Special Article

Inherent Contrast in Magnetic Resonance Imaging and the Potential for Contrast Enhancement

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Magnetic resonance (MR) imaging is emerging as a powerful new diagnostic tool valued for its apparent lack of adverse effects. The excellent inherent contrast between biologic tissues and fluids afforded by MR imaging is one of the foremost characteristics of this technique and depends on physicochemical properties such as hydrogen density and T1 and T2 relaxation rates, on magnetic field strength and on operator-chosen factors for acquiring the MR imaging signal. Pharmaceutical contrast-enhancing agents shorten the MR imaging process and improve sensitivity and diagnostic accuracy.

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As an introduction I will recount a conversation I had recently with an old friend, a surgeon, whom I had not seen for several years. When he asked what type of research I was involved in, I explained that our group was studying magnetic resonance (MR) imaging, formerly known as nuclear magnetic resonance imaging, and, in particular, we were attempting to develop new pharmaceutical contrast agents for this technique. Being a well-informed physician, my friend explained that he knew a little about MR imaging and that he understood that it had excellent inherent contrast. He asked, "Why do you need contrast agents at all for MR imaging?" He also asked, "How do these new contrast agents work?" Had I the time at the occasion of our meeting, I would have offered the following as answers to his questions.

Determinants of Contrast on Magnetic Resonance Images

Hydrogen MR images of the human body are now being obtained by adding small amounts of energy to the body's protons in the form of radiofrequency pulses, or radiowaves, after the patient has been placed within a strong external magnetic field. Following the radiofrequency pulse, the magnetic axes of the protons, which have a natural tendency to oscillate or "resonate," return to equilibrium by emitting radiofrequency energy. This energy is detected by the MR device and converted into a two-dimensional tomographic image in any one of three orthogonal planes (transaxial, coronal or sagittal). The process of nuclei returning to equilibrium is called "relaxation" and the time constants for relaxation for a tissue vary depending on the chemical environment of the protons within the tissue.[1-3] For example, hydrogen protons in bone are in a rigid matrix and tend to relax slowly, whereas protons in bone marrow, a relatively fatty tissue, relax quickly. The differences in hydrogen concentration and relaxation times of hydrogen within different tissues are primary determinants of contrast on MR images. There are, in fact, two relaxation constants for each tissue called the T1 and T2 values. For a more detailed discussion of the principles of hydrogen MR imaging, the reader is referred to one of several excellent reviews.[1,4-6]*

There are factors important to MR imaging contrast in addition to hydrogen concentration, T1 and T2. Certain of these factors depend on the MR imaging device used; others are dependent on physical conditions of the tissue such as viscosity and temperature. Contrast between tissues will vary among imaging systems operating at different magnetic field strengths. The commercially available imaging systems offer

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ABBREVIATIONS USED IN TEXT

CT = computed tomography
DTPA = diethylenetriaminepentaacetic acid
LD_{50} = median lethal dose
MR = magnetic resonance
NSL = nitroxide spin labels
TE = echo delay time
TR = pulse interval

a range of magnetic field strength from 0.15 to 2.0 tesla. The optimal choice of field strength for MR imaging is a controversial subject and goes beyond the scope of this discussion; it is sufficient to note that contrast differences will tend to decrease at higher field strengths. But other variables such as signal-to-noise ratio tend to improve at higher field strengths.

Another important determinant of contrast is the sequence and spacing of radiofrequency pulses used to excite the body's protons. These pulses are applied repeatedly. The commonly available choices of pulsing sequences include inversion recovery, spin echo and saturation recovery sequences.[5,6] Each pulse sequence emphasizes different magnetic characteristics of tissues and each produces distinctively different tissue contrast and grey scales. Further, there is virtually an infinite variety of pulse intervals (TR) and echo delay (TE) times, each TR-TE combination yielding a different intensity value (shade of grey) for the same tissues. No single pulse sequence or TR-TE combination is best to emphasize contrast between all normal tissues and pathologic processes. Accordingly, an MR imaging examination will generally include multiple pulse sequences, TR-TE combinations or both in hopes of obtaining a good or best contrast scale.

Thus, numerous factors determine the observed contrast on an MR image, some factors inherent to the tissues themselves and others depending on the equipment used or operator-chosen pulse sequences. One can easily appreciate a possible disadvantage—too many choices. A radiologist could gather dozens of different images from a single patient over many hours without exhausting all possibilities. There must be a limit to the number of images obtained without a major loss in available information or diagnostic confidence. Pharmaceutical contrast agents may help to alleviate this problem by selectively increasing the intensity of pathologic processes and thereby minimizing the need for additional imaging sequences. Contrast enhancement could shorten the total time for the MR imaging examination and thus improve the cost effectiveness of the technique.

