CHAPTER 1

A history of endoscopic ultrasonography

Michael B. Wallace MD MPH
John C Andersen Professor of Medicine, Mayo Clinic, Jacksonville, FL, USA

The first report of endoscopic ultrasonography (EUS), to my knowledge, is that of DiMagno et al., published in 1980 [1]. These investigators described a prototype echoendoscope assembled by attaching a transducer to a duodenoscope. Although images were obtained only in dogs, this work established the feasibility of EUS. As with nearly all seminal advances in endoscopy, EUS was basically an amalgamation of existing technologies. 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.

For practical purposes, the inception of EUS as a clinical entity in the United States can be traced to a meeting between Dr. Michael Sivak and Mr. Hiroshi Ichikawa of the Olympus Optical Company, most likely around 1981. Olympus was developing several new technologies and sought advice on priorities for the development of EUS, or enteroscopy. Dr. Sivak advised Olympus to focus on EUS, largely because the idea of endosonography seemed especially intriguing; it offered a greater challenge but also the promise of a much wider range of prospective applications. At the time, there was little thought or appreciation of the formidable obstacles to the clinical realization of this potential or the investment of time and effort needed to reach this goal. Mr. Ichikawa did, in fact, lay emphasis on the obstacles, warning that the instrumentation was in the early stages of development. Because of the scope and difficulty of the project, Olympus proposed to work with two investigators in the United States (actually, the western hemisphere), the other being Dr. Charles Lightdale in New York City, as well as a few individuals in other countries. As it turned out, this was the beginning of a long and rewarding professional association, for which EUS became the basis. Thus, EUS in the United States began with Michael Sivak and Charlie Lightdale.

Given the technical sophistication of present-day EUS systems, it is important to recognize that during the early years, the viability of endosonography was far from certain. Until about 1985, there was substantial skepticism concerning the future of EUS, even among those most closely involved with and committed to its development. The ample tribulations facing the very small cadre of nascent endosonographers became strikingly evident with the arrival of the first EUS system, a prototype in the truest sense. Despite the obvious problems, however, early pioneers remained encouraged; the best description of their mindset during these formative years might be "doggedly enthusiastic."

An early all-encompassing protocol written by Dr. Sivak allowed the use of the instrument as an investigational device in patients. The protocol, essentially, had no hypothesis other than the assertion that EUS was going to be a good thing. It listed almost every possible indication conceivable and minimized the risks, which were unknown in any case. By today's standards, it is doubtful it would be approved by any institutional research committee.

The major problems that had to be addressed in the beginning can be divided into four categories: the technical limitations and deficiencies of the equipment; the development of efficient and safe techniques for the use of the echoendoscope in patients; the interpretation of the ultrasound images; and the need to define and establish indications for EUS in clinical practice. More issues, some even more complicated, became evident over time.

The prototype echoendoscope itself was, by modern standards, incredibly cumbersome. The electronic (video) endoscope had not been introduced into clinical practice, so the prototype echoendoscope was a fiberoptic instrument; the optical (endoscopic) component consisted of an ocular lens and focusing ring, coupled to a coherent fiberoptic bundle, with another lens at the distal end of the insertion tube to focus an image on the bundle. The latter provided a limited, 80° field of view, oriented obliquely at an angle of 70° to the insertion tube. Of these two parameters, the narrow field of view was more of a limitation than the oblique orientation, which was not especially problematic for endoscopists accustomed to the side-viewing duodenoscope.

The ultrasound component of early echoendoscopes consisted of a transducer coupled to a rotating acoustic mirror at the distal tip of the insertion tube. The mirror was turned by means of an electric motor within a motor housing situated between a standard design control section and the insertion tube; thus the designation, "mechanical, sector-scanning echoendoscope." Because the mirror turned around the long axis of the insertion tube, the ultrasound scanning plane was oriented perpendicular to the insertion tube. In retrospect, this was the best choice because it seemed to simplify the problems of image interpretation. But this arrangement also had its limitations, mainly that it was unsuitable for guiding a needle to a target. Needle aspiration was, in fact, attempted with the

Endoscopic Ultrasonography, Fourth Edition. Edited by Frank G. Gress and Thomas J. Savides.

sector-scanning (now called "radial") instrument, albeit unsuccessfully, because the width of the tissue within the circular scan was much too narrow.

