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ULTRASONIC LESIONS IN THE MAMMALIAN CENTRAL NERVOUS SYSTEM

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Early histological studies of nerve tissue of animals irradiated with intense focused ultrasound at this laboratory indicated that nerve cell bodies were more susceptible than nerve fibers to changes by the ultrasound.[1] These preliminary histological results have not been substantiated in subsequent studies. Rather, it has been found, as was previously reported,[2] that white matter is more readily affected by the sound and that higher ultrasonic dosages are required for producing changes in gray matter. It can be readily seen that this selectivity provides a unique tool for basic neurological studies. Recent publications of this laboratory present results on the production and time sequence of changes in relatively large white-matter lesions of controlled shape.[2,3] This paper, however, is concerned primarily with small ultrasonic lesions in both gray and white matter.[4]

Selective, accurately positioned lesions as small as 2 to 3 mm in maximum diameter can be produced. The lesions, which can be localized at any desired depth in the brain without affecting intervening tissue, are quantitatively reproducible from one animal to another, so that dosage studies made on a series of animals can be used as a guide in choosing the conditions of irradiation for neuroanatomical or functional studies. The blood vessels are most resistant to the action of the sound. It is, therefore, possible to interrupt fiber tracts without destroying neighboring gray matter and without breaking blood vessels even within the site of the lesion. It is also possible, by appropriate choice of the ultrasonic dosage, to affect irreversibly the nerve tissue (fibers and cell bodies) in gray matter without causing hemorrhage.

The results reported here were obtained from histological studies of ultrasonically irradiated cats and monkeys. Extensive dosage studies have been completed, and the time course of development of the lesions has been followed in animals sacrificed from immediately after irradiation (5 min) up to 30 days. The preparation of the animal and the technique of irradiation are described in previous papers.[2,3] Results of investigations concerned with the physical mechanism of the action of the sound on the nerve tissue have been published.[5]

When a region of the white matter of the central nervous system is irradiated at one spot with a single exposure of ultrasound at a dosage just above the minimum required to produce an effect, a small lesion about 2 to 3 mm in maximum diameter is produced. Figure 1 illustrates such a lesion in the subcortical white matter 12 days after irradiation (dose 40 atm acoustic pressure and 3.9 $(10)^2$ cm/sec acoustic particle velocity for 1.00 sec). It shows a sharp boundary between the affected white matter (lower end) and the neighboring unaffected gray matter.

A lesion such as that shown in Fig. 1 is first seen 10 to 15 min following irradiation in tissue sections prepared with Weil's myelin stain. The lesion area is first recognized as a light-staining matrix as compared with normal tissue. One hour after irradiation the myelin sheaths appear beaded. The perivascular spaces are dilated, and some separation appears between the fibers. Within 6 to 12 hr (depending on the dosage) the myelin sheaths break down into separated spheres. During this same period axis cylinder fragments increase in the lesion area. These changes are followed by the hematogenous and microglial responses until all of the debris is cleared away. Other neuroglia then form a glial scar.

A greater dosage (41 atm acoustic pressure and 4.0 $(10)^2$ cm/sec acoustic particle velocity for 1.50 sec) produces a slightly larger lesion containing a central normal staining area or island of myelinated fibers surrounded by a zone or moat containing completely disrupted nerve tissue and large clear fluid-filled spaces (Fig. 2). No hemorrhage is present. These more severe lesions may involve neighboring gray matter, causing changes that are described in the following paragraphs. Lesions of the same order of size can be produced in fiber tracts at any depth in the brain without affecting the intervening nervous tissue.

Figure 3 illustrates a small lesion produced by ultrasound in the cerebral cortex of a cat. To produce such a lesion in gray matter, greater dosages of ultrasound are required than for white matter. When a region of gray matter is irradiated with a single exposure at a dosage (41 atm acoustic pressure and 4.0 $(10)^2$ cm/sec acoustic particle velocity for 2.50 sec) above the minimum required to produce a lesion, the effects that appear first (10 min after exposure) are a lightening in the staining ability of the background matrix and a slight dilation of the perivascular spaces. Nerve cells stain more faintly than normal within 1 hr.

