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Special Historical Article at the Millennium

FIFTY LANDMARK DISCOVERIES IN GASTROENTEROLOGY DURING THE PAST 50 YEARS

A Brief History of Modern Gastroenterology at the Millennium: Part I. Gastrointestinal Procedures and Upper Gastrointestinal Disorders

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The millennium provides an opportunity to contemplate and review the recent past and to plan for the future. The last half century, in particular, has been the golden age of gastroenterology, wherein rigorous, scientifically based medicine has revolutionized gastrointestinal diagnosis and therapy. The technologic fantasy and scientific fiction of 50 years ago has become the real and commonplace. The peptic ulcer that was treated by the Sippy meal, gastric freezing, or gastric radiation 50 years ago is now treated by scientifically based pharmacotherapy, including potent proton-pump inhibitors and antimicrobial therapy. The cecal adenoma that required inpatient laparotomy and colotomy for polypectomy 30 years ago is now simply removed by ambulatory colonoscopic polypectomy. The surgical gastrostomy for long-term enteral feeding of 20 years ago is replaced by percutaneous endoscopic gastrostomy. The awkward, painful, and sometimes dangerous semiflexible endoscope of 42 years ago has been replaced by the simple, convenient, and safe flexible endoscope.

The word *abdomen* is derived from the Latin *abdere*, meaning hidden or concealed. [46] The flexible endoscope, the computed tomography (CT) scan, and the abdominal ultrasound study have opened this previously inaccessible body cavity to observation and inspection by the gastroenterologist, radiologist, and surgeon without surgery. The surgeon's knife has become the endoscopist's papillotome, and the laparotomy has become a laparoscopy. The diagnostic laparotomy has become nearly obsolete.

The excitement at novel discoveries yields to complacency with time as the inconceivable becomes ubiquitous. Yet what human endeavor has contributed more to the betterment of humanity than medicine? For example, one simple gastroenterologic therapy--oral rehydration with glucose and electrolyte solution--has saved millions of lives per year worldwide from cholera. This revolution was accomplished not by the sword but by the pencil, not by rhetoric but by statistics, and not by climbing the ramparts but by toiling in the laboratory and clinic. This revolution is largely undocumented, unrecognized, and unpraised. The furious

pace of magnificent discovery and invention and the preoccupation of the discoverers and inventors with discovery and invention have left little time for writing a history.

A gastroenterologic history provides manifold salutary effects. First, individuals who toiled, created, and invented receive overdue and well-deserved recognition. Second, a history provides role models to the initiate in gastroenterology. Should not society encourage heroes and role models other than adults who can hit a round hard object with a stick beyond a wall or who can mimic human emotions and gestures before a camera? Third, a historical perspective provides the discipline an identity, purpose, and mission. Fourth, a history collates, categorizes, and clarifies the important issues in gastroenterology. A historical perspective helps outline important ongoing areas of controversy and research interest and suggests strategies, approaches, and techniques for further research. Fifth, a history that celebrates great past gastroenterologic achievements may cause legislators to reconsider draconian cutbacks in funding future worthy projects. If the need is great, the time is short. A contemporaneous history is most meaningful because a contemporary can evaluate the impact of changes, with knowledge of the before and after. Immediacy provides impact.

This article is included in this issue of the *Gastroenterology Clinics* in honor of the millennium. To provide a proper perspective, Cappell asked several senior luminaries to vote as a committee on the 50 great landmarks during the past 50 years. The vote revealed surprising concordance in the decisions, with the largest discrepancy being a difference in six of the selected landmarks. The importance and history of each landmark achievement was discussed to provide an appropriate vehicle for a modern history of gastroenterology. The landmarks are segregated into 10 categories presented in two articles.

DIAGNOSTIC GASTROINTESTINAL ENDOSCOPY

1. Basil I. Hirschowitz-- invented and developed the flexible gastroscope using fiberoptic bundles. Harold H. Hopkins, N. S. Kapany, and Lawrence Curtiss-- made technical contributions to fiberoptic gastroscopy.

Before 1957, gastrointestinal endoscopy was rarely performed. The American Gastroscope Society in 1957 was in decline with a minuscule membership that was incapable of sustaining the society journal, and the journal survived only through a $2000 contribution. At the time, most gastrointestinal complaints were evaluated by barium studies. [58] Barium studies, however, lack sufficient sensitivity because of an inability to visualize directly mucosa and lack sufficient specificity because of an inability to sample tissue histology. The only endoscopic alternatives were the semiflexible gastroscope and the gastrocamera. Flexible fiberoptic technology revolutionized and rejuvenated gastrointestinal endoscopy. Today, several gastrointestinal endoscopy journals are flourishing with circulations in the many thousands; the American Society for Gastrointestinal Endoscopy has more than 6500 members; and gastrointestinal endoscopy is a multibillion dollar industry.

Bozzini developed in 1805 a primitive rigid endoscope, for cystoscopy, called the *Lichleiter*, with illumination provided by a burning candle. [69] Kussmaul, a German physician, in 1868 fashioned and employed the first gastroscope, based on cystoscopes. The instrument was a straight, rigid metal tube passed over a previously inserted flexible obturator. The instrument was first tested on sword-swallowers. According to endoscopic legend, one sword-swallower on seeing the bulky instrument exclaimed, "I'll swallow a sword anytime, but I'll be damned if I'll swallow a trumpet." [53] Soon after the invention of the incandescent light bulb by Edison, miniature versions of the light bulb were used for endoscopic illumination. [69] General applicability of rigid upper gastrointestinal endoscopy was limited by patient discomfort and risk.

The semiflexible gastroscope, an ingenious device invented by Schindler, consisted of a rigid telescope-like cylindrical steel tube with a flexible tip that permitted flexion to 30° to facilitate intubation and to visualize tangential lesions. Images were transmitted through the flexed tip by a series of short-focus lenses, based on a concept proposed by Hoffmann. By 1947, Schindler had performed

more than 2500 semiflexible gastroscopies. The disadvantages of the semiflexible gastroscope were patient discomfort from neck hyperextension during intubation of the mostly rigid instrument, a moderately high procedure risk, and the inability to visualize parts of the stomach and the entire esophagus or duodenum at endoscopy. [58] The gastrocamera advanced by Uji and the Olympus Corporation of Japan used a miniature intragastric camera and flash lighting to photograph various parts of the stomach according to preset camera positions. The gastrocamera was inconvenient in that the instrument was intubated blindly into the stomach, the stomach was photographed without visual guidance, and the stomach was visualized only after film development following the examination. Tyndall, a British physicist, showed that light would follow the curved path of a stream of water in 1870. [54] Baird in 1927 proposed transmitting light through glass fibers around turns. [63] In 1930, Lamm, a third-year medical student in Munich, Germany, reported the successful transmission of a visual image via fiberoptic bundles. In January 1954, Hopkins and Kapany constructed a bundle of oriented and insulated glass fibers that transmitted light or visual images through a nonlinear path. [63] Their laboratory models were a few inches long and did not transmit enough light sufficiently far for gastroscopy. [58]

For flexible gastroscopy, many optical fibers had to be arranged precisely in the same relative position at both ends of a fiberoptic tube to transmit an image with high resolution and without distortion. In particular, cross-talk between adjacent fibers would degrade the image. Hirschowitz, Curtiss, and coworkers embedded thin optical glass fibers in a matrix of glass with a low refractile index; the glass matrix served as an insulating coat for the individual optical fibers to permit nearly total internal reflection of light waves around turns. [28] This breakthrough led to production of a prototype gastroscope within 6 weeks. Hirschowitz, with the help of American Cystoscope Makers Inc. (ACMI) of New York, added manual steering controls to develop a fully flexible fiberoptic gastroscope. In the grand medical tradition of Hunter, Hirschowitz tested the instrument in humans on himself. The prototype flexible gastroscope was presented in May 1957 at the American Gastroscopic Society Annual Meeting at Colorado Springs to an audience of

approximately 40 people, including Schindler. [58] Hirschowitz first published reports of the instrument in 1957 and 1958. [60] ACMI introduced the first commercial model, ACMI#4990, in 1960, which originally sold for $600. In the early 1960s, Hirschowitz replaced the side-viewing objective with the safer and simpler end-viewing objective. The side-viewing objective was subsequently revived for endoscopic retrograde cholangiopancreatography (ERCP). In 1963, Hirschowitz added a channel for endoscopic biopsies, and an external light source to provide cold light transmitted by fiberoptic bundles. [57] In the 1980s the fiberoptic cables in endoscopes were replaced by charged coupled device (CCD) chips that transmit images to a television screen via electrical wires.

The flexible gastroscope led to flexible endoscopes for the diagnosis and therapy of hepatobiliary, pancreatic, and colonic disorders, as described subsequently, as well as flexible endoscopes to examine bronchi, renal tract, and other body tubes. Hirschowitz was awarded the Julius Friedenwald Medal by the American Gastroenterology Association (AGA) in 1992.

2. Ian J. Wood, R. K. Doig, R. Motteram, and A. Hughes-- developed a flexible tube to take peroral gastric biopsy specimens without the aid of gastroscopy or fluoroscopy and used this instrument to take gastric biopsy specimens safely in hundreds of patients. Margot Shiner, and M. Royer, O. C. Croxatto, P. Mazure, and V. Sileoni-- modified Wood's instrument to perform peroral duodenal biopsies. William H. Crosby and Heinz W. Kugler-- developed a spring-operated capsule, called the Crosby capsule, to obtain peroral small intestinal biopsy specimens. Arnold L. Flick, Wayne E. Quinton, and Cyrus E. Rubin-- developed an improved biopsy tube, called the Rubin tube, that used suction and a hand operated guillotine-type blade for taking multiple peroral intestinal biopsy specimens. Basil I. Hirschowitz-- performed peroral biopsies using a flexible endoscope.

Kenamore in 1940 [71] introduced a peroral forceps to perform gastric biopsies under direct vision using Schindler's semiflexible gastroscope. Wood et al [155] in Australia developed a simple flexible tube for performing gastric suction biopsies without the aid of gastroscopy or fluoroscopy. With this technique, they demonstrated decreased gastric acid and pepsin secretion in atrophic gastritis. Wood et al

demonstrated the technique was safe in hundreds of patients. Tomenius developed an alternative tube instrument for gastric biopsies in 1950. Royer and colleagues in Argentina and Margot Shiner in England modified Wood's instrument in 1955 by lengthening the instrument and increasing its flexibility to intubate the duodenum for intestinal biopsies. [129] Their tubes were, however, cumbersome.
In 1953, Crosby assembled a medical team to analyze tropical and nontropical sprue in Puerto Rico. [7] Crosby and Kugler [27] constructed a capsule containing a spring-loaded knife activated by air suction to obtain a biopsy specimen of the jejunum to study both forms of sprue. In the grand tradition of Hunter and Hirschowitz, Crosby tested the capsule on himself by swallowing it and snipping off bits of intestinal mucosa while working at his desk on correspondence. [7] Crosby was awarded the sixth McCollum Award by the American Society for Clinical Nutrition in 1970. Flick et al [40] improved the peroral biopsy tube, using a hydraulic mechanism, to enable performance of multiple intestinal biopsies. Intestinal biopsies were important in demonstrating by pathologic analysis that gluten caused intestinal injury in celiac disease. [132] In 1963, Hirschowitz [57] in collaboration with ACMI of New York fabricated a biopsy channel to perform peroral biopsies using fiberoptic flexible endoscopes. This technology rapidly supplanted the prior instruments because of simplicity of operation, patient safety, and the ability to perform biopsies under visual guidance.

