smaller so that they are no longer part of it and therefore are inaccessible to enzymes that copy the genes into RNA.

Not unexpectedly, since adult hemoglobin consists of two β globin and two α globin proteins, thalassemias can result from deficiencies in α as well as β globin synthesis. The α thalassemias, Bank explains, have been considered "relatively boring," because they result mostly from gene deletions rather than deficiencies in gene regulation. But recently, several laboratories have revived interest in these disorders by discovering how the deletions seem to occur. It is postulated that they occur by a form of gene shuffling called unequal crossing-over that can take place whenever sequences are repeated on DNA.

Unlike the β globin genes, the α globin genes are tandemly repeated. There are two α globin genes on each copy of chromosome 16, so each person normally inherits four such genes—and in abnormal situations from one to all four can be deleted. Kan found that, as more α genes are deleted, the corresponding α thalassemias vary in severity. Most of the α thalassemia carriers who have clinically normal hemoglobin production have a deletion of one α globin gene. When two α genes are deleted, Kan discovered, some anemia occurs. When three are deleted, the anemia is severe, and when all four are deleted, the anemia is fatal and affected fetuses are stillborn.

Stuart Orkin recently studied the DNA sequences deleted in individuals who seemed to have one α globin gene missing. He discovered that the left-hand portion of the first α gene was present and the right-hand portion of the second α gene was present. But, Orkin says, "it looked as though the middle was taken out" of the two-gene sequence. In effect, the equivalent of one α gene was deleted. He proposed that one way to account for such a deletion pattern is to suppose that unequal crossing-over occurs. Kan subsequently found another sort of α globin gene deletion in which the middle of the two-gene sequence was gone, but the deletion was shifted somewhat to the right of the one that Orkin discovered. This deletion, too, could be accounted for by unequal crossing-over. If unequal crossing-over causes the deletions of α globin genes, some individuals should have three α globin genes on a chromosome whereas others should have one. Kan and David Weatherall of Oxford University recently, and independently, reported finding people with three α globin genes.

Further evidence for this mechanism was obtained by Joyce Laver, James Shen, and Maniatis. They put α globin genes on bacterial viruses and allowed the viruses to multiply in bacteria. He and his colleagues found that two kinds of α globin gene deletions occurred by unequal crossing-over and that these are the same deletions that occur in α thalassemias.

In the past few years, then, researchers have been able to describe the molecular basis of the thalassemias—an entire class of genetic disorders—in a detail previously unimaginable. "To me, that is intellectually satisfying," says Nathan.

—GINA BARI KOLATA

Additional Reading

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NMR Opens a New Window into the Body

The use of nuclear magnetic resonance for medical diagnosis hovers on the brink of practical application

The goal is far simpler to describe than to achieve. All that is wanted is a completely noninvasive—and risk-free—method for seeing what is happening inside the human body.

No technique that is currently available fits this description. Even devices that require x-rays, such as the well-known CAT (computer-assisted tomography) scanners, are invasive in the sense that they expose the patient to varying doses of ionizing radiation, which has been linked in animal studies to an increased risk of cancer and birth defects.

A new approach, in which nuclear magnetic resonance (NMR) signals are used to construct two- and three-dimensional images of portions of the human body, may provide what appears to be at least a very-low-risk, if not a risk-free, diagnostic technique. Within the past 6 months to a year, researchers have begun to produce NMR images in 2 or 3 minutes that are able to distinguish features with dimensions as small as 2 millimeters, a marked improvement over the situation just 3 or 4 years ago, when the first images began to appear. At that time, image production required as much as 30 to 40 minutes, far too long to be practical for medical diagnosis; furthermore, the resolution was poor.

With the recent improvements in hand, investigators are just beginning to move from laboratory studies, usually with themselves as the subjects, to clinical evaluation of NMR imaging in patients with known pathological conditions. One potential application is in cancer diagnosis; additional applications, such as heart attack detection, may be possible even if they are not imminent.

Chemists have used NMR for almost three decades as a tool for working out the molecular structure of pure, homogeneous samples. Suggestions that NMR might also be applied to the far more complex problem of producing body images are more recent, dating back only about 10 years.

