

Ultrasound in Neurology

William J. Fry

THE CHANGES produced in nerve tissue resulting from intense ultrasonic irradiation under controlled dosage conditions have been described in detail in a number of publications from this laboratory.¹⁻⁴ This paper is concerned with a discussion of the microscopic selectivity and a description of the instrumentation and the technic of irradiation of the animal. The types of lesions which can be produced are illustrated with low power photographs of stained tissue sections and instrumentation and technic of irradiation⁵ are discussed.

The focussed ultrasonic multiple beam method of producing lesions in the central nervous system constitutes a considerable advance over the older procedures for destroying tissue. Changes can be produced at any desired depth without damaging intervening tissue. The selectivity, which under proper ultrasonic dosage conditions can be realized in the lesion region, is not attainable by any other method demonstrated up to the present time, and it provides an entirely new approach to many neurologic problems. The fact that all neural components in a given region can be de-

stroyed without interrupting the blood vessels in the same region completely eliminates the difficulties inherent in older procedures, namely the spread of the lesion to regions supplied by interrupted blood vessels which traverse the site of the primary lesion. Since white matter is more readily affected by ultrasound than gray matter, it is possible to completely destroy nerve fiber tracts bordering or surrounded by nerve cell body regions without damaging the tissue of the gray matter, that is to say, the practically complete prevention of invasion of a lesion into gray matter can be readily attained. Consequently, any complex-shaped fiber tract can be destroyed without encroaching on neighboring gray matter. Lesions can, of course, be produced in gray matter by increasing the ultrasonic dosage over that required to produce lesions in the white matter. In addition to the selectivity already mentioned, which can be readily realized, 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

From the bioacoustics laboratory, University of Illinois, Urbana, Illinois.

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cylinders. Such naked axis cylinders have been observed microscopically four days after irradiation. The ultimate fate of these axis cylinders is not known at the time of writing of this paper. Precise positioning, small size (as small as 1 to 2 cubic millimeters), and accurate reproducibility of lesions are consistently obtained with a suitably designed instrument yielding precisely controllable dosages. In addition, the procedure is well tolerated by the animals so that treatment mortality can be kept very low.

Extensive histologic studies of the ultrasonically produced selective lesions have been accomplished. Histologic preparations of the brains of over 300 ultrasonically-irradiated cats and monkeys have been examined in the course of this study, in which the time course of the development, the degree of selectivity, and the accuracy of localization have been investigated. This ultrasonic method is being applied in this laboratory for neuroanatomic and neurophysiologic studies on experimental animals. Preparations for application of this method to human neurosurgery are in progress.

The term "ultrasound" refers to sounds whose frequencies are above the range of human audibility (human audible limit is 15,000 to 20,000 cycles per second). Since the velocity of propagation, V , of sound waves in a fluid medium is practically independent of the frequency and since the propagation velocity is equal to the product of the frequency f and the wavelength λ ($V=f\lambda$), it is evident that the higher the frequency the shorter the wavelength. A short wavelength is necessary for this work since the minimum focal spot size which can be produced is proportional to the

wavelength. Thus, if a focal spot size of the order of two millimeters in diameter is desirable, it is necessary to use sound waves with a frequency in the neighborhood of a million cycles per second or higher. At a frequency of a million cycles per second, the wavelength of the sound in physiologic saline and soft tissue is about 1.5 millimeters (velocity of sound propagation in saline is about 1,500 meters per second). The sound waves can be focussed by a lens in a fashion similar to that used for visible light. Such a focussing device is illustrated schematically in figure 1. The sound is produced by an element E (such as a quartz crystal plate) which is excited electrically to vibrate at resonance (vibration consists of an alternating change in thickness of the element). The sound traverses medium M

