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# Multicenter Double-Blind Placebo-Controlled Study of Gadopentetate Dimeglumine as an MR Contrast Agent: Evaluation in Patients with Cerebral Lesions

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**A multicenter double-blind randomized study was designed to evaluate and compare the safety and diagnostic efficacy of gadopentetate dimeglumine (Gd-DTPA) (0.1 mmol/kg) against a saline placebo for use as an IV contrast agent for MR. The randomization code provided for a 2:1 ratio of Gd-DTPA and saline patients. Six investigators studied 88 patients with signs and symptoms of a cerebral lesion. Although safety data were complete in all 88 cases, only 83 had valid efficacy data (57 received Gd-DTPA, 26 placebo). Three patients were excluded from efficacy evaluation because of incomplete scans or scans with severe motion artifacts. Two patients were excluded for protocol variations (did not have a mass lesion). The protocol required that spin-echo MR images be acquired both before and after infusion at mode 1, 500/30/2 (TR/TE/excitations), and at a single-echo mode 2 sequence within a selected range, 1500–2000/56–90/2. Additional TEs could also be used at the discretion of each investigator. Efficacy was determined by comparing post- with preinjection images for relative degree of enhancement and improvement of diagnostic ability after injection, and by comparing these results with placebo results. Enhancement was reported in 43 (75%) of 57 Gd-DTPA patients and in none of the 26 placebo patients. Improvement of diagnostic ability was noted in 37 of 57 Gd-DTPA patients and in no placebo patients. Of 17 patients receiving Gd-DTPA for whom no diagnosis could be made before infusion, nine of 17 were diagnosed after infusion. By comparison, none of five patients not diagnosed before infusion of placebo could be diagnosed after infusion. Of 43 patients in whom lesion enhancement was observed after Gd-DTPA infusion, the diagnosis changed after infusion in 16 (37%) and the number of lesions detected after infusion increased in 10 (23%). Safety studies showed no clinically significant abnormal trends. Minor changes in blood pressure, pulse, and serum iron levels were noted in a higher percentage of Gd-DTPA patients.**

**This study confirms that Gd-DTPA is an efficacious contrast agent for use with MR and that it exhibits excellent patient tolerance. Enhancement allows for a decisive diagnosis to be made in selected cases in which such capability had previously been lacking with unenhanced MR.**

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It has been suggested that the lack of a suitable contrast medium limits the specificity and sensitivity of MR imaging. Nonenhanced MR images may fail to detect certain lesions that appear isointense relative to normal brain on one or more pulse sequences, and may fail to reliably define a distinct margin between focal cerebral masses and areas of perifocal edema [1–9]. The search for such an MR contrast medium has led to the development of a new class of agents, paramagnetics, which cause enhancement by locally affecting the magnetic environment of brain water. One such agent, gadopentetate dimeglumine (Gd-DTPA), has been tested extensively in clinical trials both in the United States and Europe [10–16]. Gd-DTPA is a hydrophilic chelate that readily crosses the damaged blood-brain barrier in a manner similar to iodinated radiographic contrast media. It influences tissue relaxation times, resulting in T1 and T2 shortening. Although these effects are contradictory in terms of image signal intensity, a desirable increase in intensity in areas of blood-brain barrier breakdown may be achieved by

using T1-weighted pulse sequences, reducing the undesired signal lowering effect of T2 shortening.

Considering early results obtained in clinical trials, a multicenter double-blind placebo controlled study was designed and performed to compare the safety and efficacy of Gd-DTPA with saline placebo, and to compare pre- and postinfusion images for improvement of diagnostic ability and lesion detection. The results of this study are presented here.

## Subjects and Methods

This multicenter double-blind randomized clinical trial evaluated gadopentetate dimeglumine (0.1 mmol/kg) against a saline placebo in hospitalized patients with signs and symptoms of a cerebral lesion. The study population consisted of 88 patients at six medical centers in the United States. The randomized code provided for a 2:1 ratio of Gd-DTPA and saline placebo patients. All 88 patients had valid data for safety scoring; 83 of 88 had valid efficacy data, with five patients excluded from efficacy evaluation due to incomplete or artifactually degraded scans or to variations from study protocol (patients without a mass lesion). Of the 83 patients with valid efficacy data, 57 patients received gadopentetate dimeglumine (Gd-DTPA) and 26 received placebo. Strict patient inclusion and exclusion criteria were adhered to (Table 1); these were selected in part to exclude medically unstable individuals. Vital statistics defining the study group are summarized in Table 2, and the specific presumptive diagnoses are listed in Table 3. The study drug, Gd-DTPA, was provided to the investigating sites as a sterile, clear, and colorless aqueous solution in one 20-ml vial, which contained the di-N-methylglucamine salt of the Gd-DTPA complex in a concentration of 0.5 mol/l. Drug osmolality at 37°C was 1.94 osm/kg $H_2O$, and viscosity was 2.9 cp. All drugs were supplied to the investigators by the sponsor.* One numbered medication package was assigned to each patient entered into the study. Each package contained 20 ml of either Gd-DTPA or saline (0.9%) placebo.

After obtaining informed consent, the patient's participation in the study began after baseline evaluations were initiated and baseline laboratory values were examined and found to qualify the patient. Before injection of contrast material or placebo, a flexible angiocatheter was inserted into a convenient antecubital vein. The undiluted contrast agent or placebo was then injected at a dose of 0.1 mmol/kg body weight, at a flow rate of 10 ml/min. The mean volume of contrast material or placebo administered was 15.2 and 14.8 ml, respectively.

MR images were obtained on several MR systems at various field strengths: 0.15, 0.35, 0.5, 1.0, and 1.5 T. Before imaging, a flexible plastic tube filled with Gd-DTPA (0.4 mmol/l) was placed beside the patient's head to serve as a signal-intensity standard. Spin-echo images in mode 1, 500/30/2 (TR/TE/excitations), and mode 2, 1500–2000/56–90/2, were then obtained before injection and repetitively after injection in the following sequence. Preinjection: (1) mode 1 and (2) mode 2; postinjection: (1) mode 1, (2) mode 2, (3) mode 1, (4) mode 2, and (5) mode 1. Additional T2-weighted echoes were obtained at the discretion of each investigator. Postinjection images were acquired at 3, 25, and 55 min (mode 1) and at 8 and 35 min (mode 2). Films were collected and subsequently interpreted by the principal investigator at each test site, who then filled out an extensive report form designed to evaluate the efficacy of the injected material for improving lesion detection and subsequent interpretive diagnostic accuracy. The series of efficacy evaluation questions asked of each investigator are summarized in Table 4.

