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REVUE

SAFETY AND POTENTIAL HAZARDS IN THE CURRENT APPLICATIONS OF ULTRASOUND IN OBSTETRICS AND GYNECOLOGY

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Abstract—The safety and potential hazards in the current applications of ultrasound in obstetrics and gynecology are discussed. The author has made an attempt to provide a perspective to enable interpretation of future experimental results in terms of health hazards for humans.

Key words: Diagnostic ultrasound, Safety, Hazards, Obstetrics and gynecology, Ultrasonic damage mechanisms, Ultrasonic teratology, Hyperthermic teratology.

INTRODUCTION

An editorial on Application of Ultrasound in Medicine, in the 15 June 1972 issue of the New England Journal of Medicine drew attention to the various specialities in medicine in which ultrasound was generally accepted as the diagnostic modality of choice. With the challenge of computerized X-ray tomography, a reassessment of the comparative value of diagnostic ultrasound may be in order for some of the specialities. But the position has remained unchanged in obstetrics and gynecology, because of the well known hazard of *X*-rays to the embryo, the fetus, and the gametic cells. Meanwhile with the availability of higher resolution and "real-time" instrumentation ultrasound has become even more useful in studies of the developing fetus, while maintaining its record of safety, at least thus far. It would be imprudent to believe that diagnostic ultrasound would be safe to the fetus under all conditions of use or regardless of relentless technological innovation and exploitation, since like other modalities ultrasound too can damage biological tissues at certain "dosage" levels or under certain biological conditions. This article will present some of the current uses of diagnostic ultrasound in obstetrics and gynecology only briefly, since these have been discussed thoroughly by Thompson and Bernstine (1978), succinctly summarized by Scheer (1977) and are continually evolving and reported in professional literature. It shall then discuss the question of safety—specially as it relates to the fetus.

CURRENT APPLICATIONS

B-Scan ultrasonic examination can establish the existence of early pregnancy (after 5.5 weeks of amenorrhea) by visualization of the gestational sac with an accuracy of 95% (Blackwell *et al.*, 1975) which compares quite favorably with standard immunologic or hormonal tests. By 8–10 weeks, fetal heart motion can be detected by Doppler ultrasound techniques. Real-time imaging makes this possible as early as 6 weeks of gestation. The definite diagnosis of pregnancy and determination of fetal age is particularly important in management of cases of amenorrhea following withdrawal of steroidal contraceptives. The usefulness of prudently-timed serial examinations in providing assurance of viability, normal growth and development of the embryo is obvious. But, it is precisely at this stage that the embryo is most vulnerable to physical or chemical agents, and hence the need for prudence. Equally obvious is the fact that it could be justifiable to assume a reasonable amount of calculated risk when pregnancy is already threatened or an abnormality of early pregnancy such as ectopic pregnancy, hydatidiform mole, or co-existence of other pelvic pathologies is suspected.

After the first trimester, ultrasonic examination can furnish reliable data on the presence of multiple pregnancies, location of the placenta, and on the fetal head size and growth rate and also lead to early detection of neural tube defects such as anencephaly, hydrocephalus, meningomyelocele. Other fetal pathologies and anomalies such as

sacrococcygeal teratoma, omphalocele, ectopic liver, ascites, obstructive uropathies, osteogenesis imperfecta, achondrogenesis, conjoined twins and monstrosities, can often be detected. If the fetus is male, ultrasonic scans can frequently demonstrate this fact through visualization of its perineal region. It also appears probable that in the near future it may be possible to identify fetal heart structures and gain information on their dynamics. Yet later, it can provide valuable information on fetal presentation and position and aid in amniocentesis, fetoscopy and fetal intrauterine transfusion. The importance of this information to proper clinical management of the pregnancy cannot be overstressed. After parturition, it is useful in diagnosis of retention of placental fragments or other products of conception.

Motion detection by Doppler ultrasound is used extensively in office practice to monitor fetal heart rate to ascertain fetal viability, and during labor to gauge fetal cardio-respiratory distress.

In gynecology, ultrasonic examination can yield definitive information on abnormalities of the uterus and the adnexa by anatomical localization and differentiation of solid and cystic masses, localization of intrauterine contraceptive devices, etc. It is also beginning to provide useful information in pediatric gynecology, a field in which many of the procedures conventionally used in the adult cannot be applied. Its use in radiation therapy planning and in evaluation of the results is already well established.

Clearly, ultrasound provides substantial amounts of significant information vital to proper clinical management of pregnancy as well as some gynecological pathologies. The comparatively greater usefulness, reliability and safety of diagnostic ultrasound relative to other physical methods—both active and passive—of investigating the fetus and the placenta was borne out in a study by Docker (1975) in which he compared ultrasonic scanning and fetal heart detection with radiography and radioisotope techniques for usefulness, reliability and safety. It is no wonder that currently one-third of all obstetrical patients at some teaching institutions undergo sonographic evaluation at least once during their pregnancies and, routine scanning of all gravid patients in the 20–30 week range is advocated (Scheer, 1977). Much of this information is obtainable by manually operated, single transducer, gray scale *B*-scan equipment which is now almost commonplace. Manual scanning with a single transducer takes time, and during the examination the fetus often moves and the outlines and details of dynamically moving structures are blurred. To capture the motion of such structures, as for example, the heart, and to reduce the time required for each examination, multiple ultrasonic transducers or an array of transducers, scanned mechanically or more often electronically, have been developed. The use of such arrays to visualize the fetus in its dynamic state has yielded some interesting information on the various activities of the fetus within the uterus. For example, it has been possible to visualize, in real time, its gulping, swallowing, yawning and respiratory motions as well as thumb sucking (Stephens and Birnholz, 1978). Demonstration of the activities of the fetus is not only comforting and reassuring to the mother but also should provide valuable information on the physiological development of the fetus which might well prove to be of diagnostic importance. There are also indications that further improvements in ultrasonic imaging by use of higher resolution focused beam systems and electronic signal processing may enable detection of fetal malformations at early stages of gestation with greater consistency thus leading to better advised management of the pregnancy. These advantages must be carefully weighed against the potential to cause damage to the embryo, since not only can the focused beam, high resolution, faster scanning, real-time imaging systems deliver more ultrasonic energy to the tissues but also because they are likely to be used earlier in the pregnancy, for longer periods and repeatedly.

