Osmotic Blood-Brain Barrier Modification: Clinical Documentation by Enhanced CT Scanning and/or Radionuclide Brain Scanning

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Osmotic Blood-Brain Barrier Modification: Clinical Documentation by Enhanced CT Scanning and/or Radionuclide Brain Scanning

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Results of initial clinical trials of brain tumor chemotherapy after osmotic blood-brain barrier disruption are promising. In general, the procedure is well tolerated. The major complication has been seizures. In this report, data are presented which indicate that the etiology of these seizures is related to the use of contrast agent (meglumine iothalamate) to monitor barrier modification. A series of 19 patients underwent a total of 85 barrier modification procedures. Documentation of barrier disruption was monitored by contrast-enhanced computed tomographic (CT) scanning, radionuclide brain scanning, or a combination of both techniques. In 56 procedures (19 patients) monitored by enhanced CT, seizures occurred a total of 10 times in eight patients. Twenty-three barrier modification procedures (in nine of these 19 patients) documented by nuclear brain scans alone, however, resulted in only one focal motor seizure in each of two patients. In eight of the 19 patients who had seizures after barrier disruption and enhanced CT scan, four subsequently had repeat procedures monitored by radionuclide scan alone. In only one of these patients was further seizure activity noted; a single focal motor seizure was observed. Clearly, the radionuclide brain scan does not have the sensitivity and spatial resolution of enhanced CT, but at present it appears safer to monitor barrier modification by this method and to follow tumor growth between barrier modifications by enhanced CT. Four illustrative cases showing methods, problems, and promising results are presented.

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Osmotic blood-brain barrier (BBB) opening is a technique to increase the delivery of a variety of drugs to the central nervous system (CNS). Delivery of chemotherapy to CNS malignancies and surrounding tumor-infiltrated brain is facilitated by opening of the tight junctions between capillary endothelial cells. This is accomplished by the infusion of hypertonic mannitol into the artery supplying the tumor-bearing part of the brain. The degree, extent, and time course of barrier modification can be monitored by contrast-enhanced computed tomography (CT) and/or radionuclide brain scanning.

With CT we have demonstrated that the degree, distribution, extent, and reversibility of osmotic barrier opening can be monitored [1–6]. In a canine model, the timing of administration of iodinated contrast agent was shown to be crucial in order to obtain optimum enhanced visualization of the brain in the area of the disrupted BBB [2]. Meglumine iothalamate given intravenously resulted in excellent enhancement on CT scan. When this contrast agent was given into the internal carotid artery, enhancement was seen, but the verification of BBB opening (i.e., comparison of enhancement in the contralateral hemisphere) was less satisfactory. Metrizamide, a much less neurotoxic agent, was also evaluated [2, 7]. Enhancement was less marked and much more transient with an equivalent iodine dose of this agent than that observed with meglumine iothalamate.

In the canine model, systemically administered methotrexate after osmotic BBB disruption resulted in increased brain methotrexate levels in areas that closely correlated with CT scan enhancement [1, 2, 4]. Radionuclide brain scanning was also examined in animal studies to evaluate its ability to document

BBB modification; these scans proved less satisfactory than CT scans because of the increased absorption of the radionuclide substance in the large muscle mass overlying the cranial vault in the canine.

After careful evaluation in various animal models, clinical evaluation of osmotic BBB disruption in terminal patients with malignant brain tumors was begun. Barrier modification was documented both by enhanced CT and by radionuclide scanning. In initial clinical reports, CT and radionuclide brain scanning have both been useful in monitoring osmotic BBB modification. The greater sensitivity of enhanced CT compared with the nuclear brain scanning resulted in the predominant use of enhanced CT [3, 5]. These studies permitted us to document that osmotic BBB modification resulted in increased enhancement in the tumor as well as in the surrounding brain. This effect is illustrated by one patient, in whom a tumor that was seen after barrier modification had not been visible on the routine enhanced CT scan [3]. Using region of interest analysis to determine changes in CT number, we have been able to document and to quantify the changes in enhancement in tumor and surrounding brain after barrier modification [5]. Drayer et al. [8] showed a linear relation between CT number and delivery of iodinated contrast.

With continued experience at opening the BBB with intracarotid mannitol, we have noted a concomitant increase in incidence of focal-motor and grand mal seizures. The purpose of the present report is to demonstrate that these seizures are a direct result of the use of meglumine iothalamate, a known epileptogenic agent. Since we have now documented tumor regression in patients with microglioma (primary CNS lymphoma), medulloblastoma, glioblastoma, and metastatic disease, the problem of seizures has taken on serious significance. Indeed, seizures are the primary complication of osmotic BBB modification followed by cytoreductive chemotherapy. As a result, we have extended our observations in the use of radionuclide scanning as an adequate and safe, albeit less sensitive, means to monitor barrier modification. By using this method, it appears we have markedly reduced the problem of seizures after osmotic BBB modification and chemotherapy administration.

