ULTRASOUND DOSIMETRY AND INTERACTION MECHANISMS

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I. INTRODUCTION

Ultrasonic biophysics is the study of mechanisms responsible for how ultrasound and biological materials interact. As shown in Fig 1, when one studies how ultrasound affects biological materials, this can be viewed as bioeffect studies or risk studies. On the other hand, the study of how tissue affects the ultrasound wave can be viewed as the basis for diagnostic ultrasound. Thus, an understanding of the interaction of ultrasound with tissue provides the scientific basis for understanding image production and risk assessment.

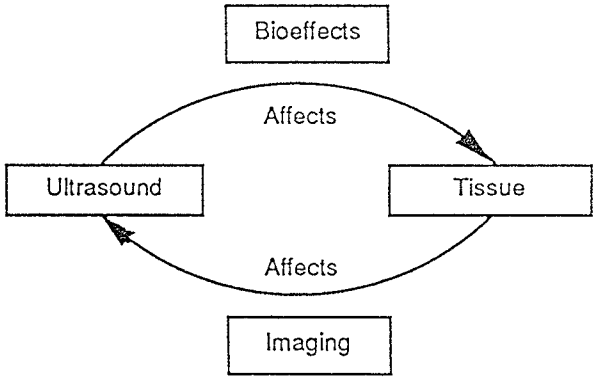

Figure 1

Ultrasonic dosimetry (O'Brien, 1978; O'Brien, 1986) is concerned with the quantitative determination of ultrasonic energy interaction with biological materials, that is, defining the quantitative relationship between some physical agent and the biological effect it produces. To understand more fully ultrasound dosimetry and interaction mechanisms, it is first

appropriate to develop common nomenclature. Then, general dosimetric concepts will be presented since a large body of literature and history exists to quantitate the interaction of various propagated energies and biological materials. Ultrasonic dosimetry and its current status will be presented. To conclude, interaction mechanisms, both thermal and nonthermal, are discussed.

II. FIRST-ORDER AND SECOND-ORDER QUANTITIES

There are many buzz words to describe a general class of events such as the terms *first-order quantity* and *second-order quantity*. *Quantity* represents what is measured and *unit* represents the amount (see Table 1).

TABLE 1

Typical ultrasonic quantities and units

QUANTITY	UNIT
charge	coulomb (C)
current	ampere (A = C/s)
displacement	meter (m)
energy	joule (J = Ws)
energy density	joule per meter cubed ($J/m^3 = N/m^2$)
force	newton (N)
frequency	hertz (Hz)
intensity	watt per centimeter squared (W/cm^2)
length	meter (m)
mass	kilogram (kg)
power	watt (W)
speed	meter per second (m/s)
temperature	degree celsius (°C)
time	second (s)
ultrasonic pressure	pascal ($Pa = N/m^2$)
voltage	volt (V)
wavelength	meter (m)

First-order quantities are known as amplitude quantities and second-order quantities as energy quantities and are listed in Table 2. The basic ideas of first-order and second-order quantities are (1) both first-order and second-order quantities deal with the transport of energy, (2) all first-order quantities are directly proportional to each other, (3) all second-order quantities are directly proportional to each other, and (4) the product of any two first-order

quantities is directly proportional to any second-order quantity, that is,

$$\text{any first-order quantity} \propto \text{any other first-order quantity} \quad (1a)$$
$$\text{any second-order quantity} \propto \text{any other second-order quantity} \quad (1b)$$
$$(\text{any first-order quantity})^2 \propto \text{any second-order quantity} \quad (1c)$$

TABLE 2

List of first-order and second-order quantities used in ultrasound.

FIRST-ORDER QUANTITIES	SECOND-ORDER QUANTITIES
current	energy
particle acceleration	energy density
particle displacement	intensity
particle velocity	power
ultrasonic pressure	
voltage	

All ultrasonic amplitude quantities are directly proportional to each other. These quantities are (O'Brien, 1992)

$$\xi_o = \frac{U_o}{\omega} = \frac{A_o}{\omega^2} = \frac{p_o}{\omega \rho_o c_o} \quad (2a)$$

$$U_o = \omega \xi_o = \frac{A_o}{\omega} = \frac{p_o}{\rho_o c_o} \quad (2b)$$

$$A_o = \omega^2 \xi_o = \omega U_o = \frac{\omega p_o}{\rho_o c_o} \quad (2c)$$

$$p_o = \rho_o c_o \omega \xi_o = \rho_o c_o U_o = \frac{\rho_o c_o A_o}{\omega} \quad (2d)$$

where ξ_o, U_o, A_o and p_o are the particle displacement, particle velocity, particle acceleration and ultrasonic pressure, respectively, and ω is the angular frequency. In addition, the characteristic acoustic impedance is defined as

$$Z = \rho_o c_o \quad (3)$$

where ρ_o and c_o are the undisturbed density and propagation speed, respectively.

