Reprinted from AMERICAN JOURNAL OF PHYSICAL MEDICINE
Vol. 37, No. 3, June, 1958
Printed in U.S.A.

USE OF INTENSE ULTRASOUND IN NEUROLOGICAL RESEARCH[1]

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One of the more fruitful methods used for studying both structure and function of the central nervous system employs the procedure of destroying a region and then following any subsequently identifiable changes in behavioral or physiological function. This, in turn, is followed by study of stained tissue sections for precise localization of the lesion and for tracing degenerating neural pathways. Although this procedure has yielded a great deal of information, it has suffered from several serious drawbacks. These drawbacks have been primarily associated with the methods (mechanical, chemical and electrolytic) of producing the lesions. Until the advent of the ultrasonic procedure, a principal difficulty was that destruction of tissue in deep regions of the brain entailed the destruction of intervening tissue. This difficulty resulted, in many instances, in confusion of interpretation since it may not be clear whether the effects obtained, both functional and anatomical (degenerating pathways), result from the destruction of tissue at the desired site or whether they are the consequence of the destruction of intervening tissue. This inadvertent or unavoidable destruction of intervening tissue has prevented the realization of unambiguous results in studies of many of the deeper brain centers. Consequently many such regions remain relatively unexplored.

A second major difficulty was that the nonselective nature of the destruction implied in many instances major interference with the vascular system. This confuses the interpretation in many instances because the interrupted blood vessels supply regions of the brain other than that at the desired lesion site. Such other regions may degenerate if the blood supply is sufficiently reduced. The possibility of misinterpretation of results would then at least be clear from the histological results. However, situations may obtain in which the blood supply is sufficiently reduced to a region to cause dysfunction but is not lowered to a level where degeneration of tissue takes place. Under such circumstances the possibility of misinterpretation might not be considered because of the absence of histological changes in the neural components.

Both of the difficulties just discussed, which are inherent in the older methods of producing lesions, are eliminated when lesions are produced by focused ultrasonic beams at dosages which result in selective destruction of tissue components (1, 2, 3, 4). The focusing procedure eliminates the damage to intervening tissue for even the deepest lesions. Small size and accuracy of placement are readily obtained with suitable instrumentation.

Figure 1 shows the interruption of the mammillothalamic tract in cat brain by a suitably chosen dosage of high level focused ultrasound. (The frequency of the ultrasound was 980 kc./sec. The acoustic pressure amplitude was approximately 50 atmospheres and the acoustic particle velocity amplitude was approximately 400 cm./sec.) The tract has a diameter of about one millimeter and, as can be seen in the figure, it was essentially completely interrupted without appreciable spreading of the lesions into the surrounding tissue. The accuracy of "geometric" positioning of the focal spot in the brain is within a few tenths of a millimeter for even the deepest portions of a human brain. The position accuracy with respect to a given internal brain structure depends upon the variation in position, from one brain to another, of that structure with respect to chosen landmarks. For the cat and rhesus monkey the usual interaural, Frankfort and midsagittal planes are used. For the first human neurosurgery with high level focused ultrasound, the same coordinate system will be

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Various phases of the research reviewed here were supported by the following contracts: Nonr 336(00)NR 119-075 with the Physiology Branch of the Office of Naval Research; AF 33(616)-3306 with the Aero Medical Laboratory, Wright Patterson Air Force Base; and USPH B-613 with the Institute of Neurological Diseases and Blindness, National Institutes of Health, U. S. Public Health Service.

Presented as part of the scientific program of the International Conference on Ultrasonics in Medicine, sponsored by the American Institute of Ultrasonics in Medicine, Los Angeles, California, September 6–7, 1957.

Received for publication January 6, 1958.

