Endoscopic Ultrasonography: From the Origins to Routine EUS

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Endoscopic Ultrasonography (EUS): The Beginning

“The first report of endoscopic ultrasonography [EUS] to my knowledge is that of DiMagno et al....although images were only obtained in dogs, this work established the feasibility of EUS. ...But in 1980 the potential of this hybrid technology was scarcely apparent to anyone probably including these first endosonographers who did not expand on their demonstration of the feasibility of EUS” [1].

“The resultant high-resolution scans may improve the ultrasonic diagnosis of cardiac, gastrointestinal and renal diseases. A similar adaptation in other endoscopes may be useful in the investigation of genitourinary and respiratory tracts and other areas” [2].

“...it should be possible to determine whether or not a disease process is mucosal, intramural or extraluminal...point out the wide potential clinical applicability of intracavity endoscopic ultrasonography (e.g. within the gastrointestinal tract, peritoneum, pancreatic ducts, intravascular spaces etc.). It is likely that specialized

ultrasonic probes will be developed to detect small lesions anywhere within the human body” [3].

Introduction

The first quotation [1] represents the prevailing opinions regarding the origins of EUS (an instrument that combined fiber-optic endoscopic and ultrasonic capabilities). The second and third quotations are from the first report of the use of EUS in *The Lancet* [2], and our article in *Gastroenterology* [3] are reports of our initial experience with the use of EUS in humans. In this article, which primarily recounts my (Professor DiMagno’s) experience, we will discuss the:

- Brief history of early development of ultrasound (US) in medicine from sound navigation and ranging (SONAR) in diagnosing valvular heart disease, rectal cancer, and urologic disease.
- Time line (Fig. 1) of the development of EUS leading up to the initial performance of EUS in humans, including pre-EUS transgastric US, preclinical proof-of-concept studies in animals using a prototype EUS instrument to assess transesophageal and transgastric imaging of thoracic and abdominal viscera, including cardiac and non-cardiac tissues, vessel enhancement, and three-dimensional imaging.
- Design of EUS instruments.
- Later studies of diagnosis of foregut duplication cysts, computer-assisted analysis (neural net or artificial intelligence) programs and the combination of EUS and pancreatic function tests for the diagnosis of pancreatic diseases, and some possible future directions of EUS.

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Fig. 1 Timeline of (left) development of fiber-optic scope and EUS and (right) publications pertaining to early development of ultrasound (US) in medicine and the development of EUS leading up to the initial performance of EUS in humans

Sonar (Ultrasound) and Echocardiography

Clinical US arose from several incipient discoveries [4]:

- 1700s Spallanzani (1729–1799) discovered (without publishing) that bats used ultrasound-guided navigation.
- 1880 Jacques and Pierre Curie [5] discovered the piezoelectric effect in quartz crystals.
- 1916–1917 Constantin Chilowsky (1880–1952) and Paul Langévin (1872–1946), a former doctoral student of Pierre Curie, proposed the use of SONAR for underwater navigation and detection of submarines [6, 7].
- 1941 Dussik was the first to apply ultrasound to medical diagnosis [8].

As an important contribution to gastroenterology, a 1946 graduate from the University of Pennsylvania Medical School, George D Ludwig, while serving on active duty 1946–1949 at the Naval Medical Research Institute, was the first to use pulse echo US similar to SONAR and radio detection and ranging (RADAR) to detect human gallstones inserted into canine gallbladders [9, 10]. At the University of Pennsylvania, I first became aware of the possible diagnostic use of US in medicine in 1957–1958, when I was a 4th year medical student on an elective with cardiologists Claude R. Joyner (a pioneer in echocardiography) and Harry F. Zinsser. Dr. Joyner and an electrical engineer John Reid were exploring the use of US to detect valvular heart disease in humans [11]. Previously, in 1952, Reid and John Julian Wild built a B-mode ultrasound instrument under the auspices of a National Cancer Institute (NCI) grant [12]. Joyner and Reid expanded on the earlier efforts (1954) of Hertz and Edler (father of clinical echocardiography) [13, 14] and confirmatory studies by Effert [15] involving the application of US to record continuous cardiac wall movements [13] and to detect mitral valve disease [14]. In the afternoons, I observed them examine normal persons and patients with valvular heart disease, usually mitral stenosis. In 90 patients with mitral stenosis, they reported a distinctive abnormal pattern of echoes in comparison with normal persons [11, 16, 17]. Their instrument was the first such system devised and used in the US. These early studies were the forerunners of transcutaneous and transesophageal cardiac echography.

