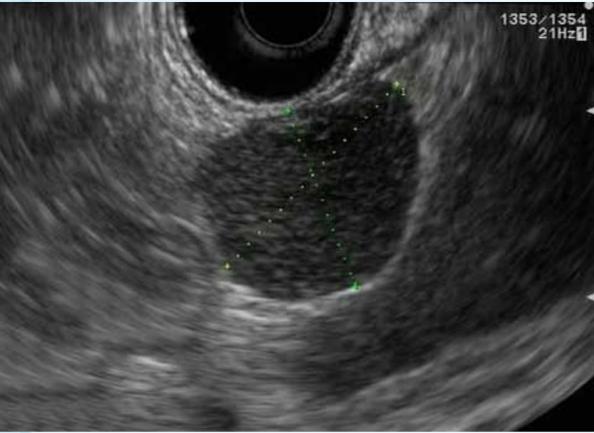


Identification and Treatment of GISTs at Penn Medicine



Endoscopic ultrasound image of a GIST. (Image: V. Chandrasekhara)

thought to have minimal malignant potential. Recently, however, aggressive behavior in GISTs smaller than 2 cm in size has been reported. Given the uncertainty of the clinical significance of smaller GIST lesions, says Nuzhat Ahmad, MD, of Penn Gastroenterology, all GISTs are now considered to have malignant potential and require long-term follow-up if they are not surgically removed.

“In this context, an accurate diagnosis, and if possible, risk stratification of GISTs, is critical,” Dr. Ahmad and colleague Vinay Chandrasekhara reported in the journal *Digestive Diseases and Sciences*. [1]

GISTs are typically diagnosed at Penn via endoscopic ultrasound (EUS) with or without EUS-guided fine needle aspiration (EUS-FNA), a modality found to provide both a high yield for sampling submucosal lesions and high accuracy for diagnosing GISTs. Lesion samples are treated and discovered via immunohistochemistry for the presence of CD117.

Risk stratification for GIST malignancy can be calculated according to the size of the lesion, location and mitotic rate. However, mitotic rate can only be reliably calculated with surgical resection specimens. At Penn, treatment of GISTs is dependent on lesion location and size. Lesions >2 cm are referred for surgical resection; gastric GISTs <2 cm can be observed with annual surveillance. Neither approach has been shown to improve outcomes. Survival is improved, however, in patients in whom the lesion is well contained in the absence of metastases.

RESOURCES

[1] Chandrasekhara V, Ahmad, NA. EUS-Guided Fine Needle Aspiration of Gastrointestinal Stromal Tumors: The GIST of the Matter. *Dig Dis Sci* 2011;56:1596-1598.

Clinician researchers at Penn Gastroenterology are identifying better ways to diagnose and treat gastrointestinal stromal tumors (GISTs), a rare subset of mesenchymal neoplasms specific to the gastrointestinal tract.

Once thought to be leiomyomas or schwannomas, GISTs are now recognized as a distinct entity arising from the interstitial cells of Cajal in the walls of the gastrointestinal tract. This clarification owes much to hematopoietic cell research in the 1990s and the subsequent observation that the expression of CD117, the c-kit proto-oncogene, is unique to GISTs among the mesenchymal neoplasms, and that mutations in the c-kit receptor tyrosine kinase play an important role in GIST pathogenesis.

With a better understanding of GIST classification, a reconsideration of their clinical behavior came about, as well. For many years, smaller GISTs (<2 cm) were

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For more information about research developments at Penn Gastroenterology, visit: <http://www.med.upenn.edu/gastro/news.shtml>

The following individuals were awarded K Grant and other career development grants.
Meenakshi Bewtra, MD, MPH
Rotonya Carr, MD
Kimberly Forde, MD, MHS
David Goldberg, MD, MSCE
Blair Madison, PhD
Andrew Rhim, MD
Frank Scott, MD, MSCE
Gregory Sonnenberg, PhD
Marie-Pier Tetreault, PhD
Vesselina Tomov, MD, PhD
Christina Twyman-St. Victor, MD

