A HISTORY OF HIGH INTENSITY FOCUSED ULTRASOUND (HIFU) THERAPY

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***Abstract*— Therapy ultrasound has, for many decades, been thought of as the poor relation of diagnostic ultrasound imaging. However, its roots predate the scanning applications of this most versatile of energy forms used in medicine. In this review the history of high intensity focused ultrasound (HIFU) is traced from its first mention in 1942 until 1970 at which point there was a lull in interest until its resurgence in the 1980's.**

***Keywords*— therapy ultrasound, minimally invasive, brain, transducer, cancer**

I. Introduction

It could not easily have been predicted that the report by Wood & Loomis in 1927 that ultrasound energy can adversely affect living organisms would trigger areas of research that have led to the development of a number of different therapies [(1)]. The appeal of ultrasound energy for therapeutic purposes is enhanced by its physical characteristics when propagating through water at low megahertz frequencies. These allow tight focusing into volumes and distances from the source that are clinically relevant.

While ultrasound has many potential therapeutic uses, including for physiotherapy treatments of soft tissue injuries [(2, 3)], the acceleration of healing of bone fractures [(4)], and the improvement of drug delivery through the skin (sonophoresis) [(5)], it has been its applications in neurosurgery and cancer therapy that have been the most commonly adopted to date, with the use of high intensity focused ultrasound beams being the most highly favoured, especially in the early days. This technique is referred to interchangeably as HIFU or FUS (focused ultrasound surgery). Historically, it was the applications in the brain that largely drove the development of HIFU devices. In this review, the history of HIFU from its inception until 1970 will be presented.

As can be seen from Figure 1, there was a lull in developments in this area in the 1970's, with a rapid resurgence of interest from the mid 1980's.

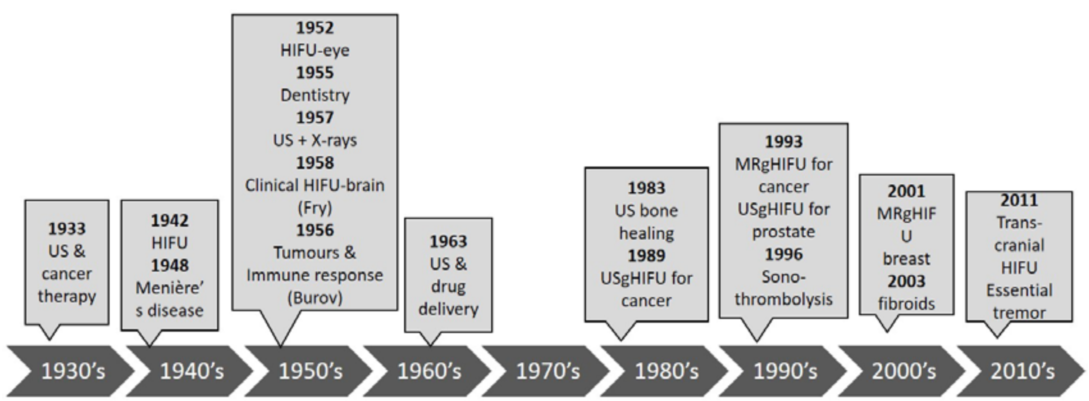

Fig. 1 Timeline, showing introduction of new HIFU applications

From a medical physics perspective HIFU provides many challenges. The different aspects of a HIFU treatment involve initial imaging and treatment planning, treatment delivery and its monitoring, and then follow up. Although early HIFU was always performed under ultrasound guidance (USgHIFU), more recently, magnetic resonance imaging (MRgHIFU) has found favour, largely because of the ability to run thermometry sequences.

II. PRINCIPLES OF HIFU

It has been known since the time of the early Egyptians that heat can play a role in cancer therapy [(6, 7)]. The field of hyperthermia, in which tumours are subjected to either radio- or chemotherapy and elevated temperatures has been extensively explored clinically, and pre-clinically. For this application temperatures of 42-45^{o}C are maintained for times of up to 60 minutes. The heat and adjuvant therapy are applied simultaneously, or, where this is not possible, as close together in time as possible. There are a number of disadvantages to this technique as it requires repeated treatments and, perhaps more difficult technically, it is important that the chosen temperature remains within defined limits for the duration of the heating period. This is difficult to maintain as the body's response is to increase blood flow to provide cooling, adding to the problem of accurate intratumoural thermometry over the entire heated volume.

