Biophysical-Medical Acoustics:

Sounds in Diagnosis and Therapy

WILLIAM J. FRY

Head, Biophysical Research Laboratory, University of Illinois

Sonics and ultrasonics are used in fascinating clinical applications today. Internal tissues are "visualized," brain function is modified, cancers are reduced in size—to name a few. Current research on modification of biological systems with sound points to still further, even more valuable, uses.

EVEN before Hippocrates, sound was a tool of the physician. Ancient Egyptian healers thumped chests and backs and listened for sounds of pathology. Centuries later, the French physician, Laennec, had an obese women patient who was too modest to let him put his ear to her chest. He solved the problem by designing the prototype for the modern stethoscope. This has brought the inner sounds of man—those from the heart, the lungs, the intestines—to the ear of the physician.

Now, however, sound is being used in diagnosis *and* in treatment in ways that would amaze physicians of even a decade ago. And the future of medical sounds that seems indicated by current research is even more promising. For example, the employment of intense focused ultrasound—that is, acoustic energy beyond 20,000 cycles a second, the limit of human hearing—to study and modify brain mechanisms, a field in which I have been closely associated, constitutes a major step forward in the analysis of brain anatomy and operation. The implications for the treatment of human neurological disorders have so far only been lightly touched.

For convenience, most current research and medical applications utilizing acoustic energy can be classified into two major categories—those employing sounds or ultrasounds that leave the biological system relatively unmodified, either permanently or temporarily (called here *passive* uses), and those employing acoustic field conditions that modify the structure or mechanisms of operation of the biological systems (called here *active* uses).

invention, the stethoscope, made
mportant tool in diagnosis. Now,
used in treatment as well.

Passive Uses of Acoustic Fields

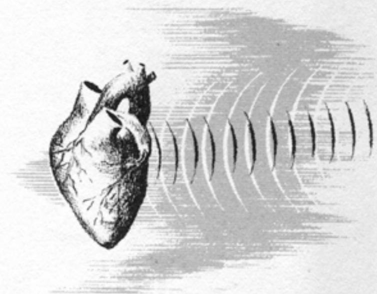
Sonic techniques of the nondisruptive or *passive* type can be used to study biological systems from the submicroscopic level of structure to macroscopic anatomy of gross tissue. Such studies utilize sound absorption or reflection, or both, as tools.

Soft-Tissues Visualized

Development of instrumentation for visualization of soft tissue structure is well along. Much of the detail of soft tissues that cannot be seen with x-ray techniques can be exhibited by ultrasound. Moreover, it is desirable to minimize the use of x-rays, in view of the cumulative effects they produce.

The more fruitful approach in this field is to detect ultrasonic energy reflected from interfaces in the tissue, rather than to measure the amount of transmitted energy after absorption has taken place along a given path. In fact the latter approach does not permit one to obtain a three-dimensional picture of the tissue structure. Although perhaps only one part in 1000 of the acoustic energy in an incident pulse may be reflected from an interface, it is possible both to detect and derive from the received signals a three-dimensional ultrasonic picture of the tissue structure.

In order to resolve structure in depth, i.e., along the axis of propagation, it is necessary to use short-duration acoustic pulses, and this means operation at high ultrasonic frequencies. A single cycle of the ultrasound is produced by a transducer and transmitted through the coupling medium into the tissue. The time delay of a returning echo indicates where in the tissue the reflection occurred. To identify structure elements close to one another, a beam of small diameter or a focused beam is used. In order to obtain a complete, unambiguous, three-dimensional view of the tissue structure, the transducer must be moved about.



Study of reflected ultrasonic pulses gives information on the dynamic characteristics of the heart in action.

Good quality ultrasonic pictures have been obtained of human structures, such as muscle, fat, and skin interfaces, the larger blood vessels of the limbs and neck, other neck structures, the liver, eye, etc. One of the major goals of this work is the detection and diagnosis of tumors in soft tissue.

