Pitt Digest

Summer 2010

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Pitt Digest
is a publication of the University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition

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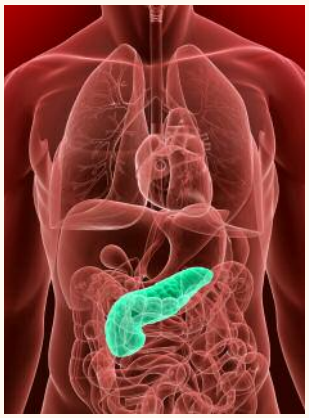
Auto Islet Cell: **Pancreatitis Advances at UPMC**

by Andres Gelrud, MD, MMSc

Total pancreatectomy with auto-islet cell transplantation has emerged as a viable option for the treatment of debilitating pain in patients with chronic pancreatitis (CP) and recurrent acute pancreatitis (RAP).

CP is a complex syndrome resulting from interactions of multiple risk factors such as genetic variance (i.e., cystic fibrosis [CFTR] and hereditary pancreatitis [PRSS1, SPINK]), environmental stressors such as alcohol and smoking (Yadav D, Whitcomb DC The role of alcohol and smoking in pancreatitis. *Nat Rev Gastroenterol Hepatol* 2010; 7[3]:131-45), metabolic alterations such as hyperlipidemia and hypercalcemia, or trauma, and worsens with an altered host immune response. It is characterized by progressive inflammation of the pancreas leading to destruction of pancreatic parenchyma with loss of exocrine and endocrine function, fibrosis, pain and high pancreatic cancer risk. The most distressing feature of CP is pain, which may be intermittent or continuous and may be out of proportion to the level of inflammation or fibrosis. Initial treatment options for CP and RAP include dietary modifications, pancreatic enzyme supplementation, pain management and, finally, narcotics. A subset of CP patients with pain benefit from surgical decompression of the pancreatic duct, particularly those with underlying strictures or stones from chronic alcohol use. However, patients with inflammatory or neuropathic pain seldom benefit from pancreatic duct decompression surgery. For CP caused by toxic, metabolic or genetic conditions, an "acinar cellular condition" is involved, and focusing on "plumbing problems" will not alter the long term disease course or relieve continuous pain. In serious pain cases, only partial or complete pancreatectomy will control pain, usually leaving the patient a brittle diabetic.



One way to minimize diabetes risk is to separate the islet cells after pancreatectomy and reinsert them into the patient. The University of Pittsburgh Medical Center (UPMC) offers total pancreatectomy with auto-islet cell transplantation (TP AICT). During this procedure, the pancreas is removed surgically, and the pancreatic islet beta cells (insulin producing) are isolated and transplanted back into the patient's liver. This prevents the development of brittle diabetes in most cases.

At UPMC, teams of experienced gastroenterologists, surgeons and social service professionals independently evaluate each patient, whether adult or pediatric. The decision to proceed with surgery is determined during a multidisciplinary pancreas conference, where team members come together and discuss in detail each individual case.

In our experience, the best TP AICT candidates are those with debilitating pain from CP or RAP. Patients with underlying genetic conditions, those with a history of alcohol abuse or other etiologies and for pancreatic pain may be good candidates for this surgery as well.

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We are honored to partner with our surgical colleagues for this issue of *Digest*, which features advanced pancreas clinical and research programs at the University of Pittsburgh Medical Center. As a team, we are providing some of the most outstanding multidisciplinary pancreas disease evaluation and care available anywhere in the world.

Pancreas diseases which we study and treat in depth include acute pancreatitis, hereditary pancreatitis, cystic fibrosis, recurrent acute pancreatitis, autoimmune pancreatitis, chronic pancreatitis, benign and malignant pancreatic masses and cysts, intrapancreatic mucinous neoplasias (IPMN), early, locally advanced or metastatic pancreatic cancer, rare genetic disorders, and the complications of pancreatitis to include pancreatic insufficiency, pancreatic necrosis, diabetes mellitus, fibrosis, pain and medical coping.

