1st Int. Symp. Stereoencephalotomy, Philadelphia 1961.
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Ultrasonic Method of Modifying Brain Structures

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The high intensity focused ultrasound method of permanently modifying tissue, and in particular brain structure, differs in principle and sophistication from methods which result in the destruction of essentially all tissue components in an affected region [1]. It provides a flexibility with respect to the modification of structure at a multiplicity of sites, including complexities of shape, which no method requiring the insertion of a mechanical device into the brain can remotely achieve. By contrast with ionizing beams, whether in the form of electromagnetic radiation or high energy particles, ultrasound does not produce cumulative action on tissue through which it passes on the way to the focus and therefore tissue intervening between the port of entry of the sound into the brain and the structures to be affected can be subjected to an unlimited amount of acoustic radiation without deleterious action. With appropriate dosage control, either permanent or temporary ("reversible") changes can be produced as desired [1, 2].

As implemented at the present time and briefly reviewed here, the application of ultrasound to the modification of brain structure requires the two auxiliary procedures of bone removal and X-ray ventriculography [3, 4]. These accomplished, bilateral irradiation of arrays of sites in any single structure or combination of structures in the thalamus, subthalamus, or brainstem can be achieved in any desired number of irradiation procedures separated by selected time intervals. Irradiation through the intact scalp eliminates the need for repetitive major surgery. Accurate re-positioning of the patient in the apparatus eliminates repetitive ventriculography. The overall method, including auxiliary and irradiation procedures at present employed for the

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human, represents a considerable improvement over that originally [5, 6] used by the authors and is now accomplished as a series of relatively short-duration procedures [3, 4]. The average elapsed time for an irradiation procedure, from arrival of the patient in the irradiation room to his departure, is two hours.

The present stage of evolution of the ultrasonic method is only an interim one which will be outmoded by developments now foreseeable. Ultimately it will probably be possible to employ focused ultrasound for precision modification of brain structure without the necessity of any surgical or X-ray ventriculographic procedures. In fact, the elimination of the X-ray ventriculography procedure (and incidentally its elimination for neurological diagnosis and neurosurgical work in general) is expected to follow from the development of ultrasonic visualization instruments based on principles recently formulated and treated analytically by one of us (W.J.F.). This new method will permit the "*direct*" visualization of major brain structures and any mechanical devices (electrodes, cannulae, etc.) inserted therein. It will also be possible to view "directly" the focus of a modifying beam of ultrasound at a specific site in a specific brain structure before inducing permanent changes in the tissue. Pathologic lesions already imbedded in brain structures, including those deliberately placed for experimental and/or therapeutic purposes should be visualizable. The availability of such a method will also eliminate a number of the basic difficulties which prevent the present use of transcranial ultrasound for the precision modification of deep brain structures, i.e., uncertainty in positioning the intense portion of the acoustic field at desired sites within specific brain structures, defocusing of the beam, and imprecision in the control of the acoustic dosage parameters at the focus, by providing direct measurement and consequent control of all of the requisite physical parameters. Of course, the instrumentation required to achieve such an objective will make the present equipment appear trivial by comparison; but when such is realized, the illumination of many morbid brain changes and the modification of brain structures for the treatment of many neurological and allied disorders will become an elegantly simple procedure, requiring only a few minutes time, and entailing neither surgical or X-ray localization methods. While most of our work up to now has involved the use of ultrasonic exposure parameters which result in irreversible lesions, it should be noted here that temporary ("reversible") changes have also been demonstrated. The principal emphasis on the use of irradiation

parameters which cause permanent changes is a consequence of the fact that for want of appropriate financial support it has not been possible to develop properly the much more elaborate instrumentation required for realizing the function-mapping potential of ultrasonic field parameter values which cause only temporary effects.

Before outlining the ultrasonic techniques and describing the instrumentation currently employed on the human it is desirable to make a few preliminary remarks regarding the precision necessary to realize the advantages peculiar to ultrasound since such determines the characteristics of the instrumentation.