SAFETY IN DIAGNOSTIC APPLICATIONS

With the need for caution inculcated by the Thalidomide disaster of the early 1960s (Kerr, 1970) and the report of increase in predisposition to leukemia in individuals who were exposed to X-rays as fetuses during X-ray pelvimetry of their mothers in the early 1970's (Stewart, 1971), the safety of diagnostic ultrasound has received close scrutiny both by researchers and practitioners working with ultrasonic techniques, as well as by governmental regulatory agencies. It is worth noting that, as with X-ray pelvimetry, ultrasonic examination of the pelvis of the

mother constitutes a whole body radiation for the fetus. And it is all the more imperative to ascertain—to the extent that it is possible—that diagnostic ultrasound is free of the dangers of the modality it has displaced in obstetrical diagnosis. Obviously, no diagnostic technique in which energy is radiated into tissues can be totally safe regardless of the power, intensity and/or biological conditions. Thus the question is not if ultrasound can cause harm but does it do so under the conditions of use. What are the potential risks to the patient? Do the benefits outweigh assuming these risks?

POSSIBLE ADVERSE EFFECTS

The possible risks associated with the use of or exposure to any physical or chemical agents may be:

1. Gross injury—structural or functional, irreversible or reversible—to the somatic cells of the fetal or maternal tissues. Even a totally reversible or transient effect may, on occasion be dangerous, e.g. induction of transient tachycardia in a patient with myocardial infarction or occurrence of temporary immunodepression in a patient under physiological stress. Also repeated minimal asymptomatic injuries may cumulate and result in dysfunction or contribute to aging or shortening of life-span.

2. Gross injury to the differentiating cells of the embryo leading to teratological effects.

3. Injury to the chromosomes or mutations induced in the somatic cells of the mother or the fetus leading to death, malfunction, malformation or carcinogenesis.

4. Injury to the chromosomes (intergenic or intragenic) of the reproductive cells of the fetus or the mother resulting in genetic damage which may or may not become manifest in one or more generations.

All these risks may be relevant to ultrasound. The ultrasonic irradiation or insonation threshold for damage to these different loci may be different and may vary with insonation parameters and variables as well as with biological characteristics of different tissues or organs. It would therefore be appropriate to look into which ultrasonic parameters and variables, and biological characteristics need be considered and what are the modes and levels of exposure under clinical conditions.

Clearly, for evaluation of probable hazards, the peak intensity, the maximum power, the pulse duration and pulse repetition rate, the total exposure time and the minimum spatial dimensions of the ultrasonic beam within the tissue are important factors. Also, since the amount of ultrasonic energy absorbed by a tissue is frequency dependent, the frequency content in the ultrasonic output of the transducer also needs to be known. Ultrasound is used both as continuous waves (c.w. Doppler systems, transmission imaging systems) and as brief pulses (as in *A*-mode pulse-echo systems for paracentesis, *B*-scan and Phased-Array systems). In the c.w. mode the energy varies spatially in planes parallel to as well as normal to the transducer. In pulse mode the energy distribution in the ultrasonic wave propagating through a medium varies both spatially and temporally. Thus, the above data need be considered both as instantaneous local intensities as well as intensities averaged in space and time. In examinations performed using the scanning systems (*B*-mode, Phased-Arrays) the ultrasonic beam is continuously moved through a sector of tissue. The exposure received by any point or volume of tissue is thus related to the speed of the angular motion and is much lower than if the target was held in a stationary beam. The definition and explanation of the terminology and the measurement and specification of the acoustic output is beyond the scope of this article and can be found in some recent publications (Eggleton, 1978; Kossoff, 1978). It should, however, be pointed out that in pulse-echo systems, the instantaneous spatial peak intensities are several orders of magnitude higher than the average intensities, since the total ON-time of the pulsed transducer is very brief.

Consideration of the properties of the target tissue relevant to the question of damage needs prior knowledge of the mechanisms of ultrasound-tissue interactions. These will be discussed in some detail later, but it may suffice here to state that the mechanisms of damage to "organized" mammalian tissues are believed to be primarily thermal or cavitational. Existence of some so-called "direct" mechanisms such as streaming, shearing and agglomeration (Nyborg, 1977) has been demonstrated in plant tissues and in *in vitro* experiments but not in mammalian tissues *in vivo*. Heat dissipation capabilities of the target tissues, vascularization or absence thereof, ultrasonic absorption coefficient, viscosity, gas content, density of cellular packing or the

proportion of extracellular fluid to the cell mass, anchoring or cohesiveness of the cells would thus appear to be important considerations. Also any information on the relative sensitivity of the target tissue compared to other tissues in general, such as the higher susceptibility to damage of dividing celt populations as compared to stable, mature cells, any differences in thermal denaturation thresholds or mechanical fragility, must be included in assessment of risk to ultrasound.

ULTRASONIC OUTPUT CHARACTERISTICS OF CURRENT DIAGNOSTIC SYSTEMS

The acoustic power output and intensities of many of the current commercially available systems have been measured by several investigators. Data obtained by Carson *et al.* (1978) being recent is specially relevant, in spite of difficulties in identification of some of the instruments because of errors in their numbering. A wide range of values was found to exist. The instantaneous spatial peak intensity in current pulse-echo systems, for example, was found to range from 0.4 W/cm^2 to an astoundingly high value of 1700 W/cm^2! The ultrasonic power output of c.w. obsetrical Doppler instruments varied from a low of 0.95–37 mW. It should be pointed out that higher output levels do not necessarily imply better resolution or other diagnostic performance and may or may not be related to the complexity of the electronics system or the price. Furthermore, it is often assumed that the output from ultrasonic transducers is at its maximum when the system is well adjusted and functioning optimally, and thus, if the performance deteriorates over time or malfunction develops, the acoustical output will be lower. Unfortunately, this "fail-safe" assumption is incorrect. For example, if a transducer "delaminates", that is, gets separated from its backing (damping material), its output could be several times greater than when it is functioning optimally.