Another rationale for the use of contrast enhancement of selected tissues is to increase the contrast differences between magnetically similar tissues. Studies of animals with MR imaging and anecdotal clinical experiences indicate that contiguous normal and abnormal tissues may have identical or closely approximating relaxation values and hydrogen concentrations.[7-9] These "isomagnetic" tissues cannot be differentiated by MR imaging regardless of imaging system or operator-dependent variables. The precise incidence of isomagnetic pathologic processes is unknown but may be relatively low compared with the occurrence of "isodense" lesions on computed tomographic scans. Regardless of the incidence, pharmaceutical contrast agents could permit the differentiation of isomagnetic lesions and increase confidence that a lesion is not being missed.

Inherent Contrast on Magnetic Resonance Images

Normal Physiologic Contrast

The intensity differences—that is, the variations in grey—among many normal tissues on MR images are often striking and uniquely valuable. Many contiguous tissues that cannot be reliably separated by computed tomography, ultrasound or conventional radiography without extrinsic contrast media can be easily differentiated by MR imaging.[9] Noteworthy examples of useful inherent MR imaging contrast differences include grey and white matter of the brain (Figure 1), cortex and medulla in the kidney, compact bone and medullary spaces (Figure 2), the spinal cord and the subarachnoid space, the annulus fibrosis and nucleus pulposus in intervertebral discs (Figure 3) and even concentrated and dilute bile.[10]

Another extremely useful property of MR imaging is the sharp contrast observed between rapidly moving blood and static tissues such as blood vessel wall (Figure 4.)[11] Emitted radiofrequency signals from fast-moving blood are totally or nearly totally missed by the MR detector system so that blood appears low in intensity (black). Blood vessel walls and the heart, particularly on electrocardiographic-gated MR images, have a relatively high intensity. These properties of MR imaging, in effect, provide angiographic detail of vascular structures without contrast medium administration. Addition-

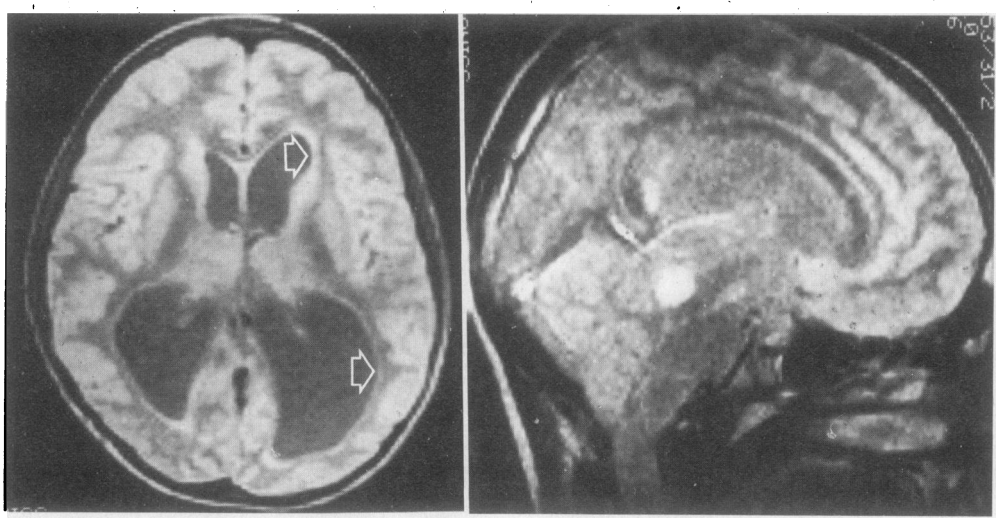

Figure 1.—Left, A transverse spin-echo magnetic resonance image of the brain without contrast enhancement shows excellent grey- and white-matter contrast differences, substantial ventricular enlargement and a rim of periventricular edema (arrows) from cerebrospinal fluid (CSF) obstruction. **Right,** A sagittal image of the same patient clearly defines a high-intensity midbrain glioma, the cause of CSF obstruction.

ally, it may be possible to quantitate the rate of blood flow within vessels using only the nonenhanced MR images.

