ROLE OF NMR IN THE CONTEXT OF EXISTING MEDICAL DIAGNOSTIC TECHNIQUES

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Abstract

Assessment of the future of cyclotron-based positron tomography (PT) necessitates consideration of nuclear magnetic resonance spectroscopy (MRS) as an alternative path to the same goals. Current performance levels lead to the conclusion that MRS is not likely to become a productive clinical tool. Even so, knowledge of the limitations of PT is common in the radiologic community, and because of the technique's maturity dramatic breakthroughs are not expected. For MRS, knowledge is scant and expectations are high. Entry into MRS requires fewer financial resources, and the expectation level is such that even a cautious person would be led to conclude that MRS will be useful even if a small fraction of what is promised comes to pass. Because of these factors we predict that during the next 3 - 5 years a potential new entrant user base for PT will be lost to MRS.

Background

Nuclear magnetic resonance (NMR) imaging, or magnetic resonance imaging (MRI) as it is being renamed by the radiology community is a diagnostic, economic, news-media and politic-academic phenomenon that surpasses the introduction of x-ray CT as an "event" (1). As has been the case with the advent of new diagnostic modalities in the last twenty years, MRI is being vastly oversold. Commercial producers and would be producers tend to oversell in almost direct proportion to the lateness of their entry into the market place. The rationale for this is clear. Companies that deliver a working product have marketing policies that need to be closer to reality. Those without a ready product hype specifications to help raise questions as to the adequacy of existing products. Academicians feed this cycle by using the forum of scientific discourse to speculate, wish and dream. Their expectations are also in direct proportion to their distance from the technology (Figure 1). Academic departments, afraid of having been passed over by the first wave, are scrambling to get the resources to study the "next frontier". An important component of the cycle is the positive feedback of expectations operating between users and providers of the technology. The fuel for this development has not been US governmental research dollars. Rather, x-ray CT manufacturers have invested unprecedentedly in basic MRI R&D. The earlier entrants had done poorly in CT and were hoping for a way to use their existing plants and product capacity to recover their investments. The more successful CT companies followed to protect their existing market when they realized the threat posed by MRI. For natural reasons this realization came later to those that were most successful in CT, and this forced them to feed back into the hype cycle described above. Outside the US, in the major industrialized countries, governmental funds are being used to, whenever possible, nurture and foster locally produced equipment, a logical use of a country's taxpayer's monies. With this situation as background, it is not surprising that the diagnostic instrumentation R&D community is confronted internally and externally by questions that in different forms ask: Is it worth investing in anything but MRI and its sequela, MRS? To answer this question we need to understand what MRI/S is, what it is capable of doing today, what its near term prospects are, and the niche it fills.

Introduction

In MRI a strong magnetic field establishes a preferred direction in space for the orientation of the spin of magnetic nuclei. Changes of the direction of the vectors are associated with the absorption and emission of energy, which can be in the form of oscillations of a magnetic field in the frequency range of 1 to a few hundred MHz. This frequency is linearly dependent on the strength of the magnetic field in the locale of the nucleus. Lauterbur demonstrated that suitable spatial and temporal variations of the main magnetic field could be used to encode position information (2). The basic approach used by Lauterbur, even though not the particular form of implementation, remains in use in all of the current commercial MRI devices. These aspects of the technique are expanded upon in references 3 and 4. The hardware has taken varied manifestations, dictated by different philosophies regarding the economics, availability, risk component and maintainability of different subsystems (5). The magnet has attracted most of the attention, based on the questionable assumption that it, by itself, drives cost and performance (6). This is evidenced by the increasing frequency with which a magnetic resonance imager is referred to by physicians as a "magnet". The highest performance systems incorporate superconducting magnets, of over 1 m room-temperature bore and 2 m-length. Resistive and permanent magnets are also used commercially. Temporal and spatial gradients are established by sets of resistive coils driven by linear or switched amplifiers capable of delivering up to 200 A with rise-times of 1 msec or better. This often-ignored subsystem is the key to the performance of an imager, both in terms of image quality (7) and the type of imaging procedures that can be implemented. Computers control every aspect of the imaging process. Typically, a large minicomputer such as a VAX 11/730 is used, aided by smaller computers.

