3.
Clinical Applications of NMR

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INTRODUCTION

When a new imaging modality is evolving as rapidly as NMR imaging, it is impossible to publish a review that accurately describes the "current status" of its clinical use, By the time such a review is published, it is out of date. Therefore, the goals of this chapter are: to provide a "snapshot" view of the state of the clinical applications of NMR in mid-1983 and to attempt to put the current status of various clinical applications into perspective, highlighting current limitations as well as advantages and distinguishing between potential applications and those that have been demonstrated with scientific rigor. More detailed clinical reviews are available (see, for example, 27,86,125,137,142,148,166) .

The first section in the chapter provides a brief overview of potential biological hazards of NMR. The rest of the chapter is organized around the three clinical applications of NMR in which the most research had been performed as of this writing: 1) imaging of protons to assess normal and abnormal structure, metabolic processes, and fluid flow; 2) use of proton relaxation times[1] in the diagnosis of disease; and 3) use of the chemical shift phenomenon to assess biochemical processes in vivo (in vivo spectroscopy).[2]

The second section provides a clinical overview of proton (hydrogen) imaging, briefly summarizing results of research on proton imaging of the brain, mediastinum, hilum, lung, heart, breast, abdomen, kidneys, pelvis, musculoskeletal system, clinical oncology, and blood vessels. Readers without clinical background may wish to skip the second section and proceed directly to the third section *(Putting Proton NMR Imaging Into Perspective),* which discusses the advantages and disadvantages of NMR imaging and addresses a number of clinical and practical issues which help put the status of proton imaging into perspective, Section 4 *(Relaxation Parameters)* provides a brief overview of research relating to the clinical use of measurements of proton relaxation times. Again, readers without clinical or scientific background may want to skip this section and proceed directly to section 5 *(Putting T_1 and T_2 Relaxation Times Into Perspective),* which discusses the conclusions to be drawn from the research described in section 4. Finally, sections 6 and 7 briefly address in vivo spectroscopy. Non-scientists may wish to read only section 7, which attempts to place the current status of in vivo spectroscopy into perspective.

'These relaxation times are estimated from NMR images.

'Imaging of nuclei other than hydrogen, such as sodium or phosphorus, has recently been accomplished, but is not included in this list. A discussion of the accumulated experience with such imaging is beyond the scope of this case study.

POTENTIAL BIOLOGICAL HAZARDS OF NMR

One of the primary advantages of NMR imaging is that it does not employ X-rays. Although there is thus no safety concern regarding X-irradiation with NMR imaging, concern has arisen regarding other potential hazards associated with use of NMR.

NMR safety concerns have focused on three NMR parameters: 1) time-varying magnetic fields, 2) radiofrequency electromagnetic fields, and 3) static magnetic fields.

Although the possibility exists that time-varying magnetic fields could induce electric currents that could cause ventricular fibrillation, cardiac arrest, inhibition of respiration, or tetanization (sustained muscular contraction), none of these potential adverse effects has been observed in over **2,000**

NMR studies performed in England (179). Nor have significant problems relating to local heating induced by radiofrequency pulses, or pathological, developmental, genetic, or behavioral hazards caused by prolonged exposure to static NMR fields been observed (161). In fact, the only complications reported at a July 1983 FDA Radiologic Devices Panel meeting by Professor Robert Steiner, of Hammersmith Hospital, London, in his discussion of the British NMR studies, were that one baby had vomited and aspirated during positioning in the NMR scanner and that 3 percent of the subjects had opted out of having an NMR scan secondary to development of a feeling of claustrophobia when positioned in the magnet. Other centers have reported claustrophobic feelings in 1 percent of subjects (147).

Potential nonbiological hazards include projectiles of metallic objects in the vicinity of NMR magnets and damage to computer tape or other objects in the surrounding environment.

The unblemished NMR safety record is perhaps related to the extreme caution that has been exercised by clinical researchers working with NMR. Researchers have, for example, tended to exclude from their studies patients in whom cardiac pacemakers, large pieces of metal (such as an artificial hip), metallic cranial aneurysm clips, or metallic intrauterine devices have been implanted. Pregnant women have also tended to be excluded. It is possible that these restrictions will be relaxed in the future. For now, however, no harmful effects have been associated with NMR imaging under existing conditions of use.

