# ULTRASONICALLY PRODUCED LOCALIZED SELECTIVE LESIONS IN THE CENTRAL NERVOUS SYSTEM[1]

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Accurately localized, quantitatively reproducible focal destructive lesions can be produced in the central nervous system by focussing a beam of ultrasound in the region to be affected (1, 2, 3, 4). Lesions can be produced at any desired depth in the brain without disturbance to intervening tissue and without disruption of blood vessels within the site of the lesion. Lesions as small as 1–2 mm in maximum diameter can be produced. Under the dosage conditions used in our experiments, the white matter of the central nervous system is readily affected. In a barely threshold effect, as observed histologically, the myelin undergoes drastic changes, but the axis cylinders do not appear to be damaged. In a more complete effect the myelin and the axis cylinders are both destroyed.

Histological results obtained on 104 cats in which either the internal capsule or parietal cortex was irradiated on one side are the basis of this report. A sample selected from this group is described here to illustrate the types of lesions that can readily be produced. For all the cats discussed in this paper the frequency of the ultrasound was one million cycles per second.

Figure 1 shows in a transverse section of a cat's brain, Weil's myelin stain, a small lesion about one millimeter in diameter in the internal capsule on the right side which is evident as a light patch in the darkly stained fiber tracts in the lower right quadrant of the section. This cat was irradiated at a sound level of 210 watts/cm$^2$ for 4.0 seconds and was sacrificed 12 days later. The sound entered the brain from the top surface and traversed two centimeters of brain before coming to a focus at the site of the lesion. There is no damage to the intervening tissue. The vascular system in the lesion was not disrupted by the sound.

Figure 2 shows, under intermediate magnification, the interruption of the deeply staining myelin of the fiber tracts of the internal capsule as they enter the region of an ultrasonic lesion produced 13 days before the animal was sacrificed. An earlier state of myelin breakdown is illustrated in figure 3. The border region of an ultrasonically produced lesion in the parietal cortex is shown at intermediate magnification. This animal, which received the same dose as that of figure 2, was sacrificed 4 days after exposure to the radiation. The degenerating myelin appears as weakly staining spheres. Examination of the brains of cats sacrificed at various times after irradiation shows that histologically the lesion is readily evident 2 hours after exposure.

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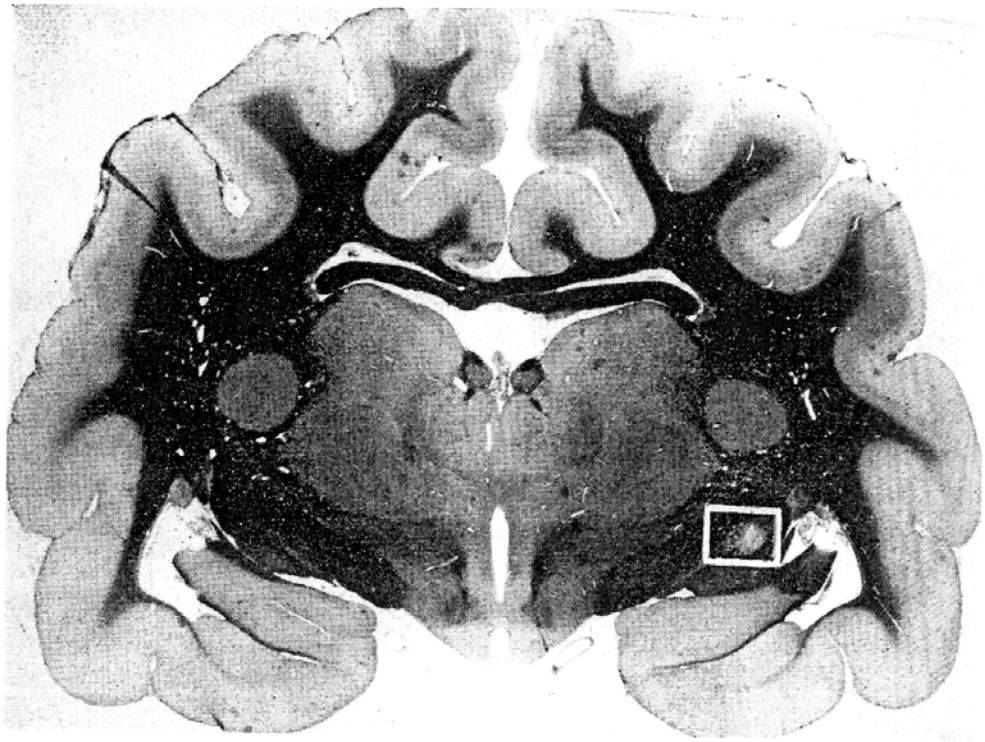

FIG. 1. Small lesion about 1 mm in diameter (light patch in rectangle) in the internal capsule and optic tract produced by a focussed beam of ultrasound which entered the brain from the top and traversed almost its entire thickness before coming to a focus in the affected region. Animal sacrificed 12 days after exposure. Weil stain. (× 3)

To produce a lesion of the desired size and shape in any desired region of the brain the focussing transducer (sound source) is moved about by a supporting structure which makes feasible the moving of the focal spot in a precise pattern.

