Fundamental Neurological Research and Human Neurosurgery Using Intense Ultrasound*

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Summary—**Focused high intensity ultrasound can be used, under accurately controlled dosage conditions, to produce either temporary or permanent changes in practically any desired brain structure. Volumes of tissue smaller than one tenth of a cubic millimeter can be affected in deep brain structures of experimental animals (cats and monkeys), and regions as large as desired can be changed by moving the focal spot of the ultrasonic beams through an appropriately chosen path. The changes can be induced without adversely affecting intervening brain structure and without interrupting the vascular system even within the site in which irreversible or permanent changes in the neural components are produced. The selectivity and absence of effects on the intervening tissue make focused ultrasound a tool of considerable power for investigating basic brain mechanisms. It is now being used in an extensive experimental animal program involving neuroanatomical, behavioral and physiological studies. It is also being used to study and modify the symptoms of various neurological disorders in humans. The signs and symptoms which have been and are under investigation in human patients at the present time include abnormal movements (tremor and nonpatterned), muscular rigidity), intractable pain (following amputations, cerebral vascular accidents, the acute phase of herpes zoster) and hypersensitivity to stimulation of the body surface.**

This paper includes brief descriptions of the instrumentation which has been developed for this type of fundamental neurological research and medical applications, the techniques of preparation and irradiation of the experimental animal and human patient, the types of research results which are obtained from experimental animal studies in which the ultrasonic dosage parameters are chosen for producing either irreversible or reversible changes, the results obtained from producing arrays of ultrasonic lesions in deep brain structures of patients suffering from various neurological disorders, and the present status of investigations of the physical mechanism of the action of the intense sound on the tissue.

Introduction

An ULTRASONIC field may interact with a biological system in a number of ways. The discovery of the manner in which such interactions occur results in methods of accumulating information on the structure and mechanisms of operation of such systems and, in some instances, in ways of modifying their structure and functions. A single type of interaction or effect may be of predominant importance for a specific range of irradiation parameters and a specific state of the system. For example, at low intensities, ultrasonic absorption or reflection may constitute the most important interaction of interest.

At high acoustic energy levels the selective permanent disruption of components of tissue structure and function may be the objective. Or, on the other hand, temporary interruption of function may be the primary effect of interest. These objectives obtain when high level ultrasound is used to study the microanatomy and modify the mechanisms of operation of the central nervous system. The discovery of specific interactions of high level focused ultrasound with tissue, which make it especially useful in studies of neuroanatomical structure and in investigations of brain mechanisms and their modification, has resulted from extensive experimental animal research carried out and reported during the past ten years by members of this laboratory [1]-[21]. This research has established the following: 1) Permanent changes confined to arbitrarily specified regions of predetermined shape, size, and orientation can be produced at almost any site in the brain without disrupting intervening tissue [6]-[9]. 2) By appropriate choice of the parameters of irradiation, it is possible to produce either reversible (temporary) [17], [20], [21] or irreversible (permanent) [1]-[4], [6]-[20], [22] changes in the tissue. 3) The blood vessels within the region in which the changes are produced can be left intact and functioning even when all neural elements are destroyed [1], [2], [6]-[11], [13]-[15]. 4) Fiber tracts (nerve fibers) of white matter can be interrupted without damaging the neural elements of neighboring or surrounding gray matter (regions of nerve cell bodies) which receives a dosage of ultrasound equal to that received by the white matter [6]-[11], [13], [15], [22]. 5) Mortality and morbidity are rare if brain structures not involved in maintaining a responsive (awake) state are not irradiated to produce permanent changes. 6) No evidence for the existence of long-term cumulative effects, comparable to those produced by X-rays and high energy particle radiation, exists [10], [11], [17], [20], [22]. 7) Some evidence exists to indicate that the myelin sheaths are more sensitive to the action of the sound than the nerve axis cylinders which they surround [8], [11], [15]. As a result of these discoveries, intense focused ultrasound is now being employed in neuroanatomical, neurophysiological and behavioral investigations employing experimental animals [22]. In addition, ultrasonic human neurosurgery of deep brain struc-

* Received by the PGBME, January 6, 1960. Presented in part at the Twelfth Annual Conf. on Electrical Techniques in Medicine and Biology, Philadelphia, Pa., November 10-12, 1959.

Figs. 1-4, 6-9, 12, 13, 15, 16, and 18-20 taken from "Intense ultrasound in investigations of the central nervous system," in "Advances in Biological and Medical Physics," Academic Press, New York, N.Y., vol. 6; 1958. Figs. 5 and 10 taken from *Am. J. Phys. Med.*, vol. 37, p. 152; 1958. Figs. 14 and 17 taken from *Am. J. Phys. Med.*, vol. 37, p. 148; 1958.

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tures has been in progress for the past two years as a collaborative effort between the Biophysical Research Laboratory of the University of Illinois and the Division of Neurosurgery of the State University of Iowa [23]-[26].

In this paper an attempt will be made to describe briefly the instrumentation which has been developed for this type of research and medical applications, the techniques of preparation and irradiation of the experimental animal and human patient, the types of research results which are obtained from experimental animal studies in which the ultrasonic dosage parameters are chosen for producing either irreversible or reversible changes, the results obtained from producing arrays of ultrasonic lesions in deep brain structures of patients suffering from various neurological disorders, and the present status of investigations of the physical mechanism of the action of the intense sound on the tissue.

Instrumentation, Technique of Preparation and Irradiation

Experimental Animal

In order to produce changes in deep brain structures without disruption or disturbance to the intervening tissue through which the ultrasound must travel, it is essential that the sound beam(s) be focused. By irradiating at an array of positions—by moving the focus of the beam—it is possible to produce lesions of complex shape and large size [6]-[9], [13], [22]. The wavelength of the sound and the angle of convergence of the ultrasonic beam or beams are the important factors which determine the minimum size of region which can be affected and consequently the degree of complexity of shape of larger regions which can be affected without corresponding effect on neighboring tissue. The design of the ultrasonic irradiator is thus of primary importance. The minimum dimensions of the focal region, which can be realized in the tissue, decrease as the frequency increases since the wavelength is an important determining factor. At a frequency of 1 mc the wavelength of sound in brain tissue is 1.55 mm [41] at 37°C, and at this frequency it is readily possible to produce lesions involving only a couple of cubic millimeters of tissue. Most of the reported experimental animal work and the human neurosurgery that have been accomplished using focused ultrasonic beams have employed this frequency [6]-[11], [14], [15], [19], [24]-[27]. However, some work has been accomplished at higher frequencies, at 2.5 mc [28], [29] and at 4 mc.[1] At the latter frequency the effects of interest can readily be restricted to volumes of tissue less than 0.05 cubic mm.

An upper limitation is imposed on the frequency by the thickness of tissue which must be penetrated in order to reach the desired site. This follows because the ultrasonic absorption coefficient per unit path length of brain tissue is directly proportional to the frequency (the average value of the intensity absorption coefficient per unit path length for the adult mammalian brain at normal body temperature is approximately 0.20 per cm at 1 mc [22]. Thus, the upper limitation is imposed by the fact that the sound level must be lower along the path through the intervening tissue than it is in the focal region itself. The results which have been obtained on reversible effects indicate that a maximum permissible sound intensity (square of the pressure or particle velocity amplitude if intensity is not appropriate for describing the field) one-tenth the value at the focus is an appropriate criterion.

One type of focusing irradiator which has received extensive use in this laboratory is the multibeam instrument illustrated in Fig. 1(a) [6], [13], [30]. This irradiator employs four individually focused beams of ultrasound. The sound is produced by circular X-cut quartz crystal plates vibrating in thickness mode. Spaced a short distance in front of each crystal plate is a lens (polystyrene has been used most extensively) which focuses the acoustic energy. The electroded face of the crystal adjacent to the lens is maintained at the electrical potential (ground) of the stainless steel housing which supports both. The coupling material between lens and crystal is castor oil. The irradiator housings are provided with tilt adjustments to permit the individual beams to be brought into coincidence in a common region and with phase adjustments to permit maximizing the sound level in this region of intersection. The tip of the retractable pointer, illustrated in the figure, is adjusted so that in the lowered position it coincides with the midpoint of the focal region. This pointer permits placing the common focus of the beams at desired sites with respect to landmarks on the instrument. A second type of focusing irradiator [22], [30], [31], is illustrated in Fig. 2. As can be seen from the schematic diagram of Fig. 2(a), the sound is again produced by a crystal plate vibrating in thickness mode. It is then reflected with a uniform angular distribution in all directions at right angles to the axis of the irradiator by a cone with an apex angle of 90°. Finally, a parabolic reflector focuses the acoustic energy. An important advantage of the reflector type of irradiator as compared with the present multibeam lens type is that the side lobes of the beam, in the focal region, of the reflector irradiator are considerably reduced over those characteristic of the multibeam irradiator. This is important, since it is essential that changes induced by the sound be restricted to the tissue irradiated by the main beam. It has been necessary to employ with the present designs of reflector irradiators, as compared with that required for the multibeam lens designs, a larger cone of convergence of the acoustic energy to obtain focal regions of equal size. This represents a disadvantage of the reflector irradiator, since it is then more difficult, in some cases, to prepare appropriate skull bone openings to admit the converging sound when deep structures are to be irradiated. The advantage of the multibeam lens design—that is, short length of focal region for a given cone of convergence—can be at least partially realized together with the advantage of the low side

[1] Unpublished work of this laboratory.

lobes exhibited by the reflector irradiator by designing transducers to employ a single lens with an aperture and cone of convergence equal to that of a multibeam instrument. The use of quartz crystal plates in such an irradiator would require that the transducer be constructed in the form of a multicrystal array. Future work, requiring continuous operation at high power levels, will make it necessary to develop transducers utilizing materials other than plastics for lenses. The lens irradiators used at present produce high power pulses of ultrasound of relatively short duration—two to three seconds at the highest sound levels (particle velocity amplitudes up to 400 cm/second employed at a frequency of 1 mc). Such pulses are used to induce requisite changes in the tissue where an array of temporally spaced exposures is used. Plastic lens materials such as polystyrene overheat and suffer mechanical flaws if transducers employing them are operated continuously at the highest power levels in order to *sweep* the focus of the beam through the tissue.

