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Review

Kinetics of Water-Soluble Contrast Media in the Central Nervous System

Michael R. Sage[1]

In neuroradiology, intraarterial, intravenous, and intrathecal injections of water-soluble contrast media are made. With the growing importance of water-soluble myelography, interventional angiography, and enhanced computed tomography (CT), it is essential to have a clear understanding of the response of the nervous system to such procedures. The blood, cerebrospinal fluid (CSF), and extracellular fluid of the parenchyma form the fluid compartments of the brain with three interfaces between, namely, the blood-brain interface, the CSF-brain interface, and the blood-CSF interface. One or more of these interfaces are exposed to water-soluble contrast media after intraarterial, intravenous, or intrathecal administration. The behavior of water-soluble contrast media at these interfaces is discussed on the basis of local experience and a review of the literature.

Water-Soluble Contrast Media

Grainger [1] recently reviewed the history of intravascular contrast media, tracing their development from Moniz in 1929 to the present day. In 1923, faint visualization of the urinary tract was noted after the therapeutic administration of intravenous sodium iodide [2], and, since then, iodine has remained the one element suitable for injection into the circulation as a radiographic contrast agent [1]. Sodium iodide, an inorganic iodine salt, was far too toxic, but the development of organic iodine compounds led to the clinical introduction of Uroselectan in 1929 [3]. This was soon superseded by two other improved pyridine products, diodrast (Diodene) and neo-iopax (iodoxyl, Uroselectan B) [1, 4].

It was not until the early 1950s that the suggestions and work of Swick [5], Wallingford [6], and Hoppe et al. [7, 8] led to the first tri-iodinated contrast media. Acetrizoic acid was developed, leading to great improvements in tolerability and opacification. Further derivatives of tri-iodobenzoic acid followed (fig. 1). These were made soluble by salification with sodium, meglumine, or both. Such ionic contrast media dissociate in solution to form an anion and a cation; only the anion carries iodine atoms and is radiopaque. The cation has no function except as a solubilizing agent. All conventional ionic contrast media are monomeric salts of tri-iodinated substituted benzoic acid (fig. 1).

In 1966, a dimer of iothalamic acid, iocarmate (Dimer X), was developed; it was less neurotoxic than available contrast media, being a methylglucamine salt of iocarmate acid (fig. 2) [9]. This, however, did not get widespread acceptance. The next major advance in water-soluble contrast media was the synthesis of metrizamide (Amipaque) by Nyegaard, Oslo, following a suggestion by Almén [10].

By transforming the ionizing carboxyl group of conventional ionic contrast medium salts into a nondissociating group, such as an amide ($CONH_2$) group, the solute concentration could be reduced without loss of iodine content (fig. 3) [1, 10] Such nonionic contrast media do not require a salifying agent and,

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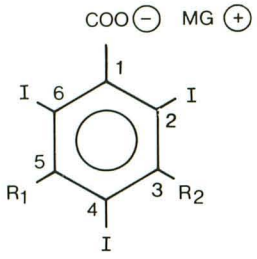
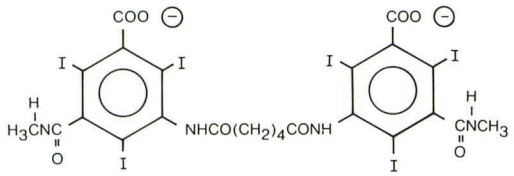


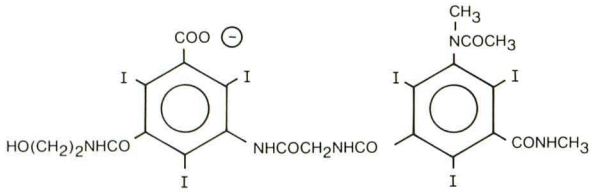
2,4,6 — triiodobenzoic acid

R_1	R_2	COMPOUND
H	$-NHCOCH_3$	Acetrizoate
$-NHCOCH_3$	$-NHCOCH_3$	Diatrizoate
$-CONHCH_3$	$-NHCOCH_3$	Iothalamate
$-NHCOCH_2CH_3$	$-NHCOCH_2CH_3$	Diprotrizoate
$-N(CH_3)COCH_3$	$-NHCOCH_3$	Metrizoate

Fig. 1.—Structure of conventional ionic contrast media, being monomeric salts of tri-iodinated substituted benzoic acid. Meglumine (MG) is preferred cation in neuroradiology.



