The Use of Ultrasound in Neurosurgery

By William J. Fry, Francis J. Fry, Russell Meyers, and R. C. Eggleton

SUMMARY

The use of accurately focused ultrasound at high amplitude levels to modify, either permanently or temporarily, arrays of sites in deep brain structures in the experimental animal and in the human is discussed. The types of selective lesion arrays that can be attained for basic research in neuroanatomy, neurophysiology and behaviour are described, and some representative examples are illustrated. The spectrum of human neurological disorders which has so far received attention in the medical application of this method is indicated, and the modifications of symptoms realised up to the present are briefly outlined. Procedures preparatory to irradiation and pertinent information concerned with the determination and control of the acoustic parameters of exposure, auxiliary factors including tissue temperature and absorption in intervening tissue are considered. Design features of the instrumentation including the various types of transducers employed for producing the focal beams, stereotactic apparatus for supporting the skull, X-ray equipment for landmark determination, calibration instruments for measurement of acoustic field parameters and distributions, and equipment for control of the physical parameters which determine the level and biological effects of the radiation (e.g. heat exchangers, electronic regulating comparators, digital timers, etc.) are briefly described.

The present use of high-intensity ultrasound in the field of human neurosurgery[5, 8, 9, 17, 18, 23-26] stems from the following facts, initially established in extensive experimental animal studies:[1-4, 6, 7, 10-14, 16, 19-21]

(*a*) By focusing the ultrasound it is possible to confine the induced changes (permanent or temporary) to a desired array of deep brain sites without corresponding effects on intervening tissue.

(*b*) Lesions of almost any desired shape and spatial dimensions can be produced by placing the focus successively at sites in an appropriate array. Uniformity of change over regions of arbitrarily large dimensions is accomplished by control of the exposure conditions and the time intervals between successive exposures at the sites of the array.

(*c*) Selective action on specific tissue components can be accomplished by accurate control of the irradiation parameters and the temperature of the tissue. For example, the vascular system can be left anatomically intact and functioning in both white and grey matter when all neural components have been destroyed. In addition, the fibre tracts of white matter can be irreversibly changed without disruption of nerve cell bodies in grey matter which are subjected to the same irradiation conditions. Lesions of various predetermined forms and sizes and the selective action on the fibre tracts of white matter are illustrated in Fig. 1.

(*d*) No delayed cumulative action is produced in intervening irradiated tissue. Therefore it is possible for the ultrasound on its way to the focus, at which site a lesion of the desired array is intended, to pass through a specific tissue volume any number of times without producing undesirable changes.

The work up to the present time in the human has been almost completely restricted to the production of 'permanent' (i.e. irreversible) changes in the tissue structures, although temporary effects have already been demonstrated in both the experimental animal and the human[4, 6, 10, 25]. Since the production of such changes requires, in general, additional sophistication in the equipment, the extensive use of the procedure of producing reversible changes in the human brain awaits further instrumentation.

The flexibility of ultrasonic methods for studying and favourably affecting the signs and symptoms of neurological disorders in the human becomes apparent when it is observed that any combination of brain structures can be modified in tens, hundreds or more sites in a single patient without penetrating the brain with a mechanical device, such as an electrode or cannula. The removal of a *single* portion of the vault of the skull of appropriate size and location as a preliminary procedure makes it possible to modify *bilaterally* a wide variety of deep structures in the thalamus, subthalamus, basal ganglia and brain stem by irradiating through the intact skin in any desired temporal sequence of procedures without subjecting the patient to repetitive surgery[5, 25]. When the ultrasonic methods cited above are employed, one is not committed to any single plan of attack in the attempt to modify favourably the symptoms of a neurological disorder in a particular patient, i.e. structures in each patient's brain can be modified in accordance with the changes observed at each step during the irradiation procedure. Since modification of structures on both sides of the patient's brain can be accomplished through a single bone opening, it is possible to relieve, for example, the severe symptoms of tremor and rigidity in parkinsonism during a single irradiative procedure[18, 25]. This can be accomplished in many cases without the direct destruction of as much neural tissue as is often destroyed by a single insertion of a metallic or plastic cannula into a deep brain structure.

