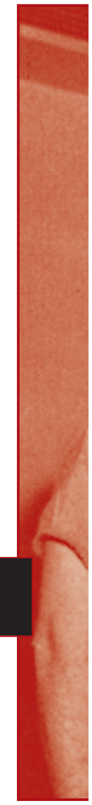
Physics Today

An early history of high-intensity focused ultrasound

William D. O'Brien Jr and Floyd Dunn

Citation: Physics Today 68(10), 40 (2015); doi: 10.1063/PT.3.2947
View online: http://dx.doi.org/10.1063/PT.3.2947
View Table of Contents: http://scitation.aip.org/content/aip/magazine/physicstoday/68/10?ver=pdfcov
Published by the AIP Publishing



An early history of high-intensity focused ultrasound

William D. O'Brien Jr and Floyd Dunn

Foresighted leadership, the GI Bill, and research conducted in an unventilated steam tunnel all contributed to the development of a now ubiquitous medical tool.

When the Fry brothers—Bill and Frank—arrived at the University of Illinois in 1946, their highest priorities were to establish a laboratory that would develop ultrasonic surgical procedures for the mammalian brain and to study the detailed neuroanatomy of the mammalian central nervous system. Within a couple of years, much of the laboratory was up and running—animal quarters included. The faculty and staff of the electrical engineering (EE) department were not accustomed to having colleagues conduct live-animal studies in their building. So when the department's candy machine started to deliver mouse-scarred candy bars, the culprits were rumored to be escapees from the laboratory cages. The grumbling stopped only after the mice were caught and discovered to be wild ones—the kind found in the fields of central Illinois.

Two years before the Frys came to the university, William Everitt had been appointed as head of the EE department. He was a renowned communications engineer and was immediately given a leave of absence until 1 May 1945 to continue his service to the country as chief of operational research of the US Army Signal Corps. When he returned to head the department, he took it upon himself to develop research to a high degree.

Bill O'Brien is the director of the Bioacoustics Research Laboratory and the Donald Biggar Willett Professor Emeritus of Engineering at the University of Illinois at Urbana-Champaign. **Floyd Dunn** (1924–2015) joined the electrical engineering faculty at the University of Illinois at Urbana-Champaign in the mid 1950s and became an emeritus professor 40 years later. His obituary is in the spring 2015 issue of *Acoustics Today*.

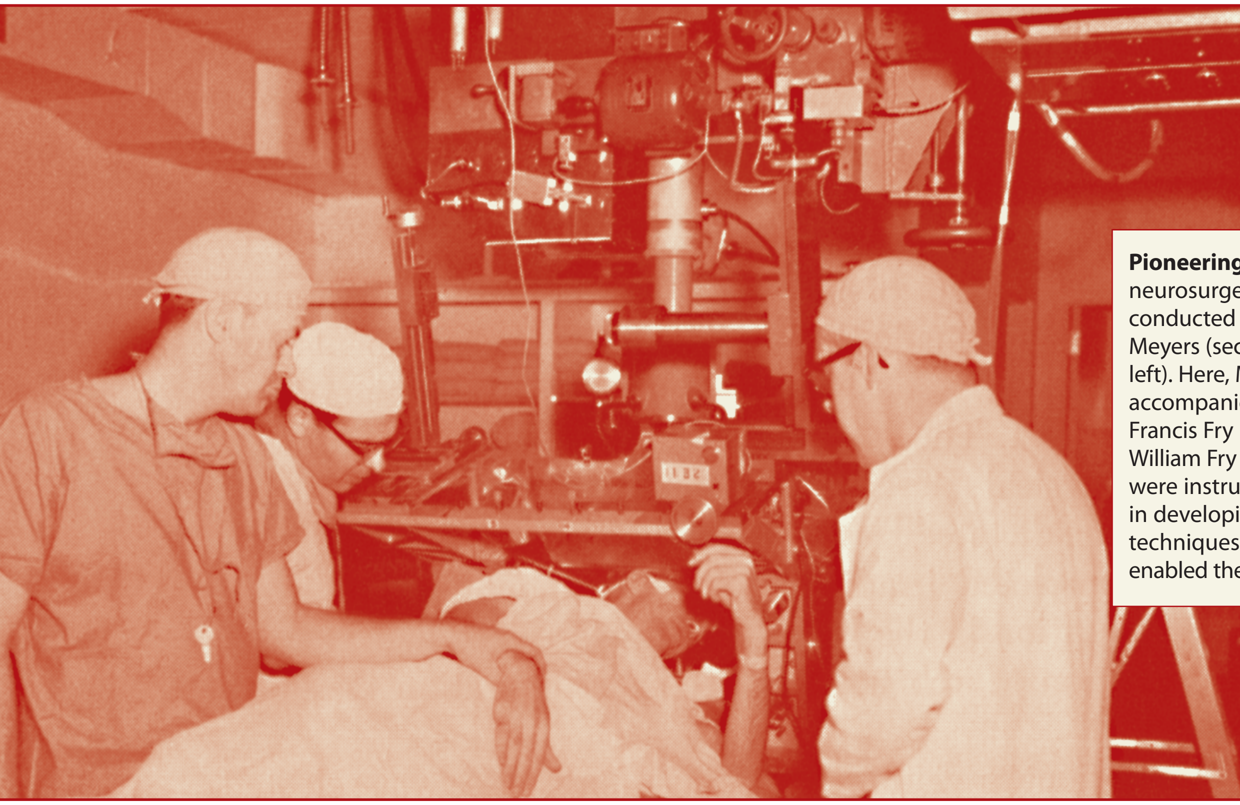
Everitt was the right person at the right time. When he arrived at the University of Illinois, on-campus engineering research was not common. A typical attitude voiced by nonresearch faculty was, "If General Electric can't do it and Westinghouse can't do it, we certainly can't do it." That attitude really bothered Everitt, who did indeed succeed in building up significant levels of research.