Other advances of intraluminal echography were transrectal and urological endosonography. Here again Wild and Reid led the way when in 1956 they used a mechanically rotating echoprobe to diagnose a recurrent rectal cancer [16]. Other early reports included transrectal ultrasonography of

the prostate and seminal vesicles [17], rectal cancer [18], and tumor infiltration of the rectal wall [19]. These instruments were US probes without optical capability. The initial attempt to use intragastric US to distinguish between pancreatic cystic and solid lesions compressing the stomach was published by Lutz and Rosch [20] in 1976. They placed an ultrasound A-mode probe within the stomach by passing the probe through the accessory channel of a therapeutic TGF-Olympus fiber-optic endoscope. The development of EUS occurred shortly thereafter.

Early History of EUS

Prior to our EUS studies, I investigated the accuracy of the diagnostic tests available at that time, including transcutaneous US, to diagnose pancreatic disease [21]. In this study, we reported that transcutaneous US was ~80 % sensitive and specific [21]. The imperfect performance of transcutaneous US led to the formulation of the hypothesis that placing the US probe within the gastrointestinal tract, closer to the pancreas, would improve the accuracy of diagnosing pancreatic diseases.

Likely as a consequence of this study [21], Philip S. Green of SRI (formerly Stanford Research Institute International) contacted me regarding my interest in an US endoscope. Philip Green and his team at SRI International, including JL Buxton, DA Wilson, and JR Suarez, developed a system incorporating US into endoscopes. Phillip Green is better known for inventing the Green Telepresence System [22], later called Mona, now called the da Vinci surgical robot in honor of Leonardo da Vinci, who is credited with inventing the robot.

The development, preclinical, and clinical testing of EUS was supported by the NCI from 1978 to 1981 [Contract CB 74136, Development of Ultrasonic Endoscopic Probes for Cancer Diagnosis]. The rationale of this contract was that current clinical US was hampered by low resolution due to intervening gas and bone. The underlying hypothesis was that EUS could simultaneously visualize the gastrointestinal lumen and accomplish high-resolution scans of adjacent structures with an aim to improve the accuracy of the diagnosis of pancreatic cancer. My responsibility was to perform the initial animal experiments to evaluate the safety and potential applicability of EUS and assess what modifications of the instrument would be necessary to use EUS in humans. The Mayo team that performed the preclinical and clinical studies included co-investigators PT Regan, RR Hattery, B Rajagopalan, JF Greenleaf, JE Clain, and EM James.

Fig. 2 Initial “animal” (a) and subsequent “human” EUS instrument (b)

Initial Design of the EUS Instrument and Its Experimental Application

The initial EUS instrument consisted of a 13-mm-diameter American Cystoscope Manufacturers Inc. (ACMI) FX-5 side-viewing endoscope with an 80-mm rigid tip containing a 10-MHz 64-element real-time image array (30 frames/s) with a 3×4 cm field-of-view US probe (Fig. 2a). The endoscope had a now obsolete “flag” handle to maneuver the tip.

EUS Safety, Collaborations, and Early Results

The aims of the animal studies were to determine safety, to define US characteristics of thoracic and abdominal viscera viewed from within the gastrointestinal tract, and to specifically explore EUS visualization of the pancreas. Prior to initiating the animal studies and approval by the Animal Safety Committee, the instrument underwent extensive testing by the Mayo Engineering and electrical safety committees to assure the instrument was safe, particularly with regard to electrical safety. The initial studies were performed in miniature pigs and in dogs (Fig. 3a) with Drs. Patrick Regan and Robert Hattery. Dr. Regan was a consultant gastroenterologist at Mayo and a former GI fellow in my laboratory, who later moved to Milwaukee where he is now an Emeritus Clinical Professor of Medicine at the Medical College of Wisconsin School of Medicine. Dr. Hattery was a radiologist expert in clinical transcutaneous US who now is an Emeritus Professor

of Radiology. The importance of the addition of the radiologists Drs. Hattery for the animal studies and EM James (now also an Emeritus Professor of Radiology) for the human studies was to help with the interpretation of the images.