Contrast Differentiation of Normal and Abnormal Tissues

The high sensitivity of MR imaging for a variety of pathologic processes is described in numerous articles now appearing in the radiologic and MR imaging literature.[9-12] Of note, there are at least two journals devoted exclusively to MR applications in medicine. Recognized applications of MR imaging include the detection of demyelinating processes of the central nervous system, infarction of various tissues including the brain and heart, inflammatory processes, edema collections from any cause (Figure 1—Left), blood collections (Figure 2), deposits of iron-containing compounds and neoplasms (Figure 1—Right).[10-17]

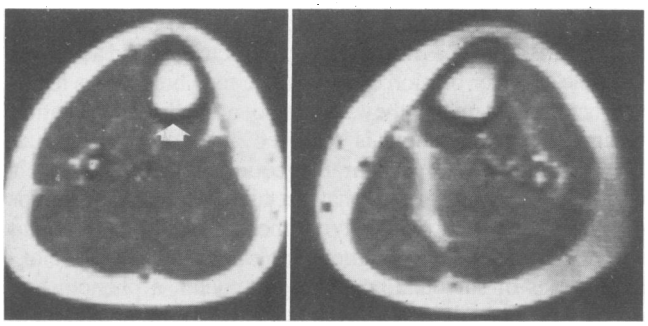

Figure 2.—A transverse spin-echo image of the lower leg in a boy with hemophilia shows high contrast between clotted blood in a hematoma and surrounding muscle. Notice the high intensity of marrow in the tibia contrasted by the low-intensity (black) cortical bone (arrow).

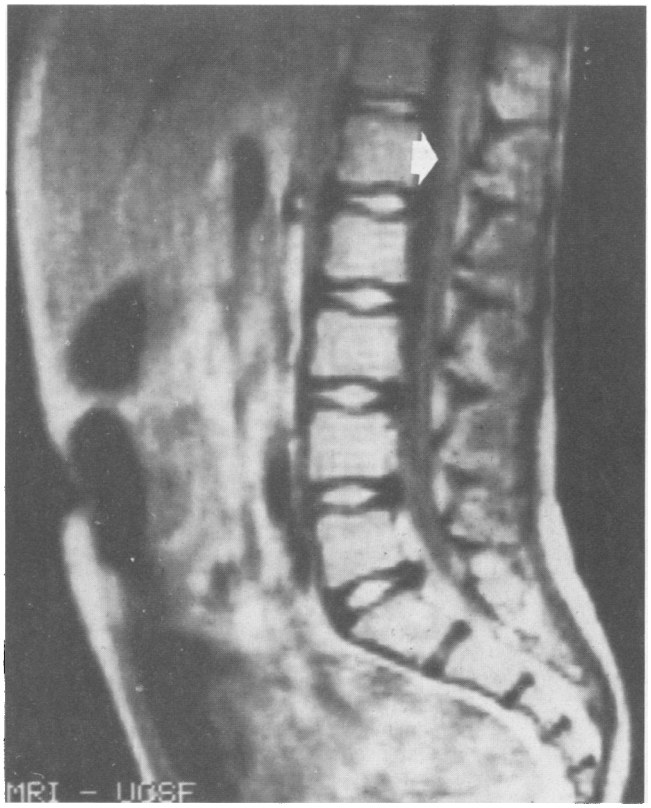

Figure 3.—Magnetic resonance (MR) imaging produces a sharp contrast difference between the nucleus pulposus (high intensity) and the annulus fibrosis (low intensity) and further produces a clear delineation of the spinal cord (arrow) in the subarachnoid space. Myelography using MR imaging does not require contrast medium instillation.

Identifying and characterizing tumors are the most promising of MR imaging uses; a great variety of neoplasms has been examined with an apparently high rate of detection.[7,9,10,13,15] Studies are not yet available to define the false-negative rate for detecting tumor by MR imaging but many investigators estimate that this will be rare. An operator's decisions about the type and number of pulsing sequences may critically affect the sensitivity of MR imaging for detecting tumor.

Disappointingly, available data do not indicate that inherent contrast from MR imaging can reliably differentiate benign from malignant processes. There is wide variation in T1 and T2 times of tumors compared with normal tissues, which themselves vary widely in relaxation characteristics.[9] These overlaps should limit the specificity of MR imaging and may even diminish sensitivity for detecting certain diseases.

Possible Applications for MR Imaging Contrast Media

Modern medicine has several precedents for the augmentation of diagnostic imaging examinations with pharmaceutical contrast enhancers. Examples include barium for gastrointestinal examinations, iodinated organic compounds given intravenously for x-ray urography and computed tomography (CT), myelographic contrast media instilled into the subarachnoid space, radiolabeled compounds for nuclear scintigraphy and, more recently, microsuspensions of air bubbles for echocardiography. With the same intent, researchers are now trying to define pharmaceutical agents that can safely alter the magnetic properties of specific tissues to change the contrast differences for MR imaging.

