INTENSE ULTRASOUND IN INVESTIGATIONS OF THE CENTRAL NERVOUS SYSTEM*

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I. Introduction

A study of the effects of intense ultrasound on the central nervous system shows that under appropriately chosen and accurately controlled conditions acoustic waves constitute a powerful tool for investigating such systems. The affecting of a specified region without disturbance to intervening tissue can be accomplished by focusing the sound waves (W. J. Fry et al., 1954; W. J. Fry, 1956; Ballantine et al., 1956). Effects can be limited to extremely small volumes if desired, and regions of large size and complex shape can be affected by movement of the focus of the beam through the tissue (W. J. Fry et al., 1955a; W. J. Fry, 1956; Barnard et al., 1955). Selective action on specific tissue components is accomplished by control of the dosage (W. J. Fry, 1956; W. J. Fry et al., 1954, 1955a, 1957; Barnard et al., 1955, 1956; Ballantine et al., 1956). Either irreversible (W. J. Fry et al., 1950, 1954, 1957; Barnard et al., 1956; Ballantine et al., 1956) or reversible (F. J. Fry et al., 1957) changes can be produced by appropriate choice of exposure conditions.

Investigation in this field has reached the point where intense ultrasound is in use in fundamental neurological research on experimental animals (in preparation) and ultrasonic human neurosurgery (Meyers et al.; W. J. Fry et al., 1958) of deep brain structures is in progress. However, the basic mechanism of the action of the sound on the tissue is not understood at present although considerable effort has been expended in order to elucidate the physical mechanism and to determine the site or sites in the tissue at which the initial or direct effect of the sound occurs (W. J. Fry et al., 1950, 1951; W. J. Fry, 1953; Huetter et al., 1956; W. J. Fry and Dunn, 1956; Dunn, 1956, 1958; Dunn and W. J. Fry, 1957b). An understanding of the mechanism of the action of the sound is important not only from the viewpoint of inherent interest but also because it may result in the prediction of dosage conditions which would produce types of selective changes in the tissue not previously observed. In addition, such an understanding might well lead to the development of ultrasonic methods of elucidating intracellular structures and associated functions.

This chapter is a review of research on the effects of intense ultrasound on the tissues of the central nervous system and on the use of controlled dosages of ultrasound as a tool in investigations of such systems. The chapter includes sections treating the following topics: (1) Techniques employed to subject selected regions of the central nervous system to accurately controlled dosages of ultrasound, including (a) the methods of using various irradiation systems (both focusing and nonfocusing types), (b) the methods of supporting the experimental animal or patient, (c) positioning of the focal regions at the desired sites, (d) coupling methods, (e) specific procedures used in the electrophysiological study of ultrasonically induced
reversible changes, and (f) ultrasonic field configuration and calibration procedures. (2) Histological results; (a) the description of selective ultrasonic lesions as a function of the dosage conditions and as a function of the time after exposure, (b) the accuracy of placement of lesions, (c) the use of the ultrasonic method of producing lesions for neuroanatomical studies illustrated by a study of the mammillothalamic tract. (3) Production of reversible changes in localized regions of the central nervous system by ultrasound, ultrasonic mapping of central nervous system function illustrated by a study on the visual system. (4) Physical mechanism of the action of intense ultrasound on the tissue components of the central nervous system; (a) the role of temperature and cavitation, (b) summation effects, (c) the determination of quantitative dosage relations and their use in determining the acoustic or concomitant variable or variables responsible for the primary action of the sound on the tissue. (5) Ultrasonic instruments used in producing selective changes in the central nervous system, including (a) equipment for accurately placing the focus of an ultrasonic beam or beams at desired sites in the brains of mammals under accurately controlled dosage conditions, (b) auxiliary equipment including calibration instrumentation, (c) synchronization and control apparatus, (d) positioning systems (manual and automatic), (e) head holders, (f) coupling devices for supporting transmitting liquids and electrodes, (g) sound tanks provided with temperature and pressure controls and positioning devices. (6) Application of the focused ultrasonic beam method to human neurosurgery of deep brain structures.

It is not possible to treat these topics in a comprehensive fashion in a review of this length, but it is hoped that sufficient detail is included to convey to investigators not working in the field some knowledge of the results already obtained, an acquaintance with current work, an introduction to some of the problems for future investigation, and an indication of the value of intense ultrasound as a tool in fundamental research on the central nervous system and in medicine (neurosurgery).

This review is subdivided into three major sections each semi-independent of the others. Readers primarily interested in the results may wish to consult Sections III and IV without detailed examination of Section II which is primarily concerned with technique and instrumentation.

II. Technique and Instrumentation

Two distinctly different types of ultrasonic field configurations are extremely useful for producing changes in the central nervous system (and in other tissue structures as well): focused fields and uniform "plane wave" fields. Focused beams of ultrasound are essential to the production of changes in deep structures without the simultaneous production of changes
in intervening tissue. By irradiating the tissue with a focused beam in a series of positions, it is possible to produce lesions of almost any desired size and shape. Uniform ultrasonic field configurations are useful in, for example, studies of physical mechanism. If a considerable volume of tissue must be affected in order to result in a given functional change, then it is extremely desirable in studies of physical mechanism that the entire volume of tissue involved in the control of the specific function receive precisely the same dosage\(^1\) of radiation at the same time. Specific reasons for this statement are given in the section on physical mechanisms.

1. Focused Field Instrumentation, Preparation and Irradiation Technique

The minimum dimensions of the focal region of an ultrasonic beam which can be realized decrease as the frequency increases since the wavelength is a determining factor (Hueter and Bolt, 1955). However, an upper limitation is imposed on the frequency by the thickness of tissue which must be penetrated in order to reach the desired site. The ultrasonic absorption coefficient of brain tissue increases with the frequency (linear dependence in the frequency range of interest here), and the limitation is imposed by the fact that the sound level must be lower along the path within the brain than it is in the focal region itself. The maximum permissible dose to the intervening tissue is dependent upon a number of factors, including the number of exposures to the radiation and the time interval between successive exposures. These factors and 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 a conservative criterion.

At a frequency of one megacycle per second (1 Mc./sec. = 10\(^6\) cycles/sec.), the wavelength of sound in brain tissue is 1.55 mm. \((V = 1.55 \times 10^5 \text{ cm./sec. at } 37^\circ C., \text{ and the “average” value of the intensity absorption coefficient for the adult mammalian brain at “normal” body temperature is approximately 0.20/cm. From a consideration of this absorption coefficient value and the gain of either single or multibeam focusing systems and with the conservative choice of safety factor just stated, it follows that this frequency is about the maximum which can be employed for the production of changes in the deep portions of the human brain. At this frequency, it is readily possible to produce lesions involving only a couple of

\(^1\) The term dosage includes a specification of the value of the appropriate acoustic field variable (intensity, particle velocity amplitude, pressure amplitude, etc.), the time duration of exposure, and the shape of the acoustic envelope, the environmental conditions (temperature of the preparation, hydrostatic pressure, state of anesthesia, etc.).
cubic millimeters of tissue, and many lesions of no more than a single cubic millimeter have been produced at this laboratory (see Section III, 1a). Most of the reported experimental animal work on the production of changes in the brain by focused ultrasonic beams has been accomplished at a frequency of 1.0 Mc./sec. (W. J. Fry et al., 1954, 1955a, b; Barnard et al., 1955, 1956). However, some work has also been accomplished at a frequency of 2.5 Mc./sec. (Bakay et al., 1956; Ballantine et al., 1956). Lesions with volumes less than 0.02 mm.³ have been produced at this higher frequency.²

a. Focusing Transducers. In order to place precisely controlled doses of focused ultrasound at a wide variety of sites in the brains of experimental animals (or humans), it is essential to have available versatile focusing transducers. A multibeam device of the type illustrated schematically in Fig. 1a and photographically in Fig. 1b is a convenient focusing system since the individual beams can be used together in various combinations as required by (1) the geometry of the port of entry of the sound into the brain and by (2) the configuration of the tissue path available for transmission of the sound.

The ultrasound is produced by circular X-cut quartz crystals vibrating in thickness mode. The individual crystals are supported in housings which also provide mechanical support for the lenses which focus the ultrasound. The face of the crystal adjacent to the lens is maintained at the same electrical potential as the metal housing. This is accomplished by placing a ring of 0.001 in. gold foil under the rubber gasket as shown in Fig. 1. The ring of foil which is in contact with the crystal electrode and with the housing extends only partially under the gasket so that a rubber gasket seal is realized. The polystyrene lens is placed a short distance (approximately 0.010 in.) in front of the crystal face and is acoustically coupled to it by a thin layer of castor oil.

The acoustic output (for a fixed driving voltage on the quartz plate) of such focusing systems with large separation distances between crystal face and lens, is markedly dependent upon the temperature. This is the result of the change in loading on the crystal caused by the variation in the acoustic length (i.e., number of wavelengths) of the separating oil column (Huetter and Bolt, 1955). The multibeam transducer illustrated in Fig. 1 is designed for operation near a frequency of 1 Mc./sec. The principal dimensions are given in Fig. 1 for an experimental animal irradiator. The planoconcave lens focuses the ultrasound at a distance in front of the lens which is determined by the radius of curvature of its front face. For a radius of curvature of 13/16 in., the midpoint of the focal region is at a distance of 33/4 in., from the center of the lens.

² E. Bell, (1957), private communication.
In order to bring the individual focal regions of the beams into coincidence in a common region, it is necessary to provide the multibeam irradiator with suitable adjustments. The device illustrated is provided with tilt adjustments which enable the individual beam axes to be swung in any direction approximately 7° from the central position. In addition to the adjustments for coincidence, the individual housings can be moved in the direction of the beam axes. This is accomplished by rotating the knurled wheel, labeled "phase adjustment" in Fig. 1. This motion permits the
beams to be brought into appropriate phase relationship in the common focal region.

When the focused ultrasonic beams from the individual lenses impinge on an interface separating a second medium such as brain tissue from the primary transmitting medium (salt solution) a small fraction of the incident acoustic energy is reflected because of the slight difference in acoustic impedance between the two media (of the order of 1% in the case of brain tissue and physiological saline). As a result, slight changes in the amount of acoustic energy transmitted through the interface can occur as the position and orientation of the irradiator is changed with respect to the interface. This effect can be observed by measuring the acoustic field variables by a thermocouple probe of the type described in Section II-3. If the orientation of the thermocouple probe (which consists essentially of a thermocouple junction imbedded in a disk of absorbing liquid, e.g., castor oil) is arranged so that acoustic energy is reflected from the interface be-
tween the transmitting liquid and the absorbing medium of the probe back to the focusing lenses, then the effect of reflection at the interface is seen as a “fine structure” in the measured axial field distribution. This is apparent as the probe is moved relative to the irradiator. The phase adjustments provided on the irradiator permit the reduction of these “fine structure” variations in the combined beam. This is illustrated in Figs. 2(a) and 2(b).

Figure 2(a) shows the axial distribution of the “square of the particle velocity amplitude” with the phase adjustments set to obtain a maximum value for this amplitude at a specific point on the axis as determined by the thermocouple probe. The amplitude of the variations are of the order of 8% of the “average” total amplitude. With the phase adjustments changed slightly the amplitude of the variations can be reduced to practically zero as illustrated in Fig. 2(b). This reduction of the amplitude of the “fine structure” is accomplished by reducing the total amplitude of the “square of the particle velocity amplitude” less than 10%. The type of adjustment just described is desirable since in irradiating tissue (brain) it is necessary to move the focus from one site to another and it is essential that the same percentage of incident sound energy enter the tissue on each exposure if accurate control of dosage is to be accomplished. Since the interface between the absorbing medium of the thermocouple probe and the saline simulates at least partially the effect of the interface between the saline and the soft tissue, it is possible to reduce the effect of a slight impedance mismatching during tissue irradiation by making the adjustments described with the aid of thermocouple probe measurements.

The multibeam irradiator suffers the disadvantage that the side lobes of the focused beam are large as compared with the side lobes of the focused beam produced by a single lens or a cylindrically symmetrical reflector irradiator. The side lobes of the beam at the focus of the irradiator illustrated in Figs. 1a and 1b are shown graphically in Fig. 3. The amplitude of the side lobes vary with the value of the angle variable which measures rotation about the axis of the main beam. This results from the fact that the irradiator is not cylindrically symmetrical about this axis. The transverse beam patterns corresponding to two values of the angle variable are shown in Fig. 3. The pattern with the smaller side lobes was obtained in a direction determined by passing a line through the “centers” of diagonally opposite housings (the direction labeled A in Fig. 3). The second transverse beam pattern was obtained along a direction at an angle variable of 45° with respect to the first direction (the direction labeled B in Fig. 3). This is the direction of the largest side lobes.

The multibeam irradiator is provided with a retractable pointer which is illustrated in Figs. 1a and 1b. The pointer provides a means of placing the

* F. Dunn, F. Brunswig, and W. J. Fry, unpublished work.
focal region of the irradiator at any desired geometric position with respect to a reference coordinate system. After adjusting the beams for "coincidence," the pointer's tip (in the lowered position) is placed at the center of the common focal region by an optical method. The pointer is retracted during calibration and for the irradiation of tissue.

