SCIENCE

New method delivers life-saving drugs to the brain—using sound waves

An emerging technique harnessing ultrasound may revolutionize treatment of fatal or hard-to-cure conditions, from cancer to Alzheimer's and Parkinson's diseases.

Prior to focused ultrasound treatment, microbubbles are injected into the bloodstream. The low intensity focused ultrasound causes the microbubbles to vibrate, which leads to the temporary opening of the blood-brain barrier allowing for the delivery of chemotherapy to the...Read More

PHOTOGRAPH BY KEVIN VAN PAASSEN, SUNNYBROOK HEALTH SCIENCES CENTRE

BY **CLAIRE SIBONNEY**

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At 6 a.m. on a spring morning in 2021, a jovial and spry 63-year-old named Michael Butler is wheeled into a special MRI suite at Sunnybrook Health Sciences Centre in Toronto. The retired sales executive and motorcyclist is hooked up to an IV and dressed in a hospital gown. Aside from a trim white goatee, his head is freshly shorn—a style he's sported since getting craniotomy surgery to remove as much as possible of an aggressive, plum-size brain tumor three months earlier.

Today he is part of a clinical trial testing a new method of delivering drugs directly into the brain, with a technique called focused ultrasound. Many experts believe this therapeutic technology will one day revolutionize brain medicine for a range of impossible or hard-to-cure conditions, from brain cancer to Alzheimer's, Parkinson's, and ALS.

In Butler's case, the procedure is designed to deliver drugs that will try to destroy any cancer cells left behind after his surgery. Complete removal by surgery wasn't possible without severely damaging the rest of his brain. Focused ultrasound is his only chance to prolong life with glioblastoma, a catastrophic form of cancer that is incredibly difficult to treat.

Sunnybrook's research team prepares a participant in the Breast Cancer Brain Metastases clinical trial for focused ultrasound treatment.

PHOTOGRAPH BY KEVIN VAN PAASSEN, SUNNYBROOK HEALTH SCIENCES CENTRE

Waiting for him are Nir Lipsman, his neurosurgeon and a scientist at the a medical physicist, and an anesthesiologist. Butler is given a mild sedative and his skull is fastened with four pins into a lightweight frame

to prevent any movement. After lying down on the bed of the MRI machine, his head is attached to a helmet-like transducer capable of transmitting more than a thousand intersecting beams of ultrasound energy deep within the brain with extraordinary precision.

Focused ultrasound is "science-fiction medicine that is rapidly becoming non-fiction," says Brad Wood, director of the National Institutes of Health Center for Interventional Oncology.

The novel procedure gets drugs into the brain by overcoming a major hurdle: the blood-brain barrier, a thin protective layer of specialized cells lining the very small blood vessels guarding the human body's most privileged organ. It keeps out the bad stuff, such as pathogens, but it also prevents potentially useful things from getting in. As a result, virtually all medications for conditions such as brain cancer and neurodegenerative diseases are effectively unable to reach the site where they are needed most.

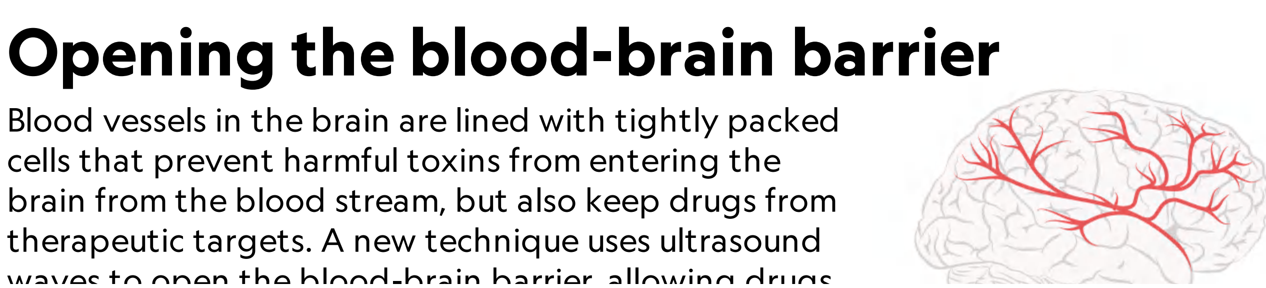
The challenge is that the brain is extraordinarily fragile and damage is irreversible, which is why surgeons want new strategies to bypass the blood-brain barrier. Methods such as surgical injection have been tried in the past but involve skin incisions, holes in the skull, and passing instruments through the brain, which all risk infection, bleeding, and swelling and could cause permanent brain damage. "When treating the brain, we have to remember the person, too," says Lipsman, who is also the director of Sunnybrook's Harquail Center for Neuromodulation. "Treating the heart, limbs, or lungs, won't change someone's personality, memory, or affect. Harming the brain will."