As discussed later, no danger is threatened with the use of any of the current instruments. But obviously, the margin of safety is reduced in use of those with high power outputs. And unless some diagnostic benefit is to be gained, the use of any more power than absolutely necessary is, *a priori*, unjustifiable.

THE EVIDENCE OF EPIDEMIOLOGICAL STUDIES

An irrefutable and realistic assessment of clinical hazard or risk is possible only in prospective or retrospective clinical studies of the effects of ultrasonic examination of the fetus. Unfortunately only a few such studies have been conducted. In a group of 1,114 pregnant women examined by pulse-echo techniques Hellman *et al.* (1970), found that "neither the frequency of ultrasonic examination nor the time of the first examination seemed to affect adversely the incidence of fetal abnormality and abortion; nor are abnormalities any more common than in the general population". Bernstine (1969) examined the incidence of congenital malformation, abortion and premature labor in 720 patients examined with c.w. Doppler ultrasound and found these to be slightly lower than in patients not so examined. This is to be expected if ultrasonic diagnosis contributes to better patient care. Ziskin (1972), in response to a questionnaire, received no reports of any adverse effects in 17,869 ultrasonic examinations using pulse-echo techniques and 7,667 examinations using c.w. Doppler techniques. In addition to these reassuring studies, it is rather remarkable that in spite of the widespread use of ultrasound in obstetrical diagnosis, there have been no reports of any adverse effects. In the mid-1970's several statistically designed, controlled, prospective studies were initiated in the U.S. and in Europe to determine the effects of prenatal diagnostic ultrasound on the growth and development of individuals. No untoward effects have yet been reported. However, it may be a decade or longer, before any definitive statements on the absence of any deleterious effects could possibly be made. Until then, however, laboratory studies conducted on animals, under conditions simulating clinical usage should provide some guidance.

LABORATORY STUDIES

The fact that ultrasound can produce irreversible structural alterations is well established and has been studied extensively in many organs and tissues, but specially in the central nervous system (c.n.s.). Many of such studies have been conducted either to establish dosimetric relationships for surgical applications or to elucidate the mechanisms operant in ultrasonic damage to tissues which will be discussed later. The intensities and total "dose" employed in some of these studies, spanned a range from orders of magnitude higher than those used in diagnosis to diagnostic levels. But since it is well known

that cells undergoing division, as in the fetus, are more susceptible to damage by a variety of agents than mature or post-mitotic cells Bergonie and Tribondeau (1906), caution must be exercised in extrapolation of this numerical data to the fetus. Some of this is discussed later.

STUDIES ON FETUSES

Several studies (Kirsten *et al.*, 1963; Sunden, 1964; Smyth, 1966; Woodward *et al.*, 1970; Warwick *et al.*, 1970; Mannor *et al.*, 1972; Muanaka *et al.*, 1972; Shimizu and Shoji, 1973; Sikov and Hildebrand, 1976; O'Brien, 1976; Rugh and McManaway, 1977; Fry *et al.*, 1978) have also been conducted on pregnant mice or rats, with fetuses insonated during the stage of organogenesis. In one of the studies (Smyth, 1966) the gonads of both parents were also insonated each day for 5–10 days during gametic maturation prior to mating and the insonation of one ovary of the mother was continued for 10 min a day for 17 days during pregnancy. No effects on the ovaries, ovulation, fertilization; implantation, abortion or continuation of the pregnancy to term, prenatal or subsequent development of the offspring, litter size, birth weight of the fetuses, or occurrence of abnormalities in the first or second generation progeny was observed in any—but one (Shimizu and Shoji, 1973)—of the investigations until the insonation "dosages" were several fold those employed in clinical practice. Sikov and Hildebrand (1976) summarize their results by stating, "Extrapolation of these results suggest that current clinical procedures with Doppler techniques have a safety factor of at least 1,650, ranging to a possible maximum of 75,000". This seems to be in agreement with the conclusions of other investigators as regards both Doppler and pulse-echo type insonations. Shimizu and Shoji (1973), on the other hand, reported an increased frequency of abortion and fetal malformation in pregnant mice insonated with c.w. ultrasound from a clinical diagnostic instrument for 5 hr on the ninth day of pregnancy. As will be discussed later, the etiology of these teratological effects is related to fetal hyperthermia rather than ultrasound and is unlikely to occur under normal clinical conditions.

The results in mice and rats thus confirm the evidence of clinical experience. But caution must be exercised in interpretation and extrapolation of results obtained in animals, specially when they are so much smaller than man, for two reasons. Firstly, the relation of ultrasonic field characteristics such as the number of wavelengths in the fetus, size of the ultrasonic beam relative to the fetus, and attenuation of intensity in tissues between the transducer and the fetus are grossly different in the two situations. And secondly, in spite of the care exercised in defining the ultrasonic field characteristics in water as in some of the recent studies (O'Brien, 1976) the insertion of the small experimental animal into the field so severely distorts the field that it is impossible to know the actual intensity at each of the fetuses. This distortion results from the presence of gas in the lungs and in the loops of intestines of the mouse, which unavoidably lie within the ultrasonic field because of the size, shape and location of the bicornuate uterus. This field distortion can also be aggravated by reflection of ultrasound back into the fetus from the distal abdominal wall of the animal. The use of avian eggs (Rivers *et al.*, 1972) as a test system for ultrasonic teratological studies is also untenable as the shell reflects most of the energy (Sofia and Lele, 1975). Trephination is needed for coupling ultrasound to the embryo. This enables effective coupling but dosimetry remains uncertain due to multiple reflections of the energy within the shell (Sofia and Lele, 1975). In studies on insects such as drosophila, the small size and presence of chitinous exoskeletons, almost impervious to ultrasound, render dosimetry and extrapolation of results to man, almost impossible.

