SESSION 3:1 INTERACTION OF ULTRASOUND AND TISSUE

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As is true in many instances in scientific endeavors phenomenological observations are made before an adequate theory is available to predict the discovery. In these cases, of which ultrasound and its interaction with tissue is an example, utilization of the phenomena for achievement of beneficial effects goes forward at a pace not entirely dependent on elucidation of fundamental underlying mechanisms. It is essential however, to pursue fundamental studies which in most cases greatly expands the range of applicability of the observed phenomena. At this time a number of interactive effects between ultrasound and tissue have been observed but a comprehensive understanding of the underlying mechanisms is not available.

Much needs to be done to identify the possible hazards of ultrasonic energy as applied to medical diagnostics and therapy through adequate toxicity studies. Additionally fundamental research seeking to provide an understanding of the basis of the observed interaction phenomena is urgently needed to define broader areas of application to medicine. It is also anticipated that such research will be valuable in enhancing our understanding of some basic biological processes.

In the ultrasonic intensity range below a few watts per square centimeter and frequencies, of essentially 1 MHz, a considerable amount of therapeutic benefit has been achieved in human medicine. This field of ultrasonic diathermy has been studied by Lehmann, Gersten, and others and most generally the conclusions seem to relate the observed therapeutic effect to a heat mechanism (*1-3*). Differential acoustic absorption properties of body tissues (bone, muscle, fat, etc.) (*4*) provide the basis for selective heating and the subsequent beneficial results. There has been a continual underlying train of thought which implies that heating may not alone explain all of the observed results. Although ultrasonic intensities in this range have been demonstrated to produce cellular changes, these observations are made at lower frequencies (20kHz) and on cells in liquid suspension (*5, 6*). Such changes have generally been presumed to occur as a result of shear stresses associated with microstreaming near bubbles, which might apply in the vascular system but not in bulk body tissues. What role any mechanism other than heat might play in low intensity ultrasonic therapy seems not to have been determined although additional studies should shed more light on this issue.

With the introduction of ultrasound in the diagnostic field, a number of techniques utilizing ultrasonic intensities varying from milliwatts per square centimeter to as much as 100 watts/cm^2 peak intensity over a wide frequency range (1 - 20 MHz) have evolved. The low intensity applications include doppler methods which deliver ultrasound in a cw regime (these generally operate in the milliwatt range). Presently conceived pulsed doppler and holographic methods would utilize similar low intensities.

Solution to the low intensity problem will be immediately applicable to possible hazards involved in ultrasonic diagnostic techniques which utilize continuous wave operation. Involved here are doppler methods for monitoring dynamic events in tissue (heart walls and valve motions in the adult and in the fetus), as well as fluid flow (blood vessels). Some holographic visualization methods would also fall in this category.

There is an area of need from both a toxicity viewpoint and elucidation of mechanism (or mechanisms) of interaction for cw ultrasound in the intensity range below several watts per square centimeter sound intensity and in the frequency range from 1 to perhaps 10 MHz. It should be emphasized that in vivo studies are to be encouraged since extrapolation from in vitro data, particularily those involving liquid suspensions of molecules, bacteria,

and so forth, must be made with great care.

The interactive effects of high intensities of ultrasound (in the range from hundreds to several thousands of watts per square centimeter) must also be considered in the light of their potential application to medical practice. The primary effect which has been recorded for cw operation in this intensity range is associated with lesion production. Central nervous system tissue has been most extensively studied in this regard and a variety of tissue selective effects are in evidence (*7-9*). The dosage conditions for the production of focal lesions in brain have been obtained over a wide range of intensities and exposure times. A plot of the time and intensity conditions necessary to produce structural and/or functional changes at or near threshold are shown in figure 1. Although there is no question about the validity of the observed dosage conditions leading to the indicated changes, there is not universal agreement as to the mechanisms involved over the entire dosage range explored (*10-13*). It seems fairly well agreed that below some value of intensity (100 to 800 W/cm^2) the primary mechanism for lesion production is heat in the adult brain at 37° C. ambient temperature.