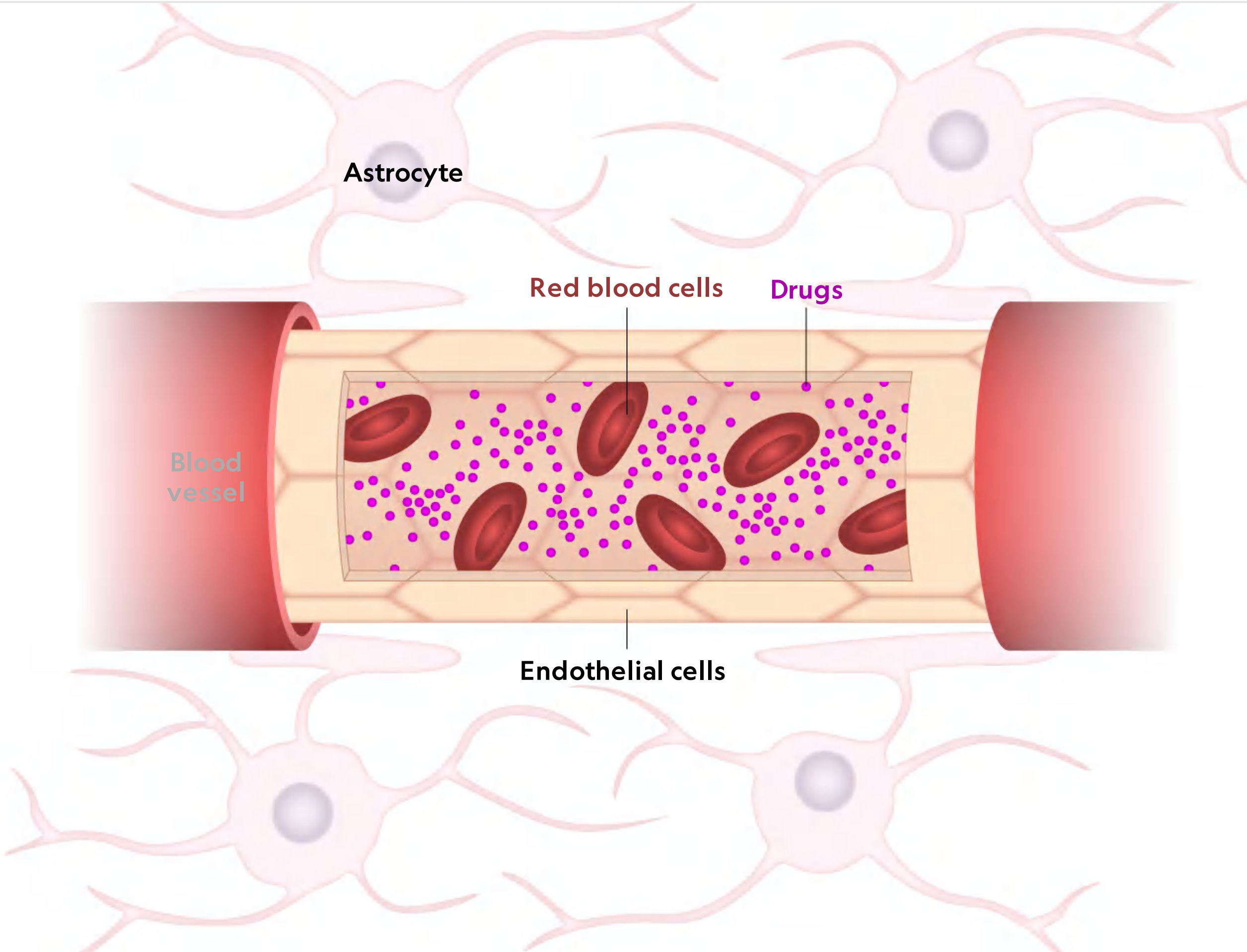
Numerous teams around the world have now shown that opening the blood-brain barrier with ultrasound is safe and feasible, so the next hurdle is proving the medical benefits.