A second type of focusing irradiator (Hueter, 1944) is illustrated

![Graph](image)

Fig. 2. (a) Axial distribution pattern of the square of the particle velocity amplitude of a multibeam irradiator—"fine structure" of large amplitude present. (b) Axial distribution pattern of the square of the particle velocity amplitude of a multibeam irradiator—"fine structure" reduced in amplitude by changing of the phase adjustments.
Fig. 3. Transverse beam patterns of multibeam focusing irradiator (center of focal region)—directions of highest and lowest side lobes illustrated.

Fig. 4. (a) Schematic diagram of reflector focusing irradiator.
schematically in Fig. 4a and photographically in Fig. 4b. This irradiator focuses ultrasound by a double reflection method. The sound produced by the vibrating X-cut quartz crystal, mounted in a fashion similar to that described for the multibeam irradiator, passes into the medium which serves as the transmitting liquid to conduct the sound to the tissue. The sound beam is interrupted by a solid metallic cone, with an apex angle of 90°, which reflects the waves radially away from the axis of the irradiator. The sound then is incident upon a parabolic reflector surface which focuses
the waves into a region in front of and on the axis of the irradiator. An important advantage of this type of irradiator design as compared with the multibeam lens type is that it dispenses with the plastic lenses which are unable to withstand continuous operation at high intensity levels. The advantage of a plastic lens, such as one of polystyrene (a plastic material which has a comparatively low ultrasonic absorption coefficient in the megacycle frequency range) is that, for equal driving voltages across the crystal, higher sound levels are more readily obtained at the focus than when metal lenses such as aluminum or magnesium are used (see Hueter and Bolt, 1955, p 265).

In addition to eliminating the use of a plastic lens, other advantages of the reflector irradiator design over the multibeam design are that it is much simpler to construct, and the side lobes are greatly reduced (Fig. 4c). However, the reflector irradiator suffers from the disadvantage that the aperture area is larger than that of the multibeam irradiator for equal lengths of the focal region, and therefore its entire beam is not as readily passed through practical bone openings made in the skull. It is possible that further research on reflector type irradiators could result in units which might be provided with adjustments to permit the choice of portions of the beam from the parabolic surface. Such a design is necessary if the flexibility of a multibeam irradiator is to be realized. Experimental measurements (unpublished) show that the length of the focal region of the reflector irradiator discussed here is longer than that of a multibeam irradiator of the same aperture size and focal length.

b. Acoustic Coupling. The high level ultrasound is conducted from the irradiator to the brain by physiological salt water which differs only slightly (approximately 2% difference) in its characteristic acoustic impedance (the product of the density of the medium and the velocity of sound in the medium) from that of brain tissue. The sound velocity for physiological saline at a temperature of 37°C. is $1.537 \times 10^5$ cm./sec., while that of brain tissue at the same temperature is approximately $1.55 \times 10^4$ cm./sec., as estimated from data for hog and dog brain published by Ludwig (1950). Thus refraction of the sound at the interface between saline and brain tissue, for angles of incidence as large as 45°, can produce a shift of the focal spot of approximately 3/4 mm. for the greatest depths (11-12 cm.) in a human brain.

Experimental measurements of such shifts for fresh (excised within 2 hr. after death) human brains are in rough agreement with this calculated value, which is therefore a measure of the accuracy of "geometric positioning," i.e., placement accuracy with respect to a reference coordinate system. The shape and size of the focal region, after the sound passes through the brain, is practically identical with that when the sound passes entirely
through water. The multiple interfaces in the brain reflect only a very small fraction of the incident acoustic energy, and scattering thus does not interfere with the production of results of the type reviewed in this chapter. The reflected energy may, however, be great enough to permit tissue structure visualization, particularly the outlining of the cerebral ventricles.

The physiological saline, which transmits the sound, must be degassed to eliminate cavitation nuclei, which could produce bubbles and thus interfere with the transmission of the intense sound by scattering and absorption. By direct test, freshly boiled saline is suitable for transmitting ultrasound at 1 atm. pressure and room temperature, at a frequency of 1 Mc./sec., up to a maximum intensity of approximately 8 kw./cm.². This figure was obtained by determining the sound level at which visible cavitation occurs at the focus of an irradiator operating at this frequency. The tissue of the central nervous system is either free of cavitation nuclei, or if present they are unable to grow under the ultrasonic dosage conditions of interest here (Dunn and W. J. Fry, 1957b). This is evidenced by the fact that there is negligible scattering of the ultrasound at high levels, e.g., as occurs in salt water which is not degassed.

For experimental animal work, the transmitting liquid is supported by a coupling pan of the type illustrated in Figs. 5a and 5b. A wire tourniquet secures the skin tightly against the flanged bottom of the pan and thus insures a liquid-tight seal (Fig. 5b). Since the dosage of ultrasound required to produce a given change in the tissue is a function of the temperature of the tissue, it is essential that the transmitting liquid be maintained at a constant temperature (normal body temperature is the usual choice) during the experiment. This is accomplished by means of the heat exchange coils shown in the top view of the pan (Fig. 5a). For studies involving the use of electrodes on the cortex, or within the brain, the coupling pan is provided with electrode clamps as illustrated in Fig. 5a.

c. Animal Head Holder. A holder must be provided to support the head of the experimental animal or human patient. The head holder can also be provided with a means of supporting the coupling pan. For experimental animals (cats and monkeys), a structure (Fig. 6) is used in which the usual interaural, horizontal, and midsagittal planes are employed as zero references (Jasper et al.; Olszewski, 1952). This structure utilizes ear bars, infraorbital clamps, and an oral fixture (which bears against the teeth of the upper jaw) to support the skull of the animal.

d. Technique of Preparation and Irradiation—Animal. Before the anesthetized animal is placed in the apparatus, the pointer, which is attached

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¹ The value given by Eache (1952) for a frequency of 1 Mc./sec. is approximately 2 kw./cm.². The latter value was determined by an acoustic method which Eache indicates is more sensitive than the visual procedure.
Fig. 5. (a) Top view of coupling pan (animal). (b) Schematic diagram of pan (cross-sectional view) illustrating assembly to cutaneous tissue.

to the irradiator and whose tip coincides with the focal spot when in the lowered position, is positioned so that the tip lies on the midline of the head holder and is also collinear with the line through the centers of the ear bars. The coordinates, on the system which supports the irradiator,
corresponding to this ear bar zero are recorded. One can then transform from the coordinates of stereotaxic brain atlases, based on the zero reference planes of the head holder, to the coordinates of the system supporting the irradiator. The pointer is then retracted, or removed from the irradiator, and the anesthetized animal is mounted in the holder. The soft tissues over the appropriate area of the brain are incised, and the skull cap is removed.

![Diagram of experimental animal head holder](image)

**Fig. 6.** Experimental animal head holder (for cats and monkeys).

The bone must be removed if precise positioning and accurate control of dosage are to be realized. The acoustic velocity of bone is considerably different from that of soft tissue (Theismann and Pfander, 1949). It is this fact and its nonuniform thickness and variable radius of curvature that prevent the desired degree of control if the bone is left in place. In addition, the high acoustic absorption coefficient of bone (Hueter, 1952) can lead to such a high rate of heating in the sound field, that neighboring brain tissue is damaged. The dura mater need not be opened. The arrangement of the irradiator, coupling pan, head holder, and skull of an animal are illustrated in Fig. 7. After the coupling pan is engaged in water-tight
connection with the skin of the animal, it is filled with degassed sterile physiological saline. The saline is transferred to the pan in a manner which prevents the formation of bubbles which would introduce gas nuclei into the liquid.
The irradiator (immersion sterilized) is then moved into position to place the focal spot at the appropriate position in the brain. Although a number of different designs for the carriage unit supporting the irradiator are possible, it is especially convenient to use the type illustrated in Fig. 8, which has evolved as a result of previous experience with other positioning carriage units. The unit illustrated in Fig. 8 is housed above the irradiation room, and a tube projects through the ceiling of this room to support the irradiators. It is desirable to have available a number of different types of irradiators which can be readily coupled to the lower end of the tube illustrated in the general view of the irradiation room shown in Fig. 9. Each of the mutually perpendicular linear motions of the carriage system is provided with a continuously-variable-speed motor drive. The movements of the carriage are limited in each excursion by switches, which can be arranged so that the focal spot of an irradiator cannot leave a prescribed volume of tissue even if the operator continues to manipulate the controls for continued motion.

Fig. 8. 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.
A spot irradiation procedure has been used in most of the work accomplished to the present time. In this procedure, the tissue is irradiated with the focal spot of the irradiator in a stationary position. After the exposure at this position is completed, the carriage unit is moved so that the focal spot is placed at the next position at which an exposure is desired. The placement of the carriage unit is accomplished by reading linear scales, calibrated in millimeters, which lie along the three orthogonal directions of motion. These three scales are viewed by television camera tubes, and magnified images (about $20\times$) of the scales appear on three picture tubes in the irradiation room. The closed circuit television systems circumvent mechanical coupling devices and thereby make it possible to position the focal spot of the sound beam(s) from an irradiator with a geometric accuracy of $\pm 0.1$ mm.

The irradiator support tube passes through a movable electrical shield at the floor level of the room which houses the positioning system. The tube
is provided with a concentric conductor which transmits the electrical excitation to the irradiator. The metal box at the upper end of the tube (Fig. 8) houses the interchangeable components which permit electrical impedance matching of an irradiator to the driver.

In the illustration of the irradiation room (Fig. 9), the animal head holder is shown mounted on a table which provides two rotational degrees of freedom. This supporting structure is designed to ride on the positioning track also illustrated in Fig. 9. The background of the photograph shows, mounted in the wall of the room, the electrical equipment necessary for: calibration, frequency control, time duration, and level of exposure, and positioning of the carriage unit (one positioning control is mounted directly on the control panel wall, and a second positioning control is mounted on the narrow tube which projects from this wall). Speed controls for the motor driving units, electrical stimulators, amplifiers, instrumentation for controlling a sequence of events (such as the time of initiation and termination of irradiation, time of stimulation—visual, auditory, electric, 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. The frequency is set by comparing the signal generator frequency with that of a crystal calibrator. The uncertainty in the frequency (1 Mc./sec.) is ±100 cycles/sec. The duration of the exposure period is controlled by a digital timer with a unit time interval of 1 msec. (millisecond). A temperature controlled electronic tuning fork provides the reference time base. The exposure interval can be set in integral multiples of 1 msec. for durations of irradiation up to 100 sec. (This is dependent only on the number of digital timer stages.) The envelope of the ultrasonic pulse is accurately rectangular with rise and delay times of approximately 10 μsec. The sequence control unit operates on a counter principle with a time unit interval of 1 msec. (Dunn, 1956). Standard commercial equipment is used for recording electrical events of neurophysiological interest. This includes a series of amplifiers which can be used to drive a double-beam oscilloscope provided with a recording camera and an EEG machine.

The tube which supports the control station near the irradiator (Fig. 9) also contains tubes providing a heat exchange liquid which can be coupled to the heat exchange coils mounted in the coupler pan. The temperature of the heat exchange liquid can be controlled over a wide range (0°–40°C.). The usual procedure consists in maintaining the temperature of the coupling liquid close to the “normal” temperature of the animal. This eliminates temperature gradients in the tissue. The control of the tissue temperature is necessary for the accurate specification of dosage conditions to obtain
reproducible lesions for given ultrasonic dosage parameters. (See Fig. 35 for quantitative information on the variation of dosage with temperature.)

The electronic control instrumentation includes metering and other equipment to enable the driving voltage across the transducer to be set and maintained at a desired value. The transducer driving voltage to obtain the required sound level is determined from calibration measurements (Section II, 3e).

From a knowledge of the dosage required to produce the desired change in the tissue, the calibration measurements, and the path length in the tissue which must be traversed by the sound to the site of the focus, it is readily possible to compute the voltage necessary to excite the irradiator (at a frequency of 1 Mc./sec., the average pressure absorption coefficient for brain tissue is approximately 0.10/cm.). If a lesion larger than that produced by a single spot irradiation is desired, the procedure most commonly used up to the present time consists in irradiating the desired region of the central nervous system in a series of adjacent positions spaced a fixed distance apart. At a frequency of 1 Mc./sec., with the focusing systems illustrated in this chapter, spacing distances from \( \frac{1}{2} \) to 2 mm. are used, the specific value depending on the dosage and the degree of uniformity desired. A rectangular array of spots is placed in the brain with a fixed time interval between the exposures at adjacent positions. (If a fixed time interval is not possible, then the criterion is "an interval not less than some minimum value"—usually not less than 1 min.)

The use of the fixed 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. A second irradiation procedure utilizes the method of sweeping the focus of the sound beam (or beams) through the tissue at a uniform rate. 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 of reversible effects. The simplest sweeping procedure of this type 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.

