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Review

Blood-Brain Barrier: Phenomenon of Increasing Importance to the Imaging Clinician

Michael R. Sage[1]

Research during the past decade has greatly extended our appreciation of the blood-brain barrier (BBB) and its functional importance [1–3]. Although disturbance of the barrier has been recognized for many years as the basis for radionuclide imaging of cerebral abnormalities [4], enhanced computed tomographic (CT) images also reflect changes in the BBB produced by various disease processes. For optimum application of imaging methods of the brain, clinicians should have a knowledge of the normal BBB and the pathologic conditions that may alter it. Our current understanding of the barrier, its structure and properties, and the mechanisms of alterations by major disease is reviewed.

Concept of the Blood-Brain Barrier

In most nonneural tissues, the endothelium of the capillary wall is permeable and allows free passage of ions and nonelectrolytes up to the molecular size of albumin between blood and interstitial fluid [3]. In the nervous system, the situation is very different. The endothelial cells of the cerebral capillaries restrict the movement of many molecules from the blood to brain, and, in many substances, fail to equilibrate with the brain tissue water even under steady state conditions [1]. This has given rise to the concept of the blood-brain barrier, which is now known to be a complex physiologic phenomenon [1–3].

Historically, the concept of the BBB developed from observations that intravenous injections of certain dyes resulted in staining of various organs while the brain, except for the choroid plexus, remained unstained [5–7]. In 1898, Biedl and Krauss [8] noted that the brain was not stained with bilirubin in jaundice, while many other tissues were saturated with the bile pigment. In contrast, Goldmann [9] noted that trypan blue introduced directly into the cerebrospinal fluid (CSF) did produce staining of the nervous system tissues. There appeared to be a barrier preventing the escape of dye from cerebral blood vessels into the brain but this barrier could be circumvented by direct injection into the CSF.

The concept was expanded in 1921 by Stern and Gautier [10], and they introduced the term *blood-brain barrier*. Further studies with dyes [11–13], bacterial toxins [12], ions [14], metabolites [15], and drugs [16] added further support to the fact that the permeability of the cerebral capillaries was different from those of other tissues.

Morphologic Aspects of the Blood-Brain Barrier

Many authors have reviewed various theories to explain the phenomenon of the BBB [1–3, 12, 17–22]. These generally relate to differences in capillaries throughout the body [22–25]. In most nonneural tissues, there appear to be large water-filled channels crossing capillary walls, formed both between adjacent endothelial cells and by transient fusion of vesicles across their cytoplasm (fig.

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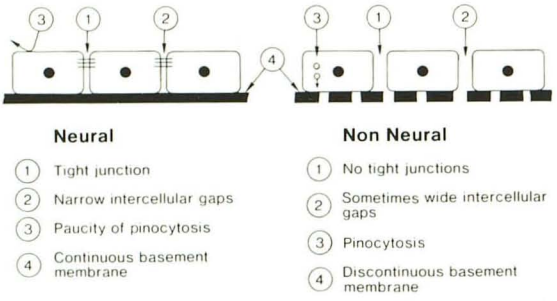

Fig. 1.—Comparison of neural and nonneural capillary endothelium characteristics.

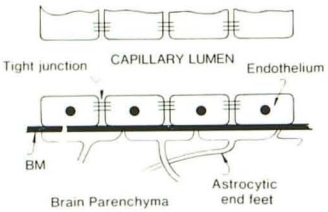

Fig. 2.—Neural capillary. Closely investing glial sheath of astrocytic "end feet." BM = basement membrane.

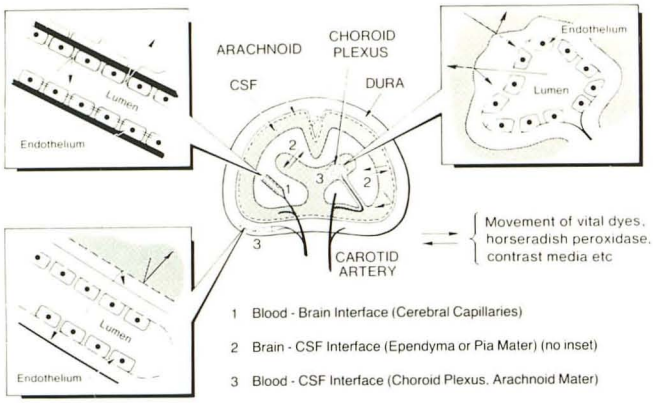

Fig. 3.—Major compartments of CNS and interfaces between blood, CSF, and brain tissue. Relatively free passage (*straight arrows*) of vital dyes, horseradish peroxidase, and contrast media occurs between CSF and brain tissue and between vessels and tissue of choroid plexus. However, such substances are prevented (*deflected arrows*) from passing freely between cerebral blood vessels and tissues by tight junctions: between dural vessels and CSF by arachnoid mater and between tissues of choroid plexus and CSF by ependyma.

