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Review Paper

Assessing the Risks for Modern Diagnostic Ultrasound Imaging

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Some 35 years after Paul-Jacques and Pierre Curie discovered piezoelectricity, ultrasonic imaging was developed by Paul Langevin. During this work, ultrasonic energy was observed to have a detrimental biological effect. These observations were confirmed a decade later by R. W. Wood and A. L. Loomis. It was not until the early 1950s that ultrasonic exposure conditions were controlled and specified so that studies could focus on the mechanisms by which ultrasound influenced biological materials. In the late 1940s, pioneering work was initiated to image the human body by ultrasonic techniques. These engineers and physicians were aware of the deleterious ultrasound effects at sufficiently high levels; this endeavored them to keep the exposure levels reasonably low. Over the past three decades, diagnostic ultrasound has become a sophisticated technology. Yet, our understanding of the potential risks has not changed appreciably. It is very encouraging that human injury has never been attributed to clinical practice of diagnostic ultrasound.

KEYWORDS: ultrasound medical equipment, safety considerations, ultrasound regulation, historical development

1. Introduction

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 be cautious to 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. Yet, this experiential data base strongly suggests that the clinical use of modern diagnostic ultrasound instrumentation represents a risk-free diagnostic modality. An examination of the historical developments of diagnostic ultrasound equipment, and other issues that surrounded these developments, is provided here in an effort to provide perspective as to why this important diagnostic modality appears safe.

2. Early History (up to the late 1940s mostly)

The earliest history of the science of sound has been recorded by Hunt[1] in his manuscript which was completed following his untimely death. Another interesting and readable history of acoustics was prepared by Lindsey.[2] Hunt recounts the period from antiquity to the age of Newton, and Lindsey brings us mostly to the age of Rayleigh with special emphasis of Rayleigh's impact on modern acoustics. Both of these histories provide a view of how acoustics then was highly interdisciplinary, a situation not too different from that which exists today. Sir Isaac Newton put forth the first serious theory regarding sound being a wave in his 1687 *Principia mathematica.*[3] Modern acoustics as we know it today was put forth in the classic 1877 work by Lord Rayleigh.[4]

The transduction device has always been central in the effective production of ultrasound wherein both the magnetostrictive and piezoelectric effects have played important roles. The magnetostrictive effect was discovered by Joule[5] in the mid 1800s. More than three decades after the 1880 discovery of the piezoelectric effect by the Curie brothers,[6] a discovery which revolutionized the production and reception of high-frequency sound, the French scientist Paul Langevin developed one of the first uses of ultrasound for underwater echo ranging of submerged objects with a quartz crystal at an approximate frequency of 150 kHz.[7] Langevin was, perhaps, the first to observe that ultrasonic energy could have a detrimental effect upon biological material wherein he reported[8] "fish placed in the beam in the neighborhood of the source operation in a small tank were killed immediately, and certain observers experienced a painful sensation on plunging the hand in this region." Langevin also reported observing incipient cavitation in water when the source was active.

Langevin, however, was not the first to propose echo ranging. Richardson, in 1912 in response to the *Titanic* disaster, suggested both airborn[9] and underwater[10] echo-ranging schemes, and, in 1914, Fessenden[11] experimentally demonstrated echo-ranging underwater detection of an iceberg.

Another decade passed before a more detailed, experimental study was conducted by Wood and Loomis[12] to investigate Langevin's 1917 observation. Although the ultrasonic levels were not specified, their experimental studies showed that ultrasonic energy had a range of effects from rupture of Spirogyra and Paramecium to death of small fishes and frogs by a one- to two-minute exposure the latter also observed by Langevin with a Poulsen arc oscillator. Considerable work followed and in the earliest review paper on this subject, Harvey[13] 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.

