Present and Future Applications of Ultrasonics in Biomedicine*

WILLIAM J. FRY†, MEMBER, IRE

Summary—**The current importance of ultrasonic energy for the investigation and modification of biological systems is reviewed and the immediately foreseeable potential apparent to the author is predicted. The uses of ultrasound in basic research studies of biological systems and medical applications are conveniently grouped into two major categories: passive uses, or those in which the acoustic field does not significantly modify either permanently or temporarily structure and/or function of the system, and active uses, or those in which modification of the system is the objective. Included within the first category are: absorption spectroscopy of solutions of macromolecular species, microscopy of cells and tissues, absorption characteristics of gross tissue, and visualization of soft tissue structure and its dynamics. The second category includes: the use of ultrasound in neuroanatomical and neurophysiological studies and the treatment of neurological disorders by the production of selective permanent or temporary changes in arrays of sites in the central nervous system, destruction of carcinogenic tissue, modification of endocrine glands, investigation of contractile and other properties of muscle, and the potentiation of ionizing radiation by simultaneous application of ultrasound. Applications of ultrasound in the biomedical field of a primarily technological nature are either mentioned only briefly or omitted entirely from the review.**

The "socioeconomic" factors which determine the level of financial support, and thus the rate of scientific progress, for a field are also briefly mentioned.

Introduction

THE STUDY of the interactions of various forms of energy with a system furnishes information on its structure and dynamics. Appropriately controlled ultrasonic energy (arbitrarily defined as sound above 20-kc frequency) constitutes a tool of considerable power for the elucidation and modification of biological systems. This potential of ultrasound, for the investigation of biological material, has been glimpsed partially as a result of work already accomplished with the methodology and instrumentation that various investigators have developed under scantily supported research programs. This glimpse of the potential future is also indicated by ideas for immediate advances, a number of which are mentioned in this paper, but which are not active experimentally at the time of writing.

A review of this length cannot hope to be exhaustive and therefore some of the important work included under the title is either mentioned only briefly or in some cases entirely omitted. However, the specific directions of investigation discussed here include most of the major ones which appear fruitful to the author at the present time. These directions, both basic research (including animal and human) and technological applications (including medical therapy), are conveniently considered in two categories: 1) passive uses; that is, those employing acoustic field conditions which do not significantly modify either permanently or temporarily the biological system, and 2) active uses; that is, those employing acoustic field conditions which modify either permanently or temporarily the structure and/or dynamics of the biological system.

A paper of this type in which both past accomplishments in a field are scrutinized and future potential is predicted might well consider, in addition to the scientific and technological features of such endeavor, the associated "socioeconomic" factors. These latter are equal in importance to the former in determining the rate of progress that can be achieved in any discipline and their prominence in determining the present status of the field of ultrasound in biomedicine is strikingly apparent. Brief reference to these nontechnological factors is included here as a specific example of the way scientific progress in general is determined by the philosophy and/or modus operandi of an organization or social structure which provides the financial support for research.

I. Passive Uses of Ultrasonic Fields

Ultrasonic fields conditions, which do not disrupt or significantly modify biological systems, can be used to detect structure from microscopic to macroscopic levels and to elucidate function. Measurements of ultrasonic absorption and/or reflection characteristics usually constitute the basic information from which such knowledge is deduced. The study of biologically significant structure at the microscopic and submicroscopic levels is subdivided here into two categories: 1) ultrasonic absorption spectroscopy of solutions of biologically important macromolecular species, and 2) ultrasonic microscopy of cells and tissues. Similarly, the investigation of biological systems with passively employed ultrasound on the macro level is divided into two categories: 1) ultrasonic absorption characteristics of gross tissue, and 2) ultrasonic visualization of soft tissue structure and its movement. The present state of development in each of these subdivisions is considered briefly and future potential is indicated.

A. Ultrasonic Absorption Spectroscopy

From measurements of the ultrasonic absorption characteristics of macromolecular configurations and molecules of biological interest such as proteins, information on the states of aggregation and organization of these species in solutions and suspending media can

* Received by the IRE, September 5, 1961; revised manuscript received, November 8, 1961.

† Biophysical Research Lab., University of Illinois, Urbana, Ill., and Interscience Research Corp., Urbana, Ill.

be deduced. Work in this field is in the early stages and no *specific* mechanism to account for the major portion of the absorption has yet been formulated and verified. However, a phenomenological approach in which relaxation theory is applied to explain the frequency dependence of absorption of some of the materials on which data is available has received some attention. That the ultrasonic absorption coefficient might well constitute a sensitive indicator of configuration states of macromolecular species in solutions or embedding media is already suggested by the work of Schwan, Carstensen and collaborators. These investigators have reported the most precisely determined and comprehensive velocity and absorption results on erythrocytes in suspension, hemoglobin in solution, plasma, extracts from liver, etc., as a function of the concentration, temperature, and ionic content over the frequency range from 0.3 to 10 Mc [1], [2]. However, measurements over a considerably wider frequency range will probably be required before much information on structural features of biological macromolecular species in solutions and in cells can be deduced from such data.

The type of ultrasonic instrumentation employed in this work is illustrated in principle [3] in Fig. 1. The method makes possible the attainment of a high degree of accuracy in the measurement of absorption coefficients and velocity differences. The basic principle is the comparison of the acoustic properties of the medium of interest with those of water or other standard liquid. To achieve this, the sound tank is divided into two compartments by a diaphragm as illustrated. One compartment contains the standard solution, the other contains the medium. The ultrasonic transducers, which generate and detect the acoustic pulses, are moved by a precision sliding mechanism. Movement of this mechanism makes possible the substitution of any desired pathlength of the solution or suspension for an equal pathlength of the standard. Absorption coefficient values with an uncertainty as small as 0.002 cm^{-1} are computed from measurements of attenuation. By determining the phase of the signal at the receiver transducer with respect to the signal at the generator, it is possible to accurately measure acoustic velocity differences, and determinations to one part in 100,000 are reported.

The method just discussed for measuring absorption coefficients of biologically significant media is not useful if both the volume of material available and the magnitude of its absorption coefficient are small since the apparatus of Fig. 1 then requires a quantity of material of the order of 0.1 to 1 liter. When the volume of material available is small, for example, a few cubic millimeters, the thermocouple method illustrated in Fig. 2 can be used. This is an adaptation of the thermoelectric probe developed at this laboratory for measuring absorption coefficients of tissue and for determining acoustic field configurations [4]–[6]. From the recording of the transient rise in temperature of the medium surrounding the junction, following exposure to a pulse of ultrasound of rectangular envelope, it is possible to calculate the absorption coefficient of the embedding medium. This method, which requires that the absolute sound intensity and the heat capacity of the medium per unit volume be known to the same degree of accuracy as that desired in the absorption coefficient,

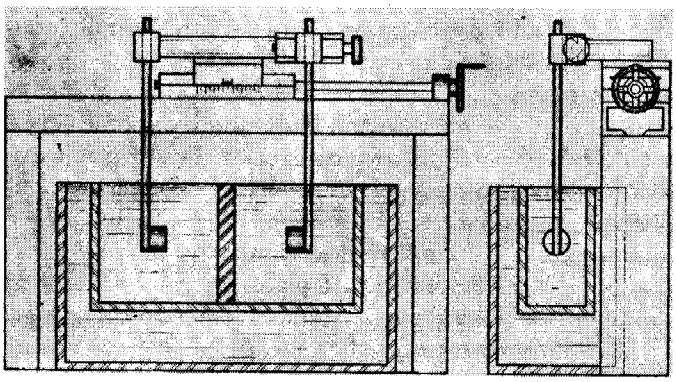

Fig. 1—Apparatus for precision measurement of ultrasonic absorption coefficients and velocity differences. Comparison of the acoustic properties of the medium of interest, which fills the left compartment of the sound tank, with a reference or standard liquid filling the right compartment of the tank, is achieved by this type of instrument. After choosing an appropriate spacing for the transmitter-receiver separation, the relative amplitude and phase of the received signal are determined as a function of the path length of the medium substituted for an equal path length of the standard by movement of the transmitter-receiver assembly relative to the two-compartment sound tank. The duration of the plane wave pulses and the dimensions of the tank are chosen so that reflection of ultrasonic energy from the tank walls does not interfere with the measurements.