Using one of a variety of imaging techniques available (8,9) it is possible to study the whole head in 10-20 min with a highly sensitive signal acquisition mode (10). These images have a spatial resolution ranging from 2.5 to the sub-millimeter level, and section thicknesses between 1 and 10 mm.

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Data Content of MRI

Human imaging is performed with the signals produced by hydrogen nuclei in the body. Hydrogen is the most abundant and sensitive nucleus per unit weight. The information is not solely dependent on hydrogen distribution. The imaging procedure consists of a repetition of excitations of the nuclei at regular rates. Each excitation demagnetizes the sample and requires that a certain period elapse so that the magnetization is re-established and with it the sample's ability to produce a signal. The growth of magnetization is characterized by an exponential time constant called the T1 relaxation time. T1 times in human tissues at 3.5 KGauss range from 250 msec for fat to 3 sec for pure fluids. Relaxation times are dependent on magnetic field strength. In the range of interest for imaging, the higher magnetic fields result in longer relaxation times (11), an effect that we shall return to later. Following excitation the available NMR signal decays with an exponential time constant called the T2 relaxation time. T2 times in human tissues, measured as part of an imaging procedure, range from 25 msec for muscle to 200-300 msec for liquids. T2 times do not change much with field, generally showing a very small drop as field increases (11). T1 and T2 are dependent on the molecular environment surrounding the excited nuclei.

The sequence of excitation and encoding pulses needed to form an image requires tens of milliseconds. If nuclei move during that time they are subjected to a different sequence, and their response is different from that produced by stationary nuclei. Consequently, blood flow is one of the factors that affect the MR image (12). Signal response to these four endogenous contrast agents or labels can be manipulated using the imaging sequence. For instance, longer intervals between subsequent repetitions of a sequence (TR) result in increasing signal from tissues with longer T1 values. Similarly, increasing the time (TE) between excitation and reception of a signal (a spin echo), permits tissues with long T2 values to provide relatively larger amounts of signal. Hydrogen density is a sometimes subtle and sometimes dominant contributor to the image. Blood flow information can be obtained by a myriad of barely explored techniques. Figures 2-5 show examples of pathology highlighted by one of these processes. The NMR signal is obtained from any part of the body without the administration of pharmaceuticals, and without hindrance from bone, air or sharp interfaces. FDA guidelines assume that based on existing data, within certain operational limits the process is risk free.

The promise of MRI was that tremendous specificity to disease was built into the relaxation times of tissues (13), leading to an almost automatic diagnostic process. What we have found is that these relaxation times are specific to normal tissues, even though to achieve this specificity both T1 and T2 need to be considered simultaneously, and there exists considerable variability from individual to individual. In-vivo work in rats has shown that water is the major determinant of relaxation times, which lengthen as water content is increased (Figure 6). The second major determinant is fat content (14). Predictive modeling of relaxation times agree with these observed results (15). In some instances the presence of para- or ferromagnetic materials modify or dominate the effects of water (Figures 7,8). If water and fat content are the major determinants of relaxation times, what can be expected about MRI's ability to detect and characterize disease? Work with hundreds of rodents has shown superb sensitivity to the presence of disease, so that benign lesions such a abscess and hematomas were detectable along with diverse tumors. Basically, any lesion larger than (usually) three resolution elements was detected. Brain (16) and muscle (17) infarcts showed lengthening in relaxation times almost immediately after injury. The same lengthening in relaxation time was, unfortunately, observed in tumors with elevated water content. Tumors with low water content had shorter relaxation times (18). We were led to conclude then that MRI is very sensitive but not as specific, and that a physician still needs to interpret the MR image, to use not only relaxation times as criteria, but also lesion morphology and anatomic information and to integrate these data with the clinical status of the patient and with results from other tests.