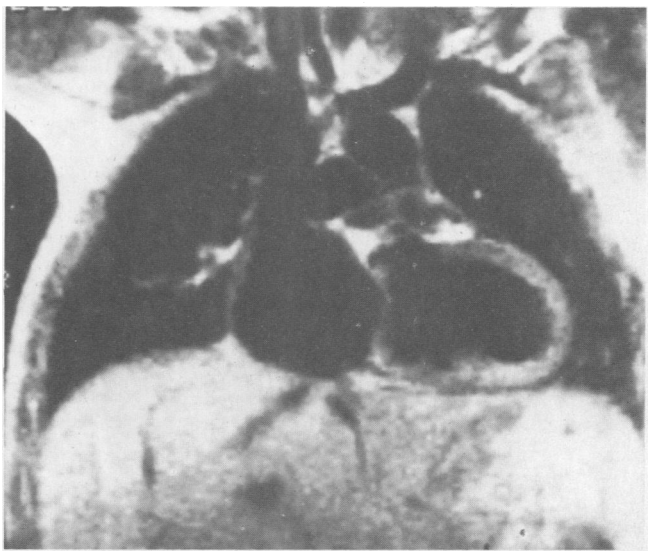

Figure 4.—A coronal image of the heart was obtained by synchronizing the radiofrequency pulses of the imager to the cardiac rhythm. Notice the high contrast between rapidly flowing blood in the heart and great vessels and the myocardium. This child has transposition of the aorta and pulmonary artery.

Certain applications of contrast media already familiar from our experience with x-ray techniques have been obviated by the intrinsic properties of MR imaging. For example, there appears to be little need for a myelographic contrast agent because we can define the subarachnoid space; cardiovascular anatomy can be easily depicted on MR imaging without an intravascular pharmaceutical (Figures 3 and 4).

Magnetic resonance intensity differences, as we have learned, reflect differences in tissue chemistry, which in turn affect T1, T2 and hydrogen density. Motion, as exemplified by rapidly flowing blood, also influences intensity. Yet none of these factors is directly related to tissue function. MR imaging contrast agents distributed on the basis of a particular tissue function would add an important new dimension to MR imaging diagnostic yield.

Familiar examples of function-dependent imaging tests include the intravenous urogram and the contrast-enhanced CT scan of the brain, the latter for assessing the blood-brain-barrier integrity. In parallel fashion, contrast-enhanced function-dependent studies have been shown for MR imaging. MR imaging contrast media injected intravenously can show renal functional abnormalities such as hydronephrosis, ischemia and congestion (Figure 5).[18] The same types of agents can also enhance the sites of blood-brain-barrier disruption.[19,20]

However, MR imaging contrast applications may be able to extend beyond these familiar radiographic applications. Possible applications might include functional assessments of pancreatic tissue, of the brain's metabolic pathways and of liver conjugation pathways. Combining the technologies of monoclonal antibodies and MR imaging contrast media may improve the detection and characterization of malignant lesions and other antigenically distinct pathologic lesions, an exciting possibility for MR imaging contrast investigation.

Mechanism of Paramagnetic Contrast Medium Enhancement

There are important differences between MR imaging contrast agents and iodinated contrast media. The principles of contrast enhancement differ. Radiographic contrast agents, having high electron density, absorb x-rays to produce their contrast effect. MR imaging contrast agents generally belong to a group of chemicals with strong paramagnetic properties; these function by altering local magnetic environments. Paramagnetic contrast agents are not observed directly on the images; rather, their magnetic effects on neighboring hydrogen nuclei are the means of contrast enhancement.[21,22]

All forms of matter possess magnetic properties, a fact described by Faraday in the 19th century. Paramagnetic substances are defined as those that are attracted toward and align with the stronger portion of a magnetic field but, unlike ferromagnetic substances, they return to a random orientation when the magnetic field is removed.[23] When placed in an external magnetic field, paramagnetic agents possess their own local magnetic fields that act as relaxation centers for other nuclei in their microenvironment (Figure 6). The local magnetic field of a paramagnetic molecule shortens the relaxation times of surrounding hydrogen nuclei, a phenomenon called "proton relaxation enhancement."[2] Proton relaxation enhancement shortens T1 and T2 values for neighboring hydrogen nuclei over a short range. This relaxation effect, dependent on the concentration of paramagnetic agents, causes a higher intensity MR signal.[14,21]

Substances are paramagnetic because they possess one or more fundamental particles—proton, neutron or electron—with a spin that is not canceled by another like particle with opposite spin.[23,24] Although there are numerous paramagnetic substances, only a relatively few deserve consideration as possible pharmaceuticals for MR imaging contrast en-

