

6-1985

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### Recommended Citation

Froelich, Jerry W.; Hearshen, David O.; Halpert, Robert D.; and Patel, Suresh (1985) "Nuclear Magnetic Resonance: Current and Future Clinical Applications," *Henry Ford Hospital Medical Journal* : Vol. 33 : No. 2 , 122-127.

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## Nuclear Magnetic Resonance: Current and Future Clinical Applications

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*Nuclear magnetic resonance has evolved from a laboratory analytical tool to become a rapidly developing discipline in clinical medicine. We present a brief historical overview, an introduction to the basic principles of the phenomenon, and a statement of the current status of clinical imaging.*

Over the past decade, significant technological developments and clinical interest in applying nuclear magnetic resonance (NMR) techniques to in vivo spectroscopy and imaging have occurred. The technical hurdles that once prevented placement of whole human bodies within magnets have been overcome, and clinical data are becoming available to help assess the role of nuclear magnetic resonance imaging (NMRI) in clinical practice. The clinical use of NMR spectroscopy (NMRS) is lagging slightly behind that of NMRI, and at present its application appears limited. Following is a terse introduction to the basic principles of NMR as applied to clinical medicine.

Traditional and laboratory NMR studies involve the quantitative analysis of spectral data from such nuclei as <sup>1</sup>H, <sup>13</sup>C, <sup>19</sup>F, <sup>23</sup>Na, and <sup>31</sup>P. Quantitative techniques yield information regarding the chemical environment of the nuclei of interest, and thus help to determine the structure and function of the molecules of interest. In addition to analysis of spectral data, NMR techniques are available for measuring relaxation parameters (T1 and T2) that follow excitation; these also provide data about the chemical environment and mobility of nuclei but, in vivo, do not provide precise information regarding molecular structure. In 1971, Damadian (1) reported that various neoplastic tissues analyzed in the laboratory NMR spectrometer had prolonged T1 and T2 relaxation times as compared with those of matched normal tissues. These data acted as a catalyst for the development of in vivo NMR analysis to evaluate neoplastic tissues, with the hope that neoplastic tissues, could be distinguished purely on the basis of NMR data (1,2).

In 1973 Lauterbur produced an image of biological tissue using NMR principles (3). Following his initial description, considerable individual and corporate efforts have been made to facilitate whole body NMRI.

NMR in medicine has diverged into two separate pathways: imaging and spectroscopy. Initially, this divergence came about because of the different equipment requirements for imaging and spectroscopy. As the technology advances, however, the two pathways will most likely converge and

*We have elected to use the traditional terminology **nuclear magnetic resonance** to refer to the imaging component of the field rather than the American College of Radiology (ACR) modification **magnetic resonance**. We do this out of respect for the founders of the field.*

yield a single system capable of producing high-quality images as well as spectroscopic data.

Spectroscopic studies have centered on in vivo metabolism, primarily <sup>31</sup>P spectroscopy. The <sup>31</sup>P spectra can be used as metabolic markers of the status of adenosine triphosphate (ATP), phosphocreatine, and free phosphates within tissues. The quantitative nature of NMRS provides precise insight into tissue metabolism; as tissues become hypoxic, there is reduction in ATP and phosphocreatine with a corresponding increase in free phosphates (4).

Since the amount of phosphate signal within the body is several orders of magnitude less than that of protons, there is considerable interest in proton spectroscopy. Early work suggests that lactic acid levels and intracellular pH can be measured in vivo, but to date the data are only suggestive, and we must await further work before we know if there is clinical utility in analysis of proton spectra.

NMR images have primarily been of the proton (<sup>1</sup>H) because of its large magnetic susceptibility and its natural abundance. High-quality images based on proton density and T1 and T2 behavior can be obtained.

### Basic Principles

It is useful to conceptualize the structure of an atom as a nucleus around which electrons rotate. Just as the planets rotate around the sun, we can visualize both the electron

Submitted for publication: March 15, 1985

Accepted for publication: June 18, 1985

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and the nucleus rotating around an axis. Since all nuclei are positively charged and all moving charges produce an electric current that in turn creates magnetization, the nucleus behaves as a tiny bar magnet situated in the center of the atom. All nuclei behave as tiny bar magnets, but for our purposes we will limit the discussion to the proton ( $^1\text{H}$ ).