So far, the instrumentation currently in use on the human has been employed to modify favourably in a step-wise fashion (*a*) the patterned tremors and rigidity of Parkinson's disease, (*b*) the non-patterned movements encountered in choreo-athetotic cerebral palsy and dystonia musculorum, (*c*) spasmus nutans and cerebellar dyssynergia, (*d*) certain clinically anonymous hyperkinesias akin to myoclonus, (*e*) the intractable pains and disturbing paresthesias and dysesthesias ('thalamic' syndrome) that sometimes follow cerebrovascular accidents, (*f*) phantom images and pains in amputees, and (*g*) pituitary function (in repetitive fashion) in cases of extensive and metastasizing cancers of the breast[5, 9, 18, 22, 24-26]. In addition, the authors have recently employed it to irradiate a surgically inaccessible tumour (hamartoma) of the base of the hypothalamus.

The *geometric* accuracy of positioning of the focus of the sound beam in the tissue is sufficient to accomplish all types of investigations contemplated so far. However, the accuracy of locating specific brain structures with respect to landmarks requires improvement. In the latter problem the extensive use of those ultrasonic parameters of irradiation which result in

Messrs. W. J. Fry, F. J. Fry and R. C. Eggleton are at the Biophysical Research Laboratory, University of Illinois, U.S.A.
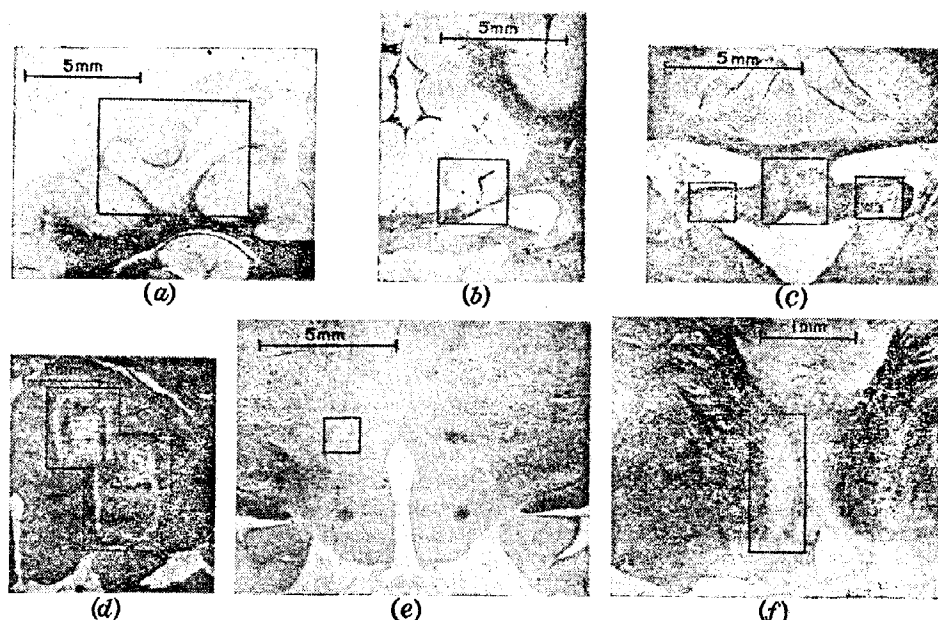Mr. R. Meyers is in the Division of Neurosurgery, State University of Iowa, U.S.A.

Fig. 1.—Lesions in various structures of the cat brain produced by focused ultrasound using appropriate values of the irradiation parameters and auxiliary conditions.

For all the lesions illustrated the focus of the ultrasonic beam was placed successively at sites in a suitably chosen geometric array.

(a) Lesion in the subcortical white matter with no invasion of the immediately adjacent cortical grey matter. The brain cross-section shown exhibits the maximum dimensions of the lesion. Its extent perpendicular to the cross-section is small. It was produced by moving the focus (1 Mc/s sound) in the plane of the section with a 1 mm spacing between adjacent sites.