It is not known when scientists initially recognized the two principal biophysical mechanisms that are currently invoked, *viz.*, thermal and cavitation. The application of ultrasound to therapeutically heat tissue was suggested as early as 1932.[14] Also in the 1920s Boyle and his colleagues were perhaps the first to observe ultrasound-produced gas bubble formation in liquids, and recognized this phenomenon as cavitation.[15–17] The ultrasound-induced biological observations

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by Langevin,[8] and by Wood and Loomis[12] were caused by gas bubbles as demonstrated with overpressurization experiments.[18]

Ultrasound-induced tissue heating was applied extensively as a therapeutic agent in the 1930s and 1940s. However, while it was clear that ultrasound could effectively heat tissue, and excess enthusiasm resulted in numerous clinical applications being proposed and tried, the inferior clinical experience caused this modality to fall into disfavor (see discussion of 1949 Erlangen resolution[19]). Thus, as Hill[20] observed of this time, "it is perhaps unfortunate that the generation of ultrasound proved to be so relatively simple and cheap that a considerable practice was built up."

During this time period, with an understanding that ultrasound at sufficient levels could have a dramatic effect on tissues, and produce large temperature increases, the potential for ultrasonic surgery was proposed. This ability to noninvasively burn focal tissue volumes deep in the body using ultrasound was first proposed in 1942[21,22] as a neurosurgery technique. Ultrasound surgery and its biophysical mechanism (heating) were further developed in the late 1940s and early 1950s.[23] Also proposed in 1948 and applied in 1952 was the application of ultrasound surgery to destroy the vestibular function to treat the symptoms of Menière's disease.[24]

There was very little activity for about a decade in the development of ultrasound imaging capabilities following Langevin's SONAR work during the First World War. In 1928, Sokolov proposed and a few years later demonstrated a through-transmission technique for flaw detection in metals.[25] Firestone's 1942 patent[26] for flaw detection in metals, and his later demonstration, is considered the first modern pulse-echo ultrasound technique for flaw detection,[27,28] and the basis for pulse-echo imaging in medicine. A technique that was never developed into clinical application was based on the principle of differential attenuation, a through-transmission ultrasonic technique which was constructed in 1937 for brain imaging by the Dussik brothers,[29] and by others in the late 1940s.[30]

The development of diagnostic ultrasound instrumentation as we know it today was initiated around the time of the end of the Second World War, a time when fast electronic circuitry was becoming available as a result of the wartime RADAR and SONAR efforts, both of which utilized the pulse-echo principle. In the late 1940s and early 1950s, Howry[31] showed that tissue interfaces could be detected in ultrasound echoes, Wild[32–34] showed that tissue structure could be differentiated (cancer from benign) in ultrasound echoes, and Ludwig and Struthers[35] showed that gall stones could be detected in ultrasound echoes, these being A-mode applications; and Howry and Bliss[36] and Wild and Reid[37,38] independently built and successfully demonstrated the earliest B-mode, bistable, ultrasound scanners.

Transduction materials had a central role in the diagnostic ultrasound developments. Quartz-based transducers had limited application, being first used by Langevin for underwater echo ranging. Quartz was used because other transduction devices and/or materials had not been developed, and it possessed high mechanical strength and low internal friction. However, large amplitude voltages were required to drive quartz transducers. Around the 1930s, Quartz started to be replaced for underwater ultrasound applications by Rochelle salt and was used up to the time of the Second World War[39] at which time it was replaced with piezoelectric ceramics, the first of which was barium titanate.[40] The strongly piezoelectric Rochelle salt was replaced because its properties were very susceptible to moisture. Piezoelectric ceramics had two major advantages, improved efficiency to convert electrical into acoustic energy and could be processed into varying shapes and sizes. Also, piezoelectric ceramics did not require large amplitude voltages to drive them. Pure barium titanate's principal disadvantage was its low-temperature Curie point (−5°C) and to improve this, small amount of calcium titanate and/or lead titanate were added. A major advancement in transducer materials occurred in 1954 when Jaffe[41] discovery lead titanate-zirconate compositions, a piezoelectric material which retained most of the advantageous properties of the titanates while extending its operating temperature range.

It is interesting to observe that both Howry's first system and Wild's system in the late 1940s used quartz as the transduction material. However, Howry's later systems employed some of the newer transduction materials,[31] and Reid and Wild[42] had evaluated the applicability of an annular array made from barium titanate.

