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Review

Rapporteur report: Mechanisms and interactions

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Abstract

The first two talks of this session described the basic characteristics of the interaction of ultrasound with matter, the first (by V.F. Humphrey) concentrating on the physical interactions, with the second (by W.D. O'Brien, Jr.) focusing on the biophysical effects and mechanisms. The regimes covered by the first and second talks were of primarily high-frequency (O(MHz)) ultrasound in liquids and tissue, respectively. In contrast, the third and final talk of the session (by M. Alves-Pereira) discussed observations made by her group of the vibroacoustic effects of low-frequency noise and infrasound, propagating through air, on humans and animals.

Keywords: Ultrasound; Infrasound; Bioeffect

Contents

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1. Ultrasound and matter—physical interactions

The aim of this talk was to describe the basic characteristics of ultrasound, the ways it interacts with matter and the effects produced. It was noted at the start that the content would be given from a perspective and context that related primarily to the use of medical ultrasound.

1.1. Wave basics

The talk opened with a description of the basic features of the interaction of ultrasound with matter, showing how an ultrasonic compressional wave can be described at any point on that wave through the time-varying characteristics of the particle velocity, amplitude and displacement, and of course the acoustic pressure. Although new technologies are being explored, historically it is the pressure which has been easiest to measure, and therefore most discussions of acoustic wave amplitudes are in terms of pressure. Comparing ultrasonic waves in air and water, it was noted that, whilst the accelerations were large ($O(10^5$–$10^7\,\mathrm{m\,s^{-2}})$ in the example waves shown), the brevity of the wave period means that the displacements were small ($O(0.1$–$1\,\mu\mathrm{m})$). It was noted that two particles which are close to each other will undergo similar types of motion at the same time. Therefore if one considers the hazard to a cell, then the differential motions across the length of the cell will also be small, because the spatial variation is determined by diffraction.

Because a fluid cannot support shear, it was noted that in fluids shear waves do not propagate to distance. Therefore discussions of ultrasound in fluids are dominated by consideration of longitudinal waves, where the displacements is aligned with the direction of propagation. It was noted that soft tissues do have a finite shear modulus, but that it is characterized by very low values. As a result, shear waves in soft tissue typically have low velocities and high attenuations. Because of this, soft tissues are sometimes described as 'fluid-like'.

1.2. Interfaces

The effects associated with the presence of interfaces in the medium through which the wave is propagating were then considered. These effects include reflection, transmission and mode conversion. Several examples were discussed, based the properties of a plane wave which is initially propagating in one medium, and then is incident on an interface with a second medium. If the specific acoustic impedance of the second medium (Z_2) exceeds that of the first (Z_1), the acoustic pressure generated on the side of the interface in the second medium (p_2) can exceed that in the first (p_1) (although the displacement may decrease in going from the first to the second medium). Of course in such circumstances the intensity (based on the ratio of the square of the pressure to the specific acoustic impedance) cannot be greater in the second medium than it was in the first, from conservation of energy. In the specific case where the first medium is a liquid and the second is a solid, shear waves and surface waves can also be generated in the solid. If the angle of incidence is greater than the critical angle, then it becomes impossible to generate the compressional wave, and consequently the energy invested in the shear and surface waves can be enhanced. Since the absorption of shear waves is generally higher than that for compressional waves, shear waves are not only likely to be more rapidly attenuated than compressional waves, but can also generate shear in tissue. When $Z_2 < Z_1$, inversion of the pressure pulse occurs. If the

incident pulse had been distorted by nonlinear propagation in medium 1, then the resulting asymmetry would mean that its peak positive pressure amplitude may be very much greater than its peak negative amplitude before the wave meets the interface. As a result, if the wave were then reflected at a pressure-release interface, tension could be generated in the first medium. The example of a wave in a kidney stone becoming incident on a pressure-release interface was given.

1.3. Absorption

On the topic of attenuation, the loss of wave amplitude as it propagates, the discussion concentrated on two causes: absorption and scattering. In a uniform medium the intensity of a plane wave would decrease exponentially, such that if the initial intensity were I_0, then the intensity after it had propagated a distance z would be $I(z) = I_0 e^{-2\alpha z}$. Here α is the attenuation coefficient, which can be thought of as consisting of the sum of a component relating to absorption losses (α_a) and, if the material is inhomogeneous, a component which reflects the scattering losses associated with these inhomogeneities (α_s), such that $\alpha = \alpha_a + \alpha_s$. For biomedical ultrasound in soft tissue, the major component of this is thought in most circumstances to be due to absorption. Consequently, the description then focused onto the topic of absorption. It was noted that absorption in tissue is generally much greater than that found in water *at a given frequency* (although one must be careful not to make too simplistic an interpretation of this statement—see Section 1.4). This has implications for translating in vitro measurements to the in vivo case, particularly for calibration measurements. The absorption coefficient is dependent on the ultrasonic frequency (f), such that $\alpha_a \propto f^n$ where n is a characteristic exponent, which takes a value of 2 for pure water, and is typically in the range 1.0–2.0 for fluids like amniotic fluid and blood. Generally, the more protein is present in the tissue, the nearer the exponent tends to unity, and these sorts of values typify many soft tissues.

1.4. Nonlinear propagation

The discussion then moved on to the phenomenon of nonlinear propagation, including its sources in the material and convective nonlinearities. If these effects are deemed to be small, then the linearized plane wave equation can be derived. However if the hazard associated with biomedical ultrasound is under consideration, the amplitudes are often sufficiently large that these terms cannot be neglected, and this is reflected in the observation of nonlinear effects during propagation. Sources of nonlinearity manifest themselves when the acoustic Mach number is large, and in any nonlinearity in the equation of state. Indeed, even were the pressure/density relationship in the equation of state of the medium to be linear (which is not the case), nonlinearity could still be introduced through convection during the propagation of waves of finite amplitude. As a result, a point on a wave will not travel at the sound speed for waves of infinitesimal amplitude (c_0), but rather at $c_0 + u(1 + B/2A)$, where u is the local particle velocity and B/A is the nonlinearity parameter, which has a value of 5.0 for pure water, 6.3 for blood, between ~6 and ~7 for liver and ~10 for fatty tissue.

The generation of harmonics as a result of nonlinear propagation, the generation of shock waves, and the consequent enhancement in attenuation, were then discussed. The possibility of acoustic saturation was raised. In this, the wave amplitude at some point remote from the source will not increase when the source amplitude is raised. This is because the higher source amplitude augments the nonlinearity and therefore enhances the attenuation. This can not only be potentially misleading for observations at a distance, but in addition several practical devices (in both the biomedical and the sonar regimes) have approached these conditions, whereby the increase in signal level detected at range is much less than the increase applied to the source amplitude in order to improve signal-to-noise levels.