In 1978, after receipt of the animal instrument (Fig. 2a) and after approval by institutional committees, we began the animal studies and presented our preliminary studies in October 1979 in Chicago at the Central Society of Clinical Research and the Midwestern Section of the American Federation of Medical Research [23]. The results of the initial experiments using the experimental instrument in dogs were published in March 1980 in *The Lancet* [2]. We reported that the instrument was safe in dogs, provided <1-mm resolution real-time images of the heart, great vessels, spleen kidney, porta hepatis, gall bladder, and gastric mucosa, free of bone and air artifacts. Due to the very long 80-mm rigid tip, however, we were unable to enter the duodenum. Because of the limitations of this initial instrument, a second instrument was developed, which we hypothesized would be suitable for human studies.

Vessel and Tissue Enhancement, Three-Dimensional Imaging, Leading to Human Transesophageal Echocardiography

We conducted further investigations with the experimental EUS in dogs to explore vessel and tissue enhancement and three-dimensional imaging. These studies included vessel

Fig. 3 EUS procedures. **a** One of the first dog studies. Dr. DiMagno sitting; Dr. Regan standing. The dog was part of other studies (I had an active animal laboratory as well as doing clinical investigation), which is the reason for the cannulas. The crate is the shipping container for the EUS instrument. **b** Human study. Eugene P. DiMagno (endoscopist), masked patient (gurney), and technician (right)

and tissue indocyanine green (ICG) enhancement of the aorta, splenic and renal arteries, heart, renal cortex, gallbladder, and pancreatic ducts [23–26]. The Mayo investigators for the cardiac studies in dogs included James Greenleaf, a Mayo pioneer in ultrasound, and Bala Rajagopalan, a research fellow in Dr. Greenleaf's laboratory. With the experimental EUS, we obtained transesophageal images of the aorta and canine heart. In addition, after insertion of a catheter into the cardiovascular system and injection of a contrast medium (ICG), we visualized the right ventricular outflow tract (Fig. 4a–c), aortic bulb (Fig. 4d–f), contrast enhancement of the left atrial chamber (Fig. 4g–i), and scans of the left atrium during incremental rotation about the axis of the endoscope. These canine cardiac studies demonstrated that in comparison with transcutaneous US imaging, EUS provides unobstructed

high-resolution imaging of the heart, which led to early studies of human transesophageal echocardiography at Mayo [27], the possibility of constructing 3-D images by collecting incremental transverse cross sections [28], and with contrast media to enhance visualization of the myocardium (an indication of myocardial perfusion) and possibly coronary arteries.

Clinical EUS

The clinical instrument was a 13-mm-diameter ACMI FX-8 endviewing endoscope that had the same US system as the animal instrument, but had a shorter 35-mm rigid tip (Fig. 2b). The aims of the human EUS study were to determine the safety of the procedure, determine the normal US characteristics of thoracic and abdominal viscera, and the gastrointestinal mucosa viewed from within the gastrointestinal tract, and to assess the ability to visualize pancreatic and extra-pancreatic lesions such as tumors, metastases, and cysts.

Prior to initiating the clinical EUS studies and approval by the institutional review board (IRB), the human instrument was extensively tested by the Mayo Engineering and electrical safety committees to assure the instrument was safe and did not pose a significant shock hazard. During EUS, we were required to continuously monitor cardiac (ECG) and respiratory function (rate and oxygen saturation). After obtaining a signed informed consent, each participant was given intravenous conscious sedation. Finally, the procedure was videotaped (with audio) and limited to 45-min duration (Fig. 3b).

We (gastroenterologists Drs. EP DiMagno, PT Regan, and JE Clain and radiologist EM James) performed 32 EUS examinations in 15 normal persons (4 studied twice), in 10 patients suspected or known to have pancreatic disease (4 with pancreatic carcinoma [1 cystadenocarcinoma, 1 non-functioning islet cell tumor, and 2 ductal adenocarcinomas] and 6 with chronic pancreatitis [1 studied twice]), and in two patients suspected of having pancreatic disease who had a normal pancreas at examination (1 a gastric ulcer and 1 suspected to have a pancreatic abscess). Two gastroenterologists and the radiologist attended each procedure.