Fundamentally, ultrasonic wave propagation transports energy. The total energy in a particle volume element is the sum of the particle's kinetic and potential energies, given by (Pierce, 1981; Kinsler et al., 1982; Hall, 1987; Ensminger, 1988)

$$\Delta E = \Delta KE + \Delta PE \tag{4}$$

The particle's kinetic energy represents the motion of the particle from

$$\Delta KE = \frac{1}{2}(\text{mass})\,(\text{velocity})^2 \tag{5}$$

From the development of the continuity equation (Eq 16 in O'Brien, 1992), the undisturbed and disturbed incremental masses are, respectively,

$$M_u = \rho_o A\, \delta x \tag{6a}$$

$$M_d = \rho A \left(1 + \frac{\partial \xi}{\partial x}\right) \delta x \tag{6b}$$

which are the products, respectively, of the undisturbed and disturbed densities (ρ_o and ρ) and volumes $A\,\delta x$ and $A\left(1 + \frac{\partial \xi}{\partial x}\right)\delta x$. Since $M_u = M_d$ (conservation of mass), Eq 5 becomes

$$\Delta KE = \frac{1}{2}(\rho_o A\, \delta x)\left(\frac{\partial \xi}{\partial t}\right)^2 = \frac{1}{2}\rho\left(1 + \frac{\partial \xi}{\partial x}\right) A\, \delta x \left(\frac{\partial \xi}{\partial t}\right)^2 \tag{7}$$

where the particle velocity $u(x, t) = \frac{\partial \xi}{\partial t}$.

The particle's potential energy represents the compressed fluid state of the particle from

$$\Delta PE = -\int p\, dV \tag{8}$$

From the development of the continuity equation (Eqs 17 and 22 in O'Brien, 1992),

$$dV = -\frac{V_o}{\rho_o c_o^2}\, dp \tag{9}$$

which yields

$$\Delta PE = -\int p\left(-\frac{V_o}{\rho_o c_o^2}\, dp\right) = \frac{V_o}{\rho_o c_o^2}\,\frac{p^2}{2} + \text{constant} \tag{10}$$

where V_o (= $A\,\delta x$) is the undisturbed particle volume. The constant is zero because under conditions in which the acoustic pressure is absent (the undisturbed condition), the particle's potential energy is zero. Therefore, the particle's total energy (Eq 4), from Eqs 7 and 10, becomes

$$\Delta E = \frac{1}{2} V_o \rho_o \left(u^2 + \frac{p^2}{\rho_o^2 c_o^2}\right) \tag{11}$$

The total energy per particle volume, or the total energy per volume, is the instantaneous energy density and is found from Eq 11 to be

$$\mathcal{E}(x, t) = \frac{\Delta E}{V_o} = \frac{1}{2}\rho_o \left(u^2 + \frac{p^2}{\rho_o^2 c_o^2}\right) \tag{12}$$

where u and p are the respective instantaneous values of particle velocity and acoustic pressure.

To evaluate the average energy density, the one-dimensional, harmonically varying particle velocity is assumed to be

$$u(x, t) = U_{op} \cos(\omega t - kx) + U_{on} \cos(\omega t + kx) \tag{13}$$

where U_{op} and U_{on} are the amplitude particle velocities for the positive and negative directed components, respectively, and the one-dimensional, harmonically varying ultrasonic pressure (from Sec IX of O'Brien, 1992) is

$$p(x, t) = p_{op} \cos(\omega t - kx) + p_{on} \cos(\omega t + kx) \tag{14}$$

where $p_{op} = \rho_o c_o U_{op}$ and $p_{on} = -\rho_o c_o U_{on}$. Therefore, the average energy density is

$$\langle \mathcal{E} \rangle = \frac{1}{T}\int_0^T \mathcal{E}(x, t)\, dt = \frac{\rho_o}{2}\left(U_{op}^2 + U_{on}^2\right) \tag{15}$$

The same expression for $\langle \mathcal{E} \rangle$ results whether $\mathcal{E}(x, t)$ is averaged over either time or space.

