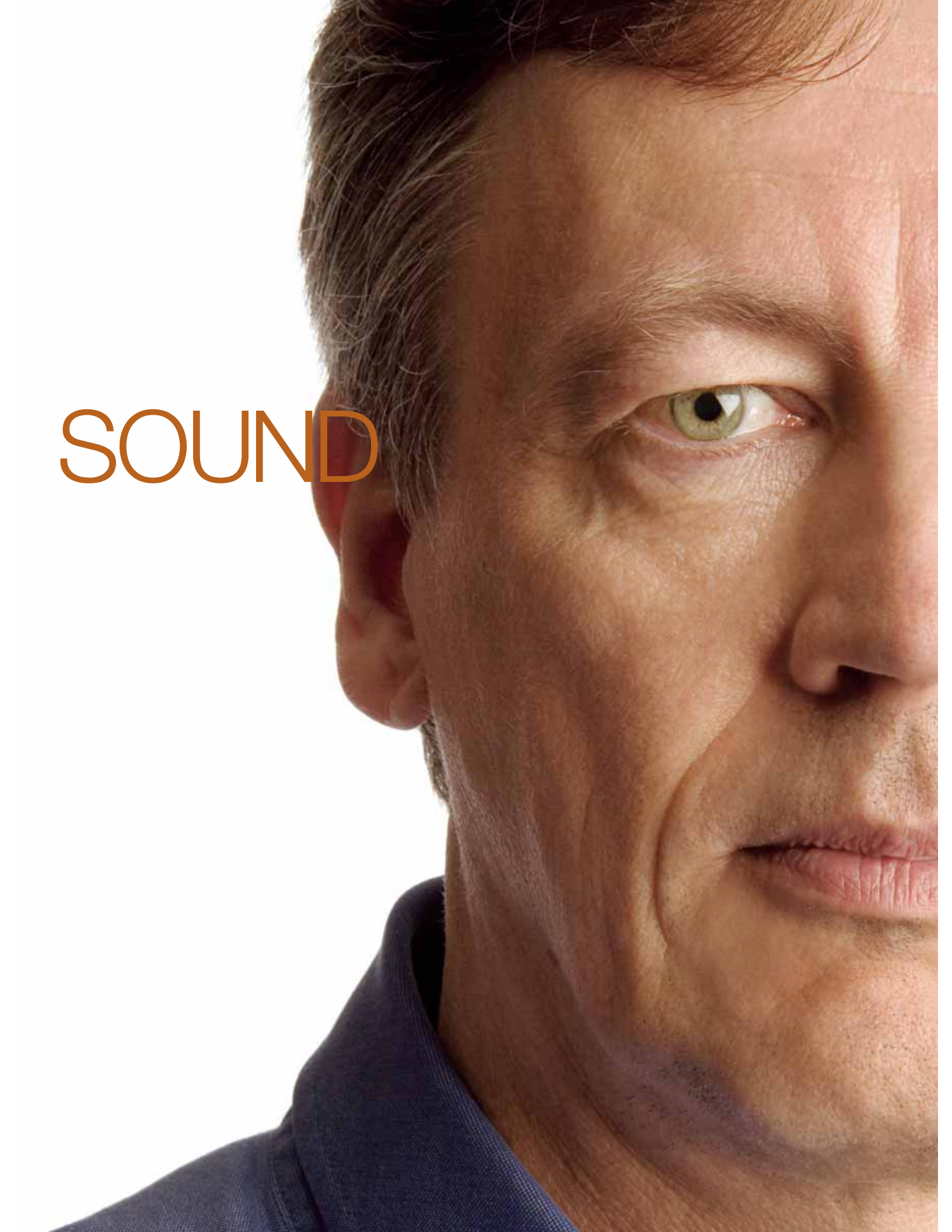


SOUND



THE PROMISE AND REALITY OF THERAPEUTIC ULTRASOUND ARE FINALLY IN HARMONY. KULLERVO HYNYNEN IS ONE REASON WHY

FOCUS

tumours; and low-intensity ultrasound to disrupt reversibly the blood-brain barrier, thereby enabling drug delivery and gene therapy in previously inaccessible parts of the brain: these and Hynynen's other discoveries have shaped the evolution of ultrasound from simple imaging tool to futuristic, noninvasive surgical paradigm, and helped push us to the cusp of a new era in medicine.

