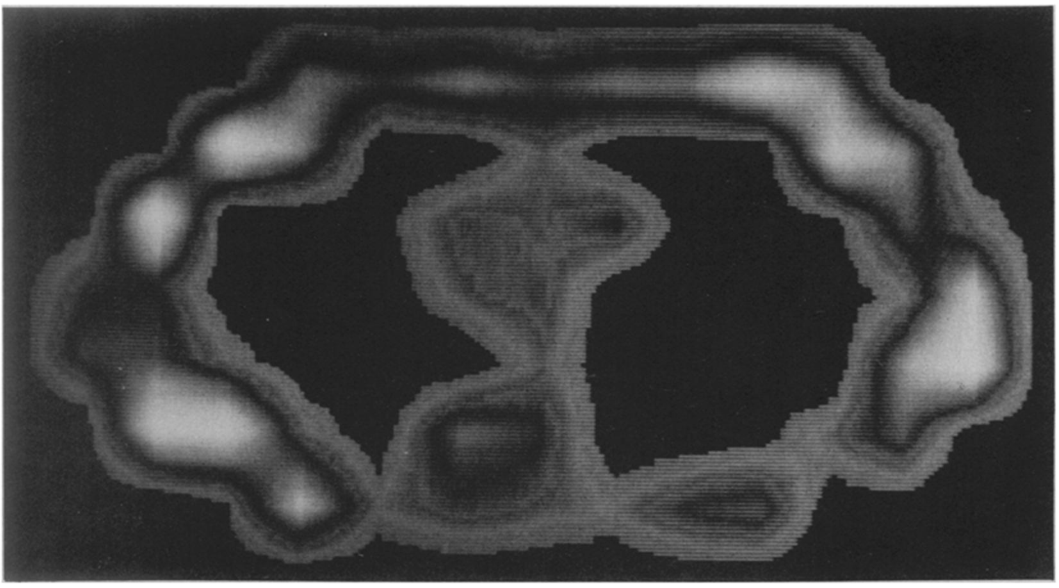
Medical 3-Dimensional Chemistry

Scientists are attempting to probe the human body with the same technique that now gives biochemists a glimpse into living cells

BY LOIS WINGERSON



Raymond Damadian

The chest of a researcher as seen with NMR spectroscopy. The two large dark areas are lungs and the gray shapes in the center are the heart and the descending aorta.

High technology medicine aims at gathering information from deep within a patient without touching the body with a surgeon's scalpel or a catheter probe. The best-known space-age diagnostic tool is computerized axial tomography (CAT)—a 5-year-old technique for taking information gathered from multiple X-rays and, with a computer, drawing an image of the interior (SN: 3/13/76, p. 170). Now other technological developments, such as improved NMR spectroscopy, may crowd yet more sophisticated equipment into the physician's figurative little black bag.

A CAT scan is very pretty, says NMR scientist Paul Lauterbur. But a doctor can't tell from looking at it whether the patient is alive or has been dead for several days. But if you could take NMR spectra at many points along a single line through a patient's chest, collect all the lines through a cross-section of it, and compile them all in the way X-rays are stacked to make a CAT scan, you'd have more than just an anatomical map of the chest. You'd have chemical information from deep inside it.

Imagine being able to image the distribution of ATP inside the heart muscle, or track the blood flow inside the brain. These feats could be achieved if researchers like Lauterbur overcome the obstacles to NMR scanning, which at the moment seem about as vast as its potential. Though some NMR images already exist, as a medical tool NMR is still on the drawing board. Will it turn out to be a brilliant vision or a crazy idea?

To the science establishment it was definitely the latter in 1971, when Raymond Damadian first proposed NMR scanning. Damadian, an associate professor of medicine and biochemistry at Brooklyn's Downstate Medical Center, forecast that NMR would "convert medicine from the practice of anatomy into the practice of chemistry." A veritable NMR evangelist, he has often been either ignored or ridiculed by colleagues, and funding committees have generally rejected his proposals.

In 1977, after winding a giant magnet coil by hand and building an NMR scanner himself (in part from cast-off equipment in the center's basement), Damadian became the first to produce an NMR image of a cross-section of a living person. Still, he is regarded as a maverick by other NMR scientists — who are scrambling to fulfill his prophecy.