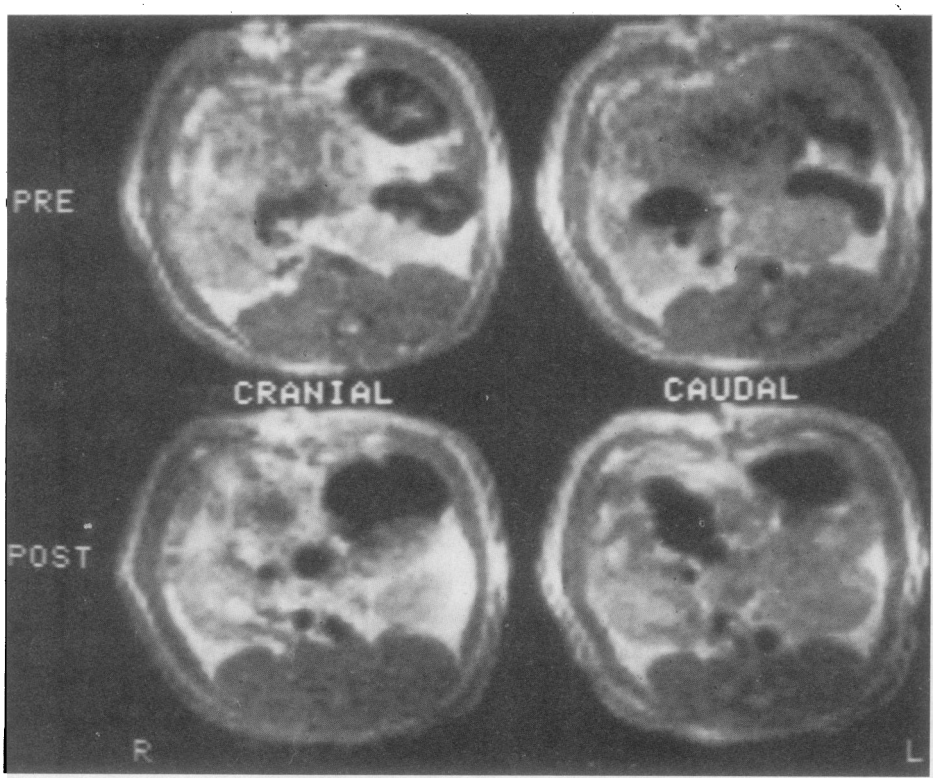

Figure 5.—Contrast-enhanced magnetic resonance images of a rat showing renal functional impairment. Spin-echo images of rat kidneys were obtained before and 15 minutes after administration of a nitroxide spin label (0.5 grams per kg). The precontrast images show equal intensities from the normal right and ischemic left kidney 4 hours after renal artery ligation. The postcontrast images show asymmetric enhancement with increased intensity on the right and no intensity change in the diseased left kidney. (From Brasch et al[18]; reproduced with permission from *Radiology.*)

hancement by virtue of being strongly paramagnetic and being well tolerated by animals. Additional requisites for a paramagnetic contrast agent include stability, wide availability, low cost and appropriate biodistribution and excretion. More than one MR imaging contrast agent, because of different biodistributions, may have clinical efficacy. Yet, all must have low toxicity in doses necessary to produce observable effects on MR images.

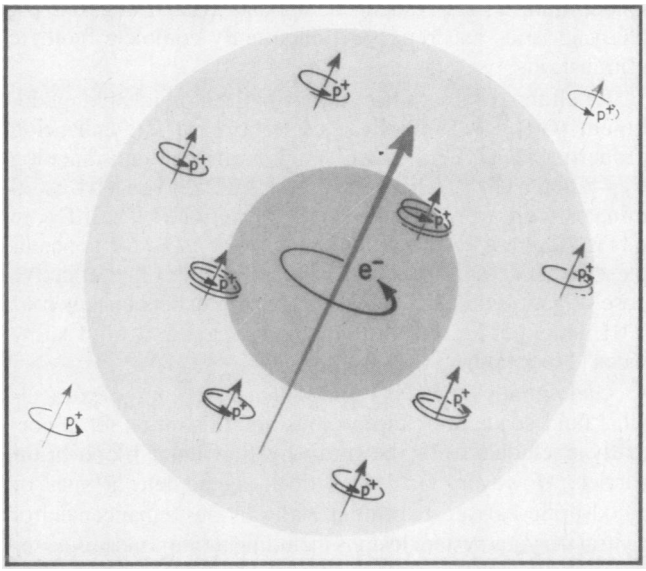

Figure 6.—Proton relaxation enhancement. This schematic of a molecule with a spinning, unpaired electron (symbolized by the large central arrow) depicts the local, microchemical effect (shaded area) of a paramagnetic substance on neighboring hydrogen nuclei (small arrows with unpaired protons). The paramagnetic molecule tends to enhance proton relaxation of nearby hydrogen nuclei and thereby shortens T1 and T2 values. (From Brasch[22]; reproduced with permission from *Radiology*.)

