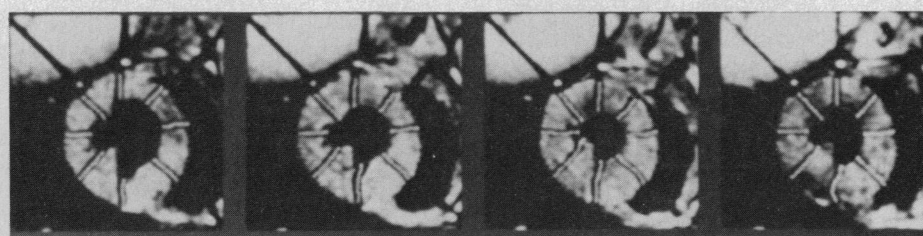
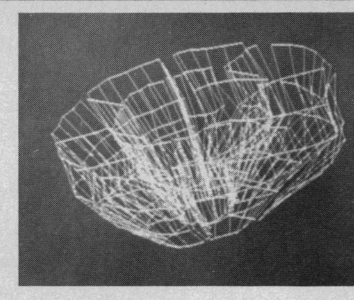
Making 3-D Movies of the Heart

When scientists in diverse disciplines pool their talents to devise a new, noninvasive way of imaging the heart, it pays off in research opportunities and clinical applications



Jerry Prince



Jerry Prince

Hearts on display. *Heart "tags" (black radial lines) reveal a twisting motion as the left ventricle contracts (top); a three-dimensional line drawing shows the entire ventricle at once (bottom).*

ON THE COMPUTER screen, a heart pumps. Elias Zerhouni, a radiologist at Johns Hopkins School of Medicine in Baltimore, points to a section of the heart wall that is moving less vigorously than the surrounding muscle. "That sluggishness tells us," he says, "that this region is getting less oxygen than the rest of the heart." Such ischemia—the medical term for the oxygen deprivation caused by lessened blood flow—causes heart attacks in an estimated 1.5 million people each year in the United States.

Until now, there has been no easy way to pinpoint the damage done to the heart by ischemia or heart attacks, says Myron Weisfeldt, director of cardiology at Johns Hopkins Hospital. Although doctors have various ways to gauge how well the heart is functioning as a whole, "The methods we have for measuring regional function are second-rate," Weisfeldt says, and this is a major handicap for doctors trying to determine the best way to treat a heart attack victim. But now, using a modification of magnetic resonance imaging (MRI), Zerhouni and co-workers have developed a noninvasive way to make three-dimensional "movies" of a beating heart with enough detail to pick out small abnormalities, as well as to give cardiac researchers new information on how the heart works normally.

"There's really nothing like this," says Ed Shapiro, a Johns Hopkins cardiologist who collaborates with Zerhouni. "It's opening up doors to [heart] physiology that have great promise." Already Shapiro, Weisfeldt, and other cardiologists are using Zerhouni's technique to judge the effectiveness of therapies, such as clot-dissolving drugs and balloon angioplasty, which is used to open the blocked coronary arteries of heart attack patients. Eventually, the technique could become a standard tool for diagnosing the location and extent of damage to the heart muscle.

But the new MRI technique is more than just another medical breakthrough. The history of its development is an edifying tale of how scientists from several disparate fields can cooperate to create something much greater than would be possible for any of them working individually. The Johns Hopkins team consists of cardiologists, radiologists, electrical engineers, biomedical engineers, a mechanical engineer, and a physicist, each with his own research interests. How Zerhouni has kept them working toward a common goal for more than 2 years is an important lesson for other researchers in this day of increasing cross-disciplinary collaboration.

The research grew out of a need to see the beating heart in greater detail than is possible with existing methods, Zerhouni says. Echosound, for instance, allows doctors to image two-dimensional slices of the heart many times a second, but it can probe at the heart only from certain angles because the sound waves used to produce the images can't "see" through bone or the air in the lungs. In contrast, computerized tomography, which is based on x-rays, can see through anything in the body, but is not fast enough to take a series of pictures of the heart through a beat cycle. And both techniques suffer from an even more serious shortcoming: They see the heart in silhouette and cannot make out what's going on inside the heart wall.

Cardiac researchers have tried various methods to obtain more details of the heart's function. In one, which has been in use for two decades, metal beads are surgically implanted into the hearts of lab animals. Since these beads show up clearly in x-rays, they serve as "markers" that identify particular points in the heart muscle and allow researchers to watch exactly how these points move relative to each other as the heart beats. But even this technique is severely limited. Researchers can put only a few beads into the heart, so they can monitor only small sections at a time; the presence of the beads may disturb the heart's function; and even though Stanford researchers did insert beads into a few human volunteer heart patients in the 1970s, the technique has little clinical value—doctors can't surgically implant beads into patient's hearts just to get more details of the heart's functioning.