“There are early glimmers of hope,” Lipsman says, referring to multiple clinical trials he’s overseeing to tackle everything from tumors to neurodegeneration. The field is also advancing to enhance drug delivery, improve patient comfort, and make the technology more accessible.

A confounding barrier

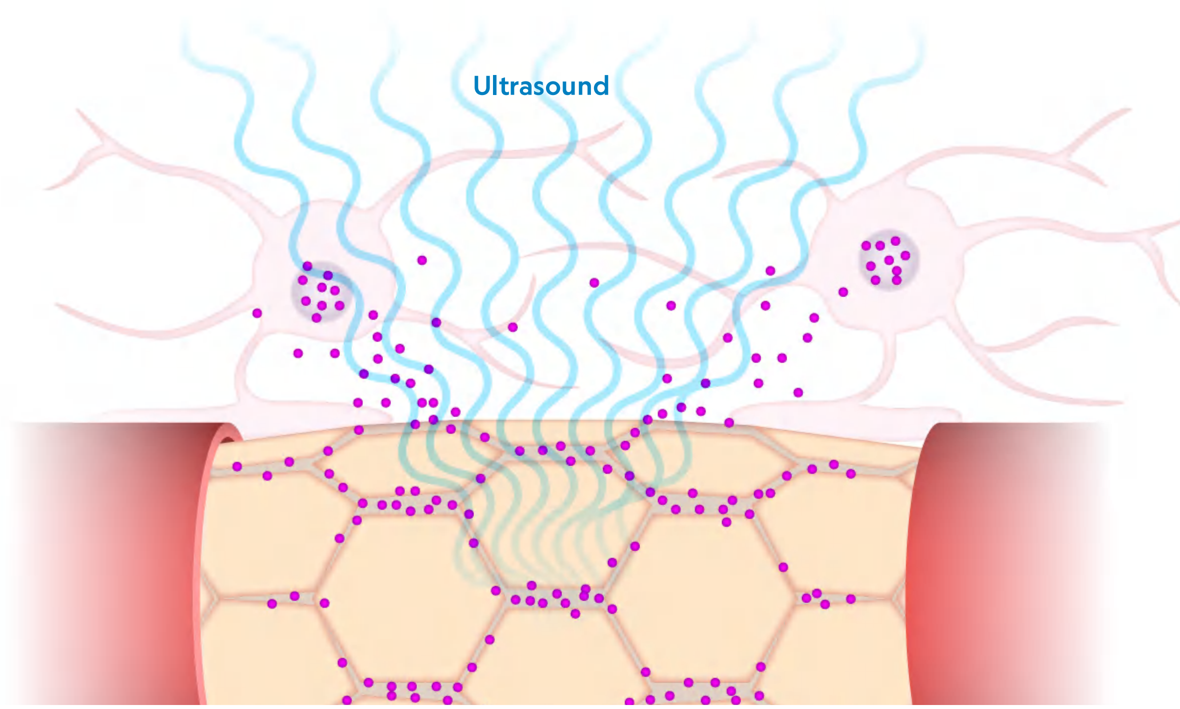
Focused ultrasound is not a new idea and has been used as a medical treatment since the 1950s. Beginning 15 years ago physicians used it to destroy uterine fibroids and prostate cancer and treat prostate gland enlargement. Today the procedure is being applied to more than 160 diseases and conditions at various stages of research and commercialization. Some of the FDA-approved techniques are used to treat tremors and some motor symptoms of Parkinson's disease—but these efforts are unrelated to opening the blood-brain barrier.





Impermeable barrier

Tightly packed cells in the walls of blood vessels called endothelial cells prevent drugs in the blood stream from reaching brain cells called astrocytes, which connect to neurons.



Opening the barrier

Focused ultrasound beams excite microbubbles infused in the bloodstream, causing them to vibrate and open up the junctions between endothelial cells, allowing therapeutic drugs to reach targeted parts of the brain.

Jason Treat, NG Staff.
Focused Ultrasound Foundation; Columbia University.

