NMR Imaging in Medicine

Nuclear magnetic resonance, or NMR, can reveal the distribution of atoms in a sample of material. It can do the same in the body, generating images of internal structure without the use of X rays

by Ian L. Pykett

The medical need to see inside the human body from the outside has been met for many decades by recording the differential absorption of X rays. A major deficiency of the standard method of radiography is its inability to discriminate among overlapping structures. This deficiency has been remedied in recent years by the development of X-ray computerized tomography, or CT scanning, a technique in which X-ray data recorded from many different directions are reconstructed mathematically to yield cross-sectional views of selected regions of any part of the body. Although CT scanning has proved to be an extremely useful diagnostic tool, the information its images provide is basically anatomical; they tell little about the functional or physiological state of the internal organs. Moreover, some pathological lesions have X-ray absorption properties so similar to those of the surrounding tissues that the lesions can go undetected in a CT scan unless they are large enough to change the size or shape of the organ. Beyond that X rays, even in small doses, carry a finite risk of doing physiological harm.

A new technique for obtaining cross-sectional pictures through the human body without exposing the patient to ionizing radiation is on the threshold of clinical application: nuclear-magnetic-resonance imaging. NMR imaging not only yields anatomical information comparable in many ways to the information supplied by a CT scan but also promises to discriminate more sensitively between healthy and diseased tissue. The latter prospect is founded on the well-established ability of NMR spectroscopy to elucidate the intricate conformation of organic molecules and to provide insight into dynamic chemical processes. For several years biochemists have exploited NMR techniques to monitor metabolic reactions in experimental animals and human beings. It is the recent development of methods for presenting NMR information in pictorial form that is now providing clinicians with a powerful new diagnostic tool.

The experimental foundations of NMR spectroscopy were laid by Felix Bloch of Stanford University and Edward M. Purcell of Harvard University more than three decades ago, work for which they were awarded a Nobel prize in 1952. It had been known since the 1920's that many atomic nuclei have an angular momentum arising from their inherent property of rotation, or spin. Since nuclei are electrically charged, the spin corresponds to a current flowing about the spin axis, which in turn generates a small magnetic field. Each nucleus of nonzero spin therefore has a magnetic moment, or dipole, associated with it. Only nuclei with an odd number of nucleons (protons or neutrons) exhibit a net spin and therefore lend themselves to NMR spectroscopy.

In general the magnetic dipoles of the nuclei with spin will be pointing in random directions. When they are placed in a magnetic field, however, they will orient themselves with the field's lines of induction, or lines of force. For nuclei of the spin designated 1/2, such as protons (hydrogen nuclei, ^1H), the only allowed orientations of the dipoles are parallel to the field or antiparallel to it (in the opposite direction). The two orientations have slightly different energies, described as a Zeeman splitting of the energy levels. In the case of protons the difference between the number of protons with spin "up" (parallel) and spin "down" (antiparallel) is very small: only about one part in 10^8, with a slight excess in the lower energy state (spin up).

The magnetic behavior of the entire population of nuclei can be predicted by defining a macroscopic, or bulk, magnetization vector, M, that represents the net effect of all the magnetic moments of the nuclei of a given nuclear species in the sample of material being examined. In the absence of an external magnetic field the bulk magnetization is of course zero. When a magnetic field is imposed on the sample, however, the nuclear dipoles become oriented to yield a finite equilibrium bulk magnetization that will point in a direction parallel to the applied magnetic field. This direction conventionally defines the z axis.

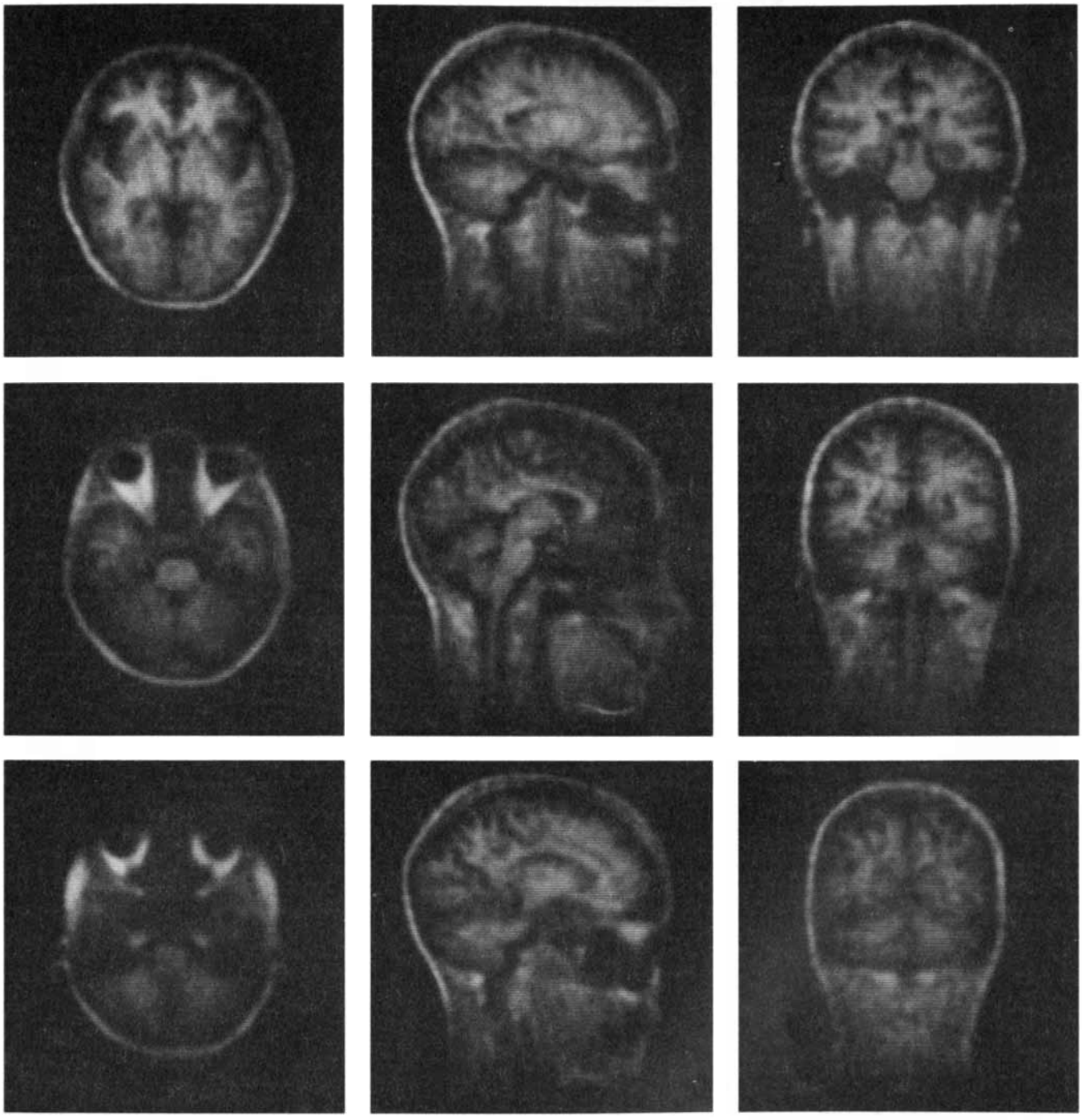
Spinning nuclei behave rather like tiny tops or gyroscopes. If the axis of a spinning gyroscope is tipped away from the vertical, the gyroscope will rotate about its former axis in a motion describing the wall of a cone. It is the motion called precession. Similarly, if the bulk magnetization M, corresponding to an assembly of spinning nuclei in a magnetic field, is tipped away from the z direction, M will precess about the z axis. Such a tipping can be achieved by applying a much smaller magnetic field that is rotating in the x-y plane, at right angles to the static (nonrotating) field. In practice the rotating magnetic field is applied by surrounding the sample with a coil connected to a source of radio-frequency power. In order to tip the macroscopic spin vector away from the z axis the frequency of the applied electromagnetic radiation must match the natural precessional frequency of the nuclei of the sample, hence the term nuclear magnetic resonance.

A simple mathematical relation links the resonance frequency, often called the Larmor frequency, to the value of the externally applied static magnetic field. The frequency is equal to the strength of the field multiplied by the "gyromagnetic ratio," which is unique for each nuclear species of nonzero spin. For hydrogen nuclei (protons) in a magnetic field of one tesla (10,000 gauss) the resonance frequency is 42.57 megahertz (MHz), or 42.57 million cycles per second. For nuclei of the isotope phosphorus 31 (^{31}P) in the same field the resonance frequency is 17.24 MHz; for nuclei of sodium 23 (^{23}Na) it is 11.26 MHz. These frequencies are in the radio-frequency band of the electromagnetic spectrum. Such frequencies, far below those of X rays or even visible light, are powerless to disrupt the molecules of living systems.

