Endoscopic Retrograde Cholangiopancreatography (ERCP) was developed more than 30 years ago and allows trained gastroenterologists to use x-rays as a guide to enter the bile ducts and pancreatic duct for diagnostic and therapeutic maneuvers. ERCP is the treatment of choice for gallstones in the common bile duct, certain injuries to the biliary tree, stones and strictures in the pancreas and malignant obstruction of the bile ducts. Despite the widespread use and success of ERCP, shortcomings include reliance on the use of x-rays and the injection of contrast material needed to visualize the bile ducts and pancreatic duct.

Over the past 20 years, miniature scopes were designed which pass through the working channel of a standard ERCP scope to visualize the bile ducts and pancreatic ducts directly and to assist in diagnostic and therapeutic maneuvers. Direct visualization is a great advantage over contrast enhanced x-rays.

Disadvantages of these scopes include the requirement of two operators, limited steering capability, extreme fragility and high cost.

Early in 2007, Boston Scientific developed a new generation miniature scope designed for direct visualization of the biliary tree during ERCP. Named “Spy Glass” due to its ability to peer into a cavity not accessible by conventional approaches, this system consists of a dedicated light source, image processor and irrigation channel housed in a mobile cart. The optical component is a fiber optic “spy glass” barely the diameter of several strands of human hair. The scope is disposable with a one-time use for each patient. A series of tools have been designed which pass through the scope to assist with tissue acquisition for malignancy and the removal of common bile duct stones. The scope is 3mm in diameter.

Figure 1: text to come

continued on page 2
In the February issue of Gastroenterology (2008, 134: 597-616), the AGA Institute’s Future Trends Committee reported on a consensus conference designed to:

• assess the premise that academic gastroenterology (GI) divisions face growing and potentially untenable pressures;

• explore the nature of and understand these pressures; and

• consider approaches to ensure that academic GI divisions can continue to pursue their research and educational missions.”

I had the privilege of presenting key elements of our successful University of Pittsburgh Model at the consensus conference, and remarks about our program were included in the committee’s published report. For me, most rewarding was its consensus statement that the “Ideal Division” of the future describes, in essence, the University of Pittsburgh’s Division of Gastroenterology, Hepatology and Nutrition today.

In this issue of Pitt Digest, we feature key outcomes of the University of Pittsburgh’s pancreas research, including Dr. Dhiraj Yadav’s article to your on page 6 describing the critical assessment of the role of alcohol in pancreatic disease. Additional articles highlight advancements in pancreaticobiliary diseases, including Dr. Adam Slivka’s review of the novel Spy Glass procedure and Dr. Randall Brand’s reflections on UPMC as a premier center for translational research and this attracting him to join our faculty to pursue his own research in gastrointestinal cancer. Complementing our faculty, three of our outstanding GI fellows review notable teaching cases from our clinical services. These highlights continue to affirm our Division’s mission and commitment to unite “physicians and scientists for excellence in patient care, education and research, providing the best of tomorrow’s medicine, today!”

In good health,

David C. Whitcomb, MD, PhD

Giant Eagle Foundation Professor of Cancer Genetics
Professor of Medicine, Cell Biology & Physiology and Human Genetics
Chief, Division of Gastroenterology, Hepatology and Nutrition

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UPMC’s LPI Acquires Spy Glass®

continued from page 1

with four-way steering capability and has four channels running through it, including one through which instruments may be passed.

In 2007, 22 human subjects were evaluated using the Spy Glass Direct Visualization System, which facilitated patient care in approximately 90% of the cases. Later in 2007, the company engaged 15 experienced endoscopists from the U.S. and Europe to use this system and determine effectiveness with pancreaticobiliary patients. The University of Pittsburgh was chosen as one of these centers.

Our therapeutic endoscopy team and I used Spy Glass on almost 300 patients and carefully monitored results through April, 2007. Interim analysis of the first 146 patients was reported at Digestive Disease Week (DDW) in May, 2008. Results demonstrate that Spy Glass was extremely valuable in improving the diagnostic yield in at least two clinical scenarios: in patients with suspected cancer of the biliary tree, and in patients with slow-growing bile duct cancers surrounded by extensive scar tissue.