Subjects and Methods

Informed consent was obtained from each patient in accordance with the regulations of the Human Research Committees of the Oregon Health Sciences University and the University of Texas Health Science Center at Dallas.

The patients underwent a thorough neurologic evaluation [5] and were maintained on therapeutic (serum) levels of phenytoin and phenobarbital. Except at the time of their initial barrier modification, most patients were off all steroids before each barrier opening. Serial pretreatment enhanced CT scans were obtained with a G.E. CT scanner (model 8800, Milwaukee), an Artronix (neuro-CAT) CT scanner (St. Louis), or an EMI Scanner (model 5005, Hayes, Middlesex, England). Contrast-enhanced control scans were obtained 30 min after the administration of 90 g of meglumine iothalamate (150 ml of Conray 60; Mallinckrodt, St. Louis) by intravenous infusion. Double-dose contrast CT scans were obtained after 300 ml of Conray 30 by intravenous drip after 150 ml of Conray 60 by intravenous bolus. Pretreatment radionuclide brain scans were obtained on a Picker 4/15 large-field-of-view 3/8 inch (0.97 cm) crystal gamma camera interfaced with a Medical Data Systems nuclear medicine computer (Ann Arbor, MI) at 1 hr after injection of ^{99m}Tc-DTPA (diethylenetriaminepenta-acetic acid), 15 mCi (555 MBq).

On the day of BBB opening, oral diazepam (10 mg) was used as premedication and oral antacids were given. Phenobarbital 1.0 mg/kg and diazepam 0.14 mg/kg were given intravenously on arrival in the angiography suite; standard monitoring was used (electrocardiograph, blood pressure cuff, and precordial stethoscope). The procedures were performed under general endotracheal anesthesia with thiopental, N_2O/O_2, and small amounts of halothane if required; ventilation was controlled to maintain a P_{CO_2} of about 30 mm Hg. Diuresis was established with intravenous mannitol (1.0 g/kg) and furosemide (0.5 mg/kg); and, immediately before barrier disruption, thiopental (1–4 mg/kg) was administered and the patients were hyperventilated with O_2 for 1 min. Atropine (0.4 mg) was given before intracarotid drug administration to block the effect of carotid sinus stimulation.

After anesthesia induction, a 6.5 French Headhunter catheter (Cook, Bloomington, IN) was inserted percutaneously into the femoral artery and then passed cephalad into the internal carotid or vertebral artery. The rate of mannitol infusion into the internal carotid artery was generally 9–10 ml/sec via a Medrad Mark IV arterial injector (Medrad, Pittsburgh) since this infusion rate was required to produce reflux from the internal into the external carotid artery. In vertebral artery injections, a rate of 6–8 ml/sec provided contrast reflux down the ipsilateral and the contralateral vertebral artery and was thereby used for BBB opening. Since the intravascular lumen must be filled with undiluted 25% mannitol for barrier opening, an infusion rate that results in these patterns of reflux is important.

The contrast agent (meglumine iothalamate) was administered at the same dosage as for the pretreatment control CT scan and was given intravenously 2 min after the intracarotid mannitol infusion. When a brain scan was to be used to document barrier modification, the radionuclide was given by intravenous bolus 2 min after mannitol. Five min after the mannitol infusion, methotrexate was administered into the internal carotid artery over 15 min using the Medrad Mark IV arterial injector. The exact chemotherapy regimen has been described elsewhere [9]. The extent and degree of the barrier opening was defined by a CT scan obtained 30 min after contrast agent infusion and/or by brain scan obtained 1 hr after radionuclide administration. The general anesthesia was terminated after the CT scan or brain scan.

The quality of BBB disruption on radionuclide scans was assessed by visually inspecting the rainbow color-coded output from an interfaced Medical Data Systems Nuclear Medicine Computer with 1981 A^2 revision B software (Ann Arbor, MI). The display unit used was a Conrac Model J-211RS19 video display monitor (Covina, CA). The rainbow translation table producing this response is based on a sliding scale response that assigns shades of color to 1 to 292 levels depending on the maximum counts in the "hottest" pixel. A sample of this response was calculated and is shown in table 1, and representative brain scans are illustrated in figures 1–4.