3. Bergein F. Overholt-- developed the flexible sigmoidoscope. Saburo Oshiba, Akihiro Watanabe, F. Matsunaga, and H. Niwa-- developed the colonoscope. Luciano Provenzale and Antonio Revignas-- pioneered an alternative (now obsolete) technique of performing colonoscopy by pulling an orally passed string tied to an anally inserted gastroscope.

Although barium enema can outline the entire colon, this technique lacks sufficient sensitivity because of an inability to visualize mucosa directly and lacks sufficient specificity because of an inability to sample tissue histology. Before the 1960s, only the distal 25 cm of the colon was visible by rigid sigmoidoscopy. Rigid sigmoidoscopy was uncomfortable and caused mucosal trauma. The semiflexible gastroscope developed by Schindler was not sufficiently flexible to negotiate the

turns in the sigmoid colon beyond 25 cm from the anal verge. Matsunaya et al in 1957 and Niwa in 1960 reported on attempts, mostly unsuccessful, to intubate the colon using a modified flexible gastrocamera, called the *sigmoidcamera*. The instrument could not be safely passed beyond the distal sigmoid colon. [69] Lemire and Cocco in 1966 were occasionally able to view the descending colon with the flexible fiberoptic gastroscope developed by Hirschowitz. This flexible gastroscope was not suitable for colonoscopy because greater torque and better steering controls were needed to intubate the tortuous sigmoid.

During an interview for a fellowship position, Overholt, a medical resident, heard the interviewer complain about the pain he had just experienced during rigid sigmoidoscopy and was stimulated to adapt the fiberoptic principles that had been recently applied in fiberoptic gastroscopy to develop a flexible sigmoidoscope. [52] Overholt, with the help of Kapany and the Dow-Corning Company, injected into the rectum of human volunteers silicone latex molds, which maintained their original shape after rectal expulsion, to made a lifelike model of the human distal colon. He then constructed a fiberoptic instrument with steering controls to negotiate the turns in the sigmoid colon. A prototype instrument that provided tip deflection in only one axis was first tested clinically in 1963. [106] Overholt [105] in 1968 and 1969 reported on the ability to examine beyond the 25-cm limit of rigid sigmoidoscopy by flexible sigmoidoscopy.

Oshiba in conjunction with the Machida Instrument Company and Niwa, Matsunaga, and coworkers in conjunction with the Olympus Corporation developed prototype flexible colonoscopes for complete colonoscopy. [72] [96] ACMI of New York built the first commercial true colonoscope in the late 1960s. [106] Shinya and Wolff succeeded in routinely intubating and examining to the midtransverse colon during 1969 using an 86-cm-long fiberoptic colonoscope and performed the first complete colonoscopy with examination to the cecum in June 1969. [152] Shinya and Wolff were soon able to examine routinely to the cecum using a 186-cm-long flexible colonoscope.

Provenzale and Revignas pioneered an alternative technique of colonic endoscopy by passing transnasally a long soft polyvinyl tube with a mercury bag at the tip.

After the tube tip was transported to the rectum by way of peristalsis, they tied an anally inserted Hirschowitz gastroscope to the tube, then pulled the gastroscope retrograde through the colon using the tube exiting the nose as a pulley. They performed 260 partial colonoscopies and 150 complete colonoscopies by this technique with no gastrointestinal perforations. [114] This method required about 5 days to complete. Flexible colonoscopy rendered this cumbersome technique obsolete. Other pioneering colonoscopists included Waye in New York City and Williams in England. Colonoscopy revolutionized the diagnosis and therapy of lower gastrointestinal disorders and permitted the development of colonoscopic polypectomy for removal of premalignant colonic lesions. Overholt received the Schindler Award by the American Society for Gastrointestinal Endoscopy in 1975.

4. Eugene P. DiMagno, James L. Buxton, Patrick T. Regan, R. R. Hattery, D. A. Wilson, J. R. Suarez, and P. S. Green; and W. D. Strohm, J. Phillips, F. Haggenmuller, and Meinhard Classen-- first used endoscopic ultrasonography in the gastrointestinal tract. The instrument had been proposed by John J. Wild and John M. Reid.

Conventional abdominal ultrasound produces degraded images of structures that are distant or behind gas-filled viscera because of ultrasound wave attenuation. An internal probe is closer to many internal organs and provides greater resolution. Wild and Reid were the first to suggest attaching an ultrasound transducer to an endoscope for internal recordings. In 1957, Wild and Reid developed a 15-MHz frequency probe and introduced this probe blindly intrarectally to scan the human rectum. [150] Nishi first performed transurethral ultrasound in 1968. Watanabe and others then blindly inserted probes into the vagina to assess gynecologic disorders or into the rectum to assess urologic or gynecologic disorders.

Visual guidance helps in intubating and properly orienting a probe for transgastric and transduodenal ultrasonography. In 1976, Lutz and Rosch [80] passed a miniature catheter echoprobe through the biopsy channel of a gastroscope to obtain transgastric A-mode sonographic images. Green in the late 1970s attempted to scan the pancreas by attaching a linear array probe to the tip of a flexible gastroscope. Hisanage et al in Nagoya, Japan, intubated a probe under

endoscopic guidance for transesophageal echocardiography in 1978. DiMagno et al in 1980 attached an 8-cm-long linearly arrayed ultrasonic probe to the tip of a side-viewing ACMI endoscope. In a linear array, multiple transducer elements are sequentially activated to provide a longitudinal gut image. The 13-mm diameter tip contained the optics and the ultrasound mechanisms in-line. They used a 10-MHz frequency to obtain a 3-cm-wide and 4-cm-deep ultrasound field. They achieved acceptable ultrasound images of the gallbladder and liver by aspirating air, even without a balloon attached to the probe. They initially tested this version in animals because of concern about possible perforation in humans resulting from an 8-cm-long rigid tip. [31] They reported the instrument was safe in dogs at the Fourth European Congress of Gastrointestinal Endoscopy in Hamburg in 1980 and reported their initial clinical experience in humans in 1982. [32]

At the same 1980 meeting, Strohm et al [141] reported their experience in 18 patients with a prototype radial scanning ultrasonic endoscope manufactured by Olympus. A radial scanning device employs one rotating transducer to provide a circumferential ultrasound image perpendicular to the axis of the scope. They initially used an 8-cm ultrasonic probe incorporated into the tip of a side-viewing GF-B3 Olympus gastroscope. Images were scanned in a 90° sector in the direction of visual observation by a rotating mirror that reflected the ultrasonic waves generated by a transducer at the tip of the gastroscope. [123] A 5-MHz frequency provided an adequate acoustic focus at a depth of 3 cm. The ultrasonic probe was covered by a balloon containing olive oil as the transmitting medium. The initial instrument was unwieldy because of an 8-cm-long rigid tip. [141] The examinations lasted 30 to 40 minutes. The authors observed that despite the long tip, gastroscopy "could be performed easily." They were unable to traverse the pylorus in two of their first five patients. They considered that the distal choledochus was better evaluated by their echoendoscope than by conventional abdominal ultrasound.

In 1983, Alzin et al, [3] Dragsted and Gammelgaard, and Hildebrandt et al reported application of endorectal ultrasound to stage rectal cancer accurately. In 1985, Dancygier and Classen reported on the value of endoscopic ultrasound in staging

esophageal cancer according to the tumor node metastasis (TNM) system. The first commercial model endoscopic ultrasound, the Olympus GF-UM2 or EU-M2, developed in the late 1980s, provided ultrasonic images of internal organs superior to those obtained by conventional transabdominal ultrasonography. Endoscopic ultrasound was shown to be superior to conventional ultrasound or CT to evaluate depth of tumor invasion, extent of lateral tumor involvement, and associated lymphadenopathy. This instrument provided excellent delineation of the bowel wall and of organs not well seen by conventional transabdominal ultrasound, such as the pancreas and choledochus. An ultrasound colonoscope first became available in 1989.

During the last 2 decades, considerable progress has been made in developing narrower, more flexible, and more maneuverable echoendoscopes. An exciting application of endoscopic ultrasound is for guided biopsies or aspirations for diagnosis or therapy. [26]

5. William S. McCune, Paul E. Shorb, and Herbert Moscovitz-- first performed ERCP. Itaru Oi-- developed the first modified esophagogastroduodenoscope to perform ERCP.

Before 1965, the pancreatic duct could be visualized radiographically only intraoperatively, and the biliary tree could be visualized without surgery only incompletely and indistinctly by oral cholecystography or intravenous cholangiography. Two radiologists, Rabinov and Simon, [115] in 1965 cannulated the ampulla of Vater for pancreatography with a perorally inserted tube using fluoroscopy without endoscopic guidance in two of eight attempts. A guidable cannula was passed through a basket deployed at the level of the ampulla. This technique was not clinically applicable because of the technical difficulty of ampullary cannulation without visual guidance.

McCune et al [88] at George Washington University in 1968 taped a cannula to the outside of a side-viewing flexible Eder duodenoscope for pancreatic cannulation with endoscopic visual guidance. The cannula was visible through the lateral lens. An endotracheal-type cuff balloon was placed on the scope just beyond the lens. The balloon was inflated or deflated to adjust the position of the catheter over the

ampulla and to move the endoscope away from the bowel wall to permit mucosal visualization. [72] They stated that "the ampulla of Vater ... appears as an elevated red spot on the duodenal mucosa." [88] Cannulation was achieved "by manipulation," using considerable torque on the instrument shaft without the aid of a cannula elevator. Diatrizoate sodium (Hypaque sodium) contrast agent was then injected before taking radiographs. They noted "the technic is not easy and requires considerable experience." [88] They achieved a 25% rate of pancreatography, which reflected a 50% rate of duodenal intubation and a 50% rate of cannulation after duodenal intubation. The authors did not attempt endoscopic retrograde cholangiography. Endoscopic retrograde pancreatography was performed on about 50 subjects without significant morbidity. All subjects were asymptomatic, and all had normal pancreatograms. McCune et al [88] noted that to be successful at this procedure requires "undying, blind, day and night, uncompromising persistence."

Oi et al, in conjunction with the Machida and Olympus corporations, developed a side-viewing fiberoptic duodenoscope specially designed with an elevator lever at the tip to manipulate the cannula for ampullary intubation. The first commercially available model, the Machida F. D. S. duodenoscope, had a large biopsy channel to facilitate cannula insertion but had a highly flexible endoscope tip that made pyloric intubation difficult and had an infinitely variable focus that required frequent manual focusing during cannulation to compensate for respiratory or peristaltic movements. The cannula had a metallic radiopaque tip, and contrast agent was injected under continuous fluoroscopic control. Oi first successfully injected the pancreatic duct in March 1969. Oi et al [100] [101] and Kasugai et al then extended the technique to inject and visualize the biliary tree. The procedure was renamed ERCP in recognition of visualization of both ductal systems. Using the fiber duodenoscope, in 1969, Oi [100] visualized the papilla in 94% of patients and cannulated the papilla in 41 (77%) of 53 patients, without significant complications. He stated that "after an individual endoscopist cannulates one case, he then has little difficulty ... with further cannulations."

The Olympus Corporation then developed the Model JFB-2 duodenoscope, which had an improved elevator lever for superior cannula control. [72] This endoscope

lacked the disadvantages of the earlier Machida endoscope. Pioneers in ERCP included Anacker, Vennes, Geenan, Cotton, Siegel, and Demling and Classen. ERCP has become a standard technique to evaluate pathology of the biliary tree and pancreatic duct.