1) [3]. The latter phenomenon permits transfer by vesicular transport or pinocytosis. Capillaries in nonneural tissues often have a discontinuous or fenestrated basement membrane and also often have wide intercellular gaps (fig. 1). In contrast, the endothelia of cerebral capillaries, endoneurium, retina, and inner ear have a continuous basement membrane, with cells being connected by a continuous belt of tight junctions [26]. Vesicular transport (pinocytosis) is rare (figs. 1 and 2) [23–25]. Because of these morphologic characteristics, the endothelium of cerebral capillaries has the permeability properties of an extended plasma membrane [25–27]. The continuous tight junctions prevent the passage of protein molecules from the capillary lumen through the endothelium into the extravascular space [26]. Both horseradish peroxidase (molecular weight, 43,000) and a microperoxidase (molecular weight, less than 2,000), when injected into the blood stream, remain within the cerebral capillary lumen [26, 28, 29]. On the other hand, when peroxidase is injected into the CSF, the molecule not only penetrates the ependyma and brain parenchyma, but permeates the capillary basement membrane and the clefts between adjacent endothelial cells up to the tight junctions (fig. 3).

Unlike nonneural capillaries, cerebral capillaries have a closely investing glial sheath, composed of the "end-feet" of astrocytes (fig. 2). Although the astrocytic end-feet are joined by discontinuous gaps and allow the passage of peroxidase [30], the close association between the astrocytes and the blood vessels suggests a functional relationship [31]. Davson and Oldendorf [32] speculated that the physiologic tightness of the barrier, namely tight junctions and a lack of pinocytosis, may be due to an inductive influence from such astrocytic end-feet [31]. This hypothesis has never been proven but has much substantial evidence to support it [31].

In nonneural tissues, pinocytic vesicles are important sites for transferring macromolecules out of peripheral vessels [24, 25, 31, 33]. A characteristic feature of the endothelium of cerebral vessels is the paucity of such vesicles, and it has been suggested that this represents another manifestation of the BBB [1–3, 26, 34, 35].

The BBB is notable for its resistance to a number of physical and chemical insults, but its permeability may be increased in certain specific and fairly extreme circumstances [31]. Despite extensive research, there remains great division in the literature on the ultrastructural basis of barrier breakdown [31]. Initially, it was usually attributed to opening of the tight junctions between the endothelial cells, but, more recently, increased vesicular transport activity has been suggested. Perhaps different ultrastructural changes occur in response to different insults [31].

Properties and Purpose of the Blood-Brain Barrier

The function of the BBB is to maintain the homeostasis of the neuronal environment [31]. The continuity produced by the tight junctions between individual cells allows the endothelium of cerebral capillaries to behave like a plasma membrane [2, 3, 36, 37]. Substances with a high degree of lipid solubility [1], a low degree of ionization at physiologic pH, and a lack of plasma protein binding are permitted free entry and rapid equilibration [38, 39]. On the other hand, slow entry and lack of equilibration occur with substances poorly soluble in lipids [15, 40], ions and substances mostly dissociated at physiologic pH [18, 41], and substances bound to plasma proteins [42, 43]. Being a near perfect semipermeable membrane, the barrier allows water to move in either direction to maintain equal osmotic concentrations of solutes in cerebral extracellular fluid and blood [3]. However, the changes in volume of the brain are resisted despite prolonged osmotic disturbances, and solutes such as potassium, calcium, and magnesium are maintained in very

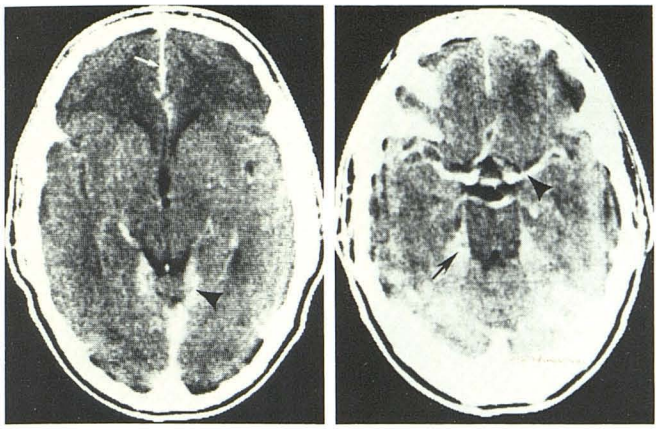

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Fig. 4.—Normal enhanced CT scan. Enhancement of tentorial incisura (*arrowhead*) and falx (*arrow*).

