Neurosonicsurgery

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Editor's note: Dr. W. J. Fry presented a 16 mm. sound, color motion picture entitled "Neurosonicsurgery." The following is an abstract of the film.

RESEARCH conducted during the past six years at the Bioacoustics Laboratory of the University of Illinois in the design of precision ultrasonic focusing instruments and their application in biological investigations has made it possible to employ ultrasonic energy in research in neuroanatomy, neurophysiology and neuropathology and now opens the way for extensive application of this tool to therapeutic procedures in clinical neurologic disorders. By proper monitoring of ultrasonic dosage, relatively reversible as well as enduring lesions of predetermined size, shape, selectivity and loci in the cortical ribbon, sub-cortical and deep-lying structures (e.g., internal capsule and mammillo-thalamic tract) have been produced in cats and monkeys. Over 250 animals have been subjected to such experiments and it has been possible to establish (a) that the procedure is extremely well tolerated by the animals and (b) that, when judged by currently available histologic criteria, structures not intended for alteration by ultrasound energy can be spared.

A serious limitation in the field of bioacoustics is the complete lack of precision ultrasonic instrumentation and auxiliary equipment designed specifically for biological research. To surmount this difficulty, a completely new laboratory designed specifically for ultrasonic irradiation of selective regions of the central nervous system of mammals has been constructed in the Bioacoustics Laboratory at the University of Illinois. The electrically shielded irradiation room (Fig. 1) contains apparatus for supporting the animal, calibration instrumentation for determining the acoustic output of the transducers, and controls for positioning the focused ultrasonic beam, as well as stimulators, amplifiers, oscilloscopes and 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 focusing transducer. The precise positioning of the sound beam is accomplished by the motor-driven coordinate system supporting the transducer. This system permits translational motion in three mutually perpendicular directions and

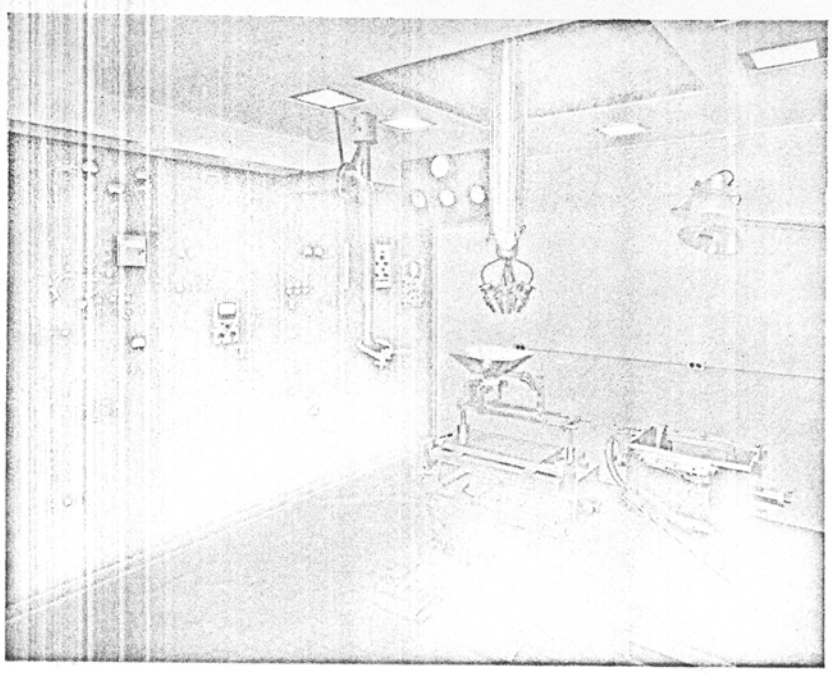


FIG. 1. Instrumentation for focused ultrasonic irradiation of tissue.

two rotational motions. The coordinate system itself, which weighs about 3500 lbs., is mounted on a steel girder framework in the room (Fig. 2) directly over the irradiation room. The controls for the coordinate system are placed in the irradiation room below. The upper room also houses the electronic driver for supplying electrical power to the transducer.

This instrumentation setup makes possible accurate location of the acoustic radiation in any desired region of the central nervous system under precisely controlled dosage conditions.

A four-beam ultrasonic focusing irradiator (Fig. 3) has been designed and is in routine use in this laboratory. In this instrument the focusing beams from each of four transducer heads are adjusted so that the focal regions are brought into coincidence. The most intense region of the ultrasonic field can produce lesions as small as a few cubic millimeters.