In 1980, Great Britain's National Radiological Protection Board (NRPB) issued interim safety guidelines pertaining to NMR imaging of humans (table 1); revised guidelines are expected to be published soon. In 1982, the U.S. Food and Drug Administration (FDA) also issued guidelines, but FDA's guidelines were intended only to assist Institutional Review Boards in making decisions regarding what constituted "significant risk. "

Table 1 .—Suggested Guidelines for Safe Operation of NMR Imagers

	National Radiological Protection Board (U. K.) 1980[a]	Bureau of Radiological Health (FDA) (USA) 1982[bc]
Static magnet field (tesla) (whole or partial body exposure)	<2.5 T	<2 T
Time-varying magnetic fields (whole or partial body exposure)	<20 T/sec for pulses for > 10 msec	<3 T/see
Radiofrequency electromagnetic fields	<15 MHz (<70 w average power absorbed)	< 0.4 W/kg[d] averaged over whole body; <2 W/kg over any one gram of tissue

[a] R.D. Saunders and J S. Orr, "Biologic Effects of NM R," in *Nuclear Magnetic Resonance (NMR) Imaging*, C L Partain, A. E James, F. D. Rollo, et al. (eds) (Philadelphia: W. B Saunders, 1983).

[b] W. E Gundaker, *Guidelines for Evaluating Electromagnetic Risk for Trials of Clinical NMR Systems,* FDA Bureau of Radiological Health, Division of Compliance, Feb. 25, 1982

[c] The NRPB guidelines specify upper limits that must not be exceeded. The FDA guidelines, in contrast, are intended to serve as an aid for Institutional Review Boards making determinations of what constitutes "significant risk" under an Investigational Device Exemption. Thus, the FDA does not prohibit use of NMR imagers that operate outside these recommendations

[d] Average specific absorption rate rather than fixed frequency.

Some attempts are underway to maintain records of individuals who have undergone NMR imaging studies so that they can be contacted in the future. The NRPB is collating this type of exposure record, and the NMR Commission of the American College of Radiology has distributed patient data forms that are to be completed each time a patient undergoes an NMR imaging study. It would be advisable to establish uniform guidelines for collection of this type of data worldwide, at least for the near future. Who should be responsible for collecting and maintaining such data and who should bear the expense need to be determined. In addition, patient confidentiality issues need to be resolved.

PROTON IMAGING: A CLINICAL OVERVIEW

Brain

Thus far, the widest and most efficacious use of clinical proton NMR imaging has been for the brain and central nervous system. NMR's prowess in demonstrating the anatomy of the central nervous system derives in large part from two facts. First, although the proton density in the gray and white matter of the brain is approximately equal, gray matter contains approximately 15 percent more water than white matter. This difference in the chemical environment in which gray and white matter protons exist, which is reflected in differences in the T_1 relaxation time of gray and white matter, results in a significant level of gray versus white matter contrast in NMR images **(30,52).** This differentiation is much more striking with NMR imaging than with X-ray computed tomography (CT) because X-ray CT's linear attenuation coefficient for gray matter is only slightly different from that for white matter **(24).** Second, because cortical bone has a very low NMR signal strength, it is possible to image with NMR areas such as the posterior fossa, brain stem, and spinal cord that are not well seen by CT because the skull and vertebrae are impervious to the X-rays used in CT **(136).** In work done in Aberdeen, Scotland **(166) and** at Hammersmith Hospital in England **(30),** for example, NMR has produced clear images of the cerebellum and brain stem, and has demonstrated brain stem hemorrhages and cerebella tumors not seen with CT.

NMR also appears to be more sensitive than X-ray CT to the demyelinating lesions that occur in multiple sclerosis *(207).*

In a report on cranial NMR scans performed on *140* patients with a broad spectrum of neurologic diseases and on 13 healthy volunteers, Bydder, et al., demonstrated NMR's ability to detect tumors, hemorrhages, infarctions, and ventricular size (30). It remains to be seen whether NMR will be superior to X-ray CT in demonstrating these types of pathologies in areas of the brain other than the posterior fossa and brain stem.

One final interesting central nervous system application of NMR is the study of brain development. Researchers at Aberdeen and Hammersmith, for example, have begun to explore the time course of myelination in newborns (166,178). Given the presumed safety of NMR imaging, further studies can be anticipated.

Mediastinum, Hilum, and Lung

Although recent evaluations of NMR imaging of the thorax suggest that the technique may prove useful in assessing mediastinal, hilar (referring to the anatomic area where the bronchus blood vessels, nerves, and lymphatic enter or leave the lung), and lung abnormalities **(71,166), the data** are still insufficient for comparing the efficacy of NMR with other imaging techniques in evaluating these structures. The possibility exists that variations in the T_1 relaxation time between blood and soft tissues might permit clinically useful discriminations between blood, fat, and hilar tumors to be made without use of intravenous contrast materials. Clinical trials are necessary, however, to assess the sensitivity and specificity of NMR imaging in these applications. Early work at Aberdeen suggests that some peripheral lung tumors may not be so well seen with NMR as with X-ray CT **(166).** If this proves to be the case, clinicians might use X-ray CT to evaluate lung parenchyma and NMR to evaluate the hilum. Finally, the possibility of exploiting differences in relaxation times between flowing, static, and clotted blood suggests that NMR might be used to diagnose pulmonary emboli. Respiratory gating (a technique in which image acquisition is coordinated with the breathing cycle) may improve the diagnostic quality of all types of NMR studies of the lung.

