Ultrasound in Med. & Biol., Vol. 26, No. 6, pp. 911–964, 2000

0301-5629/00/$–see front matter

PII S0301-5629(00)00243-X

● *Historical Review*

BIOLOGICAL EFFECTS OF ULTRASOUND: DEVELOPMENT OF SAFETY GUIDELINES

PART I: PERSONAL HISTORIES

WESLEY L. NYBORG
Physics Department, University of Vermont, Burlington, VT 05405, USA

(*Received* 4 *February* 2000; *in final form* 4 *April* 2000)

Abstract—After the end of World War II, advances in ultrasound (US) technology brought improved possibilities for medical applications. The first major efforts in this direction were in the use of US to treat diseases. Medical studies were accompanied by experiments with laboratory animals and other model systems to investigate basic biological questions and to obtain better understanding of mechanisms. Also, improvements were made in methods for measuring and controlling acoustical quantities such as power, intensity and pressure. When diagnostic US became widely used, the scope of biological and physical studies was expanded to include conditions for addressing relevant safety matters. In this historical review, a major part of the story is told by 21 investigators who took part in it. Each was invited to prepare a brief personal account of his/her area(s) of research, emphasizing the "early days," but including later work, showing how late and early work are related, if possible, and including anecdotal material about mentors, colleagues, etc. © 2000 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Biological effects, Ultrasound, Safety, Guidelines, Personal, History.**

INTRODUCTION

After vacuum technology and piezoelectric materials became available early in the 1900s, it was possible to generate ultrasound (US) at intensities sufficient to make this an interesting new modality. In the 1920s and 1930s, investigators created excitement by reports of physical, chemical and biological effects that could be produced by US at intensities up to several hundred watts per cm^2 and frequencies in the vicinity of 300–400 kHz. This led to development of applications, along with extensions of the range of intensity and frequency available, as well as research aimed at learning the basic mechanisms involved. Applications directly related to medicine included bacteriocidal use, physical therapy and surgery. In the 1950s and 1960s, the promise of diagnostic US became increasingly apparent, and the need to define conditions for its safe practice was recognized. The 1970s and 1980s saw diagnostic US established as a major part of diagnostic medicine. Also, during this period, there was much research on biological effects of US, as well as development of improved methodology for characterizing the acoustic output of diagnostic US equipment. This research and development enabled the formulation and use of scientifically based safety guidelines, and also helped to advance applications of US to therapy and surgery.

This review is divided into two parts, I and II. Part II is a general review, and the present part (I) consists of 21 short personal accounts. The authors of these accounts (whose addresses are listed in the Appendix) include investigators who made significant contributions to understanding how US produces biological effects, leaders in developing applications to therapy and/or surgery, and leaders in developing and using much-needed methodologies for characterizing US fields. (Some authors contributed in two, or all three, of these aspects of the subject.)

By invitation, each of the histories is a brief account of the development of the author's area(s) of interest from a personal perspective, emphasizing the "early days," but including later work, showing how late and early work are related, when this can be done. ("Early," of course, means different things to different people.) The accounts include memorabilia about mentors, col-

Address correspondence to: W. L. Nyborg, M.D., University of Vermont, Department of Physics, Cook Physical Science Building, Burlington, VT 05405 USA. E-mail: wnyborg@zoo.uvm.edu

leagues, etc., and sometimes recall issues that have been the focus of lively debate. It is clear that the present status of medical US owes much to the efforts and accomplishments described here.

In Part II of this review, considerable reference is made to information provided in the 21 personal histories.

The personal history of our loved and respected colleague Padmaker P. Lele, M.D., Ph.D. (Oxon), appears here, with help kindly offered by his family, almost exactly as he prepared it before his death (11 June 1998). This publication provides an occasion to remember with gratitude his many contributions to medical US generally, and his special passion for US hyperthermia.

Fig. 1. J. Angell-James.

J. ANGELL-JAMES: THE ULTRASONIC TREATMENT OF MENIERE'S DISEASE

Arslan's pioneering work

I (Fig. 1) first became interested in ultrasound on a visit to Padua in Italy in the mid 1960s. There, I saw Michele Arslan performing an ultrasonic destruction of the labyrinth, using equipment constructed by the Italian company Federici. Arslan had learned of the idea of using US for the destruction of the labyrinth from the Austrian otologist Krejci. The operation was being undertaken to treat intractable Meniere's disease. This is a condition in which the end organ of the balance system in the labyrinth becomes disorganised; there is a rise in the pressure of the endolymph, which is the fluid that fills the cavity in the temporal bone. The object of the operation was to destroy the balance function of the end organ yet leaving the hearing intact. In Meniere's disease, there is some loss of hearing accompanied by tinnitus, and the main symptoms are severe attacks of vertigo with vomiting, during which some patients may even fall down. The attacks may last for several days at a time and then cease, but recur later and the hearing usually deteriorates. At the time, most otologists who attempted surgery for Meniere's disease would destroy the labyrinth completely and, with it, the hearing on the affected side. Destruction of both labyrinths in bilateral cases of Meniere's disease was virtually impossible because of the total deafness that would result. The ultrasonic method was recommended chiefly to maintain hearing on the operated side.

At the time, I knew very little about US except that it was used in the First World War and, of course, much more extensively in the Second World War, in the technique for detecting submarines.

The Federici equipment was large and consisted of a generator and a solid rod probe. The operation was performed under local anaesthesia to observe the nystagmus resulting from the application. To apply the US, the mastoid had to be opened and the bony wall of the labyrinth exposed. Ultrasound produced nystagmus that was at first directed toward the side of the operation but, after a variable length of time, the nystagmus reversed as the US paralysed the irradiated vestibular apparatus. The reversal of nystagmus was taken as an indication of the completion of the operation. Looking at the bone after the operation, it was seen to be quite black, and so I immediately jumped to the conclusion that heat had been very considerable. I discussed with Professor Arslan the possible effect of this on the facial nerve, which runs only a millimetre or two away from the area that was treated, and noted that cases of facial paralysis were reported.

Early work in Bristol

On my return from Padua to Bristol, I consulted H. F. Freundlich, the Head of the Medical Physics Department. He was immediately interested. Much of the writing on US up to that time had been in German, and Freundlich, who was German-speaking, was a great help in looking back into the history and the literature as we made our plans for our own research. We asked our local Medical Committee to purchase the apparatus from Italy and we applied to the Medical Research Council, from whom we obtained a grant of £10,000. Although this sum sounds trivial now, at the time it was a large sum of money and it made it possible for us to investigate the performance of the apparatus by employing (now Professor) P. N. T. Wells as a research assistant, supervised by Freundlich and another physicist, M. A. Bullen. We began to investigate the function of the Italian apparatus. We examined how it was built and measured its power output and beam shape. Some of the things that we found were very alarming. The temperature of the tip of the probe was much too high for the safety of the facial nerve and, possibly, also even of the bone itself.

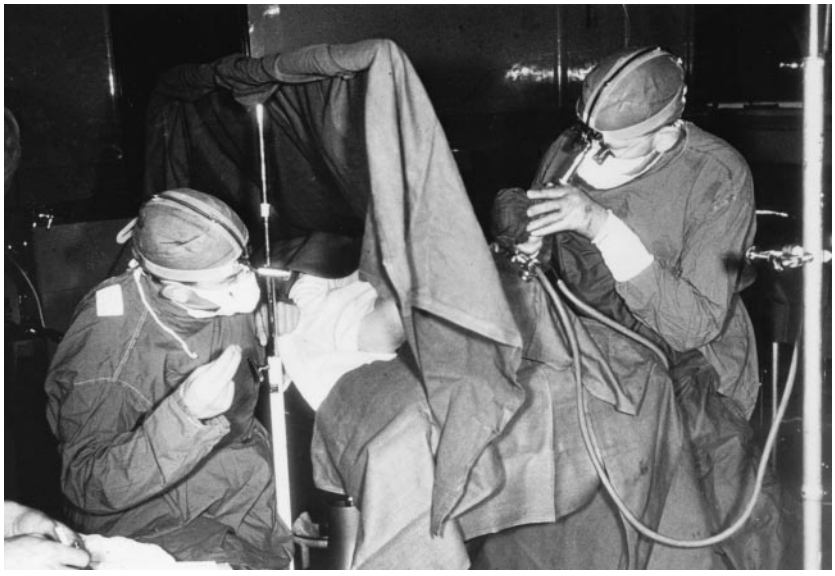

Fig. 2. Irradiation in progress, 1960. J. Angell-James is on the right, holding the Federici ultrasonic probe, and G. A. Dalton is on the left, observing the patient's nystagmus (centre).

Our own apparatus

Having identified the shortcomings of the Federici equipment, we proceeded to develop our own apparatus. We used a small hollow cone as a probe, with normal saline continuously flowing through it as a coolant and conductor of US, thus reducing the risk of bone or facial nerve damage. Temperature was monitored continuously by thermocouple. Lead zirconate titanate was used as the ultrasonic transducer, in spite of the difficulty in finding a firm capable of supplying suitable material. By means of schlieren photography, we demonstrated the shape of the ultrasonic beam and the way in which it passed through specimens of bone. In itself, this work excited a lot of interest. We felt that it was important to get as much US as possible into the labyrinth, and so we decided that we should drill down through the bone over the lateral semicircular canal until a blue line, a fraction of a millimetre thick, appeared. We believed that this would lead to the shortest exposure time and the least damage to the bony structure of the labyrinth.

Our laboratory studies on the Federici apparatus enabled us to modify Arslan's technique so that we were confident enough to embark on a clinical series. In this work, I was assisted by my senior registrar, G. A. Dalton, who later went on to become consultant otolaryngologist in Birmingham (Angell-James et al. 1960). Figure 2 shows the scene in the operating theatre.

Animal experiments

We thought that it was imperative to find out, by means of animal experiments, what effect the US had on the sensitive cells of the vestibular apparatus. Although we had learned that the labyrinth of the giraffe closely resembles that of man, experiments on giraffes were obviously impracticable for us, so we used sheep, the next most suitable animal, for our initial work. The Veterinary Faculty of the University gave us the facilities for this research and our anaesthetist was B. M. Q. Weaver, who was renowned for her work at the Langford Laboratories of the University of Bristol. One of the temporal bones of the sheep was irradiated and the other served as control. Three weeks later, the sheep was euthanized under general anaesthesia and the temporal bones subjected to intravital fixation. The bones were then sectioned by C. Hallpike of the Ferens Institute. Photomicrographs of sheep crista are shown in Fig. 3, without and after irradiation. In the irradiated crista, the hair cells show disorganisation.

With D. E. Hughes and J. T. Y. Chou at Oxford University, experiments were carried out on guinea pigs. We investigated the metabolism of Reissner's membrane and demonstrated significant changes in sodium-potassium pumps. The sodium concentration was lowered and that of the potassium raised. The results of these experiments, interesting in themselves, helped us to understand the mechanism of ultrasonic irradiation in man, and to explain the responses of the patients both during surgical procedures and postoperatively (Angell-James 1963, 1966, 1969).

At the same time, we were performing a number of hypophysectomies for the relief of breast cancer, and it occurred to us that US might offer a very good method of

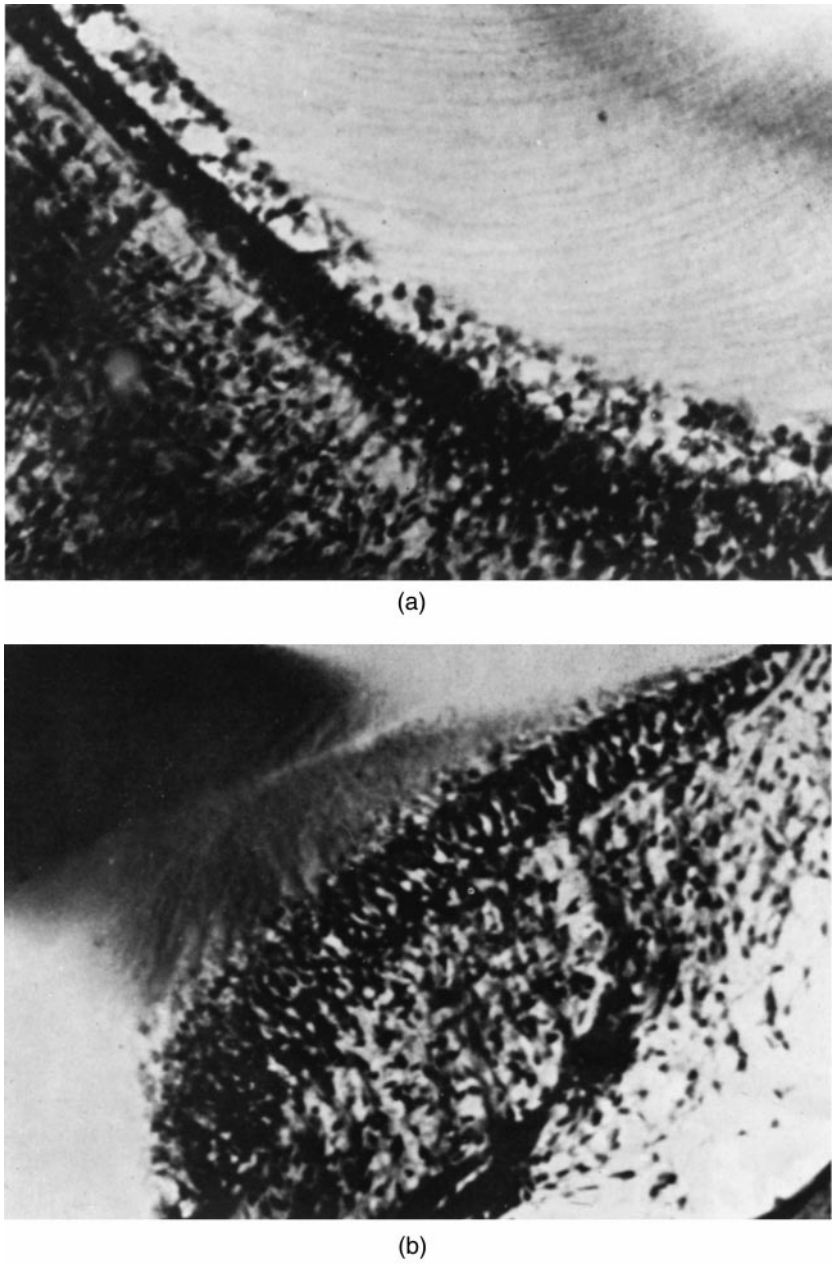

Fig. 3. Photomicrographs of sheep crista of the lateral semicircular canal (magnification approximately ×60). (a) Healthy control; (b) 28 days after irradiation with 3-MHz ultrasound.

destroying the pituitary without having to remove it entirely. The significance of this was due to the fact that the pituitary gland, like the end organ of the labyrinth, is surrounded and protected by bone, so that the surrounding tissues would not be damaged by lethal doses of US. We, therefore, tested out the effect of US on the rat pituitary, but were not satisfied with the destructive effect without the possibility of surrounding damage, so this had to be abandoned.

Clinical results

I myself treated 400 patients and, since my retirement in 1966, my colleague P. G. Bicknell has operated on a further 275. The results for the relief of vertigo have been very good. A number of patients have also reported relief from tinnitus and the feeling of pressure in the ear. Some have also experienced an improvement in their hearing (Angell-James 1967, 1969). It may well be that the US, by increasing

permeability of the membranous labyrinth, reduces the endolymphatic hydrops.

The success of our efforts has been due to the exceptional enthusiasm and the ability of our colleagues in the special departments mentioned. In the future, it would seem that further uses for the wide attributes of ultrasonic vibration may be found in medicine and surgery. These special attributes are the effect of vibration causing a rise of temperature and the wide differential between conductivity in liquids and conductivity in solid materials such as bone, the effect on the permeability of semipermeable membranes, and its reflectivity at places where neighbouring materials have different characteristics. All these will have to be borne in mind in looking at future applications.

STANLEY B. BARNETT: ULTRASOUND BIOEFFECTS RESEARCH

As an honours graduate of King's College University of London, my undergraduate thesis involved research on Molossid bats in flight, under the guidance of David Pye, an expert on echo-location techniques. Despite that early introduction, I (Fig. 4) was subsequently quite surprised to find myself directed towards a career in ultrasound. Early in 1970, I joined a small group of dedicated scientists working in a converted warehouse in what is now known as the "Historic Rocks" area of Sydney.

I can clearly remember my first meeting with a somewhat flamboyant individual, wearing a brightly coloured bow tie, who spoke English with an American/Russian accent and insisted on first-name addressing. This was quite a contrast from my days at King's College, when the head of the Department was addressed as nothing less than Professor, and then only when spoken to! George Kossoff had just returned from a 2-year visit to the University of Illinois where he worked with Floyd Dunn and a graduate student by the name of William O'Brien, Jr.

Having spent 25 years working in the same Laboratory as George Kossoff and David Robinson, it is inevitable that I have been influenced in some way by these individuals. They share a common desire to achieve, to be noticed, and to know more than anybody else around them at any time. This has inspired elements of competition and, no doubt, has contributed to the success of the Laboratory. I have considered myself fortunate to work in a high-profile Laboratory with a mix of graduates in engineering, physics and biological sciences in close association with Universities and teaching hospitals.

In the early 1970s, research at the Commonwealth Acoustic Laboratory (as it was known then) involved a

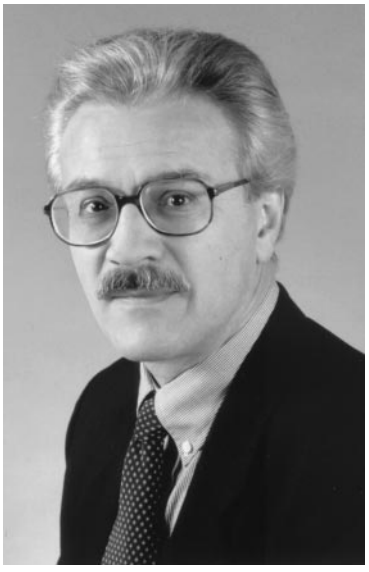

Fig. 4. Stanley B. Barnett.

range of diagnostic applications (obstetrics, ophthalmic, mammographic) and the ultrasonic treatment of Meniere's disease. The technical achievement of the therapeutic application was in the design of a miniaturised transducer and holder that could pass through the patient's external auditory meatus and be positioned adjacent to the round window of the cochlea to allow US to be transmitted into the inner ear. This procedure was considerably less traumatic than an alternative approach that coupled US to the semicircular canal after removing part of the skull bone with power saws, bone cutters and drills. The so-called "round window" procedure achieved success, with approximately 70% of patients showing removal or improvement of the debilitating symptoms of loss-of–balance and orientation (Barnett and Kossoff 1977). An advantage over alternative surgical procedures, such as labyrinthectomy, was that the patient's hearing was not destroyed. Although the technique successfully treated the symptoms in patients with unilateral affliction, the means by which this was achieved was not fully understood. This, of course, is not unusual for technological developments in medicine.

My introduction to US research, therefore, involved working in hospital operating theatres with ENT surgeons, and planning and undertaking a series of animal studies to mimic these surgical US exposures of the mammalian inner ear. Endpoints included histological examination of the vestibular and cochlear neuroepithelia, microscopic examination of surface preparations of the cytoarchitecture of the organ Corti, and measurements of cochlear microphonic responses and temperatures. Many hours were spent preparing glass microelectrodes with hand-built laboratory equipment. The char-

acter-building exercise included enduring the frustration of measuring minute signals with high-impedance KCl microelectrodes after spending hours implanting them in the surgically-exposed cochleas of anaesthetised guinea pigs. This was done in a laboratory that was only about 2 miles by line-of–sight from a naval base. The value of an electrically-shielded operating area soon achieved a great significance!

The results of approximately 6 y of work in a variety of small and large animals showed that the sensory apparatus of the vestibular labyrinth (responsible for balance in healthy individuals, but hypersensitised in patients with Meniere's disease) was selectively destroyed (Barnett et al. 1973) and damage to the cochlea was restricted to its base so that practical hearing (to about 8 kHz) ability was preserved. Using the cochlear microphonic response as a physiological indicator (Barnett 1980a, 24;1980b), it was discovered that a combination of the effects of direct interaction and bulk temperature increase was responsible for the structural changes observed in the neuroepithelia. A relatively slow increase in temperature within the endolymph fluid (8°C after 3-min continuous insonation) was accompanied by a gradual depression in microphonic response. The histopathology aspects of the small animal work were carried out with guidance and support from Professors Wilhelm and Lykke in the School of Pathology of the University of New South Wales.

In 1974, our laboratory experienced its first working visit by an overseas scientist in the form of Marvin Ziskin of Temple University Medical School, Philadelphia, PA, USA. The initial meeting left an indelible mark on my memory as this enthusiastic American had a burning desire to undertake bioeffects research on a marsupial species. He presumably came to Australia in the belief that wallabies and koalas roamed freely through the city streets! Undaunted, this intrepid adventurer's quest brought us to a meeting with Marshall (Marsh) Edwards in the School of Veterinary Clinical Sciences of the University of Sydney. After Edwards painstakingly explained the difficulties of attempting to do research with marsupials within the 6-month sabbatical period (litter sizes were small, there were no breeding programs within the University and many species are protected), a collaborative effort was established using guinea pigs.

That introduction more than 20 years ago has developed into valued personal and scientific associations. The Ultrasonics Laboratory has enjoyed successful long-term research collaborations with Marsh Edwards and other members of the University of Sydney. This has led to successful grant applications and a number of degrees conferred on students as a result of work in my (bioeffects) laboratory. I have been honoured by being appointed an Honorary Associate of the University of Sydney, School of Veterinary Clinical Sciences.

In the early 1980s, there was considerable international interest in the possible mutagenic effects of diagnostic US. A paper from a prestigious New York medical college had reported alteration in the rate of sister chromatid exchanges (SCE) in mammalian cells exposed *in vitro* to US emitted from a diagnostic device (Liebeskind et al. 1979). Although our studies were unable to confirm these results, we observed an increased rate of SCE in Chinese hamster ovary (CHO) cells when insonated with ms pulse lengths, at peak pressures that were considerably higher than those used in diagnostic imaging at that time.

This was apparently noticed by researchers at the University of Rochester, New York, NY, USA. I accepted an offer to work in the faculty of Radiation Biology with Morton (Mort) Miller during 1986/87, to further study the SCE phenomenon. While there, I also spent many hours in Edwin Carstensen's laboratory, insonating myriads of CHO cells. I quickly shared in the enthusiastic attitude of this small group of dedicated people. We all became familiar with the security officers who patrolled at night and on weekends. Although the SCE technique is highly labour-intensive, I could not match the output of Yukio Doida, a frequent summer visitor from Japan. I suspect that he slept in the cell-culture room. After 3 months, it was almost impossible to find Doida behind the bench-to–ceiling piles of thousands of petri dishes. Only the sound of quiet rhythmical counting of cell colonies gave a hint to his whereabouts.

Our studies showed a marginal, but statistically significant, increase in SCE rates (Barnett et al. 1988). However, the reliability of the SCE effect remained elusive; it is almost certainly a product of inertial cavitation. The difficulty in the procedure lies in the need for enough cells to survive the exposure, divide with abnormal DNA replication and then be detected in a test sample of a few cells from a population of tens of millions (many of which may be unaffected). The special chromatid labelling procedure also affects the SCE rate and it is, therefore, essential that this be carefully controlled so that the SCE rate (and variability) in controls does not mask a small increase induced by the exposure insult. The protocol (used by the Ultrasonics Laboratory) of holding the cell suspension on ice prior to insonation would certainly have increased the probability of gas bubble formation when the suspension was warmed to 37°C during insonation, thereby assisting cavitation. In fact, subsequent work in Miller's laboratory has demonstrated this effect by enhancing US-induced mutations in Chinese hamster V79 cells when a similar protocol was used (Doida et al. 1992). This underlines the importance

and great difficulty of standardising protocols for sensitive endpoints in studies involving short time schedules.

I am very pleased to have had the opportunity to work with Mort Miller and Ed Carstensen, and I greatly value their friendship. It was an exciting time in Rochester for a number of reasons. I have never experienced sub-zero temperatures for so long (about 3 months). Spring was heralded by the sudden appearance of masses of brightly coloured tulips. The nature of the environment is such that things happen quickly and create an impact. For the many individuals who have been associated with the "U of R," it would seem normal for new developments to take place. I was fortunate to arrive at the time when the Rochester Center for Biomedical Ultrasound was formed, and I was involved in its inaugural Symposium, together with such luminaries as Wesley Nyborg. I distinctly remember Wes quoting from the Bible in terms of Maxwell's equations and demonstrating the creation of light. He pointed out that there was no such record for the creation of sound, but speculated that it must have occurred very early to make possible the "Big Bang."

On my return to the Ultrasonics Laboratory in its new purpose-built modern facility, I set about the serious task of writing grant applications to encourage scientists to visit my laboratory and continue to develop academic liaisons. The Australian Bicentennial year of 1988 is significant for many people but, for me, it was overshadowed by the arrival of an effervescent Welshman bent on a mission to unlock the mysteries of ultrasonic bioeffects research. Alun (Roy) Williams took time out from his busy schedule to spend approximately 2 months developing a project to identify the mechanisms responsible for fetal weight loss when pregnant mice were insonated with therapeutic doses. It had troubled Roy that some reports of US-induced fetal weight reduction had referred to symptoms that indicated maternal compromise. Our study demonstrated that exposure with similar intensities that avoided the pregnant uterus, but interacted with the dam's nervous system affected the maternal physiology and also impaired fetal development (Barnett and Williams 1990). These results highlight the potential difficulties in assessing US safety from experiments where the ratio of beam size to target is not relevant to human clinical examinations. The possibility of direct effects, independent of maternal interference, was subsequently tested in another collaborative study, with the University of Sydney School of Veterinary Clinical Sciences, using an embryo culture system. It was found that development of rat embryos, specifically the forebrain, was impaired when pulsed US was applied together with a mild temperature (+1.5°C) elevation (Barnett et al. 1990b).

Research on the bioeffects of US continues to play a prominent role in Australia and the ASUM has an active Safety Committee, of which I am Chair. A merger of divisions within the CSIRO resulted in closure of the Ultrasonics Laboratory and displacement of staff in 1997. My laboratory is currently secreted securely within the confines of an impersonal monolith built in 1979 on the requirements of the National Measurement Laboratory. Despite these socioenvironmental changes and several funding challenges, research has continued through collaborative associations with academic institutions in Australia and overseas (Duggan et al. 1995; Horder et al. 1998a, 1998b). I look forward to further stimulating research opportunities.

Research on the bioeffects of US has evolved from therapeutic applications, where gross anatomical effects were recorded after exposures to intensities not relevant to diagnostic exposures. The search for effects induced by relatively low levels of US used in diagnostic applications has introduced some sophisticated test systems. The movement away from phenomenological reporting to the mechanistic approach is to be applauded. However, a number of reports of fascinating effects on mammalian cell development are not readily explained by known interactive mechanisms. Detection of subtle biochemical changes involving cell membrane-mediated signal transduction and responses at the subcellular level may help to understand some, yet to be determined, nonthermal processes in cell development. The search for effects at the level of the chromosome has involved rather crude endpoints, mostly relating to gross morphology. The possibility of altered genetic expression has not been seriously questioned by sensitive tests. It may be that the answers lie within the realm of molecular biology.

The World Federation for Ultrasound in Medicine and Biology has recognized the importance of research on bioeffects and safety by its continued support and sponsorship of symposia on the Safety of Ultrasound in Medicine (WFUMB 1992, 1998). The workshop-style meetings provide an excellent opportunity for focused debate on issues that are of global concern to the safety of diagnostic US. I am pleased to have been given the opportunity to participate in these activities. It is hoped that this positive encouragement will continue amidst the otherwise general financial restrictions on international research.

KLAUS BRENDEL: PERSONAL HISTORY

After having worked for 10 years in the field of underwater acoustics in the III Institute of Physics at the University of Göttingen as a member of Professor Erwin Meyer's staff, I (Fig. 5) took up a post at the Physikalisch-Technische Bundesanstalt (PTB), Braun-

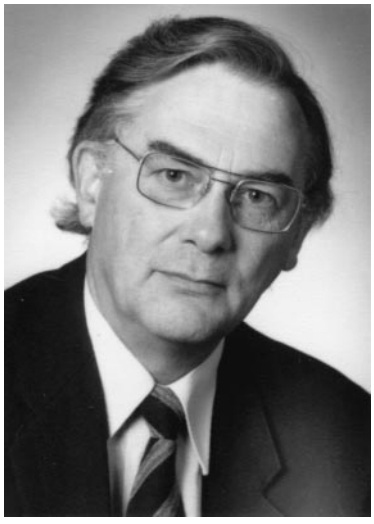

Fig. 5. Klaus Brendel.

schweig, in December 1968. There, I started with self-reciprocity calibrations of ultrasonic transducers. The experience gained was very useful in the development of an absolute calibration procedure of probe hydrophones years later. From 1971, I was put in charge of the Ultrasonics Laboratory of the PTB and was also responsible for developing, realizing and disseminating procedures for the determination of the acoustic data of ultrasonic medical devices in Germany.

The development of acoustic measurement methods at megahertz frequencies is no easy task, mainly due to the fact that calibration facilities are usually far from meeting ideal boundary conditions as assumed in theory. The length of the ultrasonic wave and the size of the objects (*e.g.*, the hydrophone diameter) are comparable, and numerous types of waves exist in finite solids. In addition, the electrical wavelength on the cable is comparable to the length of the cable. Jan Koppelmann, who was in charge of the PTB Ultrasonics Laboratory before, used to say: "The ultrasonic measurement technique was invented by God in great anger."

As to standard measurement procedures for ultrasonic diagnostic devices, no such methods were available before 1970. A pattern evaluation of therapy units using the float method was developed at the PTB in 1951–1952 and adopted as an IEC Recommendation (IEC 150) in 1965. However, the float technique employed is restricted to power levels higher than 100 mW. For determining the spatial and temporal peak pressure and intensity values, no appropriate calibrated sensor (hydrophone) existed. The hydrophones available showed so many resonances that a bad frequency-dependence resulted. A hydrophone, designed and built to the best of our knowledge in our Institute's workshop, did not bring about an improvement; on the contrary, it was one of the worst. It was built most precisely and, therefore, resonances and diffraction phenomena were extremely noticeable.

In this situation, it was both reassuring and helpful to learn of the efforts of colleagues and their troubles with ultrasonic measurement technique. Due to my appointment as a delegate to the International Electrotechnical Commission and to several other committees in 1970, I had the opportunity to get to know US experts from all over the world before very long and to discuss measurement problems of mutual interest. I have fond memories of the 2nd World Congress on Ultrasonics in Medicine in Rotterdam in 1973, at which Bill O'Brien introduced me to a number of colleagues I had not met before. In 1975, I became a member of the Advisory Board of UMB and in 1979 of the new established "Watchdog Group"—the European body equivalent to the AIUM Bioeffects Committee in the USA.

