Biological Effects of Ultrasound: Rationale for the Measurement of Selected Ultrasonic Output Quantities

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Research into the biological effects of ultrasound is a two-edged sword. On the one hand, there is the potential to show that some of the current clinical practices with diagnostic ultrasound may be more risky than previously thought. If so, clinical practice with ultrasound may have to be modified based upon a reassessment of its risk. On the other hand, such research could identify potential benefits in terms of therapeutic applications of ultrasound. In either case, the care provided to patients with ultrasound would have been improved, although the short-term impact of a newly identified ultrasonically induced biological effect might tend to affect adversely the diagnostic side.

There has been a considerable amount of research into how ultrasound affects developmental tissue because a large fraction of all pregnant women have their fetuses examined with ultrasound. In fact, virtually all of the biological effect literature has been carefully evaluated in terms of assessing the risk from ultrasound on the fetus. It is encouraging that the risk to the fetus is viewed as a "potential risk." Little, if any, examination of this literature has been brought to bear on assessing the potential risk of ultrasonic energy on nondevelopmental tissue.

In the past six years, there have been so many reviews of ultrasonically induced biological effects that it is not possible to duplicate this effort in this article. Further, these extensive reviews provide a comprehensive bibliography for anyone who desires to study this topic in greater depth than will be provided here.

This review will examine the relationship between the ultrasonic output quantities of current diagnostic ultrasound imaging equipment and the biological basis for such measurements. Specifically, the basis for measuring specific exposure quantities lies in the fundamental mechanisms responsible for causing biological alterations to living systems.

History and Perspective

Diagnostic medicine has generated an enormity of clinical experience with ultrasound. During this time, it is extremely encouraging that no deleterious clinical effects have been reported. However, one must not conclude from this experiential data base that ultrasound can be thought of as safe. There is no substitute for carefully derived scientific findings. One only needs to examine the history of ionizing radiation and other chemical and physical agents to realize that many subtle effects would not have been discovered without comprehensive experimental studies using animals. Thus, comprehensive animal laboratory studies must be an essential part of the determination of permissible dosage levels for the various medical applications of ultrasound.

Some 35 years after the 1880 discovery of piezoelectricity by the Curies,[1] the French scientist Paul Langevin developed one of the first uses of ultrasound for underwater sound ranging of submerged objects. Langevin was, perhaps, the first to report the observation that ultrasonic energy could have a detrimental effect upon biological material, that is, on small aquatic animals.[2-4] Another decade passed before a more detailed, ex-

This work supported in part by grants CA 36029, CA 09067, and HD 18877 from the US National Institutes of Health.

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perimental study was conducted[5] to investigate Langevin's observation. Although the ultrasonic levels were not specified, the experimental study showed that ultrasonic energy could kill small fishes and frogs by a one- to two-minute exposure.

In the earliest review paper on this subject, Harvey[6] reported on the physical, chemical, and biological effects of ultrasound in which alterations were produced in macromolecules, microorganisms, cells, isolated cells, bacteria, tissues, and organs with a view towards the identification of the interaction mechanisms. The ultrasonic exposure conditions of these early works were neither well characterized nor reported, but the exposure levels were undoubtedly high.

While the dosimetry was inferior to that possible today, these early studies clearly demonstrated that ultrasound, at sufficient levels, could easily destroy biological material. From the earliest considerations that ultrasound might be a feasible energy source for producing images of the human body, it was already known that high ultrasonic energy levels might be hazardous. This information must be kept in mind because many of the early pioneering engineers who were designing ultrasound imaging devices were also cognizant that ultrasound had the potential for disrupting biological materials. Additionally, they were aware of the history of ionizing radiation effects. Thus, there has been a continuing concern of the risk from ultrasound prior to and during the entire period of diagnostic instrumentation development.

Contemporary Reviews

There is an extensive literature that supports the view that ultrasonic energy can produce gross effects on biological materials. There is an equally extensive literature that has reviewed the original articles and, to some extent, has reviewed the reviews. The bulk of this literature has focused attention on assessing the risk from ultrasound on the fetus. Even so, there is value in commenting on this selected literature for it has shaped our current thinking about possible risks posed by ultrasound.

Perhaps the first major symposium on "Ultrasound in Biology and Medicine" was held at the University of Illinois in May, 1952 to examine phenomena of how ultrasonic energy interacted with and acted upon biological materials. Of the eight papers presented, six were published and dealt with the effects of high-intensity ultrasound[7–9] or the thermal mechanism of ultrasound.[10–12] Two additional symposia were held (June, 1955; June, 1962) to address similar issues. Their records were published in two books.[13–14] This literature laid the basic foundation for the mechanisms by which ultrasound is known to affect biological materials, viz., thermal phenomena and cavitation.

One of the earliest, comprehensive examinations of the causes and effects of ultrasonically induced biological effects was conducted at the 1972 Workshop on the Interaction of Ultrasound and Biological Tissues, which resulted in a thorough document dealing with virtually all aspects of how ultrasound interacts with and affects biological materials in fluids, cells, and tissues and organs.[15] One of the critical problems identified during the workshop was the need to establish safe exposure limits. Additionally, a series of "recommended actions" were proposed, which the workshop participants believed would serve as a guide for further research on the issue of ultrasonic safety. Even today, this workshop document is an extremely valuable resource.

Since then, there have been numerous reviews and assessments, which are listed in Table I. A common conclusion reached in all of these documents is that the studies necessary to support a reliable assessment of risk have not been completed. Rather than again review the ultrasonic biological effect literature, the reader is referred to one of the many more recent reviews listed in Table I.