Intensity is an extremely useful ultrasonic quantity which represents a measure of ultrasonic power flowing (time-averaged rate of flow of energy) at normal incidence to a specified unit area. The intensity concept is generally applied in connection with a traveling plane wave. Further, it is a vector quantity but, since the discussion herein is confined to an isotropic fluid and to the one-dimensional wave equation, vector notation is not used since the direction is known. The instantaneous intensity is defined as the dot product of the ultrasonic pressure and particle velocity. Its time-averaged representation is given by

$$I = \frac{1}{T}\int_0^T pu\, dt = \frac{\rho_o c_o}{2}\left(U_{op}^2 - U_{on}^2\right) \qquad (16)$$

It should be noted that for a standing wave where $U_{op}^2 = U_{on}^2$, the time-averaged intensity is zero whereas the time-averaged energy density is not.

For a plane progressive ultrasonic wave propagating in only the +x direction, $U_{on} = 0$, and Eqs 15 and 16 become

$$\langle E \rangle = \frac{\rho_o}{2} U_o^2 = \frac{1}{2\rho_o c_o^2} p_o^2 \qquad (17)$$

and

$$I = \frac{\rho_o c_o}{2} U_o^2 = \frac{1}{2\rho_o c_o} p_o^2 = \frac{p_o U_o}{2} \qquad (18)$$

and, combining these results yields

$$\langle E \rangle = \frac{I}{c_o} \qquad (19)$$

which is an extremely useful expression in terms of measuring ultrasonic intensity and ultrasonic power with radiation force techniques.

III. DOSIMETRIC CONCEPTS

Dosimetry is the determination of a dose, or similar type of physical quantity, which characterizes the physical agent as to its potential or actual interaction with the biological material of interest. Ultrasonic dosimetry's objective is to relate magnitudes of specific quantities, such as intensity, acoustic pressure, particle displacement, etc., or perhaps some quantity yet to be developed, to the likelihood of occurrence of a biological alteration. To accomplish this, it is necessary (1) to quantify the output quantity or quantities of the source, (2) to determine the effect of the material on the

propagating energy, *viz.*, reflections, refraction, scattering, absorption, etc., and (3) to relate quantitatively the first two items at the site of interest.

Typically, dose connotes something that is given or imparted in a quantitative manner. The history of other radiation forms has documented that defining dose, or dose-like concepts, is difficult, especially when the objective is to include all possible physical and biological variables. More commonly, however, special quantities are developed for the biological action under consideration. In ionizing radiation, for example, dose generally refers to the quantity *absorbed dose* which has been specifically defined as the energy imparted to matter by ionizing radiation per unit mass of irradiated material at the site of interest (ICRU, 1971). But other dose quantities have been defined for specific purposes such as genetically significant dose, cumulative dose, dose equivalent, threshold dose, etc (BEIR, 1972). In photobiology, dose sometimes refers to the quantity *dose of ultraviolet radiation* which has been defined as the energy per unit surface area applied to an object (Rupert, 1974). There has been much discussion regarding microwave dosimetry. Terms such as specific absorption rate, absorbed power density and specific absorption density and energy dose-rate have been used as a basic quantity to describe absorbed electromagnetic energy (Anderson, 1992; Bernhardt, 1992; Grandolfo, 1992; Leonowich, 1992; Sliney, 1992)

IV. SPECIFIC DOSIMETRIC EXAMPLE

For illustrative purposes, it is useful to examine in some detail the history of another radiation form with a view towards its dosimetry development. Ionizing radiation is chosen because it represents a well developed history (Spiers, 1956; Wang and Robbins, 1956; Spiers, 1964; Roesch and Attix, 1968; Taylor, 1971; Bushong, 1973). However, this examination is not meant to indicate that ultrasonic dosimetry should take this route. The mechanisms of interaction between ultrasonic and ionizing radiation are quite different. Rather, the rationale for ionizing radiation dosimetry, as with other radiations, is one of developing an acceptable and reasonable nomenclature by which researchers in various fields can compare results and from which radiation protection guidelines can be developed.