THERAPEUTIC GASTROINTESTINAL ENDOSCOPY AND OTHER AMBULATORY PROCEDURES

6. Hiromi Shinya and William I. Wolff-- developed colonoscopic polypectomy.
Colon cancer is the second commonest cause of mortality from cancer in the United States. About 56,000 Americans die from this cancer annually. Nearly all colon cancers arise from the progressive growth of adenomatous colonic polyps. Before 1969, colonic polyps proximal to the rectum could be removed only by laparotomy and colotomy, but polyps in the rectum could be removed by rigid sigmoidoscopy. Shinya, as a young surgeon in the Department of Surgery at Beth Israel Hospital in New York City, together with Wolff, Chairman of the Department of Surgery, developed a technique to remove more proximal polyps by flexible sigmoidoscopy or colonoscopy. They constructed an expandable flexible wire loop, which could be passed through the biopsy channel of the colonoscope to loop and snare polyps under visual guidance. Polyps were severed by applying cautery through the wire loop. In September 1969, they removed the first colonic polyp without laparotomy using a snare and cautery. Initially the wire loop circuit was completed for cautery by closing a Kelly clamp on the protruding ends of a wire. The clamp was attached to a standard electrosurgical generator. Wolff and Shinya [153] presented a videotape of their technique at the 1971 session of the AGA and published their preliminary data in 1971. In 1973, they reported on 303 colonoscopic polypectomies [154] and in 1975 on 2000 polypectomies.
In the last 30 years, colonoscopic polypectomy has become ubiquitous. Nearly all colonic polyps are now removed endoscopically, almost always on an outpatient basis. Polypectomy with polyp retrieval for histologic analysis is diagnostic and

therapeutic for adenomatous polyps. Polypectomy is important because nearly all colon cancers arise from adenomatous polyps. Colonoscopy with colonoscopic polypectomy has been shown to lead to earlier diagnosis and decreased mortality from colon cancer. [151]

7. Meinhard Classen and Ludwig Demling; and K. Kawai, Y. Akasaka, K. Murakami, M. Tada, Y. Kohli, and M. Nakajima-- first performed ERCP with sphincterotomy.

About 15% of patients undergoing biliary surgery have choledocholithiasis. With the advent of diagnostic ERCP, gastroenterologists were able to diagnose but not remove choledocholithiasis. Although patients without choledocholithiasis at a preoperative diagnostic ERCP avoided unnecessary common bile duct exploration, patients with choledocholithiasis diagnosed at a preoperative diagnostic ERCP still required common bile duct exploration and choledocholithotomy during biliary surgery. Common bile duct exploration and choledocholithotomy significantly increase the morbidity and mortality of cholecystectomy.

In 1973, Demling and Classen in Germany reported cutting the papilla with a high-frequency diathermy catheter (papillotome) containing a thin steel wire at its distal tip. [30] By pulling the steel wire, the papillotome tip was flexed into a bow, and the steel wire formed a bowstring that served as a diathermy knife. [81] Endoscopic papillotomy produced as wide an incision as surgical papillotomy in dogs, without hepatic or pancreatic injury or subsequent ostial stenosis. This research led to the first successful papillotomy in humans in 1973. [21] Kawai in Japan independently fabricated a papillotome with two 2-mm-long diathermy blades at the tip. [70] [93] This papillotome was useful for stones impacted at the ampulla but was otherwise inferior to Demling's papillotome and was abandoned. [81] The German group believed the major indications for endoscopic sphincterotomy were choledochal stones in either cholecystectomized patients or surgically poor-risk patients and papillary stenosis. [21] The Japanese investigators believed the major indications were stones impacted at the ampulla or lower choledochus and patients with a poor operative risk. Their contraindications were identical to those for surgical papillotomy: long bile duct stenosis, a papilla situated at the edge of a duodenal

diverticulum, and an uncertain position of the papillotome in the common bile duct. They warned against *enforced extraction* because crushing of stones had not yet been developed.

Sphincterotomy was quickly embraced by endoscopists. Short-term follow-up after sphincterotomy demonstrated its safety, without subsequent papillary stenosis or insufficiency. Important subsequent technical advances include balloon-tip catheters for stone removal, nasobiliary drainage tubes, internal biliary stents, and lithotripsy. Therapy was also extended to the pancreatic duct for pancreatic disorders. Today, endoscopic papillotomy is routinely used to manage choledocholithiasis. This advance in therapeutic endoscopy rivaled the introduction of colonoscopic polypectomy. The technique is currently available in every endoscopic unit throughout the world.

8. Jeffrey L. Ponsky, Michael W. L. Gauderer, and Robert J. Izant Jr.-- developed percutaneous endoscopic gastrostomy (PEG).

Nutritional support is essential in the critically ill to improve wound healing, immunologic function, resistance to sepsis, and patient recovery. Nutritional support by the enteral route is preferable to the parenteral route, when feasible, because of greater safety and lower cost. Slender nasogastric tubes are effective for short-term, but not long-term, enteral feeding because of long-term risks of esophageal stricture and aspiration pneumonia. Until the development of PEGs, long-term enteral feeding in patients unable to ingest orally required surgical gastrostomy or jejunostomy.

In 1980, Ponsky, an endoscopic surgeon, with Gauderer and Izant from Cleveland, Ohio, described PEG performed without laparotomy or general anesthesia on 12 children. [43] [113] They noted that the light from a gastroscope located in the stomach could be seen on the abdominal skin and provided a target for transcutaneous intragastric puncture. The authors used a standard mushroom catheter as the PEG tube and used standard, smoothly tapered intravenous cannulas as introducers. The authors decided before the PEG where to place the gastrostomy and anesthetized and incised a small slit in the skin and anterior rectus sheath. After endoscopic intubation, a smooth, tapered intravenous cannula was punched

through the abdominal wall wound into the stomach under endoscopic guidance; the intragastric end of the cannula was encircled with a polypectomy snare; then the inner metallic needle was withdrawn and replaced by a silk thread composed of suture material. The suture was grasped with the snare, and the endoscope, snare, and suture were brought out retrogradely through the mouth. This end of the suture was tied to the PEG tube. The drainage end of the gastrostomy tube was passed through the esophagus into the stomach by pulling at the abdominal end of the suture until the gastrostomy tube exited out the abdominal wall. This produced minimal trauma. [43] Further external tube traction pulled the mushroom head and stomach snugly up against the anterior abdominal wall to create a tight seal around the gastrostomy. The children experienced only minor complications except for one case of embedding of the mushroom catheter in the gastric wall after 4 months, which was treated by surgical replacement. In 1981, Ponsky and Gauderer [113] reported on PEG performed in 11 more children and 19 adults.

The original PEG design and technique have been maintained with minor modifications. A guidewire was subsequently substituted for the suture; the guidewire is grasped by the snare and pulled out the mouth similar to the suture. The gastrostomy tube is then pushed over the guidewire for gastric intubation. In 1984, Ponsky and Aszodi extended the technique of PEG to perform percutaneous endoscopic jejunostomy. Ho, Tao and Gilles, and Wills and Oglesby independently introduced radiologic guidance for percutaneous gastrostomy and gastrojejunostomy. [61]

Today, about 100,000 PEGs are performed annually in the United States. Since its introduction, an industry has developed concerning the manufacture of PEGs. PEGs are indicated for long-term alimentation in patients unable to eat orally but with an otherwise functional gastrointestinal tract. The PEG tube is occasionally used for gastric decompression in patients with chronic intestinal obstruction.

9. Philip Kramer and Franz J. Ingelfinger-- developed early techniques of esophageal manometry using static, water-filled, open-tipped catheters and external transducers and demonstrated peristaltic, circumferential esophageal pressure contractions during swallowing. Charles E. Pope, 2nd, Charles S.

Winans, and Lauran D. Harris-- contributed to modern esophageal manometry by developing constant slow infusion of intraluminal catheters to measure more accurately intraluminal squeezing pressures within the esophagus.

Before 1950, gastrointestinal motility was analyzed by radiography or by kymography, pressure recordings from large balloons. Kronecker and Meltzer first obtained pressure determinations in the human esophagus by kymography in 1883. They recorded an apparent peristaltic pressure wave in the esophagus with two large air-filled intraesophageal balloons and crude external pressure transducers. Kymography was insensitive and slow. Also, esophageal contractions created artifacts by compressing the air-filled balloons. Ingelfinger and Abbot introduced incompressible water-filled balloons in 1947 to avoid artifact from compression of air-filled balloons. Ingelfinger and Kramer applied this technique to describe esophageal motility in achalasia in 1949. Even water-filled balloons, however, alter esophageal motility by stimulating gut receptors and inducing secondary peristalsis.

In 1947, Brody and Quigley used air-filled, small-bore flexible tubing, without balloons, and optical pressure recorders to improve manometric recordings. Brody and Quigley described manometric antral pressure waves corresponding with the peristalsis seen on radiographs. In 1953, Sanchez et al replaced air-filled catheters with static water-filled catheters to avoid artifact from air compression. [20] This more sensitive technique led to improved analysis of the normal motility of the esophagus and the abnormal motility in esophageal disorders. Farrar and Bernstein [38] used telemetry capsules to monitor capsule movements and obtain pressure recordings beyond the esophagus and into the intestine.

Harris et al demonstrated that a catheter tip behaved as if it were sealed when within a sphincter. Constant water infusion was necessary to measure the strength of the seal or sphincter pressure. They developed a constant water infusion open-tip catheter in 1964 to improve recording fidelity, especially at the sphincter. [50] Rapid infusion was required to record faithfully rapid, large pressure changes. [20] Substitution of narrow rigid tubing and elimination of syringes in the infusion system decreased tube compliance and permitted accurate measurement of rapid,

large pressure changes with slow infusion. Arndorfer commercially manufactured infusion pumps.

These modern techniques permitted accurate determination of intraesophageal pressures during peristaltic contractions. Cohen and Harris [22] showed that constant infusion manometry provided an excellent correlation between lower esophageal sphincter (LES) pressure measurement and LES strength, measured as the force required to pull a 1-cm Teflon-coated ball through the LES. In the mid-1970s, Dodds et al showed wet swallows were more reliable than dry swallows in evaluating esophageal peristalsis.

10. Giorgio Menghini-- developed a simple, quick, and safe method of percutaneous needle liver biopsy.

Ehrlich performed the first percutaneous liver biopsy in 1883. Lucatello performed a percutaneous liver biopsy using a syringe and trocar soon thereafter. [124] In 1939, Baron reported on 48 hepatic aspirations using a syringe and a 9-cm-long needle. He used liver aspiration to diagnose cancer metastatic to the liver and to determine the cause of jaundice. [124] He reported one death in the 48 aspirations. Iversen and Roholm [68] reported in the same year the use of liver biopsy in acute epidemic hepatitis. Histologic analysis of liver biopsy specimens changed the diagnosis in one third of cases. Iversen and Roholm introduced the now generally accepted transthoracic approach for liver biopsy. Roholm et al published the largest clinical series of liver biopsies in the first half of the twentieth century. Kumpe et al [76] in 1947 demonstrated the reliability of diagnosis by liver biopsy and the unreliability of diagnosis by clinical criteria.