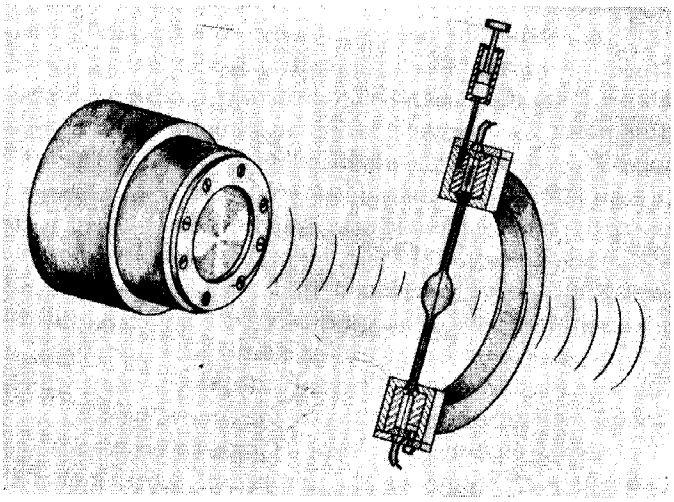

Fig. 2—Method of measuring the ultrasonic absorption coefficients of materials on samples as small as a few cubic millimeters. The material is supported in a tubular shaped container, formed of thin plastic sheet, in which a thermocouple is mounted in approximate coincidence with the long axis. The ultrasound pulses of rectangular envelope are focused in the volume of the medium surrounding the thermocouple junction and the voltage generated across the couple leads indicates the transient change in the temperature of the medium in the immediate neighborhood of the junction. From an analysis of the form of the temperature response, that part caused by absorption of the ultrasound in the body of the medium can be deduced, and from this and a knowledge of the heat capacity of the medium per unit volume and the absolute sound intensity, the acoustic absorption coefficient can be computed.

promises to be extremely useful in the further development of the field of ultrasonic absorption spectroscopy of solutions and suspensions of biological significance.

Absorption of ultrasound occurs in a *homogeneous* liquid when the changes in density are not in time phase with the changes in pressure. This type of behavior is produced by a variety of mechanisms classified into the two categories: viscosity or frictional lag and relaxation processes. The mechanism of the first category results from the fact that liquids exert resistance to shearing forces and for a Newtonian liquid this force is proportional to the velocity gradient and to the *constant* coefficient of shear viscosity. In non-Newtonian liquids the value of the viscosity coefficient depends upon the velocity gradient. The term "relaxation" process is used to include heat conduction, which is relatively unimportant for biological systems, and thermal and structural relaxation mechanisms [7]. Thermal relaxation results when the temperature of a fluid is changed due to the propagation of a sound wave, and the transfer of energy between external and internal degrees of freedom of components of the medium requires a time interval comparable to the period of the wave. The out-of-phase relations which result cause a conversion of acoustic into thermal energy. Structural relaxation results when a time interval comparable to the period of the sound wave is required for redistribution of the mutual orientation or degree of association of the components of the medium in response to the pressure changes produced by the sound field. Since configuration changes entail energy transfer, some acoustic energy is converted into heat when the rate of the redistribution process is too slow to follow the variations in pressure produced by the sound field without appreciable lag. If the equilibrium state of a chemical reaction is dependent to a sufficient degree upon the pressure of the reactants then acoustic absorption of the relaxation type takes place.

Absorption of ultrasound can occur as the result of relative motion between suspended structures and imbedding medium [8]–[11], *e.g.*, in cell suspensions or tissue. Such relative motion results since the densities of the suspended particles or their constituent parts are not, in general, equal to that of the suspending matrix. This relative motion gives rise to friction forces which cause absorption of acoustic energy.

Liquids can be subdivided into three classes on the basis of their ultrasonic absorption characteristics [12]–[14]. Members of the first group have ultrasonic absorption coefficient values close to those calculated on the basis of shear viscosity losses. Monatomic liquids such as mercury are in this group as well as some diatomic liquids such as oxygen and nitrogen. As far as is known at the present time, no biologically interesting materials are in this class. The second group is characterized by a positive temperature coefficient of absorption; that is, the magnitude of the absorption coefficient increases as the temperature increases and reaches values from three to four hundred times those calculated on the basis of a shear viscosity mechanism. Unassociated liquids such as benzine and carbon tetrachloride are in this group. The "excess" absorption of these liquids may be the result of a slow rate of exchange of energy between the external and internal degrees of freedom. The third group, the associated polyatomic liquids, exhibit a negative temperature coefficient of absorption. Liquids of this type include water and alcohols. The blood proteins exhibit such a negative temperature coefficient of absorption [15] but nerve tissue exhibits a positive temperature coefficient [7].

It is not possible in a review of this length to consider in any detail the methods of analysis leading to the identification and separation of shear viscosity mechanisms from relaxation processes and the identification of specific relaxation mechanisms and their characteristic frequency distributions. (See, for example, reference [7] for a discussion.)

The primitive state of knowledge of this field is apparent when it is compared with the present status of electromagnetic spectroscopy of atoms and molecules. In the ultrasonic case only a single molecular species—hemoglobin—has been studied in any detail and the underlying mechanism of absorption of not a single macromolecular structure has been worked out. When it is realized that classical electromagnetic spectroscopy (infrared, visible and X ray), which has yielded such a vast amount of information on the structure of molecules, atoms and crystals, can furnish little essential information on the macromolecular features of structures of interest here, and that electron microscopy is not readily adapted to the examination of solutions or suspensions, it is apparent that ultrasonic spectroscopy methods, in which the values of the absorption coefficient are critically dependent upon the macromolecular configurations in the embedding media, should receive major attention. It is emphasized here and it will be increasingly apparent from subsequent sections of this article that ultrasonic methods of the type described are particularly useful for the study and examination of structure on the biologically significant level.

B. Ultrasonic Microscopy of Cells and Tissues

Since different protein solutions and presumably other macromolecular species of biological significance are characterized by different values of the ultrasonic absorption coefficient [2], it is possible to develop an ultrasonic absorption microscope [7] to determine distributions of molecular species on an intracellular level. Since the mechanisms of absorption of ultrasonic and electromagnetic energy are completely different in general, components of cells and tissues would not exhibit the same differential absorption of these two forms of energy. Consequently, it is reasonable to expect to detect and visualize structures ultrasonically which are not seen by microscopes using visible light or electromagnetic energy in other portions of the spectrum and vice versa.

The principle of operation of one form of an ultrasonic absorption microscope is illustrated in Fig. 3. Acoustic waves are generated in a coupling medium by a piezoelectric element such as an X-cut quartz plate vibrating in thickness mode and this liquid conducts the sound to the specimen which is interposed between the source and a small thermoelectric probe or array of such probes. This array detects the acoustic energy transmitted through the portions of the specimen adjacent to the individual probes and thus an acoustic image of the structure can be reproduced by moving the specimen relative to the probe array [7], [16].

It should be noted here that this same device provides a method for measuring acoustic absorption coefficients of solutions or suspensions in the kilomegacycle frequency range. For this use the fluid medium, whose absorption coefficient is to be measured, fills the chamber and a single thermocouple probe is moved along the direction of propagation of the sound in the medium. The transient change in the temperature at the thermocouple junction, resulting from conversion of a fraction of the energy of the acoustic pulse into heat in the immediate neighborhood of the junction, measured as a function of the spacing distance between the source and probe, provides the necessary information to permit a calculation of the absorption coefficient of the medium. Work now in progress at this laboratory has shown that such a device can be used to measure absorption coefficients from the Mc frequency range into the kMc frequency range. At the present time it appears that an operating frequency spectrum of four orders of magnitude will be feasible.