Results

Osmotic BBB modification has been performed in 19 patients with malignant brain tumors over the past 3 years. These 19 patients have undergone 85 barrier modifications which were documented by enhanced CT alone on 56

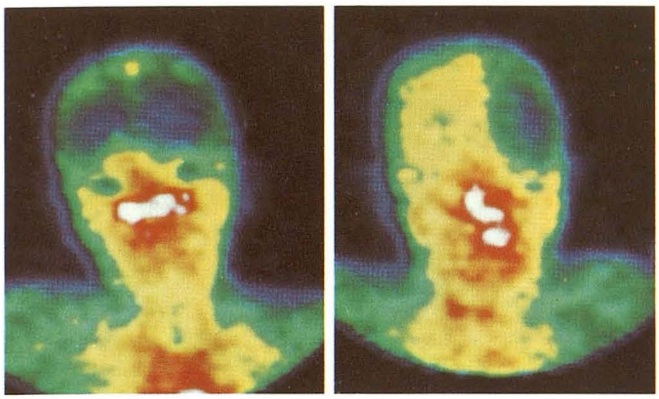


Fig. 1.—Case 12. Medulloblastoma. Radionuclide brain scans, anteroposterior views. **A,** Control scan. **B,** 7 days later. Markedly increased uptake of radionuclide in right cerebral hemisphere due to barrier opening. (The patient's right is on the reader's left).

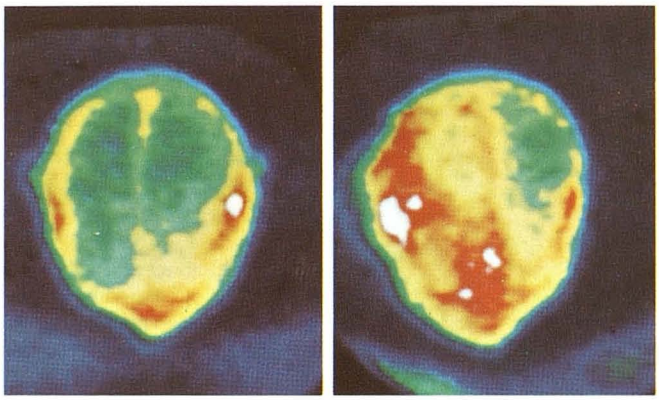


Fig. 2.—Case 16. CNS lymphoma. Radionuclide brain scans, vertex view. **A,** Control scan 5 months after initiation of protocol. **B,** 24 hr later, after BBB disruption via right internal carotid artery. (The patient's right is on the reader's left).

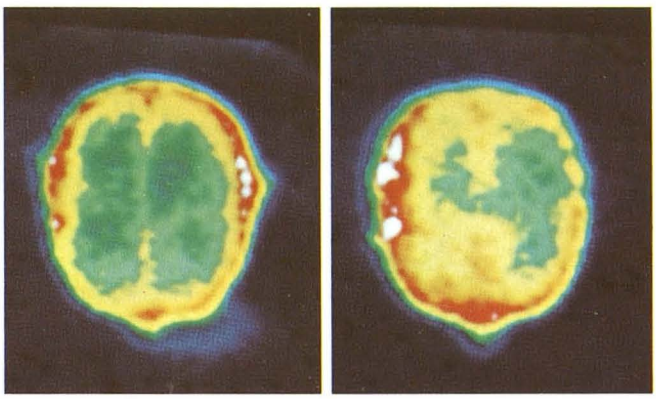


Fig. 3.—Case 17. Glioblastoma. Radionuclide brain scans, vertex view. **A,** Control scan. **B,** 24 hr later, after osmotic BBB modification via right internal carotid artery. (The patient's right is on the reader's left).

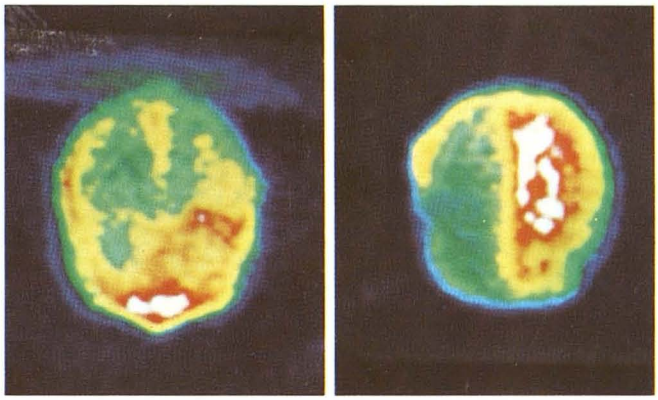


Fig. 4.—Case 19. Metastatic carcinoid tumors. Radionuclide brain scans, vertex view. **A,** Control scan. Increased uptake in left frontal and temporal areas due to two metastatic tumors in this region. **B,** Markedly increased uptake of radionuclide in anterior, middle, and posterior cerebral artery distributions after osmotic BBB disruption after osmotic BBB disruption. (The patient's right is on the reader's left).