Fig. 5.—Normal enhanced CT scan. Vessels of circle of Willis (*arrowhead*) due to iodinated contrast media in blood pool. Normal enhancement of tentorium (*arrow*).

constant CSF concentrations despite severe and prolonged disturbances in blood plasma concentrations [1–3].

Cerebral capillaries are unique in comparison with other capillaries in the distribution of a variety of enzymes [1, 3]. A lack of nucleoside phosphatase activity may represent one aspect of the BBB. The entry of glucose into the brain appears to be an enzyme-mediated process [15, 44] and several carrier systems for the uptake of amino acids have been described [45].

Sites of the Blood-Brain Barrier

The BBB separates the major compartments of the central nervous system (CNS), the brain and the CSF, from the third compartment, the blood [1–3]. Interfaces between the blood and these two compartments are found in the blood vessels of the brain and the subarachnoid space, the choroid plexus, and the arachnoid membrane overlying the subarachnoid space (fig 3).

Unlike the brain parenchyma, the choroid plexus stains after intravenous vital dyes. It is also the site of active transfer of some substances from the blood to CSF [1] and acts as an effective barrier to the diffusion of some lipid-insoluble substances. A blood-CSF barrier is sometimes proposed to explain why intravascular substances enter the CSF and brain at different rates [22], but this may simply reflect the gross anatomic relation between the three compartments [2].

The ependyma and the pia constitute the brain-CSF interface (fig 3). The ependyma allows rapid equilibration between the extracellular fluid of the cerebral tissues and the CSF [2, 3, 14, 46, 47]; the easy passage of horseradish peroxidase and other smaller molecules between the lining ependymal cells has been clearly demonstrated [2, 3, 30, 48].

Certain specialized areas of the brain appear devoid of the BBB. These include the choroid plexus [9], hypophysis [49], tuber cinereum [50], area prostrema [51], paraphysis [52], pineal gland [53], and the preoptic recess [54]. Unlike other cerebral capillaries, vessels in these areas appear to have fenestrations, greater pinocytotic activity, and differences in enzymes [35, 55–57]. The blood vessels of the dura also have a discontinuous endothelial cell layer and allow rapid diffusion of peroxidase and vital dyes into the tissue [2]. However, although the three layers of the meninges are all mesodermal in origin, the outermost layer of the arachnoid has capillaries with tight junctions, and peroxidase introduced into the CSF will not penetrate through this outer layer, which, therefore, represents the barrier between the CSF and the mesoderm [58–60]. Similarly, vital dyes injected intravenously stain the dura that covers the arachnoid membrane but do not penetrate into the CSF [11].

Blood-Brain Barrier and Contrast Enhancement in CT

The BBB renders cerebral capillaries impermeable to iodine contrast agents [61], and, normally, intravenous injection of contrast media demonstrates only vascular structures. The cerebral parenchyma shows a slight increase in density since the cerebral blood volume represents 4%–5% of total brain volume [61, 62]. Normal white and gray matter show a very slight increase in attenuation in contrast-enhanced CT (average enhancement, 1.9 Hounsfield units [H] for gray matter and 1.4 H for white matter [63]).

The dural vessels are fenestrated and allow passive diffusion of contrast agents into their extracellular space. Normally, intense enhancement of the dural folds of the falx and tentorium occurs (fig. 4) [64]. The choroid plexus vessels also lack an impervious barrier between capillaries and the extracellular space and show marked enhancement [64]. Naidich et al. [64] also report that at times there is a distinct blush of the lateral walls of the lateral ventricles after contrast enhancement. The explanation for this is unknown but it may be due to the caudate nucleus and the subependymal veins.

It has been shown that an iodine concentration of 1 mg/ml raises the average attenuation of a solution by 24–30 H [65–67]. The high values of the tissue-blood ratio of enhancement in pathologic conditions in CT cannot be explained by the iodinated blood volume per unit volume of tissue alone [65]. From recent studies [68, 69], it must be concluded that cerebral contrast enhancement by iodinated material in CT is to a great extent a reflection of a loss of the integrity of the blood-brain barrier, except where large vascular channels contain a sufficiently large pool of iodinated materials to be visualized directly (fig. 5) [67].

