacity, divided by flow rate of pump. SAS, subarachnoid space. (From Dakhil S, Ensminger W, Kindt G, et al. *Cancer Treatment Reports*, 1981; 65: 405.)

CSF infusion circumvents blood-CNS barriers and exploits pharmacokinetic factors. Drug metabolism and protein binding are usually less problematic in CSF than in plasma. Central administration of drugs largely avoids renal/hepatic metabolism. Because CSF has a meager protein level, there is low probability that a drug effect will be diminished by extensive binding to a large central reservoir of extracellular albumin or other protein.

There is advanced technology of implantable pumps to deliver drugs via CSF. Some pumps hold 50 mL and deliver at 75 to 100 μL/min. Variation in delivery rate is ±5%. Drug dose is regulated by adjusting reservoir concentration. Therapeutic agent stability is required for many weeks at 37 °C in a CSF-like buffer. Vehicles are set to a certain pH and osmolality and cannot contain a solubilizer harmful to exquisitely sensitive brain.

A big plus for CSF drug delivery is localized pharmacologic effect. This is significant because many neurologic diseases are circumscribed. Central drug delivery is efficacious when there is optimal blending of pharmacodynamics and pharmacokinetics. Intrathecal morphine, used successfully in pain control, avoids systemic narcotic effects like anorexia and oversedation. Intraventricularly administered bethanechol (an acetylcholine agonist) has improved Alzheimer patients. Future investigations should reveal how higher brain center functions can be effectively modified with intraventricular infusions or CP-mediated delivery of therapeutic agents (6).

15. NEW OUTLOOKS FOR CSF TRANSLATIONAL RESEARCH AND THERAPY

Appreciation of the circulatory vitality of the CP-CSF-arachnoid nexus for brain metabolism is prompting novel investigations in basic and clinical neuroscience. In animal models, the burgeoning CSF dynamics in early development coincides with a brain growth spurt (3). Gene expression in the maturing CP is key to understanding the impact of CSF growth factors and neurotrophins on the SVZ. There, the birth and migration of neurons is pivotal for "architecturally" shaping the brain. Because of secretion of multiple growth factors at the BCSFB, the CP generates a "hotbed environment" for the brain interior (3, 5, 13). A disrupted flow of vitamins and modulating proteins in ventricular CSF substantially alters

fetal brain morphing (3, 35). Congenital hydrocephalus models demonstrate that disordered CSF dynamics has dire consequences on neuron generation in germinal matrix (35). To alleviate pediatric hydrocephalus, rational prophylactic measures (e.g., CSF growth factor manipulation) are on the horizon.

Experimentally, the BCSFB is gaining attention in regard to homeostatic and pharmacokinetic modeling. New insights strengthen the construct that CP makes major contributions to brain health (3, 16). Choroid epithelial cells not only *distinctively* transport plasma-borne micronutrients and particular hormones but also *uniquely* synthesize and secrete proteins such as transthyretin. Transport *specificity* at the BCSFB points to pharmacologic opportunities (6) for regulating the movement of neurotrophic and reparative agents to neuronal networks. Biomedical devices and strategies for stem cell augmentation (8), as well as CP transplants and transgene manipulation (6, 36), may also be feasible by intraventricular instillation (6). Boosting trophic factors, antagonists, and chelators in CSF will benefit neural repair in trauma (37), ischemia (38), hyperthermia (39), and infectious disease.

Another advance, with potential to expedite translational research, is appreciation that the BCSFB and BBB should *both* be incorporated in paradigms of metabolic and fluid balance (3). The multicompartmental nature of CNS dictates that experimentation should factor the CP functions along with the cerebral capillary transport phenomena (influx and efflux). Two examples are the translocation of water and amyloid peptides by aquaporins (3) and the LRP-1 transporter (3, 40), respectively. Conceptualizing *both* plasma and CSF as potential sinks (40, 44) on water and solutes will enhance pharmacotherapy to ameliorate hydrocephalus and Alzheimer's disease (3, 41).

Aging exacts a great toll on CP mechanisms that protect brain from systemic perturbations (42). In aging, free radicals and other oxidative products injure the choroidal epithelium, thus interfering with CSF production and solute homeostasis (16). The decline in CSF turnover rate with age places the brain at risk because the CNS does not receive adequate micronutrition (4) or properly remove catabolites (41, 43). Consequently, amyloid peptide fragments are retained in ISF and likely wreak havoc with cognitive neuronal networks and the stem cell environment. A worthy goal is to identify agents that stabilize the BCSFB and allow CP to maintain CSF formation in senescence. This would maintain CSF sink action (44) and the clearance of harmful toxins (3, 41, 43). Otherwise, stagnated CSF dynamics in advanced aging predisposes to the dementia of chronic hydrocephalus (41). PET scans and refined MRI analysis (45) of CP-CSF status in the elderly will identify vital links among distressed CSF circulation, compromised cognitive abilities, and impaired conversion of stem cells to neurons.

Several salient questions await answers for the field of CSF dynamics. Can peptidergic agents (12, 46, 47) be used to therapeutic advantage in controlling CSF formation? To what extent does reduced CSF formation in aging (42) and neurodegeneration compromise ISF movement throughout brain and to drainage sites (48) and thus predispose to plaque formation (3, 41, 43)? In addition to bulk flow, do molecular transport and unconventional mechanisms facilitate CSF reabsorption by arachnoid (30, 49, 50)? Resolving these questions should enhance therapeutic regulation of the renal-like CP transporters (24) and arachnoid efflux systems, thereby sustaining CSF-brain throughout life.

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