Knowledge of the energy deposition of the tissue site of interest is one of the critical elements in understanding the interaction between the radiation form and matter. One of the earliest ionizing radiation dosimetric concepts was the *skin unit dose*, more commonly known as the *skin erythema dose* or *threshold erythema dose*. One skin unit dose was the amount of ionizing radiation which just produced skin erythema within a period of about one week. The detector, human skin, was very imprecise but the skin unit dose was, nevertheless, used as a basis for the first radiation protection guideline

in the mid 1920's. The *tolerance dose* was suggested to be a small fraction, around one percent, of a skin unit dose, averaged over a one month period.

Not until sensitive and reproducible measurement devices were developed was there a physical measurement of ionizing radiation. The concept and value of the unit *roentgen* (R) was established in 1928 and defined in terms of the ionization, or interaction, of x-ray radiation in air (ICRU, 1928). It was a special unit of exposure but no specific quantity was defined at that time for which the roentgen was its unit.

In an effort to relate the tolerance dose to a physical quantity, radiotherapists were polled as to the number of roentgens required to produce one skin unit dose. Based upon a rough value of 600 R for one skin unit dose, the tolerance dose worked out to be 6 R on a monthly basis, or 0.2 R/day. In the early to mid-1930's national and international organizations endorsed a tolerance dose of 0.2 R/day. Later this value was reduced to 0.1 R/day and remained at this level for 12 years. The term tolerance dose created many problems because it was impossible to predict just what level was tolerable over a long period of time. With the realization in the mid-1930's that ionizing radiation effects may not be threshold type reactions, the term *maximum permissible dose* was substituted for tolerance dose.

As a result of biophysical and biological effect studies with various types (qualities) of ionizing radiation, it was recognized that broader dosimetric concepts were required to define and describe quantitatively ionizing radiation fields. This was especially important when applying dosimetry to radiation protection in that the roentgen was inadequate because of its limitation to x- and γ-rays and because it was not a measure of absorbed energy. In the early 1930's, it was shown that the biological effect of ionizing radiation depended not only upon the exposure intensity and time but also upon the quality of radiation since differences between x-rays and γ-rays were observed in growth reduction and mortality studies (Failla and Henshaw, 1931). This was termed the *relative biological effectiveness* (RBE) concept and became even more important in the 1940's with the production and discovery of other ionizing radiation particles. In terms of the absorbed dose unit rad, which will be discussed shortly, this meant that the same number of rads of neutrons, for example, would produce a greater biological effect as compared x- or γ-rays.

In the late 1930's a unit, termed the *energy unit*, was suggested as dose of γ-rays delivered to tissue in terms of absorbed energy per gram tissue (Gray and Read, 1939). Also, around this time, another unit, the *gram-roentgen*, was suggested (Mayneord, 1940) as the amount of energy absorbed by one gram of air when irradiated to about 1 R. In the late 1940's another unit was suggested to describe energy absorption, *viz.*, the *rep* for *roentgen-equivalent-physical* (Parker, 1948). Originally, one rep was defined as that dose of ionizing radiation which produced an energy absorption of 84 ergs/cm^3 in tissue. It was based upon the roentgen in that this was meant to be the energy absorbed by tissue when exposed to 1 R. That meant that the definition depended upon a calculation of energy absorption and upon other tissue parameters which were subject, in some cases, to wide uncertainty. These difficulties were reflected in redefining one rep from the original value to other values in order to reflect actual tissue absorption properties and to remove dependence of tissue density.

The rep concept led to what is currently the quantity *absorbed dose* with the unit *rad* for radiation absorbed dose. The advantage of the unit rad over the rep was that the one rad was arbitrarily defined as 100 ergs/gm and thus was independent of material properties (ICRU, 1954).

At the same time the rep was being suggested as a unit to describe dose, the unit *rem*, for *roentgen-equivalent-man*, was also being suggested for radiation protection purposes. The rem was defined as the product of energy absorption (in reps) and the relative biological effectiveness (dimensionless) of the energy under consideration. If there were energies of different RBEs, then the rem was the sum of each respective product (Parker, 1948). In the mid-1950's, the rem concept was adopted, using the rad instead of the rep. The quantity *RBE dose* in rems was equal to the product of absorbed dose in rads and the RBE and, in the case of multiple RBEs, the sum of each product (ICRU, 1956).