As already indicated, bone absorbs ultrasound very strongly in the fre-

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1 The reduction in pressure or particle velocity amplitude in a path length \( x \) of tissue is given by \( P = P_0 e^{-0.1x} \) and \( v = v_0 e^{-0.1x} \), respectively, where \( P \) designates the pressure amplitude and \( v \) designates the particle velocity amplitude (the subscript zero designates the values for zero path length).
quency range of interest here (Hueter, 1952); its temperature rises rapidly in an intense sound field. Thus damage to adjacent brain tissue may result from heating by conduction (Barnard et al., 1955). This situation arises when the focus of the ultrasonic beam (or beams) must be placed close to bone in order to produce a lesion in nerve tissue adjacent to, or in the immediate neighborhood of bone. In many instances it is not convenient or practical to remove the bone (particularly at the base of the brain), and it is therefore necessary to devise methods of preventing disturbances to neural tissue by heat conducted from the bone. In some cases, the irradiation of nerve tissue close to the bone can be accomplished by orienting the direction of propagation of the sound along a path approximately tangential to the bone surface.

In instances where this procedure is not practical, a procedure can be used which consists of subdividing the dose into exposure intervals short enough so that bone heating during each interval is not sufficient to produce tissue damage by conduction. These exposure irradiation intervals can be spaced in time so that the bone temperature returns to the base value between exposures. With respect to this latter procedure, dosage studies indicate that a series of "subdamaging" doses of ultrasound (separated by time intervals) can sum to produce an irreversible effect. However, after the tissue is subjected to a "subdamaging" dose, a decay process follows (W. J. Fry et al., 1951). Therefore, the total time required for such a summation procedure may be much greater (1/2 hr.) than the time required for a single exposure (1-3 sec.) to produce the desired change. This procedure can therefore become extremely time consuming particularly if a large lesion is to be produced by the successive placement of the focal spot in a number of positions.

A technique, practical in many cases, which permits the use of a single exposure (at each position), consists in flowing a thin layer of degassed saline between the heated bone and the brain tissue. The liquid is conducted to the region by small-diameter, flexible plastic tubes, the open ends of which are placed near the region of interest. It is preferable to place these tubes outside the dura. In many instances, however, this is not possible because of the strong adherence of the dura to the bone, particularly near the base of the brain. In such circumstances, it has been possible to place the tubes inside the dura without damage to the adjacent brain tissue. Sterile degassed saline is flowed through the tubes under slight pressure (approximately 1/2 p.s.i.) before, during, and for some time (1 min.) after the exposure period. The thin film of saline, flowing between the bone and the brain tissue, removes the heat conducted from the bone and thus prevents damage to the adjacent brain tissue. 6

6 F. J. Fry and W. J. Fry, unpublished work.
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. 5a. Figure 10 shows a set of four bipolar subcortical electrodes in position in the visual cortex of a cat. These electrodes are supported by the coupling pan. 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 so constructed that electrical artifacts are not introduced by action of the flow of the coupling liquid (produced by the intense sound field) on the leads by interaction between the ultrasonic field and the insulation of the electrode leads. Electrode leads (0.010 in. diameter nichrome) covered with a layer of thin insulation are stiff enough to withstand the acoustic flow without appreciable motion, and the use of such electrode leads prevents the introduction of artifacts either during or at the ends of the exposure periods. Increased stiffness of the electrode leads cannot be accomplished by using wires of large diameter since this would interfere with the passage of the sound from the irradiator to the brain.
A number of different materials were used to insulate the portions of the electrode leads which must be in the sound field. The use of Formvar\textsuperscript{7} insulated nichrome has reduced the artifact due to interaction between the sound field and the insulation to a negligible level. The ends of the electrode wires are first flattened and sharpened. They are then plated with silver to reduce the electrical impedance at the tissue-metal interface. The electrode leads can be covered with heavy rubber insulation up to the position of clamping as illustrated in Fig. 5a. The bipolar electrode leads are tied together at intervals with a strand of fine thread to reduce the electrical artifacts produced by slight relative motion between the wires.

On the basis of the results obtained up to the present time, it appears that the production of quantitatively reproducible reversible changes by the ultrasound requires that the level of anesthesia be controlled more accurately than can be realized from the use of widely spaced injections. Accurate control can be attained by the use of an automatic anesthesia injector which provides an intravenous injection of an accurately controlled amount of anesthetic at short time intervals. For example, with a tube placed in the femoral vein of an adult cat (weight approximately 5 lb.) an injection of approximately 0.2 mg. of pentobarbital sodium every 2 min. makes it possible to realize adequate control of the anesthesia level, which enables quantitatively reproducible reversible effects to be produced in the brain by focused ultrasound. Since it is desirable to vary the level of anesthesia, in studies of reversible effects, over a range which includes a depth sufficient to interfere with respiration, it is necessary to use a respirator in conjunction with these experiments. If a sense receptor is to be stimulated, a controlled source of stimulation is required. The sequence timer provides appropriate control pulses.

c. Technique of Preparation and Irradiation—Human. The head of the human patient is supported in a different fashion from that of the experimental animal. The midsagittal, Frankfurt, and interaural reference planes are determined, as in the case of the experimental animal, by ear bars and by fixtures which rest on the infraorbital ridges (Spiegel and Wycis, 1952). However, the ear and eye bars are not used to support the head but are employed only for orientation with respect to the holder. The human head holder is illustrated in Fig. 11. One ear bar and the infraorbital fixtures can be seen in Fig. 11. For the patient in a reclining position, the head is supported during the orientation procedure by a movable rubber-covered platform which surrounds the lower ear bar as shown in Fig. 11. The lower ear bar can be moved, in a snugly fitting hole in the platform, in a direction perpendicular to the platform surface so that the ear bar tip fits snugly in the ear canal, and the surface of the platform is in contact with the side.

\textsuperscript{7} Driver-Harris Co., Harrison, N. J.
of the head. The assembly of platform and ear bar can then be moved together to permit easy centering of the head of the patient in the holder. Scale marks on the ear bars are provided to facilitate this adjustment.

Four pins, which mount on universal supports, are brought into position to support the skull after the head is appropriately positioned with the ear bars and infraorbital fixtures (see Fig. 11). The tips of these sterilized pins are rounded to fit into previously prepared indentations of equal radius in the skull. The pins are moved into place after the skin has been opened over the positions of the indentations in the skull. The universal support for each pin permits the hemispherical tip of the pin to be brought into any desired position to fit the corresponding hemispherical indentation in the skull. The adjustments permit motion along the axis of the support, an angular rotation about this axis, and motion of the pin in the direction of its long axis. Three micrometer mounts on each universal support permit accurate reproduction of the pin tip position from one time to another. This
is necessary since the same 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.)

If internal reference landmarks (ventricles) are to be used for positioning, it is necessary to provide the head holder with a suitable X-ray unit. Accordingly, a bracket arrangement which supports an X-ray tube in two positions on the head holder is provided. This is illustrated in Figs. 12a and 12b. The X-ray film holders are provided with pins which enable them to be placed accurately in position on the head holder. Since the X-ray tube is not a great distance from the head of the patient, it is necessary to account for the distortion in scale, on the film, of the projected X-ray images of the brain landmarks when calculating position coordinates for the focus of the ultrasonic irradiator. The evaluation of position coordinates involves the use of correction scaling factors plus a knowledge of the position of two mutually perpendicular undisplaced projected lines. (Any two mutually perpendicular lines through the point, on the film, of perpendicular pro-
jection by the X-rays. For ease of operation and simplification of the procedure, it is desirable that these undisplaced coordinate lines remain in the same position for every picture. The X-ray cassettes are provided with four appropriately placed lead pointers whose tips appear on every X-ray picture and thus designate the positions of the desired undisplaced lines. This means that the X-ray tube position and orientation must be identical for all pictures. This is accomplished by the bracket arrangement illustrated in Figs. 12a and 12b.

The head holder is also provided with a positioning system which supports a tungsten crosshairs. This facilitates the placement of the focus of the ultrasonic beams at the desired site within the brain when X-ray landmarks are used. The directions of motion of the hand-operated positioning system coincide with the axes of the head holder. This system is especially useful whenever the coordinate directions associated with the head holder are oriented at non-zero angles with respect to the directions of motion of the positioning system which supports the irradiator. Under such circumstances it is inconvenient and extremely time consuming to use the pointer (whose tip coincides with the focal spot of the sound beam) attached to the irradiator since this entails numerous trigonometric computations. Such calculations are completely eliminated by the use of the hand-operated positioning system which supports either the crosshairs or a matching pointer.

For a lateral X-ray picture, the crosshairs (supported on the hand-operated system) is first positioned at the anterior-posterior and vertical coordinates of the brain structure of interest, which are obtained from maps of the brain using the ear bar center as zero reference. This first approximation to the position (anterior-posterior and vertical coordinates) is then corrected by examination of the X-ray photograph showing the internal reference landmarks and the crosshairs. The required movements of the crosshairs are obtained by simple scale measurements on the X-ray film and by taking into account the scaling factors. The correct lateral coordinate position (corresponding to the structure of interest) of the crosshairs is determined by placing it in front (back) of the patient's head and taking an X-ray picture in the anterior-posterior direction.

After the patient's head is disengaged from the head holder, the crosshairs is replaced by the matching pointer whose tip is placed at the geometric position or positions in space at which the structure to be irradiated in the brain lies when the head is supported by the holder. The tip of the pointer, which is attached to the irradiator, is then brought into coincidence with the tip of the pointer of the positioning system by moving the irradiator.

Previous to placing the tips of the pointers in coincidence, it is necessary to determine the position and size of the required bone opening and the
angular orientations of head holder and irradiator. This is accomplished by mounting in the head holder a skull containing a model of the structure to be irradiated at the appropriate interior position. Cones simulating the beam shapes are fastened to the irradiator and the bone openings and angles for irradiation are determined. A template for the skin flaps and bone openings on the patient's head is then prepared. The position of the flaps on the patient's head can be duplicated accurately by providing the template with marking holes, the positions of which are determined by coordinate readings on the positioning system (pointer's tip placed at marking hole) which which the head holder is provided.

When the pointer tips are brought into coincidence, the coordinate values on the irradiator supporting system are then read and are thus available for the irradiation procedure. It is emphasized that, in general, the use of the positioning system which supports a crosshairs or matching pointer simplifies the procedure of determining the coordinates on the irradiator positioning system to be used for the irradiation. This is a consequence of the fact, already mentioned, that the directions of the motions on the irradiator positioning system are not, in general, along the coordinate directions of the head holder.

The head holder is also provided with structures to support the coupling pan illustrated in Fig. 11. The lower portion of the pan can be readily disassembled from the upper portion. This is desirable since it is convenient to have available a number of contoured bottom portions to conform to different shapes of skull configurations for different positions of bone openings. The conforming rim of the bottom portion of the pan contains a channel which supports an inflatable rubber tube. After the pan is placed in close proximity to the skin of the patient, it is firmly fastened to its supports, and the skin and muscle are tied to stubs provided in the pan base. When this procedure is completed the tube is inflated with air. This procedure results in a liquid-tight seal between the coupling pan and the skin of the patient.

2. Unfocused Field Instrumentation, Preparation, and Irradiation Technique

Uniform ultrasonic field configurations are especially useful in dosage studies for the elucidation of physical mechanisms of ultrasound on tissue. This follows from the fact that a considerable volume of tissue, by comparison to the focal region size of the irradiators already described (Section II, 1) must be affected to produce a given functional endpoint in many systems of interest. The complication of interpretation which arises when the irradiation of the desired volume of tissue is not accomplished by a single uniform exposure is discussed in the section on physical mechanisms.

Because of the difficulties involved in the production of uniform high intensity ultrasonic beams, it is desirable to choose a preparation, for
studies of physical mechanism, which requires the irradiation of a relatively small amount of tissue. The young mouse was chosen for such studies for a number of reasons (W. J. Fry and Dunn, 1956; Dunn and W. J. Fry, 1957) in addition to the fact that it is small in size, and these reasons are discussed in the section on physical mechanisms. It is possible to obtain rather precise results in a dosage study with appropriate ultrasonic instrumentation. The

![Diagram of sound tank](image)

Fig. 13. Sound tank, viewed from above, showing positioning system and absorber in place.

instrumentation and techniques which have proved successful for obtaining appropriate data for such studies will now be described.

a. Sound Tank. The acoustic energy is produced by a circular X-cut quartz crystal. One face of the crystal is in contact with the transmitting liquid and is at ground potential. The cylindrical tank, Fig. 13 (Dunn, 1956), which supports the crystal assembly and positioning system, for holding the preparation, also contains an absorption chamber which makes contact with the transmitting liquid by means of a Teflon-rubber diaphragm. The plane of the diaphragm is placed at an angle of 45° with respect to the axis of the sound tank in order to minimize the effect of small amounts of reflected energy and thus assure a traveling wave field. The tank is provided with a
port through which positioning systems supporting preparations, acoustic probes, and other associated instrumentation can be introduced. The transmitting liquid is physiological saline and is degassed by boiling. The sound tank is built to withstand pressure differentials (up to 20 atm.) so that the pressure coefficients of dosage relations can be determined. The positioning system, which supports the preparation, can be accurately placed in a fixed position in the tank.