The high intensity ultrasound is conducted from the irradiator to the brain by degassed saline—physiological salt water. This liquid differs only slightly—approximately 2 per cent—in its characteristic acoustic impedance (product of the density of the medium and the velocity of sound in

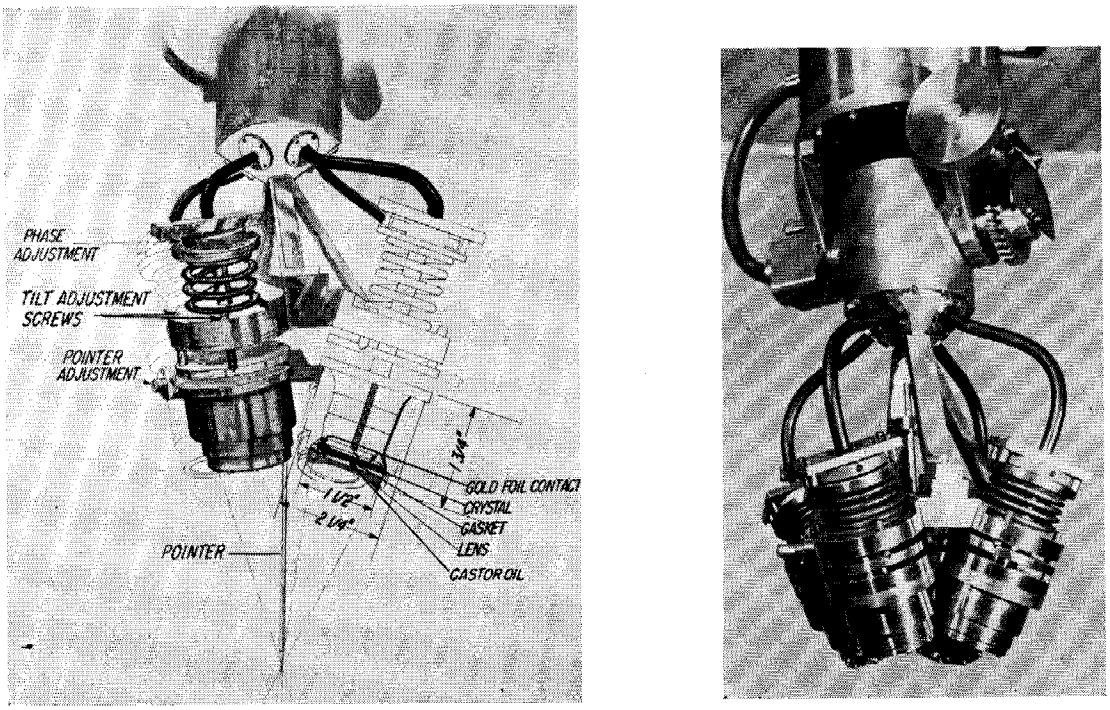


Fig. 1—(a) Schematic diagram of multibeam focusing (animal) irradiator. (b) Multibeam focusing irradiator.*

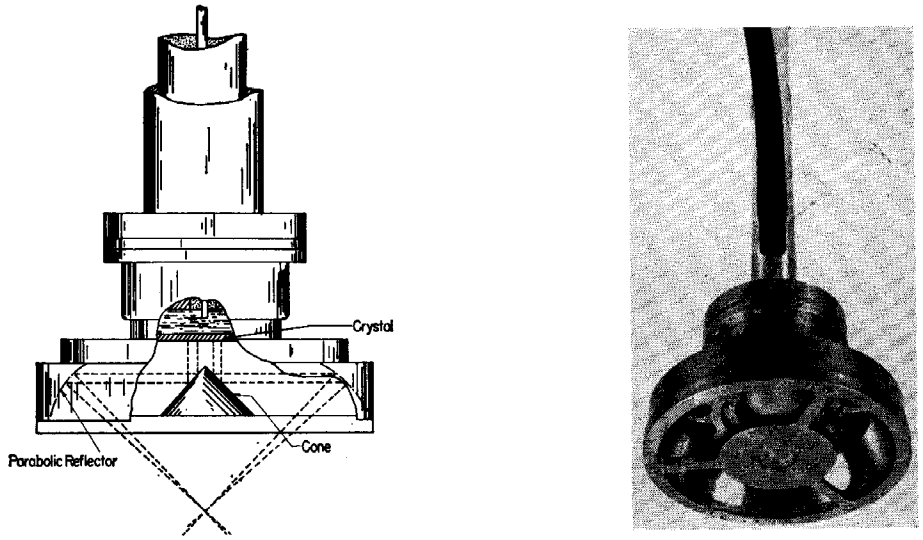


Fig. 2—(a) Schematic diagram of reflector focusing irradiator. (b) Reflector focusing irradiator.*

the medium) from that of brain tissue. Consequently, it is not necessary in determining the dosage parameters to correct it for the small fraction of the incident acoustic energy which is reflected at the interface between the saline and the tissue. The sound velocity in physiological saline at a temperature of 37°C is $1.537(10)^5$ cm/second while that in brain tissue at the same temperature is approximately $1.55(10)^5$ cm/second as estimated from data available for hog and dog brain [41]. Thus, refraction of the sound at the interface between the saline and the brain tissue, for angles of incidence at this interface as large as 45°, can produce a shift lateral to the axis of propagation, of the focal spot, from its position in saline, of approximately two-thirds of a millimeter for the greatest depths in the human brain (11 to 12 cm). Experimental determination of the magnitudes of such shifts for freshly excised brains are in approximate agreement with these calculations which therefore constitute a measure of the accuracy of "geometric positioning" of the focus—that is, placement accuracy with respect to a reference coordinate system—if refraction shifts are not taken into account in positioning the beam [22]. The shape and size of the focal region, after the sound passes through the entire thickness of the brain, are practically identical with the shape and size when the sound passes entirely through saline. The multiple interfaces within the brain reflect only a very small fraction of the incident acoustic energy, and scattering does not interfere with the production of results of the type described here. The saline, which transmits the sound, must be degassed to eliminate cavitation nuclei which produce bubbles when subjected to the tension forces of the intense acoustic field. Bubbles cannot be tolerated since they interfere with the transmission of sound by scattering and absorbing the acoustic energy. Freshly boiled saline is a suitable medium, at a hydrostatic pressure of one atmosphere, for transmitting ultrasound at a frequency of 1 mc and at body temperature up to a maximum intensity of approximately 8 kw/cm^2 [22], [32]. The tissue of the central nervous system is either free of cavitation nuclei or, if the nuclei are present, they are unable to grow under the ultrasonic dosage conditions of interest here.

Bone, present in the path to be traversed by the converging sound beams, must be surgically removed since it has a high ultrasonic absorption coefficient [33] which would result in heating to cause damage to underlying cortex. In addition, the acoustic velocity and impedance of bone [34] differ so much from those of brain tissue that the nonuniform thickness and variable radii of curvature of the skull would cause both undesirable modification of the beam shape and difficulties in precision positioning.

In current experimental animal work, the transmitting liquid is supported by a coupling hopper of the type illustrated in Fig. 3. A wire tourniquet secures the skin of the animal tightly against the flanged bottom of the hopper and thus assures a watertight seal. In the experimental animal work accomplished up to the present, the irradiation sequence is performed at the time the bone flap is removed. Since the dosage of the ultrasound required to produce a given change in the tissue is a function of the temperature, it is necessary that the transmitting liquid be maintained at a constant temperature during the experiment especially if tissue close to the saline interface is irradiated. The maintenance of the saline bath at a given temperature is accomplished by circulating a heat exchange liquid through coils within the hopper (Fig. 3). The clamps shown in the interior of the coupling unit are provided to permit mounting of electrodes for recording and/or stimulating during irradiation.

A head holder illustrated in Fig. 4 is provided to support the skull of the experimental animal and the coupling pan rigidly. For cats and monkeys a structure utilizing the usual fixtures—ear bars, infra-orbital and oral clamps—is employed. Before the anesthetized animal is placed in the head holder, the irradiator is positioned so that the tip (tip coincident with the position of the center of the focal region) of an attached pointer lies on the midline of the head holder and on the line through the center of the ear bars. When this is accomplished, the coordinate readings on the positioning system, which supports the irradiator, are recorded. One can then transform from the coordinates of brain structures given in atlases [35], [36] based on the

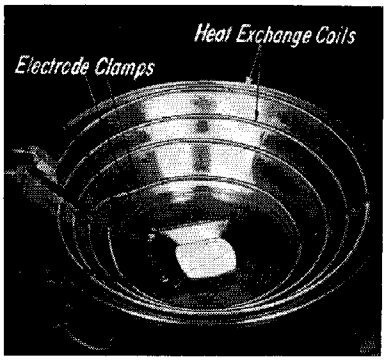


Fig. 3—Top view of coupling pan (animal).*

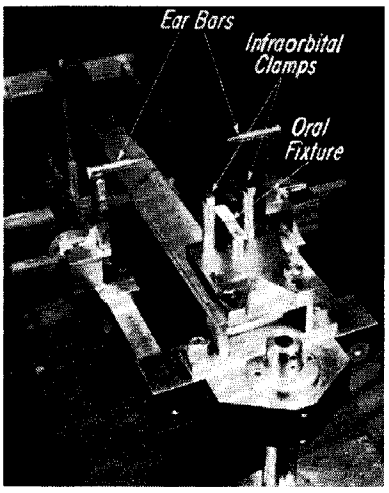


Fig. 4—Experimental animal head holder (for cats and monkeys).*

ear bar midpoint as the zero reference to the coordinates, of the same structure, on the irradiator positioning system.

