NUCLEAR MAGNETIC RESONANCE IN BULK MATTER

Basic research on assemblies of nuclear gyromagnetic moments led to powerful techniques for studying molecular structure and solid lattices—and to a modern medical diagnostic tool.

George E. Pake

George Pake is a retired group vice president of Xerox Corporate Research and director emeritus of the Institute for Research on Learning, in Palo Alto, California.

In early 1946 the *Physical Review* published letters from the two discoverers of nuclear magnetic resonance describing their independent detections of nmr in bulk matter.[1] In recognition of their pioneering research, which they carried out simultaneously, albeit in different places and with different conceptual bases, Felix Bloch and Edward Purcell were awarded the 1952 Nobel Prize for Physics.

Neither Bloch nor Purcell discovered the phenomenon of magnetic resonance, which I. I. Rabi had already described and demonstrated in molecular-beam experiments in the latter 1930s. (See Norman Ramsey's article on page 40.) Rabi's research had been aimed primarily at measuring nuclear moments—which until then were either unknown or only very approximately estimated from small splittings (hyperfine structure) of atomic spectra. Whereas beam experiments benefit from the isolation of the atom or molecule, the power of postwar nmr in many applications lies in the interaction of the atomic nucleus with its natural surroundings in the molecule or in the bulk matter sample.
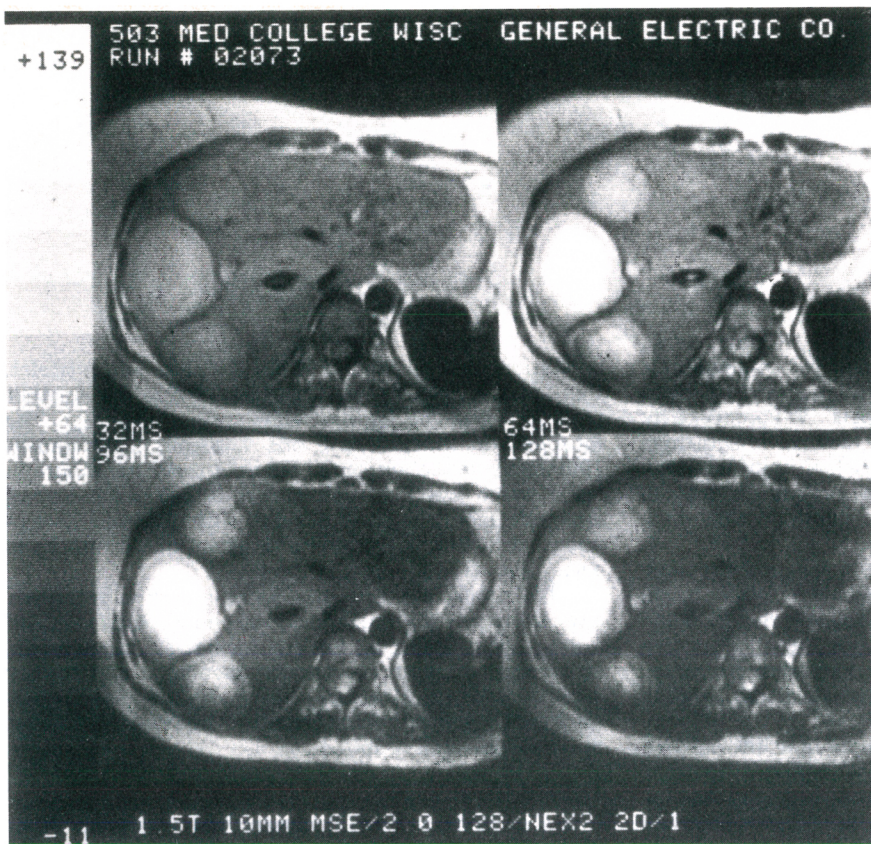
Physical picture

Perhaps the most easily grasped physical picture of magnetic resonance involves viewing the nuclear gyromagnetic moment μ as a precessing top in a laboratory magnetic field $\mathbf{H}_0$. The magnetic moment μ of the nuclear gyromagnet is given by

$$\mu = \gamma \, \mathbf{I}$$

where $\mathbf{I}$ is the nuclear angular momentum, and γ is the gyromagnetic ratio. Then the rotational statement of Newton's second law (the rate of change of angular