In regard to the standardization of measurement methods, Kit Hill, the secretary of the IEC working group on "Ultrasonic diagnostic devices," reported at the London Meeting in 1971 that the preparation of a document on measurements of ultrasonic diagnostic devices had been started and Martin Grützmacher, the chairman of the subcommittee on "Ultrasonics," stated that a round-robin test on ultrasonic medical equipment should be one of the first steps of this working group. Nobody would have believed that these projects would take so much time, more than 10 years.

After only 1 year at the IEC meeting in Oslo, it was agreed to dispense with detailed references to Doppler equipment in the document under preparation. Only the characteristics of the complete system, and not those of system components, should be covered. This was the first realization that the input of information was higher than the output in preparing a document.

At the Moscow meeting in 1974, the task was split. Instead of the aforementioned document on measurements of ultrasonic diagnostic devices, it was decided that three documents should be prepared: "Methods of measuring the performance of ultrasonic pulse-echo diagnostic equipment," "Methods of measuring the performance of ultrasonic Doppler diagnostic equipment," and "Measurement of the acoustic output of medical ultrasonic equipment." The third document led to extensive discussions between Hill, Peter Edmonds and myself on the question as to whether or not the power measurement using the radiation force is a primary method. The result was: "Yes, it is." A further point of discussion concerned the measurement problems at frequencies above 10 MHz.

In the meantime, in most laboratories engaged in the field of medical ultrasonics, more or less sophisticated

measurement devices for the determination of the radiated power, also in the milliwatt range, have been installed. An excellent device was the "Rooney balance" in Nyborg's laboratory. I was even allowed to "play" with this measurement setup on the occasion of a visit to Burlington in 1973. A handy and rather accurate measurement of the sound pressure with high resolution in both space and time was not possible until the piezoceramic material was replaced by the piezoelectric high-polymer polyvinylidene difluoride (PVDF) as sensitive material. I still vividly remember Gail ter Haar's enthusiasm when talking about the advantageous properties of this material and the membrane hydrophones in London in 1982. Also, a calibration method for probe hydrophones—the two-transducer method—was developed by Gerhard Ludwig and myself. I presented this measurement procedure in Bethesda in 1974. To be sure that there was no error involved, I had given the manuscript several days before to W. J. Trott and his staff from the Naval Research Laboratory, Washington, DC. The experts' answer was only that in one formula a letter had been mixed up. In the 1980s, round-robin measurements were performed with PVDF needle-type and membrane hydrophones, and also with power standards developed by the National Bureau of Standards (NBS) and later by the PTB.

Also, the IEC work became more and more successful. However, during the Sydney meeting in 1980, it became apparent that the explosive development in the field of ultrasonic diagnostics could not be handled by one working group. The Subcommittee Ultrasonics 29D was changed to the Committee 87 Ultrasonics with Joachim Herbertz as chairman and Roy Preston as secretary. The working group on ultrasonic diagnostic devices was split up into three groups: "Ultrasonic field measurement," "Pulse-echo diagnostic equipment" and "Doppler diagnostic systems." In 1985, a fourth working group, "Ultrasonic exposure parameters," was established. At the IEC meeting in Berlin in 1982, in the working group "Ultrasonic field measurements," the "homework" was distributed: The delegates of the UK should mainly promote the measurement technique using hydrophones, the delegates of Japan, Russia and the USA the thermal measurements, and the German delegates the power determination using the radiation force.

Since the early 1990s, IEC recommendations for most essential measurement procedures have been available, and most ultrasonics laboratories are equipped with appropriate measurement devices. For example, at the PTB, Rainer Reibold, Klaus Beissner and Walter Molkenstruck have built several devices for the determination of the total radiated power between 10 μW and 40 W. In particular, Beissner has been engaged in the development of the basic radiation force theory. A setup using double-exposure holography allows the intensity and its distribution within the sound field to be determined. The PTB interferometer implies a stabilized version for displacements of up to $\pm$ 50 nm and a quadrature version for greater displacements in one optical setup. Also, the methods of light diffraction and light deflection are occasionally used. Basic investigations on the ultrasonic scattering process were performed by Burkhard Fay and coworkers in the 1970s (Fay 1973; Fay et al. 1976). At present, Dr. Fay is engaged with the development of thermoacoustic sensors for US power measurements (Fay et al. 1994). The two-transducer reciprocity method was combined with time-delay spectrometry for quasifrequency continuous calibration. A useful survey on the PTB activities can be found in the book *Ultrasound Exposimetry* edited by Marvin Ziskin and Peter Lewin (Ziskin and Lewin 1993). Hans Georg Trier has excelled in the field of quality assurance of ultrasonic diagnostic devices in Germany since the mid1980s (Trier 1994).

In spite of the success achieved in the field of ultrasonic metrology, the challenge does not cease to exist: including the finite size of the hydrophones, the increasing number of measurements in the nonlinear region due to the higher outputs of modern diagnostic devices working in the pulsed-Doppler mode in particular, and the effect of contrast agents. The total radiated power of pulsed-Doppler devices should be restricted by the manufacturer to 10 W s/min (167 mW) to exclude irreversible thermal bioeffects, according to a regulation under consideration, at present, in Germany.

I have focussed my report on the IEC activities. Statements and regulations on the performance and safety of ultrasonic diagnostic equipment by national and international bodies, such as AIUM, NEMA, BMUS, ECURS, NCRP, BRH, NIH, WHO, DIN and others come together at the IEC and influence international recommendations, and also the development of the respective measurement techniques.

I should not conclude this brief historical review without emphasizing the frank and friendly contacts and cooperation I have experienced during my commitment in the field of ultrasonics.

PAUL L. CARSON: SAFETY GUIDELINES AND STANDARDS

A relatively large fraction of my professional time has been spent on ultrasound safety and safety-related efficacy issues, compared with the smaller mandate for these activities from my funding sources. My interest in safety is in keeping with the examples of many medical physicists, including my mentor at the University of Colorado, William Hendee. I (Fig. 6) will also acknowl-

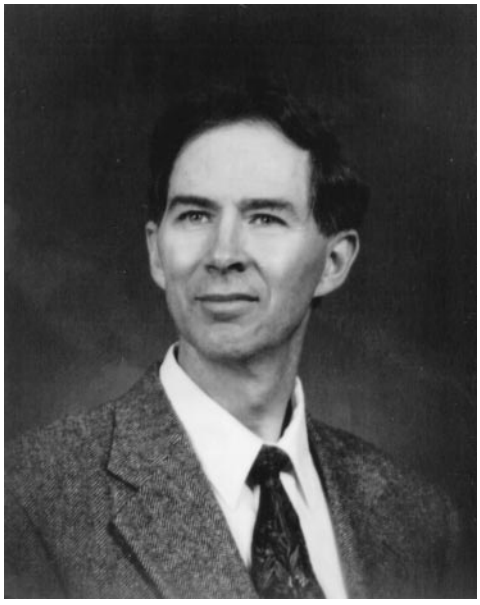

Fig. 6. Paul L. Carson.

edge ambivalence about completely separating bioeffects and safety from quality control and other efforts to help assure that the patient is free from unnecessary risk from inadequate equipment.

Because of the preference of NIH for new science and new applications, general safety activities were often performed in my work as investigations of the possible effects of new techniques or as other extensions from the knowledge gained in the research. For example, a project on fetal lung and liver tissue characterization included assessment of intervening maternal tissues for their effects on US beams for fetal maturity measurements and, later, for fetal safety considerations. This led to development of the fixed path and maternal-weight–dependent models for estimating obstetrical exposures (Carson 1989; Carson et al. 1989; NCRP 1992; WFUMB 1992). Similarly, in a recent project on ultrasonic generation and use of microbubbles for diagnosis and therapy, the aim has been to acoustically create and sustain microbubbles as a contrast bolus for possible urinary and vascular tract diagnosis. This project rightfully involves a substantial proportion of bioeffects and safety research because acoustic pressures well within the range of potentially harmful bioeffects apparently are required for visible contrast generation (Fowlkes et al. 1991; Gardner et al. 1993; Ivey et al. 1995; Hwang et al. 1998).

Upon joining the University of Colorado faculty in 1971, my responsibility to provide modest clinical and research support for Holmes' US laboratory led rapidly to the enclosed-test–object concept (Carson et al. 1973a) and to committee activities in performance evaluation, such as the American Institute of Ultrasound in Medicine (AIUM) enclosed 100 mm test object (AIUM 1975; Erikson et al. 1976). Acoustic output and safety was also an immediate question to a beginner in the field (Carson et al. 1973a; Carson 1975).

Ken Erikson (then at Rohe Scientific) was a great supporter and manager of my early efforts with the AIUM Ultrasound Standards Committee, which he chaired. I followed Ken as standards committee chairman and helped expand the range and number of standards efforts (Erikson et al. 1982; AIUM 1976; Carson et al. 1979; AIUM 1980). In 1978, these efforts included formation of a task group from the AIUM Bioeffects and Standards Committees and a group from the Technical Committee of the National Electrical Manufacturers' Association (NEMA) to develop the AIUM/NEMA Safety Standard for Diagnostic Ultrasound Equipment (AIUM/NEMA 1983). Bill O'Brien, Chairman of the Bioeffects Committee, was a major organizer of that joint undertaking. A 1979 contract from NEMA helped me, along with Dick Banjavic, Chuck Meyer and several students develop some of the necessary measurement procedures for the above AIUM/NEMA safety standard (Fischella and Carson et al. 1979; Jones et al. 1981; Carson and Banjavic 1981). I have continued to try to make these safety and performance (AIUM 1991) measurements compatible so that they can be cross-checked, for example, for center frequencies and beam areas when the transmit and receive apertures are the same.

The output measurement techniques we developed or refined were employed in the laboratory and in the field on numerous diagnostic systems. A survey of data obtained using these techniques (Carson et al. 1978) and some subsequent unpublished measurements were influential in a panel of the U.S. Food and Drug Administration (FDA) recommending reclassification of US equipment in a low risk category, one which only required the "510(k)" (FDA 1985) clearance, rather than a much more extensive proof of safety and efficacy *via* premarket approval. While doing the survey, during interviews with the developers of the original Physionics three-jointed–arm compound scanner, I was impressed with how they and many other early manufacturers limited the peak acoustic pressures to levels (at which there was a great deal of experience) that were well below the levels at which biological effects were known to occur in mammals or mammalian-like systems.

In 1974, I began the chairmanship of the General Medical Physics (*i.e.*, nonionizing radiation) Committee of the American Association of Physicists in Medicine (AAPM). The first published work from that committee was a position statement on the use of diagnostic US instrumentation on humans for training, demonstration and research (Carson et al. 1975b). The statement is not a bad guide for the current controversies on the scanning

of models at meetings and training sessions, and has been reflected in many other official guidelines; for example, an AIUM statement on training and research (AIUM 1985a) is not very different. The 1975 statement (Carson 1975) was motivated in part by discussions at the 1974 AAPM summer school in Boulder, Colorado, generated by my demonstration of US scanning techniques on young volunteers.

Beginning with that summer school in Boulder, I developed a number of workshops on quality control and safety, including a 1976–1978 series of 10 workshops through the Centers for Radiological Physics. At one of the workshops in Cleveland, Earl Gregg recounted his 1940s or 1950s experience with hydrophones to measure sonar fields, and wondered why we were making hydrophone measurements sound so tough. One might wonder why hydrophones are still one of the limiting factors in our exposimetric armamentarium and an active area of development (Carson 1980, 1988; Schmitt and Carson 1990).

At the instigation of the FDA, my colleagues and I worked on an anthropomorphic abdominal phantom (Scherzinger et al. 1983) to reduce the need for scanning live subjects by the least-experienced trainees and for some equipment demonstration purposes. Unfortunately, ours and other phantoms were rather expensive to produce and of rather limited diversity in comparison with live studies (of apparently minimal risk). It is interesting to see that a new 3-D electronic simulator is gaining acceptance for training. As the second person to serve on the Board of the American Registry of Diagnostic Medical Sonographers in charge of the physics exam, I included a significant emphasis on bioeffects understanding that has continued in sonographer registry and training.

My intermittent work on international standards and biological effects of US through the International Electrotechnical Commission (IEC) and World Federation of Medicine and Biology (WFUMB) resulted in contributions to several papers and reports on performance evaluation and safety (WFUMB 1992; Carson 1989a; Carson et al. 1989), and it has contributed to international standards such as IEC 1157 on acoustic output measurement (IEC 1992). Wes Nyborg was responsible for my membership on NCRP Committee 66—Biological Effects of Ultrasound, which he formed and chaired. During long-standing efforts on that committee, I enhanced my understanding of biological effects and continued my concern for balance between considerations for safety and considerations for present and future diagnostic performance. In the 1983 report (NCRP 1983), I contributed mainly to the sections on acoustic properties of tissues and extant medical US fields. The impact of findings that the attenuation of US in mammalian tissue is much lower than had been reported in the earliest measurements was stressed. (Textbooks and some not-so–old estimates of diagnostic exposures *in vivo* have continued to quote old typical soft tissue attenuations of 1 dB cm^{-1} MHz^{-1}, about twice the appropriate value.) For that report, I presented the concept and initial estimates of maximum diagnostic dwell time for various examinations.

An NCRP report (No. 113) on thermal mechanisms (NCRP 1992) was released 9 y later, after extensive discussions and research had been motivated during its development. It was a joy to see informal discussions of possible worst-case scenarios lead to calculations and experiments on acoustic heating of bone that have dramatically affected our understanding of thermal limitations to diagnostic US examination. While working on conclusions for this report, it became apparent to several of us independently that an actual on-screen estimate of, or indicator of, potential *in situ* heating might be achievable. From those discussions, the concept of the output display standard (ODS) (AIUM/NEMA 1992) was developed. For use of that standard to allow adherence to less stringent acoustic output guidelines, representatives of the FDA insisted that there be an indicator of cavitation potential, as well. The ODS, in my opinion, is the most innovative and bold standard for medical imaging equipment safety in many decades. X-ray equipment standards still call for no such examination-specific and speculative calculated indicators of potential bioeffects. The lack of apparent thresholds for x-ray bioeffects reduces the need for such indicators on x-ray systems. My major contributions to the NCRP report No. 113 and to deliberations for the ODS were in modeling of attenuation of the US propagation prior to the focus or to particularly sensitive tissues, and in attempting to assess the intensity and power needed to obtain appropriate diagnostic information (Carson 1992). Although the latter is a question diagnostic US system designers and policy makers must face, there is very little written specifically on the subject.

The move from the University of Colorado to the University of Michigan in 1981 increased my incentives and capabilities in development of imaging techniques and instrumentation, but reduced my activities in safety/quality control topics. At Michigan, I have also had more diverse administrative and clinical support responsibilities. My funded US research probably would not have survived without the accomplishments and support of Charles Meyer, who was among those who came with me from Colorado. It has similarly been my pleasure to work with Brian Fowlkes, who is part of another generation of basic scientists with specific training and interests facilitating development of medical US capabilities as well as bioeffects and safety.

During my service on the NIH Radiology Study

Section, as a regular member from 1984–1988, I was asked several times by researchers in other fields whether we needed to keep pouring money into US bioeffects research; that is, whether we didn't already know what was really needed. Well, much of the important bioeffects research and standards development has occurred since 1990 and important discoveries are continuing, particularly in relation to US nonlinear propagation (Carson 1999) and its interactions with gas bodies.

One area where we lag is in educating users to interpret and apply the thermal (TI) and mechanical indices (MI) provided by systems complying with the ODS. A strong effort in this direction is required from individual leaders, scientific societies, companies and government. Good information for such efforts is being provided by the AIUM (*e.g.*, Thomenius 2000).

The indices do not make it possible, however, for scientists to calculate the potential risk from many anatomic situations that violate the assumptions about tissue properties and other assumptions in the index calculations. The position that many of us have held is that a few physicians, engineers and US scientists do, indeed, interpret the available peak acoustic field data, as well as the ODS indices, as information enabling us to raise flags when exposures may approach a danger point in some specific situation. How those data should be obtained and made available is controversial. I have supported the current requirements for company provision of the data (FDA 1985; IEC 1992; AIUM 1998). We have also summarized the available USA data (AIUM 1985b).

It has been an exciting time to help evaluate and, hopefully, improve the safety and utility of diagnostic ultrasound.

EDWIN L. CARSTENSEN: PERSONAL HISTORY

My (Fig. 7) introduction to ultrasound came at the beginning of World War II, testing underwater sound detection and guidance systems for the U.S. Navy. Earl Gregg, a colleague during those years, opened for me the possibility of combining physics and biology. Soon, biomedical US became my principal research interest, and it remains so today. In retrospect, it is interesting how certain conceptual threads have woven their way from the early days to the present.

Bubbles

German submariners in WWII developed evasive techniques that tricked Allied forces into dropping depth charges on the echoes of their wakes rather than on the submarine itself. The Underwater Sound Reference Laboratory (USRL) under Robert Shankland, on loan from the Physics Department of Case School of Applied Science to the National Defense Research Council, was asked to investigate. Around 1944, Lyman Spitzer, astrophysicist on loan to USRL from Princeton, prepared a detailed quantitative hypothesis identifying bubbles as the probable source of the echoes in the submarine wake. The USRL test facility in Orlando, Florida set out to test Spitzer's predicted acoustic properties of bubble screens. Donning diving helmets, we would go to the bottom of Lake Gem Mary to adjust an array of bubble generators. When all was ready, a pulse of bubbles was released and, as they floated upward, they separated according to size. Sound transmission through these bubble screens confirmed the frequency-dependent attenuation that corresponded to their predicted resonance properties. Leslie Foldy took over and expanded the theoretical aspects of the bubble program and we published a paper on the acoustic properties of bubbles (Carstensen and Foldy 1947).

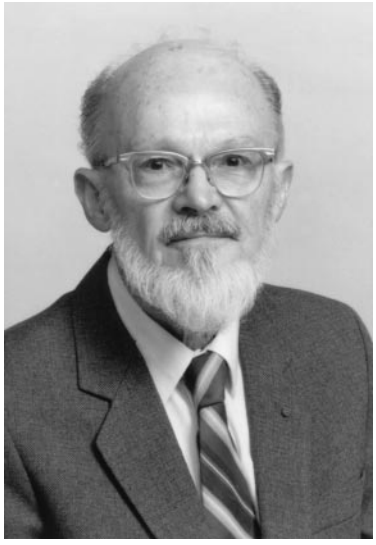

Fig. 7. Edwin L. Carstensen.

About 20 y later, Raymond Gramiak and his colleagues at the University of Rochester reported observations of intense echoes from the heart chambers when injecting radiographic contrast agents (Gramiak et al 1969). In an approach like the submarine problem, Fred Kremkau tested three alternate hypotheses, and concluded that the echoes came from small bubbles generated by flow cavitation during the injection (Kremkau et al. 1970). Marvin Ziskin independently reached the same conclusion. Today, the manufacture of stabilized microbubbles for use as US contrast agents has become a major industry.

A decade later, we were checking out some promising reports of bioeffects of diagnostic ultrasound when bubbles returned to the spotlight of our studies. D. J.

Pizzarello, radiologist at NYU, had observed that fruit fly larvae were killed by diagnostic US exposure and that miniature flies developed from exposed larvae (Pizzarello et al. 1978). We were never able to show an association between US exposure of larvae and the development or anatomical characteristics of adult flies (Child et al. 1980), but killing of larvae became probably the first confirmed nonthermal effect of diagnostically relevant exposures of US (Child et al. 1981). The evidence suggested that the sites of action of the US were the small gas bodies contained within the respiratory systems of the larvae. More recent observations show that very similar effects lead to hemorrhage in the mammalian lung (Child et al. 1990; Penney et al. 1993; Tarantal and Canfield 1994; Zachary and O'Brien 1995; Raeman and Child 1993; Raeman et al. 1996; Baggs et al. 1996) and intestine (Dalecki et al. 1995a). Lung hemorrhage appears to be the first, clearly established, adverse, nonthermal effect of pulsed US with parameters similar to those used in diagnosis.

With the advent of lithotripsy in the mid 1980s, it became evident that cavitation would be a major factor, not only in the destruction of stones, but also in the side effects that the exposures would have on tissues in the lithotripter fields. Until that time, the evidence for any nonthermal biological effects of diagnostic US was extremely weak (Carstensen et al. 1985). The large fields of lithotripters, however, opened the floodgates and nonthermal biological effects were found almost everywhere we looked. Systematic studies of the thresholds for cavitation damage from lithotripter fields on a variety of tissues were launched. These included adult and fetal lung (Hartman et al. 1990a), adult and fetal intestine (Raeman et al. 1994; Miller and Thomas 1995; Dalecki et al. 1995b; Dalecki et al. 1996), kidney (Mayer et al. 1990; Raeman et al. 1994), embryos (Hartman et al. 1990b) and heart (Dalecki et al. 1991b). Effects first discovered with lithotripter fields in many cases have been found to occur with diagnostically relevant pulsed US. Many of these nonthermal biological effects can be attributed to the physical action of acoustic cavitation, but others may be purely mechanical in origin (Dalecki et al. 2000; Carstensen et al. 2000). These discoveries are attributable to the skill and insight of a remarkable team—Sally Child, Carol Raeman and Diane Dalecki.

Heating

In the days of Sister Kenney, before polio vaccines, the standard treatment for paralyzed muscles in polio patients was the application of heat packs. The Polio Foundation (now the March of Dimes) supported a small research program in the Departments of Physical Medicine and Electrical Engineering at the University of Pennsylvania to develop methods for deep heating (diathermy) of tissue. I came to Penn as a Research Associate under this program from war work in underwater sound, thinking that US might be used as a kind of diathermy. After arriving at Penn in 1948, I discovered that ultrasonic diathermy had been introduced by Pohlman in Germany 10 y earlier. Herman Schwan joined the University and, with his guidance and collaboration, my graduate research turned to mechanisms of absorption in biological tissues with particular emphasis on blood. After testing a few unproductive hypotheses, it soon became apparent that, although the cellular composition of the blood made a small contribution to the absorption (Carstensen and Schwan 1959a), almost all of the losses originated from macromolecular relaxation (Carstensen and Schwan 1959b). Subsequent work has shown that the same pattern is true for almost all of the organs of the body. Ultrasonic diathermy soon became the most popular method for producing heat in the deep tissues of the body, and remains so today.

Ultrasonic surgery has not found a large-scale acceptance in the medical community. Bill Fry, at the University of Illinois, in collaboration with neurosurgeons in Iowa, initiated one of the first and most ambitious efforts in this direction. My limited experience in this field can be attributed to Charles Linke, an urologist at the University of Rochester. In the mid 1970s he approached me with his interest in destroying tumors of the kidney by localized heating. The kidney is a difficult organ for excision surgery because it is highly vascularized. He postulated that, if a tumor was killed by heat, the body would eventually scavenge the dead tissue and that, as a bonus, the system might develop an immunological response to the tumor tissues. Ultrasound was the ideal heating tool and, after a series of studies (Linke et al. 1973; Elbadawi et al. 1976; Fridd et al. 1977; Frizzell et al. 1977; Hare et al. 1982), 1. the basic concept was validated, 2. ultrasonic treatment did not accelerate metastasis, and 3. although there was a suggestion of an increased immunological response to the tumors, we did not establish that conclusion with 95% confidence. The 1990s have seen a resurgence of interest in thermal surgery with a number of brilliant innovations from investigators throughout the world.

For me, the most interesting result of the thermal surgery program came from a problem that arose during our work on an experimental surgical technique called autotransplantation. To simplify surgery on a kidney, it was removed from the host, treated *in vitro* and then returned to the animal. Our job was to produce an ultrasonic thermal lesion in a dog kidney in a bath of cold saline. When we placed the organ at the Rayleigh distance from a 5-MHz source, regardless of the input power, we were unable to produce a lesion. When the transducer was near the source, we experienced no prob-

lems. In this way, we had our introduction to the phenomenon of acoustic saturation and, from this, began a program of studies of nonlinear propagation of US in tissues that has intensified up to the present time, and has included major contributions by Tom Muir and David Blackstock at the University of Texas in Austin, David Bacon formerly of the National Physical Laboratory in Teddington England, and Kevin Parker, Diane Dalecki, and Ted Christopher at the University of Rochester (Muir and Carstensen 1980; Carstensen et al. 1980; Bacon and Carstensen 1990; Dalecki et al. 1991; Christopher and Parker 1991).

FLOYD DUNN: EARLY HISTORY OF THE BIOACOUSTICS RESEARCH LABORATORY (BRL) AT THE UNIVERSITY OF ILLINOIS

I (Fig. 8) recall that the Bioacoustics Research Laboratory was founded in 1946 by the late William J. Fry. Bill, as he was known with affection by colleagues and friends alike, was studying physics at Penn State University when World War II broke out and he soon found himself during the war years at the Naval Research Laboratory in Washington, DC developing principles for SONAR system design and development. The French physicist Langevin had experimented with ultrasound as a means of detecting submarines when they appeared in World War I, but none had ever been detected during hostilities prior to World War II. Thus, as instruments designed between the wars were found lacking in many respects, the creation of more adequate design principles and useful instruments was crucial. Bill coauthored a book on these topics during this period that may still be referred to for analysis.

Immediately after the war, many such as Bill, who were part of the scientific and engineering war effort, found themselves in the position of wanting to conduct research activities of their own choosing in the freer university atmosphere. University faculties and facilities were expanding rather rapidly at that time, due to the fact that much stagnation in growth had occurred during the depression and war years and because returning military service personnel were flocking to campuses for higher education. At the University of Illinois, William L. Everitt, an already renowned communications engineer, was in the process of building up the Electrical Engineering Department, and he had induced Lloyd DeVore, who had been a professor of theoretical physics at Penn State, and Bill Fry's teacher, and who had spent the war years at Wright Field in Ohio directing electronics research projects, to become a member of the EE Department and to promote and develop a superior research program. It must be understood that, prior to World War II, research was not an important undertaking of EE faculty members. If they conducted any scholarly activities at all, it was usually in the form of consulting. Lloyd DeVore knew Bill Fry to be an unusually clever, independent and ingenious solver of theoretical physics problems, as they were treated in graduate course work. Bill came to the University of Illinois in late 1946 and immediately endeared himself to many of the old-time, nonresearch oriented, EE faculty by removing, for trash disposal, their numerous cherished World War I electrical instruments to make room for the only space that could be found for him, which was in a tunnel under the then EE building (later to become the Electrical Engineering Research Laboratory, EERL). Bill's brother Frank joined him at that time and the two worked closely for the next 22 y.

Fig. 8. Floyd Dunn.

Bill Fry wanted to study the central nervous system with sufficient comprehensiveness to begin to understand intimate details of structure and function. The methods employed up to that time had been rather crude, requiring invasion of brain tissues by physically rigid electrodes and the consequent production of unreasonably large lesions. Such methods were employed with the hope of identifying those structures that might involve particular types of neural activity. Bill had envisioned that US, which he knew could be focused to very small volumes, would comprise a vastly superior tool by providing for noninvasive alteration of brain tissues. He set out toward two related goals: first, to develop ultrasonic surgical procedures for affecting the mammalian brain, both reversibly and irreversibly, which would provide for animal experiments and clinical surgical procedures, and second, to study the detailed neuroanatomy of the mammalian central nervous system and determine, if you will, a complete "circuit diagram" of the neural components. The first of these was accomplished with extreme success and, by the late 1950s, had been well-demonstrated in animal experiments and was being utilized in medical practice in a cooperative program at the University of

Iowa. Numerous patients were treated for hyperkinetic and dystonic disorders, including Parkinson's disease and intractable pain. The procedures, though extremely complex, were successful and Time Magazine discussed these in the December 2, 1957 issue.

The project dealing with determination of the "wiring" diagram of the central nervous system also achieved significant success, although, because of the enormous complexity of the media being studied and many attending difficulties, only details of small sections of the cat brain were studied. Nevertheless, the methodology was well demonstrated.

Throughout the approximately 20-y period from the mid 1940s to the mid1960s, and to reach the abovementioned goals, instruments were invented and developed for generating, detecting and measuring US; crucial details regarding how US propagates in biological media were discovered; the propagation properties important for diagnostic, as well as therapeutic and surgical US, such as speed of sound, absorption, attenuation, scattering and impedence, were determined; the physical mechanisms of interaction of US were studied in some detail and phenomenological theories were developed; toxicity and dosimetry were treated in some detail; and nonlinear acoustic properties were begun to be studied. Measuring methods, as well as instruments, were invented and developed to their full usable potential and are still employed throughout the world. Technicians were trained, graduate students were educated and approximately 100 papers were published in high-level peer-reviewed journals describing all of these scientific and technological developments.

Additional research topics were also undertaken. The 1957 meeting of the AIUM was held in Los Angeles, in early September, and Bill and I drove there and returned with Dr. Oka, of Osaka, who spent about a month learning our neurosonic surgery methodologies.

During the several-day automobile trip back to Illinois, Bill developed the view that it was time to initiate a program to develop an artificial heart. This was discussed to some degree while traveling and, by the time the group arrived in Illinois, Bill had worked out a scheme involving piezoelectric devices which, though it seemed promising in the car, turned out to be very inefficient when detailed calculations were made in the comfort of the laboratory.

Nevertheless, less dramatic or more conventional ideas were employed and devices capable of sustaining animals for extensive periods were developed and patented by Bill and Frank.

The ultraconservative attitude of the University of Illinois, at this time, toward the promotion by faculty of their innovations, prompted Bill to organize the Interscience Research Institute to exploit these heart devices, and they were no longer treated in BRL. Other topics that were undertaken in the laboratory, largely at Bill Fry's design, were studies of excitable tissues, with and without ultrasonic stimulation, investigations of the organ of Corti, and studies of the modification of animal behavior produced by neurosonic surgical methods.

Thus, the Laboratory emerged as preeminent in this area and Bill, recognizing the necessity for supporting all those working in this field, created what has come to be known as the Allerton Conferences—closed, invited-only to participate—held at an estate owned by the University, approximately 25 miles from the campus. Thus, the acknowledged world leaders in the field were able to convene and discuss in detail, in isolated pleasant surroundings, the then important problems of investigation. These continue under the leadership of Bill O'Brien and Leon Frizzell and the organizational skills of Wanda Elliott.

It would, however, be entirely wrong to have the view that this was only a very narrowly focused bioultrasonics laboratory of inquiry. Such a view would belie the character of Bill Fry who was, in actual fact, a most extraordinarily well-read, highly cultured, near Renaissance individual.

An example of BRL undertakings under Bill Fry's direction, suggesting its scope of activity, is to be found in a strangeness of the time. Unusual objects called "flying saucers" were being sighted, and unusual abilities embodied in the term ESP (extrasensory perception) were being promoted with seriousness for contention with the established sciences. Rhyne had established a laboratory at Duke University for the investigation of some of these unusual abilities. The military were, of course, not unaware of these goings on, but completely unprepared in any way to evaluate them. Thus, Bill was asked if he would consider investigating persons, or groups of persons, alleged to have rather special abilities; for example, the ability to see through dense media. Such an ability as of interest to the military, who were ever on the look-out for providing personnel the possibility of "seeing" in night darkness. Examining such persons provided curious diversions, as people came to the Laboratory to be examined and members of the Laboratory traveled to other places to conduct tests.