After the coordinates of the ear bar midpoint are determined, the pointer is retracted or removed from the irradiator and the anesthetized animal is mounted in the holder. In order to improve upon the accuracy of positioning using the ear bar zero as the reference, X-ray views of the animal's head, mounted in the holder, are now employed at this laboratory. Both lateral and vertical roentgenograms are taken to reveal internal bony landmarks whose use permits the attaining of greater accuracy of positioning of the focus of the sound beam(s) with respect to deep brain structures. Placement errors are, in some cases, reduced by a factor of approximately five. In order to accomplish this increased precision, it is essential that the X-ray film cassettes be placed in reproducible positions with respect to the head holder when the roentgenograms are taken. This is accomplished by providing the cassettes with guide pins which bring them into the same positions on the head holder each time. In order to take account of the divergence of the X-ray beams, appropriate scaling factors are used in computing the positions of the various landmarks from measurements made on the films. After the roentgenograms are taken, the soft tissues are incised and a skull cap of appropriate position, shape and size is removed. The dura mater need not be opened. After the coupling pan is engaged in watertight connection with the skin of the animal, it is filled with degassed sterile physiological saline in a manner which prevents the introduction of bubbles which would introduce gas nuclei into the liquid. The irradiator (immersion sterilized) is then moved into position to place the focal region at the position in the brain to be irradiated first.

Although a number of different designs for the carriage unit which supports the irradiator are feasible, it is especially convenient to use the type illustrated schematically in Fig. 5, which has evolved as a result of previous experience with other positioning systems [30]. The diagram shows the irradiation instrumentation in the form of a double-deck arrangement. The upper deck or room houses the motor-driven positioning system which supports and moves the irradiator. (Three rectangular degrees of freedom and one rotational motion are provided.) The lower room contains the structure for supporting the head of the animal, the calibrating system for determining the ultrasonic dosage parameters, equipment for controlling the positioning system, apparatus for recording the responses of the animal (including electrical changes in the brain), and stimulating instruments of a variety of types. The positioning of the irradiators is facilitated by employing closed circuit television systems to view the scales on the positioning system and to provide magnified images (approximately 20 ×) of these scales in the irradiation room. Speed controls provided in the irradiation room permit the focus of the transducer to be moved at a variety of speeds through the tissue structure. The positioning unit housed above the irradiation room is illustrated in Fig. 6. The photograph shows

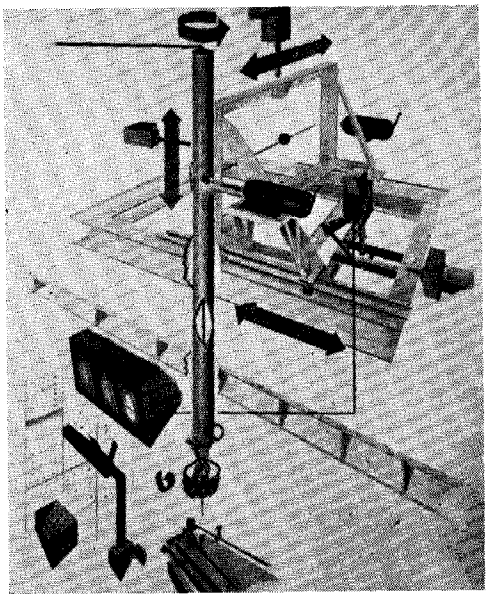


Fig. 5—Schematic diagram of ultrasonic irradiation rooms.*

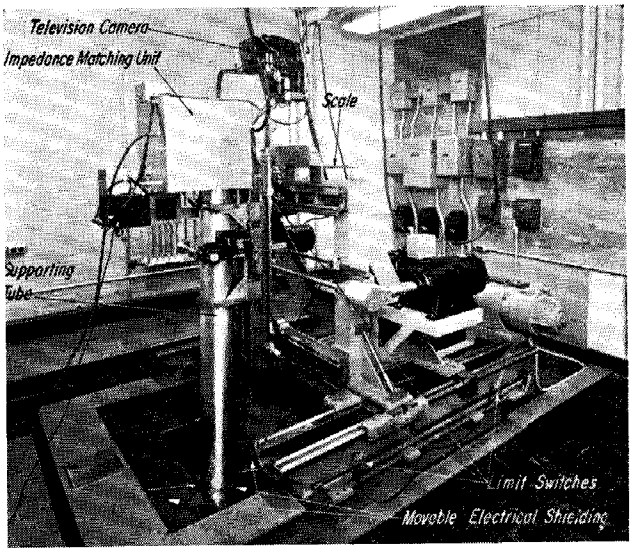


Fig. 6—Carriage unit for supporting and moving the irradiators. The tube which supports the transducers is shown passing through the movable shield, at floor level, to project into the irradiation room below.*

the tube which projects through the ceiling of the irradiation room to support the transducer, the continuously variable motor drives for moving the tube, the adjustable limit switches which restrict the range of motion of the irradiator, the television cameras for viewing the scales mounted on the positioning system, and the electrical coupling unit which matches the impedance of the driver to the transducer.

A stepwise irradiation procedure has been used in most of the work accomplished to the present time. In such a procedure, the tissue is irradiated with the focal region of the irradiator in a stationary position. After the exposure at a position is completed, the carriage unit is moved so that the focal region is placed at the next position at which an exposure is desired. The successive positions of the fo-

cal regions are made to overlap, and the time interval between exposures at such adjacent positions is kept constant when uniform selective changes are desired in contiguous volumes of tissue larger than that covered by the focal region placed in a single position.

The support tube passes into the irradiation room through a movable electrical shield which is continuous with the shielding of that room. This shielding is provided so that low level electrical measurements can be carried out on the nervous system during irradiation.

In the photographic illustration of the irradiation room (Fig. 7), the animal head holder is shown mounted on a table which provides two rotational degrees of freedom. This table is designed to ride on the positioning track seen in the figure. The photograph also shows, mounted in the wall of the room, the electrical equipment necessary for calibration, frequency control, adjustment of time duration and acoustic parameters of exposure, and positioning of the carriage unit which supports the irradiator. One positioning control is mounted directly on the panel wall, and a second positioning control is mounted on the narrow tube which projects from this wall and provides a number of other services to the neighborhood of the irradiator (heat exchange liquid, suction, terminals for electrical pickups and stimulation). The speed controls for the motor driving units, electrical stimulators, amplifiers, instrumentation (sequence control unit) for controlling a sequence of temporally spaced events (such as the initiation and termination of irradiation, periods of stimulation—visual, auditory, electrical, etc.), and equipment for recording electrical activity of the central nervous system are also mounted on this wall.

The frequency at which the crystals of the irradiator are excited is controlled by a commercial signal generator with added voltage regulation. This frequency is set by comparing the signal generator frequency with that of a crystal calibrator. At one mc the uncertainty is ± 100 cps. The duration of the exposure period is controlled by a digital timer with a unit time interval of one msec, a temperature controlled electronic tuning fork providing the reference time base. The acoustic exposure interval can thus be set in integral multiples of 1 msec. The envelope of the ultrasonic pulse is accurately rectangular. The sequence control unit also operates on a digital basis with a unit time interval of one msec. Standard commercial equipment is used for recording electrical events of neurophysiological interest.

As indicated above, the tube which supports the control station near the irradiator (Fig. 7) contains tubes which provide a temperature controlled liquid for circulation in the heat exchange coils mounted in the coupler pan. The usual procedure consists in maintaining the temperature of the coupling liquid within 0.2°C of the rectal temperature of the animal. This eliminates temperature gradients in the brain tissue. The control of the tissue temperature is necessary for the accurate specification of dosage conditions to obtain reproducible lesions for given values of the

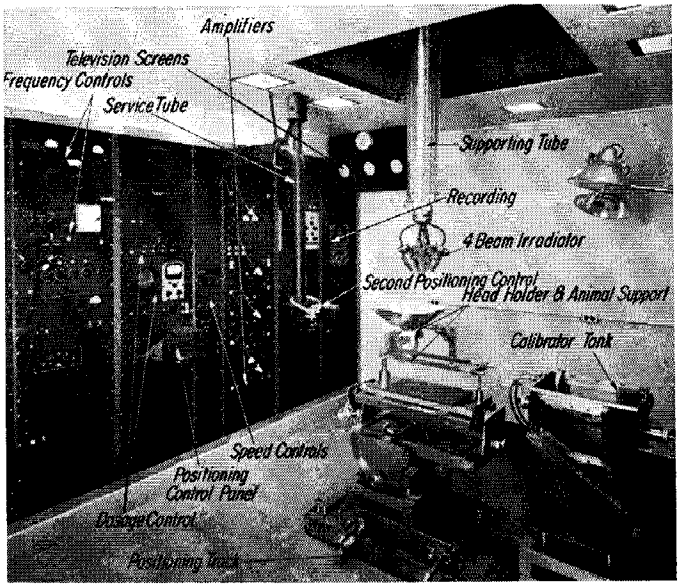


Fig. 7—Irradiation room showing tube supporting transducer and animal head holder, and supporting table, calibration tank and electrical control, calibration and recording equipment in background.*

ultrasonic dosage parameters. (See the last section of this portion of the paper for quantitative information on the variation with temperature of the acoustic dosage parameters required to produce a specific change in the tissue.)