IOCARMATE (Dimer X)



IOXAGLATE (Hexabrix)

Fig. 2.—Structure of ionic dimer contrast media, with six atoms of iodine/molecule.

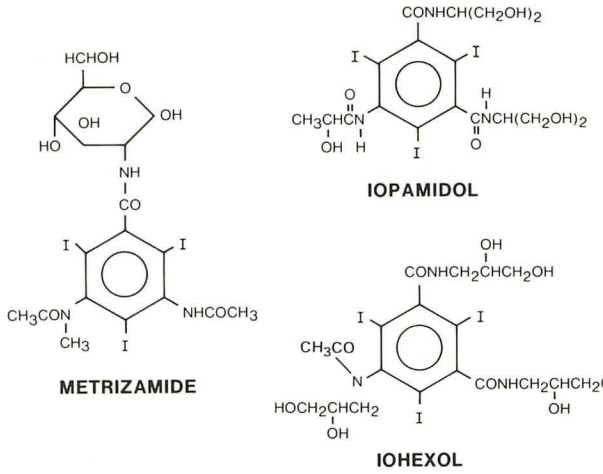


Fig. 3.—Modern nonionic contrast media. A salifying cation, such as meglumine, is not present, producing a lower osmolality than corresponding ionic contrast media without loss of iodine content.

TABLE 1: **Viscosity and Osmolality of Various Water-Soluble Contrast Media Used in Neuroradiology**

Contrast Medium	Concentration (mg I/ml)	Viscosity (37°C) (mPa.s)	Osmolality (mol/kg H_2O)
Ionic:			
Meglumine iothalamate	280	4.3	1.46
Iocarmate (Dimer X)	280	7.2	1.04
Ioxaglate (Hexabrix)	320	7.5	0.58
Nonionic:			
Metrizamide	280	5.0	0.43
Iopamidol	280	3.8	0.57
Iohexol	280	4.8	0.62

Note.—Measurements derived from [11, 12].

therefore, have greater tolerability and a lower osmolality than corresponding ionic contrast media (table 1). An ionic contrast medium with a low osmolality was developed by the synthesis of a monoionized dimer, Hexabrix or ioxaglate (fig. 2). This has six atoms of iodine per molecule, which dissociate into two ions, providing the same iodine:particle ratio of 3:1, as do the nonionic preparations. This dimer has an intermediate position between conventional ionic and more recent nonionic contrast media [1].

Unfortunately, metrizamide is unstable in solution, necessitating lyophilization and preparation of a fresh solution before use [11]. The major problem in preparation of a second generation of nonionic contrast media was the difficulty in achieving sufficient water-solubility [11], but further efforts have led to the introduction of iopamidol by Bracco, Milan, and iohexol by Nyegaard (fig. 3). The development of a third generation of low-osmolality contrast agents is already well advanced [1] with the synthesis of a dimer like Dimer X or Hexabrix, but in a completely nonionic form. Such nonionic dimers are iotasul [1] and DL-3-117 [13], which allow the maintenance of a high iodine concentration while retaining a very low osmolality.

When compared with equivalent iodine solutions of ionic contrast media, nonionic contrast media have the advantage of a lower osmolality and viscosity (table 1) and also do not require a potentially toxic cation to ensure water solubility (fig. 3). Therefore, they are particularly suitable for use in neuroradiology.

Intracarotid Injections of Water-Soluble Contrast Media

Blood-Brain Interface

The blood-brain interface constitutes the so called blood-brain barrier (BBB) [14] and this concept as it relates to neuroradiology was recently reviewed [15]. In nonneural tissues, the endothelium of the capillary wall allows free passage of ions and poorly fat-soluble nonelectrolytes up to

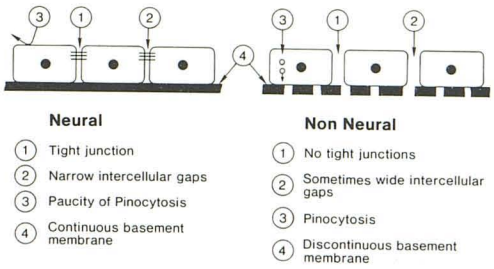


Fig. 4.—Comparison of characteristics of neural and nonneural capillary endothelium. (Reprinted from [15].)

the molecular size of albumin between the blood and interstitial fluid [16]. In contrast, the endothelium of the cerebral capillaries has a continuous basement membrane, with cells being connected by a continuous belt of tight junctions [14, 17], and vesicular transport (pinocytosis) is minimal (fig. 4) [18]. Because of these morphologic characteristics, the endothelium of the cerebral capillaries has the permeability properties of an expanded plasma membrane [17, 19, 20], controlling the free passage of many substances between blood and brain, hence maintaining the homeostasis of the neuronal environment.