It is evident, therefore, that by the proper choice of frequency one can "tune in" to specific nuclear species and observe their response in isolation. All medical NMR images produced so far,

however, have been obtained with the resonances only of hydrogen nuclei. Other nuclei not only have a lower intrinsic NMR sensitivity but also are found in much lower concentrations in biological material.

From the quantum-mechanical viewpoint the tipping of the bulk magnetization vector of an assembly of nuclei away from its equilibrium position is equivalent to a transition from a lower energy state to a higher one. The transition is effected only when the energy of the quanta carried by the radio-frequency field exactly equals the difference in magnetic energy between the two energy states. The fact that medical NMR images can be most easily generated from the resonance of hydrogen nuclei is fortunate, because the human body is 75 percent water, each molecule of

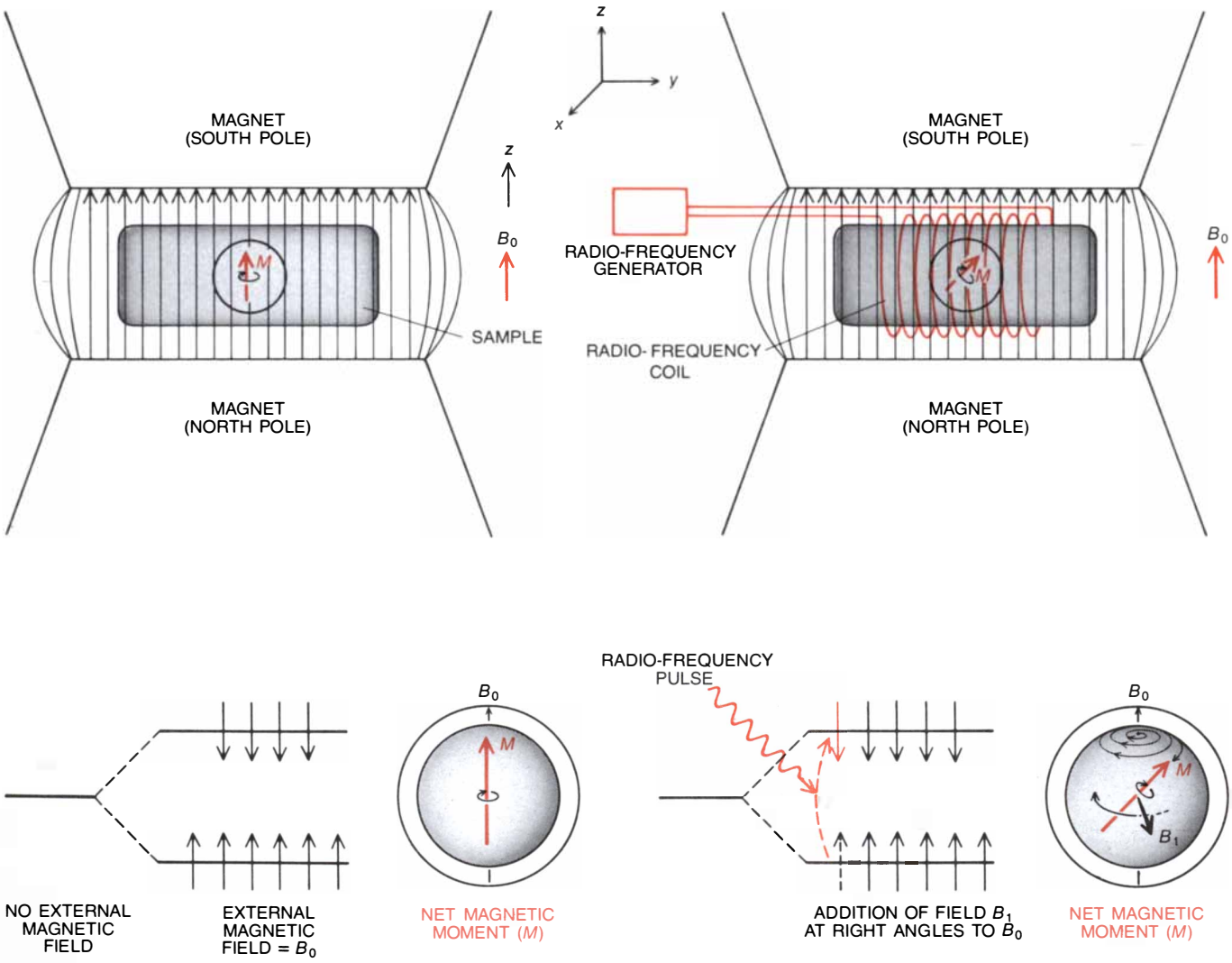


NMR IMAGES are cross-sectional pictures of thin slices through the body obtained by using radio waves to interrogate susceptible atomic nuclei that have been precisely oriented in a magnetic field. The susceptible nuclei are those that have an odd number of nucleons (protons or neutrons) and therefore exhibit a net spin. Hydrogen nuclei (protons) are the most ubiquitous in living matter. After radio excitation the nuclei reveal their location by emitting a signal of precise frequency for a brief period. With computer techniques pictorial images can be reconstructed from the emitted signals. Here are nine images of a human head, reconstructed from a single three-dimensional data collection, showing primarily the distribution of proton-containing water and lipid molecules in blood and tissue. The three transverse images at the left show sections at three levels: through the center of the brain (*top*), at eye level (*middle*) and just below eye level (*bottom*). The three images in the middle show a section at the midline (*center*) and parallel sections about three centimeters to the left and right. The three images at the right show the head from the front at the brain's widest point (*top*) and at two regions farther to the rear. The images, which were made in the NMR research laboratory of the Massachusetts General Hospital, were generated with NMR apparatus built by the Technicare Corporation of Solon, Ohio. The apparatus had a magnet operating at .15 tesla (1,500 gauss).

which has two hydrogen nuclei. Moreover, the distribution of water, together with that of various other small, hydrogen-rich molecules (for example lipids), is known to be altered by many disease states.

The displacement angle between the nuclear magnetization vector M and the direction of the static magnetic field continues to increase for as long as the rotating field is applied to the sample, and the rate of increase depends on the power of the field. A pulse long and strong enough to tip M from its initial position until it is just rotating in the x-y plane is termed a 90-degree pulse. But how does one know that there has been any tipping? Immediately after the application of a 90-degree pulse the magnetization vector continues to rotate freely in the x-y plane, and in so doing it generates a small electromotive force that can be detected either by the same coil that transmitted the pulse or by a separate receiver coil. The emitted signal is called the free induction signal or free induction decay. In quantum-mechanical terms the signal is generated as the nuclei drop back from the excited energy level to the ground state, the lowest energy level.

After the excitation pulse ends, the magnetization vector of the nuclei eventually returns to its original position directed along the z axis. The return to equilibrium is characterized by two principal "relaxation" times, T_1 and T_2. To discuss T_2 first, it is called the spin-spin relaxation time or the transverse relaxation time. Spin-spin relaxation phenomena influence the natural lifetime of the free induction signal, during which the various components of magnetization in the x-y plane remain more or less in phase. When the excitation pulse ends, each nucleus continues to "feel" not only the external static field but also local fields associated with the magnetic properties of neighboring nuclei. The nuclei will therefore acquire a range of slightly different precessional frequencies, causing the free induction signal to go out of phase. In a liquid, where the atoms and their nuclei are continuously in motion, the internuclear magnetic fields responsible for spin-spin relaxation tend to average out. As a result the signal decays much more slowly than it would in a solid, where the nuclei



IN THE PRESENCE OF A MAGNETIC FIELD, B_0, nuclei with nonzero spin orient themselves with the magnetic field lines, which point in the z direction (*left*). A net magnetic moment M, aligned parallel to the field, is therefore generated within the sample. In quantum-mechanical terms the alignment corresponds to the creation of multiple magnetic energy levels. For nuclei with the spin designated 1/2, which include protons, two levels are established, with a small excess of nuclei in the lower energy state. The vector M can be made to precess about the magnetic field direction as if it were a falling top. This is done (*right*) by applying a second magnetic field, B_1, which has a rotating component in the plane x-y at right angles to the static (nonrotating) field. Only when the frequency of the rotating field exactly matches the Larmor frequency (the natural resonance frequency) of the nuclei is M tipped toward the x-y plane. B_1 is generated by placing around the sample a coil that applies radio-frequency energy to the spin system. In quantum-mechanical terms quanta of radio energy that exactly match the gap between energy levels will cause some nuclei to "flip" from the lower energy state to the higher one.