From a knowledge of the dosage parameters required to produce the desired change in the tissue at a given temperature, the calibration measurements, and the path length in the tissue which must be traversed by the sound to the site of the focus (at a frequency of one mc, the average pressure absorption coefficient per unit path length for brain tissue is approximately 0.10/cm), it is possible to compute the voltage necessary to excite the irradiator. In general, lesions larger and more complicated in shape than those produced by single position irradiation are desired. The procedure most commonly employed up to the present time to accomplish this consists in irradiating in a series of adjacent positions spaced a fixed distance apart [6]-[9], [22]-[26]. At a frequency of one mc spacing distances from ½ to 2 mm are used, the specific value depending on the dosage and the degree of uniformity desired. An array of lesions is thus placed in the brain with a constant time interval between the exposures at adjacent positions to insure uniformity of effects. (If a fixed time interval is not feasible, then irradiation in neighboring positions is not performed within a time interval shorter than one minute.) The use of the constant interval procedure standardizes the temperature conditions in the tissue and aids in the production of uniform reproducible lesions, particularly if the time interval between exposures is not sufficiently long to enable the temperature of the tissue to return entirely to the base value between exposures. A second irradiation procedure[1] employs sweeping the focus of the sound beam (or beams) through the tissue (at a uniform rate if the

structure is homogeneous with respect to the dosage required to induce the desired change). This procedure has not received much attention up to the present time, but it is expected that it will be used extensively in the future, especially in studies employing reversible effects induced by the ultrasound. The simplest type of sweeping procedure consists in moving the focus of the beam (or beams) along a linear path with appropriate endpoints. A second linear sweep through the tissue can then be placed adjacent to the previous path after an appropriately chosen time interval. In this fashion a volume lesion of arbitrary shape and size can be produced.

If electrical measurements on the brain are to be accomplished during exposure to ultrasound, or in the intervals between exposure periods, it is convenient to use a coupling pan with electrode clamps as illustrated in Fig. 3. In order to record either spontaneous activity or evoked electrical potentials during exposure and at the beginning and end of the irradiation period, it is essential that the electrodes be constructed so that electrical artifacts are not caused by direct action of the intense sound on the insulation of the electrode leads or by the flow of the coupling liquid in the intense field. Electrode leads of 0.010 inch diameter nichrome, covered with a thin layer of Formvar insulation, are stiff enough to withstand the acoustic flow, and the artifact level is negligible.

On the basis of the results obtained up to the present time, it appears that the production of quantitatively reproducible reversible changes in the brain by ultrasound requires that the level of anesthesia be controlled more accurately than can be realized from the use of widely spaced injections of the anesthetizing agent. Appropriate control can be attained by the use of a device which provides an intravenous injection of a controlled amount of anesthetic automatically at short (two minute) time intervals. The electrocorticograph pattern can be used as a monitor. In studies in which ultrasonically induced reversible effects are produced, it is desirable to vary the level of anesthesia over a wide range in order to realize the potentialities of the method for acquiring information on brain mechanisms.

Human

The head of the human patient is supported in a different fashion from that of the experimental animal. Three mutually perpendicular reference planes are determined, as in the case of the experimental animal, by ear bars and by fixtures which rest on the infra-orbital ridges (see, for example, [37]). However, the ear and eye bars are not used to support the head but are employed only for orientation with respect to the holder which is illustrated in the lower half of Fig. 8.

Four stainless steel rods or pins, mounted individually on universal supports, are brought into position to support the skull after the head is appropriately positioned with the ear bars and infra-orbital fixtures (see Fig. 8). The tips of these sterilized rods are rounded to fit into previously prepared indentations of equal radius in the skull. The rod tips are moved into place after the skin has been opened over the positions of the indentations. Three micrometers mounted on each universal support permit accurate reproduction of the rod tip position from one time to another. This is necessary since the patient must be placed in the holder a number of times—at least twice, since the X-ray procedure for locating landmarks is accomplished previous to the day of irradiation.

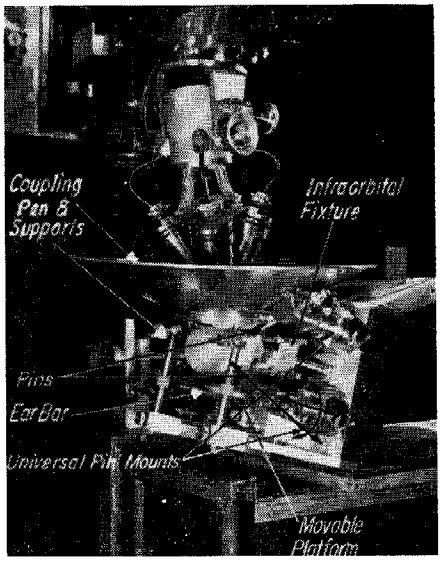
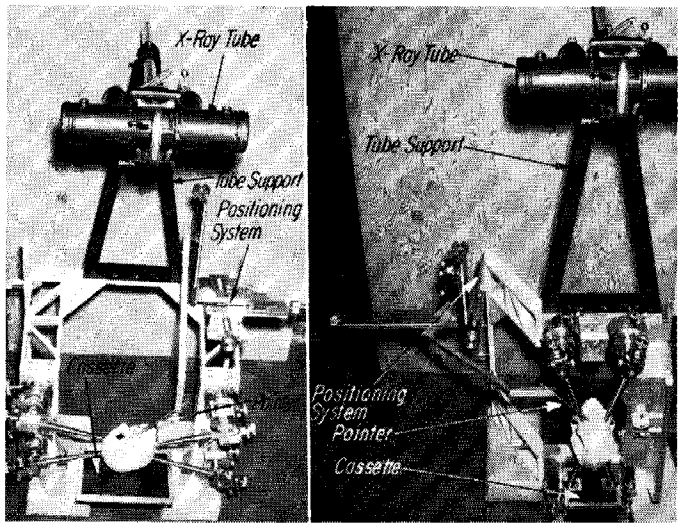


Fig. 8—Human head holder.*

Since internal brain structures are used as reference landmarks for positioning the focus of the ultrasonic beams, it is necessary to provide the head holder with suitable X-ray units. Accordingly, bracket arrangements support X-ray tubes in two positions on the head holder as illustrated in Fig. 9. One tube and corresponding film cassette are provided for obtaining a lateral view of the ventricular system and a second X-ray tube and cassette are provided to obtain an anterior-posterior view. The brain landmarks, which are used as references, are made apparent by placing a suspension of radiopaque material in the ventricular system.

A positioning system, fastened to the head holder, is provided in order to support and move a tungsten crosshair in directions parallel to the axes of the head holder. The projected images of this crosshair appear on the roentgenograms. From measurements made on the roentgenograms of projected images of brain landmarks and crosshair, it is readily possible to compute the positions of the internal brain landmarks in the coordinate system of the axes of the head holder. An appropriate transformation of coordinates then provides the coordinate readings for positioning the focus of the transducer at the desired position in the brain. In order to facilitate this transformation of coordinates, the crosshair is replaced by a pointer whose tip coincides with the position of intersection of the crosshair. By bringing the tip of the pointer of the irradiator into coincidence with the tip of the pointer which re-



(a) (b)

Fig. 9—(a) Human head holder showing X-ray tube in position for a lateral picture. (b) Human head holder showing X-ray tube in position for an anterior-posterior picture.*

placed the crosshair, one can thus obtain the irradiator coordinates for any given coordinates of the head holder system. From a series of coincidence measurements it is, of course, readily possible to compute a set of transformation equations which can be used for machine computation of the irradiator coordinates of any desired sites in the brain structures of interest. It is then not necessary to make coincidence measurements for each new series of sites to be irradiated.

The procedure which was first employed for the irradiation of the human patient was similar to that used for the experimental animal—that is, irradiation was accomplished at the time the bone flap was removed. (The patient was conscious during the entire procedure.) However, instead of tying the skin of the patient to the hopper with a tourniquet, a series of stitches were placed around the periphery of the incision and the skin was pulled tightly against the hopper lip. Inflation of a pneumatic cuff in a groove at the lip then provided the necessary watertight seal. With the technique currently employed, the time consuming procedure of tying the tissue to the hopper is eliminated and in addition a number of considerably more important advantages have been realized as will be indicated later. This latest technique employs the procedure of irradiating directly through the skin—an appropriate bone flap having been removed earlier (at least two weeks) and the skin and underlying tissue sutured back in place [38], [25], [26]. The patient is not irradiated before the incision heals. It is then only necessary at the time of irradiation to open the four small incisions to admit the hemispherical tips of the supporting rods. The neurological disorders presently under investigation in the human being are treated by irradiating structures on both sides of the brain through a single "lateral" opening in the skull. The position and shape of the bone flap removed are determined by means of a template which is positioned by utilizing an indicator supported on the coordinate system of the head holder, to place it in the required location on the patient's scalp and exposed skull.