In addition to the specific features already mentioned, the present use of high intensity ultrasound in both basic and applied neurology and endocrinology, including the modification of carcinogenic tissue, depends upon selective action. Under appropriate dosage conditions, including control of the tissue temperature, it is possible to leave the vascular system in both white and gray matter structurally intact and functioning in a region in which all neural components are destroyed [1]. It is also possible to modify irreversibly the fiber tracts of white matter without disrupting nerve cell bodies in immediately adjacent gray matter which receives the same dosage of the ultrasonic radiation. In an analogous fashion it is possible to depopulate the hypophysis of glandular cells without disrupting its vascular system, thus providing a unique method for modifying and studying endocrine function [7]. Typical examples of ultrasonically produced lesions in various brain structures and in the hypophysis are shown at low magnification in Fig. 1. These photomicrographs of sections from the brain and pituitary of cat illustrate the flexibility of the method from the viewpoint of shaping and selectivity and interruption in depth *without* disruption of intervening tissue. It should be emphasized here that reproducibility of lesions of the type illustrated requires: accurate control of acoustic field parameters and duration of exposure; reproducibility of the sound level (within 1 %) at the target sites; and precise positioning and movement of the acoustic focus in the tissue. Uniformity of effect is critically dependent on the spacing accuracy between adjacent positions of the array and, at the higher ultrasound frequencies currently employed, where the transverse diameter of the focus can be ½ mm or smaller, a geometric positioning and reset accuracy of 1/100 mm is extremely desirable and realizable. The accuracy of geometric positioning of the focus in the tissue structure (for example within 0.1 mm for the deepest structures in cat brain) is

