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Acoustic Surgery

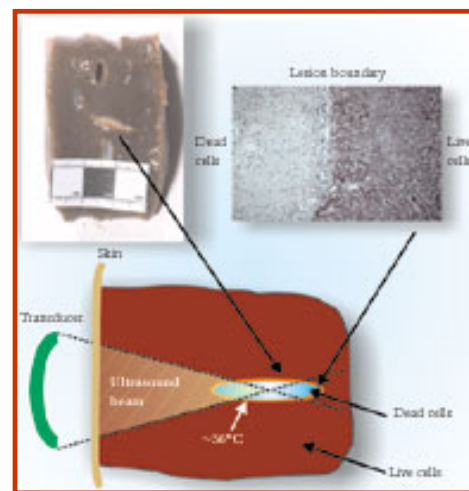
Bursts of focused ultrasound energy three orders of magnitude more intense than diagnostic ultrasound are emerging as a noninvasive option for treating cancer and other medical procedures.

[Gail ter Haar](#)

There must be very few aspiring physicists (or inquisitive children) who have not at some stage used a magnifying glass to focus the Sun's rays down to a spot with the intention of setting fire to dry leaves or a piece of paper. The fascination lies in part with the fact that the tinder only catches fire when placed exactly at the focus. In a similar fashion, high-intensity ultrasound fields may be focused on targets lying deep within the human body. If sufficient sound energy is concentrated within the focal volume, the temperature in that region may be raised to levels at which the constituent cells are killed. Just as with leaves in the Sun's rays, the tissues lying outside this volume are undamaged.

[Figure 1](#) shows a schematic diagram of the principle of this technique, which is referred to synonymously as focused ultrasound surgery (FUS) or high-intensity focused ultrasound (HIFU).¹ The technique has potential applications in any medical field that may benefit from the selective destruction of tissue volumes. Recent clinical interest has concentrated on treating soft-tissue cancers and on debulking enlarged prostates (benign prostatic hyperplasia).

Elevated temperatures (hyperthermia) have been used for many years to combat disease. The 1980s saw considerable interest in using hyperthermia in combination with radiotherapy or chemotherapy for treating cancer. The goal was to raise the temperature of the tumor and a surrounding margin of normal tissue from normal body temperature (37°C) to 42-46°C for about an hour. Radio-frequency, microwave, and ultrasound energy were investigated for this purpose, and sources were developed for use outside the body (extracorporeal), within body cavities (intracavitary), and within the tissues themselves (interstitial). Researchers sought a way to kill cells through a synergistic combination of heat and either x rays or anticancer drugs in the hope that the dose of x rays or drugs could be reduced, thus minimizing side effects.



[Figure 1](#)

The main drawbacks of these hyperthermia techniques are that they are time consuming and they require maintenance of uniform temperature distributions in a narrow therapeutic range, which necessitates the introduction of thermocouples into the target tissue. This makes an otherwise minimally invasive treatment relatively uncomfortable. Real-time temperature monitoring and associated feedback to the power source are important because the presence of blood vessels can lead to local cold spots that do not reach the necessary therapeutic temperature level. A successful cancer treatment requires that all malignant cells be killed, since the tumor may regrow from remaining viable tissue.

FUS has a different philosophy from "conventional" hyperthermia. In FUS,² the temperature in the focal zone is raised to a temperature above 56°C and is held for 1-3 s. The rapid deposition of thermal energy leads to a peak temperature rise that is independent of cooling by blood flow--an important consideration for tissues in which the vascular pattern is not completely known or predictable. It also obviates the need for inserting thermocouple probes into the target volume, because thermal modeling can give a good prediction of temperature distribution.