In parallel with the early history of ultrasound were the developments of ionization radiation starting with Röntgen's 1895 discovery of X-rays,[43] 15 years after the Curie brothers discovered the piezoelectric effect, and for which he won the first Nobel Prize in physics in 1901. Becquerel, in 1896, discovered natural radioactivity wherein he found that uranium gave off some "invisible rays" that darken a photographic plate. In 1898, Marie and Pierre Curie discovered the two new radioactive elements *polonium* and *radium*, the same year Rutherford identified what we now know as alpha and beta particles. Almost immediately, medical application of X-rays were developed, and the science and technology of radioactivity was born. An ironic history with ionizing radiation resulted in Marie Curie, using piezoelectric techniques devised by her husband Pierre Curie to carefully measure radiation in pitchblend, an ore that contained uranium; she died in 1934 from pernicious anemia, presumable from an over exposure to radiation. This view gained support when, in 1942, Dunlap[44] provided strong evidence that ionizing radiation was responsible for human leukemia. In the mid 1920s, Müller[45] and Stadler[46,47] discovered the mutagenic effects of X-rays, thus identifying the potential hazards of ionizing radiation. Major national and international activities originated to quantify exposure from ionizing radiation from which radiation protection guidelines were developed.[48] In the mid 1920s, the first radiation protection guideline was the *tolerance dose* which was based on the *skin unit dose*, the amount of ionizing radiation just required produced skin erythema (skin redness) in humans within a period of about one week. The tolerance dose was about one percent of a skin unit dose averaged over a one month period. Later when the concept and value of the unit *roentgen* (R) was established in 1928,[49] the skin unit dose was quantified to roughly 600 R; thus the tolerance dose worked out to be 6 R on a monthly basis, or 0.2 R/d, later to be lowered to 0.1 R/d. The term tolerance dose created many problems because it was impossible to predict just what level was tolerable over a long period of time and with the realization in the mid 1930s that ionizing radiation effects may not be threshold-type reactions, the term *maximum permissible*

dose was substituted for tolerance dose. In the early 1930s, it was shown that the biological effect of ionizing radiation depended not only on the exposure intensity and time but also on the quality of radiation since differences were observed in growth reduction and mortality studies between X-rays and γ rays.[50] This was termed the *relative biological effectiveness* (RBE) concept and became even more important in the 1940s with the production and discovery of other ionizing radiation particles. In the late 1940s the *rep* for *roentgen-equivalent-physical* was proposed[51] and represented the energy absorbed by tissue when exposed to 1 R. The rep concept led to what is currently the quantity *absorbed dose* with the unit *rad* for *radiation absorbed dose*.[52] At the same time the rep was being suggested as a unit to describe dose, the unit *rem*, for *roentgen-equivalent-man*, was suggested for radiation protection purposes and defined as the product of energy absorption (in reps) and the RBE (dimensionless) of the energy under consideration.[51] In the mid 1950s, the rem concept was adopted, using the rad instead of the rep. The quantity *RBE dose* in rems was equal to the product of absorbed dose (in rads) and the RBE.[53] Also, concerns for the protection of the fetus from the possible effects of low doses of ionizing radiation were being raised in the 1950s.[54–56]

The scientific and engineering advances during the 1940s had enormous influences on the development of diagnostic ultrasound. In 1943, the Moore School of Electrical Engineering at the University of Pennsylvania was contracted to construct the Electronic Numerical Integrator and Computer (ENIAC), the first electronic computer with design specifications to calculate 5000 operations per second. Up to then, the only computing capabilities were basically analog computers. Another major program was the radar activity at the Radiation Laboratory at MIT from which the need was identified for fast electronic circuitry in order to achieve higher frequencies for better imaging resolution. Radar was also responsible for much of the diagnostic ultrasound nomenclature. In the mid 1930s, the American Telephone and Telegraph Company identified a need to develop fast electronic switching to replace electromechanical switching. This lead AT & T's Bell Labs to initiate a solid-state research program which lead to the invention of the point-contact transistor for which its 50th anniversary was celebrated in December, 1997.

While ultrasound exposimetry was inferior in these early times to that possible today, these early bioeffect 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 known that high ultrasonic energy levels had the potential to be hazardous. This information must be kept in mind because many of the early pioneers who were developing ultrasound imaging devices were also cognizant that ultrasound had the potential for disrupting biological materials. Additionally, they were aware from the history of ionizing radiation to be concerned with the potential for hazardous effects. Thus, it must be presumed that there has been a continuing concern of the risk from ultrasound prior to and during the entire period of diagnostic instrumentation development.