There are, however, three documents that have been developed within the last several years by expert groups that are worthy of note. They would be an important starting point for individuals who would like to pursue this literature individually. In 1981, the Geneva office of the World Health Organization produced a criteria document[16] that addressed the issue of risk from ultrasound. The basis of the WHO document came from a merging and expert evaluation of two separate reviews, one generated by the US Food and Drug Administration[17] and the other by the Canadian Department of Health and Welfare;[18–19] both agen-

TABLE I

Major Compilations and Reviews of the Ultrasonic Bioeffect Literature

Ulrich WD: Ultrasound dosage for nontherapeutic use on human beings—extrapolation from a literature survey. *IEEE Transactions on Biomedical Engineering* BME-21:48, 1974.

Wells PNT: The Possibility of harmful biological effects in ultrasonic diagnosis. In RS Reneman (Ed): *Cardiovascular Applications of Ultrasound.* New York, American Elsevier, 1974, pp. 1–17.

Dunn F, O'Brien WD Jr: *Ultrasonic Biophysics.* Stroudsburg, PA, Dowden, Hutchinson and Ross, Inc., 1976.

Hazzard DG, Litz ML (Eds): *Symposium on Biological Effects and Characterizations of Ultrasound Sources.* HEW Publication (FDA) 78-8048. Washington DC, US Government Printing Office, 1977.

O'Brien WD Jr: Safety of ultrasound. In M deVlieger et al (Eds): *Clinical Handbook of Ultrasound.* New York, Wiley, 1978, pp. 99–108.

Lele PP: Safety and potential hazards in the current applications of ultrasound in obstetrics and gynecology. *Ultrasound Med Biol* 5:307, 1979.

Fry FJ: Biological effects of ultrasound—A review. *Proceedings of the IEEE* 67:604, 1979.

Repacholi MH, Benwell DA (Eds): *Ultrasound Short Course Transactions.* Ottawa, Canada, Radiation Protection Division, Health Protection Branch, Canadian National Health and Welfare, 1979.

O'Brien WD Jr: Biological Effects of Ultrasound. In GD Fullerton, JA Zagzebski (Eds): *Medical Physics of CT and Ultrasound: Tissue Imaging and Characterization.* AAPM Medical Physics Monograph No. 6. New York, American Institute of Physics, 1980, pp. 578–615.

Carstensen EL: Biological effects of low-temporal, average-intensity pulsed ultrasound. *Bioelectromagnetics* 3:147, 1982.

Hill CR, ter Haar G: Ultrasound. In MJ Suess (Ed): *Nonionizing Radiation Protection.* Copenhagen, World Health Organization Regional Publications, European Series No. 10, 1982, pp. 199–228.

Dunn F, Frizzell LA: Bioeffects of ultrasound. In JF Lehman (ed): *Therapeutic Heat and Cold.* Baltimore, Williams and Wilkins, 1982, pp. 386–403.

Repacholi MH, Benwell DA (Eds): *Essentials of Medical Ultrasound.* Clifton, NJ, The Humana Press, Inc., 1982.

Williams AR: *Ultrasound: Biological Effects and Potential Hazards.* New York, Academic Press, 1983.

Sarvazyan AP: Some general problems of biological action of ultrasound. *IEEE Transactions on Sonics and Ultrasonics* SU-30: 2, 1983.

Lizzi FL, Coleman DJ, Driller J, et al: Ultrasonic hyperthermia for ophthalmic therapy. *IEEE Transactions on Sonics and Ultrasonics* SU-31:473, 1984.

O'Brien WD Jr.: Ultrasonic bioeffects: A view of experimental studies. *Birth* 11:149, 1984.

Petitti DB: Effects of *in utero* ultrasound exposure in humans. *Birth* 11:159, 1984.

Nyborg WL: Optimization of exposure conditions for medical ultrasound. *Ultrasound Med Biol* 11:245, 1985.

Nyborg WL, Ziskin MC (Eds): *Biological Effects of Ultrasound. Clinics in Diagnostic Ultrasound 16.* New York, Churchill Livingstone, 1985.

Stratmeyer ME, Lizzi FL (Eds): Special issue on the biological effects of ultrasound (16 papers). *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control* UFFC-33:137, 1986.

cies have regulatory authority in their respective countries. These documents provide an extensive catalog of biological effects and mechanisms. Further, they list safety recommendations (not enforceable requirements), which include labeling requirements, upper intensity limits, and exposure timers.

The second document was developed through the US National Institutes of Health consensus development conference processes[20] by convening an expert panel of physicians, basic scientists, epidemiologists, nurses, educators, and sonographers to provide answers to the following questions:

1. What types of ultrasound scanning are currently used in obstetric practice? How extensive is this use? What is known about the dose/exposure to the fetus and the mother from each type?
2. For what purposes is ultrasound now used in pregnancy? For each use, what is the evidence that ultrasound improves patient management and/or outcome of pregnancy?
3. What are the theoretical risks of ultrasound to the fetus and the mother? What evidence exists from animal, tissue culture, and human studies on the actual extent of the risk?
4. Based on the available evidence, what are the

appropriate indications for, and limitations on, the use of ultrasound in obstetrics today?
5. What further studies are needed of efficacy and safety of use of ultrasound in pregnancy?

The document indicated that the increasing use of ultrasound during pregnancy is safe and effective for 28 medical conditions. This was, perhaps, the first time that the issue of effectiveness of diagnostic ultrasound was critically reviewed. Further, it was suggested that while diagnostic ultrasound does not appear to be associated with any known hazards, investigators should continue to evaluate risks. Understanding how ultrasound and tissue interact is necessary to appreciate the effect of ultrasound on tissue (for risk assessment) and of tissue on ultrasound (for image details).