One consequence of the rapid heating to cytotoxic temperatures is that there is a very narrow boundary between live cells and dead cells at the edges of the focal volume. Electron microscopy reveals this boundary to be only about six cells wide (see [figure 1](#)). The damage has a characteristic appearance under the microscope, with an "island" of instantaneously heat-fixed cells that are apparently normal--but are clearly dead under examination with an electron microscope--surrounded by a "moat" of cells that are obviously damaged and have undergone coagulative necrosis. Their outlines are still recognizable, but they have lost their nuclei and other organelles. The volume of dead cells is referred to as a lesion. This method of cell killing is commonly called thermal ablation, but that term is technically inaccurate because ablation--from the Latin *abfero*, "I carry away"--implies that damaged tissue is cleared from the site in some fashion. In reality, cells that become heat-fixed are removed only by the body's natural mechanisms (phagocytosis).

Medical uses of ultrasound

Ultrasound applications in medicine fall into two principal classes, diagnostic imaging and therapy, which differ in the power, intensity, and duration of the ultrasound.

Medical ultrasound is perhaps best known for its diagnostic use in obstetrics. In many parts of the world, an ultrasound scan is now routinely offered to women early in pregnancy. This scan is used to determine the baby's gestational age and to look for abnormalities. Ultrasound imaging is used in many other fields of medicine, because it gives useful diagnostic information from a number of anatomical sites. As with any diagnostic technique, the goal is to obtain information from tissues of interest without inducing biologically significant changes in them. Ultrasound's limitations derive mainly from its rapid attenuation by both bone and gas at the frequencies used, commonly 1-20 MHz. Thus it cannot form good images of the lungs, for example, since they not only lie behind the rib cage but also are filled with air.

The most common ultrasound imaging technique is the pulse-echo method, which is similar in principle to radar. A short acoustic pressure pulse emitted from the source (the transducer) is reflected from tissue structures within the body. The piezoelectric transducer receives the reflected pressure pulse and converts it into a voltage that may be displayed on a screen. The

amplitude of the returning pulse depends on the acoustic properties of the structure reflecting it, and the time delay between its transmission and receipt provides information about the structure's position. Sweeping an interrogating beam over the region of interest can thus yield a two-dimensional gray-scale image, known as a B-mode image, in which the brightness indicates the reflectivity of the tissues. Conventionally, the highly reflecting bone surfaces appear bright, and fluids that contain no scatterers are dark. In addition to pulse-echo techniques, the Doppler effect is used to obtain information from flowing blood. Frequency shifts provide information about speed and direction of flow, which is particularly useful in cardiology and oncology.

The therapeutic uses of ultrasound fall into two categories: inducing nondestructive heating or other, mechanical effects to stimulate or accelerate normal physiological response to injury; or the production of controlled, selective destruction of tissue. The first category includes physiotherapeutic applications; FUS falls into the second. Ultrasound is used by physiotherapists for a number of purposes, including relieving pain, accelerating wound healing, and reducing swelling. It may also be used to enhance the transport of drugs across the skin (sonophoresis).

Ultrasound's nonthermal mechanisms of action are not well established but are thought to arise from cavitation, radiation pressure, and acoustic streaming. Acoustic streaming is unidirectional circulation set up in a fluid by an acoustic field, due to momentum transfer from the field to the liquid. The velocity gradients associated with such fluid motion may be quite high, especially in the vicinity of boundaries within the field, and the shear stresses may be sufficient to cause biological changes or damage.

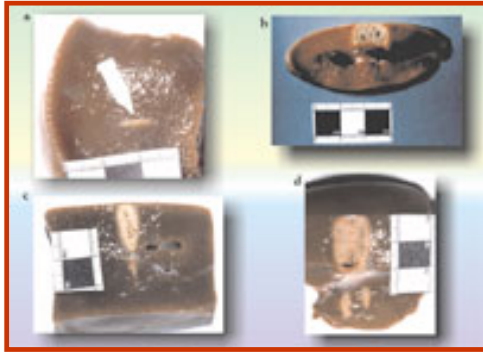
Typical Parameters of Medical Ultrasound

	Frequency (MHz)	Source area (cm ²)	Power (W)	Maximum intensity (W cm ⁻²)	Pulse Length
Diagnostic imaging					
Pulse-Echo (B-Mode)	1-20	1-30	0.05	1.75	0.2-1 μ s
Pulsed Doppler	1-20	1	0.15	15.7	0.3-10 μ s
Physiotherapy	0.5-3	3	<3	2.5	2-8 ms or continuous
Surgery	0.5-10	50	~200	1.5 x 10 ³	1-16 s

The table on the next page (see above) summarizes the differences in ultrasound exposure conditions used for these different applications. It shows that FUS uses energy levels that are approximately three orders of magnitude greater than those of diagnostic techniques. The sources for supplying these intense ultrasound pulses are described in [box 1: Ultrasound Sources for Acoustic Surgery](#).