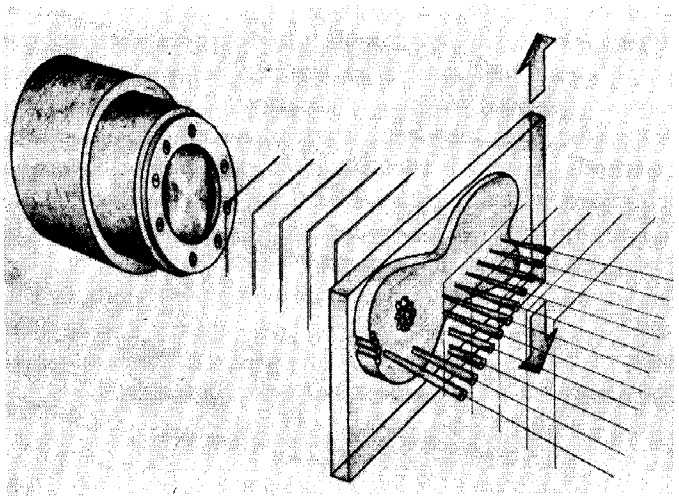

Fig. 3—Principle of operation of an ultrasonic microscope capable of resolving structure on an intracellular level. Plane pulsed waves of sound are generated by a piezoelectric plate element vibrating in thickness mode at any of a series of odd harmonics of the fundamental resonant frequency. After passing through the structure under examination, which is coupled in close proximity to the transducer element by a fluid medium, the acoustic energy passes into a medium imbedding an array of thermocouple junctions immediately adjacent to the specimen. Since differential absorption of the sound occurs in the specimen it is apparent that the temperature distribution defined by the different thermocouple outputs is a manifestation of structure in the specimen. By moving the specimen in its plane and in a direction at right angles to the direction determined by the linear array of junctions it is possible to obtain a two dimensional ultrasonic picture of microstructure of the specimen. The resolution of such a device is dependent on the size of the thermocouple junction, the thermal properties of the couple leads and of the imbedding medium, the ultrasonic pulse duration and intensity and the magnitude of differential absorption characteristic of the microstructural features.

Instruments designed on the basis of the principle illustrated in Fig. 3 have not yet been employed to examine or study the micro detail of cells or tissue structures since such devices are still in an early stage of development at this laboratory and much additional sophistication will be required before the microstructure of biologically interesting materials can be studied. However, a form of this device employing a single thermocouple junction is in use on the measurement of absorption coefficients of liquids from the low Mc into the kMc frequency range.

Calculations of the resolving power of an ultrasonic absorption microscope of the type discussed have been made [7], and it appears feasible on the basis of the analysis to expect a resolution of a few tenths of a micron at the higher operating frequencies. High resolving power requires operation in the kMc frequency range, not because of wavelength limitations, but rather because its attainment requires the use of short pulse lengths to minimize the effects of thermal conduction. The use of increasingly shorter pulse lengths requires increasingly higher ultrasonic absorption coefficient values in order to achieve a sufficient temperature change to be detectable, and since the absorption coefficient per unit pathlength increases with the frequency it is necessary to operate in the UHF range.

It should be noted here that an ultrasonic microscope based on lenses or reflector focusing principles would not be practical at the frequencies necessary to obtain high resolution since the acoustic absorption coefficient values per unit pathlength at these frequencies in liquid media are too high for the pathlengths which would be required in such designs.

Ultrasound employed in the manner indicated in this section would appear to have considerable potential for the examination and elucidation of biological structure on a microscopic level. It not only constitutes a new way of detecting structural features but it is also well suited for the examination of tissue or cells *in vivo*.

C. Ultrasonic Absorption Characteristics of Tissue

The absorption and the propagation characteristics of tissue for ultrasound must be determined to provide information basic to the utilization of this form of energy for: examination of the gross anatomy and normal dynamics of organs *in vivo*, diagnosis of malfunction and pathological states, modification or destruction of internal structure without incising of the intervening tissue in animals and humans. Quantitative information is essential for a basic understanding of the manner in which proteins and other macromolecular species contribute to the absorption in tissue and for an understanding of absorption mechanisms related to tissue

structure as contrasted with that resulting from processes occurring on the "molecular" level.

As will be indicated in Section I-D of this paper, the ultrasonic visualization of soft tissue structure offers enormous potential for the examination of the anatomy of intact organisms and the associated dynamics but the acoustic propagation characteristics of such tissue must be understood in order to achieve the potential. In addition, the entire field concerned with the modification of tissue structure, reviewed in Section II, is dependent upon an accurate knowledge of the propagation characteristics of ultrasound in tissue. Both velocity [17] and absorption characteristics [18], [19] must be known.

In view of the incompleteness of the acoustic propagation data [20] in this field it is apparent that much experimental work and theoretical analysis must be accomplished before the absorption characteristics of a variety of tissue structures in the ultrasonic frequency range are both known and understood [8], [9], [11], [21]. A recent example of the type of data and analysis required for a basic understanding of absorption mechanisms in tissue in the megacycle frequency range is that reported from this laboratory on the absorption in lung [22].

Not only is it essential that the acoustic propagation characteristics of normal tissue be measured and understood but it is also necessary that the characteristics for pathological tissue be determined. This latter is particularly important if ultrasound is to be useful passively for diagnostic purposes.

D. Ultrasonic Visualization of Soft Tissue Structure

Nearly all soft tissue components possess essentially the same X-ray density, and therefore structural features of soft tissue cannot be visualized directly by using this radiation. By contrast, since soft tissue structure is not acoustically homogeneous (slight differences in acoustical impedance are present), small fractions of the ultrasonic energy incident on interfaces within or between such tissues are reflected. Since under the ultrasonic irradiation conditions required, no deleterious effects are produced in tissue, this form of energy provides a method of visualizing tissue structures (both normal and pathological) in three dimensions [23], [24]. In addition, their dynamic characteristics can be studied; for example, it is possible to observe the movements of major blood vessels and characteristics of heart motion [25]–[29]. Ultrasonic visualization methods have been applied in ophthalmology [30], and tumor localization and diagnosis have received the attention of a number of investigators [31]–[33].

The wavelength of the radiation determines the resolution which is obtainable and since the velocity of sound in soft tissue is close to that of water it is necessary to operate at frequencies of 1 Mc and above if resolution of the order of a millimeter is desired. At these frequencies the absorption per centimeter of tissue path is relatively high so that the received acoustic energy reflected from interfaces at different tissue depths is considerably affected in magnitude by this factor. By the use of focused beams and short pulse lengths it is possible to obtain resolution in both azimuth and range.

The instrumentation required for visual presentation of the reflected ultrasonic signals as a reconstruction of the tissue structure and for detection and processing the signals for the presentation system is quite sophisticated. It is necessary because of the tremendous range of amplitudes of the returning reflected signals to design the system with gain compensation. Since the orientation of the reflecting interface with respect to the direction of the incident beam is important in determining the direction of the reflected acoustic energy, and consequently the amount of energy which is returned to the receiving transducer, it is necessary to view each site in the structure from a number of different directions. The importance of this is apparent when it is observed that, for example, an angular shift from normal incidence of 10° can cause a reduction of the amplitude of the received signal by a factor of 100. Compound scanning techniques thus improve the picture detail and eliminate artifacts (see, for example, reference [7] for further details).

The ultrasonic method of soft tissue structure visualization just described—that is, one depending upon existing small differences in the acoustic impedance at tissue interfaces to provide reflected energy—although furnishing a tremendous amount of information not obtainable previously, does not permit the visualization of all tissue structures of interest. In addition, increased contrast between structures now detectable is extremely desirable in many cases. A considerable advance in these two directions can be expected by a new ultrasonic visualization method recently proposed and evaluated analytically by the author. The advantages offered by the new method can be illustrated by the following specific comparison. Present ultrasonic visualization methods do not detect boundaries between any internal brain structures since the acoustic impedance differences are not of sufficient magnitude to provide detectable amounts of reflected energy. However, it is presently possible to detect the ventricular system since the impedance difference between brain tissue and cerebrospinal fluid is sufficiently great to provide the necessary reflection. Since the study and modification of brain structure and function requires the placement of beams of radiation, electrodes, cannulae, etc., at specified sites in particular structures it is extremely important to have a system which permits visualization of all major brain structures (that is the boundaries between the major gray and white matter masses). This can be achieved and presently undetectable structural details in other tissues and organs of the body can be visualized by designing an instrument to induce temporary impedance differences at tissue interfaces. Such impedance changes can be induced at interfaces where the ultrasonic absorp-

tion coefficient changes in value; for example, in the brain the white matter exhibits an ultrasonic absorption coefficient approximately $1\frac{1}{2}$ to 2 times that characteristic of gray matter.