A moderate sized lesion in the internal capsule of another cat is shown in figure 4. To produce a lesion this large in width (6 mm), fourteen positions of the focal spot, ½ mm apart, in the lateral direction were required. This animal was irradiated at each position with a moderately heavy dosage (400 watts/cm² for 4.0 seconds).

A series of ultrasonically produced lesions in the parietal cortex illustrates the differential destruction of nerve fibers as contrasted with cell bodies and the formation of a lesion of any desired shape and size with sharp boundaries.

Figure 5 illustrates a large ultrasonically produced lesion in the cortex of a cat, sacrificed 12 days after irradiation, obtained by successively placing the focal spot of the beam in a series of positions. The dosage used on this animal was 250 watts/cm² for 4.0 seconds. All nerve fibers in the lightly stained region under the left cortex are destroyed. The section is prepared with Weil's myelin stain. The sharp boundaries between the degenerate white matter and the intact gray matter above and the normal fiber tracts below should be noted. This type of preparation demonstrates the greater susceptibility of fibers as compared to nerve cells, since the gray matter in the sulci (lateral and middle suprasylvian) received as much radiation as the white matter which was irreversibly affected. The irradiated cortex does not differ from the corresponding region on the opposite

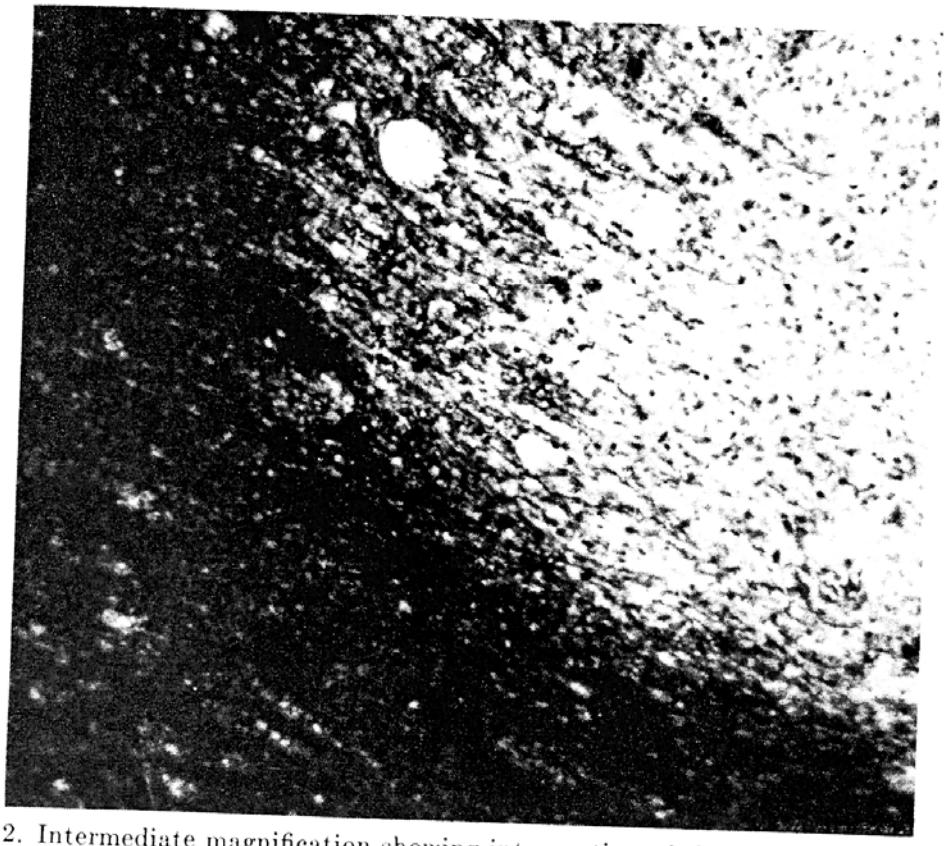

FIG. 2. Intermediate magnification showing interruption of the deeply staining myelin of the fiber tracts of the internal capsule as they enter the region of an ultrasonically produced lesion. Animal sacrificed 13 days after exposure. Weil stain. (× 160)