When nonlinear propagation is actually measured, the asymmetry between the positive and negative pressures (mentioned in Section 1.2) was attributed to diffraction which occurs in waves generated by real sources (of finite size) as opposed to the idealized plane wave. As the real wave propagates, diffraction occurs as a result of the finite source size. As a result, the phase of the fundamental component of the wave is continually changing relative to that of a plane wave, the harmonics are always trying to catch up with that phase change, resulting in the observed asymmetry.

Measurement problems can arise from this. Since the asymmetry results in the majority of the higher-harmonic component energy being invested in the peak positive (as opposed to the peak negative) measures of the waveform, a consequence of this could be that the limited bandwidth of the receiver system can result in underestimations of the peak positive pressure. Measurement errors can arise through failure to compensate for the phase response of the hydrophone, which can distort the waveform reported by the hydrophone, such that it differs from the waveform which is actually present in the water.

Attitudes to nonlinear propagation have changed over the years. When nonlinear propagation was first detected in water, there was considerable scepticism as to whether it would ever occur in tissue. Nowadays nonlinearity in tissue is exploited in the modality known as harmonic imaging. However there is a difference between the nonlinearities in water and tissue. The fields in water contain tens of harmonics, or more; in tissue the highest frequency containing any significant energy is usually around the third harmonic: there is very little energy invested in tissue at the frequencies of the higher orders of harmonic which would be detectable in water. In tissue, as a rule-of-thumb, the second harmonic has a level which is about $-10\,\mathrm{dB}$ compared to the level of the fundamental, and the third harmonic has a level of around $-20\,\mathrm{dB}$ compared to the fundamental. An important consequence of this is as follows. From Section 1.3, it is clear that the attenuation coefficient *at a given frequency* is less for water than for tissue. However it is too simplistic to say that a wave will suffer more absorption in tissue than water. This is because, if the same high amplitude wave were to propagate nonlinearly in both water and tissue, the wave in water would have more energy invested at higher frequencies. These frequencies are more strongly attenuated. Therefore the absorption of that waveform in water would be greater than expected from a consideration of only linear propagation. Therefore, in transferring ideas from in vitro to in vivo, it is not satisfactory simply to consider water as lossless (compared to the magnitudes of the losses in tissue) as far as nonlinear propagation is concerned. Indeed, losses in water as a result of this could be as much as $1\,\mathrm{dB\,cm^{-1}}$, i.e. similar to tissue.

1.5. Ultrasonic heating

The absorption of energy discussed in Sections 1.3 and 1.4 leads to heating of the medium. Understanding of both of the previous topics (absorption and nonlinear propagation) is of course key to predicting and interpreting the heating that can occur when high amplitude ultrasound propagates through a medium, and the consequent temperature rises that may be observed in, for example, liquids and tissue. The rate at which acoustic energy is converted to heat per unit volume of the medium (q_v) depends on the *local* intensity I of the wave and the absorptive characteristics of the medium: $q_\mathrm{v} = 2\alpha_\mathrm{a} I$. As a result of this, the temperature T will initially rise at a rate $\mathrm{d}T/\mathrm{d}t = q_\mathrm{v}/(\rho_0 C_\mathrm{p}) = 2\alpha_\mathrm{a} I/(\rho_0 C_\mathrm{p})$, where C_p is the specific heat at constant pressure, and ρ_0 is the equilibrium density, of the medium through which the wave is propagating. However this heating effect will be countered by cooling processes, such as conduction and fluid flow (convection, streaming, etc. and, in the special case of living tissue, perfusion of blood from and to cooler regions). One approximate way in which these effects can be incorporated into modelling is through use of the Pennes' bio-heat transfer equation, which assumes that excess heat is removed from the system (rather than being deposited at another locality, possibly nearby). Despite this unphysical assumption, the Pennes' equation is popular because it is simple to implement in many types of modelling, and it has been used effectively for many years. A historical example was then given, based on the modelling of a focused field from a 3 MHz transducer (modelled as a heated disk of 20 mm diameter, 100 mm focal length, and having source power of 100 mW). For these parameters, Thomenius (1990) predicted the temperature rise in tissue (with an assumed absorption coefficient of $1.3\,\mathrm{dB\,cm^{-1}}$) for various distances on-axis from the transducer. Such modelling shows that, while initially the greatest heating occurs at the focus because the local intensity is high there (which one might require for use in ultrasonic surgery), over time the greater temperature rises are seen in the tissue which is adjacent to the transducer, because the power deposition is greatest there. Moreover, in reality there is an additional factor which was not included in the above modelling example of Thomenius (1990), which would further increase heating in the tissue near the transducer. Specifically, the temperature of the transducer itself can rise, because it is mechanically not perfectly efficient. Such temperature rises can cause heat conduction directly into the tissue next to the transducer (a particular effect to note with the use of intracavity transducers). Results from tests on a bone mimic at the UK National Physical Laboratory were presented, showing the expected

increased temperature rise (compared to that seen in water or soft tissue) which is attributed to the greater absorption of bone (both of the compressional waves, and of the shear waves that can be generated).

1.6. Cavitation

Two examples were given of ways in which cavitation might generate physical effects. As regards noninertial cavitation, the familiar observation of microstreaming in liquids was extrapolated to speculate on the possibility of similar effects generating shear in an elastic medium. With respect to inertial effects, the possibility of mechanical damage through bubble involution and jetting was outlined.

1.7. Secondary nonlinear physical effects

The talk then progressed to discussing the so-called 'secondary' nonlinear physical effects, which result from the inherent nonlinearity of the propagation. The first such effect to be discussed was radiation pressure. For a continuous wave, this is a steady small pressure in the direction of propagation, observed at interfaces in the medium. The second effect in this class is acoustic streaming in fluids. This is a movement of fluid away from the transducer in the direction of propagation.

If the acoustic signal is modulated, the radiation force can similarly be modulated. Such audio-frequency modulation of ultrasonic radiation pressure could be a mechanism by which audio-frequency signals might be generated from the interaction of ultrasound with matter.

1.8. Conclusions regarding the physical interactions between ultrasound and matter

The conclusions were that:

- the interactions of ultrasound with matter can be complex;
- nonlinearity cannot be ignored (especially in water);
- the presence of bubbles or cavitation can significantly alter behaviour and/or further complicate the situation;
- arrangements used for bioeffects studies may significantly affect field characteristics (as a result of scattering, reflection, etc.).