The third document, developed under the auspices of the National Council on Radiation Protection and Measurements (NCRP), which traditionally had concentrated its efforts on ionizing radiation issues, has expanded its efforts into the area of nonionizing radiation.[21] The document rigorously covers the basic physics of ultrasound with an emphasis on medical ultrasound fields and on the quantification of various ultrasonic field quantities to which humans are exposed during the course of an ultrasound examination. Also included are mechanisms by which ultrasound interacts with biological material and effects caused by ultrasound on biological materials such as plants, animals, and in vitro systems, the latter is considered quite thoroughly. Finally, this document sets forth a number of recommendations that fall into the categories of research needs, industrial practices, education, and exposure criteria. It is interesting that a number of the recommendations are consistent with those put forth by the Workshop on the Interaction of Ultrasound and Biological Tissues[15] a decade earlier.

Labeling Requirement Basis

In the early to mid 1970s, there was great uncertainty with respect to the safety of ultrasound (there were serious questions about whether ultrasound affected genetic material—the initial reports were subsequently shown to be incorrect) and what authority and role the US Food and Drug Administration would take in terms of regulating diagnostic ultrasound (e.g., would there be upper intensity limits that such equipment could not exceed). There was apprehension among the public, patients, physicians, sonographers, basic scientists, manufacturers, and the government. One of the fundamental difficulties was the lack of an accurate (closeness to the true value) and precise (reproducible) procedure to quantify the output from diagnostic ultrasound equipment. Such measurements were, and still are, extremely difficult to make. Because of these difficulties, the output levels from diagnostic ultrasound equipment were not well known, and human exposure levels could not be compared to results of laboratory experimental studies.

In response to this uncertainty and the lack of a suitable measurement scheme, the American Institute of Ultrasound in Medicine (AIUM), a medical and scientific professional society, and the National Electrical Manufacturers Association (NEMA), a trade organization that represents many of the ultrasound manufacturers, joined efforts in 1976 to develop a standard that would assure that sufficient information on the characteristics of diagnostic ultrasound equipment was supplied to allow medical personnel to make informed judgments regarding the application of this equipment to patients. The AIUM/NEMA Safety Standard for Diagnostic Ultrasound Equipment[22] was developed over a five-year period and sets forth precise definitions of quantities relating to ultrasonic output levels. Specifically, the standard relates only to those characteristics of ultrasound equipment that pertain to patient exposure and safety. As such, this voluntary standard calls for manufacturers to make available, through labeling requirements, the maximum values of the following ultrasonic quantities: ultrasonic power; spatial peak, temporal average intensity (I_{spta}); and spatial peak, pulse average intensity (I_{sppa}).

The US Food and Drug Administration requires manufacturers and importers to report to them the output of ultrasonic diagnostic equipment before that equipment is introduced into interstate commerce.[23] Such a report is termed "the 510(k) premarket notification" and results from the Medical Device Amendments to the Food, Drug and Cosmetic Act, which the FDA

enforces. This notification is used by the FDA to determine if the new devices are substantially equivalent, in safety and effectiveness, to diagnostic ultrasound devices on the market prior to May 28, 1976, when the Medical Device Amendments were enacted. The 510(k) guidelines for reporting this information are quite detailed and call for reporting the maximum values of the following ultrasonic quantities: ultrasonic power; spatial peak, temporal average intensity (I_{spta}); spatial peak, pulse average intensity (I_{sppa}); and spatial peak, maximum intensity (I_m).

The rationale for specifying these particular ultrasonic quantities is related to their potential for producing biological effects. This fact in no way signals that diagnostic equipment produces biological effects. Instead, these ultrasonic quantities are those most often reported in the basic science literature to relate the strength of ultrasound to the production of biological effects in laboratory experimental studies. What follows is an exploration of the rationale for specifying these ultrasonic quantities by considering how they are believed to relate to biological effects or to a cause, or mechanism, underlying biological effects. To explain these topics requires a brief discussion of the nature of diagnostic ultrasound fields. With this background, a discussion of mechanisms associated with these specific ultrasonic quantities will be more meaningful.

Nature of Diagnostic Ultrasonic Fields

Sound is a form of acoustic or mechanical energy. It is *not* radio waves, or microwaves, or X-rays. Sound is classified as infrasound, audible sound, or ultrasound, depending on its rapidity of vibration, or frequency. In the audible range, frequency is associated with that characteristic called pitch. Audible sound has an approximate and somewhat arbitrary range of frequencies (due to human hearing variability) from 20–100 hertz (Hz) or cycles per second at the lower end to 15,000–20,000 Hz (15–20 kHz, for kilohertz) at the upper end. Infrasound has frequencies less than those of audible sound, and ultrasound has frequencies greater than those of audible sound.

The ultrasound frequencies used in diagnostic medicine are more than 50 times higher than the highest audible sound frequency so it is not possible to hear these sounds. These frequencies are in the 1 to 10 MHz (megahertz for a million hertz) range. Such high frequencies are necessary to obtain a very detailed, or high resolution, image.

Resolution is related to wavelength and, in practice, resolution is about twice the wavelength; as the frequency increases, the wavelength decreases. The smaller the wavelength, the smaller the object that can be imaged. For example, at an ultrasonic frequency of 1 MHz, the wavelength is about 1.5 mm, while at 10 MHz it is only 0.15 mm. Hence, there is a trend to push the ultrasonic frequency higher to obtain a more detailed image. However, there is an opposing phenomenon at work, that is, ultrasonic attenuation, or loss of acoustic energy, which increases as frequency increases. Attenuation will be discussed in conjunction with thermal mechanisms below. But the importance of this interrelation between resolution and attenuation is the demand to obtain better resolution images while maintaining the capability to image to the same depth. To accomplish this penetration at the high frequencies needed for fine resolution, the transmitted ultrasonic signal has to be increased in amplitude to counteract the increase in attenuation. How high can the ultrasound amplitude be increased before undesirable biological effects occur? Currently, the answer to this important question is not known!