Unlike contrast media, xenon is fat-soluble and passes freely across the normal blood-brain barrier. Therefore, specific damage to the BBB cannot be detected by xenon enhancement [70]. However, having a high atomic number (54), xenon results in enhancement in the extravascular tissue, and experimental studies suggest that such enhancement may have a place in blood flow studies [71, 72]. Recently, xenon, as inhaled gas, was used for contrast enhancement in CT of the brain, spinal cord, and other tissues [72–75]. Theoretical considerations and possible

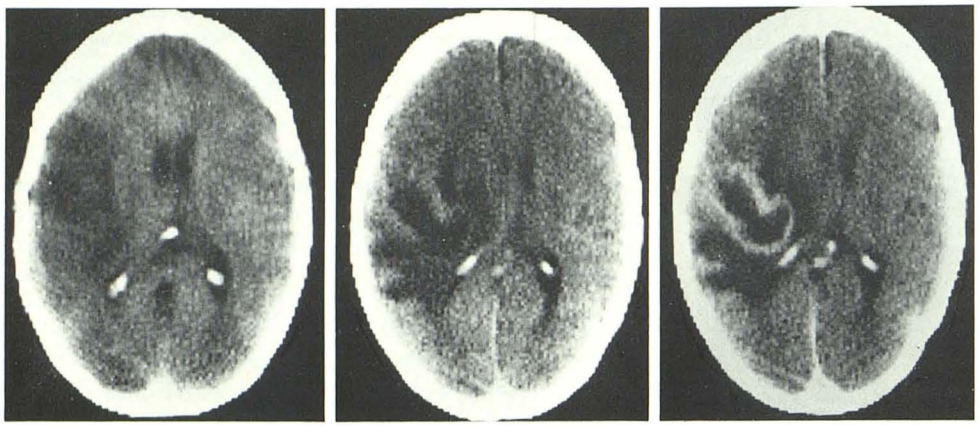

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Fig. 6.—Enhanced CT scan of patient with large low grade astrocytoma of temporal lobe. Extensive area of hypodensity but no enhancement because new tumor capillaries resemble normal cerebral capillaries with maintenance of BBB.

Fig. 7.—Glioblastoma multiforme. **A**, Plain study. Extensive vasogenic edema. **B**, After contrast. Intense enhancement of tumor due to disturbance or even complete absence of BBB.

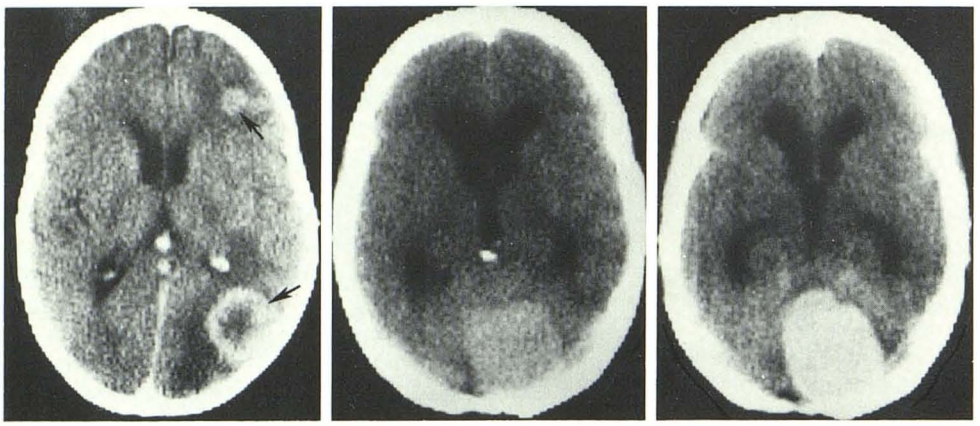

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Fig. 8.—Enhancement of two metastatic tumors surrounded by rim of edema. Proliferation of nonneural capillaries, similar to tissue of origin, allows passage of contrast from blood pool into tumor tissue.

Fig. 9.—Obstructive hydrocephalus due to meningioma in posterior fossa. Hyperdense lesion in plain study (**A**) shows intense enhancement after contrast (**B**), illustrating absence of BBB in these tumors.

use of contrast agents other than those incorporating iodine in CT have been discussed [75].

Pathologic Alterations in the BBB and Their Relevance to CT Enhancement

Intraaxial Tumors

Normally, the cerebral capillary endothelium has a close investment by a glial sheath, the "end feet" of astrocytes (fig. 2) [31], and the physiologic tightness of the BBB may be due to an inductive influence from these astrocytic end-feet [31, 32]. Disruption of this glial sheath by mitotic activity may make the capillaries more permeable [3].