Concerns regarding the occurrence of reflections within the human pelvis resulting in concentration of energy at the fetus would seem to be unfounded. The ultrasonic intensity is greatly attenuated (approximately 20 dB) in its passage to the posterior wall of the pelvic cavity (Pl. see Table 2) which is covered with highly attenuating muscles. The overlying neuro-vascular structures would tend to scatter the incident ultrasonic energy rather than reflect it in a symmetric manner to focus within the pelvic cavity.

STUDIES ON OTHER DIVIDING CELL POPULATIONS *IN VIVO*

Dyson *et al.*, (1970, 1976) have reported stimulation of tissue regeneration by bursts of plane-wave 3.5 and 3.0 MHz ultrasound at intensities of 0.1–8.0 Watts/cm^2 in wounds placed in the pinnae of rabbits, as well as, in varicose ulcers in man. In experiments on rabbit ears, there was little correlation be-

tween the response and the intensity used—greater response being obtained at medium intensity levels. In varicose ulcers, the investigators found that although there was considerable variation in the response, healing of the insonated ulcers was more marked than that exhibited by controls, using an intensity of 1 Watt/cm^2. No comparable studies have been reported by any other investigators.

Kremkau and Witcofski (1974) studied the effects of insonation on rat liver, stimulated into regeneration by partial hepatectomy and concluded, despite great variability in both the control and experimental groups, that ultrasound caused a reduction in the number of mitoses, that is in the amount of regeneration. A repetition of the experiments by Miller *et al.* (1976) in consultation with Kremkau, using intensities 10 and 100 times greater than those used by Kremkau and Witcofski however failed to show any difference between the insonated and control group.

STUDIES ON CELLS IN CULTURE *IN VITRO*

Effects of insonation have also been studied on cultured mammalian cells *in vitro*. Most of these studies have been principally concerned with cell lethality without reference to age-distribution of the cell populations. The LD_{50} thresholds reported vary over a wide range. Some of this variability obviously could be due to different age-distributions of cells or to different susceptibilities of different cell lines to ultrasound. But even with synchronized cells, different cell lines have been reported to be most sensitive to ultrasound at different stages of the cell cycle. For instance, Clark and Hill (1969) reported that L51784 mouse leukemia cells are most sensitive to ultrasound in the *M* phase, whereas, Martins *et al.* (1977) found that Chinese hamster V-79 cells were most resistant in the *M* and early G_1 phases. The reported values for LD_{50} thresholds vary from a low of 0.7 Watts/cm^2 for 1 min at 750 kHz for HeLa S3 cells in suspension (Watmough *et al.*, 1977) and 2 Watts/cm^2 for 5 min at 1 MHz in HeLa and CHO cells in suspension (Kaufman *et al.*, 1976) to "more than 11 Watts/cm^2 for 60 min at 1.5 MHz in CHO cells in suspension" (Bleaney *et al.*, 1972) and more than "30 times greater intensities and ... 100 times higher exposure times than any treatments shown to produce pathological lesions in mammalian tissues" at approximately 1 MHz in monolayers of single CHO cells (Moore and Coakley, 1977).

Studies conducted in the author's laboratory show that the variability in the results and the thresholds for cell lethality for any cell line is dependent both upon the method of insonation and dose uniformity. Cells in suspension or in monolayers exhibit extreme variability in results, particularly when insonated with a non-uniform spatial intensity distribution. However, when the cells were anchored in a viscous medium, approximating body organs in acoustical, physical and thermal properties, and insonated with a uniform intensity field the thresholds for cell lethality were consistently reproducible and comparable to those for histologically detectable morphological damage to fetal tissues (Lele *et al.*, 1975). Under these conditions, cavitation and acoustic streaming, which are significant in suspension cultures, were found to be respectively absent or insignificant as they are in organized tissues at these intensity levels. Similarly, in other experiments, blood platelets suspended in plasma could not be made to aggregate even at spatially uniform intensities up to 15 W/cm^2. But in non-uniform ultrasonic fields, with vigorous acoustical streaming or with a magnetic stirrer placed within the specimen chamber during insonation, platelet aggregation occurred at intensities of 2–3 W/cm^2, confirming the results of Williams (1977). Platelets can apparently be made to form clumps at an intensity as low as 16 mW/cm^2, through enhancement of acoustical streaming by introducing stabilized microscopic air spaces (Nyborg *et al.*, 1978). It is, however, not clear as to how these data relate to or can be made to relate to the question of hazard *in vivo* under diagnostic conditions.

STUDIES OF EFFECTS ON CHROMOSOMES

In addition to any lethal action on the cells of the embryo leading to teratological effects, the possible existence of sublethal effects on chromosomes is rightly of considerable concern because of its latency and profound genetic implications. Thus, the first report of the occurrence of chromosomal aberrations in lymphocytes by Macintosh and Davey (1970) led to the repetition of their experiments in many different laboratories, none of

which could confirm occurrence of these effects (Lele, 1972). Furthermore, repetition of the experiments by Macintosh *et al.* failed to yield any confirmation of their earlier results (Macintosh *et al.*, 1975), and showed that they could have been due to the effects of a toxic chemical eluted from their sample holder. Presently, it is reasonable to assume that c.w. insonation of human lymphocytes *in vitro* with intensity up to 300 mW/cm^2 and durations up to 2 hr, does not cause chromosomal aberrations. Similar absence of aberrations has been found by several investigators (Coakley *et al.*, 1971; Abdulla *et al.*, 1971; Boyd *et al.*, 1971; Rott *et al.*, 1972; Coakley *et al.*, 1972; Mermut *et al.*, 1973), using pulsed ultrasound. Lyon and Simpson (1974) carried out a comprehensive study of the probable genetic effects, by insonation of the gonads of male and female mice prior to mating. No evidence of the occurrence of genetic damage was found even with intensity levels and durations of insonation considerably higher than those used in diagnostic ultrasound.