The basic principle underlying the method proposed by the author is illustrated in Fig. 4. Two pulsed properly synchronized scanning beams of ultrasound are employed, one (the modifier) of relatively long pulse duration and the other (the analyzer) consisting of a series of pulses short compared to the first. These sound beams are, in general, of different frequencies. The long-pulse focused beam or modifier is used to produce in a relatively small volume of tissue (the site within the specimen receiving immediate attention) transient changes in temperature by conversion of acoustic energy into heat. In the boundary regions between tissue structures characterized by different values of the ultrasonic absorption coefficient transient steep gradients of temperature would thus be produced. Since the velocity of sound is temperature dependent corresponding gradients in the acoustic velocity would thus exist temporarily in these boundary regions. The second focused beam, the analyzer, would then be partially reflected from regions exhibiting such gradients. Calculations demonstrate that sufficient acoustic energy can be reflected when temperature differences which would not produce damage to the tissue are employed. This new method will achieve not only visualization of structures which are undetectable by instruments employing the present methodology, but will also permit increased contrast to be achieved between structures detectable with the present equipment, but for which improved contrast would be extremely advantageous. The new method is well suited to the centering of attention on chosen small volumes of tissue to provide enhancement of echoes from this region compared to those from surrounding or embedding structure. This is achieved since the temperature gradients which either induce or increase acoustic impedance differences at boundaries are of appropriate magnitude only in the region of the focus of the modifying beam. Thus, three major advantages over present methods of ultrasonic visualization of soft tissue structure are provided: visualization of structures not now detectable, increased contrast between presently detectable structures, and relative suppression of reflected energy from embedding and intervening tissue.

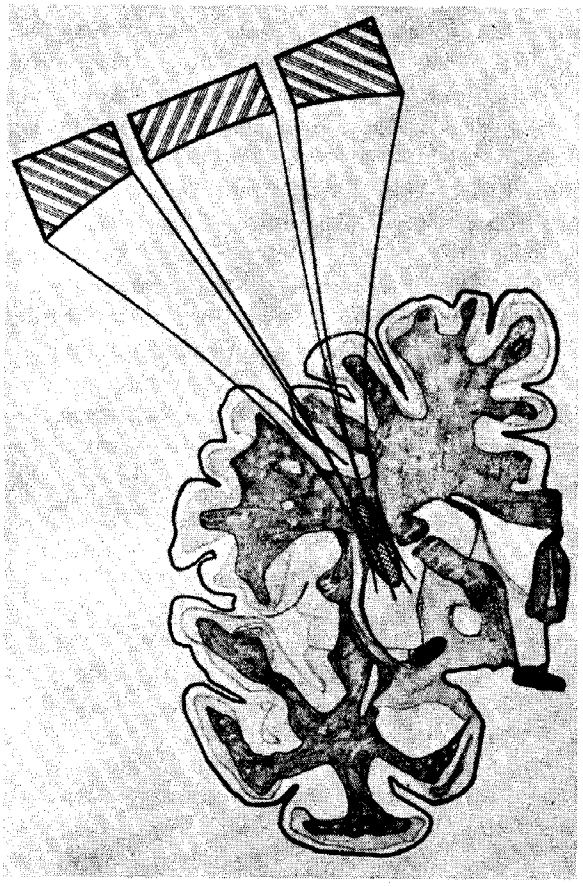

Fig. 4—Schematic diagram of ultrasonic method of visualizing soft tissue structure by employing one focused and pulsed beam of sound (included within the two concentric cones which surround the inner beam illustrated in the diagram) to induce temperature gradients of small nondamaging amplitude at tissue interfaces (brain, gray-white matter interface in the figure) and other structural features at which changes in acoustic absorption occurs. Since the velocity of sound is temperature dependent acoustic velocity gradients are thus induced in the regions of structural change. These gradients are then detected and their geometric positions determined by a second pulsed and focused ultrasonic beam (included within the innermost cone of the diagram) appropriately synchronized with the first. Both the temperature modifying and the examining beams are moved to scan the specimen. The duration of the pulse length of the former is relatively long (0.1 to 1 sec) in order to induce velocity gradients of appropriate amplitude without the use of extremely high ultrasonic intensities and the pulse length of the latter is very short (1 μsec) in order to provide appropriate resolution (0.1 to 1 mm).

The potential of ultrasound for examination of tissue is apparent when it is observed that the present widespread use of X rays in diagnosis is based on the visualization of a much more restricted range of structure than that which will be possible with instruments based on ultrasonic methods. The implications can again be emphasized by reference to the neurological field. No present method can achieve visualization of internal brain structures (nuclei and fiber tracts) and a variety of landmarking methods have been devised to provide systems of reference which at best furnish meager information. The direct visualization of all major brain structures, which the new ultrasonic method outlined briefly here is expected to provide, now appears to be within our grasp.

II. Active Uses of Ultrasound

Modification of structure and/or function at deep sites in tissue both for basic research on experimental animals [34]–[36] and humans [37], [38] and for routine treatment of disorders in medical therapy can be achieved with ultrasound. By focusing it is possible to produce changes at any desired depth without damage to intervening tissue and by appropriate control of the irradiation parameters selective action on components of tissue structure can be accomplished [34], [39]–[46]. Either permanent or temporary [34], [47] changes can

be produced as desired. The central nervous system has been the object of the most intensive study using precisely controlled intense ultrasound and the present status of this area of activity will be briefly reviewed and future potential indicated.

A. Central Nervous System

In the central nervous system the selectivity that can be realized at the present time by employing ultrasonic field parameters corresponding to pressure amplitudes of 5 to 50 atmospheres and appropriate durations of exposure constitutes an extremely powerful tool for investigation of normal structure and function. By moving the focused beam about with an appropriate precision positioning system changes in regions of arbitrary sizes, shapes and orientations can be produced in deep sites without damaging intervening tissue. Microscopic studies of irradiated tissue show that blood vessels are the part of the brain most resistant to the action of the sound and also demonstrate that it is possible to interrupt selectively the neural components of white matter (the regions which contain only nerve fibers) without damaging gray matter (the regions containing the nerve cell bodies) subjected to the same irradiation conditions. No evidence of long term cumulative action comparable to that produced by ionizing radiation and ionizing particles exists.

The minimum size region that can be affected is determined by the volume of the focal region and this is, in turn, dependent upon the wavelength of the sound. At 1 Mc the wavelength in brain tissue is $1\frac{1}{2}$ mm and therefore the minimum size tissue volume that can be affected in easily reproducible fashion in homogeneous tissue is a few cubic millimeters. At higher frequencies changes can readily be restricted to smaller volumes of tissue if so desired. For example, at 4 Mc the tissue volume affected for a single exposure position can be as small as a few hundredths of a cubic millimeter. However, it is not possible to decrease the wavelength indefinitely, by increasing the operating frequency, to affect smaller and smaller tissue volumes in depth because as the frequency increases the absorption per unit path length also increases—linearly in the range of interest (at 1 Mc the pressure absorption coefficient is 0.1 cm^{-1}).

The procedure employed at the present time for the irradiation of brain structures requires that a portion of the skull be removed since bone has a much higher absorption coefficient [19] than soft tissue and, therefore, if left in place, thermal damage to underlying tissue would occur as the result of heat conduction from the irradiated bone. In addition, the irregularities of skull thickness and orientation would modify the beam shape and reduce the accuracy of positioning the focus. When the new ultrasonic visualization method discussed in the previous section is in operation, it may be feasible to develop instrumentation to eliminate the present requirement of bone removal since it will then be possible to view directly the focus of the ultrasonic beam, used for modification or disruption of neural structure, in the specific sites to be affected. The attainment of such a goal must however await the development of very elaborate instrumentation. Obviously all possible effort should be bent toward this objective since its realization would make the precision modification of brain structure for the treatment of a variety of neurological and other disorders in the human extremely simple to achieve in practice since no preliminary or auxiliary procedures such as the present surgical and ventriculographic preparations would be required.

Much work has been carried out on experimental animals to investigate the types of tissue changes which are produced (see references listed in the introduction to this section) and as a result ultrasonic methods are currently being employed at this laboratory in fundamental research studies of a neuroanatomical and behavioral nature. Anatomical investigations [35] heretofore not feasible are now possible since changes can be confined to selected volumes of tissue without *any* damage to other structures. When the desired "lesion" is achieved there is no ambiguity regarding interpretation of results such as ordinarily arises because of damage to other tissue. Fig. 5 illustrates in cross-section lesion arrays of various configurations in cat brains produced by focused ultrasound.