The multicenter North American Pancreatitis Study 2 (NAPS2) and Study of Nutrition in Acute Pancreatitis (SNAP) projects represent major multidisciplinary pancreas research projects. Other current University of Pittsburgh studies investigate the severity of acute pancreatitis, early detection of pancreatic cancer, learning to optimize biomarker information, mathematical modeling for outcome prediction/intervention, genetics, cancer treatment (multiple studies), minimally invasive surgical techniques, methods of islet cell preservation and expansion (through Endocrinology) and studies on the mechanism and treatment of pancreatic pain from basic science to pancreatectomy and islet autotransplantation. See articles in this issue for more information about the groundbreaking SNAP research as well as UPMC's success with auto-islet cell transplantation.

If this issue gets you interested in pancreas disease advancements, attend *PancreasFest 2010* this summer (July 29 – 31, 2010), an annual international meeting of clinical pancreatologists and related scientists. In addition to physician education at *PancreasFest*, we will discuss and develop multicenter studies to further understand and treat pancreatic disease. Other physician education programs include our GI Division's *Postgraduate Course: Multidisciplinary Strategies for Common Digestive Diseases* on October 21 & 22 and Surgery's *Minimally Invasive Approaches to Pancreatic Disease* on November 12 & 13.

See **http://deptmed.pitt.edu/gi** for more Division event and educational information, including archived copies of the *Pancreas Education and Research Letter (PEaRL)*, designed for pancreas patients.

Sincerely,

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

Study of Nutrition in Acute Pancreatitis (SNAP):

An NIH U-01 Multicenter Study

by Stephen J. D. O'Keefe, MD, MSc

Acute pancreatitis (AP) results from premature activation of the proteolytic proenzyme trypsinogen to trypsin within the gland, leading to self-digestion or autophagia. Since food is the most potent stimulant of trypsin synthesis, the mainstay of medical management has been to hold feeding and apply gastric suction. This is an imperfect solution, since patients with severe AP (SAP) have extremely high protein catabolic rates, and the degree of ensuing nitrogen loss correlates directly with mortality. In the 1970's, total parenteral nutrition (TPN) was introduced to avoid pancreatic stimulation and prevent nitrogen loss, but septic and metabolic complications ensued. The late 1990's introduced enteral nutrition (EN) tube feeding with delivery into the jejunum in elemental form to minimize pancreatic stimulation. Over the past two decades, several randomized trials by the University of Pittsburgh and others have compared EN to TPN. Findings confirmed the superiority of EN, particularly with regard to infective and metabolic complications and cost.

Two recent studies from India and Scotland compared jejunal vs. gastric EN delivery and found no difference in outcome, questioning the fundamental importance of pancreatic rest. The results were surprising, since most patients with SAP have antro-duodenal compression due to the inflammatory mass leading to poor gastric emptying. These authors deemed gastric feeding preferable to jejunal feeding due to ease and speed of initiation as well as evidence that early enteral feeding prevents some complications and organ failure in critically ill patients. Our group is concerned that these two new studies ignore the importance of pancreatic rest. Both used duodenal and proximal jejunal feeding, and pancreatic rest can only be maintained if feeds are delivered >40cm past the ligament of Treitz. Consequently, both study arms were stimulatory, possibly

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1-888-623-PANC

Pancreatic Surgery Supplement

Summer 2010

Dear Colleagues:

UPMC Pancreatic Surgery is delighted to share pancreas surgery updates in this newsletter. We will highlight exciting improvements in the surgical care of pancreatic disease patients which are being pioneered at UPMC. We are now one of the highest volume centers for pancreatic surgery in the world.

A multidisciplinary approach to pancreatic disease is essential for optimal patient outcomes, and our devotion to this approach is apparent in every aspect of the surgical program. Surgery and gastroenterology share clinic space which is immediately adjacent to the GI lab. This facilitates real-time, bi-directional consultation while eliminating patient inconvenience. Treatment plans for patients are determined collaboratively during a weekly pancreatic disease conference, which is attended by gastroenterologists, pancreatic surgeons, medical oncologists, radiation oncologists, radiologists and pathologists. Timely communication with and accessibility to referring and primary care physicians are top priorities.