MRI in The Context of Other Imaging Modalities

As it now exists NMR can be considered a highly sensitive, benign procedure. Its niche is clearly that of x-ray CT. Compared to ultrasound, MRI requires larger capital and space expenditures, and cannot be done at the patient bedside. Compared to nuclear medicine, MRI is not suited to whole body surveys such as those provided by the bone and gallium scans, and heart studies cannot be performed at the bedside of a sick patient, as can be done with portable gamma-cameras. MRI does not match angiography in temporal or spatial resolutions. It will undoubtedly erode the utilization of these techniques, specially as capacity grows, but the impact will not be significant. Of the imaging modalities now in use, MRI more closely resembles x-ray CT. Both provide cross-sectional views with superb anatomic detail, although the former permits direct imaging along planes other than transverse (Figure 9). Both require a great deal of space, and high capital outlays, as well as significant maintenance expenditures. Patients cannot be examined at the bedside. X-ray CT poses less problems in regards to the use of patient life support systems, which in their present form cannot be used with MRI because of the hazards posed by ferromagnetic materials. MRI, conversely, avoids ionizing radiation and the well known problems associated with reactions to iodinated contrast agent injections. Given the similarity of utilization factors, it becomes apparent that there will be little utility for the combined use of MRI and CT on the same patient, except in a small number of particular cases. There is little question that third party reimbursement sources will be reluctant to pay for both. Therefore, the role of MRI as a generalized diagnostic technique will be decided on the basis of its capabilities vis-a-vis CT. Considering that when this is being written the number of patients imaged by all of the MRI units in operation is probably no larger than the number of patients scanned in one year by one or two busy CT scanners, the favorable reports about MRI cannot be considered as the definitive answer to the choice between techniques.

Research & Development on High Field Systems

Hydrogen imaging is by no means a mature field. Although we understand reasonably well the methodology for highlighting T1 and T2 effects in the image, surprises are still present. Blood flow imaging has barely been explored. The impact of hydrogen density has been undervalued. Even so, the

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community's attention has been sequestered by an even more basic endeavor: To observe metabolic processes in humans in-vivo and non-invasively. Well before NMR imaging was demonstrated, biomedical investigators were using the technique to identify the location of nuclei within a molecule. The principle is the same as in imaging. The local magnetic field for a nucleus is the sum of the external field and the local fields produced by surrounding electrons. Since the electron orbits are modified by chemical binding, each chemical has a unique electron field value. Thus, each nucleus is identified by its frequency, or chemical shift. With such a tool we could assess organ viability from its phosphorous kinetics, observe the pathways of C-13- labeled compounds, and so on. Implementation of this technology is not straight forward. High magnetic fields are needed, since the amount of shifting is directly proportional to field strength. The magnets required higher uniformity than that needed for imaging, since it is undesirable to mask the chemical shift with spatial shifts. These high field magnets are suboptimal for hydrogen imaging because of two major basic factors: As the magnetic field strength increases, T1 lengthens. The longer values of T1 result in smaller signal differences between tissues, and, for any one tissue, TR needs to lengthen in direct proportion to T1 to produce the same response. Since the longer T1 values are relatively closer to each other, contrast decreases even for the longer TR values. The scant hydrogen clinical work done at high fields (15 KGauss) does not yet indicate any advantages over 3.5 KGauss work, and may actually prove to be less sensitive to the presence of disease.

Irrespectively, even suboptimal or equivalent imaging performance at high field is accompanied by the potential for obtaining chemical shift information. Although different in principle from the information available from positron tomography (PT) using cyclotron-produced radiopharmaceuticals, it can be argued that MRS would reach the same endpoint: Assessment of the metabolic state of tissues, and the tracking of metabolic chains. MRS, although considerably more expensive than MRI (by about $500K for equipment and at least as much for installation, as discussed in reference 6) has significant price advantages over PT when the cost of cyclotron, hot chemistry and imaging facilities and personnel are factored in (Appendix I). Therefore institutions that may not be have considered PT within their means, are reaching for MRS as an alternative. Even institutions with the funds for PT are considering MRS because of a perceived increase in the rate of returns on invested dollars and by the "unexplored frontier" aura of MRS.