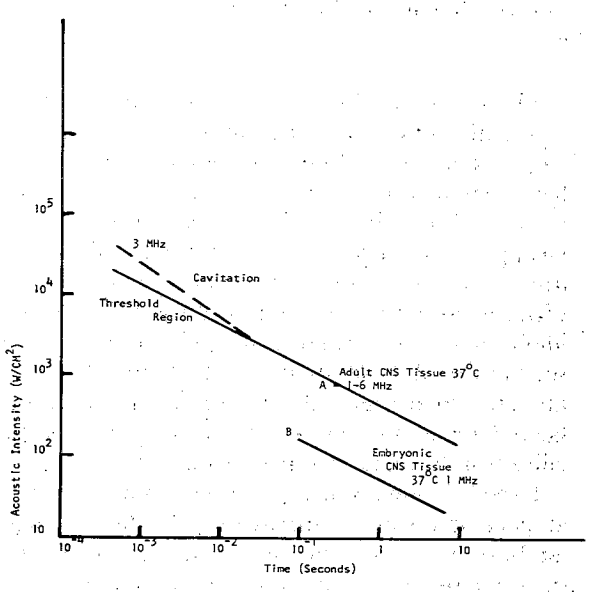

Figure 1. Ultrasonic threshold dosage curves for adult and embryonic mammalian central nervous tissue.

Vagueness in the intensity values required to produce thermal damage is due primarily to lack of information concerning ability of tissue to withstand transient temperature rises for short time periods (10 seconds to a fraction of a second). From the available data obtained on neural tissue, using direct thermocouple measurements in the adult rat brain (*12*), it appears that a temperature time description for tissue survival can be described by the curve of figure 2. The maximum allowable steady state ΔT for various body tissues including neural tissue has been well established, but data are meager from which the remainder of the curve has been constructed. Resolution of the question concerning the tissue survival versus time and temperature rise should aid in our understanding of the role of the heat in lesion production in the intensity range from 100 to approximately 1,000 W/cm^2. Above 1,000 W/cm^2, in the adult mammalian brain, both measured and computed temperature rises are below those normally considered lethal.

For some multiple pulse regimes involving neural tissue (viz., 1 millisecond on, 15 millisecond off, 5 second total delivery time, 3 MHz and 2,200 W/cm^2) it has been demonstrated that the curve of figure 1 is applicable, although the temperature rise at the lesion site is essentially one-fourth of that produced by a single pulse of sound of the same intensity leading to a lesion.

There is a body of data involving functional and structural changes in the spinal cord of day old mice which indicates that sound intensities of the order of 50 watts/cm^2 at 1 MHz frequency will produce effects without lethal temperature rises (*14*). This condition has been demonstrated by reducing the temperature of the irradiated mice so that temperatures below 46°C. (which are lethal on a continuous basis) are not achieved during the irradiation period. Fine thermocouples imbedded in the spinal cord have been used to record the temperature rise during irradiation. The phenomena observed have a positive temperature coefficient in that although the temperatures reached during irradiation are not lethal, the effect is produced at lesser ultrasonic dosages as the base temperature is raised, at a given frequency (*14, 15*). The relative dosage required to produce a functional and/or structural change for the day old mouse cord is smaller than that for adult brains. This result is shown from the data presented in