In one instance, BRL investigators were convened for the purpose of examining an individual alleged to be able to float very high in water, in violation of Newton's law of gravity. In this particular instance, a swimming pool at the University of Illinois was engaged for the test, during which it was found that the writer, then the skinniest of the BRL investigators, probably floated as high in the water as did the protagonist, his wife doing even better.

In all, approximately a half dozen individuals and

groups were examined. Of course, all were found to be either extraordinarily clever performers or frauds. This fruitless activity, though, was often a source of fun.

The WFUMB and the AIUM have benefited well from the existence of BRL. Early on, when Bill Fry took an active interest in AIUM affairs and during his tenure as President, he nurtured it through a very traumatic transition period, when it seemed on the verge of self-destruction.

Since that time, I a second-generation BRL member have been elected to national academies and have served the profession with officerships in acoustical societies. A third-generation laboratory member, W. D. O'Brien, Jr., has held the highest offices in the AIUM and the WFUMB, as well as being intimately involved in scientific affairs of the profession. BRL members and former students have contributed very significantly to the progress of the field to its present state.

It is hoped that these few remarks have conveyed some feeling of what it meant to work in the laboratory Bill Fry founded and led. It is also hoped that the reader will have gleaned some of the excitement experienced during those days when Bill was actively driving and creating science in BRL. Bill Fry suffered a rather serious heart attack in 1965, and he used the few years following to prepare himself for the Ph.D. degree, which he had never had the opportunity to pursue, because of the war interrupting his graduate education at Penn State and the great demands he put upon himself thereafter. He was to receive the Ph.D. degree at the University of Texas in early 1969; he died in July 1968.

It has been most interesting to reflect on those earlier times, in preparing this note, and to speculate on what might have occurred had Bill Fry and some of the other giants of our field continued to live beyond their lifetimes and on into the present era.

FRANCIS J. FRY: PERSONAL HISTORY

My undergraduate degree in Electrical Engineering in 1940 was vintage power with a smattering of electronics. With this background, I (Fig. 9) was employed by the Westinghouse Electric Corporation in power circuit breaker engineering development. Our division became a prime contractor on the Manhattan Project, so I spent considerable time during the World War II years at the Radiation Laboratory at Berkeley and at Oak Ridge, Tennessee.

After the war in 1946, my brother Bill left the Naval Research Laboratory and went to the University of Illinois in Urbana, Illinois. I joined Bill at this time, which was the inauguration time of the Bioacoustics Research Laboratory in the Department of Electrical Engineering. We set up experimental animal facilities for the laboratory, and began the historically documented work on the interaction of high-intensity focused ultrasound on biological tissue and brain, in particular.

Fig. 9. Francis J. Fry.

Bringing together the significant biological and medical research people using US was inaugurated at the first Allerton Conference in 1952, and this conference continues to be a gathering place for the international research group. Another interesting outgrowth of this interaction was the reformulation of the AIUM in its present format, which was guided and directed by Bill in its initial stages.

Originally, our overall thinking involved developing an understanding of the mechanism of action between US and biological tissue. Questions about cavitation and temperature were investigated. Out of the temperature-rise studies emerged the use of thermocouples to determine the absorption coefficient in tissue and the use of thermocouples as US probes.

Because brain was a primary point of interest, there evolved an extensive study of focused US interaction with this system. These basic studies led to a series of human neurosurgical procedures in which some 100 patients were treated for hypokinetic disorders. This series started in 1955 and remains, to this time, the only clinical brain study using US for such treatment. Another small series of 10 patients was conducted in the early 1970s. These patients had tumors that were generally treated in relatively small areas of the total tumor volume.

In addition to exploring focused US as a clinical surgical method, an extensive study was conducted using the method in neuroanatomical studies in the experimental animal. This extensive work revealed a quantitative organization of neuron populations in the limbic system in the cat. What the study revealed was a set of combining proportions of identifiable neuron subpopulations in the medial and lateral mammillary nuclei of the adult cat.

These laws of combining proportions are quite accurate and are independent of the total number of neurons in the individual nuclei, which are quite variable. No other such study of this specific type exists to this day, nor has the significance of the information been studied or revealed.

Although intense focused US was a primary concern, we branched out into combining the pulse-echo method of US visualization with the focal therapeutic mode, and this combination was used in the 10-patient series mentioned above.

I was involved in an ultrasonic toxicity study on the pregnant mouse using both pulsed and cw (continuous-wave) US. This study is of interest because it showed that pulsed US of the same average intensity as cw US produced no more bioeffects than did the cw US.

Nonlinear US fields are a significant component of intense focused US used in tissue irradiation. I was involved in studying the effects of nonlinear focused US fields on tissue absorption, particularly in liver and, of course, these same types of fields were involved in the pregnant mouse toxicity studies.

Starting in 1972, when I moved to the Indianapolis Center for Advanced Research, there developed a more intensive effort to move the basic research studies on tissue interaction with US into the clinical arena. This clinical activity represents a continuum from the initial work at the Bioacoustics Research Laboratory at the University of Illinois and provided a unique opportunity to pursue such work in a large medical hospital environment.

Over the past 50 y, I have been involved with US at the basic research level, development of instrumentation to conduct research, clinical activity and development of instrumentation for this work, startup of new companies to pursue medical instrumentation, and involvement with activities supporting the growth of US in medicine and biology. These studies involved developing a brain-lesioning system, a gallstone-dissolution device and a transrectal system for the treatment of human prostate disease. All three of these systems are approved by the FDA for a series of human patients. The brain system has not yet been used in the clinic. The gallstone system was used in a 10-patient clinical series, and the prostate system is undergoing extensive clinical trials.

I have had the opportunity to work with many people in my years in US and I owe them a profound depth of gratitude. I would like to think that US in medicine and biology remains a vital area of expansion and discovery.

LEONID GAVRILOV: PERSONAL HISTORY

Fig. 10. Leonid Gavrilov.

I (Fig. 10) was born in 1938 in Russia and lived in Leningrad (now Sankt-Petersburg) until 1967. After graduating from the Electrotechnical Institute, Department of Electronic Engineering, in 1961, I began to work in the Central Institute of Turbo-Machines and organized a group of engineers developing electronic devices for testing of turbo-machines. I had aspired to work in science and, so, from that point of view, it was not interesting work. So, I was considering leaving this Institute when, unexpectedly, A. D. Pernik, the author of the excellent book "Problems of Cavitation," which, unfortunately, was not translated in English and therefore was unknown in the West, began to work in our Department. This event was the first big break in my scientific life. Immediately after our acquaintance, he told me in a very vivid and fascinating way about the phenomenon of cavitation and the causes of its appearance. Very soon, research into cavitation and cavitation nuclei became my first and fondest pursuit in science. Pernik also told me that a famous American scientist, M. Strassberg, had developed a setup for acoustical measurements of US attenuation in tap water due to an existence of very small invisible gas bubbles therein. He said that if I could develop an installation for similar measurements and make clear how one can calculate from the values of sound attenuation the distribution of the size and number of these bubbles and, then, could obtain these data for tap water or any water in natural conditions, it would be a good grounding for my future Candidate Dissertation (the same as a Ph.D.). After that, books and journals on physical acoustics became fundamental and, in 1966, I finished and defended my Ph.D. entitled "Experimental methods of the investigation of cavitation in liquids." In addition to this work, I developed the setup for measurements of cavitation thresholds in liquids and a device for the rapid analysis of the volume content of free gas in

water (*e.g.*, for the cases of model and natural hydroturbines, keel-water streams beyond ships, etc.). The principle on which this device worked was based on the measurements of the phase velocity of the sound, whose frequency was much lower than the resonance frequencies of all bubbles existing in water. During this work, I had constant communications with the scientists from the Acoustics Institute in Moscow. The person who had the most influence upon me was the Head of the Ultrasound Department, L. D. Rozenberg, the author of a number of famous books and articles related to theory and practical applications of focused US transducers and various aspects of US technology.

In 1967, due to personal circumstances, I moved from Leningrad to Moscow and received two offers for work: one, as a Senior Research Scientist in the Institute of Hydraulic Machines, and the second, as a Junior Research Scientist, with half the salary, in the Department of L. D. Rozenberg in the Acoustics Institute. Without any hesitation, I chose the second invitation. So, the opportunity to work together with Rozenberg and side-by–side with his younger, active and talented collaborators was the second break in my scientific career. By inertia, from the beginning, I continued my work on the acoustical measurements of gas bubbles in liquids (Gavrilov 1969, 1970, 1973). Then, together with the very active and keen Victor Akulichev, who later became a well-known specialist in acoustical cavitation and bubbles dynamics, I dealt in 1968–1969 with the application of US for the visualization of traces of high-energy ionized particles in the bubble chambers.

In 1969, the Head of the Laboratory where I was working, M. Sirotyuk, invited me to organize and carry out feasibility studies into the application of focused US in medicine and physiology. The reason was that our Laboratory and the Department of Ultrasound had considerable experience in the theory, development and application of high-intensity US focusing systems, but had never used them in medicine before. I accepted this unexpected proposition with great enthusiasm and, from the beginning of 1970, I began research into the feasibility of application of focused US in different fields of medicine and physiology. First of all, it was a "classical" field (*i.e.*, its use for brain tissue ablation for applications in neurosurgery and neurophysiology) where such scientists as W. Fry, F. Fry, F. Dunn, P. Lele, J. B. Pond and others were working actively. Here, I was working together with specialists from the Brain Research Institute, Moscow (O. S. Adrianov, N. A. Vyhodtseva, etc.). In this field, two most important results were obtained. To the best of my knowledge, we were the first to measure cavitation thresholds in brain tissues of animals *in vivo* and, then, present these data in juxtaposition with ablation thresholds of tissues and results of calculations of the temperature elevations in tissues due to US absorption. Thus, one could obtain from these data quantitative information on the dosage corresponding to pure thermal and pure cavitation mechanisms of tissue ablation in tissues (Gavrilov 1974a). In addition, we showed the possibility of ablating deep brain structures by US irradiation through the intact skull bone (Tyurina et al. 1973). Unfortunately, the main results of these studies, including the work involving ablation through the skull of cadaver brain tissues, were published only in Russian in 1974–1975. Fry published the results of similar research 3–4 y later in the USA.

The other field of medical application of focused US was ophthalmology. We were working in this area with the Helmholtz Ophthalmologic Institute (F. Fridman, N. Narbut), using focused US as a means for artificially accelerating the "maturing" of cataracts (Gavrilov et al. 1974b). Much later, we also used focused US for the treatment of glaucoma.

Inspired by works of Woeber, we tried to use US in therapeutic dosages in experimental oncology as a means of improving the treatment of superficial cancer in animals. In particular, we showed that ultrasonic irradiation of transplanted sarcoma tumours in mice with 0.9-MHz US in the range 0.5 to 2.5 W/cm^2 for periods of 1 to 5 min before gamma irradiation, enhanced the sensitivity of the tumour cells to its action (Gavrilov et al. 1975). We had shown also that the combined action of US and cryoablation enhanced the destructive action of the latter on tumours.

All of the abovementioned studies were in well-developed fields of medical applications of US where many scientists from the USA, UK and other countries had been working actively for a number of years. However, at the beginning 1970s, we discovered a new and very promising application of focused US in medicine and physiology—the stimulation of receptor neural structures of human beings and animals. We worked in this area for many years together with I. M. Sechenov Institute of Evolutionary Physiology and Biochemistry, Sankt-Petersburg (G. V. Gersuni, E. M. Tsirulnikov, I. A. Vartanyan, etc.). We demonstrated that the focused US stimuli of short duration and relatively high intensity can induce a variety of somatic sensations, *e.g.*, tactile, thermal (warmth and cold) and pain, without any attendant damage to tissues (Gavrilov et al. 1976; 1977, 1980; Gavrilov 1984; Vartanyan et al. 1985). The main advantages of using focused US were: first, that this technique was principally noninvasive (*i.e.*, it did not require surgical intervention to stimulate deep-seated neural structures). Second, the locality of the stimulation could be controlled and changed by altering the resonant frequency of the US transducers to stimulate predetermined volumes of tissues and selected neural structures. Precise

control of the stimulus parameters (*e.g.*, intensity, duration of stimuli, volume of stimulated region etc.) is possible. Finally, the possibility of inducing a wide variety of different sensations was available with the same equipment. As a result, this method was very convenient for research into physiology of reception, and we obtained many interesting data on this subject that were discussed in several books published in Russian (Gavrilov and Tsirulnikov 1980; Vartanyan et al. 1985).

To date, two wide and promising fields of medical applications of focused US for the stimulation of neural structures have arisen. The first one is concerned with the stimulation of the receptor structures of the somatic system of humans (Gavrilov et al. 1976, 1977; Gavrilov and Tsirulnikov 1980; Vartanyan et al. 1985). It is possible that, in the near future, a new broad field of ultrasonic medical diagnostics will open up, based on precise measurements and comparison of thresholds of various sensations in persons with normal perception and in patients with different kinds of pathology. This method has been used for diagnosis of neurological, skin and other diseases that involve changes of perception thresholds for different sensations from normal ones. The second large and promising field of medical applications of the methods is related to diagnosis of hearing disorders and prosthesis of hearing function, for example, for the introduction of hearing information to some deaf people (Gavrilov et al. 1980; Gavrilov and Tsirulnikov 1980; Tsirulnikov et al. 1988; Vartanyan et al. 1982, 1985).

Of special interest for me was the study of the physical mechanisms of stimulation effects of focused US on neural structures. The main effective factor of focused US as a stimulus of neural structures was shown to be a mechanical one (Gavrilov 1984). The direct action of sign-altering ultrasonic oscillations during the use of comparatively long US stimuli is probably the main effective factor for induction of pain sensations, and can also change the thresholds of other sensations (*i.e.*, thermal, hearing, etc).

In 1982, I finished and defended my second (D.Sc.) dissertation entitled: "Investigations of the effects of focused ultrasound on biological structures for application in medicine and physiology." Two years before, the Scientific Council of our Institute elected me to the position of the Head of newly-created Laboratory of Medical Acoustics. After that, the main part of my time became devoted to teaching 10–12 newcomers who had no experience of work in medical acoustics. The remainder of my time was dedicated to solving various conflicts between some persons in the Laboratory. Sometimes, I despaired because I felt that the productivity of our work was no greater than when I was working alone or with one assistant. I understood then that the efficiency of work of any scientific group does not depend at all on the number of persons in it. However, I must note that, after several years, all my colleagues became very experienced and, in my opinion, the Laboratory became the best in medical US in the USSR.

The main direction of our activity became US hyperthermia of tumours with the use of single or multielements, plane or focused US transducers. From our work of this period, I can note research into hyperthermia of eye tumours and tumours in brain using the US irradiation through the intact skull. I also investigated the effect of cavitation on the contraction force and action potential of animal papillary muscle (Zakharov et al. 1989).

The next direction that I initiated in our Laboratory was the use of focused ultrasonic receivers for the remote measurements of acoustical fields, cavitation, elevation of temperature and different acoustical and thermal parameters of biological tissues (Gavrilov et al. 1988). Another subject of our interest became the use of focused US for ablation of the definite structures of the heart for the treatment of arrhythmia.

The total number of my publications is about 150, including five books (all in Russian), 13 Russian patents, about 100 journal articles (more than 70 in English). In 1988, I was awarded the Certificate of the World Federation of Ultrasound in Medicine and Biology and American Institute of Ultrasound in Medicine "History of Medical Ultrasound. Pioneer Award."

In 1975, I was elected Chairman of the Section "Ultrasound in Medicine and Biology" of the Scientific Council on Acoustics, Russian Academy of Sciences. Together with my friend and colleague A. P. Sarvazyan from the Institute of Biological Physics, we organized and carried out (in different cities and towns of the former USSR) a number of conferences, symposia and meetings on medical ultrasound, including ones with international participation.

Unfortunately, as a result of the well-known events in the former USSR after 1991, the economical situation in Russia became extremely difficult. In 1992–1993, the salaries of scientific workers became totally inadequate to support their families, and they were forced to look for other work to survive in these circumstances. Thus, almost all my colleagues from the Laboratory, who by this time had become specialists of very high level, had to leave the Institute. As a result, by 1994 only three persons from the previous staff of the Laboratory, including myself, were still continuing to work in it.

In 1995–1998, I worked by invitation in the Hammersmith Hospital, London, in the Radiological Sciences Unit (Head of the Unit, J. W. Hand) on a project related to the development of a transrectal phased-array US system for thermotherapy of benign prostatic hyperplasia (Gavrilov et al. 1997). After my coming back to the Acoustics Institute, Moscow in 1998, I have been con-

tinuing with J. Hand work on computer modeling of 2-D multielement phased arrays intended for application in US surgery (for tissue ablation). The aim of this study is to show that a random distribution of elements on a shell of an array, in combination with rational choice of characteristics of the elements, leads to marked improvement of the array performance, in terms of the intensity distribution, compared with cases in which regular annular, hexagonal or square packing is used (Gavrilov and Hand 2000).

After coming back to the Institute where I had been working since 1967, I looked for the faces of young keen scientists, but saw very few. I still believe that, in time, the situation with science in my country will change for the better, but I guess that it will happen only with the next generation of our scientists.

GERALD R. HARRIS: EARLY HYDROPHONE WORK AND MEASUREMENT OF OUTPUT EXPOSURE LIMITS AT THE U.S. FOOD AND DRUG ADMINISTRATION

In 1970, the U.S. Bureau of Radiological Health (BRH), now a part of the U.S. Food and Drug Administration (FDA)'s Center for Devices and Radiological Health, began its US measurement program with the formation of a group under the direction of Hal Stewart and Steve Smith. In addition to myself (Fig. 11), early members included Mike Haran, Bruce Herman and Ron Robinson. As part of BRH's responsibilities under the Radiation Control for Health and Safety Act of 1968, we set out to establish a measurement and calibration laboratory applicable to medical US output levels and frequencies. Initial efforts were to focus on US therapy equipment, in part because of a larger BRH concern about radiation therapeutics. Because it was not clear which of the available measurement methods would be best suited for characterizing US therapy fields, we decided to evaluate several promising approaches. In particular, Mike chose acousto-optics (because of his previous study at Georgetown University under Walter Mayer), Bruce worked on thermal methods, Ron took radiation force techniques, and I selected hydrophones.

It was Bill O'Brien who first showed me a miniature ultrasonic hydrophone. He was working with Mel Stratmeyer in BRH's bioeffects division at the time, and he was using a hydrophone probe whose sensitive element was a hollow, piezoelectric ceramic cylinder. The maker had stopped selling the assembled hydrophone, so I purchased some of the cylinders and constructed a few probes for our laboratory and field use. They worked out well for the narrowband, $>$ 1-mm wavelength therapy fields we were measuring and, soon thereafter, we identified several companies producing "needle" hydrophones having piezoelectric ceramic discs as the sensitive element that also were suitable for these measurements.

Fig. 11. Gerald R. Harris.

Our efforts eventually led to a USA standard for ultrasonic therapy products published by the FDA in 1978. However, during this time, we also had begun to make measurements of diagnostic device outputs, as well as to evaluate hydrophones for this purpose, and it became apparent that the nonuniform frequency response associated with most ceramic hydrophones made them generally unacceptable for measuring broadband diagnostic pulses. (At the time, we were unaware of the distortions introduced by finite amplitude effects, a complication that places even more stringent requirements on hydrophone bandwidth.)

This inability to measure diagnostic pulses faithfully was a critical problem, because, in 1976, the U.S. Congress passed the Medical Device Amendments, and it soon was recognized that BRH and FDA's Bureau of Medical Devices eventually would be combined due to their similar responsibilities. (The official merger, creating the Center for Devices and Radiological Health, occurred in 1983.) Under the Amendments, diagnostic US was categorized as a Class 2 device, which meant that, for a new device to be marketed, the submission to FDA of a "510(k)" (named for a section of the Amendments) premarket notification was required. In this submission, the manufacturer had to demonstrate that the device was substantially equivalent in terms of safety and effectiveness to devices marketed before May 28, 1976, the date of the Amendments.

With regard to demonstrating equivalent safety, we needed somehow to measure the output exposure levels of preAmendment devices and, then, have manufacturers characterize their new equipment in a similar manner. There were several published papers we were aware of that contained output data for a number of older devices, the two largest surveys being by Hill in the UK and Carson and coworkers at the University of Denver (Hill 1971; Carson et al. 1978). Both of these papers were

significant contributions, but each identified the ceramic hydrophones used as being potential sources of measurement error. Furthermore, there was no general agreement at the time that the quantities reported in these papers were the most relevant to safety. Thus, we had three problems to overcome: what measurement device(s) to use, what output quantities to measure, and how to obtain a representative sample of measurements for preAmendment devices.

Our answer to the first problem arrived somewhat serendipitously. In 1977, in a conversation between the head of our machine shop and one of his neighbors, it came out that the neighbor was working with a relatively new type of US sensor material. After being told of this conversation, I decided to contact the neighbor, who turned out to be Aimé DeReggi of the National Bureau of Standards (now National Institute of Standards and Technology) Polymers Division. We soon began what was to become a productive collaboration, developing single-layer and bilaminar spot-poled membrane hydrophones using the piezoelectric polymer polyvinylidene fluoride (PVDF). Our development of these types of hydrophone, along with their performance and use at medical diagnostic frequencies, was first reported at the Fall 1978, meeting of the Acoustical Society of America and, later, at the 1980 AIUM Convention and IEEE Ultrasonics Symposium. Subsequently, three patents were obtained for various hydrophone embodiments.

Also, around this time, others were experimenting with PVDF. For example, at the 1979 AIUM annual meeting, Eggleton and McGlinn from the Indianapolis Center for Advanced Research described a polymer hydrophone probe developed by Nigam and later sold by Nuclear Associates and, at the 1979 IEEE Ultrasonics Symposium, Wilson and coworkers from Raytheon described a polymer probe of similar design that was later sold by Machlett. Meanwhile, across the Atlantic, in 1980 the UK National Physical Laboratory in collaboration with Marconi Instruments published their initial membrane hydrophone work and, in 1981, Lewin described his PVDF needle hydrophone developed at and sold by the Danish Institute for Biomedical Engineering (both published in Ultrasonics). Other contributions followed, of course, but these early efforts helped establish PVDF as the *de facto* standard material for hydrophone use in medical diagnostic field measurements, a situation that still exists today. (For an extensive review of PVDF hydrophone work, see Harris et al. 2000.)

The second problem, what to measure, was answered in a standard developed and published jointly by the AIUM and the National Electrical Manufacturers Association (NEMA), a trade association representing the majority of diagnostic US manufacturers. Titled "Safety Standard for Diagnostic Ultrasound Devices," and published in 1981, this standard defined several intensities that were derived from hydrophone measurements, including spatial-peak, temporal-average (SPTA) and spatial-peak, pulse-average (SPPA). This standard also recommended that PVDF hydrophones be used. We adopted these intensities as a means of characterizing and categorizing equipment but, for the purpose of comparing new and preAmendment device outputs, we added the additional step of estimating an *in situ* (derated) value based on an attenuation factor of 0.3 dB/cm-MHz.

By the early 1980s, then, we were satisfied that making accurate measurements of standardized and relevant field quantities was possible, so the third problem could be addressed (*i.e.*, making actual measurements on preAmendment devices). Through our regulatory work, we had occasional access to older clinical instruments, and we also solicited the loan of preAmendment devices from both users and the industry. Using four categories for clinical applications (peripheral vessel, cardiac, ophthalmic and general imaging, including fetal), we created a small data base of intensity values.

In 1985, we were ready to publish a 510(k) submission guidance for measuring acoustic output, which would include the highest known preAmendment intensities. We compared the intensity values calculated from measurements we had made with our spot-poled membrane hydrophones to the values in the literature and, in one category, general imaging, the values in the Carson et al. (1978) paper were larger. If we were to use these results, we would need the SPPA intensity as defined in the AIUM/NEMA standard but, understandably, this value was not calculated because the definition did not exist when the paper was written. Fortunately, however, a picture of the hydrophone-measured waveform was given in the paper, which we were able to digitize and, thereby, calculate a derated SPPA intensity using additional information provided about the exposure conditions. A more troublesome problem in adopting these intensities was that they were determined using a ceramic hydrophone. However, the reported SPTA intensity seemed acceptable, given the ultrasonic power and f-number for the 2.25-MHz transducer. Also, the pulse distortion characterized in the paper as a hydrophone artefact appeared, instead, to be reasonably attributable to the finite amplitude effects associated with nonlinear propagation in water. Therefore, data from this paper were included in the intensity tables in the December 1985, 510(k) guidance.

(Note: There was a fifth application category in our guidance, not mentioned above: unfocused fetal Doppler monitors. We considered these devices a special case because of the nature of their use, and we took the spatial-average, temporal-average intensity of 20 mW/cm^2 from the paper of Carson et al. (1978) as the max-

imum preAmendment level. This value was determined from a radiation force balance measurement, and it is still used in our current guidance.

The process of application-specific derated intensity comparisons then in place provided an effective means to make determinations of substantial equivalence based on relative safety considerations. Nonetheless, there was a growing resistance to the use of these tables, both from a philosophical standpoint (the intensities sometimes were being interpreted as absolute safety levels) and from the practical viewpoint that the values may not have represented the highest available prior to 1976, especially in the category containing fetal imaging. With regard to this latter point, in 1986, the AIUM published a NEMA request in its newsletter for any clinical user having a device marketed before May 1976, to make it available for output testing. Some individual manufacturers renewed their efforts as well and, soon, we heard that a Hoffrel device marketed in 1965 had been identified with derated intensities approximately 4–6 times higher than the preAmendment values then in use for fetal imaging.

Sid Soloway of Hoffrel had made these measurements with a Lewin needle hydrophone. He sent the unit to us along with three different transducers he had located, so that we could make confirmatory measurements with our spot-poled membrane hydrophones. One of the three, a 3.5-MHz transducer, initially did have the high output described. However, with time, the output decreased and the transducer eventually failed. It later was discovered that this was a relatively new transducer and was not designed to withstand the >1000-v pulses produced by the generator. A second transducer, however, which operated at 2 MHz, was confirmed to have higher outputs; so, in 1987, the tables were modified accordingly with derated SPTA and SPPA intensity values of 94 mW/cm^2 (previous value, 46 mW/cm^2) and 190 W/cm^2 (previous value, 65 W/cm^2), respectively. (A fortuitous consequence of this change was that the ceramic hydrophone data were replaced, meaning that all of the spatial-peak intensity values in the tables then came from spot-poled PVDF membrane hydrophone measurements.) This Hoffrel transducer also had a maximum mechanical index of 1.9, a value now in use. No other high output units were identified, and the limiting intensity values have remained unchanged; in part, because the search for higher outputs was soon supplanted by efforts to replace the current regulatory scheme with one based on an acoustic output display, which is another story.

So, in summary, it can be said that the development and use of piezoelectric polymer hydrophones enabled the FDA and industry to make accurate measurements of the acoustic pressures produced by diagnostic US devices and, thus, allowed issues of device safety and regulation to be addressed in a more rational, methodical manner. Technology is seldom complacent, however, and new measurement problems continue to arise. For example, the increasing use of high-frequency diagnostic US has created a need for hydrophones with smaller sensitive areas, as well as for standardized high-frequency hydrophone calibration techniques. Thus, significant challenges still remain in the area of ultrasonic exposimetry.

C. R. HILL: EXCURSIONS IN ULTRASOUND BIOEFFECTS AND METROLOGY

Commencing in 1957, I (Fig. 12) had been a Ph.D. student under W. V. Mayneord at the Institute of Cancer Research working on investigations of natural environmental background radiation. By 1961, I was on the scientific staff of the Institute, with considerable freedom to choose my own line of scientific pursuit and, having begun to feel that the physics and engineering content of work in natural radiation was beginning to wear thin, was looking for other possibilities. I was attracted to work that was then going on in investigating the action of US (particularly focused beams) for therapeutic or quasisurgical purposes. In physics and engineering terms, the most interesting work in this line was that of Bill Fry and his group at the University of Illinois, but also exciting was the more clinically oriented work being done by Ballantine and Lele at MIT. I discussed the situation with Mayneord, who encouraged me to follow this interest, but also remarked that it would not be an easy field in which to work.[1] At that time, there was some related work going on in the UK, particularly that of David Hughes, who was interested in the mechanisms for the processes of ultrasonic cellular and molecular disintegration. At the same time, Roger Warwick, at Guy's Hospital in London, was following up some of the American work on the use of US for inducing focal lesions in brain. Also, a group at Bristol, under the ENT surgeon Angell-James, was developing clinical and some experimental work in relation to ultrasonic treatment of Meniere's disease. I visited these groups and, then, in 1962, had the opportunity of taking a trip to the USA to visit Fry's laboratory (unfortunately missing out on meeting Bill Fry himself, who tragically died some 2 y later, Lele's laboratory, and also the very interesting work that was being done at the University of Vermont, under Wesley

[1] Mayneord's primary interest was in ionizing radiation, but he had long been involved also with US. In the mid1920s, he had worked with F. L. Hopwood, who was one of the first to follow up the pioneering work of Wood and Loomis (1927) on US bioeffects (Hopwood 1931). Then, in 1951, he became the first investigator outside the USA to take up the work on pulse-echo diagnostics (BECC 1971; Donald 1974).

Fig. 12. Left to right: D. L. Miller, W. L. Nyborg, C. R. Hill, Susan Hill, at an outing during the 7th WFUMB Congress in Sapporo, Japan, 1994.

Nyborg, on the visible and morphological changes taking place in cells exposed to US in various ways. Nyborg and colleagues had produced some fascinating film showing the remarkable movements of intracellular structures in response to exposure to US.

I was, at that time, working in a laboratory building that was largely devoted to ionizing radiation biology and, in view of my great interest in the work that was being done in US, and the possible potential that I saw for the application in cancer treatment, I decided to set up work in which I would provide carefully controlled sources and measuring techniques for US and apply these to cellular and animal experimental systems that were already well-documented in radiobiology. To the best of my knowledge, this was the first occasion on which radiobiological know-how and expertise was to be brought to bear on questions of the biological action of US.

This prospect of achieving an improved understanding of the biological action of US through use of techniques familiar in ionizing radiation biology; thus, leading to the possibility of intelligent therapeutic use of US in cancer, has been a central interest of mine since that date, and I will return below to try to give some account of the way that I see it having progressed over the years in question. However, it has brought with it an interest and involvement in two other related strands of medical ultrasonics, which it will be convenient to deal with first. These involve the question of whether the biological action of US represents any substantial hazard in its use in medicine, particularly in diagnostic procedures, and the closely related question of how one should best approach the matter of achieving a coherent and biologically meaningful system of metrology or "dosimetry" of US.