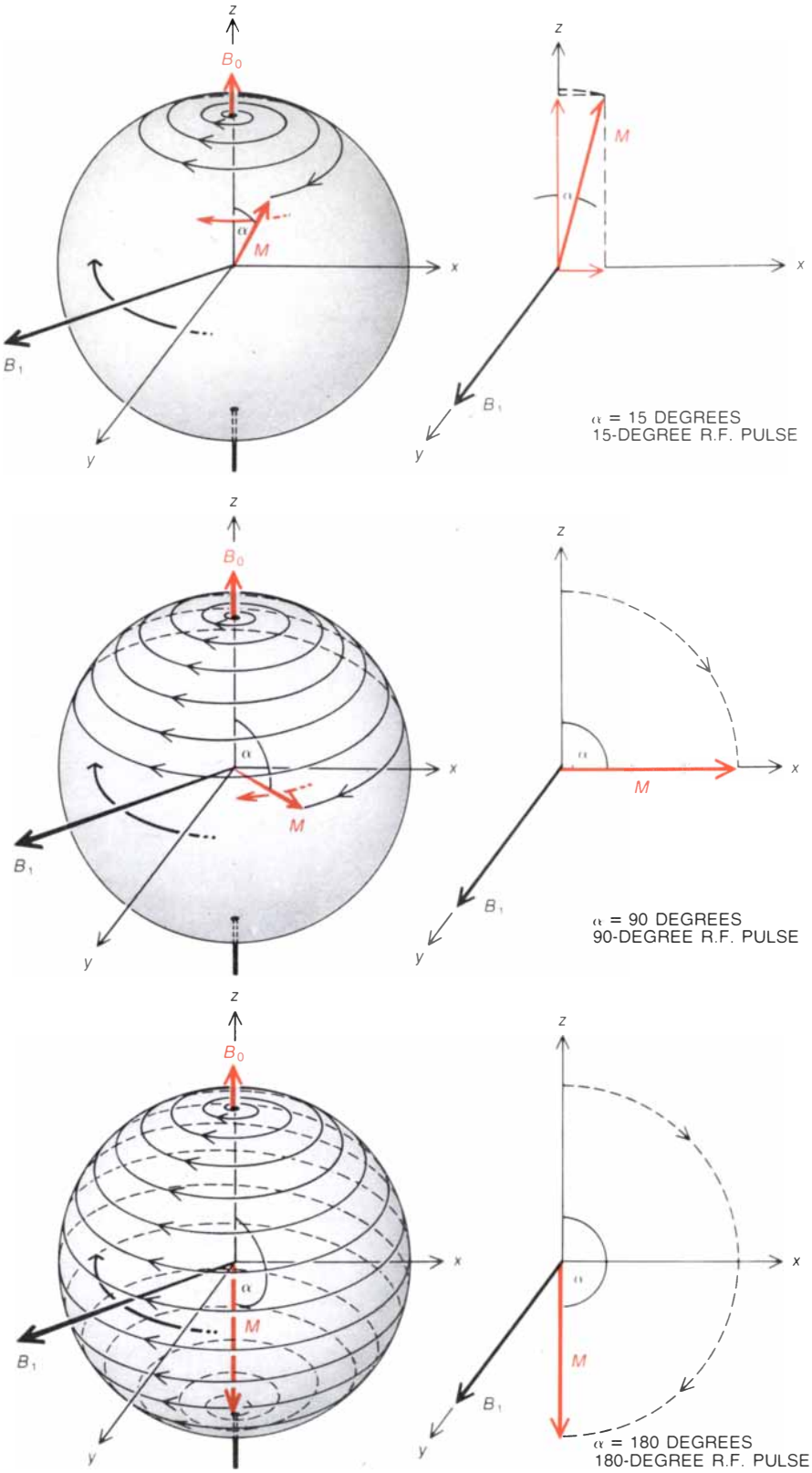
remain essentially fixed in space. In a pure liquid T_2 can be as long as several seconds. In a solid it is usually only a few microseconds; indeed, the signal decays so fast that it is generally undetectable.

If the static magnetic field were perfectly uniform, T_2 could be determined simply by measuring the rate of decay of the free induction signal. The fields generated by real magnets, however, are always less than perfect. Even though the imperfections in the best magnets used for NMR spectroscopy are extremely small, they cause the free induction signal to decay faster than it would if the magnetic field were perfectly homogeneous. The time constant defining the actual rate of signal decay in an imperfect field is designated T_2^* ("T two-star") to distinguish it from the true relaxation time T_2.

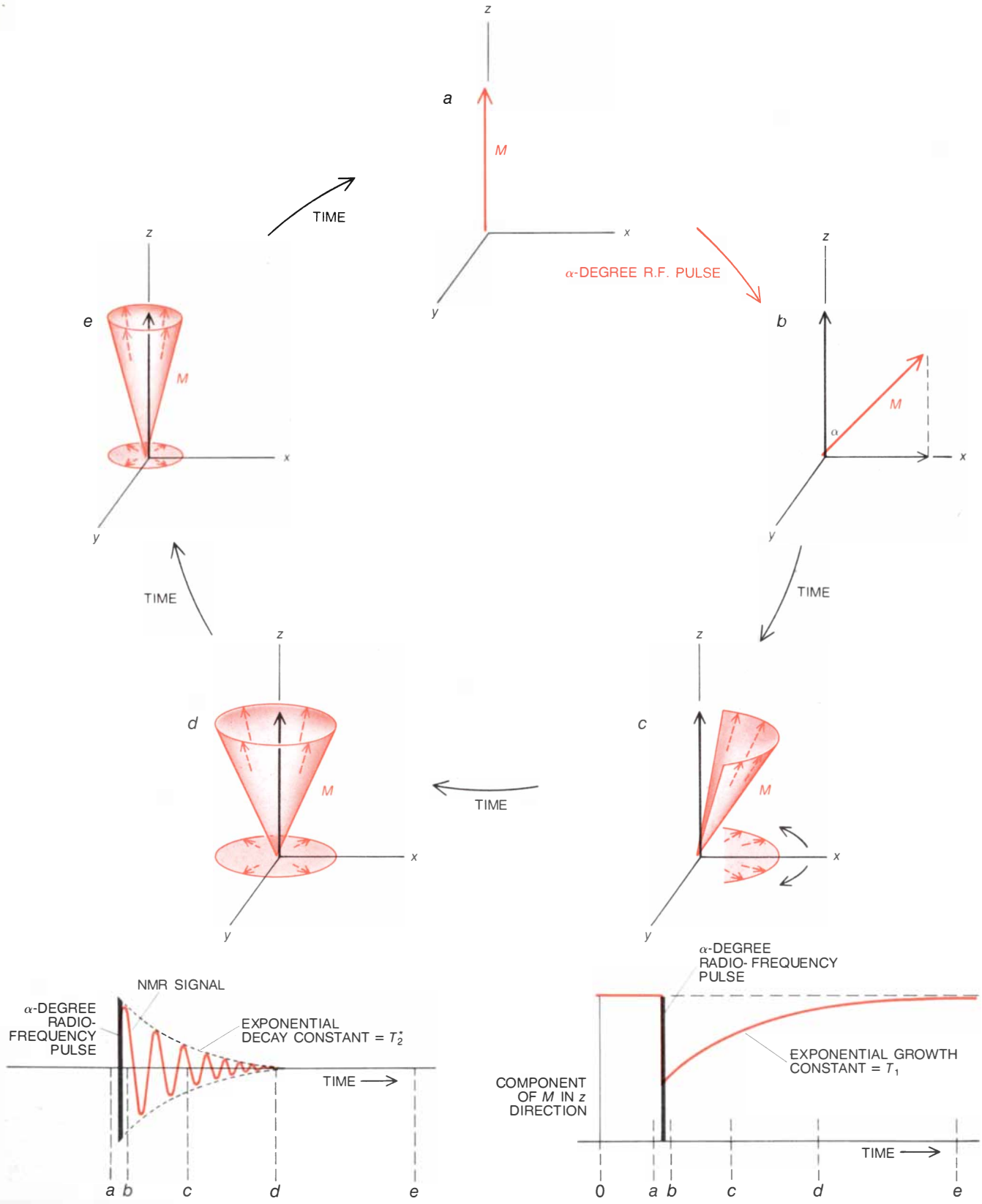
It is nonetheless possible to determine the intrinsic T_2 value for a sample of material even when it is in an imperfect field, because the nonuniformities in the magnetic field are constant and can in effect be identified and canceled. For this purpose one can recall the signal in the form of a "spin echo," or a series of echoes, by applying a special pattern of radio-frequency pulses called the Carr-Purcell pulse sequence. In such a sequence the initial free induction decay signal and each of the individual spin echoes decay with a time constant T_2^*, but the peak heights of successive spin echoes decay with a time constant equal to the intrinsic T_2 value of the sample.

The other relaxation time, T_1, is known as the spin-lattice relaxation time or longitudinal relaxation time. T_1 is characteristic of the time required for the spin system to return to thermal equilibrium with its surroundings (the "lattice") after the excitation pulse ends. In quantum-mechanical terms the fluctuating magnetic fields of the nuclei making up the lattice must have appropriate frequency components to stimulate transitions from the upper magnetic energy level back down to the ground state. In solids or in samples of material at low temperatures, where the atoms and molecules move about very little, there will be few components at the right frequency, and T_1 can last for hours. For protons in pure, simple liquids, such as distilled water, T_1 and T_2 are approximately equal (a few seconds), an indication of the mutual dependence of the relaxation times on the fluctuating, internal magnetic fields.

