Biological and Medical Acoustics

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RELATIVELY recent investigations show that acoustics has considerable potential value in studies of the structure and function of biological systems. Ultrasonic methods are now proving extremely useful for examining both the macro- and microstructure of such systems. Although gross effects of intense ultrasound on biological systems, such as many of those caused by cavitation, have been known for some time, it is only within the last few years that the development of more precise instrumentation for the production, control, and application of such intense sound has opened up new vistas which indicate that this form of energy will play a major role in the study of biological structures in the immediate future.

Since the application of acoustics in medicine is the result of fundamental research involving (1) the study of the physical mechanism of the action of the sound or the characteristics of its propagation in biological structures (tissue), (2) the determination of the site or sites of interaction in the structure, and (3) the utilization of this knowledge in fundamental studies (experimental animal work), this discussion on some of the unsolved problems in bioacoustics includes all of these aspects.

An acoustic field or acoustic energy may interact with a biological system in a variety of ways. The discovery of the manner in which such interaction occurs results in methods of accumulating information on structure and function in such systems. A single type of interaction or effect may be of predominant importance for a specific dosage range and a specific state of the system. For example, at very low intensity levels absorption or reflection of the sound may constitute the only important interaction of interest. However, at high intensities selective disruption of structure may be the primary effect of interest.

Figure 1 indicates in a simple schematic fashion the relation between fundamental research studies and applications. Everyone is familiar with this relationship but it is exhibited here in this schematic form since it is important to outline in this manner the current status of a number of problems (not an exhaustive list) in bioacoustics which are in various stages of development or solution. The following brief comments are made on the various terms appearing in the boxes of this figure. The term "physical mechanism" refers to the determination of the physical variable or variables which cause the observed effect of interest. For example, increased temperature caused by absorption may bring about the observed change in a biological system. A number of physical variables may be involved in the interaction and the isolation of the important ones may constitute a difficult problem. The term "biological mechanism" refers to the determination of the sites or substructures at which the sound affects or interacts directly with the biological structure (tissue) to produce the effect of interest. For example, intense ultrasound may disrupt weak bonds in giant macromolecules. The term "biological research applications" refers to the use of the interaction or effect to examine biological systems or to produce specific changes in such systems. If changes are produced the system is then examined for subsequent modifications

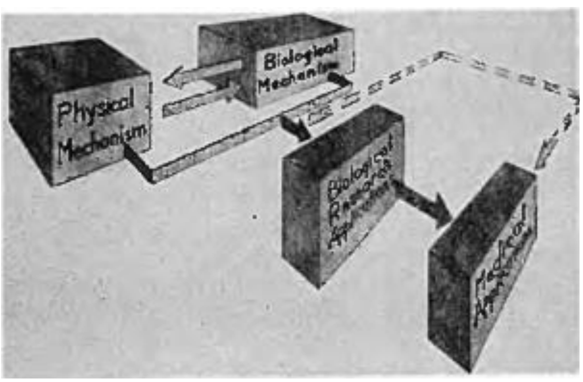

FIG. 1. Relation between fundamental research studies and applications.