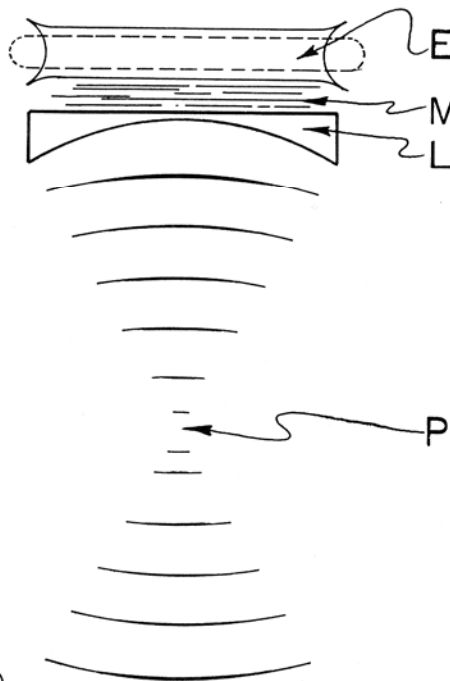


FIG. 1. Focussing system (lens) for ultrasound. For description of symbols see text.

and passes through the plano-concave lens L , which focusses it at P . Four of these focussing devices can be combined into one unit as illustrated by the irradiator shown in figure 2. The four individual focussed beams can be brought into coincidence by adjustments provided on the irradiator. This focussed multiple beam irradiator has been used to produce the types of localized selective lesions discussed in this paper.

It is not practical to increase the frequency indefinitely in order to obtain smaller and smaller focal spot sizes if the beam must penetrate much tissue before coming to a focus. This limitation is imposed by the fact that the absorption of the sound by the tissue increases as the frequency increases. The sound level must consequently be increased at the port of entry into the brain to offset the absorption losses which occur along the transmission path. The losses may become so great at higher frequencies that the increased sound level required would result in damage to the brain where it enters and along its transmission path. A frequency of one million cycles per second is about the maximum practical if the sound must penetrate the maximum depth of a human brain before coming to a focus to produce a lesion.

Even in the one million cycle per second frequency range, the absorption in bone is so great that it must be removed to prevent damage to adjacent nerve tissue caused by flow of heat from the bone to the soft tissue. However, there is an additional reason for removing the bone overlying the surface of the brain at which the sound is to enter, namely, the sound propagation velocity in bone is quite different from its value in brain tissue. Therefore, the sound

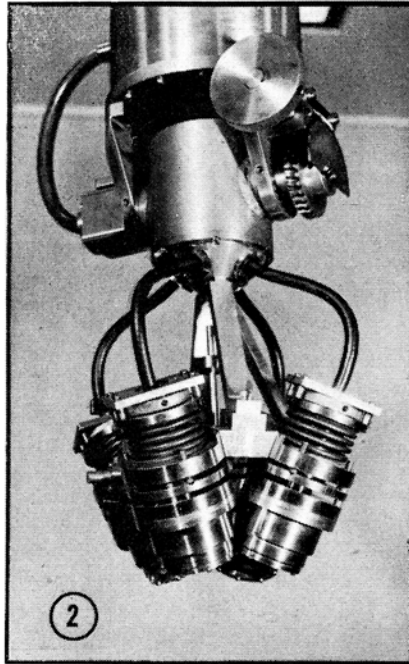


FIG. 2. Four beam focussing ultrasonic irradiator.

beams would be distorted if they traversed the skull bone prior to being focussed in the brain. The removal of the bone eliminates the difficulty of distortion and the sound can then be conducted from the lenses to the exposed dura through sterile physiologic saline. Since the acoustic levels used are quite high, it is necessary to degas the saline before using it to prevent the formation of bubbles in the transmission path. Degassing can be accomplished by boiling for a few minutes and then cooling.

The physical mechanism of the action of the sound on the tissue is not understood at the present time, although it is clear that the primary effect is not the result of heating. That the action is not the result of temperature changes resulting from the conversion of acoustic energy into heat has been demonstrated

in a number of ways. Experiments on cooled animals, in which the increased temperature due to the sound never exceeds a "normal" temperature for the animal, demonstrates this convincingly.⁶ Additional evidence for this viewpoint is the fact that sound pressure amplitude or sound particle velocity amplitude is more simply related than sound intensity to the exposure time necessary to produce a specified effect on the central nervous system.⁷ The time rate of heating produced by passage of the sound through the tissue is directly proportional to the acoustic intensity for a progressive wave (no standing waves). The sound pressure amplitude is a measure of the fluctuating or alternating pressure in the medium resulting from the pas-

sage of the acoustic waves. The particle velocity amplitude is the maximum value of the alternating speed of the particles of the medium during passage of the sound waves. Greater intensities correspond to larger alternating pressure and particle velocity amplitudes, and these two latter quantities are in fact directly proportional to the square root of the intensity in a plane progressive wave. As a result of the fact that the pressure and/or particle velocity are probably more basic in the mechanism of the action of the sound on the tissue than is the intensity and since values for the space distribution of intensity do not completely describe the acoustic field conditions in a sound field of the type produced by the multibeam focussing