My interest in the hazard question was brought to a focus by being recruited to the Radiation Protection Committee of the British Institute of Radiology and being asked by them to write a committee paper on the scientific basis of the possibility of any hazard arising from the use of US. This paper evolved into a review article for the British Journal of Radiology (Hill 1968) that became the first published systematic review of the question. It is also, I believe, the first instance of a publication in which two particular classifications were set out: it was proposed 1. that it could be useful to classify the biophysical mechanisms by which US had its effect in three groups, namely, thermal, cavitational and "other;" and 2. that it would be useful to consider attenuation of US in tissues as taking place through two distinct mechanisms: absorption and scattering. Both of these classifications are now common currency, but most people seemed not to have been thinking explicitly in these terms before that date.

At the time of that article, 1968, there had already been considerable interest in the question of safety of US, certainly going back to the early work of Wild nearly 20 y before. However, from then on, the subject grew in interest, partly because of the rapid growth of use of diagnostic US (particularly in obstetrics), but also because of publication of some disturbing claims as to the biological action of US, particularly in relation to production of chromosomal abnormalities. Much of the subsequent history of the subject is probably common knowledge to many people in the field. My own involvement included the drafting of texts for two World Health

Organisation documents on the subject, in both of which I was collaborating with Gail ter Haar. This was part of a development that took place during the 1970s, initially, and in which I was one of the protagonists, particularly because of my close association with the work of the International Commission on Radiological Protection (ICRP). This was a move for the medical ultrasonic community, initially at national and regional levels but, later, at an international level, to obtain comprehensive documentation and corresponding expertise in its interpretation of the biological effects of US. The object was, on the ICRP model, to distill from the world literature some coherent set of advice for practicing diagnosticians and their patients as to the prudent or appropriate approach to clinical use of US. I believe that these early attempts (which took place through the AIUM Bioeffects Committee in North America, the EFSUMB Watchdog Group in Europe and a corresponding group in Japan, and were subsequently brought together in the WFUMB Safety Committee) will be seen by future historians of the subject as a key development in the sense that the profession was starting to collaborate internationally in ensuring that its activities were carried out in a professionally responsible manner.

Closely related to the matter of safety (but also, of course, to that of therapeutic use) is the subject of metrology, more commonly referred to as dosimetry or, perhaps more appropriately, as "exposimetry" (Hill 1974). A very considerable proportion of the early reports on biological action of US were almost entirely devoid of any quantitative basis; thus, making the observations, however fascinating, essentially anecdotal and without any basis for using them to deduce evidence on the mechanisms behind the phenomena observed. Eventually, more systematic workers, such as those in Fry's laboratory, did start to make some measurements; these were almost always based on the phenomenon of the radiation force that is exerted on an object that intercepts a progressive radiation beam. This approach to measurement was adopted, I believe for reasons predominantly of convenience, and led to the use of intensity as a measure of exposure of an object to a US source. This was a useful step, but was somewhat arbitrary, and many would now say, unsatisfactory, because the quantity intensity is not a satisfactory fundamental measure of the ultrasonic field, itself. My personal interest in this subject was focused as a result of two circumstances that occurred in the early 1970s. In the first place, on a committee of the UK Medical Research Council that was planning a large scale prospective epidemiological study of the possible hazards of US in obstetrics and, as the only physicist, I found myself first asking the question—and then being asked to find the solution to it—"How should one ensure that such an epidemiological study could be carried out so that exposure of the patient was documented in a manner that would have permanent relevance?" At about the same time, in 1970, I became chairman of the new working group of the International Electrotechnical Commission (IEC-29D-WG4) that was to deal with matters concerning medical ultrasonics, and in which we set ourselves the task of producing recommendations on how to carry out scientifically-valid measurements of relevant ultrasonic fields.

In both of these connections, I became a member of a small school of thought at that time who considered that the ideal approach was to try to measure one or more of the fundamental acoustic field variables (displacement, velocity, acceleration, pressure) with as high temporal and spatial precision as possible. The best possibility here seemed to be to set out to measure local values of pressure using a hydrophone; this has now become very much the internationally-agreed optimum approach. In the progress of this work, it happened that a very useful symposium on the subject took place within a framework of a slightly broader meeting in the USA (Reid and Sikov 1972); this probably constitutes what is historically the first systematic review of the metrology of US from a biomedical standpoint. Much of the scientific groundwork for this approach came from the West German Standards Laboratory (PTB) in Braunschweig, under Klaus Brendel. My own involvement included setting up a research and development project, funded by the Medical Research Council at the University of Surrey, in which, from the start, I encouraged the UK National Physical Laboratory (NPL) to take an interest; the eventual result was that the work moved over to NPL, who subsequently became an international focus for the work, initially under Keith Shotton and, subsequently, under Roy Preston. Finally, in connection with this development in metrology, it is perhaps worth recalling that, for most of the first 10 y of the efforts of the IEC Committee to prepare international recommendations for this type of measurement, most of us knew what ought to be done, but none of us knew how it would be possible to do the job properly; hydrophones would need a piezoelectric element, and piezoelectric materials at that time did not have anything like the right properties to give a broad bandwidth device, and one that would not itself seriously perturb the ultrasonic beam. It was only with the emergence of piezoelectric PVDF in the late 1970s that the solution to this problem became apparent.

I will now pick up again the topic of the therapeutic or surgical use of US, particularly in relation to cancer, which I indicated as being one of my particular interests dating back to the early 1960s. At that time, the concept of using US for treating cancer was not a new one (as I have indicated above) and, indeed, was in considerable disfavour, partly as a result of some of the earlier poor

and uncontrolled work, and partly due to a suspicion (which I believe has never been substantiated (see Hill and ter Haar 1995) that therapeutic US might act to disseminate cells from a primary tumour and, thus, promote metastasis. Also, at that time, there was a virtually complete lull in any interest in the use of hyperthermia in relation to cancer therapy. This led me to assume (probably without thinking about it clearly) that something as clear and obvious as the effect of varying temperature on the progress and control of cancer must have been fully studied and found to be of no interest. Partly for this reason (and, perhaps, partly because I suspected that other phenomena might be more interesting), I deliberately set out to study nonthermal effects of US in cells and tissues, to the extent of trying to control quite carefully the temperature of cells and tissues being exposed so that they remained at 37°C. The main point of historical interest relating to work in the 1960s is, perhaps, that the scientific community generally seemed to exclude the possibility that cavitation and related phenomena could have any substantial part in producing the observed biological effects of US exposures; at least, when the intensities and acoustic pressures were in the fairly modest range used for physiotherapy and also for much biological experimentation. This assumption seemed to be based on results of Esche (1952), who had stated that the threshold for cavitation induction at frequencies around 1 MHz was in the region of 1000 W cm^{-2} or more. In retrospect, this seems to have been a very strange situation, because there was a very considerable body of work, perhaps outstandingly exemplified by the publications of El'piner (1964) and colleagues in the USSR, which indicated very marked and substantial changes to cells and macromolecules in aqueous suspension or solution and which, although now explicable as a result of cavitation type processes, was then not attributed to any known mechanism. In fact, I believe it was work in our laboratory that, partly due to an artefact of the particular manner in which we carried out our exposures of cells and DNA solutions, led to the realization that cavitation-type phenomena were, indeed, taking place in these aqueous systems, and which we were then able to demonstrate and quantitate (Hill et al. 1969; Hill 1972). One of the intellectual puzzles that I see as having run through the study of the mechanistics of the biological action of US has been whether, when you rigorously exclude the action of both temperature and cavitation type phenomena, you can really demonstrate in a systematic and repeatable manner that there are any remaining mechanisms that have interesting biological consequences. It is now known from the work of Li, ter Haar and others that such mechanisms do indeed exist, even though they have not yet been properly identified and explained; from an historical point of view, I believe that it is correct to say that such evidence was absent until sometime around 1980.

During the 1970s and 1980s, much of my time and energy was taken up in work on the physics and engineering of diagnostic US in relation to cancer and, later, as Chair of a very busy, multidisciplinary department of medical physics. By 1991, however, I had the good fortune to be able to return to my early love of focused US surgery research and development, as a member of Gail ter Haar's small, but remarkably productive team. Here, in addition to being designer, driver and chief technician for our mobile, clinical/large-animal prototype equipment ("Teleson:" see Vaughan et al. 1994), I busied myself with some of the conundrums relating to how focal lesions are formed (Hill 1994), how to optimize treatment (Hill 1994; Hill 1995), and how to carry out appropriate exposimetry: an exercise that led to proposing the "Fry," as the suitable unit of absorbed dose, where 1 kJ/kg = 1 Fry (Hill et al. 1994).

In summary, I had the great good fortune to join the biomedical US world at a stage where it made sense for an engineering- and radiation-oriented physicist, such as myself, to involve himself in working on a wide variety of largely unexplored problems. Accounts of much of the resulting work, most of it due to students and colleagues, is recorded in a recent book (Hill et al. 2000).

IVO HRAZDIRA: MY JOB AND MY HOBBY

I (Fig. 13) first became familiar with US in the early 1950s, when I was a medical student at Masaryk University in Brno. At that time, I was working in the laboratory of the Department of Medical Physics, where a new US therapeutic device was tested. My task was to develop a simple method for detection of the biological effects of US. Being aware of the mechanical nature of US vibrations and the possibility of cavitation, I selected human erythrocytes for my studies. The extent of mechanical impairment of red cells was easy to assess by a photometric method based on the degree of haemolysis. The results were included in my first scientific paper entitled "Contribution to the problem of ultrasound haemolysis," which was published in Scripta Medica, the Journal of the Faculty of Medicine, in 1955 (Hrazdira 1955).

This first encounter with the biological effects of US became a decisive moment for all my future career. I have been involved in these studies for over 40 y. To broaden my knowledge of biophysics in general, and of the biophysics of US in particular, I started postgraduate study at the Medical Faculty of Comenius University in Bratislava in 1957. The title of my Ph.D. thesis was, "The Effect of Ultrasound on Blood and its Components."

Fig. 13. Last UBIOMED VIII Symposium held in Brno in 1989. I. Hrazdira is at the center. To his right (speaking) is Professor Ceresnak, Rector of Masaryk University and, to his left, is Dr. Placheta, Regional Health Care Director.

With a fresh Ph.D. degree, I entered my academic career as an assistant lecturer at the Department of Medical Physics of the Brno University in 1962. I taught medical students the principles of medical physics and, at the same time, tried to establish a research team that would carry out systematic investigations of the bioeffects of US used for therapy and diagnosis.

The period of the 1960s was marked by busy and rewarding research activities. Our team published a number of original papers that met with favourable response, both at home and abroad; consequently, our first international contacts could be established in spite of the existing "iron curtain" (Dvorak and Hrazdira 1966; Horak and Hrazdira 1968; Hrazdira 1963, 1965a, 1965b, 1967; Hrazdira and Bilkova 1963; Hrazdira and Konecny 1966; Pospisilova et al. 1963). However, hopes for more freedom represented by the Prague Spring were destroyed by military force with a profound negative impact on every sphere of life, research included. I had to leave the country and take a teaching position abroad. During that time, our successful research team broke up. Three years later, after I came back from Africa, I had to start from scratch and form a new team from my younger colleagues (Hrazdira and Skalka 1970; Hrazdira 1971, 1973, 1975, 1978, 1981, 1983, 1984). The political climate of the 1970s was not in favour of any international cooperation; thus, making us seek contacts within the countries behind the iron curtain. This brought about fruitful cooperation with Millner from Halle (former GDR), Filipczynski from Warsaw, Greguss from Budapest and with Sarvazyan, Akopyan and Gavrilov from the former Soviet Union. One of its successful results was the establishment of a tradition of international symposia known under the abbreviation UBIOMED (Ultrasound in Biology and Medicine). These regularly-held meetings helped to initiate new international contacts and provided a platform for exchange of information and experience also with western scientists. In the 1970s and 1980s, 8 symposia were held, the last taking place in Brno, the former Czechoslovakia, two months before the "Velvet Revolution" (Fig. 13).

During those 40 y, the objectives of research on US bioeffects have changed markedly: from studies of morphological changes in cells and tissues with the aim of differentiating between direct and indirect effects of US, to the assessing of functional changes in cells at subcellular and molecular levels (Hrazdira et al. 1974, 1988, 1995, 1998; Hrazdira and Prochazka 1983; Hrazdira and Doskocil 1988). The rapid development of ultrasonic diagnostic methods in the 1960s and 1970s accentuated the need for evaluation of hazards of US applications. Research at that time became focused on the two main risk factors: heating and cavitation. In our department, we were concerned with the investigation of potential embryotoxic effects of noncavitational US and with attempts to determine the cavitation threshold under therapeutic and diagnostic conditions (Forytkova et al. 1995). Through these research activities, I became involved in several international organisations concerned with the safety of US. In the fall of 1979, at the WHO meeting of a working group of advisors in London, I joined specialists for the biological effectiveness of US.

For the first time, I met scientists who, until that time, had been only famous names I knew from the literature, such as Hill, Dunn, Harder, Nyborg, Rott, Brendel, Bang and others. Three years later, I was appointed a member of the European Committee for Ultrasound Radiation Safety, better known under the name Watchdogs, and I worked there for 16 y.

Reflecting on those 40 y of my activity in the biomedical US field, I can conclude that quite a lot of work has been done, and many scientific observations and findings have been made that broadened our understanding of US as a therapeutic and diagnostic tool. However, no definite answer has been obtained as to the mechanisms of US action on biological systems, nor have all the problems of safe medical application of US been solved. These will remain as a challenge to our successors.

Fig. 14. T. F. Hueter.

T. F. HUETER: FOUNDATIONS AND TRENDS IN THE 1950s

When I (Fig. 14) arrived at the Massachusetts Institute of Technology (MIT) in 1950, the war was over, and new technology was in the offing, for the benefit of mankind. One of the foremost beneficiaries was to be medicine. But there was not yet a common language between M.D.s and Ph.D.s; the term "bioengineering" was not yet coined, and interdisciplinary research was a new *modus operandi*. Radar and sonar signal processing had made great strides during the war, but much of this was still shrouded in secrecy. Newly-available isotopes gave strong impetus to the new field of nuclear medicine. Such was the stage on which the joint MGH/MIT program on brain tumor detection was launched by the Massachusetts General Hospital (MGH), combining resources with MIT.

Prior to my arrival in the USA, I had been involved, at the Siemens electromedical laboratories in Erlangen, Germany, in ultrasonic propagation experiments in animal tissues (1946–1949). Measurements were made at various frequencies near 1 MHz, which held promise for reflections at interfaces and for differential absorption through the tissue layers traversed (Hueter 1948). It was hoped that this would lead to diagnostic or therapeutic applications of an energy that could be easily beamed.

Ultrasonic metal inspection using A-scan presentations was finding general acceptance in industry in the late 1940s, notably through the Sperry "reflectoscope." Crude reflectograms could be obtained from various parts of the human body, but were difficult to interpret and lacked stability (early work by J. Wild and Howry). However, medical diagnosticians at that time envisioned "ultrasonograms" that would resemble the familiar roentgenograms (X-ray films), hopefully with better contrast and delineation of the soft tissues. Clearly, they were not looking for complex pulse reflection trains on an A-scope, but for a two-dimensional (2-D) rendering of internal body topography, for an analogue to the X ray. This amounted to what I would like to call the "visualization paradigm" that, for many years, biased the preferences for tissue visualization in ultrasonic diagnostics.

At the MIT/MGH project, I collaborated with T. Ballantine and R. H. Bolt (Hueter and Bolt 1951) in exploiting some earlier (1945) attempts at ultrasonic cerebral ventriculography by the Dussik brothers in Austria. The original objectives of the MGH/MIT study were strongly influenced by the abovementioned visualization paradigm. It turned out that ultrasonic mapping of the brain tissues within the human skull was prone to great error due to the very large bone contrast encountered at useful diagnostic frequencies. Efforts to compensate for bone effects by use of the different absorptions at different frequencies—a very modern kind of a scheme—were marginally successful at that stage of the computational art.

However, in the course of these pursuits, a good many basic data essential for tissue characterization were assembled and proved useful for later diagnostic work on other body regions accessible through natural windows. This research benefited from lively interaction between the various groups at Urbana, Minnesota, Denver and Boston.

A particularly important product of this early work at MIT/MGH was the establishment of guidelines for dosimetry (Ballantine et al. 1954). The need for this had been recognized by my mentor, R. Pohlman, during the early postwar years at Siemens, in Erlangen, Germany. Pohlman was a superb experimenter and a man of many inventions. He showed me how to take advantage of E. Hiedemann's ultrasonic Schlieren techniques for the probing of ultrasonic fields. Among several clever pat-

Table 1. Early pioneers and their contributions

	Biological response of tissues	Calibration and dosimetry	Clinical applications
U. of Penn; also Vermont; Schwan, Carstensen, Nyborg	Fundamentals; heat vs. cavitation, bubbles	Some thermal, some pressure	None tried
MIT/MGH; Ballantine, Hueter	Velocities, absorption models	New standards, damage thresholds	Some disproved, some experiments
Urbana; Fry, Dunn	Mechanism of action	Refined instrumentation	Equipment capable of clinical trials, but later abandoned
Minnesota; Wild, Reid	Search for specific tissue characteristics	Some	Basis for diagnostic imaging, impetus to industrial development
Denver; Howry	Search for structural detail	Some	Basis for diagnostic imaging, impetus to industrial development
U. Washington; Baker, Reid, Strandness	Cardiovascular Doppler visualization	Velocity calibration	Technology transfer to industrial equipment tage

ents in the application of US, he came up with an ingenious design for a device to measure ultrasonic intensity (in W/cm^{-2}) by radiation pressure. It was produced and sold by Siemens as an ultrasonic dosimeter, one of which I brought with me to the USA at that time.

Our work at MGH on controlled lesions in animal brains with focused US (in parallel with W. Fry's group in Urbana) was much concerned with dosimetry and the underlying questions of the "mechanism of action" of US of any intensity on cell tissues. At a symposium held by the American Society of Chemical Engineers in Columbus, Ohio, I summarized the state of our knowledge in this area based on the literature available up to 1951 (Hueter 1951; Hueter et al. 1953). Later, in 1956, D. E. Goldman and I pulled together all the then available data on ultrasonic propagation in mammalian tissues for publication in the Journal of the Acoustical Society of America (Goldman and Hueter 1956).

From then (Rosenblith and Hueter 1954) until the present time, including the recent controversy on damage thresholds in sonic lithotripsy, there has been a lively debate in the literature on the role of heating vs. mechanical (or cavitational) effects. Only recently (in the 1990s), some more light is being shed on the physics of bubble collapse through the study of sonoluminescence from a single bubble (*e.g.*, Putterman 1995).

During my 6 y at MIT/MGH, I benefited from many discussions at the Acoustical Society of America and other meetings, with my fellow players in the biomedical ultrasonics field who, likewise, enjoyed NIH sponsorship of their research. Schwann and Carstensen, Fry, Howry and Nyborg are names that stand out. My own research interests focused on the behaviour of tissues as viscoelastic materials with frequency-dependent relaxational properties. This work is documented in a report to the Aeromedical Laboratory of ASAF (Hueter 1958).

Some of the early pioneers and their contributions are listed in Table 1 (Ballantine et al. 1956; Hueter 1956, 1972; Hueter and Bolt 1955; Hueter and Fry 1960). In doing this work at the Acoustics Laboratory of MIT, I came to realize that the art of industrial flaw detection, as well as tissue visualization, with US would benefit considerably from the unleashing of the technologies (still partly classified) developed in radar and sonar during World War II. Thus, when an opportunity came to join the Submarine Signal Division of Raytheon and to expand my knowledge in the area of signal processing and transducer design, I switched my allegiance from sponsorship by the National Institutes of Health to that of the U.S. Navy. This turned out to be the beginning of a new career in industrial research and development, with a strong management flavor. Finally, in 1960, I moved with my family from Boston to Seattle to work for Honeywell until my retirement in 1982.

It was the combination of these industrial advances (Howry's radar background) with the results of the spreading research activities in ultrasonic tissue characterization (Schwan, Wild, Dunn et al.) that finally brought to life the present era of widespread diagnostic ultrasonics. In the 20 y it took to make this new modality acceptable, if not indispensable, the visualization paradigm had finally been overcome; medical doctors became used to "windows" and "sector scans," to computer-corrected imagery, to color-coding and to use of the Doppler effect. The grandfathers of the pioneering effort in medical ultrasonics, such as Loomis, Schmitt, Harvey, and Pohlman, would be pleased by the progress made, even though it took almost half a century to get there.

Fig. 15. Panel of speakers at the Seventh Congress of the World Federation for Ultrasound in Medicine and Biology, Sapporo, Japan, 1994. Left to right: M. Ziskin, M. Ide, F. Duck, W. Nyborg.

MASAO IDE: SAFETY AND STANDARDIZATION

I (Fig. 15) graduated from Musashi Institute of Technology in March 1953 with major in electrical communication engineering (in the Department of Electrical Communication Engineering). I was engaged in the college as Assistant within a month of graduation and, in the first year, made some studies on electrical communication. About 1 y later, I met Jun'ichi Saneyoshi, an authority in the field of ultrasonics, who was famous for his research in ultrasonic engineering. He was at the Tokyo Institute of Technology, which was located about 10 min by car from my college. Because I was interested in US, I became an unpaid Research Assistant at the Tokyo Institute of Technology to receive Saneyoshi's guidance. Thus, my researches on US began as an odd job, my main business being at the Musashi Institute of Technology, and then became my life work. Following is a history of my research on US in medicine and biology, and of my work on standardization of medical ultrasonic equipment. During my career, I have had many opportunities to apply my background in physics and engineering to advance the field of medical US.

Ultrasonic power output indicator for therapeutic equipment

My first research assignment was given to me and supervised by Saneyoshi. (Although I was interested in medical applications of US, it was not until after I met Toshio Wagai of Juntendo University School of Medicine that I began the studies of medical US in full scale.) For preliminary work in evaluating the therapeutic value of US and defining US "dose," there was need for measurement of the power (in W) or intensity (in Wcm^{-2}) of the US with which the human body was irradiated. I measured the acoustic load impedance at the surface of the body at frequencies of about 1 MHz. Using a Q-meter, I measured the electrical admittance of the quartz transducer that was the source of US for the ultrasonic therapeutic apparatus, when it was acoustically loaded with water, and when coupled to the body. Because the acoustic impedance of the body surface was almost the same as water, except in specific regions, the load to the transducer (hence, also the efficiency) was almost constant. With this result in mind, I thought a direct indication of ultrasonic power was possible, by measuring the electric input power to the transducer using a high-frequency power meter. I developed the abovementioned ultrasonic power indicator from this idea (Saneyoshi and Ide 1957).

Traveling-wave type sonde for ultrasonic pressure measurement

It is necessary to know the acoustic pressure in various applications of US. Together with Saneyoshi and others, I developed a traveling-wave type sonde (a kind of hydrophone) for this purpose. This sonde can measure high acoustic pressures and their distribution in US fields of wide frequency range, without becoming damaged in the high-pressure fields produced by cavitation. The

sonde has a long rod that guides the ultrasonic wave to a transducer, and has an absorber part at the rear of the transducer that absorbs the reflected wave. Because only a traveling wave exists in the rod, which acts as a wave guide to the transducer, we named this type of hydrophone as "traveling-wave sonde" ("sonde" from the German word for "catheter"). Several types were developed with small rod diameters (1 mm to several mm), so that they do not disturb the sound field, with measurable frequency range of 10 kHz to 2 MHz. This type of sonde has been used in various medical and biological applications (Saneyoshi et al. 1963, 1966).

Ultrasonic apparatus for destroying bacteria

Around 1957, together with Saneyoshi and others, I developed an apparatus to destroy cell-walls of bacteria, to make extractions of enzymes, proteins, toxins, etc., from the bacteria. In this kind of application, it is desired to destroy the cell wall with mechanical action, while suppressing chemical action. Because the apparatus used at this time employed X-cut crystals that produced US at frequencies in the range of several hundreds of kilohertz, effects of chemical action were strong and the efficiency of destruction was poor. Instead, our apparatus used ferrite transducers and produced frequencies in the range of 10 and 20 kHz. Moreover, acoustical doses in the vessel were controlled during the operation. This was achieved by determining 1. acoustic pressures with the traveling-wave sonde described above, and 2. the vibrating velocity of the transducer by measuring the motional voltage of the transducer (Saneyoshi et al. 1958; Saneyoshi and Ide 1957; Ide 1958).

Stereotaxic encephalotomy instrument with focused ultrasound

Around 1960, stimulated by the works of W. J. Fry and colleagues on focused US, with T. Wagai and others, I developed several items of focused US equipment, such as single-beam equipment with focused transducers, transducers with focusing lenses, and four-beam equipment for concentrating the US. In the four-beam equipment, the maximum intensity at the focal point reached several kilowatts per square centimeter. Hence, measurement of the intensity was a problem and it was necessary for us to develop apparatus for this purpose. One instrument was the traveling-wave sonde discussed above. An ultrasonic power indicator constructed with thermosensitive paint, sandwiched between plastic plates, was also one of the items of measuring equipment we developed (Ide 1962; Ide and Wagai 1965; Ide et al. 1984).

Studies on bioeffects of ultrasound

I began studies of biological effects of US about 25 y ago, together with about 10 researchers of obstetrics and gynecology, including Kazuo Maeda of Tottori University and Shoichi Sakamoto of the University of Tokyo, in a group organized by the Ministry of Health and Welfare. In the first several years, we investigated bioeffects of continuous-wave US. After that, we investigated those of pulsed US (Maeda 1981). In these studies, we used about 10 specially manufactured ultrasonic irradiation devices, the output intensity of which were known and adjustable. Similar devices, which had the same performance characteristics, were delivered to the researchers who belonged to the study group. Data on effects of ultrasonic irradiation on bacteria, animal egg and animal fetuses were accumulated. Epidemiological investigations on the effects of ultrasonic diagnostic examinations on pregnant women were also made among the researchers in the the group. Results of these investigations were published as reports (Maeda 1981). This study was very useful for the enactment of JIS standards afterward.

Standardization of ultrasonic diagnostic equipment

As chairman of the JIS Enacting Committee, I drafted several standards of ultrasonic diagnostic equipment. Standards for A-mode, B-mode, M-mode and Doppler fetal equipment including the output powers, were completed first. Then, standards for electronic linear scan equipment were completed. In this process, much effort and time were needed to adjust the differences between two Ministries: the Ministry of Health and Welfare and the Ministry of International Trade and Industry. The reason was that the drafting was first made by the Ministry of Health and Welfare, but then the matter was placed also under control of the Ministry of International Trade and Industry for developing industrial standards. Several years passed after the first draft was completed before the standards were enacted. The JIS standards enacted by both Ministries are:

JIS T 1501; General method of measuring the performance of ultrasonic pulse-echo diagnostic equipment (1984)

JIS T 1503: A-mode ultrasonic diagnostic equipment (1984)

JIS T 1504: Manual scanning B-mode ultrasonic diagnostic equipment (1984)

JIS T 1505: M-mode ultrasonic diagnostic equipment (1984)

JIS T 1506: Ultrasonic Doppler fetal diagnostic equipment (1984)

JIS T 1507: Electronic linear scanning ultrasonic diagnostic equipment (1989)

In these standards, output powers were specified; these were based on determinations of the total power from the ultrasonic probe obtained from radiation force measurements using an electronic balance. "Output power" is

calculated by dividing the total power by the effective area of the probe; this value is equivalent to the spatial-average temporal-average intensity (I_{SATA}). Limiting values for I_{SATA} intensities specified in the above standards 1503, 1504, etc., were, respectively: JIS T 1503, 100 mW/cm^2; JIS T 1504, 10 mW/cm^2; JIS T 1505, 40 mW/cm^2; JIS T 1506, 10 mW/cm^2; JIS T 1507, 10 mW/cm^2.

The limiting value for each standard was based on a "safety factor" specified for the body parts to which the equipment was applied. In A-mode, which was applied to intracranial diagnosis, attenuation of the US in skull bone was considered; in M-mode, which was applied to diagnosis of the heart, a safety factor for muscle was employed. In the equipment applied to fetal diagnosis, the largest safety factor was specified because fetal tissue was considered to be most sensitive to US (Maeda and Ide 1986). JIS standards are written in Japanese, the official language of Japan, except that the back cover is written in English. This is inconvenient for people outside of Japan. However, we have heard that, in the main Western countries, translation services have become more popular than before so that reading Japanese is not so difficult at present.

Survey of the acoustic parameters of ultrasonic diagnostic equipment on the market

I made the first research survey of acoustical output data for commercial equipment to report them at the WFUMB Safety/Standardization Committee meeting held in 1988 at Airlee House, Virginia, USA. As Chairman of the Standardization Committee of the JSUM at that time, I made the request, with the help of the President of the JSUM, that manufacturers of Japan report the data on output power of their equipment. It was not easy to obtain the cooperation of the manufacturers but, at last, data on 71 models (including multi mode equipment) were obtained from 11 companies. I reported the analyzed results of the 160 measured quantities categorized with mode at the second WFUMB Safety/Standardization Symposium (Ide 1989).

The second research survey was made to report at the Congress of the JSUM in 1992. Data were presented for 97 transducers of 26 models from 15 companies. The data were mainly those required according to the 510 (k) Guidelines of the U.S. Food and Drug Administration (FDA) (FDA 1985). These often included many items of data for a given equipment system because modern systems are usually multifunctional, with several modes and numerous probes. For such equipment, many measurements were made for the respective modes and probes. Data were graphed for the I_{SPTA}, I_{SPPA} and I_m intensities categorized with the intensity levels and the number of products. It was found that output intensities of the Doppler equipment were higher than those of B- and/or M-mode equipment (Ide 1992).

Connections with organizations

IEC. In September 1970, together with J. Saneyoshi, I participated in a meeting of IEC SC29 that was held at the German Standards Laboratory (PTB) in Braunschweig, Germany. This was my first participation in an IEC meeting. At this meeting, it was decided to form a working group in medical US. Since then, I have proceeded with the standardization of medical US both as a member of SC29D and as a member of TC87, the latter being the Technical Committee (TC) for US. As Secretary of Working Group 10 (WG10) of the above TC, I have made efforts to produce documents on Doppler equipment.

JSUM. In 1962, together with Toshio Wagai and others, I established the Japan Society of Ultrasonics in Medicine (JSUM). At present, the number of members is about 15,000, but it was about 200 during the first several years. For the development of the Society, I made much effort as a board member and as chairman of the standardization committee, and served as President for 2 y since 1976.

WFUMB. The World Federation of Ultrasound in Medicine (WFUMB) was formed in June 1973 and the JSUM was affiliated with it at the same time. Together with other members of the JSUM, I participated in the first Congress of the WFUMB, which was held in August 1976 in San Francisco, CA. At the general assembly, I received a recognition award that contained the statement that the award was given me "for advancing the uses of ultrasound in medicine on both national and international levels." In August 1979, the Second Congress of the WFUMB was held in Miyazaki City, Japan, hosted by the JSUM. I served as Co-President of the organizing committee. The Seventh Congress of the WFUMB was held in Sapporo, Japan in 1994, at which I was also present (Fig. 15).