Unfortunately, the ultrasound imaging sector provided by the first instruments was not a full 360° but only 180°. To obtain a complete, circumferential sector scan of the surrounding tissue – a circumferential esophageal tumor, for example – it was necessary to rotate the insertion tube 180° while maintaining the same scanning plane. This was a considerable feat, especially with the instrument deeply inserted, for example, in the third part of the duodenum. In truth, it was largely impossible because any application of torque to the insertion tube invariably altered the scanning plane. This was but one among many difficulties.

Owing to the mechanical components, principally the motor and its housing, the instrument was much heavier than a standard endoscope. Because EUS had no established clinical purpose, the first procedures can only be described as exploratory. Consequently, procedure length was determined largely by patient endurance, and with an especially tolerant patient, the weight of the instrument seemingly increased exponentially. After two or three examinations, it was often difficult (and painful) to straighten your left arm.

The combination of optical and acoustical components at the distal end of the insertion tube conferred other penalties, including some potential hazards. The outer diameter of the insertion tube was 13 mm, which is substantially greater than that of the upper endoscopes of the time. To make matters worse, the distal end was rigid over a length of 4.5 cm, that is, the distance from the tip to the bending section. Together with the limited field of view, this increased the difficulty of inserting the instrument through the mouth and pharynx and into the esophagus. Although we assumed that the risk of complications with EUS was no greater than that with upper endoscopy, and informed our patients the same, in reality, the risk of perforating the pyriform sinus was probably greater – a fact subsequently substantiated. Moreover, attempts at insertion of the large-diameter echoendoscope through a constricting tumor in the esophagus were no doubt associated with an appreciable risk of perforation.

In addition to developing techniques for the safe insertion of the echoendoscope, the learning curve for EUS imaging can only be described as long and steep, like a line with a slope approaching straight up. According to Yogi Bera, "ninety percent of everything is half mental," and this was definitely true of EUS. The first quandary was the need to uncouple endoscopic imaging from ultrasonography. This relates to the need for acoustic coupling, that is, the creation of a suitable interface between the tissue and the transducer (in this case, the acoustic mirror). We discovered in short order that ultrasound images cannot be obtained through the air. The obvious solution is to remove the air. But this proved impractical for several reasons. The alternative was to interpose water between tissue and "transducer," which could be accomplished in two ways: by placing a balloon over the transducer section of the instrument and filling it with water, or by filling the gut with water. However, it was not simply a matter of choosing between these two options. Depending on the circumstances, including location within the gastrointestinal tract, one or the other is usually a better choice. With the balloon method in particular, the endoscopic view was lost as the balloon was brought into contact with the gut wall, meaning that ultrasound imaging could only proceed by abandoning the endoscopic view. For technical reasons, therefore, EUS imaging was, of necessity, endoscopically blind. Although this decoupling might seem inconsequential today, it was a mental leap of faith in the early days, inasmuch as endoscopic dogma deemed "blind" use of an endoscope hazardous.

The use of the balloon with early-model echoendoscopes was so exasperating that it deserves a digressive paragraph of its own. The latex material that constituted the balloon was not of uniform quality, which made it nearly impossible to place the balloon on the echoendoscope without tearing it. When expanded, the balloon had an asymmetric bulge, and according to the instructions, the bulge was to be placed over the transducer on the same side as the optical component; this was never accomplished. Assuming that the balloon could be maneuvered intact into the correct position, it was next necessary to tie it in place with small sutures. The design of the instrument was such that the proximal end of the balloon sometimes occluded the opening of the channel for air insufflation and water irrigation, which would not be evident until it was securely tied in place and tested. Subsequent attempts to nudge the balloon into the proper position usually result in tearing. Since the objective was to create a water–tissue interface, it was necessary to remove all the air from the balloon (without breaking it). The balloon, if not placed exactly, could occlude the tiny-diameter channel provided for this purpose. Once all of the delicate parameters were attained and the balloon was in gloriously correct position and functioning properly, the most maddening occurrence was the rupture of the ill-fated bag in the middle of an examination, usually at the most inopportune moment. Early adopters dealt with some of these frustrations by persuading support staff from the biomedical engineering department (designated the "balloon man") to take on the task of balloon placement prior to each procedure.