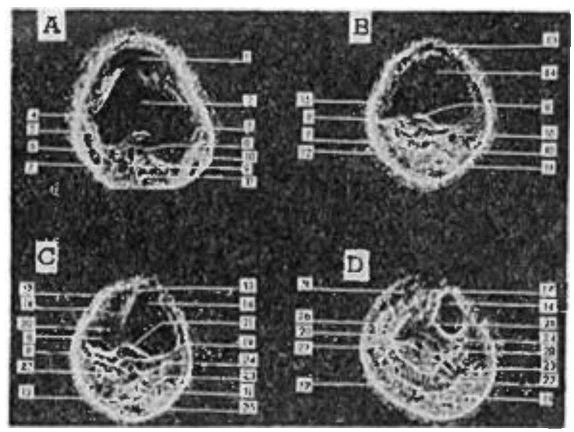

FIG. 2. Serial somagram—left leg. A. Section through mid-patella, B. section 6.33 cm below A, C. section 1.27 cm below B, D. section 10.16 cm below C (mid-calf). 1. Patella, 2. femur, 3. medial epicondyle, 4. lateral epicondyle, 5. gastrocnemius tendon (lateral head), 6. biceps femoris M., 7. plantaris M., 8. popliteal artery, 9. popliteal vein, 10. sartorius M., 11. gastrocnemius M. (medial head), 12. gastrocnemius M. (lateral head), 13. patellar ligament, 14. tibia, 15. biceps femoris M. tendon, 16. semitendinous M. tendon, 17. tibialis anterior M., 18. extensores longi digitorium et hallucis, 19. sartorius gracilis et semitendinous tendons, 20. fibula, 21. tibialis posterior M., 22. soleus M., 23. plantaris M. tendon, 24. popliteus M., 25. small saphenous vein, 26. peroneus longus et brevis, 27. peroneal artery et vein, 28. posterior tibal artery et vein.

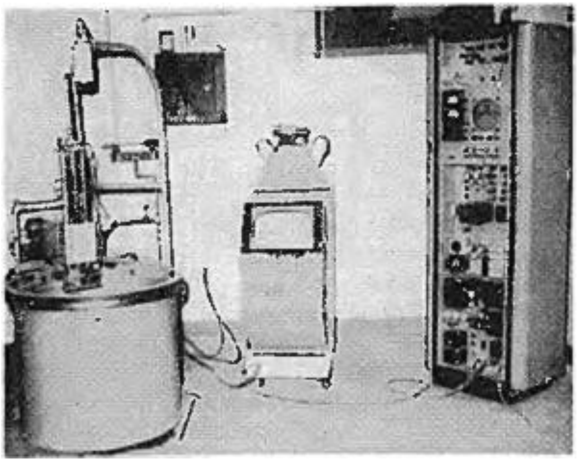

FIG. 3. Dr. Douglass Howry's equipment for the visualization of macrostructure of soft tissue.

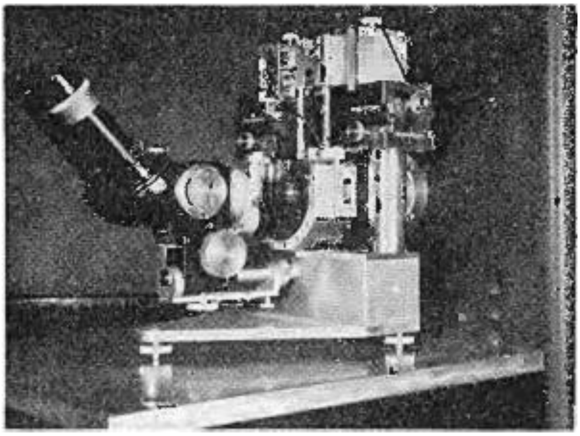

FIG. 5. Closeup view of ultrasonic micrograph. The associated electronic components are housed in the cabinet on the right. The optical microscope is used to locate the general region of tissue to be examined.

in behavior which may be chemical, neurological, psychological, etc.

The problems in bioacoustics to be discussed fall into a number of research fields. Before proceeding, however, I should first like to indicate that no reference is made to problems of ultrasonic diathermy. In the short space available it does not appear fruitful to include this subject although it is applied rather extensively in the practice of physical medicine.

Consider first research on functions of intracellular structures. From a number of recent studies it begins to appear that intense ultrasound may constitute a tool of considerable power for selectively disrupting some such structures. The forces involved in even an intense ultrasonic field are not sufficient to disrupt small molecules (in the absence of cavitation) but they may exert sufficient force on large molecular species to break relatively weak bonds. Such disruption of bonds can be expected to affect drastically the subsequent behavior of the cell. A determination of the sites of action of such intense ultrasound under various ultrasonic dosage conditions and for various states of the tissue may result in medical applications of considerable importance. For example, recent Russian reports on the use of intense ultrasound on tumors indicates that the controlled application of such high level sound constitutes a means of destroying at least some types of malignant neoplasms in humans.[1,2] The sound levels employed by the Russian workers are of the order of 500 w/cm^2 with uniform beams of the order of 50 cm^2 in area. It is reported that such ultrasound can selectively destroy cancer tissue and that successful transplantation of the same type of tumor (Brown-Pierce) to the experimental animal (rabbit) could not be accomplished after irradiation. This implies that a type of immunity to cancer has been produced.

