REVIEW OF LITERATURE
Although human use of sound must have extended far back into pre-history, the physical nature of sound was not understood until the time of Newton, in the 17th century. Little was known about the physiology of hearing until Helmholtz's researches in the 19th century, when methods became available to generate and detect ultrasound.

The effects of intense ultrasound on living organisms were among the early observations of Langevin during World War I. By far the major events of the period influencing the future development of ultrasonics were the Titanic disaster of 1912. Rayleigh's study on the pressure of collapse of a bubble in a liquid (1917), which was the pioneer model for ultrasonic cavitation. However, there were few practical applications of ultrasound until the 1920's.

Wood and Loomis (1927) observed the destruction of Spirogyra and killing of small fish and frogs when they were exposed to 300 KHz ultrasound for several minutes. Harvey and Loomis (1928) reported streaming within cells
and cellular destruction, at 404 KHz. Schmitt (1929)
developed an apparatus that used glass tubes to transmit the
ultrasonic vibrations from a crystal into a glass micro-
needle, which could be inserted into single living cell
contained in a hanging-drop microscope preparation. Effects
observed in amoeba and "marine eggs" included rotation of
granules about the needle, decreased viscosity of protoplasm, "churning" of cellular contents and coagulation of protoplasm
into a gel.

Schmitt and Uhlemeyer (1930) reported ultrasonically induced lysis of protozoa; the frequency and
intensity were unspecified. Freundlich (1932) suggested its
use as a diathermic agent. Gyorgi (1933) investigated the
chemical and biological effects of ultrasound. Dussik and
Dussik (1937) studied the possibility of making images of
the brain by recording vibrations in the intensity of an
ultrasonic beam transmitted across the head. Pohlman (1939)
mentioned its first physical therapeutic use.

Harvey et al., (1944) observed all living systems
examined are known to possess cavitation nuclei. William
J. Fry (1947) undertook the study of the central nervous
system using ultrasonics as a means of exploration. In
addition to lethal effects on roaches and mice, momentary
dizziness and heating of exposed parts of the body were noted in humans by Allen et al., (1948). Ludwig (1949) had demonstrated the feasibility of detecting gallstones implanted in dogs from their ultrasonic reflections.

Fritz-Niggli and Bonf (1950) found no increase in lethal mutation frequency after irradiation of eggs, larvae and pupae with 0.3 to 1.8 w/cm$^2$ at 800 KHz for 25 min. Fry et al., (1950) observed the physical factors involved in changes produced in the physiological characteristics of tissues by ultrasound and the temperature changes resulting from absorption of acoustic energy while irradiation was in progress. John J. Wild along with John Reid (1951) gave a correct diagnosis for a malignant cerebral tumour. Wolff (1951) demonstrated that when the excised cray fish ventral nerve cord exposed to ultrasound (35w/cm$^2$, frequency 1mc) exhibited a reduction of spontaneous activity after several seconds exposure and recovered its original activity about one minute after the ultrasound was turned off. Wild and Reid (1952) and Howry et al., (1952) explored the use of this modality for the diagnosis of breast disorders. Selman (1952) and Spencer (1952) showed ultrasound to be disruptive to the root meristem. Carstensen et al., (1953) measured the absorption and velocity of sound in blood, plasma and solutions of albumin and haemoglobin, in the
frequency range 800-3000 Kc and temperature range 5-45°C. Mazoue et al., (1953) observed the excitation of nerves when exposed to high-frequency ultrasound. Lehmann et al., (1954) suggested the ultrasonic effect on the potentials measured across the frog skin was created by both a thermal and a mechanical component. Lehmann (1955) demonstrated an increase in sodium transport in isolated frog skin with therapeutic levels of ultrasound by measuring changes in membrane potential caused by ultrasound.