2. Ultrasound—biophysical mechanisms

The biophysical mechanisms associated with the propagation of O(MHz) ultrasound through tissue are classified as thermal and nonthermal mechanisms. This reflects the established importance of the thermal effects to the question of hazard. That importance has become established in this way because those scenarios which have dominated interest with respect to the question of hazard concern ultrasonic exposure of foetuses and neonates. The importance of bubble-related effects to the question of hazard by nonthermal mechanisms is reflected by the further subdivision made by the speaker in this category: mechanisms involving contrast agents; mechanisms not involving contrast agents; and mechanisms which are not thought to be related to either bubble activity or thermal effects.

The interaction between ultrasound and tissue was discussed. Ultrasound affects tissue through bioeffects, but in turn the tissue affects the ultrasound (a process which of course is fundamental to ultrasonic imaging). Prof. O'Brien drew attention to the issue of ultrasonic dosimetry which overrides the use of biomedical ultrasound. Ultrasonic dosimetry is concerned with the quantitative determination of the interaction of ultrasonic energy with biological materials. He recalled the comment, made the previous day by Prof. ter Haar, who had stressed that 'exposure' should refer to what was measured in water, while 'dosage' should refer to the quantitative determination of the interaction of ultrasonic energy with tissue. He recalled that she had emphasized that there was no clear understanding of the dosimetric unit in ultrasound. In agreeing with this, he added that there have been some attempts to understand this dosimetric unit. However this had only been done for very specific biological effects induced under very specific conditions. In general the issue of

ultrasonic dosimetry is far from solved. He concluded the introduction with the clear statement that the discipline lacks a dosimetric unit.

2.1. Thermal mechanisms

To summarize the state of affairs with respect to thermal mechanisms for generating ultrasonic bioeffects, Prof. O'Brien reiterated key facts from the previous talk (see Section 1.3). He recalled that whenever ultrasonic energy propagates in an attenuating material such as tissue, the amplitude of the wave decreases with distance. Absorption and scattering contribute to the observed attenuation. Absorption is a mechanism that represents the conversion of a proportion of the ultrasonic energy into heat. He emphasized that a temperature rise can occur as long as the rate of heat production is greater than the rate of heat removal.

There are a number of concepts of dose that are receiving attenuation with respect to thermal mechanisms. The Thermal Isoeffect Dose has principally been used with respect to hyperthermia therapy. However it is currently being explored for incorporation into the field of diagnostic ultrasound. It attempts to provide a method of converting thermal exposure into an equivalent duration, in minutes, at 43 °C (t_{43}). This Thermal Isoeffect Dose can be calculated through $t_{43} = tR^{(43-T)}$. Here t corresponds to the duration of the temperature rise, and the index R can take two values depending on whether the temperature in question is greater than, or less than, 43 °C. Specifically $R = 0.5$ for $T > 43$ °C and $R = 0.25$ for $T \leqslant 43$ °C. Different tissues have different characteristic values of t_{43}, covering a wide range (from $t_{43} = 240$ min for muscle and fat in pig, to $t_{43} = 20$ min for mouse brain). This can be used to provide a basis for comparing thermal doses. O'Brien then discussed the processes which might characterize heating with very short exposures. He referred to two studies which summarized a large amount of data on thermal bioeffects, and interpreted the findings in the light of guidelines under a thermal statement regarding nonfoetal tissue, currently under discussion by the AIUM (American Institute of Ultrasound in Medicine). Prof. O'Brien indicated that there was evidence that adult tissue is less sensitive to thermal effects than foetal tissue (he was later asked to clarify this point in the discussion—see Section 4.1.2).

The other popular thermal dose concept is the output display standard, the Thermal Index value, TIS. This Thermal Index has been incorporated as a real-time on-line index displayed on-screen during clinical diagnostic ultrasonic procedures. He demonstrated how the Thermal Index could be considered to be a conservative estimate of heating. The full calculation of the TIS is complicated, and is based on calculations involving the source power W_0 (in mW), the centre frequency f_c (in MHz) and the active area A_{aprt} (in cm^2). Prof. O'Brien demonstrated simplified expressions, $TIS_{new(1)} = W_0^{0.85} f_c^{0.58}/168A_{aprt}^{0.33}$ and $TIS_{new(2)} = W_0^{0.73} f_c^{0.62}/130$. These have not been adopted by any organization, but have been found to be useful for application in some specific cases. Prof. O'Brien showed that the second expression, $TIS_{new(2)}$, can be calculated without inclusion of the active area of the transmitter, at the cost of allowing somewhat greater scatter in the results when processed in this way.

The effect of the anatomy for *in utero* exposure was discussed in the context of a three-layer model for *in utero* exposure (such layering is not currently included in calculation of TIS), where the layers are: 1 cm of abdominal wall, 5 cm of bladder, and then fetal tisuue. This model was used to predict the changes in the spatial distribution of temperature rises for different values of TIS. These calculations indicated that the heating of the abdominal wall, through absorption there, could be an important effect.

2.2. Nonthermal mechanisms

Prof. O'Brien reiterated the classification of nonthermal mechanisms into: those involving ultrasound contrast agents (UCAs); those not UCAs; and those which are not thought to be related to bubble activity.

He summarized that most attention with respect to nonthermal mechanisms for bioeffect is based upon the phenomenon of acoustically generated cavitation, which he defined for the purposes of this presentation as the interaction of ultrasound with a gas body. It is potentially a potent mechanism for biological effects of ultrasound, acting through a range of bubble-related mechanisms, including radiation forces, microstreaming, shock waves, free radicals, microjets and strain.

2.2.1. Nonthermal mechanisms involving UCAs

UCAs are stabilized microbubbles that enhance the ultrasonic echogenicity of blood. Their presence in blood greatly increases the contrast in ultrasonic images and, in addition, their motion provides a useful diagnostic tool. The possibility of side effects was introduced, primarily in terms of the potential bioeffects generated as a result of any cavitation nucleated by contrast agents.

The medical and pharmalogical communities that developed these contrast agents have chosen to categorize their effects in terms of the Mechanical Index (MI). Real-time on-screen values of the MI are provided for medical ultrasonic diagnostic imaging devices, although when UCAs are present, the value of the calculated MI is not well related quantitatively to the conditions in the tissue. Nevertheless the community still chooses to categorize the effects of contrast agents into three general clinical regimes of MI. These are, specifically, 'low MI' levels (where the contrast agents behave linearly); 'moderate MI' levels (where the contrast agents behave nonlinearly); and 'high MI' levels (where the contrast agents nucleate inertial cavitation). The purpose of this classification is to emphasize to users that it is important to appreciate whether the UCAs are behaving linearly, nonlinearly or nucleating inertial cavitation. However currently clinicians cannot be certain to what extent the conditions in vivo reflect the regime in which they believe they may be operating.