The following articles offer further details regarding our treatment and research programs devoted to patients with pancreatic neoplasms and pancreatitis. Perhaps the greatest point of interest lies in our ongoing efforts to develop and refine minimally invasive pancreatic surgery, including laparoscopic and robotic-assisted radical pancreaticoduodenectomy (the Whipple procedure). Equally important efforts include a comprehensive portfolio of clinical trials including neoadjuvant therapy for pancreas cancer and improved outcome prognostication using novel methods of imaging assessment and molecular analyses of neoplasms.

Steven J. Hughes, MD

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Minimally Invasive Surgery for Pancreaticobiliary Disease

by Stephen J. Hughes, MD, Kenneth K.W. Lee, MD, A. James Moser, MD and Herbert J. Zeh III, MD, PhD

In 2002, our group initiated a dramatic improvement for patients facing pancreatic surgery with the performance of the first successful laparoscopic distal pancreatectomy performed at UPMC. Since then, our program has applied minimally invasive surgical techniques to increasingly complex pancreatic disease procedures. In what is now the largest, single-institution experience in the world (n > 200), we have proven that laparoscopic distal pancreatectomy outcomes result in equivalent surgical margins and lymph node counts, clearly surpassing standard techniques. This approach results in reduced time in the ICU, less blood loss, fewer blood transfusions and shorter lengths of hospital stay.

Upon this foundation, the UPMC pancreatic surgery group has evolved its approach to the management of necrotizing pancreatitis, performing pancreatic necrosectomy and drainage procedures laparoscopically, thus virtually eliminating wound complications and shortening recovery. Similarly, the management of pancreatic pseudocysts via laparoscopic cyst gastrostomy and Roux-en-Y cyst jejunostomy is now routine. Even longitudinal drainage approaches including Frey, Beger and Peustow procedures are now safely performed laparoscopically on appropriate patients at our center. Capitalizing on these successes, the first laparoscopic radical pancreaticoduodenectomy (Whipple procedure) at UPMC was performed in 2008.

Such complex, minimally invasive, reconstructive surgical techniques are optimal applications for robotic surgery. The UPMC pancreatic surgery program is actively pioneering robotic surgery for pancreatitis complications and pancreatic neoplasms. In addition to multiple robotic distal pancreatectomy and drainage procedures, this program can now boast the successful completion of more than 30 robotic Whipple procedures. Our multidisciplinary pancreatic disease conference selects appropriate patients based on collective and careful review of oncologic principles, and the program has collectively performed over 50 minimally invasive/robotic Whipple procedures. With its refined surgical technique and mortality rates below five percent, the UPMC Pancreatic Cancer Center is now studying if and/or why minimally invasive/robotic Whipple is superior to standard, open surgery techniques.

Personalized Medicine for Pancreatic Cancer

▸ Multidisciplinary Treatment

Pancreatic cancer is a therapeutic dilemma requiring multidisciplinary specialty care. The spectrum of evidence-based management includes variable combinations of surgical intervention, neoadjuvant and/or adjuvant chemotherapy, radiotherapy, palliation of pain, prevention of malnutrition and evaluation for clinical research. Traditional care patterns often require multiple visits to different specialists resulting in delays in definitive care, heterogeneity of care plans within the same institution and barriers to data collection and clinical trial enrollment.

The UPMC Pancreatic Cancer Center inaugurated the first Specialty Care Center (SCC) within the UPMC Cancer Center network in 2007. The mission of this Pancreatic Cancer SCC is to improve and personalize pancreatic cancer patient treatment at all stages of the disease and to offer cutting edge clinical trials. The Pancreatic Cancer SCC offers multidisciplinary cancer care to patients during a single clinic visit. Cindy Valko, RN (1-888-623-PANC), coordinates pancreatic cancer patients' experiences with surgery, gastroenterology, medical and radiation oncology, cancer nutrition, cancer genetics, pain/palliative care, integrative/holistic medicine and clinical trial information. Most often, these various patient consultations are combined into a single patient visit. This multidisciplinary team evaluates patients every Wednesday and rotates between the UPMC Presbyterian and the Hillman Cancer Center campuses. The SCC evaluated more than 250 patients in 2009, most of whom traveled more than 50 miles for care. Patient satisfaction surveys indicated that 96 percent of patients were satisfied with their evaluation and the efficiency of the multidisciplinary process. The average time from initial evaluation to initiation of definitive oncologic care was 17 days, as compared to an average delay of 49 days prior to the implementation of the SCC.

