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In diagnoses, a tale of two specialties



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Cover Story

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The clever folks at The Methodist Hospital Research Institute, Houston, are busy creating the future of pathology.

It doesn't have a name yet, though a few possibilities are being tossed around. Diagnostic medicine. Molecular radiology. Radiologic pathology.

None of these labels are particularly elegant, perhaps because they reflect the field itself—a work in progress. No one is fully comfortable predicting what the new practice will look like. Pathologists may have a clear view, but don't know what they'll see. Radiologists may know what they'll see, but may not know how to read it. Yet it's all evolving according to plan at the Research Institute, or TMHRI, which has set out to do nothing less than redefine the shape and practice of both fields by trying to meld them.

When this happens (no one's using the word "if"), pathologists will become in vivo specialists, and radiologists will absorb in vitro duties. Basic anatomic pathology will use real-time imaging at the cellular level. Ultimately, those reading the images—exactly who that will be is an intriguing if unanswerable question right now—may do so based only on in vivo pictures, without any tissue processing.

It's not so much that TMHRI and like-minded colleagues at other institutions are dreaming up a new future, as simply looking down the road and seeing the logical destination.

Actually, they're looking down two roads—pathology and radiology. Until recently, both imaging sciences have been separated by matters of scale—the microscope versus the MRI, to shorthand it. But that's changing, says King C. Li, MD, the M.D. Anderson Distinguished Chair in Radiology and Imaging Sciences and chair, Department of Radiology, The Methodist Hospital.

Dr. Li likes to start with the basics to explain why he and his colleagues see pathology and radiology cozying up in the not-too-distant future. In fact, he says, it's happening now.

Pathology developed through analog methods—using eyes, later enhanced by microscopes, to analyze samples obtained from tissues. Radiology followed a similar path, starting with the development of x-rays, and using eyeball analysis as well.

Despite these similarities, the paths have been segregated—separate but equal, and not necessarily in the best interest of those receiving the service.

At the same time, adds Steve Wong, PhD, the two fields have been limited by a bottom-up approach to medicine, with pathologists identifying biomarkers for molecular diagnostics and radiologists doing imaging studies before handing cases over to surgeons. The radiologists and pathologists don't interact. "It's quite a waste of talents," says Dr. Wong, vice chair and chief of medical physics, Department of Radiology, The Methodist Hospital, and director of bioinformatics, TMHRI. (Dr. Wong also has a joint faculty appointment in the Department of Pathology.)

Now the two paths are merging, thanks to shifts that allow both groups to analyze molecular information with digital methods. As it turns out, while pathologists have been debating whether molecular diagnostics falls into the domain of anatomic pathology or clinical pathology, the answer may be "neither."

Dr. Li and his colleagues are developing a methodology to visualize molecular events at the macroscopic level, using, for example, PET or CT-PET to look at an area of abnormality that expresses specific molecular or functional information, such as the trapping of fluorodeoxyglucose. Physicians could then guide a tiny fiber to the area, inject a stain that highlights a molecular probe, and assess tissue without removing a sample. "This is in vivo immunohistochemistry and bioassays—it's doing pathology in vivo," Dr. Li explains.

At TMHRI, researchers are developing a multimodality platform to do such work, combining a multitude of imaging tests to localize the molecular event with guided optical imaging tools and chemical probes. They're also developing ways to look at the area microscopically, removing samples for gene and protein analysis. Yet even this is an improvement, with the use of a very thin fiber that allows users to slice through a huge area and avoid sampling error. "Using in vivo analysis, you can look at everything, then decide to take samples from the representative area," Dr. Li explains.

There is likely to be an expanded role for special stains as well, says Mike Lieberman, MD, PhD, chair of the Department of Pathology and CEO and director of TMHRI, as well as professor of pathology at Weill Cornell Medical College, New York City. This will very much be a partnership with interventional radiologists, who will place the catheter and take pictures for pathologists to interpret. He views it as similar to current frozen and permanent sections in the OR, with pathologists taking a preliminary look at images to assess sample adequacy and underlying processes, then making a diagnosis later on. "As we all get more comfortable with the technology, we may be reading some of these simply from the in vivo image, without any tissue processing," Dr. Lieberman says.

Not only are pathology and radiology inching toward each other, but so are AP and CP. This shouldn't be a real shock to anyone. As Dr. Lieberman points out, in hematopathology the morphologic diagnosis of hematopoietic neoplasms depends on flow cytometry, molecular diagnostics, and chromosomal analysis. The leading edge of the clinical lab will be molecular diagnostics and proteomics, he says. IHC and proteomics "are exactly the same thing. When we test for ER or PR in a breast biopsy we're analyzing protein. So it may be possible to do real-time genomics as well—that is, we may be able to visualize DNA and RNA in these same biopsies, and do things that are the equivalent of FISH or even other kinds of staining technologies that will allow us to look for oncogene expression and similar processes."

Such techniques are not likely to replace FNA techniques for superficial masses, such as thyroid, but will be important for deep tissues, such as pancreas, liver, masses of unknown origin in the abdomen, possibly kidney and colon masses. Nor is it

inconceivable the technique could be used on brain masses, Dr. Lieberman says.

It's more than a futuristic dream. "A lot of it you can do with things you already have," says Dr. Li, noting that some optical imaging dyes have already been approved for clinical use. Similarly, FDG, gadolinium, and other contrast agents can be used for microscopic imaging. "We are well on our way," says Dr. Li.

He seems rather unfazed by the magnitude of developing a new branch of medicine. Miniaturizing fibers is one challenge, he concedes, and clearing FDA hurdles will be another. "But the concept is in front of us," he says, "All our images are digitized, right? But we're still using our eyeballs to analyze them. So it seems to be obvious that this is going to happen. It's just a matter of time."