The cylindrical sound tank is housed in a modified deep-freeze unit which provides refrigeration to permit lowering of the temperature of the transmitting liquid, which controls the temperature of the preparation. The young mouse, 24 hr. after birth, is an essentially poikilothermic animal. Consequently, the temperature of the animal comes to equilibrium at a value dependent upon the state of the animal and the temperature of the environment. For example, a young mouse 24 hr. after birth in a saline bath at 10.0°C. comes to equilibrium at 10.2°C. (Stier and Pincus, 1928; Dunn, 1956). By varying the base temperature of the preparation, it is possible to obtain temperature coefficients of dosage relations. The temperature control for the studies reported in this review is ±0.1°C.

The electronic instrumentation for providing power to drive the irradiator and to control the duration and level of exposure has characteristics similar to that described for focusing irradiator instrumentation.

b. Technique of Preparation and Irradiation. It is essential, as in the case of the focused beam work, that the volume of tissue irradiated be placed accurately in the position in the sound field at which the calibration measurements are made. For the type of dosage study described in this chapter, the two instruments which are positioned in the field are the calibration probe and the mouse holder. To facilitate the positioning of these instruments, a coordinate support system capable of continuous variation in three orthogonal directions is mounted in the irradiation chamber (Dunn, 1956). An accurately machined tongue is used to attach either the calibration probe or the mouse holder to the coordinate positioning system. The positioning system is shown supporting the thermocouple probe in Fig. 14 and supporting the mouse holder in Fig. 15. The calibration probe, the sensitive element of which is a small (0.001 in. diameter) thermocouple junction, is used in determining the field configuration and the sound level. The transverse field distribution, approximately 10 cm. from the crystal face, is shown in Fig. 16.

The first step in the preparation for irradiation is the calibration of the sound field at the position at which the tissue structure of interest will be placed (Dunn and W. J. Fry, 1957b). This is accomplished by attaching the calibration probe to the supporting tongue and then fastening this assembly to the positioning system. This geometric configuration is ac-
Fig. 14. Thermocouple probe mounted on positioning system.

Fig. 15. Mouse holder mounted on positioning system.
curately duplicable because alignment is accomplished by a dowel pin arrangement. After the necessary calibration measurements are made, the tongue-probe assembly is removed from the positioning system in the tank and dismantled. A cross-hair attachment and the mouse holder are then fastened to the tongue. The cross-hair attachment is aligned on the tongue by a dowel pin arrangement, so that the position (set by an optical method) of the cross hairs of the attachment accurately duplicates the position of the thermocouple junction of the probe in a plane perpendicular to the axis of propagation and is displaced a few millimeters along the axis in order to allow for the preparation. The anesthetized young mouse is supported in the holder, which is provided with adjustments which permit positioning of the animal with respect to the cross hairs. This is accomplished optically as described below.

A specific change in motor function serves as a convenient and unambiguous endpoint for an ultrasonically induced effect in the irradiated animals. The lumbar enlargement of the spinal cord is chosen as the region to be irradiated with the ultrasonic energy, and paralysis of the hind legs then serves as the functional endpoint. This region of the cord contains a high density of the neurons associated with the femoral, sciatic, and obturator nerves (see, e.g., Greene, 1955). Thus, alteration of motor neurons of the lumbar enlargement produces functional changes in the hind limbs of the animal. The functional changes are easily detected, for example, by observing the
response to electrical stimulation of the skin of the animal in the foot region of the hind limb. In the case of no alteration by ultrasound, the animal displays a strong reflexive action to stimulation by violently jerking the limb away from the origin of the stimulus. In the case where the spinal cord has been altered in such a fashion as to produce motor paralysis of the hind limbs, very strong stimuli will not produce a reflexive action of these limbs.

Ossification is not complete in the 1-day old mouse (Walker and Wirschafter, 1957). Histological examination shows that the tissue overlying the dorsal side of the cord is nonosseous, while that over the lateral and ventral sides shows a slight degree of ossification. Therefore, it is not necessary to perform surgery to expose the spinal cord for irradiation since the configuration of the ultrasonic beam is not appreciably disturbed by the soft tissue and the absorption coefficient of the overlying tissue is not high as it is for bone.

When an intense light beam is passed through the animal from the ventral side, the vertebrae from the first lumbar through the sacral and caudal regions can be seen clearly when viewed from the dorsal side. The sacrum and the sacral vertebrae are therefore taken as convenient reference loci for locating other skeletal structures of the young mouse. Thus any vertebra in this region can be identified by first identifying the sacrum and the sacral vertebrae and then counting the vertebral segments until the desired one is located (Dunn and W. J. Fry, 1957b).

During the irradiation of the mouse, the axis of the acoustic beam is centered on the third lumbar vertebral segment. Histological examination of the mouse spinal cord shows that the region of the third lumbar vertebra is the approximate center of the lumbar enlargement which contains the high density of the motor neurons. The histological study also indicates that the spinal cords of the animals used in this investigation very nearly fill the vertebral canal. Therefore, a close 1:1 spatial correspondence between the vertebral segments and the cord segments exists (Dunn, 1956).

Previous to placing the mouse in the holder, it is examined by the electrical stimulation method described above to insure that a specimen possessing normal motor facility is utilized. The animal is then cooled to render it dormant so that it can be properly positioned in the mouse holder and to insure that it will remain in that position until it is placed in the sound tank and irradiated. When the mouse is sufficiently cooled, it is placed in the mouse holder, which holds the head, the hind limbs, and the tail firmly. The animal is then fully extended to reduce possible lateral movement. The mouse holder, the tongue, and cross-hair attachment are then assembled and placed over an intense, cool light source. The mouse holder is then adjusted to place the center of the third lumbar vertebra under the intersection of the cross hairs. The cross-hair attachment is then removed, and the mouse holder is ready to be placed in the sound tank.
The mouse-holder assembly is then placed in the sound tank, which is filled with the degassed 0.9% saline. Several minutes are permitted to elapse before irradiation in order that the animal can reach temperature equilibrium, which is realized, as checked by measurement with imbedded thermocouples, in this period of time. When the mouse reaches temperature equilibrium, a single acoustic pulse of rectangular envelope (having rise and decay times of approximately 10 μsec.), predetermined intensity (plane wave case), and time duration is then initiated. After the cessation of the sound, the mouse-holder assembly is removed from the sound tank, the cross-hair attachment is placed in position, and the assembly is again placed over the intense, cool light source to determine whether or not the position of the animal has moved with respect to the intersection of the cross hairs. In cases where such changes are observed, the animals are discarded from the compilation of the results. After checking for a possible change in position of the animal in the mouse holder, the mouse is removed from the holder and rapidly warmed to room temperature. The animals are examined for paralysis or overt movements by the electrical stimulation method outlined above, approximately 15 min. after exposure and again after 6 hr.

The accuracy of placement of the third lumbar vertebra with respect to the axis of the sound beam can be determined from the following: (1) The accuracy of the machined parts is ±0.002 in. or ±0.05 mm. (2) The position of the axis of the beam can be determined to ±0.1 mm. (3) The accuracy of locating the center of the third lumbar vertebra, which is approximately 0.6 mm. in length, is ±0.1 mm. Thus, the overall uncertainty in the position of the center of the third lumbar vertebra with respect to the axis of the sound field is ±0.25 mm. Since the beam width (see Fig. 16) at 95% of the peak intensity is 2.6 mm., and since in the lumbar region, the vertebral segments are 0.67 mm. long, measured from corresponding edges, then nearly four vertebral segments of the cord are irradiated with an acoustic intensity variation of not more than 5%.

3. Field Configurations and Calibration

Precise control of the ultrasonic dosage is required both to realize reproducibly selective changes in the central nervous system and to obtain quantitative data for the determination of physical mechanisms. Therefore, it is essential to use probes which are capable of detecting fine structure present in the fields and which have a stability permitting determination of the absolute sound levels (intensities) to an accuracy of 2-3%. Both of these requirements are satisfied by the type of thermocouple probe described here (W. J. Fry and R. B. Fry, 1954b; Dunn and W. J. Fry, 1957a). This section includes a description of: the design and construction of these
probes, the principles of operation (including typical measurements), and probe calibration and auxiliary equipment.

a. Thermocouple Probe Design and Construction. The general design principle for thermocouple probes, of the type described here, is the imbedding of a small thermocouple junction in a sound-absorbing material which closely matches in density and sound velocity the values for physiological salt water. Since both focused sound beams and plane-traveling wave fields are of interest in the research reviewed in this chapter, a thermocouple probe configuration of the type illustrated schematically in Fig. 17 is convenient. A photographic illustration of such a probe is shown in Fig. 18.

The housing for the probe is in the shape of a thick disc, the inner diameter of which must be greater than the cross-sectional dimensions of the ultrasonic field so that a traveling wave can pass through the probe absorbing material without interference from the supporting ring structure. The supporting rings are provided with "Kovar" lead-throughs to enable the thermocouple to be mounted along a diameter of the housing. The thermocouple is assembled from 0.003-in. diameter wire (e.g., copper and constantan), which is tapered by etching to 0.0005-in. diameter in the neighborhood of the junction. Thin windows (0.003-in. polyethylene sheet) separate the absorbing medium (castor oil) from the external medium (salt water). The thermocouple wires are fastened together by a lapped solder junction, which is positioned in the approximate center of the housing.

Since the fine tapered wires and the junction may be subjected to considerable shock, especially if the probe housing does not receive delicate treatment, it is desirable to incorporate a small spring in the thermocouple leads within the housing. This can be accomplished by forming a spring directly in the constantan lead. Since castor oil closely matches physio-
logical saline in acoustic impedance (a difference of less than 7% at a temperature of 30°C, where a major fraction of the calibration and field distribution measurements are made) and also has a relatively high acoustic absorption coefficient at a frequency of 1 Mc./sec., it is a convenient choice for the imbedding liquid at the present time. It is extremely desirable, from the viewpoint of determining the geometric position of the focal spot of an irradiator relative to a given structure (pointer tip on the ir-

**Fig. 18. Thermocouple probe.**

radiator) to construct the probe so that the small thermocouple junction can be seen visually. It is therefore desirable that both the imbedding material and the window be optically transparent.

*b. Principles of Probe Operation.* The behavior of such a thermocouple probe in response to a pulse of ultrasound has been described in quantitative detail in the literature (W. J. Fry and R. B. Fry, 1954a, b; Huetter, 1957; Dunn and W. J. Fry, 1957a). The temperature change at the thermocouple junction, resulting from an exposure to an ultrasonic pulse, is the result of heating by two mechanisms. The liquid in the immediate neighborhood of the wires is heated by the action of the viscous forces resulting
from relative motion between the wires and the imbedding medium. It is also heated because of the absorption of the sound in the body of the medium. A recording of the thermoelectric emf produced by the thermocouple in response to a 1-sec. pulse of ultrasound (rectangular envelope, frequency 1 Mc./sec.) is shown in Fig. 19.

The initial rapid increase, which occurs during the first 0.1 sec., is caused by the viscous force action at the wire boundary. The slower increase, which follows, is the result of volume absorption in the body of the imbedding medium. The percentage deviation from linearity of the slow rise is dependent upon (see W. J. Fry and R. B. Fry, 1954a): the time elapsed after initiation of the exposure, the temperature, the thermocouple wire diameter (at the junction), the heat conductivity coefficients of the constituent metals of the thermocouple, the beam configuration, the acoustic pressure amplitude (or intensity), the heat conductivity coefficient, and heat capacity per unit volume of the imbedding medium,

![Diagram](https://via.placeholder.com/150)

**Fig. 19.** Thermocouple probe output in response to a 1-sec. pulse of ultrasound.

and the change in the acoustic absorption coefficient of the imbedding medium with the temperature.

As a specific example (W. J. Fry and R. B. Fry, 1954b), the deviation of the slow rise from linearity is approximately 4% with the junction (copper-constantan 0.0005 in. diameter) on the axis of a focused beam 4 mm. in diameter (width at one-half the peak intensity) and at a sound intensity of 20 w./cm.² for 1 sec., and with castor oil at 25°C. as the absorbing medium (frequency 1.0 Mc./sec.). Under the same conditions, except for an intensity of 15 w./cm.², the deviation from linearity is approximately 1% (W. J. Fry and R. B. Fry 1954b). The relatively rapid decrease in temperature (Fig. 19), following termination of the acoustic pulse, is the result of the removal of the viscous force action which contributes a heat source confined to the immediate neighborhood of the wires during the acoustic pulses. The subsequent slow phase of the temperature decline is a consequence of the cooling of the imbedding medium previously heated by acoustic absorption in the body of the medium. The component of the temperature increase at the junction, resulting from absorption in the body of the imbedding medium, is independent of the orientation of the wire in the field. However, the time rate of heating and consequently the increased temperature resulting from the action of
the viscous forces between the wires and the fluid imbedding medium is
dependent upon the angle between the direction of the particle velocity
and the direction of the wire.