Transition Series Cations	Electron Distribution in 3d Orbitals	Spin Quantum Number
Vo^{+2}	$3d^1$	1/2
Ti^{+2}	$3d^2$	2/2
Cr^{+3}	$3d^3$	3/2
Cr^{+2}, Mn^{+3}	$3d^4$	4/2
Mn^{+2}, Fe^{+3}	$3d^5$	5/2
Fe^{+2}, Co^{+3}	$3d^6$	4/2
Co^{+2}, Ni^{+3}	$3d^7$	3/2
Ni^{+2}, Cu^{+3}	$3d^8$	2/2
Cu^{+2}	$3d^9$	1/2
Cu^{+1}	$3d^{10}$	0

Figure 7.—Electron subshell diagrams of first-transition-series ions are listed with the corresponding spin-quantum numbers. Unpaired electrons with uncanceled spins producing paramagnetic characteristics are shown with single arrows. Electron pairs with zero net spin are depicted by double arrows. Manganous ion (Mn^{+2}) and ferric ion (Fe^{+3}) both contain five unpaired electrons, giving a spin-quantum number of 5/2. Generally, the larger the number of unpaired electrons, the stronger the paramagnetic behavior.

The most powerful paramagnetic agents, and thus those with the greatest proton relaxation enhancement, are substances that contain unpaired electrons (Figure 7). The elements or ions of the periodic table with unpaired electrons are found in the transition series, such as manganese, iron and copper, and lanthanide series, such as gadolinium. A second group of strongly paramagnetic substances are the organic nitroxide stable free radicals, also known as nitroxide spin labels (NSL). These are synthetic organic chemicals that have been used in biomedical research for two decades.[25] Nitroxide spin labels, metals and metal complexes have all been tested as MR imaging contrast agents with some very promising results. Clinical trials using a complex of gadolinium and diethylenetriaminepentaacetic acid (DTPA) are already under way in Europe.[26,27]

Promising Paramagnetics for MR Imaging Contrast Enhancement

In 1978 Lauterbur and co-workers proposed the injection of paramagnetic agents in vivo to change MR imaging tissue contrast; they tried Mn^{+2} as a possible myocardial perfusion agent.[28] Although Mn^{+2} is still being considered for clinical application, the use of free metal ions in humans may be limited by their long retention in the body and a small margin between effective MR imaging dose and toxic dose.

Oral Agents

Although metal ions may not be ideal as intravenously given agents, oral Fe^{+3} (ferric) ions can be used with apparent safety as contrast enhancers for the gastrointestinal tract.[29] Most experts agree that a gastrointestinal contrast enhancer for MR imaging is essential to differentiate bowel from other abdominal structures; this necessity is familiar to those interpreting abdominal CT examinations. Ferric ammonium citrate is the major ingredient in Geritol and has been shown to be safe in a large population as a dietary supplement. A 500-ml dilute solution, 1 mmol, of ferric ammonium citrate has been used effectively for gastrointestinal contrast enhancement on MR imaging (Figure 8), the total dose being

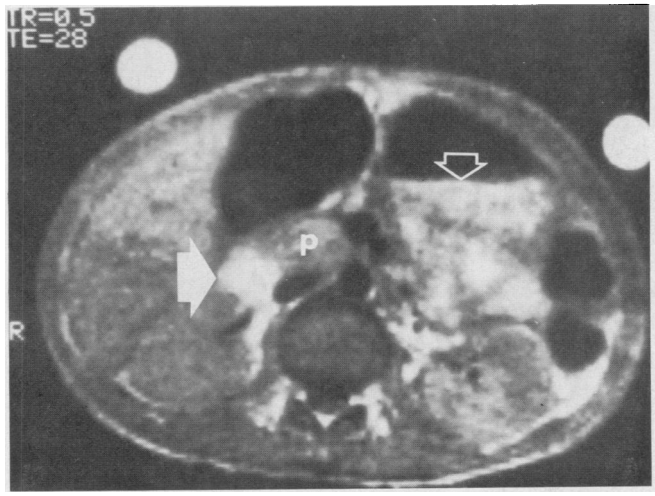

Figure 8.—A spin-echo image of the upper abdomen after oral ingestion of 500 ml of 1 mmol ferric ammonium citrate shows high intensity in the dependent portion of the stomach **(open arrow)** and in the duodenal sweep **(solid arrows)**. The contrast enhancement of the gastrointestinal tract helps to define retroperitoneal structures such as the pancreatic head **(p)**.

less than the usual daily recommended dose of Geritol. Orally administered iron may be the simplest and safest answer to the requirement for abdominal MR imaging; other nonabsorbed paramagnetic formulations may also be effective.[22]