Although the term implies a wall, the blood-brain barrier is not a single structure but a network of tightly packed cells that are bound together. These so-called endothelial cells line the inside of blood vessels everywhere in the body. Around the brain, says Lipsman, they function the way linked hands do in the children's game Red Rover, keeping out the opposing team. It's a vital function for protecting this important organ—and a huge challenge for treating brain conditions.

The floodgates opened in 2015, when Canadian neurosurgeon Todd Mainprize and scientists at Sunnybrook showed it was possible to safely open the blood-brain barrier of a patient with the skull intact using focused ultrasound. The technique temporarily separates the barrier's joined cells for several hours, long enough to allow drugs to get into the brain. It's also fully reversible: the barrier closes naturally within 24 hours

The Sunnybrook team passed another milestone in October 2021. Using a therapeutic antibody with a radioactive tag, the team tracked the antibody as it crossed the barrier and entered the brain, reaching cancer cells that had metastasized there from the breast.

The ability to measure drug delivery like that was the "missing link" in a field that will transform medicine, says Neal Kassell, a former co-chair of neurosurgery at the University of Virginia and the founder and chairman of the Focused Ultrasound Foundation, which helps fund and promote international research. "It's going to revolutionize therapy to the same degree that MR scanning revolutionized diagnosis."

Today the University of Maryland School of Medicine is one of the leading U.S. centers for focused ultrasound research, and its chair of neurosurgery, Graeme Woodworth, is especially encouraged by recent multicenter clinical trials for enhanced drug delivery by opening the blood-brain barrier, including his work with the Toronto team treating patients with glioblastoma.

"We can perform the treatments monthly, we can accomplish this with a high degree of control and safety, and the patients tolerate it quite well each month," Woodworth says. The potential to personalize the treatments is "very exciting," he adds. "That's a game-changing concept

Cautious optimism

Pre-clinical trials for treating Alzheimer's with focused ultrasound also have shown some encouraging results. For starters, simply opening the blood-brain barrier appears to have positive cognitive effects such as improving memory function. Elisa Konofagou, a professor of biomedical engineering and radiology at Columbia University, and other researchers have found that the debris of beta amyloid plaque—one of the hallmarks of Alzheimer's disease—gets cleared from the brain when the barrier is open. No one knows exactly why, but it's a start.

Other potential uses of focused ultrasound, such as gene therapy, aren't as close to the clinical trial stage, but researchers are hoping that's not far off.

At the Comprehensive Center for Neuroscience in Madrid, neurologist and professor Jose Obeso and his research team have found that viral vectors, which use harmless viruses as a delivery system for genes, can slip through the blood-brain barrier in non-human primates after focused ultrasound treatment and deliver the instructions for healing proteins that fight neurodegeneration such as Parkinson's disease. In theory, the brain cells will absorb the genes and then manufacture proteins that restore brain function or block unwanted activity in a certain brain region. The principle has been shown to work and be effective in rodents but the unpublished results would be the first to show this is also the case in monkeys. "If it works in monkeys, chances are it will work in humans."

There are currently no therapies proven to modify the course of brain illnesses such as Parkinson's, so "any hope you have of providing a treatment where none was available before is obviously something to peer-reviewed medical journal *Movement Disorders*.

Still, Stoessl cautions against raising people's hopes prematurely. Focused ultrasound for neurodegenerative diseases is generally not as advanced as it is for cancer. With cancer, doctors have a much clearer understanding of where to deliver the drugs. That's not the case with conditions such as Parkinson's and ALS, where researchers are still trying to figure out what parts of the brain are affected and how.

Huge demand

For many experts and patients, though, approved focused ultrasound treatments can't come soon enough. Consider the effects of Alzheimer's: The disease and its related forms of dementia affect 57 million people worldwide, a number expected to triple by 2050. Hundreds of drugs for Alzheimer's have failed in clinical trials at a cost of billions of dollars. Some researchers speculate that's because they don't get to the brain in adequate concentrations. Providing high doses by conventional means would require potentially toxic doses. An obvious benefit of focused ultrasound is that because the dose is targeted to the brain, lower quantities would be effective.

While these applications address diseases that tend to impact older people, there are others who would benefit from this new form of drug delivery. At Columbia, Konofagou has been using the technology to treat pediatric patients with a deadly form of brain cancer called diffuse fatal within a year of diagnosis. The challenge for her has been making the technology more accessible.