On 1 September 1949, Everitt became the dean of engineering at Illinois. During the 19 years he held that position, he continued his support and encouragement of high-level research in the College of Engineering. He was also a founding member of the National Academy of Engineering.

Cramped quarters

Just after World War II ended, colleges and universities across the US experienced a rapid growth in their faculties, facilities, and enrollments. In part that was a reaction to the stagnation that had set in during the Depression and war years. But it was also fueled by the young men who had returned from wartime service and enrolled in large numbers to take advantage of the GI Bill. Engineering attracted many students because the advances and discoveries made during the war raised awareness of the profession. The University of Illinois was no exception to the general trend of rapid growth. In 1946 it welcomed one of us (Dunn) as an undergraduate EE student after his return from the European theater.

In the immediate aftermath of the war, many in the scientific and engineering war effort wanted to conduct research of their own choosing in the freer university atmosphere. William J. Fry, shown with



Pioneering ultrasonic neurosurgery was conducted by Russell Meyers (second from left). Here, Meyers is accompanied by Francis Fry (left) and William Fry (right), who were instrumental in developing the techniques that enabled the operation.

his brother in figure 1, was hired by Everitt in late 1946, and he established the university's Bioacoustics Research Laboratory that same year. Bill, as he was known with affection by colleagues and friends, had pursued graduate work in theoretical physics at the Pennsylvania State University, the same institution that had granted him a bachelor's degree in 1940. After the US entered World War II, he had left his graduate studies to work at the Naval Research Laboratory in Washington, DC. There he'd spent the war years working to develop principles for designing and building sonar systems.

Sonar dates back to French physicist Paul Langevin, who during World War I developed one of the first uses of ultrasound for underwater echo ranging: the detection of submarines, which had been introduced as an implement of war. Sonar instruments designed between the two world wars were lacking in many respects, though, and before World War II, submarines had never actually been spotted during hostilities. Thus when Bill left Penn State, there was a crucial need to create better devices.

Francis J. Fry, two years younger than Bill, joined his brother at Illinois in 1946. Like Bill, Frank went to Penn State, received his bachelor's degree in 1940, and was hired by Everitt. But unlike his brother, Frank had studied EE. After graduation he worked at Westinghouse Electric Corp on power circuit breakers. His division became a prime contractor for the Manhattan Project, so Frank spent considerable time during World War II at the Radiation Laboratory in Berkeley, California, and at the Clinton Engineer Works in Oak Ridge, Tennessee. During that time, he also earned his EE master's degree from the University of Pittsburgh.