Liver biopsy needles before 1958 required manual needle rotation after hepatic puncture to cut loose a specimen core. This rotation took experienced hepatologists 5 to 10 seconds. Menghini realized that decreasing the time a biopsy needle is within liver parenchyma would greatly decrease the risk of hepatic laceration and intrahepatic hemorrhage. Menghini designed a special biopsy needle that cut loose a liver specimen core without requiring needle rotation; this device reduced needle insertion into the liver to about one tenth of a second during liver biopsy. [90] [124] Menghini attached a syringe to the needle to apply suction for

biopsy specimen retrieval. This technology greatly increased liver biopsy safety and simplicity so that today liver biopsy is a relatively standard and indispensable diagnostic test for liver disease.

RADIOLOGY

11. Y. Tsuchiya and Kunio Okuda; K. Tanikawa, T. Emura, S. Kuratomi, and S. Jinnouchi-- developed a safe and widely adapted method of percutaneous transhepatic cholangiography (PTC). John Evans, Alan G. Redeker, G. G. Karvountzis, R. H. Richman, and N. Horisawa-- advanced the modern technique of PTC in the United States.

In the 1920s, oral cholecystography was developed to detect gallstones in the gallbladder. Oral cholecystography, however, did not provide clinically useful images of the biliary tree or pancreatic ducts. Burckhardt and Muller first successfully visualized the biliary tree in 1921 by injecting percutaneously kolargol, an iodinated compound, into the gallbladder using narrow-caliber needles. This method was abandoned because of the risks of severe allergic reactions or bile leak. In 1925, Cotte of Lyon performed the first postoperative cholangiogram by injecting Lipiodol, an iodized oil, through a percutaneous drain to detect biliary strictures and retained stones. In 1932, Mirizzi and Losada of Argentina introduced Lipiodol into the gallbladder during surgery for intraoperative cholangiography. [4] Huard and Hop performed the first percutaneous, transhepatic cholangiogram in 1937 in Indochina. They punctured the bile ducts, rather than the gallbladder. In one patient with a clinically suspected hepatic abscess, percutaneous cholangiography demonstrated a bile duct stricture. [65] The general medical community was unaware of their technique because the communication was written in French and published in a local Indochinese journal with a small circulation. Carter and Saypol [19] performed the first PTC study, via the hepatic ducts, in the United States in 1951.

Japanese clinicians advanced percutaneous transhepatic puncture of the gallbladder without laparoscopy. In 1954, Suzuki at Tokyo University performed percutaneous puncture of the gallbladder for cholecystocholangiography and demonstrated a cancer in the head of the pancreas. Gallbladder puncture was indicated by aspiration of bile. Major improvements in safety during the 1950s included direct puncture of bile ducts and the prophylactic administration of antibiotics to prevent biliary sepsis. Arner et al in Sweden and Glenn in New York used televised fluoroscopy during contrast agent injection to recognize bile duct puncture. Ohto and Tsuchiya applied all the prior advances of a skinny unsheathed needle, right flank approach, horizontal needle direction, direct bile duct injection, and monitoring by fluoroscopy during contrast agent injection. Tsuchiya [144] reported in 1972 only 13 complications in 554 procedures. Okuda et al [103] established the safety of a skinny needle, even in the presence of obstructive jaundice. The skinny needle was called the *Chiba needle* in honor of the city in which it was invented. The needle was safe because of limited puncture trauma owing to a narrow caliber and flexibility.

During the 1960s, interest in PTC slowly increased in the United States. Redeker et al [118] in Los Angeles introduced and popularized the use of a skinny flexible needle in the United States. This technical advance led to widespread clinical use of PTC for diagnosis and treatment of biliary disease. Currently, PTC is a useful alternative to ERCP and sphincterotomy in the diagnosis and treatment of obstructive jaundice.

12. John Julien Wild and John M. Reid and Ian Donald-- first applied abdominal ultrasound to distinguish benign from malignant abdominal masses. Ian Donald also simplified the technique of abdominal ultrasound by eliminating the need to immerse the patient in water to obtain readable ultrasound images. Joseph H. Holmes and Douglass H. Howry-- further pioneered application of ultrasound to diagnose abdominal diseases.

Ultrasound was first developed by the military to detect enemy submarines. [94] Dussik and Dussik used a primitive ultrasound transducer to analyze the internal structure of the human brain in 1937. They detected variable sound transmission

because of variations in skull thickness but were unable to visualize the cerebral ventricles. Ludwig and Struthers, at the Naval Medical Research Institute in Bethesda, Maryland, detected gallstones using external ultrasound transducers first with the gallstones surgically implanted in muscle and later with the gallstones in the gallbladder of dogs. [94]

Wild after World War II applied ultrasound to distinguish between mechanical and functional intestinal obstruction at Wangenstein's laboratory at the University of Minnesota. [94] In 1950, Wild [148] measured bowel wall thickness and detected the different bowel wall layers by ultrasound. Wild and Reid [149] reported in 1956 that cancer could be distinguished from benign tissue by sonographic characteristics. Wild developed an ultrasound scanner to screen for breast cancer and developed transrectal and transvaginal ultrasound probes.

Douglas Howry became interested in ultrasound while an intern in radiology at Denver University Hospital in 1948. [62] With engineers Bliss and Posakony, he modified surplus U.S. Air Force radar equipment to build the first B-mode, two-dimensional scanner in 1949. Later, an ultrasonic transducer was mounted on a wooden rail within a water tank, fabricated from a cattle-watering container. [64] The water bath provided better resolution than early contact scanners, and the wooden rail permitted probe rotation to improve resolution. During the procedure, patients were immersed in water, which precluded examination of sick patients. [5] Patients had to hold lead weights during the examination to maintain their position in the water-filled tub. [62] In the late 1950s, Holmes developed a scanner in which the transducer rotated on a water-filled pan that was strapped to the patient to eliminate the need for total body immersion. In the early 1960s, Howry, in collaboration with engineers Wright and Meyer, developed a direct contact scanner manually controlled by the operator that did not require any water immersion. Howry compared ultrasonic images made on live animals with anatomic cross-sections obtained after sacrificing the animals. He found that an experimentally produced liver abscess in a cat was detected as multiple irregular echoes by abdominal ultrasound at the same location as determined by pathologic dissection

at postmortem. Howry and Holmes, a nephrologist, analyzed abdominal structures by two-dimensional sonography in 1963. [62]

Donald, an obstetrician at the University of Glasgow, used radar as a member of the British Royal Air Force during World War II. In 1955, Donald used a commercial metal flaw detector to distinguish tissue layers by sonography in pathology specimens. Donald with engineers McVicar and Brown developed a contact scanner without water immersion. In June 1958, Donald et al [33] diagnosed a cystic mass by ultrasonography in a 64-year-old woman who had presented with weight loss and increased abdominal girth believed to be due to gastric malignancy. The mass was successfully resected and found to be a benign mucinous ovarian cyst. Donald et al applied ultrasound to visualize small pelvic tumors, ectopic pregnancy, and placental location and to determine fetal biparietal diameter. The diagnostic application of abdominal ultrasonography rapidly expanded with the development of two-dimensional B-mode sonography, real-time imaging, gray-scale imaging, and other technical improvements. Today, ultrasound is routinely used to evaluate jaundice or suspected intra-abdominal abscess.

13. George R. Leopold and Joel Sokoloff; Uve F. Hublitz, Paul C. Kahn, and Larry A. Sell; Bruce D. Doust and Nabil F. Malakad; and Francis Weill, J. C. Becker, J. R. Krachenbuhl, G. Heriot, and J. P. Walter-- demonstrated the value of ultrasonography in the diagnosis of gallstones.

Buxbaum in Europe in 1898 and Beck in the United States in 1900 first visualized gallstones in vivo by plain abdominal radiography. Plain abdominal radiography, however, has limited sensitivity because most gallstones are radiolucent. Gallstones could be visualized radiographically as a filling defect in the gallbladder if enveloped by a radiopaque agent that is delivered to and concentrated in bile. Cole and Graham analyzed 89 bromine or iodine derivatives of phenolphthalein and injected two of the most promising of these compounds intravenously into dogs to attempt to opacify the gallbladder by using phenolphthalein as a vehicle to deliver and concentrate the bromine or iodine contrast agent in the gallbladder. [24] This technique failed more than 200 times before finally succeeding after the animal caretaker had forgotten to feed the dog the morning of injection. [47] Graham

and Cole then successfully reproduced the experiment by fasting dogs overnight before injection. After 15 unsuccessful attempts in humans, on February 21, 1924, a patient underwent cholecystography for right upper quadrant pain, which revealed a normal opacified gallbladder. [4] [47] The patient was subsequently diagnosed with ureteral obstruction. In 1925, Whitaker, Milliken and Vogt, and Menees and Robinson independently reported successful cholecystography by oral rather than intravenous administration. Clinical applicability was limited by unpleasant drug side effects, however. In 1951 Hopes and Archer demonstrated that iopanoic acid (Telepaque) provided superior gallbladder opacification and was well tolerated.

Ultrasound has replaced oral cholecystography for gallstone detection because of greater patient safety, higher test sensitivity, and avoidance of radiation exposure. Ludwig and Struthers at the National Naval Institute in Bethesda, Maryland, pioneered in the 1940s the use of ultrasound to detect gallstones. They detected gallstones first with the gallstones surgically implanted in muscles and later with the gallstones in situ in the native gallbladder of dogs. [94] Leopold, while a resident in radiology at Presbyterian Hospital in Pittsburgh in 1965, studied ultrasound using a Picker machine. On arriving at the University of California at San Diego in 1968, Leopold acquired the first such machine on the West Coast and applied ultrasound to study the abdomen, including the use of ultrasound to detect gallstones. [78] In 1970, Weill et al [146] in France also demonstrated the sensitivity of ultrasound in detecting gallstones. While a resident in radiology at the Einstein Medical Center in Pittsburgh in 1964, Goldberg published several important studies on abdominal ultrasonography. [44] In 1968, after he became a staff radiologist at Hahnemann Hospital, Goldberg confirmed the value of ultrasonography in gallstone detection. [45] Goldberg also applied abdominal ultrasound to detect and evaluate ascites and to drain abscesses percutaneously. [94] Other pioneers in the ultrasonographic detection of gallstones include Doust and Maklad [34] and Hublitz et al. [66]

14. Elizabeth Harvey, James Ryan, Michael Loberg, Malcolm Cooper, and Steven Sikorski-- demonstrated use of 99m-technetium- labeled HIDA to visualize the liver,

gallbladder, and bile ducts. This became the standard test to diagnose acute cholecystitis.

Hevsey in 1923 was the first to use radioisotopes in biology. He first realized the biologic applicability of radioisotopes when he was living in a boarding house that he suspected served food scraps, left after a meal, the next day. He placed a radioactive tracer in his leftover food one day and demonstrated the serving of old food by detecting radioactivity in the food he was served the next day. He studied calcium metabolism in plants using radioactive lead and the Geiger-Muller tube, a crude recording instrument. In the 1930s and 1940s, radioactive iodine was used to study thyroid metabolism. [79] In 1946, the U.S. Atomic Energy Commission made artificial radioisotopes available to clinical and biologic researchers. Moore [91] in 1947 detected brain tumors using radioactive iodide. Benedict in the United States and Cassen and Mayneord [87] in England independently developed techniques to map the distribution of radioactive tracers in the human body around 1950. Yuhl et al [157] in 1952 produced the first cholescintigram at the University of California at Los Angeles. This cholescintigram was unsatisfactory because of use of radioactive diiodofluorescein (iodine-131), a weak radioisotope, and because of the crude measuring instruments then available. In 1970, rose bengal was labeled with iodine-131 for cholescintigraphy. Rose bengal, however, provided suboptimal resolution of the biliary tree and was not excreted into the biliary tree in the presence of jaundice.