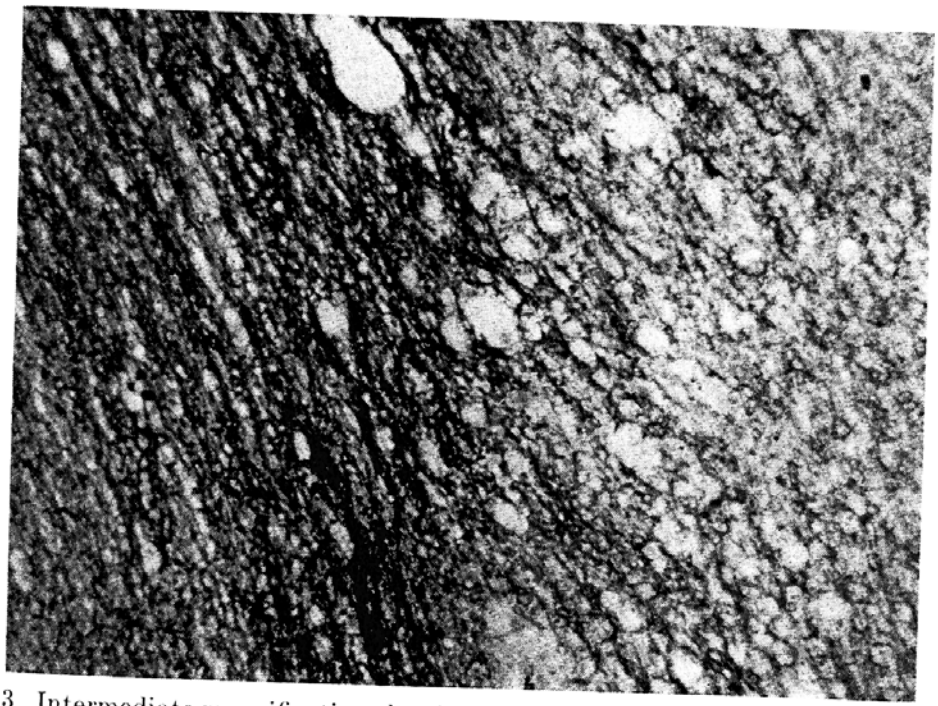

FIG. 3. Intermediate magnification showing border region of an ultrasonically produced lesion (lighter stained area) of the white matter of the parietal cortex. Four days after the ultrasonic irradiation, the degenerating myelin appears as weakly staining spheres. This is an earlier stage of myelin breakdown than that illustrated in figure 2. Weil stain. (× 160)

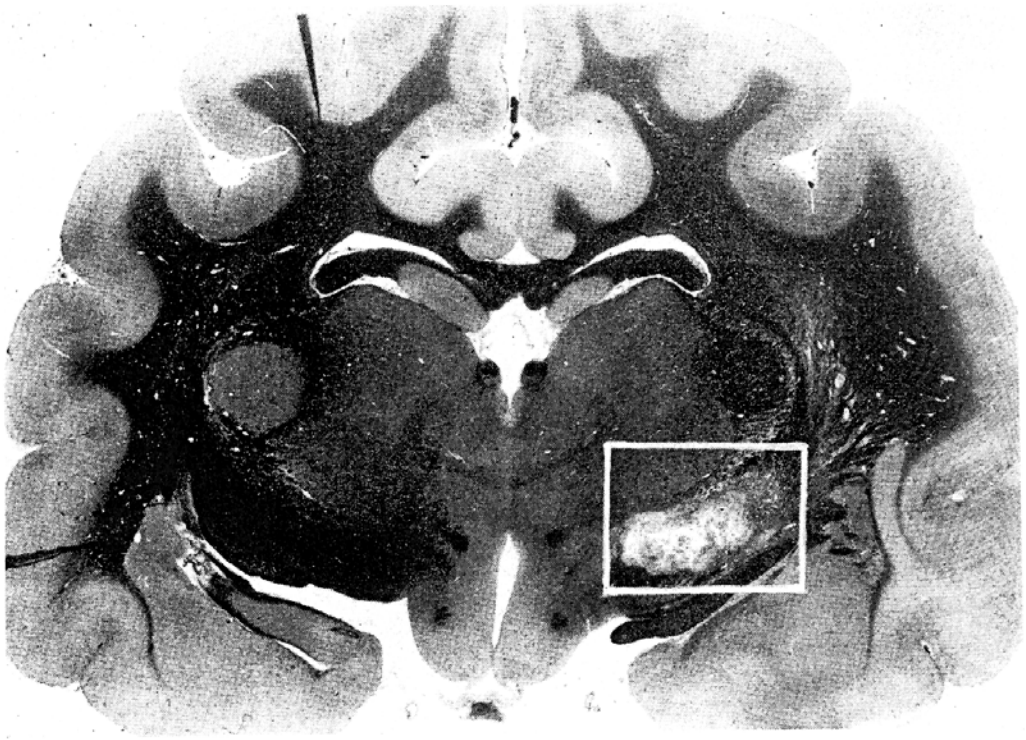

FIG. 4. Large lesion (in rectangle) confined to the internal capsule produced by a beam of ultrasound whose focus was located successively in a series of positions laterally to produce an effect in a large area. Animal sacrificed 4 days after exposure. Weil stain. (× 3)