Heart

Researchers have begun investigating the potential for using NMR to produce tomographic images of the heart muscle, chambers, and valvular structures **(27,43,56,83,142).** Although the spatial resolution in images of the heart obtained to date is crude compared to that of images of the brain, advances in cardiac imaging are being made as techniques for gating of images to the electrocardiogram are developed (114) and refinements

are made in the application of high-speed imaging techniques (such as the echo-planar technique—a particular type of NMR imaging in which an image of a plane is obtained from an excitation pulse) (124) to visualization of the beating heart (27,142). Although NMR tomographic imaging of the anatomical structures of the heart must for now be considered experimental, evidence is accumulating that NMR may emerge as the modality of choice in the imaging of certain structures. (See, for example (176), relating to imaging the pericardium with NMR versus X-ray CT.)

Another potential cardiac application of proton NMR imaging is discrimination between infarcted, ischemic, and normal myocardium (27,142). In early work performed at Massachusetts General Hospital, researchers were able to distinguish ischemic from non-ischemic canine myocardium with, but not without, use of a paramagnetic (a substance with a small but positive magnetic susceptibility (magnetizability) that may increase the contrast between tissues and NMR images) **(4)** contrast agent *(76).* Although manganese, the contrast agent used, may be too toxic to be used in humans, other less toxic paramagnetic agents might be developed *(23,76).* More recently, investigators at the Massachusetts General Hospital have used anti-myosin (antibodies directed against myosin, a component of muscle) monoclinal antibodies labeled with manganese and injected into the coronary arteries to visualize acutely infarcted myocardium in dogs (110). Finally, researchers at the University of California at San Francisco have been able to distinguish in vivo between normal tissue and experimentally induced infarcts in the lower extremities of rats within 24 hours of infarction (89). Further research needs to be performed before the implications of these findings to the diagnosis of myocardial ischemia and infarction in humans can be determined.

Breast

Ross, et al., reported on a series of NMR scans of *128* breasts examined in *65* patients (155). Scans were obtained using a magnetic field strength of 0.045 T. The investigators found that although normal breast tissue could often be distinguished from abnormal breast tissue, there was some difficulty in localizing abnormalities, as well as some degree of overlap of T_1 values obtained from benign and malignant breast tissues. The latter may limit NMR's diagnostic efficacy in this application.

Ross, et al., also cited the prolonged time required to do an NMR breast scan as a possible limitation of the technique (at a relatively low magnetic field strength). In Ross' study, the average total examination time per patient was 1 hour. Pairs of transverse sections of the breasts were produced in 10 minutes; T_1 measurements were made in 6 minutes. The average total examination time per patient exceeds the time required to produce individual transverse sections because images of several sections are used in the process of completing a patient examination.

Yousef, et al., employing a 0.3 T superconducting magnet, recently reported experience with NMR imaging of two patients with breast abnormalities (58). Three-dimensional NMR images in one case and single-slice planar images (images taken through a single plane) in the other correlated well with mammograms performed in the same patients. The authors suggest that NMR imaging may prove useful as a noninvasive probe of breast lesions, but acknowledge that it is premature to predict the efficacy of NMR in the assessment of human breast disease **(58).**

Abdomen

Although the T_1 values of the major abdominal organs are sufficiently specific to make recognition of those organs relatively easy with proton NMR imaging, there may not be sufficient difference between the values in normal and diseased states to permit pathologic diagnoses to be made with a high degree of accuracy (166). Results of small clinical series of NMR imaging of the liver (53,132,167) and pancreas (169,175) have been reported, but further comparative studies need to be performed before the clinical utility of NMR imaging of space-occupying lesions in the abdomen can be defined.

There is some indication that metabolic liver disease may also be amenable to evaluation by hydrogen NMR imaging techniques. NMR can be

used to measure liver iron overload in patients with hemochromatosis (173), for example, and to demonstrate focal areas of inflammation in patients with chronic active hepatitis (174).

Kidneys

Although several studies of proton NMR imaging of the kidney have been reported (98,118, 168,170), NMR investigations of the anatomy and function of the kidneys must be considered experimental at this time. The possibility of distinguishing between renal cortex and medulla with NMR *(98)* has been demonstrated, but further studies are needed before the clinical utility of such NMR data can be defined. Similarly, NMR's role in the clinical evaluation of renal diseases such as glomerulonephritis remains to be demonstrated **(98).** One potential disadvantage of using NMR to evaluate the kidney is its inability to detect calcifications. In another area, Ackerman, et al., have begun exploring the possibility of employing NMR to evaluate transplanted kidneys (2).