Walter Welkowitz (1956) demonstrated that under appropriate ultrasonic dosage conditions, the propagated action potential of an excised striated muscle can be permanently reduced or completely blocked. Goldman and Heuter (1956) gave tabular data on the velocity and absorption of high-frequency sound in mammalian tissues. Dunn (1958) demonstrated the physical mechanisms of the action of intense ultrasound on tissue (e.g. cavitation, thermal mechanism etc.). Fry et al., (1958) showed the production of irreversible changes in the central nervous system by high intensity ultrasound. Carstensen et al., (1959) measured the absorption and velocity of sound in the range 0.5 to 10 Mc for solutions of haemoglobin under various conditions of temperature, concentration and chemical environment.
Paul et al., (1960) observed that ultrasound had also been used to promote healing of pressure sores. Hughes and Rodgers (1960) reported the lysis of bacteria by 20 KHz ultrasound and came to the conclusion, that lysis was a function of cavitation via mechanical stresses and not via chemical activity. Dunn and Fry (1961) experimentally determined the acoustic reflection and absorption coefficients of both normal and diseased (Pneumonitis) excised lung tissue (dog) at a frequency of 0.98 Mc/sec. Dunn (1962) studied the acoustic intensity absorption coefficient of tissue of the central nervous system at the sound frequency of 1 Mc/sec in the temperature range from 2° to 28°C at incident intensities ranging from 5 to 200 w/cm². Hughes and Nyborg (1962) reported that the streaming associated with needle oscillation (85 KHz, 2-14 mm displacement amplitude) ruptured cells, no cavitation was present. Prudhomme and Constantin (1963) denied the existence of a direct connection between the formation of free radicals or other chemically active substances and injury to the cells, leading to their lysis. Hawley and Dunn (1964) observed the complete cessation of all movements when rotifers were irradiated with ultrasound at intensities of the order of $10^{-3}$ w/cm² in the frequency range from 200 Mc to 600 Mc. Woeber (1965) reported the marked improvement in the treatment of human superficial
cancer for simultaneous employment of ultrasound and x-rays. Fukuda and Wagai (1965) reported that when localized, irregular, intense reflections are detected within the breast, these reflections are an indication of the presence of carcinoma.

Dvorak and Hrazdira (1966) reported the changes in the properties of the cell surface following ultrasound treatment in vitro. Pritchard et. al. (1966) studied the degradation of solutions of calf thymus DNA in the presence of vibrating air bubbles in ultrasonic fields of low power which would not normally induce ultrasonic cavitation. Slotova et. al. (1967) studied the chromosome abnormalities generated in Vicia faba root tips by 800 KHz ultrasound. Sichel and Brown (1967) have found changes in the thresholds for electrical excitation of Nitella, when vibration at 85 KHz was applied to part of its wall. Tissue regeneration in response to ultrasonic irradiation has been studied by Dyson et. al. (1968, 1970). Nyborg (1968) discussed specific aspects of nonthermal sonic action, especially those involving steady stresses, displacements and circulatory movements. Kessler and Dunn (1969) measured the excess ultrasonic absorption and the speed of sound in aqueous solutions of bovine serum albumin at 20°C over the frequency range 0.3
to 163 MHz and over the pH range 2.3 to 11.8. Johnsson and Lindvall (1969) observed changes in Elodea leaf cells, caused by relatively low levels of 1 MHz ultrasound.

Clarke and Hill (1970) reported that therapeutic levels of ultrasound causes damage to the outer membrane of the cells in suspension, leading to their lysis. Fry et al., (1970) studied a threshold lesion in the cat brain when irradiated with focussed ultrasound of 1,3 and 4 MHz with intensities ranging from $10^2$ to $2 \times 10^4$ w/cm$^2$ with the corresponding pulse durations from 7 to $2 \times 10$ sec. respectively. Rooney (1970) studied the haemolysis effect in detail at 20 KHz using a single hemispherical bubble, 26 um in diameter, in a small exposure chamber. Taylor and Pond (1970) noted nonthermal damage, including haemorrhage, which had the property that the damage decreased with increasing frequency. Pauly and Schwan (1971) investigated the dominant part of the acoustic absorption of liver tissue and its components results from macromolecular relaxation process over the frequency range 1-10 MHz. Coakley and Dunn (1971) observed the reduction in molecular weight of gassy and degassed aqueous solutions of DNA when treated ultrasonically at intensities greater than about 500 w/cm$^2$. Taylor and Pond (1972) studied haemorrhages and paralysis.
produced by exposure of rat spinal cord to ultrasound which were seemed to be caused by nonthermal processes, possibly cavitation. Rooney (1972) and Williams (1972) have reported cell lysis when shear forces ranged from 3.0-4.5 kdyn/cm\(^2\) to 130-200 dyn/cm\(^2\), respectively. Thacker (1973) noted that yeast was more sensitive to 1 MHz 3.25/cm\(^2\) cw ultrasound when budding (i.e. bigger) or with increased ploidy (diploid vs. haploid). Holmer et al., (1973) irradiated amoebae on glass plates with an ultrasound crystal attached below. At the stated exposure conditions (1 MHz, 0.4 w), amoebae were observed to contract, rotate, aggregate and suffer membrane damage.

