Review

Studies on the foundation and development of diagnostic ultrasound

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Abstract: In recent years, various types of diagnostic imaging methods, such as CT, MRI, PET and Ultrasound, have been developed rapidly and become indispensable as clinical diagnostic tools. Among these imaging modalities, CT, MRI and PET all apply electromagnetic waves like radiation rays. In contrast, an ultrasound imaging method uses a completely different mechanical pressure wave: “sound”. Ultrasound has various features, including inaudible sound at very high frequencies, which allows its use in medical diagnoses. That is, ultrasound techniques can be applied in transmission, reflection and Doppler methods. Moreover, the sharp directivity of an ultrasound beam can also improve image resolution. Another big advantage of diagnostic ultrasound is that it does not harm the human body or cause any pain to patients. Given these various advantages, diagnostic ultrasound has recently been widely used in diagnosing cancer and cardiovascular disease and scanning fetuses (Fig. 1) as well as routine clinical examinations in hospitals. In this paper, I outline my almost 50-year history of diagnostic ultrasound research, particularly that performed at the early stage from 1950-56.

Keywords: CT, MRI, PET, ultrasound, diagnostic ultrasound, Ultrasono-tomography

Introduction—principles and history of diagnostic ultrasound research

Ultrasound is an inaudible sound of high frequency. The advantages of ultrasound are that it can transmit via any medium including solids, liquid and air with different propagation velocities and with a sharp beam based on its short wave length. In addition, reflection, Doppler effect and attenuation of the sound can be detected along its pathway. Inspective applications of ultrasound has been used since 1912 after the Titanic collided with an iceberg. Since then, ultrasonic safety navigation employing a reflection method has been widely used. During World War II, ultrasound was used to detect submarines. After the war, it found such peaceful applications as in ultrasonic flow detectors for metallic materials and ultrasonic fish finders. At the same time, research into diagnostic applications of ultrasound (diagnostic ultrasound) was advanced by applying the same reflection method. The principle of diagnostic ultrasound is to apply the characteristic features of transmission, reflection and Doppler effect generated within the human body.

Research on diagnostic ultrasound began around 1950 almost concurrently but independently by K.T. Dussik (Austria 1949)1) R.H. Bolt (MIT, MGH, USA 1950),2) J.J. Wild (Minnesota, USA 1950)3) and myself T. Wagai (Juntendo University, Japan 1952).4) K. Dussik (neurologist) and R. Bolt (physicist) stressed the fact that it was impossible to detect weak echoes generated inside the brain through the skull and, therefore, they applied a transmission method aimed at diagnosing brain tumors. They succeeded in displaying ultrasonic transmission images of the human brain and ventricle in a fixed head inside a water tank, and named them “Hyperphonographie” and “Ultrasonic ventriculography” respectively. They failed, however, in clinical applications because of poor image

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quality and procedural complexity. Subsequently, J. Wild (surgeon) and myself (surgeon) applied a reflection echo method to the same purpose of diagnosing brain tumors, and succeeded in creating the foundation of diagnostic ultrasound. Applying a very high frequency ultrasound, such as 15 MHz, J. Wild was able to obtain a fine image of soft tissue structure using reflection method. He reported a range of possibilities for diagnostic ultrasound. However, he failed in clinical applications because of large ultrasound attenuation, which limited the examination of tissue to a depth of 1.0 cm. On the other hand, I continued my research by applying rather low frequency ultrasound such as 1–10 MHz, and succeeded in displaying ultrasonic images of the whole human body. After about a 40-year research effort, diagnostic ultrasound has seen remarkable development and become an indispensable tool in clinical medicine.