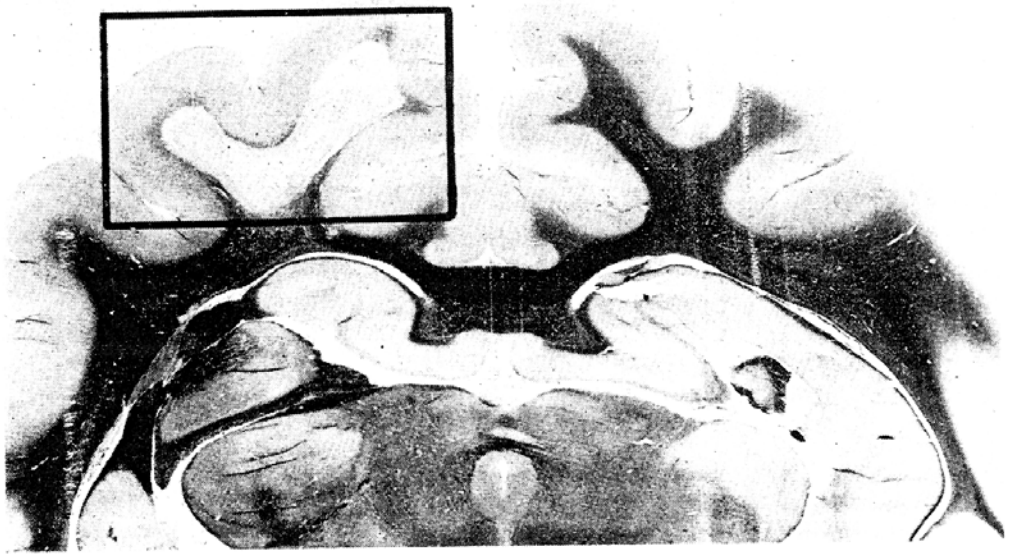

FIG. 5. Large lesion (in rectangle) in the white matter of the parietal cortex produced by a focussed beam placed successively in a series of positions. Note the sharp boundary between the degenerate white matter and the intact gray matter above and the normal fiber tracts below. Animal sacrificed 12 days after irradiation. Weil stain. (× 3)

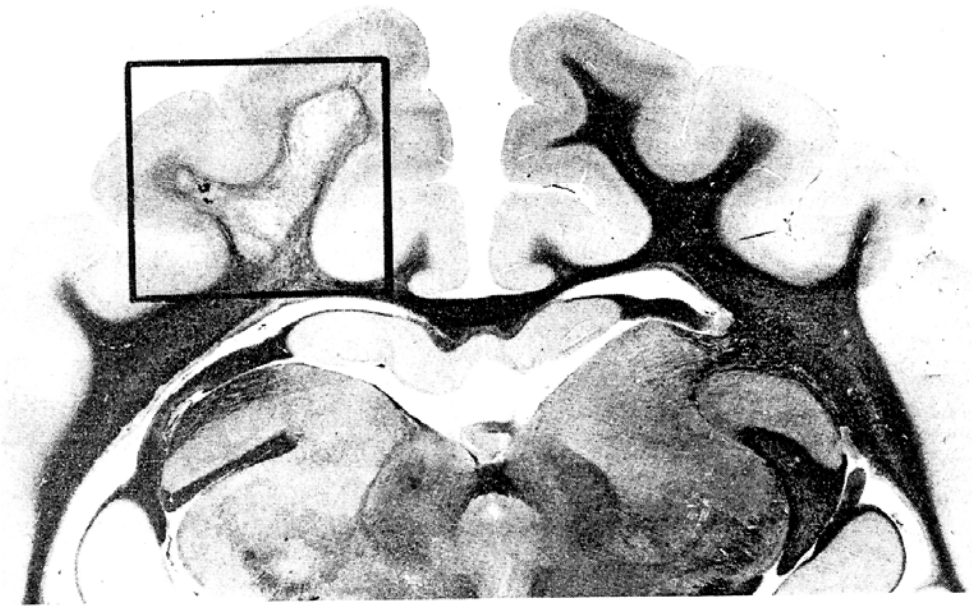

FIG. 6. Large lesion (in rectangle) in the white matter of the parietal cortex produced in similar fashion to the lesion illustrated in figure 5. This animal was sacrificed 2 days after irradiation. The myelin spheres have now broken down, and the necrotic area is filled with the debris of nerve fibers. Weil stain. (× 3)

side except that some of the large pyramidal cells of layer 5 are beginning to show early chromatolysis which is probably a retrograde reaction to axon injury. Edema which usually is in evidence for a number of days following the production of such a large lesion has disappeared. The cell density of the irradiated cortex is the same as the corresponding region on the opposite side of the midline.

As indicated previously, to produce a lesion of this large size with the focussed beams used at present, the focal spot must be placed successively in a series of positions. Recently, large lesions comparable in quality with those described in this paper have been produced by continuously moving the ultrasonic transducer by a motor drive which causes the focal spot to map out a desired trace in the brain. This latter technique requires considerably less time for the radiation procedure than the former.

An earlier stage of a lesion like that illustrated in figure 5 is shown in figure 6, again in Weil's myelin stain. The cat of figure 6 was irradiated in the same area as that of figure 5. The lesion is evident in the lightly stained white matter underlying the middle suprasylvian and lateral gyri. The myelin spheres have broken down at this stage, and the necrotic area is filled with the debris of the nerve fibers.