Agents Given Intravenously

Nitroxide spin labels. Many successful MR imaging experiments using nitroxide spin labels have been carried out in our laboratory. The synthetic NSL compounds have increased the diagnostic efficacy of MR imaging for assessing renal function in animals, providing information not available without the use of paramagnetic pharmaceuticals. In animal models of renal artery (see Figure 5) and vein ligation, implanted renal cell carcinoma, unilateral hydronephrosis and acutely infarcted myocardium, enhanced relaxation rates using NSL have been shown.[18] Also, focal disruptions in the blood-brain barrier have been contrast enhanced by intravenously administering NSL.[19] These compounds do not breech the normal blood-brain barrier, but NSLs do accumulate at sites of disease where the barrier has been broken (Figure 9). The least effective diagnostic dose for NSL is less than 0.15 mmol per kg and the median lethal dose (LD_{50}) in rats is about 15 mmol per kg, suggesting a wide margin of safety. Nitroxide spin labels and their metabolites also showed no abnormalities in a sensitive assay of mutagenesis, the sister-chromatid exchange assay.[30] A potentially disadvantageous feature of current nitroxide spin labels is that they can be partially reduced in vivo to nonparamagnetic metabolites. New NSL derivatives with greater in vivo stability, better tolerance and greater relaxation effects are being sought before initiating clinical trials.

Metal complexes. Strongly paramagnetic but relatively toxic metal ions can be largely detoxified by complexation within various chelators. Metal-chelator complexes are being selected to retain strong paramagnetic characteristics but to favor a rapid and complete elimination of the metal from the body. A major challenge confronting the use of intravenously administered metal complexes in biologic systems is the potential for in vivo dissociation of the metal complex, freeing the relatively more toxic metal ion. Thus, selecting metal complexes with high formation constants (K_F) is mandatory. Gadolinium-DTPA is such a compound, with strong relaxing characteristics and rapid and apparently complete biologic elimination.[26]

Of all the paramagnetic cations in the atomic table, gadolinium (Gd^{+3}) has the strongest relaxation rate-enhancing properties. DTPA has a very high formation constant (log $K_F=22$) for Gd^{+3}. The half-life of Gd-DTPA in vivo is 20 minutes with a predominant renal excretion.[26] The LD_{50} in rats is 10 mmol per kg compared with the LD_{50} for noncomplexed gadolinium ions of 0.4 mmol per kg. The effective dose of gadolinium-DTPA for renal contrast enhancement is 0.01 mmol per kg or less, thus suggesting a very high safety index (1 to 1,000).

Gadolinium-DTPA is rapidly distributed in the extracellular fluid space after intravenous administration. It is normally excluded from the brain by the intact blood-brain barrier. However, Gd-DTPA does accumulate at sites of blood-brain-barrier disruption with obvious enhancement of central nervous system lesions including tumors and abscesses (Figure 10).[20,27] Urographic MR imaging experiments using gadolinium-DTPA indicate rapid, easily observable increases in renal parenchymal and renal pelvis signal intensities after intravenous administration of doses as low as 0.01 mmol per kg.[20] This same agent has been shown to be diagnostically