It should be noted that as early as 1951,[57] individuals working on the development of diagnostic ultrasound equipment had an awareness of a potential risk to patients. Also in the early 1950s the same investigators active in image system developments were also investigating the nature of ultrasound-induced tissue damage,[58–62] thus demonstrating a concern for the safety of this diagnostic modality.

3. Mid History (between early 1950s and late 1960s)

By the early to mid 1950s, the basic ideas of producing and acquiring reflected ultrasound echoes using either water path or direct contact methods, and displaying them in either A-mode and B-mode formats had been identified. These early investigators made their observations and findings public through presentations and publications which no doubt stimulated others to pursue pulse-echo system improvements and/or diagnostic imaging applications in, for example, echoencephalography,[63–65] ophthalmology,[66–68] echocardiography,[69,70] obstetrics and gynecology,[71,72] breast,[73] direct-contact two-dimensional ultrasonic scanner,[74,75] ultrasonic scanner with two articulated arms[76,77] and dynamic focusing.[42] However, progress was modest and the bistable images were often challenging for diagnostic interpretation in the late 1950s and 1960s. It was a time when most of the progress was being made in university and/or hospital settings by true pioneers.

The equipment developments for assessing flow and motion (Doppler) developed rapidly during this period. One of the first proposed was a two-transducer, transit-time, continuous wave technique,[78–80] but it did not prove to be a satisfactory method for measuring blood flow. The first successful system was a continuous wave, nondirectional, backscatter technique.[81,82] Directional Doppler was proposed in 1964[83] which lead to various pulse-wave techniques.[84–88] Most of these techniques have now been replaced with more sophisticated two-dimensional, real-time approaches. Like with the pulse-echo imaging developments, progress during this time was made principally in university and/or hospital settings.

During these two decades, the ability to quantify ultrasonic fields improved but only to a limited extent; there were still no national-based ultrasound measurement standards or procedures. All of the improvements dealt with absolute procedures to quantify second-order quantities, and consisted of ultrasonic intensity via thermocouple probe[89–92] and electrodynamic method,[93] and ultrasonic power via calorimetry[94] and radiation pressure balance.[94–96]

This period saw only a few advances in our understanding of how ultrasound interacted with biological materials. Perhaps the first major symposium on "Ultrasound in Biology and Medicine" was held at the University of Illinois in 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[34,97,98] or the thermal mechanism of ultrasound.[99–101] Two additional symposia were held (June, 1955 June, 1962) to address similar issues.[102,103] This literature laid the basic foundation for the biophysical mechanisms by which ultrasound is known to affect biological materials, *viz.*, thermal and cavitation.

There were scattered reports about ultrasound having an effect on biological systems during this period, but these reports in general did not deal with the types of exposure that would be expected from diagnostic ultrasound equipment, nor did they provide any kind of a consistent message. Two sum-

maries identify a number of these early reports.[104,105] However, during the 1950s and 1960s, as diagnostic ultrasound equipment started to be used in clinical medicine, there continued to be concerns about its safety which could not be dispelled because of the paucity of well-conducted and comprehensive experimental studies.

One interesting observation made in the late 1960s that would wait more than two decades before it would become an active area of basic and clinical research was the identification of the production of cavitation at the tip of catheters when various liquids were injected through the catheter. The cavitation was a primary source of echoes in an echocardiograph image, and the first application of an injected contrast agent was identified.[106,107]

Ancillary activities in the late 1950s which would have an enormous impact on future diagnostic ultrasound instrumentation included the first integrated circuit using discrete wire interconnections by Kilby and the first integrated circuit using vapor deposited metal connections by Noyce,[108] and in 1960, DEC announced its first minicomputer, the PDP-1, and in 1965, announced the PDP-8, the first minicomputer to use integrated circuits.[109]