There is some controversy about who should get credit for the development of the new NMR methods. Raymond Damadian, who is affiliated with the Downstate Medical Center of the State University of New York (SUNY) claims that the idea originated with him, but so does Paul Lauterbur, who is at SUNY's Stony Brook campus. Some of the investigators now actively pursuing NMR imaging research attribute their own interest to the work of Lauterbur. For example, Waldo Hinshaw of Massachusetts General Hospital says, "I consider Lauterbur to be the father of the field; I think the literature shows that the idea originated with him." Damadian published the first paper, however.

It appeared 9 years ago in *Science* (19 March 1971, p. 1151), and presented evidence indicating that cancerous and normal tissues might be distinguished on the basis of their NMR signals. Damadian followed that up in 1972 by filing for a patent on an NMR technique, called Field Focused NMR (FONAR for short), that he suggested could be used for focusing on, and obtaining NMR signals from, localized regions within the body. (The patent was granted in 1974.)

Then in 1973, Lauterbur, in a paper published in *Nature* (16 March 1973, p. 190), outlined an approach to NMR image formation that is now the basis of a half-dozen or so imaging techniques that are variations on his original theme.

All NMR techniques depend on the fact that certain atomic nuclei behave like tiny magnets. When they are placed in a static magnetic field, the nuclei align themselves with the direction of the field and precess (spin like a top) about it at a resonance frequency that depends on the strength of the applied field. The nuclei are then exposed to an alternating magnetic field of the same frequency, which lies within the radio-frequency range. The second, exciting field perturbs them from their condition of equilibrium with regard to the static field and this perturbation gives rise to the NMR signal. Because the chemical environment of a particular nucleus can affect the magnetic field to which it is subjected, the resonance frequency of a given nucleus in one environment can differ from that of the same nucleus in another. Structural information can be gleaned from these differences.

In addition, the physical environment affects the speed with which the perturbed nuclei return to equilibrium when the exciting radio-frequency field is turned off. Two relaxation times, T_1 and T_2, describe the return to equilibrium, and measurement of these parameters can also give information about the state of the nucleus in question.

The nucleus of most interest in NMR imaging is the proton, both because it gives a comparatively strong signal and because it is the most abundant nucleus in living tissue. The difference between normal and cancerous tissue that was noted by Damadian was an increase in the T_1 and T_2 for protons in the tumor material. Because most of the proton NMR signal from living cells can be attributed to the protons of water, Damadian suggests that the elevated relaxation time values reflect an increased water mobility in cancer cells. The exact biological alterations that might bring about this change are unclear.

In traditional analytical NMR, the magnetic field applied to the sample must be homogeneous so that signals from one part of the sample are indistinguishable from those originating in other regions. No information about the relative locations of the resonating nuclei can be deduced from conventional NMR signals.

An NMR headscan of William Moore

The eyes and optic nerves are visible at the top. The bright outer rim is the scalp and the dark region underneath it is the skull, which gives a negligible signal under these conditions.

About 30 years ago, however, R. Gabillard of the Université de Lille I in Villenneuve d'Ascq, France, noted that it is possible to get such spatial information by using a nonuniform magnetic field. In the method originated by Lauterbur, this is achieved by superimposing a linear magnetic field gradient on the uniform magnetic field applied to the object to be imaged. When this is done, the resonance frequencies of the precessing nuclei will depend primarily on their positions along the direction of the magnetic gradient. "The result," says Lauterbur, "is essentially a one-dimensional projection of the structure of the three-dimensional object. By taking a series of these projections at different gradient orientations, you can derive a two- or even three-dimensional image of the object." The mathematical procedures for constructing these images from one-dimensional projections is very similar to those used for the analogous process of constructing the images obtained by x-ray CAT scanning.

But there is a fundamental difference between the two kinds of images. Those produced by x-ray methods reflect differences in electron densities within the object (or subject), whereas NMR images as currently done are maps of proton densities, which also may vary from tissue to tissue.

Lauterbur points out that forming an image by NMR methods requires that the object interact with two magnetic fields, a static one that may have a superimposed linear magnetic gradient and one alternating at radio frequencies. Because the object thus joins the two fields together, he christened the procedure "zeugmatography" from the Greek word ζευγμα which means "that which joins together."