REVIEWS AND SUMMARIES OF BIOEFFECTS LITERATURE

The voluminous, but often cursory, data on the biological effects of diagnostic ultrasound including those on plants and invertebrates was collated by Wells (1974) and by Ulrich (1974) and has been reviewed in the U.S. by at least two independent panels in addition to others set up by the governmental regulatory agencies. In 1973, the National Science Foundation (NSF) Survey Team on Ultrasonic Imaging noted the absence of any biological effects, in animal or plant tissues, with c.w. insonation (as from Doppler fetal heart monitors) at levels below 100 mW/cm^2 average intensity at frequencies between 0.5 and 10.0 MHz (Report of the NSF Survey Team on Ultrasonic Imaging, 1973). After a further study of the biological effects reported with the use of c.w. as well as pulsed ultrasound, the American Institute of Ultrasound in Medicine (AIUM), in August 1976, issued a "Statement on Mammalian *In Vivo* Ultrasonic Biological Effects" (AIUM Committee Report, 1977). This in part states:

"In the low megahertz frequency range there have been (as of this date) no demonstrated significant biological effects in mammalian tissues exposed to intensities† below 100 mW/cm^2. Furthermore, for ultrasonic exposure times‡ less than 500 sec and greater than 1 sec, 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."

After the AIUM statement was issued, investigators in the U.S. became aware of several papers reporting the occurrence of biological effects at lower intensity or power levels. The statement was, therefore, modified in October 1978 by substituting "independently confirmed" for "demonstrated" (AIUM, 1978a). It now also points out that "it is reasonable to expect at least some lowering of the observed 'threshold' level for some biological systems, especially as more sensitive biological tests are discovered and as more critical physical conditions are identified". The data which prompted this revision is discussed below, since, it is also cited by the U.S. Food and Drug Administration (FDA) as the rationale for their "Intent to Propose Rules and Develop Recommendations for diagnostic ultrasonic equipment" (FDA, 1978). It should, however, be first pointed out that biological effects and hazard are not synonymous. For example, a temperature rise of a few degrees in the skin, when warming oneself in front of fire, is a biological effect but not necessarily a hazard. Release of adrenalin with emotion is an effect but not normally a hazard. Even a reversible ultrastructural change does not necessarily signify damage. For instance, the mitochondria of the muscles of the leg show a swelling of their cristi for a short period after exertion such as climbing a flight of stairs, but this too cannot be construed as a hazard. Thus, biological effects are not synonymous with hazards. On the other hand, irreversible destruction of the tissue can sometimes be the first and the only biological effect produced.

The papers, reporting the occurrence of biological effects at intensity and power levels lower than those currently accepted as safe, not unexpectedly, are based on the use of functional or transient phenomena as end points. Anderson and Barrett (1977) reported immunosuppression of IgM in mice by

†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.

exposure of the spleen to c.w. ultrasound for 5 min at an average intensity of 10 to 50 mW/cm^2. The report of the AIUM Bioeffects Committee (1978b), which reviewed these results states, "Questions have been raised by reviewers about the numbers of animals used, about the statistical interpretations, and about the adequacy of the controls". The report also states, "—two independent groups of investigators have carried out experiments in order to test the replicability of results, and extend the observations. With the end points studied to date by these groups, working with mice under conditions similar to those of Anderson–Barrett, they have not confirmed the results". Unfortunately, neither these negative findings, not the details of Anderson and Barret experiments have yet been published. It is probably germane to point out here that even if the report of immunosuppression by splenic insonation is eventually confirmed, it is unlikely to be of clinical significance in the practice of diagnostic ultrasound. It is almost impossible to avoid the exposure of the entire mouse spleen using a diagnostic transducer and it is equally impossible to expose any significant portion of human spleen for more than fractions of a second, using the same transducer.

Other recent studies, or rather reports, that apparently are of serious concern to the FDA include developmental effects such as delayed neuromotor reflex development (Murai *et al.*, 1975a), altered emotional behavior (Murai *et al.*, 1975b), increased levels of glutamic oxaloacetic transaminase in the cerebrospinal fluid of dogs (Tsutsumi *et al.*, 1964), evoked electroencephalographic responses in non-human primates (Hu and Ulrich, 1976) and reports of increased fetal movements during clinical examination of pregnant women using Doppler instrumentation (David *et al.*, 1975). The validity and significance of most of the results described in these papers cannot be properly evaluated because of the complexity of the experimental procedures, inadequacies in design of experiments and the use of very small samples in face of the large scatter in the results obtained. For example, perusal of the data presented by David, Weaver and Pearson (1975) shows that though there was an increase in the fetal activity during examination of patients between 28 and 40 weeks of gestation using c.w. Doppler ultrasound, there was an equally large progressive increase in the number of fetal movements in their controls (non-activated ultrasonic head), as the study progressed from case numbers 1 to 8, through 9 to 15 and 16 to 21.

The AIUM Bioeffects Committee (1978c) points out the facts that many of these studies do not represent the exposure conditions of the clinical situations, that the dosimetry in these studies is lamentably imperfect, that the sample sizes are inadequate, the experimental design cannot preclude observer bias, many of the end points are subjective or very labile or affected by a variety of uncontrollable factors and thus subject to artifacts, that the data have not been verified by other investigators and that most of the data involve continuous wave exposure. But whereas the AIUM finds the reports unconvincing and inconclusive because of these defects, the FDA argues "that not all such studies can be dismissed as irrelevant, particularly since some of the studies involve the use of clinical devices" (FDA, 1978). It is of course gratifying that the agency entrusted with ensuring the safety and effectiveness of medical diagnostic equipment, is watchful of any potential dangers. But on the other hand, it is debatable if the zeal for safety justifies assumption of a hazard for any and every biological effect and application of vastly different standards in evaluation of reports that imply the possible existence of a biological effect than of those which do not.