Series of sections through the body shows the progressively more prominent image of a cancerous growth in the liver as the time allowed for relaxation is increased from 32 milliseconds to 128 msec. (Courtesy of John D. Roberts, Caltech.)

momentum equals the applied torque) gives

$$d\mathbf{I}/dt = \mu \times \mathbf{H}_0 = -\gamma \, \mathbf{H}_0 \times \mathbf{I}$$

This equation tells us that the nuclear precession angular frequency, or Larmor precession frequency, is

$$\omega = -\gamma \, \mathbf{H}_0 \qquad (1)$$

Consistent with this picture, one can readily see that a smaller field $\mathbf{H}_1$ at right angles to $\mathbf{H}_0$ and rotating in synchronism with the precession frequency $\omega_0 \equiv \gamma H_0$ applies a torque to $\mathbf{I}$ or μ that tends to tip it, thus changing its orientation with respect to $\mathbf{H}_0$. Because the potential energy of μ in the magnetic field is proportional to its component along the field, a nucleus with spin angular momentum $\mathbf{I}$ has $2I + 1$ energy levels in the field $\mathbf{H}_0$. Application of the Bohr frequency quantization condition to these levels suggests that transitions should occur between adjacent levels for $\hbar\omega$ agreeing with equation 1 for the classical top picture. For a nuclear magnet in a typical large laboratory magnetic field $\mathbf{H}_0$, the frequency ω_0 corresponds to a few tens of megahertz, in the radiofrequency range.

The extension of magnetic resonance experiments to nuclei in bulk matter began with the two pioneering groups: Purcell's at Harvard[2,3] and Bloch's at Stanford.[4,5] John Rigden[1] traces these discoveries, showing how Purcell's conceptual approach relating to energy absorption between adjacent nuclear spin energy levels was a natural follow-on to the MIT Radiation Laboratory's wartime effort to decrease radar wavelengths to 1.25 cm. That wavelength happened to fall upon a strong absorption band of atmospheric water vapor, precluding practical radar operation. Consistent with these perspectives, Purcell and his coworkers labeled their experiments "nuclear magnetic resonance absorption."

Bloch's nuclear induction discovery built on the classical precessing-top picture that leads to equation 1. In 1942 Bloch had collaborated with Luis Alvarez in an ingenious experiment to measure the magnetic moment of the neutron.[6] They used a neutron beam and incorporated a magnetic resonance transition region (a radiofrequency field) in the beam path. This experiment, limited only by the precision with which the magnetic field could be measured, determined the neutron moment to 1% accuracy, compared with the one or two significant figures available previously.

Bloch was motivated to do postwar research that would lead to more accurate field measurement—for example, using the known magnetic moment of the hydrogen nucleus, the proton, as a measure. Bloch, William W. Hansen and Martin Packard made a step in this direction in 1946 by detecting nuclear induction by the protons in water.[4] Bloch visualized that when his team swept the magnetic field through the resonance condition, the collective nuclear magnetic moment of the assembly of precessing nuclei was tipped at resonance to produce a minute flux change in a small pickup coil, thereby inducing a radiofrequency voltage (at the Larmor frequency).[5] Hence his apt name "nuclear induction" for the process.

The Purcell and Bloch experiments were completely independent and nearly simultaneous. (The Purcell group's letter[2] to the *Physical Review* was dated 24 December 1945, whereas the Bloch group's letter[4] was dated 29 January 1946.)

Applications to physics and chemistry

Nuclear magnetic resonance researchers in the early days probably thought they were doing nuclear physics. The

technique made accessible the resonances of numerous nuclear moments that were previously either unknown or only approximately measured. Robert V. Pound's early discovery and recording of electric quadrupole splittings of nmr in crystals made possible nuclear spin measurements and very rough estimates of nuclear quadrupole moments.[7] These advances surely qualified nmr as a boon to nuclear physics.