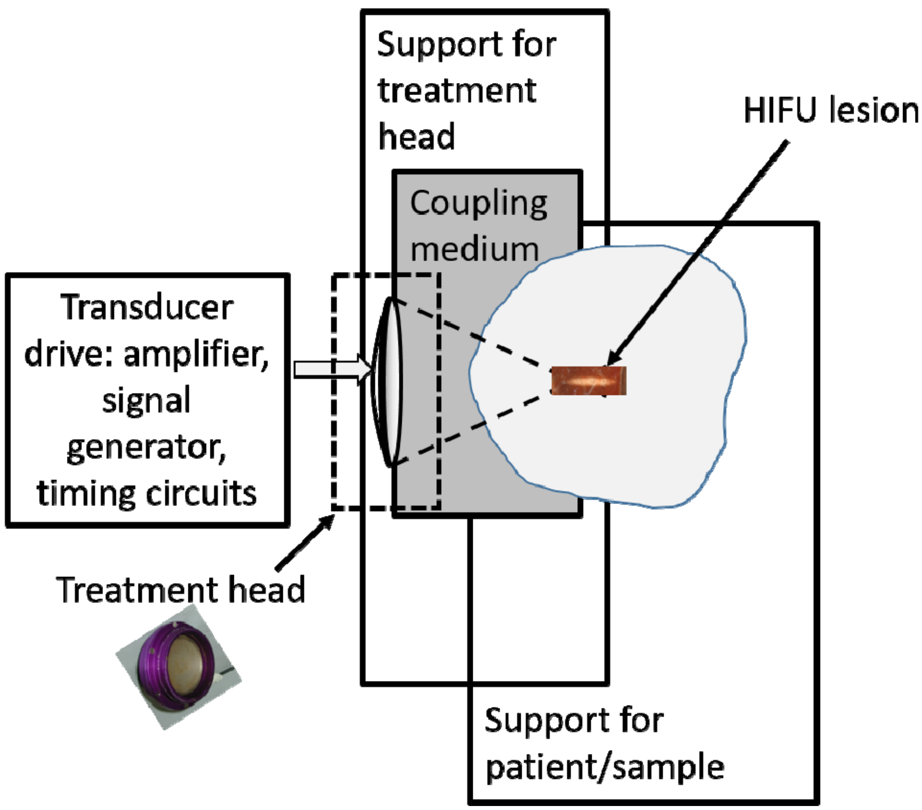

Fig 2. Schematic showing the necessary components of a HIFU system.

HIFU, in contrast, relies on the fact that higher temperatures (in excess of 56^{o}C held for ~ 1 second) can lead to instantaneous cell death (thermal ablation). This can be achieved in a single, short treatment, and as long as thermal necrosis is seen, there is no need for thermometry. Thus, if heating to these temperatures can be achieved selectively in a desired volume (for example, a tumour), with no damage to surrounding tissues, then thermal ablation becomes a viable therapeutic option. While it is often possible to insert a probe capable of generating ablative temperatures into the target (and indeed the Egyptian Edwin Smith papyrus [(8)] suggests the use of a 'fire drill' – a heated stick – inserted into a breast tumour), the non-invasive solution offered by HIFU appears to have significant advantages,

Figure 2 shows a schematic of the principles on which a HIFU treatment works, and the components that are essential to delivering such a treatment. Histologically, the ellipsoidal region of damage created (the 'lesion') has what has been described as an 'island and moat' appearance [(9, 10)], with the boundary between normal and affected tissue being very sharp. Tissue within the 'island' appears almost normal, with cells being heat fixed, and in the 'moat' cells are severely disrupted, with liquefaction, deformed nuclei, and absence of structure.

III. HIFU DELIVERY

While Wood & Loomis' 1927 observations of stimulating and lethal effects in unicellular organisms, small fish and animals, made using a plane transducer [(1)] generated a considerable amount of interest, Lynn et al [(11)] (working in Columbia University, New York) were the first to publish biological effects in focused fields (1942). They claimed that it was the finding of Grűtzmacher that ultrasound waves could be focused with a gain of 150 using a curved quartz surface [(12)] that stimulated their studies. Grűtzmacher had described a constant thickness spherical piezo-electric quartz shell (concave – convex) cut so that the X- crystallographic axis coincided with the beam axis (X-cut), and with electrodes plated on both surfaces.

In their first published paper, Lynn et al describe using 835 kHz ultrasound, generated by putting an oscillating electric potential across the opposite faces of such an X-cut concave quartz crystal. This potential was supplied by "what amounts to a small 0.5 kW radiotransmitter, such as used for code signaling". The power supply design is described as a "full wave mercury rectifier circuit (type 866) with choke input filter". Lynn et al's design of crystal mount [(11)] is one that has been replicated by many. The mounting of a transducer to maximize its acoustic output for therapy has specific requirements. The crystal must be held securely and evenly around its circumference, with as little damping of its vibrations as possible. The

