BIOLOGICAL IMAGING

Scanners Get a Fix on Lab Animals

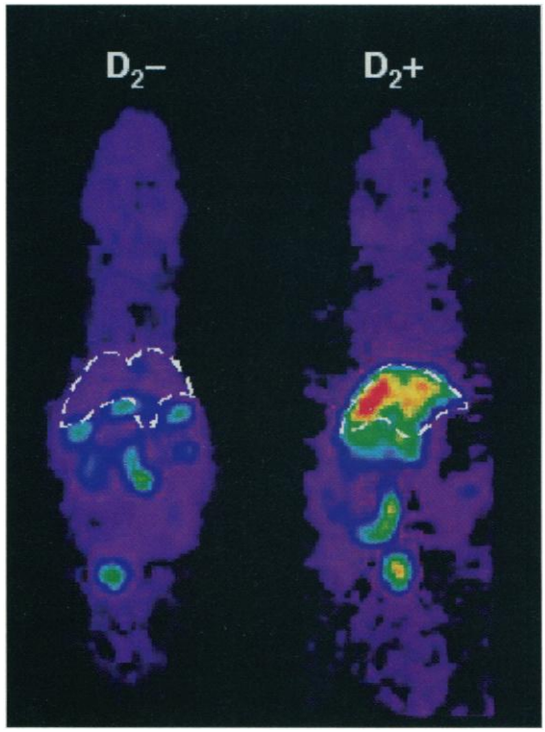
Purpose-built machines with improved resolution are allowing researchers to monitor novel drugs in vivo and watch gene expression, without wielding a scalpel

To see what is going on inside the human body, physicians can turn to advanced medical imagers such as computed tomography (CT) scanners and magnetic resonance imaging (MRI) machines. But for biomedical researchers working with animals, the standard tool has been the scalpel. Imagers lacked the necessary resolution to make out the tiny features inside the brains or other organs of small animals such as mice. And in any case, the companies building the machines have had their sights fixed on clinical settings, drawn by the multibillion-dollar market—until now.

"The interest in small-animal imaging has been growing exponentially," says G. Allan Johnson, who specializes in producing high-resolution MRI images of small animals at Duke University in Durham, North Carolina. The reason, paradoxically, is a revolution in human imaging: These techniques are no longer limited to simply mapping the internal anatomy. Thanks to new probes that give off a detectable signal when they encounter specific molecules, medical imaging is now beginning to shine a spotlight on particular molecular events within cells, such as illuminating when genes get turned on or when a cancer cell turns malignant (*Science*, 15 May 1998, p. 1010). Because the probes—like drugs—can be tested more easily in animals than in people, imaging research has been turned on its head, sending researchers and imaging companies rushing to develop scanners able to see fine detail in rats, mice, and rabbits. "Virtually all the imaging techniques are being developed for small animals," says Johnson.

This month, for example, a Knoxville, Tennessee–based company called Concorde Microsystems is set to roll out the first commercially available positron emission tomography (PET) scanner for small animals, dubbed Micropet. Already the company has back orders from drug companies, academic researchers, and government research labs for some 13 machines. MRI and CT machines for small animals are already on the market. And researchers at the University of California, Los Angeles (UCLA), are working on a new scanner that combines PET's ability to monitor activity in particular tissues with CT's ability to reveal general anatomy. MRI specialist Kamil Ugurbil of the University of Minnesota, Minneapolis, says of the new class of machines: "I think these will become relatively abundant and popular in the near future."

Along with allowing researchers to test new molecular imaging techniques before they are used in human patients, all this new hardware is starting to generate handsome research payoffs, many of which were on display at a recent meeting entitled "Imaging in 2020" in Jackson Hole, Wyoming. The meeting, the first of its kind, brought together everyone from radiologists and surgeons to physicists and chemists working to design novel imaging probes and advance the state of molecular imaging. The results on display included images tracing specific neural connections in the olfactory bulbs of rats to maps showing the activity of newly introduced genes in genetically engineered animals.



Light duty. A PET scanner lights up gene expression in the liver of a genetically engineered mouse (right).