Williams (1974) has observed increased serotonin release from platelets exposed to a 20 KHz vibrating needle, with 6/\mu m displacement amplitude. Dyson et al., (1974) showed the arrest of blood cell flow in living tissue by exposing it to ultrasound in a stationary wave field. Brown et al., (1975), using a uniform shear force flow, have noted release of ADP, ATP and serotonin at 50 dyn/cm\(^2\), lysis and fragmentation at 100 and 250 dyn/cm\(^2\). Thacker (1975) has indicated that shear forces sufficient to degrade DNA in solution probably would not disrupt DNA in chromosomes. Harvey, et al., (1975) found that in fibroblasts ultrastructural changes resulting from mechanical stress after ultrasonic
treatment at levels which stimulate protein synthesis. Longo et al., (1975) studied the irradiation of subcutaneously implanted rat Wilm's tumours with 1 MHz CW ultrasound at 1.5 \text{ w/cm}^2 to achieve reduction in tumour volume, reduction in tumour weight and increase in mean rat survival time. Harvey et al., (1975) reported that protein synthesis in fibroblast cells was stimulated 4 days post sonation at 1 MHz pulse-echo ultrasound. O'Brien (1976, 1983) reported a small but significant foetal weight reduction on the 18th day of gestation resulting from in utero ultrasonic irradiation, on the 8th day of gestation. Coble and Dunn (1976) found in excised preparations of isolated frog skin, an unlinking of the membrane potential and short circuit current as a result of exposure to 1 MHz focussed ultrasound. Prasad et al., (1976) reported that 1 MHz pulse-echo ultrasound inhibited DNA synthesis.

Kaufman et al., (1977) showed that those cells remaining intact in suspension have reduced viability and growth rate when exposed to therapeutic ultrasound. Chan and Frizzel (1977) showed the threshold for irreversible structural change, produced by focussed ultrasound in cat liver to be about twice that for brain. Miller et al., (1977) reported giant cell formation from CHO cells exposed
to 1.1 MHz CW ultrasound at 5 w/cm$^2$ for 5 min. Nyborg (1978) studied the nonlinear phenomena which may act as nonthermal mechanisms for ultrasonic bioeffects include radiation pressures, bulk acoustic streaming, radiation forces and torques. Pizzarello et. al., (1978) studied that 88 per cent of late third instar larvae of Drosophila were killed by pulsed 2.25 MHz ultrasound. Coakley and Nyborg (1978) observed that transient cavitation brings into play additional mechanisms including shock waves, hydrodynamic jets and free radical generation with concamitant chemical activity. Wolff (1979) stated a wide variety of chemical and physical agents can induce SCEs but neither the mechanism of formation nor the genetic significance of SCEs in known. Chapman et. al., (1979) reported that thymocyte sensitivity to ultrasound was inversely related to frequency. Liebeskind et. al., (1979b) reported an increase in SCEs when human lymphocytes were exposed to 2.5 MHz pulsed ultrasound. Anderson and Barrett (1979) reported a dose dependent immuno-sensitive effect in mice exposed for 5 min, over the area of the spleen, to ultrasound, which results in slight reduction of haemagglutinin and haemolysis antibody titers.