Space was at a premium in the University of Illinois EE building when Bill and Frank arrived. Virtually the entire department was crowded into a too-small, antiquated space that had been expanded and rearranged in every direction as much as possible. The Frys were each assigned a small office, but they were informed that laboratory space simply did not exist. However, they did not intend to wait until space was freed up; a functioning laboratory was more important than office space. They found an unoccupied location in a steam tunnel under the EE building that they decided could work. When we

Figure 1. The Fry brothers, William (left) and Francis (right), joined the electrical engineering faculty of the University of Illinois in 1946.

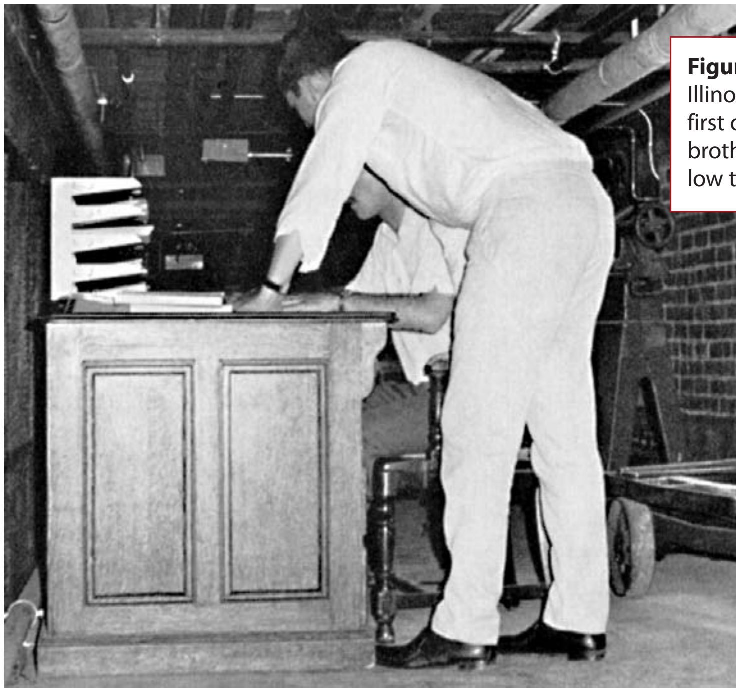


Figure 2. A steam tunnel below the University of Illinois electrical engineering building served as the first office and lab space for Bill Fry (seated) and his brother, Frank (leaning over). The ceiling was so low that the brothers couldn't stand up straight.

say "unoccupied," we mean unoccupied by faculty—the tunnel actually housed many cherished World War I electrical instruments that had been used by the old-time, nonresearch EE faculty. Removing that equipment for trash disposal did not exactly endear the brothers Fry to their faculty colleagues. As figure 2 shows, the tunnel was so low that it was impossible for a person to stand upright. Moreover, during the hot summer months, the unventilated tunnel became like a steam bath. None of those obstacles or inconveniences deterred Bill and Frank from setting up their offices and laboratory space.

Everything built from scratch

Bill wanted to study the central nervous system so comprehensively that he could begin to understand intimate details of structure and function. At the time of his arrival at Illinois, the experimental methods in use were rather crude; they required that physically rigid electrodes be implanted in brain tissue. The idea was to identify specific anatomic structures related to brain activity that, for example, caused pain in a particular site of the body. However, the invasive electrode-based procedure produced unreasonably large lesions—damaging or mortal tissue changes.

Bill knew that ultrasound could be focused to very small volumes. He envisioned it as a vastly superior tool to rigid electrodes, one that would allow for noninvasive alteration of brain tissues. But Bill and Frank's research goals of developing clinical surgical procedures and determining a "circuit diagram" of the mammalian central nervous system would require high-intensity ultrasound: When focused to a pinpoint, HIFU (high-intensity focused ultrasound) could affect deep tissue without harming intervening tissue.