The reality of MRS would indicate that some caution should be exercised. Financially, a hospital that has spent over $2M on a MRI/S high field system and paid half as much to install it, will quickly become impatient if the S part of the work interferes with the I's role in patient care. But more fundamentally, even a dedicated research system needs critical assessment as a substitute for a PT installation. Just as MRI's successful use has to be considered in comparison to x-ray CT, the technique it most closely matches, MRS needs to be compared in performance to PT if it is to be considered as an alternative. Presently, spatial resolution of MRS is characterized by a sphere of 6cm-diameter, and more recently "fist-sized". Since surface coils are used, significant averaging of skin, muscle, fat, marrow and CSF occurs in studying the head. Noninvasive liver, head and kidney work in humans is presently beyond the reach of surface coils. Thigh and arm muscle can be studied. Using a surface coil, phosphorous spectra require minutes of data acquisition to obtain adequate information from over 100 cm^3 of tissue. If a deep seated spot of 1 cm^3 of brain tissue were to be studied, there would be a loss of signal to noise of 100 due to the smaller volume, and an additional 5-10 from antenna efficiency, pushing the time into the many hour range. MRS using point localization techniques are inadequate even for a generalized clinical research program. Point techniques were used early on for MRI, and even though for hydrogen the sensitivity is many thousandths of times higher than for phosphorous (19), they were abandoned because multi-point reconstructions are at least 100 times more efficient. There is no reason to expect that point MRS will fare any better. It is possible to perform spectroscopic imaging, where data are obtained from entire planes at a time. We have estimated (20) that in hour-long imaging periods a resolution of 3 cm on the side would provide barely adequate S/N levels. Current 15 KGauss systems may not be able to do whole-section imaging, as reported in reference 21. Surface coils may permit improvements for peripheral regions, by maybe as much as a factor of 10. Magnets with higher specifications for the ratio of field strength/field non-uniformity may also help, but the basic limitation in signal availability remains. Until the resolution and study time of MRS reach clinically useful levels, its utility remains a matter of speculation.

Discussion

MRI does not significantly overlap with PT as an imaging technology. There could be significant overlaps between MRS and PT, the former being a lower cost modality to implement. Our current understanding of MRS would lead us to conclude that image quality specifications are such that MRS will not be competitive with PT. For the near future, such considerations are irrelevant. PT is a mature technology with well understood limitations. MRS has only recently come to the attention of the medical community and its conceptual potential has not yet been tainted by reality. Even when limitations are understood, there is always the expectation that "next week" a new breakthrough will occur, so that not even reality tempers expectations. This process is amplified because in response to the perception of the value of MRS, manpower, government funds and commercial resources are drawn to it. This in turn further enhances the value of MRS in the eyes of the user community to the detriment of the perceived value of PT (and other techniques). It is very probable that during the next 3-5 years a large fraction of institutions that would have entered the PT field will divert their resources to MRS.

Appendix I: Comparison of MRI, MRS and PT Costs

It is always difficult to assess the full costs of a technology, since these vary on the basis of locale, accounting methods, allocation among institutional subunits, etc. In fact, not even equipment costs are straightforwardly accounted for: Most cyclotrons and PT imagers have been paid for by NIH funds, and cost the institution little or nothing. Many PT imagers have been built by research institutions and do not carry the usual margins found in industry for items such as warranty, marketing, insurance, regulatory, inventory, and other. The

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situation is as undefined in MRS: Although list prices exist, today, there is no specification as to the performance of a whole-body MR spectrometer, no indications for its use, and not even a hint of FDA approval. In fact, the application for FDA approval by the manufacturer that has made the strongest claims regarding the ability to perform imaging and spectroscopy jointly has been returned to the company (22). MRS units are being "placed" in universities so that we may find what they can do. Others are being "sold" at prices that do not reflect real costs. Many are being "bundled", i.e., for full price on a MRI/S unit a "free" x-ray CT and other equipment are also delivered. Often a company pays for the housing facility. Payment terms are extended. A university's lack of prestige can be gauged by how close to list price their real costs are.