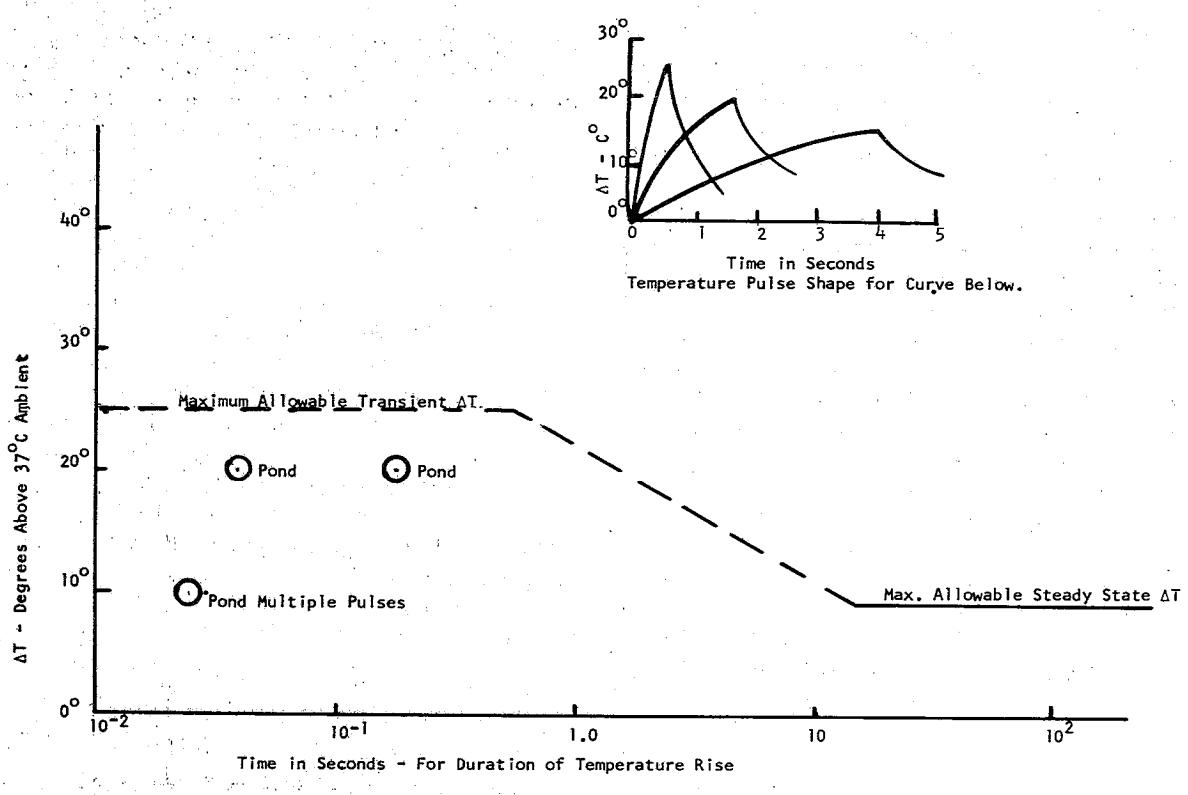

Figure 2. Relationship between maximum temperature rise above 37°C and the duration of the temperature pulse (for specific pulse shapes) for mammalian central nervous system tissue destruction.

figure 1. The difference in dosage conditions for the day old mouse spinal cord and adult animal brain structural or functional effects cannot be completely attributed to the animal age since adult rat cord data indicate it may be similar to day old mouse spinal cord (*16*). Presumably the difference could be associated with a difference between brain and cord in response to ultrasound.

Studies involving multiple irradiation of the frog spinal cord with 980 kHz ultrasound show that it is possible to produce addition of ultrasonic dosages if very specific conditions apply (*15*). Specifically for a sequence of two irradiations spaced at varying time intervals from 0 to 500 seconds apart paralysis of the hind legs of the frog can be achieved. A complex relationship (conditions leading to paralysis) exists between the time interval between irradiations and the dose delivered in the second irradiation starting with a fixed dosage for the first irradiation which is subparalytic. The full implication of the role of temperature and other factors in this study has never been completed.

There is no evidence to support any long term cumulative effects of ultrasound in neural tissue. Approximately 2,000 experimental animal brains have been irradiated under a variety of continuous wave conditions in experiments having animal survival periods of up to 5 years with virtually the entire brain of all these animals studied histologically with the light microscope in serial sections. No evidence of any abnormal tissue generation has been seen in any of these brains. Further, in no case has any abnormal cage behavior or functional deficit been detected in those cases involving lesions specifically induced to produce a functional change.

Irradiation times of a few milliseconds were used at peak intensities approaching 20,000 W/cm² to establish the region shown in figure 1 at which tissue cavitation is produced. Cavitation is most apt to appear at a weak structure in the tissue, such as blood vessel wall-blood interface. Intensities above several kW per square centimeter have been seen to initiate cavitation at specific sites in neural tissue. Thus, the full range of irradiation times and in-

tensities shown in figure 1 involves regions in which heat, cavitation or other mechanical effects predominate but that a number of mechanisms interplay at any region making the problem of separating one from the other somewhat difficult (*10, 11*).