But other early discoveries of splittings and structure in nmr lines showed the nucleus to be a sensitive probe of the submicroscopic atomic environments in which the nuclear moments are embedded. Now, nearly 50 years after the discovery of nmr, its value to condensed matter physics, chemistry, biochemistry and medicine exceeds its value to nuclear physics.

The first detection of splitting in an nmr line induced by the nuclear magnetic environment (which I reported[8] in 1948) was a consequence of local magnetic dipolar fields at the resonating protons in gypsum crystals ($CaSO_4 \cdot 2H_2O$). These fields are generated at each proton by the nuclear moment of its partner proton in the water molecule, which is rigidly bound into the crystal lattice. The linewidths and splittings contrasted with liquid water's sharp lines, whose natural widths and thermal relaxation times were explained in the doctoral dissertation research of Nicolaas Bloembergen, reported[3] in the *Physical Review* in 1948. Improved spatial uniformity of the large magnetic field revealed smaller splittings of nmr lines. First discovered was the so-called chemical shift, a local variation in the amount of diamagnetic shielding that each "kind" of nuclear environment experiences from the molecular electrons in its immediate neighborhood.[9]

Higher-resolution nmr revealed a multiplet structure that was subsequently shown to arise from a so-called indirect nuclear spin–spin coupling.[10,11] The ethyl alchol (CH_3CH_2OH) spectrum that had earlier exhibited only three chemically shifted peaks of relative intensity 3:2:1

exhibits further resolution of the CH_3 line into a triplet, the CH_2 line into an octet and the OH line into another triplet.[12] (See the figures below and on page 49.) The form and the magnitude of this small interaction (about 100 hertz) can be accounted for by a small admixture in the electron bonding of electronic excited states having magnetic moments that interact with the nuclear moments, in effect "telegraphing" nuclear spin couplings to each other via the bonding electrons.[13]

The nature of a line splitting at a particular nuclear site can reveal the number and chemical equivalency of a group of neighboring nuclear moments. Much of the significance of nmr spectra for chemistry and biology depends upon the structural information provided by the combined influences of the chemical shift and the indirect nuclear spin–spin coupling.

Transient excitation

Erwin L. Hahn in 1949 generated and interpreted spin echoes—the response of the nuclear magnetization to appropriately spaced radiofrequency pulses of particular durations at the Larmor frequency. Hahn reported his discovery in the *Physical Review*.[14]