(b) Lesion placed to interrupt longitudinally running fibres—the cingulum running perpendicular to the plane of the section—in the white matter of the cingulate gyrus. The lesion was produced by placing the focus at an array of sites space 0·2 mm apart—4 Mc/s sound.

(c) Three lesions in the subcallosal fornix. The longitudinally running fibres are interrupted in the lateral half of the structure bilaterally and the fibres in the medial portion of the structure in the plane of the section are destroyed. No damage was produced in the corpus callosum and underlying thalamic structures—0·2 mm spacing between adjacent sites of the array, 4 Mc/s sound.

(d) Two thin rectangular sheet lesions in the thalamus and subthalamus. These lesions are thin in the direction perpendicular to the section shown—4 Mc/s sound used.

(e) Interruption of the mammillothalamic tract—0·2 mm spacing, 4 Mc/s sound.

(f) Lesion in the medial part of the medial mammillary body. The lesion extends throughout the length of this structure, i.e. for 1½ mm in the direction perpendicular to the section shown. The lesion is shown in cross-section—0·2 mm spacing, 4 Mc/s sound.

temporary changes in function to locate arrays of sites at which permanent structural changes should be made will almost certainly constitute a major advance. The use of this method may be expected to eliminate implicit dependence upon brain atlases for positioning, other than for obtaining a rough, first approximation of the target site(s).

Instrumentation with the flexibility, reproducibility and accuracy now technically possible for producing permanent changes at deliberated arrays of positions in the human brain is quite elaborate and not inexpensive. The instrumentation must include a head holder with X-ray equipment for landmark localization, ultrasonic-focusing transducers, apparatus for positioning the focus at predetermined arrays of sites in the brain, electronic apparatus for supplying the necessary electrical excitation to the transducers and for accurately controlling the acoustic output with respect to both sound level and duration of exposure, and calibration instrumentation for precisely determining acoustic field configurations and measuring the sound levels to be employed for irradiating.

The instrumentation required for realizing the full potentials of temporary, i.e. reversible, changes induced by ultrasound will not be available until sometime in the future. It will be considerably more elaborate than the present equipment, but will constitute an extremely powerful analyser for examining brain function(s) in pathological states and therefore for indicating desirable changes to be made on a permanent basis. Some of these possibilities become immediately apparent when one considers that the resolution obtainable with the ultrasonic method can make a moving sound focus the equivalent of 10 000 to 100 000 electrodes, capable of disturbing threshold relations and temporal sequences of neural events in a combination of

structures in a single brain. With such an analyser, one need not destroy any brain tissue in searching for an anatomical or functional landmark. Thus it might prove possible to modify favourably the symptoms of any neurological disorder in which the disruption of a specific neural structure or structures would relieve the symptoms.

The instrumentation and certain aspects of the procedure currently being employed in the irradiation of arrays of sites in the human brain will now be discussed. Consider first the ultrasonic-focusing irradiators. The wavelength of the sound and the apex angle of the cone of convergence of the beam are the important factors determining the minimum size of the focal region[15], since both the diameter of the focus in the direction of the beam axis and that transverse to the axis are determined by these two factors. Because the wavelength is inversely proportional to the frequency, the minimum dimensions of the focal region obtainable in the tissue structure decrease as the frequency increases. Since the velocity of sound in soft tissue is approximately $1·5 \times 10^5$ cm/s, at a frequency of 1 Mc/s the wavelength is 1·5 mm, and therefore at this frequency it is possible to produce changes involving only 2-3 mm³ of tissue. Much of the work done in both the experimental animal and the human has been implemented at this frequency. However, at a frequency of 4 Mc/s, which has also been extensively employed at the University of Illinois in fundamental neuroanatomical and behavioural studies involving experimental animals, the wavelength is slightly less than 0·4 mm. At this frequency it is readily possible, if desired, to restrict the volume of the affected tissue for each exposure to a few hundredths of a cubic millimeter.