During the examination, the balloon was filled with water via a Luer lock fitting located between the control section and the motor housing. Unfortunately, this design meant that the attached syringe protruded in a perpendicular fashion. Accordingly, as the endosonographer moved his right hand from the control section to the insertion tube, he invariably broke the syringe. In order to fill the balloon, it was necessary to set a small lever on the motor housing to the balloon-filling position, clearly labeled as "B." The other choice was "G," which, when selected, channeled the water into the gut. Since it was not possible to see this lever, it was advisable to remember which position it was in. Otherwise, the balloon might be filled with water beyond its capacity.

One of the most gratifying aspects of endosonography, readily apparent at the very first examination, was the ability to obtain a structured image of the gut wall. Believe me, all of us knew intuitively and immediately that this was going to be very big. But the interpretation of these images was something else again. There was a natural tendency to assume and hope that the five-layer structure corresponded in exact fashion to the actual layers of the gut wall as seen microscopically in a histological section. This betrays a near total ignorance of the principles of ultrasound imaging, and over time, it became evident that the physical basis for the endosonographic representation of the bowel wall is much more complex. For reasons unknown to me, the main ultrasound frequency selected for the first EUS systems was 7.5 MHz, a frequency that happens, under the usual conditions, to render the wall structure of the stomach as five layers. I suspect that this choice of frequency was based on technical considerations rather than experimental data. In any case, it took some time to work out the actual physical basis for the ultrasound images of the gut wall.

During the initial discussions with Dr. Sivak and Hiroshi Ichikawa, they soon realized that EUS might have a positive impact on the problem of pancreatic cancer. By 1980, it was clear that

endoscopic retrograde cholangiopancreatography (ERCP) could never alter the natural history of this disease, but perhaps EUS might provide an opportunity, under certain circumstances, for earlier detection and therefore improved survival. In retrospect, this was a worthy but naïve notion. Nevertheless, they resolved to pursue EUS of the pancreas. Dr. Charlie Lightdale, on the other hand, took a more sensible and practical path by studying the applications of EUS in staging esophageal cancer.

Imaging the pancreas presented many challenges to early endosongraphers, and it was soon obvious that the only way to move forward was to seek the partnership of a radiologist with expertise in ultrasonography. Many of the first endosonographers adopted a similar approach. And so, a radiologist by the name of Craig George joined the team at University Hospitals Cleveland. Dr. George would look over Dr. Sivak's shoulder during the EUS procedure and essentially interpret the images. By this time, a second-generation prototype EUS system was available. In contrast to the first prototype, the second system included an extremely bulky image processor with a tiny display screen, probably no more than 8 inches on the diagonal. Moreover, the quality of the image was poor, which made it necessary to get close to the screen to see anything. Furthermore, the screen was placed in the box so that it was only about 4 feet above the floor.

Although this arrangement was cumbersome, the endosonographer and sonographer soon mastered pancreatic imaging and the principles of ultrasonography and gradually returned to independent imaging by the GI physician.

Until June 1982, the struggle to develop EUS was a lonely one; only a handful of endoscopists had any practical experience with EUS, and all were working essentially alone. This changed that June, when Olympus sponsored the first "International Workshop on Endoscopic Ultrasonography" at the Grand Hotel in Stockholm, Sweden – a time and venue selected to coincide with the World Congress of Gastroenterology. They met in a very small room, as there were, according to timely notes, only about 15 active participants, including two invited guests with expertise in areas of digestive ultrasonography other than EUS and excluding about a half dozen representatives from Olympus.