To produce a precisely localized lesion by ultrasound, the head of the anaesthetized animal (cat, monkey) is engaged in a stereotaxic substructure in which the usual interaural, Frankfort and midsagittal planes are employed as "zero-references." The skull cap is removed and the dura mater exposed. The bone must be removed because of its high acoustic absorption coefficient, which results in excessive heating, and its disturbance

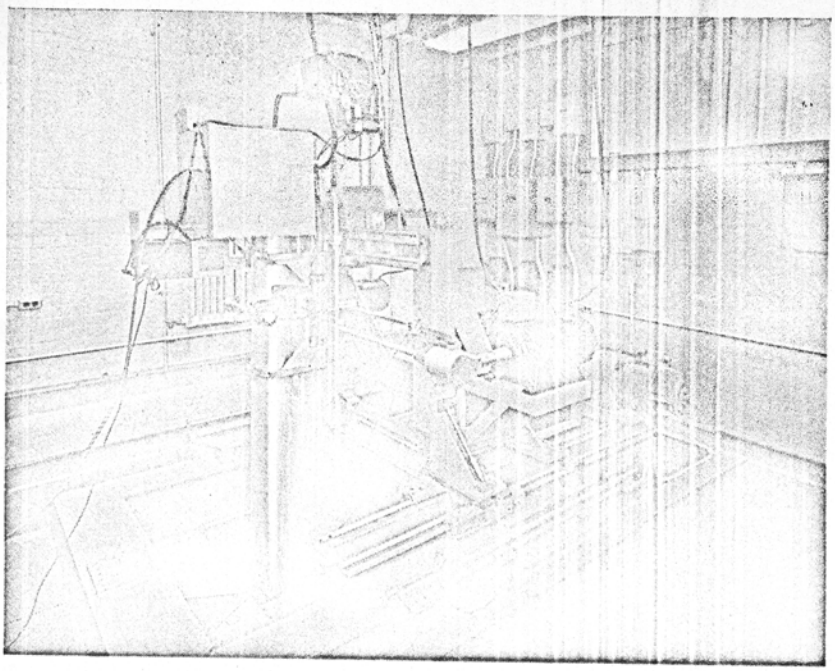


FIG. 2. Coordinate and positioning system for control of the placement of the focus of the ultrasonic beam(s) in the tissue.

of the beam shape. 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 metallic hopper in such fashion as to provide a "pan," the bottom of which consists of the exposed dura mater. This "pan" holds the degassed physiological saline which acts as the transmitting medium for the sound.

The substructure of the stereotaxic instrument (and the engaged animal) is now moved under the superstructure which supports the four-beam ultrasonic focusing transducer which generates the acoustic waves.

The sterilized four-beam transducer is supported on and moved by a single carriage (Fig. 2). All parameters are suitably checked at this point. The ultrasonic dosage is now delivered. At the highest intensities used the duration of irradiation is usually in the range from one to three seconds. The frequency employed is close to 1 megacycle. For the smallest lesions the tissue is irradiated with the focal spot in a single position but for larger lesions the focal spot is placed successively in a number of positions.

The substructure is now disengaged from the superstructure and the animal returned to the operating room where closure of the cranial muscles and scalp is accomplished.