* Berlex Labs., Cedar Knolls, NJ.

**TABLE 1: Criteria for Entry of Patients into Controlled Gd-DTPA Study**

| Criteria |
|---|
| Inclusion: |
| Between 18 and 75 years old |
| If female, not of childbearing potential |
| Prediagnosed by CT to verify or localize lesion to be studied |
| Willing to sign written informed consent document |
| Willing or required to remain hospitalized for a continuous period of 48 hr after infusion MR |
| Exclusion: |
| Over 100 kg body weight |
| Medical instability |
| Contrast-enhanced CT study within 44 hr before study |
| Concurrent cytostatic or radiation therapy |
| Severe or uncontrolled hypertension |
| Cardiac pacemaker |
| Intracranial clips or external metallic clips within 10 mm of lesion to be studied |
| Elevation of one or more laboratory parameters: |
| Serum iron in excess of laboratory normal |
| Total serum bilirubin in excess of 1½ times normal |
| SGPT in excess of two times normal |
| Serum creatinine above 2.0 mg/dl |
| Receipt of any investigational drug within 30 days of baseline evaluation |

**TABLE 2: Vital Statistics of Patients in Controlled Gd-DTPA Study**

| Variable | Gd-DTPA | Placebo |
|---|---|---|
| Gender, no. (%): | | |
| Male | 42 (70) | 16 (57) |
| Female | 18 (30) | 12 (43) |
| Age (years): | | |
| Range | 18–75 | 22–69 |
| Mean (males) | 47.4 | 49.6 |
| Mean (females) | 60 | 56.5 |
| Weight (kg): | | |
| Mean (males) | 78.9 | 77.6 |
| Mean (females) | 70.5 | 68.4 |

**TABLE 3: Presumptive Diagnosis at Time of Patient Entry into Controlled Gd-DTPA Study**

| Diagnosis | No. of Patients | |
|---|---|---|
| | Gd-DTPA | Placebo |
| Tumor | 36 | 19 |
| Infarct | 13 | 5 |
| Inflammatory | 3 | 1 |
| Vascular | 3 | 1 |
| Degenerative | 2 | 0 |
| Congenital/metabolic | 1 | 0 |
| Demyelinating | 1 | 0 |
| Other | 1 | 2 |
| Total | 60 | 28 |

**TABLE 4: Global Efficacy of Gd-DTPA as Evaluated by Six Investigators**

| Question | No. of Patients (%) | |
|---|---|---|
| | Gd-DTPA ($n$ = 57) | Placebo ($n$ = 26) |
| (1) Did injection facilitate making a diagnosis? | 37 (65) | 0 |
| (2) Are postinfusion T1-weighted images sufficient for diagnosis? | 39 (68) | 11 (42) |
| (3) Are postinfusion T2-weighted images sufficient for diagnosis? | 37 (66)[a] | 17 (65) |
| (4) Did the lesion enhance? | 43 (75) | 0 |
| If yes to question 4:[b] | | |
| (5) Which sequence was best for lesion conspicuity? | | |
| T1-weighted | 41 (95) | – |
| T2-weighted | 2 (5) | – |
| (6) Which postinfusion scan was most diagnostic (minutes after injection)?[c] | | |
| 0–14 | 24 (56) | – |
| 14–27 | 6 (14) | – |
| 28–41 | 10 (23) | – |
| 42–54 | 0 | – |
| 55–69 | 3 (7) | – |
| 70–100 | 0 | – |
| (7) Did infusion change the diagnosis? | 16 (37) | – |
| (8) Was there an increase in the number of lesions after infusion? | 10 (23) | – |

[a] Of 56 instead of 57 patients.

[b] Questions 5–8 refer to the 43 patients for whom the answer to question 4 was Yes.

[c] The six time intervals represent time elapsed between infusion of contrast material and performance of imaging.

The efficacy of Gd-DTPA was determined by comparing pre- and postinfusion images to demonstrate the relative ability of the agent to improve contrast between the lesion and normal tissue compared with the ability of placebo injection to do the same. Similarly, such comparison was made to determine whether either injection could facilitate the establishment of a definitive diagnosis. Relative pre- and postinfusion intensities were obtained for the detected focal lesion and for surrounding normal brain tissue, and also for any related lesion necrosis and perifocal edema. Film contrast scores were reported on a four-point scale for conspicuity: 0 = no contrast (no enhancement), 1 = equivocal, 2 = good, and 3 = excellent enhancement.

Gd-DTPA and placebo groups were compared for possible adverse reactions and side effects by extensive clinical examination and laboratory testing. Physical and neurologic examinations were performed at baseline (patient entry into the study) and at 2, 24, and 48 hr after injection. ECG and EEG studies were performed at baseline and 2–4 hr after injection. Laboratory examinations performed at baseline and 2, 24, and 48 hr after injection included urinalysis, serum chemistry studies (blood urea nitrogen, creatinine, lactate dehydrogenase, SGOT, SGPT, potassium, sodium, chloride, calcium, inorganic phosphorous, glucose, total protein, alkaline phosphatase, total and direct bilirubin, cholesterol, iron, magnesium, and uric acid) and hematologic studies (hematocrit, hemoglobin, RBC, WBC, differential leukocyte count, mean corpuscular hemoglobin, mean corpuscular volume, partial thromboplastin time, and platelet count).

In addition, all patients were closely monitored for any adverse reactions immediately after injection and for another 48 hr. Reactions, if noted, were graded by individual investigators as mild, moderate, or severe, and were classified according to clinical review by each investigator as definitely, probably, possibly, remotely, or not related to the study drug or study conditions. Date and time of onset and resolution of reactions were recorded. If the study drug was discontinued, this was indicated also.

## Results

### *Efficacy Evaluation*

The results of the global efficacy evaluation are summarized in Table 4. Postinfusion images in all 26 patients receiving placebo were judged to be unenhanced and devoid of any added diagnostic information when compared with preinfusion scans. In patients receiving Gd-DTPA, film contrast scores indicated the relative enhancement of mass lesions provided by infusion. Contrast (intensity) scores were graded for normal tissue, mass lesion, perifocal edema, and necrosis, and values obtained were used as a quantitative measure of enhancement. The percentage of Gd-DTPA patients with a higher intensity score after infusion was statistically significantly greater than that found for placebo patients. Higher intensity scores were noted after injection vs before injection for mass lesion in both modes 1 and 2 ($p < .05$) and for mass vs healthy tissue in mode 2 ($p < .01$). A higher contrast ranking was found after injection in 40 (70%) of 57 Gd-DTPA patients in mode 1 and in 14 (25%) of 56 patients in mode 2. No placebo patients had higher contrast rankings after injection in either mode.