In the border zone surrounding the necrotic center of the lesion, the end bulbs of retracting axis cylinders are readily observed in silver preparations. Figure 7 shows normal axis cylinders of nerve fibers of the white matter of the unirradiated parietal cortex stained with silver and photographed under high power.

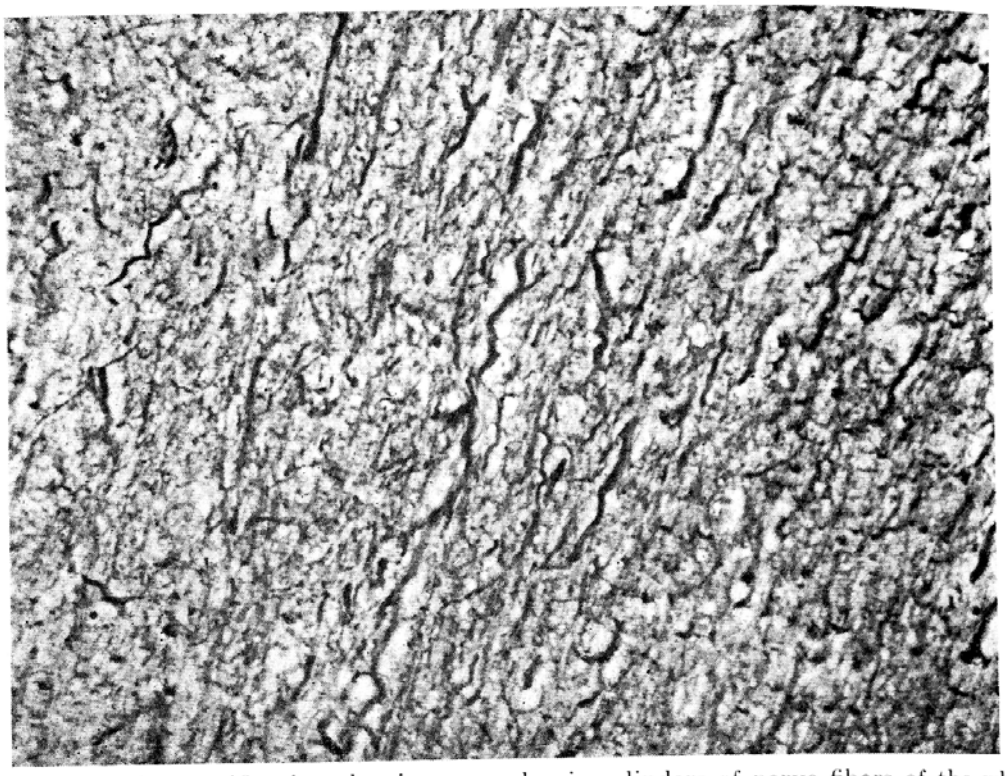

FIG. 7. High magnification showing normal axis cylinders of nerve fibers of the white matter of the parietal cortex. Romanes silver stain. (× 360)