Another quantity that affects resolution is pulse duration (the time duration that the pulse is on). Diagnostic ultrasound equipment transmits repeated pulses of ultrasound. After each pulse is transmitted, there is a listening period during which time these pulses are reflected and scattered off of structures within the body. This is schematically depicted in Figure 1 where the distance between the source and the reflector is noted as x_1. The time between when the pulse is transmitted from and received by the transducer is noted at T_1. Some of this reflected and scattered energy comes back to and is detected by the ultrasonic transducer and is eventually processed into an image. The received signal has a much lower amplitude than that of the transmitted signal. The narrower the pulse, the better the resolution along the direction that the pulse traveled, that is, better axial resolution. Typical pulse du-

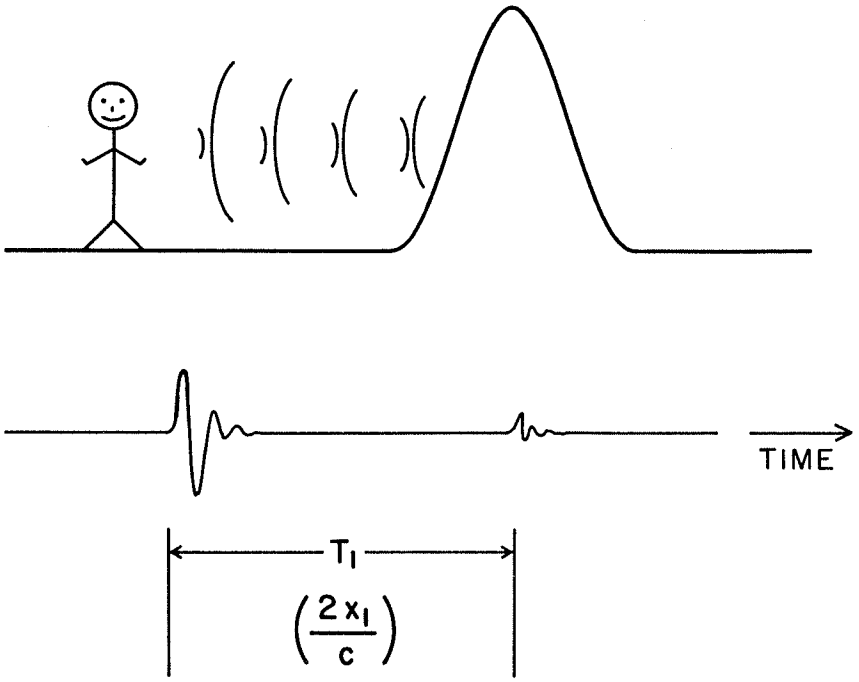

Figure 1. *Schematic representation of an ultrasonic pulse that is transmitted from and received by the ultrasonic transducer. T_1 represents the time between transmission and reception and equals the round trip distance ($2x_1$) divided by the ultrasound speed (c).*

rations are around 1 microsecond with about 1 millisecond (1,000 microseconds) of listening time (or pulse repetition period) before the next pulse is transmitted. The reciprocal of pulse repetition period (PRP) is pulse repetition frequency (PRF) and is typically 1 kHz (but ranges up to 7 kHz for some imaging systems).[24] The ratio of the pulse duration to the pulse repetition period is called the duty cycle (the fraction of time that the ultrasound is on) and is typically about 0.001.

Pulsed-Doppler systems employ a much greater PRF (up to 30 kHz) in order to satisfy certain sampling criteria so that a useful signal is obtained. Hence, the duty cycle is much greater, which causes higher values for some of the intensity quantities.

The transmitted signal should have a high amplitude (for better depth of penetration) and a small pulse duration (for better axial resolution). Both high amplitude and small pulse duration contribute directly to increased difficulties of accurately and precisely measuring the output from diagnostic ultrasound equipment. These engineering and measurement trade-offs are outside the scope of this paper and are addressed elsewhere.[22] However, they contribute to some of the measurement uncertainty and, thus, to why manufacturers are somewhat reluctant to make available their measured output level. Quantities reported by different manufacturers do not necessarily represent the same thing. The minimization of these uncertainties through a unified measurement process (a standard such as the Safety Standard for Diagnostic Ultrasound Equipment[22]) has contributed to more meaningful quantification of output levels so that the same quantities reported by different manufacturers have comparable meaning.

The concepts presented in this section are important to the understanding of ultrasonic fields of clinical, diagnostic equipment. The quantities whose magnitudes define the output characteristics of diagnostic ultrasonic equipment will now be introduced in a more rigorous fashion. Then,

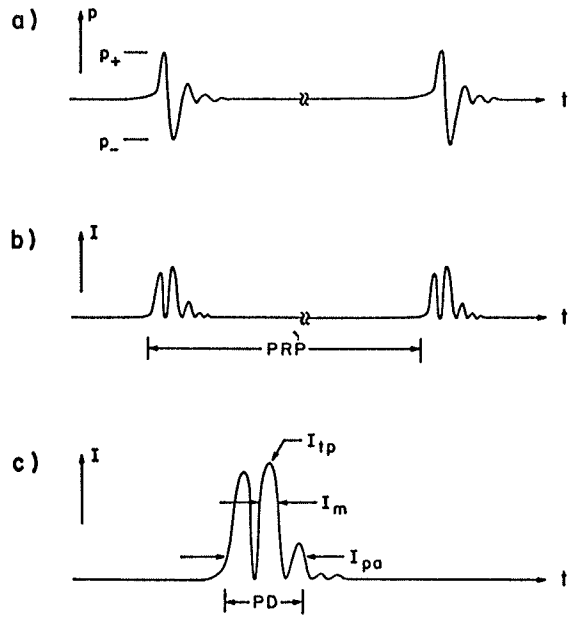

Figure 2. *Temporal representation of an ultrasonic signal in terms of its pressure (a) and intensity (b,c). The maximum positive (p_+) and maximum negative (p_-) ultrasonic pressures are indicated. The pulse repetition period (PRP) is the time between the same position on two adjacent pulses. The details of a single ultrasonic intensity pulse show the pulse duration (PD), the temporal peak intensity (I_{tp}), the maximum intensity (I_m), and the pulse average intensity (I_{pa}).*

the basis underlying the choice of the above ultrasonic quantities will be discussed in the context of their risk assessment role.