Prof. O'Brien presented results from experiments using passive cavitation detectors. These were deployed to measure the threshold acoustic pressures required to cause inertial cavitation to be generated when UCAs are used to nucleate the cavitation. He demonstrated the surprising ease with which inertial cavitation could be obtained when UCAs are exposure to diagnostic ultrasound. Specifically, the data referred to the use of a passive cavitation detector to determine the thresholds for generating inertial cavitation using Optison^{TM}, one of only three contrast agents which have FDA approval for clinical use in the USA. While the threshold pressure required to produce inertial cavitation increased with frequency as expected (the equivalent 'value of MI' was also indicted), there was little difference in the threshold for varying the pulse length between 3 and 7 cycles.

A list was provided of bioeffects which could be occurring in vivo at diagnostic levels with UCAs. Probably one of the more serious ones is haemorrhage in petechiae (skeletal muscle). However it is difficult to obtain data on this because research grants in this area are difficult to obtain. Premature ventricular contractions have been observed primarily in rodent models, although there is evidence of it occurring in humans. Cardiac capillary damage and erythrocyte extravasation have been observed in rabbits exposed to diagnostic levels of ultrasound. Observations of rat hearts had detected blood plasma troponin T elevation, and petechiae and microvascular leakage. In addition, renal capillary haemorrhage has been detected in rats, and endothelial cell damage observed in rat liver.

Another aspect of tissue bioeffect generated by UCAs at diagnostic levels of ultrasound was discussed. The ability of UCAs to evoke in vivo therapeutic effects when activated by diagnosed levels of ultrasound is currently being investigated. The possible therapeutic effects include: sonoporation for gene and drug delivery; drug delivery (in skeletal muscle and myocardium); and gene delivery (in the myocardium). Prof. O'Brien emphasized the importance of the fact that these agents, which had been developed to enhance contrast with diagnostic ultrasonic modalities, were now being investigated for therapeutic applications (such as drug delivery).

Given the uncertainty regarding the possible bioeffects and potential damage which UCAs might cause at diagnostic exposures, Prof. O'Brien explained the impasse which has been recently reached by the FDA and NEMA (the US National Electrical Manufacturers Association, the trade organization which represents manufacturers of medical ultrasound equipment). The FDA has said that it will not approve any more UCAs for use in the USA unless the manufacturers of the UCAs can prove the safety of their agents. Specifically, they are required to provide in vivo data regarding their safe use in the vascular system. It appears that the development and introduction of new UCAs into the USA healthcare market are on hold until this matter is resolved.

2.2.2. Nonthermal mechanisms not involving UCAs

Other nonthermal, but possibly bubble-related, mechanisms which could occur at diagnostic levels include: thrombolysis; the effects which allow ultrasonically assisted transdermal drug delivery; and the observed

acceleration of bone growth and healing. It was noted that while these effects might be bubble-related, there is the possibility that they are not (e.g., that radiation forces and piezoelectric effects may contribute to bone growth and healing).

2.2.3. Nonthermal mechanisms which are not thought to be related to bubble activity

Many nonthermal and noncavitational mechanisms, which are though to occur at diagnostic levels, are believed to be caused by radiation force effects. They include: tactile perception; auditory perception in air and *in utero*; the mechanisms behind vibroacoustic imaging; the banding and stasis of blood cells in standing waves; vasodilation; and macroscopic streaming.

A notable exploitation of such effects is found in Acoustic Radiation Force Impulse (ARFI) imaging, in which high-energy, focused acoustic pulses of short duration are used to generate radiation forces in tissue. These forces cause tissue displacements that can be detected using ultrasonic correlation-based methods. In this way, images are formed which show the relative mechanical properties of the tissue.

Lung damage has also been observed in animals at diagnostic levels. It is one of the most intensively investigated bioeffects from diagnostic ultrasound in recent years. Prof. O'Brien speculated that this effect might possibly be generated in humans, on the basis of two factors: first, the effect had been observed in a range of animals (mouse, rat, rabbit, and pig); second, Prof. O'Brien pointed out that, with the exception of two studies involving pigs, lung damage had been observed at values of the MI less than or equal to 1.9 (the legal FDA limit for exposure).

3. Vibroacoustic effects

The talk by Dr. Alves-Pereira consisted of a report spanning nearly 25 years of research by her group, which today resides at Lusófona University in Portugal. The research concentrated on the effects of exposure to sound having frequencies less than 500 Hz (the range termed 'low frequency' for the purposes of the presentation), and including infrasound (<20 Hz). One overwhelming problem experienced by the group has been the failure by the medical community to characterize the relevant sound fields properly. A particular problem is the extensive use of the standard dB(A) protocols for environmental noise fields, in order to reduce exposures which contain low frequency and infrasonic spectral content to a single dB(A) value. This is clearly incorrect. Given these circumstances, their findings have not been confirmed by other groups and are inadequately funded.

Since 1980 her group has studied the effects on both animal models and human populations exposed to occupational low-frequency noise. They have collated their observations in their attempts to define a pathology for 'vibroacoustic disease', described as a systemic pathology characterized by abnormal growth of extra-cellular matrices. Specifically, their observations include an abnormal proliferation of collagen and elastin fibres in the absence of inflammatory processes. It is of course unusual to have collagen production without an accompanying presence of an inflammatory process.

Dr. Alves-Pereira began by noting that until 1987, they had been studying a group of aircraft technicians, 10% of whom had been identified as having late onset epilepsy (as opposed to an occurrence rate of 0.2% expected in the general Portuguese population). As a result, until 1987 her group considered that the biological effects of low-frequency noise exposure in an occupational setting were likely to be in the form of neural psychological damage. They instituted studies of the central nervous system, including brain MRIs, evoked potentials, etc. and detected a variety of pathological signs amongst these aircraft technicians.