A few years later, RBE was changed to *quality factor*, QF, and assigned fixed values which were closely representative of actual RBE's for specific conditions and energies. This was done because RBE itself was dependent upon a large number of variables and for radiation protection purposes, the quality factor values chosen were representative of RBEs. Thus, the quantity *dose equivalent* was adopted, its unit the rem, and was equal to the product of absorbed dose, quality factor and other dose modifying factors to account for spatial and temporal dose distribution (ICRU, 1962).

In the history of ionizing radiation dosimetry is reflected the rationale for which national and international commissions have labored to develop concepts and define units and quantities. Initially, the threshold dose was defined as a monthly fraction of the skin unit dose and later, following proper instrumentation development, in terms of an exposure in roentgens. The term threshold dose was later called maximum permissible dose because of the realization that risk from ionizing radiation may not be represented by a threshold. Because of the desire to express the effect of ionizing radiation in terms of the interaction with or absorption by tissue at the site of interest, the absorbed dose concept was defined. Eventually the dose

equivalent quantity evolved to embody both physical and biological quantities.

V. ULTRASOUND DOSIMETRY

By comparison, the field of ultrasonic dosimetry has not developed to the extent of ionizing radiation dosimetry. The most widely used quantity in ultrasonic bioeffect and biophysical studies is intensity in the unit of W/cm^2. The principal reason for the use of intensity is, perhaps, convenience since it is understood how it's measured (Lewin, 1992). However, intensity represents many of the same problems as does the ionizing radiation quantity "exposure" in that it is not a measure of dose. Yet the majority of bioeffect and biophysical reports use intensity as the measured physical quantity of the ultrasonic field. This extensive literature documents the actions of ultrasound but, in most cases, lacks the necessary characterization of the field at the site of interest. An ideal situation would be to know the instantaneous particle velocity, the instantaneous acoustic pressure and the phase between these two field parameters at the site or sites of interest (O'Brien et al, 1972; O'Brien, 1978; O'Brien, 1986).

There have been three ultrasonic dosimetric quantities which are noteworthy of comment in that they represent, in concept, the basic approach to dosimetry. The *cataract-producing unit*, CPU, was a quantity defined as the length of exposure necessary to produce a grossly observable cataract and expressed in units of seconds (Purnell et al, 1964). The dosimetric concept *damage ability index* with the unit second is a quantity intended to describe the effect of ultrasound on spinal cord hemorrhage (Taylor and Pond, 1972). It has been suggested (Johnston and Dunn, 1976) that a universal dosimetric response to ultrasonic exposure may exist for different tissues but the response has only been demonstrated, in a limited manner, in mammalian brain tissue. The response is in terms of *energy absorbed per unit volume* for histologically observable lesions at superthreshold levels as a function of the *delivered intensity*. It is shown that at two different ultrasonic frequencies, 3 and 4 MHz, identical constant volume curves result even though there are two different threshold levels (Dunn and Fry, 1971).

In another category of ultrasonic dosimetric studies, *in utero* ultrasonic intensity in both the gravid and nongravid human uterus have been estimated (summarized in Stewart and Stratmeyer (1982) and NCRP (1983)). In these early studies, a model of the tissue layers between the skin surface and fetal sac yielded a total attenuation in the range of 2 - 20 dB at frequencies between 2 and 5 MHz. The distances between the abdominal surface and the uterine cavity in early pregnancy ranged between 2 and 11 cm. In more recent work (Carson et al, 1989), similar distances were estimated to be 2.6

cm.