For plane-traveling wave fields, the relation between the acoustic
intensity \( I \) at the junction and the time rate of change of the temperature
\( dT/dt \) during the linear portion (before conduction becomes important)
of the second or slow phase of the thermocouple response is

\[
\mu I = \rho C \frac{dT}{dt},
\]

(1)

where \( \mu \) designates the acoustic intensity absorption coefficient of the
imbedding medium per unit path length, the product \( \rho C \) designates the
heat capacity of the imbedding fluid per unit volume (\( \rho \) designates the
density and \( C \) the heat capacity per unit mass), and \( (dT/dt) \) designates
the initial time rate of change of the temperature of the imbedding medium
resulting from absorption in the body of the medium. The identification
of the time rate of change of the temperature indicated by the slow phase
of the thermocouple response with the quantity \( (dT/dt) \) of Eq. (1) is
permissible, for a specified accuracy, only if the wire diameter is less than
some maximum value which is dependent upon the beam structure to
be resolved and the material of the thermocouple wires (W. J. Fry and
R. B. Fry, 1954a). The sound level must also be limited or appropriate
correction made because of the dependence of \( \mu \) and \( \rho C \) on the tempera-
ture. As a specific example, an iron-constantan thermocouple (imbedded
in castor oil) with a wire diameter, in the neighborhood of the junction,
of 0.001 in. is suitable for making measurements, with an accuracy of
approximately 1%, on beams approximately 2 mm. or more in "diameter"
(width at a pressure amplitude equal to 0.707 of the peak value).

If the absorption coefficient of the imbedding material is not known
sufficiently accurately at the frequency of interest, it is then necessary to
calibrate the thermocouple probe. This can conveniently be accomplished
in a plane wave field as indicated in the next section.

c. Probe Calibration and Auxiliary Equipment. The two methods illus-
trated schematically in Fig. 20 (A and B) have been used to display and
record the emf produced by the thermocouple. Figure 20A shows the probe
connected directly to a magnetic oscillograph. The deflection of the light
beam is recorded photographically. Figure 20B shows the probe connected
to a low noise amplifier which is coupled to an oscilloscope. The deflection
of the oscilloscope beam can be observed visually and also recorded photo-
graphically, if desired. The amplifier-oscilloscope method is especially
convenient for determining field configurations. By observing the responses
produced by 0.1-sec. pulses, it is possible to determine quickly details of
a relatively complex field. The oscilloscope and a camera, or the magnetic oscillograph with its associated camera unit, can be used for recording the response to 1-sec. pulses for the purpose of absolute determinations of sound levels (pressure amplitude, particle velocity amplitude, intensity).

As indicated previously, the thermocouple probe cannot be used as an absolute measuring device in accordance with Eq. (1) if the absorption coefficient of the imbedding material is not known sufficiently accurately. Under such conditions, a radiation pressure method (Fox and Griffing, 1949) can be adopted for calibrating the probe (W. J. Fry and R. B. Fry, 1954b). Such a calibration is conveniently performed in a plane-traveling wave field. The radiation pressure detector is comprised of a small stainless steel sphere (\(\frac{3}{16}\)-in. diameter is suitable for measurements at a frequency of 1 Mc./sec.) suspended at a specific position in the medium. The unidirectional force resulting from radiation pressure deflects the steel sphere from the initial equilibrium position with no sound field present. The sphere can then be returned to this position, with the sound field present in the medium, by moving the positioning system which supports the bifilar suspension, which in turn supports the sphere. When the sound field is then cut off, the sphere deflects from this position and the amount of this deflection, measured by a cathetometer, is used to compute the sound level (intensity, pressure amplitude). In practice the deflection is observed for a number of different sound levels.

For a piezoelectric crystal transducer (X-cut quartz plate), a linear relation is obtained when the deflection is plotted as a function of the square of the crystal driving voltage. From the graphical relation and appropriate computation [see the formula and graphs of Fox and Griffing (1949)], the absolute value of the sound level is expressed in terms of the crystal driving voltage. The thermocouple probe is then placed in the sound field with

![Fig. 20. Methods used to observe the thermoelectric emf produced by the thermocouple probe.](image-url)
the junction at the position in the medium previously occupied by the sphere (W. J. Fry and R. B. Fry, 1954b). The thermoelectric response of the probe to a 1-sec. pulse of sound (rectangular envelope) is obtained for a number of driving voltages across the transducer. The deflection amplitudes of the first and second phases of the probe response are then plotted as a function of transducer driving voltage and consequently related to the previously determined values of the acoustic field variables.

Thus from the calibration data, the first or rapid phase of the response is expressed in terms of the particle velocity amplitude, and the second or slow phase is expressed in terms of the pressure amplitude. The magnitude of the response of the slow phase is independent of the orientation of the thermocouple wire in the field (see Section 11, 3b). Therefore, it is possible to determine the acoustic pressure amplitude at a point in a field of unknown configuration from measurements made with the junction at the position of interest.

To determine the particle velocity amplitude directly, it is either necessary to know the field configuration, so that the thermocouple wire can be oriented, relative to the particle velocity vector, as it was during the calibration procedure, or to vary the probe orientation until a minimum response is obtained, i.e., particle velocity vector perpendicular to the wire direction. It is not necessary to consider the two phases of the response separately for measurements in plane wave fields. In this case, it is only necessary to orient the probe so that the thermocouple wire is perpendicular to the direction of propagation and to express the acoustic intensity in terms of the total emf developed by the probe at the termination of an acoustic pulse of proper length, e.g., 1 sec. (Dunn and W. J. Fry, 1957a).

As indicated previously, the second phase of the thermocouple probe response deviates from linearity as the sound level increases. This is a consequence of thermal conduction, acoustical streaming, and the change in value of the acoustic absorption coefficient of the imbedding medium with the temperature. Therefore, in many instances, it is desirable to calibrate the overall electroacoustical system against the thermocouple probe at relatively low sound levels (up to approximately 20 w./cm.² at a frequency of 1 Mc./sec., for example) and then extrapolate to higher sound levels. This requires that the electroacoustical system possess a component which indicates relative sound levels, e.g., a vacuum tube voltmeter measuring a fixed fraction of the voltage applied across a piezoelectric crystal. An example of the type of calibration data obtained is illustrated in Fig. 21. The specific data was obtained in a plane wave field. For such a field, the total probe response following a pulse of ultrasound (1.000 sec.) is expressed in terms of the acoustic intensity. The pressure amplitude and particle
velocity amplitude are then readily computed, and it is therefore not necessary to analyze the different phases of the response data in this case.

Thermocouple probes of the type described here are extremely stable and accurate; calibration of sound fields can be accomplished relatively rapidly. With the instrumentation available at the present time, it is possible to determine the absolute acoustic intensity in a plane wave field to an accuracy of ±2-3% (Fig. 21). Figure 21 does not, however, represent a limit for this type of probe.

![Graph](image)

Fig. 21. Calibration curve of sound field (unfocused) using thermoelectric probe.

### III. Effects and Applications

Intense ultrasound can, over specific dosage ranges, produce accurately localizable changes in the tissue structure and in the functions of the central nervous system. By appropriate control of the dosage conditions, it is possible to produce either reversible or selective irreversible changes. The ultrasonic method of producing such changes is presently being used in neuroanatomical and neurophysiological studies on experimental animals, and it is also in use in human neurosurgery for the precise interruption of deep brain structures.

Although ultrasonic dosage conditions have been established for the

\[ I = \frac{P_1}{2\rho V} = \frac{\rho V^2}{2} \]

where \( P \) designates the acoustic pressure amplitude, \( V \) designates the acoustic velocity, and \( \rho \) designates the particle velocity amplitude.
production of specifically desired changes (W. J. Fry et al., 1954, 1955b; Barnard et al., 1955, 1956; Ballantine et al., 1956), the physical mechanism of the action of the sound, and the primary site or sites of action in the tissue are not known (W. J. Fry, 1953; W. J. Fry and Dunn, 1956; Dunn and W. J. Fry, 1957b; Dunn, 1958). The physical mechanism of the ultrasonically induced changes has been the subject of considerable investigation, and this work is reviewed in the following subdivision of this chapter.

The effects of the ultrasound on the tissue have been studied by extensive histological work and by observation of induced functional changes. Functional change of the system, e.g., motor paralysis, blocking of transmission over neuron pathways (observed electrically), cessation of tremor, relief of muscular rigidity, occurs soon (the minimum time has not been determined, but it is certainly no longer than a few seconds) after the exposure of the desired site to a dosage sufficient to produce an irreversible change. However, histological evidence of a lesion, in response to an ultrasonic dosage within the selective range, has not yet been observed earlier than about 10 min. after exposure (W. J. Fry, 1956; Barnard et al., 1956; Dunn, 1958). Tissue sections from brains of animals sacrificed within 5 min. after exposure do not exhibit evidence of a lesion when prepared with the following stains: Weil for myelin sheaths, tissue matrix, and blood elements; Nissl (thionin, toluidin blue) for nerve cell bodies and glia; iron hematoxylin as a general stain; silver (Romanes, Bodian protargol) for axis cylinders; and Mallory’s phosphotungstic acid-hematoxylin. This does not, of course, imply that it will not be possible, with other stains, impregnations, or techniques (Bakay et al., 1956) to obtain histological evidence of a lesion 5 min. or less after an exposure to an ultrasonic dosage which produces irreversible selective changes, but such evidence has not yet been reported.

In this section, a histological description of ultrasonic lesions of different degrees of selectivity will be given, and the application of the ultrasonic lesion method in neuroanatomical and neurophysiological studies will be discussed. A neuroanatomical study of the mammillothalamic tract in cat is briefly reviewed as a specific example. The use of intense focused ultrasound to produce localized reversible changes in the brain is illustrated by a study on the visual system. Although the study of such reversible changes is in the early stages, it already appears that this method will constitute a powerful procedure for three-dimensional ultrasonic mapping of brain

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Footnote: The term “dosage” includes a specification of the value of the appropriate acoustic field variable (intensity, particle velocity amplitude, pressure amplitude, etc.), the time duration of exposure, and the shape of the acoustic envelope, the environmental conditions (temperature of the preparation, hydrostatic pressure, state of anesthesia, etc.).
“function” (pathways and accompanying time relations for information transfer for relatively complex activity) (F. J. Fry et al., 1958). The application of the method of selective, ultrasonic lesions in human neurosurgery is illustrated by the successful results obtained on patients with hyperkinetic and hypertonic disorders.

1. Irreversible Effects

Focusing of the ultrasound produces values for the acoustic intensity, particle velocity, and pressure amplitudes in the focal region which are much greater than the values for these variables elsewhere in the field. This makes it possible to produce changes at any desired depth in the brain without damage to intervening tissue if the fraction of the incident acoustic energy absorbed along the tissue path traversed is not too great. Since, as discussed in a previous section, the ultrasonic absorption coefficient per unit path length increases linearly with the frequency, an upper “limit” is imposed on the usable frequency for a given depth and safety factor. A frequency of 1 Mc./sec. is sufficiently high to yield a focal region small enough so that lesions involving only a few cubic millimeters (unbounded homogeneous tissue) of tissue can be readily produced, and this frequency is low enough so that any depth in a human brain can be reached safely. (See the specific examples given later in this section.) Larger lesions of prescribed shape and size can be made by the procedure described in the previous section of this chapter. Accordingly, comprehensive histological studies have been made on tissue exposed to various ultrasonic dosages at a frequency of 1 Mc./sec. This does not imply that other frequencies (Ballantine et al., 1956) are not important for such work but simply that ultrasound at a frequency in the neighborhood of 1 Mc./sec. constitutes a good choice for a variety of uses in this field.

a. Histological Changes. All neural components in a given region of the brain can be destroyed without interrupting the blood vessels in the same region (Barnard et al., 1956). This eliminates the difficulty, inherent in older procedures of producing lesions, of spreading of the lesion to regions supplied by interrupted blood vessels which traverse the site of the primary lesion. The noninterruption of blood flow does not imply that the blood vessels are not affected. This is evident histologically especially for higher dosages (W. J. Fry, 1956; Barnard et al., 1956), and it is shown by results reported on changes induced in the blood brain barrier (Bakay et al., 1956). Both the histological work and the blood brain barrier studies indicate that the effects on the blood vessels are reversible.

Since white matter is more readily affected by ultrasound than gray matter, it is possible to completely destroy nerve fiber tracts bordering on or surrounded by nerve cell body regions without damaging the tissue of the gray matter (W. J. Fry et al., 1954, 1955a; Barnard et al., 1955). Con-
sequently, any complex-shaped fiber tract can be destroyed (by placing the focal spot of the beam in a number of adjacent positions) without encroaching on neighboring gray matter. Lesions can be produced in gray matter by increasing the ultrasonic dosage over that required to produce lesions in the white matter (W. J. Fry et al., 1955b; Barnard et al., 1956; Ballantine et al., 1956). In addition to the selectivity already mentioned, evidence exists which indicates that, under certain ultrasonic dosage conditions, nerve fibers in both white and gray matter can be demyelinated without destruction of the axis cylinders (W. J. Fry et al., 1957; Barnard et al., 1955). Such naked axis cylinders have been observed histologically 4 days after irradiation; however, their ultimate fate is not known at the present time.

