

## History of Ultrasound in Medicine from its birth to date (2022), on occasion of the 50 Years Anniversary of EFSUMB

A publication of the European Federation of Societies for Ultrasound In Medicine and Biology (EFSUMB),  
designed to record the historical development of medical ultrasound

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### Abstract

The history of the European Federation of Societies in Ultrasound in Medicine and Biology (EFSUMB) is closely related to the general history of ultrasound. In the presented paper the physical background and history of technologies including A-mode, Time motion or M-mode, 2D Imaging (B-mode) are summarized. In addition, ultrasound tissue characterization, Doppler ultrasound, 3D and 4D ultrasound, intracavitary and endoscopic ultrasound, interventional ultrasound, ultrasonic therapy, contrast enhanced ultrasound (CEUS) and key developments in echocardiography are discussed.

**Keywords:** history; EFSUMB; ultrasound

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### Introduction

Medical ultrasound (US) is continually developing. New techniques producing better and better images with more clinical applications are continually evolving, and this document can only provide a snapshot of progress to date.

“What is happening beneath the skin?” is a question that has puzzled physicians and anatomists, at least from the times of Galen and Leonardo. Some answers started to emerge with Röntgen’s 1895 discovery of X-rays, and their use in forming shadow-images (so-called radiographs). The extension of this idea to another physical phenomenon – sound waves – was explored by the Austrian neurologist (psychiatrist) Karl Dussik and his brother Friedrich, a physicist, who began using ultrasonic transmission through the head and photographic plates to record the results, rather than X-rays and dyes, to discover abnormalities in the shape of the ventricles in the brain. By moving the transmitter around the skull and registering the energy of the transmitted beam, a pattern of dark and light patches, somewhat like a television image, was built up on a photographic plate, producing what they called a “hyperphonogram”. The physical principle involved was the attenuation of the sound as it passed through the head. The Dussiks published their findings in 1942 and 1947 [1,2]. Unfortunately, the aberrations introduced by transmission through the skull gave rise to artifacts that distorted and degraded the image, and the method did not provide useful diagnostic information. Güttner and colleagues in Erlangen, Germany, showed in 1952 that the “hyperphonogram” images were artefacts, which resulted almost entirely from attenuation of the ultrasonic energy by the skull and not by the brain. Similar images could be made from just the skull [3].

Dussik’s work built on earlier uses of US, namely for testing materials. The Soviet physicist Sergei Sokolov and also the German Otto Mühlhauser [4] both proposed that US could be used for non-destructive testing of metals to detect hidden flaws [5]. What they seemed not fully to have considered was that X-rays and sound waves are quite different in the ways they transmit through tissues. In both methods energy is lost, and the beam is attenuated. However, absorption of the energy into the tissue, and scattering of the energy out of the beam, occur in quite different ways and contribute differently to the total transmission loss. Moreover, unlike X-radiation, US is easily reflected, refracted, and diffracted, altering the direction and amplitude of the wave. Later works exploited the very small amount of reflection and backscatter as the basis for modern practice. Now the effects of attenuation, the basis of radiography, are greatly reduced [6].

### The Physical Background

The basic properties of sound were described in the classic work of Rayleigh, whose ‘Theory of Sound’ was written during an 1871 honeymoon sailing trip up the Nile [7]. The key to obtaining numerically useful information

from sound waves came from the 1880 discovery, by the brothers Pierre and Jacques Curie, of the (direct and reverse) piezoelectric effects. Pulse-echo ultrasonic medical imaging did not start to develop for another seventy years, until the 1950s. Then, the first pioneers explored whether the echoes from the newly developed industrial ultrasonic flaw detectors could reveal internal body structures. Much of the associated electronic technology was developed for radar during the Second World War. The ultrasonic pulse-echo technique itself was invented during the First World War, by a joint investigation of the French and British governments into methods for submarine detection. This earlier development had brought together three separate ideas to make it successful. The first was that pulsed sound could be used to measure underwater distance by timing the echo, as shown by Alexander Behm [8] in 1912. The second was that, by using US rather than audible sound frequencies, a torch-like beam could reveal both the distance and direction of an object. In 1912, shortly after the “unsinkable” Titanic had hit an too late seen iceberg, and sunk, Lewis Richardson took out two patents on his acoustic method to detect obstructions at sea [9]. As a Quaker pacifist he did not promote it for submarine detection [7]. Then, in 1915, Constantin Chilowsky described an ultrasonic pulsed system for submarine detection. This was brought to the attention of the French physicist Paul Langevin, another pacifist, who had agreed to investigate means for submarine detection for the French navy.

The third, and most important, development was due to Langevin. Several methods were suggested to produce US, including magnetic vibrations, capacitive vibrations, underwater whistles, and sirens. None worked well. The piezoelectric properties of quartz had been considered and rejected by the French, by Robert Boyle and the nuclear physicist Ernest Rutherford, working in parallel for the British navy. It was Langevin, who had been a student of the Curie brothers, who realized that the quartz crystal should be cut in a particular direction, ‘x-cut’, to create an US wave powerful enough to form a sensitive receiver. By 1918, both French and British navies had completed successful sea trials using pulsed quartz transducers, aided by the new technology of thermionic valves, developed for radio communications [10]. This work formed the basis of SONAR (sound navigation and ranging) detection, which was more fully developed during World War II [11-13].

Langevin carried out his experiments in Toulon harbour in France during the first World War time, and Frank Hopwood, member of the British group of Rutherford, noted that “fish entering a beam of high-frequency sound waves were frequently killed by it” and

that certain observers, who plunged their hands in the same region experienced “a painful sensation” [7,14].

Several important and influential texts on ultrasonics were available. Among them was L. Bergmann’s book [15], which appeared in a 1939 English edition, and Benson Carlin’s *Ultrasonics*, published in 1949 outlining the physical principles of industrial US applications [16].