An upper limitation upon the frequency employed for a particular purpose is imposed by the thickness of the brain tissue

which must be penetrated in order to irradiate the target sites. The ultrasonic absorption coefficient per unit path length in soft tissue increases in direct proportion to the first power of the frequency. At 1 Mc/s at a temperature of 37°C, the 'average' intensity absorption coefficient for brain tissue is 0·20 per cm. Since the sound level along the path through the intervening tissue should be considerably less than the level in the focal region, it is probable that frequencies no higher than those in the neighbourhood of 2 Mc/s would be practical for irradiating structures requiring the maximum penetration in the human brain.

range from approximately 5 atm to 100 atm acoustic pressure amplitude. The acoustic particle velocities lie in the range from approximately 50 cm/s to 1000 cm/s. To illustrate the acoustic power levels involved, the intensity in a plane-wave field in water for an acoustic pressure amplitude of 50 atm is approximately 1 000 watts/cm². In order to realize the necessary stability and accuracy of scaling of the driving voltage across the transducer, it is essential to employ an amplifier system with an appropriate feedback arrangement and comparator. In the present equipment a precisely known fraction of the driving
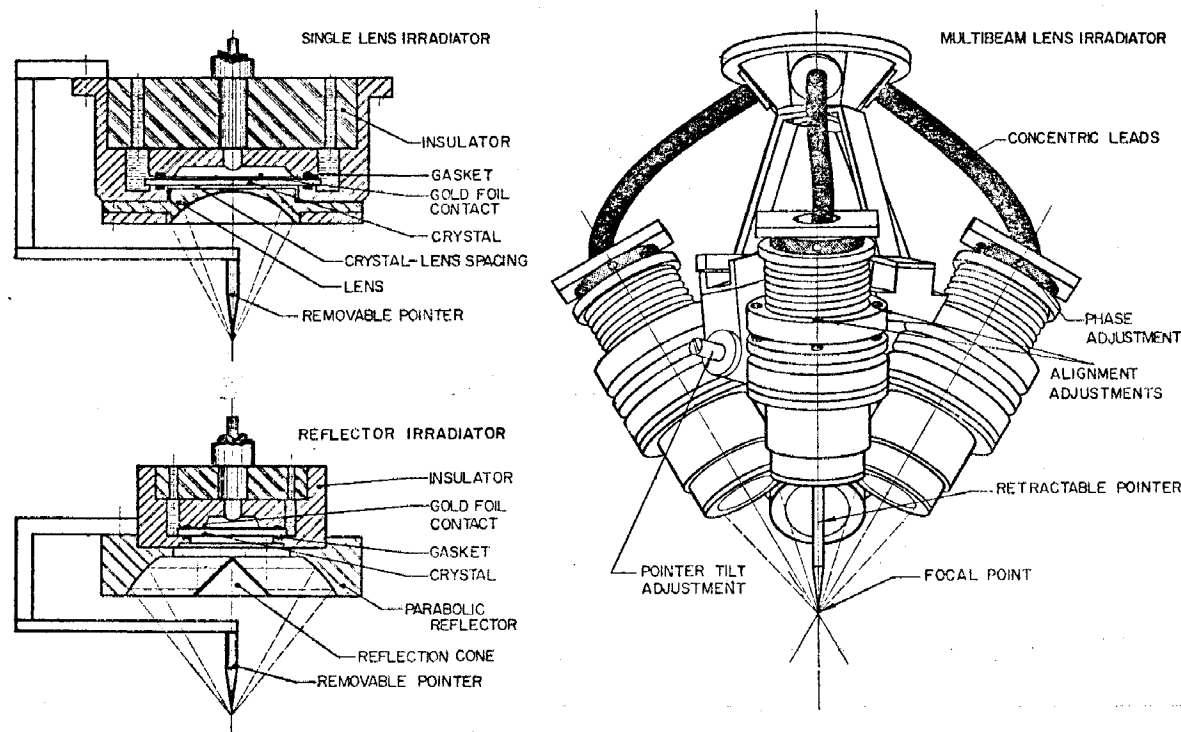

Fig. 2.—Schematic of single-beam lens, multi-beam lens, and reflector irradiators.