For Butler's procedure in Toronto, doctors designed the treatment to precisely deliver the drugs to what remains of his tumor and its immediate surroundings while sparing the nearby tissue. Before administering the therapy, Lipsman sat in an adjacent control room creating a high resolution three-dimensional map of Butler's brain and pinpointing where he wanted to open the blood-brain barrier to target his chemotherapy.

From there the team followed a highly coordinated sequence of events. Butler swallowed a chemo pill about 45 minutes into the procedure. As the chemo reached peak concentration in his bloodstream, technicians injected gas-filled microscopic bubbles into his veins via IV. These bubbles are smaller than red blood cells and pass harmlessly through the body while absorbing ultrasound energy.

For the next 90 seconds, Lipsman directed the focused ultrasound helmet to emit targeted energy to a precise, egg-size location in Butler's brain. The ultrasound waves triggered the microbubbles to rapidly expand and contract—loosening the tight junctions of the blood-brain barrier and opening passages for drug molecules to flow through and come in direct contact with the tumor, plus its rim around the surrounding region.

"Scientifically and medically, the feat is groundbreaking," says Lipsman.

hospital or clinic will have these resources.

Impatient with a lack of funding, MRI access, and technology partners, Konofagou developed a portable neuro-navigation system that does not depend on MRI to guide focused ultrasound to open the blood-brain barrier. By making do without a dedicated MRI machine, she came up with a simpler solution that uses existing MRI images to find the target and then opens the barrier with ultrasound waves from a hand-held device. It doesn't offer as much fine control as MRI-guided systems, but it works.

Kullervo Hynynen, the University of Toronto medical physicist who pioneered MRI-guided focused ultrasound and microbubble use, is also developing a more sophisticated, next-generation customizable focused ultrasound helmet that can be used without the real-time guidance an MRI machine provides when a patient is inside the machine.

The reusable helmet will cut the cost for image guidance to an estimated $500 for the total series of treatments, compared with the current cost of approximately $1,000 per session, he estimates. With further advances in technology, it may eventually be possible for patients to have the treatments in the comfort of their own homes. "That's the long-term dream," says Hynynen, who is also VP of research and innovation at Sunnybrook. He believes Canadian government approval for the device itself is only five years away.

Given all the excitement, various teams are already working on refining the technology involved in focused ultrasound. Insightec, Sunnybrook's Health Canada sponsor, currently manufactures one of the most widely used MRI-guided focused ultrasound devices to open the blood-brain barrier. Lipsman says that the company is developing ways to make the treatment more tolerable for patients, for example, by eliminating the need to shave their heads and have pins secured in their skulls.

And when it comes to government approval, Lipsman believes cancer applications, such as primary or secondary brain cancers, have the best shot at moving forward within the next two to three years. That's because the desired results, such as reduced tumor size or increased survival rates, are much simpler and less time-intensive to define than those for neurodegenerative diseases. From there, he hopes larger neurodegenerative disease trials won't be too far behind.

In February Michael Butler celebrated his one-year prognosis anniversary, the minimum for how long he was expected to survive when diagnosed in 2021. The maximum he was given—18 months—is coming up in August. He is using every minute of it. Following his final focused ultrasound treatment in October 2021, he and his wife, Valerie, took an epic train ride through the Canadian Rocky Mountains for their 15th wedding anniversary. More recently they took their children and grandkids to Disney World.

In March 2022, after scans showed concerning new tissue in the same chemo-treated area as Butler's original tumor, he had another surgery immediately. The lab results provided immense relief. It was only scar

The self-described dreamer says he volunteered for these sometimes laborious—and certainly not guaranteed—clinical trials to ultimately have

more time with his children and grandkids. He also did it for Valerie and all the ski trips and Harley Davidson rides they have planned. “I’ll be a lab rat,” he says, adding that he hopes there will be more focused ultrasound clinical trials he can participate in. “I’ll take any chance I can get.”

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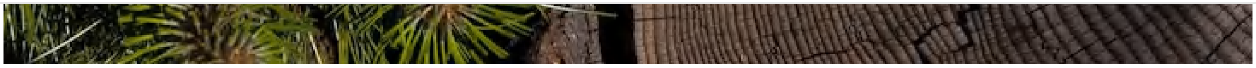

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