Medical pulse-echo imaging only became feasible with the advent of the fast electronics that was being developed by Firestone (his instrument was called a “reflextoscope” [17] in the USA and also in Britain by Watson-Watt and others, for use in radar. In 1941 the engineer Donald Sproule (UK) developed a pulse-echo ultrasonic instrument with a second, non-generating transducer to detect returning echoes. This particularly enabled methods of non-destructive testing in metals (NDT), with a device for the purpose – “Supersonic Flaw Detector” – being developed and manufactured in Glasgow by Henry Hughes & Son (later Kelvin-Hughes) [7].

Sproule befriended John Julian Wild in 1944 whilst he was a trainee surgeon working in London at the North Middlesex Hospital and seems to have given him an idea of using US to measure bowel thickness in the diagnosis of acute intestinal diseases. Two years later Wild was practicing in the Department of Surgery, University of Minnesota in Minneapolis and happily discovered a nearby US naval base (Wold-Chamberlain Naval Air Station) that was using an ultrasonic pulse-echo Navy Radar device operating at 15 MHz as a trainer for aircraft pilots [18]. Wild gained entry, and was soon starting to measure the thickness of excised tissue and published in 1949 the first of a remarkable series of papers that effectively set the agenda for much of the future work in the field of ultrasonic imaging [7,18-22]. His finding that echoes from tumor-invaded tissue could be distinguished from those produced by normal tissue in the same sample led him to apply US to cancer detection, particularly in the breast [22-24], and to lecture on “The use of ultrasonic pulses for the measurement of biologic tissues and the detection of tissue density changes” [18].

In 1952 together with Jack Reid, a recent graduate in engineering, Wild described the first real time B-mode scanner, which they used on patients to examine the breast [23]. In more detail, they built a B-mode contact scanner, which provided a cross-sectional, two-dimensional picture of the plane of the body scanned (and thus more accurate position information than one-dimensional A-mode). This scanner had electronics that permitted real-time scanning (images appeared directly on the screen at the time of scanning without the necessity of intervening film development) [23,25]. John Wild designed his flexible and rigid transrectal scopes for imaging the

bowel and deeper abdominal structures in the course of his ultrasonic research [19].

The potential of US to provide diagnostic information was more widely described at the First International Congress of Ultrasound in Medicine held in Erlangen in 1949 [2]. The earliest diagnostic applications of US to abdominal disease was the work of George Ludwig, in the late 1940s and early 1950s, on detection of gallstones embedded in the muscles of animals [26].

## Technology

### *A-mode*

The early development, the “A-mode”, displayed information about the size of the returning echoes as a function of time. The horizontal axis represented the time between ultrasonic pulse transmission and the received echoes (which corresponded to the depth where the echoes were generated), whilst the vertical deflection of the trace represented the amplitude of the reflected pulse from that corresponding depth. These systems were able to detect echoes from significant acoustic boundaries such as gallstones, brain tumors, and hemorrhage [27].

In Japan, this pioneering work was done with 15 MHz transducers by the physicist Rokuro Uchida at the research laboratories of Nihon Musen Company (later to become Aloka) and by physicians Kenji Tanaka and Toshio Wagai at Juntendo University School of Medicine in Tokyo [28]. In 1951 Tanaka and Wagai used an industrial A-mode 2 MHz flaw detection equipment as a medical ultrasonic scanner. They reported detection of intracerebral hematomas and brain tumors [27,29,30]. Wagai demonstrated the ability of US to detect gallstones and breast cancer, and Douglas Howry in Denver in 1952 published results using a 2 MHz industrial flaw detection equipment to study abdominal masses [31]. US was also widely used for ophthalmology during these early years [32-34].

A-mode was first constructed in Germany in 1949 by “Krautkrämer”, a company founded in Cologne by the brothers Dr. Josef and Herbert Krautkrämer. “Krautkrämer” was taken over by Siemens in 1956 to develop their devices for medical diagnostics [35].

### *Time motion or M-mode*

In 1953 the M-mode technique, a development of the A-mode technique, was introduced to record the movement of structures within the body. In the earliest implementation, the horizontal axis continued to represent the depth of the reflecting surfaces, but the size of the echo was shown by the brightness of the trace rather than the vertical deflection of the trace (a B-mode scan). The

movements of the bright areas, representing the surfaces, could then be recorded by scrolling light sensitive paper past the face of the oscilloscope. Once storage scopes were developed the same result could be obtained, by slowly sweeping the brightness traces perpendicular to the depth time-base and thus generating a graphical display of the movement of interfaces against time [35].

In 1953, virtually simultaneously with the early Japanese work in Doppler echocardiography, Dr. Inge Edler, a physician at the University of Lund in Sweden, began a collaboration with the German physicist Carl Hellmuth Hertz that launched clinical echocardiography using the pulse-echo technique [36-39]. Edler and Hertz improved upon A-mode by developing M-mode to examine the movement of tissue structures, such as those of the heart valves and heart wall. Their first echocardiogram in 1953 used an industrial A-scope to make M-mode recordings on continuously moving 35 mm photographic film. The joint efforts of Edler and Hertz using an advanced Siemens ultrasonic reflectoscope for flaw detection was the beginning of cardiac US or echocardiography [38].

The first attempts to scan the heart with US had been made by Wolf-Dieter Keidel in Erlangen in 1949 when he had used transmitted US with the goal of measuring cyclical variations in cardiac volume [39]. After visiting Lund, Sven Effert who worked in Düsseldorf and then in Aachen, pioneered M-mode echocardiography in Germany from the late 1950s. In the USA echocardiography was developed from 1963 by Harvey Feigenbaum in Indianapolis; he wrote the first textbook, which was published in 1972 [40].