In the past 5 or 6 years, several investigators have developed a number of additional approaches to NMR imaging. Damadian's and Lauterbur's methods represent the extreme ends of this spectrum of approaches. Damadian's FONAR method depends on the shape of the magnetic field produced by the magnet he uses to focus on a given point within the object. This field is shaped somewhat like a saddle, with the magnetic field strength varying sharply with distance along its sloping surfaces. The exciting radio frequency is chosen to correspond to the field strength at the "saddle point" in the field center. Only this point will give an NMR signal because the nuclei in the parts of the sample lying outside of it will be resonating at the wrong frequencies or will be at a location where the field strength is so steeply graded that a signal cannot be produced. An image can be built up by moving the saddle point in ordered fashion through the object to be examined and determining the signal at each location.

In contrast, each one-dimensional projection taken by Lauterbur's method contains signals from the entire sample volume. Between these two extremes are various approaches that yield NMR signals from lines or planes within the object. Some of these focus on the desired region by effectively wiping out the signals from all other parts of the sample. One such method was devised by Hinshaw when he was a postdoctoral fellow in the laboratory of Raymond Andrew at the University of Nottingham, a center of NMR research that was recently visited by *Science*.

William Moore, during an interview in his laboratory there, said, "Hinshaw came up with a unique idea—to isolate a point, a line, or a plane in space with oscillating gradients." If a single oscillating magnetic gradient is applied to the object, only the nuclear spins within a thin slice at the null point of the field can be detected. Two oscillating gradients at right angles to one another limit the sensitive region to a line, and three such gradients limit it to a point. Both the line and the point must be scanned through the object in order to build up the image. Images of the plane can be acquired by image reconstruction techniques similar to those developed by Lauterbur.

Peter Mansfield and his colleagues, who are also at the University of Nottingham, have developed a different approach to obtaining NMR signals from a line through the object. Whereas the technique originated by Hinshaw effectively wipes out the signal, except in the region of interest, Mansfield has devised a method for selectively exciting NMR signals from a given segment.

. . . diagnosis of brain abnormalities is likely to be the first medical application of NMR.

Lawrence Crooks of the University of California at San Francisco also makes use of selective excitation of a line to generate NMR signals.

Finally, two investigators, Richard Ernst of the Eidgenössiche Technische Hochschule in Zurich and David Hoult of the Biomedical and Instrumentation Branch of the Division of Research Services of the National Institutes of Health, have developed their own approaches to generating NMR signals from planes.

Which of these many approaches will find widest application is still unclear. They each have their own strengths and weaknesses. Because NMR signals are inherently weak, methods that collect them from larger portions of the sample, planes or volumes, are more efficient because they obtain signals simultaneously from all the elements throughout the sample. Consequently, these techniques may have an edge in speed and sensitivity over the point- and line-scanning methods. Nevertheless, the technical difficulties of focusing on the sample and of collecting and analyzing the data increase with each dimension added in progressing from a point to a volume.

Many investigators think that diagnosis of brain abnormalities is likely to be the first medical application of NMR. Imaging of the trunk and abdomen is still hampered by the fact that movements, such as the rise and fall of the chest during respiration and the normal peristalsis of the digestive tract, can cause blurring and distortion.

Moore and his Nottingham colleagues, G. Neal Holland and Robert Hawkes, have begun the clinical evaluation of a method that they have developed for obtaining images of planes through the head. They are testing it on patients who have known brain abnormalities, including brain tumors and blood vessel disorders.

Says Moore of these initial tests, "We have achieved what we set out to do. For most kinds of pathology of the head, NMR has something to offer. In some cases it was better than x-ray." All in all, the NMR images showed what they were supposed to show in the patients. And in one incident, with an apparently normal visitor to the laboratory, they even showed the unexpected. The head image of the visitor, who had asked to have it done just to see what it was like, contained an abnormality that turned out to be a benign growth in the back of his eye. The growth was removed and the man, who had been having severe headaches of previously unknown origin, is now fine.