Tumors stimulate the proliferation of abnormal capillaries by releasing specific angiogenic factors in the brain [76–78]. The nature of these capillaries in glial tumors is somewhat predictable [61]. In low-grade gliomas, such as grade 1 astrocytoma, new capillaries resemble normal cerebral capillaries with maintenance of the BBB, and, therefore, no CT enhancement is demonstrated (fig. 6) [61]. On the other hand, in more malignant tumors, the capillaries are fenestrated with vesicule formation (pinocytosis), have an incomplete BBB, and allow enhancement with contrast material (fig. 7) [61, 79]. In malignant tumors, Long [77] suggested that it was more correct to speak of a complete absence of the BBB rather than a breakdown by endothelial hyperplasia or extensive vesicle formation. The basement membrane of malignant tumor capillaries is often difficult to define and glial processes are often absent. Fenestrated capillaries have been demonstrated in experimental tumors [80], while rupture of the endothelial cells themselves has been postulated with tumor growth [81]. Barrier breakdown allows protein and other blood solutes to be taken up by the astrocytes, particularly in relation to the capillaries, and this has been reported in the case of tumors [80, 82]. This may also upset the postulated influence of the astrocytic end-feet on barrier integrity.

There is no relation between the angiographic architecture of a particular tumor on the one hand and enhancement at CT on the other [61, 65]. The major influence on enhancement of such lesions is a change or alteration in the BBB due to the factor above. Gado et al. [65] suggested that the vascular pool of angioblastic tumors represents at best only 20%–30% of enhancement.

Metastatic tumors in the brain induce proliferation of

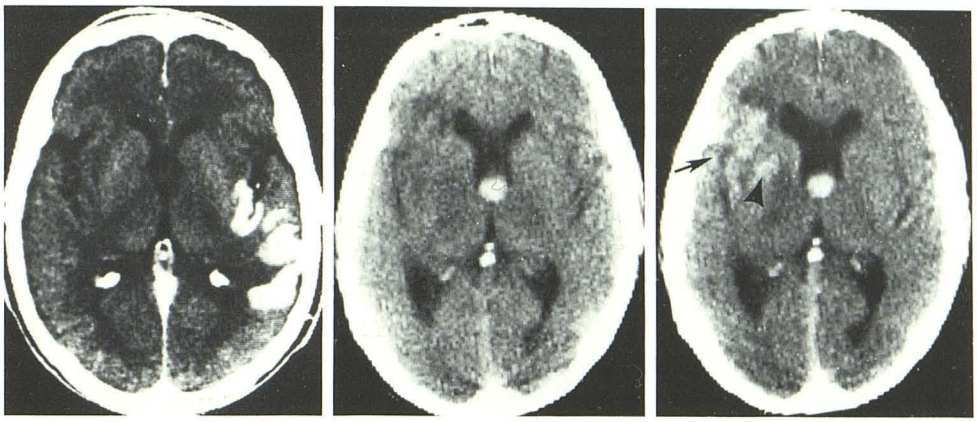

Fig. 10.—Enhanced scan 7 days after cerebrovascular accident. Intense cortical enhancement in area of recent infarction. Luxury perfusion and stasis may be factors in such enhancement transiently but increased permeability of BBB is dominant factor.

Fig. 11.—Patient with known colloid cyst who developed left hemiplegia 10 days before. **A**, Plain series. Vague areas of low density in anterior temporal region on right side. **B**, After contrast. Enhancement of both cortical mantle (*arrow*) and deep central gray matter of basal ganglia (*arrowhead*) indicates extensive area of infarction.

10 **11A** **11B**

nonneural capillaries, characteristic of the tissue of origin. For example, capillaries of cerebral metastatic lymphoma have regular endothelial cells with pinocytotic activity and fenestrations characteristic of a normal lymph gland rather than of cerebral capillaries [83]. Such capillaries have no BBB, and, therefore, show CT enhancement (fig. 8). Although the change in the BBB is the most important factor in enhancement, the volume of the extracellular space in both primary and secondary tumors is also important [65].

Extraaxial Tumors

Meningiomas arise from arachnoid rests in the dura. Because of the mesenchymal origin of such tumors, the capillaries are fenestrated and, therefore, have no significant BBB. This absence explains the intense enhancement seen, particularly with meningiomas (fig. 9). Similarly, the anterior lobe of the pituitary normally has no blood-brain barrier and the normal gland, therefore, enhances uniformly [84], being isodense with cerebral vessels. Therefore, typically, pituitary macroadenomas appear hyperdense compared with brain tissue after contrast enhancement [61]. On the other hand, the density and contrast enhancement in prolactin-secreting microadenomas is often less than that of the surrounding normal gland [84, 85].