I have many memories of the WFUMB. One of them is about its official Journal, Ultrasound in Medicine and Biology (UMB). I requested the Editor-in–Chief, Denis White, to add JSUM members to the Advisory Board because there were few from Japan at that time. White replied that this would be difficult because reviewing English papers is necessary, and this is difficult for Japanese. I continued the negotiation and insisted that the number of the Japanese who are good at English has increased. For a Japanese author, an effective style of writing is achieved by obtaining professional revision of English. However, Japanese readers can judge whether English papers are good or not. At present, five JSUM members are appointed to the Advisory Editorial Board.

Fig. 16. Elizabeth Kelly-Fry.

I have participated in the WFUMB Safety/Standardization Symposia from the beginning, reporting advances that have been made in Japan and helping to make well-informed decisions.

ELIZABETH KELLY-FRY: WORKING WITH PROFESSOR WILLIAM J. FRY AT THE UNIVERSITY OF ILLINOIS AND THE INTERSCIENCE RESEARCH INSTITUTE

The early history of the University of Illinois' Bioacoustics Research Laboratory (BRL) has been presented here in Floyd Dunn's personal history. William J. Fry (Bill Fry) was Director of BRL during its first decade and during its second decade, when the name of the laboratory was changed to the Biophysical Research Laboratory (also designated BRL). In addition, for the second decade time period, Fry was Director of Interscience Research Institute (IRI). This personal history is based on my (Fig. 16) experience, first as a research associate at BRL, and later as Associate Director of Research and Vice-President of IRI, both BRL and IRI positions taking place during the time period of the second decade. I had an M.S. in Physics-Biophysics and had completed 1 y of graduate studies in physiology at the time that I joined the research staff of BRL. After I became a faculty member of Indiana University School of Medicine, I completed a Ph.D. in Science Education.

Bill Fry and I married after I joined BRL; but I continued to use my maiden name (Elizabeth Kelly) in publications. After his death, in his memory, I changed my name to Elizabeth Kelly-Fry. As one of the members of Bill's research teams, and as his wife, I had a unique insight into his research goals. With this personal history, I hope I can convey, in a limited way, what Bill hoped to accomplish by his own research and by his intense efforts to encourage colleagues, myself included, to maximize their individual research talents.

Bill was a physicist with a talent for analytical evaluation of complex systems. He had a unique appreciation of the complex mechanisms associated with the central nervous system of both animals and humans. He believed that use of physics research techniques in combination with sophisticated instrumentation methods could increase knowledge of some of the basic operating mechanisms of the human brain. In pursuing that goal, in the early years of BRL, major efforts were devoted to building and applying US instrumentation designed to investigate the central nervous system of experimental animals. One of the primary accomplishments during that early period was the use of focused, high-intensity US for production of selective and precisely localized changes in the gray and white matter of the brains of experimental animals. Various members of the BRL staff were involved in this instrumentation development, with a major contribution made by Francis J. Fry, Bill's brother. A total of 41 research papers were published by Bill and his associates during the decade 1947–1957. Space limitations do not allow the listing of most of them, or other significant later publications. (Fry et al. 1954; Barnard et al. 1955). However, publications by this writer, on two of the Allerton Conferences, provide insight into the status of bioacoustics research at BRL and

other research facilities during the 1950s and 1960s (Kelly 1957, 1965).

Bill, an individual who was extremely sensitive to human suffering, believed that certain medical problems, then considered beyond the capabilities of medical science, could be solved by development of more advanced instrumentation approaches. In that context, while carrying out the animal based research at BRL, he gave constant attention to the possible applications of the same or similar instrumentation techniques to human subjects. In 1955, in response to a request from Russell Meyers, a neurosurgeon associated with the State University of Iowa Hospitals, in Iowa City, Bill agreed that he, and his brother, Francis, would design and build a high-intensity US instrumentation system that was appropriate for application to human patients. By 1958, an elaborate ultrasonic operating theater was in operation at the Iowa City hospital. Over the next several years, a variety of patient afflictions were treated, with particular emphasis on Parkinson's disease, but including such conditions as cerebral palsy, the after-effects of stroke, phantom images and pain following amputation. Bill and other members of the BRL team, under the medical guidance of Myers, carried out the irradiation procedures. A number of "firsts" came from this series of US surgeries (Fry et al. 1958; Fry and Meyers 1962; Meyers et al. 1959, 1960; Hickey et al. 1961, 1963; Bauserman et al. 1963). Based on the knowledge gained after 3 y of experience with US irradiation of human patients, Bill proposed to design an US surgery center that included further advancements in the US instrumentation. Extensive financial support would have been required to achieve this next phase of neurosonic surgery. After attempts to obtain financial support for the proposed expansion were not successful, Bill made the decision to dismantle the US operating theater and resume basic research investigations at BRL. In terms of a historical review, it is of interest to consider why a well-proven, precise technique for US irradiation of the human brain, based on long-term studies of experimental animals followed by application to human subjects, was not, in subsequent years, further developed and medically applied by other investigators. An analysis by E. Breckenridge Koch presents relevant data on this question (Koch 1990). The early comments of William J. Fry on the limited number of scientists with interest and expertise in this research area are still relevant (*i.e.*, ". . . sound produced, controlled, and utilized under precisely controlled conditions with precision instrumentation constitutes an extremely powerful tool for investigating biological systems and for use in medicine. Unfortunately, the research areas discussed in this paper have not yet caught the imagination of many investigators. It is not unusual to find only one or two laboratories investigating a field which may well occupy the efforts of a score of laboratories") (Fry 1958). Fortunately, at the present time, there is increasing interest in the application of high-intensity US for a variety of medical applications.

At the time I joined the Bioacoustics Research Laboratory, all of the biological studies included the application of US for modification of tissue. My early research was based on the effect of ultrasound on muscle (Kelly and Fry 1958; Kelly et al. 1959) and on application of high-intensity US to modify the functions of the anterior pituitary of cats (Kelly 1965). In 1958, the name of the laboratory was changed to the Biophysical Research Laboratory (BRL). As an early proponent of interdisciplinary research, Bill decided it would be best if the biological research was not limited to just a single aspect of physics (*i.e.*, bioacoustics). This broadening of laboratory goals allowed research investigators greater freedom in choice of research topics. In that regard, I halted my investigations on the effects of high-intensity US on muscle because it was clear from my initial results that some fundamental mechanisms of muscle contraction needed to be experimentally determined before reaching conclusions on the effects of US (Kelly and Fry 1958; Kelly et al. 1959). Following the laboratory name change, I carried out extensive investigations on muscle contraction that did not include the use of US techniques (Kelly et al. 1964, 1965; Kelly and Fry 1964, 1965). After Bill's death, the title of Bioacoustics Research Laboratories was reinstated.

Interscience Research Institute (IRI), in Champaign, Illinois, a not-for–profit organization founded in 1957 with Bill as President, had uniquely broad goals for that time period. The first goal was to have biological scientists, physicists, engineers and physicians working as a research team. The institute was designed to allow both animal-based research and application of new instrumentation to human subjects. Two of the primary programs carried out at IRI were instrumentation for US visualization of soft tissue and testing of an artificial heart on dogs. After I joined IRI in 1964, my investigations, at BRL, on US irradiation of the anterior pituitary and muscle came to a close.

The development of a double-beam US system for distinguishing two adjacent soft tissues not normally detectable because their acoustic impedance values are similar was achieved at IRI under Bill's direction (Kelly 1965). The double-beam system consisted of an US perturbing beam that changed the acoustic impedance of the tissue with the higher absorption coefficient. Bill and associates also evolved the theory and instrumentation for a US "search and destroy" system for treating tumors, in particular, brain tumors. With this system, the tumor is located by the low-intensity US visualization method,

and then an attempt is made to selectively destroy the tumor by application of high-intensity US.

IRI maintained close communication with Japanese medical US scientists, including arrangements for Japanese investigators to be visiting IRI scientists. Daitaro Okuyama, one of the visiting Japanese scientists, and I worked together on a number of research projects, including US instrumentation development and US imaging of livers of different animal species. George Kossoff from Australia and Chihiro Kasai from Japan were also IRI visiting scientists.

I was one of the team members (with Bill as chief scientist) who developed, at IRI, an omnidirectional US visualization system using an online digital computer that allowed a resolution of 1 mm and an accuracy of location of 0.5 mm (Fry 1968; Fry et al. 1968). For the year 1968, this elaborate instrumentation represented a significant advancement. After Bill's death, I became Chief Investigator on a 3-y grant for US imaging of the *in vivo* human breast with this computer-based system (Kelly-Fry et al. 1972). The knowledge gained from that IRI-based investigation was the preamble for my subsequent long-term research as Professor of Radiology at Indiana University School of Medicine and as Research Scientist at the Indianapolis Center for Advanced Research on the use of US imaging techniques for breast cancer detection and diagnosis.

A brief word follows on Bill Fry's concept that the relatively short life span of humans was the greatest impediment to solving the many complex problems of humanity.

In terms of human life span, Bill seriously felt that, with sufficient long-term, world-wide research, human life could be extended to the order of a thousand years. He did not expect, in our lifetime, that this was possible, only promising both of us about 200 years. He emphasized the extent of the research that would be required for such life extensions, ranging from the relatively simple, practical approach of maintaining the heart function to gaining complete understanding of all aspects of the brain and the systems it controls. In terms of solving the heart muscle problem, he was the first person to conceive and design (in 1954) an artificial heart as a complete replacement for the human heart. His final publication, which appeared 2 y after his death, concerned the application of high-intensity US in a manner that demonstrated quantitative data on brain neural networks not previously known or understood (Fry 1970). He showed that questions concerning the relationships between structure and function, at the level of neuron groups and their connections, can be answered on a quantitative basis. From a therapeutic viewpoint, this research may prove to be important in our understanding of a variety of neural disorders that lead to neuron population imbalances.

GEORGE KOSSOFF: PERSONAL HISTORY

In March 1959, on graduation as B.A. first class honours in Electrical Engineering, University of Sydney, I (Fig. 17) was approached by Norman Murray, the Director of the Commonwealth Acoustic Laboratories, who invited me to set up and head its program on Medical Ultrasound. I had at that time considered taking up an offer of appointment as a nuclear scientist at the Atomic Energy Commission. Norm Murray persuaded me to accept his invitation on the basis on his description of medical ultrasound as a field in the early stages of development when it would be easier to make a meaningful contribution. Not by accident, he also proposed that the appointment would be at a grade higher than that normally offered to raw graduates. In other words, he made an offer that I just could not refuse.

The initial tasks I was given were 1. to develop a calibration facility to measure the acoustic output of physiotherapy equipment and 2. to provide recommendations as to the direction for research into medical US in Australia. The first was in response to concern regarding possible induction of abortion by unlawful US physiotherapy procedures, the second as result of interest in publications by John Wild, Doug Howry, Bill Fry, Toshio Wagai and Ian Donald into potential applications of medical US.

My first international publication (Kossoff 1962) described the method we developed for calibration of ultrasonic therapeutic equipment. The acoustic power output was measured using the Cartesian float method

Fig. 17. George Kossoff.

described in draft form by the IEC Technical Committee 29, Working Group 7. The intensity distribution was measured by a densitonometric evaluation of the degree of starch-iodine reaction on a starch-coated plastic film developed for the application. The Cartesian float method has proved to be remarkably age-resistant, and we still occasionally use the method for quick, first cut assessment of power output of acoustic output in the 1–10 W range.

The publications by Alice Stewart on increased incidence of leukemia in children exposed to X rays *in utero* indicated that there was immediate need for research into obstetrical applications of diagnostic US. In collaboration with Dave Robinson from our laboratory and Bill Garrett at the Royal Hospital for Women, Paddington, we constructed our first obstetric echoscope in 1962 and began to examine patients that year. We found the Cartesian float to be too unstable to allow measurement of the low acoustic output generated by diagnostic equipment. We, therefore, developed a balance technique to measure the acoustic output (Kossoff 1965) and the peak acoustic intensity (Kossoff 1969) generated by diagnostic equipment, and described the methodology for specification of acoustic parameters generated by such equipment (Kossoff 1978).

A major brief of the Commonwealth Acoustic Laboratories was to undertake research and provide services into hearing conservation. It was, therefore, a natural extension for the medical US program to investigate the therapeutic application of US for the treatment of Meniere's disease, which causes vestibular disturbance and progressive hearing loss. The work by Michele Arslan demonstrated that ultrasonic irradiation of the semicircular canal abolished vertigo attacks while conserving hearing in patients with this disease. Our research with several ENT specialists in Sydney confirmed these results but, unfortunately, also demonstrated that the procedure induced partial facial paralysis in a significant number of patients. Experiments demonstrated that this was due to conductive heating of the facial nerve from the surrounding temporal bone irradiated by the large applicator used by the original equipment. We, therefore, developed equipment employing a smaller and more efficient applicator that dramatically reduced the risk of this complication. The equipment was successfully used in Australia and overseas in many otologic centres for several years (Kossoff and Khan 1966).

Part of my responsibility in assisting with the ultrasonic treatment was the monitoring of nystagmus during the irradiation. Initially, the eyes of the patient would swing slightly in the direction of the irradiated ear in response to treatment. The direction of the swing would, after 10 to 20 min of treatment, change in the other direction as the other ear took control. On one occasion early in the series, I was tested by our ENT colleagues by being asked to comment on my observation of the direction of nystagmus on a patient who, unknown to me, had a glass eye. Fortunately, I was sufficiently honest to tell them that I could not make sense of the erratic movements of the artificial eye and, so, passed their reality check. In the process of performing temperature elevation measurements on temporal bones, I became proficient with the anatomy of the inner ear. This knowledge allowed me to realise that the round window of the inner ear could be used as a natural opening through which to apply the ultrasonic irradiation. The approach simplified the prerequisite surgical approach from a major mastoidectomy to a simple reflection of the tympanic membrane. The round window was also a larger and, therefore, more efficient approach and less energy was needed for the treatment. This eliminated any possibility of causing facial paralysis (Kossoff et al. 1967). The technique attracted international interest and was used for several years until it was superseded by newer US therapeutic methods.

In 1967–1969, at invitation from Bill Fry, I spent a 2-y sabbatical at the Bioacoustic Research Laboratory, University of Illinois and the InterScience Research Institute in Champaign/Urbana, Illinois. I appreciated the opportunity to enlarge my experience, working, not only with Bill Fry, but also people like Frank Fry, Reg Eggleton, Elizabeth Kelly and Floyd Dunn and with young graduate students like Bill O'Brien. The two groups were eminent in research into focused US for surgery and were at that time pioneering the application of computers to diagnostic US. They had excellent facilities and I was impressed by their dedication to their research. It was there that I was also introduced to the intricacies of cavitation-induced phenomena (Fry et al. 1970).

Stan Barnett joined our Laboratory in 1970, and we have had a close working relation on bioeffects and exposimetry over the ensuing 25 y. Originally, Stan undertook research to determine the histological effects of the round window irradiation on the inner ear (Barnett et al. 1973). The last author (G. M. Clark) in this publication went on to develop a distinguished career as Professor of Otolaryngology at Melbourne University, with his pioneering research into the bionic ear.

At the completion of the inner ear program, Stan and I focused our attention on exposimetry and mechanisms of interaction of diagnostic US with soft tissue. At times, our publications would be influenced by my technically-oriented outlook (Barnett and Kossoff 1982) and, in others, his biology expertise would form the dominant theme (Barnett and Kossoff 1984).

In 1983, in my capacity as President of WFUMB, I chaired the WFUMB Council Meeting held in New York. It was agreed, at that meeting, that the World

Federation should take a proactive role in sponsoring activities of interest to its membership. I was requested by Council to organise the WFUMB First Symposium on Safety and Standardization of Ultrasound in Obstetrics. This was a major undertaking in that the Symposium was to be held immediately after the WFUMB 85 Congress, the staging of which taxed most of our available resources. Stan was of great assistance in helping to organize the Symposium and, together, we coedited its proceedings (Kossoff and Barnett 1986). The Symposium proved to be highly successful in bringing together leading experts in the field, giving them opportunity to present international perspective and to get to know each other. It also acted as a catalyst encouraging several organizations to sponsor national conferences on the subject.

Encouraged by its success, WFUMB decided to continue to sponsor these symposia. As result, while I was on sabbatical leave at Emory University, Atlanta, Georgia, Wes Nyborg and I cochaired the WFUMB Second Symposium on Safety and Standardisation in Medical Ultrasound, which was held in Airlie, Virginia (Kossoff and Nyborg 1989).

It became apparent at the second symposium that a carefully prepared draft document that could be widely circulated for comment was needed before international consensus on WFUMB recommendation could be developed. WFUMB and several national US organizations generously supported a limited-attendance workshop I helped to organize, which was held in Geneva in May 1990. After a 1-week intensive effort by all participants, Stan Barnett was able to produce the Geneva draft document on WFUMB Recommendations Regarding Thermal Mechanism for Biological Effects of Ultrasound. The document was produced having access to only one word processor, and a major task was the allocation of time on a 24-h basis over the 1-week duration of the workshop for participants to get into a queue to type in their section for the recommendations. The ultimate outcome of this Herculean effort was the publication of the Special Issue of the WFUMB Symposium on Safety and Standardization in Medical Ultrasound (Barnett and Kossoff 1992) that, for the first time, published WFUMB recommendations on thermal mechanisms for biological effects of US.

Although I am no longer as involved, I'm pleased that WFUMB continues to support such symposia. There are many topics where official recommendations by WFUMB can affect Government policy in the provision of ultrasonic diagnostic services and I'm pleased that I had the opportunity to contribute to the development by WFUMB of this activity.

Over the years, I also participated in a number of activities by organizations such as the IEC and societies such as the AIUM on standards on safety and on standardization. In particular, I was Chairman of the WFUMB Committee on Standardization from 1985 until 1994, and Chairman of the Australasian Society for Ultrasound in Medicine Committee on Safety and Standardization from 1979 until 1994.

PADMAKER P. LELE: PERSONAL HISTORY

Ultrasound has been a hobby that has consumed most of my (Fig. 18) postdoctoral years and kept me from engaging in the business of practicing medicine—which I spent 12 y to learn!

During my internship in neurology, I became interested in the problem of intractable pain. So, I went to work with Graham Weddell at Oxford to study its mechanism and wrote my D.Phil. thesis on a new theory of pain. To put the theory to some practical use (for relieving intractable pain in patients), what was required was a method to perform noninvasive (trackless) focal surgery on the spinal cord. Focused US was the unique modality in that respect. And, so, in 1959, I went to Massachusetts General Hospital (MGH) in Boston to work with Ballantine, one of the earliest pioneers in medical US, both diagnostic and therapeutic. He was keenly interested in the development of an ultrasonic neurosurgical system that could be replicated and used by practicing neurosurgeons everywhere, in contrast to the one-of–a-kind installation of Bill Fry at the University of Illinois at Urbana. It was great to work with Tom Ballantine. He was very enthusiastic and gave me initial support, as well as freedom to pursue my ideas. Because our main motivation was utilization of focused US for neurosurgery,

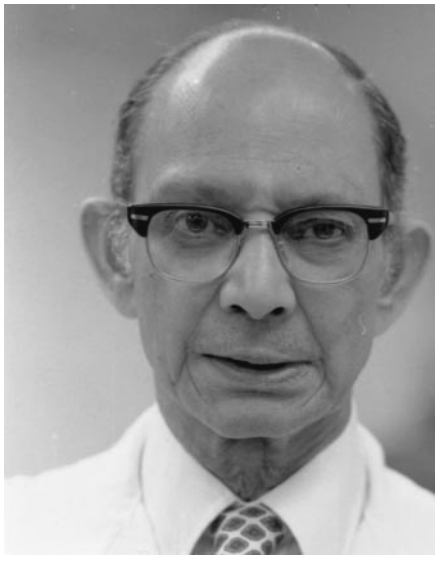

Fig. 18. Padmaker P. Lele.

my early program concentrated on refinement and standardization of the equipment and on statistically sound dosimetry. I was lucky to have L. Basauri, a neurosurgeon from Chile as a coinvestigator and Ida Giriunas, Ballantine's neurosurgical nurse, as the technician. We conducted our first dosimetric studies in 654 anesthetized cats (Basauri and Lele 1962). Thanks to the fact that the studies were conducted rigorously, the data are still valid and accurate. As can be imagined, it would now be impossible for anyone to conduct such extensive studies in mammals. These studies formed the basis upon which Ballantine and I later successfully performed ultrasonic commissural myelotomies (*i.e.*, procedures for placing lesions in the spinal cord of patients to relieve their intractable neurogenic pain without producing any sensory loss).

But, these dosimetric studies had another interesting feature. Because we were interested in using US during and for surgery, we wanted to be sure about dosimetry under conditions during neurosurgical procedures, which meant surgery under hypothermia to reduce blood loss, etc. These studies highlighted, in a statistically defensible manner, the differences in the response of different tissues, or of the same tissue under different conditions of circulation or at different temperatures, to identical insonation. Those studies, and subsequent studies on plastics (Lele 1962) and on peripheral nerves (Lele 1963) pointed to the importance of thermal mechanisms in US - tissue interactions. Thanks to my naivete, and my innocence of the strength of the entrenched dogma that denied any role to thermal mechanisms, I did not feel intimidated enough to disown or suppress the results of our studies (Lele and Hsu 1970). The leading bioacousticians at that time held that "the lesions are formed by a mechanical mechanism which is thus far not well understood" (Fry et al. 1950; Barnard et al. 1955; Dunn 1958; Fry et al. 1970).

In 1968, to be able to devote more time to research in US than was possible in a clinical setting, I moved to the Massachusetts Institute of Technology (MIT). Several doctoral students at MIT, Tom Robinson and Bill Hsu, to name the first two, looked at this problem from the nonbias a graduate student in an unrelated field can afford (Robinson 1968; Robinson and Lele 1972; Lele and Hsu 1970; Hsu 1974). They developed an analytical predictive model based on ultrasonic and thermophysical properties of tissue *in vivo* to "forecast" the volume of tissue necrosis (or coagulation) that a particular "dose" of ultrasonic burst will produce. This proved to be very accurate in the regimen of "surgical" or "therapeutic" US. Its extension to diagnostic US was not feasible at MIT because the basic principles had already been examined and, thus, the topic was not challenging enough even for an M.S. or Ph.D. thesis at MIT. The data they generated kept on emphasizing the importance of thermal mechanisms and led to the formal enunciation of the "thermal hypothesis" at the Workshop on "Interaction of Ultrasound and Biological Tissue" held at Battelle Seattle Research Center in 1971 (Lele and Pierce 1972a, 1972b). It is now widely accepted by bioacousticians that thermal mechanisms are important in tissue modification by US.

Heat generation, it turns out, is such an important component of the effects of ultrasonic wave propagation in organized tissues (that is, tissues in which the constituent cells are tethered, and not mobile as in blood) that it was the first mechanism I examined to determine if it was responsible for the production of teratological effects described by Shimizu and Shoji (1973) in fetal mice insonated by diagnostic transducers. Fetal hyperthermia, occurring at a specific gestational stage, can cause teratological effects, and it was found that insonation, as in the Shimizu and Shoji experiments, could, in fact, have caused fetal hyperthermia (Lele et al. 1973; Lele 1975a). It is, indeed, gratifying that the recommendations now proposed for safe use of US in diagnosis and management of pregnancy are based to a considerable extent on considerations of ultrasonic hyperthermic teratology. Furthermore, the analytical and modeling studies by Robinson (1968) and by Robinson and Lele (1972) for prediction of ultrasonically-induced damage at high intensities have been very astutely adapted by Nyborg for calculation of threshold intensities for damage by diagnostic US.

The recognition of heat generation as one of the most important bioeffects of US also has had a salutary effect in the field of therapy, particularly in cancer therapy by localized hyperthermia of tumors. Fortunately, I was successful in having an NIH research grant (CA 16111)—a very modest one to be sure—awarded through peer review in 1974 to demonstrate the feasibility of using focused US for localized heating of deep tumors. This award was noteworthy because it was made in spite of the fact that a Blue Ribbon Panel appointed by Frederick W. George (then chief of the radiotherapy branch of Division of Cancer Treatment of the National Cancer Institute) had just concluded that "ultrasound has no place in hyperthermia." Since the first publication of the results in 1975 (Lele 1975b), the basic concepts have been amply vindicated in clinical trials in over 300 patients, by their acceptance by hyperthermia physics community, and by duplication of the system by several research groups and the industry.

During the period that Tom Robinson, Bill Hsu and others in my laboratory were busy testing the thermal hypothesis, others, including Senapati (1973), Matison, Namery, Mecca and I started to look into cavitation, scattering, frequency-dependent absorption, acoustical

streaming, bubble resonance, etc. Many graduate and undergraduate students contributed to these studies. It was a very active period in my laboratory and the pace was so hectic that most of the data and analyses have been published only as theses, although in one paper (Lele 1987), summarizing the results, the references to the original theses are given. To the best of our knowledge, the phenomena of cavitation and heat generation in organized mammalian tissues *in vivo* had not been studied so intensively or extensively by any other group in the intervening 20 y! The results of the cavitation studies were rather interesting. Bubble oscillation was found to contribute a little to temperature rise, but not to tissue destruction. Bubble collapse not only led to tissue fragmentation, but also to significant temperature rise that, in turn, lowered the cavitation threshold. The earlier studies on scattering were recently continued and completed by Sleefe and Lele (1988). Bubble resonance and acoustic streaming were not found to affect nerve conduction in mammalian nerves (Lele 1977).

One of the very exciting findings during this hectic phase of our activities was in the field of tissue characterization. We found that the slope of a plot of attenuation vs. frequency for any tissue varied with the state of its viability and proposed to utilize it for detection and mapping of myocardial infarction by focused US (Lele and Namery 1972a, b; 1974). It is gratifying that the validity of this phenomenon is amply confirmed by many investigators who are using it for tissue characterization of organs that do not move about as rapidly as the heart. For its successful application to detection of myocardial infarcts, faster and cheaper data-acquisition systems and more visionary and less petty leadership at the Heart and Lung Institute than were available in the late 1970s, are essential.

In the light of the excitement of the work and the fruitful and pleasant interaction with scores of students and colleagues—undergraduate, graduate, postdoctoral and faculty—that I had the good fortune to have, I do not in the slightest regret that my hobby kept me from pursuing my business, except as it directly applied to my research!

FREDERIC L. LIZZI: ULTRASONIC BIOLOGICAL EFFECTS IN OPHTHALMOLOGY

My involvement in ultrasonic bioeffects research started in the late 1960s, when I (Fig. 19) was a graduate student at Columbia University (CU) and had a position at the CU Electronic Research Laboratories, which is now Riverside Research Institute. D. Jackson Coleman was a resident in Ophthalmology at the CU College of Physicians and Surgeons, and we embarked on collaborative bioeffects research that has continued to the present.

Fig. 19. Frederic L. Lizzi.

The 1960s were a very active time in ophthalmic US bioeffects research. Zeiss had earlier demonstrated ultrasonic cataract production (in 1938!), and Baum, Purnell, and Sokollu had established early results for both ocular damage and potential therapeutic applications. Coleman was working with Ben Carlin to liquefy the vitreous body ultrasonically and, thereby, promote the dispersion of vitreous hemorrhages. Donn had previously shown that the vitreous body, normally in a gel-like state, could be liquefied if an air bubble was introduced into the vitreous prior to insonification; unfortunately, this technique also produced opaque vitreous strands, so that the technique was impractical. Coleman's hypothesis was that, using higher intensities with sharper focussing would obviate the need for the bubble and, therefore, not result in vitreous opacities.

My first bioeffects task was to modify a power amplifier that had been carefully designed to function above 50 MHz, so that it would function at 1 MHz. The power amplifier was the size of a small closet, and it used light-house power tubes with air cooling through "chimneys." We would receive shipments of bovine and porcine eyes from a New Jersey slaughterhouse, and inject them with radioopaque dyes to simulate vitreous hemorrhages. We would then insonify the eyes, put them in plastic containers and take a taxi to the radiology department to determine whether dispersion had been induced (Coleman et al. 1969). Control eyes served to verify that dispersion was not induced by the cab ride through Manhattan. We also used Schlieren observations to determine how therapy beams were affected by ultrasonic refraction and absorption in ocular media (Lizzi et al. 1970).

These early experiments helped us to redesign transducers, power amplifiers and experimental procedures. We then were able to address more systematically

a number of topics related to safety in ophthalmic US. Concern was being expressed that the eye might be at particular risk because of the high diagnostic center frequencies (10 MHz), the high absorption coefficient of the lens and its lack of blood flow cooling. Purnell and Sokollu had performed pioneering research, defining a cataract production unit (CPU) as the intensity level needed for cataractogenesis near 4 MHz. We were able to produce cataracts in rabbit lenses at 10 MHz, and to show how their sizes and shapes were consistent with a thermal mechanism (Lizzi et al. 1978c). We also produced the first threshold curves (Lizzi et al. 1978a) for chorioretinal lesions, showing how these curves resembled those for laser exposures and for the thermal computations of Carstensen and Dunn. At sufficient intensity levels, chorioretinal exposures produced a transient blanching of the choroid, due to local blood-vessel compression, as reported by Purnell and Sokollu. We found that the thresholds for chorioretinal lesions could be lowered by using pulsed exposures at a low pulse-repetition rate (near 1 Hz); this lowering seemed to be due to repeated vascular blanching, which reduced average blood-flow cooling (Lizzi et al. 1978b). All of these data showed that damage levels were far above diagnostic exposure levels, and our attention shifted towards therapeutic applications, an area we are still exploring.

Over the next years, we conducted a series of animal experiments treating a rather broad scope of simulated ocular disorders (Lizzi et al. 1985). We showed how intravitreous blood could be dispersed by induced hemolysis and mechanical agitation; how vitreous membranes could be disrupted by pulsed mechanical forces; how torn lens capsules could be "sealed" to prevent total cataract formation; how chorioretinal lesions could be used in retinal detachment procedures; and how cataracts can be made to develop through the entire lens (with the goal of denaturing lens proteins that can trigger severe immune responses, complicating simple ocular procedures). We also studied ultrasonically facilitated infusion of pharmacological agents. Most attention was given to glaucoma treatments and to tumor therapy.