Ultrasound is a pressure wave. During its transit through the body, it loses energy due to both scattering and absorption. Sound scattered out of the main beam may be used to form images;

absorbed energy gives rise to tissue heating (see [box 2: Tissue Heating by Ultrasound](#)). In FUS, the absorption is maximum in the focal volume, where the intensity is at its highest. In addition to heating, the pressure wave, during its negative swing, can draw gas out of solution, and the bubbles thus formed may be set into oscillation. This phenomenon is acoustic cavitation³ (described in liquid helium in *Physics Today*, February 2000, page 29^{*}). The mechanically driven bubbles cause damage to their surroundings, especially when the bubbles grow to a size that renders them resonant at the driving frequency (about 3 μm at 1 MHz).



[Figure 2](#)

Damage due to heating is relatively uniform, and the spatial extent may be predicted. Cell killing due to acoustic cavitation, however, occurs only in close proximity to an oscillating bubble and is therefore more random in nature. Examples of thermal and "bubbly" lesions are shown in [figure 2](#). Cavitation-damaged tissue contains holes or tears, but viable cells are still present. Cavitation on its own, therefore, is an inappropriate method for treating cancer, in which it is essential to destroy all cells.

In practice, heating and cavitation are inseparable for the types of ultrasound exposure used in FUS. Bubbles are drawn out of solution only above a threshold acoustic pressure. At these pressures, the ultrasound beam heats the tissue to biologically significant levels. As the tissue is warmed, gas comes out of solution more readily, and the acoustic pressure needed to create cavitation is reduced.

There are two schools of thought about optimum exposure regimes for FUS treatments. A purely thermal technique has the advantage that the shape and position of the lesion can be accurately predicted. Cavitation renders the tissue destruction less predictable, but the gas bubbles that are produced act as scatterers that allow the lesion's position to be readily seen in an ultrasonic image.

History of acoustic surgery

The first report of tissue destruction by HIFU was published in 1942. The technique was originally conceived as a tool for neurobehavioral studies. Most of the early work was carried out at the University of Illinois by Bill and Frank Fry.⁴ They noted that the lesion produced was well circumscribed and "trackless." Once the necessity of first creating an acoustic "window" by removing a portion of skull bone was realized, the researchers could destroy small regions in the brain selectively without damaging overlying or surrounding tissues. The Illinois team applied this technique to attempt the treatment of subjects with Parkinson's disease. Despite early reports of apparent success, they did not pursue this course, most probably because the effective drug levodopa was introduced at the same time.

Considerable effort was put into seeking ophthalmology applications of high-intensity ultrasound by Fred Lizzi's group at the Riverside Research Institute in New York.⁵ They investigated the use of FUS to treat glaucoma and retinal and capsular tears. Again, the timing was not right: The introduction of lasers into ophthalmology occurred at the same time, and lasers were perceived as

being easier to use. FUS has therefore not been extensively explored in this field.

The recent resurgence of interest in focused ultrasound techniques has been fueled by the drive to find minimally invasive therapies. Such therapies are attractive to patients and clinicians alike since they reduce the length of hospital stays, thus saving money. Particular interest lay in FUS as an alternative treatment to transurethral resection of the prostate (TURP) for debulking enlarged prostates. The FUS revival is timely: Imaging techniques are now sufficiently sophisticated to allow accurate placement of lesions in the target volume and, in some instances to enable real-time monitoring of the cell killing as it occurs.