In very recent work wherein direct *in utero* intensity measurements were made (Daft et al, 1990; Siddiqi et al, 1991), the average attenuation was reported to be 6.2 ± 3.5 dB under full bladder conditions and 7.3 ± 4.9 dB under empty bladder conditions. Applying the fixed-attenuation tissue model (attenuation dependent upon frequency and independent of distance), and normalizing to the center frequency of 2.4 MHz, the attenuation coefficient was estimated to be 2.56 ± 1.47 dB/MHz for the full bladder condition whereas, with the overlying tissue model (attenuation dependent upon frequency and non-fluid distance), the attenuation coefficients were estimated to be 0.89 ± 0.71 dB/cm-MHz and 0.45 ± 0.32 dB/cm-MHz, respectively, for full and empty bladder conditions. The mean values for the fixed-attenuation tissue model's attenuation coefficient were about a factor of 3 greater than the values proposed to model the attenuation coefficient by Carson et al. (1989). FDA's Center for Devices and Radiological Health uses a value of 0.3 dB/cm-MHz as a derating factor for manufacturers in their 510(k) process to estimate ultrasonic intensity quantities in tissue (FDA, 1985; Harris, 1992). The measured mean values for the overlying tissue model's attenuation coefficient were a factor of 2 to 3 greater than the values used by FDA suggesting that FDA's values error on the side of safety.

In general, it is necessary to determine a firm data base from which various dosimetric modeling approaches can be explored. In one approach (Carson et al, 1989), a worst-case approach was employed to overestimate safety whereas, in another approach (Siddiqi et al, 1991), the mean values of the results and their distributions were reported so that the scientific community could make the appropriate safety judgements.

VI. ULTRASOUND DOSIMETRY RELEVANCE

Ultrasonic biological effect studies and biophysical research have shown that ultrasound can produce changes in living systems. The AIUM/NEMA Ultrasound Safety Standard for Diagnostic Ultrasound Equipment (AIUM/NEMA, 1983) and AIUM Acoustic Output Measurement and Labeling Standard for Diagnostic Ultrasound Equipment (AIUM, 1992) labeling requirements were based on the philosophy that there is a possible risk from diagnostic ultrasound exposure. The specific labeling requirements of these and other (Harris, 1992) safety standards were selected to include those quantities whose magnitudes are known or believed to be related to actual damage or to risk of damage to biological tissues as a result of ultrasonic irradiation. The Food and Drug Administration's 510(k) premarket notification requirements (FDA, 1985) have a similar basis, owing to the FDA's requirement to determine the safety and effectiveness of ultrasound

equipment.

The basis for this rationale lies in an understanding of the mechanisms by which it is known that ultrasound can affect living systems. Such knowledge comes from fundamental laboratory studies (O'Brien, 1984; O'Brien and Withrow, 1985; O'Brien, 1991). These mechanisms can be classified and discussed in terms of whether heat is or is not believed to be the principal cause for the biological effect. The applicable ultrasonic exposure quantities will be identified during the course of this discussion. Both thermal and nonthermal mechanisms will be considered.

VII. THERMAL MECHANISM

Whenever ultrasonic energy is propagated into an attenuating material such as tissue, the amplitude of the wave decreases with distance. This attenuation is due to either *absorption* or *scattering*. Absorption is a mechanism that represents that portion of the wave energy that is converted into heat, and scattering can be thought of as that portion which changes direction. Since the medium can absorb energy to produce heat, a temperature rise may occur as long as the rate at which heat is produced is greater than the rate at which the heat is removed. In tissue, at the site where the ultrasonic temporal average intensity is I_{TA}, the average rate of heat generation per unit volume per unit time is given by the expression (Nyborg, 1981; Cavicchi and O'Brien, 1984)

$$Q = 2\alpha I_{TA} = \frac{\alpha p p^*}{\rho c} \qquad (20)$$

where

$$I_{TA} = \frac{p p^*}{2\rho c} \qquad (21)$$

where α is the ultrasonic amplitude absorption coefficient which increases with increasing frequency, p and p* are the instantaneous ultrasonic pressure and its complex conjugate, respectively, ρ is density and c is sound speed. The product of p and p* in Eq 21 is equal to the ultrasonic pressure amplitude (see Eq 2d) square, p_o^2, at the specific location in the medium where Q is determined and can be thought of as a temporal average quantity.

The temporal average intensity is not necessarily at the location where it is maximized, that is, at the spatial peak location. If it were, however, then the I_{TA} in Eq 21 would be I_{SPTA}, which would maximize Q for that tissue site. AIUM's Statement on Mammalian *In Vivo* Ultrasonic Biological Effects (see Table 3), sometimes referred to as the *100 mW/cm²*

Statement, is a generalization about the state-of-affairs with respect to an intensity (in terms of I_{SPTA})-time limit below which there have been no independently confirmed significant biological effects in mammalian tissues (AIUM, 1988).