Armour (1980) exposed CHO cells to 1 MHz CW ultrasound at an intensity of 1 w/cm$^2$ and noted no effects on suspension cells at 37°C; but at 3°C survival of cells was
greatly reduced at intensities between 1 and 3 w/cm$^2$. Weissler et al., (1980) noted the production of free radicals in a sonicated aqueous suspension of cells or nucleosides appear to be mediated by transient cavitation. Kashkooli et al., (1980) demonstrated that microsonation with a 20 KHz transversely oscillating wire could even inactivate certain enzymes such as malate dehydrogenase. William and Miller (1980) studied the release of ATP from cells subjected to the localized ultrasound exposure at the micropores.

Child et al., (1981) observed an apparent threshold for killing of the Drosophila larvae at about 10 w/cm$^2$ spatial average temporal peak intensity. Carstensen et al., (1981b) observed lesion production in liver tissue exposed to 2.25 or 4.4 MHz ultrasound. Martin et al., (1981) studied the effects of 2 minutes exposure of 0.8, 1.5 and 3 MHz ultrasound in vivo on mouse liver. At 0.8 MHz, localized areas of damage occurred at the liver surface and penetrated the tissue up to 2 mm. Bailey et al., (1981) exposed mouse testis to CW ultrasound and observed a more severe form of tubule damage with significant interstitial tissue involvement. Sachs et al., (1981) have examined sonated EMT 6 mammary sarcoma multicellular spheroids and observed immediate loss of normal cell morphologies and a concurrent
appearance of a mottled, fibrous like surface features, production of surface holes suggestive of cell loss and production of small holes in cell membranes.

Child and Carstensen (1982) found that the eggs of Drosophila are most vulnerable to ultrasonic action shortly before hatching, when they contain small, stabilized gas bodies. Forester et al., (1982) stated that ultrasound alters the contractility of myocardial tissue in isolated papillary muscle. Ross et al., (1982) demonstrated that a major effect of ultrasound exposure is the inhibition of \( \text{Na}^+ - \text{K}^+ \) activity. Marchal et al., (1982) studied local ultrasound induced hyperthermia combined with other modes of therapy was effective in treatment of superficial malignant tumours in man.

The propagation of ultrasound is fundamentally a nonlinear process, secondary phenomena, which are not expected from consideration of purely linear propagation and heating, emerge at relatively high ultrasonic amplitudes (NCRP, 1983). Miller et al., (1983) exposed whole human blood cultured in vitro to pulsed ultrasound at 2 MHz and did not observe a difference in SCE yield between control and exposed cultures. Bailey et al., (1983) observed that short time exposure to varying intensities of ultrasound
damaged the ovarian and surrounding tissue of mouse, seen as pycnosis and vacuolization. Williams (1983) detected ATP release from platelets at spatial, peak temporal average intensities as low as 4 mW/cm². Bamber et al., (1983) used a 10 MHz CW ultrasonic Doppler system to obtain information about the blood flow characteristics of the normal human breast and of malignant breast tumours.

Apfel (1984) stated that cavitation involves transformation of a "cavitation nucleus" into an active form, typically upon exceeding a threshold exposure level. Mortimer et al., (1984) studied membrane potentials in isolated papillary muscles and found that there was an increase in transport of both sodium and calcium into the cell for the duration of the action potential during irradiation with therapeutic ultrasound.

Gross et al., (1985a) and Miller et al., (1985) searched for cavitation bubbles in canine arterial blood proved negative for moderate intensities of 0.51 - 1.61 MHz ultrasound. Kumar and Bhargava (1985) observed the growth arrest of the breast tumour of mouse when exposed in vivo to continuous plane wave ultrasound. Vivino et al., (1985) found that cell death, clumping and apparent reduction of DNA synthesis resulted from 1.6 MHz exposure of stimulated
lymphocytes. Hynynen (1985) showed experimentally that the nonlinearities had a significant effect on the temperature produced by focused ultrasound fields in dog's thighs in vivo.