In liquid and liquidlike materials, then, the ratio of T_2 to T_1 tends to approach unity, but in solid materials the ratio is very small. The internuclear ("dipole-dipole") magnetic interactions that cause T_2 to be extremely short in solids can be effectively canceled by resorting to complex multiple-pulse cy-



PRECESSIONAL ANGLE, α, continues to increase as long as the rotating magnetic field, B_1, is applied. The precessional frequency, however, remains constant, being fixed by the inherent properties of the nuclei and the strength of the static field, B_0. The radio-frequency pulse needed to tip the vector of the net magnetic moment M through an angle of 15 degrees is described as a 15-degree pulse. Pulses of 90 and 180 degrees cause corresponding increases in the precessional angle. To an imaginary observer rotating with the magnetization vector at the Larmor frequency (*right*) the increase in the precessional angle would appear to be a simple rotation of M about the applied field B_1, which would appear to be stationary. Whenever a net component of M exists in the x-y plane, an electromotive force is generated that can be detected by a coil surrounding the sample. This electromotive force is the origin of the NMR signal.



IN A PULSED NMR EXPERIMENT the emitted signal is observed after the radio-frequency energy that induces precession is turned off. In these diagrams the frame of reference is assumed to be rotating at the average Larmor frequency. After a radio-frequency pulse tips the vector of net magnetic moment M through some angle, α, there will be a component of M in the x-y plane (*b*). For a brief instant the NMR signal is at a maximum (*curve at bottom left*). Nuclei immediately begin to precess, however, at slightly different rates because of magnetic interactions between nuclei and slight nonuniformities in the magnetic field. The net component of M in the x-y plane therefore diminishes, and the signal amplitude decays exponentially with a time constant T_2^* (*c, d*). If the magnetic field B_0 is perfectly uniform, the signal decay time is longer, and the time constant is T_2, called the spin-spin relaxation time. Simultaneously the longitudinal component of magnetization increases as M returns to its equilibrium position, aligned with the z axis (*e*). This relaxation, designated T_1 (spin-lattice relaxation time), measures the time needed for the spin system to return to thermal equilibrium (*curve at bottom right*).

cles. Such cycles, however, have not yet been employed for medical NMR imaging; only liquidlike regions in biological materials yield any appreciable signal.

We have seen that it is possible to determine the material's intrinsic relaxation time T_2. It is also possible to determine the intrinsic value of T_1. This is done by applying a second pulse after the signal has decayed but before there has been full spin-lattice relaxation. The second pulse will evoke another free induction signal, but the amplitude in this case will be smaller. The explanation is that the strength of the evoked signal is proportional to the longitudinal component of magnetization along the field direction z just before the pulse is applied. Before the initial pulse all the nuclei are aligned with the field, and the evoked signal is therefore maximal. The second pulse, however, is applied while the component of magnetization is still in the process of returning to the aligned position, so that the evoked signal is not as strong as the original one. Since the component of magnetization returns to its equilibrium value exponentially with a time constant T_1, the respective amplitude of the two signals is a measure of that constant.

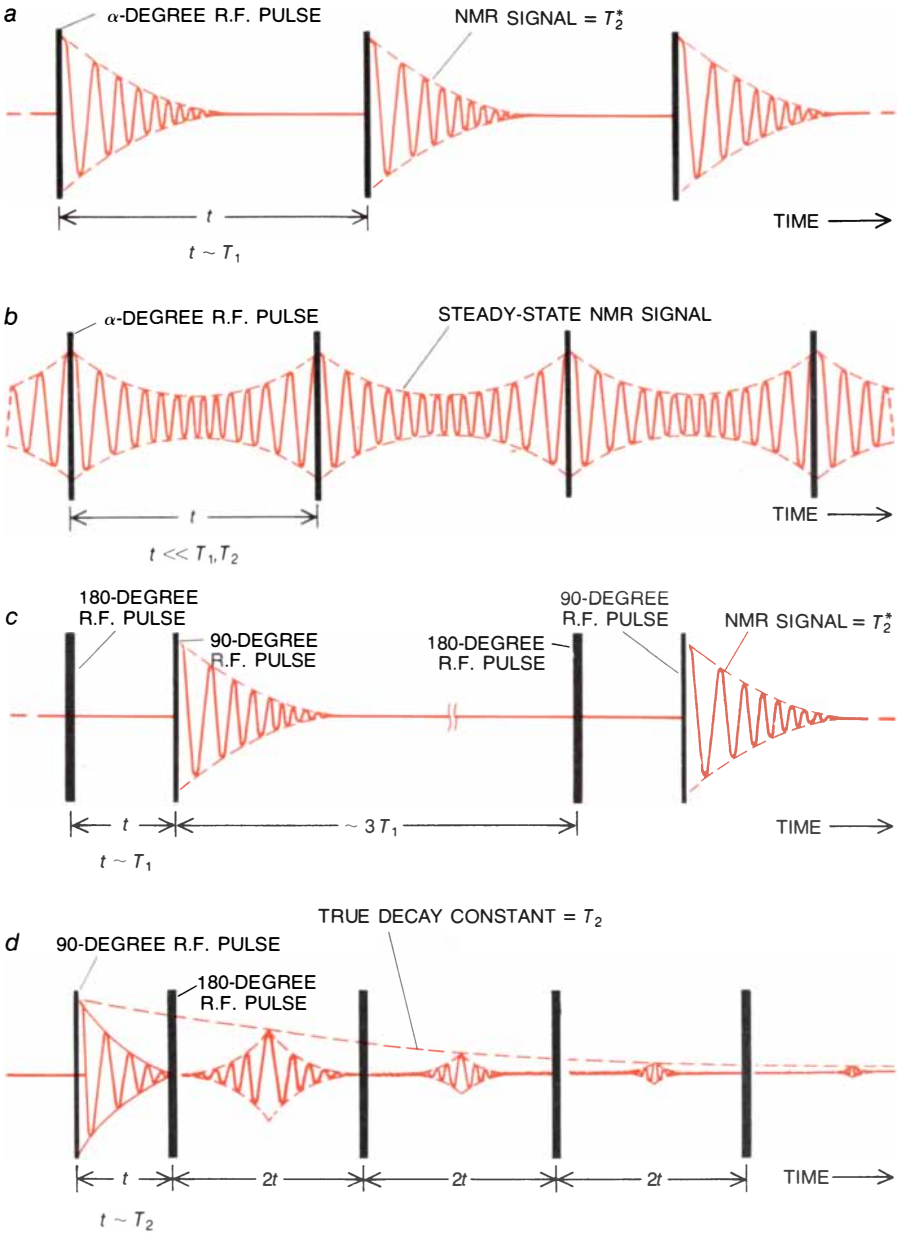
Variations in the value of T_1 can be exploited in NMR imaging to increase the contrast between different regions in samples of soft tissue. Differences in T_1 values can be brought out by means of special pulse sequences, for example the "saturation-recovery" sequence. Here the sample is exposed to a train of radio-frequency pulses with a constant spacing between pulses. Provided that complete spin-spin relaxation (T_2) occurs in each pulse interval, the amplitude of free induction decay signals will reach a steady-state value that is dependent on both the value of T_1 and the density of liquidlike nuclei contributing to the signal. The relation to signal strength is such that for areas in the image where T_1 is long compared with the interval between pulses the image intensity is weak.

This imaging procedure yields images that are said to be T_1-weighted. If two or more images are obtained with different spacings between pulses, it is possible to calculate from the data a T_1 value for each pixel, or picture element, in the image, independent of spin density. The result is a "T_1 map." The T_1 differences identified in this way are extremely useful in proton NMR imaging because proton T_1 differences among various soft tissues are much greater than corresponding differences in mobile proton density.