Histological preparations of the brains of over 400 ultrasonically irradiated cats and monkeys have been examined in the course of this work. The results show that accurate reproducibility of lesions is consistently obtained with a suitably designed instrument yielding precisely controllable dosages. The time course of the development, the degree of selectivity, and the accuracy of localization of the ultrasonically produced lesions have been investigated. The results obtained from the histological study of both small gray and small white matter lesions (single position of irradiation) are summarized in Charts 1 and 2, which are organized to exhibit the time sequence of events (following irradiation) and the “degree” of the selective response of the tissue elements to the dose of radiation.

The numbers at the top of each block in the columns of the charts refer to specific cats with lesions which are representative of the condition described. The time of survival of the tissues after exposure to ultrasound is indicated along the vertical axes of the charts. Along the horizontal axes, the charts are subdivided into columns in which the changes in the individual tissue components are described. The light-, medium-, and heavy-lined columns designate the classification of the lesions (light, medium, and heavy for white matter lesions; mild, moderate, and severe for gray matter lesions). The single, solid vertical lines above the vertical columns indicate that no histological change is observed in the tissue at the time indicated, and the dotted lines indicate an absence of information. Hatching denotes that a particular tissue element, normally present, is absent. The statements appearing in the charts are necessarily brief. The following semiquantitative designations apply to the populations of nerve cell bodies and glia: Very few, $\frac{1}{10}$ or less; few, approximately $\frac{1}{4}$; some, approximately $\frac{1}{2}$; many, approximately $\frac{3}{4}$; most, $\frac{3}{10}$ or more. In the description of the nerve fibers and blood elements, the same terms are employed, but in a qualitative sense. The choice of term employed to describe a specific lesion is decided by comparison with a set of arbitrarily chosen standards.

The lesions produced in white matter are classified as light, medium, or
heavy, and this classification scheme, used in the charts, is based purely on the histology. Other methods of classifying lesions do exist, of course, and are extremely useful. For example, a functional change can be used as a measure of the "degree" of an ultrasonic lesion, and this is done in the dosage studies for elucidation of physical mechanism, as summarized in the next section of this chapter. It is possible to correlate two or more such classification methods with each other when they can both be applied to the same preparation.

It is possible, of course, to produce a continuous gradation in the severity of tissue damage by varying the ultrasonic dosage conditions. However, lesions in the categories already indicated represent an adequate picture of the type of selectivity and graded damage that have been observed so far. It should be noted that the same type of lesion can be produced at different sound levels by varying the duration of exposure. However, for the results reviewed in this section, a single sound level will be stated and the ranges of exposure times necessary to realize the different types of lesion will be indicated.

The terms used for classifying the lesions are defined as follows: A lesion possessing a relatively homogeneous field of necrosis is called light, Fig. 22, (acoustic particle velocity amplitude 440 cm./sec., duration of exposure 1.1–1.4 sec.). A lesion which contains a central region (island), staining like normal tissue, surrounded by peripheral necrosis (moat) is called medium, Fig. 23, (acoustic particle velocity amplitude 440 cm./sec., duration of exposure 1.5–1.7 sec.) if it does not encroach on neighboring gray matter. A lesion is classified as heavy, Fig. 24, (acoustic particle velocity amplitude 440 cm./sec., duration of exposure 1.8–2.1 sec.) if it possesses an island and moat and also encroaches on neighboring gray matter.

No histological change (stains indicated above) is observed in the irradiated brains of animals killed within 5–9 min. after exposure at a dosage at which selective destruction occurs. Twelve to 14 min. after treatment, the first evidence of lesion formation is visible as a lighter staining tissue matrix. At 1 hr., a heavy lesion shows a distinct moat of lightly staining material surrounding a central island. A light response, which is produced by a lower ultrasonic dose, is readily detectable at 1 hr. The entire area of the light lesion resembles the moat of the heavier lesions, i.e., the tissue undergoes rapid morphological change.

The structure in the white matter most sensitive to the action of the sound at these high levels appears to be the myelin sheaths. These are followed in order of decreasing sensitivity by the axis cylinders, the glia (sufficient information is not yet available to determine whether the various glial cell types can be ordered in sensitivity to the ultrasonic radiation),
Fig. 22. Subcortical white matter lesion (light)—single position irradiation, Weil's myelin stain (Barnard et al., 1950).

Fig. 23. Subcortical white matter lesion (medium) exhibiting the island-moat structure—single position irradiation, Weil's myelin stain, (Barnard et al., 1950).
and the blood vessels. A description of the changes which occur is organized in the charts into accounts of individual tissue components, in the following order: axis cylinders, myelin sheaths, glia, matrix, blood elements, and blood vessels. For a detailed account of these changes see W. J. Fry et al. (1957) and Barnard et al. (1956).

The same sound levels used to produce white matter lesions can be used to produce selective gray matter lesions, but the time duration of exposure necessary to produce a lesion (at 440 cm./sec. particle velocity amplitude) is $1\frac{1}{2}$–2 times as great.

Fig. 24. Subcortical white matter lesion (heavy) showing invasion into the gray matter—single position irradiation, Weil's myelin stain, (Barnard et al., 1956).

The selective lesions produced in gray matter by intense ultrasound, are classified as mild (440 cm./sec. particle velocity amplitude, 2.0–2.3 sec. duration of exposure), moderate (440 cm./sec. particle velocity amplitude, 2.4–2.6 sec. duration of exposure), or severe (440 cm./sec. particle velocity amplitude, 2.7–3.0 sec. duration of exposure). It has not been possible, during the course of the histological investigations reviewed here, to formulate histological criteria for the classification of gray matter lesions which can be as readily applied as those formulated for the classification of white matter lesions. In fact, the assigning of a gray matter lesion to a particular class is decided primarily on a comparative basis. At 10 to 15 min. after irradiation, gray matter lesions are characterized by a slightly pale-staining background in the moderate response. In the severe lesion, a pale-staining region surrounds a normal-staining central region (island).
The changes which occur, as a function of the time after exposure in the individual tissue components, i.e., nerve cells, nerve fibers, glia, matrix, and blood vessels are summarized in Chart 2. As in the case of white matter, the myelin sheaths appear to be the tissue element most sensitive to the action of the sound. The sheaths are followed in order of sensitivity by the nerve cell bodies, the axis cylinders, glia, and blood vessels. Again W. J. Fry et al. (1957) and Barnard et al. (1956) should be consulted for details.

It is possible to illustrate some of the important characteristics of the ultrasonic method of producing lesions in the central nervous system by low-power photographs of stained tissue sections. If the subcortical white matter of the brain of a cat is irradiated in a single isolated position, a lesion (2 hr. after exposure) of the type illustrated in Fig. 22 is produced, as indicated previously, when the dosage is just above that required to produce a minimal effect. There is no invasion of the lesion into bordering gray matter. This lesion, which is about 1 mm. in maximum diameter, possesses the extremely sharp boundaries which are characteristic of ultrasonically produced lesions. As the ultrasonic dosage is increased, the lesion (Fig. 23) exhibits a central region (island) which stains more nearly like normal tissue than the peripheral necrotic region (moat) even many hours after irradiation. Even at such a dosage, however, the gray matter bordering on the lesion area is not disrupted, and a sharp boundary between the affected white matter and the neighboring gray matter is apparent under the microscope. As the ultrasonic dosage is further increased, the gray matter becomes affected, and a lesion such as that shown in Fig. 24 is obtained. The dosage used in producing the lesion illustrated was sufficiently high that the gray matter was directly affected.

A lesion can, of course, be restricted entirely to gray matter by suitable positioning of the focal region of the beams in the tissue (Fig. 25). As indicated previously, the ultrasonic dosage required, for the adult mammal at approximately normal body temperature, to produce changes in gray matter is greater than that required for white matter changes. Therefore, if it is desirable to destroy a gray matter region without disrupting bordering white matter, the focal region of the beam must be positioned geometrically within the gray matter so that the fiber tracts of the white matter are not subjected to the high sound level used to affect the gray matter.

The lesions illustrated and discussed thus far were produced by irradiating the tissue with the focal spot of the ultrasonic beam in a single position. Since it is possible, by proper dosage control, to destroy fiber tracts without disrupting neighboring gray matter, one can destroy practically any complex-shaped white matter region of any size without disrupting
cell body regions which border on the tracts to be affected. Such large complex-shaped lesions are illustrated in the next two figures. The stained tissue section illustrated in Fig. 26 shows a large subcortical white matter lesion produced by irradiating the brain (cat) with the focal spot of the ultrasonic beam placed successively in a number of positions spaced 0.5 mm. apart. The ultrasonic dosage conditions used to produce this lesion were: frequency 980 kc./sec., particle velocity amplitude approximately 200 cm./sec., duration of exposure (at each position) 4.00 sec.

Fig. 25. Small cortical gray matter lesion—single position irradiation, Weil’s myelin stain, (W. J. Fry et al., 1955b).

Sharp boundaries are exhibited by these large lesions, and the gray matter which borders on the lesion region is not disrupted even though it receives the same dosage of ultrasound as the neighboring fiber tracts which are completely destroyed. The blood vessels in a lesion as large as this one are still functional after irradiation, i.e., no interruption of blood flow is produced by the sound. Another example of a large, shaped, white matter lesion is illustrated in Fig. 27. This tissue section is from the brain of a monkey irradiated bilaterally at 52 positions (1 mm. between adjacent positions) at a dosage sufficient to destroy the fiber tracts of the white matter without disrupting the gray matter. The shaping of the lesion around both the cortical gray and deep nuclei is clearly shown. The brain was irradiated to within 1.5 mm. of the midline at the level of the sub-
cortical white matter of the superior frontal gyrus, but at the deeper levels
the tissue within 6.5 mm. of the midline was not irradiated. This is clearly
shown in the tissue section where it can be seen that the white matter of
the cingulate gyrus is intact.

The ultrasonic dosages chosen to produce lesions in monkeys are based
on a knowledge of the dosages required to produce such selective lesions
in cat brain. Histological studies show that the production of selective
lesions in adult cat and monkey brains requires essentially the same ultra-
sonic dosages, Fig. 27 (W. J. Fry, 1956). Although no histological results

![Fig. 26. Large subcortical white matter lesion—multiple position irradiation, Weil's myelin stain, (W. J. Fry et al., 1955a).](image)

are yet available on irradiated human brains (Section III, 3), dosages
chosen on the basis of the animal results have been successfully employed
in treating neurological disorders in human patients.

b. Neuroanatomical Studies. The procedure of producing a lesion and
subsequently determining pathways of degeneration and neuron depopu-
lations has been extremely fruitful in neuroanatomical studies. Unfortu-
nately, the procedure has been limited by the methods of producing lesions:
mechanical, chemical, and electrolytic. [See, e.g., the bibliography follow-
ing Chapter 2 of Spiegel and Wycis (1952).] Difficulties associated with
these older methods are: damage to intervening tissue and major inter-
ference with the vascular system in the lesion region. These difficulties
have, in many instances, resulted in confusion of interpretation. In some cases, they have completely prevented the realization of unambiguous results in studies of many of the deeper brain centers, and consequently many such regions remain relatively unexplored. Since these difficulties are eliminated when lesions are produced by focused ultrasonic beams, at dosages which result in selective destruction of tissue components, the ultrasonic method is an extremely powerful tool for use in studies of neuroanatomy and the relation of neuroanatomical structure to physiological function and to behavior.

The use of selective lesions, produced by focused ultrasound, in neuroanatomical studies can be illustrated by summarizing briefly the work on a specific problem. The anatomy of the mammillothalamic tract—course and terminations of the fibers and the locations of the cells of origin—has been studied in cat by interrupting the tract at selective ultrasonic dosages (in preparation). This tract which is at a depth of approximately four-fifths of the total brain thickness is approximately 1 mm. in diameter along most
of its length. The illustration of Fig. 28 shows the normal tract on the right side and the ultrasonic lesion (maximum diameter illustrated) which interrupts the tract on the left side.