▸ Clinical Trials for Pancreatic Cancer

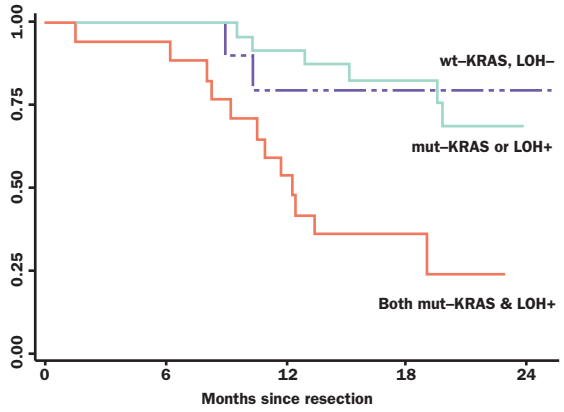
Although surgery remains the mainstay of treatment for patients with early-stage pancreatic cancer, recent data from the ESPAC and CONKO-01 medical oncology trials demonstrate clearly that optimal survival outcomes are only achieved through a multimodality approach combining surgery with adjuvant chemotherapy. Expanding on this approach, the Pancreatic Cancer SCC offers innovative clinical trials to patients with all stages of pancreatic cancer with an emphasis on the provision of novel treatment to patients before surgery (neoadjuvant therapy). Currently, we have clinical trials or innovative treatment plans for all

stages of disease. Early stage resectable patients are offered UPCI clinical trial 06-035, the novel combination of high-dose chemotherapy (gemcitabine), with the vascular growth factor inhibitor bevacizumab (Avastin) and radiation. For metastatic disease, we are honored to participate in several national consortiums including the Pancreatic Cancer Research Team. Through this organization, our group has access to the latest and most promising new agents. We are participating in a phase III clinical trial using the exciting new chemotherapy agent nab-paclitaxel (Abraxane) with gemcitabine for metastatic pancreatic cancer. Other innovative therapies offered currently include combining stereotactic radiosurgery (Cyberknife) with systemic chemotherapy for unresectable tumors. Lastly, we have a vigorous phase I clinical trial program for patients who have received unsuccessful treatment elsewhere including UPCI 06-041, a clinical trial of a genetically-engineered vaccinia virus used to kill metastatic pancreatic cancer upon injection into tumors.

▸ Improving Outcomes of Surgery for Pancreatic Cancer

Although surgical techniques have evolved tremendously since Whipple published the operation which bears his name in 1935, basic surgery principles for pancreatic cancer have not changed significantly. The objective of any surgical procedure for pancreatic cancer is to resect localized tumors with a microscopically-negative surgical margin and to assure the patient's rapid recovery so that adjuvant gemcitabine chemotherapy can be initiated within eight weeks.

The status of the surgical margin is the major predictor of survival following surgery. Of concern are recent reports indicating that as many as 42 percent of patients undergoing radical pancreatoduodenectomy (the Whipple procedure) have residual disease after resection, **all** of whom will eventually die of cancer. The UPMC Pancreatic Cancer Center is dedicated to using high-technology preoperative predictive modeling to reduce the need for cancer patients to endure nontherapeutic surgery. We have recently validated a predictive model which uses preoperative imaging characteristics obtained from CT and EUS to categorize patients into high-risk and low-risk groups for residual cancer following surgery. The high-risk characteristics are commonsense features such as large tumor size (>2.6 cm diameter), evidence of *any* vascular involvement (including minor degrees of venous or arterial abutment) and evidence for abnormal lymph nodes during EUS. Using this predictive model reduced the positive surgical margin rates among surgical patients significantly and improved survival by more than ten months.