Pressure, Power, Energy, and Intensity

Acoustic pressure, p, is the fundamental quantity with respect to describing the propagation of an ultrasonic wave. By analogy, pressure is to acoustics as voltage is to electricity. When an ultrasonic pulse is transmitted into tissue, a pressure disturbance is propagated, and this pressure disturbance travels at the speed of sound, typically 1,540 m/s in tissue. Pressure is force per unit area so its unit is the newton (N), a force, per meter squared (m^2), an area. Another unit of pressure is the pascal (Pa). One Pa is equal to one N/m^2. A more common unit for pressure is the atmosphere (atm). One atm is equal to approximately 10^5 Pa.

Acoustic pressure varies with time. If an ultrasonic pressure detector, a hydrophone, were placed in water in the path of an ultrasonic pulse, the detected ultrasonic pulse would show changes with time like that shown in Figure 2; the maximum pressure at any point is denoted by the symbol p_+ and the minimum pressure by p_-. The maximum and minimum ultrasonic pressure values (denoted $p_{+/-}$ in Table II) are typically up to 50 atm.

The propagated ultrasonic pulse transports ultrasonic energy. Energy, the product of power (in watts) and time (in seconds), which has the unit of joule, is the capacity to perform work. Ultrasonic energy is required to produce an image and to cause a biological effect. Ultrasonic power is a measure of the rate of work being done by an

TABLE II

Summary of the Maximum Ultrasonic Output Quantities for Diagnostic Ultrasonic Equipment*

Equipment Type	W (mW)	I_{sata} (mW/cm^2)	I_{sppa} (W/cm^2)	I_m (W/cm^2)	$p_{+/-}$ (atm)
Manual Compound Scanners	20	200	300	700	50
M-Mode	75	225	700	300	30
Auto-sector Scanners	50	30	200	250	30
Sequential Linear Array Scanners	55	10	200	100	20
CW Doppler—Obstetrics	40	80			
Pulsed Doppler—Cardiac	70	1900	100		
Pulsed Doppler—Peripheral Vascular	10	700	12		

* Ultrasonic power (W); spatial peak, temporal average intensity (I_{spta}); and spatial peak, pulse average intensity (I_{sppa}) maximum values were summarized from [24] and maximum intensity (I_m) and maximum/minimum ultrasonic pressures ($p_{+/-}$) maximum values were summarized from [21].

ultrasonic field. Power describes the potential for the ultrasonic field to interact with the medium in which it is propagating. Maximum values of ultrasonic power from diagnostic equipment are typically in the tens of milliwatts (see Table II).

The quantity most often used to describe the strength of the ultrasonic field is intensity. Intensity describes the spatial concentration of power and accordingly has the unit of power per unit area (W/cm^2 or mW/cm^2). There are both spatial and temporal variations of intensity. To imagine the spatial variation of intensity, think of visualizing a flashlight beam shined onto a wall where the center of the beam is brighter (higher intensity) than the rest of the beam. This brighter position occurs in the center of the beam, on the beam axis. If one were to vary the distance between the flashlight and the wall and determine the maximum brightness, since the intensity is at its peak value there, the light intensity at that position would be termed the spatial peak (SP) intensity. This quantity is denoted as I_{sp}. If the flashlight were focused by a lens, the I_{sp} would be expected to occur at the focal point.

Intensity changes from point to point across the beam for the flashlight as it does for the ultrasound beam. This is shown in Figure 3, which is a three-dimensional perspective plot of ultrasonic intensity distribution from a 1 MHz source. At positions away from the beam axis, the intensity is less. The spatial average (SA) intensity, I_{sa}, is determined by taking some predefined area of the beam, called the beam cross-sectional area, and spatially averaging the intensity over this area of the beam. The I_{sp} is greater than the I_{sa}.

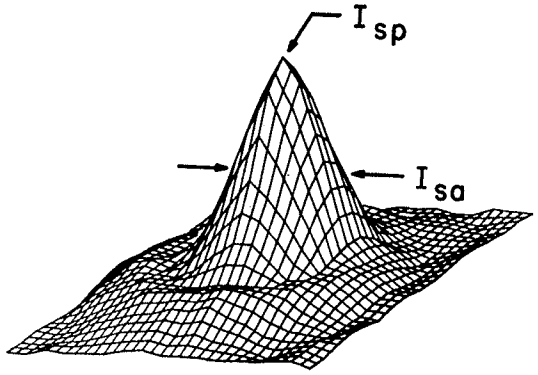

Figure 3. *Spatial representation of ultrasonic intensity distribution from a 1 MHz source. The three-dimensional perspective plot of intensity across the beam shows that the peak intensity (I_{sp}) is located in the beam center. I_{sa} represents the spatial average intensity.*

Diagnostic ultrasound equipment transmits repeated pulses of sound and, therefore, additional terms are used to describe the temporal nature of the ultrasonic field. Imagine the ringing of a bell. When the clapper strikes once, a pulse of sound is transmitted. Figures 2a and 2b graphically show two consecutive ultrasonic pulses, as a function of time, in terms of their acoustic pressure and intensity, respectively. Figure 2c is an enlarged version of one of the Figure 2b intensity pulses. At some instant of time within the pulse, the intensity will be at its peak value, the temporal peak (TP) intensity, I_{tp}. If you think of the sound from the bell in the form of a beam like that of the flashlight, and you located the position where the sound amplitude is the greatest, then the time when the pulse reaches its greatest value would be quantitatively described as the spatial peak, temporal peak intensity, I_{sptp}. Moving away from the location of greatest amplitude, the value of the I_{tp} would decrease (as would the ultrasonic pressure values of p_+ and p_-).