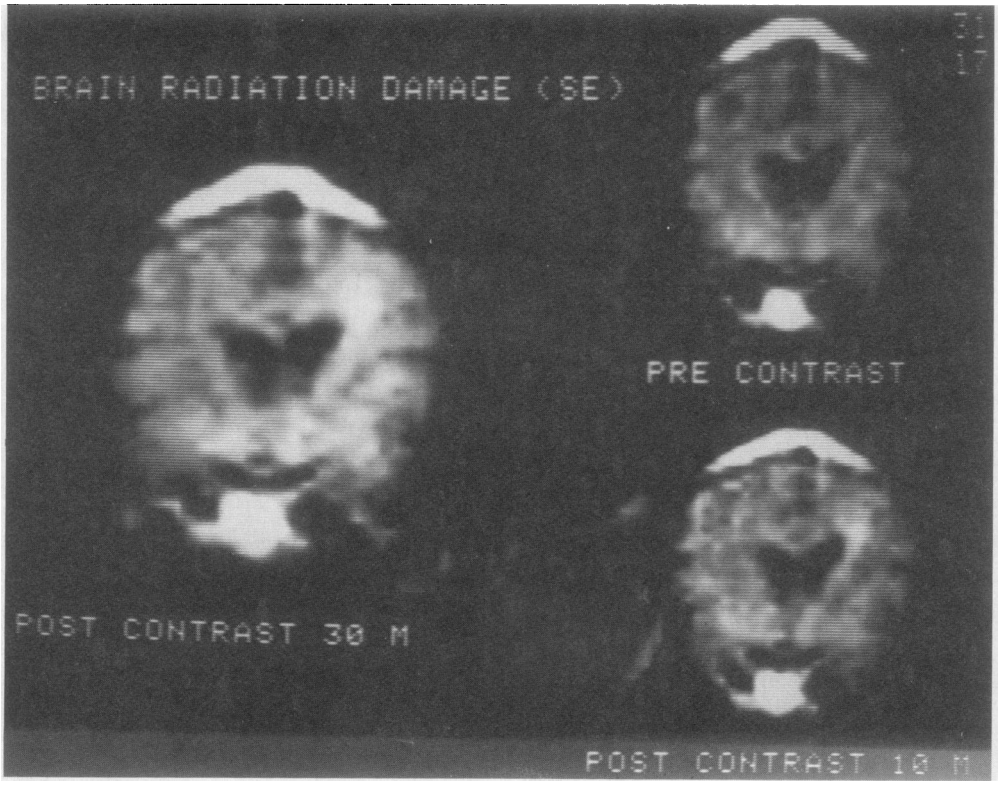

Figure 9.—Nitroxide spin label (NSL)-enhanced cerebral radiation damage. A series of magnetic resonance (MR) images of a dog having radiation-induced brain necrosis before contrast (upper right) and 10 minutes (lower right) and 30 minutes (left) after intravenous administration of NSL (9.9 grams per kg) shows greatly enhanced intensity at the site of brain necrosis. This isomagnetic focus of brain damage was not shown on nonenhanced MR images using pulse-interval times of 0.5 to 1.0 seconds and echo delay times of 28 and 56 ms.

useful in the MR imaging evaluation of sterile abscesses (Figure 11) and of canine myocardial ischemia.[16,20]

On the basis of available data, gadolinium-DTPA appears to be effective not only in experimental animals but in humans.[27] More than 50 patients have received this contrast agent in Europe with no evident toxicity and with striking contrast enhancement of various lesions.[27]

Conclusions

The ultimate role of pharmaceutical contrast enhancement in the MR imaging process is now uncertain, but the possibility of safe, useful agents seems very promising. The manner of administering contrast media is uncertain, in part because the limits of nonenhanced MR imaging are yet to be defined and technologic improvements are still rapidly evolving. However, it appears that contrast media may extend the diagnostic yield of MR imaging and thereby contribute to the general acceptance of this new technique. Accordingly, the development of MR imaging contrast media should parallel, rather than follow, the development of MR imaging instrumentation. Contrast enhancement may be particularly important if the contrast media can shorten the time required to produce with confidence either normal or abnormal imaging examinations. As with all medical decisions, the risk-to-benefit ratio for the use of MR imaging contrast agents will be pivotal.

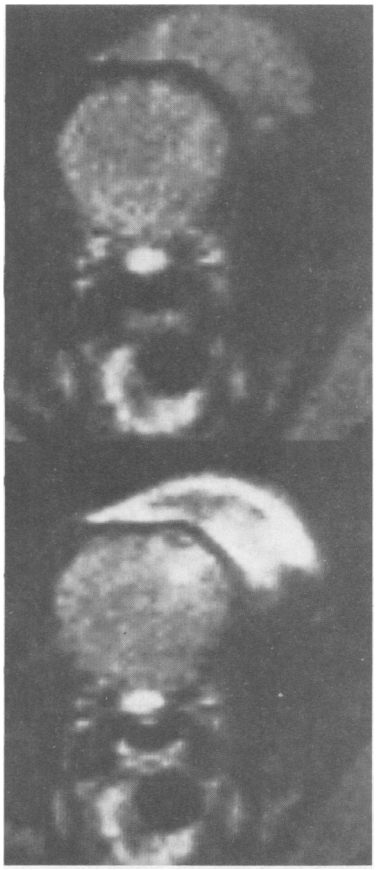

Figure 10.—Gadolinium-DTPA enhancement of canine radiation-induced necrosis and a surgical wound. Magnetic resonance images before (above) and 25 minutes after (below) intravenous administration of Gd-DTPA (0.5 mmol per kg) show pronounced contrast enhancement of both the surgical hematoma of the scalp and the intracerebral focus of necrosis. (From Brasch et al[20]; reprinted with permission from the *American Journal of Roentgenology.*)

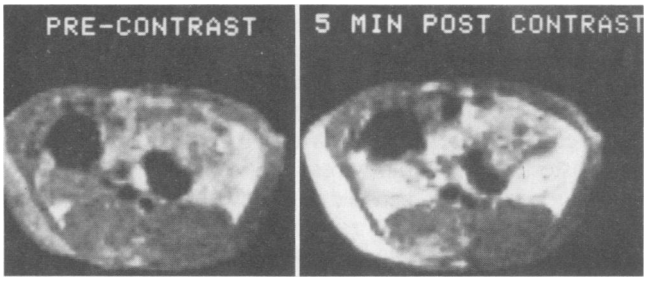

Figure 11.—Abscess and renal enhancement using gadolinium-DTPA. Magnetic resonance images of a rat before and after intravenous administration of Gd-DTPA (0.1 mmol per kg) shows substantial intensity increases in a sterile right flank abscess and in the kidneys due to the local accumulation of the paramagnetic complex. (From Brasch[20]; reprinted with permission from the *American Journal of Roentgenology.*)

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