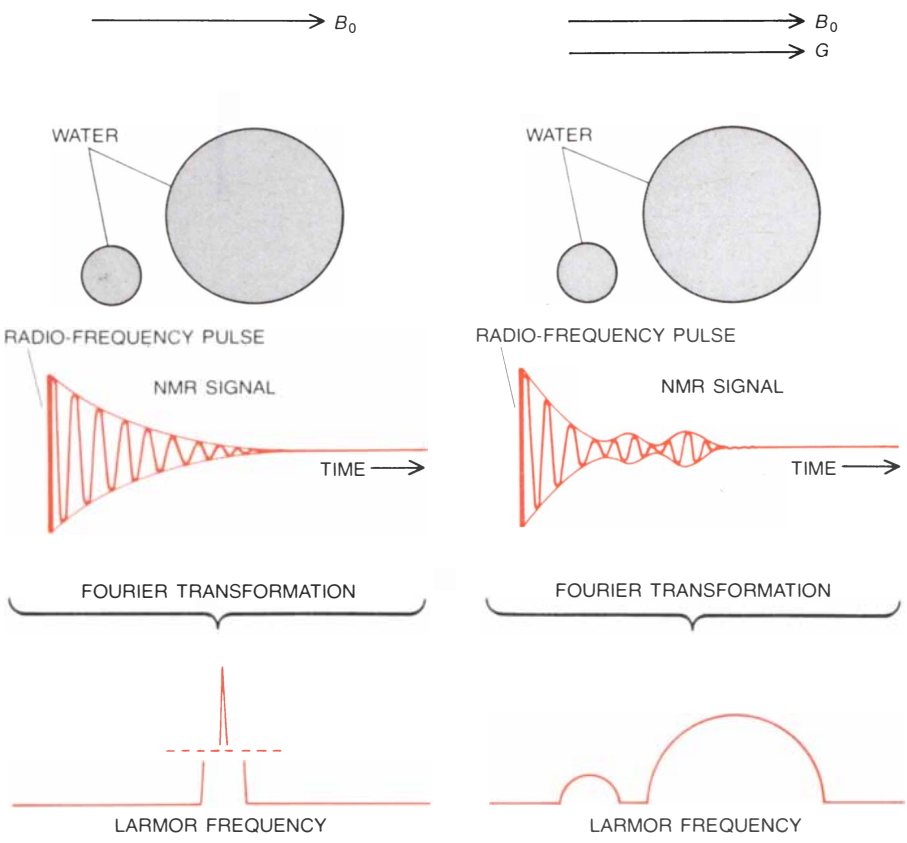
If the pulses are applied so rapidly that the signal does not decay to zero between successive pulses, a different steady-state condition arises in which the signal intensity is dependent on T_2 as well as T_1. This pulse sequence is called steady-state free precession, or SSFP. Although images of very high quality have been generated with the SSFP sequence, it is not easy to separate the individual contributions of T_1 and T_2 to the resulting image intensity.

Another frequently adopted pulse pattern is the "inversion-recovery" sequence, which resembles the saturation-recovery sequence in that T_1 variations in the sample are emphasized. In this pattern the bulk magnetization vector is first completely inverted by applying a 180-degree pulse to the sample. T_1 relaxation proceeds during a selected pulse interval, after which a 90-degree "read" pulse is applied. The free induction signal that follows the read pulse serves to generate the image.

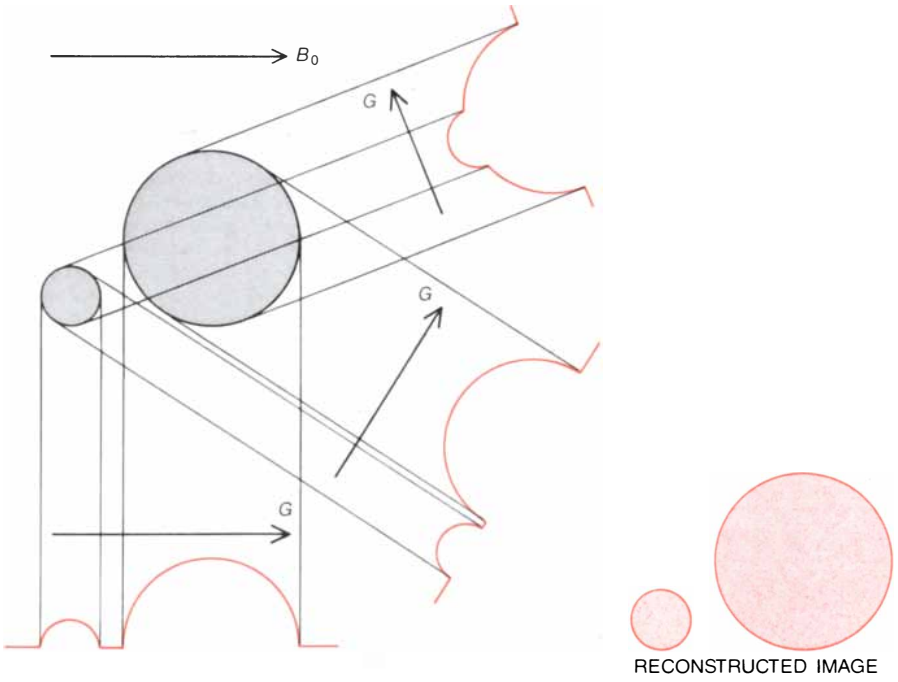
The inversion-recovery sequence gives



VARIOUS PULSE PATTERNS that emphasize different aspects of the evoked NMR signal can be exploited to alter the contrast of NMR images. In a "saturation-recovery" pulse sequence (*a*) a series of 90-degree pulses is applied with an interpulse spacing, *t*, longer than the decay time T_2 and roughly the same length as T_1. When the value of *t* is changed, variations in T_1 in different parts of a sample will show up as differences in image intensity and a "T_1 map" can be generated. If *t* is much shorter than T_2, the signal will not decay to zero between successive pulses, creating a condition known as steady-state free precession, or SSFP (*b*). Now image contrast can be altered by changing the pulse angle α. In the "inversion-recovery" pulse sequence (*c*) the magnetization vector is inverted by first applying a 180-degree pulse and then a 90-degree "read" pulse. This sequence also emphasizes T_1 variations in the sample. The "Carr-Purcell spin echo" sequence (*d*) consists of a 90-degree pulse followed by a series of 180-degree pulses. Here the resulting images are strongly dependent on the spin-spin relaxation time T_2.



METHODS OF CREATING NMR IMAGE call for spatial "encoding" of the NMR signal. Here the sample is water in two cylinders, viewed from above. The hydrogen NMR signal obtained in NMR spectroscopy (*left*) appears as a single tall spike after Fourier transformation, a mathematical process that converts a curve representing signal strength v. time into one representing signal strength v. frequency. If a linear magnetic field gradient, *G*, is now added to the original static field, B_0, the evoked signal, after Fourier transformation, takes the form of a curve that is representative of the shape of the sample (*right*). The area under the curves represents the total number of protons in the sample, and therefore the area is equal for both.



IN PROJECTION-RECONSTRUCTION IMAGING a magnetic field gradient is rotated to obtain "snapshots" of the sample at many different angles covering an arc of at least 180 degrees. From such a set of data a computer can reconstruct a cross-sectional image of the sample. The method is analogous to the one in X-ray computerized tomography (CT scanning).

an image of higher contrast than the saturation-recovery sequence, but a penalty is paid in the form of either longer imaging time or reduced spatial resolution. The reason is that if errors in T_1 determinations are to be avoided, a delay time equal to at least three times the value of T_1 should be allowed to elapse before repetition of the 180- and 90-degree pair of pulses. T_1 maps can also be derived from inversion-recovery pulse patterns. The spin-echo pulse sequence mentioned above is useful for creating images that are primarily or solely dependent on the spin-spin relaxation time, T_2.

Therefore by choosing an appropriate pulse sequence, the intensity of an NMR image can be made to reflect one or more of several NMR parameters inherent to the tissue being examined. Such parameters in turn are sensitive to the physicochemical environment of the nuclei and underlie the conviction that NMR imaging holds promise for detecting disease early and for monitoring its progress.

The foregoing methods for manipulating the NMR response apply not only to NMR imaging but also to NMR spectroscopy, in which the signal elicited represents a summation of the NMR response from the entire sample of material. But if the nuclear signal comes from the entire sample, how can it be encoded with spatial information? As long ago as 1951 Robert Gabillard of the École Normale Supérieure in Paris was puzzled by the reverse question: he noted that the NMR signal could be distorted according to the shape and size of the sample. This was correctly attributed to nonuniformities in the static magnetic field. The degree of distortion depends on how much of the sample is in nonuniform parts of the field and on the magnitude of the nonuniformities.

A continuing effort in NMR instrumentation has therefore been to remove the influence of sample shape on the NMR signal by making magnets with fields of ever increasing homogeneity and stability. The quest may conceivably have delayed the advent of NMR imaging, because in imaging it is necessary to make the field nonuniform deliberately, albeit in a controlled manner, usually by superimposing on it a linear magnetic field gradient.

The primary motivation for perfecting the static field of magnets has come from the desire of NMR spectroscopists to measure the subtle "chemical shift" in samples incorporating molecules of complex structure. One might expect all nuclei of the same species in a homogeneous magnetic field to have the same resonant frequency; that is to say, one would expect to observe a single, narrow peak in the NMR frequency spec-

trum. For nuclei in samples consisting of very simple molecules (such as for the hydrogen nuclei of pure water) this is indeed so. For more complex molecules, however, the magnetic field is subtly altered around some nuclei as a result of "shielding currents" that are associated with the distribution of electrons around adjacent atoms. Such alterations cause shifts in the resonance frequency that are representative of particular molecular conformations and therefore directly aid in the determination of chemical structure.