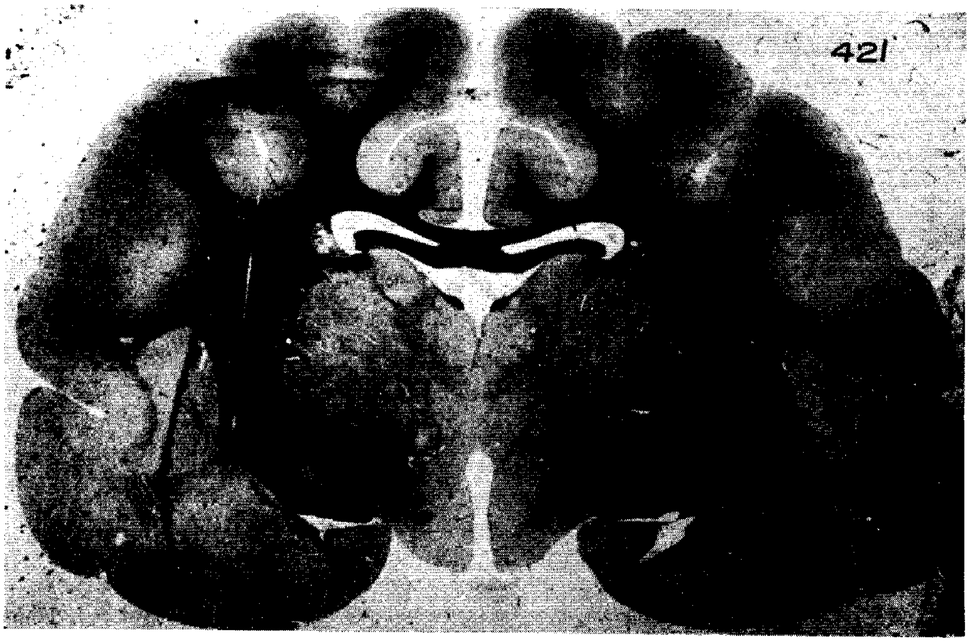

FIG. 1. Interruption of mammillothalamic tract in cat brain by focused ultrasound.

used as a first approximation, but a second reference system which uses landmarks on the ventricles as seen in x-ray photographs will be used as the principal reference system[2].

In addition to eliminating the difficulties inherent in the older methods of producing lesions in the brain, high level ultrasound, at a suitably chosen dosage, provides a means of destroying the fiber tracts of white matter without disrupting immediately adjacent gray matter which receives the same dosage of ultrasound. This is possible since white matter is affected at lower dosages of ultrasound than gray matter. At sound levels (frequency in the neighborhood of one megacycle per second) corresponding to particle velocity amplitudes of approximately 400 cm./sec., the minimum duration of exposure required for the disruption of gray matter in the adult animal is about 50 per cent greater than that required for the complete disruption of the neural components of white matter. This selective action, realized over a specific dosage range, makes it possible to destroy complex-shaped fiber tract regions without damaging nuclear masses. This is illustrated in figure 2 by the subcortical lesion in the white matter of the cat brain. To produce lesions such as this, the focal spot of the sound beam (or beams) is positioned successively in a number of adjacent positions and a single pulse of ultrasound is applied at each of these positions. A one millimeter spacing distance between adjacent positions is used. The selective action of the ultrasound for destroying fiber tract regions will be utilized in the treatment of the first human patients[2]. The ansa-lenticularis will be interrupted in patients with Parkinson's disease. The production of selective irreversible changes by high level ultrasound is now a well established procedure at this laboratory, and the method is now in use in neuroanatomical and neurophysiological studies. The application to human neurosurgery is imminent.

Relatively recently an investigation was initiated on the effects of ultrasound on the tissues of the central nervous system when the ultrasonic dosage conditions are selected to avoid producing a histologically observable lesion. Under such dosage conditions, the manifestation of a change is the temporary suppression of an evoked electrical signal in response to a stimulus. The focus of the ultrasonic beam (or beams) is located at positions along the central pathway from the position of entry of the signal into the

[2] Since this paper was presented at the International Conference on Ultrasonics in Medicine, three patients have been successfully treated.

brain to the region in which the elicited response is detected (5). The cat has been used as the experimental animal. The arrangement of animal and apparatus is shown schematically in figure 3. A flash of light is used to stimulate one eye of the cat and several bipolar recording electrodes are placed in the appropriate cortical areas on both hemispheres, approximately 2–3 mm. below the surface. These electrodes are connected to amplifiers of a standard 6-channel electroencephalograph. A focused ultrasonic beam source is used to irradiate 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 ultrasonic irradiation. Continuous electrical recording is in progress during the course of the experiment.