Maeda et al. (1986) determined the growth of cultured JTC-3 cells of human amniotic cell origin when irradiated with CW ultrasound. Mortimer et al. (1986) described the beneficial effects of ultrasound when the supply/demand ratio to the heart is reduced by rapid electrical pacing or by a hypoxic state. Borelli et al. (1986) reported that hyperthermia is particularly damaging to the developing CNS and therefore a high dosage of ultrasound can cause various abnormalities such as excencephaly, microphthalmia. Edwards (1986) reported that hyperthermia is a potent teratogen in experimental animals. Perez et al. (1986) reported that patients with recurrent breast carcinoma exhibited significant tumour reduction when hyperthermia raised the temperature to 41° - 43°C after at 30-6 min. irradiation.

Forester et al. (1987) showed that ultrasound is protective to brain function during acute hypoxia because the delivery of oxygen although limited is greatly facilitated. Bailey et al. (1987) observed the temperature increase when
the exteriorized mouse ovaries were exposed to 1 MHz ultrasound in situ. Coleman et al., (1987) showed that similar to ultrasound, shock wave lithotripters are known to produce acoustic cavitation.

Mortimer and Dyson (1988) studied the exposure of cultured fibroblasts to sonication and observed the augmentation of intracellular calcium, a well known mediator of numerous cellular processes including protein synthesis. Mortimer et al., (1988) reported an increase in the rate of oxygen transport across excised frog abdomen skin when exposed to ultrasound. Kondo et al., (1988) have shown that ultrasound exposures which result in transient cavitation can produce free radicals.

The report of Desai et al., (1989a) showed that foetal exposure to ultrasound has no apparent effect on lymphopoiesis or haemopoiesis. Miller et al., (1989) showed the single strand breaks (SSBs) in the DNA of fresh human leukocytes exposed to ultrasound in vitro. Kumar and Raju (1989) reported an increase in dehydrogenases activity when mouse liver was exposed in vivo to CW ultrasound and observed that therapeutic ultrasound induces extensive damage to the liver of mouse.
Carstensen et al., (1990) showed the resonance lysis of the cells in the leaves of the aquatic plant Elodea at higher amplitudes. Young and Dyson (1990) studied the effect of therapeutic ultrasound on the formation of new blood vessels in full-thickness excised lesions in the flank skin of adult rats. Rubin et al., (1990) examined the acute effects of pulsed ultrasound on the microvasculature of the rat cremaster and observed the significant reduction of oxygen tension at 2.5 w/cm². Carstensen et al., (1990b) reported that mouse kidney showed no significant signs of damage even after exposure to 1 and 4 MHz pulsed ultrasound.

Suneetha and Kumar (1991) estimated lactate, malate and succinate dehydrogenases in the foetal brain and liver following in utero exposure of pregnant mice to a continuous wave of unfocussed ultrasound. Varma and Kumar (1991) reported an increase in Glucose-6-phosphatase and glycogen phosphorylase when mouse pancreas was exposed in vivo to a continuous and unfocussed wave ultrasound beam. Chicca et al., (1991) showed that lesions inflicted up on DNA by pulsed ultrasound could be ascribed to production of free radicals (O₂⁻, OH), and H₂O₂ which could mediate the production of still unidentified organic radicals likely to be responsible for DNA damage.
NCRP (1992) recognized that there is a potential for heating bone with certain diagnostic ultrasound system. Varma and Kumar (1992) studied certain biochemical enzymological changes in mouse pancreas and liver following the irradiation of pancreas in vivo. Moros and Hynynen (1992) compared the theoretical and experimental ultrasound field distributions in canine muscle tissue in vivo. Bondestam et al. (1992) correlated the echo intensity of the liver tissue of burbot fish with chemically measured fat and water content and with the tissue cytology and found that the echogenecity is a function of the liver histomorphology. Suneetha and Kumar (1993) reported the enhanced levels of the neurotransmitters in the pregnant mice when exposed to continuous-wave ultrasound of 875 KHz frequency at 1 w/cm² for 300 and 400 sec., spread over five days, starting from the sixth day of pregnancy.