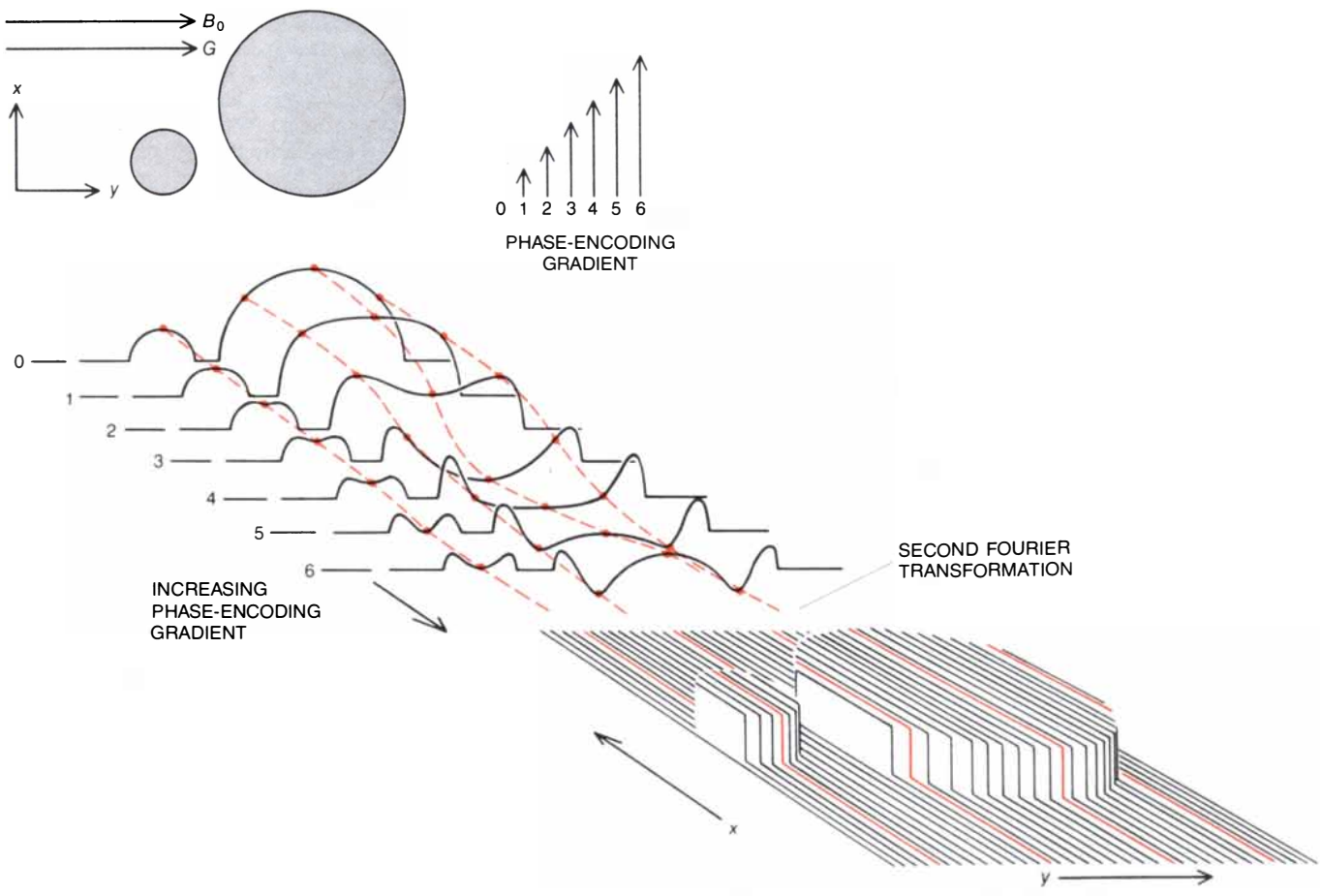
These chemical shifts are very small, being measured in parts per million with respect to the strength of the static magnetic field, and this explains why such emphasis has been placed on the construction of magnets with a highly uniform field. In the current generation of NMR imaging systems the static magnetic field is not uniform enough to show chemical shifts with a useful degree of accuracy. In any case the imaging procedure itself (specifically the application of the field gradients) often precludes the extraction of such information.

The first published NMR image can be credited to Paul C. Lauterbur of the State University of New York at Stony Brook. In a 1973 article he presented images of two water-filled capillary tubes, obtained with a modified NMR spectrometer. The sample can be regarded as a medium that couples the radio-frequency field to the gradient of the magnetic field, and so Lauterbur called his imaging method zeugmatography, from the Greek *zeugma,* that which joins together.

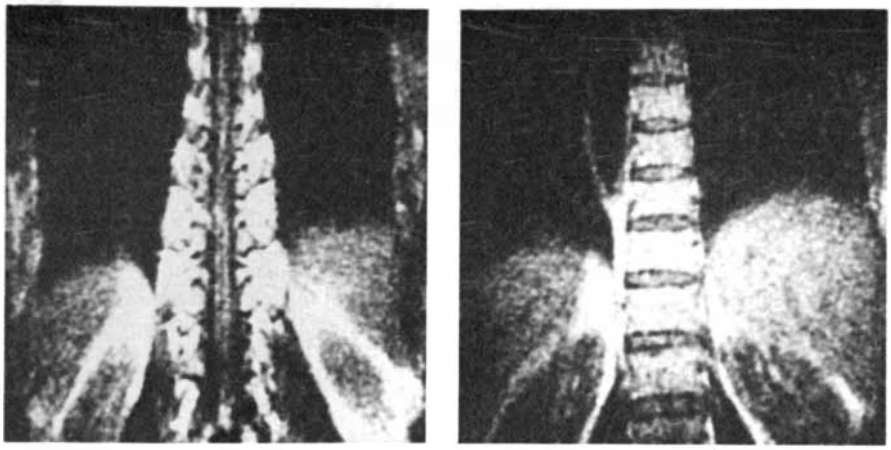
NMR imaging systems can be designed to receive data from a single point in the sample, from a line, from a plane or from the complete three-dimensional volume all at once. In point- or line-scanning methods images can be generated by electronically moving the selected point or line through the sample in a raster, or sequential pattern. Such methods, however, have been almost entirely superseded by two- and three-dimensional methods, which are much more efficient.

Most of the two- and three-dimensional methods call for the application of a linear magnetic field gradient to supply one dimension of spatial information. Resolution in the second and third dimensions can be achieved by sequentially stepping gradient magnitudes or directions through a predetermined set of values. There are other approaches. Rotating-frame zeugmatography, first reported by David Hoult of the National Institute of Dental Research, is unique in that it exploits a gradient in the radio-frequency field as well as one in the static magnetic field. Peter Mansfield of the University of Nottingham has devised a very high-speed method, echo-planar imaging, that generates a complete, spatially resolved image following a single radio-frequency pulse.

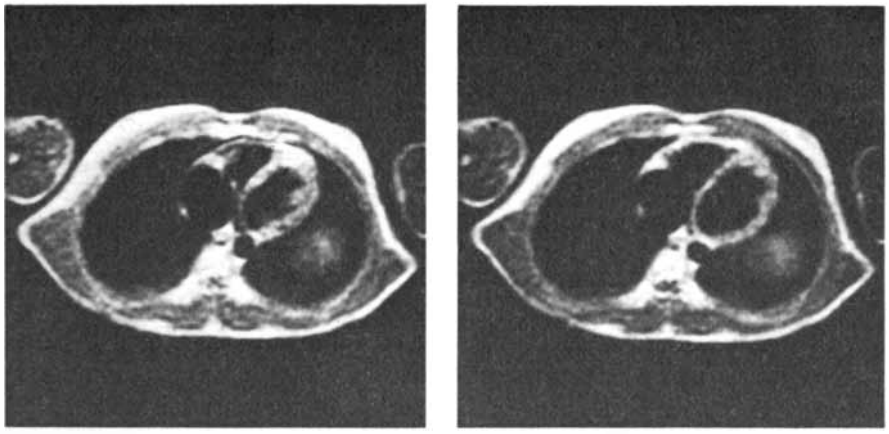
The first images produced by Lauterbur borrowed image-reconstruction computer algorithms, used also in CT scanning. If a sample of water is placed in a homogeneous magnetic field, the NMR frequency spectrum of the hydrogen nuclei in the water molecules is a single narrow line. If the magnetic field