Pelvis

Researchers at Aberdeen were able to correctly differentiate between benign prostatic hyperplasia and prostatic carcinoma with proton NMR in **27** of *30* men with symptoms of urethral obstruction. Two cases, however, were misdiagnosed as cancer when, in fact, prostatitis was present (166), again illustrating that pathologic diagnoses made with proton NMR may not be sufficiently specific to obviate the need for biopsy. Bladder tumors have also been imaged **(178).** It is too early to assess the utility of using NMR in the staging of cervical, uterine, and ovarian cancer. The fact that NMR imaging does not employ ionizing radiation, however, makes it attractive as a potential means of imaging the pelvis, particularly in children and pregnant women. More recent developments in NMR imaging of the pelvis have been reviewed elsewhere (97).

Musculoskeletal System

Although NMR does not visualize bone cortex, it can be used to demonstrate bone marrow and alterations in bone architecture. Consequently NMR has been used to demonstrate osteomyelitis and tumor metastasis in vertebral bodies and pelvic bones (166). Because of its ability to provide sagittal and coronal images, NMR may prove useful in examination of the spinal canal, but again studies comparing NMR to other techniques need to be performed before NMR's role in this regard can be defined. Early work has suggested that both the spinal cord and nucleus pulposus can be discerned in NMR images. Images of muscles, tendons, and ligaments demonstrating great detail have also been produced with NMR (131), suggesting that NMR imaging is likely to prove valuable in the evaluation of musculoskeletal disorders.

Clinical Oncology

As has been discussed, further research needs to be performed before the role of proton NMR imaging in the diagnosis of cancer can be defined (14). Additional techniques need to be developed before NMR can be used to distinguish with clinically useful accuracy between benign and malignant lesions. Because NMR does not employ ionizing radiation, it might be used frequently to closely monitor the progress of pediatric and adult cancer patients being treated with radiation or chemotherapy. Finally, the exciting possibility exists, but remains to be demonstrated, that NMR could prove capable of detecting malignant abnormalities at a stage earlier than is currently possible. If that potential is realized, the additional possibility exists that clinicians will become more successful in treating the malignancies that are detected.

Blood Vessels and Flow

NMR imaging offers two different approaches to the evaluation of vascular disease, Although it is still too early to assess the sensitivity and specificity of NMR techniques in the detection of vascular obstructions, a number of investigations have suggested that proton NMR imaging can be used not only to demonstrate atherosclerotic vascular disease, but also to qualitatively assess flow in major vessels (3,41,81,108,109). These findings are particularly interesting since NMR imaging does not require the potentially toxic radiopaque dyes and catheterization of traditional angiography.

PUTTING PROTON NMR IMAGING INTO PERSPECTIVE

NMR imaging has captured the interest of the medical profession for a number of reasons. First, it eliminates the risk of X-radiation exposure that is associated with use of devices such as X-ray CT scanners. Second, in addition to providing excellent spatial resolution (on the order of 1.0 millimeter), the technique provides excellent contrast resolution without the need for injection of potentially toxic contrast agents. Third, because of the absence of NMR signal artifact from bone, physicians can visualize areas such as the posterior fossa, brain stem, and spinal cord with NMR that were not well seen with other noninvasive imaging modalities. Finally, because NMR images are sensitive to fundamental physical and chemical characteristics of cells, the technique offers the possibility of detecting diseases at earlier stages than is currently possible and of permitting accurate pathologic tissue diagnoses to be made noninvasively. These and other potential clinical or practical benefits associated with NMR imaging are summarized in table 2.

NMR imaging is not without its disadvantages, however (see table *3).* NMR imagers, for example, are expensive and their installation is costly and difficult. In addition, the magnetic fields used to generate NMR images with resistive and superconducting systems are sensitive to radiofrequency interference and may damage computer tape or other objects in the surrounding environment. Furthermore, it is currently thought not to be safe to perform NMR imaging on certain patients (e.g., those with pacemakers or metal implants, such as aneurysm clips). Finally, until more experience with the modality is obtained, NMR imaging may require more physician time in performance of patient examinations than X-ray CT or other imaging modalities.