Various types of focusing irradiators have been designed, built and used in the basic experimental animal research and in the human work. These include single- and multi-beam lens types, as illustrated schematically in Fig. 2. In all irradiators for precision work the sound is generated by X-cut quartz plates. The lens materials currently employed are plastics, such as polystyrene or methyl methacrylate. In the reflector-type irradiator, the sound is first incident upon a cone with a 90° included angle which reflects it to a second (parabolic) surface from which it is focused. Each irradiator is provided with an appropriate pointer system whose tip can be placed coincident with the position of the centre of the focal region. The pointer permits positioning of the focal region of the irradiator at any desired reference site on the head holder, and is thus essential for its accurate placement at desired sites in space.

The driving voltage across the transducer determines the magnitudes of the acoustic field variables at the focus. The requisite voltage is determined by calibration measurements, and the authors have shown in experimental animal studies that it should be determined and controlled to within 1%. When this is accomplished, lesion boundaries are reproducible in desired dimensions and predictable selective action can readily be achieved from one brain to another. The values of the acoustic parameters, which are of current interest in this work, lie in the

voltage is accurately compared, after rectification, with a direct voltage standard, and the difference is used to shift the low-level drive appropriately.

The duration of exposure is of major importance in determining the effects produced by the ultrasound on the tissue. This is controlled by a digital timer using a tuning fork as a time-base reference. Durations of exposure of current interest at 1 Mc/s at the levels indicated range from 0·5 to 30 sec. At a particle-velocity amplitude of 350 cm/s the durations of interest are from 1·0 to 3·0 sec. (At 4 Mc/s for a particle-velocity amplitude of 550 cm/s the range of interest is from 0·4 to 1·0 sec.)

Since the base temperature of the tissue is also important in determining the changes which are produced in response to a given set of ultrasonic irradiation parameters it is important to control accurately this factor. In the case of the conscious human patient this constitutes no great problem, since the central temperature control mechanism is intact. However, in much of the experimental animal work, where anaesthetics which disturb the central temperature control mechanisms are used, it is essential to provide external means of maintaining the animal at a given selected temperature. This is accomplished by a suitable arrangement of thermo-sensing elements and heat exchangers. Both the temperature of the animal and that of the

transmitting liquid are presently held to within ± 0·3°C of that desired.

engage hemispherical indentations in the external table of the skull, are shown supported from universal mounts which permit
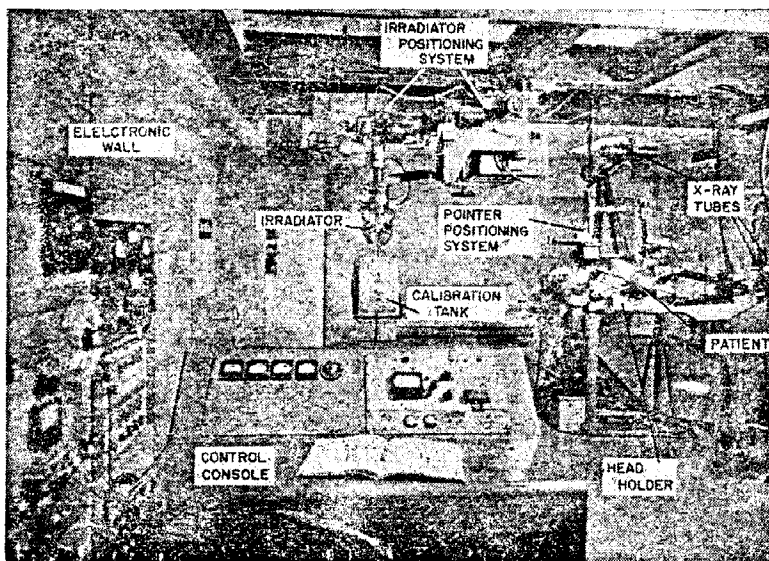

Fig. 3.—Irradiation room for treatment of human patients.