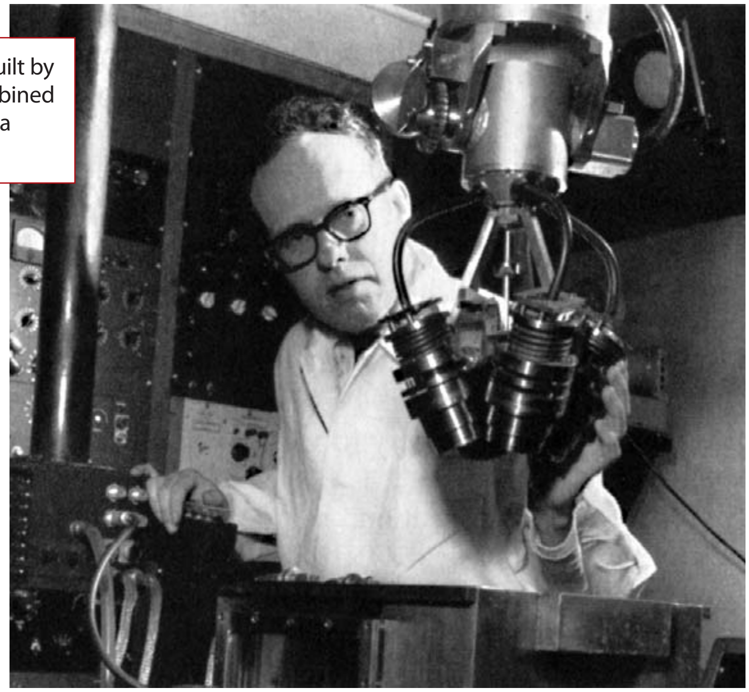
To achieve their unique research goals, the Fry brothers and their coworkers had to invent instruments for generating, detecting, and measuring ultrasound. Descendants of their inventions are now used worldwide (see the article by Gail ter Haar, Physics Today, December 2001, page 29). The researchers also had to understand in detail how ultrasound propagates in biological media. Their investigations thus addressed such issues as the speed of propagation, how ultrasound is scattered and attenuated, and the degree to which tissue can tolerate ultrasound. They developed phenomenological theories based on their data and even began to study nonlinear acoustic effects, whose understanding is important for imaging.

The equipment developed to create, detect, and analyze ultrasound was built from scratch. Many of the materials used today were not available in those days. Lack of 21st-century materials was not a problem for the Frys, but lack of 21st-century funding agencies was a challenge—many of today's funding agencies were nascent when the brothers were initiating their research. For example, the Office of Naval Research was created in 1946 and NSF came into existence only in 1950. The National Institute of Health (note the singular Institute) had been around since the 1930s, but it largely supported in-house research. In the late 1940s, the National Institutes of Health (now plural) slowly initiated a program of grants for external research. Funding of university research on ultrasound at the time was mostly from the military—in particular, the US Navy's Bureau of Ships and the Office of Naval Research—and grants tended to be for transducer developments. Fortunately, Bill was very convincing when he argued on behalf of the Bioacoustics Research Laboratory's work.

The Fry brothers began their research journey by studying how ultrasound affects biological materials. Their specially built, high-intensity, calibrated ultrasonic exposure equipment yielded promising results from the beginning.[1–5] Bill, Frank, and their colleagues learned, for example, that ultrasound affects all kinds of tissue but has different effects on different tissue components. They established that below a certain threshold ultrasound did not injure tissue and that repeated exposures below that threshold still did not harm tissue. On the other hand, at above-threshold intensities, ultrasound could affect tissues either temporarily or permanently, depending on its amplitude and exposure time. Much of what they discovered is accepted as commonplace today, but it was unknown when the Fry brothers initiated their studies.

By the mid 1950s, surgical methods based on HIFU were ready for human testing. Before that, the Frys and their coworkers had evaluated their ultrasonic neurosurgery techniques with cats and monkeys—more than 250 animals in all. The researchers showed that their procedures were well tolerated by

Figure 3. A novel transducer designed and built by Bill Fry (shown), Frank Fry, and coworkers combined four individual transducer elements to create a highly localized, intense ultrasound spot.



the animals and that structures not intended for alteration by ultrasound were not adversely affected.

Multidisciplinary work

To arrive at the point where the Frys could seriously contemplate ultrasound neurosurgery on humans, they had to pull off numerous achievements that spanned the fields of physics, biology, and engineering.

▶ The Fry lab designed and built a remarkable new transducer with a highly confined focal region.[6,7] As figure 3 shows, the Fry device combined four separate transducer elements. Each one was fabricated with a quartz piezoelectric material; a polystyrene lens positioned in front of the quartz produced a focused field. Individual transducer elements could produce high ultrasonic intensities at the focus, but a single transducer would generate a characteristic cigar-shaped focal region. When the four elements in the Fry design were properly aligned, however, the field in the focal region was localized to a spot. The most intense region of the field could produce alterations in biological tissue volumes as small as a few cubic millimeters.