In the comparison below we will use equipment list prices for MRI and MRS. Siting costs for MR will be based on an "average university" operation, which our institution certainly is not. Consider, for instance the Radiologic Imaging Laboratory and the main Campus of the University of California, San Francisco. Installation of a 3.5 KGauss unit at RIL costs well under $75,000 in 1,500 sq.ft. that can be full accounted at $22/sq.ft./year (this includes rent, utilities, security, phones, copying, secretarial, janitorial, mailing, machine and electronic shops, etc.) A 20 KGauss unit is being installed in an adjacent warehouse for about $100,000 in 3,000 sq.ft. with even lower footage costs. The respective costs on the main campus are over $250,000 for installation of the lower-field unit, and a bid of $2.2M for installation of the high field unit in a campus garage. For the cost of PT hardware and installation we use references 23 and 24.

Personnel costs vary depending on the purpose for which this equipment has been installed. We will assume a clinical operation with mostly entry level personnel. Although Evens lists only one half a radiologist for his PT operation, we will assume the need for 2 radiologists, to take into account vacations, meeting time and sick leave. For the same reasons we will use two technologists. It is worth pointing out that in a supply-limited situation as it now exists in MRI, the addition of two more techs will double the number of patients studied. Even so we will consider one shift only. Specialized personnel for the cyclotron operation will be, as listed by Evens, 2 cyclotron operators, one chemistry technician, and one half engineer, and one quarter chemistry technician.

Consumables will be assumed on the basis of a full patient load. Electrical costs include computers, air conditioning, and normal appliances as well as specialized equipment. Equipment depreciation does not necessarily reflect real life-time, but the desire to depreciate as fast as possible for tax reasons. Indirect charges, cost of money (about 13%) and tax savings or payments are not included. All monies are in 1984 dollars.

Table I: Comparison of MRI, MRS and PT Direct Costs

	MRI	MRS	PT	
Equipment	$ 1.5M (3-5 KGauss)	$ 2-2.5M (15-20 KGauss)	$ 1.65M(23) (Cyclotron tot)	$ 2.5M(24) (Hardware)
Site	250K	0.5-1M	1.4M(23) (imager tot)	1.5M(24) (site)
5yr Amortization	$ 350K	$ 600K	$ 610K	$ 800K
Personnel:				
2 Radiologists	$ 200K	$ 200K	$ 200K	
2 Techs	60K	60K	60K	
Spectroscopist	-	35K	-	
Cyclotron spec.	-	-	131K	
Maintenance	90K	90K	225K(23)	
Consumables	50K	50K	122K(23)	
Electrical	50K	50K	50K	
Cryogens	10K	10K	-	
Total/year	$ 810	$ 1,105K	$ 1,398	$ 1,588

Having been made, it is worth pointing out that a cost comparison of this type is meaningless. To choose technologies on the basis of price would be like choosing whether to go to a pediatrician or a neurosurgeon on the basis of the difference in fees between the disciplines. The first question that needs to be asked is, if a choice is necessary, which modality best serves the institution's patients and research problems? Which modality best addresses those needs? A modality that cannot provide the needed information is expensive at any price.

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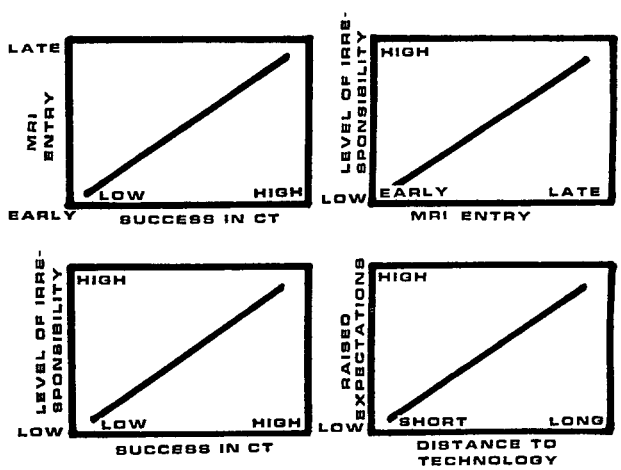


Figure 1. The response of the manufacturing community to the MRI phenomenon (upper row and lower left) can be understood in terms of their success in CT. Academicians (lower right) are part of the hype cycle.

