

A N E W A G E O F

# Imaging Agents

BY PATRICK YOUNG

**Contrast agents have been unheralded heroes in helping physicians diagnose and treat diseases. A new generation of these chemical compounds sharpens otherwise fuzzy images of internal organs, promising to sustain and enhance that rich heritage.**

**Diagnosis:** Prostate cancer

**Recommended treatment:** High-dose radiation

**First step:** CT scan enhanced by a contrast agent

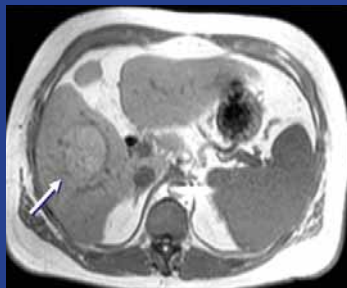
**A** radiation therapist at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University approached me carrying two small Styrofoam cups. One contained MD-Gastroview, a contrast agent that would make my colon visible on the computerized tomography (CT) scan. My radiation oncologist ordered the scan to help plan the series of X-ray treatments that lay ahead in my battle against prostate cancer.

“Some people tell me it tastes bitter,” the therapist warned, referring to the combination of diatrizoate meglumine and diatrizoate sodium in MD-Gastroview. It did, and I washed away the taste with water from the second cup.

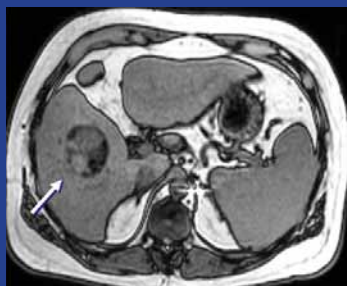
But MD-Gastroview did its job, just as many unheralded chemical compounds—invaluable aids in the diagnosis and treatment of disease—do for millions of patients each year. The results of the CT scan brought an immediate sense of relief and reassurance: My colon was situated well above the area of my urinary bladder, which would be the target of radiation therapy. That anatomical twist reduced my chances of serious bowel damage from the X-rays to less than 1%—or, as my wife Leah said, to “almost zero.”

### Example of an Hepatocellular Carcinoma (HCC) on MRI

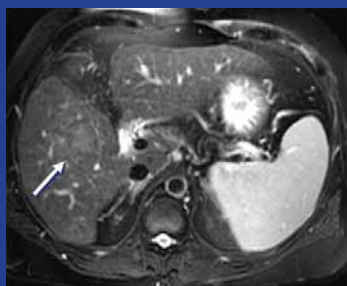
This is a tumor commonly seen in patients with cirrhosis of the liver.



T1-weighted image with the water and fat protons in-phase shows a hyperintense mass in the liver.



T1-weighted image with water and fat protons out-of-phase reveals that the mass drops out indicating fat content.



T2-weighted image with fat suppression reveals that the mass has subtle hyperintensity.



T1-weighted image post Gadolinium-chelate administration intravenously during the arterial phase reveals a hyperenhancing mass.

As their name suggests, contrast agents—also called imaging agents—provide contrast that allows physicians to more clearly distinguish a specific body part, system, or function from surrounding tissue. By doing so, they paint a valuable picture of a pathological condition or disease process.

“You can perform some imaging studies without contrast agents,” said Rendon C. Nelson, M.D., professor of radiology at Duke University Medical Center. “In other studies, contrast agents give you an order of magnitude more information than you would get without them. For example, if I do an unenhanced CT scan of the liver and see a dark spot, I know there is a mass there. But the mass may be benign or malignant, or sometimes it’s just fat. The enhancement pattern given by a contrast agent can be highly diagnostic. Often I can tell whether a mass is a metastatic tumor or completely benign and avoid doing a biopsy.”

### A Future That Depends on Chemistry

With new compounds in the laboratory and in the pharmaceutical industry’s pipeline, imaging agents are poised to make even greater contributions to medicine and patient care. One agent well along the approval path at the U.S. Food and Drug Administration (FDA) will allow the first contrast imaging of lymph nodes to detect the spread of cancer. Also on the way are blood pool agents, which do not leak from blood vessels quickly, like conventional contrast agents do; as such, they will enable the prolonged imaging of arteries and veins.