The intensity can be temporally averaged over the time that the pulse is on, that is, the pulse duration (PD) in Figure 2c. At the location of greatest amplitude, this pulse average intensity (I_{pa}) would be denoted I_{sppa}, the spatial peak, pulse average intensity, and would be lower than the I_{sptp}.

From a measurement standpoint, it is difficult to determine very high values of the I_{sptp}, and significant measurement errors can occur. Hence, this intensity quantity is not specified in any of the existing standards, not because it is unimportant, but because the large measurement errors diminish its usefulness. It should be noted, however, that continuing research is being conducted to provide a useful measure of I_{sptp}.

The I_{sppa} was developed in the AIUM/NEMA Safety Standard[22] because it could be determined more repeatedly and with less error than I_{sptp}. However, I_{sppa} does not properly represent the greatest intensity value. A temporal definition of intensity that more closely approximates the greatest temporal intensity is denoted by I_m.[25] To understand this definition, note that the ultra-

sonic pulse consists of a few cycles (Fig. 2) and that one of its half cycles is greater in magnitude than any other half-cycle within the pulse. This intensity quantity, I_m, is then defined *at the spatial peak location* to be the temporal average of intensity over the largest half-cycle. The approximate temporal duration over which intensity is averaged ranges from 0.1 microseconds (or, equivalently, 100 nanoseconds, ns) for I_m to 1 microsecond (the pulse duration, PD) for I_{pa}. Conceptually, I_{tp} is determined at the *instant* of time when it is at its maximum. The magnitude of I_m will lie between the larger value of I_{sptp} and the lower value of I_{sppa}.

For the periodic ringing of a bell, there is a period of time when sound is heard and a period when it is not. The temporal average intensity, I_{ta}, is that which is temporally averaged over all time. In practice, the temporal averaging needs only to be done over one pulse repetition period (PRP, Fig. 2b), that is, the time interval between the same point on the waveform of two successive pulses. Where the intensity is spatially maximized for the temporal average waveform, this is the spatial peak, temporal average intensity and is denoted as I_{spta}. The I_{spta} is approximately 1,000 less than the I_{sppa} because they are mathematically related by the duty factor, D, as $I_{sppa} = I_{spta}/D$ where D is approximately the ratio PD/PRP, or typically 0.001.

Table II shows three intensity quantity values for various clinical applications. These *maximum* values range from 10 to 1,900 mW/cm^2 for I_{spta}, from 12 to 700 W/cm^2 for I_{sppa}, and from 100 to 700 W/cm^2 for I_m. In Table II, I_m is lower than I_{sppa} for some applications because the measurements came from different sources. The typical values for these quantities are lower than the maximum values listed in Table II.

Temporal intensity quantities can also be determined for the spatial average intensity, I_{sa}, and, in that case, these intensities would be denoted as I_{sata}, I_{sapa}, and I_{satp}. The I_m definition is restricted to the spatial peak location.

In summary, seven intensity quantities have been introduced to quantify the output of diagnostic ultrasonic equipment. In practice, not all of them are specified. In some cases, it is too difficult to obtain reliable values even though they would be of value in assessing the potential for producing a biological effect. In other cases, they can be estimated from those quantities that are specified and have some value for risk assessment.

Relevance of Output Quantities

Ultrasonic biological effect studies and biophysical research have shown that ultrasound can produce changes in living systems. The prescribed AIUM/NEMA Ultrasound Safety Standard for Diagnostic Ultrasound Equipment[22] labeling requirements were based on the philosophy that there is a possible risk from diagnostic ultrasound exposure. The specific labeling requirements 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[23] 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 laboratory studies. One must rely on such basic science understanding of mechanisms because it has not been documented that clinical, diagnostic ultrasound equipment represents a direct hazard to the patient.

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 cavitation mechanisms will be considered.

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[26] given by the expression

$$Q = 2\alpha I_{ta} \quad (1)$$

where α is the ultrasonic absorption coefficient that increases with increasing frequency. The temporal average intensity is not necessarily at the location where it is maximized, that is, at the spatial peak location. If it were, then the intensity in equation 1 would be I_{spta}, which would maximize Q for that tissue site.

AIUM's "Statement on Mammalian *In Vivo* Ultrasonic Biological Effects," sometimes referred to as the "100 mW/cm^2 Statement," is a generalization about the state-of-affairs with respect to an intensity-time limit below which there have been no independently confirmed significant biological effects in mammalian tissues.[27] This statement (see Table III) is stated in terms of the spatial peak, temporal average intensity, I_{spta}. It will be referred to later.

In a subsequent section, use will be made of a more general expression for Q in terms of the ultrasonic pressure as[28–30]

$$Q = \alpha pp^*/\rho c \quad (2)$$

TABLE III

AIUM Statement on Mammalian in vivo Ultrasonic Biological Effects[27]

August, 1976; Revised October, 1978; reaffirmed October, 1982

In the low megahertz frequency range there have been (as of this date) no independently confirmed significant biological effects in mammalian tissues exposed to intensities* below 100 mW/cm^2. Furthermore, for ultrasonic exposure times** less than 500 seconds and greater than one second, such effects have not been demonstrated even at higher intensities, when the product of intensity* and exposure time** is less than 50 joules/cm^2.

* Spatial peak, temporal average as measured in a free field in water.