The data indicate that a large proportion of patients receiving Gd-DTPA showed lesion enhancement after infusion (43 of 57), and in 37 (65%) of 57, Gd-DTPA was found to facilitate the diagnostic process. In some patients Gd-DTPA administration resulted in enhancement without improvement of diagnostic ability (Fig. 1). Of the 43 patients with enhancement, 41 (95%) had optimal enhancement (and lesion conspicuity) on T1-weighted scans. The most diagnostic image was found within 27 min after contrast infusion in 30 (70%) of 43 patients (Fig. 2; Table 4). In two of 43 patients, T2-weighted scans showed optimal lesion conspicuity after infusion. In these cases, the additive effects of T2 prolongation and residual increased intensity due to T1 shortening provided better definition of the abnormal focus (Fig. 3). Of the 43 patients with enhancement, the initial presumptive diagnosis was changed in 16 (37%) after images were reviewed subsequent to Gd-DTPA infusion (Fig. 4). An increase in the number of lesions detected was noted in 10 (23%) of the 43 enhanced cases, accounting for a significant portion of those cases demonstrating diagnostic change (Fig. 5).

A definitive diagnosis was not possible before injection of contrast material or placebo in 22 patients. Of these, 17 received Gd-DTPA and five received placebo. Of the 17 patients receiving Gd-DTPA for whom no diagnosis was possible before infusion (on either mode 1 or 2 scans), a diagnosis *was* possible after infusion in nine (53%) (Fig. 4).

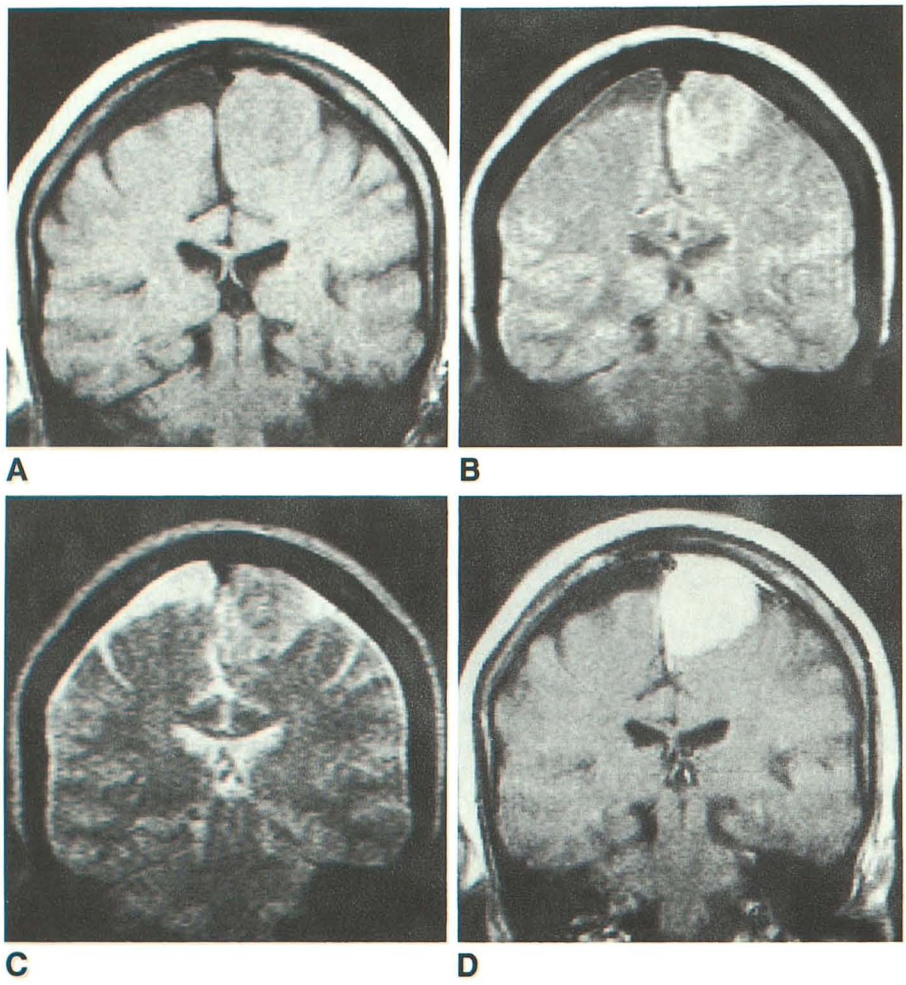



**Fig. 1.—Parasagittal meningioma in 64-year-old woman with focal seizures. Contrast enhancement without improvement of diagnostic ability is illustrated.**

***A–C*, Preinfusion coronal spin-echo images 500/30 (*A*), 2000/60 (*B*), and 2000/120 (*C*), acquired at 0.5 T near frontoparietal junction. Mass is isointense relative to brain on short TR/short TE sequence (*A*), but is still visible by way of regional displacement of gyri and sulcal effacement. Intermediate- and heavily T2-weighted images more clearly define mass and adjacent perifocal edema.**

***D*, Coronal spin-echo image, 500/30, at same level as *A* after infusion of 0.1 mmol/kg Gd-DTPA. Note marked increase in intensity of tumor improving lesion conspicuity. Improved diagnostic ability was not reported since the mass was clearly detected and delineated before infusion.**

No additional diagnostic information was reported in any of the five placebo patients after injection ($p < .01$). Although improvement in diagnostic ability was reported in 65% of all patients receiving Gd-DTPA, a statistically significant difference existed among investigators. Two of the six investigators reported a lower percentage of facilitation; this likely was related to a different case mix, since fewer cases of metastasis and infarction were examined at their institutions. Finally, while 83% of patients were correctly diagnosed after infusion of Gd-DTPA, 67% could be diagnosed on preinfusion mode 1 and 2 images alone.

### *Safety Evaluation*

All patients were evaluated for short-term toxicity to contrast material. Pre- and postinjection clinical evaluations revealed no significantly abnormal trends in physical examination, neurologic status, ECG, EEG, or urinalysis.