### **2-D Imaging**

Using the same idea of representing significant echoes by increases in brightness of a trace, there was work in the 1950s using US for anatomopathological tissue imaging – so-called B-scanning [18]. Two separate lines of work on this emerged that may be characterised as coming from anatomical and pathological points of view, the former associated with the name of Howry [31] and the latter with Wild [18,19]. Douglas Howry was a radiologist, whose approach derived from the observation that some organ boundaries – e.g., the fetal skull – give rise to strong echoes. This led to the development of scanning techniques that would optimise the chances of picking up what was considered as “specular reflections” [41]. This line of thinking also led the engineers to make use of display tubes that had been developed for radar and are “bistable”, in the sense that they would light up with strong echoes but ignore any lesser “noise”.

John Wild was a surgeon and was interested in tissues within these organ boundaries. These echoes would generally be ignored by bistable systems. A solution to the

problem was largely brought about by Kossoff’s group at the Commonwealth Acoustics Institute in Sydney, Australia, with their systematic approach to signal processing and display, which has since been largely adopted in common practice, demonstrating the importance of diagnostic information carried in the low-level “Gray-scale” echoes [7,42-44].

During the 1950s, simple B-scans and compound B-scans were applied to the neck and breast [23,24]. Nevertheless, during the early years of medical US, the most widespread clinical use was not for general soft-tissue investigations but in obstetrics and gynecology. Diagnostically critical outcomes were available, even with crude equipment, as a result of the echo contrast between soft tissue and fluid spaces, such as amniotic fluid and cystic fluid, and the contrast between the fetal skeleton and skull and other tissues. The lead was taken by Ian Donald in Glasgow, and the engineer Tom Brown, whose working partnership led to the successful commercial development of the ‘Diasonograph’ [45].

Alongside this work was the realisation that US offered the possibility of not just static but also dynamic imaging, at frame rates compatible with human visual perception (approximately 10 frames/second). Early scanner design was based on the use of a single-element transducer that could be moved in the scan plane. Several fast, “real-time” scanners were developed, some based on mechanical movement of the transducer more based on multi-element transducer array systems.

In 1962 Richard Soldner (Siemens, Erlangen, Germany) developed a completely new automatic scanning device with two and later three transducers (2.5 MHz) [46]. This was the first device with real-time technology (image frequency of 12-16/second) and gray scale display, initially introduced for breast imaging. In contrast to the bistable compound scanning systems, and depending on their strength, the brightness of echoes was displayed on the screen. Movement artifacts and tissue displacements due to transducers movements could be avoided. The results were disappointing due to the low transducer frequency and, therefore, low resolution.

In 1964 a 10-element array transducer for ophthalmology was developed by Walter Buschmann in cooperation with the Kretz company [47].

In 1965 Hans-Jürgen Holländer (Münster, Germany) and Manfred Hansmann (Bonn) introduced the Vidoson 635, electronically scanned, multi-element array scanner into clinical obstetrics and gynecology [48]. The first results were published at the 1<sup>st</sup> World Congress of Ultrasound Diagnostics in Vienna 1969 [49]. In 1972 his textbook on “Ultrasound Diagnostics in Pregnancy” was published [50]. The Vidoson technology was introduced



into internal medicine by Gerhard Rettenmaier (Erlangen, Germany) and his first results were also presented and published at the 1<sup>st</sup> World Congress in Vienna in 1969 [51]. Dieter Weitzel introduced Vidoson into pediatric medicine [52]. In summary the Vidoson was somewhat mobile, allowed point of care (bedside) imaging and shorter examination time in comparison to the compound scanning systems, and furthermore the system was cheaper.

2-D scanning of the heart was proposed by Hertz in 1967, which was before the technology was sufficiently developed for that to become routine [53]. The first electronic phased-array scanner was developed by the engineer Jan Somer in 1968 [54] and the first linear array scanner intended for the heart (but with technology more suited to abdominal scanning) was made by Nicolaas (Klaas) Bom and Charles Lancée in Rotterdam [55]. Further prototypes followed within a few years from several other groups, including a mechanical sector scanner by Jim Griffith and Walter Henry in 1973 [56,57] and a phased-array cardiac scanner by Thurstone and Von Ramm in 1974 [58].

In Europe, the Austrian Paul Kretz developed a mechanical working sector-shaped device with five rotating transducers (Combison 100) in 1979. In 1975, linear array electronic transducers were developed by ADR (2130) and later by Toshiba (SAL-20). Following the success of Vidoson Siemens introduced its Linear Array technology named Sonoline 8000, the first digital US device in 1982.

The development by the EMI company in 1970 of X-ray “Computerised Tomography” was a major step in the introduction of digital technology in medical scanning generally and was much welcomed by the manufacturers in their advertising of “Digital Ultrasound”, even if the advantages over analogue technology in terms of image processing and quality seemed minimal, at least initially.

#### **US tissue characterisation**

Wild [18,19] introduced the term “tissue comparison” in describing the different signals that he was recording from a metastatic tumor and surrounding normal tissue in the frontal lobe of an excised human brain. This opened up interest in the underlying physical phenomenon – acoustic scattering [59] – particularly as the parallel field of X-ray scattering had already led to advances such as the understanding of DNA structure. In the medical ultrasonic field, several different approaches to this topic have emerged.

The first issue of *European Medical Ultrasound*, the official journal of EFSUMB, published in August 1979, recognized the growing interest in US tissue characterization [60]. Thijssen, from Nijmegen, identified over 500 respondents working in some aspect of tissue char-

acterization, 62% of whom were physicians with the remainder from a variety of other disciplines. Thereafter, a successful series of European meetings on US tissue characterization were arranged. The associated publications facilitated scientific exchange on investigations about ultrasonic attenuation, scatter, acoustic impedance, sound speed and non-linear effects and on means to exploit these phenomena for clinical use [61]. This has led to the clinical application of Elastography – remote ultrasonic palpation – measurement of the softness/hardness, or “rheology” of different tissues similar to the palpation of superficial structures that every trainee doctor is taught [62,63].

#### **Doppler US**

Shigeo Satomura published the first medical application of Doppler-shifted US in 1956, only a few years after the first medical pulse-echo imaging was reported [64,65]. As a research engineer at Osaka University, Japan, Satomura successfully applied radar and US techniques to medical applications. These first reports showed that cardiac motion could be detected: in due course this was widely exploited for fetal heart rate monitoring and more narrowly in studies of tissue motion. Then, in 1959, Satomura showed the method to be sensitive enough to detect the movement of blood [66].