Dynamic Characteristics of Tissue

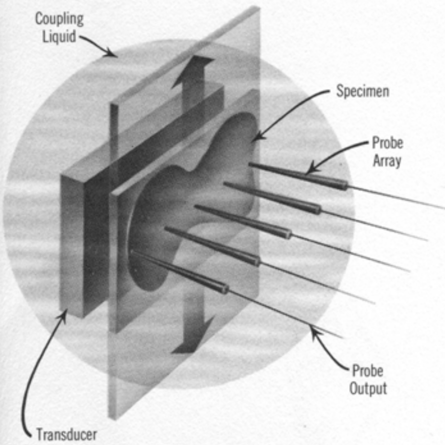
Another passive application of ultrasound is its use in the examination of the dynamic characteristics of the heart. Study of the sequence of time delays of acoustic signals reflected from a moving tissue interface provides information on the mechanical functioning of the tissue. It is also possible to obtain information on heart function by analyzing the Doppler effect (the change in pitch of a sound reflected from a moving surface) produced on the ultrasonic pulses reflected from moving tissue surfaces within the organ. Ultrasonic instrumentation for these studies is being tested at various places.

The use of ultrasound for the examination of static and dynamic characteristics of gross tissue will require instrumentation of considerably greater complexity and cost than current diagnostic x-ray equipment. Therefore, it is necessary that both high-quality engineering talent and financial backing be forthcoming to develop the necessary equipment.

Ultrasonic Microscope

A potential field of fundamental biological interest is the possible use of acoustic energy to investigate various microscopic phenomena in cells and tissues. Reports have shown that different proteins are characterized by different values of the ultrasonic absorption coefficient. By measuring the absorption coefficient of protein solutions under a variety of conditions (different temperatures, pressures, sound frequencies, ionic concentrations, etc.), information is obtained on the configuration, size, and other aspects of structure and energy exchange in such molecular species.

Since the different components of cells would not, in general, exhibit the same differential absorption of ultrasonic and electromagnetic energy, because the mechanisms of absorption are completely different, one would expect to "see" structure ultrasonically that is not seen by microscopes using visible light or energy in other regions of the electromagnetic spectrum. Calculations show that resolution down to one micron (40 millionths of an inch) is feasible for an appropriately designed ultrasonic "microscope," and work is now proceeding on the development of such a device in our laboratory.



Scheme for an ultrasonic "microscope."

The principle of operation of our microscope is illustrated schematically in the figure in the margin. A pulsed source of plane sound waves is coupled by a liquid medium to the specimen. Some of the sound energy is absorbed by the specimen, and the remainder passes through it and excites a small thermocouple probe placed immediately adjacent. The thermocouple is connected to an amplifier and a display instrument such as an oscilloscope. By arranging a linear array of such probes as indicated in the figure, a two-dimensional picture can be obtained if the specimen is moved about correctly.

Considerable ingenuity and resourcefulness are required in order to realize an appropriate instrument, so the device probably will be more complex and considerably more expensive than an elaborate optical microscope. However, we expect the instrument to furnish much new information on microscopic structure, including unicellular and multicellular organisms and tissues.

Sound in Physical Medicine

An extensive application of low intensity (1 to 5 watts per square centimeter) ultrasound to clinical medicine is ultrasonic diathermy. Here, unfocused ultrasound is applied to tissue by means of an appropriate transducer at the surface of the skin. Ultrasonic energy of this intensity—that is, where the dosage is restricted by the requirement that the patient experience no pain—is useful in the alleviation of a number of conditions, including muscle pain, muscle spasm, restricted movement, bursitis, fibrositis, periarthritis, post-operative pain in amputees, and a number of sports injuries. During the 1940's, ultrasound was used in Europe to treat other conditions, but many of these applications have been discontinued.