The head holder is provided with a structure to support the coupling hopper as illustrated in Fig. 8. The bottom rim of the hopper conforms approximately to the contour of the skull and contains a channel which supports an inflatable rubber tube. This tube presses against a soft rubber gasket which is placed on the skin of the patient to conform to the bone edge underneath the scalp. If precautions are taken to prevent any leakage of the saline transmitting liquid into the incisions admitting the supporting rods, it is not necessary to place and fill the hopper using aseptic technique. The method of irradiating directly through the skin makes it possible to subject the patient to practically any number of irradiation procedures and thus follow and modify the signs and symptoms of the disorder over an extended period of time. The bone flap can be replaced after the termination of the irradiation series, or an acrylic plate can be substituted for it.

The photograph of Fig. 10 (next page) shows the entire machine which was designed and built for the first human work. The electronic driving, control and calibration equipment is housed in cabinets seen in the right rear of the illustration. The rigid steel framework was essential since the first machine had to be installed in an existing operating room without entailing major building modifications. The machine is illustrated in use on a patient in Fig. 11.

Results and Applications

Precisely controlled high level focused ultrasound can be used to produce, as already indicated in the introduction, selective irreversible or reversible changes at practically any desired array of sites in the brain. As a result, ultrasonic methods are now in use in neuroanatomical, neurophysiological and behavioral studies on experimental animals and also in investigations of the mechanisms and modification of the signs and symptoms of a number of neurological disorders in humans.

Irreversible effects—Experimental animal

Ultrasonic dosage conditions have been established for the production of selective irreversible changes by a study involving the irradiation of a variety of brain structures in cat and monkey and the subsequent examination of histologically prepared tissue sections [6]-[11], [13], [22]. If the ultrasonic beam focus is placed at a single position (frequency of one mc) in the subcortical white matter (fiber tract) of the brain of a cat and an exposure for the selective destruction of the fiber tracts delivered, the type of "lesion" illustrated in Fig. 12 (p. 175) is obtained. This figure shows a transverse tissue section stained so that the white matter or fiber tract regions appear dark or deeply stained and the gray matter or nerve cell body regions are almost unstained. The dosage parameters used to produce the lesion illustrated were such that the neighboring gray

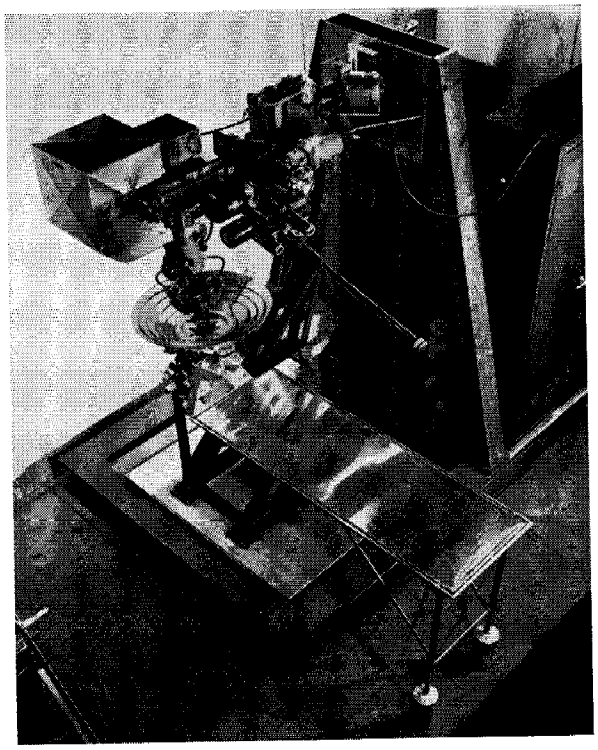


Fig. 10—Over-all view of the transportable human ultrasonic neurosurgery instrument. The 4-beam focusing irradiator is shown in position above the pan which supports the transmitting liquid. The head holder lies beneath this coupling pan. The pan itself is provided with heat exchange coils which permit the temperature of the transmitting liquid to be maintained at the desired value. The positioning system which supports the 4-beam irradiator permits the focal spot of the irradiator to be moved about in three mutually perpendicular directions. One of the X-ray tubes which are used in the determination of the position of internal brain landmarks is shown mounted on the head holder. The operating table incorporated with the instrument is shown in position for irradiation of the patient from the lateral direction. The electronic instrumentation which supplies the electrical driving power for the irradiator and the instrumentation for calibration is shown behind the framework which supports the positioning system for the irradiator.*

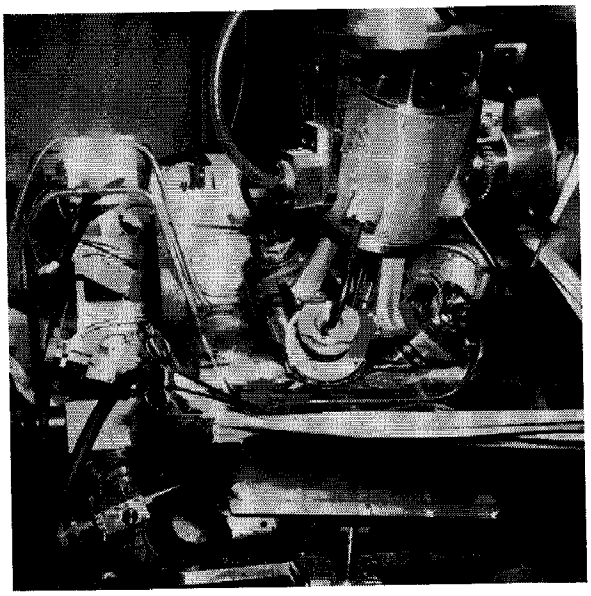


Fig. 11—Ultrasonic human neurosurgery (neurosonicsurgery) in progress on a patient with a hyperkinetic disorder. Irradiation is being performed through the intact skin, a bone flap having been removed in a previous procedure. The 4-beam irradiator is shown partially immersed in the degassed transmitting salt solution. The coils seen in the pan or hopper which supports the transmitting liquid are used for circulating a heat exchange liquid to maintain the temperature of the saline near 38°C. The hose connection to the pan on the lower left corner is provided for filling it. The support for the pan and two of the mounting posts which hold the rods for supporting the skull of the patient can be seen.

matter, even though exposed to an equal dosage of the ultrasound, was undamaged. In order to produce larger lesions in the white matter, the focus of the ultrasonic beam is moved successively from one position to another with an equal spacing distance between adjacent positions. A lesion produced by this method is illustrated in the tissue section shown in Fig. 13. Even in a lesion as large as this one the vascular system is left intact and functioning. The production of a small lesion deep within the brain is illustrated in the tissue section of Fig. 14. This section shows the interruption by focused ultrasound (frequency one mc) of the mammillothalamic tract (a small fiber tract about a millimeter in diameter deep within the brain) in the cat. The normal tract appears on the right-hand side of the figure and the tract interrupted by the focused ultrasonic beam is on the left (the light spot within the square). Microscopic examination of the intervening tissue between the port of entry of the sound into the brain and the site of the lesion indicates that no adverse effect on this tissue was produced by the converging ultrasonic beams.

To affect gray matter, the ultrasonic dosage must be increased [10], [11]. That is, either the sound level must be raised or the duration of exposure prolonged if the level is above the threshold required to produce selective effects in gray matter. Therefore, when gray matter is to be affected and neighboring white matter spared, the focal region of the converging beams must be confined to the gray matter. An ultrasonic frequency of four mc is a better operating frequency than one mc for producing such lesions in the gray matter structures of small brains (cat) since the dimensions of the focal region of the ultrasonic beam can be made much smaller at the higher frequency. Consequently, it is more readily possible to confine the focus so that it does not overlap white matter.

One of the more fruitful methods of studying both the structure and mechanisms of operation of portions of the central nervous system has employed the procedure of destroying a region and then studying the experimental animal for subsequent changes in function. The examination of stained tissue sections permits the correlation of these

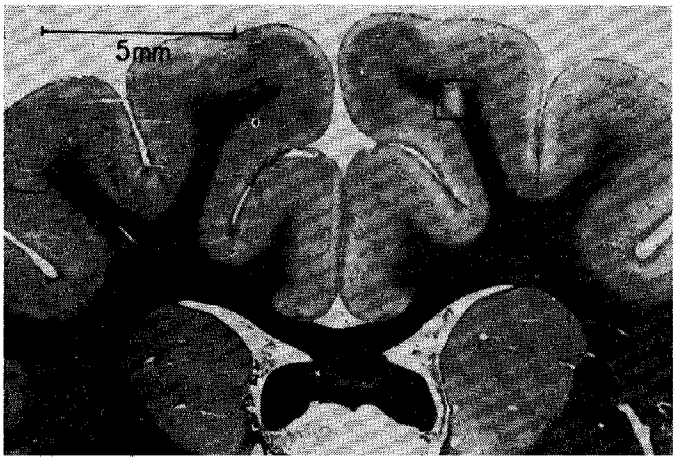


Fig. 12—Subcortical white matter lesion—single position irradiation, Weil's myelin stain.*