▶ Bioacoustics Research Laboratory scientists developed a positioning system that would allow precise movement of the new ultrasonic transducer.[8] Great precision was necessary because of the way ultrasound-induced lesions were actually created. One had to move the transducer focus to many specific spots in the brain and produce a very small lesion at each location. It was the combination of those many small, precisely located, spatially adjacent lesions that yielded the desired complex-shaped lesion. Figure 4 shows the room in which the irradiations were performed. The 3500-pound positioning system, mounted on a steel girder frame, was located in an area directly above the irradiation room and controlled from the lower room. The Frys electrically isolated the irradiation room, an effort that demonstrates the care they took to accurately locate the ultrasonic focus under precisely controlled conditions.

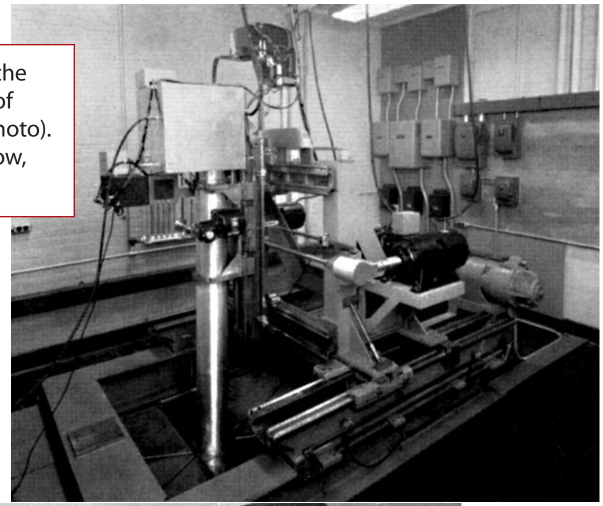
▶ Bill, Frank, and colleagues developed and validated the capacity to calibrate ultrasonic fields so that they could reliably determine field intensities. In those days, there was no National Institute of Standards and Technology to quantify ultrasound. For that matter, NIST still does not provide such a capability. The Illinois laboratory's primary calibration standard was based on the radiation force principle. When ultrasound hits an object, it acts on the body with a force that can be mathematically related to a property of the ultrasound wave, such as power or intensity. The lab's primary standard was quite accurate and precise, but it was not mobile. So lab researchers fabricated a cleverly designed, portable thermocouple probe that could be calibrated against the primary standard and then serve as a secondary standard. The thermocouple probe mostly fulfilled that role in the lab's animal-based experiments. If necessary, it could also function as a primary standard, provided that the acoustic and thermal properties of the liquid surrounding the thermocouple were known with accuracy and precision.

▶ Illinois researchers determined ultrasonic dosage curves for neural tissue. Such curves relate physically determined quantities—ultrasonic intensity, exposure time, and so forth—to measurable biological outcomes. Figure 5 presents two examples. In one, the biological outcome is paralysis in an animal's hind limb; in the other, the production of a brain lesion.

From movie theater to operating theater

As noted earlier, the Bioacoustics Research Laboratory scientists conducted a considerable number of animal tests to fully understand HIFU neurosurgery so that it could be performed on humans. They adapted existing techniques and developed new, more precise ones for locating specific anatomic brain structures. To keep an anesthetized animal perfectly still, they designed a special head holder. A pointer tip connected to the four-beam ultrasonic irradiator (figure 3) designated the location of the beam's focus.

Thanks to such innovations, the Frys and their colleagues could better calibrate the irradiator's ultrasound field and position the device so that its focus was placed at the desired location in the brain. The 22-minute-long, 16-mm movie *Neuro Sonic Surgery*, produced in 1955, demonstrated all of the ultrasonic neurosurgery procedures that the Fry brothers developed with animals. Dunn was a graduate student of Bill's during the time when many of those developments occurred, and he provided the technical supervision for the movie.