Use of ultrasound as a therapeutic technique predates its diagnostic application. Scientists began treatment studies in 1927 after finding that ultrasound could permanently alter bacteria, but these efforts were hindered in later decades by a limited ability to control application, and monitor temperature and tissue changes. Imaging capacity had improved a lot by the early 1990s, and in 1993 at the University of Arizona, Hynynen was the first to show that magnetic resonance imaging (MRI) could effectively monitor tissue death during ultrasound thermal coagulation (heating and destruction of cells) in a preclinical model. By 1996, he had moved to Harvard and expanded the use of MRI in this system to monitor precisely temperature elevation and cavitation (the occurrence of tiny gas bubbles) — two concerns for patient safety.

The same year, Hynynen sealed a renal artery with MRI-guided focused ultrasound in a preclinical model. Researchers are extending this technique to stop bleeding after internal organ damage, and to seal blood vessels following trauma. It has also shown potential as a cancer treatment, closing tumour-feeding vessels to starve tumours of oxygen.

Ultrasound appeared useful as a treatment for brain disorders including cancer as early as the 1950s, when scientists used focused beams to produce lesions in the central nervous system. But because sound waves distort on passing through bone, the need for invasive creation of a soft-tissue window limited further study. In 1998, Hynynen was among the first to show preclinically that ultrasound could produce a focused beam through an intact skull. He used two 64-element phased transducer arrays to deliver varying ultrasound frequencies, and then measured phase distortion caused by the skull for each element of the arrays and compensated for it through phase-control circuitry. "This requires," says Hynynen, "very detailed information on the skull structure, thickness and speed of sound, so you can model propagation of the sound field through the skull. In this way, beams come to a single focus inside the

Dr. Kullervo Hynynen is making time. Preparing to leave for the Sixth International Symposium on Therapeutic Ultrasound in Oxford, the new director of imaging research at Sunnybrook Research Institute (SRI) and Canada Research Chair in Imaging Systems and Image-Guided Therapy has pushed away from his LCD and settled into an armchair in his sixth-floor office to discuss research. Briefly.

"What frustrates," he says, "is slow clinical implementation." Hynynen speaks quietly and gently; his smile is infrequent but warm, and his face angular, precise. "Twenty years ago, there were lots of good ideas on using ultrasound for therapy, but developing them into treatments has been," he pauses. "Long and complicated."

It's a little surprising that Hynynen's greatest disappointment is the pace of translating physics into clinical ultrasound treatments. That he's frustrated speaks to a drive to help—to make sick people better—that has spurred several breakthroughs. High-intensity focused ultrasound to seal arteries and thermally destroy uterine fibroids, breast and brain

GETTING RESULTS SUCCESS IS A METHOD IN SCIENTIST'S LAB

Dr. Kullervo Hynynen is in the lab, but not for the reason he'd like to be. It's a photo shoot, and the photographer is encouraging him to look natural among vertical racks of green circuit boards. Hynynen uses the time to talk science with postdoctoral fellow Dr. Laura Curiel and scientist Dr. Rajiv Chopra, who will collaborate with him and share a newly renovated 3,600-square-foot lab on the seventh floor of Sunnybrook's C wing.

The lab is unique at Sunnybrook. Since arriving in January 2006, Hynynen has recruited 14 lab members, and expects to double that number in the next six months. By autumn 2007 there will be 35 students, postdocs, engineers, tissue culture assistants, animal technicians and research assistants—about the size of his previous lab at Harvard—engaged in 12 research projects.

Chopra, in his office down the hall, says, "The group gets so big because Kullervo focuses on a number of areas to get the work into the clinic." For focused ultrasound therapy of brain tumours, he explains, one team calculates algorithms on wave distortion and refocusing inside the brain. Another handles electronics driver development—how to get signals to sound transducers in the MRI unit. Yet another makes the transducers. Then there is a major effort in preclinical evaluation of prototype devices. "It's the whole spectrum of research," says Chopra.