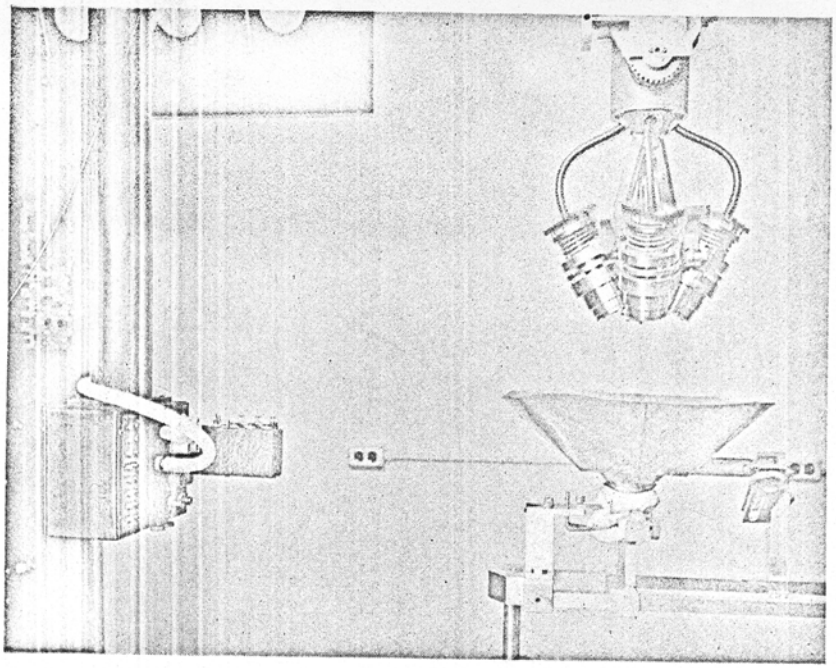


FIG. 3. Four beam focussing irradiator shown above the "pan" which supports the coupling liquid which transmits the sound from the irradiator to the tissue.

The animals are observed for varying periods of minutes to weeks following such experiments, during which time physiologic and/or psychologic aberrations may be noted. The animals are sacrificed minutes to hours, days or weeks after irradiation, the brains removed, fixed and ultimately sectioned, and stained.

A unique advantage of such a procedure is the susceptibility of the fiber tracts of the nervous system to alteration by ultrasound as compared with gray matter and blood vessels at the irradiated locus. This makes it possible to make anatomic, physiologic and pathologic differentia among neural components which, when attacked by the older mechanical, chemical and electrolytic technics inevitably underwent non-differentiated alterations. The advantages of this to research endeavors are self-evident.

It appears that at the parameters employed reversible and irreversible lesions are produced by direct alteration of intercellular structures of the tissues rather than by indiscriminate coagulation by heat. Blood vessels running through a felt-work matrix of ultrasonically damaged tissues are left intact and exhibit no hemorrhaging.

It is envisioned that a variety of neurosurgical procedures can be implemented by ultrasound. These include the hyperkinetic and hypertonic

disorders (e.g., Parkinsonism, athetosis, ballism, chorea, dystonia); psychosurgery and intractable pain.

References

Fry, W. J. and R. B. Fry. 1954a. Determination of absolute sound levels and acoustic absorption coefficients by thermocouple probes—Theory. J. Acoust. Soc. Am. *26:* 294–310.

Fry, W. J. and R. B. Fry. 1954b. Determination of absolute sound levels and acoustic absorption coefficients by thermocouple probes—Experiment. J. Acoust. Soc. Am. *26:* 311–317.

DR. W. J. FRY: Before answering questions, I would like to present a few illustrations. Fig. 4 illustrates a lesion in the sub-cortical white matter of a cat brain. The tissue section is stained so that the nerve fibers stain darkly and the gray matter or regions of cell bodies are practically unstained. In this animal, we chose dosage to produce a change in the fiber tracts without affecting the gray matter. The lesion was produced by moving the beam laterally in a number of adjacent overlapping positions spaced ½ millimeter apart. This sharp boundary between the affected white matter and the neighboring unaffected gray matter is realized, as just indicated, by the choice of dosage, but you also observe that a sharp boundary between the affected white matter and the unaffected white matter is also obtained. This is illustrated at the lower border of the lesion. In such a lesion with all the neural components of the white matter destroyed, the blood vessels remain unbroken and functional.

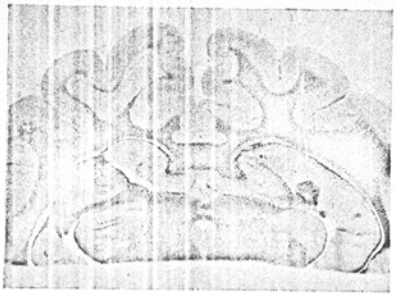
DR. BALDES: Do you sometimes irradiate with the transducer rotating?

DR. W. J. FRY: The apparatus is designed to permit operation in that manner, but we have not used the procedure. Different dosage relations would obtain if the transducer were moved continuously along a path. We have done some work with the common focus of the beams moving, tracing out a path, but we have not emphasized this procedure, because we have been interested in producing both small lesions and lesions of different shapes. We have restricted ourselves primarily to the procedure of irradiating in one spot, and after a fixed time interval irradiating in an adjacent overlapping spot.

DR. BALDES: What do you find is the most advantageous way of degassing water, vacuum or boiling?

DR. W. J. FRY: We use the boiling procedure. We have not compared the two methods.

