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Ultrasonic Threshold Dosages for the Mammalian Central Nervous System

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Abstract—**The ultrasonic threshold doses (acoustic intensity and time duration of a single pulse) to produce functional and structural irreversible effects in the mouse, rat, cat, monkey, and human central nervous systems are presented for a wide range of the pertinent parameters. There does not appear to be an important dependence upon frequency in the range from 1 to 6 MHz. Embryonic tissue is found to be appreciably more sensitive than adult tissue. From considerations of the measured outputs of commercially available ultrasonic diagnostic instruments, the experimentally determined threshold dosages necessary to produce these irreversible effects, and reports of clinical experience, it is concluded that ultrasound does not present a hazard, as currently employed for medical diagnostic purposes.**

I. Introduction

EVIDENCE that ultrasound continues to receive ever increasing attention and application as a medical diagnostic tool is abundant. Published proceedings of recent important meetings and symposia exhibit the role assumed by ultrasound and describe techniques and procedures of uncommon sophistication [1]–[3]. It is, however, common knowledge that at considerably higher acoustic intensities, and for single pulses of appropriate duration, irreversible changes are affected in tissue [4]. It thus becomes essential to have knowledge of the dosage ranges of the pertinent parameters over which safe operation of the ultrasonic instruments utilized for medical diagnostic purposes can be assured.

It is a purpose of this paper to examine selected available data to determine whether a hazard exists to the subject so examined, the safety factor necessary before potential hazards emerge, and the areas where studies should be undertaken in order to address appropriately these first two questions. Because the interest here is almost exclusively the human, data will be drawn only from studies on mammals, i.e., studies dealing, for example, with microorganisms in suspension are ignored. Also, as the mammalian central nervous system appears to be among the most sensitive of tissues to alteration by ultrasound,[1] it alone will be considered. Fortunately, due to interests in ultrasound as a neurosurgical tool and to interests associated with determining the mode of interaction of ultrasound and tissue, considerable information is available for this tissue.

There are at least two points of view which can be considered in assessing the effects of ultrasound on tissue, viz., effects manifested by changes in structure and those associated with changes in function. Both are treated in this paper and for both only irreversible changes are considered.

For the purposes of this inquiry, dose is defined as the numerical doublet consisting of the acoustic intensity at the site in question and the time duration of a single pulse of rectangular envelope, together with complete specification of temperature, hydrostatic pressure, etc.

II. Structural Changes

Structural changes have been observed mainly by suitable histological examination of the tissue following sacrifice of the specimen. Several groups of investigators have concerned themselves with such studies and a summary of these results at threshold has appeared recently [4]. Curve *A* of Fig. 1 is taken from [4] and shows the results of studies of three research groups on cat [6], [7] and rat [8] brain over the frequency range from 1 to 6 MHz.

Though there is not universal agreement, some investigators feel that the dosage region shown in Fig. 1, (curve *A*) can be divided into three regions. At intensities below about 150 W/cm², where the time durations of exposure are several seconds or greater, lesions are considered to be produced by local temperature increases due to absorption of acoustic energy in the body of the tissue. We refer to these as "thermal" lesions since the temperature has ample time to reach damaging levels as a simple computation shows.

At intensities somewhat above 150 W/cm² and extending to about 1500 W/cm², where the time duration of exposure is about 50 ms, temperature effects alone do not explain the effects produced. These structural changes are referred to as "focal" lesions. In this region several unique effects appear as follows.

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[1] See for example reports in [5].

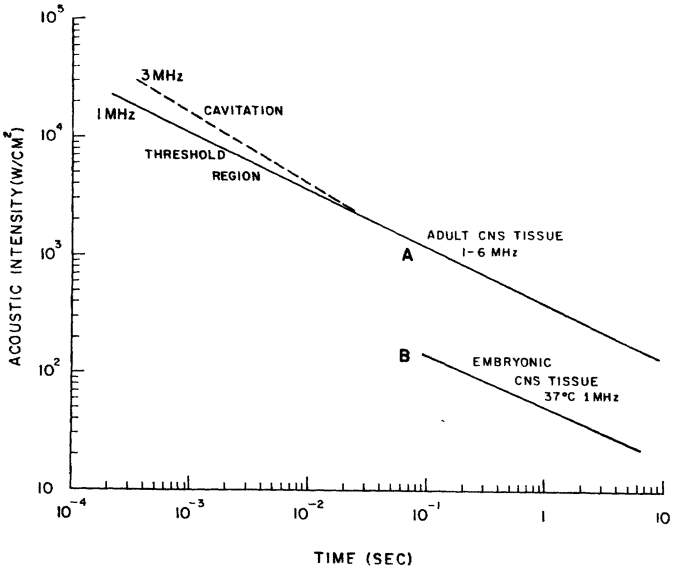

Fig. 1. Ultrasonic threshold dosage curves for adult and embryonic mammalian central nervous tissue.