Adverse reactions were graded by investigators as mild, moderate, or severe, and as related or unrelated to the injected drug. A similar percentage of patients receiving Gd-DTPA (13 [21.7%] of 60) and placebo (six [21.4%] of 28) reported at least one adverse reaction ($p > .99$). Three severe reactions were reported in two placebo patients: nausea and hiccups in one patient and headache in the other. None of these was considered to be "drug related." No severe reactions were reported in Gd-DTPA patients. The only adverse reactions reported in more than one patient included headache in three (5%) of the Gd-DTPA patients and five (17.9%) of the placebo patients; hypertension in four (6.7%) of the Gd-DTPA patients and one (3.6%) of the placebo patients; and hypotension in two (3.3%) of the Gd-DTPA patients and none of the placebo patients. Investigators categorized mild or moderate adverse reactions as possibly or definitely drug related in five patients receiving Gd-DTPA. These five patients had 13 reactions, including weakness, conjunctivitis, taste abnormality, local burning at injection site, hypertension, hypotension, nausea and vomiting, and headache.

Minor changes were noted in blood pressure and pulse rate in a higher percentage of Gd-DTPA patients. A decrease in systolic blood pressure of more than 25 mm Hg from baseline was noted 25 min after infusion in six Gd-DTPA patients. Further study of this group revealed that five of six were studied at one of the six test sites, and that three of six had baseline systolic pressures in excess of 160 mm Hg. Only

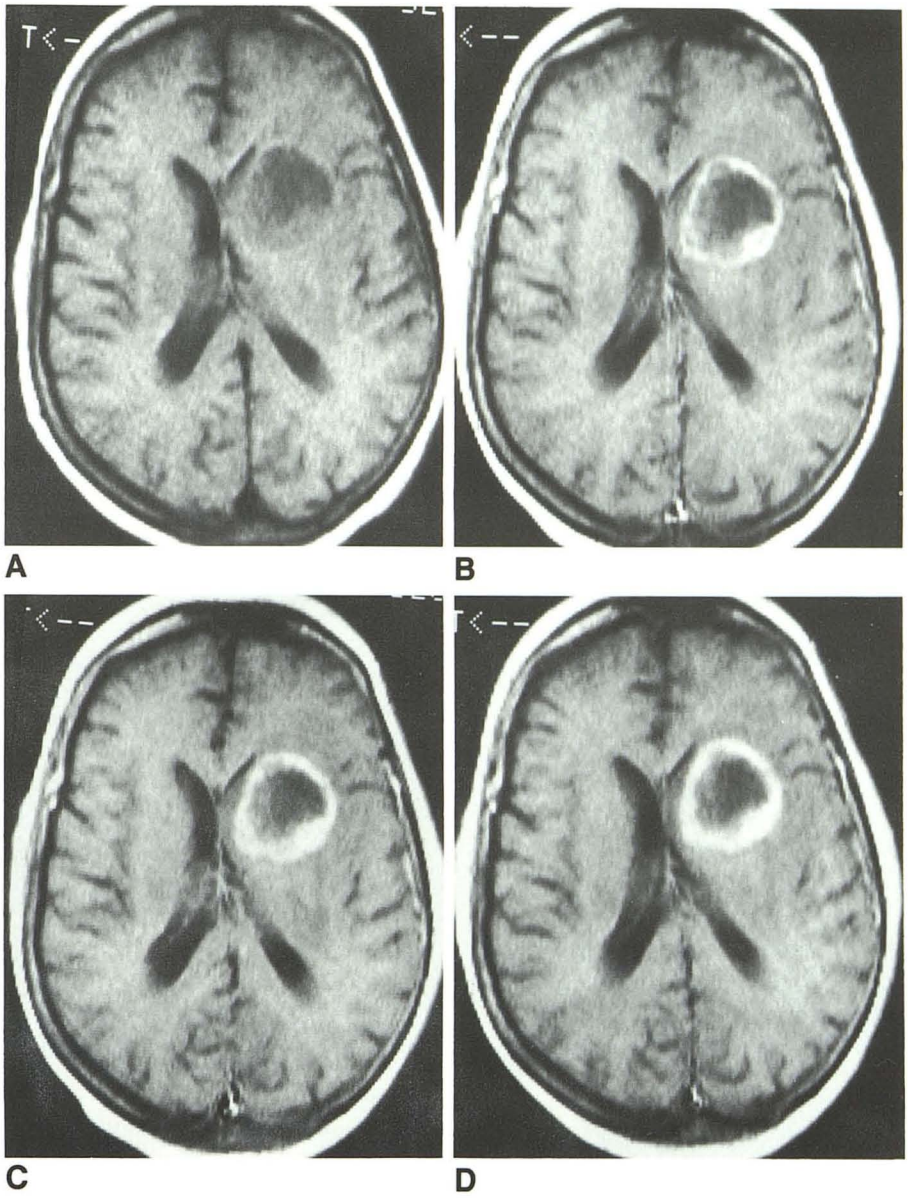



**Fig. 2.—76-year-old woman with 4-day history of memory loss and metastases from lung carcinoma. Time dependence of enhancement is illustrated.**

***A*, Axial spin-echo image, 500/30, at 0.5 T before contrast infusion. Central low signal intensity of deep frontal mass is due to necrosis.**

***B–D*, Postinfusion spin-echo images, 500/30, at 5 (*B*), 25 (*C*), and 55 (*D*) min after Gd-DTPA injection. Note relatively thin rim of enhancement observed at 5 min. Delayed scans show thickening of enhanced portion of mass.**