Perrier and Segre discovered technetium in 1937. Technetium is an excellent radioactive tracer owing to a strong radioactive signal, ability to chelate many compounds, and low radiation risks to patients. In the 1960s, various organ scans were obtained by labeling compounds with radioactive technetium. [79] HIDA and related IDA compounds are cleared from the bloodstream by the liver and almost exclusively excreted by the biliary system with negligible urinary excretion. In 1975, Harvey et al [51] [120] introduced HIDA, an iminodiacetic acid derivative, labeled with technetium for cholescintigraphy. The radioactive tracer was visualized by serial gamma camera images. This agent is well tolerated by patients. Other iminoacetic acid molecules, such as DISIDA, produce better gallbladder visualization even in

the presence of significant jaundice. This cholescintigram has become the standard technique to diagnose acute and chronic cholecystitis. Acute cholecystitis is highly reliably diagnosed by prompt visualization of the choledochus and duodenum without visualization of the gallbladder because of cystic duct obstruction in acute cholecystitis. Modern cholescintigraphy has a more than 95% sensitivity at diagnosing acute cholecystitis.

15. Sven-Ivar Seldinger-- introduced a simple method using a guidewire to introduce a central angiographic catheter percutaneously via a peripheral artery without a cutdown. Stanley Baum and Moreye H. Nusbaum-- developed diagnostic and therapeutic angiography for gastrointestinal bleeding.

Angiography began within 2 months of Roentgen's discovery of x-rays, when Haschek and Lindenthal injected contrast agent into the blood vessels of an amputated hand to visualize the vascular anatomy by x-ray. The vascular anatomy was then studied in detail in human cadavers by radiography after contrast injection by Kassabian in 1907 and by Orrin in 1920. Injection of contrast agent to visualize vessels was first performed by Franck and Alwens in live laboratory animals in 1910. Sicard and Forestier in 1923 injected Lipiodol, an iodinated contrast agent, into vessels in human subjects to visualize venous anatomy. The patients coughed as the oil reached the lungs but suffered no further ill effects. Berberich and Hirsch in 1923 and Brooks in 1924 obtained the first arteriograms in humans by intra-arterial injection of contrast agents. During the ensuing 25 years, angiography was extended to study the vascular anatomy of numerous organs. Moniz described carotid arteriography in 1928, Rousthoi described aortography in 1933, Castellanos et al delineated the cardiac chambers by angiography in 1937, and Jonson et al performed cardiac angiography in 1948. [1] Clinical application of angiography of central arteries was limited until 1953, however, because angiography required either direct percutaneous puncture of the vessel to be studied or cutdown of a peripheral artery to thread a catheter into the central artery. Both of these techniques involved considerable risk.

In 1953, Seldinger invented a simple technique to deploy a catheter peripherally through the femoral artery into central arteries without a cutdown. After introducing

a needle into the femoral artery, he passed a flexible metal guidewire into the artery. After removing the needle, he was able to pass a flexible polyethylene catheter easily over the guidewire and thread the catheter into major internal arteries. Use of a catheter and guidewire avoided a cutdown and permitted insertion of a catheter with a larger caliber than that of the initial needle. Seldinger quipped about his discovery, "I can perform the procedure faster than you can write about it. Needle in, wire in, needle out, catheter over wire, wire out, that is all." [142] Seldinger [127] in 1953 performed 35 aortographies with this technique, all but 2 of which were successful. Only one complication occurred, of partial extravascular injection of contrast agent, without clinical sequelae. Seldinger's technique rapidly became routine for angiography. Odman in 1958 extended this technique to cannulate selectively the celiac artery, one of the three major intestinal arteries. Seldinger trained in radiology at the Karolinska Sjukhuset in Sweden beginning in 1950, where he continued as a staff member until 1966. He was among the first to perform PTC, the study of which earned him a doctorate in 1966. Despite a worldwide reputation, Seldinger returned to the village of Mora, Sweden, his birthplace, to become head of the Department of Diagnostic Radiology at the local hospital.

After completing a residency at the Graduate Hospital of the University of Pennsylvania, Baum served as a fellow in cardiovascular radiology at Stanford University. Baum then returned as a staff radiologist at the University of Pennsylvania Graduate Hospital. At this institution, Nusbaum, a surgeon, and Baum tested various radiologic techniques to determine the site of experimentally induced intestinal bleeding in 25 dogs. They failed to localize the site of bleeding with radioactive isotope tracers or aortography. Selective percutaneous arteriography of the celiac, superior mesenteric, and inferior mesenteric arteries by the Seldinger technique successfully demonstrated the bleeding sites as contrast extravasation for bleeding as slow as 0.5 mL/min. [97] In 1965, Baum et al [8] extended selective angiography to determine in four patients the site of severe gastrointestinal bleeding that had been undetermined by conventional tests. This study introduced diagnostic angiography for gastrointestinal bleeding, a now

standard technique. Nusbaum et al [98] found in experiments in dogs that direct infusion of low-dose vasopressin into the superior mesenteric artery reduced flow in this artery without untoward effects to the dogs. This reduced flow offered the theoretic possibility of arresting bleeding from this artery. In 1968, they applied this therapy in two patients with bleeding from esophageal varices and portal hypertension via a catheter introduced into the superior mesenteric artery by the Seldinger technique. [98] In one patient, this technique successfully arrested the bleeding, and in the other, the bleeding was controlled by a combination of this technique and balloon tamponade. This study introduced therapeutic angiography for gastrointestinal bleeding, a now standard technique. After these discoveries, Baum went to the Massachusetts General Hospital before becoming Chairman of the Department of Radiology at the Hospital of the University of Pennsylvania. [140]

16. Josef Rosch, William N. Hanafee, and Harold Snow-- first described transjugular portal venography and percutaneous deployment of a portacaval shunt in dogs. Ronald F. Colapinto, Roger D. Stronell, Michael Gildiner, Alexander C. Ritchie, Bernard Langer, Bryce R. Taylor, and Laurie M. Blendis-- first applied transjugular intrahepatic portosystemic shunts (TIPS) successfully in humans. Julio C. Palmaz, Randy R. Sibbitt, Stewart R. Reuter, Francisco Garcia, Fermin O. Tio, David T. Kopp, Wayne Schwesinger, Jack L. Lancaster, and Peter Chang-- developed an expandable metal stent for TIPS to increase flow through the iatrogenic shunt.

Numerous therapies have been developed for esophageal variceal hemorrhage during the twentieth century to reduce the high mortality of this condition, with variable success. Before the last 25 years, the main therapies were balloon tamponade and vascular shunt surgery. [25] Balloon tamponade, however, does not correct the underlying portal hypertension, and patients are at high risk of rebleeding after balloon removal. Early enthusiasm for shunt surgery waned in the 1960s because of a high rate of postoperative hepatic encephalopathy and unimproved survival owing to death from hepatic failure. Crafoord and Freckner in 1939 introduced esophageal sclerotherapy using a rigid esophagoscope. In 1979, Williams and Dawson introduced sclerotherapy via flexible endoscopy.

Sclerotherapy began to become popular in the 1970s with the decline in shunt surgery. Sclerotherapy controls about 80% of acute variceal bleeding, but patients frequently rebleed during the ensuing years because of the underlying, untreated portal hypertension. [25]

Angiography offers another therapeutic modality for esophageal variceal bleeding. Widrich et al [147] and Viamonte et al developed transcatheter angiographic occlusion to obliterate gastric and esophageal varices. This technique only sometimes achieves hemostasis because the underlying portal hypertension is uncorrected.

Rosch et al [119] described in 1969 percutaneously inserting a catheter through the jugular vein into the hepatic vein under radiologic guidance. A needle was then deployed within the catheter and probed into liver parenchyma until puncturing a major branch of the portal vein for portal venography in six dogs and one sheep. A short tube was then inserted over the catheter to form a percutaneous portacaval shunt in five dogs. These narrow shunts had a low flow. The procedure was accomplished within 30 minutes without complications. Colapinto et al [23] successfully applied this technique clinically in 1983 in six patients with advanced cirrhosis, portal hypertension, and bleeding esophageal varices. The portal venous pressure immediately declined after shunt insertion by 10 to 15 mm Hg. Three patients survived the procedure, and two were discharged from the hospital.

Palmaz et al [108] modified Rosch's technique by deploying expandable metal stents to create a wide and high-flow shunt.

TIPS is currently indicated for acute variceal hemorrhage unresponsive to medical or endoscopic therapy and recurrent variceal hemorrhage after adequate endoscopic therapy. TIPS is particularly useful in patients with advanced cirrhosis with refractory variceal bleeding. TIPS is physiologically equivalent to a side-to-side portacaval shunt but can be performed in 1 to 2 hours often without general anesthesia.

SURGERY AND GASTROENTEROLOGIC EDUCATION

17. Development of methods to maintain continence after lower gastrointestinal surgery: Nils G. Kock-- developed a surgically created ileal pouch and ileal valve to produce a continent ileostomy. Mark M. Ravitch and David C. Sabiston, Jr.-- developed an operation to preserve the anal sphincter to maintain the normal pathway for defecation, while removing diseased rectal mucosa during colectomy. Jacques Heppell, Keith A. Kelly, Sidney F. Phillips, Robert W. Beart, Jr., Robert L. Telander, and Jean Perrault-- refined the technique of ileoanal anastomosis by creating an ileal pouch or reservoir proximal to the ileoanal anastomosis to decrease postoperative stool frequency and further promote fecal continence.

Continent Ileostomy

Total colectomy with ileostomy became an established procedure by 1950, most commonly performed for severe ulcerative colitis or familial polyposis coli. Ileostomies were initially constructed by inserting the free end of small bowel through an abdominal wall incision and suturing the serosal surface of terminal ileum to abdominal skin to create a stoma. Warren and McKittrick in 1951 reported chemical serositis and stomal malfunction from serosal exposure to stomal effluent. Brooke eliminated this problem in 1952 by everting a cuff of ileal mucosa and suturing mucosa to abdominal skin to expose mucosa rather than serosa to the stomal effluent; mucosa, in contrast to serosa, is normally exposed to stool without becoming inflamed. The Brooke ileostomy also provided a spout onto which an ileostomy appliance could fit. Turnbull independently eliminated the problem of serositis by grafting skin onto the serosal surface of the ileostomy. Ileostomy function improved with better fluid and electrolyte replacement after colectomy, with the development of comfortable disposable ileostomy appliances, and with the development of enterostomal support teams. Patients with traditional ileostomies are incontinent and require an appliance to capture and store the stomal effluent. Kock of Gothenburg, Sweden, during a sabbatical year in Zurich invented a surgical technique to maintain stomal continence by constructing a terminal ileal pouch to store ileal contents internally until voluntarily emptied. Such a pouch

obviates the need for an external appliance. The patient drains ileal contents directly into the toilet by inserting a catheter through the stoma and valve into the ileal pouch, after which the catheter is removed. Kock performed three surgical maneuvers: folding the terminal 30 cm of remaining ileum on itself to generate a pouch with a reservoir of about 500 mL, which would require drainage only once or twice daily; incising the ileum along its antimesenteric border before loop anastomosis to impair muscular contraction and produce a highly compliant pouch that fills with effluent at low pressures; and surgically creating a nipple by intussuscepting the efferent ileal limb into the pouch. Kock [75] in 1969 reported promising surgical results on five patients.