One can understand spin echoes more easily by transforming one's perspective to that of an observer residing in a coordinate frame rotating about an axis in the H_0 direction at an angular frequency corresponding to the frequency of the alternating magnetic field $2H_1$. Spin echoes are generated by first applying a pulse at the radiofrequency $\omega = \omega_0$ for a time adequate to allow the nuclear magnetization in the rotating frame to precess about H_1 through an angle accumulating to 90°. This precession puts the nuclear magnetization into the xy plane, where it is nearly stationary with respect to the rotating frame but is precessing about H_0 in the laboratory frame. A pickup coil perpendicular to H_0 will thus experience an emf induced at the Larmor frequency by the precessing nuclear magnetization. This signal will
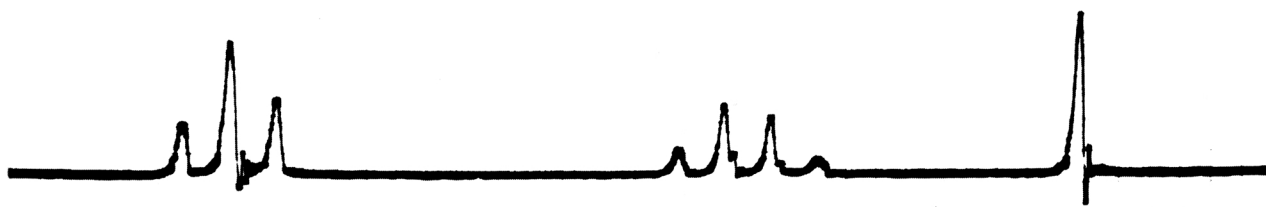
High-resolution proton nmr spectrum at 40 megahertz of ethyl alcohol, CH_3CH_2OH, shows, from left to right, the methyl (CH_3) triplet, the CH_2 quartet and the hydroxyl (OH) line. Each group is separated from the others by the chemical shift. In very pure alcohol, where chemical exchange effects are not present, the hydroxyl line becomes a triplet, and the CH_2 line is an octet. The magnetic field decreases to the right. (Courtesy of Weston Anderson, Varian Associates.)
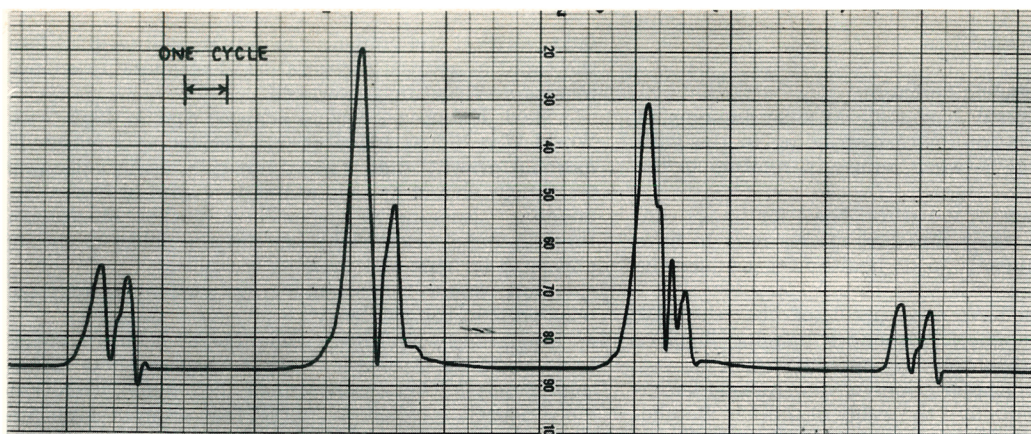
Proton nmr spectrum of the CH_2 group in ethyl alcohol shows the emerging octet structure when the hydroxl exchange is not too pronounced to allow evidence of the indirect spin–spin coupling to the OH group. The magnetic field decreases to the right. (Courtesy of Anderson.)

decay, or "relax," as the microelements of nuclear magnetization lose phase coherence. They lose phase coherence because they precess in slightly differing local fields, either because of spatial inhomogeneity of the external H_0 field or because of the small spectrum of local internal microscopic fields associated with the aggregate of neighboring nuclear spins (magnets). This decaying signal following the 90° pulse is called a free-induction decay; its relaxation time T_2 is called the transverse relaxation time.

If the external field H_0 were completely homogeneous over the sample, and if the distances between nuclear magnets within the sample were so great that local nuclear magnetic fields were negligible, the free-induction signal would still decay slowly via thermal relaxation processes. This decay would occur as the nuclear magnetization returned from its nonequilibrium precession around H_0 to thermal equilibrium along H_0, at a rate measured by the thermal relaxation time T_1, called the longitudinal relaxation time. T_1 is normally longer than T_2; in certain circumstances T_2 may equal (but not exceed) T_1. The relaxation times T_1 and T_2 are significant for medical applications of nmr.

If a 90° pulse is followed, after an interval τ shorter than T_1, by a 180° pulse, this effectively reverses the sense of precession so that after another interval τ the spins are back together. This brief "recoherence" of the nuclear magnets after 2τ provides a partial reassembly of the nuclear magnets into a magnetization comparable to that which initiated the free-induction decay. The reassembled precessing magnetization induces a voltage pulse in the pickup coil at time 2τ, a signal called the "spin echo."

Magnetic resonance imaging

Now a nearly ubiquitous medical diagnostic tool, magnetic resonance imaging may be the first context in which citizens encounter nuclear magnetic resonance. The basic nmr physics heretofore described makes this powerful imaging tool possible. Modern mri employs many clever techniques and numerous optimizations. Here we only sketch lightly the principles involved, to make it clear why mri sometimes has an advantage over other medical imaging technologies. This quick review of mri draws heavily upon articles by Felix Wehrli (see PHYSICS TODAY, June 1992, page 34, and January 1993, page 15), John

Roberts,[15] and George Levy and David Craik.[16]

How does one associate a particular nmr signal with a small localized region in the human body? Paul Lauterbur took one of the first steps toward this goal in 1973 when he proposed developing spatial maps of elements of nuclear magnetization by nmr zeugmatography.[17] The idea is to use special coils to augment the homogeneous external magnetic field H_0. These coils provide a series of linear gradients, so that a particular local Larmor frequency is associated with each volume element of the sample under observation. In this way it is possible to map the regional element onto the frequency domain. The magnitude of the gradient over a large sample can be as high as about 1 gauss per centimeter for whole-body gradient coils. Current standard magnetic resonance imaging resolution is 0.5–1 mm.