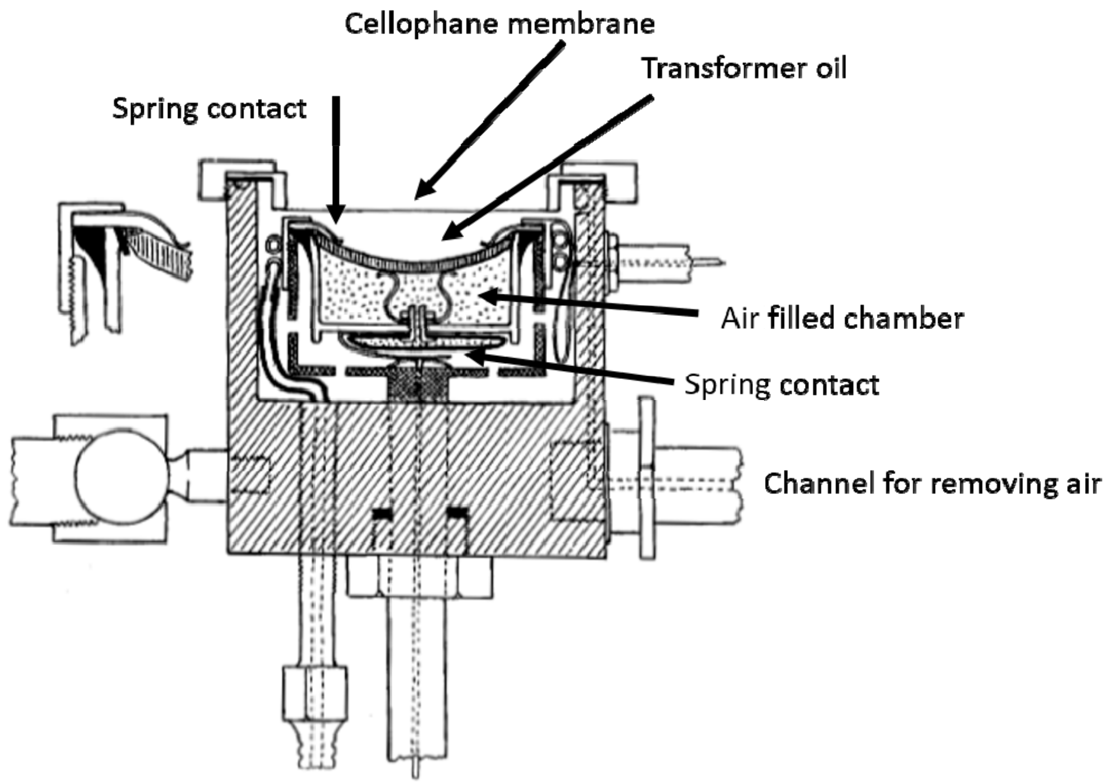

Fig. 3 Transducer mount used by Lynn et al (11).

method of mounting should be such that there is minimum restraint as this can lead to reduced output and mechanical failure. Their solution was to air back the quartz crystal, in a way suggested by earlier authors. Figure 3 shows their transducer design [(11)]. The air backing minimizes damping, but also serves as a total reflector of the sound wave, thus enhancing the forward power from this transducer. This method has been used to effect to the present day.

Changes in focal depth for this system were achieved by mounting the transducer and its immediate casing on a piston structure that enabled it to be moved forwards and backwards relative to the 'thin cellophane diaphragm' that was in contact with the skin. Cooling was provided in part by surrounding the transducer, mounted on a universal joint, with clear transformer oil.

These authors describe the calibration of their system in delightful detail. They placed 'several millimetres' of oil on the top of the front cellophane membrane, and describe the acoustic fountain obtained when the transducer is activated, pointing vertically upwards : ‘a conical column, from the top of which oil droplets were thrown upward and outward so that the entire phenomenon resembled an erupting volcanic cone’. They claimed the height of the cone to be a ‘reliable (but crude)’ indicator of output, reporting that a plate current of 220 mA, potential 2400V gave a peak output of 900 mA of RF current, and a cone 12.5 cm high with spray extending to twice this height. More details of early calibration methods are discussed in section V below.

Further studies with the Columbia group’s device showed that they could produce focal damage in blocks of beef liver only when full power was applied for 10-15 seconds. Follow up experiments in the brains of 3 cats and 2 dogs, resulted in scalp damage in all subjects, and with brain damage only being seen in the 2 animals who were exposed to maximum acoustic power. The necessity of applying sufficient energy very fast when seeking selective focal damage is discussed in this paper. They cite the work of Gohr & Wedekind [(13)] in recognizing that the presence of blood perfusion has an effect on the ability to produce focal lesions.

A. Brain studies

Lynn’s group was also the first to publish detailed histology of lesions created in the brain [(14)]. They exposed the spinal columns of 3 dogs, 30 cats and 4 monkeys to 835 kHz ultrasound from a 5.5 cm focal length transducer. They reported ‘partial success’ with trans-cranial and trans-vertebral focal lesions of the central nervous system. While they were able, at will, to produce irreversible, reversible or partially reversible damage which they refer to as ‘disabilities’, they inevitably created damage to the overlying skin and soft tissues. The damage included cortical blindness, cerebellar ataxia, monoparesis, and bilateral paresis of the hind extremities. The lesions were conical in shape, and this paper is one of the first to report mechanical tearing and formation of cavities, which, they postulated were due to the ‘sudden explosive release of dissolved gases from tissue solution’. They found that ganglion cells were more susceptible to damage than glial elements, and also that the least affected components of the brain were the blood vessels.

A number of other people were also working on this topic at this time (1949 – 1952) but were deterred by the extent of damage to the scalp, and their inability to create lesions deep in the brain when exposing trans-cranially [(15-18)]. Zubiani [(19)] managed to get lesions deep into the brain, but only by using a moving transducer and crossed beams, but he gives little detail about the exposures. He treated 30 patients with brain disorders using low intensities (0.6 – 1.5 W cm^{-2}) at 500 kHz and reported that ‘subjective symptoms’ disappeared with no concomitant cellular damage. Denier [(20)] also reported treating 3 patients with dementia, Parkinsonism and torticollis to ‘some benefit’. Wall et al [(21)] used a focused beam to create lesions in cat and monkey brains through a skull opening.

Petter Lindström (Swedish neurosurgeon, married to the actress Ingrid Bergmann for a while) performed a trephine opening in the skull vaults of dogs and rabbits in order to gain direct access to the brain for 1 MHz ultrasound. This work was published in 1954 [(22, 23)]. They used cone shaped cups of different lengths and angles filled with saline to achieve focusing and to couple sound into the brain. Unsurprisingly, he found that the degree, extent and depth of the tissue damage was a function of intensity, exposure time and size of the sound beam at the entry point into the brain. He discovered that exposing through the dura mater resulted in smaller lesions than when it was turned back. Lindström reported that he could make graded, controllable lesions extending deep into the white matter with comparatively little damage to the cortex. He therefore concluded that the risks and complications arising from the use of ultrasound to produce functional changes to replace lobotomy clinically would be minor compared to operative lobotomy. The team went on to try this on 20 patients between May & October 1953, 17 of whom had intractable pain from inoperable cancers, exposing through a 1.5 inch (3.8 cm) ‘button’ opening in the calvaria. 1MHz ultrasound was used, with the output being described as 7 W cm^{-2} ‘close to the crystal’, but being focused using the cone shaped cup described above [(23)]. It is reported that there were no post-operative complications, and 10/17 had practically complete relief from pain over the 2 week – 11 month observation period, appeared to be ‘more relaxed’ and had ‘better appetites’. Four more patients showed improvement with pain decreasing after treatment. The remaining three patients gained no relief from the treatment, although one was offered two more, after which pain relief resulted. 15 patients died from their cancers following (but not connected with) treatment, providing access to post mortem treated brain tissue. Apart from the expected minimal damage under the dural flaps that were lifted in the first patients treated, most patients appeared normal, with minimal damage, where seen, being in the white matter.