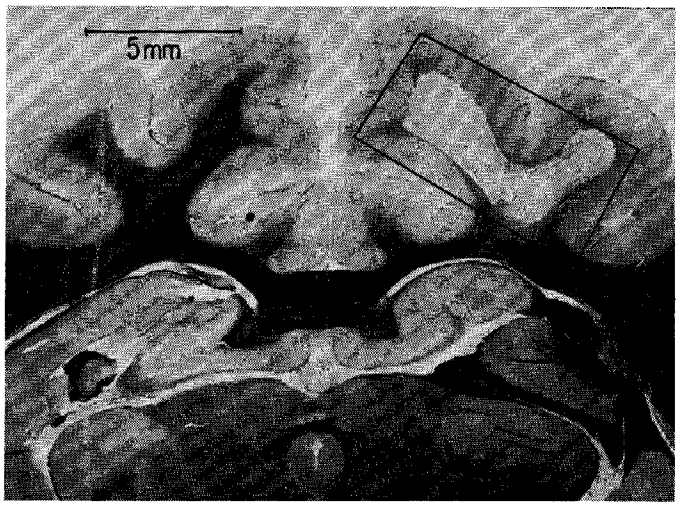


Fig. 13—Large subcortical white matter lesion—multiple position irradiation, Weil's myelin stain.*

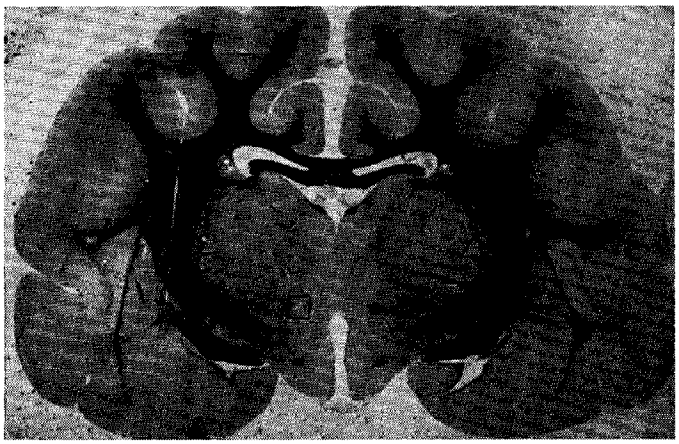


Fig. 14—Interruption of the mammillothalamic tract in the brain of a cat by properly controlled high intensity, focused ultrasound. Compare the lesion produced by ultrasound on the left side with the untreated right side.*

functional changes with specific neural structures. Various mechanical methods are used to destroy nerve tissue. They involve the use of cutting instruments or devices to remove tissue by suction. Chemical necrotizing agents are introduced into regions of the brain by means of hollow tubes which are pushed through the tissue to bring the opening to the desired site. Electrodes to permit the passage of current to coagulate nerve tissue are placed at a desired site by penetrating the intervening tissue with a cylindrical device which carries the electrodes at its tip. All these methods result in the destruction of tissue intervening between the region destroyed and the surface of the brain. As a result, the effects obtained cannot in many cases be unambiguously ascribed to the destruction of the tissue at the desired site since the destruction of the penetrated tissue may be of equal or greater importance in producing the observed changes. In addition to possible complications resulting from the destruction of intervening tissue, the use of these procedures does not result in the *selective* destruction of specific tissue components in the region affected—that is, all types of tissue or cells in the region are destroyed. This includes the blood vessels. Difficulties then result from the fact that hemorrhage may occur or that interrupted blood vessels may supply regions of the brain not within the site to be destroyed. Interruption of such blood vessels can result in the dysfunction of portions of the nervous system other than those encompassed in the region of direct destruction.

The necessity of introducing a mechanical device in order to reach the region of interest has made it impractical and in many cases impossible to produce lesions of particularly desired shapes to correspond to the forms of specific nuclei or nerve fiber tracts. Each time a tube or rod is introduced, intervening tissue is destroyed so that if a region of complex shape or of relatively large size is to be affected, more tissue may be destroyed outside the region of interest than within the region. Consequently, the number of times a mechanical device is inserted is usually restricted

to one or two penetrations to destroy any specific region. This is the case for both experimental animals and for humans neurosurgery of deep brain structures). Other agents which have been used to destroy tissue in the central nervous system are X-ray radiation and high energy nuclear particles. These two methods suffer from the disadvantage that radiation damage is produced in all intervening tissue in the path of the beams and that the effects of such damage are cumulative. In addition, no range of dosages for producing destruction of neural tissue without some interference with the vascular system has yet been demonstrated and there is no evidence indicating that reversible changes can be induced in nerve tissue components by these methods. The principal advantage of these latter two methods over the use of mechanical devices is that a surgical procedure requiring penetration of brain tissue to the sites of interest is not required.

Essentially all of the disadvantages of the methods just discussed are eliminated by using precisely controlled focused high intensity ultrasound for producing changes in deep brain structures. And, in addition, ultrasonic procedures make possible methods of attack on problems of brain organization based on principles which could not be entertained with other methods. The only disadvantage apparent in the ultrasonic procedures at the present time is that a portion of the skull bone must be removed to permit the sound to enter the brain. However, as already indicated, irradiation can be accomplished through the skin if a window has been made in the bone so that treatment need not be performed at, nor confined to the time the bone is removed.

Reversible Effects

Intense focused ultrasound can induce, under appropriate dosage conditions, reversible changes in the central nervous system [17], [20]-[22]. Studies of such changes, using the visual system of the cat, have been pursued at this laboratory. By focusing ultrasound into the region of the lateral geniculate nucleus (fibers to the "visual" part of the cerebral cortex arise from cells which synapse with incoming visual system fibers in this nucleus), temporary suppression of various components of the cortical potentials, evoked in response to a flash of light, can be produced. Such temporary (complete recovery within one to five minutes) or reversible suppression can be repeatedly obtained at the same site without producing a histologically observable lesion. Studies of these changes are in the relatively early stage of investigation, and the neural substructures at which the primary action of the sound occurs have not yet been identified. It is not yet known whether temporary interruption of information transfer (electrical manifestation) by ultrasound can be accomplished in all neural components—nerve fiber, neuron, synapse. In addition, the physical mechanism of the action of the sound to produce reversible changes has not yet received appreciable attention.

For the study of the reversible action of ultrasound on the operation of the visual system, the schematic arrangement of animal and apparatus, shown in Fig. 15 has been employed. A flash of light is used to stimulate the eye(s) of the animal, and a set of bipolar recording electrodes, placed in the appropriate cortical areas on both hemispheres, is used to detect the evoked electrical potentials. The electrodes are placed approximately one mm below the surface of the cortex. (If the observations are restricted to the determination of changes in the relative amplitudes of evoked potentials, one can record on a standard electroencephalograph. However, if the detailed shapes of the potential responses are desired, a recorder with a wider frequency response characteristic is required.)

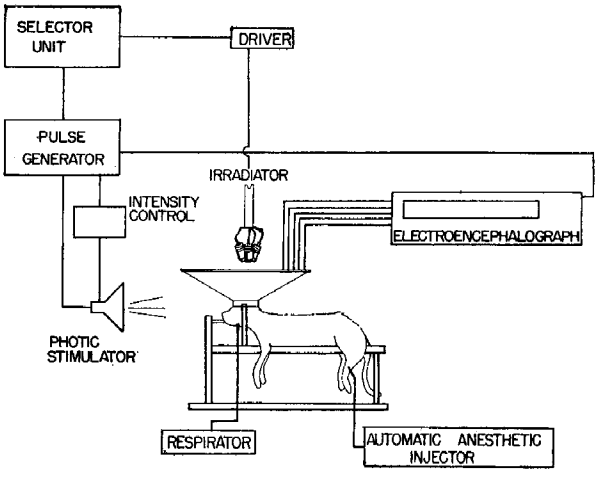


Fig. 15—Schematic arrangement of animal and apparatus for study of the reversible action of ultrasound on the visual system.*

The sound is focused at various sites in the region of one of the lateral geniculate nuclei of the animal. Stimulation of the eye(s) by light is repeated at fixed time intervals before, during, and after irradiation. Continuous electrical recording from the entire set of electrodes is in progress. The anesthetic is administered intravenously at intervals of several minutes with the electroencephalographic pattern serving as a monitor of the depth of anesthesia, and the temperature of the animal is controlled, using a rectal thermosensitive element as an indicator.

The magnitude of the transient suppression of the evoked potential components is a function of the position of the focal region of the ultrasonic beam in the brain structure, and it is thus possible to obtain by this means three-dimensional mappings of brain operation. This is illustrated in Fig. 16, which shows a plane section of such a map at the depth of the center of the lateral geniculate nucleus. The evoked potentials used for constructing this contour map were recorded from a bipolar electrode at the position indicated by the black dot in the figure. This position is close to the posterior end of the visual cortex near the midline. The level of anesthesia was adjusted so that the "normal" evoked potential was of the form indicated by the bottom record on the right. Ultrasonic dosage conditions (particle velocity amplitude—130 cm/second; du-

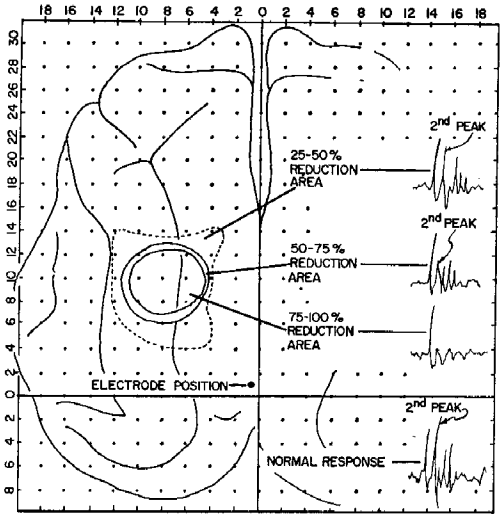


Fig. 16—Reduction by ultrasound, focused in the region of the lateral geniculate region, of the second and subsequent peaks of the evoked cortical potential to photic stimulation.*

ration of exposure—30 seconds) were chosen to cause reversible suppression of the second and subsequent peaks of this evoked potential without effect on the first component. When the focus of the ultrasonic beam was placed within the region bounded by the inner curve, the second and later peaks of the evoked potential response, following a flash of light, were reduced between 75 and 100 per cent in amplitude. In the annular region between the two inner curves, the second peak of the evoked potential response was temporarily reduced between 50 and 75 per cent of its initial value. By placing the focus of the ultrasonic beam at various depths, it is possible to obtain a series of such contour maps, the set of which constitutes a three-dimensional mapping.