The first description of the speed of light from stars was made by the Englishman James Bradley in 1727 [67]. In US, the change in frequency caused by relative movement between source and receiver is named after the Austrian Christian Andreas Doppler who developed the theory in 1842 [68,69]. Three years later the Dutch physicist Buys-Ballot demonstrated its validity for sound waves so, by the time that US was developed for underwater applications, the Doppler-shift principle was well established. During the Second World War, Sonar officers in the US Navy were tested by the Sonar Pitch Memory Test to distinguish the pitch difference between two echoes three seconds apart, to predict the presence and direction of submarine motion [70].

During the 1960s, numerous laboratories exploited this new non-invasive technique for vascular studies. The instruments were convenient and compact [71]. Continuous-wave (CW) beams of US at frequencies up to 10 MHz enabled arterial blood-flow waveforms to be recorded from peripheral arteries. Quite coincidentally, the spectrum of Doppler-shifted frequencies from the movement of blood happens to be in the audio range, because of the ratio between the speed of sound in blood to the speed of blood through the artery. Operators learned to distinguish the difference between sound from streamline and turbulent flow. Spectrum analyzers, developed for speech analysis, allowed researchers to create dis-

plays showing the changing Doppler spectrum during the cardiac cycle. In due course, commercial equipment distinguished forward from reverse flow [72], and gave a time-varying voltage for comparison with simultaneous blood pressure and electrocardiogram waveforms. Several measures were developed to characterise the Doppler waveforms, such as the pulsatility index [73] and the resistance index [74].

Whilst CW systems were simple and convenient, they suffered from several weaknesses. The sensitive volume was limited to the fixed region of beam overlap. All vessels, venous and arterial, in this region contributed to the overall Doppler signal. Necessary 'wall thump' filters removed low-velocity signals. Anatomic factors largely limited access to only the neck, iliac, and limb arteries. Apart from a specific window to the thoracic aorta via the sternal notch [75], flow from deep arteries could only be detected using miniature intra-arterial [76] intravenous [77] or intra-oesophageal [78] transducers. The first intravascular recording of blood flow was probably obtained by Cieszynski in 1956 [79]. Since the shift in frequency depended on angle, accurate measurement of absolute blood velocity and blood flow were not possible.

The development of pulsed wave (PW) Doppler systems would eventually overcome most of these difficulties. The first PW Doppler systems had emerged by 1970, developed simultaneously in several laboratories [80-82]. Using the same transducer to operate as both a transmitter and a receiver the sensitive volume was set, not by beam overlap, but by range-gating. This allowed any interference from other vessels and from some tissue movement to be removed, so allowing the detection of flow from deeper abdominal arteries. Improvements in range resolution allowed flow profiles to be measured. Nevertheless, it was only when PW Doppler was integrated with real-time imaging that PW Doppler started to be widely used clinically. The initial 'duplex' systems used real-time imaging to locate a region of interest, which was investigated by manipulating a PW Doppler device at the side of the imaging transducer. An early system for cardiac scanning was reported by Frank Barber with John Reid in 1974 [83]. By 1982, Toshiba introduced a linear array system that allowed Doppler and B-mode imaging to operate together. All the evaluation techniques for the Doppler signal that had been developed for CW Doppler, aural discrimination, spectral display, ratemeter output and flow indexes could be equally applied to PW Doppler.

Doppler imaging established a new dimension in diagnostic US. Pioneering efforts to create images of arteries by mapping the 2D distribution of the Doppler signal, either from continuous wave [84] or pulsed operation [85], whilst being of research interest, failed to gain

clinical momentum. Once a color overlay, generated by the Doppler signal, was superimposed on the real-time echo image, a powerful and unique imaging tool was introduced, which combined cross-sectional anatomical imaging with cross sectional functional imaging. The engineer Marco Brandestini working at the University of Seattle developed the first system for a cardiac scanner in 1978 [86]; the first commercially available color flow system was introduced by Aloka in 1982. Numerous developments in Doppler processing allowed direction of flow, the flow profile and eventually capillary perfusion to be visualised. Once the angle between the beam and the vessel of interest could be measured much effort was made in attempts to quantify volumetric flow from measured blood velocity vectors [87]. Fundamental limitations remain, including aliasing and power operating at the limits of safety, causing heating of both exposed tissues and of the transducer [88,89].

Although most current systems permit the angles between blood vessels and the US beam to be measured, blood flow direction in complex geometries such as bifurcations, valves, tortuous vessels and stenoses (which are often clinically of most interest) will fluctuate over the cardiac cycle, and therefore more recent developments have aimed at developing systems that display the true 2-D velocity vectors throughout the cardiac cycle, and which can detect fast transitory vortices and other complex flow at high frame rates [90]. Complex flow is of course three-dimensional in nature, and further developments will be needed before flow can be fully described.

### **3D and 4D ultrasound**

The concept of 3D US was conceived as early as the 50's and 60's [91,92]. However, it was the digital revolution in the 80's that really paved the way for 3D and 4D US as a natural extension of 2D qualitative US scanning [93-97]. The initial concept was to stack serial 2D ultrasonograms together and utilize computerized algorithms to process and display the data. First, mechanical arms were used for acquisition of regular data volumes. Second, ordinary 2D probes were inserted into motorized holders and either rotated [98,99], translated [95,100, 101] or tilted [102,103] to obtain regular data sets. Pullback devices were also constructed to aid intraluminal and endosonographic scanning where the transducer was positioned inside the body while the pullback device was outside the body [104]. Principally, data acquisition by 3D US can be performed in 3 different ways [105]. Sampling of data may be carried out either by using a 2D probe attached to a mechanical arm/motor which moves the probe in a computer-defined way, as described above, or by a spatial localizing system connected to a 2D probe, or by genuine, electronic 3D probes with direct volume

acquisition in real-time. The first spatial sensor devices applied in 3D US were acoustic sensors [106-108]. Magnetic sensor systems were also integrated to improve accuracy in registration of probe position [109-113]. Later, miniature magnetic sensors were incorporated in the scan head to optimize the acquisition procedure. Furthermore, volumetric 2D array transducers [114,115] were developed to enable dynamic real-time volumetric US, which is the main 3D/4D acquisition modality used today in various disciplines, particularly in obstetrics and cardiology.