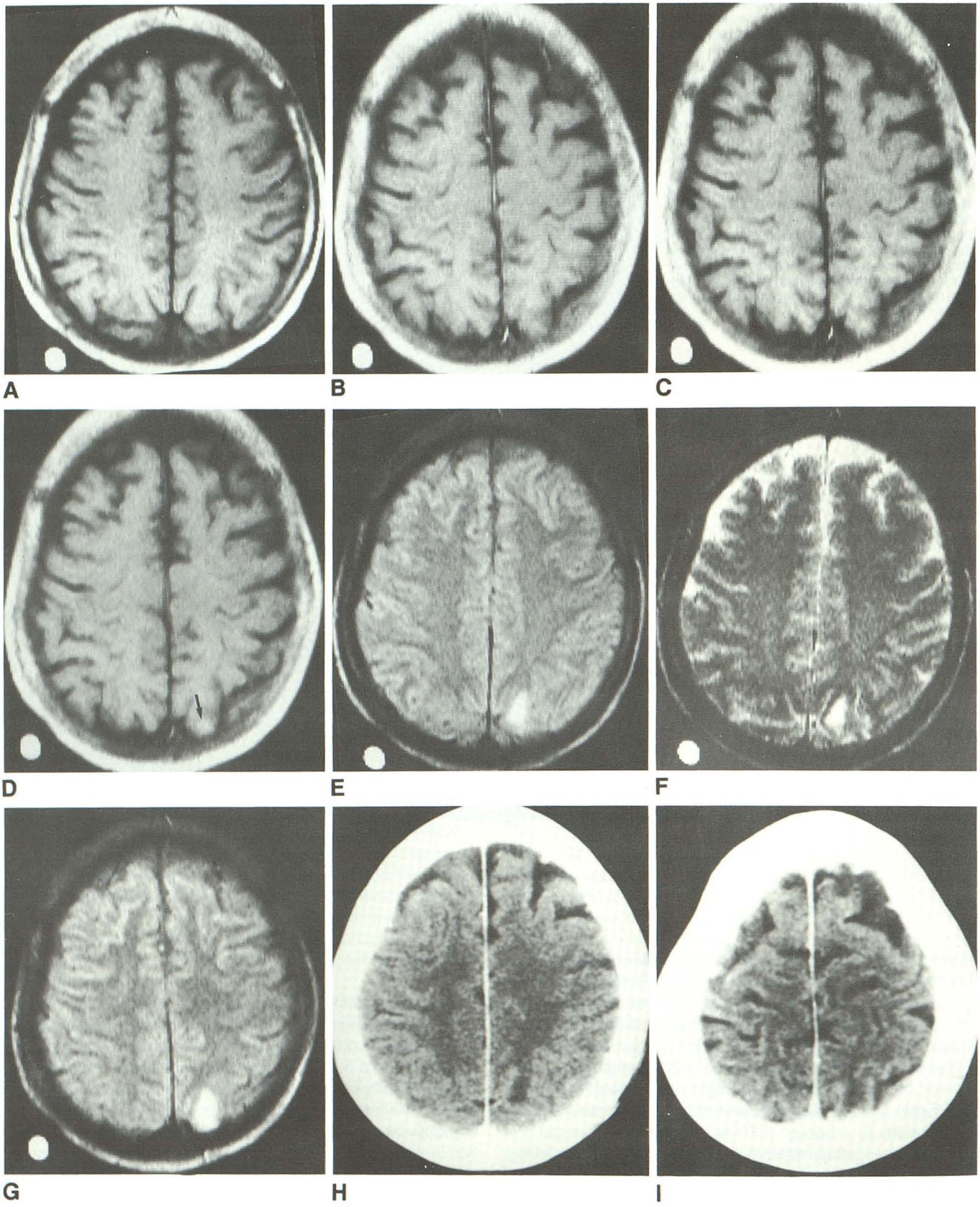
**As additional information was not available on scans delayed beyond 25 min, optimal enhancement was noted at this point. These findings were typical of cases of necrotic tumors. Immediate postinfusion scans often underestimated extent of eventual tumoral enhancement. Delayed images (most frequently within 25 min) best corresponded to enhancement observed on CT scans.**

one of six had an associated decrease in diastolic pressure. Adverse reaction reports noted that two Gd-DTPA patients experienced clinical signs of hypotension. One of the two was a 47-year-old man with symptoms of hypotension 85 min after injection, assessed as unrelated to the drug. The other was a 45-year-old woman who appeared weak and pale and had a blood pressure of 90/60 mm Hg, from a baseline of 120/62, 25 min postinjection; this was considered to be possibly drug related.

Laboratory studies revealed a generally transient post–Gd-DTPA increase in serum iron concentration. A higher percentage of Gd-DTPA patients had elevated serum iron at 2–4 hr postinjection, and several patients had mildly elevated levels of iron at 48 hr (Table 5).

## Discussion

This investigation demonstrated the effectiveness of Gd-DTPA for the detection and definition of cerebral lesions when used in conjunction with MR. It is not surprising that placebo injections were ineffective and that significant increases in signal intensity occurred in a variety of cerebral lesions after Gd-DTPA infusion. Of greater significance was the efficacy demonstrated by Gd-DTPA for providing diagnostic information in nine of 17 cases not elucidated before its administration. Although one might argue that the use of different pulse sequences (such as heavily T1-weighted inversion recovery) might have allowed a greater percentage of diagnoses to be made without infusion of contrast material and that the study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◄ **Fig. 3.—52-year-old woman with poorly differentiated metastatic lung carcinoma. Lesion is detected readily on all T2-weighted images, but only on 55-min delayed postinfusion T1-weighted study.**

***A–D*, Axial spin-echo images, 500/30, of high convexity before Gd-DTPA infusion (*A*) and at 5 (*B*), 25 (*C*), and 55 (*D*) min after infusion (acquired at 0.5 T). Note enhancement in small peripheral metastatic nodule detected by independent observers only on last delayed scan (*arrow*).**

***E–G*, Axial intermediate spin-echo, 2000/60 (*E* and *G*), and heavily T2-weighted spin-echo, 2000/120 (*F*), MR images before (*E* and *F*) and after (*G*) Gd-DTPA infusion. Nodule at periphery is easily detected on preinfusion images because of high-signal edema. Enhancing nodule is also visible posterior to edema (T1 effect) on postinfusion intermediate image (*G*) (compare with *E*). Lesion is more conspicuous than on postinfusion T1-weighted studies (*B–D*).**

***H* and *I*, CT scans after infusion of iodinated contrast material (adjacent cuts). Nodule is partly hidden by high density of inner table of skull. Contrast this with lack of obscuration by bone on MR studies (*D* and *E*).**

**(Reprinted from [17], with permission.)**

was too limited in this respect, the study sequences were representative of current clinical practice. One might also counter that the increase in lesion conspicuity observed in many cases after Gd-DTPA infusion improved diagnostic confidence in a way not indicated by the study data. Improvement in diagnostic ability was reported in 37 of 57 cases qualifying for efficacy determination. The *absence* of enhancement, which led to a more confidently negative diagnosis in some cases, was reflected in this statistic and partly explained the unexpectedly high percentage of such positive responses, although improved lesion conspicuity due to enhancement did account for the majority of these cases. Because enhancement was observed in 43 of 57 cases, and enhancement facilitated diagnosis in 37 cases, it is evident that enhancement was present in some cases without necessarily improving diagnostic ability (Fig. 1). Although the number of patients in this study is relatively small, there is clear evidence that this carefully controlled investigation supports the utility and even the necessity (in some cases) of using Gd-DTPA (or other contrast agents) in cases not diagnosable or less accurately defined by preinfusion MR alone. Our data also show that improvement in diagnostic ability (reported in 37 of 57