The diagnosis of cancer outside of the operating room has been plagued with false-negative biopsy and cytology. Historically, endoscopists could expect a positive biopsy in only half of bile duct cancer patients using ERCP or radiologically guided tissue acquisition. With Spy Glass, these bile duct tumors are visualized and biopsied directly. The accuracy of cancer diagnosis rose to 83 percent with Spy Glass, with a sensitivity of 78 percent, which compares favorably with a reported diagnostic accuracy of ≤ 50 percent in the literature.

Also, Spy Glass permitted localization and treatment of common bile duct stones which could not be removed through conventional ERCP. The Spy Glass fibers passed shock waves or lasers through the scope to fragment large stones into small easily removed pieces. Ninety-two percent of refractory stones were removed with Spy Glass, and serious complications were rare.

The therapeutic endoscopy team at the University of Pittsburgh has added Spy Glass to its arsenal to improve the care of patients with bile duct and pancreas diseases.

Dr. Slivka is a professor of medicine with the Division of Gastroenterology, Hepatology and Nutrition. He serves as the associate chief of clinical services for the Division and is the co-director for UPMC’s Liver Pancreas Institute.
Why did you come to UPMC? This is a question that I have been asked frequently by friends and colleagues across the country when I shared my decision to join the Division of Gastroenterology, Hepatology and Nutrition last September. I explain that the University of Pittsburgh Medical Center (UPMC) is one of the top centers in the country to perform translational research. I define translational research as either 1) the application of molecular and cellular biology to develop and test possible interventions in humans; or 2) investigating the biological basis for observations made in individuals with a disease or in populations at risk for a specific disease. Translational research at UPMC is enabled by the availability of a large patient population, the presence of superb clinicians and outstanding basic science support.

A multi-disciplinary collaborative approach is critical to the success of any translational research initiative and is an important part of UPMC’s Pancreatic Cancer Translational Program. UPMC patients with pancreatic cancer have easy and rapid access to physicians and other health care providers with an expertise in pancreatic cancer through a newly created multi-disciplinary clinic. Their care is standardized through the development of Pancreatic Cancer Clinical Pathways. These resources make it easier to offer patients opportunities to participate in a wide range of pancreatic cancer research protocols to diagnose pancreatic cancer at an earlier stage and to investigate novel treatment protocols.

My research efforts are focused on the early detection of pancreatic cancer. Vadim Backman, PhD and Yang Liu, PhD, colleagues from Northwestern University, and I have pioneered the use of light scattering spectroscopy to identify field effect changes in normal appearing duodenal mucosa to discriminate patients with pancreatic cancer from healthy patients (see figure above). Current funded research studies are examining whether this technology can discriminate pancreatic cancer from other diseases of the pancreas and biliary tract. Dr. Liu was recruited to the University of Pittsburgh in the spring of 2008 to explore the use of optical technology to improve the diagnosis of pancreatic cancer and other malignancies. This technology may also improve the fine needle aspiration diagnostic yield during pancreatic biopsies.

Also, I am leading a multi-center effort to create a reference set consisting of well-characterized serum/plasma specimens to use as a biomarker development resource for the early detection of pancreatic adenocarcinoma. This resource will be available to researchers across the country and will provide them with access to valuable samples from early staged pancreatic cancer patients. Furthermore, the testing of various biomarkers on the same sample set permits direct comparison among them, allowing for the development of a biomarker panel that can be validated in future studies. I will also continue to collaborate with Anna Lokshin, PhD at the Hillman Cancer Center (working on a multimarker panel to diagnosis pancreatic cancer), Surinder Batra, PhD from the University of Nebraska Medical Center (exploring the use of MUC4 as a diagnostic tool for pancreatic cancer), and Brian Haab, PhD at the Van Andel Research Institute (developing protein and glycan biomarkers for the specific detection of pancreatic cancer).

