1. Executive Summary

In developing background for scientifically based exposure criteria, this Report gives much emphasis to the means by which ultrasound can bring about changes in biological structures or processes. The intent is to consider all known mechanisms, thermal and nonthermal. Nonthermal mechanisms are taken up in Sections 3 through 8 and are divided, for convenience, into two classes: those that involve acoustic cavitation, i.e., the many-faceted activities of gas-filled cavities, and those that do not. It is the former on which there is, by far, the most information, and to which the greater part of this Report is devoted; however, the latter is of much interest, and is discussed in Section 3.

Effects of nonthermal mechanisms that do not involve cavitation include: tactile response to, and hearing of, pulsed ultrasound; aggregation of cells in blood vessels; reversible alteration of electrical and other properties of cell membranes; and irreversible cell damage. These depend on acoustic radiation pressure, radiation force, radiation torque, or acoustic streaming, all of which are time-averaged quantities that are consequences of acoustic nonlinearity.

Acoustic cavitation phenomena include a wide variety of possibilities. The kind of activity that occurs depends on the size of the cavity as well as on the nature of its immediate surroundings; it is also dependent on the characteristics of the ultrasound field, the pressure amplitude being especially important. The response to an ultrasound field of low or moderate pressure amplitude may be a periodic volume pulsation, so that the cavity becomes a secondary source of sound; this response underlies the effectiveness of the gas-based contrast agents that are now widely used to enhance ultrasound imaging. Other phenomena that occur at moderate amplitudes are best seen in modeling experiments with plants, insects and in vitro cell suspensions, but have their counterparts in mammalian tissues when contrast agents, bubbles or other gas bodies are present. These phenomena include fluid movements, bubble-particle interactions, and shearing action in the neighborhood of gas bodies with consequent effects on properties of cell membranes. The movements and actions can be partially accounted for as special forms of acoustic radiation force and small-scale acoustic streaming.
If a beam of pulsed ultrasound from commercial diagnostic ultrasound equipment is projected into water or another aqueous medium and if contrast agents or other suitable small gas bodies are present, the pressure amplitude during the pulse is often sufficient to produce inertial cavitation. This is a violent activity in which a cavity expands during part of a sonic cycle, then collapses suddenly to a very small volume which persists for a few nanoseconds, during which time the pressure and temperature of the contents are very high. If the collapse occurs near a solid boundary, a liquid jet may be formed that impinges on the boundary at high speed. Inertial cavitation is usually involved during \textit{in vitro} investigations of effects of ultrasound on cell suspensions or cellular monolayers; the cell killing, which is commonly observed, appears to be mostly from the associated mechanical forces. Biochemical damage may result from the highly reactive chemicals, including free radicals, that are often produced during the moments of high pressure and temperature that follow collapse events. \textit{In vitro} experiments have led to much information on the possible biological consequences of inertial cavitation.

While experiments with model systems, together with relevant theory, have led to valuable insights on basic mechanisms, the results cannot usually be applied with confidence to clinical situations, unless they have been tested by experiments with living animals. This is especially true when considering possibilities for nonthermal biological effects caused by various aspects of acoustic cavitation. In mice, rats, swine and other laboratory animals, diagnostic ultrasound has been shown capable of rupturing small blood vessels, with consequent leakage of red cells into extravascular space, but only under special conditions. The conditions are that the vessel walls must be near gas bodies that either (1) are present normally, as in adult lung and intestine or (2) have been injected into the blood stream, as when gaseous contrast agents are used. The use of contrast agents can significantly increase the potential for ultrasound to affect processes in organs or tissues that do not normally contain obvious gas bodies, as is shown by the recent findings of increased incidence of premature ventricular contractions when the heart is examined with ultrasound. In general, gas bodies are found to play a critical role, serving as sites where diagnostic ultrasound can alter biological structures and processes \textit{via} nonthermal mechanisms.

Biological effects produced by thermal mechanisms are taken up in Section 11, as an extension of the detailed treatment of this subject in NCRP Report No. 113. In that earlier Report, attention was given to teratological effects of heat, on which topic the information comes mostly from “whole-body” exposures in which small pregnant
laboratory mammals are subjected to elevated temperatures in heated air chambers or water baths. In the present Report, the analysis of results from such exposures is extended, in order to obtain information on situations where heat is applied more directly to the fetus, as it is when focused ultrasound is used clinically to examine the human fetus. Also included here is a review of recent advances in experimental and theoretical methods for measuring or estimating temperature fields produced by ultrasound in model systems and in mammals.

A review of existing human epidemiological studies (Section 12) of patients examined with ultrasound leads to the encouraging conclusion that these studies do not provide sufficient justification for finding ultrasound to be the cause of any of the adverse effects investigated. It is pointed out, though, that these studies would not have detected a small percentage increase in a common event. Also, it is noted that the studies are based on procedures using ultrasound equipment manufactured before 1991, and that important changes in equipment and procedures have occurred since then.

In the course of discussions in this Report on the status of knowledge about biological effects of ultrasound, specific values are given for physical parameters that define conditions of relative safety or concern; these are the “criteria” to which the title of this Report refers. For example, approximate values are given of the lowest pressure amplitudes for which lung damage has been observed in laboratory animals. These are in situ values of the pressure amplitude, i.e., they apply at the surface of the animal lung. In using these criteria for human exposures, it is necessary to estimate the pressure-amplitude values existing at the surface of the human lung. In order to do this, knowledge is required of the acoustic pressure amplitudes produced by the diagnostic equipment at various parts of the human body. These quantities cannot be measured directly but, in the United States, are estimated by manufacturers from measurements made in water, together with assumptions about ultrasound propagation characteristics in tissues. Section 9 includes a discussion of present knowledge on attenuation of ultrasound in the human body, with special consideration of obstetrical applications. Present standards adopted by the Food and Drug Administration (FDA) for estimating the attenuation appear to be sufficiently accurate for several large classes of obstetrical examinations. However, they can seriously overestimate the attenuation (and thus underestimate the exposure) in situations where there is a large fluid component in the path to the target tissue. Proposals are offered for improving the estimates.
Section 13 contains conclusions reached by weighing the information presented in the preceding sections of this Report, and Section 14 contains recommendations. The latter recognize the responsibilities users have in making decisions about procedures to be followed and control settings to be used. It is necessary to be knowledgeable about ultrasonic dosimetry and effects, and about acoustical characteristics of the equipment used, in addition to the particular characteristics of the patient being examined. Modern equipment for diagnostic ultrasound is complex, and users need considerable assistance in making decisions. The on-screen display of thermal indices (TI) and a mechanical index (MI), now provided by many manufacturers in response to requirements of the FDA, mark a significant step forward in making safety information available to users. It is recommended that there be continuous efforts to make this information more accurate and complete. In Section 14, criteria are expressed both in terms of these displayed indices, and in terms of the basic physical quantities involved.

It is noted that an appropriate benefit/risk decision does not always call for a choice of pressure amplitude, or other acoustic output parameter, low enough to assure that there is no risk. For some situations, it may be determined that the improved imaging capabilities that can come from increased output level, as discussed in Section 10, or from use of contrast agents, may offer enough benefit to make increased risk acceptable.

It is the purpose of this Report to present background for a scientifically based approach to safety assessment for diagnostic ultrasound, so that users can make informed decisions, while taking advantage of new developments in equipment and procedures.