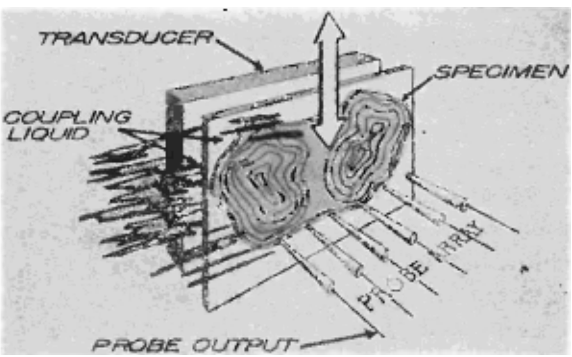

FIG. 4. Principle of ultrasonic micrograph.

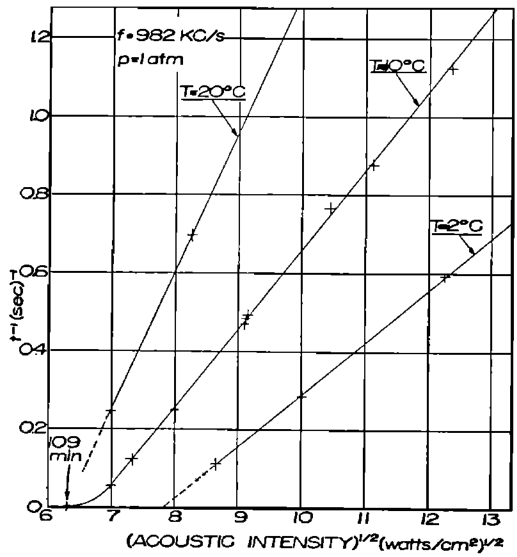

FIG. 6. Ultrasonic dosage curves for young mice at three base temperatures. The lumbar enlargement of the spinal cord is irradiated and paralysis of the hind legs is used as the end point. The reciprocal of the exposure time to produce the desired end point is shown as a function of the square root of the acoustic intensity.

[1] A. K. Burov and G. D. Andreewskaya, Repts. Acad. Sci. U.S.S.R. **106**, 445 (1956).

[2] A. K. Burov, Repts. Acad. Sci. U.S.S.R. **106**, 239 (1956).

FIG. 7. Cross section of cat brain showing localized lesion in the mammillothalamic tract.