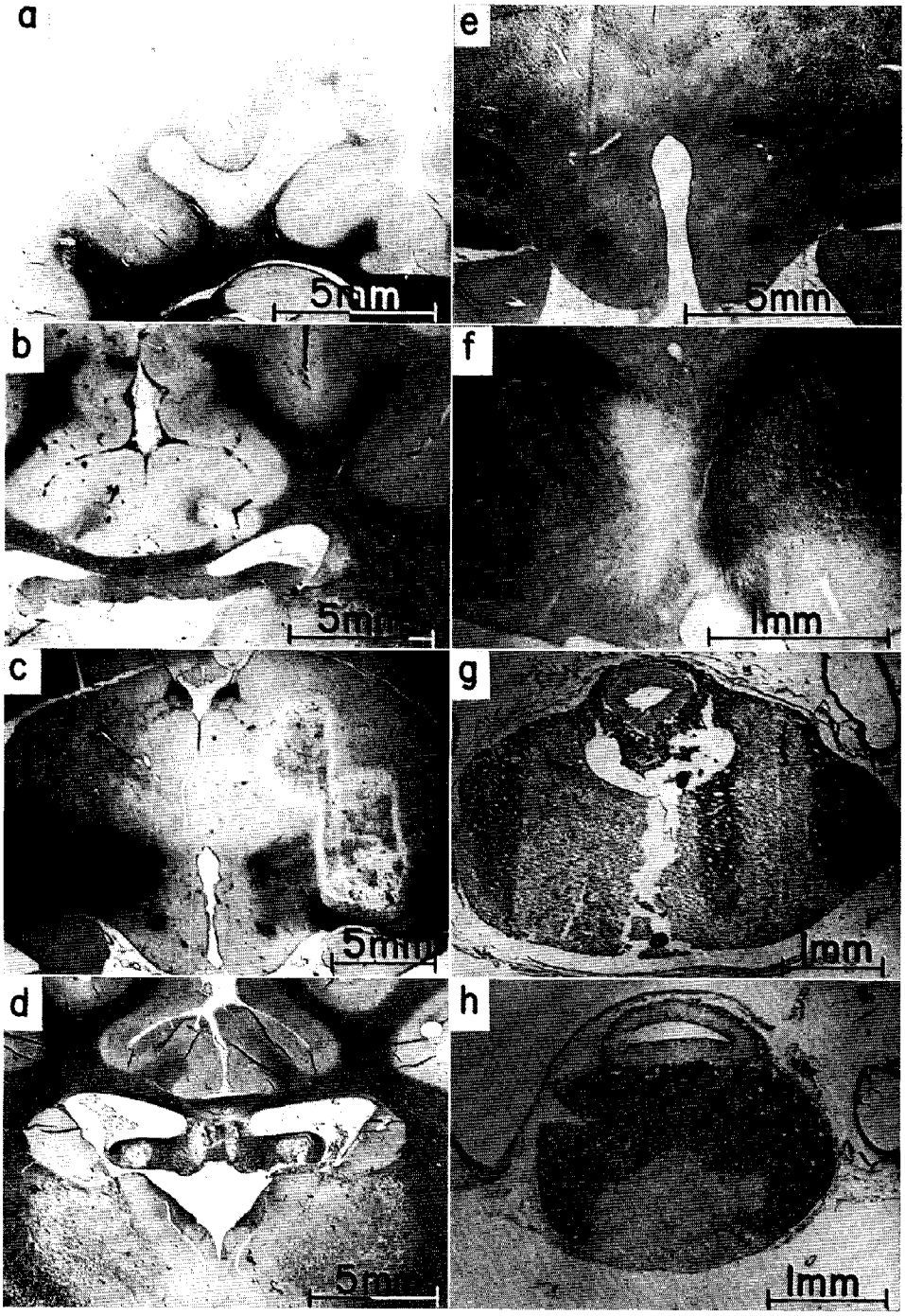

Fig. 1

adequate for work now in progress, but positioning at particular sites in specific brain structures is limited by the present landmarking method (radio opaque ventriculography employing the configuration

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Fig. 1. Histological preparations (cat) illustrating the macroscopic features of lesions of various configurations in the brain and in the hypophysis produced by appropriately controlled ultrasound focused in arrays of sites in the tissue structures. (a) Lesion in the subcortical white matter with no invasion of the immediately adjacent cortical gray 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/sec. sound) in the plane of the section with a 1 mm spacing between adjacent sites. Weil stain. (b) Lesion placed to interrupt longitudinally running fibers – 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 spaced 0.2 mm apart – 4 Mc/sec. sound. Weil stain. (c) Two thin rectangular sheet lesions in the thalamus and subthalamus. These lesions are thin in the direction perpendicular to the section shown – 4 Mc/sec. sound. Weil stain. (d) Three lesions in the subcallosal fornix. The longitudinally running fibers are interrupted in the lateral half of the structure bilaterally and the fibers 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/sec. sound. Weil stain. (e) Interruption of the mammillothalamic tract – 0.2 mm spacing, 4 Mc/sec. sound. Weil stain. (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/sec. sound. Weil stain. (g) Two "sheet" lesions oriented transversely in the anterior hypophysis produced by focusing ultrasound in two arrays of sites with 0.2 mm spacing between adjacent positions. The tissue in the base of the section was destroyed as a result of the temperature increase caused by heat produced in the adjacent bone by the ultrasound and conducted therefrom to the tissue. The ventrodorsal extent of this "heat" lesion is apparent in the illustration as indicated by the termination of the zone of normal tissue in the right center and the right lateral spread of the light stained area at the base. In the ultrasound lesion per se the gland cells have practically completely disappeared at this time after irradiation (7 days), the fibrous reticulum and blood vessels are intact. Azan-Heidenhain stain. (h) "Sheet" lesion oriented transversely in the anterior hypophysis produced by focusing ultrasound through the entire depth of the brain to sites in the ventral half of the gland (0.2 mm spacing between adjacent sites of the array, 4 Mc/sec. sound). The tissue structure in the base (⅓ of the lesion depth) of the relatively unstained (gallocyanine) area was modified as a result of the temperature increase caused by the heat produced in the adjacent bone by the high level ultrasound and conducted therefrom to the hypophyseal tissue. The selective ultrasound lesion per se exhibits acidophils and basophils in an advanced stage of degeneration at this time after irradiation (5 days). The fibrous reticulum and vascular system are intact.

of portions of the ventricular walls as coordinate references) which implicitly contains the uncertainties of localization due to variations of brain-structure loci with respect to the ventricular system. A third requirement is the accurate control of the tissue temperature. Inasmuch as the mechanism of action of the sound, while basically nonthermal, is temperature dependent, the ultrasonic dosage required to achieve a specific endpoint proves to be lower for the higher preirradiation tissue temperatures [1].

In this brief paper it is not possible to outline in technical detail the procedures currently employed by the authors and their colleagues for implementing the ultrasonic method of modifying structures of the brain and other tissues and determining the effects of such on the manifestations of neurological and other disorders, etc. Only specific aspects of the methodology and technique can be synopsized.