The successful implementation of translational pancreatic cancer research program depends on the support and hard work of fellow physicians, nurse coordinators, laboratory scientists and technicians along with our ancillary support staff. These individuals are motivated by a desire to improve the dismal survival rates for this dreaded disease with the hope that one day a diagnosis of pancreatic cancer will not be considered a death sentence.

Dr. Brand is a visiting professor of medicine with the Division of Gastroenterology, Hepatology and Nutrition. He also serves as the academic director for the Division at UPMC Shadyside and is the director of the GI Malignancy, Early Detection, Diagnosis and Prevention Program.
GRAND ROUNDS

Not the Usual Case of Diarrhea

by David Y. Lo, MD
Gastroenterology Fellow

Case Presentation

A 31-year-old male with a history of mental retardation and sarcoidosis presented with emesis and a one-year history of diarrhea. He had four to six watery non-bloody stools daily and a 12 pound weight loss over the last two months. He denied abdominal pain. Previously, he had normal stool cultures, a normal small bowel series, and biopsies of the colon showed a non-caseating granuloma in the lamina propria. He was treated with steroids for presumed gastrointestinal sarcoidosis. On steroids, his symptoms improved initially but relapsed quickly. Physical examination was unremarkable.

Laboratory studies were significant for the following: hemoglobin 10.1 g/dL (normal 14-18 g/dL), iron 14 mg/dL (normal 65-165 mg/dL), iron saturation 8% (normal 25-50%), ferritin 41 ng/mL (normal 10-282 ng/mL), albumin 1.8 g/dL (normal 3.4-5.0 g/dL), and prealbumin 13 mg/dL (normal 18-38 mg/dL). The white blood cell count, liver function tests, and coagulation profile were normal. Stool cultures were negative. An abdominal and pelvic CT scan was remarkable for mesenteric lymphadenopathy. A colonoscopy and normal random biopsies. On EGD, the duodenal mucosa appeared diffusely micronodular, and biopsies of the duodenum showed foam cells in the lamina propria. He was treated with steroids for presumed gastrointestinal sarcoidosis. On steroids, his symptoms improved initially but relapsed quickly. Physical examination was unremarkable.

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Whipple’s disease is a systemic illness caused by T. whipplei, a gram positive Actinobacteria. An oral route of infection is presumed, leading to invasion of the small intestinal mucosa and replication in monocytes and macrophages. The infection then spreads through the lymphatics to the mesenteric lymph nodes and bloodstream. Defects in the Th1 cytokine pathway may decrease macrophage activation, thus allowing infection to propagate. Immunosupression may hasten progression of disease.

Constitutional symptoms include fever, weight loss, and adenopathy. Gastrointestinal manifestations include malabsorption, diarrhea, abdominal pain and occult gastrointestinal bleeding. Given the systemic nature of Whipple’s disease, a wide spectrum of manifestations may occur, including rheumatologic (arthralgia, sacroiliitis), neurologic (dementia, delirium, supranuclear ophthalmoplegia, psychiatric symptoms, myoclonus, seizures), cardiovascular (blood culture-negative endocarditis), pulmonary (pleural effusion) and dermatologic (melanodera) manifestations.

Diagnosis is made by biopsy. On light microscopy, foamy macrophages are seen in the lamina propria. The glycoproteins of T. whipplei turn magenta with periodic acid-Schiff staining. Ziehl-Nielsen stain is used to rule out acid-fast bacilli. T. whipplei cellular structure is apparent on electron microscopy, and PCR testing for T. whipplei is performed for confirmation. A lumbar puncture with PCR for T. whipplei should be performed to rule out CNS involvement, which would require antibiotics known to penetrate the blood-brain barrier.