While this conceptualization is useful and most imaging and spectroscopic principles can be explained in terms of this classic picture, the fundamental basis of NMR is quantum mechanical. Some of the principles discussed below (that the proton is either "parallel" or "antiparallel" to the external magnetic field, for instance) can only be fully explained in terms of quantum mechanics (5,6). Nevertheless, we retain this conceptualization for its simplicity and its surprising accuracy in predicting the outcome of imaging or spectroscopic techniques.

A spinning proton behaves like a small magnet with theoretical north and south poles, and it has a property called a *magnetic moment*. The magnetic moment is a vector quantity pointing along the axis of rotation of the nucleus. Before placing protons in magnetic fields, the magnetic moments are oriented in random directions (the sum of the individual magnetic moments is equal to zero). When protons are placed in an external magnetic field, their magnetic moments orient themselves either parallel or antiparallel to the applied magnetic field. The protons do not precisely align themselves along the magnetic field, but rather precess around an axis that is parallel to the external field. The frequency of precession is called the Larmor or resonance frequency. The resonance frequency is proportional to the strength of the external magnetic field times a constant, the gyromagnetic ratio, which is unique for each type of nucleus.

The NMR experiment requires placing the proton in an external magnetic field and then applying a radiofrequency (RF) magnetic field perpendicular to the external magnetic field. This RF magnetic field is oscillating at the resonance frequency of the nuclei of interest. As the RF field is applied, the proton absorbs the energy and changes orientation relative to the external field. After the RF pulse is removed, the proton will again realign itself with the external magnetic field emitting the energy absorbed. A small antenna receives the emitted energy, and the strength of this signal is proportional to the nuclear density and the rate of realignment (relaxation times  $T_1$  and  $T_2$ ).

The imaging experiment is a variant of the traditional NMR experiment as described above. In 1973, Lauterbur (3) was able to obtain information on the distribution of protons within an object by superimposing over the static external magnetic field another field that varied linearly across the region of interest. The total external field was thus comprised of a large static field plus a small magnetic field whose direction was parallel to the static field but whose magnitude varied linearly in one direction in space (Fig 1).