Looked at another way, all this is merely a matter of extracting more information. Dr. Li views this largely as a technological hurdle, and is convinced that once the technology is there, acceptance will follow. Build the tools, he says, and the revolution will follow.

He sees this happening in three steps. The first is using existing imaging information and existing tissue analysis information to create useful composite information. This is a bioinformatics challenge if there ever was one, though Dr. Li remains characteristically optimistic. "The first phase should be simple. The data are already there; it's how to derive information by combining them. We're trying to do that, quickly."

The next step is to develop tools that will change the way biopsies are done. This will require localized probes, which could take any number of formats: chemical, optical, MR, or radiotracer. Likewise, the field will need strong platforms, which may not be all that far off. TMHRI researchers are ramping up existing CT scanners by adding optical probes as well as the capability to do electromagnetic tracking, high-intensity focused ultrasound, and in vivo microendoscopy diagnosis and localized drug discovery. "We are experimenting with a couple of these right now," says Dr. Wong. He and his colleagues are also working closely with one of the three largest imaging companies, though he declined to name names.

If any area is lagging, it's molecular diagnostics. Dr. Wong notes that microarrays continue to face problems with reproducibility, and he laments the lack of medical engineering expertise in pathology. Pathologists publish plenty of scientific papers, he says, but few of them think about bringing robust products to market—at least as compared to other colleagues. "Surgery, cardiology, radiology—they are very aggressive. Radiology is just a whole bunch of toys," he says with a laugh. "And every time we come up with a new big toy, we open up a new revenue stream and sometimes a brand-new subspecialty." On a more serious note, he says the underlying message is that radiology has excelled at embracing technology to stay ahead of the curve. "I don't know whether pathology colleagues have this same type of urgency," Dr. Wong says.

The third step will integrate these new methods into therapeutic decision-making. Rather than assessing tumor size after chemotherapy cycles, says Dr. Li, "we'll look at the molecular image and say, 'Why are you still treating with anti-VEGF therapy when there's no VEGF present?'"

"The ball is in our court to develop the technology first," Dr. Li says. If a strong bioinformatics structure is in place—and there's no question he thinks it will be—the rest will be easy. Give clinicians powerful composite information, and they'll have no reason or desire to limit themselves to older formats. "In the old days we did exploratory laparotomies. But when a CT scanner is available, you say, 'Why do I still

have to cut open the belly to see what's inside?' It didn't take long to change once the tool became available."

What would this new field mean for pathologists? James Musser, MD, PhD, shares Dr. Li's enthusiasm, though he's somewhat more circumspect. "My general feeling about this is, frankly, the crystal ball model is not the best one."

"I think what's going to happen is that two or more smart people with a particular interest around a specific topic are going to talk," says Dr. Musser, associate chair, Department of Pathology, The Methodist Hospital, and executive vice president of the Research Institute. "They're going to start formulating specific ideas. It could be, for example, liver pathology or infectious disease. I don't think we know where the solutions are going to come from. I think much of this is going to be driven very much at the grass-roots level, in my opinion, by two or more individuals who have a shared passion over some medical problem or biomedical problem. And that's how this synthesis of fields is going to move forward."

On a practice level, Dr. Musser foresees "a hybrid field filled with hybrid individuals," much like what has happened in molecular pathology. "Now we have training programs in molecular and so forth, and a society and journals, and it's a viable academic enterprise."

"Hybrid vigor is crucial to the ongoing success of any discipline," he adds, including medicine.

"If fields don't mutate they die."

Dr. Musser says that with hope, though it sounds a bit ominous. If you're a pathologist—and you probably are—it's impossible not to wonder what these changes could mean for your own practice.

Dr. Wong has little patience for this line of thought. "Traditionally, people look at pathologists as doing *ex vivo*, and radiologists as *in vivo*." That's an artificial barrier, he says, creating a "my-turf-vs.-your-turf" mentality. "That's nonsense. We can do better patient care by combining these two. Medicine needs to advance."

His advice to pathologists is simple: "Forget about your current mountain. Go to the next mountain and start climbing."

Still... Who will read new images? Pathologists? Or radiologists? Either are possibilities. "This is the one possible 'threat' to the practice of pathology," says Dr. Lieberman. "But I don't think this will happen." His reasoning? Without training in microscopy, and without the ability to do backup permanent sections, radiologists may fear to tread this territory. On the other hand, there's a long tradition of dermatologists reading their own slides and taking subspecialty boards, he notes. "And that's why I'd like pathologists to be out there proactively. The better we can prepare for this, the better we're going to fare as a discipline."

Radiology has a leg up in terms of imaging technology, which could tip the balance among practitioners, especially if future breakthroughs are driven by the imaging rather than diagnostics industry. Radiologists already do image-guided biopsies. "But I don't think there will be a desire or way for radiologists to read the results from an anatomic pathology perspective very easily," Dr. Lieberman says. And they simply may not be interested, he says—after all, they've got other procedures to do, and may not want to undertake the time-consuming practice of reading images and rendering permanent decisions.

"But no one knows where the boundaries are. This is going to be like a lot of other techniques in medicine," Dr. Lieberman says. "Who does backs—neurosurgeons or orthopedic surgeons? Who does facial reconstructions—the oral facial and maxillary surgeons or the ENT people? Who does imaging—interventional cardiologists or interventional radiologists?"

The answers may not even be important, at least at present. "Now is the time we should be asking questions, rather than think we know the answers," Dr. Lieberman says.

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