Our glaucoma treatments in animals (Lizzi et al. 1984) led to the design of a clinical system for use in our NIH research programs. We designed a therapy transducer with a central diagnostic positioning transducer and an axial aiming light to visualize beam positioning. The therapy beam was focused in the sclera and underlying ciliary body to produce well-defined lesions that had several effects. A focal lesion in the ciliary body suppressed the production of excess aqueous humor and also tended to open "potential" internal drainage pathways. In addition, rabbit experiments showed that alterations in the overlying sclera allowed excess aqueous humor to flow out of the globe under the conjunctiva, which remained intact. After successful animal experiments and initial clinical trials, a license was granted to Sonocare, Inc. for the development of a commercial version of this technique. Extensive clinical trials (Silverman et al. 1991) were conducted at 20 sites, and demonstrated that the ultrasonic procedure could lower intraocular pressure to acceptable levels in refractory glaucoma cases that had not been successfully managed with drugs, laser procedures and/or surgical filtering techniques. The U.S. Food and Drug Administration (FDA) issued the required premarket approval, permitting this system to be distributed for refractory glaucoma therapy. We have recently been able to image the small lesioned areas produced with these exposures, by using diagnostic US with center frequencies at or above 40 MHz (Lizzi 1993).

We have also concentrated on ultrasonic treatment of ocular tumors (Silverman et al. 1986). Our animal experiments have employed human tumor explants (usually of melanomas) growing subcutaneously in the thighs of nude athymic mice. When these tumors grow to a size commensurate with human ocular tumors, we treat them using a focused beam region (to study ablation) or the distal diverging region of a focused beam (to study hyperthermia). After initial successful animal results, we have applied hyperthermia clinically to treat choroidal malignant melanoma. Several types of studies are proceeding. Hyperthermia combined with radiotherapy is being applied to test the synergy between these modalities for arresting and retarding tumor growth. Hyperthermia is also being applied in melanoma patients scheduled for enucleation (surgical removal of the eye) to determine if such treatment can "sterilize" these tumors and reduce the rate of metastases associated with surgery. Our spectrum analysis procedures for diagnostic US have helped in these procedures by providing cross-section images that delineate tumor regions where effective scatterer sizes, concentrations and acoustic impedance characteristics have been altered by therapy.

To support the preceding clinical applications, we have developed a theoretical model of ultrasonically-induced temperature in thin tissue layers (*e.g.*, sclera and chorioretinal complex) and thick tissues (*e.g.*, tumors). The model can use tissue geometry derived from B-mode data, and can be used to study either ablation or hyperthermia (Lizzi et al. 1992). Temperature rises are computed as functions of time and space, and lesioned areas are predicted using a damage integral formulation. This model is being expanded to help guide research into other applications and to improve the design of therapy beams and exposure parameters.

Over the course of our research, many laboratories have contributed substantially to progress in understanding ultrasonic bioeffects. However, much still remains to

be done. The issue of safety requires constant vigilance. The goals of higher resolution, deeper penetration and more detailed flow information frequently motivate the use of diagnostic techniques with elevated exposure levels, and quantitative bases for evaluating continued safety are needed to permit the confident use of important new techniques. Currently, the emergence of very high frequencies for ocular, intravascular and dermatological examinations should motivate new bioeffects studies. Therapeutic applications have progressed significantly, but still have not reached their full potential. Here, needs exist for better mathematical modeling and more accurate data regarding tissue properties and their temperature dependencies. Aiming and monitoring facilities also require improvement if these techniques are to find practical clinical applications.

Acknowledgements—Coleman and I have been especially fortunate in being able to collaborate with a large number of very talented and resourceful researchers over the course of our investigations. Many of our colleagues are listed in the referenced articles; special mention should be made of the contributions of Ronald Silverman, Jack Driller, Mark Rondeau, Michael Ostromogilsky and Angel Rosado. The author also wishes to acknowledge the support of our research by the National Eye Institute.

KAZUO MAEDA: PERSONAL HISTORY

My graduation from Kyushu University Medical School was in 1947, 2 y after the end of World War II. My (Fig. 20) medical training in OB/GYN was at Kyushu University Hospital. Early work included taking electroencephalograms (EEGs) of pregnant patients, newborn respiration recording, fetal life detection with fetal ECG using maternal abdominal cutaneous leads, fetal phonocardiography with self-made devices, and fetal heart rate (FHR) recording. Ultrasound was introduced into my practice in 1967. The ultrasonic Doppler fetal heart-beat detection was done with a Doptone machine supplied by Smith-Kline. We were excited by its high performance in detecting fetal heart beats in an early stage of pregnancy. The machine was used in clinical practice and fetal heart signal analysis (Maeda 1977; Maeda and Nakano 1968); its electrical output frequency was demodulated for recording the fetal blood flow wave in 1969 (Maeda and Kimura 1969). This report was in the frontier of work on the ultrasonic Doppler fetal blood flow wave. Doppler fetal detection spread quickly; soon, almost 100% of obstetricians utilized the device. Objective and quantified fetal examination brought about a revolution in obstetrics. I moved to Tottori University as the chairman of its OB/GYN Department in 1968.

Initial alarm followed by the bioeffect group study

We were, however, alarmed by reports on the development of fetal animal anomalies in specially inbred DHS, A/He pregnant mice exposed to weak diagnostic level US for several h by Shimizu, Shoji and others around 1970 (Shimizu et al. 1970; Shoji et al. 1975). Many sensational topics were reported in the newspapers, warning of possible fetal anomalies produced by the ultrasonic fetal heart beat detector. The Committee on Biomedical Engineering of the Japan Society of Obstetrics and Gynecology, of which I was chairman, discussed the issue and made plans for establishing reasonable strategy for the future use of US in obstetrics. Proceeding to investigate ultrasonic bioeffects ourselves, we formed a study group of obstetricians to serve as investigators with the support of M. Ide of Musashi Institute of Technology, and obtained a grant from the Ministry of Health and Welfare.

Fig. 20. Kazuo Maeda.

We studied effects of US on chromosomes, cultured cells, fertilized ova and fetal animals, by exposing them to intense CW US produced by a standard US generator. The frequency was 1, 2 or 4 MHz, and the spatial average temporal average (SATA) intensity was about 3 W/cm^2 at 2 MHz. In the studies from 1972 to 1976, no abnormalities were observed in the chromosomes and fertilized ova after exposure in a cooled condition. The threshold for production of fetal anomalies in mice was 1 W/cm^2. These findings were consistent with those of epidemiology, which had revealed no increase of neonatal anomalies after the introduction of US diagnosis (Maeda et al. 1986).

Together with the OB/GYN group at Tottori University, I studied the growth curves of cultured JTC-3 cells exposed *in vitro* to US in water at 37°C. There was no change of the cells suspended in culture medium made of calf serum after exposure in a polystyrene tube

to CW US of maximum intensity. When the medium was changed to serum-free phosphate-buffered solution and the tube was rotated for 2.5 rpm, we found suppression of cell growth curves after exposure to CW US if the spatial average intensity was 2.6 W/cm^2, but not if it was 0.8 W/cm^2. We reported that a spatial average intensity of 1 W/cm^2 would be the critical level for producing cell damage by exposure to CW US (Maeda et al. 1986).

These results were reported in the symposium "Researches on the Ultrasound Bioeffect" of the 30th Conference of Japan Society of Ultrasound in Medicine (JSUM) organized by me in 1976. The safety of common diagnostic US devices was supported by the reports. Pulsed-Doppler flowmetry had not been used in the study of fetal circulation.

Our study group also investigated biological effects of pulsed US in 1977–1979. A pulsed-US generator, USP-1, was generally used during this period. Experiments were done using these conditions: frequency 2 MHz; pulse duration 3, 5 or 10 μs; repetition frequency 250, 500 or 1000 Hz; spatial average temporal peak (SATP) intensity 50–60 W/cm^2; and spatial average temporal average (SATA) intensity 0.5–0.6 W/cm^2. Under these conditions, no change was seen in the chromosomes or red blood cells. No change was seen in the cultured cells after exposure at intensities less than critical intensities SATP 20 W/cm^2 and spatial peak temporal average (SPTA) 240 mW/cm^2. The threshold SATA intensity level for production of abnormalities and developmental retardation after 720-min exposures of preimplantation embryos was 2.6 W/cm^2. The number of fetal anomalies was increased by 5-min exposures to 0.5 μs pulses at a 1-kHz repetition frequency and an SPTA intensity of 1.2 W/cm^2 (Maeda et al. 1981). It was stated by the JSUM that an SATA intensity of 1 W/cm^2 for CW US and an SPTA intensity of 240 mW/cm^2 for pulsed US were critical levels for production of bioeffects. An SATA intensity of 10 mW/cm^2 was chosen by the Japan Industrial Standard (JIS) as the safety limit for ultrasonic Doppler fetal detectors, B-mode equipment and electronic linear scanners (Maeda and Ide 1986).

The safety state of diagnostic devices has been changed, however, after the introduction of pulsed Doppler flowmetry in obstetrics. We reported the results in the second WFUMB Congress in Miyazaki (Maeda 1979), a WHO task group (WHO 1982) and in WFUMB US safety symposia since 1985 (Barnett et al. 1994). The thermal effect was initially discussed. Nonthermal effects were considered in WFUMB symposia held in Japan in 1994 and in Germany in 1996 (WFUMB 1998a).

Flow cytometric studies at Tottorri University on bioeffects

In Tottori University, the investigation of effects on cultured cells was extended to HeLa cell cycle change detected by flow cytometry (FCM). A clear peak of the HeLa cell distribution appeared at S phase after 15-min exposures to 10-μs pulses of 2-MHz US at an SATP intensity of 58.6 W/cm^2; the peak was small after the exposure to 5-μs pulses of the same peak intensity, and did not appear after exposure to 10-μs pulses at an SATP intensity of 20 W/cm^2. The importance of pulse length was suggested (Maeda and Kigawa 1986). It was also found that there was no change of HeLa cell cycle after exposures to 2-MHz US at an intensity of 14 W/cm^2 SATP delivered in 3-μs pulses, but that the cell DNA distribution in $G_0 + G_1$ phase was significantly decreased when the pulse duration was 10 μs (Maeda et al. 1988). Both FCM studies showed changes of cell DNA distribution after *in vitro* exposure of HeLa cells to experimental US with longer pulse duration.

Ultrasound safety in obstetric practice

Obstetrical US application has been limited by the state of knowledge on US safety. Although US autocorrelation fetal monitoring is indispensable in modern obstetrics, its use was allowed generally only after the confirmation of US safety by our group study. The ultrasound SATA intensity of fetal monitors is limited to be less than 10 mW/cm^2 in JIS T no. 1303 standard in 1994. Fetal morphology has been studied by real-time sonography in our routine work (Maeda 1989). Our recent interest lies on the antepartum fetal brain damage (Maeda et al. 1992), clinical tissue characterization by using ultrasonic grey-level histogram width (Maeda 1992), ultrasonic fetal actocardiogram, the chart record of fetal movement and FHR (Maeda 1984), fetal systolic time interval (STI) recorded by ultrasonic fetal heart valve signals (Maeda et al. 1981b), etc. In these works, US safety was guaranteed at the level of device production, because of the intensity limitation of real-time sonography in JIS. However, in fetal blood flowmetry at present, the user is requested to be prudent in the use of pulsed Doppler. Because the physical bases of US bioeffects have been studied, I may request ultrasonic engineers and manufacturers to supply us totally safe devices that need no concern in fetal use in the future.

I moved to Seirei Hospitals in 1990. Since then, the progress of US has been marvellous, as seen in the Fifth World Congress of Ultrasound in Obstetrics and Gynecology that was organized by us in Kyoto, Japan in November, 1995. I am still working on various subjects in fetal study with use of US, particularly in the analysis of ultrasonic grey-scale histograms of fetal organs and of the placenta (Maeda et al. 1998, 1999).

Fig. 21. Morton W. Miller.

MORTON W. MILLER: ULTRASOUND?

During the autumn semester of 1970, a first-year graduate student, Winborn Gregory, came to my office and indicated that he would like to work in my laboratory on a research project. Winborn was one of about 30 new students who had been admitted into the University of Rochester's graduate degree program in radiation biology, in what was then the Department of Radiation Biology and Biophysics. At that time, I (Fig. 21) being a botanist by training, was engaged in research projects using plant systems to study the mechanism(s) by which biological systems repair ionizing radiation-induced damage. Fortunately (I now write), there was an immediate problem with Winborn, in that he did not want to do any research with X rays nor with ultraviolet light. He wanted "to do something different," and he wanted to work with a plant system (which was in my favor because I was about the only botanist in the entire university). "How about chemical mutagens?" I asked. "No," was his reply. "Environmental pollutants?" "No." Eventually, Winborn departed my office without having defined "something different."

About 2 months passed before I had the pleasure of seeing Winborn again at my office. He had been busy with course work (as are all first-year students) and had also been busy reviewing various brochures prepared by other departments to lure graduate students to apply for admission into one of the many university-wide graduate degree programs. He had spent a considerable amount of time "scouting" various faculty in departments such as chemistry, electrical engineering and mechanical engineering. He told me he had settled on a research topic and hoped that I would be available to help him. I was initially noncommittal, for he had still not specified the nature of the project. I told Winborn I was interested, but needed to know more about his intended research project. It was then that he mentioned he had been talking with Edwin Carstensen of the Department of Electrical Engineering, and that Winborn was certain he wanted to do something with plant roots and ultrasound. "Ultrasound?" I asked, almost incredulously. "Yes, ultrasound," replied Winborn.

Winborn was very enthusiastic about the project and indicated it would be a great "marriage" between the biological and physical sciences. I was to provide guidance in the area of root biology, and Carstensen was to provide guidance in the area of US physics. . . . and that is exactly how my involvement in US bioeffects research began. Winborn's project resulted in the first of many papers on the topic of US bioeffects and mechanisms of action (Gregory et al. 1974).

I look back on my encounter with Winborn as representing an expanding, inverted pyramid, with an ever-increasing number and variety of projects continuously being added to the top and Winborn's project at its foundation. From it grew a large, long-term and wonderfully interesting research program, through which I have enjoyed long-term collaboration with a rich array of intelligent and highly-motivated scientists. Of course, my long-term association with Edwin L. Carstensen of our University's Department of Electrical Engineering is a matter of public record. Ed and I have coauthored 45 peer-reviewed papers (Child et al. 1975, 1989; Brayman et al. 1995). Also, part of this public record is the continuous long-term grant support from NIH (CA-392230) for my research in this area, my long-standing participation in NCRP Committee no. 66 on US, chaired by Wesley Nyborg (NCRP 1983, 1992), and my efforts with the AIUM Bioeffects Committee (AIUM 1991). And all the "blame" for this wonderful experience rests squarely on Winborn Gregory, a former graduate student who, for a research project in 1970, wanted to do "something different."

In complement to and elaboration of Winborn's project, the laboratory initially focused on additional projects dealing with various aspects of US-induced effects on plant root growth, physiology, macromolecular syntheses (DNA, RNA and protein syntheses), cell cycle kinetics and cytogenetics, with special interest in the induction of chromosomal agglomerations (for want of a better term) (Cataldo et al. 1976). The scope of the project was then expanded to include mammalian cells *in vitro* because they allowed for better control of environmental and biological parameters, and also were closer to the "cells of interest" (Kaufman and Miller 1978). Hugh Flynn, a noted authority on acoustic cavitation, began participating in the project and assisting my graduate

students. We began to explore in more depth the mechanism(s) by which US affected cells, with special emphasis on the interactions of acoustically-activated bubbles (Ciaravino et al. 1981). Additionally, theoretical analyses probing bubble dynamics in relation to acoustic pressures and frequencies were undertaken. Charles Church, now also a recognized authority in acoustic cavitation, was one of those students interacting with Hugh and, from these interdisciplinary efforts, we began to gain information on how the sound was affecting bubbles that, in turn, were affecting cells (Flynn and Church 1988). There was, and still is, much focus on bubbles and, in addition to Carstensen's laboratory, there was developing rather spontaneously throughout the University, a large amount of research concerned with many aspects of biomedical US. A Rochester Center for Biomedical Ultrasound at the University of Rochester, with Carstensen as its founder and Director was organized in 1986. Things were really rolling; it was a rich, growing and varied environment.

In addition to pursuing our own specific areas of research, we were very intrigued by reports of low-level US field bioeffects on a number of different types of organisms. For example, there emerged from other laboratories a number of reports that US induced sister chromatid exchanges (SCEs); thus, suggesting potential cytogenetic effectiveness of clinical exposures. We attempted to replicate independently nearly all of these reports, but were never successful and, to this day, remain perplexed at the disparate results (Miller 1985). Lack of independent verification of positive results has a tendency to cast doubt on the veracity of the initial observation, but I am not sure this is a correct conclusion (*e.g.*, it is possible, given the episodic nature of acoustic cavitation, that our experimental conditions did not support it and, thus, no effect was induced). There is much newer information that, even for samples identically prepared and comparably insonated, the results from bubble-cell interactions can be "all or nothing" or, as Ed Carstensen noted, "something or nothing."

Initially, when we began our US studies, there was, and still is, much speculation as to whether or not the human body contained gas nuclei, an essential "ingredient" for acoustic cavitation. Additionally, the outputs of diagnostic US devices were relatively "low" compared to what they are today. With the development and use of microbubble pulse-echo contrast for certain diagnostic US procedures, it is clear that now that sometimes certain areas of the body exposed to diagnostic US are also deliberately and extensively gas-nucleated areas. We, thus, began to explore the relationship between the presence of a microbubble pulse-echo contrast agent and the induction of US-induced hemolysis of human red blood cells *in vitro*. It was very evident that hemolysis was always greatest when the microbubbles were present during insonation (Miller et al. 1995). However much remains to be learned, it is evident that we have "come a long way" and the road ahead looks wonderfully intriguing. The only regret I have is that it is apparent that one career is not sufficient to travel the entire road. There is still much to do, and much to learn.

WESLEY L. NYBORG: ULTRASONIC OBSESSIONS

My fascination with the wonders of US began during my graduate studies at Pennsylvania State University during the 1940s. In the course of thesis research under W. H. Pielemeier and H. K. Schilling, my reading included publications by Wood and Loomis (1927) and Harvey et al. (1928), in which it was shown that US could do such things as kill bacteria, clean or erode metals, produce new chemical species and generate light. It was not very clear how this was possible, although bubbles were known to be important. I (Fig. 22) was possessed by an obsession to understand, and still am.

An opportunity to be involved with this kind of subject came in the late 1940s when, as a junior faculty member, I was given responsibility for physics participation in an Air-Force–sponsored study of possible hazards to personnel required to work in the vicinity of jet aircraft, where the sound levels can be very high. The physics group was to design and test suitable arrangements for studying effects of high-amplitude sound on bacteria, protozoa and other living things. In doing this, some earlier experience was influential in a rather odd way. In the mid 1940s, I was part of a research effort in which my special task was to develop air-driven ultrasonic whistles. Measurements showed that the acoustic

Fig. 22. Wesley L. Nyborg.

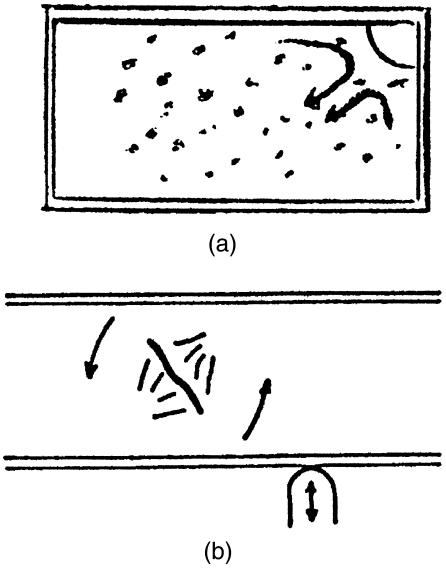

Fig. 23. (a) Small-scale acoustic streaming (microstreaming) near a vibrating gas body; (b) schematic of the whirling of an incipient cell wall observed by Dyer (1965) in his studies of inherited changes in moss protonema.

pressure levels developed at the closed end of an operating whistle were about 1000 Pa or more, about right for simulating levels near jet aircraft. It was, therefore, decided to see how protozoa would be affected by subjecting them to the sound field in a suitable compartment within a whistle made of clear plastic, so that observations could be made with a low-power microscope during the sonic exposure. It was soon found that positive results were obtained when there was considerable motion in the exposure compartment, and that this motion occurred when gas bubbles were present in the compartment after a cell suspension had been introduced. In its simplest form, the fluid movement appeared as a symmetrical eddying pattern based on the bubble, as indicated in a sketch in Fig. 23a. This was my first introduction to bubble-associated acoustic microstreaming, as it came to be called.

During the 1950s, I continued this interest at Brown University, with the help of students and colleagues, including Peter Westervelt, an authority on nonlinear acoustics, and Josef Kolb, a visiting professor from the University of Innsbruch (Kolb and Nyborg 1956). Samuel Elder made a thorough and definitive study of "cavitation microstreaming" in the course of Ph.D. research (Elder 1956, 1959). Francis Jackson and Robert Gould investigated microstreaming under various conditions in their Ph.D. researches, and demonstrated its potential for accelerating the transport of mass and heat (Jackson 1960; Jackson and Nyborg 1958; Gould 1961, 1966). Hubert Dyer, a colleague versed in plant physiology, became interested in the subject, and we investigated microstreaming induced in a plant cell by vibrating a portion of its wall (Dyer and Nyborg 1960; Dunn and O'Brien 1976). He later showed that, by vibrating a portion of moss protonema wall near a site where cell division was about to occur, the mitotic apparatus was set into rotation (Fig. 23). When the vibration stopped, the division often proceeded abnormally, producing daughter cells with altered characteristics, which were propagated for many generations (Dyer 1965, 1972).

The first application of bubble-associated microstreaming to microorganisms was made during a collaboration with David Hughes, who invited me to join him at Oxford University in 1960–1961. He and Ernest Neppiras had devised and used the "dipping probe" method, now widely used for applying US to cell suspensions. The interest then was in finding a way of releasing enzymes from bacteria with minimum damage from the free radicals that are produced by "collapse" (now called inertial) cavitation. We found that, if very small holes were drilled in the end of the dipping probe, and if the amplitude was kept very low, cell disintegration could be produced in the absence of free radical damage, evidently because of the microstreaming associated with the air-filled holes at the end of the probe (Hughes and Nyborg 1962). Pritchard and coworkers, also at Oxford, later used a similar method to study the reduction in molecular weight of DNA in solution produced by viscous stresses associated with the microstreaming (Pritchard et al. 1966).

At the University of Vermont (UVM), from 1960 until retirement in 1986, my research activities, sponsored by the National Institutes of Health, included investigations of microstreaming applied to plant and animal cells and tissues. Some of the experiments were done at the Woods Hole Marine Biological Laboratory with marine eggs and single muscle cells, done in collaboration with physiologists Walter Wilson, Ferdinand Sichel and Floyd Wierczinski; a key individual was Ronald Schnitzler, then a graduate student. Using an 85-kHz Mason horn with a very small rounded tip, and a micromanipulator, it was found that localized vibration of the surface of a normal immature egg of the starfish *Asterias* caused orbiting of the nucleolus within the large nucleus, and also caused fragmentation of the nucleolus, which was reversible if conditions were not too severe (Wilson et al. 1966). In fertilized eggs of the sea urchin *Arbacia punctulata*, similar localized vibration of the surface caused rotation of the mitotic spindle, with consequent delay in cell division (analogous to the observations of Dyer with moss protenema (Wilson and Schnitzler 1963). Also, when localized vibration was applied to single fibers from frog sartorius muscle, movements of the sarcoplasm were produced in the immediate vicinity

of the vibrated area, when calcium was present in the bathing saline (Wilson et al. 1964). This observation was followed by extended studies in Schnitzler's doctoral research (Schnitzler 1969) and in a collaboration between Ravitz and Schnitzler (1970).

Quantitative understanding of the significance of bubble-associated microstreaming for suspensions of biological cells was advanced by James Rooney's doctoral thesis on hemolysis produced by a single stable bubble vibrating at a frequency of 20 kHz (Rooney 1970a, 1970b). This was followed quickly with a demonstration by Alun Roy Williams and others (Williams et al. 1970) that (as expected from acoustical theory) similar microstreaming, with similar biological significance, is produced at the tip of a vibrating wire whose tip curvature equals that of the corresponding bubble. A series of publications followed, by Rooney, Williams and others, on microstreaming studies; these are reviewed in Williams' book (Williams 1983).

For analogous studies of bioeffect-mechanisms at the higher frequencies typical of medical applications, a microscope facility, constructed and employed at UVM by Douglas Miller in his doctoral research (Miller 1976), proved very useful. Like an arrangement developed earlier by Harvey and coworkers (Harvey et al. 1928), it allowed visual observation and photorecording of events produced during exposure to US in the megahertz frequency range. Research was done with plants with the aid of Alexander Gershoy, Professor of Botany at UVM, who joined us for many years after his retirement. In many plant leaves, roots, stems and other tissues, most of the interior of a typical cell is a liquid-filled vacuole and the intercellular space contains gas bodies. A typical finding was that, under US, eddying motions typical of acoustic microstreaming occurred readily in the vacuoles, especially those near intercellular gas bodies. Motions were slow at low amplitudes of the US, but became vigorous enough to cause damage at the higher amplitudes. The same microscope facility was used for studying acoustic microstreaming in cell suspensions near gas-filled pores of hydrophilic Nuclepore^{R} membrane, the pores being only a few micrometers in diameter.

In other studies, microstreaming has also been observed in living animals, specifically, in blood vessels: 1. near cartilaginous rods of fish tails during exposure to US, 2. near a region where a small rod had deliberately been pressed against the blood-vessel wall of mouse mesentery during exposure to US; and 3. near a portion of mesentery locally vibrated with an 85-kHz Mason horn. I shall not attempt to discuss here these and numerous other publications that have appeared in recent years, in which microstreaming is observed or assumed to occur and, instead, refer the reader to thorough reviews of the subject by Miller (Miller 1983, 1987). Suffice it to say that this subject is still on my list of obsessions.

MARVIN C. ZISKIN: PERSONAL HISTORY

I (Fig. 24) have been actively involved in US research for the past 35 y. In 1965, as a Research Associate in diagnostic US at Hahnemann Medical College in Philadelphia, I pioneered in the establishment of 2-D ultrasonography as a valuable diagnostic modality. In September, 1965, my laboratory was featured on the cover of Life magazine. The illustration was that of a pregnant wife of a medical student being examined ultrasonically, with the fetal head showing on an oscilloscopic screen. This was such a new dramatic development that it was deemed worthy of front-page coverage. Also, at that time, using a combined radiographic and through-transmission ultrasonic technique, I established the nature of an echo source giving rise to false-positive results in the ultrasonic diagnosis of pericardial effusion (Evans et al. 1967; Ziskin 1968; Ziskin et al. 1968).

In 1968, I joined the faculty of Temple University, where I have continued US research ever since. My early study there involved investigation of physiological meaningfulness of the Doppler signal. I developed a procedure for the detection of carotid arteries stenosis using Doppler ultrasound (Ziskin 1969), and was the first to use US to detect the cavitation that occurs at catheter tips during rapid IV injections (Bove et al. 1969).

While performing blood flow studies in dogs, I noted a dramatic amplification of Doppler signal several seconds following IV injections of fluids at distant sites. This led to the study of cavitation developed at catheter

Fig. 24. Marvin C. Ziskin.

tips and, ultimately, to the development of contrast agents for clinical diagnostic ultrasonography (Ziskin et al. 1972).

Because of concern about the safety of clinical US, I conducted an international survey of clinical users in 1971. The next year, I reported that no adverse effects attributed to examination by US had been identified by any of 68 respondents to the survey in over 121,000 patient examinations. The report represented a combined total of 292 institute-years of experience in the clinical use of diagnostic US (Ziskin 1972).

In 1973, I investigated the safety of ophthalmological ultrasonography using New Zealand rabbits. In this study, 33.7 mW cm^{-2} continuous-wave US was directed to the left eye for durations of 1 h and 4 h. The right retina served as a control. No damage was observed from any of the exposures, as determined by meticulous microscopic examination by an ophthalmologic pathologist (Ziskin et al. 1974).

In 1977, I was a visiting scientist for 6 months at the Acoustics Laboratory in Sydney, Australia. There, working with M. J. Edwards at the University of Sydney, I exposed pregnant guinea pigs on the 21st day of gestation to 1 MHz continuous-wave US at intensities ranging from 50 to 1100 mW cm^{-2} for a period of 1 h. Internal body temperature was monitored with a thermocouple inserted into the rectum to the level of the uterus. Results showed a reduction in the brain:body weight ratio between control animals and those in which the internal temperature rose greater than 1°C; thus, reaffirming that reduction in brain weight of the newborn is the most sensitive indicator of biological damage known to result from gestational hyperthermia. Furthermore, I showed that the temperature elevation achieved internally was the most appropriate measure of the exposure dosage because intestinal gas situated between the pregnant uterus and the skin altered ultrasonic transmission to the uterus in an unpredictable way.

From February 1979 to January 1982, I was a coinvestigator with Wesley L. Nyborg of the University of Vermont on an NIH grant entitled "Low intensity ultrasonic effects in mammalian tissue." Douglas Miller was also a coinvestigator on this grant. By subjecting various intact animals to slow pressurization and rapid decompression, we were able to conclude that microbubbles (approximately 1 μm in diameter) exist within mammalian tissue, probably in small crevices between cells. We demonstrated several blood flow disturbances when bubbles in the blood were of "resonance size" to the pulse-repetition frequency of the insonating beam. Also, during this time, multicellular tumor spheroids were developed as an experimental model to test the ability of a US beam to dislodge cells from a tumor and induce metastasis. We showed that this would not occur if the SPTA intensity was less than 1 W cm^{-2} (Conger and Ziskin 1981, 1983; Conger et al. 1981).

For a number of years, I studied the effects of image display format on diagnostic accuracy, and on the creation of US display artefacts (Thickman et al. 1983a). I described and named the "comet tail artefact," a reverberant type echo complex found distal to a highly reflective structure (Ziskin et al. 1982). The term "comet tail echo" has caught on and has become a frequently used term in the vocabulary of ultrasonographers (Thickman et al. 1983b).

While working on an NIH grant entitled "Ultrasonic bioeffects on mammalian development" from 1987 to 1991, I reviewed the pertinent literature on the biological consequences of hyperthermia, with special interest in effects on the fetus. A rather large assemblage of fetal abnormalities were gathered, and I used this database to develop a relationship between temperature elevation and exposure duration. This relationship has proven valuable in developing guidelines for the safe use of US in diagnostic US (Miller and Ziskin 1989).

I have been a member of the AIUM Bioeffects Committee since its inception in 1973, and a member of the National Council on Radiation Protection and Measurements, Committee no. 66, under the chairmanship of Wesley L. Nyborg, ever since its inception in 1980. I have been Chairman of the WFUMB Committee on Ultrasound Safety since 1985 and, in this capacity, have organized a number of international symposia on US bioeffects and clinical safety. In 1982–1984, I served as President of AIUM and in June 2000 was elected President Elect of WFUMB, to assume the presidency in 2003.