Moore notes that a big advantage of NMR imaging over x-ray methods is that images can be made of planes taken at any angle through the object. In x-ray scanning, the instrument must be mechanically moved around the patient so that projections can be taken at a variety of angles. Consequently, high-resolution x-ray images as usually done are limited to horizontal cross sections of the head or body. But in many NMR imaging methods the position and direction of the plane to be imaged can be controlled electronically. For example, Moore, Holland, and Hawkes have been making images of longitudinal planes through the head.

There are some practical difficulties that may plague the NMR methods. The structural steel present in many large buildings can interfere with the acquisition of NMR signals by distorting the magnetic field. Hoult, who was having sporadic difficulties with the magnet he is constructing, found that the operation of a fork-lift truck on the floor below was the source of the problems. Appropriate shielding of the magnet can minimize these effects.

Mansfield took a somewhat different approach, by having an essentially iron-free building erected adjacent to the physics department where he conducts his research. When he moved into the small, boxlike facility, however, he encountered another problem: interference from radio broadcasts became more severe. Mansfield says, "We exchanged one problem for another."

A more significant limitation to NMR imaging techniques is the inherent weakness of the signals. The classic answer to this problem is apparently not possible for NMR imaging. Increases in sensitivity for conventional NMR analytical techniques have been achieved principally with the use of ever more powerful magnets to evoke ever more powerful signals. This increases the resonance frequencies of the precessing nuclei and means that the instruments have to operate at high radio frequencies.

But high-frequency operation is not possible for medical imaging, according to Hoult. To begin with, the body is less transparent to the higher frequencies.

In addition, as the size of the magnet and the solenoid coils needed to detect the NMR signals increases, the operating frequencies must decrease. The magnets of analytical instruments will accommodate samples up to only 1 centimeter in diameter, whereas an instrument designed for head imaging must have a magnet opening about 30 centimeters in diameter for an infant and at least 40 centimeters for an adult.

Hoult has calculated that 6 megahertz is about the upper frequency for a 30-centimeter coil. (For comparison, analytical instruments may operate at 100 megahertz or higher.) "Nature conspires against you," is how Hoult sums up the situation.

Because of these limitations, the current capabilities of NMR imaging techniques do not quite equal those of x-ray scanning methods and may never do so. As Lauterbur puts it, "I can see no way for NMR techniques to simultaneously reach the same resolution and speed as advanced x-ray methods."

Nevertheless, the NMR researchers are optimistic about the potential usefulness of their techniques. Says Hinshaw, "Even though the NMR image quality may never be as good as x-ray images, they may be more useful medically." Hinshaw was referring to the fact that, by appropriate manipulations of the image construction techniques, NMR images can be made to reflect differences in the relaxation times of the tissues, in addition to proton density differences. Such images may contain more information about the chemical and biological state of the tissues than do the electron density maps produced by x-rays.

Although investigators think that relaxation time changes may be helpful in diagnosing cancer, as Damadian has suggested, the diagnosis of other conditions may also be facilitated by the altered T_1's or T_2's that they cause. Lauterbur has evidence that increases in T_1 accompany the accumulation of water in the lungs, such as may be caused, for example, by pneumonia or congestive heart failure. Heart attacks, which damage a portion of the heart muscle and cause it to accumulate water, may also be reflected in increased T_1 values, according to Lauterbur.

Another prospect, one that is still in the distant future but which NMR researchers nonetheless find exciting, is the possibility of producing NMR images based on nuclei other than the proton. The NMR analysis of compounds containing phosphorus-31, the naturally abundant phosphorus isotope, or carbon-13 is already proving to be a boon to investigators studying the biochemical reactions that go on in living cells (*Science*, 1 December 1978, p. 958). Investigators hope that one day it may be possible to combine the phosphorus NMR techniques with imaging procedures to obtain detailed pictures of the physiological state of an organ or body part. The main obstacle to achieving this goal is the fact that phosphorus NMR signals are much weaker than those of protons, a situation that is compounded by the low concentrations of phosphorus-containing compounds in living tissues. But says Hinshaw of phosphorus imaging, "It will be terribly difficult but it is so exciting that it is worth putting some effort into it."