Their views changed in 1987 when one of these subjects died. He had specifically requested in his will that an autopsy be conducted. The Principle Investigator of the vibroacoustic disease research programme is a pathologist. The autopsy was performed in 1987 and revealed a thickening of cardiac structures, specifically blood vessels. This was not the result of a typical atherosclerotic plaque that might typically be associated with poor diet. Rather the vessel wall itself was thickening along the length of the vessel. In addition, the autopsy also revealed thickening of the pericardium (from the 0.5 mm thickness normally expected to a thickness of $\sim$2 mm). It was noted that there had been no diastolic problems, which is unexpected given that one might suppose that such a thickness of the pericardium would hinder the expansion of the heart. In addition, the

autopsy revealed a brain tumour, a kidney tumour and lung fibrosis. Although the occurrence of lung fibrosis proved to be of great interest later, at the time the team did not place much significance on it. This is because lung fibrosis would not be unexpected given the occupational environment of this aircraft technician, which might contain dust, paint, etc. However they were intrigued by the thickening that had been detected in the cardiac structures. They therefore initiated echocardiogram studies of the surviving aircraft technicians and discovered pericardial thickening in all of the patients examined. This was not associated with pericarditis, since there were no diastolic problems and no indication of inflammatory processes. However, as might be expected, blood vessel thickening leads to a decrease in the size of the lumen. Eventually some of these patients were recommended for cardiac surgery, a process unrelated to their involvement in the vibroacoustic research programme. Therefore the team set about obtaining the informed consent of the patients, and the approval of the hospital ethics committee, for them to receive for analysis pericardial fragments from 12 low-frequency noise-exposed personnel (3 aircraft technicians, 4 aircraft pilots, 4 helicopter pilots and 1 truck driver). This was done because, while the echocardiogram did reveal that structures were changing, there was no anatomical correspondence between these observations and the occupational exposure to low-frequency noise experienced by these aircraft technicians.

Examination of the pericardial fragments by light microscopy revealed structural changes to the pericardium. Normally the pericardium contains three layers, but in the patients studied by the team, the pericardium had become an organ of five layers. The middle (fibrous) layer of the pericardium, which is composed primarily of collagen and elastin, had not only thickened extensively, but had also subdivided. Scanning and transmission electron microscopy of the pericardial wall also revealed thickening, the fibrous layer dividing into two and forming a sandwich around a layer of loose tissue, containing blood vessels, adipose tissue and neurones. This was therefore taken to be the source of the anomalies seen in the echocardiogram and is clearly not associated with pericarditis.

Thickened blood vessel walls were also seen in biopsy, with thickening along the full length of the vessel, with a narrowing of the lumen that was not caused by plaque formation but rather caused by thickening of the walls themselves.

In 1992 the team began to study animal models, because they had several patients who exhibited pleural effusion. These were unusual and atypical cases of pleural effusion: the aetiology was never discovered, the recovery times were very long, and the patients did not respond to normal therapeutic measures. Consequently the team wondered whether the immune system was compromised in some way, impairing the patients' response.

They therefore began exposing rats to acoustic environments containing low-frequency noise, and then spliced, photographed and compared the trachea of exposed rats with control animals. They observed what appeared to be cellular organization typical of what is seen in pre-cancerous lesions.

Recall that when they began to look at animal models, they were looking for explanations of the anomalous cases of pleural effusion that had been observed in aircraft technicians. During one cut that was undertaken to enable observation by microscopy, the incision that was made was deeper than intended and cut into the lung itself, where they discovered lung fibrosis. This was considered to be unusual in a rat for whom the occupational characteristics (smoking, exposure to fumes and paint) of the aircraft technicians would not be germane. They therefore returned to examination of the humans. High-resolution CAT scans revealed focal lung fibrosis in both symptomatic and asymptomatic aircraft technicians. This was independent of whether the technician was a smoker or a nonsmoker. As was mentioned earlier, lung fibrosis was also seen in the 1987 autopsy. Attention therefore focused on the respiratory system, and after further animal tests (where fibrosis was detected in the trachea, lungs and pleura of animals exposed to low-frequency noise), they concluded that vibroacoustic disease is characterized by lesions which can be detected by bronchoscopy. Although this is invasive and less simple to undertake than an echocardiogram, these bronchoscopic lesions (which they have terms 'pink lesions') have been biopsied and found to contain abnormal amounts of collagen in the absence of inflammatory processes.

This collagen production is unlike that which occurs in wound healing. In wound healing the collagen is anchored. The collagen which the team observed in their studies is functional: it is being produced in a way which generates functional units within the organs. Slides were shown demonstrating thickening of the alveolar wall in rats exposed to low-frequency noise, compared to control rats.

Having now 25 years of research and observations, the team have ideas as to the processes which might be occurring. It is well known that cell signalling can be biochemical (which was likened to a 'software' process) or mechanical (which was likened to a 'hardware' process).

Mechanotransduction is the molecular mechanism through which cells sense and respond to mechanical stress, and interact with each other and the extracellular matrix.

It therefore plays an important role regarding the connections cells have with each other and with the extracellular matrix. Consider the cell as an object with a cytoskeletal configuration, such that it is attached to other cells and the basal laminar through structures. The cell–cell junctions consist of adherens junctions (with actin filaments) and desmosomes (with intermediate filaments). The cell–matrix junctions consist of focal adhesions (with actin filaments) and hemedesmosomes (with intermediate filaments). The reason for the interest in this relates to the structural organization of the pericardium (in which, it is recalled, anomalies were observed early in the research). The mesothelial cell layer is open to the pericardial sac, and it is supposed to be one cell deep. In the pericardial fragments from the 12 low-frequency noise-exposed personnel who underwent cardiac surgery, the team observed that the intercellular connections were greatly reinforced, with three cell–cell junctions where only one is expected normally. Dr. Alves-Pereira emphasized that this had been observed in numerous images, and on many occasions using transmission electron microscopy on the anomalous pericardia.

Dr. Alves-Pereira stated that similarly consistently anomalous features were seen in the connections between the mesothelial cells and the sub-mesothelial layer (basal lamina) below it. They also saw an anomalous extrusion process happening in the mesothelial cell layer. The normal cycle of cell death is not observed in this layer: rather, older cells were observed to be extruded into the pericardial sac (only older cells were seen to do this).

Anomalies were also seen in structures based on the protein actin in rats exposed to low-frequency noise, compared to the controls. For example, in trachea, the actin-based microvilli in the brush cells of rats which had been subjected to low-frequency noise, were fused compared to the controls. In the cochlea, the hair cells are also composed of actin, and the team observed that in exposed rats the hair cells fuse with the upper tectorial membrane. Dr. Alves-Pereira speculated that there may be effects on the actin structures in the cytoskeleton.