**Foundation of diagnostic ultrasound research**

In 1950, I planned and started my research on diagnostic ultrasound by applying the reflection echo method while studying in the Department of Neurosurgery, Juntendo University School of Medicine, Tokyo, Japan. I conducted it in collaboration with engineers of Japan Radio Co, Tokyo. This work performed from 1950-56 marked the dawn of diagnostic ultrasound research in Japan. As there were no precedent trials or literature on diagnostic ultrasound research in Japan at that time, I had to begin by proving whether ultrasonic waves really transmitted within the human body; and if confirmed, whether echoes could really be detected from the inside of the human body. Also, whether ultrasonic waves are really safe for the human body. To answer these fundamental questions, I started by performing experiments.

**Pilot studies in immersion ultrasonic examination:** At first, I set out to confirm the possibility of detecting echoes from inside a brain specimen using a prototype ultrasonic flow detector with a frequency of 1 to 10 MHz. I designed a special examination method that was performed in a water vessel (Fig. 2, 1951). This method has since been used widely as an immersion water pass ultrasonic examination method. I succeeded in detecting various types of echoes from the ventricle wall, brain hemorrhage, and tumor tissue. The ultrasonic flaw detector used in this pilot study was an A mode display type that displayed ultrasonic echoes as changes in amplitude on the time axis of a cathode ray tube (CRT). Since Juntendo University was, as a newly established private school, poor in the period just after the war, I had no suitable laboratory or research funding at my disposal. Therefore, I experienced many difficulties in advancing my research. As I had no device for taking pictures of the CRT echograms, I recorded them by hand (Fig. 2, 1951).

**Measurement of acoustic impedance and attenuation of brain tissue:** To confirm these results theoretically and calculate a reflection coefficient, I tried to measure the acoustic impedance values of various brain tissues based on their propagation velocity and density. However, as there were no methods or devices for taking these measurements...
at that time, I had to design my own measurement method and device. I succeeded in measuring propagation velocity in even smaller brain specimens by using a specially designed acoustic masking method. I measured brain tissue density using a small brain specimen and employing a sulfuric acid copper method, which was usually used for measuring blood density at that time. The results of these measurements showed that the propagation velocity of brain tissue was almost the same as that of water, that the tissue density was similar to that of human blood. Also, that there was a small difference in acoustic impedance values between normal and pathological brain tissues. Through these measurements and calculations, I was able to also theoretically confirm the possibility of detecting echoes from inside brain tissue. Moreover, the slightly different propagation velocities between normal and pathological tissues allow ultrasound to detect cancer and other diseases. These results were reported at the annual meeting of the Acoustical Society of Japan on May 1952 as the first report titled “Detection of pathological anatomy of brain by using ultrasound.” At that meeting, I submitted a report of hand-written mimeographed copies (in Japanese). It was there that I first came to know of several international pioneers in this field (whose names are mentioned above), as it was difficult to get foreign literature in Japan at that time. Subsequently, I measured the ultrasonic attenuation of brain tissue in relation to the ultrasound frequency, and found a very interesting ultrasonic attenuation response between normal and pathological brain tissues, which was effective in ultrasonic differentiation between brain disease, cancer, and others later.

**Development of ultrasonic phantom and special transducer with water column attachment.** To advance the experiment more quickly, I wanted to use a phantom. After investigating various materials for this purpose, I developed an agar-agar of 3% density as a sort of phantom that showed almost the same acoustic impedance as that of human soft tissue. This phantom was very useful in conducting a variety of experiments (Fig. 6, 1953). On the other hand, to make the immersion water pass technique more convenient and to drive the experiments more rapidly, I developed a special type of transducer with a water column attachment. At first, variously shaped glass columns were designed and undesirable echoes reflected from the water column wall were investigated. Finally, I developed a new transducer with an ideal water column (Fig. 3, 1953). Using it made the immersion method much easier and more effective in conducting experiments, even clinical studies, compared to the previous ones performed in a water vessel. As the above results were all obtained using a formalin fixed brain specimen, experiments using fresh brain tissue were necessary. I used a fresh cow brain just after butchering, and was able to confirm the same results as those obtained with the fixed brain specimen.