4. The More Recent History (between early 1970s and mid 1980s)

This 15-year period witnessed the greatest expansion with diagnostic ultrasound imaging capabilities, starting with bistable, static and ending with grey-scale, real-time capabilities. One of the major ultrasonic image quality advances was the introduction of the grey scale.[110,111] Another major advance was the ability to display images in "real time," wherein there were a number of approaches including the mechanical scanner,[112] the linear array,[113,114] the phased array[115–117] and the water-path scanner.[118] Scan converter developments played an important role with the implementation of both grey-scale and real-time capabilities.[119,120]

Major Doppler advances also occurred during this period when blood velocity estimates could be displayed on a B-mode image, that is, duplex imaging,[121] and then when both theory and high-speed computational electronics provided the capability for color-flow imaging.[122,123]

During this period, the ability to quantify ultrasonic fields improved considerably. Perhaps the first intercomparison (between two universities) to assess the absolute measurement of ultrasonic intensity was conducted;[124] the comparison was conducted with the elastic sphere radiometer.[125]

A major breakthrough of earlier work occurred with Kawai's discovery in 1969[126] of the strong piezoelectric effect in polyvinylidenefluoride (PVDF) to measure the temporal characteristics of diagnostic ultrasound fields. Two types of PVDF hydrophones were developed, *viz.*, needle[127] and membrane.[128–131]

The US National Bureau of Standards (now the National Institute of Standards and Technology, NIST) developed an ultrasound power transfer standard,[132] and the UK National Physical Laboratory developed both a two-transducer reciprocity technique and an optical technique.[133]

This 15-year period had its controversies relative to whether diagnostic ultrasound was safe. Two are briefly reviewed to illustrate the level of concern the ultrasound community felt since these reports dealt with the potential of diagnostic ultrasound affecting chromosomes. In 1970 it was reported that ultrasound from a low-output commercial fetal pulse detector induced aberrations in human lymphocyte chromosomes.[134] Numerous laboratories throughout the world attempted to replicate the findings without success. The matter was brought to closure when, in 1975, the same lead author of the original report was invited to another laboratory in an attempt to duplicate the experiment; they were unable to reproduce the original findings.[135] In the late 1970s, a report appeared[136] which suggested that exposure from a diagnostic ultrasound system showed an increase in human lymphocyte sister chromatid exchange (SCE) frequency (an indication of chromosome damage). Like with the previous chromosomes aberration situation, numerous laboratories throughout the world attempted to replicate the findings. In 1984, the American Institute of Ultrasound in Medicine's Bioeffects Committee carefully and thoroughly reviewed a total of 14 ultrasound-SCE studies and concluded that these studies do not suggest a hazard from exposure to diagnostic ultrasound.[137]

In the early to mid 1970s, there was great uncertainty with respect to the safety of ultrasound as discussed above and what authority and role the US Food and Drug Administration (FDA) would take in terms of regulating diagnostic ultrasound. Regulatory control of diagnostic ultrasound in the United States can be traced to passage of the 1976 Medical Device Amendments to the Food, Drug and Cosmetic Act, but for the several years prior to its passage, the FDA coordinated a classification scheme for all medical devices. 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 and precise procedure to quantify diagnostic ultrasound equipment outputs. Because of these difficulties, the output levels from diagnostic ultrasound equipment were not well characterized, and human exposure levels could not be compared to results from 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 represented many of the ultrasound manufacturers, joined efforts in 1976 to develop a voluntary 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 *Safety Standard for Diagnostic Ultrasound Equipment*[138] was developed over a five-year period and set forth precise definitions, output measurement procedures and labeling requirements related to those characteristics of ultrasound equipment that were believed at that time to pertain to patient exposure and safety. The voluntary standard's labeling requirements called for manufacturers to make available (publicize) to the ultrasound community 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 labeling requirements were based on the philosophy that there was a *potential risk* from diagnostic ultrasound exposure and included those quantities whose magnitudes were known or believed to be

related to actual damage or to risk of damage to biological tissues; they were the quantities most often reported in the basic science literature to relate the strength of ultrasound to the production of biological effects in laboratory experimental studies. The voluntary standard did not specify upper limits.