The spectrum of interaction effects, which are nondestructive and nontherapeutic, occur in which aspects of acoustic impedance characteristics in tissue lead to delineation of soft tissue interfaces by reflection methods. Pulse echo methods employing typically 1 μs sound pulses repeated every 1,000 μs are used for tissue, generally. This short regime of ultrasonic irradiation of tissue needs both toxicity information and basic mechanisms study. It does not appear possible to produce structural and/or functional changes with such an exposure regime without employing sound intensities unachievable with present commercial diagnostic equipment. The data shown in figure 1 seem to indicate that the most likely operative interactive mechanism is thermal, if the average intensity were to reach the threshold for damage. This could be achieved for example under conditions of 1,000 watts/cm^2 average intensity in the μs pulse repeated every 1,000 μs leading to 1 watt/cm^2 average intensity concentrated in a fixed tissue volume for time periods of many hours, assuming heat conduction is stabilized and that summation of the effect for individual pulses can be made in this way. No such exposure conditions can presently be obtained from diagnostic apparatus so that there appear to be orders of magnitude of safety for ultrasonic applications operating in this mode. Data from Hill shown on figure 3 indicate the operating range of a number of present diagnostic devices (*17*).

Reversible suppression of electrical conduction in brain tissue has been achieved (*18*) without evidence of structural or functional damage. Irradiation of the lateral geniculate nucleus of the cat provided reversible modification of evoked electrical activity in the occipital cortex due to photic stimulation in the eye of the anesthetized animal. The mechanism of suppression for this type of effect has not been studied.

Acceleration of healing after ear puncture in the rabbit has been reported as being produced by low intensity ultrasound in which the temperature rise is essentially 1.5° C., leading to the supposition that a nonthermal, noncavitation mechanism is operative (*19*). This work is quite interesting and needs further study to delineate the fundamental mechanisms involved. Some ultrastructure studies are available on blood vessels in the rabbit ear subjected to a broad range of ultrasonic intensities (a few watts per square centimeter to 1,500 watts/cm^2) which shows evidence of structural change at dosages approximately the same as those in evidence for neural tissue change (*20*). A variety of structural changes are in evidence in this variable survival time series, and at the highest intensities involved, the measured temperature rises (of the order of 2 to 3° C.) cannot be considered lethal.

In a very general sense it would appear that the quantitative determination of acoustic parameters of various normal and abnormal tissues would be of considerable help in the differential diagnosis of disease entities provided of course, the different tissue states can be readily typed in vivo. Instrumentation development for collecting, processing and analyzing of acoustic signals received from the specific tissue sites is needed to implement this type of study. An understanding of tissue properties which affect acoustic parameters (velocity, absorption, and so forth) would be part of such a study. Perturbation methods such as transient thermal gradients (*21*) induced in tissues of different acoustic absorption properties can be used to aid in the derivation of the acoustic parameters. The same type of information would benefit certain types of ablative surgical procedures performed by ultrasonic means.

The general conclusion drawn from studies of the interaction of ultrasound and tissue, with most emphasis on neural tissue, is that ultrasound can produce structural and/or functional changes via a thermal, cavitation, or other mechanical mechanism not yet well understood. Although there is evidence for a small cumulative effect over a very short time base (less than 5 minutes) there is no evidence for cumulative effects on any longer time scale. Short term cumulative effects can, of course, be attributed to transient temperature rises, inherent in all ultrasonic irradiation procedures in tissue, and a careful consideration of the temporal sequence of temperature variation is needed to access the effects of ultrasonic doses repeated after time periods of less than 5 minutes. Toxicity studies are needed for all body organs and tissues. These studies should be conducted in vivo on appropriate mammals and should, if possible, duplicate the irradiation regimes used in present or anticipated clinical practice. Whenever possible the irradiation

regimes should be carried to the stage of actual production of structural and/or functional changes so that margins of safety can be determined. Fundamental mechanism studies are needed to provide a comprehensive rational basis for the application of ultrasound in clinical diagnosis and therapy.