Mappings of the type illustrated and discussed here are expected to be extremely useful in determining pathways of information transfer, and the temporal relations involved in such transfer, in the brains of experimental animals. They are expected to yield information on the mechanisms underlying the performance of complex activity of central nervous systems.

The use of focused ultrasound, at dosages which cause only reversible changes, combined with implanted electrode techniques will constitute a new and powerful tool for investigating brain function.

Reversible changes induced in brain structures by focused ultrasound will also be extremely useful in medicine. For example, in many instances the dependence upon brain or bony landmarks for accurate positioning of a lesion at a desired site in the human brain could be eliminated. If the temporary interruption of information transfer along a neural pathway results in an identifiable change in behavior or physiological function, then the application of ultrasound, at dosages which produce only reversible changes, would permit the localization of sites in the brain at which lesions are desired without recourse to landmarks except as a first approximation.

Ultrasonic Human Neurosurgery (Neurosonicsurgery)

As a consequence of the work accomplished on the induction of selective changes in structures or sites in the central nervous system of experimental animals with high intensity focused ultrasound, it became apparent that these procedures have application to the investigation and favorable modification of mechanisms underlying various neurological disorders in the human. This phase of the program has been in progress over the past two years in collaboration with Dr. Russell Meyers and his associates of the Division of Neurosurgery of The State University of Iowa.

Up to the present time ultrasonic irradiation of brain structures has been accomplished on 48 patients [23]-[26]. The neurological disorders which have received attention are: 1) tremor and rigidity of Parkinson's disease, 2) nonpatterned involuntary movements of cerebral palsy origin, 3) nonpatterned involuntary movements of unclassified hyperkinetic disorders, 4) intractable pain following cerebral vascular accidents, 5) phantom limb pain and image following amputation, 6) hypersensitivity to stimulation of peripheral sense receptors, and 7) discomforting sensations of a variety of types in addition to those already listed. In the case of Parkinsonism, the involuntary cyclic movements (tremor) and the muscular stiffness (rigidity) are the primary aspects of the disease under investigation, although some attention has also been placed on the study of the slow movement feature exhibited by some patients with the disorder. The mechanism of this latter feature is apparently not identical with that subserving rigidity, at least in some patients, since slow movement can and does exist without it.

As indicated above, the initial method of studying and modifying the signs and symptoms of these disorders was to irradiate with a skin flap open and bone flap removed. The irradiation procedure was carried out on the conscious patient on the day of surgery. This required cooperation of the patient after he had undergone the stress accompanying the bone flap removal. The more recent technique of irradiating through the intact skin [25], [26], [38], sometimes subsequent to the removal under general anesthesia of the bone flap, eliminates this stress on the conscious patient.

An array of lesions is produced in brain structures of each patient. The sites at which the focus of the ultrasonic beam(s) is placed, are determined by the sequence of events occurring during irradiation and by experience obtained on previous patients. Sites in more than one structure may be irradiated at a single procedure. A particularly useful shape of lesion is the curved sheet form which may be used to separate two or more brain structures. The formation of such lesions in deep brain structures is not feasible by methods requiring mechanical penetration of intervening tissue.

Practically any number of irradiation sequences can be performed on patients treated by irradiating through the intact skin, since repetitive surgical procedures are not required except for the opening of the four small incisions

required to admit the tips of the supporting rods. This is extremely desirable in many cases since it is possible to eliminate completely signs and/or symptoms of a disorder during one irradiation sequence and have a partial or complete return of them within a few days, weeks, or months.

The tremor and rigidity of Parkinson's disease and the nonpatterned involuntary movements of patients with other types of hyperkinetic disorders have been favorably modified and eliminated by arrays of ultrasonic lesions in a number of combinations of brain structures.[2] These structures have included: 1) the ansa lenticularis ventral to the globus pallidus, 2) portions of the medial part of the globus pallidus, 3) part of the posterior half of the substantia nigra and its superior medial border, 4) the base of the ventral lateral nucleus of the thalamus, 5) the tegmental field of Forel, 6) the fiber tract regions H 1 and H 2 and the zona incerta. In these structures it has been possible to exhibit spatial distributions of neural components, the irradiation of which results in the modification of the abnormal movements and/or rigidity in various muscles of the body. For example, tremor and/or rigidity in an upper limb may be eliminated without effect on these signs in the lower limbs and vice versa. Similarly, the irradiation sequence may be such that the rigidity and/or tremor is relieved in the muscles of the fingers or hand without relief in the arm or forearm. It should be noted that, in general, the irradiation of structures on one side of the brain produces the maximum effect in the limbs of the opposite side. However, irradiation of structures on one side may result in changes in abnormal muscle tone and involuntary movements on both sides of the body. Many patients exhibit involuntary movements, tremor or nonpatterned, and abnormal tone in muscle groups other than those of the limbs (that is, in the jaw, neck, trunk). In some cases relief occurs by irradiation of structures on one side of the brain; in other cases, irradiation of structures on both sides is required.

It has also been shown that tremor and rigidity are not necessarily simultaneously modified in the same muscle group(s).

Considerable progress has been made on the investigation of the brain mechanisms underlying abnormal involuntary movements and abnormal muscle tone in patients suffering from Parkinson's disease and other hyperkinetic disorders. However, the present status of the research would appear to indicate that a considerable amount of additional work will be required before a detailed mechanism of these signs can be formulated. After further information on mechanisms is obtained, it is expected that the routine application of ultrasonic methods will result in considerable improvement in the therapy of the hyperkinetic and hypertonic disorders.

As indicated above, some work has been accomplished on the study and modification of intractable pain and other discomforting sensations of various types and on the investigation and modification of phantom images. Only a very few cases (six) have been treated thus far, and no procedure for complete, permanent (longer than 6 months) relief of symptoms has yet been formulated. However, a considerable amount of information on the mechanism of these disorders—the identification of structures in which arrays of lesions can be placed to eliminate symptoms—has been forthcoming. It is possible to relieve completely amputation stump pain, phantom limb pain and image, the burning pain following a cerebral vascular accident (Déjèrine's syndrome), the pain and other discomforting sensations following the acute phase of shingles (herpes zoster), and the hypersensitivity and distortions of sensation (hyperesthesia and dysesthesiae) associated with these disorders without imposing any detectable neurological deficit on the individual. It remains to be determined whether a suitable array of lesions in deep brain structures can be identified to eliminate these symptoms on a permanent basis.

The work carried out to date on the human has involved the production of irreversible changes in specific brain structures. In only one instance was a dosage appropriate to induce a reversible change employed. This was accomplished in a Parkinsonian patient, and the temporary (1 to 5 minutes) suppression of tremor in the upper limb on the side contralateral to the brain structure undergoing irradiation was demonstrated. The use of dosages to affect neural function reversibly implies that placement accuracy for the production of irreversible changes would not be dependent upon the accuracy of available brain atlases. Therefore, it is imperative that the employment of dosages at which only reversible changes are produced be implemented as soon as possible. However, this requires more extensive instrumentation than that now available for the human work. Specifically, it is essential that the instrument be capable of moving uniformly and continuously the focus of the ultrasonic beam(s) along a complex shaped path in the brain.

After the mechanisms of the neurological disorders discussed briefly here become further elucidated by the ultrasonic methods currently in use, and as therapeutic procedures are formulated for handling such cases routinely, other neurological conditions in the human will be investigated and treated.

Physical Mechanism

The physical mechanism of the selective action of intense ultrasound on the tissue components of the central nervous system has been the subject of an extensive investigation at this laboratory [1], [3]-[5], [12], [16], [22], [40]. It has been shown that the temperature increase which accompanies the acoustic wave propagation in the tissue is not the primary physical variable responsible for inducing the selective action [1], [12], [16], [40]. However, the primary process does exhibit a nonzero temperature coefficient; that is, less sound is required to pro-

[2] All statements regarding placement of the lesions in the human brain should be qualified by the note that no histological results are available yet.

duce a given change at higher body temperatures than at lower temperatures. That heat is not the primary cause of the selective changes is shown by dosage studies in which the base temperature of the animal (one-day-old mouse) is cooled to such a value that the temperature of the tissue, measured directly by small imbedded thermocouples never reaches "normal" body temperature for the adult animal during irradiation. It has also been shown that cavitation is not important in the mechanism. This has been proved most conclusively by irradiating frogs under a hydrostatic pressure sufficiently high to prevent the cavitation process from occurring [3].

The young mouse, 24 hours after birth, is a convenient experimental animal for a number of reasons, one of the more important being that it is essentially poikilothermic [39] and therefore can readily be carried through temperature cycles to as low as 0°C without producing permanent changes. The mice are irradiated in a plane traveling wave field at the level of the third lumbar vertebra, the region of the approximate center of the lumbar enlargement which contains a high density of the motor neurons which are involved in the control of movement of the hind legs of the animal. Thus, destruction of the neurons of the lumbar enlargement results in motor paralysis of the hind limbs of the animal, constituting a convenient and readily observed endpoint.