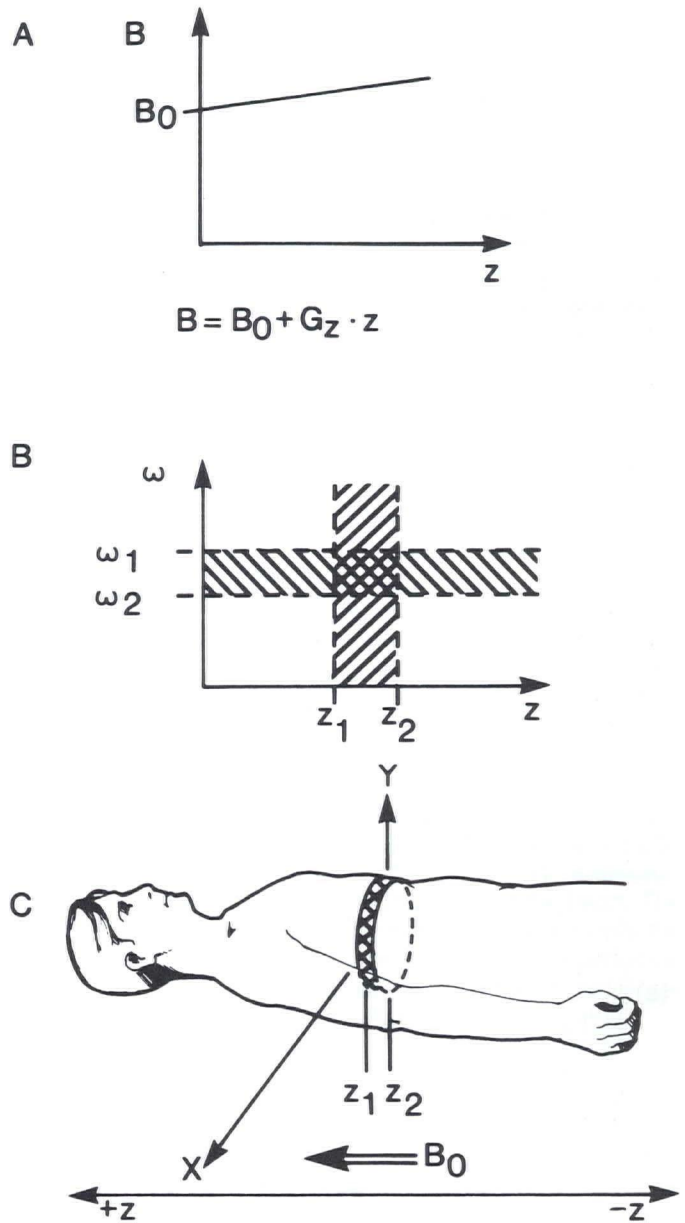


Fig 1

Plane definition using selected irradiation (narrow bandwidth) in presence of section selecting gradient. Total magnetic field,  $B$ , as function of  $Z$  for static gradient,  $G_z$  (Part A). The  $Z$  gradient is constructed such that field produced varies linearly over a specified region in space with slope  $G_z$  and intercept  $B_0$ . The incident RF, with bandwidth of which endpoints were  $\omega_1$  and  $\omega_2$ , specifies range of possible resonance frequencies (Part B). From the Larmor equation, these frequencies define set of magnetic fields, which in turn (Part A), define range of  $z$  coordinates for imaging. Typical axial section is shown in standard configuration for superconducting solenoidal type magnet (Part C). Axis of the magnet's cylinder is parallel to  $Z$  axis. Since gradients are controlled electronically, it is possible to define plane at any orientation.



The characteristic resonance frequency of a proton is directly proportional to the *total* external magnetic field; the gradient field will produce a one-to-one correspondence between resonance frequency and spatial location along the gradient direction. This principle can be used to produce a cross-sectional image in the following way: the RF energy is *transmitted* with a small bandwidth in the presence of a gradient. This defines a planar slab within the object in which all protons resonate at approximately the same frequency (Fig 1). Protons outside this slab will not satisfy the Larmor equation and will not absorb any RF energy. Analysis of the amplitudes of each frequency component of the *emitted* signal in the presence of a gradient perpendicular to the first gives information about the amount and spatial distribution of protons in *one dimension* in the plane (Figs 2,3). In other words, the NMR signal at each frequency becomes a one-dimensional projection of the spatial distribution of magnetic nuclei within an object. By changing the direction of the gradient relative to the object and obtaining multiple additional projections, a reconstruction technique similar to X-ray CT reconstruction will then produce a two-dimensional image.

Since Lauterbur's initial description, there have been considerable refinements and additions to techniques for obtaining NMR images. The projection reconstruction technique described above has been largely supplanted by the spin-warp or two-dimensional Fourier transformation technique (7), a description of which is beyond the scope of this paper. The advantages of the two-dimensional Fourier transformation technique over projection reconstruction appear to be a better signal-to-noise ratio, less susceptibility to magnetic field inhomogeneities and other artifacts, and the use of a Cartesian rather than a polar coordinate system for reconstruction (7).

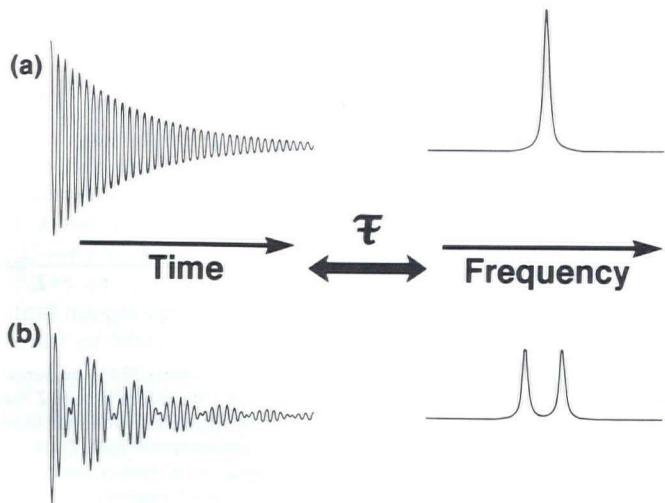


Fig 2  
Free induction decay and its frequency domain analog for single frequency (a) and two different frequencies (b). The time varying NMR signal is resolved into its frequency components by Fourier transform. (Reproduced with permission from General Electric Company, March, 1985.)