Dr. Alves-Pereira concluded the talk with the following statements. Vibroacoustic disease is a mechanotransduction disease, exhibiting changes in the extracellular matrix which are so profound that it is inconceivable to Dr. Alves-Pereira that mechanotransduction signalling is not affected by this. She stated that vibroacoustic disease has been diagnosed in several professional groups, including workers in industry, marines and disc jockeys. It has also been diagnosed in members of the general population. It has also been diagnosed in members of the general population. Dr. Alves-Pereira emphasized that low-frequency noise is not a recognized health hazard. As a post script to the talk, attention was drawn to the incongruity of characterizing noise fields using the conventional dB(A) scale when low-frequency noise and infrasound were present.

4. Discussion

The session ended with a discussion of all three contributions (see Sections 1–3 above). The following topics were discussed.

4.1. Thermal effects

4.1.1. Pennes' equation

Prof. Noble asked Prof. Humphrey to clarify his statement that one of the assumptions behind Pennes' equation was that 'the energy disappears'. Prof. Humphrey replied that, for a given region in a particular time interval, it is assumed that perfusion takes away heat energy, and the amount it takes away is proportional to the excess temperature. This removal of energy reduces the heating (or brings about cooling) in the region in question. However Pennes' equation does not deposit that heat elsewhere. This simple approach cuts through the difficulties inherent in describing the details of how perfusion actually occurs, such as the location and size

of capillaries, and the question of over what size scale the capillary acts to transfer the heat, and the details of how that transfer occurs. While there are alternative approaches, the advantage of this approach (Pennes' equation) is that it then allows the user to incorporate the effects of perfusion to the model at some later stage, after the event. Effectively, calculations can be undertaken to see what happens without perfusion, and then the effect of perfusion can be added in afterwards, an approach which will explicitly reveal the difference made by the presence of perfusion. Prof. Hand added insight into how Pennes had originally carried out this work on heat transfer. The original study investigated temperature profiles in the forearm. By insertion of a suitable numerical term to account for heat transfer via capillaries, Pennes managed to obtain a good fit of the theory to experimental measurements of the temperature profiles. These profiles were over lengthscales of a few centimetres, and subsequently many people have shown that this model works well over such lengthscales. Prof. Hand asked Prof. Humphrey and Prof. O'Brien if it was valid to use Pennes' equation for heating caused by biomedical ultrasound, where the profiles of importance can be on the millimetre scale. Reiterating, he asked if it was relevant to use Pennes' equation on the scales which typify biomedical ultrasound, given that these are so much smaller than the centimetre scale for which the numerical term was fitted by Pennes. Prof. O'Brien replied that the development of the Thermal Index does use information derived from Pennes' equation. A representative of the HPA added that he had used Pennes' equation in the context of the heating generated by microwave and radiofrequency radiation. He noted that there were more sophisticated models (such as the Utrecht model), but that these required extra input data, and more detailed knowledge of the anatomy (such as individual arteries, in the Utrecht model). This represents knowledge on a very small spatial scale. He stated that he was unsure as to the range of validity of the Pennes' model, and was aware of published instances when it has been used outside of its range of validity. To illustrate this, he cited the example of whole body exposure of a rat, where of course the assumption that the excess thermal energy is simply removed is nonsensical: it has to be deposited somewhere else within the body of the rat. He summarized by saying that there is therefore a range of lengthscales where use of Pennes' equation is valid, and that it would be invalid at very large and very small lengthscales. He was concerned that some people are insufficiently critical with respect to the validity of its application in a given situation. Prof. Hand stated that he had experience with both the Pennes' and Utrecht models, in the context of examining the temperature distribution in the cooled heads of babies. He agreed with the comments made on the importance of the lengthscale of the anatomy over which models were applied, and over which the investigator is seeking information. He said that there was probably very little difference between the results of the Pennes' equation and the Utrecht equation if the investigation is over the centimetre lengthscale, but that he thought that there would be major differences over the millimetre scale. He indicated that this issue had been the basis of the question: since the wavelengths of MHz clinical ultrasound in tissue would tend to be on the millimetre scale rather than the centimetre scale, he questioned the validity of the heat transfer approaches that were being used. Professor O'Brien replied to this by commenting that the heat is generated over regions that have dimensions much larger than the scale of a wavelength, typically five to ten wavelengths rather than one. He suggested that therefore the lengthscale that should be considered in terms of the heat transducer might be considerably larger than the scale of a single wavelength. Professor J. Wu commented that he had been involved with some heat transfer experiments, using tissue mimicking material to verify modelled thermal predictions. The most difficult item to include in the model was perfusion, but that without this term the predictive ability of the model was greatly compromised.

4.1.2. Tissue response to biomedical ultrasound

Prof. O'Brien was asked to clarify the statement he made to the effect that adult tissues were less sensitive to ultrasound than were foetal tissues. He replied this was a hypothesis put forward as one possible explanation for the particular thermal response data he had been showing. He was then asked about the data he had shown regarding the bioeffects of ultrasound on lungs tissue, specifically whether those effects are observed in foetal lungs which are fluid-filled, as opposed to neonatal lung which is air-filled. Prof. O'Brien responded that the effects were not seen in liquid-filled lung.

Prof. Duck said that, as he understood it, Prof. O'Brien was extrapolating from his data to investigate shorter time exposures and higher temperatures. He asked Prof. O'Brien to comment about the presence or absence of experimental evidence in the literature, which would allow him to undertake that extrapolation.

When asked clarify the question, Prof. Duck asked for Prof. O'Brien to quantify the amount of data he had, on which he was basing his extrapolation of the time/temperature thresholds. As he understood it, that extrapolation was based on relatively long periods of exposure, undertaken in order to estimate what the thresholds might be for much shorter periods of exposure. Prof. O'Brien verified that he was not extrapolating, but rather was putting (on one curve) a range of data that covered durations of exposure, down to 0.1 s. He confirmed that all of the data he was using for that purpose was published in the literature, and corresponded to a variety of tissue types.

Professor O'Brien was asked whether the data he had presented regarding the sensitivity of tissue to heating of tissues for varying periods of time, had been obtained by submerging the animals. The questioner commented on a paper by Henriques and Moritz which he believed might have been included in the dataset that Prof. O'Brien presented. He asked Professor O'Brien to comment on the similarities and differences between heating that had been induced by submersion, and ultrasonic heating, as pertaining to his dataset, and specifically to clarify how many different ways of heating the animals had been included when compiling that dataset. Professor O'Brien responded that the dataset which he presented, corresponding to heating from durations of 1 s down to intervals of 0.1 s, consisted almost entirely of ultrasonically induced heating. He believed that there might have been a single item that was derived from laser-induced heating.