The mechanism of action of the sound in diathermy probably depends primarily on temperature changes produced by absorption of acoustic energy in the tissue. However, effects produced by nonthermal means at these sound levels have been reported. It would appear that ultrasonic diathermy is here to stay and that increased knowledge of its mechanism should suggest further applications. The instrumentation has been fairly well developed but additional equipment, in particular calibration instrumentation, is required if we are to realize all the technique's potentialities.

Active Uses of Acoustic Fields

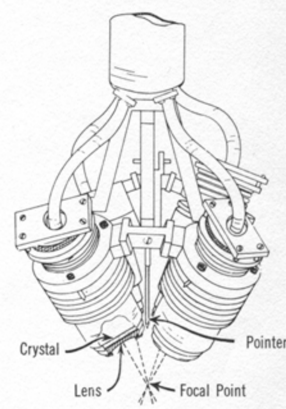
At ultrasonic dosage levels higher than those at which a biological system undergoes essentially no disturbance, selective permanent disruption of tissue structure and function can be produced. Or, with appropriately chosen dosages, it is possible to obtain temporary interruption of function. Considerable effort has been expended in the investigation of the ultrasonic dosage conditions which affect (either permanently or temporarily) specific tissue components of the central nervous system. Comparable studies of tissue components of other body systems have not yet been done, but it is important that such research be forthcoming. However, some work has been done on the modification of tumor tissue by ultrasound and by the combined use of ultrasound and ionizing radiation.

Central Nervous System

In the central nervous system, the selectivity that can be realized with appropriate dosages of high-intensity (100-2000 watts/cm^2) ultrasound is almost ideal for the investigation of normal structure and function. By focusing the sound, changes in regions of arbitrary sizes, shapes, and orientations can be produced in deep tissue without damaging intervening tissue. Microscopic studies of tissue sections show that blood vessels are the most resistant element within the brain to the action of the sound. Such studies also show that it is possible to destroy selectively the nerve components of white matter (the regions which contain only nerve fibers) without damaging adjacent gray matter (the regions containing nerve cell bodies). There is no evidence that long-term cumulative effects occur comparable to those produced by x-rays and ionizing particles.

To produce changes restricted to small volumes deep within tissue, the ultrasound must be focused. Large complex-shaped regions can be affected by moving the focus along an appropriate path or by placing it at a series of sites in an appropriate array. In determining the focus size, the rule is the shorter the wavelength, the smaller the focus that can be attained.

At a frequency of 1,000,000 cycles per second, the wavelength of sound in brain tissues is approximately 1.5 millimeters, and the minimum dimensions of the focal region of a practical irradiator at this frequency are such that one can affect a volume of tissue as small as a couple of cubic millimeters (that is, about the size of the exposed lead of a pencil). At a frequency of 4,000,000 cps, changes can be restricted if desired to a tissue volume 1/100th this size. However, it is not possible to decrease the wavelength indefinitely by increasing the frequency, because the higher the frequency, the greater the loss by absorption. A frequency of 2,000,000 cps is about the maximum that can be used to irradiate the deepest structures of the human brain in which the tissue path to be penetrated may be as great as 12 centimeters.



An ultrasonic brain irradiation device.

To irradiate the brain, a portion of the skull must be removed, since bone has a much higher absorption coefficient for sound than soft tissue. If bone were left in place, the heating that would occur as a result of absorption of the sound would result in damage to the underlying tissue, and the irregularities in skull thickness would modify the beam shape and would also disturb the accuracy of positioning of the focus.

Much work has been carried out on experimental animals to investigate the types of tissue changes produced (neurohistology) and problems of brain structure (neuroanatomy) and its operation (neurophysiology and behaviour). As a result of this fundamental animal work, the ultrasonic method is now being used to modify the symptoms of human neurological disorders that could not previously be attacked with older methods. In the case of human patients, it is especially useful for the irradiation procedures to be carried out with the skin of the patient intact (a bone flap large enough to irradiate arrays of sites in many deep brain structures having been removed at an earlier operation). Then, subtle modifications of behaviour and the symptoms of the neurological disorder can be made by interviewing and examining the conscious, unstressed patient during the irradiation procedure. The time course of the changes induced can be followed and modified by irradiation procedures spaced at any desired time intervals, from days to years.