Molecular imaging agents will one day target only a specific molecule. And far from center stage but perhaps the most exciting prospects are the biochemically activated imaging agents, each one sensitive to a specific biological process. Only when the target process occurs—say, new blood vessels form—can the agent be imaged.

“Chemistry drives the field forward,” said Thomas J. Meade (ACS ’81), the Eileen M. Foell Professor of Chemistry; Biochemistry and Molecular and Cell Biology; Neurobiology and Physiology, and Radiology at Northwestern University. “Each modality requires contrast—not just contrast in the anatomical sense but in a smart sense. The future of imaging depends on chemistry.”

### A Century’s Worth of Images

Physicians began using contrast agents shortly after Wilhelm Roentgen’s 1895 discovery of X-rays. Because bone is so dense, X-rays allowed easy viewing of the skeleton to detect fractures and, in one early case, a needle embedded in the pad of a patient’s foot. But soft tissues like lungs, stomach, and kidneys posed a challenge. Tissue that is less dense than bone often appeared as a fuzzy blur on X-rays, and because of the small density difference among types of soft tissue, distinguishing an organ from its surroundings was difficult. Physicians needed ways to highlight specific body parts.

Contrast agents were first used in the early twentieth century. Bismuth and barium outlined the stomach and duodenum (the first part of the small intestine) when administered orally and enabled the diagnosis of gastric ulcers and cancer. Other agents, administered rectally, helped physicians diagnose colon cancer and diverticulosis. New contrast agents developed between 1906 and 1912 allowed physicians to noninvasively visualize blood vessels, the bile duct, and the gallbladder. An injectable mixture of iodine and poppy seeds introduced in the early 1920s provided good-quality images of lungs and their air passages. Angiography, first performed in 1929, enabled the imaging of arteries inside the heart and the diagnosis of potentially fatal blockages that occur in people who have atherosclerotic heart disease.

RENDON C. NELSON

## Example of an Hepatocellular Carcinoma (HCC) on MRI

(continued)



T1-weighted image post Gadolinium-chelate administration intravenously during the venous phase reveals a subtle slightly hyperenhancing mass.



T1-weighted image post Gadolinium-chelate administration intravenously during the equilibrium phase shows that the mass has washed out but now demonstrates a thin capsule.

A fat-containing mass that hyperenhances during the arterial phase and has a capsule is virtually diagnostic of hepatocellular carcinoma in the appropriate clinical setting.

RENDON C. NELSON

X-ray machines were the mainstays of internal imaging throughout the first half of the 20th century. In the 1950s, however, ultrasound and nuclear medicine expanded imaging's horizons. In nuclear imaging, a small amount of a radioactive tracer concentrates in the target organ or body structure, thereby revealing size, shape, position, and perhaps information about its function. Nuclear imaging applications began in 1955 with the use of inhaled xenon-133 to image the lungs. A few years later, technetium-99m debuted and quickly became a widely used radioisotope for medical imaging. Today, about 85% of diagnostic imaging procedures in nuclear medicine—about 20 million each year—rely on technetium-99m. About half are bone scans, and the rest include kidney, heart, and lung scans.

Ultrasound proved its value in detecting atherosclerosis in the 1960s and has become the most popular technique for imaging blood vessels, partly because it is noninvasive, needs no ionizing radiation, and is less expensive. Ultrasound also is valuable for tracing blood flow in cancer tumors and in organs such as the kidney and liver.

CT and magnetic resonance imaging (MRI) were introduced in the 1970s only to become major imaging technologies in the 1980s. In 1976, researchers demonstrated that CT could produce images of metastatic tumors in the lungs. MRI, the medical application of nuclear magnetic resonance, came into its own with the demonstration that it could image tumors. Although MRI initially was envisioned as a stand-alone imaging technique, users soon found that certain scans benefited from the addition of contrast agents.