In the early 1980s, the assessment of diagnostic ultrasound risk was addressed by two major activities. One of the activities was sponsored by the US National Institutes of Health consensus development conference processes[139] by convening an expert panel of physicians, basic scientists, epidemiologists, nurses, educators, and sonographers to provide answers to specific questions related to safety and efficacy of diagnostic ultrasound in obstetric practice. 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 diagnostic ultrasound efficacy was critically reviewed. Also, this process recommended against routine scanning of the embryo and fetus. Further, it was suggested that while diagnostic ultrasound does not appear to be associated with any known hazards, investigators should continue to evaluate risks.

The other activity was conducted under the auspices of the National Council on Radiation Protection and Measurements.[140] The document rigorously covered the basic physics of ultrasound with an emphasis on medical ultrasound fields and on the quantification of various ultrasonic field quantities to which humans were exposed during the course of an ultrasound examination. Also included were mechanisms by which ultrasound interacts with biological material and effects caused by ultrasound on biological materials such as plants, animals, and in vitro systems. Finally, this document set forth a number of recommendations that fell into the categories of research needs, industrial practices, education, and exposure criteria. It is interesting that a number of the recommendations were consistent with those put forth by the Workshop on the Interaction of Ultrasound and Biological Tissues[104] a decade earlier.

When the FDA initiated the regulation of diagnostic ultrasound equipment in the mid 1980s,[141] it set *application-specific* intensity limits in their 1985 "510 (k) premarket notification" which manufactures could not exceed (see Table I). 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, the date when the Medical Device Amendments were enacted. The exposure quantities required by FDA were, in part, similar to those in the *Safety Standard for Diagnostic Ultrasound Equipment* voluntary standard's labeling requirements.[138] However, the limits were *not* based on safety considerations but rather on the maximum output limits of known diagnostic ultrasound equipment at the time when the Medical Devices Amendments were enacted, in May, 1976; hence the term *pre-amendments levels*.

To emphasize the date-base regulation approach as opposed to the safety- and efficacy-base regulation approach of the FDA, the American Institute of Ultrasound in Medicine notified[142] the FDA in mid 1986 that there existed prior to May 28, 1976 at least two diagnostic ultrasound devices (pre-enactment ultrasound devices) with intensity levels greater than those listed in Table I. In early 1987, the FDA updated their diagnostic ultrasound guidance to higher intensity levels[143] to those listed in Table II. The date-based regulation approach has been criticized by technical, scientific, and medical professionals, as well as by the diagnostic ultrasound industry[144] because of the implication that these arbitrary limits are safety based, and because they could limit future clinical benefits by preventing the development of more advanced diagnostic ultrasound systems, and hence greater clinical benefit, that may require higher output levels. Further, it must be recognized that limited diagnostic ultrasound capabilities may, in fact, be responsible for greater risk to the patient due to either an inadequate diagnosis, or to the use of an additional diagnostic procedure with a defined risk.

Table I. FDA's pre-amendments levels of diagnostic ultrasound devices (FDA, 1985).

	Derated intensity values		
	I_{SPTA} (mW/cm^2)	I_{SPPA} (W/cm^2)	I_m (W/cm^2)
cardiac	430	65	160
peripheral vessel	720	65	160
ophthalmic	17	28	50
fetal imaging and other[a]	46	65	160

[a] Abdominal, intraoperative, small organ (breast thyroid testes), neonatal cephalic, adult cephalic.

Table II. FDA's pre-amendments levels of diagnostic ultrasound devices (FDA, 1987).

	Derated intensity values		
	I_{SPTA} (mW/cm^2)	I_{SPPA} (W/cm^2)	I_m (W/cm^2)
cardiac	430	190	310
peripheral vessel	720	190	310
ophthalmic	17	28	50
fetal imaging and other[a]	94	190	310

[a] Abdominal, intraoperative, small organ (breast, thyroid, testes), neonatal cephalic, adult cephalic.

5. Where We are at Now (since the mid 1980s)

This is the period that introduced to clinical practice ideas for which the background was investigated years ago such as harmonic imaging (tissue nonlinearity properties investigated in the early 1980s[145]), contrast agents (originally proposed and demonstrated in the late 1960s[106,107]), three-dimensional imaging to a limited extent (first paper published in 1970[146]) and composite transducers to a limited extent (introduced in the late 1970s[147]).