TABLE 1: **Sample Approximation of Rainbow Translation Table Response**

Color Ranges	Counts/Pixel		
	Example 1	Example 2	Example 3
White	···	340–292	556–520
Red	125–85	282–214	460–356
Orange	···	246–222	404–368
Yellow	88–62	206–164	344–284
Green	62–45	150–110	264–228
Blue	27–2	52–2	152–64
Maximum counts	125	344	556
Levels assigned	125	172	139

Note.—Pixels having counts in the range of gaps and overlaps in color assignment result in an intermediate color in the image. For instance, in example 1 there is an overlap at 85–88 counts and a gap at 27–45 counts, both of which would result in a mixed color response in the image.

occasions and by radionuclide brain scanning alone on 23 occasions (table 2). The primary toxicity seen with barrier modification has been seizures. These occurred in eight of 19 patients with a total of 12 seizures occurring in the immediate post-barrier modification period in these patients. The use of various anticonvulsants (phenytoin, phenobarbital, Valium) has not been effective in preventing these seizures. With the exception of two focal motor seizures, seizures in every other case have occurred following the administration of iodinated contrast material after barrier modification. The seizures appear to be related to the administration of meglumine iothalamate after barrier modification. The seizures do not appear to be related to either the barrier modification or the subsequent administration of chemotherapy. The radionuclide brain scan was not as

sensitive as the CT scan in following the course of a brain tumor, but it was adequate to document barrier modification.

Representative Case Reports

Four patients with brain tumors illustrate some of the relevant issues in the use of radionuclide scanning and CT scanning following barrier disruption.

Case 12

A 12-year-old boy had an operative resection in 1978 for a medulloblastoma in the posterior fossa. This was followed by radiotherapy. He had an excellent response and was well until the spring of 1981 when he developed recurrent symptoms and had radiographic documentation of a massive frontal tumor. An extensive but subtotal resection was carried out; within 6 weeks of the operation, the tumor was as large as when he presented. He was treated with chemotherapy using methotrexate, cytoxan, and procarbazine in association with osmotic BBB disruption, as described elsewhere [9]. As illustrated in figure 5, enhanced CT was able to document not only tumor regression, but also the degree and extent of barrier modification. Similarly, both tumor regression and barrier modification were also documented by radionuclide brain scans (fig. 1), although the latter lacked the degree of spatial resolution possible with enhanced CT. Of particular note, this patient had a focal motor seizure after his *initial* osmotic BBB modification procedure, which had been documented by nuclear medicine scan. He did, however, tolerate 13 subsequent infusions (six with isotope alone, three with contrast material alone, and four with both agents) without seizure activity.

TABLE 2: **Blood-Brain Barrier Disruption: Documentation by Enhanced CT and/or Radionuclide Brain Scanning and Incidence of Seizures**

Diagnosis: Case No. (Age)	No. BBB Disruptions (No. Seizures after Administration of Contrast Agent or Radionuclide)		
	Totals	Documented by Enhanced CT	Documented by Radionuclide Scanning
Glioblastoma:			
1 (46)	2	1 (0)	0 (0)
3 (63)	8	4 (0)	4 (0)
5 (53)	6	3* (0)	3 (0)
6 (56)	8	8† (0)	0 (0)
13 (50)	1	1 (0)	0 (0)
14 (41)	5	5† (0)	0 (0)
17 (40)	4	2 (1)	2 (0)
18 (20)	1	1 (1)	0 (0)
Cranial metastases:			
2 (35)	3	2 (0)	1 (0)
7 (53)	5	5 (1)	0 (0)
8 (53)	2	2 (0)	0 (0)
10 (31)	2	2 (0)	0 (0)
19 (61)	1	1 (1)	0 (0)
Glioma:			
4 (36)	7	3* (2)	3 (0)
9 (21)	2	1 (1)	1 (1)
11 (35)	1	1 (1)	0 (0)
Medulloblastoma:			
12 (12)	14	3 (0)	7 (1)
CNS lymphoma:			
15 (62)	8	7 (0)	1 (0)
16 (37)	5	4 (2)	1 (0)

Note.—BBB = blood-brain barrier; CNS = central nervous system.
*All were double-dose contrast studies, as described in subjects and methods.
†Two were double-dose contrast studies, as described in subjects and methods.

Case 16

A 37-year-old man had multifocal mass lesions; at craniotomy these were shown to be primary CNS lymphomas. He was treated with the chemotherapeutic regimen described above after five osmotic BBB modification procedures. Remarkable tumor regression occurred. During his therapy, barrier opening was clearly and consistently documented with enhanced CT when using a GE 8800 CT scanner (figs. 6A–6C), but was more difficult to document using the same dose of contrast agent and an earlier-generation CT scanner (fig. 6D).

Iodinated contrast material was administered in conjunction with the first four disruptions, and he experienced a focal motor seizure after his third procedure and a grand mal seizure after his fourth BBB modification. The fifth barrier modification was documented by a radionuclide brain scan rather than contrast agent and CT scan, and no seizures occurred. This case illustrates our experience (see table 2) that the likelihood of seizures is reduced with postdisruption radionuclide scans rather than CT scans to monitor barrier opening. As seen in figure 2, the status of barrier modification can be clearly evaluated with a radionuclide brain scan. The drawback in changing our assessment method is a loss of sensitivity, which is documented by the following finding: after three courses of chemotherapy, this patient's residual right frontal tumor was clearly seen by enhanced CT scan but not by radionuclide scan. Currently, this patient is neurologically intact with no evidence of tumor on enhanced CT.