### Contrasting the Agents

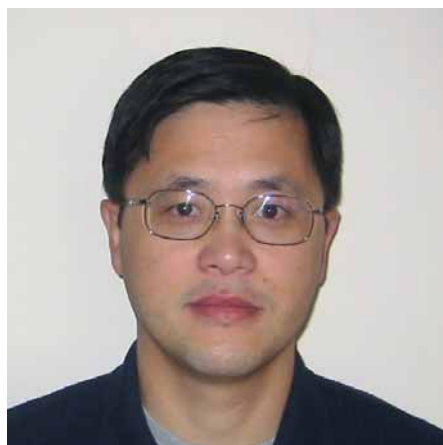
Contrast agents can be administered orally, rectally, by injection or infusion, or even as a gas (for certain lung and brain studies). Specific agents are used for each imaging technology. "For example, in angiography, the contrast agent gadolinium DTPA (diethylenetriamine pentaacetic acid) enhances the visibility of vessels," said Yantian Zhang, a program director at the National Institute of Biomedical Imaging and Bioengineering (NIBIB), part of the National Institutes of Health. "It does not create the same effect with ultrasound or a CT scanner."

Ultrasound imaging relies on three categories of contrast agents: microbubbles, liposomes, and perfluorocarbon emulsion nanoparticles, typically 0.1–0.8 micrometers ( $\mu\text{m}$ ) in diameter. Blood is less "echogenic" than tissue, and these agents increase the reflectivity of the ultrasound waves to permit the imaging of vessels as small as capillaries. CT scans use barium- and iodine-based contrast agents in concentrations that vary depending on the part of the body to be imaged. MRI contrast agents (primarily small-molecular-weight paramagnetic compounds) enhance the magnetic relaxation in tissue that underlies the technique and appear bright (positive) or dark (negative) on an image.

One major research need in this field is the invention of contrast agents that can be used with more than one imaging technique. "Developing multi-imaging modality contrast agents is high on many people's agendas," Zhang said. "One example would be an agent for MRI and optical scanning. The information provided by each imaging modality complements the other."

To all investigators developing new imaging agents, academic and pharmaceutical, the creed is the same: First, do no harm. Ultrasound has a low incidence of adverse side effects, and patients tolerate MRI contrast media better than those used with X-rays. Even though imaging agents have a good safety record, some patients experience mild side effects, such as a warm sensation, a metallic taste, or itching. More serious and much less common reactions include tissue damage, kidney problems, and severe allergic reactions.




**YANTIAN ZHANG**

“In developing a contrast agent, you have to keep in mind not only its efficacy or potential utility; you must think about safety,” said Darryl J. Bornhop (ACS ’79), professor of chemistry at Vanderbilt University.

### Excitement over Combidex

The investigational agent Combidex (ferumoxtran-10), an MRI contrast material, intrigues cancer specialists because it can reveal cancer cells that have spread to lymph nodes. It consists of iron oxide nanoparticles that accumulate in macrophages, which are present in normal lymph nodes but reduced or absent when cancer cells replace normal tissue. On an MRI scan with Combidex, cancerous tissue in lymph nodes appears light, and normal tissue appears dark.

“The FDA hasn’t approved Combidex yet, but it has huge promise,” said Nelson. “Right now, enlarged size is our only criteria for an abnormal lymph node.” So if you have a small node with cancer in it, you are going to call it normal, and if you have a node that is big for a nonmalignant reason, such as infection, you will call it cancerous. With this agent, we can find small tumors, and that is exciting.”

Combidex’s development began with a serendipitous observation. Researchers at Advanced Magnetics, Inc. (Cambridge, MA) noticed that a small amount of one of its investigational agents—now approved for liver scans as Feridex I.V. (ferumoxides)—also went to the lymph nodes. “In talking to physicians, we learned that there was a serious diagnostic problem in telling whether a patient’s cancer had spread to the lymph nodes,” said Paula Jacobs, the company’s vice president for development.

However, tailoring a drug to image lymph nodes proved difficult. The drug needed a long half-life in the blood to accumulate adequately in lymph node cells. Researchers solved that problem by creating iron oxide crystals about 6 nanometers (nm) in diameter and coating them with Dextran to yield a 30-nm particle. Still, other challenges remained. “Combidex is a colloid, and there are not a lot of injectable colloid drugs,” Jacobs said. “It had to be made sterile, endotoxin-free, and stable.” In addition, “Combidex is freeze-dried. The challenges of freeze-drying a colloid and bringing it back up as a solution are not insignificant.”

The FDA has told Advanced Magnetics that it regards Combidex as an approvable drug. But first it wants evidence of the agent’s efficacy in detecting the spread of specific cancers, such as those in the breast or prostate.