Because the number of clinical applications of NMR imaging and the utility of each is constantly evolving (table 2), NMR's role in medicine has yet to be determined. As Kaufman, Tosteson, et al., have pointed out, many of the claims that NMR will provide detailed chemical information specific enough to be diagnostically useful are premature *(109).* Although there is some plausibility to the hundreds of applications that have been

Table 2.—Demonstrated and Potential Advantages of NMR Imaging

A. Demonstrated benefits
1. Uses no ionizing radiation; currently free of known biological hazards
2. Sensitive to differences in proton density and relaxation parameters, providing a basis for a high degree of soft tissue contrast
3. Does not require injection of potentially toxic contrast agents (In the future paramagnetic contrast agents may be developed for use with NMR. The risk associated with use of such agents will have to be evaluated.)
4. Low-intensity signal from bone, resulting in improved visualization of the posterior fossa, brain stem, and spinal cord
5. Can produce three-dimensional as well as tomographic images in virtually any imaging plane without reformatting (computer manipulation of the image)

B. Potential clinical or practical benefits
1. Increased sensitivity to physiochemical characteristics of tissues may permit enhanced detection of disease (if, for example, alterations in tissue physiochemical character can be detected prior to alterations in organ function or morphology)
2. Increased sensitivity to physiochemical characteristics of tissues may permit accurate pathologic tissue diagnoses to be made noninvasively (The development of nontoxic paramagnetic contrast agents would be particularly useful in this regard.)
3. Potential for analysis of flow of blood and other fluids, such as cerebrospinal fluid
4. Absence of moving parts may decrease maintenance costs and increase the useful lifetime of NM R imagers

SOURCE E P Steinberg, Johns Hopkins Medical Institutions, Baltlmore, MD, 1983

Table 3.—Current and Potential Disadvantages of NMR Imaging

A. Current disadvantages
1. NMR imagers are expensive
2. Difficult and expensive site preparation
3. Exclusion of patients with pacemakers; metal implants, such as aneurysm clips; or claustrophobia. (Patients who have undergone brain surgery in whom there is uncertainty regarding whether metal clips were implanted may need to be X-rayed before being imaged with NMR. Metal detectors are also being used.)
4. Insensitivity to dense bone and calcifications
5. Relatively prolonged acquisition times and sensitivity to motion result in degradation of images of moving anatomic structures

B. Potential disadvantages
1. May require more physician time in performance of patient examinations compared to other imaging modalities
2. Examination times could prove to be longer than with X-ray CT or ultrasound, resulting in fewer patients examined and increased average cost. (Newer developments in imaging techniques may change this)

SOURCE: E P Steinberg, Johns Hopkins MedicalInstitutions, Baltimore, MD, 1983

cited for NMR, the majority of such applications must be considered potential rather than *demonstrated.* Although T_1 and T_2 relaxation times have been found to vary in different pathologic processes, for example, researchers have so far been unable to characterize tissue pathology as specifically as had originally been expected using T_1 and T_2 values, The possibility exists, however, that through the development of nontoxic paramagnetic contrast agents, much of the noninvasive diagnostic potential of NMR that had been hoped for can be realized.

Whether the results that have been observed in research institutions to date will be easily duplicated by other institutions remains to be seen. The NMR imaging that has been performed so far has taken place in research centers that possessed or acquired considerable background and expertise in NMR prior to initiation of an NMR imaging program. Most, if not all, such centers have utilized interdisciplinary teams consisting of physicians, physicists, engineers, and others to produce the images that have been published so far. In addition, the exquisite images that are helping to fuel excitement about NMR imaging have often required prolonged amounts of time that it may not be practical to expect most hospitals to expend, Although future NMR production models are likely to simplify image acquisition for the physician, and although the time required to produce high-quality images is likely to decrease, it should not be assumed that images of the same quality *as* those published or displayed to date will necessarily be produced *immediately* in hospitals that are not able to spend equivalent time and effort on their production.

Furthermore, although in most research studies performed to date several physicians have interpreted NMR scans independently and without access to comparative X-ray CT scans to guide them, in many, if not most, instances patients with *known* pathologies were being imaged. This is, of course, not only reasonable, but also advisable in the early stages of evaluation of a new technology. Nonetheless, NMR will not necessarily be shown to have the same sensitivity and specificity when used to image patients with unknown types of pathology.[3] (See (149), for example.)

Although researchers have reported the ability to produce head and body images with NMR in times comparable to those required for X-ray CT scanning (41), it is possible that the time required to perform NMR studies on patients with unknown types of pathology will be longer than that required by experts imaging patients with known pathology (table 3). Given the variability in NMR images depending on the pulse sequence employed, researchers are finding that certain pulse sequences are better for demonstrating one type of pathology, while different pulse sequences are better able to demonstrate other types of pathology. Optimal pulse sequences for different pathologies are therefore being sought. It is likely that in the future pulse-sequence algorithms that are best suited to imaging specific medical problems such as abscesses, hemorrhages, and tumors will be built into NMR software. Although this development implies improvement in NMR images of individual types of pathology, it also implies that patients with unknown types of pathology who are referred for a "screening" NMR scan in the workup of symptoms such as fever, weight loss, or pain will have to receive multiple scans using multiple pulse sequences to exclude an abnormality. Such use of multiple pulse sequences may increase the time required to perform NMR studies.