The accuracy of geometric placement of the focus of the ultrasonic beam is within a couple of tenths of a millimeter after passing through the entire thickness of a cat's brain. This is determined directly by first centering the focus of the beam on a probe with physiological saline as the conducting medium, then interposing a freshly excised cat's brain between the transducer and the probe, and finally repositioning the transducer to center the focus with the brain in place. The amount of shift indicates the accuracy of geometric positioning. The position accuracy with respect to a specific internal brain structure is not, in general, as good as the geometric position accuracy. This is a result of the fact that internal brain structures vary
in position, from one animal to another, with respect to the reference planes (midsagittal, interaural, and Frankfurt) determined by bony landmarks. Accordingly a series of ultrasonic lesions (single position irradiation) were produced in 34 cats to determine the accuracy of hitting a specific anatomical site along the mammillothalamic tract (W. J. Fry, 1956). In the lateral coordinate direction, approximately 9/10 of these lesions fall within ±0.5 mm. of the desired position, and in the anterior-posterior direction, approximately 3/4 of the lesions are within ±0.5 mm. of the desired anatomical locus. The vertical positioning did not constitute a test of placement accuracy in this series, since the focal region of the beam was oriented with its long axis along the vertical direction. The dimensions of the focal region are: length, 5.0 mm., with a particle velocity amplitude equal to or greater than 90% of the maximum value; transverse diameter, 0.8 mm., with a particle velocity amplitude equal to or greater than 90% of the maximum value.

It should be noted that careful microscopic examination of the tissue between the mammillothalamic tract on which the ultrasound was focused and the port of entry of the sound into brain (cerebral cortex) shows no tissue changes anywhere along the transmission path.

A series of lesions were placed in various positions along the tract for the anatomical studies. A lateral view of the configuration of the tract is shown in Fig. 29, and the positions at which lesions were placed are marked. Lesions, of the type illustrated in Fig. 28, closely restricted to the tract with no interruption of blood flow even within the lesion site and with no damage to tissue elsewhere, were produced at the different positions. The distal portions of the nerve fibers degenerate 2 to 3 weeks after interruption, and the pathways of degeneration (Fig. 30) have been followed by the Nauta-Gygax silver method. Figure 30 shows in coronal section the pathway of degenerating fibers of the mammillothalamic tract as it courses upward from the site of the lesion toward the anterior nuclei of the thalamus. The normal tract on the left-hand side of the illustration does not appear because the Nauta-Gygax silver impregnation method selectively stains degenerating fibers. (Only a small percentage of normal fibers stain.) Encapsulation of the ipsilateral anterior nuclei of the thalamus by the degenerating fibers is seen in Fig. 30.

The illustrations surrounding Part A of Fig. 30 show, on an enlarged scale, selected regions from the center illustration as designated by the lines. Illustration a shows a portion of the normal mammillothalamic tract and a1 shows the corresponding portion of the degenerating tract.

By choosing a dosage to produce selective destruction of white matter and irradiating the brain in a number of overlapping spots, it is, of course, possible to interrupt the tract in essentially every animal.
Illustrations $b$ and $b_1$ show the same regions under larger magnification. Illustration $c$ shows a region from the anterior medial nucleus on the side contralateral to the lesion (a few fibers and terminals are stained), and $c_1$ shows the corresponding region on the ipsilateral side. The extensive degeneration in the ipsilateral nucleus shows that many mammillothalamic tract fibers terminate here. A similar situation obtains for the anterior ventral nuclei as illustrated by $d$ and $d_1$. However, the anterior dorsal nuclei show extensive degeneration on both sides as shown by $f$ and $f_1$. This shows that a crossed component of the mammillothalamic tract exists and that it terminates only in the dorsal part of the contralateral nucleus. (The crossover fibers can be seen under the microscope, but they do not form a discrete bundle as does the main part of the mammillothalamic tract.) Illustrations $c$ and $c_1$ show under high magnification portions of the anterior ventral nuclei from opposite sides.

Considerably later, the proximal portions of the nerve fibers undergo retrograde degeneration, and the nerve cell bodies which give rise to the
fibers of the tract disappear. This permits a complete determination of the population and distribution of the neurons (in the mamillary bodies) corresponding to the fibers of the tract. All of these aspects of the anatomy

![Image of a diagram with labels A, B, C, D, etc., showing degeneration of mammillothalamic tract fibers (A) and degenerating fibers and their terminals in the anterior nuclei (a1, b1, d1, f1, f) of the thalamus following the production of an ultrasonic lesion in the mammillothalamic tract. Tissue prepared by the Nauta-Gygax silver method of selectively impregnating degenerating fibers. AD—anterior dorsal, AM—anterior medial, AV—anterior ventral. See text for a detailed description of the various parts of this figure.]

of the mammillothalamic tract have been determined following the production of selective ultrasonic lesions in cat.

The mammillothalamic tract study demonstrates the power of the ultrasonic method for making lesions for neuroanatomical studies of discrete fiber tracts. This includes the localization and distribution of end termina-
tions and the determination of the neuron population which gives rise to the tract.

c. Functional Studies. Functional changes, resulting from ultrasonic irradiation of specific regions of the central nervous system at dosages which produce irreversible changes (as observed histologically), are apparent as soon after irradiation as it has been possible to subject the animal to suitable tests.

A very extensive series of experiments, which supplies information pertinent to this subject, have been carried out on the spinal cords of both frogs and young mice in order to study the physical mechanism of the action of the ultrasound on the tissue of the central nervous system. In these dosage studies, a functional endpoint, paralysis of the hind legs, is used as a criterion of the induced irreversible change (W. J. Fry et al., 1951; W. J. Fry and Dunn, 1956; Hueter et al., 1956; Dunn, 1956, 1958; Dunn and W. J. Fry, 1957b). Since these experiments have been performed at base temperatures of the animals from 2° to 20°C., the temperature has served as the anesthetic agent to render the animal dormant. Under these circumstances, the animals can be checked for a functional deficit (motor paralysis) as soon as they have been warmed sufficiently. The minimum time required has been in the range from 3/4 to 1 min. when the animals were at 20°C. for irradiation, and the functional change is observed immediately after such warming. No delayed functional paralysis has been observed in over 3,000 irradiated animals.

In studies of the effect of ultrasonic radiation on the two neuron arc response, observed electrically, in rat spinal cord the interruption of propagation following irradiation of the appropriate cord segments occurs no longer than a few seconds after the termination of the exposure period. In this unpublished study, one branch of the sciatic nerve, the tibial, was excited electrically, and the reflex discharge through the spinal cord was observed electrically on the peroneal branch of the sciatic. The time required for functional disruption should be compared with the period of 10–12 min. immediately following irradiation, during which no histological evidence of tissue changes are apparent. (Tissue prepared as described earlier in this section.)

Tremor diminishes or ceases in conscious patients with Parkinson's disease within a few seconds (possibly less) after termination of a dosage required to produce an irreversible lesion. It thus appears that functional disruption, as observed both by changes in motor activity and by electrical measurements, occurs within at most a few seconds after termination of exposure. And it may well be that such disruption occurs at the termination of the exposure period, but this possibility requires further study.

11 The results of these experiments are unpublished.
2. Reversible Effects

Intense focused ultrasound can, under appropriate dosage conditions, induce in the central nervous system reversible changes. F. J. Fry (1957) and F. J. Fry et al. (1958) have been studying such reversible changes using the visual system of cat. By focusing ultrasound into the region of the lateral geniculate nucleus, temporary suppression of various phases of the evoked cortical potentials, in response to a flash of light, can be produced. Such temporary or reversible suppression can be repeatedly obtained on the same preparation without producing a histologically ob-

![Diagram of experimental setup](image)

Fig. 31. Schematic arrangement of animal and apparatus for study of the reversible action of ultrasound on the visual system.

servable lesion. Studies of such reversible changes are in the early stages, and the site or sites (neural substructures) of action have not yet been identified. It is not yet known whether temporary interruption of information transfer (electrical manifestation) in the different neural components (nerve fiber, neuron, synapse) can be accomplished by different doses of ultrasound. In addition, the physical mechanism of the action of the sound to produce reversible changes has not yet received any attention.

For the study of the reversible action of ultrasound on the operation of the visual system, the schematic arrangement of animal and apparatus is shown in Fig. 31. A flash of light is used to stimulate the eyes of the animal, and bipolar recording electrodes, placed in the appropriate cortical
areas on both hemispheres, are used to detect the evoked potentials. The electrodes are placed approximately 1–2 mm. below the surface of the cortex. If the observations are restricted to the determination of the relative amplitudes of evoked potentials, one can record the potentials on a standard electroencephalograph. This method of recording is used in the current studies. (If the details of the shapes of the potential responses are desired, a recorder of wider frequency response characteristic is required.) A focused ultrasonic beam source is used to irradiate portions of the region of one of the lateral geniculate nuclei of the animal since these nuclei are sites of synaptic stations along the visual pathway. Stimulation of the eye by light is repeated at fixed time intervals before, during, and after irradiation, and continuous electrical recording is in progress. The anesthetic is administered intravenously at intervals of several minutes by the method briefly described in the first section.

A series of three light flashes with 3–5 sec. between flashes is used to stimulate the eye of the animal. The series of three flashes is repeated at various intervals of time, before, during, and after exposure to the ultrasonic radiation. Reversible suppression of the various phases of the evoked cortical potential is accomplished by placing the focus of the ultrasonic beam or beams successively in and around the region of the lateral geniculate nucleus. The extent of this suppression is dependent upon the position of the focal region of the ultrasonic beam, and it is thus possible to obtain three-dimensional mappings of brain operation. This is illustrated in Fig. 32 which shows a plane section of such a map at the depth in the brain 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. This 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 (130 cm./sec. particle velocity amplitude, and a duration of exposure of 30 sec.) were chosen to cause reversible suppression of the second and subsequent peaks of this evoked potential. When the focus of the ultrasonic beam was placed within the region corresponding to the inner curve, the second and latter peaks of the evoked potential response, following a flash of light, were reduced between 75 and 100% 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% 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. Complete recovery
of the evoked potential from the suppressed level usually occurs, under these conditions, within 5 min.

Three-dimensional ultrasonic mappings of the type illustrated here will be extremely useful for determining pathways of information transfer and the temporal relations involved in such transfer in the brains of experimental animals. Such maps can be expected to yield information on the pathways of communication for the performance of complex activity of central nervous systems. The use of focused ultrasound at dosages which cause only reversible changes combined with the implanted electrode method will constitute a new and extremely powerful tool for investigating brain function. Reversible changes induced 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, 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.
3. Human Ultrasonic Neurosurgery (Neurosonicsurgery)

The production of selective, precisely-placed lesions deep within the brain, without disruption of intervening tissue and without interruption of the vascular system, makes focused ultrasound a powerful tool for investigating mechanisms of neurological disorders and for therapeutic treatment of such disorders in humans. At the time of writing this review, the precision ultrasonic method of producing selective lesions has been employed in a series of irradiation procedures on 18 cases of parkinsonism, two cases of cerebral palsy of the tension athetotic type, and one case of phantom limb pain (Meyers et al.; W. J. Fry et al., 1968). All procedures were carried out during local anesthesia thus making possible the active cooperation of the patients. In each case, a series of lesions was produced; the number and position of the lesions were determined by the results obtained during the course of the irradiation procedure. In all but one of the 25 irradiation procedures carried out to date, the ultrasonic frequency was 980 kc/sec., the particle velocity amplitude was 350 cm/sec. at the site of the lesion and the exposure time ranged from 1.80 to 3.00 seconds depending upon the structure affected. In one procedure acoustic parameters of such magnitude were employed which repeatedly resulted in reversible physiological effects, specifically, the abolition and reappearance of tremors. The observations on reversible effects were then followed by irradiation with dosage parameters chosen to produce irreversible abolition of tremors.

The ultrasound has been aimed, in the human brain, at the following sites: the region of the ansa lenticularis as it leaves the globus pallidus, the medial segment of the globus pallidus, the superior medial neighborhood of the substantia nigra, portions of the caudal two-thirds of the substantia nigra, the medial and inferior part of the corpus Luysi, portions of the tegmental field of Forel, and parts of the ventral posterolateral nucleus of the thalamus. After each exposure, in the case of the parkinsonian and athetotic patients, examinations were made and changes observed regarding the following: deep and superficial reflexes, vibratory and light touch perception, motor power, non-equilibratory coordination, postural set of the limbs in repose, rigidity, eupraxia, abnormal movements, speech articulation, state of responsiveness ("consciousness"), and vital signs. In the phantom limb case topological distributions of pain, deep pressure, light touch, vibratory and thermal perception were determined, and position sense and voluntary movement of muscle groups were also examined after each exposure.