4.1.3. Nonlinear propagation

Prof. Leighton asked Prof. Humphrey to what extent the effects of nonlinear propagation were taken into account when using the established procedures which are applied for the purposed of estimating the acoustic conditions in vivo. He gave the example of derating, whereby the field in tissue is estimated from measured fields in water using established practices. Errors in this would presumably propagate into the indices which are subsequently calculated from the field estimated in vivo. Prof. Humphrey replied that his current understanding was that the Mechanical Index (MI) does not include the effect of nonlinearity. He had undertaken calculations of fields in water and then applied derating to estimate what that field would be in tissue. He had then calculated the field in tissue directly. He had found circumstances where the derating process had underestimated the peak negative pressure in tissue by about 20%, presumably as a result of failure to incorporate the nonlinearities into derating. In water, the nonlinear propagation results in enhanced attenuation. As a result, the estimated in vivo level could be an underestimate, if it is estimated by applying derating to the measured fields in water.

4.2. Low-frequency noise and infrasound

4.2.1. Measures of exposure to low-frequency sound and infrasound

Prof. Noble asked Dr. Alves-Pereira if the point she was making at the end of her talk was that it is necessary to take into account the whole spectrum in considering occupational noise exposure. She said that in essence this was correct. It would be inappropriate to describe the spectrum by an average amplitude, and that the frequency information was important.

The discussion returned to this point sometime later. Dr. Shaw agreed that the fact that it is possible to assign a single value (such as dB(A)) to describe a field does not mean that that number is the correct number to use for occupational exposure or bioeffect studies. He likened this issue to the problem currently present in the field of biomedical ultrasonics, where the existence of the MI and Thermal Index can cause problems. Whilst it is possible to calculate these numbers, and use them to characterize fields for reporting in published works, such a practice might mean that many other parameter values (which represent important exposure in formation) are not reported. The perception that it is sufficient to give one or both of the MI and Thermal Index when publishing, is leading to inadequate reporting of the experimental conditions. The fact that a number exists to be used does not necessarily mean that it is the correct number to use.

Prof. Noble asked Dr. Shaw whether the basic reason for that was because the system is inherently nonlinear, such that it will be invalid to separate out the responses at different frequencies and then undertake a summation to try to predict the result that would have occurred when the full spectral exposure is used. He asked if that was the underlying physical idea behind this point. Dr. Shaw responded that this may well be part

of it, although it might also be important that the given index might be valid for discussing one phenomenon (for example, hearing sensitivity), but not for describing another.

Prof. Leighton confirmed that one of the key problems is that occupational noise levels are characterized using the dB(A), which takes the band-limited spectral and temporal characteristics of the noise field and reduces them to a single number. In doing so a great deal of information is lost. This reduction is acceptable if the noise field corresponds to a set of assumed characteristics. The dB(A) representation is only valid for fields which adhere to those assumed conditions. It is not valid, and worse still is misleading in a way which underestimates the exposure, if the noise field deviates from those characteristics. Such deviation occurs if, for example, the field contains energy outside of the bandwidth in which the dB(A) is defined, which is true of fields containing ultrasonic or infrasonic energy. The importance of spectral information was clear, and could not be conveyed by simply stating a dB(A) calculated over a limited frequency. He asked why the use of even simple measures, such as characterization of the spectrum into third octave bands, was not more widespread. Dr. Alves-Pereira affirmed that the use of third octave bands was not at all common practice. She stated that one the major difficulties her team had encountered was that there was no perception in the community that low-frequency noise and infrasound are important. There has been, and is, great international effort to examine the effect on humans of noise exposure, and one of their problems is that the vibroacoustic disease they have characterized has not been discovered or observed by other groups. As a result, there is no evidence to corroborate what her team have been finding. One of the causes of this is that the literature on occupational noise exposure is overwhelmingly dominated by the use of dB(A) to characterize sound fields. In this context, controversial results, or results that cannot be confirmed by other groups, are treated with scepticism. However without proper characterization of the sound fields, particularly in the low frequency and infrasonic ranges, confirmation would be difficult, and this is what occurs if only the dB(A) scale is used. She noted that occasionally in the literature, spectra are reported. However invariably the lower limit on them is usually 20 or 50 Hz, since these studies are generally undertaken in order to determine what is the best protection for the ear for the circumstance under investigation. It is invalid to compare two acoustic environments based only on the dB(A) level. Prof. Leighton noted that it would not be difficult to use third octave bands to characterize occupational sound fields, and to check over what frequency limits it is important to measure. He noted that acousticians and engineers had been characterizing acoustic fields in this way for many years. Dr. Alves-Pereira pointed out that whilst this may be done by acousticians and engineers, it was not the case in the bioeffects arena, where the studies undertaken by the medical community have used dB(A) almost exclusively. She commented that the reason for this is that the legislation is framed in terms of dB(A), and not in terms of third octave or a similar representation of the spectrum.

Dr. O'Hagan asked if the total exposure of humans to low-frequency noise was measured. Dr. Alves-Pereira responded that the challenges of such an experiment would be very great. She agreed that the ideal environment would be one in which she could expose humans or animals to well-controlled levels of sound within a narrow frequency band, with the ability to vary of the level and the frequency band. It would be even better to be able to expose these subjects to a range of controlled spectra. However there are many challenges preventing this, not least the absence of sufficient funding. Dr. Alves-Pereira said that, in addition, with humans is impossible to study dose responses. This is because exposure of humans occurs outside of the test site, because low-frequency noise exposure can take place at work, at home, and during leisure activities (such as motorized sports). This was the advantage of the animal studies, where the exposure could be controlled. With animals they have managed to conduct continuous exposure for 48 h, and have found that, after 7 days of post-exposure silence, the exposed creatures recover sufficiently to resemble the controls. Dr. O'Hagan responded by asking Dr. Alves-Pereira if they had undertaken dose response tests, whereby they would monitor the response of the subjects when they are subjected to exposures which increased the dose for progressively shorter periods of time. She answered that such a procedure could be done in the future, but to date they had concentrated on simulating particular occupational environments. She clarified that all of the animal results she had presented during the talk had come from simulated occupational environments. They were currently trying to study continuous exposures, such as humans might experience in ships or on the space shuttle. However such investigations presented difficult logistical problems. For example, it is not a simple matter to find a laboratory in which animals might be placed for such studies. It would not be ethical to undertake them in, for example, the basement room at her university, because of the ability of low-frequency

noise and infrasound to propagate away from the test area into remote locations of the building. Continuous exposure conditions would be particularly difficult to reconcile with the presence of other occupants in the building. She commented that Russian workers had exposed rabbits to incrementally increased tones (8 Hz, then 10 Hz, etc.), but the literature is in Russian and difficult to translate. It appears that the goal of these studies was to determine which cellular mechanism is affected by which particular frequency.