TABLE 3

AIUM Statement on Mammalian *In Vivo* Biological Effects (AIUM, 1988)
(Approved August, 1976. Revised and approved October, 1987)

A review of bioeffects data supports the following statement:

In the low megahertz frequency range there have been (as of this date) no independently confirmed significant biological effects in mammalian tissues exposed *in vivo* to unfocused ultrasound with intensities[a] below 100 mW/cm², or to focused[b] ultrasound with intensities below 1 W/cm². Furthermore, for exposure times[c] greater than one second and less than 500 seconds for unfocused ultrasound, or 50 seconds for focused ultrasound such effects have not been demonstrated even at higher intensities, when the product of intensity and exposure time is less than 50 joules/cm².

[a] Free-field spatial peak, temporal average (SPTA) for continuous wave exposures, and for pulsed-mode exposures with pulses repeated at frequencies greater than 100 Hz.

[b] Quarter-power (-6 dB) beam width smaller than four wavelengths or 4 mm, whichever is less at the exposure frequency.

[c] Total time including off-time as well as on-time for repeated pulse exposures.

For a given I_{TA}, the maximum temperature rise, ΔT_{max}, under the assumption that no heat is lost by conduction, convection, or any other heat removal processes, is approximately described by

$$\Delta T_{max} = \frac{Q\Delta t}{C_h} \qquad (22)$$

where Δt is the time duration of exposure and C_h is the medium's specific heat. This formula is valid only for short exposure times; for longer times,

heat removal processes become significant. Nonetheless, as a "ballpark estimate," using the intensities from the *AIUM Statement* in Table 3 of $I_{SPTA} = 0.1$ and 1 W/cm^2 at an ultrasonic frequency of 5 MHz, from Eq 20, Q = 0.05 and 0.5 J/cm^3-s ($\alpha \approx 0.25$/cm at 5 MHz). Since the thermal properties of biological tissue can be approximated by water (C_h = 4.18 J/cm^3-C), the maximum time rate of change of temperatures, from Eq 22, are

$$\frac{\Delta T_{max}}{\Delta t} = 0.012 \text{ and } 0.12 \text{ °C/s} \qquad (23)$$

which means that for a 1 second exposure, ΔT_{max} would be about 0.012 and 0.12 °C. If the exposure duration were longer than 1 second, the temperature would continue to rise but at a progressively slower rate, until the rate of heat generation was about the same as the rate of heat removal.

To estimate the temperature rise from a single pulse for clinical, diagnostic pulse-echo instrumentation, the local intensity of Eq 20 is considered to be the spatial peak value averaged over the duration of the pulse, that is, the spatial peak, pulse average intensity, I_{SPPA}. For typical instrumentation, a maximum value of I_{SPPA} may be as high as 500 W/cm^2. Thus, the maximum time rate of change of temperature is

$$\frac{\Delta T_{max}}{\Delta t} = 60 \text{ °C/s} \qquad (24)$$

but with the duration of the pulse, Δt, of approximately 2 μs, the maximum temperature rise, $\Delta T_{max} \approx 120$ μ°C.

There have been several studies to calculate the temperature rise in mammalian tissue from ultrasonic exposure and some of them have shown to compare favorably with experimental results (Pond, 1970; Robinson and Lele, 1972; Lerner et al, 1973; NCRP, 1984; FDA, 1985; Nyborg and Steele, 1983; Cavicchi and O'Brien, 1985; AIUM, 1988). These demonstrate that selected aspects of the theory are reasonably well understood. But there are still many unanswered concerns in terms of being able to assess *in vivo* temperature rise.

VIII. NONTHERMAL MECHANISMS

The nonthermal mechanism that has received the most attention is acoustically generated cavitation. Cavitation, in a broad sense, refers to ultrasonically induced activity occurring in a liquid or liquidlike solid material that contains bubbles or pockets containing gas or vapor. These

bubbles originate within materials at locations termed "nucleation sites," the exact nature and source of which are not well understood in a complex medium such as tissue. Cavitation can affect a biological system by virtue of a temperature rise, a mechanical stress, and/or free radical production. Even so, this is traditionally referred to as a nonthermal mechanism.