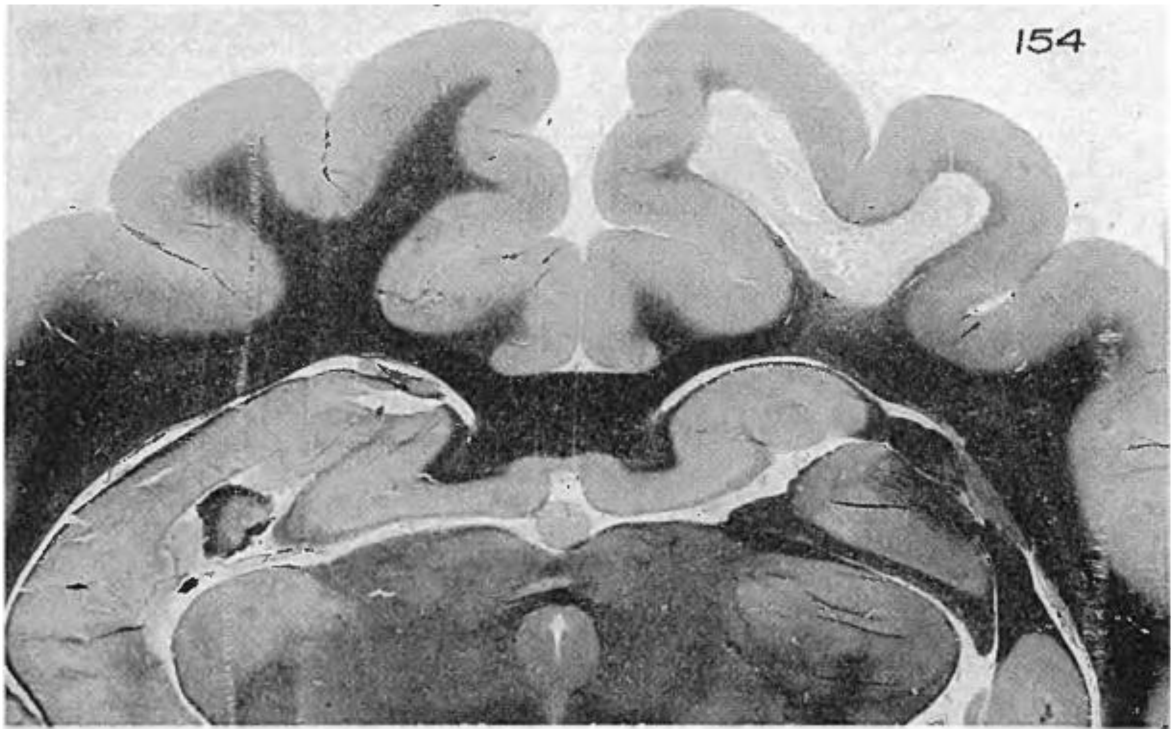

FIG. 8. Subcortical lesion in white matter produced by multiexposure of focused ultrasound.