Neurological disorders which are currently under investigation and treatment are the tremor and muscular rigidity of Parkinson's disease, nonpatterned abnormal movements in cerebral palsied individuals, unrelenting pain and hypersensitivities following amputation or stroke, and phantom "pain" in amputees.

Neurological examinations can be performed during therapy on the conscious patient to determine alterations.

In order to appreciate fully the ultrasonic method, it is desirable to compare it with other methods that have been used to destroy portions of the brain. These include mechanical, chemical, and electrical methods and the use of ionizing particles or radiation. The mechanical methods employ cutting or suction instruments; the chemicals are introduced by means of tubes; and the electrodes are placed by penetrating the tissue with an appropriate supporting structure. All of these methods cause destruction of tissue intervening between the region treated and the brain surface. In addition, these procedures do not result in the selective destruction of specific tissue components in the affected region—that is, all types of tissue or cells in the region are destroyed, including the blood vessels. High-energy ionizing particles and x-ray methods suffer from the disadvantage that changes are produced in all intervening tissue in the path of the beams, and these effects are cumulative. The single disadvantage of the ultrasonic procedure for the irradiation of the brain is the fact that a portion of the skull bone must be removed. However, a series of therapeutic procedures extending over a period of years can be accomplished without repetitive surgery, and the number of irradiation sequences that can be administered is unlimited.

Temporary Changes

Intense ultrasound can also be used to produce temporary, that is reversible, changes in the central nervous system. This has been proved by work on the visual system. When an eye of a dark-adapted animal such as a cat is subjected to flashes of light, or the optic nerve is stimulated, electrical changes occur in those regions of the brain concerned with the receipt of incoming visual information. The pattern and complexity of the electrical changes are dependent upon a number of factors, and several distinct components can readily be identified. When the focus of the sound beam is placed in regions of the brain concerned with the processing and transfer of visual information and an appropriate dosage of ultrasound administered, it is possible to produce changes in the magnitudes and times of appearance of these components. A focused sound beam used in this fashion constitutes an analyzer for the complex circuitry of the brain. In other words, nerve pathways over which information is transmitted can be located and studied by observing changes in the electrical signals received in brain structures caused by the temporary acoustically-produced disturbance to the pathways.

From the work already accomplished, it is clear that three-dimensional mapping of brain function of a type and scope heretofore unattainable will be possible by sweeping focused beams of ultrasound through brain structures and observing resultant changes. The methods will be extremely useful both in fundamental experimental animal studies and in human therapy.

On the human, irradiation can readily be performed on conscious patients. Continuous interview and examination could be used to indicate subtle changes in brain functioning. Therefore, it should be possible to investigate the relations between complex behaviour and brain mechanism. However, in order to bring such a program to fruition, major developments in the instrumentation for this work must be forthcoming. This would include equipment for data storage, analyzing machines, programming equipment, and presentation systems.

With a focused sound beam the complex circuitry of the brain can be analyzed.

Another advantage realizable from dosages of ultrasound that produce only reversible changes is the accurate localization of sites to be affected permanently for the relief of symptoms. When dosages which produce only permanent changes are employed, positioning of the irradiator depends upon certain internal brain landmarks revealed by x-ray. By using "reversible" dosages before "irreversible" ones, it should be possible in many instances to locate accurately and unambiguously the tissue structures to be affected before making permanent changes.

High-intensity, precisely-controlled, focused ultrasound methods have a tremendous potential value for fundamental research on the central nervous system and for applications in neurosurgery, neurology, and psychiatry. The realization of this potential depends upon two factors: the training of personnel to utilize the new tools; and the availability of sufficient funds to permit a number of organizations to purchase the rather expensive equipment required.