Overall survival stratified by the presence of tumor genetic aberrations. Patients with either KRAS mutations or allelic imbalance had equivalent survival (median not reached). Patients exhibiting both KRAS and LOH (n – 17) had significantly shorter overall survival (median 12.3 months, log rank test, p<0.001) after pancreatic resection.

The UPMC Pancreatic Cancer Center encourages all patients with pancreatic cancer to undergo preoperative treatment to reduce the risk of a positive margin after surgery. This is especially important for high-risk patients, since postoperative median survival among high-risk patients is only ten months.

▸ Genetic Modeling of Outcome

By adding tumor genetic variables to the anatomic predictors observed during CT and EUS, we have constructed a biological model to predict survival for patients with localized pancreatic cancer and to personalize their treatment decisions. We analyzed clinically relevant, commercially available genetic predictors for pancreatic cancer, such as the presence or absence of KRAS mutations and tumor suppressor gene loss of heterozygosity analysis, into a decision model which stratifies patient outcomes into four remarkably different survival groups. This model distinguishes patients with predicted survival as high as 65 percent from others having a 17-month life expectancy regardless of surgery and chemotherapy. The statistical validation of this prospective, predictive model is being conducted currently.

Drs. Hughes, Lee, Moser and Zeh are associate professors of surgery with the University of Pittsburgh Division of Surgical Oncology.

Minimally Invasive Management of Acute Pancreatitis

by Drs. Hughes, Lee, Moser and Zeh

In approximately 15 percent of acute pancreatitis patients, necrosis of the pancreas and surrounding tissues occurs and can result in a severe systemic inflammatory response and development of local complications. If the necrotic tissues become infected, surgical debridement is often required. Standard open surgical debridement can result in large and sometimes open incisions with prolonged recoveries plagued by complications such as wound infections and intestinal fistulae.

The pancreas surgery team at UPMC has developed minimally invasive techniques for performing these pancreatic debridements. Using instruments introduced into the abdomen through several small incisions, these techniques remove infected fluid and necrotic pancreatic and peripancreatic tissues thoroughly. Postoperative pain and surgical trauma are minimized, and the risk of wound-related complications is reduced.


Fig. 1

Figure 1 shows a patient who underwent minimally invasive debridement of his pancreas three weeks after an exploratory laparotomy. Two drains exit from the sites used to introduce the minimally invasive instruments into his abdomen. The wound resulting from his exploratory laparotomy is also visible. *Figures 2a* and *2b* show pre-and post-debridement abdominal images.

If necrosis is present with infection, the necrosis can lead to formation of a pancreatic pseudocyst. Internal drainage is advisable if the pseudocyst is symptomatic or enlarging, or if complications develop such as infection. Minimally invasive internal drainage of pancreatic pseudocysts is now our group's preferred method to achieve internal drainage of pancreatic pseudocysts into either the stomach or small intestine. Advanced laparoscopic and robotic suturing and stapling techniques enable our surgical team to perform minimally invasive pancreatic cystgastromies and Roux-en-Y pancreatic cystjejunostomies.

Figures 3a and 3b show pre- and post-drainage images of a 58-year-old woman with an enlarging symptomatic pancreatic pseudocyst after an episode of acute biliary pancreatitis. This pseudocyst bulged downward through the transverse mesentery but did not abut the back of the stomach. It was treated via a laparoscopic Roux-en-Y pancreatic cystjejunostomy.