Hypoxia, Ischemia, and Infarction

Maintenance of the integrity of the BBB in the face of hypoxia and ischemia has been confirmed by many authors [3, 86, 87]. This resistance is attributed to a differential sensitivity, of the endothelial cells on one hand and neurons and glial cells on the other, to lack of oxygen [2, 3, 88, 89]. However, extended periods of ischemia lead to focal necrosis and infarction [90, 91], and neurons, glia, and capillary endothelial fall out in sequence [2]. Edema develops at the periphery of the infarcted area, where increased BBB permeability is demonstrated, reaching a maximum at 4–5 days and remaining for 20 days or more [2]. Invading phagocytes eventually remove necrotic tissue, which is replaced by a fluid-filled cyst with normal blood vessels [91].

CT findings in the acute cerebral infarction have been well documented [92–95]. Usually, no enhancement is seen in the first few days [96] but 60%–93% of infarcts show enhancement at 7–30 days [92, 93, 96]. After 3–4 months, 50% show enhancement [95, 96] and it has been observed as late as 6 months [97, 98]. The pattern of enhancement is variable. It may be heterogenous with a fingerlike pattern, particularly in the cortical area (fig. 10), or homogenous over the entire low density area demonstrated in the precontrast series [99]. Sometimes, localized enhancement is noticed in an area apparently isodense on the precontrast scan [99].

Close inspection of a postcontrast scan obtained soon after injection shows enhancement corresponding to the irregular peripheral margin, and the normal dense bands inside the area of low density of the precontrast scan, corresponding exactly to the gray matter of the cortical mantle and basal ganglia (fig. 11) [70, 96]. On the other hand, delayed scans 3 hr after contrast administration show a diffuse spreading of contrast material in a pattern thought to indicate spread of the extravasated contrast media in the extracellular space [70, 95]. The pathophysiologic basis of enhancement in cerebral infarction still remains speculative, but destruction or increased permeability of the BBB [100, 101], luxury perfusion [102], and new capillary growth [96, 101] all play a part. Hayman et al. [70] recently investigated enhanced CT patterns after cerebral arterial embolization in baboons. No enhancement was demonstrated in the total absence of perfusion. Slow flow was associated with a transient focal cortical blush, and luxury perfusion at the margin of the infarct resulted in enhancement. However, disturbance of the BBB was thought to be the major factor. Usually, enhancement due to increased permeability of the BBB obscured enhancement due to luxury perfusion or slow flow. Therefore, delayed contrast scans are necessary to distinguish BBB damage, associated with progressively increasing enhancement, from flow abnormalities, characterized by transient enhancement.

Inflammatory Diseases

In pyogenic meningitis, bacteria multiply within the CSF or meninges. The blood vessels of the subarachnoid space

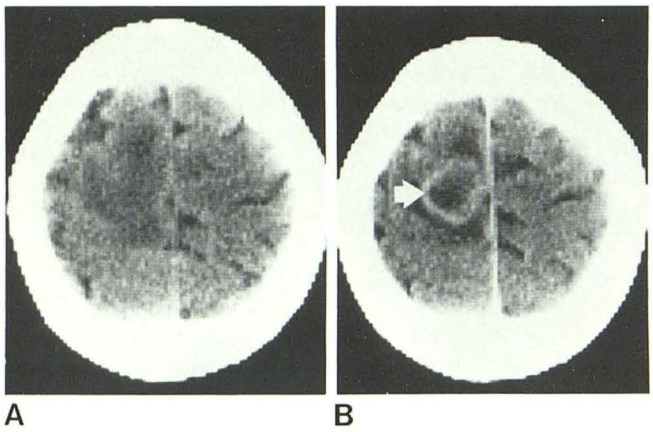

Fig. 12.—Cerebral abscess in parietal region. **A**, Plain study. **B**, After contrast. Typical rim enhancement (*arrow*) within area of edema in plain study due to inflammation and capsule neovascularity.