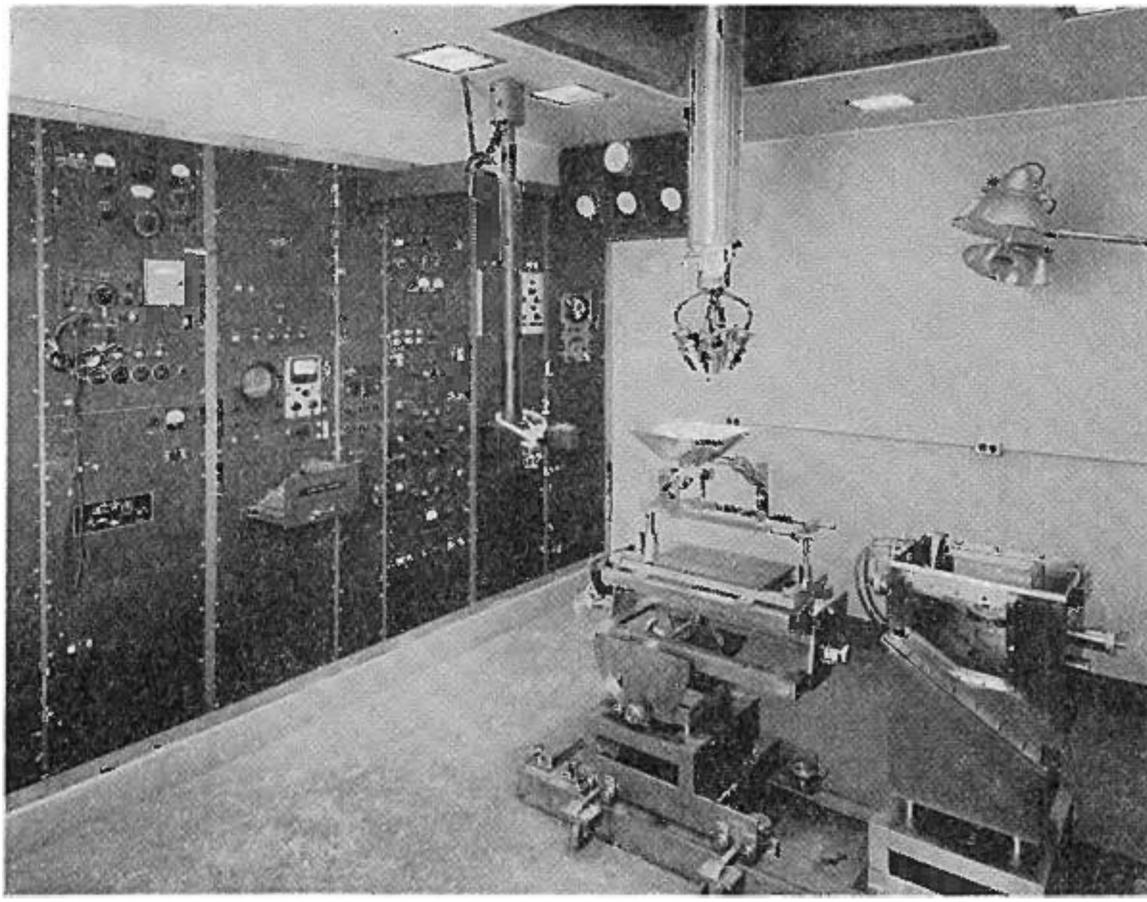

FIG. 9. Apparatus for precision ultrasonic irradiation of tissue (central nervous system) at high sound levels. A 4-beam focusing transducer is shown supported on a tube which projects through the ceiling of the irradiation room. This tube is moved about by a positioning system housed in the room above. The apparatus shown below the transducer is a holder for supporting the head of the animal (in any desired orientation) with a metal container positioned over the skull. This metal container supports the degassed sterile liquid which is used as the medium to transmit the ultrasound from the focusing transducer to the brain. At the right of the animal holder a calibration tank is shown. The 4-beam transducer dips into the degassed water of this tank and the acoustic output and field pattern are determined by utilizing a thermocouple probe mounted in this tank. The control panels on the left center of the picture provide controls for positioning, determination of ultrasonic dosage, observation of electrical activity of the central nervous system and other auxiliary instruments. Closed circuit television systems permit the positioning of the focus of the transducer by exhibiting on picture tubes a portion of the scales mounted on the positioning system in the room above.

They also report that the highly malignant tumor melanoblastoma has been treated in humans with very encouraging results. Much further work is necessary in this field, in particular the effects of intense ultrasound under a variety of dosage conditions on a variety of types of tumors must be investigated.

The cancer application represents only one aspect of the study of function of intracellular structures by acoustic means. Work in this field is in the very early stages but it already appears to have considerable implications.

We consider now the macrostructure of soft tissue. By observing the fact that tissue structure is not homogeneous and therefore might be expected to reflect at least a small fraction of ultrasonic energy incident upon it, a number of investigators have been developing methods of visualizing soft tissue structure by reflected ultrasonic pulses.[3,4] By the use of pulses in the megacycle frequency range it is possible to realize good resolution and to obtain enough reflected energy to "see" considerable detail in the soft tissue structure. No other method can yield this type of information at the present time. The method and instrumentation have been developed to the stage where preliminary clinical tests are being carried out for some body sites. This tool will be extremely useful in medical diagnosis in, for example, location of tumors and in studies of the vascular system. The type of detail which can be realized is illustrated in Figure 2 which shows a series of ultrasonic cross-sec-

[3] D. H. Howry, *Ultrasound in Biology and Medicine*, E. Kelly, editor (American Institute of Biological Sciences, Washington, D. C., 1957), p. 49.

[4] J. J. Wild and J. M. Reid, *Ultrasound in Biology and Medicine*, E. Kelly, editor (American Insitute of Biological Sciences, Washington D. C., 1957), p. 30.

tional views of a human leg. The tendon and muscle tissue interfaces are clearly shown. The bones are sharply outlined and major blood vessels can be seen. This photograph is one of Dr. Douglass Howry's and was made with his equipment which is illustrated in Fig. 3. Many problems remain for study in this field, in particular the mechanism of reflection of the sound as related to the type of tissue structure. *This area of investigation contains the possibilities for tremendous advances in the near future.*

We consider now the use of sound waves as a tool for elucidating microstructure of cells. Research in this area is in a very early stage. Measurements of ultrasonic absorption coefficients of proteins in solution indicate that absorption by these components may account for a large fraction of the absorption in soft tissue structures.[5] The absorption coefficients can be expected to be a function of the size and geometrical configuration of the protein molecules and the manner in which they are incorporated into the structure. Only a couple of proteins have been quantitatively studied so far. It is conceivable that information on the structural distribution of proteins in cells might be obtained by ultrasonic methods. This requires investigation. One method of looking for such distributions is to construct an ultrasonic microscope or micrograph. The principle of operation of one such device is illustrated in Fig. 4. A source of plane waves is coupled by a water solution to the specimen. Some of the ultrasonic energy is absorbed and the remainder passes through the specimen and excites a small probe placed immediately adjacent to the region under examination. A linear array of such probes can yield a two-dimensional "picture" of the structure if the specimen is oscillated or moved in a direction at right angles to the line of the array. To determine experimentally the type of structural detail which can be seen in a biological system a first model of such a micrograph, utilizing a single probe, has been constructed and is illustrated in Fig. 5. This illustration does not include either the electronic driver or the presentation system. Continuation of work along such lines may well lead to an ultrasonic microscope which is capable of differentiating such important aspects of cellular structure as the protein distributions which are completely undetectable directly by other types of microscopes.