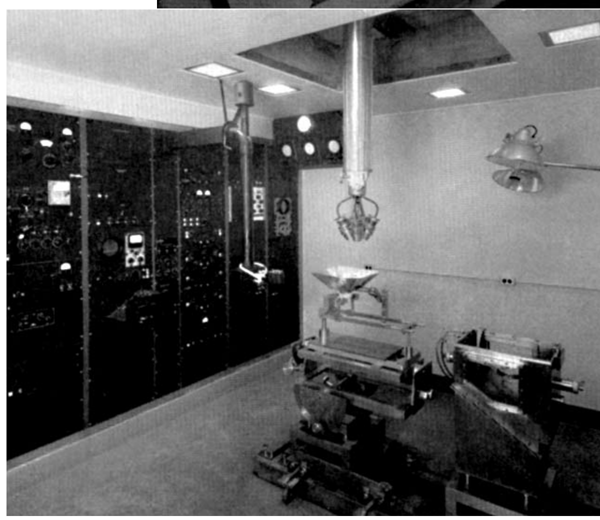


Figure 4. The heavy, elaborate structure in the upper photo allowed for precise positioning of the ultrasonic focus in a room below (lower photo). The positioning system is controlled from below, in the irradiation room.

Meanwhile, Russell Meyers, a professor of neurosurgery at the medical school of the University of Iowa, had gotten to know the Frys' work through their papers and meeting presentations and had developed an interest in human ultrasonic neurosurgery. It was still necessary to develop ultrasound equipment that could safely produce lesions in humans, and the staff at the university hospital would need years to prepare rooms for housing the equipment required for human ultrasonic surgery. But in 1957 Meyers successfully conducted what we understand to be the first ultrasonic surgery on a human brain; the medical milestone was covered in the 2 December 1957 issue of *Time* magazine. The photo on page 43 shows Meyers, along with the Fry brothers, and one of his history-making patients.

In the period 1958–62, some 88 patients underwent ultrasonic neurosurgery to treat various afflictions, including Parkinson's disease, cerebral palsy, the aftereffects of stroke, and phantom images and pain following amputation. During that time, the Bioacoustics Research Laboratory regularly sent personnel to Iowa to oversee and conduct the complex procedures involved in the surgeries.

Wiring and hiring

Human ultrasonic neurosurgery was the result of a truly synergistic effort that began with the Fry brothers' arrival at Illinois in 1946. The Frys and their colleagues faced scientific and technical challenges, but they overcame them, and quite successfully. By the end of the 1950s, HIFU therapy had been born and clinically validated. The Frys had accomplished their original goal of developing ultrasonic surgery for affecting the mammalian brain.

After the development of HIFU neurosurgery techniques, the Bioacoustics Research Laboratory's main focus turned to mapping brain structures—determining the "wiring" diagram of the central nervous system. That was the second of the Frys' goals when they came to Illinois, and they achieved significant success. However, in large part because of the enormous complexity of the media they studied, they could only detail small sections of the cat brain.

The early accomplishments of the Bioacoustics Research Laboratory were only the start. Following the early neurosonic surgery successes, the university hired new engineering faculty with biology-related interests; new personnel included Dunn, who joined the EE department as a faculty member in 1956. Research expanded significantly, but the principal focus remained the basic science and application of the interactions of ultrasound with biological material. As additional faculty came to the laboratory, it became the *de facto* center of bioengineering in the College of Engineering.

The lab's real-world-inspired basic science led to new, medically important ultrasound applications. Lab personnel were the first to quantify *in vivo* how the ultrasonic absorption coefficient in biological tissues depends on temperature, and they found a behavior considerably different from that exhibited *in vitro*. Those observations had an important influence on therapeutic ultrasound, and they continue to be valuable, particularly when ultrasonic hyperthermia (controlled tissue-temperature increase from ultrasound exposure) is considered or used for treatment of certain types of cancer. In the late 1950s and early 1960s, lab scientists conducted computational research related to ultrasonic imaging. Their goal, successfully met, was to develop a computer-controlled HIFU system that included an ultrasound image to guide therapy.