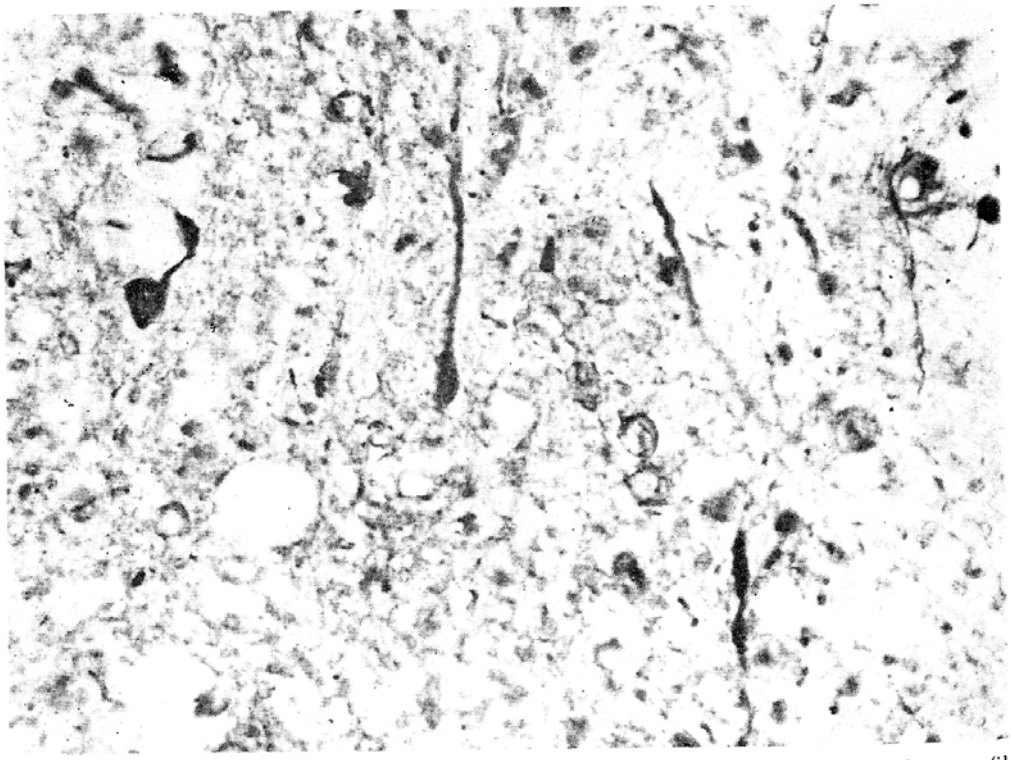

FIG. 8. High magnification showing end bulbs of retracting axis cylinders of nerve fibers of the white matter of the parietal cortex 2 days after exposure to ultrasound (border zone of lesion). The area in this figure corresponds to the area of figure 7 of the opposite cortex. Romanes silver stain. (× 360)

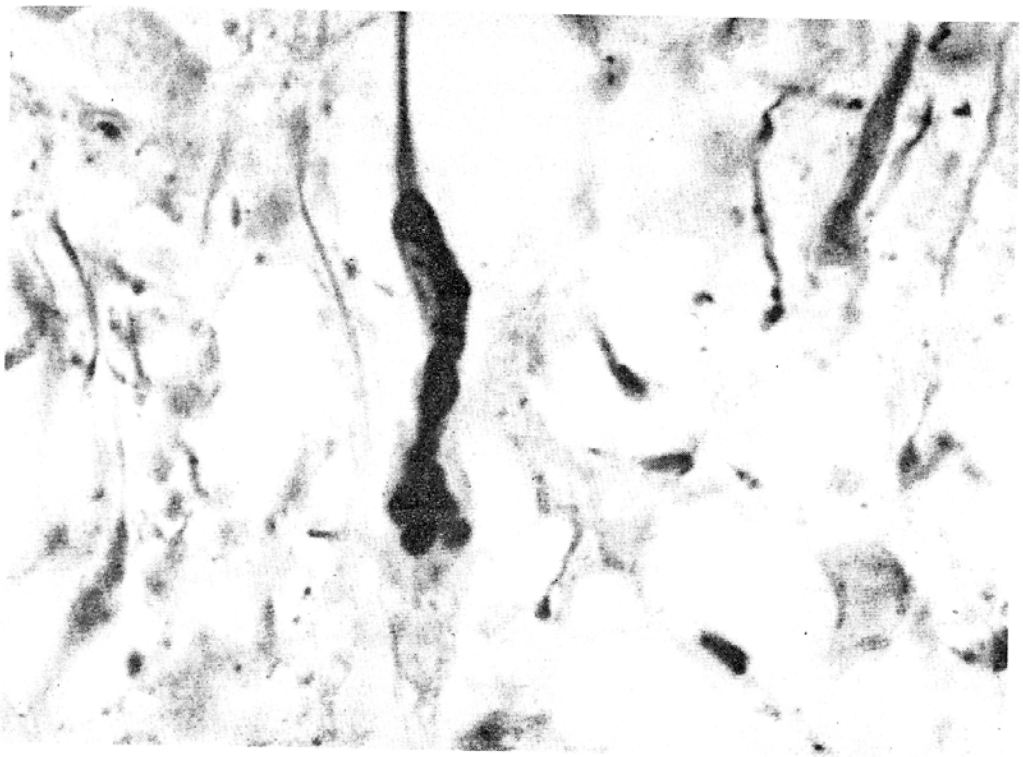

FIG. 9. High magnification showing details of an end bulb of a single retracted axis cylinder located in the border zone of an ultrasonically produced lesion in the parietal cortex. Romanes silver stain. (× 920)

Figure 8 is the corresponding area of the cortex on the opposite (irradiated) side of the midline in the border zone surrounding the necrotic center. The cat was sacrificed 2 days after exposure to the ultrasound. Figure 9 is a photomicrograph, taken at a magnification of 920 diameters, of a single retracted axis cylinder. Detailed examination of this silver stained preparation indicates that the axis cylinder has assumed the form of a spiral.

A brief description of the ultrasonic focussing transducers and the technique of irradiation follows. The high frequency sound is generated by a quartz crystal excited electrically to vibrate. It may be focussed by a lens placed in front of the crystal. Beams as small as 1.5 mm in diameter are readily attained. The sound is conducted from the lens to the tissue through sterile physiological saline. This liquid must be degassed to prevent bubble formation during irradiation, which would interfere with acoustic transmission by scattering the sound. The bone overlying the region through which the sound is to enter the brain must be removed to eliminate heating in the bone caused by absorption of acoustic energy and to insure a well defined beam in the nervous tissue.