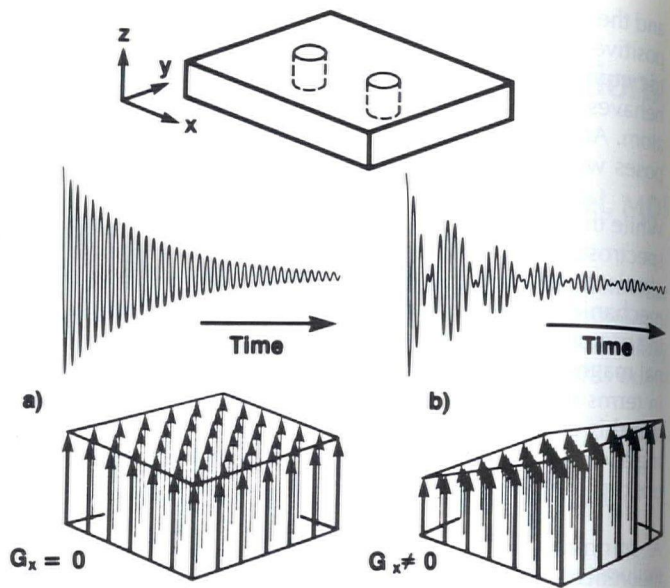


Fig 3  
Using Fourier transforms, two identical samples with different X coordinates can be distinguished. In absence of field gradient ( $G_x = G_y = G_z = 0$ ) both samples sense same field; free induction decay consists of single frequency (a). In presence of gradient  $G_x$  two samples sense different fields, resulting in free induction signal consisting of two frequencies (b). (Reproduced with permission from General Electric Company, March, 1985.)

## Clinical NMR

### Neurological imaging

From published reports (8,9), it is increasingly clear that NMRI is at least equal to and even superior to CT in the detection and characterization of various disease entities of the central nervous system (CNS).

In the supratentorial cranial space, NMR appears superior to CT in imaging those diseases that cause alterations in the cellular environments of CNS tissues. Examples include multiple sclerosis, demyelinating diseases, some primary and secondary tumors, inflammation, vascular lesions, and some metabolic and congenital conditions.

In the evaluation of the posterior fossa and spinal cord, the superiority of NMR over CT and myelography is augmented by the absence of dense bone artifacts on NMR images and the capacity of NMR to visualize anatomy and disease in different planes.

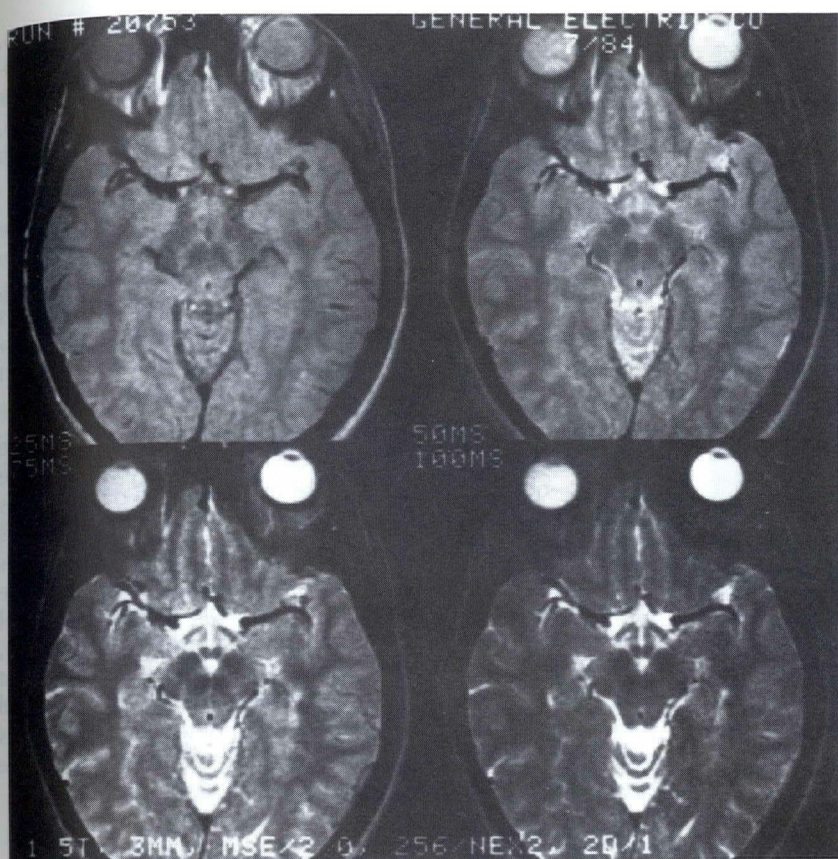
The limitations of NMRI, including its inability to distinguish acute from old hemorrhage, render NMRI ineffective in the evaluation of acute trauma, possible cases of acute hemorrhage from rupture of an aneurysm or arteriovenous malformation, and cases of hemorrhagic infarcts and tumors.