The relationship between pulse sequence and pathology suggests two additional issues. The first is the issue of how many different pulse sequences will have to be employed before an examining physician is comfortable with concluding that a patient is normal. The second is that unless examining physicians are thorough, existing pathology may be overlooked. It is thus possible that a tension will develop between the economic pressure to maintain scheduling of a reasonable number of patients and the clinical requirement that pa-

[3] On the other hand, given the rapid improvements taking place in NMR imaging, current assessments may underestimate the ultimate sensitivity and specificity of NMR in many applications.

thologic abnormalities be excluded with a high degree of certainty. To the extent that the latter predominates, fewer patients may be seen, producing a rise in average cost per NMR study. To the extent that the former predominates, the sensitivity and specificity of NMR may decrease.

Finally, since NMR imaging employs no ionizing radiation, it is possible that patients can safely have repeated NMR scans over time to monitor therapeutic progress or the natural history of disease. To the extent that such monitoring is demonstrated to provide clinically useful information, the temptation to scan a single patient more frequently may increase. Such an effect would increase demands on NMR machines, which would result in hospitals' having to either ration time on NMR machines or purchase more NMR scanners. A second potential effect of "sequential scanning" is that in the absence of prospective payment (as is now the case for patients in many States), health care bills might increase (see ch. *8).* The occurrence and magnitude of such increases depend on the extent to which sequential NMR scanning decreases or increases total patient management costs and improves patient care.

In conclusion, NMR imaging is a new modality thought to be capable of providing not only anatomic information comparable or superior to that obtainable with other imaging techniques, but also chemical and metabolic information that could yield noninvasive insights into tissue histology and function. Were NMR to be considered just another means of visually demonstrating anatomy, therefore, its true potential would be drastically underestimated. The lack of ionizing radiation or demonstrated hazard associated with NMR imaging, as well as the apparent lack of need to employ toxic contrast agents to obtain high-contrast images, would suggest an important clinical role for NMR imaging in medicine even if it proved to be no more efficacious than X-ray CT scanning. Considerably more research, such as that described in table 4, will be required before NMR's potential is determined and its most appropriate roles in clinical medicine are defined.

Table 4.—Likely Areas for Future NMR Research

1. Determination of clinical utility of NMR imaging compared to other imaging modalities
2. Improvements in magnet design (e.g., increased field uniformity; increased field strength; techniques for conserving liquid helium and nitrogen)
3. Determination of magnetic field strength that yields optimum image quality for hydrogen, for other nuclei, or for combinations of hydrogen and other nuclei)
4. Identification of pulse sequences optimal for demonstrating different types of pathologies
5. Improvements in imaging software and techniques affecting image quality, resolution, and scan time
6. Optimization of radiofrequency coils
7. Development of new and improved surface coils
8. Improvements in siting and shielding techniques
9. Development of paramagnetic agents for assessing tissue pathophysiology
10. Further development of whole-body spectroscopic techniques and applications
11. Imaging of nuclei other than hydrogen (e.g., sodium or phosphorus)

SOURCE E P Steinberg, Johns Hopkins Medical Institutions, Baltimore, MD, 1983

RELAXATION PARAMETERS

As has been mentioned previously, proton NMR images reflect not only the proton density of the tissues being imaged, but also the proton relaxation time characteristics of those tissues. In addition to exploiting these relaxation parameters to enhance the contrast of NMR images, researchers over the past decade have been investigating the extent to which quantitative measurements of T_1 and T_2 can be employed to make precise, yet noninvasive pathologic assessments.

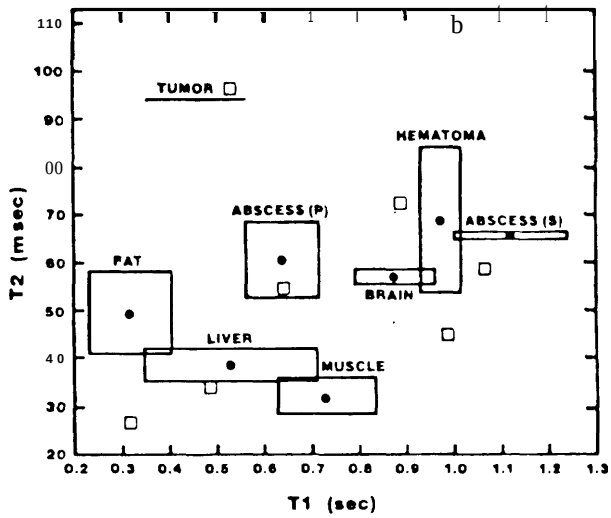
The first indication that relaxation times might have diagnostic significance emerged from the early work of Raymond Damadian at the State University of New York, Brooklyn. In *1971,* Damadian demonstrated that the proton spin-lattice relaxation time (T_1) in excised tumors that had been experimentally induced in rat livers was prolonged compared to the T_1 values of normal rat liver tissue **(42).** The T_1 relaxation times of two benign fibroadenomas were likewise found to be

