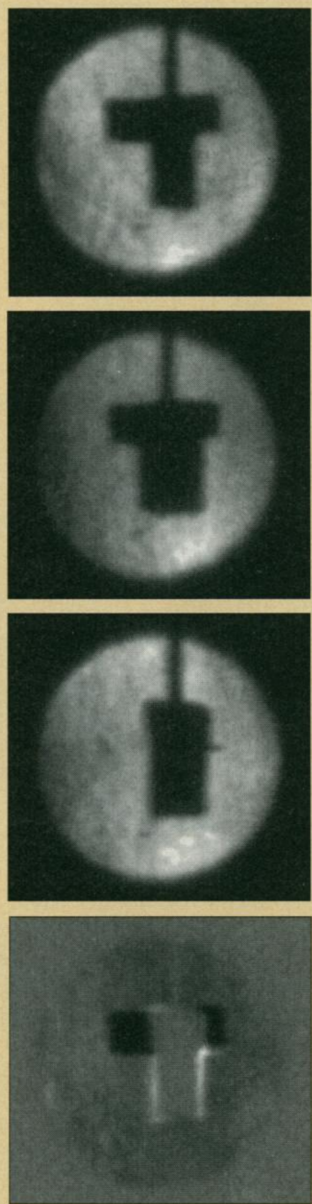
Transillumination: Looking Right Through You

As long ago as the mid-1800s, British physicians began detecting scrotal cancer by holding a lamp behind the testes and noting the shadows the tumors cast. It might seem that an idea this crude wouldn't have much application in the age of the Human Genome Project, but transillumination, as this phenomenon is known, forms the basis of a group of closely related novel imaging technologies that promise to provide finely resolved spectroscopic analyses of tissues. "We can see inside tissue with enough clarity that we're starting to see fingerprint patterns that distinguish between healthy and abnormal tissue," says Robert A. Alfano, director of the City University of New York's Insitute for Ultrafast Spectroscopy and Lasers, and a key player in the development of the new techniques.

These optical images of biological structure and function are as yet too crude for clinical use. Nevertheless, they may eventually aid in diagnosing breast cancer, assessing brain damage in newborns, and improving surgical precision. "These optical technologies are very promising, because they would be noninvasive, portable, and inexpensive, but they have a way to go before they reach the realm of clinical testing," said Deborah G. Hirtz, who as health scientist administrator at the National Institute of Neurological Disorders and Stroke convened a meeting last year to assess the potential clinical importance of various imaging technologies. But this field is moving so fast it is confounding even the experts. David A. Benaron, professor of pediatrics and neonatology at Stanford University School of Medicine and Hansen Free-Electron Laboratory, says his group already has three clinical trials in progress for imaging brain bleeding, brain hypoxia, and breast tumors. "I would expect to see early reports on the progress of many other clinical trials over the next year or two," says Benaron.

The groundwork for much of this technology was worked out in the 1970s and 1980s by Britton Chance and his students at the University of Pennsylvania and by Alfano. It was Chance who showed that by measuring both the intensity of transmitted photons and the distance light has traveled while scattering through tissue, it can be deduced where those photons are most likly to have gone and what structures they encountered on their travels, including mitochondria, nuclei, and blood vessels. Alfano, meanwhile, found that taking ultrafast slices of optical data passing through tissue improved the resolution of resulting images.



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The shadow knows. "Transillumination" images of a T-shaped block of rubber immersed in an opaque fluid; a three-dimensional image computed from them is shown at bottom.

Benaron was one of Chance's students. He and his co-workers have refined Chance's idea, using computer-assisted path reconstruction to image the internal structure of tissues. By using multiwavelength spectroscopy, they hope to monitor indicators of tissue function such as tissue oxygenation, blood flow, markers of cellular injury, and glucose and cholesterol levels, opening the way to nonsurgical "optical biopsies."

"Such techniques offer the ability to noninvasively and spatially measure the concentration of different components in tissues," said Benaron. "Thus, we may be able to not only determine that someone has had a stroke, but localize the stroke, identify other tissues at risk for future strokes, and perhaps even monitor the results of medical therapies." Such functional feedback may be important in managing heart disease, Alzheimer's syndrome, and traumatic brain injury.

In early experiments, the Stanford group has imaged an entire rat, with organs visible on the image, using this time-resolved transillumination technique. More recently, they have constructed a tomographic scanner and made images with better than 1-centimeter resolution of human and animal brains. Ultimately, Benaron would like to use this approach to image the abdomens of pregnant women to reveal information about the oxygenation and well-being of the fetus inside.

Alfano's emphasis in transillumination imaging has been on detecting ballistic photons (those that pass through tissue unscattered) and "snake light" photons (those that undergo only minimal scattering). The advantage of looking at these photons is that image processing is virtually instantaneous. "We simply use a series of lenses to spatially remove the scattered light and then open an optical shutter between 1 and 10 picoseconds after each laser flash," explained Alfano. The intensity of the arriving light, recorded with an ultrasensitive video recorder, provides a direct image of structures inside a tissue. Rotating the object relative to the scanner provides three-dimensional images in movie form.

Alfano has concentrated on fine-tuning this system for detecting breast tumors, a painstaking process of using tunable infrared femtosecond lasers to search for parameters that will identify the earliest stages of tumor formation. "Basically, we will be doing time-resolved transillumination spectroscopy in the near infrared, looking at the absorption spectra of oxygen, hemoglobin, and water in healthy and abnormal tissues," said Alfano. He believes that time-resolved transillumination techniques will eventually be used to image breast, brain, teeth, testicles, and prostate tissues.

Alfano is now attempting to extend this technology using fluorescence techniques to diagnose pathological changes in the mucosa of tissues. The idea is to increase the light available for detection by getting structures within tissue to emit photons themselves. One way to do this is to inject tissue-specific fluorescent dyes. Another approach is to tune the incoming light to the specific wavelengths that induce natural fluorescence. "There are many biological molecules, such as collagen, elastin, and NADH, that are strongly fluorescent, and that we should be able to use to assess the condition of a tissue," said Alfano. And if it is possible to put this idea into practice, the results should be, well, illuminating.

–J.A.