From this review and discussion of the experimental evidence, it is clear that there is, as yet, no evidence to suggest that diagnostic ultrasound, as currently used, threatens the safety of the fetus or the mother. Laboratory experiments can provide some data, but to be meaningful for determination of safety or potential risks they must be designed so that *all* conditions of clinical diagnostic situation are met. Studies *in vivo* on small rodents, flies and plants do not meet these requirements, because of their size, presence of exoskeleton and morphological differences, e.g. presence of air-bubbles and thick cellulose walls. Scaling for differences in size by using appropriately small wavelengths is untenable, because most of the acoustical properties of tissues are related to wavelength. Studies on model systems, such as plant cells are important from a biophysical point of view, to elucidate the possible modes of interaction between

ultrasound and biological matter, but probably can provide no insight into what actually does happen in man.

Epidemiological studies thus offer the best, if not the only, approach to obtain the needed answers. The animal studies may provide information on what questions should be addressed in the epidemiological studies. It may be extremely worthwhile for the FDA to prepare and publicize a list of possible ultrasonic effects in infants and children, which obstetricians, neonatologists and pediatricians may look for in their daily practice and thus help in accruing epidemiological data.

RISK ASSESSMENT FROM STUDIES OF DAMAGE MECHANISMS

The general recognition of the safety of diagnostic ultrasound based on empirically observed damage thresholds and in epidemiological studies, is confirmed by studies of ultrasound-tissue interaction mechanisms. In the long run, thorough understanding of the interaction and damage mechanisms is indispensable, not only for interpreting experimental results in terms of possible health hazards for humans but also to permit prediction of insonation conditions in which the damage may be incipient or the safety margin greatly reduced.

Adequate assessment of the potential hazards associated with clinical use of ultrasound requires knowledge at least of: (1) the nature and magnitude of the physical events occurring in the tissues as a result of ultrasonic perturbation, (2) the biological consequences of each of these phenomena over the range of their amplitudes, in each of the relevant tissues under different physiological and pathological states, and (3) since many, if not all, of the physical events occur concurrently in the tissues, whether their effects simply summate or they potentiate one another. This knowledge may point to the manner in which damage may occur and the site where it may become manifest and may enable the right questions to be asked in prospective or retrospective studies.

The approximate magnitudes of the physical events resulting from ultrasound propagation in biological tissues can be calculated with the oversimplified assumption of the tissue media being homogeneous Newtonian fluids. But these are of limited value in assessment of their biological hazard potential. The biological consequences of these effects and the ultrasonic dosage levels at which they first become apparent must be determined under conditions simulating clinical use, using insonation regimes typically employed in clinical practice and in structurally organized tissues or fluid tissues *in vivo*. Determination of the threshold of a biological effect in experiments designed to maximise particular effects, as for example acoustic streaming by introduction of resonant bubbles in the insonation system (Nyborg *et al.*, 1978), or induction of cavitation by inoculation of the medium with micron-sized metal particles, could be of interest as a study in biophysics. But it is obvious that the results obtained will have little relevance to the problem of ultrasonic safety or hazard in clinical medicine.

For the purpose of risk assessment, it is probably useful to classify the interactions into two broad categories, though there may be some overlap between the two: (1) those related to the mechanics of wave propagation, e.g. "Direct" effects and cavitation, (2) those related to the absorption of acoustical energy leading to heat generation and temperature rise and thus dependent upon the acoustical absorption coefficient in addition to the acoustical field parameters and variables.

There is sufficient and conclusive evidence that with c.w. or pulsed ultrasound there is no likelihood of damage to organized mammalian tissues, from wave mechanics phenomena and cavitation up to peak intensity levels of approximately 1500 W/cm^2 at a frequency of 2–3 MHz (Lele, 1977). This also includes tissues and organs containing fluids (e.g. the brain, heart, urinary bladder) or contained in fluids (e.g. the fetus). Only at intensities above these levels does collapse-cavitation, as evidenced by anharmonic acoustic emission, occur consistently (Fig. 1) and the damaged tissue show fragmentation of ultrastructure. With pulsed ultrasound, the thresholds for mechanical damage would be even higher. The margin of safety for diagnostic ultrasound, as far as cavitation damage is concerned, would thus appear to be at least two orders of magnitude. Similarly, acoustic streaming, which has been shown to be a potentially hazardous mechanism in plant cells (Nyborg *et al.*, 1977), was found to have no effects whatever on conduction of action

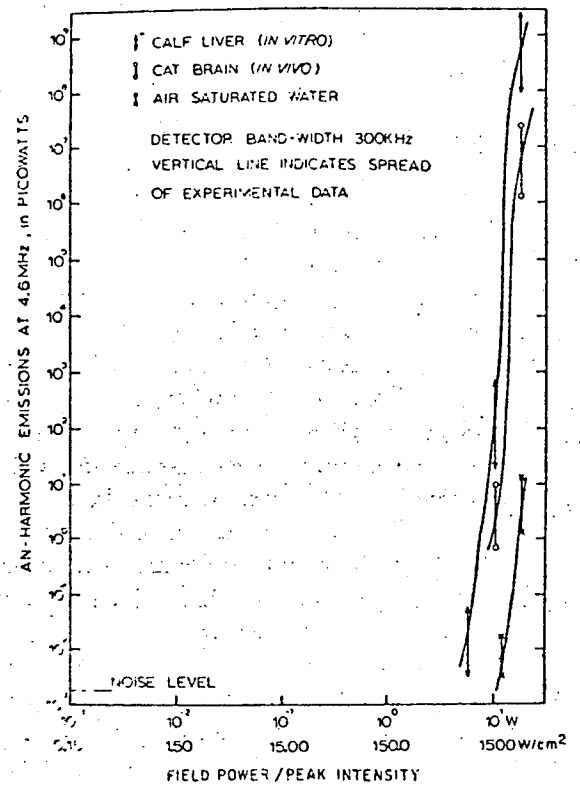

Fig. 1. Power and intensity dependence of collapse cavitation damaging to structurally "organized" mammalian tissues *in vivo* with insonation at 2.7 MHz.

potentials in exposed mammalian peripheral nerves (Lele, 1977).