Whipple’s disease is fatal without treatment. Treatment consists of the parenteral ceftriaxone or a combination of streptomycin and penicillin for two weeks followed by a daily first-line oral agent such as Bactrim, penicillin VK, doxycycline or cefixime administered for a period of one to two years. Diarrhea often resolves within several days, and weight gain occurs within a few months. Relapse rates range from two to 33 percent after an average of five years. CNS relapse signals a poor prognosis, as these cases are often refractory to therapy.
A Tale of Many Cysts

by Elie Aoun, MD
Gastroenterology Fellow

Case Presentation

A 54-year-old white male with a medical history of diabetes, hypertension and hyperlipidemia was referred for evaluation of abnormal liver function tests and pancreatic lesions. The patient had been admitted to another hospital for management of right-sided community acquired pneumonia. During that admission, blood tests revealed elevated liver function tests with AST 102 IU/L, ALT 54 IU/L and AP 195 IU/L. A right upper quadrant ultrasound was ordered and showed multiple solid masses in the pancreas and bilateral renal cysts. Amylase and lipase levels were within normal limits. The patient’s pneumonia was treated with intravenous antibiotics, and his discharge plan included follow-up with the UPMC Digestive Disorders Center.

The patient was asymptomatic during his outpatient visit. He did not exhibit nausea, vomiting or abdominal pain and denied weight loss. His physical examination was unremarkable and revealed a normal soft nontender abdomen with no organomegaly and no palpable masses. His LFT panel normalized. An MRI of the abdomen showed multiple cysts involving the entire pancreas with bilateral renal cysts. An EUS revealed a diffusely heterogeneous pancreas with hyperechoic stranding and multiple tiny cysts. A 2.3 x 1.9 cm cyst in the body of the pancreas showed internal debris within the fluid-filled cavity, and a 3.1 x 3.3 cm irregular ill-defined mass with mixed solid and cystic components was found in the pancreatic head. The cyst fluid analysis showed low CEA levels (0.8 ng/mL) and a low amylase level (<30 IU/L). The molecular analysis did not reveal K-RAS point mutations or loss of heterozygosity, and the cytology was nondiagnostic. A diagnosis of von Hippel-Lindau disease (VHL) was entertained. An MRI of the brain showed two cerebral hemangioblastomas, and an MRI of the spine revealed cerebellar and cervical hemangioblastomas. Genetic studies were positive for VHL gene mutations, and diagnosis was confirmed.

Von Hippel-Lindau disease is an autosomal dominant neoplastic syndrome resulting from a germline mutation in the VHL gene. The VHL tumor suppressor gene was identified in 1993 and has been localized to the chromosome 3p25.5. Affected individuals may develop several benign or malignant tumors as well as cysts in multiple organ systems. Central nervous system lesions are common. Visceral features include renal cysts, pheochromocytomas, pancreatic cysts and neuroendocrine tumors among others. Most often, VHL diagnosis is based on clinical criteria. In individuals with a positive family history, the presence of a CNS hemangioblastoma, pheochromocytoma or clear cell renal carcinoma is diagnostic. If family history is not available, patients must have two or more CNS hemangioblastomas or one CNS hemangioblastoma and a visceral tumor to meet the diagnostic criteria.

Thirty-five to 70 percent of VHL patients have pancreatic involvement. Pancreatic cysts and serous cystadenomas occur in 17 to 56 percent of cases with a mean age of 37 years at presentation. These lesions are usually asymptomatic and do not require treatment, although they may cause epigastric pain and discomfort. Mucinous cysts are not associated with VHL disease, and VHL patients do not have an increased risk of pancreatic adenocarcinoma. Pancreatic neuroendocrine tumors are found in eight to 17 percent of patients with VHL with a mean presentation age of 35 years. Pancreatic neuroendocrine tumors have malignant potential and may metastasize to regional lymph nodes and the liver. Typically, these tumors grow slowly and are detected incidentally. Lesions are treated by surgical resection, with the approach dictated by tumor location and size. Recommended criteria for tumor resection include the absence of metastatic disease, a size larger than 3 cm in the pancreatic body or tail or larger than 2 cm in the head of the pancreas. Serial follow up with abdominal imaging studies is recommended for patients not meeting resection criteria.
Epidemiologic studies suggest a clear association between alcohol use and pancreatitis. Pancreatitis risk increases with the amount of alcohol consumption, although the threshold is currently unknown. My research investigates alcohol's role in the epidemiology of pancreatitis, including environmental and genetic factors’ impact on susceptibility to alcohol.