A patient is shown with his head supported in the head holder. The three X-ray tubes and pointer positioning system which are used in obtaining the co-ordinates of internal brain landmarks are shown mounted on the head holder. A 4-beam focusing irradiator is shown supported on the overhead positioning system. The irradiator is shown positioned over the calibration tank in the photograph. It is swung into position over the patient for the irradiation procedure. The electronic wall and control console are in the left foreground.

Fig. 3 illustrates the arrangement of the head holder with a patient in the apparatus. The four stainless-steel rods, which
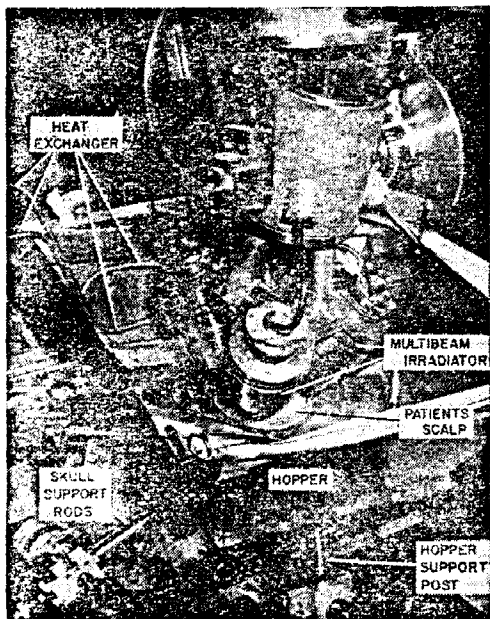

Fig. 4.—Configuration of irradiator, hopper which supports degassed transmitting liquid (normal physiological saline) and shaved scalp of patient.

The sound is transmitted through the intact scalp overlying the opening made in the skull bone at the time of craniectomy.

repositioning of the tips of the rods to within ± 0·001 in. This head holder is provided with three X-ray tubes which permit lateral, antero-posterior (A.P.) and 30°-off-the-A.P.-axis roentgenograms to be taken. When a radio-opaque material is present in the ventricles, these roentgenograms reveal landmarks on the boundaries of the ventricular system. Fig. 4 shows the arrangement for irradiation, the focusing irradiator being in position and ready for immersion in the transmitting medium (degassed physiological saline solution) which will be poured into the pan. The acoustic impedance of the degassed saline matches sufficiently closely that of the soft tissue, so that a negligible fraction of the acoustic energy, as far as this application is concerned, is reflected at the water/tissue interface. The refraction effect is readily calculated: for an angle of incidence of 45°, which is larger than that usually employed, the focal spot of the beam can shift laterally from the position it would have in the homogenous transmitting medium (the saline) about ⅔ mm for a depth in the brain tissue of 12 cm. Direct measurements show that, after the sound passes through the entire thickness of the brain, the size and shape of the focal region are close to those obtained when the sound passes entirely through saline. The multiple interfaces within the brain reflect in each case only a very small fraction of the acoustic energy incident on them, and scattering does not interfere with the production of the results of the type described here. The saline solution which transmits the sound must be degassed to eliminate cavitation nuclei which produce vapour or gas-filled cavities when subjected to the high-tension forces of the intense acoustic field. Such cavities or bubbles would, if present, interfere with the transmission of sound by scattering and absorbing the acoustic energy. Freshly boiled saline at atmospheric pressure is an appropriate degassed

medium for transmitting ultrasound at a frequency of 1 Mc/s up to intensities of about 8 kW/cm².