Lindström recognized the fact that it would be important to keep the head stationary while treating, and worked with his Swedish colleague Lars Leksell to produce a stereotactic device that would enable ultrasound treatment of psychiatric disorders. There is little published record of this, but in a 1951 paper, Leksell [(24)] shows his frustration with the need for a craniotomy, and moved on, developing stereotactic frame based radiosurgery, and later developing the gamma knife for which he is most famous (1967). Figure 4 shows the transducer and frame developed by Lindstrom and Leksell in 1949-1950. They successfully produced a system for creating periventricular lesions.

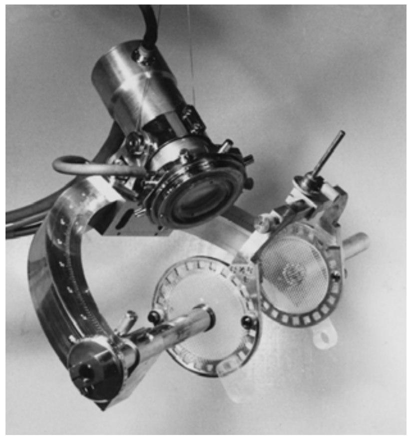

Fig. 4 Transducer head and stereotactic frame developed by Lindstrom & Leksell. (photo courtesy of Dan Leksell)

Lindström concluded that the methods he used needed further improvement. Although the required skin incision was not troublesome, the trephining was unpleasant, with patients complaining of the 'noise' and the 'shaking'. In a footnote, we are told that higher intensities (12 W cm^{-2}) had been trialed. In Lindström's opinion, a multiple beam system as described by Dussik [(25)] would only have restricted use in clinical neurosurgery since it would require several holes, or a large bone flap to be created. However, the same conclusion was not reached by the Fry brothers (William & Frank) working in the Bioacoustics Laboratory in Urbana, Illinois. After 5 years working with simple systems, they developed a treatment head that used four focused transducers mounted so that the beams overlapped at a common point, thus creating a high intensity region [(26)]. Quartz crystals, resonant at 1 MHz, fronted by polystyrene lenses were used. Coupling was achieved using physiological saline degassed by boiling. In their preclinical work, an acoustic window was created by removing a portion of bone overlying the target region. The animal's head was held in a standard stereotactic apparatus, and the depth of the focal region altered by vertical movement of the transducer mount. The system was tested on 31 cats. It was found that nerve fibres were damaged most readily, with nerve cells and blood vessels remaining intact, even in the focal zone. The paper describes the methods used to localize the focal region in the brain and to calibrate the acoustic output. This group has

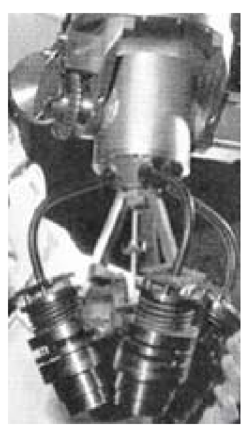

Fig. 5 4-transducer head developed by the Frys in Illinois for use producing HIFU lesions in the brain described an absorbing probe that can be used for mapping acoustic fields (see Section V below) [(27, 28)].

The Illinois team published prolifically on their research into the effects of ultrasound in the brain in the 1950's and early 60's [(10, 21, 26, 29-47)]. A publication in Science describes the lower threshold required to produce lesions in white matter (given as 51 atmospheres of acoustic pressure, acoustic particle velocity 4.8×10^3 cm s^{-1}, 1 second exposure) than in grey (53 atmospheres of acoustic pressure, acoustic particle velocity 4.9×10^3 cm s^{-1}, 2.5 second exposure) [(42)]. This was followed up a decade later by more very detailed studies in feline white matter which showed a linear relationship (with log(acoustic intensity) decreasing with increasing log(pulse duration)) in the threshold conditions for producing a lesion in the range 10^2 – 2.10^4 W cm^{-2}, 7 -2.10^{-4} seconds at 1,3 and 4 MHz [(48)]. Here they took a closer look at possible mechanisms involved, and hypothesized that at the low intensity/long pulse end of the graph the mechanism was thermal, and at the high intensity, short pulse end it was predominantly cavitational.

Frank Fry outlined the devices used by the Illinois group in a detailed, and informative paper [(31)]. He lists the required components for a HIFU system as a means for focusing the sound waves, coupling medium, rigid mechanical supports and moving devices for the transducer, supporting structure for the specimens, electronic drives and precision timing devices. They were refreshingly rigorous in also requiring a calibrating and field plotting system. The first system built by the Fry brothers was said to be designed as a prototype for human neurosurgery, and was far from portable. They used a double layer room structure. The upper room contained the positioning and support system for the transducer and the power amplifier driving it. The animal support structure, and the electronic controls were all in the lower room. The co-ordinate system and the connection between the two rooms is described as being accurate and rigid, allowing placement accuracy of 'a few thousandths of an inch' in the brain.