FIG. 3. Irradiation room.

irradiator, the ultrasonic dosage conditions are stated in terms of the frequency, pressure amplitude, particle velocity amplitude, and duration or durations of exposure. To complete the description, it is also necessary to note that the sound level rises to its maximum value at the initiation of exposure and falls to zero from its maximum value at the termination of exposure, in a time which is very short compared with the duration of exposure.

The technic of preparation and irradiation of the subject and the apparatus for control of dosage and localization will now be described. The specific machine to which the description given here applies is the prototype instrument for human ultrasonic neurosurgery. This

equipment is housed in a double room arrangement; the subject is irradiated in the lower room (figure 3) and the positioning system is housed in the upper room (figure 4). The electrically shielded irradiation room contains apparatus for supporting the animal, calibration instrumentation for determining the acoustic output of the transducers, and controls for positioning the focused ultrasonic beams, as well as stimulators, amplifiers, oscilloscopes, cameras, and other recording devices for observing electrical activity of central nervous systems during irradiation. Projecting through the ceiling of this room is a metal tube (10 feet long and 7 inches in diameter) which supports the focussing transducer. The precise positioning of the sound

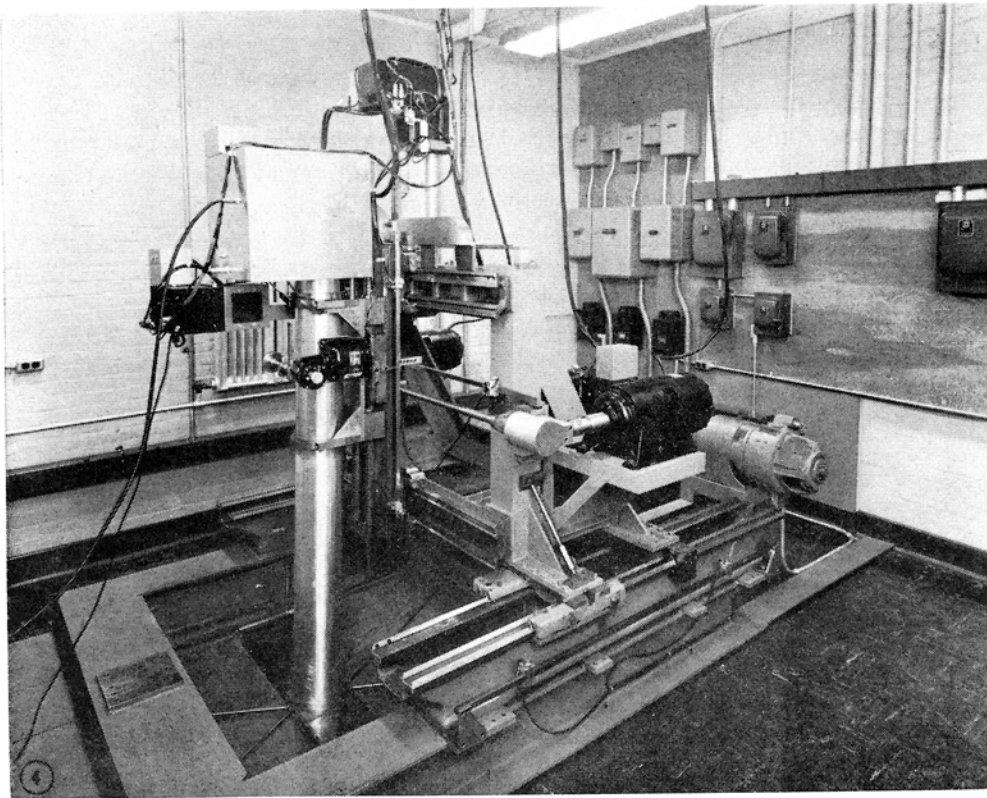


FIG. 4. Upper room housing positioning system.

beam is accomplished by the motor driven positioning system which supports the transducer. This system permits translational motion in three mutually perpendicular directions and also two rotational motions. The positioning system itself, which weighs about 3,500 pounds, is mounted on a steel girder framework in the upper room directly over the irradiation room. The controls for this system are placed in the irradiation room below. This instrumentation makes possible accurate localization of the acoustic radiation in any desired region of the central nervous system under precisely controlled dosage conditions.