** Total time; this includes off-time as well as on-time for a repeated-pulse regime.

where p and p* represent different mathematical forms of the instantaneous ultrasonic pressure. Also ρ is density and c is sound speed with its product ρc being the characteristic acoustic impedance of the medium. From an examination of equations 1 and 2, it can be seen that I_{ta} is directly related to the ultrasonic pressure by

$$I_{ta} = pp^*/2\rho c. \quad (3)$$

The product of these two ultrasonic pressure terms is equal to the square of the magnitude of the ultrasonic pressure, p_o^2, at the specific location in the medium where Q is determined. Further, p_o^2 can be thought of as a temporal average quantity.

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

$$dT_{max} = Qdt/C_h \quad (4)$$

where dt 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 intensity from the "AIUM Statement" in Table III of I_{spta} = 100 mW/cm^2 at an ultrasonic frequency of 5 MHz, from equation 1, Q is 0.03 J/cm^3 − s (α is approximately 0.15/cm at this frequency). 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 temperature, from equation 4, is

$$dT_{max}/dt = 0.007\ ^\circ C/s \quad (5)$$

which means that for a 1 second exposure, dT_{max} would be about 0.007 °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 equation 1 is considered to be the spatial peak value averaged over the duration of the pulse, that is 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

$$dT_{max}/dt = 35\ ^{\circ}C/s \qquad (6)$$

but with the duration of the pulse, dt, of approximately 1 microsecond, the maximum temperature rise, dT_{max}, is about 0.000035 °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.[21,22,30–33] This demonstrates that selected aspects of the theory are reasonably well understood. But there are still many unanswered concerns in terms of being able to assess the temperature rise.

The following example of determining the rate of heat generation, Q, illustrates some of the difficulties in assessing temperature rise within tissue.[30] The rate at which heat is removed will not be addressed. Consider a very simple tissue model geometry, a homogeneous, low-loss sphere, which has a different sound speed than the surrounding medium, here assumed to be lossless water. The

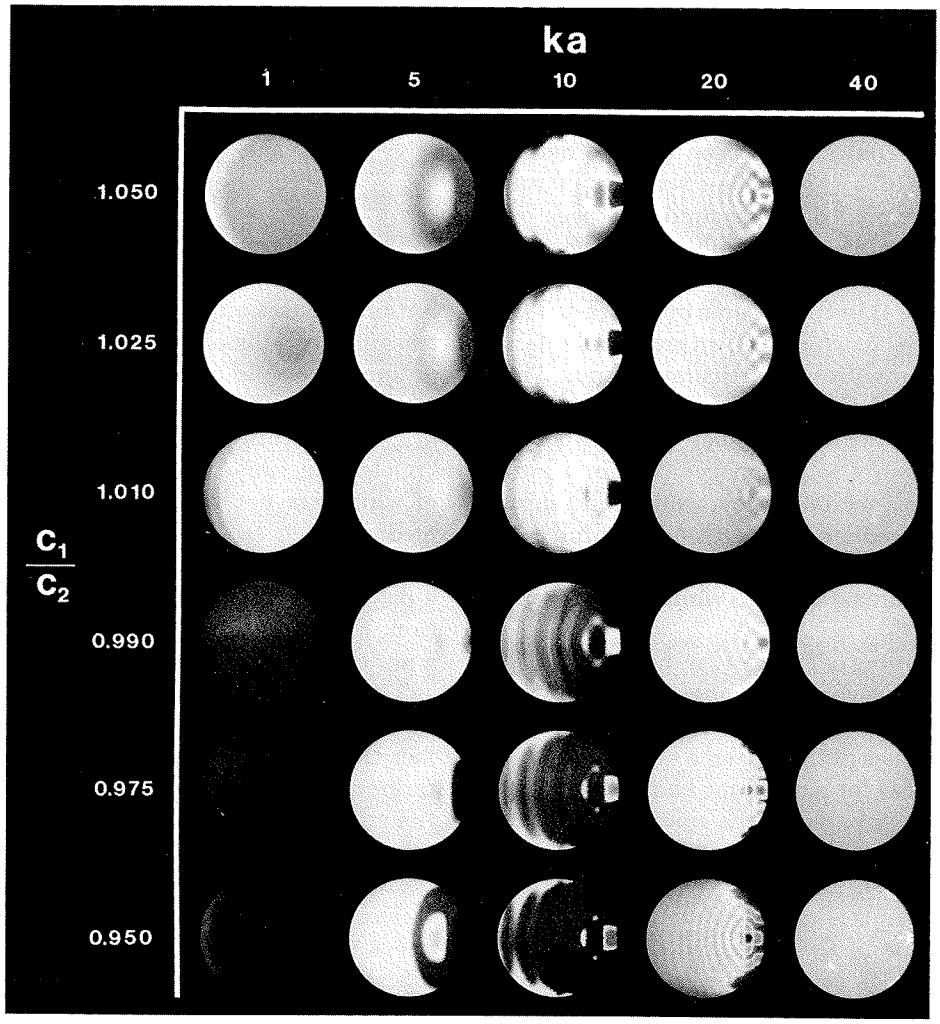

Figure 4. *Continuous gray-scale images of the spatial distribution of the rate of heat generation per unit volume, Q, in spheres for various speed of sound mismatch and size conditions. The density of the sphere and surrounding media is matched. (Reproduced with permission to reproduce this figure from the original color figure from* IEEE Transactions on Sonics and Ultrasonics©.*)*

ratio c_1/c_2, in Figure 4, is the sound speed of the sphere (c_1) to that of water (c_2) and ranges from 1.050 (sphere's sound speed is 5 percent higher than that of water) to 0.950 (sphere's sound speed is 5 percent lower). Further, consider a range of sphere sizes corresponding to a range of ka (a dimensionless, size normalization quantity) from 1 to 40, where k is called the wavenumber and is inversely related to the ultrasonic wavelength of sound in the sphere and a is the radius of the sphere. Numerically, at an ultrasonic frequency of 1 MHz, ka of 1 corresponds to a sphere diameter of 0.50 mm. For ka's of 5, 10, 20, and 40, the sphere's diameters are 1.0, 5.0, 10, and 20 mm, respectively. Doubling the frequency decreases by one-half the sphere diameter for the same ka value.