So 5 years ago, Weisfeldt and other Hopkins cardiologists approached Zerhouni with a challenge: find a way to use MRI to get more details of the heart's functions. "We had tried echocardiography and were stymied by its limitations," Weisfeldt recalls. "I thought MRI might work because we could get three-dimensional information within a reasonable amount of time."

Zerhouni responded by conceiving a new, noninvasive way to create markers in the heart. In standard MRI, a strong magnetic field first aligns the spins of all the protons (hydrogen atom nuclei) in the heart and surrounding tissue; then a radio-frequency field is applied to disturb the spins and, by monitoring the resulting signal, the MRI machine obtains an image of the proton distribution. Since that distribution differs from one type of tissue to another, the outline of the heart is clearly visible in the image.

Zerhouni realized it would be possible to "paint lines" across the heart by changing the orientation of the proton spins along various strips in the heart; these strips would show up as black lines in the MR images. By watching the shifting and twisting of these lines, or "tags," as the heart beats, a researcher could get information about the movements of the heart muscles.

To test his idea, Zerhouni hired David Parish, a software specialist at Resonex, a manufacturer of MR machines, to write a program that would produce such tags in the MR images. "We worked together for 2 weeks in August 1987 and then tested the technique on a human volunteer," Zerhouni says. The test was a success—the lines across the heart in the MR images clearly showed a slight twisting as the heart contracted, providing a rough indication of how the muscles of the heart were moving relative to one another. The technique clearly had promise, but it would take a wide array of talent to tap its full potential.

"I realized quickly that we needed expertise in three fields [in addition to cardiology and radiology]," Zerhouni says. At the very least, the team would need a physicist to calculate the magnetic and radio-frequency fields needed to create various patterns of "tags" in the MR images; an electrical engineer to take the huge amounts of MR data and process the images to provide useful information, such as the distribution of stress throughout the heart muscle; and a mechanical or biomedical engineer to create models of the heart with which to analyze the information from the images. Bit by bit, Zerhouni assembled a team to flesh out his vision.

Near the end of 1987, Eliot McVeigh arrived at Johns Hopkins for a job interview. McVeigh had recently finished doctoral work in MR physics and was interviewing at several places, but when Zerhouni described the new tagging process, McVeigh was hooked. "It was a fantastic project," he remembers thinking, and by March 1988 McVeigh was on board.

In January 1989, Jerry Prince arrived at Johns Hopkins to take a joint position in electrical engineering and radiology. Trained as an electrical engineer specializing in image processing—the art of transforming computerized data into usable images—Prince was particularly interested in medical imaging. Eventually, he spoke with Zerhouni. "I became almost instantly excited by the nature of their project—not because it was important clinically or because it would save lives, although it will, but basically because my technical interests were teased," he says. Since then, Prince has devoted much of his time to devising ways to process the data from Zerhouni's tagged MR images.

About the same time that Prince arrived at Hopkins, Zerhouni came across William Hunter, a professor of biomedical engineering at the university and medical school. Hunter was studying how the heart's pumping action could be understood in terms of the placement and behavior of its individual muscle fibers. To get details on how the fibers move with respect to one another, Hunter says, "You have to be able to see inside the walls of the heart," and at the time the only way to do that was with the implanted beads.

When he heard about Zerhouni's idea for a noninvasive technique that could do the same job as the markers, only better, Hunter was impressed. "I told Zerhouni we would really like to help him interpret what is going on." With Hunter came Andrew Douglas, a Johns Hopkins mechanical engineer who had been collaborating with Hunter on calculating the motion of the heart fibers.

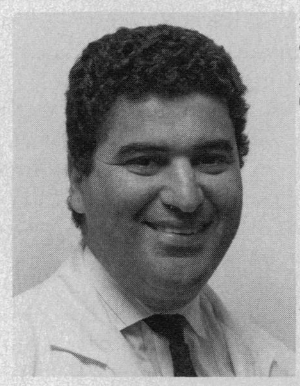
The assembly of a team of researchers with such diverse interests took time and effort, Zerhouni notes, even with a large institution to draw from, but keeping the team running smoothly has been the main challenge. What, for instance, is the best way for the team members to meet and communicate?