**Direct ultrasonic examination of the brain.** Based on the results of these fundamental experiments, it seemed possible to detect echoes from inside the brain, including brain tumors, when ultrasonic examination is performed directly on the dura mata during open-skull brain surgery. However, before conducting such a trial, the safety of ultrasonic pulsed waves on a living human brain had to be first confirmed. As there were no reports on the biological and pathological effects of ultrasonic pulsed wave on the brain, I had to resolve the problem by depending on the results of properly conducted biological experiments. First, I confirmed that ultrasonic pulsed waves did not cause a harmful effect on the human blood based on the results of a hemorrhagic experiment and subsequent animal experiments that I conducted. A living rabbit brain was radiated directly by an ultrasonic pulsed wave through a small hole in its skull using a special transducer with a metal attachment devel-
opned for this experiment (Fig. 4, 1953). During ten hours of continuous ultrasonic pulsed wave radiation directly into the living rabbit brain, physiological changes such as blood pressure and breathing were continuously monitored. I confirmed that the ultrasonic pulsed wave did not cause any change to the rabbit’s vital signs over a long duration of direct radiation. I, then, investigated histological changes in the radiated brain in laps of time until three month after the ultrasonic radiation, but detected no changes in the brain tissue. Based on these experimental results on the safety of radiating ultrasonic pulsed waves into a living brain, I tried applying this technique clinically during brain surgery and succeeded in detecting echoes from a brain tumor on the dura mata and in diagnosing its size and localization. Since then, direct ultrasonic examinations of the brain and abdominal organs have been widely employed as “intraoperative ultrasound”.

Detection of intracerebral echoes through the skull.\(^5\) However, the ideal clinical application was to detect echoes of brain diseases through the skull before surgery. At that time, however, this was thought to be impossible because of the skull’s high acoustic impedance and ultrasonic attenuation.\(^1,2\) I tried applying a new high-sensitive ceramic transducer (Barium titanate) to overcome the great barrier of the skull. After various investigations on the characteristics of the ceramic transducer, I succeeded in detecting intracranial echoes inside the brain, overcoming the barrier of the skull (Fig. 5, 1953). At the same time, I discovered that the midline echo originating from the third ventricle wall was detected at the temporal part of the head, which shift was a very important sign for diagnosing brain diseases. Another interesting phenomenon I discovered was that the midline echo showed a pulsating movement. Concurrently, I applied the A mode technique to the analysis and diagnosis of soft tissue structures such as breast, stomach and lung cancers, gallstones, and others.\(^5\)

Challenge to develop B mode.\(^5\) The above-mentioned results were all obtained by applying a one-dimensional A mode display technique. However, this technique had various limitations such as poor reproducibility and difficulty in confirming the shape of the reflective target, among others. I took up this challenge by developing a two-dimensional display of echoes by applying an ultrasonic scanning technique (B mode) to overcome the shortcomings of the A mode technique. With the B mode technique, ultrasonic echoes were displayed as changes in amplitude on the CRT time axis as bright spots (brightness modulation). This technique was usually used to display cross-sectional images by applying a scanning technique with an ultrasonic beam. At first, many engineers did not agree with my idea that a B mode technique could be used to scan the human body because it consisted of numerous echoes. Based, however, on the results of various fundamental experiments carried out using manual and other scanning techniques, I was able to develop the first immersion electrically automatic linear scanning instrument for displaying a cross-sectional image. I did this in 1953 by...
applying the same principles as used in radar and sonar (Fig. 6, 1953). Following these successful results in displaying a cross-sectional image of a phantom, I attempted to display a cross-sectional image of a human head and brain. For this purpose, the head was inserted into a water tank, covered by a rubber membrane, and bound tightly with a rubber cord to make it water tight. Using this procedure and a high-sensitive ceramic transducer, I succeeded for the first time in 1954 in displaying a cross-sectional image of a living human brain with ventricle, and named this technique “Ultrasno-Tomography” (Fig. 7). Although I obtained several interesting results by applying another method in which the head of a patient was placed in a supine position and scanned in a water tank to obtain a cross-sectional image of it (Fig. 7), I was unable to use this technique clinically because of its complicated operation and the severe pain it would cause patients. It was interesting that the same techniques were attempted by several researchers in other countries approximately 15 years after these trials. The first-stage ultrasono-tomography instrument (Fig. 7) is preserved in the National Science Museum as the oldest ultrasonic diagnostic instrument existing in the world. I also applied this scanning instrument to the analysis of soft tissue structures such as the breast, abdominal organs and extremities based on their characteristic ultrasound properties. I developed a water cup method for the breast (Fig. 8, 1954), while carrying out abdominal scanning using a bathtub. Although I succeeded in displaying various cross-sectional images of normal and pathological soft tissue organs, these results were still a long way from allowing the technique to be applied to clinical applications because of its poor image quality. I also attempted to continuously record moving echoes such as the heart valve and bowel peristalsis by applying a time-position-indication technique (TM mode). The same technique later became very widely used as Ultrasound Cardiography (UCG).