Other Tissues

Ultrasound has been employed at high intensities to modify tissue structures other than those of the central nervous system—for example, on muscle (the contractile and electrical properties) and on bone tumors.

The application of high-level ultrasound to the treatment of soft tissue tumors has been reported by Russian investigators. They employ an ultrasonic beam which is unfocused and, therefore, the work has been restricted to the irradiation of skin or immediate subsurface tumors. The Russian workers report that such ultrasound can *selectively* destroy at least some types of malignant tissue. They report that a highly malignant tumor (melanoblastoma) has been treated in a number of human patients with encouraging results.

To treat large, deep tumors by high-intensity ultrasound, a *focusing* transducer is employed that is capable of irradiating relatively large volumes of tissue simultaneously. This is necessary in order to hold the duration of the procedure within practical time limits. The sizes of the foci used in the brain work are much too small for treating large tissue masses (10 cubic centimeters or more in volume). However, a focusing system that will permit equipment for the irradiation of large, deep tumor masses is under development.

Russian investigators have treated soft tissue tumors with high level ultrasound.

During the 1940's, low ultrasonic intensities were employed in the irradiation of tumor tissue. Widely divergent effects were reported—from acceleration of tumor growth to suppression and destruction. These led to the conclusion that sound levels in this range are not suitable for treating malignant tumors. We feel, however, that this conclusion is not warranted, since in much of the reported work important irradiation parameters and auxiliary conditions were relatively uncontrolled. Precision control of dosage and the state of the tissue are essential in order to realize selective reproducible action.

For example, since increased temperature over part of the range enhances the growth of tumors and over another part of the range suppresses tumor growth, it is essential that all irradiated tissue at a given site be exposed under identical conditions. Therefore, much more investigation is necessary to determine whether ultrasonic levels in the range of 1 to 5 watts per square centimeter will be useful in the treatment of tumor tissue.

Combination Therapy

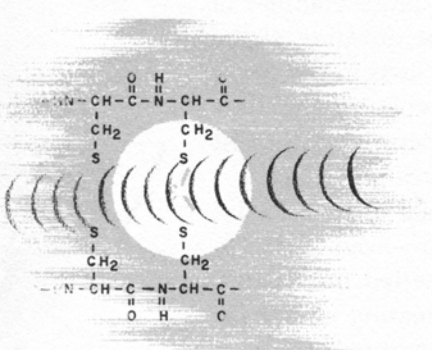
Another interesting medical application of acoustic radiation is the simultaneous employment of ultrasound and x-ray radiation to cause regression and resorption of tumors. Only a very little work has been done in this field, but x-ray dosages necessary to kill tumors have been reduced by a factor of two or more according to some reports. This is extremely important from the viewpoint of minimizing the hazards of ionizing radiation on normal tissue which is irradiated along with the tumors.

Macromolecules

Fundamental research on biologically significant macromolecules (e.g., cell components) and their functions might well benefit from the employment of intense ultrasonic fields to disrupt specific weak bonds in such structures. The forces involved in even an intense sound field in a liquid are not sufficient to disrupt strong bonds of small molecules (in the absence of cavitation), but they can exert sufficient stress on parts of large molecular species to break relatively weak bonds.

It appears, then, that high intensity sound fields may constitute a means of interrupting structure at the functioning level of the individual cells. Such breakages, when they occur in the living cell, in many cases can be expected to affect drastically the subsequent behaviour of the cellular elements involved or the cell as a whole.

The application of precisely controlled, high-level ultrasonic fields to the study of biological systems is in the very early stages. However significant results have already been obtained. Surely, increased efforts in this field, both in basic research and in medical therapy, should result in a tremendous amount of increased knowledge of the mechanisms of operation of biological systems and in extensive clinical applications.



Intense ultrasound can break weak bonds of macromolecules, thereby altering behavior of cell components.