**DARRYL J. BORNHOP (ACS ’79)**

### Blood Pool Agents

Contrast agents used in CT and MRI are small molecules that quickly leak out of blood vessels into interstitial space and reach equilibrium in 2.5 minutes or less. Blood pool agents under development for these two imaging techniques consist of large molecules that remain in the blood for extended periods and provide high-resolution images of vessels. “If you can look longer, the possibility of seeing disease will be enhanced,” said Bornhop.

Cardiologists foresee MRI blood pool agents greatly improving their ability to examine blood vessels—especially the extremely small arteries of the heart—with exquisite resolution. Cancer specialists envision the agents enhancing both the detection of solid tumors and the monitoring of therapies meant to destroy those tumors. For example, because tumors require new blood vessels to grow, several drugs aim to thwart vessel formation (called angiogenesis); oncologists then could use blood pool agents to determine whether a therapy blocks new vessel growth. “The problem now is that tumors take up a lot of contrast, and they wash out because of equilibrium. They


**THOMAS J. MEADE (ACS ’81)**

become invisible on the image,” said Nelson. “So the idea is to keep the contrast inside the tumor blood vessels longer.”

Doing so poses a formidable challenge, for several reasons. “One is toxicity,” Bornhop explained. “The body is really efficient at identifying toxins and foreign species, and its responses are considerably higher for larger molecules than for smaller molecules. The second issue is solubility. You can make large molecules that are relatively soluble, but then you have a third issue: Distribution and transport through the body is dictated by size. A large molecule is not going to make it through the liver or kidneys more than one pass, if that. It will be trapped and processed.”

Resolving these issues requires modifying the molecules so they remain in the bloodstream longer without causing toxicity. A commonly used approach is to bond a contrast agent to a common protein in the blood, such as albumin. “After bonding, the size increases dramatically, but the compound is more resistant to excretion by the kidney,” said NIBIB’s Zhang.



MALLINCKRODT

**AN IMAGING AGENT** used for radiographic examination of the esophagus, stomach, proximal small intestine, and colon.

### Molecular Imaging

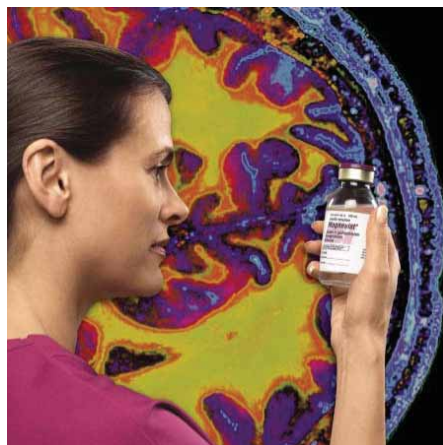
Molecular imaging has attracted interest because of its potential to diagnose disease and even treat some ailments more specifically than previous diagnostic tools. The key lies in finding a biological marker, such as a receptor on a cell, that indicates the presence of a disease—and only that disease—and then constructing a contrast molecule that will seek out and attach to that marker. “If you can design a way to visualize that marker, then you have a much more specific way of seeing what is truly going on instead of just the morphological changes,” Zhang said. “You can see the biological changes associated with the beginning of disease or its early stages.”

How applicable molecular imaging will prove to CT and MRI remains to be seen. Can researchers find ways to attach enough contrast to a biomarker for it to show up on a scan? “CT and MRI will probably not be useful for molecular imaging in the near future,” Nelson said. “Most of the hope now in molecular imaging hinges on nuclear medicine.”

Bornhop and his team at Vanderbilt have developed novel lanthanide chelates as molecular imaging agents for MRI, positron-emission tomography (PET), and CT, but their most intriguing experimental efforts concern contrast materials for optical scanning. “Our work has been oriented at developing agents that can be delivered in the blood but will localize in disease,” Bornhop explained. “We have developed some different chelate chemistry to make molecules that are brightly luminescent. The idea is to make a family of molecules for imaging agents that could be targeted to different receptors.”

For example, the team has targeted a protein called the peripheral benzodiazepine receptor, found on the membrane of mitochondria, which are the energy sources inside cells. Evidence suggests that in some cancer tumors, cells overproduce this receptor. However, the depth of optical imaging is slight, and so far, the Vanderbilt researchers have focused largely on surface malignancies, such as skin, colon, and cervical cancer.