Below these intensity levels, the potential for damage lies in the temperature rise due to the absorption of the acoustical energy. The temperature threshold for tissue damage is time dependent and is both explicable and predictable on the basis of Reaction Kinetics Theory (Johnson *et al.*, 1974; Lele, 1977). The temperature-time thresholds for tissue destruction are independent of the source or cause of temperature rise—they are the same for temperature rise produced by passing an electric current through a resistance wire implanted in the tissue, as for that produced by placement of the focus of an ultrasonic beam in that tissue and, in other studies by heating the tissues directly or with a laser. Figure 2 shows this relationship for destruction of the gray and white matter in the brain and other tissues of the cat and the monkey. There was no histologically detectable damage at points marked "*N*". Thus, elevating the temperature to 42°C for even 8 hr by continuous wave insonation did not result in any detectable damage. From available evidence (Frizzell *et al.*, 1977; Lele, unpublished data) the temperature-time thresholds for damage are believed to be the same in other mammalian tissues, e.g. the muscle, liver, kidney and testes. This correlates rather well with the cytoxic thresholds of various different somatic cells to thermal injury measured in many different laboratories (Proc. Int. Symp. on Cancer Therapy, 1975). Considering the acoustical absorption coefficients and thermal properties typical of mammalian soft tissues (Goss *et al.*, 1978), c.w. insonation at acoustic intensity levels of 1.5 W/cm^2 at 2.5 MHz for several minutes (approximately five) would be required to raise the temperature at the site of insonation to 44°C. Furthermore, it would have to be sustained for at least 15 min for damage to

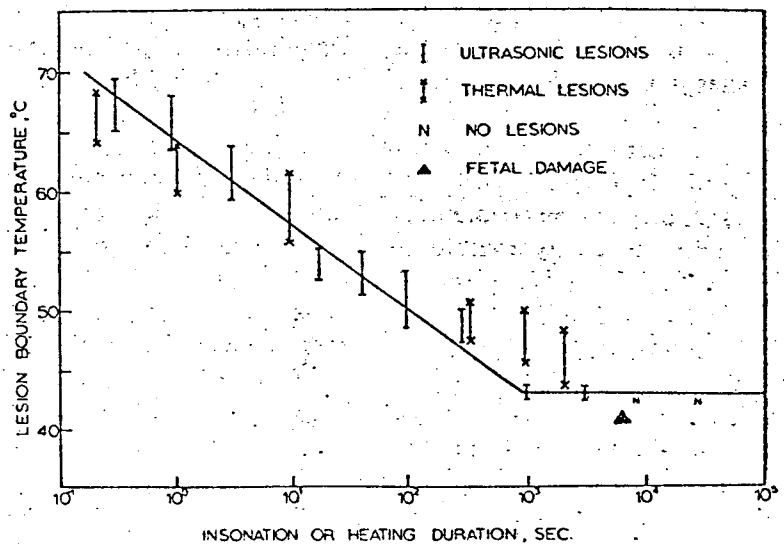

Fig. 2. Temperature-duration threshold for damage to structurally "organized" mammalian tissues *in vivo*, with ultrasonic or non-ultrasonic heating.

occur. In experiments on the c.n.s. using pulsed-ultrasound at a frequency of 3.2 MHz, pulse durations of 0.1–200μsec, repetition frequency of 1 MHz and insonation durations of up to 1 hr, no histologically detectable damage was found to occur unless the temperature-duration threshold for the c.n.s. was exceeded (Lele, 1977). Thus, both for clinical pulse-echo instrumentation and c.w. Doppler type instrumentation, the margin of safety for mature cells would again appear to be in excess of two orders of magnitude.

Experiments conducted in the author's laboratory failed to reveal any evidence that tissues have a "memory" for exposure to ultrasound. Thus, unlike X-rays, there is little likelihood of cumulative effects of ultrasound, once the heat generated has been dissipated. It should also be pointed out that, *a priori*, ultrasound, because of its long wavelengths in tissues, is unlikely to cause intracellular focal damage such as that resulting from X-radiation.

TERATOLOGICAL EFFECTS

To return to the question of safety in obstetrics: The dividing and differentiating cell populations of the embryo, specially at the stage of organogenesis are known to be particularly susceptible to damage by a variety of agents—including thermal insults. Systemic hyperthermia of 2.5°–5°C (above the normal temperature for the species) for 1 hr or longer, occurring during specific critical developmental stages of organogenesis is known to cause abortion or fetal malformation (Lele, 1975). Table 1 lists the variety of teratological effects that have been observed—the specific defect being related to the gestational stage at which hyperthermia occurred. The effect is directly on the embryo and is related not to the agent causing hyperthermia but to the hyperthermia itself. Growth retardation and microphthalmia have been observed in our laboratory in the pups born of pregnant rats rendered hyperthermic by 3°C for 1 hr on Day 9 or 10 of gestation by placement in a warm, humid incubator. (For comparison with the thresholds for damage in the adult, this data is included as ▲ in Fig. 2.) Measurements, confirmed by calculations, show that a temperature rise of 2.5°C can be produced in anesthetised mouse fetuses by their insonation *in situ* with 200 mW/cm^2, 2.7 MHz ultrasound (Fig. 3). Such hyperthermia, occurring at the stage of organogenesis, if sustained for an hour or longer could result in fetal abnormalities, such as those described by Shimizu and Shoji (1973). The ultrasonic fields and exposure durations in the Shimizu and Shoji experiments are compared with those of clinical examinations using Doppler fetal heart detectors in Table 2. It is evident that there is no real risk of ultrasonic hyperthermic teratology associated with current clinical practices unless the patient is febrile and the insonation prolonged for over 60 min. A recent report implicating hyperthermia from sauna bathing or fever during early pregnancy as an etiological factor in anencephaly (Miller *et al.*, 1978), would dictate caution in the use of ultrasound under these conditions. Organogenesis in the human embryo is completed by about Day 38 of gestation and the risk of teratogenicity should be markedly lower in the fetus, i.e. from Day 47 until birth, as is the case with ionizing radiations. Fortunately it is only at these late stages that long duration fetal monitoring is attempted and likely to be useful.