The inability to detect fine calcification hinders NMRI from providing information that could assist in diagnosis of meningioma, craniopharyngiomas, tuberous sclerosis, and other



calcified alterations that can be difficult to detect as tumors. In the evaluation of the posterior fossa and spinal cord, the superiority of NMR over CT and myelography is augmented by the absence of dense bone artifacts on NMR images and the capacity of NMR to visualize anatomy and disease in different planes. Figures 4 show techniques at different Cardiac NMRI of through the dial tissue of data d





**Fig 4**  
 Multispin echo transaxial sequence through middle of brain. Four echo images were obtained at 25 msec, 50 msec, and 100 msec. Image demonstrates superior discrimination of gray and white matter and ability of NMRI techniques to change imaging properties of tissues based on different pulse sequences. Images were obtained at 1.5-T on GE Signa System. (Reproduced with permission from General Electric Company, March, 1985.)

calcified lesions. Also, the extreme sensitivity of NMR to alterations of tissue composition may produce strong signals that can hide subtle lesions or blur the margins of normal tissue on NMR images. This is the case where edema is difficult to differentiate from adjacent disease conditions such as tumors. Contrast agents used in NMRI might solve this problem in the future.

In the evaluation of the spinal cord, NMR appears to be superior to CT due to the absence of bone artifacts on images, the ability to image in different planes, and elimination of potential toxic contrast agents used in myelography. NMRI is superior to CT in evaluation of syringomyelia, hydromyelia, spinal cord tumors, congenital conditions such as spinal dysraphism, degenerative disks, cervical myelography, and trauma.

Figures 4 and 5 demonstrate the excellent discrimination between gray and white matter achieved using NMRI techniques and the versatility of NMR for obtaining images in different planes.

**Cardiac imaging**

NMRI of the heart shows early promise since blood flowing through the chambers of the heart is discernible from myocardial tissues. Cardiac gating techniques that allow collection of data during systole and diastole are being developed. In

addition to gating, NMR images can be obtained in a multitude of angles and planes. Thus, images can be obtained orthogonal to as well as along the long axis of the heart. The combination of these image planes may allow not only the discerning of wall motion but, potentially, tissue perfusion characteristics when combined with different pulse sequences and contrast media (10,11).

**Thoracic imaging**

CT of the thorax is superior to NMRI because of its spatial resolution and rapid imaging properties. These characteristics make assessment of small pulmonary tumors and mediastinal masses both rapid and accurate. Currently NMRI suffers from motion artifacts secondary to respiration and pulsatile blood flow. At times, NMR images may be superior to CT scans, particularly when it is essential to visualize vessels as separate from soft-tissue masses within the mediastinum. Additionally, in pediatric patients the lack of ionizing radiation may make NMRI the technique of choice for evaluation of the superior mediastinum.

**Abdominal and pelvic imaging**

At present, NMRI of the upper abdomen is hindered by respiratory artifacts, inability to distinguish bowel loops from other tissues, and spatial resolution lower than that of CT.



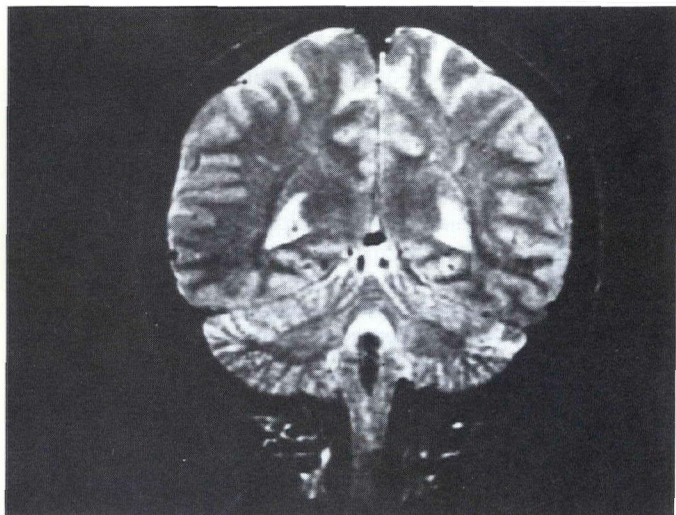


Fig 5

Single coronal image from spin echo sequence through middle portion of cerebrum and cerebellum. Note superior discrimination of gray and white matter and ability to evaluate cerebellum and spinal cord. Images obtained on 1.5-T GE Signa magnetic resonance imaging device. (Reproduced with permission from General Electric Company, March, 1985.)