1) Loss of electrical activity of nerves is immediate as are other functional alterations observed by evoked potentials.

2) The lesion must be allowed to develop for approximately 10 min before it is observable histologically.

3) It may be immediately "visible" by ultrasonic visualization techniques though the details of this interaction have not as yet been completely delineated.

4) Structural changes are more readily produced in white matter than in gray matter, the latter requiring a 30 percent longer pulse duration for the same acoustic intensity.

5) Focal lesions, as well as thermal lesions, always appear at the focus of the ultrasonic waves.

At intensities above about 1500 W/cm², where the time durations for threshold lesions become very short, the mechanism is cavitation. This is a relatively new finding and has been produced recently by two groups [4], [8]. The character of the "cavitation" lesion differs greatly from that of the focal lesion as follows.

1) The histological appearance of the lesion is instantaneous, i.e., not requiring a time delay of about 10 min for development.

2) The temperature rise as determined by absorption and time duration of exposure is virtually zero.

3) The lesion does not necessarily appear at the focus of the sound waves, but at random positions, apparently favoring locations near boundaries of different tissue structures, e.g., blood vessels, bone, ventricles.

4) The lesions are believed to occur with equal facility in gray and in white matter.

5) At the higher intensities there seems to be a complete destruction of tissue rather than the unique effects associated with focal lesions.

The random distribution of cavitation lesions is not well understood. Often they appear at positions where the calculated ultrasonic intensity should be several times less than that computed for the focal region, yet there may be no lesion appearing in the latter region. In the cavitation regions of Fig. 1, the curves *A* are plotted at the computed intensities, as no other information is available. Nevertheless, the 3-MHz data, by comparison with the 1-MHz data in this region, seem to imply that there exists a frequency dependence of the cavitation threshold in mammalian brain.

III. Functional Alterations

A functional endpoint has been utilized in a study in which young mice approximately 24 h after birth are employed [6], [9]. Here it must be considered that, compared with the adult tissue employed in the studies just discussed, these are embryonic tissues. These specimens are poikilothermic so that investigations also can be carried out as a function of temperature. The anesthetized animal is supported in an appropriate holder in a rather special ultrasonic system [9]. The lumbar enlargement of the spinal cord is exposed to a uniform plane wave distribution of sound intensity with a single pulse of rectangular envelope. If the dose is appropriate, the hind legs are paralyzed, and if the dose is not sufficient, the hind legs are functionally unaltered. The determination of whether or not paralysis occurs is accomplished easily and quickly after the ultrasonic exposure. In contrast to the noncavitation structural effect, the functional effect, as represented by these experiments, appears virtually instantaneously, i.e., as soon as a determination can be made (within a few seconds after exposure). Other evidence that the functional effect is present immediately comes from human neurosurgical procedures, e.g., where ultrasound was used to produce relief from Parkinson tremor, where it was found that the tremor disappeared virtually instantaneously with the cessation of the sound pulse. The interruption of an evoked electrical signal is another example that the time delay between the termination of the ultrasonic pulse and the manifestation of the functional effect is indeed very short.

Curve *B* of Fig. 1 shows these functional data for 50 percent of the mice paralyzed for a 37°C base temperature of the animals. Thermal effects and cavitation can be eliminated as the principal physical mechanisms responsible for these alterations and mechanical mechanisms are strongly implicated [10]. It is apparent that a discrepancy of about a factor of 8 exists between curves *A* and *B* and the question arises is this due to difference in development (i.e., adult versus embryonic tissue) or due to difference in endpoint (i.e., structural versus functional). Some evidence exists to support the view that embryonic tissue is more sensitive than adult tissue, viz., the doses required to produce the

disappearance of a Parkinson tremor and those to interrupt evoked cortical potentials, both in adult tissue, lie above curve *A* of Fig. 1.