This is also the period for which a number of equipment, techniques and/or clinical innovations are being investigated, but which have not yet made it into routine clinical practice such as elastic imaging,[148,149] high-frequency imaging,[150] three-dimensional microvascular imaging,[151] Doppler tomography,[152] nondiffracting beam transducers,[153] phase aberration corrections,[154] relaxor transducer materials[155] and two-dimensional arrays.[156,157]

Within the past decade, there have been substantial improvements, through national and international efforts, in our understanding to identify the biological interactions diagnostic ultrasound exposures may have with soft tissues, including

both thermal[158–160] and acoustic cavitation-like[160,161] phenomena. These reports have provided, in part, the basis for the development of a new approach to regulate diagnostic ultrasound equipment (see below).

It had been long thought that diagnostic ultrasound exposures could not produce biological damage. However, in the early 1990s, based on initial observations in the late 1980s from lithotropsy experiments, diagnostic ultrasound-type pulses at diagnostic pressure levels have produced significant damage (lung hemorrhage) in mice, rats, rabbits, and monkeys, the first observation being in mice.[162] There are open questions yet about whether this effect occurs in humans.

A diagnostic ultrasound educational activity was initiated with a workshop in June, 1988. This workshop set out certain principles which resulted in the initiation of a three-year process involving numerous clinicians, scientists, engineers and government regulators from many organizations; this group finalized and approved, in 1992, the *Standard for Real-Time Display of Thermal and Mechanical Indices on Diagnostic Ultrasound Equipment*, commonly referred to as the Output Display Standard.[163] The purpose of this voluntary standard was to provide the capability for users of diagnostic ultrasound equipment to operate their systems at levels much higher than previously had been possible in order to have the potential for greater diagnostic capabilities; the standard did not specify any upper limits. In doing so, the possibility existed for the potential to do harm to the patient. Therefore, two biophysical indices were provided so that the equipment operator has real-time information available to make appropriate clinical decisions, *viz.*, benefit *vs.* risk, and to implement the ALARA (**A**s **L**ow **A**s **R**easonable **A**chievable) principle, that is, the Output Display Standard provides for a real-time output display which gives the user information about the potential for temperature increase (the Thermal Index) and mechanical damage (the Mechanical Index).

Following the adoption of the voluntary Output Display Standard, the FDA revised its diagnostic ultrasound regulatory guidelines by essentially adopted the Output Display Standard. However, since the Output Display Standard did not include upper limits, the FDA added *application-nonspecific* guidelines[164,165] as regulatory upper limits based on a derated spatial peak, temporal average intensity, I_{SPTA}, value of 720 mW/cm^2 and a Mechanical Index, MI, value of 1.9. The I_{SPTA} upper limit appears to still be based on the maximum pre-1976 value since there is still no scientific basis for this value. However, the MI upper limit is, in part, based on experimental studies.[166]

To complement the Output Display Standard, a number of professional societies have developed a brochure[167] to satisfy, in part, the FDA user educational requirement.[164,165] The brochure is divided into three parts. Part One describes ultrasound-induced bioeffects and why we should be concerned about them. Part Two describes the risks and benefits of conducting diagnostic examinations and introduces the concept of ALARA. Using the ALARA principle, the intent is to obtain needed diagnostic information with minimum risk to the patient. Part Three describes how to implement the ALARA principle on equipment with and without an output display.

6. Final Thoughts

All evidence, or lack thereof, suggests that diagnostic ultrasound does not represent a risk to patients. It is the view of this author that the reason for such a remarkable record is the rigid regulatory control the FDA has exercised over this diagnostic modality, a level of control unmatched by any other radiological imaging modality. The result of this rigid control has required diagnostic ultrasonic manufacturers to limit the output of their equipment to specific output levels that were achievable more than 20 years ago. To what extent the clinical capabilities of diagnostic ultrasound systems could reach if such rigid controls were not imposed is left only to speculation. Likewise, the issue of patient risk is left to speculation. To rigidly control without a good scientific justification benefits no one, particularly the patient. The physician is a professional trained to provide health care by making informed benefit-risk judgements. The FDA's regulatory approach had denied the physician the *need* to become informed about such benefit-risk issues, and for that, we are all worse off.

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