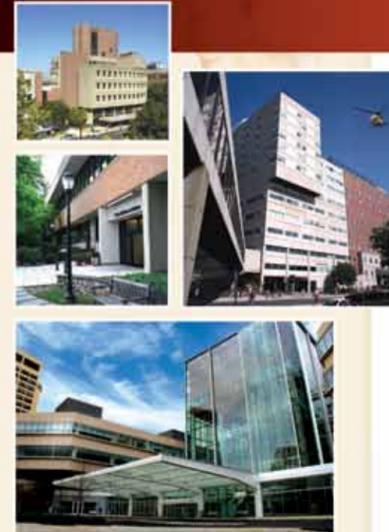
Congratulations to:
DAVID KAPLAN, MD, MSc, and his lab group on his VA merit grant award entitled “B-Cell Dysregulation in Cirrhosis due to Chronic Hepatitis C Infection.”
ROTONYA CARR, MD, is recipient of the National Harold Amos Medical Faculty Development award.
DAVID JAFFE, MD, has won a teaching award given by Penn’s medical students.

The gastroenterology team at the Perelman School of Medicine and Penn Medicine is nationally recognized for clinical research and superb care for its patients. I am pleased to announce the following recent honors and awards accorded our faculty, as well as additions to our team:



ANIL K. RUSTGI, MD

T. Grier Miller Professor of Medicine and Genetics, Chief, Division of Gastroenterology



LOCATIONS

Ruth and Raymond Perelman Center for Advanced Medicine
3400 Civic Center Boulevard
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GASTROENTEROLOGY
NEWSLETTER

WILLIAM (BOB) LONG, MD, Pioneer of Endoscopic Retrograde Cholangiographic Pancreatography, Retires from Penn Gastroenterology

William (Bob) Long, MD, a clinical researcher and pioneer of endoscopic retrograde cholangiographic pancreatography (ERCP) in the Philadelphia region, has retired after more than 40 years at Penn Medicine. A University of Pennsylvania Medical School graduate, Dr. Long began his career at Philadelphia General Hospital (PGH) in the early 1970s.

PGH was among the last hospitals operated by the city of Philadelphia, and when Dr. Long arrived, had established a renowned faculty, including Baruch Blumberg, MD, who received the Nobel Prize in 1976 for co-discovering the hepatitis B virus. An added attraction for Dr Long was PGH’s functioning GI laboratory. He soon found himself immersed in pancreatic disease research.

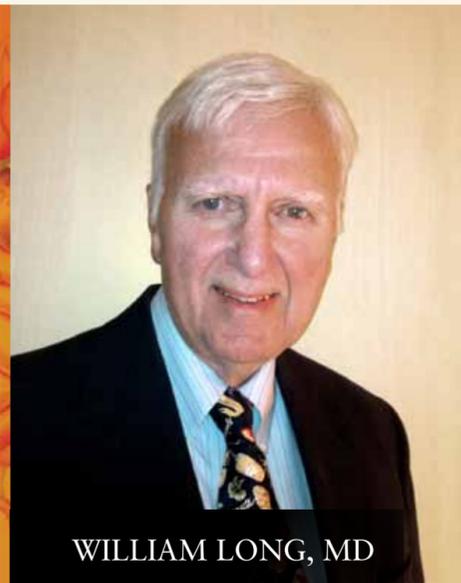
“My focus on pancreatic disease began during my fellowship, when I diagnosed macroamylasemia in a patient with chronic pancreatitis,” Dr Long observed in a recent interview. Discovered by Peter Wilding, PhD, (who, in a fortuitous development, arrived at Penn as Chief of Clinical Pathology shortly before Dr. Long’s arrival) macroamylase is a complex of amylase with a large protein leading to persistent elevation of serum amylase.

Dr. Long’s initial work involved the development of thin layer gel filtration test for macroamylasemia that, among other advantages, allowed simultaneous testing of multiple serum samples. After identifying several patients with macroamylasemia, it became apparent that the condition was more a curiosity than a bad prognostic factor. Publishing his findings in *Gastroenterology*, [1] Dr Long next developed a thin layer isoelectric focusing (IEF) test for amylase isoenzymes. Using this assay, he discovered that passage of amylase into urine was accelerated in acute pancreatitis, evidently as a manifestation of the systemic effect of the condition.

(con’t pg. 2)



(con't from pg. 1)



WILLIAM LONG, MD

Dr. Long's use of IEF would lead him to a discovery in another area.

One day at morning report, he recalls, an intern presented a multiple myeloma patient with a negative anion gap—an imbalance of positive and negative charges in the blood. “At the time, the imbalance was thought to be the result of positively charged myeloma proteins,” Dr Long says, “but no one had yet proven this hypothesis.”