For maximum acquisition of information, the patients are subjected to a battery of tests and measurement procedures at appropriate times before and after the various stages. As indicated above, two preliminary procedures, not fundamental to the ultrasonic method per se, are required at present. The object of the first, craniectomy (accomplished under a general anesthetic), is the provision of an appropriate opening in the skull through which the focused sound can enter the brain via intact scalp to affect any desired array of bilateral sites in basal ganglionic, thalamic, subthalamic and brainstem structures. The second, ventriculography, in which the patient's skull is supported rigidly in a head holder (into which it can at any later time be repositioned with an accuracy of approximately 0.2 mm) employs a radio-opaque material and is usually scheduled a month or so following craniectomy. The head holder is an integral part of the irradiation instrumentation (Fig. 2). Four stainless steel rods with rounded tips engage small hemispherical indentations in the external table of the skull. They are supported from universal mounts provided with micrometers, which permit repositioning of the tips to within $\pm$ 0.001 in. Three X-ray tubes and film cassettes mounted on the head holder are provided for obtaining lateral, anteroposterior and 30°-off-the-horizontal-axis roentgenograms. The cassettes are supported in fixed reproducible positions and markers on them provide axes from which the coordinate positions of the landmarks currently employed (the ventricular boundaries of the anterior and posterior commissures) may be measured. In general, the axes of the positioning system – the overhead structure of Fig. 2 which supports the focusing irradiator –

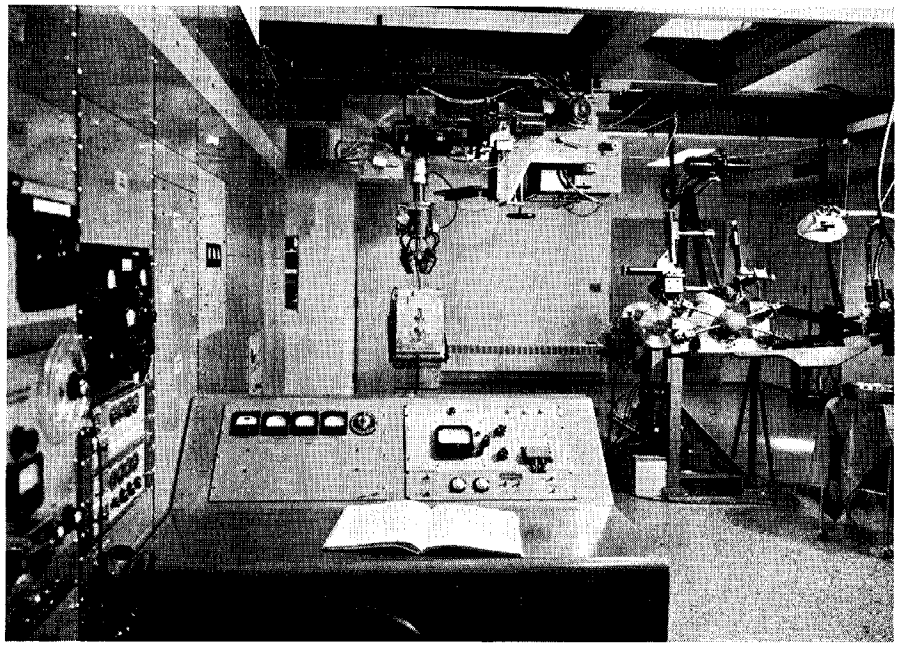

Fig. 2. View of the irradiation room for modifying brain structures in the human. An awake comfortably positioned patient is shown with head supported in the holder by four stainless steel rods whose rounded tips engage hemispherical indentations in the outer table of the skull. The tips of these rods can be accurately repositioned in space by the micrometer adjustments provided on the supporting posts in order to permit a number of irradiation procedures if desired without the necessity of determining the coordinates of the internal landmarks more than once. The three X-ray tubes and cross-hair positioning system employed in the coordinate determination of landmarks are shown mounted on the head holder. The four beam irradiator, which has provided the focused intense ultrasound for the human work accomplished up to now, is in position over the calibration tank. It swings into place over the head of the patient after a hopper which supports the coupling liquid is positioned over and engaged in water tight connection with the patient's scalp. The placement of the focus of the ultrasound in the sites of the array of positions to be modified in the brain is accomplished by the overhead structure. Since the scalp is intact during irradiation, there is no necessity for sterile procedure once the small scalp incisions at the sites where the supporting rods engage the skull are sealed. The electronic instrumentation is mounted on the panels on the left wall and in the control console in the foreground. (From reference 10.)

are oriented at non-zero angles with respect to the axes of the roentgenograms, i.e., the axes of the head holder. The appropriate coordinate transformation is accomplished on a computer. This computation

includes the use of scaling factors which adjust for the differences of interlandmark distances in the brain atlas employed as a reference and the brain of the specific patient. The arrays of sites considered for irradiation in the brain structures of each patient are represented as planar projections (one or more for the structures on each side of the midsagittal plane). As many as 100 sites are so represented for patients exhibiting some of the neurological disorders which have thus far received the attention of the authors.