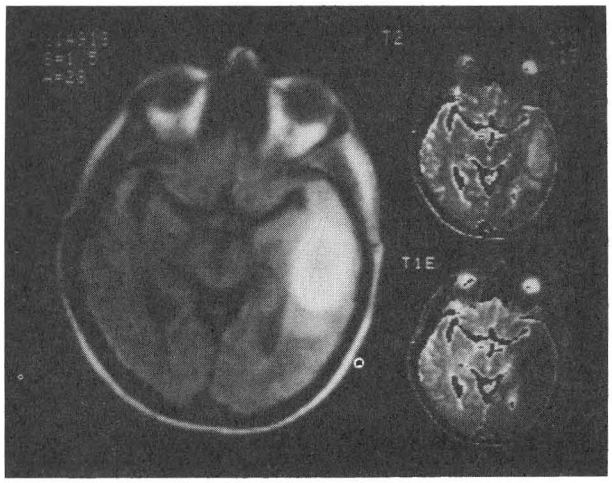


Figure 2. Pathology highlighted principally by T1 changes. In a patient with bleeding the T2 image shows a slight elevation in the lesion and surrounding tissues. The blood itself has a very short T1, which differentiates it from edema.

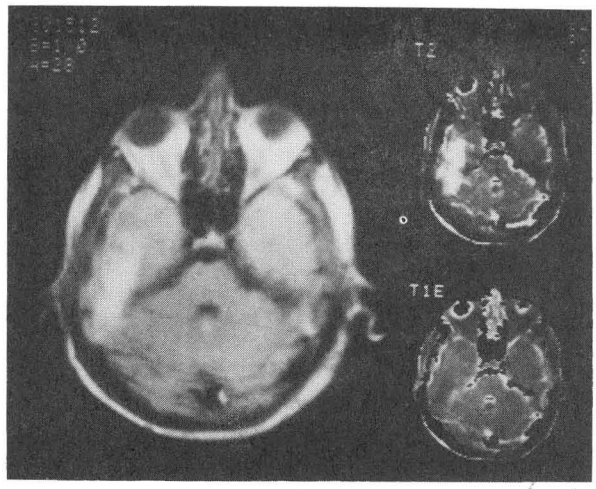


Figure 3. Pathology highlighted by T2 changes. In a patient with a brain infarct T1 is almost normal, but there is marked elevation of T2, which is responsible for the appearance of the lesion as a bright region.

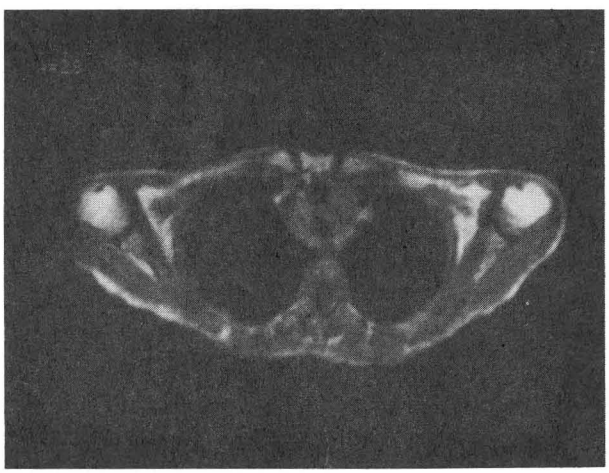


Figure 4. Pathology highlighted by large differences in hydrogen density. The low density of lung permits easy visualization of large, central mass.