Case 17

A 40-year-old man with a glioblastoma had a resection followed by postoperative cranial irradiation. Six months after surgery he

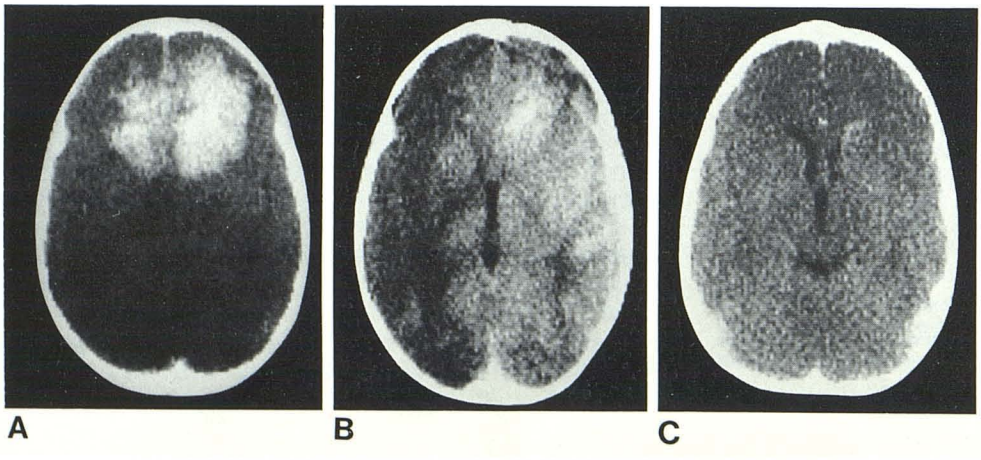


Fig. 5.—Case 12. Medulloblastoma. Enhanced CT scans. **A,** At initiation of combination chemotherapy in association with osmotic BBB disruption. **B,** 2 months later and 30 min after osmotic BBB disruption. Enhancement of entire ispilateral hemisphere and anterior cerebral circulation of contralateral hemisphere. **C,** Small residual tumor just lateral to right lateral ventricle. This scan, at nearly same level as **A,** demonstrates massive tumor shrinkage.

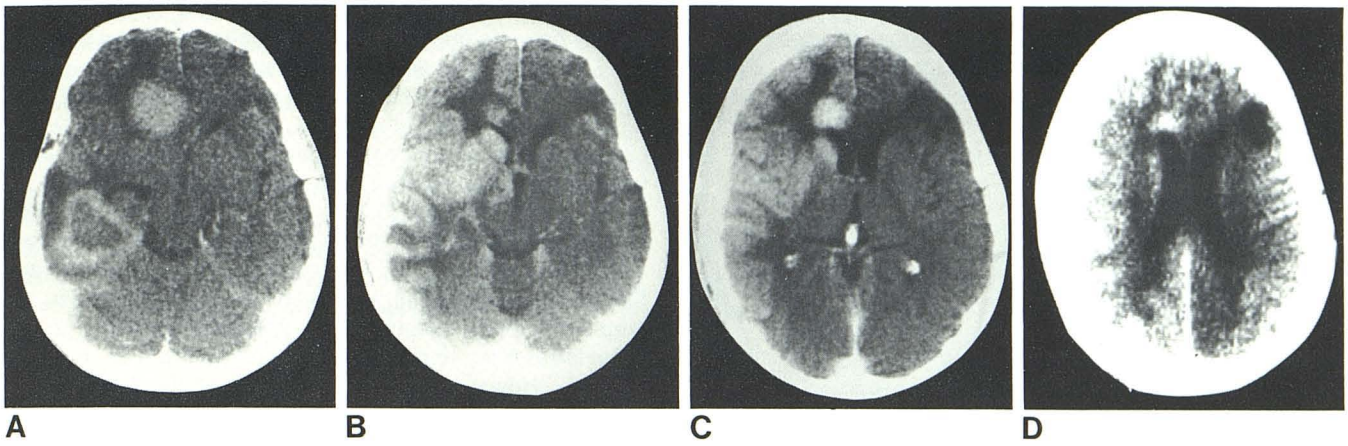
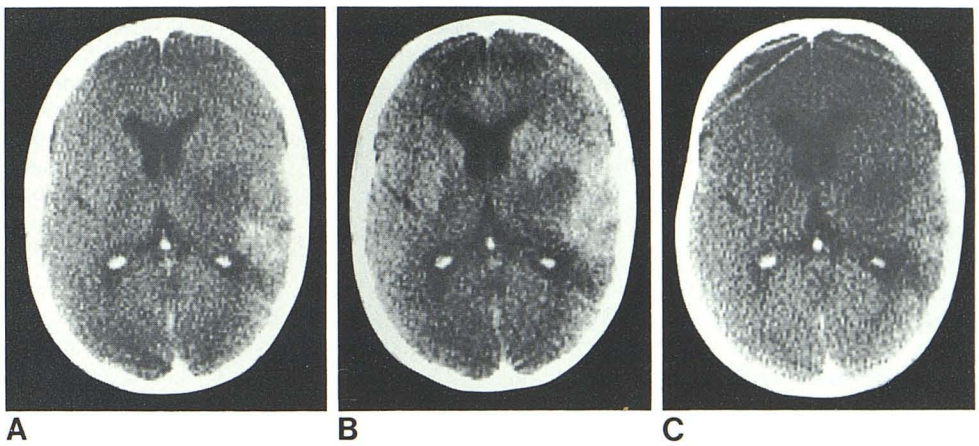