The discussion of cavitation will be less precise than that of the thermal mechanism owing to the fact that it has not been documented that cavitation occurs in biological tissue from diagnostic-like exposure conditions, whereas it is known that ultrasound can increase the temperature of tissue. So, in one sense, research continues to determine whether cavitation is a mechanism that needs to be addressed from the aspect of diagnostic, imaging equipment. In another sense, it is known that cavitation does occur in tissue at excessively high intensity levels and in "model systems" at quite low intensity levels. Excellent reviews of cavitation have been published (NCRP, 1984; Flynn, 1964; Nyborg, 1965; Nyborg, 1975; Coakley and Nyborg, 1978; Apfel, 1981; Flynn, 1982).

Cavitation can be discussed in two general categories termed transient cavitation and stable cavitation (Flynn, 1964). Transient cavitation connotes a relatively violent activity (bubble collapse) in which "hot spots" of high temperature and pressure occur in very short (of the order of microseconds) bursts at points in the sonicated medium. These bursts may be accompanied by localized shock waves and/or by the generation of highly reactive chemical species.

In contrast, a much less violent form is stable cavitation, which is associated with vibrating gaseous bodies. The nature of this form of cavitation consists of a micron-size gaseous body (at diagnostic ultrasonic frequencies) that remains spatially stabilized within but not necessarily because of the ultrasound field and, because of the ultrasound field, oscillates or pulsates. When such volumetric oscillations are established, the liquid-like medium immediately adjacent to the gas bubble flows or streams (termed microstreaming) (Nyborg, 1965). Microstreaming has been shown to produce stresses sufficient to disrupt cell membranes.

The occurrence of cavitation, and its behavior, depends on many factors, including: the ultrasonic pressure; whether the ultrasonic field is focused or unfocused, or pulsed or continuous; to what degree there are standing waves (i.e., energy reflecting back onto itself); and the nature and state of the material and its boundaries. Experimentally, since cavitation would probably affect only a single or a few cells, it would be extremely difficult to detect an adverse biological effect, unless the cavitation events were widespread among a large volume of tissue. The latter has been shown to be the case when mammalian nervous system tissue was exposed to ultrasonic levels in

excess of I_{SPTP} of 1000 W/cm^2 for a duration of at least 1 ms; these conditions are outside of the diagnostic equipment range (Dunn and Fry, 1971).

A theory has recently been put forth that results in a derived formula that predicts the conditions that will produce transient ultrasonic cavitation on a scale of a single biological cell in one ultrasonic cycle (Apfel, 1986). For sufficiently high material viscosity, a threshold pressure, p_{th}, is proportional to ultrasonic frequency, the material's viscosity, and reciprocal ambient pressure. The p_{th} quantity is the peak rarefactional pressure, p_r, quantity. This approximate analytic expression agreed reasonably well with another acoustic cavitation theory calculation (Flynn, 1982) that predicted that microsecond pulses could cause cavitation nuclei, that is, gas bubbles.

An experimental study showed evidence for cavitation from microsecond pulses of ultrasound (Carmichael et al, 1986) that qualitatively agreed with earlier theoretical predictions of Flynn (1982). Aqueous solutions were exposed to short ultrasonic pulses (approximately 6 to 20 μs) and •OH radicals and •H atoms were detected by spin trapping and electron spin resonance. These findings were ultrasonically quantified with the I_m, which is believed to be an estimator of the maximum ultrasonic pressures, either p_r or p_c.

There has been no experimental evidence to suggest that cavitation occurs in mammalian parenchymal tissue from exposure-like conditions employed with diagnostic ultrasound equipment (Apfel and Holland, 1991). However, there have been some theoretical studies that suggest that under precise conditions, cavitation may be induced by microsecond-type pulses of ultrasound (Flynn, 1982). The comments here have shown that in terms of assessing the potential for cavitation and a mechanism responsible for producing a biological effect, the important exposure quantities seem to relate to the instantaneous, and, specifically, the maximum ultrasonic pressure only.

But, there has been a suggestion that some type of ultrasonically-induded bubble activity induces lung damage in mice. Child et al. (1990) have observed an approximate ultrasonic pressure threshold for lung damage in mice of 0.8 MPa at 1 MHz. The observations of Child et al (1991) are in good agreement with the frequency dependent, *in vitro* cavitation experiments of Apfel and Holland (1991).

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