Seek and destroy

The very narrow margin produced by high-intensity ultrasound beams between dead cells and live cells enables a lesion to be placed close up against a vital structure--for example, a major blood vessel or nerve trunk--without damaging the structure itself. Lesions can also be placed side by side to produce confluent volumes of damaged tissue. In this fashion, treatments can be contoured to match the target volume closely (see [figure 3](#)).

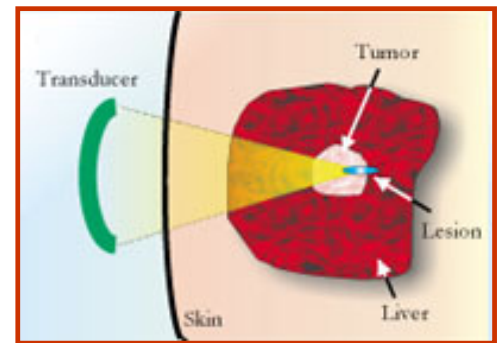


Figure 3

To capitalize on spatial accuracy, good imaging techniques are essential, both for accurate treatment planning and for monitoring in real time the tissue damage as it progresses. Ideally, a single ultrasound probe would allow both imaging and therapy, and in reality such a combination is close to being achieved. The appeal of this approach is that, broadly speaking, if a target is visible on a diagnostic ultrasound image, it should be treatable with a high-intensity beam that follows the same propagation path: Any refraction of the imaging and ablating beams should be identical. Conventional pulse-echo diagnostic imaging methods are unfortunately not optimal for visualizing thermal damage, since ablated volumes created primarily by a thermal mechanism do not scatter sound significantly differently from the normal cells surrounding them. If gas bubbles have been produced either by acoustic cavitation or by the boiling of tissue water, then they will be highly reflective and the region will be visible. However, as discussed above, exposure regimes that induce these effects are often avoided because their tissue damage is unpredictable.

Treated tissue has two properties that may be useful in developing alternative techniques for ultrasound imaging. First, "cooked" tissue is more rigid than its surroundings, so a technique that can map tissue elasticity may prove useful. Elastography is one possibility⁶ (see [box 3: Elastography](#)). Although this technique has shown potential value in acoustic surgery, it needs to be developed further before it can image in real time.

Second, although there is no change in scattering in the ablated region, a lesion has a significantly higher acoustic absorption coefficient than does undamaged tissue. Reflex transmission imaging (RTI) is a technique that may allow visualization based on this property. RTI uses an ultrasound beam, focused within the ablated region, to interrogate the tissue lying behind the region. The amplitude of returning echoes, which have passed through the treated volume, reflects the

attenuation of that region. Sweeping the imaging beam over the target volume can yield a map of attenuation. Both elastography and RTI are being actively investigated at the Institute of Cancer Research in the ultrasound groups of Jeff Bamber and myself.

It may also be possible to incorporate FUS into a magnetic resonance imaging (MRI) system, providing the problem of compatibility of the ultrasound source with high magnetic fields is overcome. This combination would allow the treatment to be planned under MRI guidance.⁷ With MRI thermometry techniques, the "thermal dose" (described in [box 4: Thermal Dose](#)) can be mapped onto the anatomical image as treatment progresses. But any deviation of the ultrasound beam from that predicted on a purely linear model--deviations due, for example, to passage through tissues with different acoustic velocities--must be understood and accounted for in treatment planning with MRI. (In ultrasound imaging, the imaging beam undergoes the same deviations as the surgical beam, thus sidestepping this problem.) Methods for combining MRI and FUS are under active development, especially in the US by Kullervo Hynynen's group at Brigham and Women's Hospital in Boston.

A disadvantage of FUS is that the volume of tissue produced by each exposure from a single-element transducer is small, typically 0.15 cm^3 . Although exposure times are short, about 1 s, time is needed between shots to allow surrounding tissue to cool. Therefore, considerable effort is going into designing phased array transducers that give larger focal volumes, about 0.5 cm^3 . The trade-off is a lower focal intensity, which necessitates longer exposure times. An alternative approach is to sweep the transducer over the target volume while it is emitting sound. This method is also being investigated, most notably in China by Feng Wu and Zhibiao Wang at the Chongqing University of Medical Sciences.