The method used to support the animal for irradiation in the acoustic field is illustrated in Fig. 17. The holder is designed so that essentially all of the acoustic energy passes through the central opening across which the mouse is suspended. This holder is placed in a heavy steel chamber containing the transducer, a positioning system for supporting and moving the animal holder (and acoustic probes) and an absorber. The chamber is housed in a modified deep freeze. This arrangement is provided so that both the temperature and the hydrostatic pressure of the animal can be varied over a wide range [12], [22], [40].

Dosage results on mice have been obtained at a frequency of 982 kc, a hydrostatic pressure of one atmosphere and base temperatures of 2°C, 10°C, and 20°C. The data show that a well-defined threshold region exists for each base temperature. If a number of animals are irradiated with identical values of the acoustic field variables for various periods of time, and the percentage of animals paralyzed at each duration of exposure is plotted as a function of the reciprocal of the time duration of exposure, a sigmoid curve, obtained by statistical treatment of the data, is obtained (Fig. 18). Each plotted point represents approximately 25 animals. From curves such as this one, a threshold range can be arbitrarily defined as the range of exposure times from 10 per cent of the animals paralyzed to 90 per cent of the animals paralyzed. The collection of these threshold ranges, obtained for various values of a specific acoustic field variable, then defines the threshold region. Fig. 19 shows the threshold region for the base temperature of 10°C. The ordinate is the reciprocal of the exposure time and the abscissa is the square root of the acoustic intensity. The plotted points (indicated by the symbol "+") are obtained from sigmoid curves similar to the one just shown, but obtained at other values for the acoustic intensity. The relation obtained for 50 per cent of the animals paralyzed displays a linear portion extending from approximately 48 watts/cm² (25 seconds time duration of exposure) to at least 160 watts/cm² (0.8 second time duration). Statistical analysis indicates that this portion of the curve is a linear relationship to a high degree of accuracy. The width of the threshold region in the range of the linear portion of the curves is 17 per cent. This includes the uncertainties in the physical measurements as well as any biological variation in the animals.

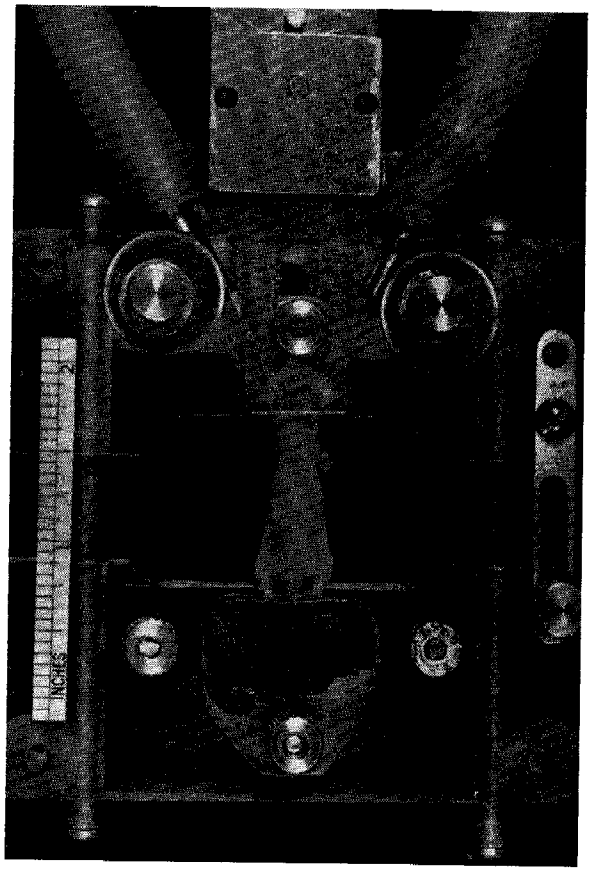


Fig. 17—An infant mouse supported in the mouseholder and ready for irradiation.*

In the course of these studies, measurements were made of the temperature increases in the spinal cords of the mice as a function of the ultrasonic dosage. This was accomplished by imbedding small thermocouples in the cords. The greatest temperature increases observed are shown in Fig. 19 plotted at the corresponding dosage coordinates (circles).

Fig. 20 shows the 50 per cent paralysis curves for base temperatures of the animals of 2°C, 10°C, and 20°C. It is clear that the relations are linear over a wide range of exposure times, but that there is an indication of a deviation from linearity for the longest exposure periods. The

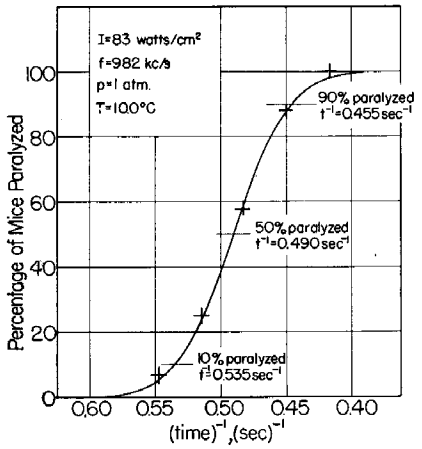


Fig. 18—Sigmoidal distribution of percentage of mice paralyzed as a function of the reciprocal of the time duration of exposure.*

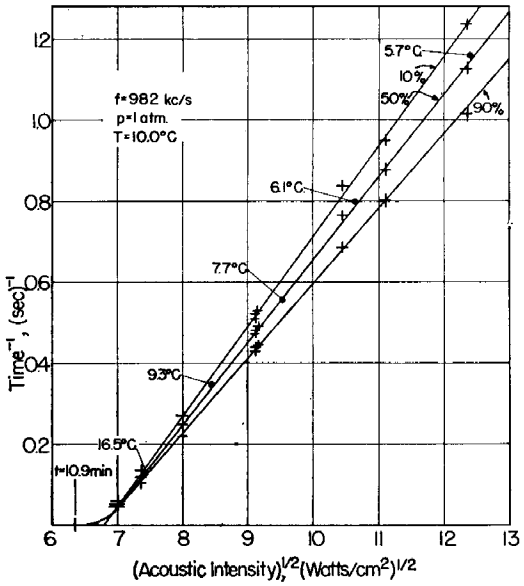


Fig. 19—Threshold region for paralysis of the hind legs of young mice under ultrasonic irradiation.*

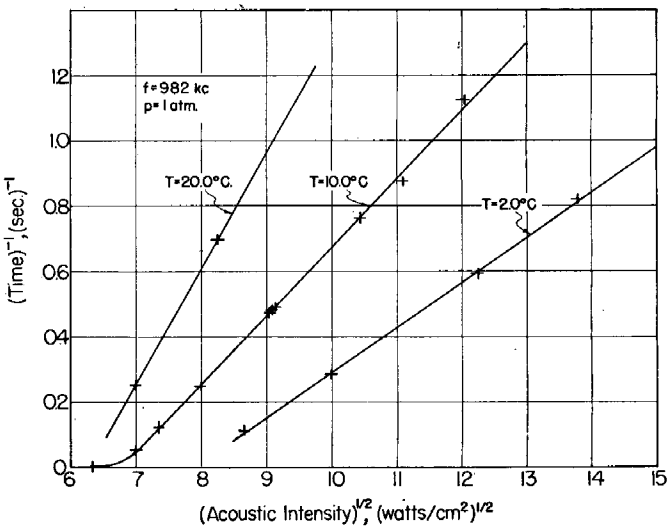


Fig. 20—Dosage relations (50 per cent paralysis curves) as a function of the base temperature of the animal. (Note that the curve for 20.0°C is determined by only two points and as such is not complete.)*

data of the graph show that in the linear range the change in the tissue is not characterized by the delivering of a fixed amount of acoustic energy (above some threshold level) since, if such a situation existed, the reciprocal of exposure time would be related linearly to the intensity rather than its square root.

A quantitative dosage study of the type described here has considerable interest aside from the contribution it is expected to make toward an understanding of the mechanisms by which ultrasonic waves act to produce the selective changes in tissue structure. A quantitative study of the dosage relations over a wide range of acoustic parameters and auxiliary conditions will indicate whether different physical mechanisms are operative over different parts of the range. A change in the *form* of the dosage relations, for example, the change in the curve for a temperature of 10°C from the linear form to the curved shape shown (Fig. 20) is an indication of a possible change in mechanism. Different physical mechanisms may result in the production of different types of selective tissue changes so that a broad quantitative dosage study will indicate the various ranges of parameters for which the irradiated tissue should be investigated histologically, cytochemically, electrophysiologically, etc.

The present status of our understanding of the physical mechanism of the selective action of intense ultrasound on tissue can be summarized as follows: Cavitation may be eliminated as a primary factor since the type of changes, produced in animals irradiated under a hydrostatic pressure sufficiently high to prevent tension forces from occurring in the tissue, are similar to those produced with the animal under a pressure of one atmosphere. Over the linear portions of the dosage relations the maximum temperatures developed in the neural tissue are considerably less than the normal temperature of the adult animal (mouse—approximately 36°C). Hence, a thermal process

may be considered unimportant as the primary mechanism in this region. The linear ranges of the dosage relations display a relationship showing that the reciprocal of the exposure time is proportional to one or a linear combination of the acoustic field variables, pressure amplitude, particle velocity amplitude, particle acceleration amplitude, etc. However, at the present time, insufficient information exists to decide the relative importance of each of these acoustic variables. The form of the dosage curves in the nonlinear range suggests that a process different from that obtaining in the linear region may be involved.

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