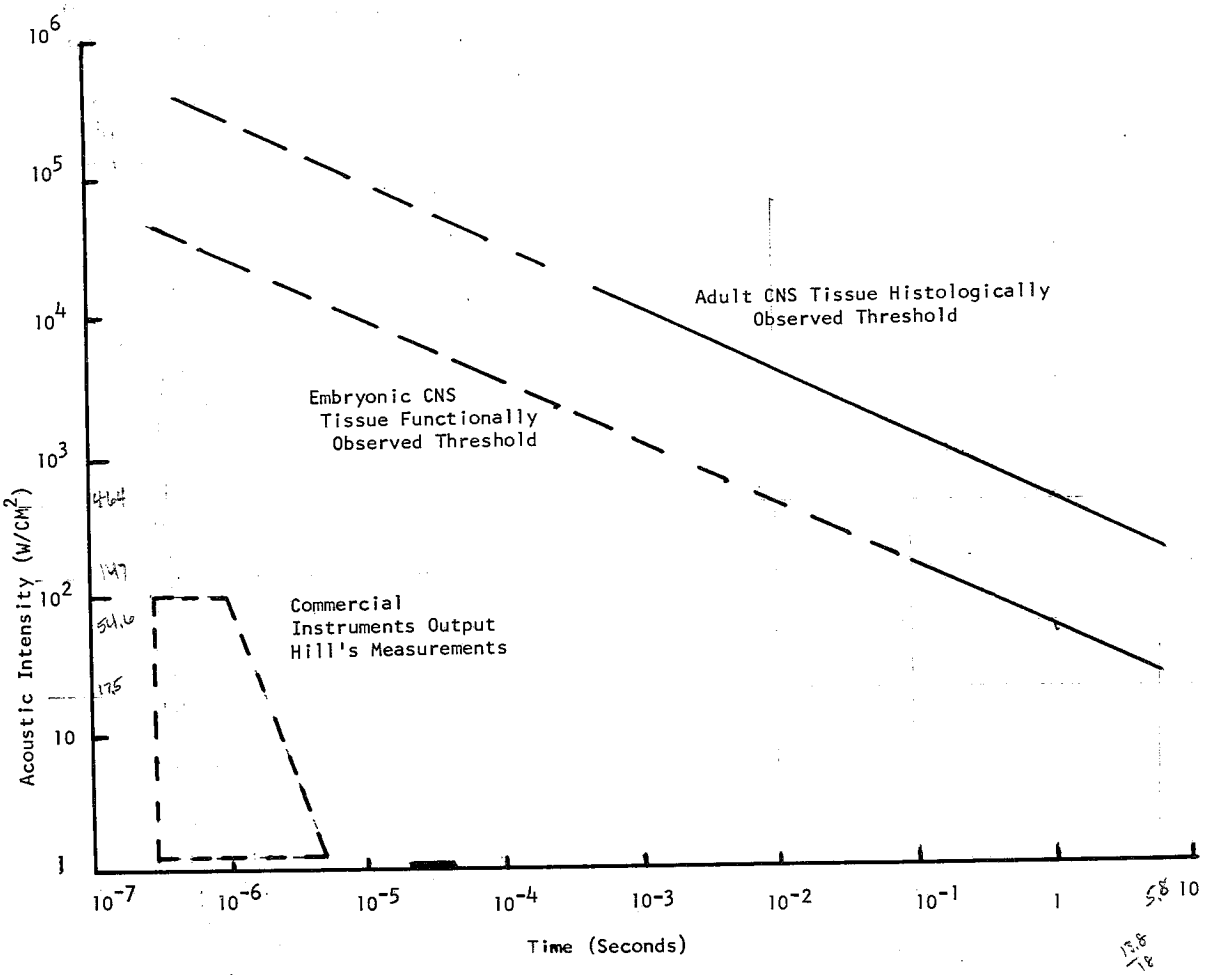

Figure 3. Comparison of threshold dosage curves for central nervous system tissue with the output of some commercially available ultrasonic diagnostic instruments.

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