The advantages for neurophysiological and behavioral studies of the ultrasonic method of producing *permanent* changes in brain structures are similar to those for neuroanatomical investigations; that is, the production of selective lesions of desired sizes and shapes in combinations of structures without damage to other regions.

The extensive work carried out on experimental animals provides the basis for employing ultrasonic methods to study and modify the symptoms of human neurological disorders and a variety of such disorders has received the attention of the author and collaborators up to the present time [34], [37], [38]. These include: the tremor and rigidity of Parkinson's disease; involuntary movements of cerebral palsied individuals; intention tremors and nonpatterned movements; intractable pain, hyperesthesias and dysesthesias following cerebral vascular accidents; and phantom images and pain in amputees. The symptoms indicated can be affected by modifying various brain structures and the ultrasonic work already accomplished has provided much new information on the identification of specific structure subserving the underlying mechanisms. The flexibility and absence of stress during irradiation of the awake human patient makes possible the subtle and consistent step-wise modification of the neurological status as determined by continuous interview and examination during the procedure.

The instrumentation necessary for attaining the flexibility, reproducibility and accuracy for producing *permanent* changes at desired arrays of sites in the hu-

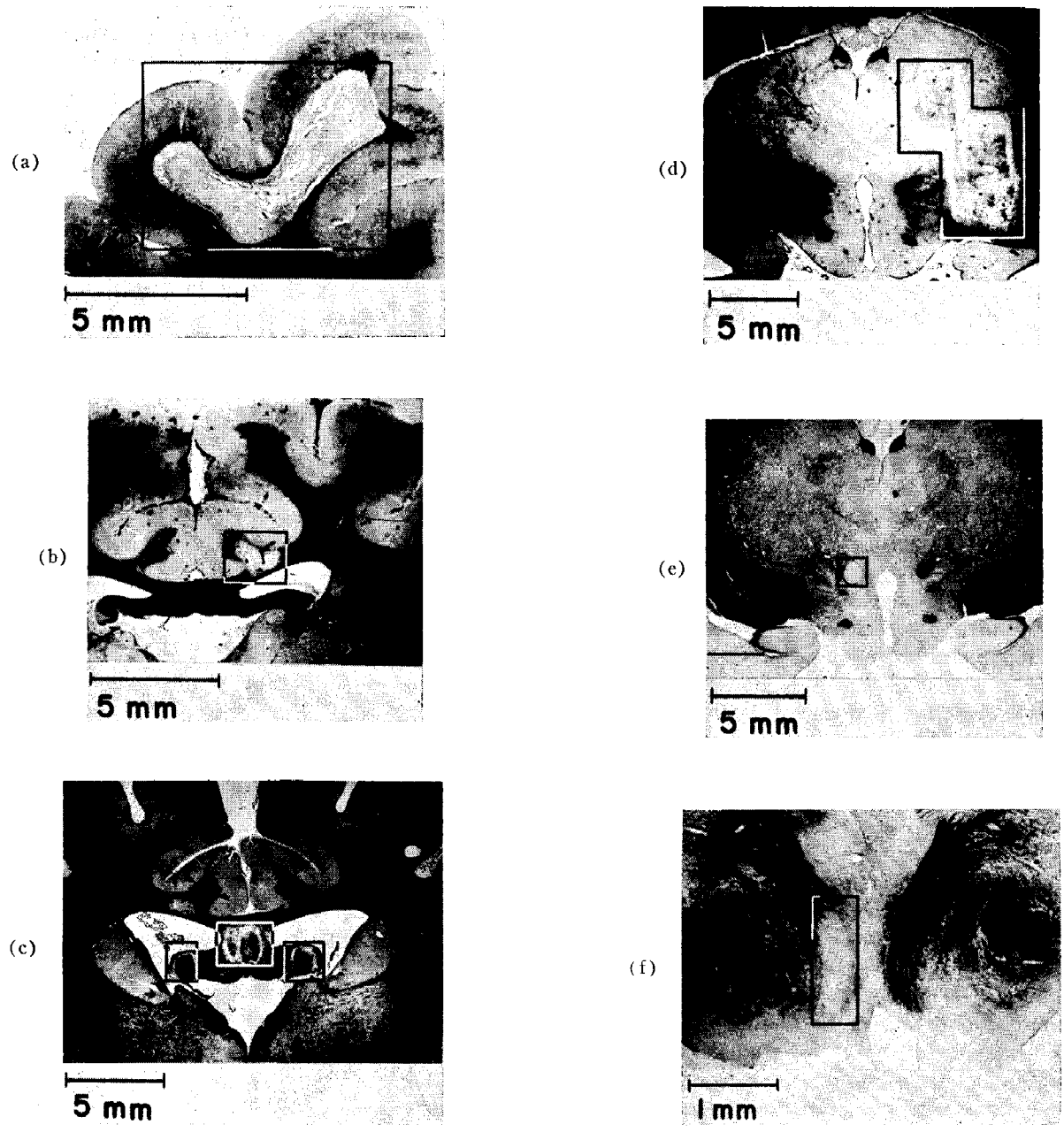

Fig. 5—Stained tissue sections of cat brain showing various shaped ultrasonic lesions in a variety of structures. The white matter or nerve fiber tract regions are stained dark and the gray matter or nerve cell body regions are relatively unstained. (a) Lesion in the subcortical white matter with no invasion of the immediately adjacent cortical gray matter. The brain cross section shown exhibits the maximum dimensions of the lesion. Its extent perpendicular to the cross-section is small, It was produced by moving the focus (1 Mc sound) in the plane of the section with a 1 mm spacing between adjacent sites. (b) Lesion placed to interrupt longitudinally running fibers—the cingulum running perpendicular to the plane of the section—in the white matter of the cingulate gyrus. The lesion was produced by placing the focus at an array of sites spaced 0.2 mm apart, 4 Mc sound. (c) Three lesions in the subcallosal fornix. The longitudinally running fibers are interrupted in the lateral half of the structure bilaterally and the fibers in the medial portion of the structure in the plane of the section are destroyed. No damage was produced in the corpus callosum and underlying thalamic structures: 0.2 mm spacing between adjacent sites of the array, 4 Mc sound. (d) Two thin rectangular sheet lesions in the thalamus and subthalamus. These lesions are thin in the direction perpendicular to the section shown, 4 Mc sound used. (e) Interruption of the mammillothalamic tract: 0.2 mm spacing, 4 Mc sound. (f) Lesion in the medial part of the medial mammillary body. The lesion extends throughout the length of this structure, *i.e.*, for $1\frac{1}{2}$ mm in the direction perpendicular to the section shown. The lesion is shown in cross section: 0.2 mm spacing, 4 Mc sound.

man brain is quite elaborate and not inexpensive. The apparatus presently employed, which is illustrated in Fig. 6, includes: a stereotaxic head holder incorporating X-ray equipment; ultrasonic focusing transducers; a positioning system for placing the focus of the beam at desired predetermined arrays of sites; electronic equipment for supplying the necessary electric excitation to the transducers and for accurately controlling the sound level and duration of exposure; calibration instrumentation for precisely determining acoustic field configurations and for measuring absolute sound levels; and auxiliary equipment for control of factors such as coupling liquid temperatures [34], [36], [48].

Intense ultrasound can also be used to produce temporary, that is, reversible changes in the central nervous system. This is demonstrated by results obtained on the visual system of the cat [34], [47]. For example, when an eye of the animal is subjected to flashes of light or if the optic nerve is stimulated electrically, electrical events occur in regions of the brain concerned with the receipt and processing of incoming visual information. The pattern and complexity of these electrical events in the visual cortex are dependent upon a number of factors and various components of the evoked response can be identified depending upon the level and type of anesthesia, the temporal sequence of exciting stimuli, the temperature of the brain, etc. When the focus of the sound beam is placed in structures (*e.g.*, lateral geniculate nucleus) concerned with the processing and transfer of information and an appropriate set of irradiation parameters are employed, it is possible to produce changes in the magnitudes and latencies of the components of the potentials evoked in the visual cortex. A focused sound beam employed in this fashion constitutes an analyzer for the complex circuitry of the brain. That is, nerve pathways and centers over which information is transmitted and processed can be located and studied by observing the temporary changes induced by focused ultrasound in, for example, electrical responses manifested in brain structures following stimuli of various types and configurations.