Several significant advances in nmr sensitivity were devised and demonstrated by Richard R. Ernst and his collaborators. This work was recognized by the award of the 1991 Nobel Prize for Chemistry to Ernst.

Generally speaking, nmr detection is more sensitive the higher the Larmor frequency is in the radio spectrum. But this high frequency requires large magnetic fields H_0 homogeneous over a region large enough to accommodate a torso or at least a head or extremity. Such high fields can be attained with superconducting solenoids.

We have yet to indicate how the image can distinguish between various kinds of tissue. One source of variation, of course, is differences in the signal intensity associated with the density of nuclear magnets. If we are looking at the proton resonance, for example, there will be different numbers of hydrogen nuclei per unit volume in muscle, fat, bone and blood.

Perhaps the most useful distinctions come from the relaxation times—the T_1's and T_2's. For a tissue with a shorter T_1, if we wait a longer time after the initial pulse before sampling the signal, more of the nuclear magnetization will have relaxed away, leaving less to induce a signal. The signal from that tissue will therefore be weak. Varying the cycle time in this way can thus modify or even enhance the contrast between various kinds of tissue.

Another way Nature helps us with relaxation time values is that in many diseased tissues—tumors, for example—the relaxation times are longer than in healthy tissues.

Magnetic resonance imaging has a number of advan-

tages for medical diagnostics:

▷ It is noninvasive.

▷ It employs no ionizing radiation.

▷ Unlike the universal gray scale in x-ray imaging, it offers a contrast continuum corresponding to the variation of the interval between pulses in relation to the relaxation times.

▷ It takes advantage of a natural basis for image contrast: the fact that many diseased tissues tend to have longer relaxation times than do healthy tissues (see the figure on page 47).

Some observers have even predicted that the 21st century may see magnetic resonance imaging displace x rays for most medical imaging applications.

Other biomedical applications of nmr include vascular flow measurements and the study of cellular metabolism.[15] An interesting feature of nmr for flow studies is that the flowing medium can carry nuclear magnetizations that have already been excited either into or out of detection regions. The parameter variations that result have potential for measurement and analysis.

Reflections on value and motivation

The spread of nmr applications from nuclear physics to structural chemistry, then on to biochemistry, and finally through biology to medical imaging is remarkable. In magnetic resonance imaging, the fundamental science of nmr, including a panoply of techniques that almost qualify to be called tricks, has merged with modern magnetic, computing and electronic technology into a robust instrument for routine medical imaging. If Bloch, Purcell and their colleagues had been told in 1946–50 that they were doing biomedical physics and were laying the foundations for medical technology, they would have been somewhat startled but not totally surprised: Everyone understands that specific ultimate applications of basic science frequently cannot be foreseen.

We did recognize in those days that we had the ability to tap a very sensitive internal probe within the submicroscopic structure of matter—the nuclear magnet—for information reflecting basic structural and dynamic properties of the matter. And we understood that our measured linewidths, splittings and relaxation times were presenting us with information about internal affairs within that matter. I recall discussions and speculations about whether we could measure nmr *in vivo* within the human body, and if so or when so, what the data might mean. Also, how could we process and analyze this rich diet of data?