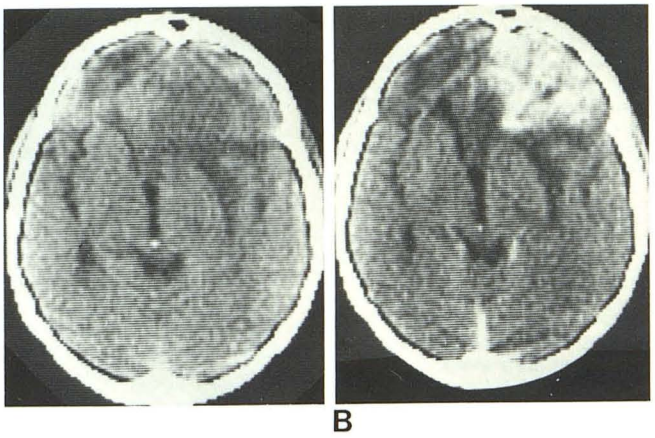

Fig. 13.—Follow-up study after radiotherapy for glioma of left frontal lobe. Plain (**A**) and enhanced (**B**) scans. Significant mass effect, edema, and intense enhancement of left frontal lobe. At craniotomy there was no obvious tumor recurrence but extensive radiation necrosis was found.

are involved in the inflammatory reaction, and migration of the leukocytes across cerebral vessels is accompanied by increased transport of substances like albumin, mannitol, and antibiotics [103, 104]. Protein in the CSF is elevated because of this barrier damage. The inflammatory process may spread into the brain parenchyma, but the increased barrier permeability appears to be limited to the blood-CSF barrier as it is usually not possible to demonstrate any brain enhancement on CT or radionuclide scans [105]. On the other hand, a heterogenous appearance with vaguely defined hyperdense areas after contrast administration has been described [106]. In tuberculous meningitis, the effect on the BBB is also poorly understood and various CT appearances have been described [105, 106].

The CT appearance of brain abscesses has been thoroughly investigated [105–110]. Enhancement is thought to be uncommon in the cerebritis stage prior to capsule formation [108, 109]. However, recently in experimental abscess evolution, ring enhancement was seen in the cerebritis stage prior to capsule formation [110]. In fact, maximum ring enhancement correlated best with the area of cerebritis, particularly with delayed scans; the diameter of the ring of enhancement decreased as cerebritis receded. Typical ring enhancement is seen is most cases, with some variation in configuration (fig. 12). In the acute phase, such enhancement is thought to represent inflammatory neovascularity, although, later, increased blood flow through the capsule may be a factor. With healing, brain abscesses show regression of the BBB disruption [108]. An increase in enhancement after withdrawal of steroids has been observed, perhaps illustrating the protective effect of the steroids on the BBB [108].

Much work has been done on the effect of viral encephalitis on the BBB [2]. Experimental encephalomyelitis has been shown to increase the BBB permeability to various markers, including vital dyes and horseradish peroxidase [111].

In uncomplicated cases of viral encephalitis, perivascular cuffs of lymphocytes surround the blood vessels but apparently do not damage the brain or interfere with function. However, in more fulminating infections, lymphocytes penetrate deeply into the brain parenchyma where they destroy myelin sheaths on direct contact and provoke an inflammatory reaction [112, 113]. BBB permeability increases either just before or at the same time as the lymphocyte migration across cerebral vessels [111].

Radiation

Various forms of ionizing radiation have been shown to increase the permeability of the BBB [3]. Large doses of photon and alpha particle irradiation will break down the barrier within 72 hr and produce a severe white matter edema [114]. The total x-ray dose needed to produce acute breakdown of the BBB is large, being about 10,000 rad (1,000 Gy) [115].

Lower experimental and clinical doses of radiation may not produce an acute effect on the BBB permeability [116]. However, they initiate changes that result in BBB breakdown 1 month to 5 years after exposure, and delayed necrosis of the brain after exposure to high doses of radiation is well recognized [117–121]. Brain edema may develop in conjunction with this increased permeability and lead to swelling of the involved tissues and, therefore, increased pressure [121, 122].

Recently, the CT appearance of such necrosis has been described [121, 122]. A low density mass is demonstrated that shows enhancement after contrast administration (fig. 13), even when the original tumor showed no contrast enhancement before radiation therapy. In the absence of tumor regrowth, radiation necrosis alone may result in significant mass effect (fig. 13) [121, 122]. Presumably, the CT appearance is explained by an increased permeability of capillaries leading to enhancement, while a mass effect results from edema due to this increased permeability. It was suggested recently that BBB function may be altered by cranial radiation to allow increased permeability to

chemotherapeutic agents such as methotrexate [123, 124].