Dr. O'Hagan asked why Dr. Alves-Pereira did not have an in vitro model. She indicated that exclusion of ambient noise during testing is a particular difficulty. She observed that it was feasible to design experiments which would provide valuable information, but that without appropriate funding these plans could not be executed.

4.2.2. Symptoms

Dr. Alves-Pereira was then asked by Prof. Hanson whether the animals tested were unwell, perhaps hypoxic or exhibiting some aspects of heart failure. Dr. Alves-Pereira replied that on the contrary, in terms of animal behaviour, the only abnormality was the response to the 'blow and kiss' test. Normal rats become tense in response to this test. In contrast the exposed rats responded to the test by trembling and raising themselves up on their hind legs. This was the only behavioural abnormality. To the best of her knowledge, there were no health defects in the animals: they did not show heart failure, respiratory deficiency etc. This agreed with the observations of the aircraft workers, who for the most part appeared to have normal health. Prof. Hanson responded that, because the exposed rats displayed such pronounced thickening of the alveolar walls, that therefore this thickening must have been relatively focal. This in turn would raise the question as to why certain parts of the system appear to be more susceptible than others. Dr. Alves-Pereira agreed that, when her team had returned to studying the aircraft workers and given them high resolution CAT scans of the lung, they had found that the fibrosis there had been focal. The autopsy had also shown that the lung fibrosis was focal. However she added that fibrosis was occurring at many more sites than just the respiratory tract: they were seeing fibrosis in the cardiovascular system, and they have recently started to study the kidney, where they have also seen fibrosis.

One questioner commented that the histological changes that Dr. Alves-Pereira had shown would suggest that the cells had been subjected to local mechanical forces. He noted however that the wavelength was very large for this low-frequency exposure. She was therefore invited to speculate on how such a large wavelength would lead to effects, which appear to be caused by local stresses. Dr. Alves-Pereira speculated that vibroacoustic disease may be associated with strengthening of the tissue surfaces. She suggested that perhaps the biological tissue is finding a need to strengthen structural integrity. She referred to the comments she had made in the talk regarding mechanotransduction. As regards the issue of the long wavelength Dr. Alves-Pereira made the following statement: the propagation of a long-wavelength infrasonic wave, over a subject at a fixed point in the field, would be experienced by that subject (with or without his/her perception) as being immersed in a near-constant pressure field. The questioner then commented that he had been studying the effect of oscillating the hydrostatic pressure in blood vessels, and had observed vasodilation. He therefore wondered whether Dr. Alves-Pereira had seen any effects on the blood pressure following exposure. She responded that they had not observed effects on blood pressure. However they had seen interesting effects in rats immediately following exposure. Specifically, they had subjected rats to 48 h of continuous exposure to low-frequency noise. They had then sacrificed the animals at intervals, until the end of 7 days. They observed that, immediately following exposure, there was swelling of cells in, for example, the trachea and the kidney. After a period these swollen cells would deflate. She did not wish to call this oedema, because she did not know whether the swelling was caused by water retention. Noting that one must treat comments from patients with caution, she did reveal some interesting comments from some patients (particularly those who had been exposed to low-frequency noise for weeks at a time, for example in ships). She said that these comments had been made before the patients were told about the swelling that had been observed in animals. These particular patients would routinely spend several weeks on a ship, and then go home for 2 weeks. They commented that, 2 or 3 days after returning home, each time they would find that their clothes were very loose on them. She cautioned the audience that this means nothing in a scientific sense.

Dr. Bouffler asked how long it took for the rats to develop respiratory fibrosis and pericardial abnormalities. Dr. Alves-Pereira stated that all the pericardial observations pertained to humans, because rats

do not possess a pericardium. She said that fibrosis had appeared within the first month of exposure of rats to simulated occupational low-frequency noise. The first symptoms appeared within around 200 h, with fibrosis initially developing and cilia being destroyed. Additional symptoms were still appearing at around 4000 h. With humans, Dr. Alves-Pereira commented that the development depends on the type of exposure that they had. She emphasized that the exposure need not be occupational: exposure outside of the workplace, in the home or through recreational activities, would tend to promote the development of the effects. When asked, she clarified that they had seen no evidence of life shortening in rats because they had not look for it: the animals have all been sacrificed. They had found dysplasia and metaplasia in rats, but had not found tumours (perhaps because their lifespans are too short for these to develop).

4.2.3. Cohort

Prof. Leighton asked how many aircraft workers were in the group that they had studied. Dr. Alves-Pereira responded that there were 306 initially. Her team have since also studied pilots, flight attendants, and of course rats. They were now looking at people who were coming forward with symptoms, and who had received low-frequency noise exposure in the urban environment. She clarified that when she had talked about twelve patients, she had been referring to the ones who had had cardiac surgery and whose pericardial fragments had been studied. She concluded that the group sizes were not large by epidemiological standards, because of funding limitations.

Prof. Mason commented that a group of people who might be of interest to Dr. Alves-Pereira were the patients who suffer from vibration white finger. This was because, in addition to the vibration that had caused of their vibration white finger, they would probably have also been exposed to low-frequency noise. Dr. Alves-Pereira countered with the comment that this might not be the case. She gave the example of the pneumatic hammer. People who work with such tools (which give rise to vibration white finger) are exposed to mechanical vibration of the hands, and are also exposed to high levels of audible noise (and should have hearing protection). She commented however that the levels of low-frequency noise and infrasound produced by such devices may well not be very great. The exception might be if these workers are using a pneumatic hammer underground, for example if they work for a water company. She also cited the example of workers using chainsaws in trees. They are exposed to hand-arm vibration and considerable audio-frequency noise, but in these environments the levels of low-frequency noise and infrasound are not great.

Prof. Humphrey stated that he believed that the human lungs exhibited resonance. Because of the size difference, he believed that it could be that the resonance of a rat lung might occur at frequencies which are several orders the magnitude greater than the frequency at which resonance occurs with the human lung. He speculated that if the resonance was important, then the relevant exposures might be in the audio-frequency regime. Dr. Alves-Pereira said that she did not know to what extent a lung resonance might, or might not, be important. In the 1960s Russian experiments on exposure of dogs to low-frequency noise found that, with increasing exposure time, the lesions in the lungs did not increase in size, but they did increase in number. The majority of lesions were found in the right lobe of the lung, as opposed to the left lobe (anatomically and biomechanically, the two lobes are very different).

5. Close of session

Prof. Noble thanked the speakers and audience for their contributions.

Reference

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