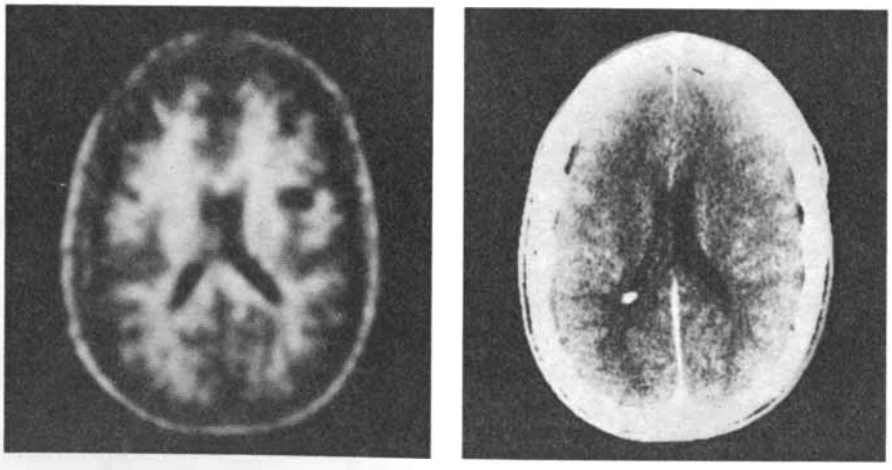
IN FOURIER ZEUGMATOGRAPHY another magnetic field gradient is applied for a short time just before the usual gradient, *G,* is turned on. This new gradient, termed a phase-encoding gradient, is applied at right angles to the original one, and its magnitude is raised from zero in a series of many small steps. The effect of the two gradients on the NMR signal is such that after Fourier transformation a series of increasingly "phase-distorted" projections are generated. Corresponding points from each of the projections (*broken lines in color*) are then subjected to a second Fourier transformation to generate the final image. The term zeugmatography is from the Greek *zeugma,* that which joins together. It alludes here to the way the sample couples the radio-frequency field and the magnetic-gradient field.



LUMBAR REGION OF THE HUMAN SPINE is depicted in two reconstructions from three-dimensional NMR data set. The image at the left shows the spinal cord within the spinal canal. In the image at the right the plane of the image has been moved a few centimeters to reveal the intervertebral disks. It is difficult to obtain clear pictures of the spine over such a large area with a CT scan or any other imaging method. The images were provided by Technicare.



"GATED" IMAGES OF THE HEART are shown in NMR cross sections of the human chest. (The two smaller shapes at each side of the chest are the arms.) The image at the left shows the heart at the end of systole, when the chambers are being emptied. The image at the right shows the end of diastole, when the chambers are filled. The images, supplied by Technicare, were made by gating, or synchronizing, the recording of data to match the stage of the cardiac cycle.



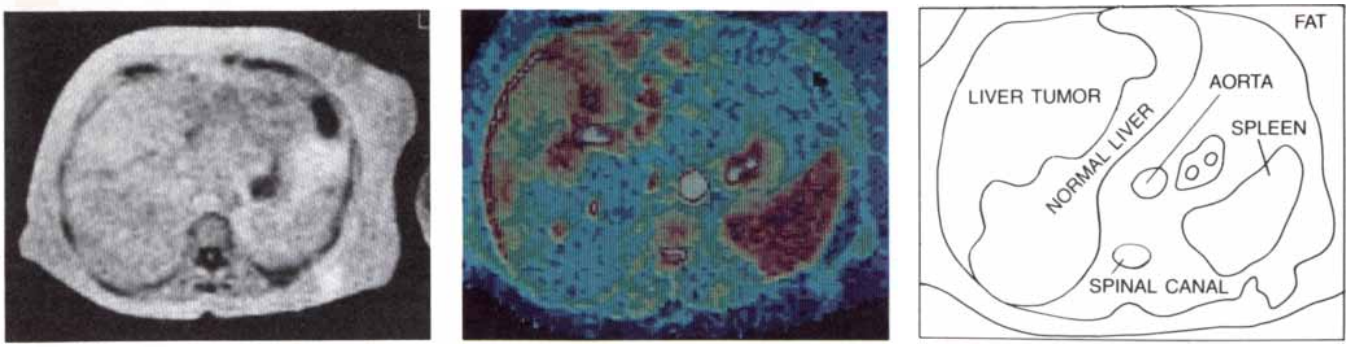
NMR IMAGE AND X-RAY CT-SCAN IMAGE can be compared in these two transverse views of the brain of a patient with a brain tumor. In the NMR image (*left*), reconstructed from three-dimensional data, the tumor is a dark circular area at the right side of the brain. In the CT scan (*right*) the tumor is all but invisible. The pictures, made at the Massachusetts General Hospital, are reproduced with permission of *Journal of Computerized Axial Tomography*.

is perfectly uniform, the shape of the line is independent of the geometry of the sample. If a linear magnetic field gradient is now superimposed, resonant nuclei at one side of the sample will feel a weaker total magnetic field than those at the other side. There will thus be a linear distribution of Larmor frequencies across the sample. Then the free induction decay signal can be subjected to Fourier transformation, a mathematical procedure that transforms the data from a curve representing signal strength v. time into one representing signal strength v. frequency.

The result is a spectrum that is broadened to a shape corresponding to the one-dimensional projection of the strength of the NMR signal onto the frequency axis. By rotating the magnetic field gradient electronically one can get a projection from a slightly different angle. Computer analysis of many such projections reconstructs the sample's geometry. In the two-dimensional application of the technique the direction of the gradient is rotated within a single plane. In the three-dimensional extension of the method the gradient is rotated in three-dimensional space through at least half a sphere.

Two-dimensional Fourier-transformation imaging, or Fourier zeugmatography, was first demonstrated in 1975 by A. Kumar, D. Welti and R. R. Ernst of the Swiss Federal Institute of Technology. Their method owes more to NMR spectroscopy than to CT reconstruction algorithms, because both amplitude information and phase information are acquired to spatially encode the signal. The first step again calls for generating a one-dimensional projection, but here a phase-encoding gradient is applied just before the original gradient is turned on. The phase-encoding gradient is applied at right angles to the original gradient, and its duration (or amplitude) is successively increased from zero, rather than the gradient's being progressively rotated, as was done in the original form of zeugmatography. The phase-encoded projections are stacked in increasing order of magnitude of the phase-encoding gradient, and the corresponding points from each projection are Fourier-transformed a second time to generate the final image [*see illustration on preceding page*].

Nuclear magnetic resonance is inherently a three-dimensional phenomenon. Since NMR signals are normally obtained from the total volume of material enclosed within the transmitter and receiver coils, considerable ingenuity is required to reduce the volume from which signals come to defined points, lines or planes. In one method, called selective irradiation, a radio-frequency pulse is applied that is specially tailored



MIDSECTION OF A CANCER PATIENT appears in two NMR images made by James M. S. Hutchison, Francis Smith and John R. Mallard and their co-workers in the Faculty of Medicine at the University of Aberdeen, using a .04-tesla imaging system. The black-and-white image is a simple record of proton density. The colored image is a computer synthesis of a series of images obtained by altering the pulse sequence to discriminate among tissues on the basis of their T_1 relaxation-time differences. Color coding was then introduced to enhance the discrimination. The patient had a cancer of the rectum that had spread to the liver. The normal liver tissue appears light blue. The cancerous regions are yellow-brown. The spinal cord and the spinal canal are more clearly seen in the proton-density image.

to consist of only a very narrow band of frequencies. Only those nuclei lying within a single slice perpendicular to the direction of a plane-selection gradient will exhibit resonant frequencies corresponding to those in the radio-frequency pulse. Hence only a thin, isolated slab of material is irradiated. The thickness or position of the plane can be altered by changing the width or the frequency offset of the irradiation spectrum electronically.

A second method, devised by Waldo S. Hinshaw, who was then working at the University of Nottingham, imposes an oscillating magnetic field to select a particular plane. In this method the direction of the plane-selection field gradient is periodically reversed, often sinusoidally. There is then just one plane at the fulcrum of oscillation within which the magnetic field remains time-independent; signals from outside this plane vary in such a way that they do not contribute to the intensity of the image. These are just two of several possible methods for selecting planes.

Although whole-volume methods offer important advantages, they also have some technical drawbacks. The sheer mass of data acquired calls for a computer with a large data-handling and storage capacity. For example, generating a three-dimensional image that shows 256 data points in each dimension, with 256 levels of signal intensity (equal to eight bits) per data point, calls for a system with more than 134 million bits of memory ($256^3 \times 8$). Moreover, many sequential values of field-gradient magnitude or direction are needed to uniquely define all the points in such a three-dimensional data matrix. This lengthens the data-collection time, particularly if T_1 maps are desired. For such reasons it is sometimes preferable to generate a small number of selected two-dimensional images. Although it is true that a single two-dimensional image can usually be acquired in less time than a true three-dimensional image, the three-dimensional one can be "dissected" at leisure into a great many slices, so that the imaging time per plane is much reduced.

The spatial resolution of a three-dimensional set of data is usually isotropic, or equal in all three dimensions. Therefore two-dimensional slices of selected thickness, with any position or orientation, can be generated at any time after the primary data have been acquired. With three-dimensional data in hand, surfaces can be detected mathematically, enabling the clinician to determine the volume of organs or of pathological lesions.