A smaller system, which also included the 4-transducer head configuration, was built in Urbana and installed in the University of Iowa hospital. This too was designed to be very rigid, with the patient's head being held in position by 4 steel pins located in 'depressions' drilled into the skull. X-ray imaging was incorporated into the system in order to establish the co-ordinates of relevant structures within the brain. The 'replacement accuracy' is quoted as being a few thousandths of an inch, allowing the patient to return for treatment after a planning session. Coupling was achieved using an air inflated 'rubber gasket' between the bottom of the open pan in which the 4-transducer head is immersed and the patient's head [(49)]. This system was used to expose the ansa lenticularis or substantia nigra of Parkinson's patients to treat their tremor [(50)]. Its use to expose human pituitary glands for patients with breast cancer met with limited success [(46)]. A second generation, simpler, clinical device was set up in the University of Indiana University Medical School in 1970. This was fully computer controlled and had 5-degrees of freedoms for spatial coordinate control. It had the added novelty that it provided B-mode ultrasound images that were synchronized with the HIFU transducer for targeting and monitoring treatments. It was used for treatment of brain cancer, and was called the "Candy machine" after a young lady who had brain cancer and was treated by Dr. Heimburger [(51)].

At the same time as the Illinois group were working in this area, there were teams in Massachusetts following similar lines. Padmaker Lele (a neurophysiologist with a laboratory at MIT) described a modified system that used a single transducer for producing lesions in the cat brain. He discussed ceramic piezo-electric transducers, but dismissed them on the grounds of their temperature dependent acoustic power output, and consequent accuracy and stability of calibration. He recommended the use of plane X-cut quartz crystal plano-concave plastic lens combinations, the lens being attached to the silvered front face of the transducer by a uniform thin film of degassed castor oil and held in place by a retainer ring. Conical applicators of different lengths were attached to the transducer/lens combination to give different available depths of the focus in tissue. The applicator's open end was sealed with a rubber condom. Coupling was achieved through distilled water or normal saline that was boiled for more than an hour, and stored under a layer of degassed mineral oil until siphoned off for use [(52, 53)]. Lele used this system to perform extensive studies of the reproducibility of lesioning in plastics and in tissue.

At Massachusetts General Hospital (MGH) a team (comprising Ballantine, Ball (a neurosurgeon), Hueter, Bell, Nauta (a neuroanatomist), and Cosman) were also creating a HIFU delivery device [(54-58)]. They describe single transducer heads operating at 1 or 2.5 MHz. These frequencies were chosen to provide appropriately sized foci for the small animal studies they were conducting. The choice made in Massachusetts from the outset was to use a single transducer head comprising a quartz crystal fronted by a tuned steel plate, a plano-concave polystyrene lens and a conical water filled applicator. They used both frequencies to study paraplegia following the exposure of mouse spinal cords. A study was undertaken to investigate the ultrasound dose (here defined by the intensity and exposure time) required to produce damage, the correlation between dose and extent of damage, interdependence of intensity and time as measured by the paraplegia endpoint, and, importantly, the mechanism of action. It was found that damage was much more extensive at 1 MHz, which was attributed to the larger focal region at this lower frequency. The mechanistic studies indicated that when the intensity exceeded 150 W cm^{-2} the damage was predominantly thermal in nature, whereas at lower intensities mechanical stresses appeared to be more important.

The studies with this system in mice led to work on larger mammals in 1960, with human exposures being the end goal [(56)]. A stereotactic device was developed. This combined a support for the subject (here, a cat), a counter-balanced column of a mobile X-ray set, a calibrated cross feed to allow vertical and lateral movement of the transducer and a commercial Horsley-Clarke machine (a stereotactic frame designed for making electrolytic lesions in the brains of large animals [(59)]). The radiofrequency generators and transducer head were developed by Bernard Cosman, who also worked on RF lesioning of the brain, and went on to start his own company, Cosman & Co., which became Radionics in the 1950's [(60)]. The frontal plane was targeted by moving the animal's support. It was still necessary to create an acoustic window by removing a portion of the overlying skull. This system was used to conduct a dosimetric study in cat brain, the exposure conditions for lesion production being found to be comparable to those used in the earlier mouse experiments. Presciently, one of the conclusions to their 1956 paper is that use of 'ultrasound lesions may offer a useful method for investigation of the nature of the blood brain barrier'[(57, 61)].

In the UK, a group working in the anatomy department of Guy's Hospital Medical School, also developed a system for studying HIFU lesions in the brains of large animals [(62-66)]. This was a collaboration between Roger Warwick (Professor of anatomy and one of the authors of the renowned Gray's Anatomy), researcher John Pond (physicist and inventor) and later Ken Taylor, research student. This team was the first to use a spherical segment (focused bowl) piezo-electric transducer to provide the acoustic field. In the reverse of the usual stereotactic procedure, the animal was placed on a milling machine that allowed its positioning with a quoted accuracy of a thousandth of an inch in 3 perpendicular planes relative to the transducer. Two different transducers were available, with focal lengths of 7.8 and 9.0 cm, and fundamental frequencies of 1 and 2 MHz respectively. Most of the work reported in their 1968 paper was conducted at 3 MHz (the third harmonic of the 1 MHz transducer, used because a 1 MHz transducer is more robust than its thinner 3 MHz counterpart). The focal position was determined using a thermocouple, its position then being indicated by a pointer fixed in relation to the transducer. In common with the other systems described above, the transducer head had a truncated Perspex cone attached to allow beam coupling to the brain. Both the Guy's and the MGH groups used goldbeater's skin to close these coupling cones. This is made from the gut of oxen, soaked in a dilute solution of potassium hydroxide, washed, stretched and beaten flat. This versatile membrane has been used to laminate gold in order that several sheets can be beaten at a time in producing gold leaf, and also, amongst other things is used for the repair of vellum, construction of early airships and the sealing oboe reeds [(67)]. In the ultrasound context, it has the attraction of being strong, elastic, hydrophilic and very thin (~25 μm), and so is better for transmitting high acoustic powers than, for example, latex.