Fig. 6.—Case 16. CNS lymphoma. Enhanced CT scans. **A,** Before osmotic BBB disruption protocol. Two large tumors in right cerebral hemishere. **B,** At second osmotic BBB opening at level just below residual right frontal tumor. **C,** At time of second osmotic BBB disruption showing residual tumor. BBB disruption in anterior and middle cerebral artery distributions. **D,** 3 months after initiation of protocol with barrier modification documented on EMI rather than GE CT scanner. Markedly decreased resolution of barrier modification compared with **B** and **C**. Residual tumor in frontal region.

Fig. 7.—Case 17. Glioblastoma. Enhanced CT scans. **A,** Enhancing tumor in right posterior temporal parietal region. **B,** Transverse-cut scan after osmotic BBB disruption. Increased uptake of contrast agent, primarily in middle cerebral artery distribution. **C,** 3 months after initiation of osmotic BBB protocol. Marked reduction in amount of enhancement in tumor region. Evidence of decreased mass effect in some other sections.



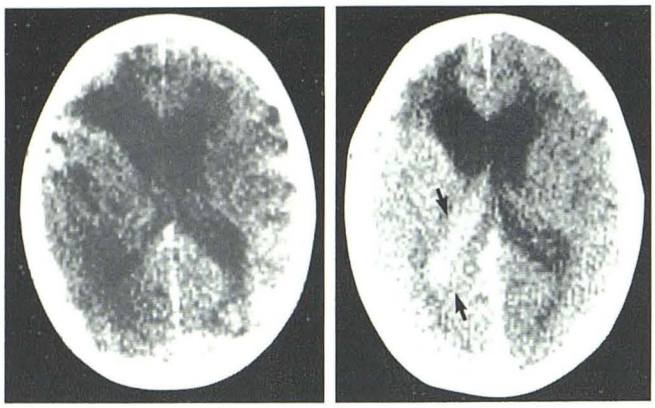
had radiographic evidence of residual tumor and was referred for our investigative treatment program. After evaluation he was begun on our combination chemotherapy regimen following osmotic BBB opening. He had a clinical response, and after four courses of therapy the tumor regression was well documented both by CT (fig. 7) and radionuclide (fig. 3) scans. Noteworthy is that the patient experienced a grand mal seizure after his second barrier modification procedure following an intravenous bolus of iodinated contrast material. For the subsequent courses of therapy we used radionuclide scans (fig. 3) to define and characterize the degree of barrier modification. No further seizures occurred. The tumor regression seen in this patient, as in the previous two patients, was not related to effects of steroid therapy, because the serial scans were obtained with the patient completely off such drugs.

Case 19

A 61-year-old woman had a variant of oat-cell carcinoma of the lung (carcinoid tumor) and two cerebral metastases (left frontal and temporal). After initial mannitol infusion via the left internal carotid artery, enhanced CT scanning (fig. 8) revealed barrier modification not only in the anterior, middle, and posterior cerebral artery circulations, but also in the choroid plexus. Because of limited sensitivity and spatial resolution, disruption in the choroid plexus was not seen on radionuclide scans (fig. 4).

Discussion

The integrity of the BBB in primary and metastatic brain tumors is a matter of some controversy. Classical doctrine is that the presence of a tumor totally disrupts the BBB focally in the area of the tumor. This view is supported by uptake of radionuclide on brain scanning and the uptake of contrast material on enhanced CT in most patients with tumors in the CNS. At the clinical level this view was questioned by the evidence that a variety of cancers have had regression of their disseminated systemic metastases while the foci in the CNS failed to respond to that treatment [10, 11]. Observations such as these have suggested that the BBB may limit the ingress of chemotherapeutic agents into tumors in the CNS. From a variety of studies it appears that the more correct view is that the barrier is defective but not



A B

Fig. 8.—Case 19. Metastatic carcinoid tumors. Enhanced CT scans. **A,** Transverse-cut control scan. **B,** At about same level, after osmotic BBB modification. Enhancement of choroid plexus (*arrows*) indicates that barrier was opened in this structure, as well as in entire left cerebrum.

absent [10, 11]. This view and the recent evidence that drug delivery to tumor and brain around tumor could be improved after BBB modification [3, 5, 12] has led to new and extended interest in the technique and problems associated with barrier opening.