Previous to preparing the animal, one calibrates the multibeam irradiator at the focal spot by choosing a convenient voltage to electrically excite the vibrating elements. An acoustic probe, which makes possible relatively rapid accurate determinations of the acoustic variables, pressure amplitude, and particle velocity amplitude, has been especially developed for this purpose.^{8,9} Both the probe and the irradiator are immersed in a calibration tank filled with salt water for the calibration procedure. The exciting voltage corresponding to the sound level desired (pressure amplitude, particle velocity amplitude) at the site of the lesion is determined. Absorption losses in the thickness of brain tissue between the port of entry and the focal region are taken into account in this determination.

To produce a precisely localized lesion by ultrasound, the head of the anesthetized animal (cat, monkey) is engaged in a stereotaxic substructure in which the usual interaural, Frankfort, and midsagittal planes are employed as "zero-references." Before the animal is

placed in the apparatus, a pointer attached to the irradiator and coinciding with the focal spot of the irradiator is positioned on the midline of the stereotaxic apparatus and is collinear with the line through the bars which support the skull of the animal at the ears. The coordinate values on the system that supports the irradiator are read corresponding to this ear-bar "zero." One can then transform from the coordinates ordinarily used with the stereotaxic apparatus to the coordinates of the system supporting the irradiator. The pointer is then removed from the irradiator and the animal is mounted in the machine. The soft tissues are incised over the appropriate area of the brain and the skull cap is removed. The dura mater need not be opened. At this point of the procedure, no definitive surgical measures beyond those of achieving hemostasis are required.

The next step consists of attaching the skin of the animal to a special flanged hopper in such fashion as to provide a "pan," the bottom of which consists of the exposed dura mater. This "pan" holds

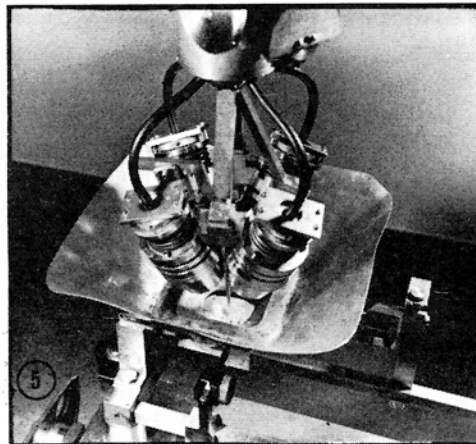


FIG. 5. A view from above showing the arrangement of irradiator, pointer, pan, skull, and head holder.