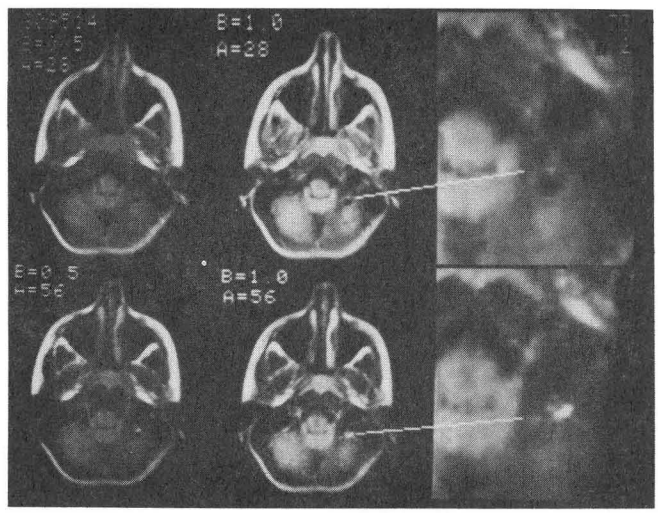
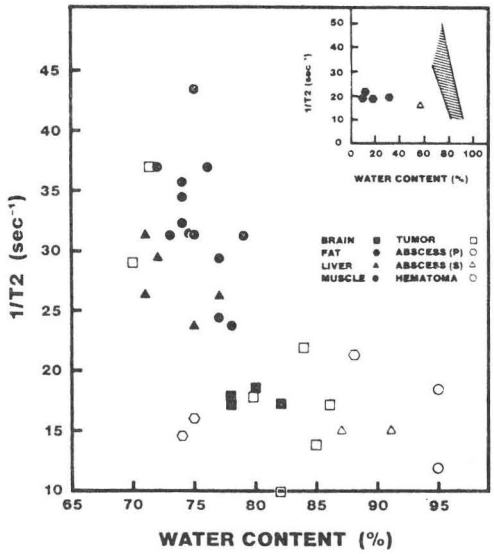


Figure 5. Pathology highlighted by flow effects. First echos (top) show low intensity for a vascular tumor, while the same region is of high intensity in the second echo (bottom). This is characteristic of relatively rapid flow.



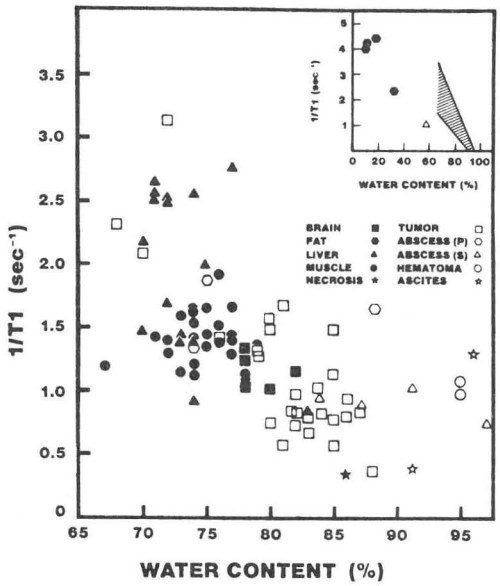


Figure 6. Relationship between relaxation rates (1/T1 and 1/T2) and water content of various tissues. Fat has a T2 that is long compared to its water content.