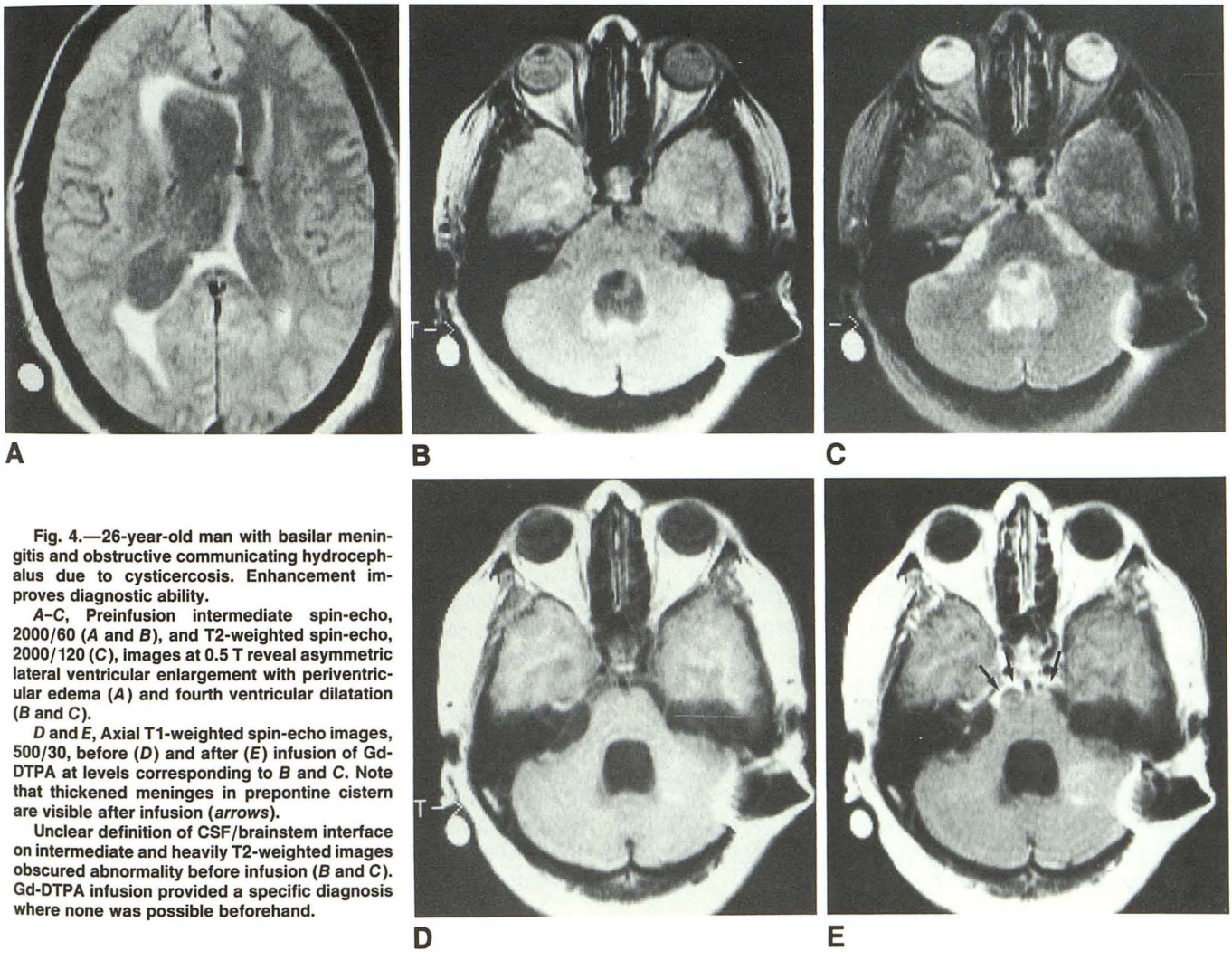


**Fig. 4.—26-year-old man with basilar meningitis and obstructive communicating hydrocephalus due to cysticercosis. Enhancement improves diagnostic ability.**

***A–C*, Preinfusion intermediate spin-echo, 2000/60 (*A* and *B*), and T2-weighted spin-echo, 2000/120 (*C*), images at 0.5 T reveal asymmetric lateral ventricular enlargement with periventricular edema (*A*) and fourth ventricular dilatation (*B* and *C*).**

***D* and *E*, Axial T1-weighted spin-echo images, 500/30, before (*D*) and after (*E*) infusion of Gd-DTPA at levels corresponding to *B* and *C*. Note that thickened meninges in prepontine cistern are visible after infusion (*arrows*).**

**Unclear definition of CSF/brainstem interface on intermediate and heavily T2-weighted images obscured abnormality before infusion (*B* and *C*). Gd-DTPA infusion provided a specific diagnosis where none was possible beforehand.**