Warwick & Pond describe in detail the microscopic appearance of the lesions obtained in the brains of cats and monkeys. They were able to confirm the 'island' and 'moat' appearance first described by Barnard et al [(10)]. While agreeing in the main with previously published histology (68) they found that whereas, for example, Bakay et al [(69)] had found that although there may be some changes in vessel walls, blood flow was not impaired, in these UK studies apparently intact blood vessels could be blocked.

The HIFU systems described above were typical of those used until the advent of phased array technology for high power applications [(70-79)]. This allows electronic movement of the focal volume without the need for mechanical translation of the transducer head. Similarly, the introduction of time reversal and other phase correction (adaptive focusing) techniques obviated the need for skull bone removal to provide an acoustic window, as judicious choice of signal phase and amplitude allows focusing behind a highly scattering medium [(80-86)].

B. Ophthalmology, cancer and other applications

Probably the first indication that high intensities of ultrasound can destroy specific ocular structures came in 1952 from Lavine et al [(87)] working at The Catholic University of America, Washington, DC, who demonstrated that cataracts were formed when the lens was targeted. Similar studies were carried out in Western Reserve University School of Medicine, Cleveland, Ohio by Purnell and colleagues [(88)]. In contrast to laser treatments in the eye, ultrasound effects are not reliant on absorption by pigmented structures, and can be focused at any point in the eye independently of the optical properties. It can be focused through the cornea and lens, through the conjunctiva and sclera, through a combination of these routes or onto the back of the eye. In the 1960's, the Ohio team used 3.5 and 7 MHz ultrasound to create circumscribed chorioretinal lesions and localized destruction of the ciliary body and suggested possible uses of this type of exposure in repair of retinal tear detachment, cyclodiathermy and destruction of intraocular tissue [(88-92)]. They used plane quartz transducers, 55 mm in diameter, with polystyrene lenses. The 3.5 MHz treatment head had an estimated maximum acoustic power at the focus of 900 W cm^{-2}, was in the form of a 'round bottomed cylinder' sealed by a polyethylene membrane, with the focal point capable of being positioned between 1 and 28 mm from the front.

For the 7 MHz head, the reach of the focal point is said to be 1-17 mm from the front of the truncated cone sealed with a vinylidene chloride membrane, and the maximum focal power is quoted as being 60 W cm^{-2}. 240 rabbit eyes were used in a study that demonstrated that selective chorioretinal lesions could be created [(90)]. Despite encouraging results, the team suggested that the danger of inadvertent cataract production and the prolonged exposure times made treatment of retinal detachment hazardous at that time.

The team best known for its work on therapy ultrasound and ophthalmology was a collaboration between the physicist Fred Lizzi at Riverside Research Institute, New York, and Jackson Coleman, an ophthalmic surgeon at Cornell University [(93-98)]. They worked on a number of conditions of the eye including the treatment of glaucoma, retinal detachment and vitreous haemorrhage, and founded the company Sonocare. The timing was perhaps unfortunate as laser techniques were being developed at the same time, with these being perceived as being simpler to use.

For many years, patients with Ménière's disease had limited options for treatment. Krejci applied ultrasound in an attempt to provide relief from the vertiginous attacks that are a symptom of this affliction [(99, 100)]. He used a narrow ultrasound beam to irradiate the vestibular portion of the inner ear, after doing an operation to expose the bony labyrinth. He eliminated the vestibular function, but preserved cochlear function. Michele Arslan, working in Padua took his technique further, using a narrow beamed 0.8 – 1.0 MHz ultrasound transducer to expose the bony wall of the lateral semicircular canal in order to destroy vestibular function [(101, 102)]. He took care to prevent lateral transmission of sound to the facial nerve by shielding, and heating was prevented by cooling. The technique appeared to resolve the problem of vertigo in 95% of patients, and so was taken up by a number of other centres [(103-114)]. In some cases, it was not possible to get sufficient intensity through the lateral semi-circular canal to get the require effect. A Bristol team under Angell James therefore developed a method of reducing the thickness of this structure to aid transmission.

Although there is now considerable interest in using HIFU (sometimes in conjunction with radiotherapy or chemotherapy) for the treatment of cancer, in the time frame under discussion here, there was little activity in this area. Probably the first mention of the use of ultrasound for the treatment of cancer was in 1933. Szent Györgyi from Budapest wrote a letter to Nature about an ultrasound exposure of 723 kHz; 'The effect of this radiation on Ehrlich's carcinoma has been studied by B Gözzi and found to have no specific effect on this tumour' [(115)]. The final sentence of this letter is dispiriting : 'For lack of funds our investigation has been broken off'. This discouraging view of ultrasound in cancer therapy (albeit, not strictly for HIFU) continued for more than 2 decades, despite some encouraging pre-clinical results from Carl Dittmar in Frankfurt [(116)]. The Congress on Ultrasound in Medicine in Erlangen, Germany in 1949 published a resolution (unsurprisingly, the 'Erlangen Resolution') which stated that 'Ultrasound is not suitable for cancer therapy and its clinical use should be discontinued'. Pohlman [(117)] performed an analysis of 133 clinical cases, finding improvement in only 17% of patients. Stuhlfauth [(118)] added to this stance, pointing out that, apart from Woeber's work combining X-rays with ultrasound therapy [(119)], '..the fact that …. tumours have never been successfully treated in human beings is due to the too low ultrasound intensities used which may also lead to an opposite effect'. He therefore called for people to 'refrain from sound treatment of tumors, since rapid growth of metastases was observed after sound treatment'. It is clear that there was little outside knowledge of research being carried out in the USSR in the 1950's, most probably because the publications were only in the Russian literature. An extraordinary man, Andrey Konstantinovich Burov, was head of the Laboratory of Anisotropic Structures, Academy of Sciences, and corresponding member of the Academy of Construction and Architecture