Increased permeability of the BBB after carotid injection of various ionic contrast media has been well documented in both experimental animals [21–26] and in humans [27]. The neurotoxicity of such contrast media is probably related to this [27–30]. The increased permeability of the BBB also appears to depend on the hyperosmolality of the solution [23, 32]; osmolality is also a definite factor in neurotoxicity [28, 29, 32]. The mechanism of breakdown is uncertain, but it has been suggested that the hypertonic contrast media lead to shrinkage of the endothelial cells and subsequent separation of the tight junctions [33]. However, the action is probably multifactorial, as increased pinocytosis (vesicular transport) has been observed with Renografin-76 compared with Amipaque, Isopaque, and Reno-M-60 in experimental animals [34]. The disruption of the BBB by hypertonic contrast media and other solutions has been shown to be reversible [23, 25, 35].

Hypertonic solutions of glucose, sodium chloride [30], and mannitol [36–38] produce similar but less pronounced effects on the barrier than ionic contrast media with an equivalent osmolality. Accordingly, the effect on the BBB and the toxicity cannot be explained by osmotic action alone [24, 39, 40]; the contrast media have a chemotoxic action as well.

Recent experiments have indicated a close correlation between the qualitative assessment of BBB disruption as indicated by Evans blue staining and quantitative assessment using enhanced CT [36–38]. The use of selective disruption of the BBB by hypertonic solutions for chemotherapy of brain tumors has been suggested [36, 37], using CT to monitor the degree and distribution of such breakdown (fig. 5).

The actual molecular structure of various ionic contrast media is important, as sodium salts of particular contrast media have been shown to cause greater disruption of the

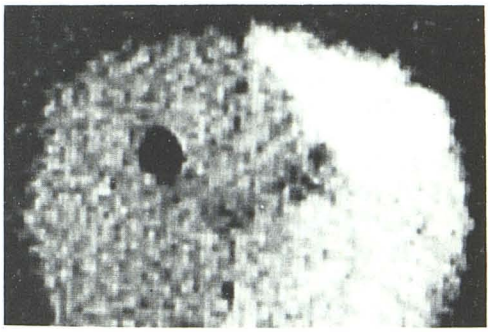


Fig. 5.—Coronal CT scan of canine brain removed 1 hr after unilateral intracarotid meglumine iothalamate and intravenous sodium iothalamate. Enhancement in distribution of middle cerebral artery on same side indicates disruption of BBB [38].

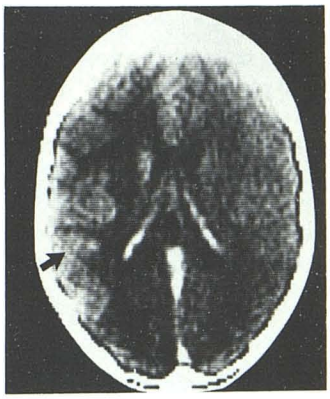


Fig. 6.—CT scan after accidental unilateral injection of Renografin-76. Cortical enhancement indicates disruption of BBB on side of injection (*arrow*). Unlike pure meglumine salts used in neuroangiography, Renografin is a mixed salt (meglumine 66%, sodium 10%) with a higher osmolality. (Reprinted from [27].)

BBB and greater neurotoxicity than equivalent methylglucamine salts [21, 24, 29–31]. If ionic contrast media are to be used for cerebral angiography, pure methylglucamine salts should be preferred, as even a mixed salt with a small amount of sodium has been shown to disrupt the BBB in humans (fig. 6) [27].

Nonionic contrast media have a lower osmolality than equivalent iodine concentrations of ionic contrast media (table 1) and should cause less disruption of the BBB by osmotic action. They also do not require a cation such as sodium or methylglucamine to increase their water solubility, and, therefore, the chemotoxic action of such cations is not present (fig. 3). It would, therefore, be expected that nonionic contrast media would lead to less disruption or breakdown of the BBB, and this has been confirmed experimentally [41–46]. In the future, nonionic contrast media will probably replace ionic contrast media for cerebral angiography.