As Chairman of the AIUM Ultrasound Terminology Subcommittee, I played an important role in developing the AIUM publication entitled, "Recommended ultrasound terminology" (AIUM 1997); it is already in its second edition. As a member of the AIUM Technical Standards Committee, I developed a statistical method of expressing uncertainty in the measurement of the outputs of ultrasonic instruments (Ziskin 1993). I take an active part as an American delegate to the International Electrotechnical Commission, in which I am the project leader on ultrasound terminology, and have been the Chairman of the Working Group on biophysical effects of ultrasound.

As of this date, I have been the author or coauthor of over 200 scientific publications and a coeditor of 4 books (Goldberg et al. 1975; Wells and Ziskin 1980; Nyborg and Ziskin 1985; Ziskin and Lewin 1993).

REFERENCES

AIUM. The AIUM Standard 100 mm test object and recommended procedures for its use. Reflections 1975;1:74–91.

AIUM. AIUM standard presentation and labeling of ultrasound images. J Clin Ultrasound 1976;4:393–398 (revised 1986).
AIUM. AIUM recommended nomenclature. Reflections 1980;6:37–52.
AIUM. Safety in training and research—Official statement. Official guidelines and statements on obstetrical ultrasound. Laurel MD: American Institute of Ultrasound in Medicine, 1985a.
AIUM. Acoustical data for diagnostic ultrasound equipment. Laurel MD: American Institute of Ultrasound in Medicine, 1985b, 1987, 1993 (revised 1987, 1993).
AIUM. Evaluation of research reports: Bioeffects literature reviews (1985–1991). Bethesda, MD: American Institute of Ultrasound in Medicine, 1991.
AIUM. Standard methods for measuring performance of pulse-echo ultrasound imaging equipment. Laurel MD: American Institute of Ultrasound in Medicine, 1991.
AIUM. Recommended ultrasound terminology. 2nd ed. Laurel, MD: American Institute of Ultrasound in Medicine, 1997.
AIUM. Acoustical output labeling standard for diagnostic ultrasound equipment. Laurel MD: American Institute of Ultrasound in Medicine, 1998.
AIUM/NEMA. Publ. UL 1-1981. Washington DC: National Electrical Manufacturers Association, 1981.
AIUM/NEMA. Safety standard for diagnostic ultrasound equipment. J Ultrasound Med 1983;2/4:S1–50.
AIUM/NEMA. Acoustic output measurement and labeling standard for diagnostic ultrasound equipment. Laurel, MD: American Institute of Ultrasound in Medicine, 1992.
Angell-James J. New developments in the ultrasonic therapy of Meniere's disease. Ann Roy Coll Surg Eng 1963;33:226–244.
Angell-James J. Meniere's disease. In: Rob C, Smith R, eds. Clinical surgery. Oxford: Butterworth, 1966:109–121.
Angell-James J. Clinical aspects of the surgical treatment of Meniere's disease with ultrasound. Ultrasonics 1967;5:102–104.
Angell-James J. Meniere's disease: treatment with ultrasound. J Laryngol Otol 1969;LXXXIII:771–785.
Angell-James J, Dalton GA, Bullen MA, Freundlich HF, Hopkins JC. The ultrasonic treatment of Meniere's disease. J Laryngol Otol 1960;LXXIV:730–757.
Bacon DR, Carstensen EL. Increased heating by diagnostic ultrasound due to nonlinear propagation. J Acoust Soc Am 1990;88:26–34.
Baggs R, Penny DP, Cox C, Child SZ, Raeman CH, Dalecki D, Carstensen EL. Thresholds for ultrasonically induced lung hemorrhage in neonatal swine. Ultrasound Med Biol 1996;22:119–128.
Ballantine HT, Hueter TF, Bolt RH. On the use of ultrasound for tumor detection. J Acoust Soc Am 1954;26:581.
Ballantine HT, Hueter TF, Nauta WJH, Sosa DM. Focal destructions of nervous tissue by focused ultrasound. Biophysical factors influencing its applications. J Exp Med 1956;104:337–360.
Barnard JW, Fry WJ, Fry FJ, Krumins RF. Effects of high intensity ultrasound on the central nervous system of the cat. J Comp Neurol 1955;103:459–484.
Barnett SB. The influence of ultrasound and temperature on the cochlear microphonic response following a round window irradiation. Acta Otolaryngol 1980a;90:32–39.
Barnett SB. Structural and functional changes in the cochlea following ultrasonic irradiation. Ultrasound Med Biol 1980b;6:25–32.
Barnett SB, Kossoff G, Clark GM. Histological changes in the inner ear of sheep following a round window ultrasonic irradiation. J Otolaryngol Soc Australia 1973;3:508–512.
Barnett SB, Kossoff G. Round window ultrasonic treatment of Meniére's disease. Arch Otolaryngol 1977;103:124–127.
Barnett SB, Kossoff G. Ultrasonic exposure in static and real time echography. Ultrasound Med Biol 1982;8:273–276.
Barnett SB, Kossoff G. Temporal peak intensity as a critical parameter in ultrasound dosimetry. J Ultrasound Med 1984;3:385–389.
Barnett SB, Kossoff G. WFUMB Symposium on safety and standardization in medical ultrasound. Ultrasound Med Biol 1992;18:731–814.
Barnett SB, Williams AR. Identification of the mechanisms responsible for fetal weight reduction in mice following ultrasound exposure. Ultrasonics 1990;28:159–165.
Barnett SB, Miller MW, Cox C, Carstensen EL. Increased sister chromatid exchange frequency in Chinese hamster ovary cells exposed to high intensity pulsed ultrasound. Ultrasound Med Biol 1988;14:399–405.
Barnett SB, Walsh DA, Angles JA. Novel approach to evaluate the interaction of pulsed ultrasound with embryonic development. Ultrasonics 1990;28:166–170.
Barnett SB, ter Haar GR, Ziskin MC, Nyborg WL, Maeda K, Bang J. Current status of research on biophysical effects of ultrasound. Ultrasound Med Biol 1994;20:201–218.
Basauri L, Lele PP. A simple method for production of trackless focal lesions with focused ultrasound: statistical evaluation of the effects of irradiation on the central nervous system of the cat. J Physiol 1962;160:513–534.
Bauserman S, Meyers R, Fry WJ. Special variations between certain cranial and cerebral structures and the anterior and osterior commissures of the living human. Anat Rec 1963;146:1.
BECC. 29th Annual Report of the British Empire Cancer Campaign. 1951:42 (report from the "electrical" Dept. of the Royal Cancer Hospital, referring to investigations on use of ultrasound for location of cerebral tumors).
Bove AA, Ziskin MC, Mulchin WL. Ultrasonic detection of *in vivo* cavitation and pressure effects of high speed injections through catheters. Invest Radiol 1969;4:236–240.
Brayman A, Azadniv M, Makin I, Miller MW, Carstensen EL, Child SZ, Raeman C, Meltzer R, Everbach EC. Effect of a stabilized microbubble contrast agent on hemolysis of human erythrocytes exposed to high intensity pulsed ultrasound. Echocardiography 1995;12:13–21.
Carson PL. Statement on the use of diagnostic ultrasound instrumentation on humans for training, demonstration and research. Radiology 1975;116:737.
Carson PL. Diagnostic ultrasonic emissions and their measurements. In: Fullerton GD, Zagzebski JA, eds. Tissue imaging and characterization with computerized tomography and ultrasound. AAPM Technical Monograph No. 6. College Park, MD: American Association for Physicists in Medicine 1980:551–577.
Carson PL. Medical ultrasound fields and exposure measurements. In: Non-ionizing electromagnetic radiation and ultrasound (Proceedings of the Twenty-second Annual Meeting of the National Council on Radiation Protection). Bethesda: NCRP, 1988:308–328.
Carson PL. Constant soft tissue distance model in pregnancies. Proceedings of the Second WFUMB Symposium on Safety and Standardization in Medical Ultrasound. Ultrasound Med Biol 1989;15:27–29.
Carson PL. Intensity and power needed in diagnostic ultrasound. In: Ziskin MC, Lewin PA, eds. Diagnostic ultrasound in ultrasonic exposimetry. Boca Raton: CRC Press, 1992:345–370.
Carson PL, ed. Effects of nonlinear propagation on output display indices (TI and MI). J Ultrasound Med 1999;18:27–86.
Carson PL, Fischella PR, Oughton TV. Ultrasonic power and intensities produced by diagnostic ultrasound equipment. Ultrasound Med Biol 1978;3:341–350.
Carson PL, Banjavic RA. Radiation force balance system for precise acoustic power measurement. J Acoust Soc Am 1981;70:1–31 (AIP document No. PAPS JASMA-70-1220-31).
Carson PL, Hendee WR, Hallberg JR. A portable system for diagnostic ultrasound intensity measurements. In: Proceedings of the 28th ACEMB. Chevy Chase: Alliance Eng Med Biol, 1975:457.
Carson PL, Hendee WR, Leung SS. Performance evaluation and dosimetry in diagnostic ultrasound. AAPM Q Bull 1973a;7:200–205.
Carson PL, Leung SS, Hendee WR, Holmes JH, Linsey LF. A sealed test tank for echoscope performance evaluation. J Clin Ultrasound 1973b;1:208–218.
Carson PL, Pickering N, Erikson KR. AIUM standard specification of echoscope sensitivity and noise level including recommended practice for such measurements. Reflections 1979;5:12–19.
Carson PL, Rubin JM, Chiang EH. Fetal depth and ultrasound path lengths through overlying tissues. Ultrasound Med Biol 1989;15:629–639.

Carstensen EL, Foldy LL. Propagation of sound through a liquid containing bubbles. J Acoust Soc Am 1947;19:481–501.
Carstensen EL, Gates AH. Ultrasound and the fetus. In: Nyborg WL, Ziskin MC, eds. Biological effects of ultrasound. New York: Churchill Livingstone, 1985:85–95.
Carstensen EL, Schwan HP. Absorption of sound arising from the presence of intact cells in blood. Acoust Soc Am 1959a;31:185–189.
Carstensen EL, Schwan HP. Acoustic properties of hemoglobin solutions. J Acoust Soc Am 1959b;31:305–311.
Carstensen EL, Law WK, McKay ND, Muir TG. Demonstration of nonlinear acoustic effects at biomedical frequencies and intensities. Ultrasound Med Biol 1980;6:359–368.
Carstensen EL, Gracewski S, Dalecki D. The search for cavitation *in vivo*. Ultrasound Med Biol 2000 (in press).
Cataldo FL, Miller MW, Kaufman GE. Partial elucidation of the derivation of agglomerated nuclei in ultrasonicated *Vicia faba* roots. Environmental Exper Botany 1976;16:89–91.
Child SZ, Carstensen EL, Davis HT. A test for 'miniature flies' following exposure of *Drosophila melanogaster* larvae to diagnostic levels of ultrasound. Experimental Cell Biol 1980;48:461–466.
Child SZ, Carstensen EL, Lam SK. Effects of ultrasound on Drosophila: III, Exposure of larvae to low-temporal–average-intensity, pulsed irradiation. Ultrasound Med Biol 1981;7:167–173.
Child SZ, Carstensen EL, Miller MW. Growth of pea roots exposed to pulsed ultrasound. J Acoust Soc Am 1975;58:1109–1110.
Child SZ, Hartman CL, McHale LA, Carstensen EL. Lung damage from exposure to pulsed ultrasound. Ultrasound Med Biol 1990;16:817–825.
Child SZ, Hoffman D, Strassner D, Carstensen EL, Gates AH, Miller MW. A test of I^2t as a dose parameter for fetal weight reduction from exposure to ultrasound. Ultrasound Med Biol 1989;15:39–44.
Christopher T, Parker KJ. New approaches to nonlinear diffractive field propagation. J Acoust Soc Am 1991;90:488–499.
Ciaravino V, Flynn HG, Miller MW. Pulsed enhancement of acoustic cavitation: a postulated model. Ultrasound Med Biol 1981;7:159–166.
Coleman DJ, Konig WF, Lizzi FL, Weininger RB, Burt WJ. Vitreous liquefaction by ultrasound. In: Ophthalmic ultrasound; Proceedings of the 1968 International Congress of Ultrasonography in Ophthalmology. Gitter KA, Keeney AH, Sarin LK, Meyer D, eds. Philadelphia/New York: CV Mosby, 1969.
Conger AD, Ziskin MC. Detachment of tissue culture cells by diagnostic ultrasound. Radiology 1981;139:233.
Conger AD, Ziskin MC. Growth of mammalian multicellular tumor spheroids. Cancer Res 1983;43:556–560.
Conger AD, Ziskin MC, Wittels H. Ultrasonics effects on mammalian multicellular tumor spheroids. J Clin Ultrasound 1981;9:167–174.
Dalecki D, Carstensen EL, Parker KJ, Bacon DR. Absorption of finite amplitude focused ultrasound. J Acoust Soc Am 1991;89:2435–2447.
Dalecki D, Child SZ, Raeman CH, Xin C, Gracewski S, Carstensen EL. Bioeffects of positive and negative acoustic pressures in mice infused with microbubbles. Ultrasound Med Biol 2000 (in press).
Dalecki D, Keller BB, Carstensen EL, Neel D, Palladino JL, Noordergraaf A. Thresholds for premature ventricular contractions caused by lithotripter shocks. Ultrasound Med Biol 1991;17:341–346.
Dalecki D, Raeman CH, Child SZ, Carstensen EL. Intestinal hemorrhage from exposure to pulsed ultrasound. Ultrasound Med Biol 1995;21:1067–1072.
Dalecki D, Raeman CH, Child SZ, Carstensen EL. Thresholds for intestinal hemorrhage in mice exposed to a piezoelectric lithotripter. Ultrasound Med Biol 1995b;21:1239–1246.
Dalecki D, Raeman CH, Child SZ, Carstensen EL. A test for cavitation as a mechanism for intestinal hemorrhage in mice exposed to a piezoelectric lithotripter. Ultrasound Med Biol 1996;22:493–496.
Doida Y, Brayman AA, Miller MW. Modest enhancement of ultrasound-induced mutations in V79 cells *in vitro*. Ultrasound Med Biol 1992;18:465–469.
Donald I. Sonar—the story of an experiment. Ultrasound Med Biol 1974;1:109–117.
Duggan PM, Liggins GC, Barnett SB. Ultrasonic heating of the brain of the fetal sheep *in utero*. Ultrasound Med Biol 1995;21:553–560.
Dunn F. Physical mechanisms of the action of intense ultrasound on tissue Am J Phys Med 1958;37:148–151.
Dunn F, O'Brien WD Jr, eds. *Ultrasonic biophysics*. Stroudsburg, PA: Dowden, Hutchinson & Ross, Inc., 1996.
Dvorak M, Hrazdira I. Changes in the ultrastructure of bone marrow cells in rats following exposure to ultrasound. Ztschr mikr-anat Forsch 1966;75:451–4606.
Dyer HJ. Changes in behaviour in mosses treated with ultrasound. J Acoust Soc Am 1965;37:1195.
Dyer HJ. Structural effects of ultrasound on the cell. *In*: Interaction of ultrasound and biological tissues DHEW Publication (FDA). 1972;8008:73–75.
Dyer HJ, Nyborg WL. Ultrasonically induced movements in cells and cell models. IRE Trans Med Elec 1960;7:163–165 (Reprinted in Dunn and O'Brien 1976).
Elbadawi A, Linke CA, Carstensen EL, Fridd CW. Histomorphologic features of ultrasonic renal injury. Arch Path Lab Med 1976;100:199–205.
Elder SA. Cavitation microstreaming. Ph.D.Thesis. Brown University, 1965.
Elder SA. Cavitation microstreaming. J Acoust Soc Am 1959;31:54–64 (Reprinted in Dunn and O'Brien 1976).
El'piner IE. Ultrasound: chemical and biological effects (translated from Russian). New York: Consultants Bureau, 1964.
Erikson KR, Carson PL, Stewart HF. Field evaluation of the AIUM standard 100 mm test object. Ultrasound Med 1976;2:445–451.
Erikson KR, Banjavic RA, Carson PL, et al. Standard methods for testing single element transducers—AIUM Interim Standard. J Ultrasound Med 1982;1:1–18.
Esche R. Untersuchung der Schwingungskavitation In Flussigkeiten. Acustica 1952;2:208.
Evans GC, Lehman JS, Segal BS, Likoff W, Ziskin MC, Kingsley G. Echoaortography. Am J Cardiol 1967;19:91–96.
Fay B. Theoretische Betrachtungen zur Ultraschallstreuung. Acustica 1973;28:354.
Fay B, Brendel K, Ludwig G. Studies of inhomogeneous substances by ultrasonic back-scattering. Ultrasound Med Biol 1976;2:195–198.
Fay B, Rinker M, Lewin PA. Thermoacoustic sensor for ultrasound power measurements and ultrasonic equipment calibration. Ultrasound Med Biol 1994;20:367–373.
FDA. 510(k) Guide for measuring and reporting output of diagnostic ultrasound medical devices. Rockville, MD: Center Devices Rad Health, U.S. FDA, 1985 (revised 1995).
Fischella PS, Carson PL. Assessment of errors in pulse echo_ultrasound intensity measurements using miniature hydrophones. Med Phys 1979;6:404–411.
Flynn HG, Church CC. Transient pulsations of small gas bubbles in water. J Acoust Soc Am 1988;84:1863–1876.
Forytkova L, Hrazdira I, Mornstein V. Effect of ultrasound on DNA synthesis in tumor cells. Ultrasound Med Biol 1995;21:585–592.
Fowlkes JB, Carson PL, Chiang EH, Rubin JM. Acoustic generation of bubbles in excised canine urinary bladders. J Acoust Soc Am 1991;89:2740–2744.
Fridd CW, Linke CA, Barbaric Z, Elbadawi A, Carstensen EL. Unfocused ultrasound localized tissue destruction in rabbit kidneys. Invest Urol 1977;15:19–22.
Frizzell LA, Linke CA, Carstensen EL, Fridd CW. Thresholds for focal ultrasonic lesions in rabbit kidney liver and testicle. IEEE Trans Biomed Eng 1977;BME-24:393–396.
Fry WJ. Unsolved problems in acoustics—biological and medical acoustics. J Acoust Soc Am 1958;30:387–393.
Fry WJ. Intercranial anatomy visualized *in vivo* by ultrasound. Invest Radiol 1968;3:243–265.
Fry WJ. Quantitative delineation of the efferent anatomy of the medial mainmillary nucleus of the cat. J Comp Neurol 1970;139:321–336.
Fry FJ, Kossoff G, Eggleton RC, Dunn F. Threshold ultrasonic dosages for structural changes in the mammalian brain. J Acoust Soc Am 1970;48:1413–1417.
Fry WJ, Leichner OH, Olalyama D, Fry FJ, Kelly-Fry E. Ultrasound

visualization system employing new scanning and presentation methods. J Acoust Soc Am 1968;44:1324–1338.
Fry WJ, Meyers R. Ultrasonic method of modifying brain structure(s), First International Symposium on Steroencphalotomy. Confinia Nuerologica 1962;22:315–327.
Fry WJ, Meyers R, Fry FJ, Schultz DF, Dreyer LL, Noyes RF. Topical differentia of pathogenic mechanisms underlying Parkinsonian tremor and rigidity as indicated by ultrasonic irradiation of the human brain. Trans Am Neurol Assn 1958;83:16–24.
Fry WJ, Mosberg WH Jr, Barnard JW, Fry FJ. Production of focal destructive lesions in the central nervous system with ultrasound. J Neurosurg 1954;1:471–478.
Fry WJ, Wulff VJ, Tucker D, Fry FJ. Physical factors involved in ultrasonically induced changes in living systems: I. Identification of non-temperature effects. Acoust Soc Am 1950;22:867–976.
Gardner EA, Fowlkes JB, Carson PL, Ivey JA, Ohl DA. Bubble generation in excised urinary bladders using an electrohydraulic lithotripter. In: Levy M, McAvoy BR, eds. Ultrasonics Symposium Proceedings. IEEE Cat. #93CH3301-0. Piscataway, NJ: Institute for Electrical and Electronics Engineers, 1993:905–908.
Gavrilov LR. On the size distribution of gas bubbles in water. Sov Phys-Acoust 1969;15:22–24.
Gavrilov LR. Free gas content of a liquid and acoustical methods for its measurement. Sov Phys-Acoust 1970;15:285–295.
Gavrilov LR. The free-gas content of liquids and methods for measuring it. In: Rozenberg LD, ed. Physical principle of ultrasonic technology. Vol. 2. New York: Plenum Press; 1973:98–141.
Gavrilov LR. Physical mechanism of the lesion of biological tissues by focused ultrasound. Sov Phys Acoust 1974;20:16–18.
Gavrilov LR, Tsirulnikov EM. Focused ultrasound in physiology and medicine. Leningrad: Nauka, 1980 (in Russian).
Gavrilov LR. Use of focused ultrasound for stimulation of neural structures. Ultrasonics 1984;22:132–138.
Gavrilov LR, Narbut NP, Fridman FE. Use of focused ultrasound to accelerate the "maturing" of a cataract. Sov Phys-Acoust 1974;20: 229–231.
Gavrilov LR, Kalendo GS, Ryabukhin VV, Shaginyan KA, Yarmonenko SP. Ultrasonic enhancement of the gamma-irradiation of malignant tumors. Sov Phys-Acoust 1975;21:119–121.
Gavrilov LR, Gersuni G, Ilyinski OB, Sirotyuk MG, Tsirulnikov EM, Shchekanov EE. The effect of focused ultrasound on the skin and deep nerve structures of man and animal. In: Somatosensory and visceral receptor mechanisms. Iggo A, Ilyinski OB, eds. Progress in Brain Research. Vol. 43, Amsterdam, Oxford, New York: Elsevier, 1976:272–292.
Gavrilov LR, Gersuni GV, Ilyinski OB, Tsirulnikov EM. A study of reception with the use of focused ultrasound. I. Effect on the skin and deep receptor structures in man. II. Effects on the animal receptor structures. Brain Res 1977;135:265–277, 279–285.
Gavrilov LR, Gersuni GV, Pudov VI, Rozenblyum AS, Tsirul'nikov EM. Human hearing in connection with the action of ultrasound in the megahertz range on the aural labyrinth. Sov Phys-Acoust 1980; 26:290–292.
Gavrilov LR, Dmitriev VN, Solontsova LV. Use of focused ultrasonic receivers for remote measurements in biological tissues. J Acoust Soc Am 1988;83:1167–1179.
Gavrilov LR, Hand JW, Abel P, Cain CA. A method of reducing grating lobes associated with an ultrasound linear phased array intended for transrectal thermotherapy of prostate. IEEE Trans Ultrason Ferroelec Freq Contr 1997;44:1010–1017.
Gavrilov LR, Hand JW. A theoretical assessment of the relative performance of spherical phased arrays for ultrasound surgery and therapy. IEEE Trans Ultrason Ferroelec Freq Contr 2000;47:125–139.
Goldberg BB, Kotler MN, Ziskin MC, Waxham RD. Diagnostic uses of ultrasound. New York: Grune & Stratton, Inc., 1975.
Goldman DE, Hueter TF. Tabular data of the velocity and absorption of high-frequency sound in mammalian tissues. J Acoust Soc Am 1956;28:35–37.
Gould RK. Effects of acoustic streaming on heat transfer, Ph.D.Thesis, Brown University, 1961.
Gould RK. Heat transfer across a solid-liquid interface in the presence of acoustic streaming. J Acoust Soc Am 1966;40:219–225.
Gramiak R, Shah PM, Kramer DH. Ultrasound cardiography: contrast studies in anatomy and function. Radiology 1969:939–948.
Gregory WD, Miller MW, Carstensen EL, Cataldo FL, Reddy MM. Non-thermal effects of 2 MHz ultrasound on the growth and cytology of *Vicia faba* roots. Br J Radiol 1974;47:122–129.
Hare JD, Linke CA, Child SZ, Fridd CW, Carstensen EL, Davis HT. Transplant immunity in hamsters treated with ultrasound. J Clin Ultrasound 1982;10:257–260.
Harris GR, Preston RC, DeReggi AS. The impact of piezoelectric PVDF on medical ultrasound exposure measurements, standards, and regulations. IEEE Trans Ultrason Ferroelec Freq Control UFFC 2000 (in press).
Hartman C, Child SZ, Mayer R, Schenk E, Carstensen EL. Lung damage from exposure to the fields of an electrohydraulic lithotripter. Ultrasound Med Biol 1990;16:675–679.
Hartman C, Cox CA, Brewer L, Child SZ, Cox CF, Carstensen EL. Effects of lithotripter fields on development of chick embryos. Ultrasound Med Biol 1990b;16:581–585.
Harvey EN, Harvey EB, Loomis RW. Further observations on the effect of high frequency sound waves on living matter. Biol Bull 1928;55:459–469.
Hickey RC, Fry WJ, Meyers R, Fry FJ, Bradbury JT. Human pituitary irradiation with focused ultrasound. AMA Arch Surg 1961;83:620–630.
Hickey RC, Fry WJ, Meyers R, Fry FJ, Bradbury JT, Eggleton RC. Ultrasonic irradiation of the hypophysis in disseminated breast cancer. Am J Roent Radium Therapy Nuclear Med 1963;89:71–77.
Hill CR. The possibility of hazard In medical and industrial applications of ultrasound. Br J Radlol 1968;41:561–569.
Hill CR, Clarke PR, Crowe MR, Hammick JW. Biophyslcal effects of cavitation in a 1 MHz ultrasonic beam. In: Ultrasonics for industry conference papers. London: Illiffe, 1969:16–30.
Hill CR. Acoustic intensity measurements on ultrasonic diagnostic devices. In: Boch J, Ossoinig K, eds. Ultrasonographia medica: 1st World Congress on Ultrasonic Diagnostics in Medicine. Vienna: Vienna Academy of Medicine, 1971:21–27.
Hill CR. Ultrasonic exposure thresholds for changes in cells and tissues. J Acoust Soc Am 1972;52:667–672.
Hill CR. Proposed faculty for ultrasound exposimetry and calibration. Proc. Colloquium on Ultrasound Bio-effects and Dosimetry. (Abst.) London: Chelsea College, 1974.
Hill CR. Physical Principles of Medical Ultrasonics. Chichester, Ellis Horwood; 1996.
Hill CR, Bamber JC, ter Haar GR. Physical Principles of Medical Ultrasonics. 2nd ed. London, Wiley, 2000.
Hill CR. Optimum acoustic frequency for focused ultrasound surgery. Ultrasound Med Biol 1994a;20:271–277.
Hill CR, Rivens I, Vaughan MG, ter Haar GR. Lesion development in focused ultrasound surgery: a general model. Ultrasound Med Biol 1994b;20:259–269.
Hill CR, ter Haar GR. High intensity focused ultrasound: potential for cancer treatment. Br J Radiol 1995;68:1296–1303.
Hopwood FL. Ultrasonics: some properties of inaudible sound. Nature 1931;128:748–751.
Horak F, Hrazdira I. The ultrasonic detection of pregnancy in sheep. Acta Univ Agricult Brno 1968;16:723–728.
Horder MM, Barnett SB, Vella GJ, Edwards MJ, Wood AKW. *In vivo* heating of the guinea-pig fetal brain by pulsed ultrasound and estimates of thermal index. Ultrasound Med Biol 1998a;24:1467–1474.
Horder MM, Barnett SB, Edwards MJ. Effects of pulsed ultrasound on sphenoid bone temperature and the heart rate in guinea-pig foetuses. Early Human Dev 1998b;52:221–223.
Hrazdira I. Contribution to the problem of ultrasonic haemolysis. (in Czech) Scripta Med 1955;28:145–153.
Hrazdira I. Uber die Ultraschallwirkung auf die elektrische Leitfahigkeit des deionisierten Wassers. Naturwissenschaften 1963;50: 398.
Hrazdira I. Anderungen der Uberlebenszeit mit ^{51}Cr markierter Eryth-