“One main target is oral cancer,” Bornhop said. “One would give this as a topical agent, let it equilibrate, wash off the excess, shine blue light on it, and look for reddish-pink fluorescence. It could serve for early detection and as a guide during biopsy and surgery, to ensure the removal of the entire tumor.”



BERLEX IMAGING

**FIRST MRI CONTRAST AGENT**  
 When Magnevist (gadopentetate dimeglumine) was introduced in 1988, it ushered in the revolutionary concept of contrast-enhanced magnetic resonance imaging (MRI). Magnevist became the world's first contrast agent for use in MRI. The product is still the MRI market leader, used in imaging the head, neck, and parts of the body. MAGNEVIST has been used in more than 45 million MRIs in more than 100 countries.

**Targeted Therapy**

Even more exciting than disease detection is the concept of using imaging agents in treatment. Could the same agent that detects atherosclerosis deliver a means to reduce it? “Why not?” answered Bornhop. “That is what nanomedicine is all about—making a molecule that has more than one function. We would like to make agents that signal a disease, deliver a therapy, and tell you if the disease has been abated or cured.”

Targeted therapy delivers a treatment—a drug, toxin, or radioactive particle—directly to the disease site without exposing other tissues. By altering the surface of a contrast agent that homes in on a biomarker for a specific disease, researchers could create a means of both diagnosing and treating the ailment. “That is one side of targeted contrast agents,” Zhang said. “The other is using contrast agents in the drug-discovery-and-development process.”

The FDA often uses the survival rates of patients treated with an experimental drug as the gold standard of its efficacy. However, a statistically significant survival curve can take years to develop. Using targeted contrast agents to determine whether a treated condition persists could provide a means of assessing survival rates. “You see not only a cancer shrinking with the treatment, but the specific biological changes and bioactivity related to the treatment,” Zhang explains.

Researchers are working on targeted contrast agents for all the major imaging techniques. For example, ultrasound specialists have attached various biologically active molecules to microbubbles and liposomes in searching for ways to noninvasively detect disease and study gene expression, drug localization, and the molecular mechanisms of diseases.

**Biochemically Activated Agents**

At the cutting edge of contrast media research stand the teams—perhaps half a dozen worldwide—exploring the creation of imaging agents that become activated only by a specific biochemical process. “These new classes of MRI agents represent a substantial leap in the type of information derived from imaging experiments,” said Meade. “We developed the first multimodal contrast agent for MRI and optical imaging in 1998, and we have been using it for years in a number of applications, including stem cell migration. We can make these agents for use inside or outside cells, inside or outside organs.”

Meade and colleagues at Northwestern have created multimodal agents that consist of gadolinium resting inside a cage structure that resembles a tennis ball cut in half, then secured at four opposing points by a specific enzyme whose presence serves as a marker for a targeted process. The cage and cap prevent the gadolinium from being detected by MRI. Upon cleavage, however, the cap and cage open, exposing the gadolinium. The MRI's detection of gadolinium indicates the presence of the targeted biochemical process.

“By coupling the unique properties of nanomaterials with new types of biochemically activated contrast agents, we can develop an entirely new generation of probes,” Meade said. “Researchers want to correlate the genetic activity during a developmental event. Now we’ve got a family of contrast agents that allows us to peer into physiological and biochemical processes, not just anatomy.”

*Patrick Young is a freelance science and medical writer and is former editor of Science News magazine. He is writing a book about his experiences as a prostate cancer patient.*

**CROSSWORD solution**

TO SPRING 2006 CHEMISTRY PUZZLE.

T	A	N	S	U	N	Q	A	T	E	A											
F	E	L	O	N	Q	U	A	R	T	E	R	S									
A	L	E	L	I	P	A	R	C	H	E	R	S									
R	A	D	I	A	T	I	O	N	O												
A	M								T	E	R	R	O	R							
B	E	A	M	M	G	U	P				S	O	P								
L	I	D				R	E	M	I	S	S			U	R						
I	N	F	R	A	R	E	D			P				T	I						
N	A					R	F	E			G	L	A	S	S	E	S				
P	H	O	T	O	N	S				I				W	O	R	M				
W	E	A	R			P	O			G	R	A	B								
H	P	S				T	R	I		H	A	Y									
I	M	P								V	I	O	L	E	T		S	T	A	R	
R	O	E				I	C	Y													
L	E	N	S	E	S					Y	E	L	L	O	W						E