### ***Intracavitary and endoscopic US***

The history of intracavitary use of US began in 1956 with Wild and Reid, who used a rigid and blind radial A-scanner transrectally to measure rectal wall thickness and evaluate the prostate and diagnosed recurrence of rectal cancer [116]. Japanese researchers introduced thin A-mode US probes into the abdominal cavity to detect gallstones using a laparoscopic approach [117]. The first two-dimensional B-mode imaging of the prostate was published by Hiroki Watanabe in 1967 [118]. In the early 1980's Hans Henrik Holm (Denmark), Bernd Frenzel-Beyme, N Jaeger and Hagen Bertermann (Germany) reported on transurethral and transrectal US scanning of the urinary bladder, seminal vesicles and prostate including local staging of bladder and prostate carcinoma [119-122].

Based on the first flexible fiberoptic endoscopes, introduced by Hirschowitz in 1957 [123], transcavitary application of US to the upper digestive tract became a realistic option in the late 1970s. The first flexible intracavitary US application was published in 1976. Rösch and Lutz used a miniaturized A-mode probe inserted through the instrumentation channel of a gastroscope to detect and measure pancreatic pseudocysts [124]. Because of the limitations of transcutaneous US in diagnosis of pancreatic diseases, the idea of trans gastric US imaging of the pancreas by using a fiberoptic endoscope equipped with an US transducer emerged. Almost simultaneously, technical developments and experimental investigations with endoscopic US began in the USA (at the Mayo Clinic in Rochester), Germany (at the Medical University Hospitals in Frankfurt and in Erlangen), and in Japan. The Mayo group's first prototype consisted of a side-viewing gastroscope with an 80-mm rigid tip incorporating a 10-MHz linear array with 64 elements and a frame rate of 30/s. High-resolution images of the heart, great vessels, portal vein, gallbladder, spleen, kidneys, and stomach wall of miniature pigs and dogs were presented in October 1979 [125] and the results of this experimental study published in *Lancet* in March 1980 [126]. Unpublished animal experiments included initial

3D reconstructions, echocardiographic studies, and contrast studies using intravascular injection of indocyanine green [125]. Between 1979 and 1980, 32 EUS studies were performed in 15 healthy volunteers and in 10 patients with suspected or confirmed pancreatic diseases using a modified forward-viewing scope with the same array, but a shorter rigid tip (35 mm). Results were published at congresses in 1980 [125] and in *Gastroenterology* in 1982 [127].

In parallel, probes were being developed for transoesophageal examination of the heart. The principle was established by Frazin and colleagues in 1976, with an M-mode technique on a non-steerable probe [128]. The first steerable mechanical sector scanner was developed in Japan by Hisanaga in 1977 [129] but the breakthrough came in 1981 when Jacques Souquet, working with the clinician Peter Hanrath in Hamburg, developed a phased-array transducer that was incorporated into an endoscope [130].

In Germany, at about the same time, experiments were conducted using the first prototype of a radial echoendoscope. An Olympus side-viewing gastroscope was equipped with an 85-degree sector transducer (5 MHz) from Aloka with a rotating acoustic mirror (45 degrees). The first experience on 18 patients with known liver, pancreas and biliary diseases were published in September 1980 [127]; further German-language publications followed in 1981-1983, including the visualization of pancreatic pseudocysts and bile duct stones. In addition to the Frankfurt group, the team of the Erlangen University Hospital around Ludwig Demling and Harald Lutz stood at the cradle of endosonography in Germany. Starting in 1981, patients with various abdominal diseases were examined with further developed Olympus prototypes with a rotating 90 or 180 degree 7.5 MHz sector scanner. In addition, a Pentax gastroscope was used in conjunction with a 7 MHz-48-element linear array operated with a Siemens US scanner [131-134].

In Japan, investigators from Nagoya University of Medicine published their first experiences with a "blind" flexible probe with a 2.25 or 3.5 MHz mechanical transducer rotating in an oil-filled sheath and a Toshiba US system as early as in 1978. Using this device, transgastric endosonographic 180-degree pancreatic imaging was achieved in 16 healthy volunteers in 1979/1980 [135]. The same research group used a similar flexible device also for transesophageal pulsed wave Doppler and B-Mode echocardiography [136,137]. In 1983, a research group from Tohoku University in Sendai reported their experience with a 36-element 3.5 MHz linear array mounted on the tip of a Machida side-viewing endoscope and operated with a Toshiba US unit [138]. In 1984, Kei-

ichi Kawai's research group from Kyoto reported their first 118 pancreatic endosonography cases performed with the three Olympus prototypes including three cases of small pancreatic carcinoma (<20 mm) [139]. The first commercially available radial US endoscopes were offered by Olympus in 1982 (7.5 MHz, 180 degrees) and 1984 (7.5/12 MHz, 360 degrees). The first studies relating endosonographic visible gastric wall layers to anatomy and investigating infiltration depth of gastrointestinal cancers were performed by the Erlangen group, the Amsterdam group (Tio and Tytgat), and the group of Kawai and published between 1983 and 1986 [132,140-143]. In addition to the pioneers already mentioned, Michael Sivak, Charles Lightdale, G.A. Boyce, and Giancarlo Caletti were particularly pacesetters of the technology, devoting much of their initial research to EUS anatomy [144]. The first International Endosonography Workshop was held in June 1982 at the World Congress of Gastroenterology, chaired by Keiichi Kawai, which had about 15 participants, and resulted in the publication of a special US supplement of the Scandinavian Journal of Gastroenterology in 1984 [145].