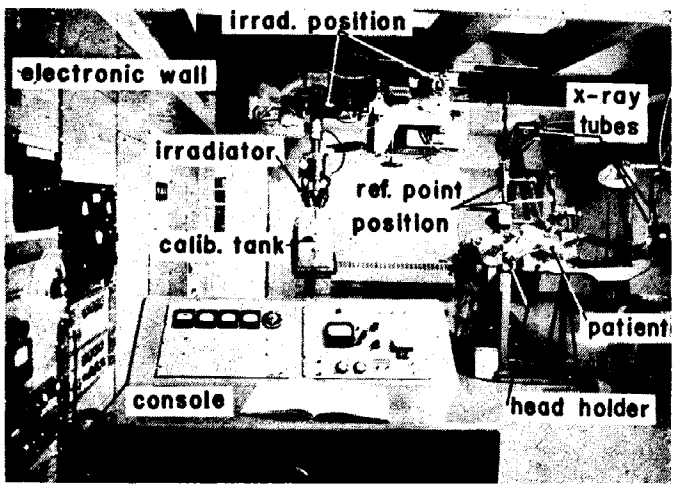

Fig. 6—View of the irradiation room for modifying brain structures in the human. An awake comfortably positioned patient is shown with head supported in the holder by four stainless steel rods whose rounded tips engage hemispherical indentations in the outer table of the skull. The tips of these rods can be accurately repositioned in space by the micrometer adjustments provided on the supporting posts in order to permit a number of irradiation procedures if desired without the necessity of determining the coordinates of the internal landmarks more than once. The three X-ray tubes and cross hair positioning system employed in the coordinate determination of landmarks are shown mounted on the head holder. The four beam irradiator, which has provided the focused intense ultrasound for the human work accomplished up to the present, is in position over the calibration tank. It swings into place over the head of the patient after a hopper which supports the coupling liquid is positioned over and engaged in water tight connection with the patient's scalp. The placement of the focus of the ultrasound in the sites of the array of positions to be modified in the brain is accomplished by the overhead structure. Since the scalp is intact during irradiation (an appropriate portion of the skull bone is removed at an earlier procedure) there is no necessity for sterile procedure once the small scalp incisions at the sites where the supporting rods engage the skull are sealed. The electronic instrumentation is mounted on the panels on the left wall and in the control console in the foreground.

From the work that has been accomplished it is apparent that three-dimensional mapping of brain function of a type and scope heretofore completely unattainable will be possible by moving appropriately controlled focused beams of ultrasound through brain structures and observing resultant changes. Some of these possibilities are apparent when one considers that the resolution obtainable with ultrasonic methods can make a moving sound focus the equivalent of 10,000 to 100,000 electrodes capable of disturbing in controlled temporal sequences threshold relations of neural events in essentially any combination of structures in a single brain. Such methods will be extremely useful both in fundamental research studies on experimental animals and on humans and in human therapy. In the latter application it will not be necessary, for example, to destroy any brain structure to locate regions involved in specific malfunction or pathological behavior.

If will be possible to investigate relations between complex behavior and brain mechanisms with some hope of obtaining a basic understanding of the operation of the maze of inter-connections and inter-relations which exist. However, to bring such a program to fruition, major developments in instrumentation must be forthcoming. The instrumentation which is required (at an estimated cost of several million dollars for a single installation) will include: data storage equipment; data analyzers, programming apparatus, presentation systems for results of data analysis; anatomical and functional presentation systems; a multiplicity of focusing transducers; positioning systems; ultrasonic visualization instrumentation; and a variety of types of control equipment.

The study and correction of malfunctions of the human brain—the most complex mechanism yet identified by man—would appear to warrant the development and use of instrumentation which is at least comparable in sophistication to that currently in use in investigations of the "physical" world. We have a long way to go but it is to be hoped that support for such activity can be ob-

tained so that the major contributions promised by new methodology, for example the ultrasonic procedures indicated herein, are forthcoming.

B. Other Structures

High-level ultrasound can be used to modify tissue other than that of the central nervous system but other structures have not received comparable attention. The application of intense ultrasound to the treatment of soft tissue tumors has been reported [49], [50]. An unfocused beam of large cross-sectional area (50 cm^2) and intensity levels up to 500 w/cm^2 were used to modify and destroy malignant tissue. The treatment of deep tumors by high intensity ultrasound will require the development of focusing transducers capable of irradiating relatively large volumes of tissue simultaneously. This is necessary in order to confine the duration of the procedure to practical time limits. The "effective" sizes of the foci employed for the current work on the central nervous system are much too small (0.1 to 10 mm^3) for treating large tissue masses (1 to 10 cm^3). The development of focusing transducers with focal regions large in cross sectional area uniform, within a few per cent, in acoustic field parameters presents difficulties. Some headway on the development of appropriate focusing systems using modified cylindrical lenses has been achieved at this laboratory [51], [52].

It should be noted here that work accomplished during the 1940's on the use of relatively low intensity ultrasound to modify tumors with enhancement reported in some cases and suppression in others does not constitute an appropriate basis on which to judge the possible applicability of high-level ultrasound for the favorable modification of carcinogenic tissue. This view is reasonable since desirable effects may only be achieved above certain threshold levels, as has been demonstrated in the case of the central nervous system. Investigations into the possible production of selective changes in carcinogenic cells, that is, for example, the possible action of high-level ultrasound to *selectively* destroy such material when embedded in normal cellular masses is extremely desirable and should receive major attention in the immediate future.

The endocrine status of both experimental animals and humans has been modified by irradiation of the pituitary in work accomplished by the author and collaborators [53], [54]. This work has application not only to the study of normal endocrine balance but also to the modification of endocrine function in, for example, patients with endocrine tumors—metastasizing breast tumors [54]. From the work accomplished it is apparent that the endocrine state of an organism can be drastically modified by hypophyseal irradiation with ultrasound and made to undergo a series of changes with various recovery rates either to pre-irradiation or altered endocrine status. The histological work of this laboratory [53] indicates that it may be possible to alter the ratios of the gland cellular populations of the pituitary and thus the interesting possibility of redesigning the hypophysis by the application of controlled dosages of ultrasound is suggested. If this can be achieved it will constitute a powerful procedure for the study and modification of endocrine physiology.

Another type of tissue, which has been the object of basic investigative work employing ultrasound in attempts to obtain fundamental information, is muscle [55]–[58]. Such work continues and it is hoped that increased knowledge of muscle structure and its relationship to the contractile and electrical characteristics of the tissue will be forthcoming.

The action of ultrasound on cells and tissues other than those already mentioned has received the attention of various investigators. For examples of work reported within the last ten years see [59] through [61] for liver, skin and some embryonic tissues and reference [62] for a specific plant tissue.

Before concluding this section it is of interest to call attention to another intriguing use of ultrasound in the study of biological systems, that is, in combination with ionizing radiation. An extremely small amount of work has been accomplished in this direction and it has been shown that X-ray dosages necessary to irreversibly destroy some types of tumor tissue can be reduced by a factor of two or more by simultaneous irradiation with relatively low-intensity ultrasound [63], [64]. The mechanism of such action should receive attention and studies must be extended to the use of high-level ultrasound in combination with ionizing radiation.

III. Technological Applications

It has not been the intention of this review of the present status and future potential of ultrasound in biomedicine to consider various developments of a strictly technological nature. A number of these, both apparatus and nonresearch applications, have already been developed and more are expected in the future including equipment for use in basic research and for medical technology. Present examples of equipment development include: ultrasonic apparatus which produces cavitation to disrupt cells and tissues in order to free intracellular contents in a form unaffected by chemical agents, equipment for separation of layers of tissue by the use of ultrasonically induced cavitation [65] and ultrasonic blood flowmeters [66], [67]. In medical therapy the use of ultrasound at low level as a diathermy procedure might well be classified as technological in character [68], [69]. These few examples serve to indicate the range of developments that have been thus far conceived and applied. It is, of course, practically impossible to predict at any one time the specific apparatuses which will be invented for future use in research and technology. However, it does appear possible to predict investigative directions which will produce fruitful research and to indicate new fields of applications which can be expected to arise therefrom. Such has been the theme of this paper.