A week after ventriculography the patient is ready for the first and in some cases only irradiation procedure. An adjustable table with a fluctuating air mattress is provided for the comfort of the wakeful individual while his head is engaged in the instrument. Degassed normal saline is the coupling medium provided to conduct the sound from the irradiator to the intact scalp. A thin polyethylene sheet with an adhesive-bordered opening corresponding in size and shape to the cranial defect is employed to achieve a liquid-tight seal with the scalp. This plastic sheet is supported by a hopper-shaped container positioned in appropriate orientation on the head holder and fully supported by it. A heat exchanger is provided to maintain the bath temperature to $\pm$ 0.1°C of the desired value. The focusing transducer shown above the calibration tank in Fig. 2 is rotated into position, lowered into the degassed coupling medium and checked for air bubbles on the surfaces of the lenses. The irradiation procedure is initiated by placing the focus at a chosen site, setting the driving voltage for the desired sound level (taking absorption in the intervening tissue into account), and completing the exposure (duration in the range 1 to 3 seconds at the sound levels currently used). The changing status of the patient's abnormal manifestations, objective and/or subjective, during the procedure determines in part the course of the succeeding steps, that is, the form and extent of the irradiation arrays. One is not committed to any single plan of attack, i.e., the modification of any one or predetermined specific combination of brain structures in attempting to modify favorably the manifestations of a disorder in a particular patient. The duration of the procedure is determined to a considerable extent by the time taken for interview and physical examinations. All together the various procedures involved in irradiation require approximately 1 ½ to 2 hours. In order to follow the time course of induced changes irradiation can be terminated at any time without concern that the patient must be subjected to involved repetitive stressful procedures. Repositioning in the head holder is a process of

short duration. Hence a series of irradiation procedures distributed over a time interval of six months can well be contemplated. Careful stepwise modification of brain function separated, when indicated, by periods of protracted observation enhances, in many cases, the possibility of an overall favorable result (usually a minimum of two irradiation procedures is now employed when the patient exhibits bilateral symptoms).

The bony defect resulting from craniectomy does, however, inconvenience some patients; hence, attention is now being given to its coverage at the time of craniectomy by a prosthesis having suitable acoustic characteristics. Such an agent will simultaneously eliminate the operative procedure now required to either replace the previously excised bone or to insert an acrylic substitute after all irradiation procedures are completed.

The ultrasonic instrumentation currently in use by the authors and collaborators on the human has been employed to modify singly and in various combinations portions of a variety of brain structures to affect in a stepwise fashion [3, 4, 5, 8]: (a) the patterned tremors, rigidity and bradykinesia of Parkinson's disease (tegmental field of Forel, fiber tracts H_1 and H_2, medial and basal parts of ventrolateral nucleus, superior medial portion of substantia nigra, and the medial globus pallidus); (b) the non-patterned movements encountered in choreo-athetotic cerebral palsy and dystonia musculorum (structures listed under [a]); (c) spasmus nutans and cerebellar dyssynergia (tegmental field of Forel); (d) certain clinically anonymous hyperkinesias akin to myoclonus (structures listed under [a]); (e) intractable pains and disturbing paresthesias and dysesthesias (basal and lateral border region of centromedian nucleus, medial dorsal nucleus, ventropostero-medial nucleus); and (f) phantom images and pain in amputees (ventropostero-lateral and medial nuclei, basal and lateral border region of centromedian nucleus). In addition, endocrine function has been modified in cases of extensive and metastasizing cancers of the breast by ultrasonic irradiation of the hypophysis [9] and, in a single case, direct irradiation of tumor tissue (a surgically inaccessible, presumed hamartoma at the base of the hypothalamus) has been performed.

The ultrasonic method as now employed by us on the human provides a flexibility, safety and generality of approach not possible by any method requiring the insertion of probes, cannulae, etc. into regions of brain to be affected. It represents in its present state a

major step in the evolution of ultrasonic methodology as applied to neurologic, endocrinologic and similar problems [10]. The authors look forward to the next phase of development, in which all major brain structures and the foci of ultrasonic beams positioned at sites within these structures to effect modifications will be "directly" visualized.