The array of sites to be considered for irradiation within the brain is represented in terms of a map whose scales represent the axes of the positioning system which supports and moves the irradiator. This positioning system provides three rectangular degrees of freedom whose axes lie, in general, at non-zero angles with respect to the axes of the head holder. Consequently, it is necessary to transform from the co-ordinate system of the axes of the head holder to that of the irradiator. Using measurements of the positions of internal brain landmarks determined from the roentgenograms, it is possible to obtain the positions of these landmarks with respect to the co-ordinate axes of the head holder. From available atlases and the appropriate use of scaling factors it then becomes possible to compute co-ordinates for arrays of sites in desired structures of the brain of any given patient. These computations and the transformation from the co-ordinate system of the head holder to that of the irradiator positioning system are accomplished on a computer. The results of this computation furnish the co-ordinates in the irradiator positioning system of arrays of sites in a variety of brain structures in the patient of interest. As many as 100 such sites are often computed for the clinical types of patients currently under investigation and treatment.

The irradiation procedure is commenced by placing the focus at a chosen site. The exposure is then completed. In appropriate cases, the patient is examined during and immediately following each exposure for changes in signs and symptoms. The wakeful patient is interviewed periodically during the course of the procedure. In parkinsonian cases, in which tremor and rigidity are prominent symptoms, the subjects are regularly examined for changes in muscle tonus (extensor and flexor) and tremor (amplitude, frequency and duty cycle) in the various muscle groups of the body. The changing status of the symptoms during the procedure determines in part the course of the succeeding steps of the irradiation, i.e. the form and extent of the irradiation arrays.

In addition to the range of disorders already indicated, the authors currently plan to extend their investigations to include the direct irradiation of a variety of neoplasms. As stated above, this has already been initiated in one inoperable sub-hypothalamic tumour (hamartoma) attended by pubertas praecox and epileptic seizures. The investigation of the possibility of favourably modifying 'deep' brain mechanisms in individuals with various forms of mental disorders by ultrasonic methods is also contemplated.

ACKNOWLEDGMENTS

BIBLIOGRAPHY

(1) BARNARD, J. W., FRY, W. J., FRY, F. J., and BRENNAN, J. F.: 'Small Localized Ultrasonic Lesions in the White and Grey Matter of the Cat Brain', *Archives of Neurology and Psychiatry*, 1956, 75, p. 15.

(2) BARNARD, J. W., FRY, W. J., FRY, F. J., and KRUMMINS, R. F.: 'Effects of High Intensity Ultrasound on the Central Nervous System of the Cat', *Journal of Comparative Neurology*, 1955, 103, p. 459.

(3) DUNN, F., and FRY, W. J.: 'An Ultrasonic Dosage Study: Functional Endpoint' from 'Ultrasound in Biology and Medicine', E. Kelly, Ed. (American Institute of the Biological Sciences, 1957), p. 226.

(4) FRY, F. J.: 'Production of Reversible Changes in the Central Nervous System by Ultrasound', Abstracts of National Biophysics Conference, U.S. Air Force Office of Scientific Research, March, 1957, p. 30.

(5) FRY, F. J., FRY, W. J., and MEYERS, R.: 'Investigation and Modification of the Signs and Symptoms of some Neurologic Disorders in Humans by High Level Focused Ultrasound', Abstracts of Biophysics Society, Paper J5, 1959.

(6) FRY, F. J., ADES, H. W., and FRY, W. J.: 'Production of Reversible Changes in the Central Nervous System by Ultrasound', *Science*, 1958, 127, p. 83.

(7) FRY, W. J.: 'Action of Ultrasound on Nerve Tissue—a Review', *Journal of the Acoustical Society of America*, 1955, 25, p. 1.

(8) FRY, W. J.: 'Neurosonic Surgery', Proceedings of the 4th Annual Conference, American Institute of Ultrasonics in Medicine, 1955, p. 40.

(9) FRY, W. J.: 'Ultrasound in Neurology', *Neurology*, 1956, 6, p. 693.

(10) FRY, W. J.: 'Intense Ultrasound in Investigations of the Central Nervous System' from 'Advances in Biological and Medical Physics', J. H. Lawrence, and C. A. Tobias, Ed. (Academic Press, 1958).

(11) FRY, W. J., BARNARD, J. W., FRY, F. J., KRUMMINS, R. F., and BRENNAN, J. F.: 'Ultrasonic Lesions in the Mammalian Central Nervous System', *Science*, 1955, 122, p. 517.