Compared to the many subsequent EUS meetings, this first gathering was by far the most important. By the time of the meeting, each participant had discovered many things about EUS, but none had a complete picture of its limitations or true potential. Thus, there was a remarkable and exhilarating exchange of information and ideas that, in retrospect, amounted by aggregation to a significant advance. Dr. Sivak led a long discussion on EUS of the pancreas that solidified the concept of stationed withdrawal of the echoendoscope from the duodenum. Essentially, they made a list of the organs and structures that should be imaged at each station. But, most importantly, each of the dozen participants left the meeting with a revitalized sense of purpose as well as a stronger sense of confidence in the future of EUS.

Another aspect of EUS that was clarified by the 1982 meeting was the incredible value of cooperation in the effort to establish EUS as a clinically useful technology. In many ways, the meeting revealed more about what we did not know than what we did, and it showed how much had to be done before EUS could be considered clinically relevant. Shortly thereafter, and in response to the lessons learned at the meeting, Mr. Mark Donohue of Olympus and Dr. Sivak helped organize a small group of investigators that would meet two or three times each year. Our purpose was to grapple collectively with the problems of EUS and, in general, find ways to advance its development. In addition to Dr. Sivak, the original membership included Charlie Lightdale and Drs. H. Worth Boyce and Lok Tio. Over the eight or so years of its existence, the membership changed somewhat, but it was always strictly limited to no more than six (usually five). Together with two or three people from Olympus, the total number attending each meeting was never more than eight or nine. Naturally, when the existence of this group became known, albeit not widely, Olympus was besieged by individuals who felt they had the qualifications for membership. But, to the credit of Olympus, Mr. Donohue resisted all requests in order to preserve the small-group dynamic. The group was aptly named the "EUS Users Group."

These EUS Users Group meeting topics covered much of the developmental history of EUS from about 1982 to 1989. The subject matter was divided into two major areas: technical development and the application of the technology to clinical practice and training. As interest in EUS increased, it became glaringly evident that training constituted a formidable problem, all the more so inasmuch as clinical relevance would never be achieved if EUS were performed by a small number of experts. This issue was further compounded by the high cost of the equipment (relative to that of standard endoscopes) and the absence of reimbursement. In those days, echoendoscopes were also fragile and as expensive. The need for frequent maintenance and repairs substantially increased the cost of operation. In the hands of an inexperienced operator, this fragility frequently pushed repair costs well beyond those normally anticipated by an endoscopy unit. All of these factors constituted a significant "cost barrier" to involvement with EUS.

There was a certain division within the "Users Group" as to the best approach to the problem of training. There was unanimity concerning the value of didactic teaching, resulting in a number of short symposia. However, it was clearly recognized that this was no substitute for so-called "hands-on" instruction. With respect to the latter, one viewpoint held that short periods of training, ranging from a few days for an accomplished endoscopist to 6 months for the less experienced, would be adequate to "get started." Some others felt that a "quick and dirty" approach was doomed to failure and advocated more formal and prolonged training. The caveat to this approach, however, was that EUS might never become established. As late as 1988, the programs with the capability for training numbered only five; that is, the members of the group. Even if the group trained 10 endosonographers per year, it would take many years before EUS became widely available.

It was fortunate that EUS was introduced during the decade of the 1980s, a period when endoscopists were under less pressure to be ultra-efficient and financially productive. The commitment to screening colonoscopy, for example, had not yet arisen, even as a concept. Had the introduction of EUS been attempted 10 years later, the probability that it would become an established procedure would have been substantially reduced.

The establishment of EUS as a clinical procedural entity stands as a tribute to the perseverance of a relatively small group of people as well as to the resolve of the Olympus company. Although this was not generally known, EUS also constituted a substantial cost barrier for the company; in fact, it was a financial loss for more than a decade. That any company would invest so much time and talent for so long, despite an uncertain prospect of financial gain, is remarkable. There is a story, admittedly apocryphal, that Mr. Ichizo Kawahara, then the director of the Medical Instrument Division of Olympus, was once asked why the company persisted in its efforts to develop EUS despite the obstacles and the uncertain chance for

success. He is said to have replied, "Because the doctors want it." This, I believe, also reveals the different nature of those times.