In 1990, miniature high-frequency radial US probes that were insertable through the working channel of gastrointestinal endoscopes were first marketed and could be used in the lumen of the gastrointestinal tract, endobronchially, and intraductally, especially in the bile duct [146,147]. The development of a gastroscope with a curved-array microconvex transducer by Pentax and Picker in 1989 ushered in a completely new era of endoscopic US. The Copenhagen working group led by Peter Vilmann and Søren Hancke first published diagnostic results [148] in 1991 and shortly thereafter the first EUS-guided fine-needle aspirations with this instrument [149]. This groundbreaking development ultimately initiated a paradigm shift in visceral oncology diagnostics, particularly in the tissue diagnosis of pancreatic diseases [150], but at the same time also opened the way to EUS-assisted therapeutic interventions, which were developed and published from 1996 onward, particularly by the US research group led by Maurits Wiersema [151]. Milestones in therapeutic endosonography were the development of echoendoscopes with a large instrumentation channel, which also allowed the application of 10 FR instruments and stents, the one-step EUS-assisted drainage of pancreatitis-associated fluid by the Frankfurt working group of Hans Seifert, Christoph Frank Dietrich, and Till Wehrmann in 2001 [152] and the first EUS-assisted drainage of congested bile ducts by Eike Burmester and Mark Giovannini in 2003 [153,154]. In addition to the possibility of performing fine-needle-assisted interventions under direct endosonographic view, the new elec-

tronic microconvex array ecoendoscopes allowed the introduction of multiparametric US techniques (color-coded duplex sonography, contrast-enhanced techniques and elastography) into the world of endoscopic US [155-160].

### Interventional US

Interventional US, as we understand it today, was born at the "First World Congress on Ultrasonic Diagnostics in Medicine" in Vienna in 1969, when Alfred Kratochwil, a young Austrian obstetrician, presented an US transducer with a central canal through which an amniocentesis could be performed guided by A-mode to avoid the placenta [161].

A few months later a Danish urologist, Hans Henrik Holm, and his research group in Copenhagen, Denmark, inspired by Kratochwil's A-mode puncture-transducer developed a new system for intervention under guidance of static B-mode scanning transforming needle guidance from a deflection on the x-axis into an anatomic map to guide the needle. The first puncture guided by this new manual B-scanning system, was of a large renal cyst which turned out to be malignant. These events took place late in 1969 and the first scientific report on the new US-guided puncture system was presented at the 1970 annual meeting of AIUM in Cleveland, USA in a film entitled "Ultrasound in renal diagnosis" [162].

To the best of our knowledge, the first peer-reviewed article on the use of US for interventional procedures seems to be the publication by Berlyne in 1961. He used US as a guide to renal biopsy. By use of an unmodified industrial A-mode device for flaw detection, a technique was described on how to identify depth and position of the kidney before performing free hand, non-imaging-guided, renal biopsy for parenchymal disease [163].

While Kratochwil never published his A-mode technique in a peer-reviewed article, the principle of static B-scanning US as a guide for intervention, developed by Henrik Holm's group, was published in 1972 [164].

In 1974, the first puncture guided by dynamic scanning was carried out by the Danish group of interventional US pioneers when Fog Pedersen designed a multi-element transducer with a puncture device, through which a needle could be inserted and visualized on the monitor [165]. Almost a decade later the concept of interventional US was taken to the next level with endoluminal US guidance when Holm and the French radiologist Fornage published their techniques for prostate biopsy guided by transverse and linear transrectal US, respectively [166,167]. Another ten years later another new and important technical achievement for interventional US



appeared when the Danish surgeon, Vilmann, developed a technique for endoscopic US guided biopsy obtained through very long needles that enabled pancreas biopsy through a gastroscope [149].

There has been an impressive evolution in clinical use with new areas being added every year. This multitude of potential uses can be divided into two major groups: diagnostic and therapeutic intervention. Diagnostic interventions include biopsy of solid tissue and tumors, aspiration of fluid and instillation of diagnostic material such as contrast agents through a catheter. Therapeutic interventions comprise drainage of fluid collections like ascites, pleural and pericardial effusions, lymphoceles, and abscesses, tubulation of hollow organs as in nephrostomies, gastrostomies and cholecystostomies and tissue ablation by means of heat, freezing, or radiation.

In the years following Kratochwil's groundbreaking presentation at the Vienna 1969 World Congress, interventional US gained interest worldwide and extensive research took place in many centers all over the world. This diverse and extensive work included all aspects of the field covering technical refinement, clinical applications, scientific publication, and congress activities.

During the 1970s the first diagnostic applications were investigated and US-guided fine needle biopsies of almost all intra-abdominal organs were introduced from researchers around Europe with a major contribution emerging from the group around Holm. Notable highlights were, biopsy of liver metastases by Rasmussen 1972 [168] and biopsy of renal tumors by Kristensen [169] and Bahlmann & Otto [170], amniocentesis by Bang & Northeved [171], in 1972 and biopsy of pancreatic masses by Hancke a few years later in 1975 [172]. Along this diagnostic track were reports on therapeutic applications when in 1973 and 1974, respectively, Fog Pedersen published the first written scientific reports on US-guided abscess drainage [173] and percutaneous nephrostomy [174].

Since the very beginning, applications for interventional US have continuously increased in number and range and today apply to almost all body organs. Obviously, it is not possible to rank these multiple uses in any fair way but nevertheless a few applications have had an enormous impact on modern medicine. Drainage of abscesses, tubulation of hollow organs and ablation of malignant tumors, all performed percutaneously guided by US is an integral part of the therapeutic armamentarium and considered state of the art procedures worldwide. Only a generation ago many patients now treated with these minimal-invasive techniques, would have undergone major surgery, or perhaps not have had any possible cure offered.