References

1. *Fry, W. J.:* Intense ultrasound in investigations of the central nervous system, in: Advances in Biol. and Med. Phys. (J. H. Lawrence and C. A. Tobias, Academic Press) *6:* 281–348 (1958).
2. *Fry, F. J.; Ades, H. W.* and *Fry, W. J.:* Production of reversible changes in the central nervous system by ultrasound. Science *127:* 83–84 (1958).
3. *Fry, W. J.* and *Fry, F. J.:* Fundamental neurological research and human neurosurgery using intense ultrasound, IRE transactions on medical electronics, *7:* 166–181 (1960).
4. *Fry, W. J.; Fry, F. J.; Meyers, R.* and *Eggleton, R. C.:* The use of ultrasound in neurosurgery, Proc. third international conference on medical electronics, 453–458 (1961).
5. *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 Am. Neurol. Assn., 16–24 (1958).
6. *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. J. Neurosurg. *16:* 32–54 (1959).
7. *Krumins, R.; Fry, F. J.; Fry, W. J.* and *Kelly, E.:* Use of high intensity ultrasound for study of the hypophysis. Absts. fifth annual meeting of the Biophysical Society (1961).
8. *Meyers, R.; Fry, F. J.; Fry, W. J.; Eggleton, R. C.* and *Schultz, D. F.:* Determinations of topological human brain representations and modifications of signs and symptoms of some neurologic disorders by the use of high level ultrasound. Neurology *10:* 271–277 (1960).
9. *Hickey, R. C.; Fry, W. J.; Meyers, R.; Fry, F. J.* and *Bradbury, J.:* Human pituitary irradiation with focused ultrasound in advanced breast cancer. An initial report. Arch. Surg., Chicago *83:* 620–630 (1961).
10. *Fry, W. J.:* Present and future applications of ultrasonics in biomedicine. Proc. Inst. Radio Eng. *50:* 1393–1404 (1962).

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Discussion

H. Hamlin (Providence R. I.): What evidence do you and Dr. *Meyers* have for histologic and functional changes induced by ultrasonic irradiation of the human hypophysis? Exactly where do you open the human skull to make a portal for ultrasound and what is the precise direction of the focused beam to the sella?

V. Mark (Boston): Dr. *Fry*, can you make temporary or reversible lesion with your ultrasound technique; if so, do you do this clinically?

E. A. Spiegel (Philadelphia): May I inquire what histologic methods were used in order to study the effect of ultrasound irradiation upon cells. In view of the fact that lesion of parts of the mesencephalic tegmentum adjoining the substantia nigra (cells of the reticular formation, Forel's field) may favorably influence rigidity and Parkinsonian tremor, I am wondering whether it could be histologically proven in the cases treated by Drs. *Fry* and *Meyers* that the lesions produced by their ultrasound method were limited to the substantia nigra.

B. Hughes (Birmingham, England): Dr. *Fry* told us in the early part of his talk that he would hope in the future to eliminate all radiological and surgical procedures by means of ultrasonic scanning. Does he mean by this that ultrasonic irrad'ation will be carried out without the necessity of removing any bone?

P. Lindstrom (Salt Lake City, Utah): The four-beam ultrasonic equipment for stereotactic cerebral irradiation was developed by the *Fry* brothers after many years of hard work. Through the ingenuity and foresight of these two physicists, neurology has been enriched with a new tool, for which we are thankful. Their recent therapeutic application, in collaboration with Dr. *Russell Meyers*, has opened a new approach to the treatment of some dyskinesias.

The improvements in the ultrasonic instrumentation which Dr. *William Fry* anticipates are fascinating but his thought that an ultrasonic scanning technique could replace ventriculography seems a little overoptimistic. The structural elements, like the various nuclei in the brain, may not show sufficient difference in acoustic properties to allow identification by scanning beams. The echo-technique which *Leksell* is using for diagnosis of subdural hematomas appears valuable but we still do not know for sure which structure, the pineal gland or the falx, or something else, causes the variation in the echo readings when there is a shift of intracranial structures from one side to the other.