CREDIT: M. PHELPS *ET AL*./UCLA SCHOOL OF MEDICINE

"There is very significant work you can do with animals that you can't really do in humans," says Ugurbil. Researchers can keep animal subjects immobilized for extended periods of time, inject them with potentially toxic image-enhancing contrast agents, alter their genes, and subject them to higher magnetic fields or levels of x-rays than they can with human patients. And compared to the snapshots obtained by dissecting a research animal, images can be cross-indexed to produce complex digital atlases that track key molecular players in tissues throughout the body.

Building the hardware hasn't been easy. That's because most imaging schemes have relatively poor resolution, explains Michael Huerta, who helps oversee extramural funding at the National Institute of Mental Health in Rockville, Maryland. Clinical MRI systems, for example, can see features about 1 cubic millimeter in size. "In humans, that resolution is not bad," says Huerta. "But in a mouse, that volume occupies a lot of the brain."

Much finer detail is now within reach of virtually all types of imaging systems. MRI, for example, uses a combination of strong magnetic fields and radio waves to make certain atomic nuclei in a sample, typically those of protons in water, resonate and reveal their location. By boosting these magnetic fields and using advanced software algorithms, researchers have managed to improve the resolution in animal systems to about 50 micrometers on a side, an 8000-fold reduction in volume. With Micropet, meanwhile, new detectors capable of picking up fainter gamma ray signals from the radioactive probe compounds used in PET have improved resolution to 2 millimeters on a side, a 10-fold reduction in volume.

In one demonstration of what these new high-resolution machines can do, Ugurbil reported using a high-field animal MRI scanner on cats to produce the first-ever MRI pictures of activity in brain structures called ocular dominance columns. An MRI variant called functional MRI, or fMRI, can measure metabolic activity in various tissues by tracking blood flow. But it had lacked the resolution to see these columns—collections of cells in the brain that all respond to particular visual cues, such as horizontal or vertical lines—forcing researchers to map the columns with tiny electrical probes inserted into the brain. Now, with their new high–magnetic field MRI machine, Ugurbil and his colleagues were able

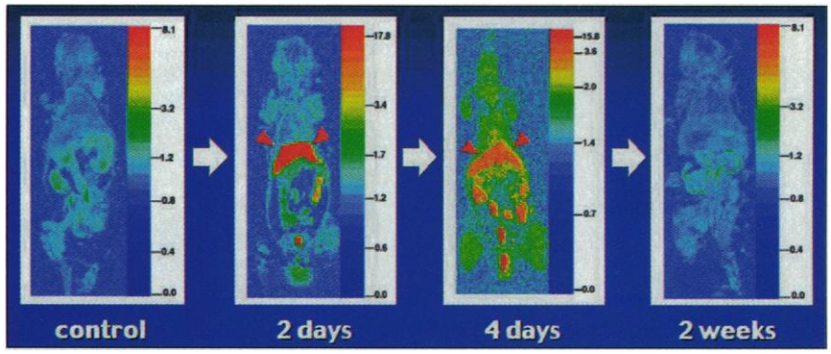
to see the columns, each a mere 300 micrometers or so in size. "It's not a new neuroscience discovery. But for fMRI, it's a very big discovery to map such small regions," says Ugurbil. And that advance, he adds, should allow his team to make detailed studies of the development of vision in individual cats over time without ever having to harm the animals.

Other teams got equally impressive results. Johnson and his Duke colleagues, who were among the first to wind MRI resolution down to 50 micrometers on a side, were able to make MRI movies of the lungs of a guinea pig as it breathes. What makes this feat particularly impressive is that MRI normally can't see lungs at all. The lungs contain very little water, which MRI normally tracks. To get around this problem, Johnson and his colleagues used another trick besides their high-resolution imager: hyperpolarized helium. Like other magnetic atoms, helium atoms act like tiny bar magnets. In a typical helium gas, these magnets point in all directions, meaning that the gas has no net magnetic field. But in recent years, labs around the world have come up with schemes to use circularly polarized light waves to align the bulk of the atomic magnets in helium gas. When the inert gas is then breathed by a subject, such as a guinea pig, it gives off a strong magnetic signal that is picked up by the MRI machine.