Concluding Statement

It is apparent from the basic research work in progress and accomplished and current applications that precisely controlled ultrasound constitutes an extremely powerful tool for the investigation and modification of structure and function in biological systems. This form of energy is particularly useful for perturbing or disrupting structure on the micro-level characteristic of biological organization. Although some of the results already achieved are rather exciting when compared with past capabilities, it is apparent that the field is in a primitive state compared to the future potential. Although it is possible at the present time to outline at least some of this extensive potential for basic biological and biomedical investigations and medical technology, its rate of attainment is determined to a major extent by the economic status of the field as decided by agencies which provide the financial support. It is to be hoped that the "socioeconomic" status of this field will soon change to permit the necessary increased support to be provided so that a major fraction of the potential now visualized is realized within this decade. A support level at least two orders of magnitude greater than that currently available to the field will be necessary in order to achieve the indicated research objectives and initiate the consequent applications during this period of time. Application of the results of the basic research in routine medical practice will require additional funds both for the acquisition of appropriate sophisticated instrumentation and the training of individuals to utilize it.

References

[1] E. L. Carstensen and H. P. Schwan, "Absorption of sound arising from the presence of intact cells in blood," *J. Acoust. Soc. Am.*, vol. 31, pp. 185–189; February, 1959.

[2] E. L. Carstensen and H. P. Schwan, "Acoustic properties of hemoglobin solutions," *J. Acoust. Soc. Am.*, vol. 31, pp. 305–311; March, 1959.

[3] G. M. Piersol, H. P. Schwan, R. B. Pennell and E. L. Carstensen, "Mechanism of absorption of ultrasonic energy in blood," *Arch. Phys. Med.*, vol. 33, pp. 327–332; June, 1952.

[4] W. J. Fry and R. B. Fry, "Determination of absolute sound levels and acoustic absorption coefficients by thermocouple probes—Theory," *J. Acoust. Soc. Am.*, vol. 26, pp. 294–310; May, 1954.

[5] W. J. Fry and R. B. Fry, "Determination of absolute sound levels and acoustic absorption coefficients by thermocouple probes—Experiment," *J. Acoust. Soc. Am.*, vol. 26, pp. 311–317; May, 1954.

[6] W. J. Fry and R. B. Fry, "Temperature changes produced in tissue during ultrasonic irradiation," *J. Acoust. Soc. Am.*, vol. 25, pp. 6–11; January, 1953.

[7] W. J. Fry and F. Dunn, "Ultrasound: Analysis and experimental methods in biological research" in Physical Techniques in Biological Research," W. L. Nastuck, Ed., Academic Press, New York, N. Y., vol. 6, 1962.

[8] O. A. Angerer, G. Barth and W. Güttner, "Über den Wirkungsmechanismus biologischer Ultraschallreaktionen," *Strahlentherapie*, vol. 84, pp. 601–610; May, 1951.

[9] W. J. Fry, "Mechanism of acoustic absorption in tissue," *J. Acoust. Soc. Am.*, vol. 24, pp. 412–415; July, 1952.

[10] O. Brandt, H. Freund and E. Hiedemann, "Schwebstoffe im Schallfeld," *Z. Phys.*, vol. 104, pp. 511–533; March, 1937.

[11] P. S. Epstein, "On the absorption of sound waves in emulsions and suspensions," in "Theodore von Karman Anniversary Volume," California Inst. Tech., Pasadena, pp. 162–188; 1941.

[12] J. M. M. Pinkerton, "Absorption of ultrasonic waves in liquids and its relation to molecular constitution," *Proc. Phys. Soc. (London) B*, vol. 62, pp. 129–141; February, 1949.

[13] J. J. Markham, R. T. Beyer and R. B. Lindsay, "Absorption of sound in fluids," *Rev. Mod. Phys.*, vol. 23, pp. 353–411; October, 1951.

[14] K. F. Herzfeld and T. A. Litovitz, "Absorption and dispersion of ultrasonic waves," Academic Press, New York, N. Y.; 1959.

[15] E. L. Carstensen, K. Li and H. P. Schwan, "Determination of the acoustic properties of blood and its components," *J. Acoust. Soc. Am.*, vol. 25, pp. 286–289; March, 1953.

[16] F. Dunn and W. J. Fry, "Ultrasonic absorption microscope," *J. Acoust. Soc. Am.*, vol. 31, pp. 632–633; May, 1959.

[17] G. D. Ludwig, "The velocity of sound through tissues and the acoustic impedance of tissues," *J. Acoust. Soc. Am.*, vol. 22, pp. 862–866; November, 1950.

[18] T. F. Hueter, "Messung der Ultraschallabsorption in tierischen Geweben und ihre Abhängigkeit von der Frequenz," *Naturw.*, vol. 35, pp. 285–288; September, 1948.

[19] T. F. Hueter, "Messung der Ultraschallabsorption im menschlichen Schädelknochen und inre Abhängigkeit von der Frequenz," *Naturw.*, vol. 39, pp. 21–23; January, 1952.

[20] D. E. Goldman and T. F. Hueter, "Tabular data of the velocity and absorption of high frequency sound in mammalian tissues," *J. Acoust. Soc. Am.*, vol. 28, pp. 35–37; January, 1956.

[21] H. E. von Gierke, H. L. Oestreicher, E. K. Franke, H. O. Parrack and W. W. von Wittern, "Physics of vibrations in living tissues," *J. Appl. Physiol.*, vol. 4, pp. 886–900; June, 1952.

[22] F. Dunn and W. J. Fry, "Ultrasonic absorption and reflection by lung tissue," *Phys. in Med. and Biol.*, vol. 5, pp. 401–410; April, 1961.

[23] J. J. Wild and J. M. Reid, "The application of echo ranging techniques to the determination of structure of biological tissues," *Science*, vol. 115; pp. 226–230; February, 1952.

[24] D. H. Howry, "Techniques used in ultrasonic visualization of soft tissue structures of the body," 1955 IRE National Convention Record, pt. 9, pp. 75–88.

[25] I. Edler and C. H. Hertz, "The use of ultrasonic reflectoscope for the continuous recording of the movements of heart walls," *Kungl. Fysiogr. Sallsk. I. Lund. Forh.*, vol. 24, NR 5; March 10, 1954.

[26] D. H. Howry, "Techniques used in ultrasonic visualization of soft tissues," in "Ultrasound in Biology and Medicine," E. Kelly, Ed., Amer. Inst. Biol. Sci., Wash., D. C., pp. 49–65; 1957.

[27] S. Satomura, "Ultrasonic Doppler method for the inspection of cardiac functions," *J. Acoust. Soc. Am.*, vol. 29, pp. 1181–1185; November, 1957.

[28] I. Edler and A. Gustafson, "Ultrasonic cardiogram in mitral stenosis," *Acta. Med. Scand.*, vol. 159, pp. 85–90; 1957.

[29] S. Effert and E. Domanig, "The diagnosis of intra-atrial tumors and thrombi by the ultrasonic echo method," *Ger. Med. Monthly*, vol. 4, pp. 1–3; January, 1959.

[30] G. Baum and I. Greenwood, "The application of ultrasonic locating techniques to ophthalmology," *A.M.A. Arch. Ophthalmol.*, vol. 60, pp. 263–279; August, 1958.

[31] J. J. Wild and J. M. Reid, "Progress in the techniques of soft tissue examination by 15 Mc pulsed ultrasound," in "Ultrasound in Biology and Medicine," E. Kelly, Ed., *Amer. Inst. Biol. Sci.*, Wash., D. C., pp. 30–48; 1957.

[32] D. H. Howry, D. A. Stott and W. R. Bliss, "The ultrasonic visualization of carcinoma of the breast and other soft tissue structures," *Cancer*, vol. 7, pp. 354–358; March, 1954.

[33] Y. Kikuchi, R. Uchida, K. Tanaka, and T. Wagai, "Early cancer diagnosis through ultrasonics," *J. Acoust. Soc. Am.*, vol. 29, pp. 824–833; July, 1957.

[34] W. J. Fry, "Intense ultrasound in investigations of the central nervous system," in "Advances in Biological and Medical Physics," J. H. Lawrence and C. A. Tobias, Eds., Academic Press, New York, N. Y., vol. 6, pp. 281–348; 1958.