The ultrasonic and other associated instrumentation used in these studies are described in the accompanying paper by Professor Frank J. Fry, page 152 of this issue (6). With this equipment it is possible to irradiate either at single isolated spots or to scan volumes of any desired size. The ultrasonic energy must, of course, be transmitted from the irradiator to the brain through degassed Ringer's solution, and the intervening skull bone must be removed. The bipolar electrodes used are constructed from 0.010 inch diameter nichrome wire with "formvar" insulation. Since the electrode leads are immersed in Ringer's solution, it is important that all insulation be liquid tight. The tip of each wire

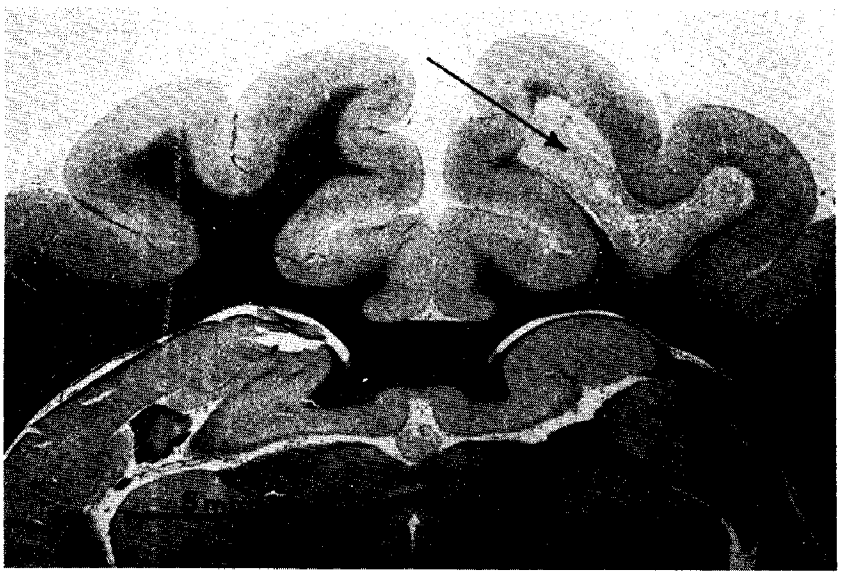

FIG. 2. Selective destruction of subcortical white matter in cat brain.

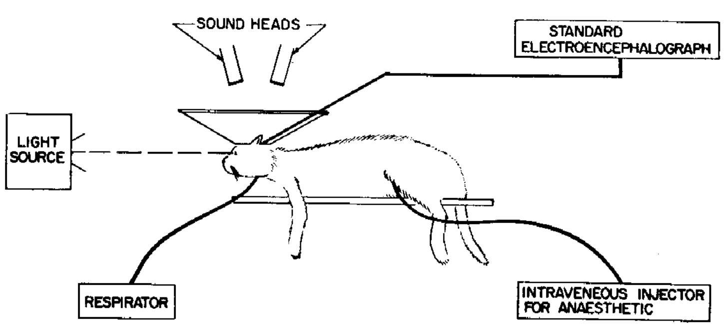

FIG. 3. Schematic diagram of animal and apparatus for study of reversible changes produced by focused ultrasound.

is cleared of insulation and plated with silver. The lateral position of the electrodes in the cortex is one to two millimeters off the midline in the lateral gyrus. They are spaced in the anterior-posterior direction along the cortex from about 15 mm. posterior to the cruciate sulcus to the most posterior region of the lateral gyrus. Sodium nembutal has been used as the anesthetic and is administered as controlled repetitive injections into the femoral vein. The EEG records and the type of the response to light stimuli are used to determine the time rate of administration. Injections are spaced several minutes apart.