Intravenous Injections of Water-Soluble Contrast Media

Because of routine and high-dose enhanced CT, dynamic CT, and digital angiography, it is mandatory for all neuroradiologists to have a thorough knowledge of the kinetics of water-soluble contrast media after intravenous administra-

tion. After an intravenous bolus injection, there is a rapid distribution of the contrast medium throughout the vascular and extracellular spaces of the nonneural tissue [47]. Peak blood levels are reached almost immediately after injection and there is a rapid fall during the next 2 min as the contrast media equilibrate between the plasma and the extracellular fluid [48]. After this, there is a more gradual fall in plasma level related to renal excretion. In normal nonneural tissues, practically no water-soluble contrast medium is bound to cell membranes or taken up by the cells, but instead it is rapidly and extensively distributed outside blood vessels into volumes approaching that of the extracellular fluid [49–52].

In contrast to the bolus injection, when the contrast medium is given as an infusion, no prompt peak blood levels are obtained; rather, there is a gradual rise in blood levels until the rate of renal excretion equals that of the rate of infusion [48]. The plasma level will only be maintained as long as the rate of infusion equilibrates with renal excretion. Once the infusion is stopped, the plasma level will drop in a similar fashion to a bolus injection, depending on the rate of renal clearance [48].

As peak blood levels are only maintained for a short time after a bolus injection, dynamic CT and digital angiography must be performed within seconds of the injection. On the other hand, for conventional enhanced serial CT scanning, there appears to be little advantage in giving the contrast medium as a bolus injection.

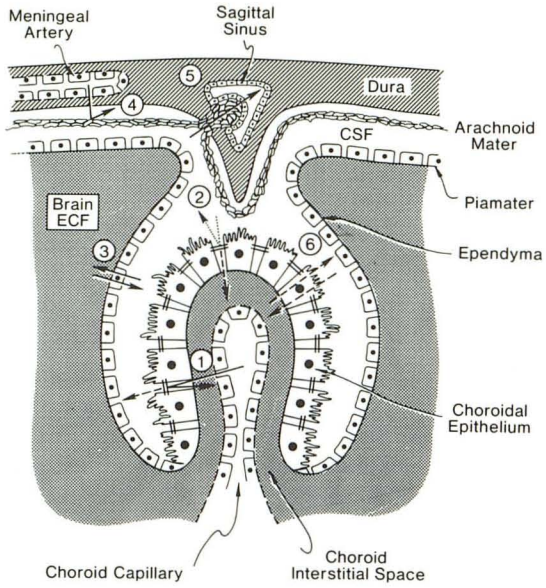


Fig. 7.—Contrast medium kinetics. Intravascular contrast medium passes freely through choroidal capillary endothelium but not tight junctions of overlying epithelium (1) (*deflected arrow*), which also prevent reabsorption of intrathecal contrast media by choroidal plexus (2) (*deflected arrow*). Intrathecal contrast medium passes freely through ependyma (3) (*straight arrows*) and pia mater by simple diffusion, but reabsorption depends on CSF absorption into arachnoid proliferations (5). Intravascular contrast medium passes freely through fenestrated endothelium of dural capillaries, but is prevented from entering CSF by arachnoid (4) (*deflected arrow*). CSF secretion and selective solute reabsorption across choroidal epithelium is an active process (6) (*straight arrows*).

Blood-Brain Interface

In contrast to nonneural tissue, the BBB prevents rapid distribution of water-soluble contrast media into the brain extracellular fluid after intravenous administration [15]. Unlike nonneural tissues, which show generalized marked enhancement, brain tissue only shows a minimum increase in density once the dynamic phase is finished [53]. Although contrast medium does not remain totally in the intravascular space [54], the slight increase in brain attenuation is due predominantly to contrast within the cerebral blood volume [15, 55].

After intravenous infusion, contrast material is delivered to the brain via the carotid arteries. As discussed before, direct injection of contrast material into the carotid arteries has been shown in certain circumstances to lead to breakdown or disruption of the BBB. The suggested use of high doses of intravenous contrast media for enhanced CT [56] will lead to an increase in the hyperosmolality of the cerebral circulation and, hence, potential BBB breakdown. Although alterations in the cerebral capillaries [34] and the permeability of the BBB [57] have been demonstrated in experimental animals after large doses of intravenous contrast media, Neuwelt et al. [58] produced no significant neurologic deficit in patients given large doses of intravenous contrast media after deliberate breakdown of the BBB with mannitol.