Modern magnetic resonance imaging depends upon numerous technological advances that I could not even begin to foresee in 1948. We could not sense the forthcoming electronics (and therefore computer) revolution. When I was awarded my PhD in June 1948, John Bardeen and Walter Brattain were just filing their first transistor patent. None of us—including, I feel certain, Bloch and Purcell—knew of the transistor at that time. And if we had, would we have foreseen integrated circuits with a million transistors on a chip, or could we have foreseen the microprocessors that help to make computing power plentiful and relatively cheap? It seems unlikely. I am less certain that none of my colleagues in 1948 would have foreseen commercial use of superconducting solenoids—but I can readily confess that I, only 22 years before becoming a research vice president for a major US technological corporation, had no inkling that superconducting magnets would now be almost a standard article of commerce.

Whereas we recognized the wealth of information inherent in nmr, we could not 45 years ago conceive of

data retrieval and analysis capabilities that would afford the rapid integrated presentation of magnetic resonance images now routinely practiced.

Next, let me ask you to suppose that in 1946, with World War II just ended, it was decided as a matter of national priority that a new, versatile medical imaging technology should be sought and developed to rival x-ray imaging. Imagine, if you will, a kind of Manhattan Project's being organized to recruit the ablest scientists and push for this new imaging technology.

How would the scientists in such a group have responded to the challenge?

▷ How many would have said, "Let us begin by trying to measure the strengths of the nuclear magnets within some atoms"? That surely sounds like a dumb, irrelevant idea—especially when you recall that all even–even nuclides (I guess about half of all the kinds of nuclides in nature) have zero spin.

▷ Once the early Bloch and Purcell experiments were—by some miracle—done within this new Manhattan Project, who would then have said, "Let's learn how to measure and calculate T_1 and T_2 for various classes of bulk matter, such as liquids, crystals and biomolecules"?

▷ Finally, who would have said, "Let's play games with pulses and see how many ways we can induce the nuclear magnetizations to dance to our radiofrequency tunes"? And while we were playing these esoteric and improbable games, of course, we would write quarterly research progress reports saying we do these things so we can build an instrument that we know will provide images that detect a multiple sclerotic brain, track the progress of a cerebral bleeding episode or diagnose a diseased liver.

Magnetic resonance imaging could arise only out of the nondirected research, not focused upon ultimate applications, that gave rise to what we know today as nmr. The key was the series of basic quests to understand the magnetic moments of nuclear spins; to understand how these nuclear magnets interact in liquids, crystals and molecules; and to elucidate the structures of molecules of chemical interest. Out of these basic quests came the knowledge that enabled a vision of an imaging technique. Without the basic research, magnetic resonance imaging was unimaginable.

Magnetic resonance imaging is an irrefutable testimonial to the enormous value of basic research.

References

1. J. S. Rigden, Rev. Mod. Phys. **58**, 433 (1986).
2. E. M. Purcell, H. C. Torrey, R. V. Pound, Phys. Rev. **69**, 37 (1946).
3. N. Bloembergen, E. M. Purcell, R. V. Pound, Phys. Rev. **73**, 679 (1948).
4. F. Bloch, W. W. Hansen, M. Packard, Phys. Rev. **69**, 127 (1946).
5. F. Bloch, Phys. Rev. **70**, 460 (1946).
6. L. W. Alvarez, F. Bloch, Phys. Rev. **67**, 111 (1942).
7. R. V. Pound, Phys. Rev. **73**, 1247 (1948); **79**, 685 (1950).
8. G. E. Pake, J. Chem. Phys. **16**, 327 (1948).
9. H. S. Gutowsky, C. J. Hoffman, J. Chem. Phys. **19**, 1259 (1951).
10. E. L. Hahn, D. E. Maxwell, Phys. Rev. **88**, 1070 (1952).
11. H. S. Gutowsky, D. W. McCall, C. P. Slichter, J. Chem. Phys. **21**, 279 (1953).
12. W. A. Anderson, J. T. Arnold, Phys. Rev. **94**, 498 (1959).
13. N. F. Ramsey, E. M. Purcell, Phys. Rev. **85**, 143 (1952).
14. E. L. Hahn, Phys. Rev. **80**, 580 (1950).
15. J. D. Roberts, Engineering and Science (Caltech), January 1986, p. 10.
16. G. C. Levy, D. J. Craik, Science **214**, 291 (1981). (This article is rather outdated but quite readable.)
17. P. C. Lauterbur, Nature **243**, 190 (1973). ■