We obtained views of the normal heart, pancreas, spleen, renal cortex, and vessels (celiac axis, portal and splenic veins, renal arteries) (Figs. 5, 6) and of pancreatic diseases (Fig. 7) and accessory signs of pancreatic diseases (dilated common bile duct and portal vein, hepatic metastases, and dilated intrahepatic ducts). We concluded with EUS one could determine whether a lesion was mucosal, intramural, or extraluminal. Also we could obtain high-resolution images of pancreatic lesions and of structures as small as 1–2 mm. Lastly, EUS eliminated the need for

(a) Before

(b) After

(c)

(d) Before

(e) After

(f)

(g) Before

(h) After

(i)

◀**Fig. 4** Sequential canine heart images before and after indocyanine green injection, the latter depicted by diagrams (*far right column*). *Right* ventricular outflow tract (**a–c**). Aortic bulb (**d–f**). Enhancement of the *left* atrial wall (**g–i**). Adapted from Figs. 4 and 6 of Ref. [26]

X-ray positioning of a fiberscope probe [29] (see below). Our initial examinations in humans with the clinical EUS (Fig. 2b) began in 1979, and the preliminary results were reported at several meetings and published as abstracts

Fig. 5 Normal anatomy. Images from **a** the esophagus [coronary sinus (CS), left atrium (LA), mitral valve (MV), left ventricle wall (LVA)]; **b** posteriorlateral stomach [spleen (S), splenic vein (SV), pancreas (P)]; **c** posteriorlateral stomach [pancreas, interlobular

pancreatic septa (SE), renal cortex (C)]; and **d** posteriorlateral stomach [aorta celiac axis (CA), left gastric artery (LGA) and hepatic artery (HA)]. Adapted from Fig. 2 of Ref. [3]

Fig. 6 Normal anatomy. Images from **a** lesser curve stomach [liver parenchyma (LP), hepatic vein (HV)]; **b** posterior antrum [portal vein (PV), splenic vein (SV), inferior vena cava (IVC), spine (S)]; **c** posterior antrum [portal vein (PV), splenic vein (SV), aorta (A), superior mesenteric artery (SMA), renal or lumbar arteries (RA)]; and **d** duodenal bulb [gallbladder (GB), liver (LP)]. Adapted from Fig. 3 of Ref. [3]

[30–34] beginning in May 1980 and ultimately as a peer-reviewed manuscript in *Gastroenterology* in 1982 [3].

In addition to the two ACMI EUS instruments, we evaluated a 9.5-mm-diameter Fujinon ATL-Fast Physical Optics (FPO) instrument, which had the same US system, except that the probe was 7.7 cm from the tip (Fig. 8). Although the US images were similar and it was easier to visualize the probe within the stomach and to enter the duodenum, it was more difficult to position the probe within the stomach to obtain US images. Ultimately, we

concluded that the Fujinon EUS had no distinct advantage over the SRI-FX8 instrument [35].

Development of Other EUS Instruments

At approximately the same time we were conducting our experimental and human studies, Professor M. Classen and his group were using a prototype instrument consisting of a 5-MHz transducer mounted on the tip of a side-viewing

Fig. 7 Pancreatic diseases. **a** Adenocarcinoma pancreas pushing against gastric wall; **b** adenocarcinoma head of pancreas [common bile duct (CBD), pancreatic duct (PD)]; **c** islet cell carcinoma pancreas pushing against lesser sac (LS) and gastric wall (GM); and

d pancreatic pseudocyst (PS) at junction of head and body of pancreas. Artifacts due to degeneration of electrical cabling. Adapted from Fig. 4 of Ref. [3]

gastroscope (Olympus GR-D3) [29]. The rigid ultrasonic probe was 3 cm long, but the terminal end including the probe was 8 cm long, the same length as the SRI experimental EUS, much longer than the 3-cm rigid end of the SRI clinical EUS. The US image was an 85-degree sector

scan generated by a motor-driven 45° acoustic mirror rotating at 4–8 revolutions/s.