[35] W. J. Fry, R. Krumins, F. J. Fry, G. Thomas, S. Borbely and H. Ades, "Origins and distributions of several efferent pathways from the mammillary nuclei of the cat," *J. Comp. Neurol.*, to be published.

[36] W. J. Fry and F. J. Fry, "Fundamental neurological research and human neurosurgery using intense ultrasound," IRE Trans. on Medical Electronics, vol. ME-7, pp. 166–181; July, 1960.

[37] W. J. Fry, R. Meyers, F. J. Fry, D. F. Schultz, L. L. Dreyer and R. F. Noyes, "Topical differentia of pathogenetic mechanisms underlying parkinsonian tremor and rigidity as indicated by ultrasonic irradiation of the human brain," *Trans. Am. Neurol. Assoc.*, pp. 16–24; June, 1958.

[38] R. Meyers, F. J. Fry, W. J. Fry, R. C. Eggleton and D. F. Schultz, "Determination of topological human brain representations and modifications of signs and symptoms of some neurologic disorders by the use of high level ultrasound," *Neurology*, vol. 10, pp. 271–277; January, 1960.

[39] W. J. Fry, W. J. Wulff, D. Tucker and F. J. Fry, "Physical factors involved in ultrasonically induced changes in living systems: I. Identification of non-temperature effects," *J. Acoust. Soc. Am.*, vol. 22, pp. 867–876; November, 1950.

[40] W. J. Fry, D. Tucker, F. J. Fry and V. J. Wulff, "Physical factors involved in ultrasonically induced changes in living systems: II. Amplitude duration relations and the effect of hydrostatic pressure for nerve tissue," *J. Acoust. Soc. Am.*, vol. 23, pp. 364–368; May, 1951.
[41] W. J. Fry, "Action of ultrasound on nerve tissue—A review," *J. Acoust. Soc. Am.*, vol. 25, pp. 1–5; January, 1953.
[42] W. J. Fry, W. H. Mosberg, Jr., J. W. Barnard and F. J. Fry, "Production of focal destructive lesions in the central nervous system with ultrasound," *J. Neurosurg.*, vol. 11, pp. 471–478; September, 1954.
[43] J. W. Barnard, W. J. Fry, F. J. Fry, and R. F. Krumins, "Effects of high intensity ultrasound on the central nervous system of the cat," *J. Comp. Neurol.*, vol. 103, pp. 459–484; December, 1955.
[44] W. J. Barnard, W. J. Fry, F. J. Fry and J. F. Brennan, "Small localized ultrasonic lesions in the white and gray matter of the cat brain," *Arch. Neurol. Psychiat.*, vol. 75, pp. 15–35; January, 1956.
[45] W. J. Fry, "Ultrasound in neurology," *Neurology*, vol. 6, pp. 693–704; January, 1956.
[46] H. T. Ballantine, T. F. Hueter, W. J. H. Nauta and D. M. Sosa, "Focal destruction of nervous tissue by focused ultrasound: Biophysical factors influencing its application," *J. Exptl. Med.*, vol. 104, pp. 337–360; September, 1956.
[47] F. J. Fry, H. W. Ades and W. J. Fry, "Production of reversible changes in the central nervous system by ultrasound," *Science*, vol. 127, pp. 83–84; January, 1958.
[48] W. J. Fry, F. J. Fry, R. Meyers and R. C. Eggleton, "The use of ultrasound in neurosurgery," *Proc. Third Internatl. Conf. on Medical Electronics*, to be published.
[49] A. K. Burov, "High intensity ultrasonic oscillations for treatment of malignant tumors in animals and man," *Doklady Akad. Nauk SSSR*, vol. 106, pp. 239–241; January, 1956.
[50] A. K. Burov and G. D. Andrewskaya, "The effect of ultraacoustic oscillations of high intensity on malignant tumors in animals and man," *Doklady Akad. Nauk SSSR*, vol. 106, pp. 445–448; January, 1956.
[51] W. J. Fry and F. S. Brunschwig, "Study of methods for producing uniform high intensity ultrasonic fields," Annual Progress Rept. on Grant G7421 with Natl. Science Foundation, pp. 1–17; July, 1958.
[52] W. J. Fry and F. W. Brunschwig, "Study of methods for producing uniform high intensity ultrasonic fields," Annual Progress Rept. on Grant G7421 with Natl. Science Foundation, pp. 1–17; August, 1960.
[53] R. Krumins, F. J. Fry, W. J. Fry and E. Kelly, "Use of high intensity ultrasound for study of the hypophysis," *Abstracts of Fifth Annual Meeting of the Biophys. Soc.*, St. Louis, Mo.; February, 1961.
[54] R. C. Hickey, W. J. Fry, R. Meyers, F. J. Fry and J. T. Bradbury, "Human pituitary irradiation with focussed ultrasound in advanced breast cancer—An initial report," *AMA Arch. Surgery*, vol. 83, pp. 620–633; October, 1961.
[55] W. Welkowitz and W. J. Fry, "Effects of high intensity sound on electrical conduction in muscle," *J. Cellular Comp. Physiol.*, vol. 48, pp. 435–458; December, 1956.
[56] E. Kelly and W. J. Fry, "Isometric twitch tension of frog skeletal muscle as a function of temperature," *Science*, vol. 128, pp. 200–202; July, 1958.
[57] J. W. Gersten, "Nonthermal neuromuscular effects of ultrasound," *Am. J. Phys. Med.*, vol. 37, pp. 235–236; August, 1958.
[58] R. G. Busnel, J. Gligorijevic, P. Chauchard and H. Mazoue, "Contribution a l'etude des effets et des mechanismes d'action des ultrasons sur le systeme neuro-musculoire," *Der Ultraschall in der Med.*, vol. 6, pp. 1–25; March, 1953.
[59] E. Bell, "Some changes in liver tissue which survives irradiation with ultrasound," in "Ultrasound in Biology and Medicine," E. Kelly, Ed., Amer. Inst. Biol. Sci., Wash., D. C., pp. 203–225; 1957.
[60] E. Bell, "The action of ultrasound on the mouse liver," *J. Cellular Comp. Physiol.*, vol. 50, pp. 83–104; August, 1957.
[61] E. Bell, "Action of ultrasound on adult and embryonic organ systems," *Am. J. Phys. Med.*, vol. 37, pp. 184–191; August, 1958.
[62] J. F. Lehmann, E. J. Baldes and F. H. Krusen, "Destructive effects of high intensity ultrasound on plant tissues" in "Ultrasound in Biology and Medicine," E. Kelly, Ed., Am. Inst. Biol. Sci., Wash., D. C., pp. 177–190; 1957.
[63] K. Woeber, "Studium der wirkung von hyperthermie durch überwarmungsbad, ultrakurzwellen und ultraschall auf krebsgewebe sowie biologische grundlagen einer kombinierten röntgen und ultraschallbehandlung oberflachlicher tumoren," *Strahlentherapie*, vol. 95, pp. 333–366; November, 1954.
[64] K. Woeber, "Die bedeutung des ultraschalls für die dermatologie und seine anwendung bei hauttumoren in kombination mit röntgenstrahlen," *Strahlentherapie*, vol. 98, pp. 169–185; September, 1955.
[65] E. Bell, M. E. Kaighn and L. M. Fessenden, "The role of mesodermal and ectodermal components in the development of the chick limb," *Developmental Biol.*, vol. 1, pp. 101–124; April, 1959.
[66] E. J. Baldes, W. R. Farrall, M. C. Haugen and J. F. Herrick, "A forum on an ultrasonic method for measuring the velocity of blood," in "Ultrasound in Biology and Medicine," E. Kelly, Ed., Amer. Inst. Biol. Sci., Wash. D. C., pp. 165–176; 1957.
[67] D. L. Franklin, R. M. Ellis and R. F. Rushmer, "Aortic blood flow in dogs during treadmill exercise," *J. Appl. Physiol.*, vol. 14, pp. 809–812; September, 1959.
[68] Proceedings of the 4th annual conference on ultrasonic therapy," *Am. Inst. Ultrasonics in Med.*, pp. 41–46; 1955.
[69] "Proceedings of the international conference of ultrasonics in medicine," *Am. J. Phys. Med.*, vol. 37, p. 152–156; June, 1958.