Intense focused ultrasound has recently become an important tool for use in studies of the central nervous system. Accurately controlled reproducible, irreversible, selective changes can be produced with precision instrumentation.[6] It is now known that these changes are not the result of heating, but it also appears that much further investigation will be required before the physical

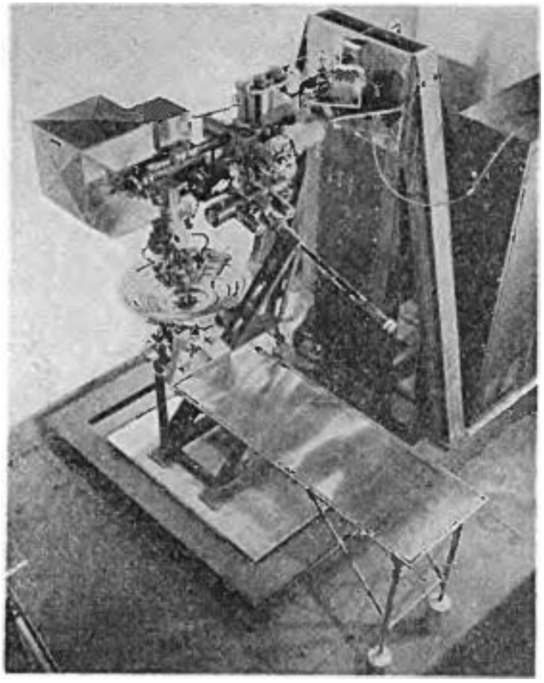

FIG. 10. Transportable equipment designed for human neurosonic surgery.

mechanism will be understood.[7,8] Quantitative dosage studies, which constitute the basis upon which a picture of physical mechanism can be built, are in progress and the type of results obtained can be illustrated by the relations in Fig. 6. Here the reciprocal of the exposure time required to produce a given functional change in the animal (paralysis of the hind legs of the young mouse following irradiation of the lumbar enlargement of the spinal cord) is shown as a function of the square root of the intensity for three base temperatures of the animal. Such dosage relations can be reproduced with an accuracy of 1% to 2%. Much further work is necessary in order to determine a series of such relations as a function of irradiating frequency, base temperature, and hydrostatic pressure, etc.

With respect to biological mechanisms much work has already been accomplished and it is clear that the neural components of the central nervous system can be selectively destroyed by intense ultrasound while the vascular system can be left intact and functioning.[9–11] Focusing of the beam prevents damage to intervening tissue. These results plus the fact that the nerve fiber tracts are more sensitive to the action of the sound than the nerve cell body regions make focused ultra-

[5] E. L. Carstensen and H. P. Schwan, *Ultrasound in Biology and Medicine*, E, Kelly, editor (American Institute of Biological Sciences, Washington D. C., 1957), p. 1.
[6] W. J. Fry, Neurology **6**, 693 (1956).
[7] Fry, Wulff, Tucker, and Fry, J. Acoust. Soc. Am. **22**, 867 (1950).
[8] W. J. Fry and F. Dunn, J. Acoust. Soc. Am. **28**, 129 (1956).
[9] Fry, Mosberg, Barnard, and Fry, J. Neurosurg. **11**, 471 (1954).
[10] Barnard, Fry, Fry, and Krumins, J. Comp. Neurol. **103**, 459 (1955).
[11] Ballantine, Hueter, Nauta, and Sosa, J. Exptl. Med. **104**, 337 (1956).