Dr. Long proposed using IEF to see whether a positive charge existed in the myeloma protein at serum pH. With a sample of the patient's blood and that of several

“Generations of GI trainees and countless patients owe a debt to Dr. Long. He was a leader amongst a generation of true innovators in gastroenterology.”

*-Michael L. Kochman, MD, FACP
Wilmott Family Professor of Medicine
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other patients, he subsequently demonstrated that high isoelectric points were the cause of negative anion gaps in multiple myeloma. This work was reported in the New England Journal of Medicine in March, 1975. [2]

Another avenue of research for Dr. Long in these years involved maldigestion in patients with advanced pancreatic disease.

“We'd been using oral pancreatic enzyme therapy to treat maldigestion in these patients with suboptimal results,” said Dr. Long—an effect, he suspected, caused by gastric acid inactivation. Fortunately, the H2 blocker cimetidine had recently been FDA approved, and thus provided the fulcrum for an experiment that would, in time, supplement the standard treatment for pancreatic insufficiency.

With physicians from St. Christopher's Hospital and Children's Hospital of Philadelphia, Dr. Long initiated a comparative study in children with cystic fibrosis-associated severe pancreatic insufficiency. The study demonstrated that cimetidine significantly improved the effectiveness of enzyme therapy in children with pancreatic insufficiency, and gastric acid inhibitors became a standard supplemental treatment for cystic fibrosis.

Having examined maldigestion in pancreatic disease, and after observing rapid emptying of a fatty meal in a patient with long-standing pancreatic insufficiency, Dr Long and his colleague, Jordan Weiss, MD, began a study to assess maldigestion as a cause rapid post-prandial emptying of liquid fatty meals. Administering fatty meals to normal subjects and patients with pancreatic insufficiency (who were subsequently treated with pancreatic enzymes) the two concluded that maldigestion was a likely precedent of rapid emptying in pancreatic insufficiency, and that pancreatic enzyme replacement both retarded gastric emptying and increased gastric pH after liquid fatty meals. The results of this groundbreaking study appeared in Gastroenterology. [3]

As with earlier studies, an aspect of the rapid post-prandial emptying trial soon prompted another investigation.

In the 1970s there was no clinical means of measuring emptying of solids from the stomach, though liquid emptying could be done with a cumbersome intubation technique. It occurred to Dr. Long that the process could

be improved by employing radioactive colloidal materials like those radiologists had been using for some time to perform liver scans.

“I thought that this colloid could be trapped in cooked egg as a marker for solid gastric emptying,” Dr Long explains. He and his colleagues prepared an egg meal marked with a minute amount of radioactivity, and after serving it to a trial subject and aspirating the gastric contents, demonstrated that all radioactivity remained in the solid particles. Reported in Gastroenterology in 1979, [4] the technique has since become the international standard for measuring gastric emptying.

Endoscopic Retrograde Cholangiographic Pancreatography (ERCP)

Dr. Long's involvement in endoscopic retrograde cholangiographic pancreatography (ERCP) began with a volunteer assignment.

The introduction of contrast material to the pancreatic duct with endoscopic visual guidance for the purpose of radiography had been performed as early as 1968 in the US. By 1970, a surgeon in Japan had extended visualization to the biliary tree, and a combined procedure, named endoscopic retrograde cholangiographic pancreatography (ERCP) for its visualization of both ductal systems, was introduced there. [5]

The GI staff at PGH recognized the diagnostic potential of ERCP at once, but published reports emphasized the difficulty of the procedure. “I was the newest member of the staff,” Dr Long recalls. “So I offered to give it a try.” But where to begin? Dr. Long knew of no one in the U.S. performing the procedure.

His first case proved challenging, but after struggling for three hours, he succeeded in injecting X-ray contrast into the bile duct. The resulting X-ray demonstrated an obstructing gallstone, and the patient went immediately to surgery for stone removal.

For Dr. Long, the event was memorable not only for its achievement, but for his own prognostication for the future of ERCP. “I told the radiologist I'd teamed with that day that I doubted anyone could make a living doing ERCs,” he recalls. In the following years, Dr. Long would prove himself wrong, eventually becoming the leading practitioner of diagnostic ERCP in the Delaware Valley.

Until the introduction of CT, ultrasound and MRI technology, ERCP was often the best diagnostic procedure available to gastroenterologists. In 1973, however, the first therapeutic ERCP—in which the orifice to the bile duct was cut (sphincterotomy) and a gallstone removed—was reported from Europe. Shortly thereafter, Dr. Long began performing therapeutic ERCs himself, procedures involving increasingly sophisticated techniques, including sphincterotomy, passage of stents and balloon dilation.