NMR examination of the pelvis appears to provide images superior to those of other modalities, because NMR is able to offer soft-tissue discrimination and has the ability to image in coronal and sagittal planes. Early clinical data suggest that NMR is superior to other modalities in the staging of prostate tumors (8,12).

#### Musculoskeletal imaging

NMR is superior to CT in evaluation of the musculoskeletal system in patients who have tumor, infection, or trauma. In particular, NMRI appears to be ideal for noninvasive evaluation of tendons, ligaments, and muscular injuries (8,9,13).

#### Renal imaging

Where respiratory artifacts can be corrected, NMR is superior to CT in its ability to distinguish soft tissues, identify masses, identify inflammatory processes, and to image in sagittal and coronal planes. The ability to distinguish soft tissues without the use of contrast media increases its superiority over contrast-enhanced CT scanning.

#### Miscellaneous

A number of other body regions can be evaluated with NMR. The ability to obtain coronal and sagittal images within the neck suggests the superiority of NMRI for staging tumors in this region.

Obtaining NMR images near prosthetic devices does not appear to pose any danger to the patient, and it allows imaging in areas where significant artifacts occur on CT scans. Exceptions to this include neurovascular clips and cardiac pacemakers.

#### In vivo spectroscopy

In vivo spectroscopy implies the analysis of selected nuclei

to identify cellular and metabolic activity in intact systems. The quantitative nature of NMR makes it ideal for determining concentrations of intracellular metabolites and their change with various conditions (ie, ischemia). In addition, intracellular and extracellular pH can be measured through the chemical shift of the inorganic phosphate peak.

Phosphorus-31 is by far the most widely used nucleus since it is the key spectroscopic component of ATP, adenosine diphosphate (ADP), inorganic phosphate, creatine phosphate, and sugar phosphates. The NMR sensitivity for phosphorus is high, and  $^{31}\text{P}$  is naturally abundant. The signal from protons is considerably greater than the signal from  $^{31}\text{P}$ , but it does not lend itself to evaluation of cellular metabolites.

Because the concentration of atoms must be greater than one millimole to be observed by NMR spectroscopy, the type of studies that can be performed is limited. To date, studies have used surface coil probes for measuring  $^{31}\text{P}$  metabolites over multicubic centimeter volumes (ie, large muscle groups of the upper or lower extremities, portions of the brain). These techniques have also limited the field of view to superficial structures as well as to gross anatomical regions (ie, kidney, hemispheres of the brain). Developments are underway that will allow the probing of structures that are not superficial (brain stem, heart, liver, etc). A number of technical problems must be resolved and physical limitations overcome before spectroscopy becomes a clinical tool (14-17).

#### Future

To date, tissue characterization that permits separation of malignant from nonmalignant tissues has not been performed in vivo. National Institutes of Health studies are underway to achieve a better understanding of tissue-relaxation parameters in the hope of being able to characterize tissues. Currently, the literature is littered with discussions of T1 and T2 relaxation times of pathologic conditions, but there is considerable variability between institutions, and no statistical information supports the clinical applicability of any reported findings.

The future holds the potential for a number of technological improvements. Surface coil techniques will allow higher resolution images over selected regions and will offer the ability to obtain spectroscopic information. Respiratory and cardiac gating will be further refined, thus minimizing respiratory and flow artifacts and improving image resolution. Further evaluation of various pulse sequences must be performed to determine the optimal sequence for specific pathologic conditions. The development of paramagnetic contrast media to define anatomical structures and perhaps tissue properties such as perfusion and metabolism is hoped for. Perhaps the most significant contribution that the field is awaiting is the determination of the clinical efficacy and the exact role of NMRI in clinical practice, established by well-controlled studies.

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