These results obtained through research carried out at Juntendo University School of Medicine from 1950-56 marked the dawn of diagnostic ultrasound research in Japan. Although the reporting of such results at meetings of various medical societies was not practiced at that time in Japan, I was able to continuously report all of my findings mainly at meetings of the Japan Acoustical Society,
which specializes in scientific and engineering systems. Under such stringent circumstances, I was very lucky to have been given a good opportunity to present the results of my early research carried out from 1950-56 at the 2nd International Congress on Acoustics (ICA) held at MIT, Cambridge, Mass. USA in June 1956. My invitation came from R.H. Bolt, who was the Congress president and one of the pioneers of diagnostic ultrasound research. My report was titled “Early cancer diagnosis through ultrasonics”. By virtue of this presentation, the state of research in Japan was highly appraised and recognized internationally as pioneering.

**Further development of diagnostic ultrasound**

The above-description is of the progress I made in research carried out mainly at its early stage from 1950-56. Following that, I engaged in research to develop diagnostic ultrasound for application to clinical use in cooperation with Japan Radio Co., Tokyo and other manufacturers in Japan. I took up this challenge despite the fact that many overseas pioneers had abandoned the idea. I will briefly outline chronologically my research carried out after 1957.

With regard to immersion automatic scanning instruments, I developed a second-stage ultrasonotomography instrument (Fig. 9, 1957) to which I applied a special plastic water bag and a long-life CRT used for radar so as to observe ultrasonic afterimages. I succeeded in obtaining whole breast and breast cancer images at a frequency of 5 MHz. Subsequently, I developed a third-stage instrument aimed at clinical application (Fig. 10, 1958). However, these instruments turned out not to be suitable for clinical use because of their poor ultrasonic image quality. Improving these techniques, I was able to make these instruments suitable for clinical use in diagnosing breast and liver diseases (Fig. 11, 1960), and they came on the market for the first time in Japan.

At the same time, I developed a new technique for performing laparoscopic ultrasonic examinations in diagnosing cholelithiasis and liver and stomach cancer. It later became widely used as “endoscopic ultrasound”. I also developed a portable ultrasonic diagnostic instrument for exclusively A mode usage and applied it effectively to intraoperative and endoscopic ultrasound and others. Furthermore, I
developed a new manual contact scanning technique and succeeded for the first time in displaying a cross-sectional image of the human brain and brain tumors (Fig. 12, 1963). These results were reported at the Symposium on Ultrasound in Biology and Medicine, held at the University of Illinois, Urbana, USA in 1962.\(^9\),\(^{10}\) I continued my research on improving ultrasonic image quality and developed a new instrument (Fig. 13, 1968) which used an arc scanning method and improved image resolution and grey scale display property by applying a logarithmic amplifier.\(^{11}\)–\(^{15}\) It was very effective for diagnosing breast and thyroid gland diseases. Then, I developed a compact immersion watertight scanner with similar properties for mass screening of breast cancer (Fig. 14, 1975), and it was effectively used widely in Japan.\(^{16}\)–\(^{18}\),\(^{20}\),\(^{27}\),\(^{30}\),\(^{31}\) On the other hand, I developed a manual contact compound scanning technique for diagnosing abdominal organ diseases (Fig. 15, 1968) and fetuses. This technique also became widely used throughout the world.\(^{12}\)