Applications of FUS in medicine

The most significant body of clinical experience with FUS has been in treating benign prostatic hyperplasia. Although thermal ablation of the gland with a transrectal approach has been demonstrated, the clinical results have been disappointing and have not matched those of the "gold standard" TURP procedure. The reason for this is not clear.

Another application in benign disease lies in the treatment of uterine fibroids. Thermal ablation using lasers has already been shown to give symptomatic relief, but that is a relatively invasive procedure. Extracorporeal FUS is looking promising as a noninvasive method.

Many current cancer therapies have unpleasant side effects that are often the limiting factor for treatment. For example, neurotoxic effects may limit the dose of a cytotoxic agent in chemotherapy. Similarly, in treating a tumor with radiotherapy, some normal surrounding tissues always receive an x-ray dose, as well. The dose that can be received by critical normal structures before they become irreversibly damaged determines the maximum irradiation--the so-called tolerance dose--that can be given. The search, therefore, continues for therapies that treat the tumor without having significant effect on normal tissues. FUS may provide just such a therapy.

Cancers that have been targeted with FUS have mostly been in the liver, kidney, breast, and prostate. Two different approaches have been used for placing the focal volume within the target organ. For the liver, kidney, and breast, an extracorporeal transcutaneous technique has been used,

whereas a transrectal approach shows the most promise for treating prostate cancer.

The largest published clinical trials to date have been for transrectal treatment of prostate cancer. The results are showing considerable promise, provided the whole gland is treated.⁸ Total exposure is necessary because a cure is only effected if every malignant region is destroyed.

Current clinical trials led by David Cunningham and myself at the Royal Marsden Hospital in London, in which 68 patients have been treated to date, have demonstrated that FUS treatment of liver cancer is well tolerated by fully conscious patients who are treated on an outpatient basis and have not needed local anesthesia or sedation. Wu and his colleagues at Chongqing have reported encouraging results in the treatment of 164 patients with a range of malignancies.⁹ In that study, patients were under general anesthesia.

Handheld FUS probes are being developed for the intraoperative treatment of liver cancer. They would be useful for surgeons who have performed an open procedure with the intent of excising part or all of the liver (hepatectomy) but have found previously undiagnosed disease that renders the intended radical surgery inappropriate. With such handheld devices, tumor masses could be ablated during the operation.

A number of groups, including those of Ian Rivens at the Institute of Cancer Research, Larry Crum at the University of Washington's Applied Physics Laboratory, and Hynynen, have shown that HIFU beams can be used both to seal blood vessels and to occlude or block them. Ultrasound techniques are therefore being developed for stopping the bleeding resulting from trauma or catheterization (hemostasis) and for selectively blocking blood vessels.¹⁰ Blood vessel occlusion may be useful in cancer therapy, where interruption of flow to a tumor may lead to its shrinkage.

Although it is generally accepted that tissues lying behind bone are not accessible to ultrasound beams, there is a very good chance that transskull treatments of the brain will become possible.¹¹ Time-reversal techniques (see Physics Today, March 1997, page 34^{*}) are already being investigated to solve this problem.¹² Similar to adaptive optics, this method uses the phase information available from the reflected beam to reconstruct the focus behind the bone. If achieved, transskull ultrasound may enable the exciting possibility of altering the blood-brain barrier to increase the permeability from the bloodstream into the brain of a variety of therapeutic agents. Pierre Mourad (at the University of Washington) and Hynynen are actively studying this possibility.

As these examples illustrate, FUS is an exciting technique that undoubtedly has a future in medicine. Before long, the clinical applications for which it is best suited should become clear. Further developments in transducer technology will allow increased sophistication both in the delivery of the therapeutic exposure and in the on-line, real-time monitoring of treatments using ultrasonic techniques. Early indications from clinical trials show the very real possibility that FUS will offer a practical alternative to conventional surgery.

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