The animal's head is held rigidly in position in a standard stereotaxic apparatus. Localization of the focal spot in the region of the brain to be affected is determined as follows: Before the animal is placed in the apparatus a pointer attached to the irradiator (vibrating crystal, lens, etc.) and coinciding with the focal spot of the irradiator is positioned on the midline of the apparatus and is

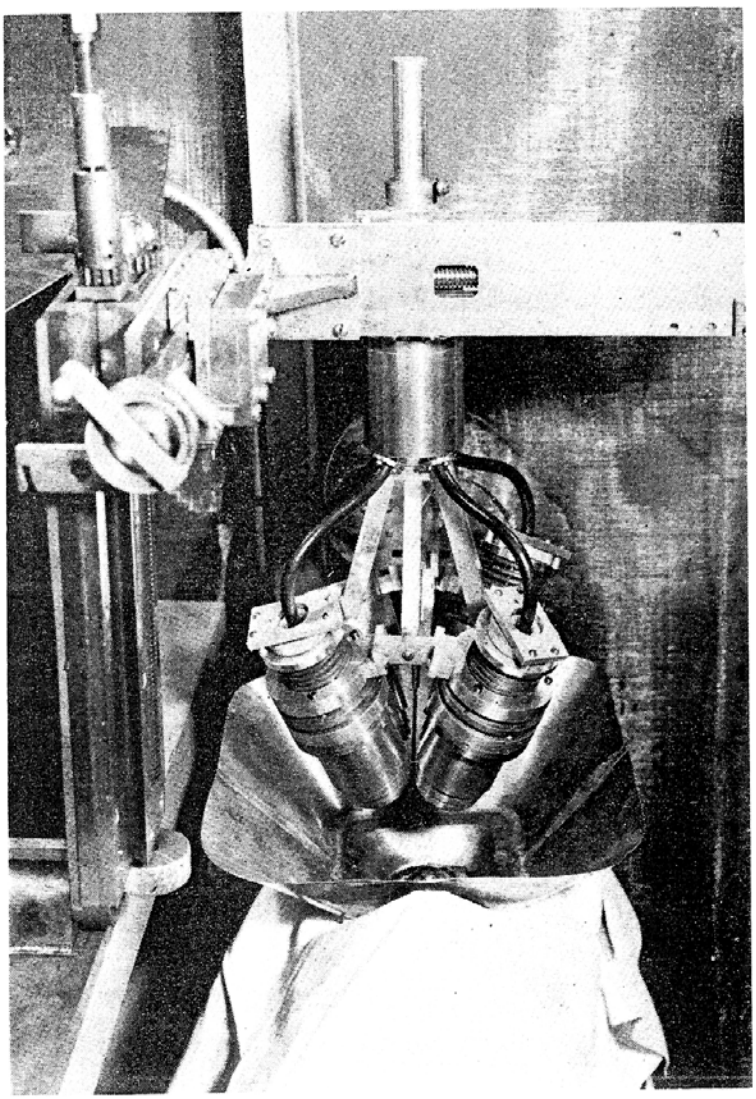

FIG. 10. Four beam focussing irradiator positioned over the exposed cerebral cortex of an animal set up for irradiation. The cap, which has a flange on the lower end to which the skin of the animal is tied to make a water tight connection, has not yet been filled with the sterile Ringer's solution which acts as the medium for transmitting the sound from the source to the brain tissue.

co-linear with the line through the bars which support the skull of the animal at the ears. The coordinate scales on the system which supports the irradiator are read corresponding to this ear bar zero. One can then transform from the coordinates of the stereotaxic apparatus to the coordinates of the system supporting the irradiator. The pointer is then removed from the irradiator, and the animal is mounted in the stereotaxic machine. The soft tissues are then incised over the appropriate area of the nervous system and the bone reflected or removed. The dura mater need not be opened. In practice a flanged cap which is used to contain the physiological saline, which acts as a transmitting medium for the sound, is tied to the skin of the animal. Figure 10 shows a four beam instrument positioned over the head of an animal as set up for an irradiation.

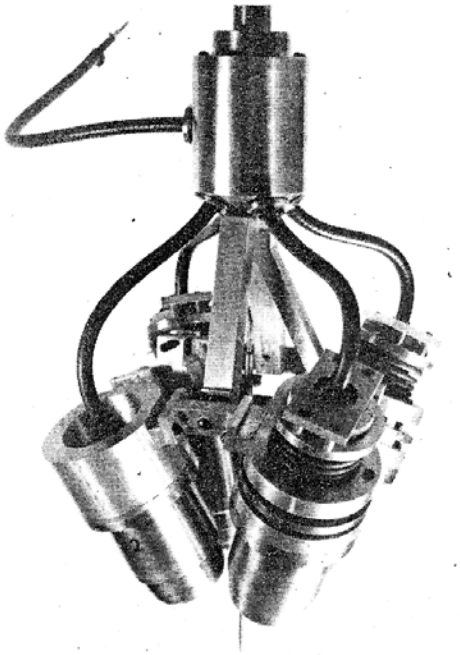

FIG. 11. Side view of the four beam irradiator

The exposure can be seen at the base on the inside of the cap which contains the saline during the irradiation. When the cap is filled with degassed sterile saline the irradiation can proceed.