Kock [74] modified this operation in 1971 because of long-term incomplete continence. He inserted the distal pouch retrogradely to create an antiperistaltic mechanism to prevent leakage of effluent from the reservoir pouch. [2] Nearly all of the first 18 patients undergoing this modified operation were continent of ileal stool, but more than half intermittently passed malodorous gas. [74] In a report from the Mayo Clinic in 1976, 72 (80%) of 90 patients had achieved complete continence with a modified Kock procedure, although one third of patients required repeat operation. The procedure was further developed and popularized by Beahrs at the Mayo Clinic in Rochester, Minnesota, and Gelernt at Mount Sinai Hospital in New York City.

Ileoanal Pull-Through

Another approach to establish continence after colectomy is to retain a distal rectal stump and to anastomose the ileum to the rectal stump. Theoretically, continence is maintained by the anal sphincter. Ravitch and Sebastion described ileoanal pull-through surgery in dogs in 1947. Ravitch [116] then performed this operation in two young adults with preservation of continence in 1948. Wangenstein also performed ileoanal anastomosis in 1948, but the result was so poor that the surgery had to be revised to a conventional ileostomy within weeks. This surgery was attempted by several other surgeons but was largely abandoned because of nocturnal soiling

and perianal irritation from incomplete continence. After the success of the Kock pouch to maintain continence after ileostomy, Heppell et al [55] and several other groups [41] [95] [110] [111] pioneered the construction of a pouch or reservoir proximal to the anal pull-through, to promote continence. Mucosal proctectomy was performed to excise the diseased rectal mucosa in ulcerative colitis or familial polyposis coli, while preserving the intramural muscles and sphincters to permit transanal defecation and maintain continence. This procedure avoids an abdominal stoma, preserves the anal sphincter, and avoids accidental intraoperative injury to the innervation of the bladder and genitalia.

18. Erich Muhe; Francis Dubois, G. Berthelot, and H. Levard; E. J. Reddick and D. O. Olsen; and J. Perrissat, D. Collet, and R. Belliard-- pioneered development of laparoscopic cholecystectomy. Kurt Semm-- pioneered techniques of laparoscopic surgery (including the first laparoscopic appendectomy) that provided the foundation for laparoscopic cholecystectomy.

Laparoscopic cholecystectomy, a revolutionary development in abdominal surgery, represents a marriage of the techniques of gallbladder surgery and laparoscopy. Bobbs performed the first well-documented cholecystostomy in 1868 in Indianapolis. In 1882, Langenbuch in Berlin performed the first cholecystectomy for gallstones. [9] Kelling reported on September 21, 1901, the first laparoscopy on a dog. [14] In the same year, Ott, a Russian gynecologist, introduced a speculum into the pelvic cavity of a female patient via a posterior vaginal incision. Jacobaeus and Kelling independently performed the first laparoscopy in humans in 1910, using cystoscopes. Jacobaeus reported on 45 procedures in 1912.

Semm developed many techniques necessary for laparoscopic surgery, including modifying conventional surgical instruments for these procedures and constructing mechanically controlled automatic gas insufflation for pneumoperitoneum. The adaptation of video imaging to laparoscopy in the 1980s relieved the surgeon of continuously holding the laparoscope and allowed the surgeon to operate using both hands and standing erect. After Semm performed the first laparoscopic appendectomy in 1983, [128] Muhe performed the first laparoscopic cholecystectomy in 1986. [92] Mouret performed laparoscopic cholecystectomy in 1987. Early pioneers

included Reddick and Olsen in the United States [117] and Dubois et al [35] and Perissat et al [112] in France. Laparoscopic cholecystectomy offers advantages over open cholecystectomy of decreased length of hospitalization, cost, and morbidity, with a similar mortality. Laparoscopic cholecystectomy has replaced open cholecystectomy as the procedure of choice for elective gallbladder surgery. By 1994, 80% of cholecystectomies in the United States were performed by laparoscopy.

19. Thomas E. Starzl-- pioneered liver transplantation.

Research in hepatic transplantation began in 1955 when Welch in Albany, New York, inserted an extra canine liver into the pelvis or right paravertebral gutter of a recipient dog. The allograft hepatic artery was physiologically revascularized by way of the aorta or iliac artery. The portal vein was abnormally revascularized to the inferior vena cava, a systemic vein. The allograft liver rapidly atrophied partly as a result of the abnormal revascularization, which denied the allograft liver access to circulating hepatotrophic factors, such as insulin. [138] Also, immunosuppressive therapy was not administered. In 1956, Cannon reported on several technically successful liver transplants in dogs but without dog survival. Cannon introduced surgical removal of the native liver before transplantation.

In the late 1950s, Starzl et al [134] in Chicago inserted the allograft into the vacated hepatic fossa after hepatectomy instead of the pelvis in dogs. In this operation, the graft's portal vein was physiologically revascularized to receive portal perfusion. By 1960, Starzl et al had performed 80 canine liver transplants, and Moore et al at Boston had performed 31 canine liver transplants. This canine research produced technical improvements of infusion of chilled solutions into the portal vein to cool the allograft liver to improve liver preservation before graft implantation and use of plastic external venous bypass of the occluded splanchnic and lower extremity venous beds during the anhepatic phase of transplant surgery to prevent venous pooling. [133]

By 1960, graft rejection remained the primary obstacle to transplantation. In the summer of 1962, high-dose corticosteroid pulse therapy, with maintenance azathioprine therapy, was shown to reverse impending renal transplant rejection

reliably in dogs and humans. Starzl et al performed the first human liver transplantation on March 1, 1963, in a child with biliary atresia. The child, however, died intraoperatively from profuse bleeding resulting from intractable coagulopathy. [136] Then two patients who underwent liver transplantation died after 22 and 7.5 days from pulmonary emboli, probably from the plastic venous bypass tubes. [139] A worldwide moratorium on liver transplantation was imposed for 3.5 years after four more deaths from liver transplantation. During this moratorium, donor liver preservation was improved, and immunosuppression was improved using antilymphocyte globulin, azathioprine, and prednisone.

Starzl et al [135] reintroduced liver transplantation in July 1967 and achieved significantly longer patient survival with these technical advances. The first prolonged survivor lived for more than 1 year with normal allograft function after transplantation for extensive hepatocellular carcinoma before succumbing to recurrent cancer. Calne, a surgeon, and Williams, a hepatologist, founded a second liver transplant program in London. Between 1963 and 1979, Starzl et al performed 170 liver transplants, with 56 patients surviving more than 1 year and 25 surviving more than 12 years. This work demonstrated that liver transplantation was feasible, but liver transplantation remained an experimental and generally impractical technique because of a high morbidity and mortality. The introduction of cyclosporine by Calne led to more effective immunosuppression and longer survival. [18] Liver transplantation advanced from an experimental to a clinical therapy. One-year survival increased to 70%. [137] The introduction of FK-506 (tacrolimus) in 1984 brought more effective immunosuppression and a further increase in patient survival. Starzl was awarded the William Beaumont Prize by the AGA in 1991. Today, thousands of liver transplants are performed annually in many centers in the United States and throughout the world.

20. Henry Le Roy Bockus and Marvin H. Sleisenger and John S. Fordtran-- edited the most widely accepted and authoritative textbooks in gastroenterology during the past 50 years.

A textbook is essential to the growth and development of a discipline. A textbook provides a student with the essential core of knowledge needed to master a

discipline and provides the clinician and researcher with an authoritative delineation of the known and unknown in the field. During the last 50 years, students, clinicians, and researchers have relied on two authoritative and comprehensive textbooks of gastroenterology: Five editions of Bockus' textbook have been published since 1943, and six editions of Sleisenger and Fordtran's textbook have been published since 1973. The numerous editions reflect the enduring popularity and influence of these textbooks.

Bockus graduated from Jefferson Medical College in 1917 and became a professor and chief of Gastroenterology at the Graduate School of the University of Pennsylvania in 1933. He trained hundreds of gastroenterologists in this division. [17] He was Chairman of the Department of Internal Medicine at this institution from 1945 to 1970. Between 1943 and 1946, he edited the first edition of the textbook *Gastroenterology*. [13] This three-volume textbook differed from prior publications in the comprehensiveness and depth of coverage of gastroenterology and liver disease. Many chapters were written by his colleagues at the University of Pennsylvania. [109] This textbook became the most widely used gastroenterologic reference. The textbook was nearly entirely clinical. The second edition, also in three volumes, appeared in 1963. Bockus employed five associate editors, including Berk, Haubrich, Kalser, Roth, and Vilardell, for the third edition, published in 1974 in four volumes. Many chapters were written by international authors. Berk was the editor-in-chief of the fourth edition published in 1985. Haubrich, Kalser, Roth, and Schaffner were assistant editors. This edition consisted of seven volumes by 200 international authors. When Bockus died in 1982, the textbook was renamed *Bockus Gastroenterology* in his honor. The most recent edition was published in 1995. Bockus was awarded the Julius Friedenwald Medal by the AGA in 1962.

The publication of Sleisenger and Fordtran's textbook was a serendipitous outgrowth of an aborted attempt by the publisher to have Sleisenger edit a revised edition of the Bockus textbook. A second edition had been published in 1963. In 1968, Sleisenger, the editor of *Gastroenterology*, was asked to consider editing a proposed new edition. Sleisenger wished to have Fordtran as coeditor. The format

would be revised to feature an introductory section on the pathophysiology of common symptoms and signs of gastrointestinal disease, such as diarrhea and jaundice. Each section on organ-specific diseases would contain an introductory chapter on normal organ physiology. Pediatric gastroenterology would be included. The proposed book title was *Gastrointestinal Disease* with the subtitle, *Pathophysiology, Diagnosis, and Management of Gastrointestinal Disease*. Bockus, after seeing the plan, however, changed his mind about relinquishing the editorship.

Sleisenger and Fordtran were still enthusiastic about editing a textbook that would feature physiology and pathophysiology, while preserving the important strictly clinical material on diagnosis and treatment. The contributing authors for the first edition of their textbook represented many of the best clinical investigators in gastroenterology as well as radiologists, pediatricians, surgeons, and physiologists. The philosophy and content of the textbook are well summarized in the preface to the first edition. [131]

The arrangement of material and its manner of presentation in this book are based upon two principles in which the Editors believe. The first is that excellence in medical practice depends upon an understanding of medical science and that clinical advances are made for the most part along scientific routes. The second is that diseases and deranged physiological states should be critically appraised and evaluated prior to describing the disorder to any professional audience... . Another of our guiding principles has been that all material important in the study of a clinical discipline can be written simultaneously for students at all levels--from the medical student to the accomplished and trained specialist. Hence, this work contains in a clinical context much of what is important in gastrointestinal physiology and pathophysiology and much that reflects the contributions of pathology and radiology. The more strictly clinical aspects of gastroenterology with which the practitioner, pediatrician, and surgeon are intimately concerned are critically presented.

The first edition appeared in 1973. Reviews in the *New England Journal of Medicine* and *Gastroenterology*, among others, praised the book as a

groundbreaker for teaching gastroenterology, for featuring pathophysiology, and for its comprehensiveness. The textbook won an honorable mention for Best Textbook of Medicine by the American Writers Association in 1974. Subsequent editions have appeared at approximately 5-year intervals, the latest being the 6th edition in 1998. [39] Important editorial changes were made along the way. Beginning with the 4th edition, Feldman of Southwestern Medical School in Dallas and Scharschmidt of the University of California, San Francisco, were added as associate editors. For the 6th edition, a section on liver disease and a companion atlas of endoscopic photographs by Wilcox were added. Fordtran retired as coeditor for the 6th edition. The 7th edition is being planned. Scharschmidt has joined the investigative world in the pharmaceutical setting and has stepped down as associate editor. Friedman of the Massachusetts General Hospital is to replace him.