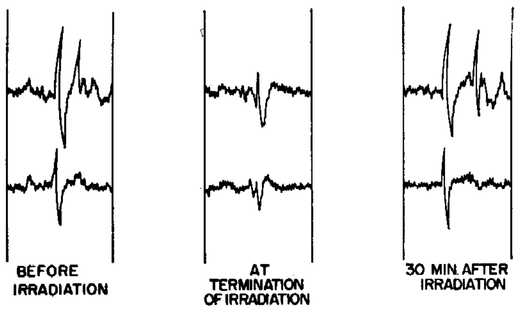

FIG. 4. Reversible suppression of evoked cortical potentials by ultrasonic irradiation of the region of the lateral geniculate nucleus.

A series of three light flashes, with approximately three seconds between flashes, is used to stimulate the eye of the cat. The series of three flashes is repeated at variable intervals of time before, during and after exposure to the ultrasonic radiation. The focus of the sound beams is placed successively in and around the region of the lateral geniculate nucleus. It is felt that

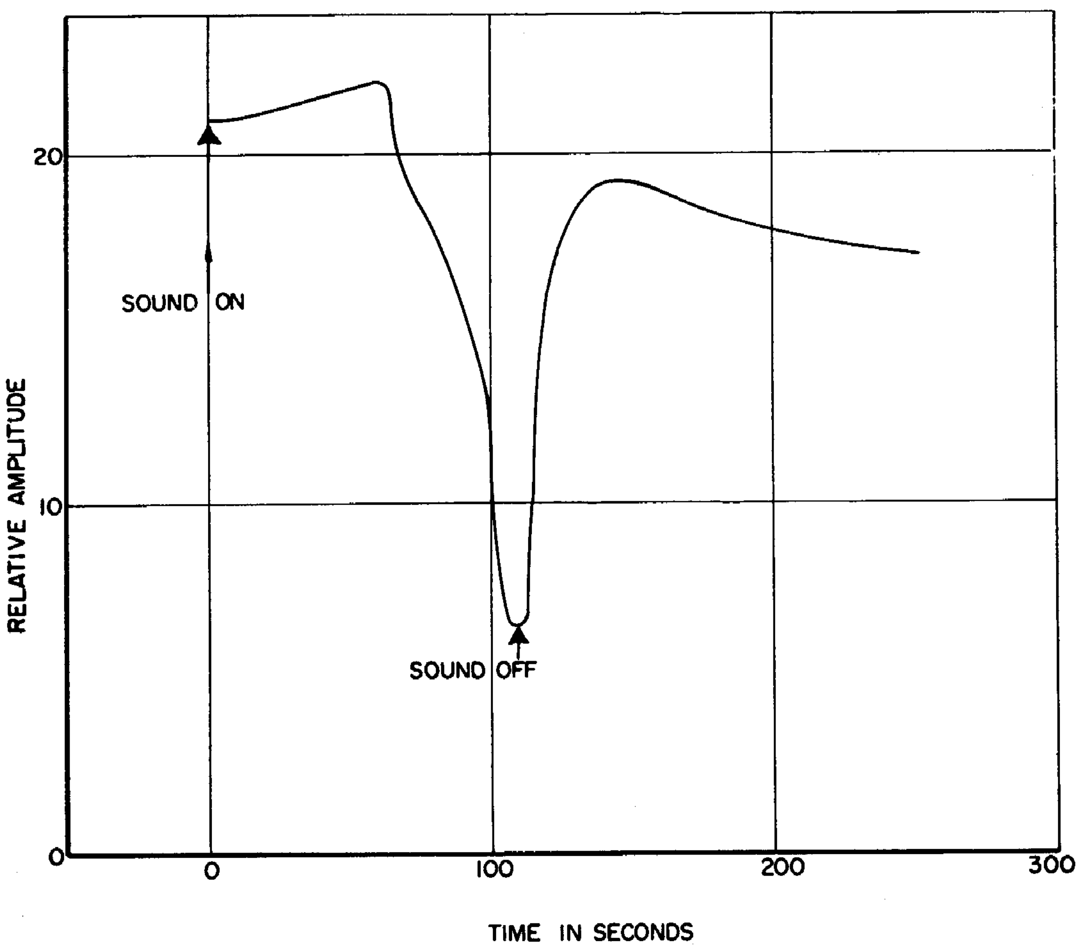

FIG. 5. Amplitude of evoked cortical potential (first peak) before, during and after ultrasonic irradiation in the region of the lateral geniculate nucleus.

mapping, illustrating functional localization in this region of the brain, is possible by successively irradiating with the focus of the sound beams at various positions. This type of mapping has been accomplished in a preliminary way, but most of the work so far has been concerned with the determination of dosage and auxiliary conditions suitable for producing an observable reversible effect.