In 1948 and 1949, Broman and Olsson [13, 14] demonstrated that the intracarotid infusion of certain iodinated contrast agents resulted in a "pronounced but completely reversible disorder of vascular permeability without any attendant signs of edema, stasis, or hemorrhages." Their reversible opening of the BBB was dependent both on the concentration of the contrast agent and the application time. In the 1970s, Rapoport et al. [15–18] refined the technique and broadened the observations of Broman and Olsson. We were subsequently able to extend the work of Rapoport to preclinical therapy trials in rodent and canine model systems [1, 2, 4, 6, 12]. We demonstrated that the degree, extent, and reversibility of BBB modification could be documented using CT [2], and that intravenous meglumine iothalamate (Conray 60) was the best agent to provide the needed enhancement. Because of the known epileptogenic potential of meglumine iothalamate [19], the nonionic iodinated contrast agent metrizamide was also evaluated in the canine [2]. The very brief duration of enhancement with metrizamide after barrier modification made documentation technically difficult, since the CT scan had to be obtained within 8 min of the modification procedure.

In the present report we have shown that nine of 19 patients who underwent barrier modification had seizures after the procedures. Of particular note is that, with the exception of two focal motor seizures, all of the seizures occurred after administration of meglumine iothalamate. Even though all of these patients had either a known history of seizures or a marked potential for seizures because of underlying intracranial malignancy, when a radionuclide brain scan was used instead of a CT scan to document barrier modification, only two focal motor seizures were observed. We attempted to suppress seizures by maintaining the patients on therapeutic serum levels of the anticonvulsants phenytoin and phenobarbital. Although Pagani et al. [19] have advocated diazepam as an effective prophylactic for contrast-induced seizures, we used intravenous Valium just before BBB opening, but were not able to eliminate the seizures that resulted from the contrast material.

As we have stated in previous publications [1–6], the degree and distribution of barrier modification is not constant. In addition, to limit the toxicity of the various chemotherapeutic agents that we administer to normal brain, the area of barrier modification is purposely limited to the region of tumor and the immediate surrounding brain as much as possible. However, a significant part of the BBB is also disrupted, which is clearly distant from the tumor. Delivery of chemotherapeutic agents to the brain distant from the tumor may not be therapeutic except in widely infiltrating tumors, and, indeed, may be harmful. When injecting mannitol into the internal carotid artery, barrier modification generally occurs in the anterior and middle cerebral artery distribution of the ipsilateral cerebral hemisphere. At times, barrier modification has occurred in the contralateral anterior cerebral artery distribution due to flow across the anterior communicating artery. More rarely, barrier modification has occurred in the posterior cerebral circulation due to the flow of mannitol via the posterior communicating artery into the posterior cerebral circulation [5]. When the tumor is located in the posterior fossa, mannitol is infused into the vertebral artery, which enables barrier modification in the entire posterior fossa and the posterior cerebral artery distribution of the cerebrum [5, 6, 9]. Therefore, it is still necessary to document by some means the degree and distribution of barrier modification after each procedure.

On the basis of the toxicity associated with the administration of meglumine iothalamate after osmotic BBB modification, it is difficult to continue to recommend the use of this agent to document barrier opening. An attempt to decrease the dose of contrast agent and to use anticonvulsant prophylaxis did not eliminate the problem of seizures and resulted in suboptimal CT scans. Other alternatives explored in our animal studies were the use of meglumine iothalamate intraarterially, thereby allowing dose reduction, or the use of metrizamide, which is less epileptogenic, but these alternatives proved unsatisfactory [2]. Therefore, we currently rely on radionuclide brain scanning to document the degree and extent of barrier modification, although we have not overcome the problem of documenting disruption in the posterior fossa, where good resolution with radionuclide scanning is difficult. We continue to follow the course of tumor size with serial enhanced CT scans between barrier modifications, since lesions smaller than 2 cm are often missed by radionuclide brain scan. In case 4, where barrier opening in the cerebrum and the choroid plexus was documented by CT after an internal carotid infusion of contrast material, a concomitant radionuclide study did not identify disruption in the choroid plexus. This had not occurred before and was probably due to barrier modification in the posterior circulation [9]. Even so, had we not obtained an

enhanced CT scan and had relied solely on the radionuclide study to monitor BBB opening, we would not have made this observation. Because of this problem of sensitivity and spatial resolution, the radionuclide brain scan is not a long-term solution. As the newer nonionic iodinated contrast agents become more readily available, it may be valuable to determine if they are more useful than metrizamide in barrier modification studies. Although objective responses have been seen in some of our patients given chemotherapy after BBB modification, it is too early to make any general conclusions about efficacy, except possibly in the case of primary CNS lymphoma [9].