Heavy alcohol use is the second most common cause, after gallstones, of acute pancreatitis. An important question puzzling investigators for decades is why only a small proportion (< 5%) of people who drink heavily develop pancreatitis. In animal models, exposure to alcohol alone does not cause pancreatitis, and an additional stimulus to alcohol (e.g., caerulein, a CCK hormone analogue) is needed to initiate this disease. It is believed that alcohol sensitizes the pancreas to other physiological or pathological stimuli. Susceptibility to alcohol may be dependent upon a combination of factors within unique patients, such as the presence of other environmental factors (e.g., smoking), genetic susceptibility factors, metabolites generated from alcohol metabolism, alteration of neurohormonal control of pancreatic secretions by prolonged drinking, or actions of alcohol on the immune system.

Heavy alcohol use is the most common cause of chronic pancreatitis. However, in contrast to acute pancreatitis, there is little population based data concerning chronic pancreatitis trends. Interestingly, at tertiary centers, many chronic pancreatitis patients report alcohol consumption in amounts much lower than what is associated with pancreatitis typically. In fact, less than half of all chronic pancreatitis cases seen at the University of Pittsburgh Medical Center's Digestive Disorders Center have classic alcoholic pancreatitis.

The reasons for this observation are unclear but may be related to several factors:

- the recognition of several genetic susceptibility factors over the last decade which may result in selective referrals to tertiary centers;
- an increase in the use of cross-sectional imaging (e.g., CT scan or MRI) for evaluation of abdominal symptoms which may affect the frequency and stage of diagnosis; and,
- population-based trends in the U.S. showing an alcohol consumption plateau as well as decreasing smoking rates.

**Dr. Yadav is an assistant professor of medicine with the University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition.**

**References upon request.**
Annual Physician Education Opportunities

PancreasFest 2008: July 24, 25 & 26, 2008

The University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition will again host one of the nation’s most innovative pancreas education and research meetings, PancreasFest 2008. Education programs are interspersed with investigative research meetings to further the multidisciplinary understanding and treatment of pancreas diseases.

This program will be held at the University of Pittsburgh Cancer Institute’s Hillman Cancer Center, and overnight accommodations are available at the Courtyard by Marriott Pittsburgh/Shadyside Hotel. For registration and overall program information, contact Carm Campbell at campbellcm@dom.pitt.edu or (412) 623-0021 or visit http://www.dom.pitt.edu/gi/education.html.

What's New in GI & Hepatology: November 13 & 14, 2008

The University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition will host its annual fall education update for physicians and medical professionals interested in gastroenterology and hepatology on November 13 & 14, 2008. This program will be held at the Rivers Club in downtown Pittsburgh.

The Thursday evening November 13 program will feature liver diseases. The full-day Friday November 14 program will feature inflammatory bowel disease and upper-GI endoscopy. Special endoscopy workshops are planned.

For more information, please contact UPMC’s Center for Continuing Education in the Health Sciences at CCEHS@upmc.edu or (412) 647-8232.

Dr. Kapil Chopra Honored at “Tribute to Excellence” Luncheon

Kapil Chopra, MD (center) was honored for his extraordinary efforts to fight liver disease at the American Liver Foundation’s (ALF) Tribute to Excellence luncheon, an event held at Pittsburgh’s Duquesne Club on June 20, 2008. ALF’s Western Pennsylvania Chapter founders, Joanne Grieme (right) and Naomi Herman, were also honored. Ms. Herman’s daughter, Lydia Blank (left), attended in her absence. Dr. Chopra is an associate professor of medicine with the University of Pittsburgh’s Division of Gastroenterology, Hepatology and Nutrition.
What Is This? Presentation: A 79-year-old man presented with an eight month history of dysphagia for solids and a 60-pound weight loss. Food was getting stuck in his mid-chest and was regurgitated. He has experienced dysphagia to liquids over the past month. Esophageal manometry is shown above.

Compare your answer to Dr. Rodemann’s answer on page 6.