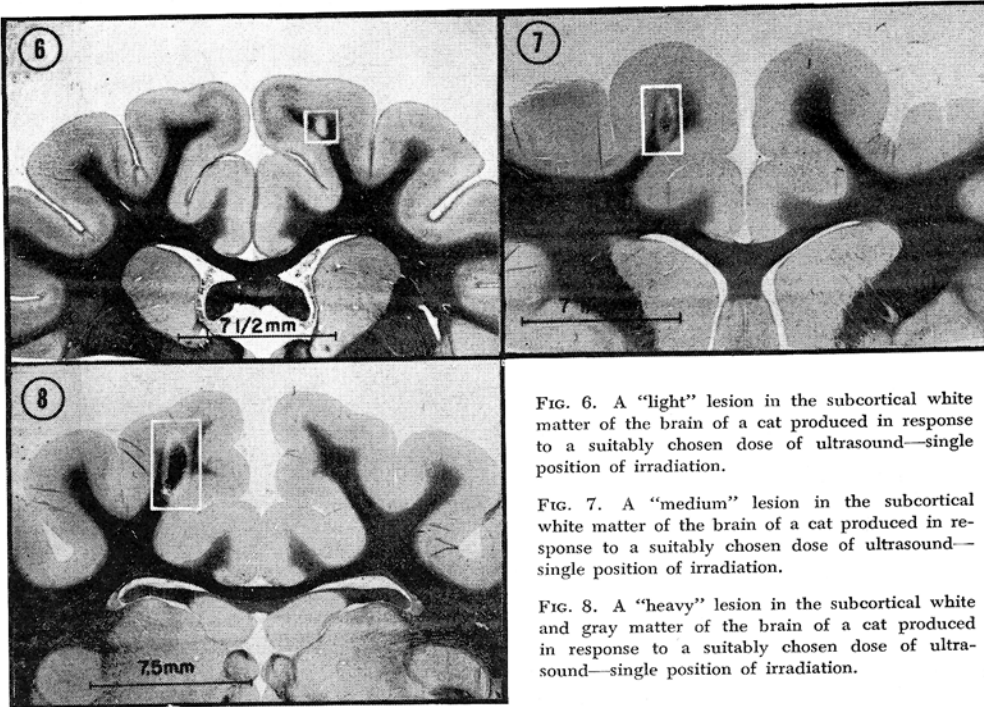


FIG. 6. A "light" lesion in the subcortical white matter of the brain of a cat produced in response to a suitably chosen dose of ultrasound—single position of irradiation.

FIG. 7. A "medium" lesion in the subcortical white matter of the brain of a cat produced in response to a suitably chosen dose of ultrasound—single position of irradiation.

FIG. 8. A "heavy" lesion in the subcortical white and gray matter of the brain of a cat produced in response to a suitably chosen dose of ultrasound—single position of irradiation.

the degassed physiologic saline which acts as the transmitting medium for the sound. The arrangement of the irradiator, pan, head holder, and skull of the animal are illustrated in figure 5. The pointer, the function of which is discussed above, is shown in the lowered position.

The sterilized multibeam irradiator, which is supported and moved about by the carriage unit (figure 4), is then positioned in the saline medium at the position or positions required to place the focal spot of the irradiator in the region in which a lesion is to be produced. For the smallest lesions the tissue is irradiated with the focal spot in single isolated positions, but for larger lesions the focal spot is placed successively in a number of adjacent overlapping positions. After exposing the brain to the proper ultrasonic dosage in the

desired number of positions, the animal is returned to the operating room where closure of the cranial muscles and scalp is accomplished. This surgical procedure may also be performed in the irradiation room, since the apparatus is designed so that the tube which supports the irradiator can be retracted sufficiently to permit the implementing of standard operative procedures below it without interference.

The animals are observed for periods varying from minutes to months following exposure, during which time physiologic and/or psychologic aberrations may be noted. The animals are then sacrificed, and the brains removed, fixed, sectioned, and stained.

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 of the type illustrated in figure 6 is produced when the dosage is just above that required to produce a minimal effect. The lesion area (the maximum cross section is exhibited in the section illustrated) possesses a relatively homogeneous field of necrosis two hours after irradiation and there is no invasion of the neighboring gray matter. This lesion, which is about one millimeter in maximum diameter, possesses extremely sharp boundaries which are characteristic of these ultrasonic lesions. As the ultrasonic dosage is increased, the lesion (figure 7) exhibits a central region which stains more nearly like normal tissue than the peripheral necrotic region, even many hours after irradiation. (See reference 4 for a complete tabulation of the time sequence of the tissue changes in both white and gray matter following various graded dosages of ultrasound.) Even at such a dosage, however, the gray matter bordering on the lesion area is unaffected and a sharp boundary between the affected white matter and the neighbor-

ing gray matter is apparent. As the ultrasonic dosage is further increased, the gray matter becomes affected and a lesion such as that shown in figure 8 is obtained. The dosage used in producing the lesion illustrated was sufficiently high that the gray matter was directly affected. Graded series of lesions of the type just illustrated are produced by ultrasound at 50 atmospheres acoustic pressure amplitude, 450 centimeters per second particle velocity amplitude, and durations of irradiation (single exposure) in the range from 1.00 to 2.00 seconds. The sharp boundaries characteristic of these ultrasonic lesions are present in both the white and gray matter, and the central darkstaining region in the white matter portion of the lesion is quite apparent at this heavy dosage. Even at this heavy dosage blood vessels which enter and are present in the lesion region are not interrupted. It is of interest to note here that even for a heavy dosage, such as that used to produce the lesion illustrated in figure 8, the changes in the tissue are not apparent under the microscope for about ten minutes after irradiation. The first change which is observed is a slight destaining,