I am pleased that the authors have now confirmed my observation of some years ago, that the white matter is much more sensitive than the cerebral cortex to the effect of ultrasound. However, the depopulation of cells in the cortex, to which the authors refer, while the capillaries are preserved following ultrasonic irradiation, must be very cautiously interpreted in studies of function of the CNS for the simple reason that by the time the ganglion cells have been destroyed, the myelin and the axons in the irradiated field have also lost their function due to the effect of ultrasound. When the cellular elements are eliminated by ultrasonic irradiation, then the conductivity and the function in general of the exposed nervous tissue have been altogether altered temporarily or permanently.

W. J. Fry: (1) Dr. *Hamlin* asked about the changes induced in the hypophysis by ultrasound, the site and size of craniectomy employed and the orientation of the

path of the sound through the superimposed brain. We have carried out preliminary histological studies of irradiated cat anterior pituitary gland and it appears that repopulation of the selectively affected tissue (vascular system and reticulum remain intact) with acidophils and basophils with different population ratios than that characteristic of the original state of the gland, may be possible. The endocrine status of breast tumor cases with ultrasonically irradiated pituitaries has been followed as a function of time. A sequence of reversible changes (17 ketosteroid level, rate of I_{131} uptake by the thyroid, blood cholesterol level, urine output, etc.) has been followed in several patients to determine if some modification of the hypophysis (other than excision or gross destruction) might favorably influence the tumor status. In one of five cases a result effective for approximately one year has been achieved. The bone plate removed measures approximately 10 cm by 13 cm and the opening is made on the lateral aspect of the cranium. The axis of the focused beam is oriented at an angle of approximately 55° from the apex which we preferred in this first work on hypophyseal irradiation in the human since the optic fibers on both sides of the midline need not be exposed to the ultrasound in the vicinity of the focus as the beam is moved from site to site to apply the same ultrasonic dosage to all parts of the gland.

(2) In answer to Dr. *Mark's* question, we have not employed ultrasound routinely to produce temporary or reversible changes in the brain. However, the potential has been demonstrated by work reported on the visual system of the cat and the reversible suppression of tremor was also demonstrated in one Parkinson patient. The method has not been routinely applied because we have not yet attained the economic status required to build the necessary instrumentation. Such equipment must include automatic movement of the focus through the tissue structure. This is necessary since the small size of the focus, which is essential to achieve complex shaping and uniformity of dosage, does not irradiate, in general, enough tissue volume, for a single position of the focus, to induce an observable change in function.

(3) In response to Dr. *Spiegel's* query concerning cell stains, we have followed histologically the changes after ultrasonic irradiation in both gray and white matter from five minutes to one year after exposure. The selective action on the components of the tissue structures has been studied as a function of dosage conditions and the order of susceptibility of the myelin sheaths, axis cylinders, nerve cell bodies, glia and vascular system to modification has been determined. With respect to the question whether lesions we have placed in the substantia nigra to relieve hyperkinetic and hypertonic symptoms have extended out of that structure, I would say that in the absence of histological data and in view of the fact that the superior medial portion of the posterior half of the structure was that receiving attention that we should not ascribe, at present, symptom elimination to destruction of parts of the substantia nigra per se. Such a conclusion would be premature particularly in view of the fact that lesion placement in the tegmental field of Forel, which is in the immediate neighborhood of the portion of the substantia nigra under consideration here, is extremely effective in eliminating tremor and reducing rigidity.

(4) Dr. *Hughes* requested amplification of my statement that it will probably be ultimately possible to eliminate the need for removing a portion of the cranium to provide a port of entry for the acoustic radiation. This information is provided in the part of the paper which could not be presented orally because of the time schedule.

(5) To conclude this discussion a remark regarding the use of complex instrumentation in therapy would appear to be in order. In the early research stage of such work the techniques and procedures might well be extremely time consuming but as the program develops evolution of methodology usually results in a considerable shortening of the time required – witness the reduction of time required for an ultrasonic irradiation procedure – a decrease from 12 hours to 2 hours. The sophistication which then becomes available to therapeutic practice widens tremendously the range of disorders that can be treated and also improves the handling of other conditions which have been previously modified by using cruder techniques accompanied by undesirable complications. I expect that further modification of ultrasonic methodology will completely eliminate the use of surgical and X-ray ventriculographic procedures for routine therapeutic brain modification and that the time required for a complete procedure will be reduced to an extremely short time – of the order of ten minutes.