Since NMR imagers have not yet gone into commercial production, although prototypes have been or are being built, their costs have not yet been established. Estimates suggest, however, that these will be in the same neighborhood as those of x-ray CAT scanners—an expensive neighborhood indeed: an x-ray scanner may cost several hundred thousand dollars.

Safety is the feature that many investigators think constitutes the biggest advantage of NMR imaging over x-ray scanning. Because of the hazard of ionizing radiation, physicians are reluctant to order repeated x-ray scans to monitor a patient's progress, or lack of it, during therapy. But if NMR methods are as safe as currently thought, the tests may be repeated as often as needed.

However, questions about NMR's safety have been raised by Thomas Budinger of the Donner Laboratory of the University of California at Berkeley, among others. All NMR methods use a static magnetic field and a radio-frequency field, and several of them also require oscillating magnetic field gradients. There is little evidence that the static and radio-frequency fields are hazardous. Hoult points out that cyclotron workers, who are exposed to static fields, do not seem to suffer any ill effects.

Radio-frequency waves may cause heating, and are used for this purpose in diathermy, but these are of higher frequency than those used for NMR imaging. Hoult has calculated that the temperature increase produced in the head by his NMR imaging technique would be only about 0.3°C.

Most of the concern centers on the oscillating magnetic field gradients. According to calculations performed by Budinger, these gradients might be able to induce electric currents in the body that are sufficiently strong to cause ventricular fibrillation, a heart arrhythmia that can cause death if not corrected within a few minutes.

Other investigators discount this possibility, at least under the conditions used in the production of medical NMR images. Says Mansfield, "Our calculations show that the gradient levels and switching rates we use are nowhere near large enough to induce fibrillation." In collaboration with biomedical researchers at a Nottingham hospital, he has even tried to induce the condition in experimental animals. As Mansfield describes the results, "There was no sign of problems in the rats' EKG's [electrocardiograms]. They were absolutely rock-steady."

Investigators, including Mansfield and Crooks, have also looked for such potential hazards as an increased incidence of mutations or chromosome abnormalities in cells and animals exposed to the conditions of NMR imaging, but have so far found nothing unusual.

"Even though the NMR image quality may never be as good as x-ray images, they may be more useful medically."

All this does not rule out the possibility that some untoward effect will turn up as more experience is gained. But, for the present, most NMR researchers see nothing to fear. Perhaps the best evidence for this is their willingness to perform experiments on themselves. Most of the NMR images currently in the literature are of one researcher or another. Moore, for example, estimates that he and Hawkes have each spent about 12 hours with some portion of their body, usually the head, in an NMR imager, without suffering any ill effects.

With the first generation of NMR imagers just now beginning to move into the clinical evaluation stage, a number of corporations are showing interest. One of the corporate pioneers in this regard is EMI, Ltd., of England, which has recently been taken over by Thorn. Partly because there is some uncertainty about the future of Thorn EMI—it is rumored to be up for sale—researchers there are very close-mouthed about the design and capabilities of their instrument. But, according to other NMR researchers, it is perhaps the most advanced of all.

Thorn EMI plans to install their imager in Hammersmith Hospital in London sometime around the end of this year. According to J. Stuart Orr of Hammersmith, the instrument is equipped with a superconducting magnet, which can generate higher magnetic fields than the conventional magnets used in the other devices, and is capable of being adapted to different imaging approaches. One thing Ian Young of EMI would say is, "I am skeptical that any one mode of operation will give people what they want."

Within the next several months, Damadian, who has formed his own company, FONAR Corporation, in Melville, New York, plans to place one of his instruments for clinical evaluation at a diagnostic center in Cleveland, Ohio, that is run by Ross-Sachs and Associates.

Among the other companies interested in NMR imaging are General Electric, Ltd. of England, Siemens AG, Philips-Eindhoven, Pfizer, Inc., which is supporting Crooks' research in San Francisco, and the Technicare Corporation, a subsidiary of Johnson and Johnson. Hinshaw has been collaborating with Technicare in the building of an instrument, which will eventually be evaluated at Massachusetts General Hospital.

If clinical testing proves any of the first-generation NMR imagers to be as useful as researchers think they are, x-ray CAT scanning will have an important new competitor.—JEAN L. MARX