In order to produce a lesion beneath the surface of the brain without damage to the intervening tissue, it is necessary to use an irradiator which produces a beam the intensity of which decreases very rapidly as one moves away from the center of the focal spot. One of the ways in which this has been realized is by

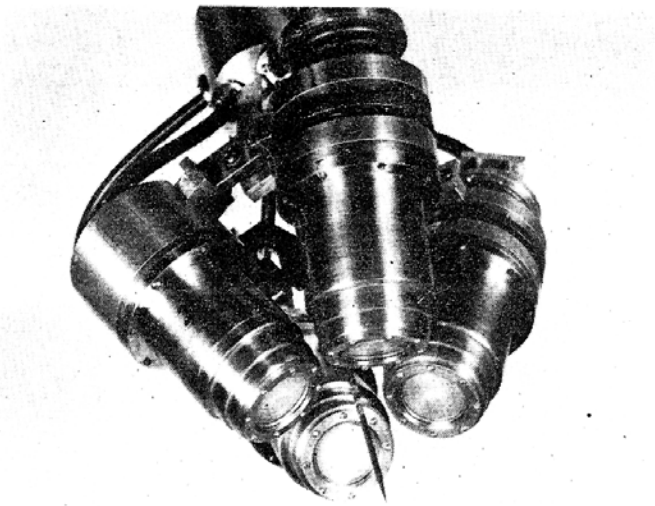

FIG. 12. View of the four beam irradiator showing individual crystals and lenses. Tip of pointer indicates the position at which all four focussed beams intersect. The distance from the face of the irradiator to the focal point is 7.5 cm.

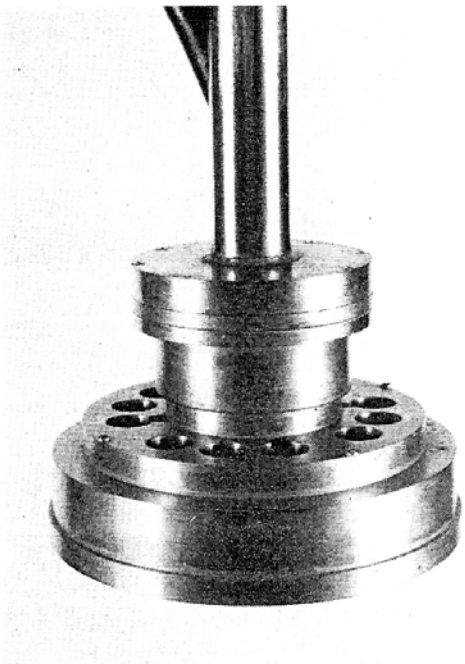

FIG. 13. Side view of the reflection irradiator

coupling together four single beam focussing irradiators with suitable adjustments to make the four beams intersect at a common point. This is the device which is shown in figure 10. Although the distance from the face of the irradiator to the focal point is fixed (7.5 cm for the irradiator illustrated), the depth of the lesion in the tissue may be varied by moving the irradiator vertically in the saline bath. Accurate relative motion between the stereotaxic apparatus and the focal spot of the sound beam is achieved by having the steroetaxic machine and the coordinate system which supports the irradiator mounted rigidly on the same supporting table. Figures 11 and 12 are close-up views of the four beam instru-

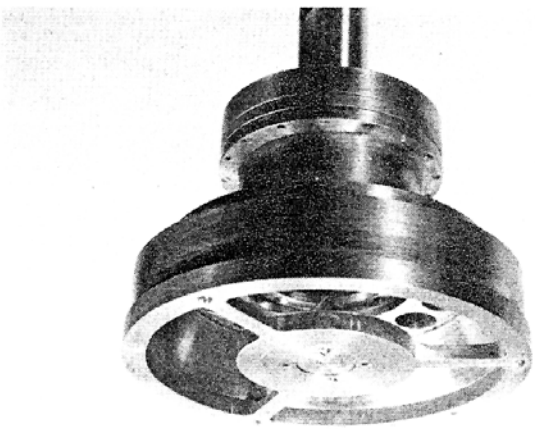

FIG. 14. View of the reflection irradiator showing a portion of the conical reflector in the center and the parabolic surface on the periphery. The beam comes to a focus on the axis of the device at a distance of 6.0 cm in front of the disc of metal which supports the cone

ment. A second instrument which can also be used to produce a focussed beam which is small in diameter is that illustrated in figures 13 and 14. This device does not use lenses. Two reflectors produce a beam of appropriate shape. The sound leaves the crystal and is first reflected from a cone which directs the sound radially away from the axis of the instrument. This cylindrical spreading wave then encounters a parabolic reflector which causes the beam to focus at a position on the axis of the device 6.0 cm in front of its face.

## SUMMARY

By employing a focussed beam of ultrasound under precisely controlled dosage conditions, accurately localized, quantitatively reproducible focal destructive lesions may be produced at any depth in the central nervous system without disturbance of intervening tissues. The white matter is readily affected. There is no disruption of the blood vessel walls even within the site of the focal destructive lesion.

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