We dilute the normal physiological saline by the amount of distilled water that is evaporated during the boiling process.



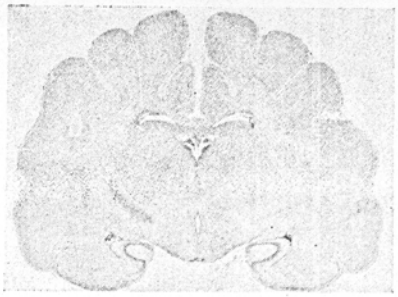


FIG. 4. Large shaped lesion in the subcortical white matter of the brain of a cat. The gray matter bordering the destroyed fiber tracts is not disrupted. This large lesion was produced by placing the focus of the beam successively in a number of adjacent positions.

FIG. 5. A small ultrasonically produced lesion in the cortical gray matter of a cat brain.

DR. HERRICK: Dr. Fry, could you explain from a standpoint of pure physics, the relative selectivity of various parts of the brain structure, particularly the blood vessels to ultrasound i.e., why you do not get damage in the blood vessels, or any degassing effects?

DR. W. J. FRY: We have made dosage studies and have observed the graded selectivity for various dosages. These results will be reviewed in the next paper. At the present time, we do not yet understand the physical mechanism. We have studied temperature and cavitation as possible contributing factors, but we have not yet isolated the physical variable(s) responsible for the primary action.

DR. NYBORG: Can you briefly describe the focussing system?

DR. W. J. FRY: We use two types of focussing systems. The system you saw in the movie is a lens type, four intersecting focussed beams produced by x-cut quartz crystals with polystyrene lenses placed in front of them. We also use a parabolic reflector type of focussing system.

DR. NYBORG: Could you state the beam size?

DR. W. J. FRY: I do not wish to imply that the half-power beam width is a critical value from the viewpoint of dosage. A factor of two change in, for example, intensity, would be quite large. However, in order to indicate the size of beam, it is convenient to state the half power width which in this case is 1.5 millimeters. The animal in Fig. 4 received 70 or 80 shots of radiation with such a beam to produce the lesion illustrated. The next illustration (Fig. 5) shows a lesion in the gray matter produced by irradiating in a single position. The length of the oval-shaped area is about 2 millimeters. This animal was sacrificed four days after irradiation.

DR. HUETER: What is the ratio of the intensities of ultrasound used in these two cases?

DR. W. J. FRY: The animal of the previous illustration (Fig. 4) was irradiated at a lower level. At 1,000 watts/cm.^{2} the time required to produce a lesion in gray matter is about a factor of 2 greater than that required for a white matter lesion.*

DR. BELL: Have you any explanation for the differential susceptibility of white matter as opposed to gray matter?

DR. W. J. FRY: No explanation. It might be noted that gray matter has a lower acoustic absorption coefficient than white matter, but we do not know that this is related to the minimum dose required to produce a lesion.

DR. QUIMBY: You do not know for certain that the irradiated gray matter in the tissue of the first illustration (Fig. 4) was unaffected. You only know that it does not appear to be affected on histological examination?

DR. W. J. FRY: We have in some instances utilized tests other than histological change. We have irradiated animals in which we produce functional changes. The particular animal in the first illustration was not irradiated in a region where you would expect to observe obvious functional changes. However, we have irradiated animals in the motor cortex, for example.

DR. HUETER: Have you ever used the same duration but varied the intensity in order to get the selectivity between gray and white?

DR. W. J. FRY: The animal in Fig. 4 was irradiated at 200 watts/cm.^{2} for 4.00 seconds. For the animal in Fig. 5 the dosage was 1,000 watts/cm.^{2} for 2.00 seconds. To produce a change in white matter at 1,000 watts/cm.^{2}, the required duration of exposure would be about one second.

DR. BELL: What is the "gain" of the multibeam system?

DR. W. J. FRY: The gain in intensity for this particular multiple beam, compared to a single beam, is about 12 times. The pressure gain is four times, if each irradiator contributes equally. The particle velocity gain is somewhat less than four because of the angle of convergence of the beams, so that the intensity gain is approximately 12.

DR. QUIMBY: What is the degree of reproducibility in your lesions, such as a small lesion in the gray matter?