distinguishable from those of the malignant tissue **(42).** Similar results were observed by others shortly thereafter (32,84,93,160). In 1974, Damadian extended this work to humans, finding the T_1 values of 106 surgically excised human tumors to be longer than the T_1 values of the corresponding normal tissues **(45,46).** About the same time, Weisman and Bennett discovered that they could use NMR to differentiate in vivo between the normal tissue of a mouse's tail and a malignant melanoma transplanted into the tail (202).

Out of *concern* that experimental malignant tumors with slower growth rates might manifest T_1 values within the range observed for normal tissues of nontumor bearing animals, Hollis, et al., studied intermediate and slow-growing malignant tumors in rats **(92).** The authors found that the T_1 values of these more slowly growing tumors were again longer than those of normal rat liver, but overlapped T_1 values of other types of normal tissues **(92).** In view of this finding, Hollis and his co-workers voiced the concern that ". . . the overlap of T_1 values for malignant and normal specimens raises the possibility of confusion between primary tumors adjacent to sites of similar or higher T_1 value, or between normal tissue and metastatic tumors having a similar or lower T_1 value" *(92).*

Similar observations were subsequently made by others. Herfkens and co-workers at the University of California at San Francisco, for example, found that the T_1 values of in vivo tumors in rats estimated by NMR imaging techniques varied widely, and, although mean T_1 values of the tumors were high, individual T_1 values overlapped the full range of normal and other types of abnormal tissues **(87).** The same group also explored the possibility of using both T_1 and T_2 values estimated by NMR imaging techniques to distinguish between different types of pathologic abnormalities and found that contrast differentiation between normal and abnormal tissues was improved, albeit still imperfect **(87) (see** fig. *8).*

Figure 8.— Mean and Standard Deviations for T_1 and T_2 of Various Tissues in a Live Rat



SOURCE: Herfkens, et al., 1981 (88).

PUTTING T_1 AND T_2 RELAXATION TIMES INTO PERSPECTIVE

A number of conclusions can be drawn from the results of studies on the potential use of quantitative T_1 and T_2 values for pathologic diagnosis. First, within certain numerical ranges, relaxation times may provide sufficient pathologic specificity (to distinguish normal from abnormal, and one disease from another) to be clinically useful in understanding disease processes. Second, in instances in which overlap exists between the T_1 and T_2 values of normal and abnormal tissues, it will not be possible to use relaxation values alone to make reliable pathologic diagnoses, despite the theoretical attractiveness of doing so. Third, even if "natural" T_1 and T_2 values do not prove to provide the pathologic specificity that had been hoped, they may be useful in understanding disease processes. In addition, there is the possibility that nontoxic paramagnetic contrast agents (21,23,156) may modify relaxation properties and enhance diagnostic specificity. Fourth, the possibility exists, yet remains to be demonstrated, that detectable changes in T_1 and T_2 values may precede the development of noticeable anatomical changes in ways that will be clinically useful. Studies of early changes in T_1 and T_2 during oncogenesis, radiotherapy, and chemo-