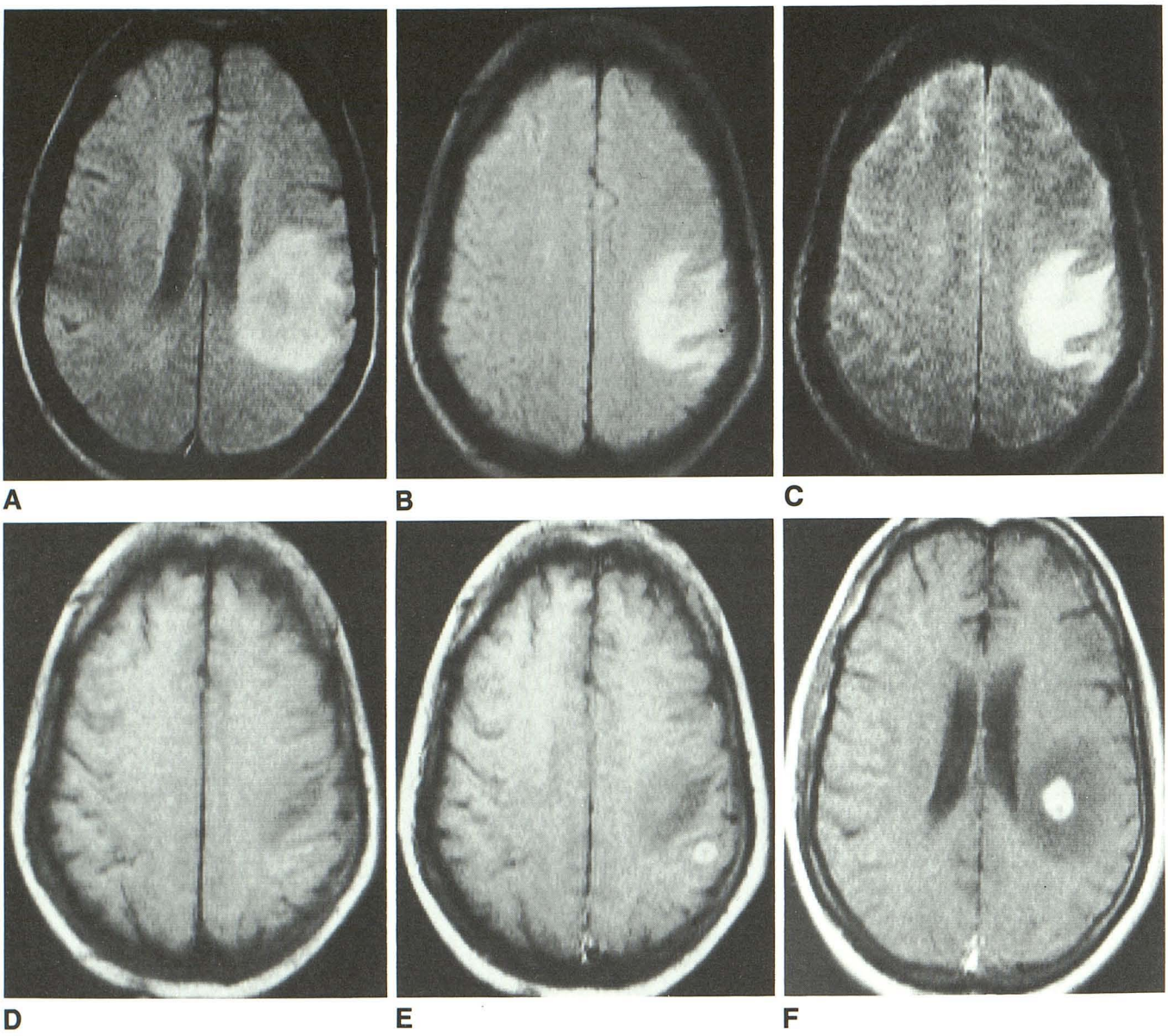


**Fig. 5.—47-year-old man with metastases from lung carcinoma. Enhancement facilitates diagnosis with an increase in number of lesions detected.**

***A–C*, Preinfusion axial spin-echo images, 2000/60 (*A* and *B*) and 2000/120 (*C*), at 0.5 T. High-signal-intensity edema is easily detected on two adjacent intermediate cuts (*A* and *B*), as is a relatively low-signal nodule surrounded by edema (*A*). Edema also is noted to circumscribe peripheral regions of apparently normal cortex (*B* and *C*).**

***D* and *E*, Axial spin-echo images, 500/30, before (*D*) and after (*E*) Gd-DTPA infusion. After contrast administration, a second tumor nodule is clearly defined. This finding is not apparent even in retrospect on any preinfusion image. Infusion studies indicate multiplicity. Improvement in diagnostic ability, therefore, was reported.**

***F*, Postinfusion spin-echo image, 500/30, shows deep lesion detected preinfusion.**

**(Reprinted from [17], with permission.)**

cases) did not always result in a change in diagnosis. Therefore, increased diagnostic confidence is reflected in these numbers; indirectly these data indicate an unexpectedly high underlying lack of confidence in the interpretation of preinfusion MR images, which may be greater than an interpreter might normally express in day-to-day clinical practice where infusion would not be available.

A change in diagnosis after contrast infusion was found most often in patients with multiple lesions. Of 16 patients in whom the diagnosis was changed after pre- and postinfusion images were compared, 10 exhibited an increase in the number of lesions detected. As previously observed in intraparenchymal cerebral metastasis [17], enhancement provides an increase in lesion conspicuity that can overcome the

**TABLE 5: Changes in Serum Iron After Infusion of Gd-DTPA or Placebo**

| Condition: Postinjection Status | No. of Patients (%)[a] | | | | | |
|---|---|---|---|---|---|---|
| | Gd-DTPA | | | Placebo | | |
| | 2–4 hr | 24 hr | 48 hr | 2–4 hr | 24 hr | 48 hr |
| | (*n* = 54) | (*n* = 52) | (*n* = 43) | (*n* = 25) | (*n* = 24) | (*n* = 21) |
| ≥15% rise from baseline | 32 (59) | 21 (40) | 16 (37) | 10 (40) | 11 (46) | 10 (48) |
| ≥15% drop from baseline | 8 (15) | 18 (35) | 16 (37) | 7 (28) | 7 (29) | 7 (33) |
| Normal baseline: | | | | | | |
| Normal | 35 (65) | 29 (56) | 24 (56) | 18 (72) | 15 (63) | 12 (57) |
| High | 7 (13) | 6 (12) | 5 (12) | 1 (4) | 3 (13) | 2 (10) |
| Low | 1 (2) | 7 (13) | 6 (14) | 1 (4) | 3 (13) | 4 (19) |
| High baseline: | | | | | | |
| Normal | 2 (4) | 4 (8) | 2 (5) | 0 | 0 | 0 |
| High | 2 (4) | 0 | 0 | 0 | 0 | 0 |
| Low baseline: | | | | | | |
| Normal | 5 (9) | 1 (2) | 2 (5) | 1 (4) | 2 (8) | 1 (5) |
| High | 0 | 1 (2) | 0 | 0 | 0 | 0 |
| Low | 2 (4) | 4 (8) | 4 (9) | 4 (16) | 1 (4) | 2 (10) |

Note.—No patients in either group with a high baseline had a low postinjection status.

[a] The results are derived from those patients with both pre- and postinjection results.

difficulty encountered in detecting small, relatively isointense lesions at the periphery of high-intensity edema, lesions that may be mistaken for regions of normal brain parenchyma (Fig. 5). The failure to detect a second tumor nodule may lead to a failure to make the diagnosis of metastasis, as a solitary mass may represent not only solitary metastasis but other primary lesions of the neuraxis. Difficulty in multilesion detectability is compounded by the failure of noncontrast MR techniques to reliably detect small parenchymal masses not associated with appreciable edema (and focal T2 prolongation) [18–21]. Gd-DTPA-enhanced scans are, in these cases, demonstrably more sensitive to subtle defects in the blood-brain barrier than are noncontrast T2-weighted images.