While percutaneous drainage of targets such as intra-abdominal abscesses and hydronephrosis is a fairly new technique, the concept of localized, in situ, ablation of malignant tumors, is ancient. The first known reference dates to approximately 2000 B.C. In ancient Egypt the use of cauterization for local tumor therapy by means of a glowing poker was described for breast cancer treatment [175]. The introduction of interventional US paved the way and brought about a revival of this ancient concept of interstitial tissue destruction when Holm and coworkers in 1981 published their work on US-guided brachytherapy, a novel technique for percutaneous precise placement of radioactive seeds in abdominal tumors [176]. This marked the beginning of a remarkable new line of cancer treatment known today as ablation used for treatment of a diverse range of neoplasia in different organs such as prostate, uterus, liver, kidney, lung, thorax, thyroid, parathyroid and the brain, and performed by means of different physical methods such as heat, freezing, radioactivity, high voltage electric current, High Intensity Focused Ultrasound (HIFU) or chemical agents. Several of these techniques are now established treatments for multiple neoplastic diseases and among these thermal ablation of liver tumors by means of heating through radiofrequency (RF), microwaves (MW) or Laser are the most widely used worldwide. Following the initial reports of brachytherapy, the 1980s quickly introduced other methods of tissue destruction [177,178]. One of the first principles to attract major interest was heating of tissue by laser light delivered interstitially through fibers placed under ultrasonic guidance. Various development and testing took place in the late 1980s and early 1990s leading to the first small clinical series of the nowadays widely accepted technique of US-guided percutaneous ablation of liver-metastases [179-182]. Throughout the 1990s and the first decade of the 21<sup>st</sup> century percutaneous ablation guided by different imaging modalities has grown tremendously and today holds an established position in many oncological protocols.

Numerous dedicated professionals took part in the early pioneering work of US-guided ablative techniques as well as all other aspects of interventional US. Since it will probably never be possible to pay fair acknowledgment to every single one of these experts, we should always bear this in mind and keep an attitude of thankfulness and appreciation towards those who paved the way and in the footsteps of whom we walk and perform our daily duties. In the early days of interventional US, congresses and smaller scientific meetings played a crucial role. Before the world wide web era with its instant access to unimaginable amounts of detailed information and data, distribution across both geographical borders

and medical specialties was no easy task. It could be time-consuming as well as associated with bureaucratic and technical difficulties for a medical breakthrough in one country to become known and implemented in countries of other regions and even more so, distant continents.

EFSUMB holds a strong tradition for supporting good clinical practice and has published clinical guidelines on many areas of medical US to facilitate evidence-based medicine. In keeping with this policy and under the leadership of the then EFSUMB President, Christoph F Dietrich, EFSUMB in 2015 undertook the demanding task of compiling the first set worldwide of clinical guidelines on interventional US. The intention of this comprehensive work was to cover all aspects of interventional US. Six articles were published and have been highly praised by interventional US practitioners all over the globe [183-188].

### The European origins of ultrasonic therapy

The first conference on Ultrasound in Medicine was held at the University of Erlangen, Germany on 3 and 4 May 1949 [189]. By far the largest number of papers concerned the use of US for therapy, exploring its scientific basis and its possible clinical uses. US therapy was first explored in France. By the mid 1930s, a suitable US transducer and electronics for therapeutic application [190] was investigated at the hospital Hôtel-Dieu in Paris by the brothers Elio and Hugo Biancani and the physicist André Dognon [191,192]. They reported 'There are substances, whose heating always remains insignificant: water, gelatine gels or proteins, whatever their viscosity or cohesion. On the other hand, a whole series of other bodies, of a fatty or lipid nature, are heated, sometimes strongly, the magnitude being linked in part to their low conductivity and specific heat, but also to their high absorption. It is natural to think that the considerable heating of fatty or lipid tissues must play an important role in the genesis of physiological disturbances caused by ultrasound of great intensity.'

The laboratory studies served to distinguish the two main mechanisms, heating and cavitation. However, in spite of the promise of this co-operation between physicist and clinician, their work was largely confined to *in-vitro* studies, and no useful clinical outcomes were reported.

It was left to the German physicist Reimar Pohlman (1907-1978) to establish the clinical potential of US for therapy. He specifically rejected the high intensity approach to cancer therapy being explored elsewhere. Instead, he proposed that US at lower intensities could be

used to stimulate healing through a combination of thermal and mechanical processes. His first experiments were designed to select the most appropriate frequency to use. 'In connection with these investigations, the question of the absorption of US in human tissues, its frequency dependence, and the depth of penetration of the radiation was of major significance', from which he selected 800 kHz for the clinical evaluation [193,194].

The first clinical trials of his US therapy were carried out before the end of 1938 in the Martin Luther Hospital Berlin-Grunewald [195]. His clinical colleagues were E Parow-Souchon and R Richter. Favourable results were reported for some neurological and neuro-muscular disorders [196]. The quartz crystal was mounted in a radiation head made of glass, which had a thin, US-permeable membrane and operated with an intensity of around 4-5 W cm<sup>-2</sup>. 'If one stroked the body part to be treated with the massage head adjusted in this way, applying light pressure, the patient had a subjective feeling of pleasant warming, and a slight hyperaemia was noticed, which resulted partly from the warming and partly from the intense vibration'.

In 1939 Pohlman was recruited by Siemens-Reiniger-Werke in Berlin to improve the design and take responsibility for further clinical trials in Berlin, Wolfsburg and Erlangen. Siemens-Reiniger-Werke partially relocated to the comparative safety of Erlangen in 1943, where Pohlman extended the measurements of the frequency-dependence of tissue attenuation up to 4.5 MHz, concluding that the absorption coefficient showed a broadly linear frequency dependence. Developments in ultrasonic metrology, assisted by the ultrasonics laboratory at Physikalisch-Technische Bundesanstalt (PTB), Braunschweig, resulted in the development of hydrophones, beam imaging and a portable power balance [197]. Pohlman left Siemens in 1948 to move to Switzerland.