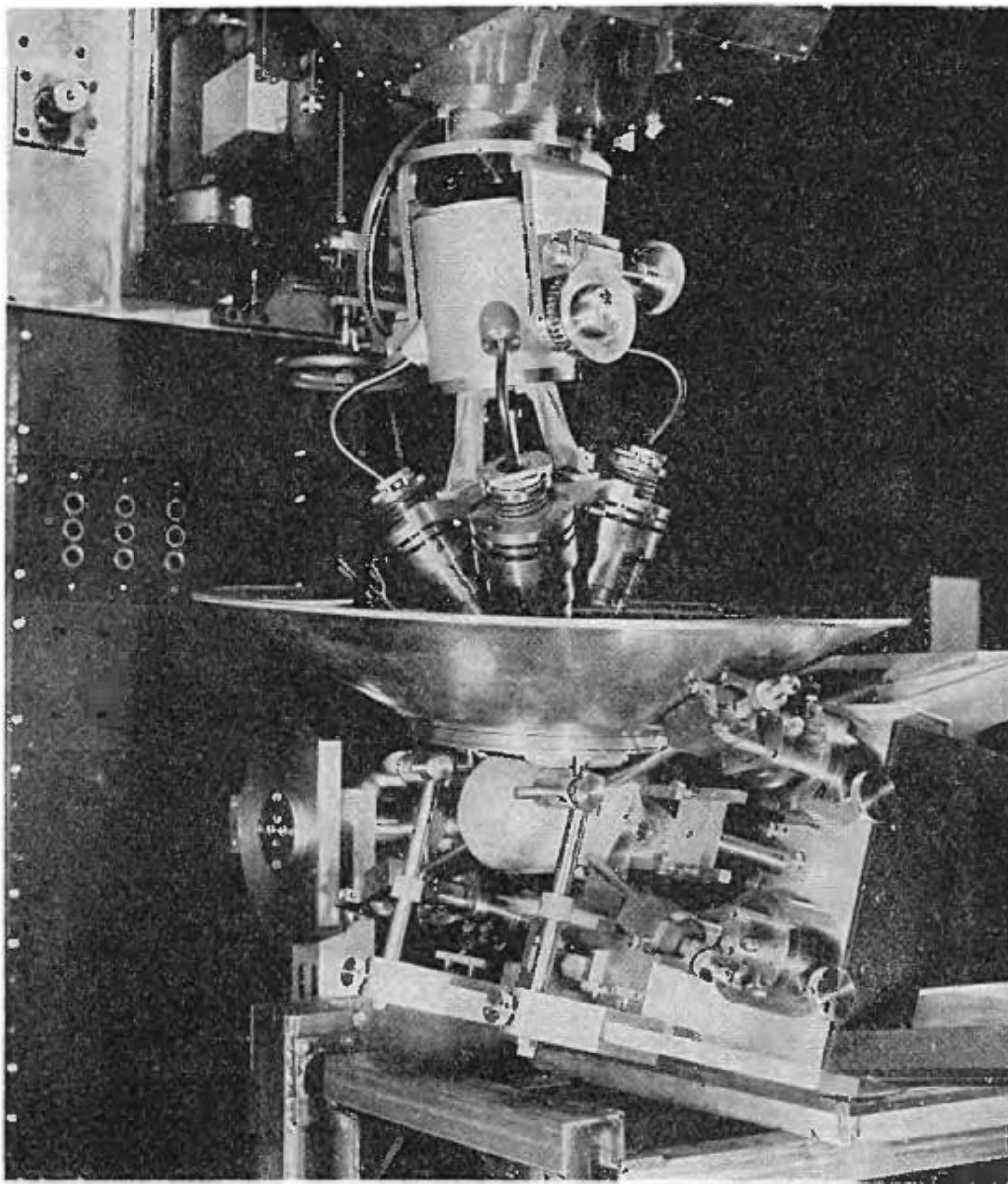

FIG. 11. Closeup view showing a human skull mounted in the head holder. The pan which supports the transmitting liquid is shown in position immediately above the skull. The 4-beam irradiator is positioned over the pan. The configuration illustrated will be that used for the first high level focused, precision, ultrasonic human neurosurgery.

sound a powerful tool for investigating the anatomy and physiology of the central nervous system. The next two figures illustrate such selective fiber tract destruction in the brain. Figure 7 shows the selective destruction of the mammillothalamic tract deep within the cat brain. No destruction of intervening tissue occurred. Figure 8 shows the selective destruction of the subcortical white matter in a cat brain produced by multiple exposures to focused ultrasound. Instrumentation used in such studies is shown in Fig. 9. *This tool* is ready *for investigating* the *brain* but its widespread application is, to a considerable extent, dependent upon the entrance into the field of more investigators with experience in acoustics.

Human neurosurgery by ultrasound is just beginning. This is expected to be a very important medical application in the immediate future. Figures 10 and 11 illustrate portions of a type of instrument which can be used in such surgery.