Finally, I developed a real-time imaging technique utilizing high-speed scanning. First, I used an electric linear array scanner, but at the early stage of this research, I was pessimistic because of its poor image quality (Fig. 16, 1978). By improving the performance of the instrument, the electric linear array scanner could be used effectively mainly for abdominal ultrasound (Fig. 17, 1985).\(^{25}\) At the same time, I was able to successfully apply a high-speed mechanical sector scanner to the breast (Fig. 18, 1981) and thyroid gland.\(^{32}\)–\(^{34}\) Building upon these research processes, in recent years real-time electric scanners have been developed and play a leading role in diagnostic ultra-
sound with Doppler color flow mapping and other newly developed technologies. These above results were reported in various international congresses, as shown in the references. The fact that all the ultrasonic diagnostic instruments developed with various modalities during this period of about forty years are buried in annals of past history reflects a common idiosyncrasy of advances made in the natural sciences.

**Conclusion**

I have mainly described the process of my diagnostic ultrasound research in its earliest stage from 1950-56 amidst my approximately fifty years of research history. In recent years, there have indeed been remarkable advances made in diagnostic ultrasound by applying various new technologies. For these, no one pioneer could have be imaginable. Actually, about thirty years were required to advance diagnostic ultrasound research from its beginning stage in 1950 to reaching the prospect of its clinical application. Achieving practical clinical application required about forty years in total. These successes owed entirely to close cooperation and great effort among many researchers in related fields of medicine and engineering. I wish to reiterate my respect to all of these parties. Furthermore, I feel lucky to have been involved in the founding and management of academic societies in the field of medical ultrasound, including The Japan Society of Ultrasonics in Medicine (JSUM), The World Federation for Ultrasound in Medicine and Biology (WFUMB), The Asian Federation for Ultrasound in Medicine and Biology (AFSUMB), and The International Congress on Ultrasonic Examination of the Breast (ICUEB), all of which help to advance and spread important research in medical diagnostic ultrasound. Finally, it is my sincere expectation that even more splendid advances in diagnostic ultrasound will contribute to the well-being and happiness of humankind.

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Profile

Toshio Wagai, M.D. was born in 1924 and started his research career in 1950 with a study on the diagnostic application of ultrasound conducted along with his study of neurosurgery at the Department of Surgery, Juntendo University School of Medicine, Tokyo, Japan, after graduating from the Faculty of Medicine, Niigata Medical College, Niigata, Japan.

He has performed pioneering work on diagnostic applications of ultrasound in both Japan and in the wider global scientific community. His research has led to extensive advances in ultrasonic imaging and diagnostic methods using CT, MRI, PET and other techniques.

He was promoted to Professor at Juntendo University School of Medicine in 1970 and became Head of the university’s Medical Ultrasonic Research Center in 1975. He was awarded the Asahi Award in 1976, the Medal with Purple Ribbon in 1986, and the Japan Academy Prize in 2006. He was elected a member of the Science Council of Japan in 1988. He was installed as the President of The Japan Society of Ultrasonics in Medicine (JSUM), The World Federation for Ultrasound in Medicine and Biology (WFUMB), The Asian Federation for Ultrasound in Medicine and Biology (AFSUMB), and The International Congress on Ultrasonic Examination of the Breast (ICUEB).