By 1986, EUS was here to stay with the introduction of the Olympus/Aloka UM2 system. The GF-UM2 echoendoscope was still a fiberoptic instrument, but the EU-M2 display unit was markedly improved. In particular, it offered a 360-sector display, a gigantic improvement with respect to pancreatic imaging. This was followed by a gradual but steady flow of technical improvements. This, together with the continuing addition of more and better data, solidified a lasting place for EUS in clinical practice. It took a lot longer than I had imagined, but it was gratifying to have played a part.

PART 1. Early history (edited by Michael Wallace)

The next phase of EUS is characterized by increasing interventional applications of EUS, beginning with the ability to extend a needle through the endoscopic into tissue, cysts, or ducts, initially for cytological sampling and then later with therapeutic applications. I entered the EUS world as a 2nd-year GI fellow at the Brigham and Women's Hospital, Boston, MA, in 1996 under the mentorship of Jacques Van Dam and David Carr-Locke. I was fascinated by the GI application to cancer detection, staging, and treatment and found myself pulled to the EUS room. In 1998, as a 3rd-year fellow, I became aware of the first EUS needles becoming available in Boston, and Dr. Bill Brugge came to the Brigham to do the first case with us. A key technological development that enabled EUS-guided fine-needle aspiration, as well as many subsequent innovations, was the curved linear array (CLA) EUS scope, where the ultrasound axis sector aligned with the scope and needle, thus allowing full visualization of the target and needle.

EUS-FNA (Fine Needle Aspiration) applications rapidly expanded, starting with pancreatic tumors, cysts, lymph nodes, other metastatic sites, the mediastinum, and virtually any site within 6–8 cm reach of the gut lumen. I soon completed my standard fellowship and received an ASGE-Olympus scholarship to train in EUS with Dr. Robert Hawes and Peter Cotton in South Carolina, where I stayed as faculty for four more years. During those years, the first therapeutic interventions, celiac plexus block/neurolysis, were reported.

The past 20 years of EUS have largely been characterized by luminal access procedures, initially through needle puncture-guidewire-standard stents from the gut lumen to any number of sites (pseudocyst/walled-off necrosis, bile duct, pancreatic duct, gallbladder, other gut lumen). The most important advance of this time was the invention and commercialization by Dr. Ken Binmoeller of the first lumen-apposing metal stent (LAMS). This device revolutionized EUS by allowing the safe, reliable anastomosis of two hollow lumens.

Twenty years ago, many skeptics of EUS predicted it would be replaced by better imaging (CT, MRI) and minimally invasive or even natural orifice (NOTES) surgery. Quite the opposite, EUS has continued to grow and thrive through innovation and scientific discovery. The need for neoadjuvant therapy for many EUS-relevant cancers (pancreas, esophagus, rectum, and lung) implies that tissue is needed before surgery. Classical NOTES was neither less invasive nor safer than laparoscopic surgery, but EUS-guided lumen apposition outperformed both. Training options rapidly increased. The first 5 founders trained 5 more per year, and then those 10 trained 10, and then 20 trained 20, and so on, leading to 1000s now trained.

Thanks to the foresight and stamina of those early pioneers, EUS is now a mainstream and, in fact, essential tool for GI care.

Acknowledgments

The first section of this chapter was written by Dr. Michael Sivak of University Hospitals, Case Medical Center, Cleveland, OH, USA. I am deeply grateful for his work in describing the early history of EUS. I have adapted Dr. Sivak's section to the third person, and have personally contributed to some of the more recent history, but much of the chapter remains the work of Dr. Sivak.

Reference

1 DiMagno EP, Buxton JL, Regan PT, et al. Ultrasonic endoscope. Lancet 1980;I:629–631.