DR. W. J. FRY: I believe generally we would say they are quantitatively reproducible. If you choose a dosage, you cannot only produce a lesion, but you can grade the lesion in degrees by choice of dosage. This aspect will be discussed in more detail in the next paper by Dr. Barnard. We classify the white matter lesions into three categories, and also the gray matter into three separate categories, depending on the extent of the damage and the selectivity obtained. It is interesting to note that in two cases we have seen

* Specification of the acoustic intensity alone does not completely describe the acoustic field. However, for a particular field configuration the intensity values constitute an indication of relative dosages.

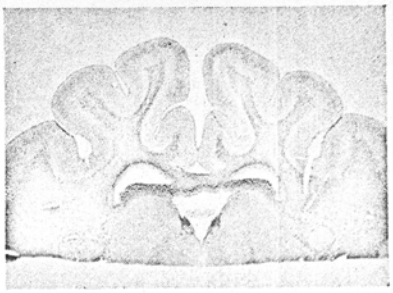


FIG. 6. Large shaped lesion in the white matter of the internal capsule of a cat brain. The dark staining material is a glial scar which has developed in the lesion region 30 days after exposure. None of the tissue intervening between the common focus of the beams and the area of entry of the sound into the brain, was disrupted.

FIG. 7. Interruption of a small (1 mm. diameter) fiber tract deep within the brain without interference to surrounding or intervening tissue.

demyelination of nerve fibers without destruction of the axis cylinders. This has been seen in both gray and white matter.

DR. BELL: What is the center thickness of the lenses that you use?

DR. F. J. FRY: 1/32 of an inch and 1 3/8 inches in diameter. The radius of curvature is about 3 inches.

DR. W. J. FRY: This illustration (Fig. 6) shows a large lesion in depth without effect on intervening tissues. The four beams entered the brain from above. The animal was sacrificed 30 days after irradiation. A glial scar is apparent in the portion of the internal capsule which was irradiated. The irradiation procedure was accomplished by moving the beam laterally and exposing the tissue in a number of adjacent overlapping positions. Fig. 7 illustrates the precision with which you can place a lesion in a deep structure. In this case we were interested in hitting the mammillothalamic tract of a cat. This tract is about a millimeter in diameter and the beam must traverse about 4/5 of the brain thickness before coming to a focus. The four beams entered from above. Coordinates were chosen from standard neuroanatomical maps. The gray matter surrounding the tract was unaffected. This is accomplished by a proper choice of dosage.

DR. SCHWAN: If you are interested in experimenting with 10 animals and trying to destroy the same area in each, how often would you succeed?

DR. W. J. FRY: If one is interested in destroying a small fiber tract such as the mammillothalamic one can irradiate, at a dosage which does not affect gray matter, in a number of adjacent positions and thus interrupt the tract practically every time. Position variation of a specific deep structure with respect to external landmarks is of the order of 1/2 millimeter in cat brain. The focus of the beam can be placed within any desired geometric location within a couple tenths of a millimeter every time.

DR. SCHWAN: Do you use bony landmarks only, or do you also look at the surface of the brain?

DR. W. J. FRY: On cat and monkey, we use the ear bar position and the base of the orbits as references.

DR. SCHWAN: I should like to inquire about the margin which exists between the minimum dosage required to cause the lesion and the optimum dosage to spread out the lesion beyond the area which you want to destroy.

DR. W. J. FRY: You mean, for example, if you are hitting a fiber tract, what would be the ratio between the minimal dosage required and that necessary to cause the lesion to spread out into the neighboring gray? This ratio varies with the sound level. For example, at 200 watts/cm.^{2}, the ratio is quite high, but at 1,000 watts/cm.^{2} the ratio would be something like 1¼, that is a 25% increase in time would be sufficient to pass from a lesion with a sharp border at the gray matter interface to a lesion which starts to invade the gray matter.

DR. SCHWAN: You may anticipate at least a certain variation in the absorption coefficient from one cat brain to another. The margin I was asking about is then sufficiently large to permit variations in acoustic properties.

DR. NAUTA: I should like to ask Dr. Fry if, in his experience, the difference in absorption rate between white and gray respectively is such that it would be difficult to produce a selective gray matter lesion close to heavy bundles of myelinated fibers.

DR. W. J. FRY: The problem is to produce and use a beam which falls off sharply enough to restrict the high level sound entirely to the gray matter. In other words, it is easy to produce a lesion in white and preserve neighboring gray matter, but more difficult to produce a lesion in gray and simultaneously preserve neighboring white matter.