Another unusual MRI tracer enabled Alan Koretsky, a chemist with the National Institute of Neurological Disorders and Stroke in Bethesda, Maryland, to track anatomy in the brain. Koretsky and his colleagues used manganese, which is chemically similar to calcium, the element that helps trigger the release of neurotransmitters from neurons so they can communicate with their neighbors. Unlike calcium, however, which exits the cell rapidly, manganese sticks around on the inside. And because the element has a strong magnetic signature, it enables MRI to track neural activity. As a bonus, manganese can also travel between cells, which allows researchers to track neural connections.

Koretsky reported that when he and his colleagues exposed mice to a strong odor spiked with manganese, images of the neural connections in the olfactory bulb—a pea-sized neural relay station in the brain's frontal lobe—lit up on their MRI machine. "We were able to watch as the manganese moves through neurons and see exactly where neurons [travel]," says Koretsky. Scott Fraser, a developmental biologist at the California Institute of Technology in Pasadena, says the new work is "really fascinating," because the technique holds out the potential to image neural development during the first months of life.

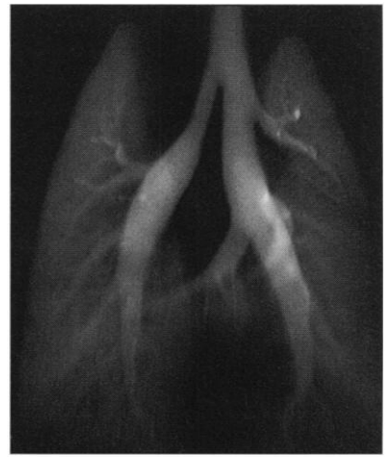
Lighting up particular tissues is only half the fun. Over the past 2 years, several labs have shown that they can also trace the activity of implanted genes that have been tailor-made to make a protein that can be picked up by an imager. Traditionally, researchers have had to sacrifice an animal to check its gene expression, only giving them a snapshot at that point in the animal's life. By imaging gene expression in live animals, researchers will get more of a movie, tracking expression over time and correlating it with the animal's behavior and health. Down the road, these techniques should also aid drug development. "You can look at what genes are turned on before or after drug delivery," says Ronald Blasberg, a PET specialist at the Memorial Sloan-Kettering Cancer Center in New York City, offering clues to how novel drugs work in the body.



Time lapse. Imaging allows researchers to track gene expression over time in mice.

Imagers will also likely prove useful for monitoring how altering a gene affects an animal's development and function. Johnson, for example, presented a technique he and his colleagues have dubbed "rapid phenotyping," which aims to correlate genetic changes with alterations in tissue development. The researchers use a technique called magnetic resonance microscopy that takes a series of digital MRI slices through an animal—1000 in this case—which they then "stack" one atop another to produce a three-dimensional reconstruction of its body. By comparing such 3D maps of one animal with maps of another that has an altered gene, they will be able to see how the change affected the animal's physiology.

Johnson and others agree that these new techniques will be a boon for understanding animal genetics. "There are 2 million genetically engineered mice sold in [the U.S.] each year," says Michael Phelps, a PET imaging specialist at UCLA. "That's expected to triple in a few years," he adds, and imaging could help researchers track the altered genes' activity and effects. Animal imaging has now gained such momentum that in September the National Institutes of Health announced that it will spend nearly $1 million on the initial development of a new computerized mouse imaging atlas. The project will attempt to duplicate the success of the human brain mapping project begun in 1993, which collects various types of imaging data—CT scans, MRI, histology, and so on—converts them all into digital form, and then allows researchers to combine the various elements in a single image that lets them see instantly how a discovery they make with one imaging method relates to everything else that has been learned.



Deep breath. MRI reveals guinea pig lungs in action.

Such maps should allow researchers to move from comparing a few animals to comparing hundreds or thousands, thus providing much more reliable information about biology and disease. Researchers interested in tracking the expression of one particular gene over time, for example, will be able to see how its expression compares to the expression of other genes detailed by other teams. Multiple teams will also be able to work together to chart the many developmental steps that take place shortly after birth, says Huerta: "It will be a very rich information space." The same will likely be said of animal imaging in general.

—ROBERT F. SERVICE

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