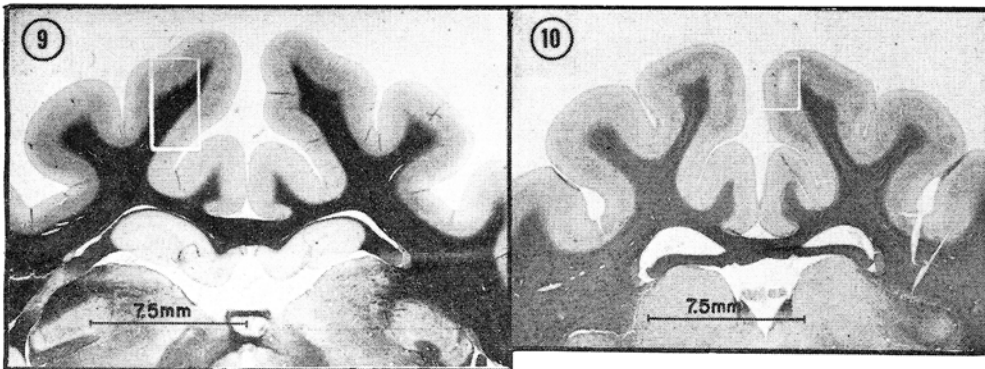


FIG. 9. The initial histologic change observed 12 minutes after ultrasonic irradiation—"heavy" lesion.

FIG. 10. An ultrasonic lesion in the midline cortical gray matter of a cat brain.

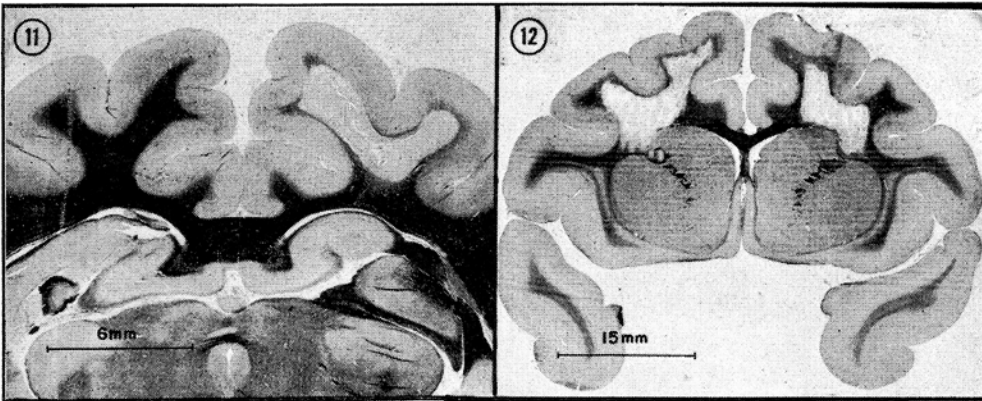


FIG. 11. A large ultrasonic lesion in the subcortical white matter of a cat brain produced by irradiating in a number of adjacent positions.

FIG. 12. A large bilateral ultrasonic lesion in the subcortical white matter of a monkey brain produced by irradiating in a number of adjacent positions.