About eight different methods now exist for converting NMR signals (the reaction of nuclei to energy in the presence of a magnetic field, see p. 378) into cross-section images of living bodies. Besides Damadian's lab, at least three labs have NMR scanners large enough to accommodate a human torso: the University of Nottingham in England, the University of Aberdeen in Scotland, and EMI Ltd., the British company that pioneered CAT scanners. Several U.S. researchers expect to have human-sized NMR scanners soon.

The various NMR imaging methods go by a bewildering variety of names: spin mapping, zeugmatography, Damadian's patented label FONAR and others. They vary in the ways they apply a magnetic field, isolate points within it and collect and compile NMR signals. All of them, like CAT scanners, use computers to record the magnitude of the signal (and its decay time) and display it in two dimensions on a grid. The resulting image looks like a foggy CAT scan.

The similarity to CAT, NMR researchers say, ends there. In fact, an NMR image is, in a way, a negative of a CAT scan because tissue and water give very strong NMR signals, while bone's response is weak. Most current NMR scanners measure the density of hydrogen ions or protons, which vary with the water content of the tissue. Since body tissues are about 80 percent water and bone only about 10 percent water (a range far greater than the difference in their abilities to absorb X-rays, according to EMI's Hugh Clow), NMR pictures should have better contrast than CAT scans.

They should also be sharper, adds E. Raymond Andrew, a professor of physics at Nottingham, because a magnetic field penetrates tissue and bone without weakening. And since NMR involves no ionizing radiation, most scientists argue that it's safer than CAT.

The fact that NMR selects soft tissue rather than bone ought to make it attractive to cancer specialists. Damadian was first to suggest (SCIENCE, Vol. 171, No. 3976, p. 1151, 1971) that tumors and normal tissue could be distinguished by NMR studies of their water content.

The National Cancer Institute, intrigued by the proposal, put Damadian and two

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other scientists on contract to pursue it. Using a complex formula of NMR indicators, Damadian claimed to discriminate between normal tissue and tumors of the breast, spleen, skin and lymph cancers. But neither of the others — Johns Hopkins biochemist Donald P. Hollis and Carlton F. Hazlewood of the Baylor College of Medicine — could find any consistent difference.

No other researcher — and several have tried — can reliably detect cancer using NMR, with one exception: breast cancer. Several teams find decay times significantly longer from breast tumors than from normal tissue and have even produced some images. In Delft, the Netherlands, researchers at the Technische Hogeschool have produced NMR images of breast tumor in a thin slice of breast tissue that are a convincing match with X-rays and photographs of the tumor. The Nottingham team even found that NMR showed the spread of cancer inside a whole dissected breast — and later confirmed it with microscopic studies.

In the United States, the National Institutes of Health may have soured on the prospect of using NMR for cancer detection after the disappointing results of the NCI contract, but NIH is going ahead with a small scanner anyway. The agency hopes to begin NMR studies of infants next summer, according to D. I. Hoult, looking for water-related congenital abnormalities such as hydrocephalus, abscesses, vascular abnormalities and brain swelling.

Scientists using pure high-resolution NMR signals (not images) of phosphorus nuclei in animal hearts are already getting promising results. Hollis at Johns Hopkins has been using phosphorus NMR to measure pH in rabbit hearts (NMR is unique in its ability to nondestructively follow pH changes in heart tissue during and after cardiac arrest). Using the NMR technique he finds that potassium chloride arrest — a method steadily gaining favor among heart surgeons because it is thought to cause less damage than simple hypothermia — allows the pH of the heart to stay more near normal and to return rapidly to normal after the heart starts beating again. Hollis hopes to use ^{31}P NMR to find other ways of stopping hearts for surgery.

At the University of Oxford in England, biochemists have been using phosphorus NMR to study phosphorus conversion between ATP and phosphocreatine in dissected mouse hearts and also, by winding a coil directly around the heart of an open-chest rat, in living animals. Similar methods may someday be used to study the suitability of organs intended for transplant.

In theory, NMR images should be available for a number of other isotopes — carbon, nitrogen, even sodium. And anything that changes the water content of tissue — inflammation, fluid-filled cysts, ischemia, even blood flow — should be visible on proton NMR images.