rocyten nach Ultraschallwirkung. Naturwissenschaften 1965a;52: 47.
Hrazdira I. Direct and indirect effect of ultrasound on bone marrow cell suspensions. Folia biol (Prague) 1965b;11:330–333.
Hrazdira I. Zeitfaktor der biologischen Ultraschallwirkung. Studia Biophys (Berlin) 1967;2:127–131.
Hrazdira I. Changes in cell ultrastructure under direct and indirect action of ultrasound. In: Bock J, Ossoinig K, eds. Ultrasonographia medica. Vienna: Wiener Med Akademie 1971:457–463.
Hrazdira I. Ultrasonic attenuation in biological media. Digest of the 10th International Conference on Medical and Biological Engineering, Dresden 1973:314.
Hrazdira I. Current opinions on the biological effect of ultrasound. Scripta Med 1975;48:3–8.
Hrazdira I. Biophysical aspects of ultrasonic tissue characterization. Proc FASE 78 (Warsaw) 1978;2:3–12.
Hrazdira I, Rakova A, Vacek A, Horky D. Effect of ultrasound on the formation of haemopoietic tissue colonies in spleen. Folia biol (Prague) 1974;20:430–432.
Hrazdira I. Cellular effects of ultrasound. In: Kurjak A, ed. Recent advances in ultrasound diagnosis. Amsterdam: Excerpta Medica, 1981:37–38.
Hrazdira I. Exposure parameters and possible risks of modern ultrasound diagnostic methods. (in Czech). Lekar a technika 1983;24: 5–7.
Hrazdira I. Biophysical approach to the problem of safety of diagnostic ultrasound. Arch Acoustics 1984;9:95–100.
Hrazdira I, Doskocil M. Chick embryo as an experimental model for ultrasound embryotoxicity investigations. Scripta Med 1988;61:75–79.
Hrazdira I, Bilkova B. Effect of ultrasound on bone marrow cell suspensions *in vitro*. Folia biol (Prague) 1963;9:397–400.
Hrazdira I, Skotakova M. Die Ultraschallwirkung auf osmotische Eigenschaften der Erythrozyten. Naturwissenschaften 1963;50:153–154.
Hrazdira I, Konecny M. Functional and morphological changes in the thyroid gland after ultrasonic irradiation. Am J Phys Med 1966;45: 238–243.
Hrazdira I, Skalka M. Changes produced by ultrasound in the deoxyribonucleoprotein complex in vitro. Folia biol (Prague) 1970;16: 121–128.
Hrazdira I, Prochazka V. Ultrasound as an echinocytogenic factor. (in Czech). Bratisl lek listy 1983;80:677–686.
Hrazdira I, Doskocil M, Dvorak M, Stastna J. An experimental approach to the problem of possible embryotoxicity due to biomedical ultrasound. In: Carson ER, Kneppo P, Krekule I, eds. New York and London: Plenum Press, 1988:127–130.
Hrazdira I, Sulcova A, Kellnerova R, Huskova B. Prenatal application of diagnostic ultrasound in mice. Ultrasound Med Biol 1995;21: 427–430.
Hrazdira I, Skorpikova J, Dolnikova M. Ultrasonically induced alterations of cultured tumour cells. Eur J Ultrasound 1998;8:43–49.
Hrazdira I, Kotulanova E, Prochazkova I. Introduction to colour duplex ultrasonography. Brno: Publisher AF167, 1998.
Hsu WL. Thermal factors in the ultrasonic destruction of mammalian tissue. Sc.D. Thesis, Massachusetts Institute of Technology, 1974.
Hueter TF. Die Absorption von Ultraschall interischen Geweben. Naturwissenschaften 1948;35:285–286.
Hueter TF. On the mechanism of biological effects by ultrasound. In: Van Anhoupen VJ, ed. Chemical engineering symposium series. New York: Am Inst Chem Eng 1951;7:57–67.
Hueter TF. Standard aid in ultrasound therapy. Magazine of Standards 1956;27:338–339.
Hueter TF. Viscoelastic losses in tissues in the ultrasound range. ASTIA Doc no. AD 142171, August 1958.
Hueter TF. Twenty years of underwater acoustics: generation and reception. J Acoust Soc Am 1972;51:1025–1040.
Hueter TF, Bolt RH. An ultrasonic method for outlining the cerebral ventricles. J Acoust Soc Am 1951;23:160–167.
Hueter TF, Morgan H, Cohen MS. Ultrasonic attenuation in biological suspensions. J Acoust Soc Am 1953;25:1200–1201.
Hueter TF, Bolt RH. Sonics. New York: John Wiley & Sons, Inc., 1955.
Hueter TF, Fry WJ. Ultrasonics: Central nervous system changes from focused ultrasound. In: Glasser OH, ed. Medical Physics Chicago: The Year Book Publisher 1960;3:671–678.
Hughes DE, Nyborg WL. Cell disruption by ultrasound. Science 1962; 138:108–114. (Reprinted in Dunn and O'Brien 1976).
Hwang EY, Fowlkes JB, Carson PL. Variables controlling contrast generation in a urinary bladder model. J Acoust Soc Am 1998;103: 3706–3716.
Ide M. Observation of bacteria destroying process with ultrasound. Tech Rep IEICE March 1958 (in Japanese).
Ide M. Acoustic field visualizing plate. Proc Acoust Soc Jpn 1962:15–16. (in Japanese).
Ide M. Acoustic data of Japanese ultrasonic diagnostic equipment. In: Kossoff G, Nyborg W, eds. Second WFUMB Symposium on Safety and Standardization in Medical Ultrasound. Ultrasound Med Biol 1989;16(Suppl. 1):49–53.
Ide M. Acoustic parameter and safety—Survey of output power of ultrasonic diagnostic equipment on market in Japan. Proc JSUM 1992:21–30 (in Japanese).
Ide M, Wagai T. Instrumentation for stereotaxic encephalotomy for animal experiment with 3 megacycle ultrasound. Tech Rep IEICE 1965:1–18 (in Japanese).
Ide M, Wagai T, Majima T. Stereotaxic encephalotomy instrument with focused ultrasound. Proc Acoust Soc Jpn 1984:119–120 (in Japanese).
IEC. Requirements for the declaration of the acoustic output of medical diagnostic ultrasonic equipment, IEC 1157. Geneva: Internat Electrotechnical Commission, 1992.
Ivey JA, Gardner EA, Fowlkes JB, Rubin JM, Carson PL. Acoustic generation of intraarterial contrast boluses. Ultrasound Med Biol 1995;21:757–767.
Jackson FJ. Sonically induced microstreaming near a plane boundary, Ph.D. Thesis, Brown University, 1960.
Jackson FJ, Nyborg WL. Small scale acoustic streaming near a locally excited membrane. J Acoust Soc Am 1958;30:614–619.
Jones SM, Carson PL, Banjavic RA, Meyer CR. Simplified technique for the calibration and use of a miniature hydrophone in intensity measurements of pulsed ultrasound fields. J Acoust Soc Am 1981; 70:1220–1228.
Kaufman GE, Miller MW. Growth retardation in Chinese hamster V-79 cells exposed to 1 MHz ultrasound. Ultrasound Med Biol 1978;4: 139–144.
Kelly E. Ultrasound in biology and medicine (Pub. no. 3). Washington, DC: American Institute of Biological Science, 1957.
Kelly E, Fry WJ. Isometric twitch tension of frog skeletal muscle as a function of temperature. Science 1958;128:200–202.
Kelly E, Fry FJ, Fry WJ. Effects of high intensity ultrasound on the mechanical response of excised biceps muscle of the frog. Physiologist 1959;11:3.
Kelly E, Fry WJ, Fry FJ. Muscle twitch tension—influence of electrical stimulating conditions at different temperatures. I. Results for chloride Ringers. Phys Med Biol 1964;9:317–388.
Kelly E, Fry WJ. Muscle twitch tension—influence of electrical stimulating conditions at different temperatures. II. Results for nitrate Ringers. Phys Med Biol 1964;9:559–567.
Kelly E, ed. Ultrasonics energy—Biological investigations and medical applications. Urbana, IL: University of Illinois Press, 1965.
Kelly E, Fry WJ. Muscle twitch tension—influence of electrical stimulating conditions at different temperatures: III. Analysis and correlation. Phys Med Biol 1965;10:251–269.
Kelly E, Fry WJ, Fry FJ. Muscle twitch tension-influence of electrical stimulating conditions at different temperatures. IV. Time rate of rise of tension. Phys Med Biol 1965;10:393–402.
Kelly-Fry E, Kossoff G, Hindman HA Jr. The potential of ultrasound visualization for detecting the presence of abnormal structures within the female breast. IEEE Sonics Ultrasonics 1972;19:25–30.
Koch EB. The process of innovation in medical technology, American research on ultrasound. 1947–1962. Dissertation, University of Pennsylvania, 1990.

Kolb J, Nyborg WL. Small-scale acoustic streaming in liquids. J Acoust Soc Am 1956;28:1237–1242.
Kossoff G. Calibration of ultrasonic therapeutic equipment. Acustica 1962;12:84–90.
Kossoff G. Balance technique for measurement of very low ultrasonic power outputs. J Acoust Soc Am 1965;38:880–881.
Kossoff G, Khan AE. Treatment of vertigo using the ultrasonic generator. Arch Otolaryng 1966;84:85–92.
Kossoff G, Wadsworth JR, Dudley PF. The round window ultrasonic technique for treatment of Meniere's disease. Arch Otolaryng 1967; 86:8390.
Kossoff G. On the measurement of peak acoustic intensity generated by pulsed ultrasonic equipment. Ultrasonics 1969;23:249–251.
Kossoff G. On the measurement and specification of acoustic output generated by pulsed ultrasonic diagnostic equipment. J Clin Ultrasound 1978;6:303–309.
Kossoff G, Barnett SB, eds. First WFUMB Symposium on Safety and Standardization of Ultrasound in Obstetrics. Ultrasound Med Biol 1986;12:673–724.
Kossoff G, Nyborg WL, eds. Second WFUMB Symposium on Safety and Standardization in Medical Ultrasound. Ultrasound Med Biol 1989;16(Suppl. 1)1–115.
Kremkau FW, Gramiak R, Carstensen EL, Shah PM, Kramer DH. Ultrasonic detection of cavitation at catheter tips. Am J Roentgenol Radium Ther Nuclear Med 1970;110:177–183.
Lele PP. Irradiation of plastic with focused ultrasound: A simple method for evaluation of dosage factors for neurological applications. J Acoust Soc Am 1962;34:412–420.
Lele PP. Effects of focused ultrasound radiation on peripheral nerve, with observations on local heating. Exper Neurol 1963;8:47–83.
Lele PP. Ultrasonic teratology in mouse and man. In: de Vlieger M, White DN, McCready VR. eds. Ultrasonics in medicine, Excerpta Medica International Congress Series No. 363 (ISBN 90 219 02974), Proceedings of the 2nd European Congress on Ultrasonics in Medicine, Munich, 12–16 May 1975. Amsterdam: Excerpta Medica, 1975a:22–27.
Lele PP. Hyperthermia by ultrasound; Proceedings of the International Symposium on Cancer Therapy by Hyperthermia and Radiation, American College of Radiology, Washington DC, April 28–30. 1975b:168–178.
Lele PP. Thresholds and mechanisms of ultrasonic damage to "organized" animal tissues. In: Hazzard DG, Litz ML, eds. Symposium on biological effects and characterizations of ultrasound sources. Rockville, MD: HED Publication (FDA) 1977:224–237 (no. 78-8048).
Lele PP. Effects of ultrasound on solid mammaliant tissues and tumors *in vivo*. In: Repacholi MH, Grondolfo M, Rindi A, eds. Ultrasound: Medical applications, biological effects and hazard potential. New York: Plenum Press 1987:275–306.
Lele PP, Hsu W. Role of thermal mechanisms in the alteration of nervous systems by ultrasound, 23rd ACEMB, Washington DC, November 15–19, 1970; Paper 14.3:174.
Lele PP, Namery J. Detection of myocardial infarction by ultrasound. 25th ACEMB, Bal Harbor, FL, October 1–5 1972a;Paper 18.2:135.
Lele PP, Namery J. Detection of myocardial infarction by ultrasonic frequency spectrum analysis; 17th Annual Meeting of the A.I.U.M., Philadelphia, PA, Oct 29–Nov 1 1972b;Paper 24:48.
Lele PP, Namery J. A computer-based ultrasonic system for the detection and mapping of myocardial infarcts, Proceedings of the San Diego Biomedical Symposium 13, 1974:121–132.
Lele PP, Pierce AD. Hypotheses on the relation of temperature to lesion formation by high intensity ultrasound. IEEE Trans Sonics Ultrasonics 1972a;SU-19:403.
Lele PP, Pierce AD. The thermal hypothesis of the mechanism of ultrasonic focal destruction in organized tissues. In: Reid JM, Sikov MR, eds. Interaction of ultrasound and biological tissues, Workshop proceedings, DHEW Publication (FDA) 73-8008, BRH/DBE 73-1. Washington DC: US Govt Printing Office, 1972b:121–128.
Lele PP, Senapati N, Msu WL. Mechanisms of tissue-ultrasound interaction. In: de Vlieger M, White DN, McCready VR, eds. Proceedings of the 2nd World Congress on Ultrasonics in Medicine, Excerpta Medica International Congress Series No. 309 (ISBN 90 219 0187 0) Rotterdam, The Netherlands, 4–8 June 1973:345–352.
Liebeskind D, Bases R, Medez R, Elequin F, Koenigsberg M. Sister chromatid exchanges in human lymphocytes after exposure to diagnostic ultrasound. Science 1979;205:1273–1275.
Linke CA, Carstensen EL, Frizzell LA, Elbadawi A, Fridd CW. Localized tissue destruction by high intensity focused ultrasound. Arch Surgery 1973;107:887–891.
Lizzi FL. High-precision thermotherapy for small lesions. Eur Urol 1993;23:23–28.
Lizzi FL, Burt WJ, Coleman DJ. Effects of ocular structures on propagation of ultrasound in the eye. Arch Ophthalmol 1970;84: 635–640.
Lizzi FL, Coleman DJ, Driller J, Franzen LA, Jakobiec FA. Experimental ultrasonically induced lesions in the retina, choroid, and sclera. Invest Oph Vis Sci 1978a;17:350–360.
Lizzi FL, Coleman DJ, Driller J, Franzen LA, Leopold M. Experimental production of chorioretinal lesions: 2. Pulsed ultrasound. In: White D, Lyons EA, eds. Ultrasound in medicine. Vol. 4. New York: Plenum Press, 1978b:579–582.
Lizzi FL, Packer AJ, Coleman DJ. Experimental cataract production by high-frequency ultrasound. Ann Ophthalmol 1978c;10:934–942.
Lizzi FL, Coleman DJ, Driller J, Ostromogilsky M. Thermal model for ultrasonic treatment of glaucoma. Ultrasound Med Biol 1984;10: 289–298.
Lizzi FL, Coleman DJ, Driller J. Ultrasonic therapy and imaging in ophthalmology. In: Berkhout AJ, Ridder J, van der Wal LF, eds. Acoustical imaging. New York: Plenum Publishing Corp, 1985;14: 1–17.
Lizzi FL, Driller J, Lunzer B, Kalisz A, Coleman DJ. Computer model of ultrasonic hyperthermia and ablation for ocular tumors using B-mode data. Ultrasound Med Biol 1992;18:59–73.
Maeda K. Functional mechanics and diagnostic monitoring of the fetal heart action and of the uterus during pregnancy and labor. Automedica 1977;2:27–57.
Maeda K. Studies on the safety of diagnostic ultrasound (results obtained in a research group of Japan) in Workshops 1, What should be the role of WFUMB in standardization and safety. 2nd WFUMB Miyazaki, July 1979.
Maeda K, Ide M, Kurachi K, Akamatsu N, Sakamoto S, Takabayashi T, Shimizu T, Morohashi T, et al. Studies on the safety of pulsed ultrasound in the diagnosis of the fetus during pregnancy. Jpn J Med Ultrasonics 1981a;8:265–299.
Maeda K, Tatsumura M, Yoneda T, Nakamura Y. Fetal mechanocardiography recorded with the processing of ultrasonic Doppler fetal heart valve signals. Jpn J Med Ultrasonics 1981b;8:150–185.
Maeda K. Special edition: Studies on the safety of pulsed ultrasound in the diagnosis of the fetus during pregnancy. Jpn S Med Ultrasonics 1981;8:265–299.
Maeda K. Studies on new ultrasonic Doppler fetal actograph and continuous recording of fetal movement. Acta Obstet Gynaecol Jpn 1984;36:280–288.
Maeda K. Ultrasonic diagnosis in perinatal medicine. Asian Med J 1989;32:551–561.
Maeda K. Tissue characterization in obstetrics and gynecology: the present state and future possibilities. Ultrasound Obstet Gynecol 1992;2:75–76.
Maeda K, Ide M. The limitation of the ultrasound intensity for diagnostic devices in the Japanese Industrial Standards IEEE Trans Ultrason Ferroelec Freq Control. 1986;33:241–244.
Maeda K, Kigawa J. Flow cytometric studies on the effect of experimental pulsed ultrasound on cultured cells in vitro. Ultrason Sympos IEEE 1986:997–1000.
Maeda K, Kimura S, et al. Pathophysiology of fetus. Fukuoka: Fukuoka Printing, 1969:183–192.
Maeda K, Murao F, Yoshiga T, Yamauchi C, Tsuzaki T. Experimental studies on the suppression of cultured cell growth curves after irradiation with CW and pulsed ultrasound. IEEE Trans Ultrason Ferroelec Freq Control, 1986;UFFC 33:186–193.
Maeda K, Morishita K, Kigawa J. The effect of ultrasound on DNA

distribution of cultured cell in vitro. JSUM proceedings. November 1988:287–288.
Maeda K, Nakano H. Experiences with the technique of ultrasonic Doppler methods in obstetrics. J Jpn Obstet Gynecol Soc 1968;15: 135–142.
Maeda K, Utsu M, Imanishi M, Naruse H, Akaiwa A. Ultrasonic assessment of intrapartum fetal brain damage. Proc L Ecografia nel decennio del cervello. Rome: CIC, 1992:517–535.
Maeda K, Utsu M, Kihaile PE. Quantification of sonographic echogenicity with grey-level histogram width: A clinical tissue characterization. Ultrasound Med Biol 1998;24:225–234.
Maeda K, Utsu M, Yamamoto N, Serizawa M. Echogenicity of fetal lung and liver quantified by the grey-level histogram width. Ultrasound Med Biol 1999;25:201–208.
Mayer R, Schenk E, Child S, Norton S, Cox C, Carstensen E. Pressure threshold for shock wave induced renal hemorrhage. J Urol 1990; 144:1505–1509.
Meyers R, Fry FJ, Eggleton RC, Schultz DF. Determinations of topological human brain representations and modifications of signs and symptoms of some neurological disorders by the use of high level ultrasound. Neurology 1960;10:271–277.
Meyers R, Fry WJ, Fry FJ, Dreyer LL, Schultz DF, Noyes F. Early experiences with ultrasonic irradiation of the pallidofugal and nigral complexes in hyperkinetic and hypertonic disorders. J Neurosurg 1959;16:32–54.
Miller DL. A review of the ultrasonic bioeffects of microsonation, gas-body activation, and related cavitation-like phenomena. Ultrasound Med Biol 1987;13:443–470.
Miller DL. An instrument for microscopical observation of the biophysical effects of ultrasound. Ph.D. Thesis. University of Vermont, 1976.
Miller DL. The botanical effects of ultrasound: a review. Envir Exp Botany 1983;23:1–27.
Miller DL, Thomas RM. Thresholds for hemorrhages in mouse skin and intestine induced by lithotripter shockwaves. Ultrasound Med Biol 1995;21:249–257.
Miller MW, Azadniv M, Doida Y, Brayman A. Effect of a stabilized microbubble contrast agent on CW ultrasound-induced red blood cell lysis *in vitro*. Echocardiography 1995;12:1–11.
Miller MW. Does ultrasound induce sister chromatid exchanges? Ultrasound Med Biol 1985;11:561–570.
Miller MW, Ziskin MC. Biological consequences of hyperthermia. Ultrasound Med Biol 1989;15:707–722.
Muir TG, Carstensen EL. Prediction of nonlinear acoustic effects of biomedical frequencies and intensities. Ultrasound Med Biol 1980; 6:345–357.
NCRP. Report No. 74, Biological effects of ultrasound: Mechanisms and clinical implications. Bethesda, MD: National Council on Radiation Protection and Measurements, 1983:1–266.
NCRP. Report No. 113, Exposure criteria for medical diagnostic ultrasound: I. Criteria based on thermal mechanisms. Bethesda, MD: National Council on Radiation Protection and Measurements, 1992: 1–278.
NEMA. UD-2-1992. Washington DC: National Electrical Manufacturers Association, 1992.
Nyborg WL, Ziskin MC. Biological effects of ultrasound. New York: Churchill Livingstone, 1985.
Penney DP, Schenk EA, Maltby K, Hartman CL, Child SZ, Carstensen EL. Morphologic effects of pulsed ultrasound in the lung. Ultrasound Med Biol 1993;19:127–135.
Pizzarello DJ, Vivino A, Madden B, Wolsky A, Deegan AF, Becker M. Effect of pulsed low power ultrasound on growing tissues. I. Developing mammalian and insect tissue. Expl Cell Biol 1978;46: 179–181.
Pospisilova J, Hrazdira I, Pospisil M. Wasserdurchlassigkeitsveranderungen des Bindegewebes nach Ultraschallwirkung *in vitro*. Rehabilitation 1963;16:63–66.
Pritchard NJ, Hughes DE, Peacocke AR. The ultrasonic degradation of biological macromolecules under conditions of stable cavitation. Biopolymers 1966;4:259–273 (Reprinted in Dunn and O'Brien 1976).
Putterman A. Sonoluminescence: sound into light. Sci Am 1995;46–51.
Raeman CH, Child SZ. Ultrasonic hemorrhage of murine lung. Ultrasound Med Biol 1993;19:507–512.
Raeman CH, Child SZ, Dalecki D, Cox C, Carstensen EL. Exposure-time dependence of the threshold for ultrasonically induced murine lung hemorrhage. Ultrasound Med Biol 1996;22:139–141.
Raeman CH, Child SZ, Dalecki D, Mayer R, Parker KJ, Carstensen EL. Damage to murine kidney and intestine from exposure to the fields of a piezoelectric lithotripter. Ultrasound Med Biol 1994;20:589–594.
Ravitz MJ, Schnitzler RM. Morphological changes induced in the frog semitendinosus muscle fiber by localized ultrasound. Exptl Cell Res 1970;60:78–85 (Reprinted in Dunn and O'Brien 1976).
Reid JM, Sikov M, eds. Ultrasonic dosimetry, session record. In: Interaction of ultrasound and biological tissues. Washington, DC: DHEW Publication (FDA), 1972:73–8008.
Robinson TC. An analysis of lesion development in Plexiglas and nervous tissue using focused ultrasound. Ph.D. Thesis, Massachusetts Institute of Technology, 1968.
Robinson TC, Lele PP. An analysis of lesion development in the rain and in plastics by high-intensity focused ultrasound at low-megahertz frequencies. J Acoust Soc Am 1972;51:1333–1351.
Rooney JA. Hemolysis with ultrasonically induced stable cavitation, Ph.D. Thesis. University of Vermont. 1970.
Rooney JA. Hemolysis near an ultrasonically pulsating gas bubble. Science 1970b;169:869–871 (Reprinted in Dunn and O'Brien 1976).
Rosenblith WA, Hueter TF. Damage risk criteria and "warning signals." J Acoust Soc Am 1954:26;453.
Saneyoshi J, Ide M. Ultrasonic power indicator for therapeutic equipment. JIEEJ 1957;77:19–22 (in Japanese).
Saneyoshi J, Mori E, Ide M. Ultrasonic bacteria destroying apparatus. Tech Rep IEICE, Feb. 1957b (in Japanese).
Saneyoshi J, Mori E, Ide M. Magnetostrictive ultrasonic bacteria destroying apparatus with a metallic horn. J Acoust Soc Japan 1958; 14:327–337 (in Japanese).
Saneyoshi J, Okujima M, Ide M, Wagai T. Ultrasonic sound pressure measuring device and an example of its medical use. Digest of the 6th International Conference ME and BE. 1963:263–264.
Saneyoshi J, Ide M, Okujima M, Wagai T. Ultrasonic sound pressure measuring device and an example of its medical use. JMEBE 1966;4:12–16 (in Japanese).
Scherzinger AL, Carson PL, Clayman W, Carter W, Johnson ML, Rashbaum C. A tissue-equivalent upper abdominal phantom. J Ultrasound Med 1983;2:455–462.
Schmitt RM, Carson PL. Acoustic beam profile, waveform and intensity measurements using piezoelectric hydrophones. In: IEEE Guide for medical ultrasound field parameter measurements (IEEE Standard 790-1989) and American National Standard, IEEE. New York: Am Nat Stds Inst, 1990:34–35.
Schnitzler RM. The effect of highly localized ultrasonic vibration on skeletal muscle, Ph.D. Thesis, University of Vermont, 1969.
Senapati N. A study of ultrasonic cavitation of biological tissues and its possible damaging effects. Sc.D. Thesis, Massachusetts Institute of Technology, 1973.
Shimizu T, Fukushima T, Shoji R. Studies on possible teratogenesity of ultrasound. Sankato-Fujinka 1970;37:1339.
Shimizu T, Shoji R. In: de Vlieger M, White DN, McCready VR. eds. Abstracts, II World Congress on Ultrasonics in Medicine, Rotterdam, June 1973. ICS 277. Amsterdam: Excerpta Medica, 1973:28.
Shoji R, Murakami U, Shimizu T. Influence of low intensity ultrasonic irradiation on prenatal development of two inbred mouse strains. Teratology 1975;12:227–232.
Silverman RH, Coleman DJ, Lizzi FL, Torpey JG, Driller J, Iwamoto T, Burgess SEP, Rosado A. Ultrasonic tissue characterization and histopathology in tumor xenografts following ultrasonically induced hyperthermia. Ultrasound Med Biol 1986;12:639–645.
Silverman RH, Vogelsang B, Rondeau MJ, Coleman DJ. Therapeutic ultrasound for the treatment of glaucoma. Am J Ophthalmol 1991; 111:327–337.

Sleefe GE, Lele PP. On estimating the number density of random scatterers from backscattered acoustic signals. Ultrasound Med Biol 1988;14:709–727.
Tarantal AF, Canfield DR. Ultrasound-induced lung hemorrhage in the monkey. Ultrasound Med Biol 1994;20:65–72.
Thickman DI, Ziskin MC, Goldenberg NJ. Effect of display format on detectability. J Ultrasound Med 1983a;12:117–121.
Thickman DI, Ziskin MC, Goldenberg NJ, Linder BE. Clinical manifestations of the comet tail artifact. J Ultrasound Med 1983b;2:225–230.
Thomenius KE, Carson PL, Harris GR, Ziskin M. Discussion of the mechanical index and other exposure parameters. Ch. 8. In: Fowlkes JB, Holland C, eds. AIUM Mechanical Bioeffects Conference. J Ultrasound Med, 2000;19:143–148.
Trier HG. Apparative Qualitätssicherung in der Ultraschalldiagnostik. Deutsches Ärzteblatt 91 1994;28/29:1949–1957.
Tsirulnikov EM, Vartanyan IA, Gersuni GV, Rosenblyum AS, Pudov VI, Gavrilov LR. Use of amplitude-modulated focused ultrasound for diagnosis of hearing disorders. Ultrasound Med Biol 1988;14:277–285.
Tyurina SI, Brazovskaya FA, Inin Yu S, Paikin DI, Sirotyuk MG, Gavrilov LR. Use of focused ultrasound for local destruction of brain structures without damage to the skull. Bul Exp Biol Med 1973;75:597–598.
Vartanyan IA, Gavrilov LR, Gersun GV, Rozenblyum AS, Tsirulnikov EM. Sensory perception. Research with the use of focused ultrasound. Leningrad: Nauka, 1985 (in Russian).
Vartanyan IA, Gavrilov LR, Zharskaya VD, Ratnikova GI, Tsirulnikov EM. The stimulating effect of focused ultrasound on the auditory nerve fibers of the frog *Rana temporaria*. J Evol Biochem Physiol 1982;17:335–341.
Vaughan M, ter Haar GR, Hill CR, et al. Minimally invasive cancer surgery using focused ultrasound: a pre-clinical, normal tissue study. Br J Radiol 1994;67:267–274.
Wells PNT, Ziskin MC. New techniques and instrumentation in ultrasonography. New York: Churchill Livingstone, 1980.
WFUMB. (World Federation for Ultrasound in Medicine and Biology) Symposium on safety and standardisation in ultrasound: Issues and recommendations regarding thermal mechanisms for biological effects of ultrasound. Ultrasound Med Biol 1992;18:731–814.
WFUMB. Reasonable-worst–case tissue models. In: Barnett SB, ed. WFUMB Symposium on safety and standardization in medical ultrasound. Ultrasound Med Biol 1992;18:759–768.
WFUMB. (World Federation for Ultrasound in Medicine and Biology) Symposium on safety of ultrasound in medicine: conclusions and recommendations on thermal and non-thermal mechanisms for biological effects of ultrasound. Ultrasound Med Biol 1998;24(Suppl. 1):1–55.
WFUMB. Conclusions and recommendations on thermal and non-thermal mechanisms for biological effects of ultrasound. In: Barnett SB, ed. World Federation for Ultrasound in Medicine and Biology Symposium on Safety of Ultrasound in Medicine. Ultrasound Med Biol 1998a;24(Suppl. 1):S1–S58.
WFUMB. Free radical production: its biological consequences. In: Barnett SB, ed. World Federation for Ultrasound in Medicine and Biology Symposium on Safety of Ultrasound in Medicine: Conclusions and recommendations on thermal and non-thermal mechanisms for biological effects of ultrasound. Ultrasound Med Biol 1998b;24(Suppl. 1):S29–S34.
WHO. Environmental Health Criteria 22, Ultrasound. Geneva: World Health Organization 1982.
Williams AR. *Ultrasound: Biological Effects and Potential Hazard*. London: Academic Press, 1983.
Williams AR, Hughes DE, Nyborg WL. Hemolysis near a transversely oscillating wire. Science 1970;169:871–873 (Reprinted in Dunn and O'Brien 1976).
Wilson WL, Schnitzler RM. The effect on cleavage of *Arbacia* eggs of ultrasound applied to a small area of the cell surface. (Abstr.) Biol Bull 1963;125:397.
Wilson WL, Wiercinski FJ, Nyborg WL, Schnitzler RM, Sichel FJ. Deformation and motion produced in isolated living cells by localized ultrasonic vibration. J Acoust Soc Am 1966;40:1363–1370 (Reprinted in Dunn and O'Brien 1976).
Wilson WL, Wiercinski FJ, Schnitzler RM. The effect of localized ultrasound on the isolated sartorius muscle fiber of frog (Abstr.). Biol Bull 1964;127:396.
Wood RW, Loomis AL. The physical and biological effects of high frequency sound waves of great intensity. Phil Mag 1927;4:417–436.
Zachary JF, O'Brien WD Jr. Lung hemorrhage induced by continuous and pulsed wave (diagnostic) ultrasound in mice, rabbits, and pigs. Vet Pathol 1995;32:43–54.
Zakharov SI, Bogdanov KY, Rosenshtraukh LV, Gavrilov LR, Yushin VP. The effect of acoustic cavitation on the contraction force and membrane potential of rat papillary muscle. Ultrasound Med Biol 1989;15:561–565.
Ziskin MC. Identification of anatomic sources of ultrasonic echoes using a combined radiographic and through-transmission ultrasonic technique. Digest of the 2nd Canadian Medical and Biological Engineering Conference, Toronto, Canada, Sept. 1968:1–3.
Ziskin MC, Lehman JS, Evans GC. An investigation of a cause of false-positive results in the ultrasonic diagnosis of pericardial effusion. (Abstract). Proceedings of the annual meeting of the American Institute of Ultrasonics in Medicine, Nov. 4–7, 1968, New Orleans, LA, 1968.
Ziskin MC. Detection of carotid artery bifurcation stenosis by Doppler ultrasound, A review. Invest Radiol 1969;4:112.
Ziskin MC, Bonakdarpour A, Weinstein DP, Lynch PR. Contrast agents for ultrasound. Invest Radiol 1972a;7:500–505.
Ziskin MC. Survey of patient exposure to diagnostic ultrasound. In: Reid JM, Sikov MR, eds. Interaction of ultrasound and biological tissues. Bethesda, MD: DHEW Publication (FDA) 73-8008, 1972b:203–206.
Ziskin MC, Romayananda N, Harris K. Ophthalmologic effect of ultrasound at diagnostic intensities. J Clin Ultrasound 1974;2:119–122.
Ziskin MC, Thickman DI, Goldenberg NJ, Lapayowker MS, Becker JM. The comet tail artifact. J Ultrasound Med 1982;1:117–121.
Ziskin MC. Measurement uncertainty in ultrasonic exposimetry. In: Ziskin MC, Lewin PA, eds. Ultrasonic exposimetery 1993:409–443.
Ziskin MC, Lewin PA. Ultrasonic exposimetery. Boca Raton: CRC Press, 1993.

APPENDIX

Addresses for authors of personal histories[2]

Dr. J. Angell-James, The Leaze, Sundayshill Lane, Falfield, Wotton-under-Edge, Gloucester GL 12 8DQ UK.

Dr. Stanley B. Barnett, CSIRO Telecommunications & Industrial Physics, Bradfield Road, P.O. Box 218, Lindfield 2070 Australia.

Dr. Klaus Brendel, Physikalisch-Technische Bundesanstalt, Mechanics and Acoustics, Bundesallee 100, 38116 Braunschweig, Germany.

Professor Paul L. Carson, Department of Radiology, Director, Basic Radiological Sciences Division, The University of Michigan Medical Center, Kresge III Research Bldg. (R3315), Ann Arbor, MI 48109-0553 USA.

Professor E. L. Carstensen, 103 Eastland Avenue, Rochester, NY 14618-1027 USA.

[2] P. P. Lele died on 11 June 1998.