In medical practice many factors must be considered when a particular imaging method is being chosen, particularly the time scale of involuntary movements of the tissue being studied. The head, for example, is particularly amenable to true three-dimensional imaging because it can be held still for the duration of the scan. The heart, on the other hand, which beats incessantly, requires either a high-speed imaging method or one that can "gate," or synchronize, the data collected over a series of cardiac cycles.

The apparatus needed for NMR imaging exploits the same basic technology developed for NMR spectroscopy. Indeed, many of the early imaging experiments were conducted with modified NMR spectrometers. The signal-to-noise ratio of an NMR image can be improved by increasing the strength of the static magnetic field of the apparatus. As the field strength is increased the Larmor-precession frequency of the nuclei in the sample of material being examined increases linearly, and a higher radio frequency is needed. The drawback is that both the transmitted and the emitted signals are more strongly absorbed as the frequency is increased. For imaging the whole human body such attenuation may become a limiting factor when the frequency exceeds about 15 megahertz, which for proton imaging corresponds to a field strength of .35 tesla (3,500 gauss). This field strength would be regarded as a low one in NMR spectroscopy, but in NMR imaging the large working volume in which uniformity of magnetic field is needed has called for novel approaches to magnet design.

At present the two commonest magnet designs are the four-coil air-core ambient-temperature magnet and the large-bore, helium-cooled superconducting magnet. NMR systems with conventional nonsuperconducting magnets are less costly and are entirely satisfactory for whole-body proton imaging at field strengths below about .2 tesla, for which the power consumption is about 50 kilowatts and cooling requirements are not prohibitive. Superconducting magnets, although they are initially much more expensive, may have lower operating costs and are able to generate magnetic fields that are both stronger and stabler than those attainable with nonsuperconducting magnets. Superconducting magnets are therefore preferred if it is intended to image nuclei other than hydrogen, which demand significantly stronger fields. For example, the observation of phosphorus 31 at 15 megahertz calls for a field strength of .87 tesla. One critical component of an NMR imaging apparatus not usually found in an NMR spectroscopy apparatus is the gradient coil system, which is needed to create linear field gradients whose magnitude must sometimes be altered very rapidly. The conflicting requirements of large-magnitude gradients and fast switching times have given rise to many original designs.

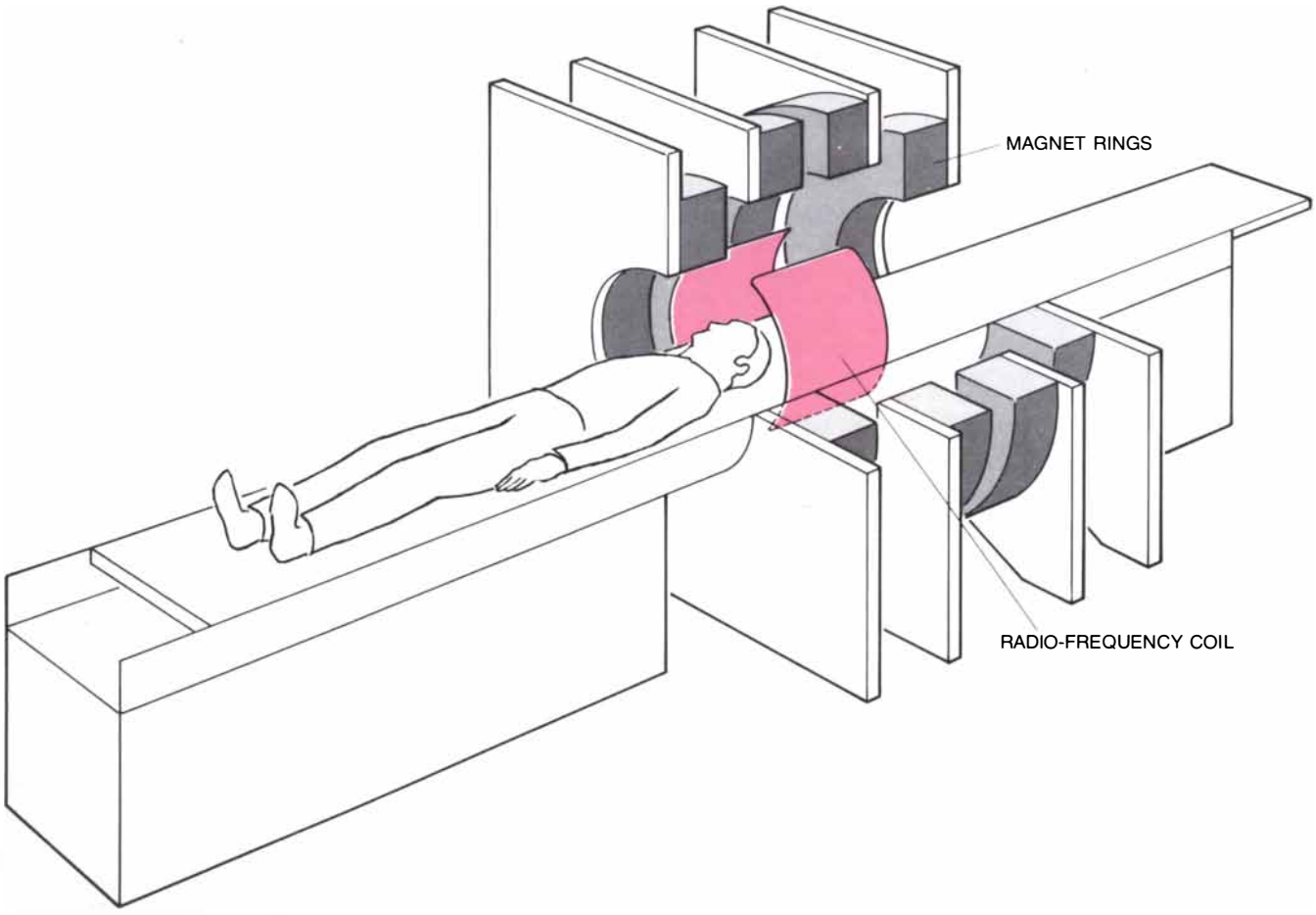
It should be emphasized that the spatial resolution of an NMR image is not dictated by the wavelength of radiation that yields the image, as it is in many imaging systems. (The wavelength of

15-megahertz radiation in free space is 20 meters.) In NMR imaging spatial resolution depends rather on the uniformity of the static magnetic field and on the strength of the gradient fields. The T_2^* relaxation time of the free induction signal is usually the dominant decay process in current NMR imaging systems, and therefore T_2^* sets a minimum line width of the NMR spectrum. The strength of the gradient fields must be high enough for the frequency increments from pixel to pixel in the final image to dominate the T_2^* line width. Some spatial encoding methods, however, require that this condition be satisfied less rigorously than others.

NMR imaging in medicine is still at an early stage. A systematic body of data must be built up so that the efficacy of the technique for detecting pathological lesions in various parts of the body can be established. Early clinical results at the Massachusetts General Hospital with two imaging systems made by the Technicare Corporation suggest that NMR may be particularly good at detecting necrotic (dead) tissue, ischemia (local anemia caused by mechanical obstruction of the blood supply), malignancies and degenerative disease of various kinds. The soft-tissue contrast is inherently superior to that of X-ray techniques, and the sensitivity for the detection of lesions in general appears to be very high.

One promising idea is to administer NMR "tracers," or contrast materials, orally or by injection. For example, paramagnetic ions such as those of manganese (Mn^{++}) have unpaired electrons, so that they have a magnetic moment and tend to align themselves in the static magnetic field of an NMR system. They increase the local magnetic field slightly and substantially modify the relaxation time of NMR-sensitive nuclei. The resulting change in image intensity would allow the distribution of the paramagnetic species to be mapped. Such tracers could play a role analogous to that of the radioactive tracers administered in nuclear medicine. Several laboratories are investigating the feasibility of using NMR to measure the velocity at which blood flows through the major vessels, and recent experiments show that the action of the heart in various parts of its cycle can be "frozen" by high-speed or stroboscopic NMR imaging.

Perhaps the greatest potential of all lies in the imaging of nuclei other than hydrogen, particularly the phosphorus nucleus. Phosphorus is a major constituent of the high-energy molecules adenosine triphosphate (ATP) and phosphocreatine, which mediate the transfer of energy in the living cell. NMR spectroscopy of phosphorus in localized volumes within the body clearly reveals several chemically shifted resonance peaks whose heights correspond to the concentration of the individual phosphorus compounds. From knowledge of such concentrations it is possible to infer the metabolic status of internal organs, and it may eventually be possible to add this capability to an imaging instrument. The next few years will undoubtedly see both an improvement in the quality of NMR images and a growing diversity of applications for nuclear magnetic resonance in clinical practice.



NMR IMAGING MAGNET is depicted schematically. The four rings hold windings that generate a static magnetic field (B_0). The radio-frequency pulse is generated by a coil in the form of two curved panels. The NMR signals evoked by the radio-frequency pulses are detected by the same coil and forwarded to a computer. Costlier systems with higher magnetic fields employ superconducting magnets.

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