DR. NAUTA: My second question concerns the possible production of inadvertent damage to fiber bundles proximal to the focal point. Is it conceivable that a relatively low concentration of ultrasonic energy, such as would prevail, say, 5 millimeters from the focus of the beam, would suffice to damage fibers passing through the area?

So far, from two limited observations in our own material, I have the impression that we should take account of such possibilities. In these cases, using parameters of exposure too low to produce visible tissue destruction at the focal point, a fairly large number of scattered degenerating axons were present in and around regions proximal to the focus. I want to make one suggestion. It is unlikely you will pick up such diffuse changes with conventional stains. I think your best chance to find them is to employ a stain for degenerating axons, because they can be identified with absolute certainty. Damaged cell bodies will be terribly difficult to detect if there are only a few of them.

DR. HERRICK: Dr. Fry, what is the minimum time between irradiation and the study of histology?

DR. W. J. FRY: We have made histological studies of the irradiated brains of cats sacrificed five minutes after exposure. At this time, no histological changes are evident with the stains employed. The first changes appear at 10 minutes

DR. BELL: When the target is deep in the brain do you have to substantially raise the intensity level or extend the duration of exposure?

DR. W. J. FRY: You raise the intensity level to get the desired value at the lesion site. The intensity absorption coefficient is approximately 20% per cm., and the resultant loss must be offset. We raise the driving voltage to compensate, and maintain constant the duration of exposure. A dosage study in the subcortical white matter thus furnishes the dosage information required for the production of lesions in deep structures.

VOICE: How do you explain the delayed evidence of lesion production?

DR. W. J. FRY: Histologically there is a delay, I don't know why. We are obviously not tearing things apart on a cellular level. We have other observations showing that electrically the lesion can be detected much sooner. We have done some work on rats' spinal cords in which we made measurements of 2 neuron arc response changes. In this case, one finds that the electrical changes occur in seconds or less.

VOICE: Have you done any electron micrography on these various animals?

DR. W. J. FRY: No.

VOICE: Do you hope to do it?

DR. W. J. FRY: Yes. It would be very interesting to see what structural components of the tissue are changed by the ultrasound. It may be that we change structure on the level of organization which is closely associated with function.

VOICE: Why do you use four concentrated beams rather than one?

DR. W. J. FRY: A single beam with the crystal and lens diameter used, has a long focal length. This beam is narrow, but the sound intensity does not vary very rapidly as one moves along the axis of the beam. By employing four of these beams, one can realize a considerable reduction in the length of the high intensity region. I again do not wish to imply that intensity is the important variable. It may be, for example, that particle velocity is much more important than intensity, but I am using the variable intensity to describe the sound levels we are talking about.

DR. FINCH: Do you feel that after four beams have traversed the material that they are still in phase?

DR. W. J. FRY: Yes, if you are speaking about brain tissue. The acoustic velocity does not vary much with position in the brain.

DR. BALDES: You indicated how you adjusted a knob to change the phase. What does that adjustment do?

DR. W. J. FRY: There are tilt adjustments which bring the beams into coincidence at a common point. The wheel adjustment or knob moves the beam in the direction of its axis.

DR. VON GIERKE: Did you ever consider the following procedure? After you produce the lesion you irradiate with a low intensity ultrasonic pulse in an attempt to receive an echo from the lesion to see if you really produced a lesion.

DR. W. J. FRY: We never attempted the possibility you suggest. You would probably have to wait for a period of time ($\geqslant$ 15 minutes) after irradiation because histologically you do not see the changes immediately after exposure. If you were willing to wait for such a period, such a procedure might work.

DR. VON GIERKE: You could observe the echo pattern before you produce the lesion, then produce the lesion and observe the pattern again.

DR. W. J. FRY: It is a possibility. We have been interested in producing reversible changes to use as a method of locating position functionally. After identification of position by this means, the dosage could then be increased to produce a permanent change.

DR. BUSNEL: Have you observed any modification of the animals' behavior after the treatment? You explained you kill the animals after 20 days. Through the 20 days period, have you observed some modification in the behavior in relation to the region where you destroyed the tissue?

DR. W. J. FRY: In the internal capsule, for example, depending upon the position irradiated we produced motor deficits which are apparent as soon as the animal recovers from the anesthetic.

DR. BUSNEL: Is it possible that you can produce some modification in the behavior without complete destruction of the tissue?

DR. W. J. FRY: This is possible. In fact, we are interested in examining ultrasonically demyelinated systems to see if they are still functional.