"At first, we had a series of big meetings for grant writing," Zerhouni says, but now, "We have meetings in small groups." The different types of meetings serve different purposes, McVeigh says. "The original ideas come out of the big brainstorming meetings." But Zerhouni adds, "If you have a general meeting, you go shallow on all subjects." So after setting the goals and coordinating the research in the larger meetings, the individual scientists retreat to their labs to follow their own lines of study, having smaller meetings to keep in touch with other researchers working in closely related areas, but not worrying about what the entire team is doing.

The team members themselves credit Zerhouni with keeping the collaboration going. A collaboration between such diverse researchers depends, they observe, on having a strong central figure—not necessarily a leader, but rather a person who can hold all the threads together. "At the large meetings, you need someone with a large overall view who connects the different pockets," McVeigh says. In this case, that person is Zerhouni.

But at the same time, Zerhouni also wants each researcher to follow his own research interests, and the team members agree that is the single most important factor in making the collaboration work. "There's no good research that gets done on order," Zerhouni says, so he tries instead to let each scientist find something interesting and challenging for himself. And he appears to have succeeded.

"The problem is nice in that it can be split into subprojects, each of which is interesting in its own right," McVeigh says. McVeigh, for instance, likes the chance to apply a magnetic resonance imaging technique called "selective excitation" to creating the tags in the heart. "It's a very interesting and important application of that theory," he says. Prince, the electrical engineer, is enthusiastic about the challenges of processing the images that result from the tagged MR studies. And Douglas, the mechanical engineer, is intrigued by the opportunity to study the kinematics of the heart, which are different from those of the structures that mechanical engineers usually study. "The heart deforms more than most metal objects," Douglas observes, "and the strains are much higher."



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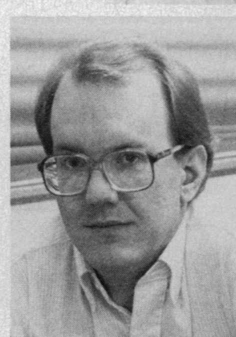
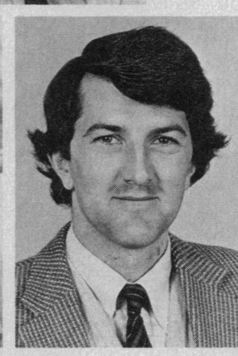
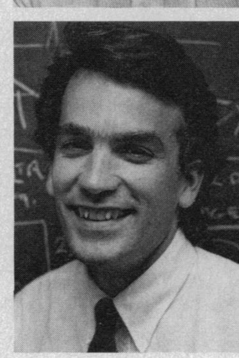






Getting together. *Radiologist Elias Zerhouni, top, assembled a team that included (clockwise from left) electrical engineer Jerry Prince, mechanical engineer Andrew Douglas, and physicist Eliot McVeigh.*

Zerhouni, in addition to acting as the central clearinghouse for the team, is responsible for taking the MR images that serve both as a testing ground for the technique and as the raw data for building a detailed model of how the healthy heart behaves—information needed to serve as a reference point for diagnosing damaged hearts. Over the next 5 years, he will be collecting such data from 100 human volunteers of all ages.

The tagging technique is already proving itself in clinical research. Cardiologist Shapiro, for instance, has recently demonstrated that the left ventricle—the main pumping cavity of the heart—twists as it contracts. Before the advent of heart tagging, no one had seen this twisting explicitly in the human heart, although it had been predicted on theoretical grounds. Now Shapiro is trying to understand the function of this twisting and subsequent untwisting and whether it is connected with certain forms of heart disease.

"We think the untwisting provides suction that helps the heart fill [with blood] very fast," he says. "This is very important because the filling of the heart is known to be the limiting step in heart function in many cases, and many diseases interfere with filling." Shapiro is now using Zerhouni's magnetic resonance tagging method to study this untwisting motion in human subjects, both normal and those whose hearts don't fill well, in order to determine if it is a faulty untwisting motion that causes the poor filling function.

In a second study, Shapiro is studying the effects of angioplasty—the medical technique in which a balloon is placed in a clogged coronary artery and then blown up to open the blood vessel—on the function of the part of a heart damaged by a heart attack. An earlier clinical study by other doctors could detect no effect of such angioplasties on damaged heart tissue, a surprising finding that called into question the way angioplasties are being used. With Zerhouni's tagging technique, Shapiro says he can perform a much more sensitive measure of heart function, and he hopes to see whether the earlier studies missed something.

Even though Shapiro and the other team members are enthusiastic about what they are learning, taking part in such a collaboration does have costs, they concede. "The obvious pitfall," Douglas notes, "is that you have to wait for a time when several of you can meet [before making decisions on how to proceed]. You have to put in some 'overhead' and spend time talking to others."