It has been possible to produce reversible changes in the elicited electrical response in the visual cortex by single, short time ultrasonic irradiation (durations of about one second, at a level which would result in a lesion if the duration of irradiation were two seconds). Reversible suppressions have been produced rather consistently with sound levels much lower than those used in the short time irradiation procedure and with an exposure time varying from 20 seconds to 120 seconds. At the present time however, it is felt that the short time, higher level, irradiation procedure will probably be more successful in exhibiting sharper functional localization in such mapping studies.

Figure 4 shows typical results taken from the records of the electrical activity in the visual cortex of a cat as seen on the electroencephalograph. Evoked cortical potentials elicited by a flash of light are shown before ultrasonic irradiation, at the termination of the ultrasonic exposure period and subsequent to irradiation. The two traces are recordings from two cortical electrodes. This record is taken from that of a cat in which the level of anesthesia, controlled by the injector, was adjusted so that a low electrical background and a relatively simple response to photic stimulation resulted. At the termination of the ultrasonic irradiation period the amplitude of the first peak was reduced to less than one third of its original value. The initial stage of recovery of the peak amplitude after exposure is relatively rapid and this is followed by a slower recovery period. The results with this particular animal indicated that about 30 minutes were required for essentially complete recovery. The relative amplitude of the response is shown as a function of the time, in seconds, in figure 5. From the graph it is observed that the initial rapid recovery phase is followed by a slight depression from which subsequent full recovery ensues.

On the basis of the electrophysiological results obtained so far and the detailed histological examination of brains irradiated at the dosage levels used to produce such changes, it is concluded that reversible suppression of transmission along neural pathways can be accomplished by applying a controlled dosage of ultrasonic radiation. Experiments are in progress to further quantify the conditions for producing controlled reversibility, to determine the site or sites (in the tissue structure) of action of the sound and to demonstrate three dimensional ultrasonic mapping of central nervous system function. Such a controlled mapping method would constitute a tool of considerable power for fundamental animal research into brain structure and function. It would also be extremely useful for precise localization of the region to be destroyed in, for example, Parkinson patients. With the patient conscious, and by irradiating at dosages below those at which irreversible changes take place, it would be possible to locate the sound beam focus at the desired site by observing the state of the patient's tremor as the focus is swept through the brain. The difficulties associated with trying to precisely position with respect to reference landmarks (skull bone, ventricular system) would then be eliminated.

REFERENCES

1. Fry, W. J. Ultrasound in neurology. Neurol., **6:** 693–704, 1956.
2. Barnard, J. W., Fry, W. J., Fry, F. J., and Brennan, J. F. Small localized ultrasonic lesions in the white and gray matter of the cat brain. Arch. Neurol. & Psych., **75:** 15–35, 1956.
3. Fry, W. J., Mosberg, W. H., Barnard, J. W., and Fry, F. J. Production of focal destructive lesions in the central nervous system with ultrasound. J. Neurosurg., **11:** 471–478, 1954.
4. Barnard, J. W., Fry, W. J., Fry, F. J., and Krumins, R. F. Effects of high intensity ultrasound on the central nervous system of the cat. J. Comp. Neurol., **103:** 459–484, 1955.
5. Fry, F. J. Production of reversible changes in the central nervous system by ultrasound. Abst. Natl. Biophys. Conf.: 30–31, 1957.
6. Fry, F. J. Precision high intensity focusing ultrasonic machines for surgery. Am. Jour. Phys. Med., **37:** 152–156, 1958.