Bioacoustics Research Laboratory scientists fol-

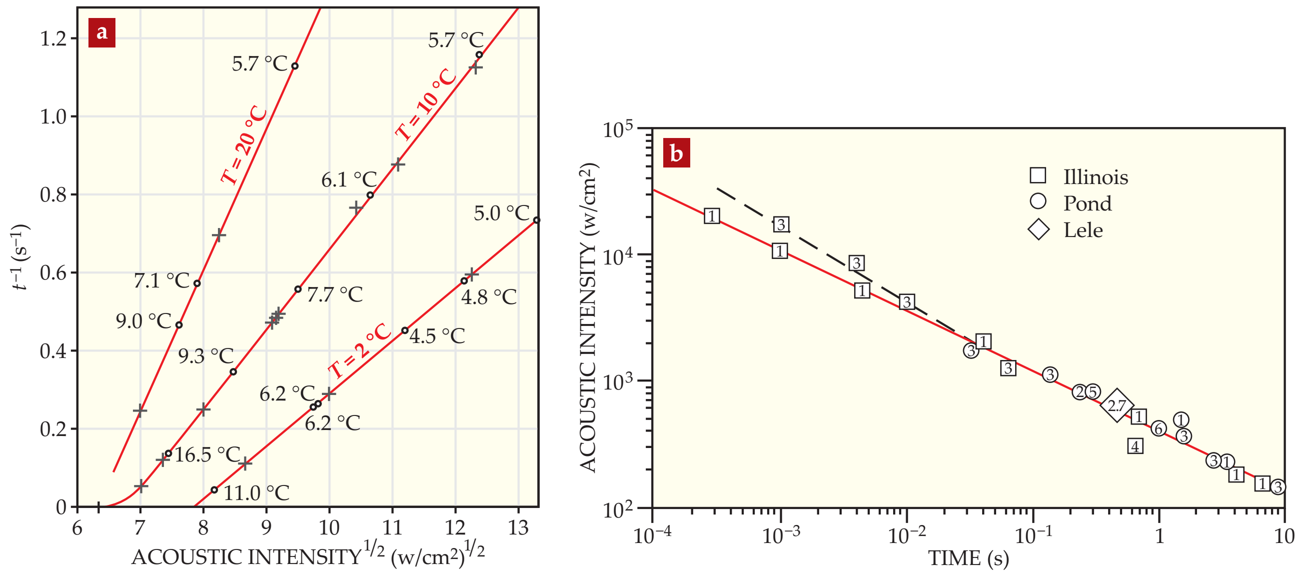


Figure 5. Dosage curves relate physical properties of applied ultrasound to a biological effect. **(a)** The curves here indicate, for anesthetized mice prepared at various temperatures T, the time (t) and intensity at which 50% of the subjects exposed to 982-kHz ultrasound experienced paralysis in a hind limb. Also indicated, near the data points expressed as circles, are maximum observed temperature rises. (Adapted from ref. 9.) **(b)** Three distinct studies, including one at the University of Illinois, determined the intensity and exposure times needed to create brain lesions in mammalian subjects. The numbers on the data points indicate ultrasound frequency in megahertz. (Adapted from ref. 10.)

lowing up on the brain-lesion studies initiated by the Frys obtained a fundamental understanding of the exposure levels that would just produce irreversible damage—in other words, they learned to identify threshold regions separating irreversible tissue damage from nondamage. In the 1970s those regions became a *de facto* worldwide reference from which government and standard-setting bodies established safety criteria.

These days the fetus of virtually every pregnant woman in the Western World is evaluated ultrasonically. Such a widespread use of diagnostic ultrasound could not have occurred without the safety assurances that followed from work initially carried out by a pair of brothers in cramped, hot quarters below the plains of central Illinois.

References

1. W. J. Fry, V. J. Wulff, D. Tucker, F. J. Fry, *J. Acoust. Soc. Am.* **22**, 867 (1950).
2. W. J. Fry, D. Tucker, F. J. Fry, V. J. Wulff, *J. Acoust. Soc. Am.* **23**, 364 (1951).
3. P. D. Wall, W. J. Fry, R. Stephens, D. Tucker, J. Y. Lettvin, *Science* **114**, 686 (1951).
4. W. J. Fry, *J. Acoust. Soc. Am.* **24**, 412 (1952).
5. W. J. Fry, R. B. Fry, *J. Acoust. Soc. Am.* **25**, 6 (1953).
6. W. J. Fry, W. H. Mosberg Jr, J. W. Barnard, F. J. Fry, *J. Neurosurg.* **11**, 471 (1954).
7. W. J. Fry, J. W. Barnard, F. J. Fry, R. F. Krumins, J. F. Brennan, *Science* **122**, 517 (1955).
8. W. J. Fry, *Neurology* **6**, 693 (1956).
9. F. Dunn, *Am. J. Phys. Med.* **37**, 148 (1958).
10. F. J. Fry, G. Kossoff, R. C. Eggleton, F. Dunn, *J. Acoust. Soc. Am.* **48**, 1413 (1970). ■