Considerable information has been acquired with respect to the mechanism of tremor and rigidity in Parkinson's disease from the work already accomplished. It is not possible in this review to discuss in a comprehensive fashion the results which have been obtained. A brief summary of the re-
sults follows. Since a number of different irradiation procedures (number
and distribution of lesions in each case) have been employed, it is necessary
to comment on each separately. By placing lesions in the region of efflux
of the fibers of the ansa lenticularis from the globus pallidus, it was possible
to reduce rigidity in the contralateral limbs and in some patients to elimi-
nate contralateral tremor. By irradiating along the medial border of the
medial segment of the globus pallidus, it was possible to abolish rigidity in
the contralateral limbs in all three patients so treated. Previous to irradia-
tion, these patients exhibited in two cases minimal tremor and in one case
severe tremor. The tremors were eliminated in the contralateral limbs in
all three cases. In a series of 10 cases, irradiation in the superior medial
neighborhood of the substantia nigra invariably resulted in abolition of
contralateral tremor. Contralateral rigidity was simultaneously reduced by
irradiation in this region. Dysarthric, monotonous and weak volume speech
were uninfluenced by the irradiation procedures just described in the
parkinsonian patients. However, bradykinesia and certain automatic as-
sociated movements were favorably affected and in some cases virtually
eliminated.
Evidence of a topological representation of the contralateral upper and
lower limbs with regard to the alleviation of hypertonus and hyperkinesia
was demonstrated both in the “ansa1” region and the superior medial
neighborhood of the substantia nigra. For example, in some parkinsonian
cases the tremor was eliminated only in the upper limbs by irradiation at
one or several sites, and this was consistent from one patient to another.
Elimination of tremor from the lower extremity required irradiation at
other sites. A comparable representation with regard to the relief of rigidity
was observed and in addition a differentiation in central topology of flexor
and extensor synergic muscle groups was obtained. A similar situation was
observed with respect to the cerebral palsy patients in whom it is ap-
parently possible to eliminate or greatly reduce athetotic movement and
fluctuating hypertonus without impairing voluntary movement. The most
recent work on parkinsonian patients, at the time of preparation of this
review, has consisted in irradiating bilaterally through a single craniotomy
opening at one operation. On the side ipsilateral to the bone flap, the su-
perior medial neighborhood of the substantia nigra was irradiated in three
patients and in two of the three the ipsilateral “ansa1” region was also ir-
radiated at a few sites. Contralateral tremor and rigidity were completely
eliminated in all cases. On the side contralateral to the bone flap, lesions
were centered in the superior medial neighborhood of the substantia nigra.
Portions of the medial corpus Luysi, the segmental field of Forel and the
fasciculus lenticularis (as it travels in field H2) were also exposed during
the contralateral irradiation procedure. Tremor and rigidity were com-
pletely eliminated from the contralateral limbs. That is, it was possible to abolishing tremor and rigidity from all four limbs during one irradiation procedure. It is of interest to note the total number of exposures which were required in each case to produce this result. The first patient so treated was given 27 exposures at different sites, the second 10 and the third 13.

Further investigation by the ultrasonic method promises elucidation of the mechanisms of the hyperkinetic and hypertonic disorders. From the therapeutic viewpoint, it now appears possible to completely relieve tremor and rigidity in all four limbs, at one procedure in most cases. While all of the results discussed above were obtained on patients under local anesthesia (cooperative individuals), the consistency of the results with respect to the duplicability of the lesion sites for the relief of symptoms indicates that it is extremely likely that such procedures can be performed successfully on patients incapable of full cooperation.

As indicated above, a single phantom limb case has been treated by irradiation at sites in the contralateral ventral posterolateral nucleus of the thalamus. It was possible to completely relieve the patient of his phantom limb pain, pain in the stump and the phantom limb image. This result was accomplished with no loss of motor power and the patient retains good coordination of his extremities. Some loss of vibratory, tactile, thermal, position, and pain sense on the contralateral half of the body was experienced. In addition to the well known topological separation of proprioception from the group of other sense perceptions (pain, thermal, tactile, etc.) some evidence was obtained for at least a partial topological separation between the central representations of pain, tactile, and thermal senses in this nucleus. Other intractible pain problems, scheduled for immediate attack by the ultrasonic methods described in this review, are postherpetic and thalamic pain, tie douloureaux, and atypical facial pain.

IV. Physical Mechanisms

1. Early Work

The early work (W. J. Fry et al., 1950, 1951; W. J. Fry; W. J. Fry and R. B. Fry, 1953), concerned with investigating the physical mechanism by which high level ultrasound (intensities in the range from 20 to 1,000 w./cm.²) selectively affects tissue structures, dealt with the possible role of heating and cavitation. In this work, the spinal cords of cooled frogs were irradiated with ultrasound in the region of the lumbar enlargement, and, under suitable conditions, motor paralysis was produced. This work indicated that the increased temperature, produced by the acoustic energy, is not the fundamental physical factor which causes the alteration in the biological system. This was shown by inserting thermocouples in the tissue
and observing that the maximum temperature rise during irradiation did not reach a damaging temperature level. This conclusion requires that microscopic "hot spots" do not exist in the tissue during irradiation.

It can be shown on the basis of a theoretical analysis that the existence of high temperatures at microscopic interfaces in the tissue is untenable, and the argument can be briefly summarized as follows (W. J. Fry et al., 1951): Assume that all sound absorbed in the tissue is absorbed at interfaces. This would result in the maximum possible temperature rise at the "hot spots." Consider a volume of material consisting of cylindrical cells of diameter 10 μ. The temperature changes would be smaller for spherical cells or cells of either shape of smaller diameter. Assume that there is one absorbing interface per cell. Let the average temperature of the tissue differ from the average interface temperature by the amount ΔT. If the heat conductivity coefficient of the material at the interface is the same as the average value for the tissue, or if the interface is of zero thickness, the following relation for the temperature difference at equilibrium is obtained:

\[ \Delta T = \frac{\mu I_0 L}{KA} \]

where \( \mu \) is the average acoustic intensity absorption coefficient per unit path length of the tissue, i.e., the usual measured value, \( I_0 \) is the sound intensity, \( L \) is the cell diameter, \( A \) is the total area of the interfaces per unit volume, and \( K \) is the coefficient of heat conductivity. At a sound intensity of 500 w./cm.² for a value of \( \mu \) of 0.4/cm. and a value for the heat conductivity coefficient equal to that of water, the calculated value of the temperature difference is less than 0.01°C. Refinements of this argument, to include, e.g., such situations as interfaces of finite thickness of different heat conductivity characteristics from the average for the tissue, do not change the general conclusion that localized heating at interfaces cannot be important in the mechanism.

That temperature change is not the fundamental physical factor is also supported by experiments in which the tissue was subjected to repeated exposures. It has been shown that the effect of repeated exposures, which individually do not produce paralysis, can sum to produce an irreversible change. With this type of procedure, the temperature increase in the tissue returned to almost zero between exposures, and the maximum temperature rise in the tissue was considerably less than that of a single exposure capable of producing paralysis (W. J. Fry et al., 1950, 1951; W. J. Fry and Dunn, 1956). Other aspects of temperature change, such as its time rate of rise and heating at microscopic bubbles, have also been considered and shown to be not of primary importance in the physical mechanism (W. J. Fry, 1953).

It was also shown that cavitation, which might be caused by tension
forces produced in the tissue at the high sound levels, is not important in the physical mechanism. This was accomplished by irradiating the animals under a hydrostatic pressure sufficiently high to prevent tension forces from occurring in the tissue (W. J. Fry et al., 1951).

The data obtained from the early work was sufficiently accurate to show that at least an approximately linear relation obtains between the square root of the acoustic intensity (i.e., a quantity proportional to the acoustic pressure amplitude or particle velocity amplitude) and the reciprocal of the exposure time required to produce the desired endpoint (motor paralysis of the hind legs).

2. Precision Dosage Study

More precise dosage relations can be obtained with improved instrumentation and technique. This instrumentation and associated technique were described in Section II, 2 of this review. The young mouse (24 hr. after birth) was chosen as the biological test specimen to be used in these dosage studies. To further elucidate the physical mechanism of the action of the ultrasound on the tissue of the central nervous system, a comprehensive dosage study involving a wide range of experimental conditions is necessary. A high degree of accuracy is necessary in order to separate the effects of the various field variables (frequency, pressure, particle velocity, particle acceleration amplitudes, etc.) and to determine the temperature and pressure coefficients of the primary mechanism. Standing wave field experiments must also be performed.

In order to realize a dosage study of the type envisioned, i.e., one for which the experimental results can be interpreted with some facility to yield information concerning the fundamental physical mechanism, it is essential that the tissue of interest be exposed only once to the radiation. If multiple exposures (both temporal and overlapping spatial-temporal) are used, uncertainty arises regarding the effect of summation since a time-dependent residual effect succeeds an exposure (W. J. Fry et al., 1951; W. J. Fry and Dunn, 1956; Hueter et al., 1957; Dunn and W. J. Fry, 1957b). Data obtained by the use of multiple exposures are thus of limited value if single exposure data are not previously available. However, the multiple exposure technique is useful in limiting the maximum temperature rise, by the choice of an appropriate duty cycle, and therefore may be used in the initial stages of a mechanism study in order to rule out the possibility of a damaging temperature level as the basic factor (W. J. Fry and Dunn, 1956). The region to be affected by the sound must be irradiated with a beam which is uniform since experimental results obtained with the use of nonuniform beams are difficult to interpret, because all of the tissue does not receive the same dose of radiation.

The type of data obtainable from an accurate dosage study designed to
elucidate the physical mechanism is now illustrated (Dunn, 1956; Dunn and W. J. Fry, 1957b): If a large number of animals are irradiated with identical values for 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 is obtained (Fig. 33). The "threshold range," at the chosen values for the acoustic field variables, is arbitrarily defined as the range of time durations of exposure from 10% of the animals paralyzed to 90% of the animals paralyzed. The collection of these threshold ranges for various values of a specific acoustic variable defines the threshold region for that variable. The threshold region includes an infinite number of "threshold relations." Three specific threshold relations are conveniently defined for discussion and analysis. These relations are defined as: the reciprocal of the exposure time as a function of an appropriate acoustic field variable (e.g., the square root of acoustic intensity) for 10, 50, and 90% of the mice paralyzed.

Figure 34 exhibits the threshold region (with the square root of the intensity as the acoustic field variable) at a frequency of 982 kc./sec., a
hydrostatic pressure of 1 atm., and a base temperature of 10.0°C. The ordinate is the reciprocal of the exposure time, and the abscissa is the square root of the acoustic intensity. Time and intensities are also indicated on the coordinate axes for convenience. The plotted points are obtained from the sigmoid curve of Fig. 33, and similar ones are obtained at other values for the acoustic intensity. The slopes of the lines for 10 and 90% of the animals paralyzed, which by definition border the “threshold region,”

\[ t^{-1} = 0.209 I^{1/2} - 1.42, \]  

where \( t \) designates the exposure time and \( I \) designates the acoustic intensity.

Fig. 34. Threshold region for paralysis of the hind legs of young mice under ultrasonic irradiation (W. J. Fry and F. Dunn, 1956).
Temperature increases in the spinal cords of the mice, as a result of exposure to the acoustic energy, were measured during irradiation by imbedding small calibrated thermocouples in the cords of the animals and recording the thermal emf's developed. The greatest temperature increases were observed on the ventral side of the cord adjacent to the spinal column. These values are plotted in Fig. 34 at the proper coordinates (Dunn, 1956; W. J. Fry and Dunn, 1956; Dunn and W. J. Fry, 1957b).

![Graph showing temperature increase as a function of acoustic intensity.](image)

**Fig. 35.** Dosage relations (50% 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.)

In addition to the dosage relation at 10.0°C, relations have been determined for base temperatures of 2.0 and 20.0°C, although the data at these latter two temperatures are not yet complete. The 50% paralysis curves for all three of these temperatures and for a hydrostatic pressure of 1 atm. and a frequency of 982 kc./sec. are shown in Fig. 35 (Dunn, 1958). Although the total range of the data covers only a factor of 2 in acoustic pressure amplitude, this corresponds to a factor of approximately 20 in the exposure time (over the linear portion of the curves).

The reproducibility of these curves can be considered by analyzing the sources of uncertainty which are involved in the various measurements. The absolute sound intensity is known with an accuracy of ±4%. However, the relative accuracy of the sound intensity is known to within ±1%. This latter figure is applicable when comparing dosage curves at a single
frequency. The uncertainty in the duration of exposure is ±0.1% for irradiation times of 1 sec. or longer. The accuracy in the ultrasonic frequency is ±0.01%. The base temperature of the animal is known to ±0.1°C. The accuracy of the dosage line is evident from Fig. 35 for the standard deviation of the points from the straight line of best fit. For the line for the base temperature of 10.0°C., the standard deviation of the points is 1.3%. An analysis performed to determine the degree of non-linearity of the "linear portion" of the threshold relation for T = 10.0°C. yields a quadratic coefficient of such magnitude that the deviation from the statistically determined linear curve is considerably less than the standard deviation (Dunn, 1956).

As already indicated, families of curves of the type illustrated in Fig. 35 must be obtained at a variety of frequencies and hydrostatic pressures. The availability of quantitative curves of this type for a wide range of conditions would provide a basis upon which to formulate a quantitative theory of the physical mechanism or mechanisms of the action of the sound on the tissue and would suggest, from the form of the relations over different ranges of the acoustic field variables, dosage conditions which might result in a number of different types of selective action of the sound on the tissue. An understanding of the physical mechanism can in turn be expected to suggest the type of structure disruption which occurs. A knowledge of the temperature and pressure coefficients of the dosage relations could contribute considerably to such studies. Further work on physical mechanism could thus lead to the development of intense ultrasound as a tool for the investigation of intercellular organization and function.

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