But so far, no one except Damadian claims to be anywhere near finding cancer or any other abnormality inside a living body. For one thing the NMR signal, though sharp, is extremely weak. The signal-to-noise ratio, according to Clow, is barely large enough to justify the effort of NMR imaging. As a result, most current images are rife with artifacts caused by wires in the magnet or metals in the laboratory building. Lauterbur, who works at the State University of New York at Stony Brook, has torn up the floor of his lab and encased the entire room in a cube of reinforced concrete.

The clearest NMR pictures to date are of phantoms — tubes of phosphoric acid or water placed in a pattern. The Nottingham team has a convincing image of a lemon slice, and a clear cross-section of a living human wrist; some cross-sections of cadaver heads look promising, too.

But try to capture an image of any breathing organism and the resolution drops discouragingly. When Nottingham physicist Peter Mansfield took a cross-section of his own thorax in the lab's body scanner, he said, "Things seemed to disappear because of my breathing motion," even though he spent 40 minutes in the scanner.

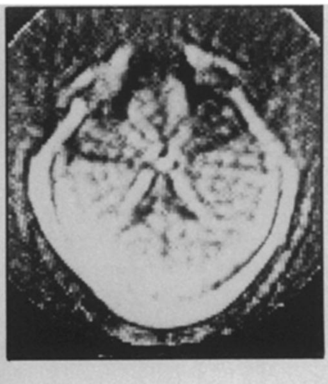
Damadian's first cross-section of a human took more than four hours to create, Nottingham's cross-section of a wrist took more than five minutes, and EMI's first NMR head-scan took six. "If we are ever to gain any credence in terms of clinical imaging, we have to get the time down. We should aim for one-second imaging," Mansfield said at a recent public meeting on NMR scanning held by the Royal Society of England.

But what NMR developers trade for time is resolution, which they can ill afford to spare. To double the resolution of current shadowy images, according to University of Nottingham's professor of physics, E. Raymond Andrew, would take 64 times as long.

Although they call NMR "non-invasive," the scientists admit no one really knows whether it's safe. Damadian says he and some of his assistants now develop headaches when they're near the magnet. A vast literature on the effects of magnetic fields predicts no danger from the level of energy used in NMR scanners (well below that used in diathermic therapy, for instance), but no one knows the effects of alternating or rapidly switching magnetic fields.

Nonetheless, NMR scanning research seems as vigorous now as the race to the CAT scanner once was. EMI gladly shows its NMR pictures, but it's keeping details of the scanner's design a close secret. The company has said it aims to have an NMR scanner on the market in five years.

In the interim, about all NMR researchers can offer medicine is the future. "In five years NMR scanning may be really taking off, or in five years it may be nothing," Hollis says. "But I have yet to see any NMR image that is medically useful." ☐



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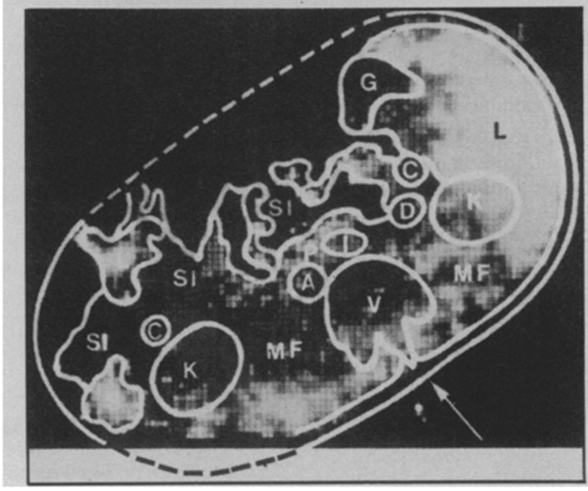

P. Mansfield, Brit. J. of Radiology

A cross-sectional image of a human head (above right). Cross-sectional scan of a human abdomen (above left). The diagram below indicates the location of the liver (L), kidneys (K), gallbladder (G), stomach (SI), vertebra (V), colon (C), aorta (A), duodenum (D), inferior vena cava (I) and muscles and fat (MF). Light areas are high proton density. The high contrast area at right within the liver has the highest proton density.