(12) FRY, W. J., BARNARD, J. W., FRY, F. J., and BRENNAN, J. F.: 'Ultrasonically Produced Localized Selective Lesions in the Central Nervous System', *American Journal of Physical Medicine*, 1955, 34, p. 413.

(13) FRY, W. J., BRENNAN, J. F., and BARNARD, J. W.: 'Histological Study of Changes produced by Ultrasound in the Grey and White Matter of the Central Nervous System', from 'Ultrasound in Biology and Medicine', E. Kelly, Ed. (American Institute of Biological Sciences, 1957), p. 110.

(14) FRY, W. J., and DUNN, F.: 'Ultrasonic Irradiation of the Central Nervous System at High Sound Levels', *Journal of the Acoustical Society of America*, 1956, 28, p. 129.

(15) FRY, W. J., and DUNN, F.: 'Ultrasound: Analysis and Experimental Methods in Biological Research', from 'Physical Technics in Biological Research', W. Nastuk, Ed. 1961 (to be published).

(16) FRY, W. J., and FRY, R. B.: 'Temperature Changes produced in Tissue during Ultrasonic Irradiation', *Journal of the Acoustical Society of America*, 1953, 25, p. 6.

(17) FRY, W. J., and FRY, F. J.: 'Neurosonic Surgery' from 'Ultrasound in Biology and Medicine', E. Kelly, Ed. (American Institute of Biological Sciences, 1957), p. 99.

(18) FRY, W. J., MEYERS, R., FRY, F. J., SCHULTZ, D. F., DREYER, L. L., and NOYES, R. F.: 'Topical Differentia of Pathogenetic Mechanisms underlying Parkinsonian Tremor and Rigidity as indicated by Ultrasonic Irradiation of the Human Brain', *Transactions of the American Neurological Association*, 1958, p. 16.

(19) FRY, W. J., MOSBERG, W. H., Jr., BARNARD, J. W., and FRY, F. J.: 'Production of Focal Destructive Lesions in the Central Nervous System with Ultrasound', *Journal of Neurosurgery*, 1954, 11, p. 471.

(20) FRY, W. J., TUCKER, D., FRY, F. J., and WULFF, V. J.: 'Physical Factors involved in Ultrasonically induced

Changes in Living Systems. II. Amplitude Duration Relations and the Effect of Hydrostatic Pressure for Nerve Tissue', *Journal of the Acoustical Society of America*, 1951, 23, p. 364.

(21) FRY, W. J., WULFF, V. J., TUCKER, D., and FRY, F. J.: 'Physical Factors involved in Ultrasonically Induced Changes in Living Systems: I. Identification of Non-Temperature Effects', *ibid.*, 1950, 22,, p. 867.

(22) HICKEY, R. C., FRY, W. J., MEYERS, H. R., FRY, F. J., and BRADBURY, J.: 'Human Pituitary Irradiation with Focused Ultrasound in Advanced Breast Cancer—An Initial Report', *Archives of Surgery* (to be published).

(23) MEYERS, R.: 'Summary Remarks: Symposium on Stereotactic Surgery', *Journal of Neurosurgery*, 1958, 15, p. 276.

(24) MEYERS, R.: 'Some Indications for and Values of Surgery of the Basal Ganglia and Thalamus', *New Physician*, 1960, 9, p. 48.

(25) MEYERS, R., FRY, F. J., FRY, W. J., EGGLETON, R. C., and SCHULTZ, D. F.: 'Determination of Topologic Human Brain Representations and Modifications of Signs and Symptoms of some Neurologic Disorders by the Use of High Level Ultrasound', *Neurology*, 1960, 10, p. 271.

(26) MEYERS, R., FRY, W. J., FRY, F. J., DREYER, L. L., SCHULTZ, D. F., and NOYES, R. F.: 'Early Experiences with Ultrasonic Irradiation of the Pallidofugal and Nigral Complexes in Hyperkinetic and Hypertonic Disorders', *Journal of Neurosurgery*, 1959, 16, p. 32.