From the studies of the mechanisms of ultrasonic damage to organized mammalian tissues, it is clear that judicious clinical utilization of calibrated ultrasonic equipment threatens no known danger to the fetus. It appears that for untoward effects to occur,

Table 1. Teratological effects of systemic hyperthermia, 2.5–5.0°C for 1 hr or longer at the stage of organogenesis in the fetus (guinea pig, sheep, rat). For details, please see Lele, 1975

General	Central nervous system	Musculo-Skeletal system
Fetal resorption/abortion	Reduction in brain weight	Talipes-like conditions
Growth retardation	Microencephaly	Arthrogryposis multiplex
Microphthalmia	Anencephaly	Amyoplasia
Cataract	Defects in the spinal cord	Hypoplasia of forefeet
Defects of the abdominal wall		Absence, defects or deformations of tibia, fibula
Renal agenesis		
Defects of the palate		Failure of incisor teeth to erupt, abnormal amelogenesis

Table 2. Comparison of the ultrasonic fields and exposure durations in experiments of Shimizu and Shoji (1973) with those in clinical diagnostic procedures in man

	Mouse†	Man‡
Average intensity at skin	40 mW cm^{-2}	10 mW cm^{-2}
Average transducer-to fetus distance	approx 2 mm	93 mm
Average attenuation to uterus	negligible	15 dB
Average intensity at fetal sac	approx 40 mW cm^{-2}	0.3 mW cm^{-2}
Field characteristics at the target site	highly non-uniform, high peak intensities possible	less non-uniform due to distance from transducer
Duration of insonation	300 min	2.5 min (during an average 20 min examination)

Data from †Shimizu and Shoji (1973) and ‡Hall (1973).

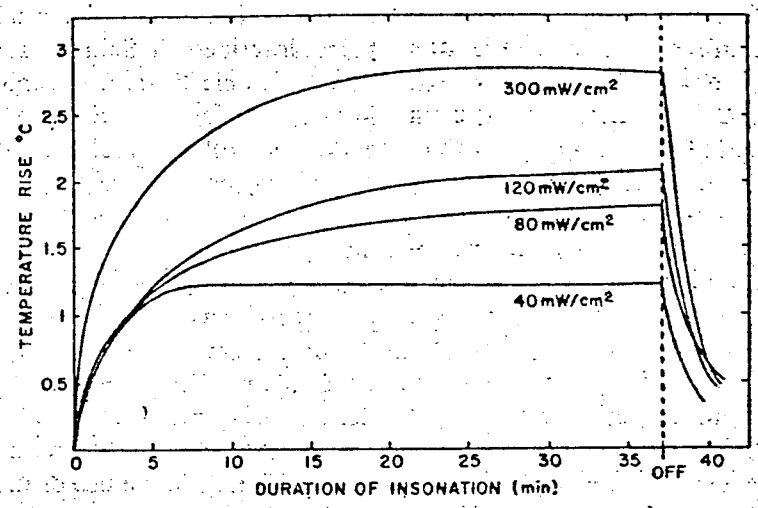

Fig. 3. Temperature elevations in mice fetuses *in vivo* during insonation under conditions in experiments of Shimizu and Shoji (1973).

the temperature in the fetus would have to be raised to over 40°C *and* sustained at that level for at least 30 min. This would suggest that ultrasonic examinations of febrile patients should not be unduly prolonged, particularly if the acoustical output of the transducer (space and time average intensity) is unknown or high. Caution would also dictate that under such conditions, ultrasonic pelvic examinations of females of child bearing age be restricted to the reproductively "safe" period—to the week following menstruation—when the probability of their being pregnant is negligible.

CONCLUSIONS

From the material presented in this article, it is obvious that there is no validated experimental evidence on which the safety of the current usage of diagnostic ultrasound can be reasonably questioned. It is comforting to note that, so far, the conclusion of safety deduced from empirical observations on man and animals is substantiated by well controlled laboratory studies on sound-tissue interactions and relevant biophysical considerations. The occurrence of transient alterations in immunological, biochemical, electroencephalographic or other functional effects at exposure levels currently considered to be safe and, whether their occurrence implies existence of a hazard, must presently be considered *sub-judice*. A diligent search must continue to be made for any possible injury or interactions which singly or together may lead to injury. It is also of utmost importance that these studies on occurrence of functional alterations at diagnostic intensity levels—or their absence—be conducted in rigorously designed experiments. Occurrence of functional alterations must also be correlated with changes in ultrastructure or microchemistry since, as there can be no function without structure, there can be no functional alterations without structural alterations. But meanwhile, with judicious use of well maintained and calibrated equipment selected on the basis of

performance capabilities and low acoustical outputs, the potential benefits of diagnostic ultrasound in better patient care seem to be so considerable and the possibility of the occurrence of somatic cell damage, teratological damage or genetic damage so negligible that hesitation in the use of this modality for diagnostic purposes would be unjustified.

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