Normal brain tissue is, therefore, thought to be protected from intravenous contrast media by the BBB. However, abnormal enhanced CT depends on leakage of contrast media across a damaged BBB into pathologic tissue. The pathologic brain tissue and, perhaps more importantly, the adjacent normal tissue is no longer protected from the contrast media by an intact BBB. The presence of the water-soluble contrast media within the extracellular fluid of the brain may have in fact a direct toxic effect. A retrospective study recently suggested that the prognosis of cerebral infarction is worse in patients who have undergone enhanced CT [59, 60]. Although such a study is not statistically significant, this suggestion warrants further consideration.

CSF-Blood Interface

The interface between the blood and CSF occurs principally in the choroid plexuses (fig. 7) [14], which are richly vascularized epithelial tissues that project into each of the four major ventricles. The choroid plexuses are responsible for at least 85% of the CSF production and also the clearance of certain solutes, such as foreign anions, and weak organic acids, such as p-amino hippuric acid and prostaglandins, from CSF back into the blood [14, 61].

Unlike the cerebral capillaries, the capillaries of the choroid plexus are fenestrated and therefore allow ultrafiltration of plasma [62, 63] and the passage of other substances such as contrast media between the blood and the choroidal interstitium (fig. 7). Because of this, enhancement of the choroid plexuses occurs during CT [15, 53]. The interstitium on the other hand is enclosed by a specialized epithelium of

cuboidal cells resting on a thin basement membrane, and each cell is joined to its neighbor at the apical surface by a tight junction (fig. 7) [14, 61, 62]. The epithelium forms an imperfect barrier between the CSF and the choroidal interstitium, restricting the passage of solutes, including contrast media, in and out of the CSF.

CSF is secreted by an incompletely understood two step process [12, 64]. First, fluid is filtered through the highly permeable core capillary into the extracellular space; second, sodium is actively transported across the choroidal epithelium into CSF and water follows obligatorily along an osmotic gradient [12]. The primary process in CSF production is therefore an active process resulting in secretion of CSF composed of sodium (Na^+), chloride (Cl^-), bicarbonate (HCO_3^-), calcium (Ca^{++}), and water from blood to ventricle, while at the same time a variety of solutes are absorbed from the CSF back into the blood [14, 61]. The passage of substances from blood to CSF depends largely on their lipid solubility [65]. Water-soluble contrast media are highly lipid-insoluble and therefore their CSF:blood ratio after intravenous injection would be expected to be very low, as only small amounts would be transported into the CSF [65]. In fact, McClennan and Becker [66] demonstrated a CSF:blood ratio of 0.05 at 1 hr after intravenous ionic iothalamate in dogs, and we recently obtained similar results [67]. A ratio of 0.04 at 1 hr has been demonstrated after intravenous nonionic metrizamide injection in rabbits [68]. These studies indicate that the suggestion that intravenous CT myelography may be possible is incorrect [69].

Another potential site of exchange between the CSF and blood is the arachnoid membrane (fig. 7) [14, 61]. The capillaries of the dura are fenestrated and allow the free passage of contrast media to escape into the dural extracellular space, producing CT enhancement [15, 53]. However, the outermost layers of the arachnoid have capillaries with tight junctions that do not allow the free passage of solutes, including contrast media, and therefore present another blood-CSF barrier [70, 71]. A number of diverse solutes, amino acids, and weak bases are in fact cleared by the arachnoid membrane from the CSF back into blood [61]. A secondary site of possible exchange between blood and CSF is via the brain tissue capillaries (fig. 8) [72]. If materials actually escape across the BBB into the brain extracellular fluid, they may diffuse freely across the ependyma or pia mater into the CSF. In the absence of disruption of the BBB after intravenous contrast media, this is unlikely, but, as indicated before, such disruption may in fact occur to a variable degree depending on the osmotic load produced by such an injection [34, 57].