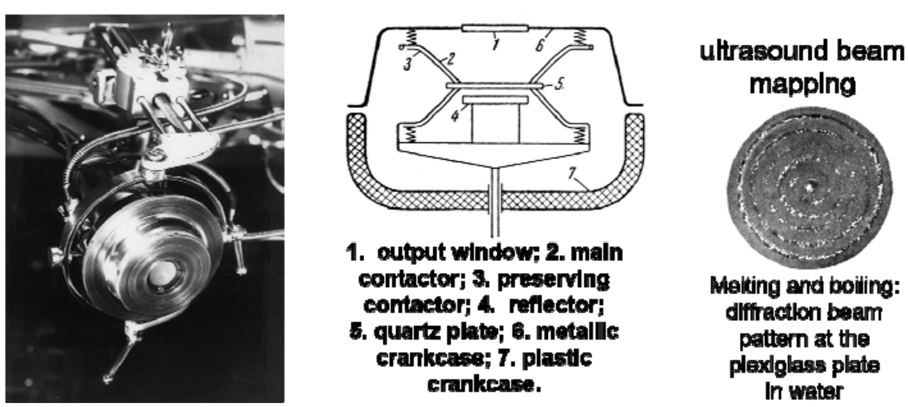

Fig. 5. System used by AK Burov & co-workers to treat Brown Pearce tumours in rabbits. (Photo courtesy of Burov archives)

of the USSR. At the end of a stellar career as an architect, where he worked with many of the greats of that era, including Le Corbusier, and he designed film sets for Eisenstein, he turned his attention to treating tumours with ultrasound. They used unfocused 1.5 MHz beams produced by quartz transducers, operating at 200 W cm^{-2} (continuous wave) (~ 500 W cm^{-2} in a pulsed regime) [(120, 121) (see Figure 5)]. They used the pulsed regime to treat Brown-Pearce tumours in rabbit testicles, finding that in 40-80% of cases, the tumour was resolved completely several months later, and a clear immune response was observed with metastases in the rabbit eyes disappearing [(122, 123)]. This was said to be a non-thermally induced response to the short (1-2 sec) exposure. The team also conducted clinical trials of melanoma treatments at the N.N.Blokhin Institute of Experimental Pathology and Therapy of Cancer. They treated 10 patients mainly in terminal stages of melanoma. Complete resorption of the tumour was seen in some, but not all, patients [(120)].

IV. HIFU TREATMENT PLANNING & MONITORING

In the 1950's and 60's pre-clinical HIFU was planned and monitored, if at all, using ultrasound imaging. The quality of the imaging was limited by the technology available in those years. Ultrasound lesions appear as hyperechogenic regions on a B-mode image. MRI was not proposed for guiding these treatments until 1992, but soon took off, especially for treatments in the brain [(83, 124-130)]. A major advantage of MR guidance of ultrasound therapies is the ability to overlay temperature rise maps on top of anatomical images. Ultrasound guidance of HIFU in patients is first mentioned in a paper by Heimburger in 1974 [(131, 132)]. Further descriptions of ultrasound guidance wait until the late 1990's with the advent of the ultrasound guided clinical devices being developed by groups in China, the UK, France and the USA for use in cancer, uterine fibroids and the prostate [(133-155)].

V. HIFU MODELLING & CALIBRATION

Gerald W. Willard and H.T. O'Neil, working at Bell Telephone Labs in New Jersey studied focused sources in some detail. In a 1949 seminal paper, O'Neil developed the theory for describing the field from a concave spherical transducer [(156)]. Despite only dealing with linear conditions, this is still used as the basis for field modelling by many people today. He was foresighted in suggesting that the results might be useful for design purposes and for correcting measured pressures and intensities to take into account the finite size of the measuring device. The solutions presented are for the distributions of pressure, particle velocity and intensity along the beam axis, but, perhaps more interestingly, also in the focal plane.

The source modelled is a concave spherical radiator with a circular boundary of diameter large relative to a wavelength (λ) and to the depth of the concave surface. Constant amplitude and phase are assumed, with the amplitude being sufficiently small that cavitation and non-linearity can safely be ignored. The pressure amplitude P_A at the centre of curvature is given by $P_A = \rho c u_0 kh$ where ρ is the mean density, c is the speed of sound in water, u_0 is the normal velocity of the surface, h is the depth of the concave surface, and k is given by $2\pi/\lambda$. This is close to the highest pressure in the field, except when kh is small. The relative pressure in the focal plane at an angle θ from the axis is the same as that at a large distance from a flat circular piston ($2J_1(ka \sin \theta)/ ka \sin \theta$) where J_1 is a first order Bessel function and a is the transducer radius. O'Neil notes that his theory matches Willard's experimental data [(157, 158)].