A recipient of the Penn GI Division's Teaching Award, Dr. Long was awarded the American Society for Gastrointestinal Endoscopy Master Endoscopist Award in 2005 in recognition of his contributions to the field of gastroenterological endoscopy. In May 2013, after 42 years of practice and research at the Hospital of the University of Pennsylvania, Dr. Long announced his retirement.

“Dr. Long was the ERCP and endoscopy authority for decades in the greater Philadelphia area,” said Gregory G. Ginsberg, MD, Professor of Medicine and Director of Endoscopic Services at Penn Medicine, and recent President of the American Society of GI Endoscopy. “He contributed substantially to the training and education of numerous Gastroenterology Fellows in endoscopy and all areas of digestive diseases during the course of his career.” Dr. Ginsberg adds that Dr Long's patience, gentlemanly manner and general kindness made him beloved by his patients, nursing staff, trainees and physician colleagues alike.

Dr Ginsberg and Dr Kochman established the annual William “Bob” Long Endoscopy Lectureship at Penn Medicine, which coincides with the annual Penn Live: GI Endoscopy course.

With characteristic understatement, Dr Long says that he is grateful that during his career he could do laboratory and clinical investigations and treat patients in a very stimulating environment. In retirement, he continues his hobbies of sculling, woodworking and playing the flute, and enjoys time with his wife of 42 years, their children and grandchildren.

RESOURCES

- [1] Gastroenterology 1972;63:564-571.
- [2] N Engl J Med 1975;292:574-575.
- [3] Gastroenterology 1974;67:920-925.
- [4] Gastroenterology 1979;77:997-1000.
- [5] Naika 1970;26:325-339.

WEIGHT AND OBESITY COUNSELING AT PENN MEDICINE

Octavia Pickett-Blakely, MD, of the Division of Gastroenterology at Penn Medicine, has a unique perspective on the clinician's role in the management of obese patients. Following the 2003 U.S. Preventive Task Force recommendation that physicians screen all patients for obesity and offer intensive counseling and behavioral interventions to promote sustained weight loss, Dr. Pickett-Blakely took part in a pair of studies to define the relationship between obese individuals and the physician community.

What she gained in the course of her investigations has since informed both

her outlook and her direction in counseling overweight and obese patients at Penn Medicine.

The first investigation, on which Dr. Pickett-Blakely collaborated with lead investigator Sara Bleich, PhD, [1] analyzed more than 2400 obese adults (BMI ≥30 kg/m2) from the 2005 National Ambulatory Medical Care Survey to assess physician practice patterns of obesity diagnosis and weight-related counseling.

“We discovered that less than a third of obese adults received an obesity diagnosis and fewer than one in five got counseling for weight reduction,” Dr. Pickett-Blakely says. “More important, perhaps, was the finding that an obesity diagnosis was among the leading predictors of weight-related counseling.”

The second (and subsequent) study, for which Dr Pickett-Blakely was the lead author, [2] examined more than 5600 obese patients from the 2005–2007

National Ambulatory Medical Care Survey. The goal of the study was to evaluate the role of patient-physician gender concordance in weight-related counseling, a phenomenon known to promote better care in patients with hypertension, diabetes and other diseases. This study found that male gender concordant pairs were more likely to receive diet/nutrition and exercise counseling than gender discordant or female gender concordant pairs.

“These studies underline the importance of physician (including subspecialist) interactions with obese patients, including recognizing obesity and providing appropriate counseling,” Dr. Pickett-Blakely says.

RESOURCES

- [1] Bleich SN, Pickett-Blakely O, Cooper LA. Pat Ed Counsel 2011;82:123–129.
- [2] Pickett-Blakely O, Bleich SN, Cooper LA. Am J Prev Med 2011;40(6):616–619.

FIG 1: Obesity prevalence and physician diagnosis of obesity among obese U.S. adults.

*Note: Obesity (BMI ≥ 30 kg/m²) prevalence based on measured height and weight. Data were weighted to be representative of the general population.
2005 National Ambulatory Medical Care Survey*

PENN GASTROENTEROLOGY RESOURCES
GI DIVISION PATIENT WEBSITE: PennMedicine.org/GI
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GI DIVISION RESEARCH: www.med.upenn.edu/gastro/research.shtml

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