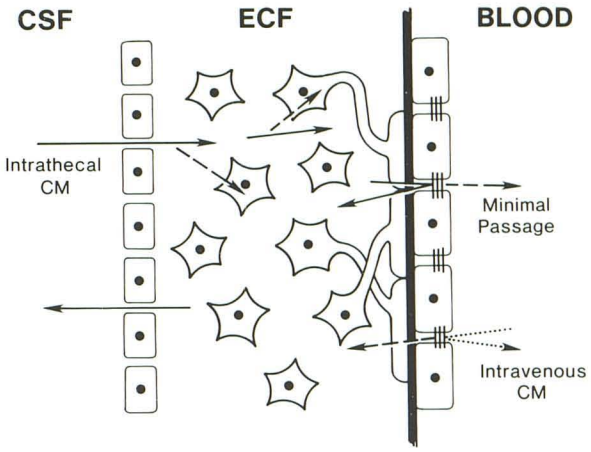


Fig. 8.—Relation of intrathecal and intravenous contrast media (CM) to CSF-brain and blood-brain interfaces. Contrast medium passes freely between CSF and extracellular fluid by simple diffusion across ependyma and pia mater (*straight arrows*), but tight junctions of capillary endothelium prevent free passage of contrast medium between extracellular fluid and cerebral capillaries (*deflected arrows*). Penetration of contrast medium into neurones appears to be minimal.

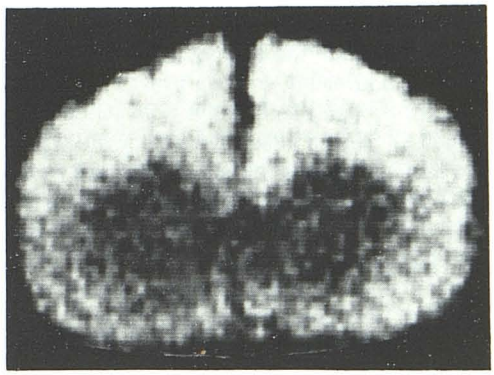


Fig. 9.—Coronal CT scan of canine brain removed 1 hr after intracranial intrathecal injection of 5 ml of nonionic contrast medium. Penetration of contrast medium into gray matter has been clearly demonstrated.

Intrathecal Contrast Media

CSF-Brain Interface

The interface between the CSF and the brain is at the pia mater overlying the brain surface and the ependyma lining the ventricular system (fig. 7). While a physiologic barrier between the blood and the brain parenchyma, the BBB, has been well documented, there is an apparent lack of a barrier between the CSF and the extracellular fluid of the brain [14, 73]. No obvious barrier seems to exist at the pia mater and the ependyma to the passage of small water-soluble molecules [14, 73–75], and it is suggested that they enter the brain parenchyma by simple diffusion into the extracellular space (fig. 8) [76]. Brain penetration by water-soluble contrast media after intrathecal injection has been well documented experimentally [77–81] and clinically [82]. The fate of intrathecally injected contrast media was reviewed recently [82]. Using a similar iodine concentration of contrast media (280 mg I/ml) we recently demonstrated that the depth of penetration was similar for both ionic methylglucamine iothalamate and nonionic metrizamide in dogs after 1 hr (fig. 9) [81]. The ionic state of the contrast medium does not appear to determine the freedom of penetration or the depth reached. Similarly, the iodine concentration in the

gray matter was similar for both contrast media. Therefore, the increased neurotoxicity of ionic contrast media after intrathecal injection is presumably related to their molecular structure rather than to an actual increase in the degree of brain penetration [81].

Intrathecal nonionic contrast media have been shown to cause electroencephalographic (EEG) changes, presumably due to brain penetration. The frequency of EEG changes appears to depend on the amount administered [77, 82]. EEG changes have been recorded with both iopamidol and metrizamide [82]. EEG changes are rarely seen after 2 hr, but are frequently demonstrated after 5 hr and disappear after 24 hr [82]. It has been suggested that there is a strong correlation between the depth and density of brain penetration and the maximum EEG changes [77], but this has not been confirmed by others [82]. The EEG changes appear to be due to the chemotoxic rather than osmotic action of the contrast media [83].

It has been suggested but not yet confirmed that the brain distribution of metrizamide after subarachnoid injection is primarily extracellular (fig. 8) [76, 78, 84]. Inulin, horseradish peroxidase, and other lipid-insoluble, metabolically inert molecules have been shown to be distributed to the extracellular fluid after subarachnoid administration and for practical purposes do not cross the BBB [14]. They have been shown to pass through the astrocytic end-feet surrounding the capillary endothelium, but are prevented from entering the lumen of the capillaries by the tight junctions between the cells (fig. 8). This is likely to hold for the water-soluble contrast media as long as the integrity of the BBB is maintained. Using Evans blue dye as a marker of BBB integrity, we were unable to demonstrate any staining of the brain in areas of maximum contrast concentration after intrathecal methylglucamine iothalamate or metrizamide in experimental animals [81]. This would suggest that the presence of a significant concentration of either ionic or nonionic contrast media within the extracellular fluid does not have a gross effect on the integrity of the BBB.