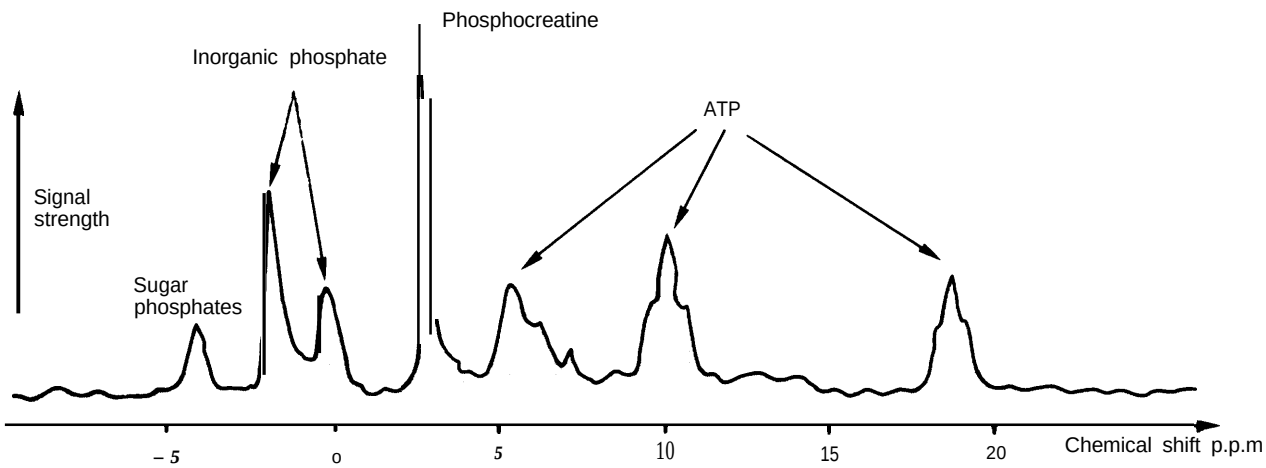
therapy, for example, may provide immediate clinical dividends, as well as insights into the etiology of cancer and new modes of cancer therapy. Finally, considerable research remains to be done in the exploration of which physical, chemical, and biological factors give rise to and influence NMR relaxation times. Only through answers to these questions will it be possible to exploit relaxation times' full medical and scientific potential.

IN VIVO SPECTROSCOPY

Although small concentrations of phosphorus are present in the body, researchers have recently detected NMR signals from phosphorus of sufficient intensity to produce images. Researchers have also been able to perform in vivo phosphorous NMR spectroscopy in which the "chemical shift" phenomenon is used to indicate the relative concentrations of compounds such as phosphocreatine, adenosine triphosphatase (ATP), and inorganic phosphate in human tissues or organs (see fig. *9).* Such a noninvasive metabolic probe has tremendous potential applications in medicine.

It has been demonstrated, for example, that levels of inorganic phosphate rise, while the concentration of phosphocreatine falls, in cells deprived of oxygen (165). The possibility thus exists that NMR spectroscopy could be employed not only to assess the utilization of ATP and the viability of oxygen-deprived brain or heart tissue (22), but also to gain insight into the functional and metabolic status of brain, heart, or peripheral muscle tissues in various physiologic and pathologic states. It has been demonstrated, for example, that the pH of oxygen-deprived tissue can be calculated from the positions of inorganic phosphorus peaks observed with NMR spectroscopy *(22,26)* and that changes in muscular metabolism during exercise can be detected by NMR (70,145), Rare diseases due to inborn errors of metabolism, such as McArdle's syndrome, can also be diagnosed using in vivo NMR spectroscopy **(146).**

Figure 9.— NMR Phosphorus Spectrogram[a]



[a]Graphic depiction of the individual components of NMR signals from phoshorus-containing compounds arranged according to the frequency of electromagnetic radiation

SOURCE: D I Hoult, "An Overview of NMR in Medicine, " U S. Department of Health and Human Services, National Center for Health Care Technology, February 1981

PUTTING IN VIVO SPECTROSCOPY INTO PERSPECTIVE

Much additional research is required before an assessment can be made of the extent to which in vivo NMR spectroscopy can be used to provide diagnostically useful clinical information regarding the metabolic and functional status of normal and abnormal tissues. It should also be recognized that the technology required for in vivo human NMR spectroscopy of organs such as the heart or brain is considerably more sophisticated than that required to perform proton NMR imaging. Superconducting magnets operating at high field strengths (on the order of 1.5 T or greater) with extremely high levels of field uniformity, for example, seem to be required to provide adequate resolution of the peaks emanating from various phosphorus-containing compounds. Thus most of the NMR imagers that are generally being installed in hospitals today (i. e., ones with field strengths less than 1.5 T) may not be capable of performing NMR spectroscopy, In addition, even though it has been proven feasible to perform spectroscopy on the 1.5 T imaging systems currently being installed, it is possible that neither proton imaging nor in vivo spectroscopy can be performed optimally at a field strength-of 1.5 T.[4] Hospitals desirous of performing spectroscopy and imaging, therefore, may need either to obtain more than one NMR machine or be content to tolerate potentially costly periods during which field strengths are changed and the NMR machine is therefore not operational.[5] Considerably more research is also required before specialized equipment, such as auxiliary surface coils, are designed that permit NMR spectroscopy of phosphorus and other nuclei to be performed optimally. For the present, therefore, in vivo NMR spectroscopy should be considered an exciting and promising area of research that is of questionable feasibility for most hospitals.

[4]High-quality images of both the head and body have recently been produced at **1.5** T. It is too early to know whether images produced at ıs T will be better or faster than those produced at lower field strengths,

[5]In addition, alterations in software may need to be made in association with adjustments in the field strength, and such software changes may prove to be too time-consuming to be practical.