IV. Discussion

It is pertinent to compare these threshold data with the output of instruments used for medical diagnostic purposes. Fig. 2 contains the information of Fig. 1 plus the results of a recent study by Hill [11] in which the acoustic output of most of the ultrasonic diagnostic instruments available in the United Kingdom were measured (12 such instruments which operated in *A*-mode, *B*-mode, Doppler regimes, etc., were examined). Fig. 2 shows the results of Hill's measurements wherein the measured peak intensity output and the time duration of the pulse is shown explicitly for some of his findings. The dashed-line boundary includes all of Hill's measurements. These represent instruments largely operating in a pulsed regime, with a low duty cycle. Some information on the question regarding the effect of such repeated exposures can be obtained from an investigation by Fry *et al.* [12], for much longer pulses and greater duty cycles, who found that subthreshold pulses would not sum to produce a suprathreshold functional effect unless the duty cycle was nearly one-half and the pulse duration approached 10^{-2} s. For such conditions, no functional effect appeared after 10 min of irradiation. Pond has recently shown that for repeated millisecond pulses to produce threshold lesions, the peak intensity of the pulse must be of the order of 10^3 W/cm^2, i.e., near the threshold curve of Fig. 2 [8]. Further, Warwick *et al.* [13], have shown that pregnant mice, utilized in experiments duplicating clinical practice of obstetric examination, but exposed to peak intensities nearly ten times those observed by Hill, yielded no statistically significant effects produced by ultrasound.

If it is permitted to extrapolate the threshold curves toward shorter exposure times, as is suggested in Fig. 2 by the dashed lines, it will be seen that there exists a safety factor of 100 relative to Hill's measurements. Even if a less favorable extrapolation is considered it appears possible to conclude, with some confidence, that ultrasonic diagnostic instruments, having outputs similar to those examined by Hill, are not likely to present a hazard. Further, it must be considered an important piece of data that physicians using these instruments have *not* reported undesirable effects resulting from their clinical practice.

During the past 15 years, 1100 cats have been irradiated in our laboratory under procedures yielding approximately 10 000 individual exposures producing lesions in the adult cat brain in the "focal" region of the dosage curve. All animals were examined histologically in the focal region of the sound beam and in the intervening tissue between the focal region and the port of

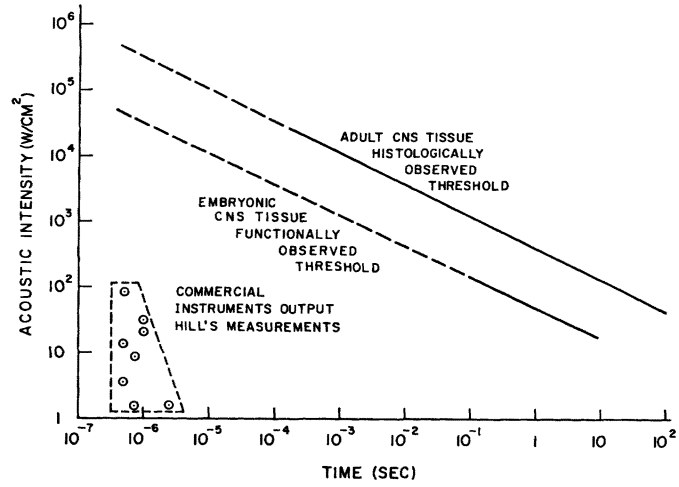

Fig. 2. Comparison of the threshold dosage curves with the output of some commercially available ultrasonic diagnostic instruments.

entry of the sound into the brain. It is pointed out here that the intervening tissue received multiple doses ranging from just below threshold values, near the beam focus, to the much lesser values, at the cortex. Animal survival was allowed to range from a few minutes to five years with more than half being sacrificed between one and two years after exposure. From all these data no evidence emerges suggesting tissue abnormalities produced by the passage of sound through the intervening tissue. Also, 247 kittens were born to irradiated mothers and 12 kittens were born to three mothers whose mothers had also been irradiated. From gross observations of cage behavior no animals exhibited abnormal conduct nor was there a greater tendency to organic disorders in any set of irradiated animals, or their offsprings, as compared to other unirradiated animals in the same colony. This is considered to be further evidence that the threshold curves of Figs. 1 and 2 provide meaningful criteria for discussions of the safety and efficacy of ultrasound in biological and medical applications.

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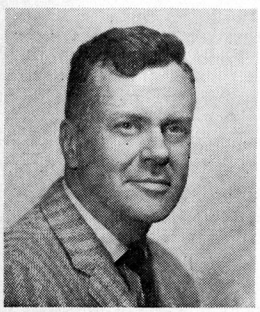

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