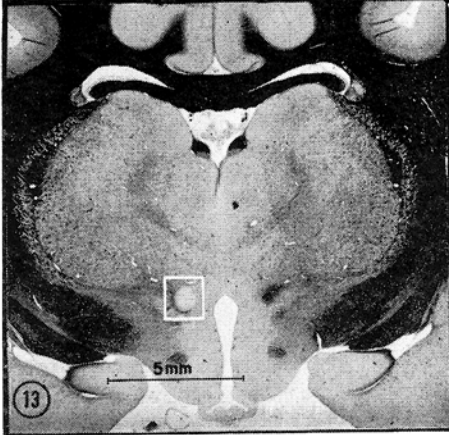


FIG. 13. The selective destruction of the left mammillothalamic tract in cat brain by ultrasound.

which becomes evident for heavy lesions about ten to 15 minutes after exposure. This is illustrated in figure 9, in which the change is more apparent in the gray matter than in the fiber tracts. A lesion can, of course, be restricted entirely to gray matter by suitable positioning of the focal region of the beams in the tissue (figure 10). As indicated previously, the ultrasonic dosage required 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 with respect to the border between the gray matter and the

fiber tract so that the white matter is not subjected to the high sound level used to affect the gray matter. A graded series of lesions can be produced in gray matter by irradiating the tissue at the pressure and particle velocity amplitudes given above for white matter, but with the duration of exposure in the range 2.00 to 3.00 seconds.

All of the lesions illustrated so far were produced by irradiating the tissue with the focal spot of the ultrasonic beams in a single position. Since it is possible to destroy fiber tracts without disrupting neighboring gray matter by proper dosage control, one can destroy practically any complex-shaped white matter region of any size without dis-

rupting cell body regions which border on the region to be affected. Such large size complex-shaped lesions are illustrated in the next two figures. The stained tissue section shown in figure 11 illustrates a large subcortical white matter lesion produced by irradiating the tissue (cat) with the focal spot of the ultrasonic beam placed successively in a number of positions spaced 0.5 millimeter apart. Sharp boundaries are exhibited by these large lesions and the gray matter which borders on the lesion area is not affected, even though it receives exactly the same ultrasonic dosage 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, that is, no interruption of blood flow is produced by the sound. Another example of a large shaped white matter lesion is illustrated in figure 12. This tissue section is taken from the brain of a monkey irradiated bilaterally at a large number of positions (52) 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 with the focal spot of the beams spaced one millimeter apart at adjacent positions. The brain became slightly distorted on imbedding and consequently the white matter in the superior frontal gyrus of the right side does not appear completely disrupted in the tissue section illustrated. However, examination of serial sections indicates that the white matter was completely disrupted in the superior frontal gyrus on this side also. The brain was irradiated to within 1.5 millimeters of the midline at the level of the subcorti-

cal white matter of the superior frontal gyrus, but at the deeper levels the tissue within 6.5 millimeters of the midline was not irradiated. This is clearly shown in the tissue section, that is, the white matter of the cingulate gyrus is not disrupted. It is of interest to note that the ultrasonic dosage chosen to produce this lesion was based on a knowledge of the dosage required to produce such selective lesions in cat brain. It is thus apparent that a dosage study based on cats is sufficient to serve as a criterion for the selection of dosages for monkeys. It is, therefore, expected that the dosages required to produce selective lesions in human beings would not be greatly different.

The next three figures illustrate the accuracy of localization in the selective destruction of the whole or a part of a small deep fiber tract. This is illustrated by ultrasonic lesions produced in the mammillothalamic tract of a cat. This tract, which is about one millimeter in diameter and is at a depth of four-fifths of the total brain thickness, constitutes a convenient test object on which to demonstrate the potency of the ultrasonic method. Ultrasonic lesions have been produced in the mammillothalamic tracts of 34 cats. Single position irradiation was used. In the lateral coordinate direction, 90 per cent of these lesions fall within ± 0.5 millimeter of the desired position, and in the anterior-posterior direction 75 per cent of the lesions are within ± 0.5 millimeter of the desired anatomic locus. The vertical positioning does not constitute a test of placement accuracy in this series, since the focal region of the beam was oriented with its axis along the vertical direction. Therefore, since the length of the focal region (5 millimeters with a