In his foreword to *Der Ultraschall in der Medizin*, the proceedings of the conference held in Erlangen in May 1949, K. Matthes, Medical Director of the University Hospital at Erlangen, was pleased to welcome non-German participants who he addressed as 'the most famous US researchers from neighbouring countries'. European citizens were rediscovering peacetime co-operation. Of the 320 delegates whose names were listed, 11 % were from outside Germany, mostly from France, Switzerland and Austria, but with a few from Sweden, England, The Netherlands and Italy. And the non-German scientists and doctors were even better represented in the presented papers, with sixteen of the 72 papers from outside German centres. Nevertheless, Germany took the lead. In his book *Die Ultraschalltherapie*, published in 1950, Pohlman could list seventeen companies manufacturing ther-

apeutic US equipment, of which twelve were German, four Austrian and one in France. He had missed several in France, Belgium and the USA but, even so, German manufacturers were dominant and German clinical users most enthusiastic. For the most part, the operating frequencies lay between 800 kHz and 3 MHz, and manufacturers limited the maximum intensity to between  $2 \text{ W cm}^{-2}$  and  $10 \text{ W cm}^{-2}$ . One manufacturer, Dr. Born of Frankfurt, offered pulsed operation at ratios of 1:5, 1:10 and 1:20.

The proceedings of the Erlangen conference included a collated review of the outcomes of all the clinical trials on US therapy available to the organisers. Cure or significant improvement was reported for treating sciatica, neuralgia, lumbago abscesses and ulcers at the other end of the scale, of 133 patents with malignant tumors, only 17.3 % were reported as showing any improvement at all, the majority exhibiting no benefit. Similarly discouraging results were reported for prostatitis, scleroderma, tuberculosis of the lung, otosclerosis, eczema and ankylosing spondylitis.

US therapy dominated the Erlangen Conference, which included only two diagnostic papers, one by Karl Dussik paper and the other by Wolf-Dieter Keidel, both using transmission methods. Within a year, the earliest experimental reports of the use of pulse-echo methods for medical diagnosis appeared.

### Contrast Enhanced Ultrasound (CEUS)

It has long been known, not only that even small gas bubbles in a condensed medium such as water or soft tissue can give rise to strong ultrasonic echoes, but also that ultrasonic fields can themselves give rise to so-called "cavitation bubbles" [198]. This led to deliberately enhancing image contrast.

Gramiak and Shah published the first report on contrast enhancement after injection of indocyanine green solution during examinations of the aortic root, caused by tiny air bubbles contained in the injected fluid [199]. Feinstein found out that sonication results in bubbles of smaller size and prolonged persistence [200], which is essential to allow passage of the pulmonary circulation and enhancement of the left heart cavity after intravenous administration. The term contrast enhanced US (CEUS) was introduced as an acronym by members of EFSUMB [201]. CEUS was initially intended to enhance Doppler signals. Contrast specific techniques were developed thereafter. After the initial experience with self-made hand-agitated or sonicated bubble suspensions, several pharmaceutical companies started the development of commercial US contrast agents. It became clear, that for

broader clinical use the bubbles had to be standardized in size and stabilized for a longer in vivo persistence.

#### *Contrast-specific US techniques*

CEUS is highly dependent on the interaction of contrast microbubbles with the US wave. In fact, the evolution of CEUS is closely correlated with the development of contrast-specific imaging techniques. The first echo contrast signals were detected in M-mode images of cardiac cavities and large vessels [199]. Already in the very early times, researchers tried also to display contrast enhancement inside of parenchymal tissue, e.g. for assessment of myocardial perfusion [202], and for detection and characterisation of focal solid liver lesions. Two major problems had to be solved: 1) the attenuation caused by high bubble concentration in the cardiac cavities and 2) the overlay of tissue signals from the cardiac wall. Shapiro therefore used an intracoronary administration to avoid cavity contrast and achieve a high local microbubble concentration. The first hepatic and pancreatic CEUS studies were performed in the 1980's and 1990's following intra-arterial injection of carbon dioxide microbubbles into the hepatic artery and the celiac trunk. Microbubbles were obtained by vigorously mixing of  $\text{CO}_2$  with Glucose and Albumine or Soja oil [203-206]. In a next step, Doppler techniques were used to obtain selective signals from microbubbles without overlaying tissue signals. The cancellation of tissue signals was based on velocity, so that only flowing microbubbles (e.g., in the heart cavity or large vessels) could be displayed. Contrast US was introduced to enhance or rescue Doppler studies [207]. Later it was found that Doppler signals could also be obtained from stationary microbubbles, when they were destroyed by high insonation power. The disappearance of the bubble signal from one frame to another is interpreted by the color Doppler autocorrelation algorithm as movement of the bubble. However, this contrast signal exists only for a very short moment (like a flash) and was named stimulated acoustic emission [208-211]. The final goal was to display the microbubble signals separated from tissue signals continuously, allowing real-time imaging of contrast wash-in and wash-out in parenchymal tissue. This requires insonation with highly reduced power (low-MI imaging) minimizing the destruction of microbubbles in the sound field. The separation from tissue signals was achieved by the introduction of frequency filtering and later pulse-summation techniques, taking benefit from the characteristic acoustic response of microbubbles oscillating in the US field (non-linear signals with harmonic frequency components) [212,213]. The method much benefitted also from the improvements in contrast agents, brought by the use of specific gas filling of microbubbles instead of ambient air. Today most

US manufacturers have a contrast mode available, based on the summation of pulses with inverted phase (phase inversion, phase modulation), modified amplitudes (amplitude modulation, power modulation) or a combination of both, and many commercial contrast agents with a variety of properties and use are now available.

Separate papers were published on the history of US in clinical subspecialties, e.g., obstetrics and gynecology [214] and cardiology [215] and additional techniques, e.g., elastography. The initiative on history of US reflects the history of member societies of EFSUMB ([www.efsumb.org](http://www.efsumb.org)).

**Conflict of interest:** none

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