The data on the optimal pulse sequence for lesion detection not surprisingly confirm the impression that T1-weighted short TR/short TE spin-echo images were superior to long TR images for lesion definition and diagnosis. In several cases, however, the long TR/intermediate TE sequence provided a nice combination of lesion depiction (as an area of short T1) and edema visualization (prolonged T2), and in one composite image all important diagnostic information was provided. Also, the intermediate sequence, in which image intensity is related to both T1 shortening and T2 prolongation, better detected two small lesions not well appreciated as areas of abnormal enhancement on postinfusion T1-weighted images alone (Fig. 3), indicating that T1 and T2 effects may be additive in these images and diagnostic information not available on either T1- or T2-weighted images alone may be produced. This additive effect explains the higher postinfusion contrast ranking and higher intensity scores noted for mass and mass vs normal tissue on T2-weighted scans. A limited number of small extraaxial lesions were studied in this investigation, and data support prior observations [22, 23] that Gd-DTPA infusion dramatically improves visualization in lesions not readily differentiable from adjacent brain substance (before infusion) by differences in inherent intensity alone.

Optimal timing of postinfusion sequences was studied by reviewing responses to question 6. The data summarized in Table 4 indicate that scans obtained within 27 min after infusion were best for detecting enhancement in 70% of cases. Immediate postinfusion imaging is particularly optimal for detecting extraaxial lesions [22, 23]. On the other hand, 13 of 43 cases were best examined after the 27-min time window. Patients best imaged late included those with small parenchymal lesions, which continued to increase in conspicuity on later T1-weighted images due to continued accumulation of contrast material. One lesion was not detected on either of the first two T1-weighted postinfusion sequences, but was noted on the third and last image obtained 55 min after infusion (Fig. 3). This (third) metastatic focus was, however, easily detected as an area of increased signal intensity on T2-weighted images obtained either before or after infusion of contrast material and, therefore, would not have been missed even if delayed postinfusion scans had not been obtained. This type of case certainly supports the need for obtaining preinfusion T2-weighted images routinely in almost all patients studied with Gd-DTPA.

Although some data are available [24], how rapidly one must study patients after Gd-DTPA injection is an issue likely to be determined more by the demands of scanner throughput than by subtle differences in lesion conspicuity, assuming that immediate postinfusion studies detect the vast majority of lesions, a premise supported by the results of our study. The fact that immediate scanning after infusion is likely to be the preferred method is further supported by the tendency of extraaxial lesions to enhance early and then fade [22, 23].

Although no patient's study went from the diagnostic to the nondiagnostic category after Gd-DTPA administration, such an occurrence is certainly possible. Such "enhancement to isointensity" can occur with contrast-enhanced CT when a subtly lucent lesion enhances just enough to blend with adjacent normal brain. One could predict that this phenome-

non would be encountered more often with MR if more heavily T1-weighted (inversion recovery) pulse sequences were used for pre- and postinfusion imaging. Inversion-recovery and very short TE spin-echo sequences show regions of prolonged T1 relaxation times as very distinct areas of low signal intensity, lower than that observed on the "T1-weighted" sequence used in this study. With these heavily T1-weighted sequences, enhancement may fail to overcome this focal low signal, producing isointensity and resulting in lowered diagnostic confidence. Preinfusion MR, therefore, is important not only for the detection of lesions with very short T1 relaxation times, such as hemorrhage (which may be masked by contrast enhancement), but also for the detection of lesions with very long T1 relaxation times to prevent this isointensity phenomenon.

A key question ultimately will be: When is contrast infusion needed? Our data show that a majority of patients are potentially diagnosable without contrast material, although diagnostic confidence and diagnostic accuracy clearly improve after infusion for a significant percentage of patients. This percentage might differ from that obtained at any particular MR facility, since image quality varied from site to site in our study group, and uniformly high-quality images might allow improved lesion detection of noncontrast images. Patients benefiting from infusion also include those who, although clinically suspected of harboring disease, subsequently are found to have a normal postinfusion MR study. We can conclude that infusion is not routinely needed in all patients, but with our current experience, it is not possible to predict with sufficient accuracy which patients do or do not need contrast studies. Unless images obtained before infusion are routinely monitored, and infusion is given only selectively in necessary cases (even this may be difficult to determine), it would appear that contrast material will be more widely used than what might, in retrospect, be required. Broader clinical experience (more widespread use of this agent) should eventually lead to specifically defined uses.

Safety studies performed as part of this placebo-controlled investigation indicate excellent clinical tolerance. No severe reactions were attributed to the drug, and few less severe reactions could even remotely be attributed to Gd-DTPA. Clinical hypotension reported in two patients was "possibly" attributable to Gd-DTPA administration in one, although cardiovascular effects are unlikely at the dose rates used in this study (maximum of 20 ml over 2 min). It is not known whether inadvertently rapid injections were related to the effects observed in this study, since none were reported or indicated in the study data. A lack of exacting technique might be implicated in view of the grouping of five patients with blood pressure abnormalities at one study site. Three of these patients had baseline systolic pressures over 160 mm Hg, suggesting that anxiety prior to the study may have affected later measurements. Such nonuniformities might be expected in a multicenter trial. It would seem likely that factors other than effect of contrast material explain the grouping of abnormal responses in these patients. To be sure, one would need to examine the exact conditions present at all sites before injection of contrast material, such as more stressful or more relaxed scanning environments, patient education, and patient comfort in each scanner, issues not addressed in this investigation.

Although transient elevations in serum iron have been known to occur after Gd-DTPA administration [15, 16, 25] and were observed in this study (Table 5), there is no evidence that these findings are clinically significant. Animal studies suggest that iron elevation may be related to extrasplenic hemolysis [14–16], although the exact mechanism is unknown. Similar effects may occur with other injected agents. In any case, the low toxicity and low necessary injection volume indicate that Gd-DTPA is well suited for use as a contrast material in patients undergoing MR.

It should also be mentioned that the admission criteria for the study excluded patients with significantly abnormal chemistry and hematology and medical instability, leaving open the possibility that exposure of such patients to the drug may lead to unexpected drug toxicity. Also, because few patients have been reexposed to the agent, the absence of allergic reactions may not indicate that such reactions will not occur when the contrast material becomes more widely used.

In conclusion, Gd-DTPA (0.1 mmol/kg), when administered to patients with presumptive diagnoses of cerebral lesions, demonstrated safety and efficacy as a contrast medium for enhancement of MR images:

1. Gd-DTPA improved diagnostic ability in 65% of the patients and provided enhancement in 75%. For placebo patients, no postinfusion improvement was reported, nor was enhancement seen in any patient.

2. Gd-DTPA permitted diagnosis in nine patients from a group of 17 patients for whom no preinjection image was diagnostic, whereas of five placebo patients for whom no preinjection image was diagnostic, none had postinjection scans that permitted diagnosis.

3. In addition, use of Gd-DTPA resulted in a change in diagnosis in 16 (37%) of the 43 patients who experienced enhancement and permitted visualization of an increased number of lesions in 10 (23%) of the 43 patients.

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