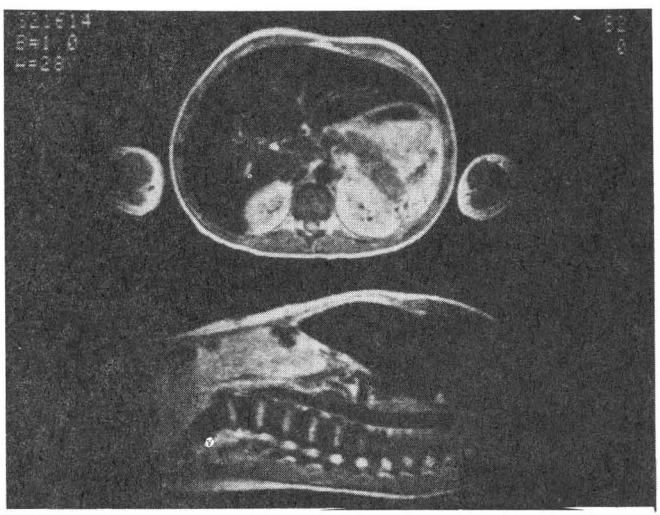


Figure 7. In a child with hemochromatosis the iron in the liver and marrow reduces the T2 relaxation time to the point that no signal is observed in these images. Top is a transverse view, and bottom is a sagittal view.

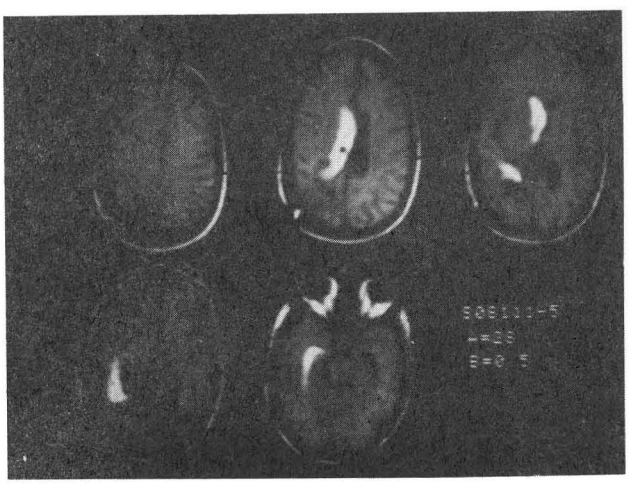


Figure 8. Blood shortens T1 due to the presence of hemoglobin. Note the bright appearance of a ventricle into which there has been bleeding, while the opposed ventricle is dark due to the long T1 of cerebrospinal fluid.

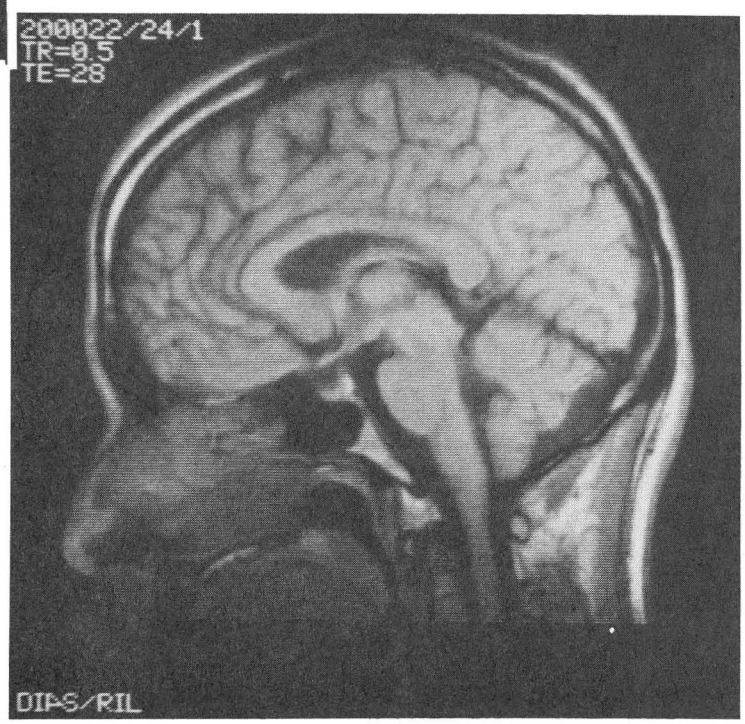


Figure 9. Sagittal view of the head through the mid-plane. The spatial resolution of this 7 mm-thick section is 0.8 mm.

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