A computer analysis has been used to determine the value of Q when a plane wave (simulates far-field conditions) of ultrasound impinges on such spheres from the left. Results were originally published in color[30] and are shown as gray-scale distributions of Q in the spheres in Figure 4. The actual value of Q to which a given gray level refers is only constant within a particular column. The gray-scale code showing the continuous range of values of Q was arbitrary: black represents the highest values in a set of images (within a particular column), white for low values, and mixtures for intermediate values. One can think of a spectrum of Q values ranging from black, representing hotter areas, down to white representing cooler areas.

The full meaning of Figure 4 has been discussed elsewhere.[30] However, a few observations are in order. The sphere's size has a dominating influence on the values of the extreme of Q. The maximum value of Q for a constant ka column (constant size) is compared to the spatially uniform value of Q for the acoustically matched sphere ($c_1/c_2 = 1.000$; not shown in the figure) in that same column. In the ka = 1 column, the ratio of maximum value of Q to the matched sphere is 1.1; in the ka = 40 column, the ratio is 4.7. This means that in the ka = 1 column, the range of values of Q does not vary greatly and that for any single sphere, the distribution of Q can be approximated to be uniform. In the ka = 40 column, the range of Q values is greater, and the range within any single object can be considerable; note the "hot spot" on the right side in the $c_1/c_2 = 0.950$ and the 0.975 spheres.

Another effect of increasing object size is the appearance of an increasing number of "bands." Constructive and destructive interference is the likely cause of these bands; in other words, the nature of the pressure wave becomes visible in the spatial distribution of pp* (see Equation 2).

The temporal average intensity quantities of I_{spta} and I_{sppa} appear to be reasonable indicators for estimating the rate at which temperature rises in an absorbing material like tissue. Fundamentally, knowledge of the complex acoustic pressure (p and p*) would provide the basis for calculating the appropriate intensity quantities but these intensity quantities can be more easily determined.

Nonthermal Mechanism

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 diagnosticlike 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.[21,34–37]

Cavitation can be discussed in two general categories termed transient cavitation and stable

cavitation.[34] 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 liquidlike medium immediately adjacent to the gas bubble flows or streams (termed microstreaming).[35] 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 millisecond; these conditions are outside of the diagnostic equipment range.[38]

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.[39] For sufficiently high material viscosity, a threshold pressure, p_{thresh}, is proportional to ultrasonic frequency, the material's viscosity, and reciprocal ambient pressure. The p_{thresh} quantity is the p_- quantity depicted in Figure 2a. This approximate analytic expression agreed reasonably well with another acoustic cavitation theory calculation[40] that predicted that microsecond pulses could cause cavitation nuclei, that is, gas bubbles.

An experimental study recently showed evidence for cavitation from microsecond pulses of ultrasound[41] that qualitatively agreed with earlier theoretical predictions of Flynn.[40] Aqueous solutions were exposed to short ultrasonic pulses (approximately 6 to 20 microseconds) and $^{\bullet}OH$ radicals and $^{\bullet}H$ 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 excellent estimator of the maximum acoustic pressure, either p_- or p_+.

There has been no experimental evidence to suggest that cavitation occurs in mammalian tissue from exposurelike conditions employed with diagnostic ultrasound equipment. However, there have been some theoretical studies that suggest that under precise conditions, cavitation may be induced by microsecond-type pulses of ultrasound.[40] 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, and in terms of quantifying the output from ultrasonic diagnostic equipment, one of the more accurate and precise measures is the maximum intensity, I_m.

Summary

Cardiac tissue is well perfused. A considerable amount of theoretical work has examined the average rate of heat generation per unit volume per unit time under conditions in which the average rate of heat removal was not considered, other than passive thermal diffusion. Perfused tissue would have a temperature rise due to ultrasonic absorption less than nonperfused tissue so the theoretical approach has been useful in identifying the worse-case temperature rise.

Some of the highest I_{spta} values have been reported for pulsed-Doppler systems used in cardiac applications (see Table II). Using the value of 2 W/cm^2 for I_{spta}, the maximum rate of change of temperature (from equation 4) is 0.14 °C/s that, for a few seconds exposure could result in a temperature increase in excess of a couple of degrees

Celsius when no heat removal mechanisms are considered. It is unlikely that cardiac tissue would reach these temperature levels, but the potential does exist. Clearly, more detailed theoretical modeling, along with appropriate animal experiments, is in order to further evaluate this phenomenon.

The higher the I_{sptp} values are, and hence higher p_+ and p_-, the greater is the likelihood to produce cavitation. Further, the use of ultrasonic contrast media such as injected microbubbles could increase the incidence of cavitation events since such microbubbles might provide the nucleation sites. There has been no experimental evidence, however, that suggests the onset of cavitation from microsecond-type ultrasonic pulses in biological tissue; thus, no suggestion of adverse tissue effects from cavitation. This also is a topic that requires further investigation.

The use of diagnostic ultrasound in cardiac applications does not appear to represent a hazard with current equipment. The ultrasonically induced mechanisms known to affect tissue continue to be evaluated but, at this time, the risk is quite low.

Acknowledgments: The author wishes to acknowledge the critical examination of the manuscript by R. A. Meyer, M.D., F. L. Lizzi, Eng.Sc.D., M. E. Stratmeyer, Ph.D., and F. W. Kremkau, Ph.D.

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