I first met Professor Classen in 1980 when we presented our preliminary human data in Hamburg, Germany, at the International Congress of Endoscopy [31]. The Classen

Fig. 8 Fujinon ATL-FPO EUS. 9.5 mm diameter and same linear array ultrasound system as other SRI EUS instruments but located 7.7 cm from tip of instrument

group published their findings of 18 patients with known hepatic, biliary, and pancreatic disorders in September 1980 [29]. In nine patients, they identified the aorta and vena cava, landmarks now recognized as necessary for a successful exam, and confirmed known pancreatic malignancies. Apparently, radiologic guidance was necessary to position the instrument.

This Olympus prototype as well as a Pentax-Siemens echoendoscope, which had a rigid metal tip, a Toshiba-Pentax prototype, and the ACMI-SRI echoendoscopes, which we used, were never produced commercially [36]. The latter 2 echoendoscopes employed a linear array transducer.

More Recent Investigations and Possible Future Directions of EUS

We described the diagnosis of foregut duplication cysts by EUS [37], and more importantly, we reported that artificial neural network (ANN) analysis of EUS images could differentiate between pancreatic malignancy and pancreatitis [38]. We hypothesized that self-teaching ANN (“neural net” or “artificial intelligence”) programs, which were developed to interpret complex waveforms such as electrocardiograms [39, 40] and US images of benign and malignant breast lesions, might aid in their differentiation [41, 42].

Briefly, we scanned and digitized the internal echo texture of EUS images from X-ray film. The rows of pixels were expressed as gray-scale displays, and by computer analysis, patterns could be distinguished that discriminated malignancy from pancreatitis. According to receiver-operated curve analysis, the diagnostic accuracies of differentiating pancreatitis from pancreatic cancer were similar for the computer ANN, the endosonographer performing the examination, an endosonographer who had no clinical

or other information, and the CA 19-9 (80, 85, 83 and 78 %, respectively). Since the differentiation of pancreatic cancer from pancreatitis by the ANN program was similar to an experienced endosonographer, ANN could be useful, particularly to endoscopists with limited EUS experience.

Other approaches aimed at increasing the general applicability and reducing observer variability of EUS, besides improving ANN-based analysis, are to add elastography to EUS for evaluation of lymph nodes [43–47] and pancreatic lesions [43, 47–53], to combine ANN with EUS elastography [50], and to use probe confocal endomicroscopy via EUS guidance [54–57]. Even more futuristic is the idea of “driverless” EUS and image acquisition (as in driverless car). Another approach is to combine EUS with a pancreatic function test to measure pancreatic enzyme activity and/or bicarbonate concentration in duodenal samples after secretin or cholecystokinin-octapeptide stimulation [58, 59]. These tests are highly predictive of the absence of pancreatic disease, but have poor positive predictive value (false positives) [58]. Thus, this test is widely applicable and valuable to exclude pancreatic diseases but has poor positive predictability, which hampers its utility.

In summary, we have presented a personal view of the early history of EUS. From these early studies, EUS has rapidly become an integral part of the gastroenterologist’s toolbox to diagnose and manage gastrointestinal diseases, particularly of the pancreas and biliary system. In this cohort of patients, EUS is a fundamental tool “because of its ability to provide superior visualization of a difficult anatomical region, but also because of its valuable role as a problem-solving tool and ever-improving ability in an interventional capacity” [75]. In addition, the ever-increasing application of EUS has improved the diagnosis of other gastrointestinal and non-gastrointestinal diseases and provided a delivery system for therapies. EUS has an important role in the evaluation of Barrett’s esophagus, cancer of the esophagus, stomach, and rectum, gastric lymphoma, submucosal lesions, fecal incontinence, perianal disease, lymph nodes, mediastinal adenopathy, and heart and vascular structures [76]. Therapeutic EUS is increasingly used to treat pancreatic diseases, including intratumoral chemotherapy drug delivery [63, 64], EUS-guided endoscopic cystogastrostomy [65–67], EUS-guided celiac plexus blockade [68–70], or neurolysis [70, 71]. The future certainly will bring further EUS innovations in scope design, probes, and devices to enhance the diagnosis and treatment of our patients.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest.

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