Certain metabolically active molecules such as cycloserine and 2-deoxyglucose are distributed intra- as well as extracellularly [72, 80] after subarachnoid injection. Although the brain distribution of subarachnoid metrizamide is predominantly extracellular [76, 78, 84], deoxyglucose is part of the metrizamide molecule (fig. 3) [80, 84]. Therefore, it has been suggested that metrizamide may compete with glucose for ultimate penetration into the intracellular space (fig. 8) [80]. After their extensive study, Fenstermacher et al. [84] concluded that nothing precise could be said about the intracellular penetration of metrizamide at this time. However, they did conclude that metrizamide passes through gray matter by simple diffusion, being largely distributed in the extracellular fluid, and that back movement across the BBB is small (fig. 8). Metrizamide has also been shown to have anticholinesterase activity, and this may be a factor in the generation of metrizamide-induced nausea, vomiting, and seizures [85]. Further work on the action of water-soluble contrast media at the cellular level is obviously required.

CSF Circulation

In an adult man, the total volume of CSF is about 140 ml, with 25–35 ml in the ventricles and a similar amount in the lumbar sac [14, 86]. The production rate is 0.4%–0.6% of the total volume per minute [63] or about 0.35 ml/min [87]. About 500 ml is secreted over 24 hr in man, which is slower than in most other mammals [88]. Most CSF is secreted by the choroid plexuses [14, 62], but the ependyma may contribute a fraction of the total production [14, 89, 90]. The movement of CSF is secondary to small hydrostatic pressure changes [14], with the net formation of CSF by the choroid plexuses plus the bulk absorption into the venous sinuses resulting in a net movement or circulation of CSF [12, 91]. Pulsation of arteries in the skull, changes in venous pressure due to respiration and other factors [92], and cilia on the ependyma presumably help with mixing, but probably only contribute a small amount to actual circulation. There is no evidence to indicate any consistent flow or circulation of CSF within the spinal subarachnoid space [14]. Although there is experimental evidence to suggest a spinal circulation in cats [93], this does not appear to be the case in man [14, 91]. Radionuclides introduced into the subarachnoid space in animals kept immobile in a horizontal position spread evenly cranially and caudally [92]. Differences in the venous pressure in the skull and the vertebral column are obviously transmitted to the CSF and therefore changes in posture, coughing, and hyperventilation will contribute to the mixing of the CSF [92].

The physiology of CSF reabsorption was recently reviewed [12, 62]. Most CSF absorption is by the cranial arachnoid villi and granulations, and only a relatively small fraction (15%) occurs through the arachnoid villi and granulations in the spine [62, 94]. CSF appears to pass from the subarachnoid space into the venous system via the arachnoid villi and granulations through pathways that act as open passages large enough to transmit large protein molecules without significant resistance (fig. 7) [81, 95]. A pressure difference of about 6.5 cm of water normally exists between the subarachnoid space and the adjacent venous sinuses [96], giving a "driving pressure," which is the major factor in the rate of CSF absorption. The rate of CSF absorption has been shown to increase linearly with CSF pressure once a critical opening pressure of about 70 mm of water has been exceeded [12]. The arachnoid villi and granulations appear to function as values, permitting relatively free flow of CSF toward the veins, but not in a reverse direction even if venous pressure is increased [12, 62]. However, the exact mechanism by which CSF and its constituents are absorbed by "bulk" flow through the arachnoid proliferations remains unknown [12]. Human arachnoid granulations are large and are commonly situated lateral to the superior sagittal sinus in the lacunae laterales [62]. Granulations and villi do occur in the spine in various animals including man [94, 97], being related to spinal nerve roots where they are surrounded by the small extensions of the subarachnoid space. The relation between the venous system and the granulations in the spine is similar to that in the

cranium [51]. In man, spinal arachnoid proliferations occur relative to most spinal nerves at all levels throughout the spinal column [62, 94].