It is imperative that, when these high intensity focused fields are used for therapeutic benefit, they can be accurately characterised. Willard and Virginia Griffing & Francis Fox (from The Catholic University of America, Washington, DC) [(159)] were amongst the first to take this seriously, with both teams describing the use of the fountain obtained when the beam is fired through water on to an angled reflector, and thence to an air interface, to assess transducer output, as first described by Wood & Loomis [(1)].

Willard's 1949 paper [(157)] shows some of the first Schlieren images of focused fields, although probably the first reference to this method is in Richardson in 1940 (160) who in turn cites its description by Hiedemann & Osterhammel in 1937 [(161)]. While focused fields can be readily visualized using Schlieren techniques, this has only recently become quantitative [(162, 163)]. He also describes the use of highly attenuating, non-reflecting materials placed at the beam focus for investigating the beam. He refers to rubber, phenol fibre and methacrylate plastics (eg. Lucite) as being suitable. He described the appearance of 'little protuberances of melted material, and an 'odour of overheating' in rubber and phenol fibre. He was able to produce localized internal heating using plastics that were less absorbing. This builds on the work of the Columbia group who used paraffin blocks to demonstrate melting [(11)].

Willard also mentions, as an aside, that 'when a person's finger is placed at the focus, an input of >100 volts (1W) produces a sensation of burning, though none of the normal burn characteristics (redness or blistering….). He does not recommend this as a method of determining the focal position, providing the caveat that there may be considerable danger of causing 'serious internal injury' if the feeling of discomfort is ignored.

This paper also describes a simple radiation force balance [(157)]. This allowed what Willard termed 'fairly quantitative' estimation of the acoustic intensity. An absorbing target is mounted on a vertical arm mounted on to a horizontal bar resting on two supports. Two horizontal arms are attached to the axle supporting the vertical bar. These have moveable weights mounted on them. On one side is a counterweight whose position can be adjusted to give a zero (horizontal) setting in the absence of a sound beam. The other arm mounts a balance weight. The radiation force from a sound beam incident on the absorber upsets the equilibrium until the position of the balance weight is adjusted to bring the system back to the zero position. Hill [(164)] also describes this type of system. The insertion of a diaphragm with a hole between the target and the source allows assessment of, for example, the intensity at the focus. Figure 6. shows the radiation force balance used to perform acoustic power measurements at the Institute of Cancer Research. The reflecting stainless steel coated target (A), horizontal rod (B), masses (D) and counter-balance masses (C) are shown. The length of the vertical rod (l), mass displacement (x) and direction of the acoustic field are also seen. Measurements were made after first balancing the horizontal rod following submersion of the target in degassed water. On the horizontal bar, accurately known masses (m) were placed at measured distances from the pivot (l_1) in order to counter-balance the radiation force. The radiation force (F_{rad}) could then be calculated by equating moments around the pivot, $F_{rad}\, l_0 = m\, g\, l_1$ where the target is a distance l_o from the pivot. The conversion of force to acoustic power for an absorbing target is 69 mg/Watt [(54)]. The development of radiation force methods for the measurement of acoustic power and intensity is described in more detail elsewhere in this history: www.mpijournal.org/pdf/2021-SI-05/MPI-2021-SI-05.pdf pp519-536.

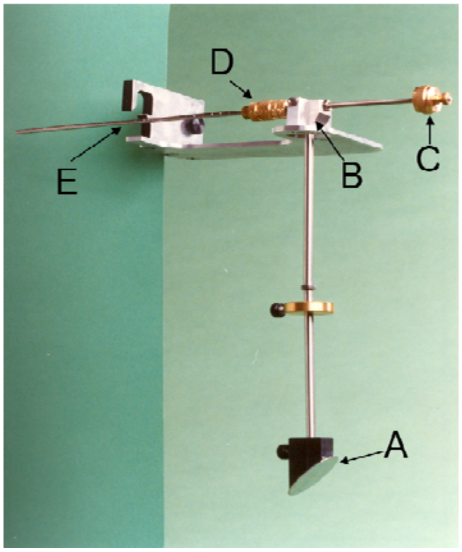

Fig. 6 Equilibrium balance for measuring radiation force

Safe and effective delivery of an ultrasound treatment also necessitates detailed knowledge of the pressure distribution. Fry & Fry described the use of thermocouples for this purpose [(27, 28)]. The probe consisted of a 12 µm wire thermocouple whose junction was imbedded in sound absorbing medium (a thin disc of castor oil) that matched the impedance of water. The oil is encased in a thin polyethylene membrane. The thermal emf is recorded on a galvanometer. They describe an initial steep temperature rise when the probe is in an ultrasound field, followed by an 'almost linear' portion of the curve. The steep rise is attributed to viscous heating due to the relative motion of the wire and the oil. These probes have been described in more detail in www.mpijournal.org/pdf/2021-SI-05/MPI-2021-SI-05.pdf p540. More recently thermistor probes coated in absorbent rubber have also been explored [(165)]. Modern beam plotting is more likely to use miniaturized ceramic piezoelectric probes or PVDF membrane hydrophones [(166)].

VI. Conclusions

Therapy ultrasound in general, and HIFU in particular has generated considerable interest with consequent potential applications in the 21st century. While it is generally recognized that this field has its roots in the 1940's and 50's, even before imaging ultrasound techniques, the intervening history is often overlooked. In many ways, current pre-clinical knowledge of HIFU and the way in which it interacts with tissue has not moved on far, but what has changed is technology. We now have the ability to image targets at depth within the body, to reconstruct a focus after transit through a strong scatterer such as the skull, and create ablated volumes using phased arrays. Used judiciously, for appropriate applications, there is no doubt that HIFU will continue to play a role in a number of medical specialties.

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