Sleisenger, after graduating from Harvard Medical School in 1947, rapidly rose to become Professor of Medicine at Cornell University and Chief of the Division of Gastroenterology at New York Hospital before moving to San Francisco to become Vice-Chairman of the Department of Medicine at the University of California at San Francisco and Chief of Medical Services at the San Francisco Veterans Administration Hospital. [16]

Sleisenger's research was focused on intestinal malabsorption. Sleisenger et al described regeneration of intestinal villi after institution of a strict gluten-free diet for celiac disease and provided crucial evidence for the existence of intrinsic factor antibodies in pernicious anemia. Other notable studies were in intestinal malabsorption, protein-losing enteropathy, and the role of estrogens in recurrent cholestasis of pregnancy. [99] Sleisenger was awarded the Julius Friedenwald Medal in 1989 and the Distinguished Educator Award in 1994 by the AGA. He served as President of the AGA in 1976.

Fordtran, after graduating from Tulane Medical School in New Orleans in 1956, eventually became Chairman of the Department of Medicine at the Baylor University Medical Center in Dallas in 1979. Fordtran's research was focused on intestinal transport. He greatly extended the use of polyethylene glycol as an indicator solution to study intestinal absorption and secretion. He made major

contributions to understanding the distinction between secretory and osmotic diarrhea, carbohydrate malabsorption, the antidiarrheal effects of opiates, and diarrhea in microscopic colitis. [37] Fordtran et al invented the use of polyethylene glycol electrolyte solution for cleansing the colon for colonoscopy, barium radiography, and colonic surgery. He served as editor of *Gastroenterology*. He was awarded the Julius Friedenwald Medal by the AGA in 1993.

ESOPHAGUS, STOMACH, AND DUODENUM

21. Roderic Gregory and Hilda Tracy-- isolated gastrin, the first identified enteric hormone.

Gastrin was discovered in 1905 by Edkins, 3 years after the discovery of the first hormone, secretin, by Bayliss and Starling. Edkins demonstrated that injection of ground antral mucosa, extracted from cats or pigs, into the jugular vein of an anesthetized cat stimulated gastric acid secretion and decreased systemic blood pressure and called the unidentified active compound *gastrin*, derived from the term *gastric secretion*. [36] After pioneering work by Komarov in the 1930s, Uvnas in the 1940s established that gastrin is released from the antrum by vagal stimulation and partly isolated active gastrin extracts from cat, dog, and hog antrum. In 1952, Jorpes and Mutt discovered that gastrin activity remained after boiling in 0.1 N hydrochloric acid and was soluble in acidified methanol, but this technique failed to provide a pure active product.

Gregory and Tracy attempted to isolate gastrin in the early 1960s. They purchased hog antrums from a local Liverpool company that specialized in making pork pies. They dissected 600 hog antrums per week for several years and "some 50,000 hog antrums later" purified gastrin by an improved method of trichloroacetic acid precipitation, followed by cellulose and Sephadex chromatography. [143] They assayed for gastrin activity by measuring gastric acid secretion in vivo after extract injection.

In collaboration with Kenner, they determined the amino acid sequence of gastrin using only a fraction of a milligram of purified gastrin and demonstrated the existence of two forms of gastrin in hogs that differed by a single sulfation at a tyrosine residue. [48] They then determined the composition of both forms of human gastrin, which proved to be similar to hog gastrin. [49] Gastrin was the first gastrointestinal hormone whose chemical structure was determined.

In 1955, Zollinger and Ellison [158] described a syndrome of peptic ulceration associated with pancreatic islet cell tumors. Gregory and Tracy and McGuigan and Trudeau demonstrated that peptic ulceration in the Zollinger-Ellison syndrome was due to increased gastrin production using the radioimmunoassay technique. The DNA nucleotide sequence of the gene encoding for gastrin was identified by Yoo et al 1982, and the gene encoding for the gastrin receptor was identified and cloned by Kopin et al in 1992. Nearly half of all papers written on gastrointestinal hormones have been about gastrin. [145] Gregory was awarded the William Beaumont Prize by the AGA in 1976.

22. Barry J. Marshall and J. Robin Warren-- identified Helicobacter pylori *and appreciated its relationship with peptic ulcer disease.*

Marshall and Warren's discovery of the role of *H. pylori* in ulcer pathogenesis represents a triumph of persistence, determination, and questioning of accepted dogma in the face of criticism and initial rejection. They were not the first to detect gastric spiral bacteria; they were, however, the first to pursue the pathophysiologic significance of these bacteria. Bizzozero had described gastric spiral bacteria in mammals in 1892. Kreinitz in 1906 first described gastric spiral bacteria in humans on postmortem examination. [83]

In 1979, Warren, a pathologist at Royal Perth Hospital, Western Australia, detected gastric spiral bacteria and severe active chronic gastritis on pathologic examination of a routine hematoxylin and eosin stain of an antral biopsy specimen from a man with dyspepsia. In 1981, Marshall, a resident in internal medicine, began analyzing the spiral bacteria with Warren. In September 1981, Marshall treated a 76-year-old Russian man with abdominal pain with tetracycline after esophagogastroduodenoscopy with endoscopic biopsy demonstrated antral spiral

bacteria and antral gastritis. The patient's symptoms and antral gastritis resolved as demonstrated by a follow-up endoscopy with endoscopic biopsy.

Marshall prospectively studied the relation between the bacteria and gastritis in 100 consecutive patients undergoing esophagogastroduodenoscopy beginning in 1982. At every endoscopy, antral biopsy specimens were obtained for histologic analysis and bacterial culture. Warren performed histologic analysis of the biopsy specimens, blinded to the clinical and endoscopic findings. [84] Marshall failed to culture the bacteria in the first 30 attempts using numerous culture media. In retrospect, this failure was due to slow bacterial growth and the laboratory policy of discarding agar culture plates if no bacterial growth was apparent 48 hours after inoculation to prevent overgrowth by contaminants. The bacteria were first isolated on April 8, 1982, when Royce left a gastric biopsy culture in the incubator for 5 days over the Easter holiday weekend. Using longer incubation, Royce and Kosaris isolated the bacteria in 10 more study patients. In the study, 57 of the 58 patients with the *Campylobacter*-like organism had gastritis or ulcers, whereas only 14 of 42 patients without the organism had gastritis or ulcers. In particular, all 13 patients with duodenal ulcers had bacterial infection. These data were presented at a local meeting of the Royal Australian College of Physicians in October 1982. Marshall noted "to gastroenterologists our observations were perhaps equivalent to noting the presence of *E. coli* in the feces of patients with colitis." [83] In September 1983, Skirrow and Marshall named the organism *Campylobacter pyloridis*. In 1987, the name was linguistically corrected to *Campylobacter pylori*. Based on ultrastructural characterization by Armstrong, the organism was reclassified in a new genus and renamed *Helicobacter pylori*.

Marshall demonstrated that bismuth rapidly killed this bacterium in vitro. [84] In January 1983, Marshall claimed in an abstract submitted to the Australian Gastroenterology Society, "They (the spiral bacteria) may be responsible for the high relapse rate in ulcers treated with cimetidine." [83] The reviewers rejected this momentous discovery for publication as an abstract. The rejected abstract was then submitted to the International Workshop on *Campylobacter* Infections in Brussels, where it was accepted for publication. In 1983, Marshall presented at this

workshop his findings and published with Warren a landmark letter announcing this discovery. [82] In a landmark publication in 1984, Marshall and Warren [86] stated "pyloric campylobacter is etiologically related to chronic antral gastritis and, probably, to peptic ulceration also." In 1988, Marshall et al [85] showed in a randomized, controlled study that eradication of *C. pylori* after therapy resulted in 92% healing of ulcers with only a 21% relapse rate, whereas persistence of *C. pylori* after therapy resulted in a 61% healing rate with an 84% relapse rate. Marshall in 1984 reported the first description of acute *H. pylori* infection after orally self-administering an innoculum of *H. pylori*. [83] In 1984, Langenberg et al reported that *H. pylori* had potent urease activity. In 1984, Marshall et al used immunofluorescent microscopy to demonstrate antibody in the serum of infected patients and developed a passive hemagglutination test. A rapid urease test, called the CLO (for *Campylobacter*-like organism) test, became commercially available to detect *H. pylori* infection in 1990. The association of *H. pylori* with gastritis and peptic ulcer disease became increasingly accepted during the 1990s. Marshall was awarded the Lasker prize in 1995. Chronic long-term infection with gastritis can lead to intestinal metaplasia, associated with gastric carcinoma.

23. Robert M. Zollinger and Edwin H. Ellison-- described severe peptic ulcer disease associated with islet cell tumors of the pancreas (gastrinomas).

Zollinger and Ellison, [158] surgeons at Ohio State University, presented to the American Surgical Association in April 1955, two patients who had severe and recurrent upper gastrointestinal ulcers, profound hyperchlorhydria, and non-beta islet cell tumors of the pancreas. The two patients required total gastrectomy to relieve severe ulcer diathesis. They extended several prior similar case reports, [122] by postulating the tumors produced a humoral substance, released into the circulation, that stimulated gastric acid secretion and promoted peptic ulceration. They incorrectly speculated the humoral substance was glucagon. The existence of this syndrome was rapidly confirmed, and 260 cases were reported worldwide by 1964.

In 1960, Grossman hand-delivered by airplane a frozen specimen from a patient with this tumor from Los Angeles, California, to Liverpool, England, for acid

secretory studies. [67] Gregory et al in 1960 confirmed that the primary tumor and hepatic and nodal metastases contained a potent acid secretagogue, which might be gastrin. In 1968, McGuigan and Trudeau [89] applied the radioimmunoassay technique developed by Berson and Yallow in 1958, to develop a highly sensitive radioimmunoassay for gastrin, and then demonstrated highly elevated serum gastrin levels in patients with the Zollinger-Ellison syndrome. The tumor producing the Zollinger-Ellison syndrome was called a *gastrinoma*.

The discovery of gastrinomas led to rapid progress in understanding the physiology of gastrin and the pathophysiology and therapy of peptic ulcers. Since the discovery of gastrinomas, researchers have identified the various biologic forms of gastrin, described their amino acid sequences, characterized the gastrin receptor, and identified the structure of the gastrin-producing gene. [67]

Zollinger authored more than 260 publications and was editor-in-chief of the *American Journal of Surgery* for many years. [107] He also served as president of the American Surgical Association, the Society for Surgery of the Alimentary Tract, and the American College of Surgeons.

24. James W. Black-- identified histamine-2 (H_2) receptors and developed H_2 receptor antagonists.

Many bizarre or ineffectual therapies were attempted until the mid-twentieth century to suppress gastric acidity and cure ulcers, such as gastric radiation, gastric freezing, and the Sippy meal, before the development of scientifically based pharmacotherapy. [59] In the 1950s, anticholinergic therapy was developed to suppress acid secretion, but this therapy was only partly successful and had frequent side effects. The development of H_2 receptor antagonists in the 1970s represented a revolutionary breakthrough in the scientifically based therapy of acid-related diseases.