REFERENCES

1. Neuwelt EA, Maravilla KR, Frenkel EP, Rapoport SI, Hill SA, Barnett PA. Osmotic blood-brain barrier disruption: computerized tomographic monitoring of chemotherapeutic agent delivery. *J Clin Invest* **1979**;64:684–688
2. Neuwelt EA, Maravilla KR, Frenkel E, Barnett P, Hill S, Moore R. Use of enhanced computerized tomography to evaluate osmotic blood-brain barrier disruption. *Neurosurgery* **1980**;6:49–56
3. Neuwelt EA, Frenkel EP, Diehl JT, Vu LH, Hill SA. Reversible osmotic blood-brain barrier disruption in humans: implications for the chemotherapy of malignant brain tumors. *Neurosurgery* **1980**;7:44–52
4. Neuwelt EA, Frenkel EP, Rapoport SI, Barnett PA. Effect of osmotic blood-brain barrier disruption on methotrexate pharmacokinetics in the dog. *Neurosurgery* **1980**;7:36–43
5. Neuwelt EA, Frenkel EP, Diehl JT, Vu LH, Hill SA. Monitoring of methotrexate delivery in patients with malignant brain tumors after osmotic blood-brain barrier disruption. *Ann Intern Med* **1981**;94:449–454
6. Neuwelt EA, Diehl J, Frenkel EP, Barnett P. Osmotic blood-brain barrier disruption in posterior fossa of the dog. *J Neurosurg* **1981**;55:742–748
7. Maravilla KR, Neuwelt EA, Diehl JT. Application of metrizamide in the radiographic evaluation of the neurologically diseased patient. *Neurosurgery* **1979**;5:389–406
8. Drayer BP, Schmeckel DE, Hedlund LW, et al. Radiographic quantitation of reversible blood-brain barrier disruption *in vivo*. *Radiology* **1982**;143:85–89
9. Neuwelt EA, Frenkel E, Diehl J, Hill S, Balaban E. Successful treatment of primary central nervous system lymphomas (microgliomas) with chemotherapy after osmotic blood-brain barrier opening. *Neurosurgery* **1983**;12:662–671
10. Neuwelt EA. CT monitoring of chemotherapeutic agent delivery after osmotic blood-brain barrier disruption. *Clin Neurosurg* **1980**;28:520–531
11. Neuwelt EA, Frenkel E. Is there a therapeutic role for blood-brain barrier disruption? *Ann Intern Med* **1980**;93:147–149
12. Neuwelt EA, Bigner D, Frenkel EP, Barnett P, Pagel M. The effects of osmotic modification of the blood-brain barrier and adrenal steroid administration on methotrexate delivery to gliomas in rats: the blood-brain barrier is a factor. *Proc Natl Acad Sci USA* **1982**;79:4420–4423
13. Broman T, Olsson O. Experimental study of contrast media for cerebral angiography with reference to possible injurious effects on the cerebral blood vessels. *Acta Radiol* (Stockh) **1949**;31:321–334
14. Broman T, Olsson O. The tolerance of cerebral blood vessels to a contrast medium of the diodrast group. *Acta Radiol* (Stockh) **1948**;30:326–342
15. Rapoport SI. *Blood-brain barrier in physiology and medicine*. New York: Raven, **1976**:229–232
16. Rapoport SI, Fredericks WR, Ohno K, Pettigrew KD. Quantitative aspects of reversible osmotic opening of the blood-brain barrier. *Am J Physiol* **1980**;235:421–431
17. Rapoport SI, Ohno K, Fredericks WR, Pettigrew KD. Regional cerebrovascular permeability to ^{14}C-sucrose after osmotic opening of the blood-brain barrier. *Brain Res* **1978**;150:653–657
18. Rapoport SI, Mathews K, Thompson HK, Pettigrew KD. Osmotic opening of the blood-brain barrier in the rhesus monkey without measurable brain edema. *Brain Res* **1977**;136:23–29
19. Pagani JJ, Hayman LA, Bigelow RH, Libshitz HI, Lepke RA, Wallace S. Diazepam prophylaxis of contrast media-induced seizures during computed tomography of patients with brain metastases. *AJNR* **1983**;4:67–72, *AJR* **1983**;140:787–792

Addendum

Since submission of this manuscript, we have altered two technical aspects of our radionuclide brain imaging protocol. First, ^{99m}Tc-DTPA images at 1 hr have been replaced by ^{99m}Tc-glucoheptonate images at 3 hr. Second, the sliding scale computer color table has been replaced by 12 equal fixed-percentage color-coded intervals, taking the hottest pixel as 100%.