Fortunately, the Johns Hopkins team has managed to avoid one common plight of collaborative efforts, Douglas adds. "As an engineer, I've been warned about working with M.D.'s" because of their "big egos," he says. But in this case, those egos never materialized. "No one's acting like a prima donna." ■ ROBERT POOL

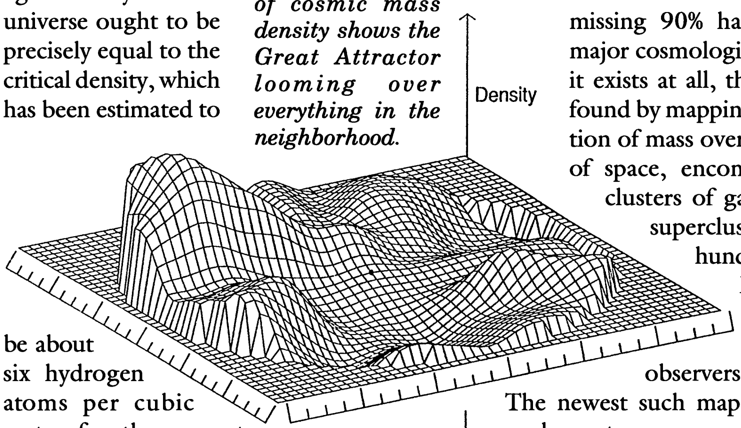
Cosmologists Begin to Fill in the Blanks

They are mapping out more Dark Matter than ever before—but is there enough to reach "critical" density?

Brighton, England—COSMOLOGY, WHICH has spent generations being a playground for theoretical abstractions and little else, is fast becoming an observational science. Witness an international conference* held here last month, where several independent groups reported intriguing, if preliminary, evidence that apparently confirms a longstanding conjecture: that the universe is poised in a state of "critical density," balanced precisely between an endless expansion and an ultimate recollapse into a "Big Crunch."

"It's one of the revolutions in the subject," said University of Sussex astronomer Bernard Jones in his summary talk at the symposium. "Certainly it is the thing that has impressed me the most at this conference."

Jones had good reason to be excited. Many cosmologists believe that the average density of the universe ought to be precisely equal to the critical density, which has been estimated to be about six hydrogen atoms per cubic meter for the present epoch of the universe. If the density had started out even slightly less than critical at the Big Bang, they argue, then the superheated cosmic plasma would have expanded so fast that neither stars nor galaxies would have had a chance to form. Conversely, if the average density had started out even slightly higher than critical, then the universe would have expanded and recollapsed in less than a microsecond—more of a Big Burp than a Big Bang. Since the universe is billions of years old, and since there are stars and galaxies all around us, the density must have somehow been just right.



Mountainous mass. *A new plot of cosmic mass density shows the Great Attractor looming over everything in the neighborhood.*

However, anyone who accepts this argument also has to live with a serious embarrassment: Astronomers can't find anywhere near that much matter in the universe. The mass in all the visible stars and galaxies, averaged over the immense distances between them, adds up to only about 1% of the critical density. To make up the difference, researchers are forced to assume the remaining 99% of the mass consists of invisible "Dark Matter"—presumably a haze of some kind of massive but weakly interacting elementary particles left over from the Big Bang.

That assumption is not quite as ad hoc as it sounds. Astronomers have found ample evidence for Dark Matter by observing its gravitational influence on the internal motions of galaxies and clusters of galaxies. Yet even in the largest clusters, the Dark Matter never seems to account for more than about 10% of the critical density. That missing 90% has thus become a major cosmological conundrum. If it exists at all, then it can only be found by mapping out the distribution of mass over truly vast regions of space, encompassing not just clusters of galaxies, but whole superclusters on a scale of hundreds of millions of light-years.

And that is precisely what the observers are starting to do.

The newest such maps come from two complementary survey techniques. One technique, discussed at Brighton by Avishai Dekel of the Hebrew University in Israel, is based on measurements of galaxies' "peculiar" velocities: their motions relative to the overall expansion of the universe. Since these motions are presumably caused by gravitational forces, explained Dekel, they can in principle reveal the existence of lumps and gaps in the cosmic mass distribution.

That possibility was dramatically confirmed in 1986, when a group of seven astronomers published convincing evidence that our galaxy and most of the other galaxies for hundreds of millions of light-years in every direction are streaming toward a cer-

* Texas/ESO-CERN Symposium on Relativistic Astrophysics, Cosmology, and Fundamental Physics, 16-21 December 1990, Brighton, United Kingdom.