In 1910, Dale et al demonstrated that histamine caused smooth muscle constriction and vascular dilation. Popielski reported in 1920 that histamine also strongly stimulated gastric acid secretion. [29] In the 1930s, histamine antagonists that selectively blocked vasodilation and uterine contraction without affecting gastric acid secretion were discovered. After Ahlquist described dual alpha- and

beta-adrenergic receptors, Folkow et al in 1948 postulated the existence of two different histamine receptors to explain this selective antagonism of histamine actions. In 1966, Ash and Shield demonstrated, by selective histamine blockade of visceral muscle contraction, two classes of histamine receptors and called the receptors in visceral muscle *histamine 1 receptors*.

In 1964, Black at Smith, Kline and French Company began to study the histamine receptor responsible for stimulating acid secretion. [10] After testing more than 700 histamine derivatives for nearly 10 years without success, Black et al [11] developed burimamide, which contained the imidazole ring structure of histamine but was modified to inhibit selectively histamine-stimulated acid secretion. Burimamide blocked acid secretion but did not block the hypotensive effect of histamine mediated by histamine 1 receptors. Black et al called the receptor inhibited by burimamide the *histamine 2 receptor*. They quantitatively described the H_1 and H_2 receptors in 1975. [12] Burimamide was too toxic for clinical use. Soon thereafter, cimetidine was developed at Smith, Kline and French Company and was shown to block selectively gastric acid secretion produced by histamine, pentagastrin, vagal stimulation, and food. [11] Cimetidine efficacy and safety were demonstrated by randomized, placebo-controlled endoscopic clinical trials. [59]

H_2 receptor antagonists revolutionized the management of peptic ulcer disease and acid-related disorders. The number of operations for duodenal ulcer decreased by 38% within 2 years of introducing cimetidine in the United Kingdom. [156] The first commercially available H_2 receptor antagonist became the best-selling drug in the world. Black was awarded the William Beaumont Prize by the AGA in 1982 and the Nobel Prize in 1988. Black's success was due to his commitment and perseverance despite more than 700 failed attempts at synthesizing an antagonist during many years of research.

25. George Sachs, Hsuan H. Chang, Edd Rabon, Robert Schackman, Miguel Lewin, and Gaetano Saccomani-- identified the K^+ -H^+ -ATPase (proton pump) on the surface of parietal cells. Hakar Larsson, Enar Carlsson, Ulf Junggren, Lars Olbe, Sven-Erik Sjostrand, Inger Skanberg, and Gunhild Sundell; and Lars Olbe, Thomas Berglindh, Berit Elander, Herbert Helander, Erik Fellenius, Sven-Erik

Sjostrand, Gunhild Sundell, and Bjorn Wallmark-- developed proton-pump inhibitors.
Stanley G. Schultz and Ralph Zalusky-- adapted the voltage clamp technique with the Ussing chamber, originally used to study ionic flux across frog skin, to analyze quantitatively absorption and secretion in mammalian intestinal mucosa. They demonstrated active sodium absorption and stimulation of active sodium absorption by glucose resulting from a glucose-sodium cotransport process.

Discovery of the Proton Pump and Proton-Pump Inhibitors

The search for a biochemical basis for gastric acid secretion began in the 1930s after Roughton discovered carbonic anhydrase. Davenport proposed that this enzyme produced gastric acid, but he disproved this theory in 1945 by showing this enzyme was incapable of producing the potent acidity contained in gastric juice. In 1945, Relm postulated active transport of hydrogen by an electrogenic pump. Ussing devised a simple method to measure ionic fluxes across mucosa under voltage clamp (short circuit) conditions. He demonstrated in 1951 active sodium transport (absorption) in frog skin by this method. In the 1950s, Hogben applied Ussing's method to study active ion transport in gastric mucosa. Hogben placed dissected frog gastric mucosa in an Ussing chamber, applied electric currents, and used radioactive isotopes of chloride to demonstrate active secretion of chloride ions into the gastric lumen by a chloride pump present in gastric mucosa. [29] Durbin and Heinz then bathed frog gastric mucosa in chloride-free solutions in an Ussing chamber and found evidence for another gastric pump that actively transported hydrogen ions. Forte et al identified a potassium-stimulated phosphatase in gastric mucosa and confirmed that gastric mucosa required adenosine triphosphate (ATP) for acid secretion in frogs. In 1973, Ganser reported a novel potassium-stimulated ATPase in amphibian gastric mucosa that differed from the then known sodium-potassium ATPase. In 1976, Sachs et al [121] identified in gastric mucosa the proton pump, an electroneutral H^+ -K^+ exchange driven by a hydrogen-potassium ATPase.

Substituted benzimidazoles were then developed to block this hydrogen pump and to inhibit acid secretion. These benzimidazoles were designed as weak bases to diffuse across the cell membrane. The first effective agent, timoprazole, was too toxic for clinical use. Picoprazole, developed by Hassle in Sweden, also had toxic side effects. Omeprazole, a subsequent modification, was shown to block irreversibly the proton pump and to inhibit acid secretion potently in humans without significant toxicity. [77] [104] The use of omeprazole was initially restricted to Zollinger-Ellison patients, in whom it was life-saving, because administration in rats led to the development of gastric carcinoids. This restriction was lifted after studies showed that the development of carcinoids occurred only in rats and not in humans. Omeprazole proved to be a reliable, effective therapy for ulcers associated with gastrinomas, for severe reflux esophagitis, for nonsteroidal anti-inflammatory drug-induced ulcers, and, in combination with antibiotics, for *H. pylori*-associated ulcers.

Sodium Absorption

Schultz and Zalusky [125] [126] at the Air Force Medical School of Aerospace Medicine in San Antonio adapted the Ussing chamber technique to study ion fluxes in rabbit ileal mucosa. They demonstrated that sodium is actively absorbed in the rabbit ileum, that this sodium absorption is electrogenic, and that sodium absorption is stimulated by glucose as a result of glucose-sodium cotransport. This technique became commercially available when WPI Corporation marketed an automatic voltage clamp apparatus. The pioneering work of Schultz and Zalusky led to numerous applications by gastrointestinal researchers of the Ussing chamber to study intestinal absorption and secretion and by nephrology researchers to study renal absorption and secretion. The stimulation of sodium absorption by glucose is clinically applied in oral rehydration therapy for cholera.

Special Award for Founding the Journal Gastroenterology, a Gastroenterology Journal Owned and Operated by a Society of Gastroenterologists

Walter Alvarez, Andrew C. Ivy, Morton I. Grossman, and Abraham H. Aaron.

A journal is a perquisite to develop a discipline into a science and to transform a focus of interest into a recognized medical subspecialty. A milestone in the maturation of a discipline is the establishment of a professional journal owned and operated by a nonprofit professional society of peers because, in contrast to for-profit proprietary journals, a nonprofit journal can focus exclusively on accepting the best science, regardless of controversy or financial consequences. The discipline of gastroenterology is currently served by many first-class journals, such as the *American Journal of Gastroenterology, Digestive Diseases and Sciences, Gut, Journal of Clinical Gastroenterology*, and *Gastroenterology*. This review honors the founders of the journal *Gastroenterology*. Two other historically significant subspecialty journals, the *American Journal of Gastroenterology* and *Digestive Diseases and Sciences*, were established in 1933 and 1934 and are not within our purview.

The AGA was founded in 1897. [42] Papers presented at the annual AGA convention were published in its annual *Transactions* from 1903 through 1939. In March 1934, the rival National Gastroenterological Association, the forerunner of the American College of Gastroenterology, published the inaugural issue of its official society journal, the *Review of Gastroenterology*, the forerunner of the *American Journal of Gastroenterology*. [73] Another distinguished journal, the *American Journal of Digestive Diseases and Nutrition*, the forerunner of *Digestive Diseases and Sciences*, published its inaugural issue the same month. Spurred by the rival society publication, the AGA arranged in August 1934 for the *American Journal of Digestive Diseases and Nutrition* to be its official journal under joint editorial control by the AGA and the journal's editorial council. [6] The AGA's Governing Board later became dissatisfied with the advertising policy and editorial decisions of this journal. On June 15, 1942, the AGA terminated the publishing contract, and on July 15, 1942, Alvarez, Ivy, and Aaron, representing the AGA, signed a contract to publish a gastroenterology journal with editorial control vested exclusively in the AGA. [6]

Gastroenterology was adopted as the journal name on the second straw ballot of the AGA convention on August 31, 1942. During the first year, the journal published nearly 1000 pages and had about 1500 paid subscribers. Five years later, the journal published about 2000 pages and had about 2000 subscribers. Despite a small circulation, the journal was slightly profitable during the early years, although the first three editors-in-chief received no renumeration for the job and provided their own office space and their own secretarial support without compensation by the journal. By 1968, the journal had approximately 6000 paid subscribers and by 1999 had more than 10,000 paid subscribers.

The first editor-in-chief was Alvarez, with Ivy as assistant editor and Grossman as Ivy's assistant. In 1950, Ivy was promoted to editor, and Alvarez was appointed Chairman of the Editorial Board. Subsequent editors-in-chief included Aaron from 1952 to 1959, Grossman from 1959 to 1963, and Sleisenger from 1965 to 1970.

Alvarez as an intern confirmed Schaudinn's discovery of *Treponema pallidum* as the cause of syphilis in 1906. Alvarez studied rhythmic intestinal motor gradients in Cannon's laboratory at Harvard Medical School. Alvarez and Mahoney described gastric and intestinal electromyography in 1922. Alvarez authored four books from 1922 through 1943. [6] Alvarez was editor of the *American Journal of Digestive Diseases* before accepting the editorialship of *Gastroenterology*. Alvarez was awarded the Julius Friedenwald Medal by the AGA in 1958.

Ivy was Chairman of the Department of Physiology and Pharmacology at Northwestern University Medical School from 1925 to 1946. He later became Chairman of the Department of Clinical Science at Northwestern University Medical School. Ivy trained more than 500 gastrointestinal physiologists in his laboratory, including more than 60 who received a doctorate. Ivy studied regulation of gastric secretion, particularly by hormones, and contributed to the discovery of cholecystokinin. Ivy was awarded the Julius Freidenwald Medal by the AGA in 1970.

Aaron attended the University of Buffalo Medical School and was a house officer at Buffalo General Hospital. He apprenticed under his uncle, also Aaron, an AGA founder. He was Professor of Medicine at the University of Buffalo from 1940

through 1957 and was Chief of Medicine at Buffalo General Hospital from 1944 through 1957. He was known as an outstanding bedside teacher of gastroenterology and medicine. [17] Aaron was awarded the Julius Friedenwald Medal by the AGA in 1958.

Grossman received an M.D. and Ph.D. degree from Northwestern University of Chicago. He became a professor at the University of Illinois at age 32. He conducted research with Ivy and Robertson that conclusively established the existence of gastrin. He became Chief of Gastroenterology at the Wadsworth Veterans Administration Hospital in 1955. Grossman was editor of *Gastroenterology* from 1959 through 1965 and chairman of the editorial board of *Gastroenterology* from 1973 through 1978. He was President of the AGA in 1968. He was awarded the Julius Friedenwald Medal by the AGA in 1978.

Special Award for Landmark Discoveries in General Medicine of Particular Significance in Gastroenterology

Godfrey Newbold Hounsfield and Allan M. Cormack-- developed computerized tomography that has found innumerable applications for gastrointestinal imaging (awarded Nobel Prize in 1979).[25A] [25B] [63A] [90A]

Rosalyn S. Yalow and Solomon A. Berson-- discovered radioimmunoassay technique that has had broad implications in gastrointestinal physiology, pharmacology, and endocrinology, as well as numerous clinical gastrointestinal applications (Yalow awarded Nobel Prize in 1977).[9A] [140A] [156A]

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