Many contain large clear vacuoles in their cytoplasm; others have ruptured cell membranes, and only ragged strands of cytoplasm remain around the still intact nucleus. The nerve cells have disappeared by the end of 1 day. The background contains many clear spaces, and in the more severe lesions large fluid-filled clefts may appear in the tissue. The myelin sheaths and axis cylinders of nerve fibers begin to break down within 1 hr and undergo the afore-described changes for white matter. Some blood-filled capillaries are present at 1 hr. The hematogenous response is manifest within 6 hr by the presence of leucocytes. Microglial multiplication is evident at 4 days, and 12 days after irradiation the glial response is well developed.

The ultrasonic method of producing localized selective lesions in the central nervous system constitutes a unique and potent tool for experimental neurological and neurosurgical applications.[6] The technique is currently being used in this laboratory in a variety of neurological studies.

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REFERENCES AND NOTES

1. P. D. Wall *et. al., Science* 114, 686 (1951).
2. W. J. Fry *et. al., Neurosurg.* 11, 471 (1954).
3. J. W. Barnard *et. al., J. Comp. Neurol.,* in press.
4. This study was partially supported by the Biophysics Section of the Physiology Branch of the Office of Naval Research under contract Nonr 336(00)-NR 119-075.
5. W. J. Fry, *J. Acous. Soc. Amer.* 25, 1 (1953).
6. No commercial equipment is yet available.

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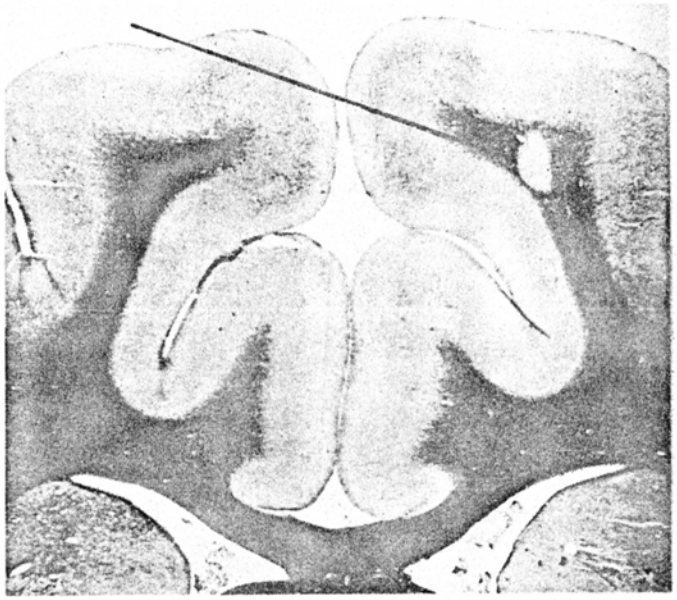

Fig. 1. Small ultrasonic lesion in the subcortical white matter of the brain of a cat. Dosage used selectively affects the fiber tracts, and no damage is produced in the neighboring gray matter. (PTAHstain)

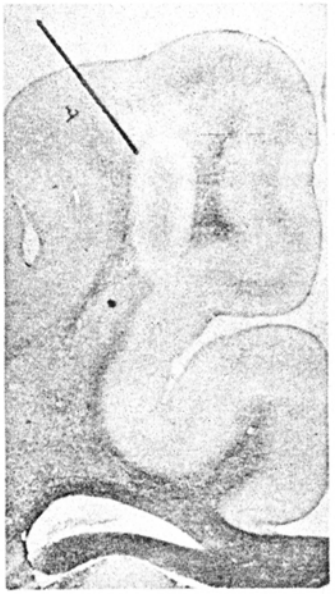

Fig. 2. Ultrasonic lesion in the subcortical white matter of a cat brain exhibiting a central region of dark-staining fibers and some invasion of neighboring gray matter. (PTAHstain)

Fig. 3. Small ultrasonic lesion in the cortical gray matter of a cat brain. (PTAHstain)