Recent work also demonstrates that intense ultrasound can also be used to produce reversible changes in the central nervous system.[12,13] From the work already

[12] F. J. Fry, Abst. Natl. Biophys. Conf. p. 30 (1957).
[13] Fry, Ades, and Fry, Science 127, 83 (1958).

accomplished it is clear that three-dimensional mapping of brain function of a type and power heretofore completely unattainable will be possible by sweeping focused beams of ultrasound through the tissue and observing the resultant changes. Such studies will aid in the elucidation of structure, pathways of communication, and temporal relations in the central nervous system. I would like to illustrate the type of result which has been obtained by a single example. By subjecting the eye of a cat to a flash of light or stimulating the optic nerve electrically an evoked electrical potential is obtained in the visual cortex. Such electrical potentials may exhibit a series of peaks of different magnitudes. Figure 12 shows a mapping of one type of reversible change obtained by focusing the sound into the region of the lateral geniculate nucleus of the left side of the brain during stimulation of the eyes with flashes of light. This nucleus is a site of synaptic junctions along the visual pathway. Reversible suppression of the second peak of the evoked potential is the basis of the map. The electrode position at which these changes occurred is indicated by the black dot. The magnitude of the suppression is dependent upon the position of the focus of the ultrasonic beam and the figure shows a contour map of the magnitude of the depression. Examples illustrating the types of records obtained in various regions of the mapping are shown on the right-hand side. This method has tremendous potential value for fundamental research on the central nervous system. The method will also be extremely useful in medicine; for example, it could be used to locate sites at which irreversible changes are to be effected in the human brain.

Another area of investigation in which acoustic methods are useful is concerned with what I have labeled "biological organ mechanics." This might be considered as included in the field "macrostructure of soft tissue" but it has been separated here to emphasize the dynamic aspects. Reflected ultrasound may be used, as in the case of the ultrasonic visualization of macrostructure, but in this case we are interested in the movements of the tissue. One Japanese study which is currently in progress utilizes the Doppler effect on the reflected ultrasonic pulses from the moving tissue surfaces.[14] Instrumentation has been developed for preliminary clinical testing of cardiac function. This method would appear to have considerable potential value in diagnosis of cardiac disfunction and disturbances to the vascular system.

[14] S. Satomura, J. Acoust. Soc. Am. 29, 1181 (1957).

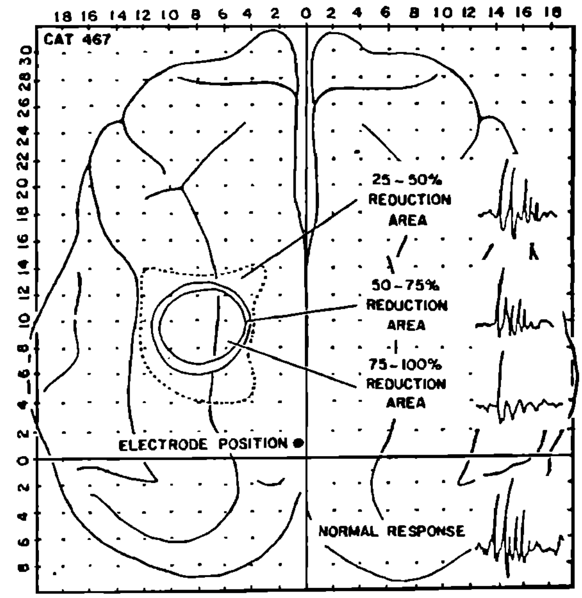

FIG. 12. Reduction by ultrasound, focused in the lateral geniculate region, of the second peak of the evoked cortical potential to photic stimulation.

I would like to conclude this brief survey of some of the partially solved and unsolved problems in biological and medical acoustics by observing that sound produced, controlled, and utilized under precisely controlled conditions with precision instrumentation constitutes an extremely powerful tool for investigating biological systems and for use in medicine. Unfortunately, the research areas discussed in this paper have not yet caught the imagination of many investigators. It is not unusual to find only one or two laboratories investigating a field which might well occupy the efforts of a score of laboratories. Contrast this with the present activity in the field of x-ray and radiation as applied to fundamental studies of biological systems. Let us hope that the potentialities of the area of bioacoustics, briefly reviewed here, will be recognized on a much larger scale in the immediate future.