While the range of activity in Hynynen's lab is unusual, his interaction with his staff is most striking. "One thing that sets Kullervo apart is communication," says Chopra. "He doesn't sit isolated from the students." Students face agonizing forks in the road during experiments, and Chopra admits that there's something to be learned from going down the wrong path, seeing it and coming back. But

at the same time, he says with some understatement, "You don't want to make your career out of it. Kullervo really uses his experience to guide his students."

Curiel, recently arrived from France, agrees. "It's astonishing he finds time to speak with each person in the lab, often every day...to check progress and make suggestions." She believes this unusual for an established scientist, but is grateful that he does so. "It saves a lot of lost time," she says adamantly.

Hynynen's short commute from his new home close to Sunnybrook helps him to find time, as does a daunting schedule of dawn-until-dusk workdays. But Hynynen nonchalantly regards the hours and the complex range of his work as requisite for his ultimate goal—clinical implementation. **10**



CONTINUED FROM PREVIOUS PAGE

skull." Remarkably, these corrections produced enough focused heat to destroy tumour tissue.

By 2002, Hynynen and colleague Dr. Greg Clement had constructed a helmet-shaped 320-element array to achieve a more precise application in human skulls. They developed wavevector-frequency models to dictate sound delivery; these allowed for reconstruction of a more sharply focused beam after distortion. Hynynen is now starting clinical trials of these models at Toronto Sunnybrook Regional Cancer Centre (TSRCC) to treat brain tumours—no hair out of place.

MRI-guided ultrasound is adaptable to treat tumours in other areas of the body, and Hynynen was the first to show its potential in the breast. In 2001, Hynynen was a part of a group that eliminated benign tumours up to 6.5 cubic cm. Ablated tumour tissue was absorbed by the body with no adverse effects. He has since collaborated with other scientists in applying this technique to the more complex challenge of cancerous breast tumours. Results are promising, and Hynynen plans to start a clinical trial at TSRCC with SRI scientists Drs. Greg Czarnota and Peter Burns next year.

Three in four women will develop uterine fibroids at some point in their lifetimes, and one in four will experience symptoms, which include pain, bleeding and infertility; they're also the main reason for hysterectomy. In 2003, Hynynen and collaborators zapped uterine fibroids up to 10 cm in diameter in a clinical trial. The procedure took less than three hours, produced only mild discomfort, and patients were released immediately. The treatment is now federally approved in the United States and Canada. Despite the bureaucratic frustrations of pushing the treatment into the

marketplace, its success is the accomplishment that pleases Hynynen most. "I'm very happy ultrasound surgery is now in clinical practice—it will most likely make a huge difference in the lives of people," he says.

While Hynynen is pleased ultrasound surgery is finally a clinical reality, he believes his work on disruption of the blood-brain barrier holds the most promise. The blood-brain barrier is a membrane that controls movement of substances between blood and the central nervous system. In 2001, Hynynen and his lab were the first to use MRI-guided ultrasound with microbubbles as cavitation nuclei to open specific parts of the barrier—a feat thought impossible by many scientists. The preclinical procedure required removal of skull bone, but was done at relatively low frequency, thus leaving surrounding tissue intact and ensuring the opening was transient. In 2004, by combining this technique with earlier work on algorithmic correction of distorted sound waves, the team achieved the same effect noninvasively. Clinical translation of this procedure could have profound implications in brain cancer and other diseases of the nervous system for which treatment is difficult or even impossible.

Hynynen is keen to get into the lab. End of interview in sight, he becomes almost expansive looking back at his career. On developing an interest in science during high school in Finland, he recalls, physics quickly became his strongest subject. At the University of Kuopio, he was accepted in all physics streams, but says, "Medical physics seemed to be the area which could most benefit others. That was a deciding factor, and it felt right." Interview over. Standing up, Hynynen laughs, adding, "There are easier choices where you make more money, but I'm happy and have never looked back." **10**