The intracranial "driving pressure" between the subarachnoid space and the venous system appears to remain constant in dogs no matter what position [96], and it is probable that the pressure difference in the spine is also constant in all positions [62].

Clearance of Intrathecal Contrast Media

The clearance of intrathecal contrast media depends on the mixing within the CSF and the rate of CSF absorption. Unlike blood to CSF transfer, the transfer of substances from CSF to blood is not related to lipid solubility [65] but more to simple "bulk flow" reabsorption of CSF, particularly above a certain molecular size [98].

As discussed, there appears to be an absence of active circulation of CSF within the spinal subarachnoid space, mixing depending more on variations of the venous pressure and diffusion. In monkeys, water-soluble contrast media injected into the lumbar region are eliminated predominantly directly by the vascular circulation, presumably through spinal arachnoid villi into the epidural veins [99].

Reabsorption of water-soluble contrast media in humans has been shown to commence almost immediately after the lumbar injection [100], and therefore some contrast material is reabsorbed by the spinal villi and granulations [62, 100]. The transfer is delayed slightly if the patient is maintained in an erect position, but is increased significantly if the patient is maintained in a supine position immediately after the examination [100]. The slight delay in the erect position is presumably due to the poor mixing of the water-soluble contrast within the CSF, allowing it to stay in the lumbar region only, and therefore only those arachnoid granulations or villi related to the contrast media would take part in the reabsorption. In the horizontal position, however, mixing brings water-soluble contrast media in contact with the granulations throughout the spinal canal and hence helps with rapid clearance.

Therefore, absorption of contrast media from CSF to blood is not only dependent on the rate of CSF production and reabsorption but also on the location and volume injected. Absorption appears to take place through arachnoid granulations nearest the site of injection [65]. When mixing is more complete, as occurs during total myelography, the passage of contrast material into the cranial cisterns is more rapid [62].

The effects of leakage at the lumbar puncture site after myelography with water-soluble contrast media probably depends on the concentration of contrast medium in the fluid leaking from the subarachnoid space [62]. In view of the role of the spinal arachnoid granulations in the clearance of water-soluble contrast media from the CSF, the presence of arachnoiditis would be expected to decrease the rate of excretion. In 1980, Eldevik et al. [99] showed that after repeat water-soluble myelography, the transfer from CSF to blood was slowed in monkeys, presumably due to arachnoiditis affecting elimination. In the same animals, this led to an increase in the intracranial contrast medium concentrations and a prolongation of the exposure of the lumbar arachnoid to the contrast media. Meglumine iocarmate was shown to have a more significant effect than metrizamide. In monkeys, dehydration also appears to slow the elimination of contrast media in the lumbar subarachnoid space [101], and dehydration has been shown to be a factor in human toxicity.

The rate of CSF formation is reduced with hypothermia, alkalosis, and drugs including acetazolamide, frusemide, ouabain, spiralactone, amphotericin, and vasopressin [88, 103]. A drop in CSF pressure of only 4 cm of H_2O in monkeys has been shown to cause cessation of CSF absorption [62, 104], and it is therefore possible in man also that a small reduction in CSF pressure would reduce the rate of absorption to zero and hence cause stagnation of fluid in the subarachnoid space. Therefore, in myelography, if a large amount of CSF is removed, greater than the amount of water-soluble contrast material introduced, a drop in pressure and therefore a drop in the rate of reabsorption could result [62].

As already mentioned, transfer of water-soluble contrast media from CSF to blood starts almost immediately after intrathecal injection in humans [100], being slightly delayed in the erect versus supine positions. However, subsequent transport is similar, with a maximum blood concentration being reached at 1–3 hr with a half-life of 3.9 ± 2.4 hr. There is therefore considerable individual variation in the rate of reabsorption. Two half-lives have been demonstrated because of renal excretion from blood. The velocity of actual transport does not appear to be influenced by the position [100], apart from the initial delay in the erect position. With a mean half-life of 4 hr, the greater part of the contrast medium has been transferred to blood by 12 hr after administration, and less than 5% of the contrast medium remains after 24 hr [100]. In experimental rabbits, rats, and cats, 97%–98% of contrast material is cleared in the urine and feces within 48 hr after injection into the cisterna magna [105]. In humans, most is excreted in the urine within 2–3 days [106], and less than 5% enters the feces. A very small amount appears to remain in the body, being excreted slowly over 7 days [106].

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