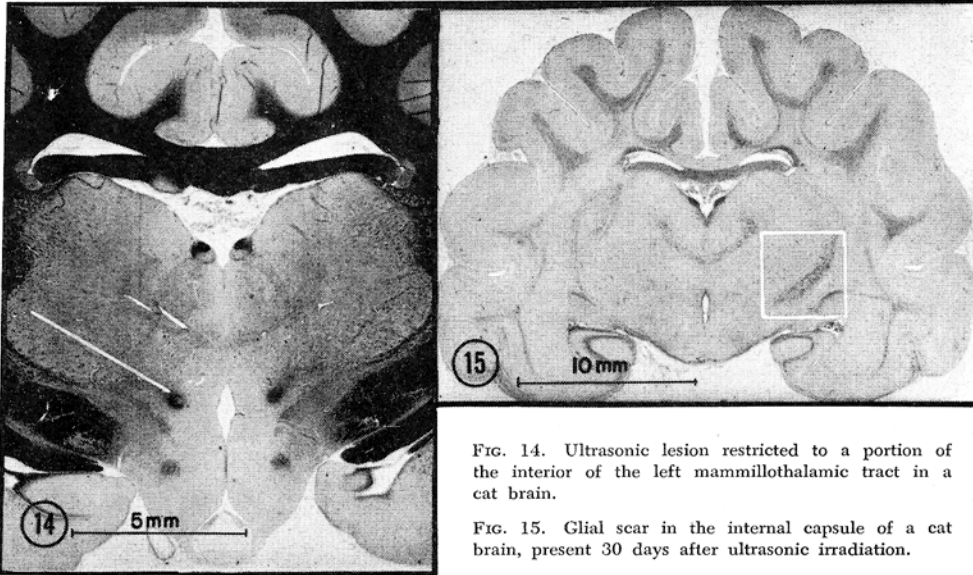


FIG. 14. Ultrasonic lesion restricted to a portion of the interior of the left mammillothalamic tract in a cat brain.

FIG. 15. Glial scar in the internal capsule of a cat brain, present 30 days after ultrasonic irradiation.

particle velocity amplitude equal to or greater than 90 per cent of the maximum value) of the beam is several times greater than its diameter (0.8 millimeters with a particle velocity amplitude equal to or greater than 90 per cent of the maximum value), there was no difficulty in hitting the tract every time as far as the vertical position was concerned. The numerical values quoted for placement uncertainty include, of course, the variation in the position of the structure (mammillothalamic tract) with respect to the external reference landmarks on the skull which are used in positioning the head of the animal in the holder.¹⁰ Since the dosage was chosen to selectively destroy the tract without disrupting the surrounding gray matter, the variation in position is exhibited as a lesion in which the tract is only partially destroyed. In figure 13 the left mammillothalamic tract is essentially completely destroyed. Figure 14 exhibits a lesion in the interior of the tract. In this last example, the ef-

fective size of the focal region of the beam to produce a lesion was so small that only a small portion of the interior of the tract was destroyed. The stained tissue sections of the figures show the maximum size of the lesion in each case. Microscopic examination of the tissue between the mammillothalamic tract on which the ultrasound was focussed, and the port of entry of the sound into the brain (cerebral cortex) shows no tissue changes anywhere along the transmission path.

The mammillothalamic series of lesions, examples of which are illustrated here, was produced to determine the accuracy of placement of a single tiny ultrasonic lesion within the deepest portion of a cat brain. The series also furnishes material for an anatomic study of this tract, its course, and terminations. If the severing of the entire tract in essentially every animal were the objective, without disturbance to neighboring gray matter, this could be readily accomplished by irradiating with the

focal spot of the sound beams placed successively in a number of positions to cover a region which includes the total space variation of the tract with respect to the external landmarks. The ultrasonic dosage delivered at each position would, of course, be chosen so that the radiation does not affect gray matter.

Large lesions of almost any desired shape can be produced in fiber tracts in the depths of the brain. The tissue section of figure 12 illustrates a lesion in the brain of a monkey which has a lower border following the boundaries of the gray matter masses at intermediate depth. The tissue section of fig-

ure 15 shows a glial scar which has formed and is present 30 days after the production of a crescent-shaped lesion in the deep fiber tracts of the internal capsule of a cat brain. This lesion in the capsule was produced by irradiating the tissue in a number of positions with beam centers spaced 0.5 mm. apart.

From the work that has already been accomplished, it is clear that the ultrasonic method of producing accurately localized selective lesions in the central nervous system constitutes a new and powerful tool for experimental neurology and it has considerable potential value for neurosurgery.

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