Brain Trauma and Cerebral Edema

Cerebral edema may be intracellular, extracellular, or a combination of the two. Mechanisms of formation have been considered cytotoxic and vasogenic [125, 126]. Cytotoxic edema is conceived when the primary lesion and accumulation of fluids is in the parenchymatous cells, neurons, and glia, as in hypoxic and ischemic damage. Therefore, BBB breakdown is unusual and occurs late, if at all. Most other types of edema are vasogenic and are due to excessive exudation of fluid from the cerebral capillaries [13]. Most insults that rupture the barrier will cause cerebral edema if applied with sufficient intensity [22, 31]. Direct injury to the brain, such as a stab wound, results in local destruction of the brain cells and blood vessels [127]. The damaged endothelial cells separate from each other, rupturing tight junctions and leaving gaps in capillary linings, while pinocytosis increases in the remaining cells [2]. During this stage, therefore, some enhancement on CT would be expected. With healing, phagocytes remove destroyed tissue while proliferating astrocytes lead to the formation of a glial scar. After 1 month, the region is invaded by new normal capillaries with normal barrier properties [13, 128, 129]. Therefore, in the healed phase, such injuries would not show enhancement.

Miscellaneous Causes of Changes in the Permeability of the BBB

Multiple Sclerosis

Computed tomography has demonstrated a spectrum of abnormalities in patients with multiple sclerosis, including small focal areas of contrast enhancement [130–133]. The contrast-enhancing lesions, typically periventricular in distribution, are usually demonstrated in the presence of acute, active, or exacerbating disease [130, 131, 133] and represent areas of active demyelination. This association has been proven pathologically [133–135].

Such enhancement presumably results from changes in the integrity of the BBB produced by acute demyelination, which allows extravasation of contrast medium [136]. This is supported by the fact that such lesions are better visualized by the use of an expanded dose of contrast medium [136, 137] and also delayed contrast examinations [130, 136]. With clinical improvement, contrast-enhancing lesions become isodense [130, 131] while corticosteroids may also reduce enhancement [138], presumably by reestablishing the integrity of the BBB [130, 132, 138].

Epilepsy

Using vital dyes and radioactive tracers, increased permeability or breakdown of the BBB has been demonstrated after induced convulsions [3, 139, 140]. The increase in permeability correlates with the duration of seizure activity [3], while experimentally low blood pressure, pentobarbitone [141], and glucocorticoids [142] have a protective effect. The degree of neuronal activity [143] and vasodilation [3] may play a part in the extent of these temporary barrier alterations. All changes are reversible within 1 hr after cessation of the convulsions [3, 144]. Structural abnormalities have been identified on enhanced CT in one-half of epileptic foci identified by electroencephalography and clinical evaluation, while further lateralization is possible using the region of interest technique [145].

Seizures induced by intravenous contrast media for enhanced CT have been described [146], particularly in the presence of metastases. This may be due to the direct effect of the contrast media itself. The underlying lesion may alter the BBB and allow contrast media to leak into the brain parenchyma [147].

Disturbance of Normal Autoregulation

Experimentally induced severe hypertension leads to increased permeability of the BBB [148], susceptibility being increased by irradiation [149] and reduced by dexamethasone [150]. In hypertensive encephalopathy, characterized by an acute rise in blood pressure above 200 mm Hg, increased BBB permeability and clinical disorders of the nervous system have been described [2].

Other conditions including hypercapnia, profound metabolic and respiratory acidosis, cerebral concussion, and intracranial hypertension may also alter normal autoregulation [2]. Increased luminal pressure results in capillary dilatation and this may widen intercellular tight junctions leading to increased BBB permeability and brain edema. When autoregulation is restored, changes are reversible.

Similarly, certain other metabolic disturbances may alter the permeability of the BBB in experimental animals, including thiamine deficiency [151] and portocaval anastomosis [152], while clinically, heavy metal poisoning such as lead, may lead to an encephalopathy characterized by increased BBB permeability [3].

Hypertonic Solutions, Including Contrast Media

Various hypertonic solutions of electrolytes and nonelectrolytes have been shown to disrupt or increase the permeability of the BBB, often in a reversible fashion [153–159]. Recent studies of intravenous hypertonic mannitol suggest that reversible osmotic BBB disruption may increase markedly the delivery of chemotherapeutic agents to the cerebral parenchyma [155].

Increased permeability of the BBB after carotid injection of various contrast media has been well documented [160–165], and the neurotoxicity of such media is probably related to this. The osmolality of contrast media is a definite factor in neurotoxicity [166, 167]. However, hypertonic glucose and sodium chloride solutions produce similar but less pronounced effects [168] on the BBB so that toxicity cannot be explained by osmotic action alone. The actual molecular structure of various contrast media is important and, hence, sodium salts of a particular contrast medium cause a greater disruption of the BBB and greater neurotoxicity then equivalent solutions of methylglucamine salts [160, 163, 167–

169]. Recently developed nonionic contrast media, such as metrizamide, appear to have a less toxic effect on the BBB than equivalent ionic methylglucamine salts [170].

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