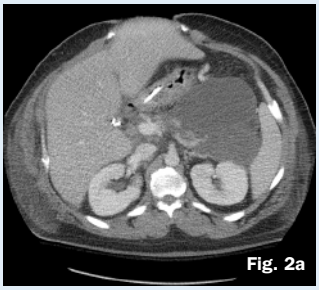


Fig. 2a

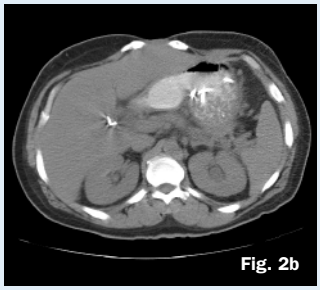


Fig. 2b

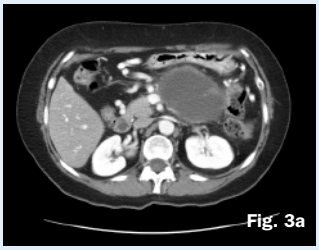


Fig. 3a

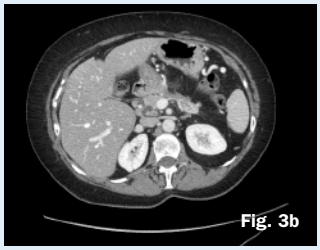
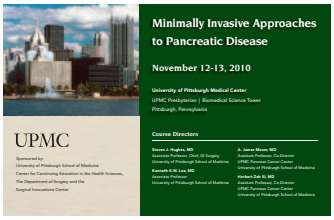


Fig. 3b

Minimally invasive drainage of pancreatic pseudocysts achieves high success rates. Postoperative pain and wound complications are minimized, and postoperative ileus and postoperative hospitalizations are shortened to facilitate the patient's earlier return to normal activities.

Physician Education Opportunity

The UPMC Surgical Innovations Center (SIC) will host a two-day symposium that will focus on the technical performance of Minimally Invasive Procedures for Pancreatic Diseases. A one-day didactic session will be composed predominantly of procedure videos including laparoscopic Whipple, distal and central pancreatectomy, enucleation, cyst gastrostomy, Roux-en-Y cyst jejunostomy and hepatico-jejunostomy, and debridement and drainage of infected necrosis. The second day offers two options: participation in a human cadaver practical lab (limited to 10 participants) or observation of live procedures presented via telesurgery.



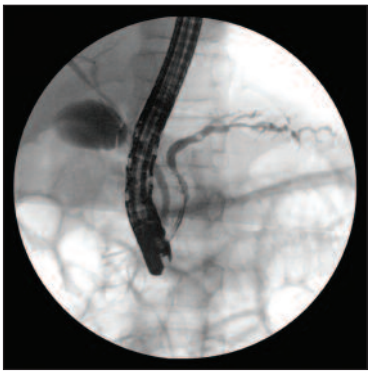
The symposium will be held at the UPMC Presbyterian Biomedical Science Tower in Pittsburgh, Pennsylvania. For more information or to register, contact Penny Sauvageot by phone (**412**) **647-3516** or e-mail **sauvageotp@upmc.edu**.

New Approaches to Pancreatic Pain

by Ari Wiesen, MD
Gastroenterology Fellow

Case Presentation

An 11-year-old boy was seen for a long term history of painful chronic pancreatitis. His mother had gestational diabetes, and the patient was delivered by cesarean section at 38 weeks gestation due to macrosomia. He weighed 10 pounds 14 ounces. Through age two, he experienced respiratory problems and was diagnosed with asthma. Beginning at 13 months, this young patient required multiple admissions for chronic abdominal pain and, at four years, was diagnosed with pancreatitis (amylase and lipase levels both above 1,000). He progressed to chronic pancreatitis with debilitating pain and became opiate dependent. Genetic testing was performed at age nine, and the patient was found to have a *PRSS1* (cationic trypsinogen gene) mutation, indicating a diagnosis of hereditary pancreatitis.



Pancreatogram revealed a dilated main pancreatic duct with multiple dilated side branches and filling defects.

This child's chronic pancreatitis was characterized by recurrent documented episodes of pancreatitis without specific triggers, despite evidence of good hydration and a low fat diet. Abdominal CT imaging revealed pancreatic fibrosis, dilated pancreatic duct, and multiple stones in the main pancreatic duct with obstruction. He underwent multiple ERCPs with stone extraction and stent placement to treat the pain and prevent duct obstruction, but the symptoms recurred soon after stent removal. At age ten, he was diagnosed with pancreatic endocrine insufficiency (diabetes mellitus), and exocrine insufficiency was documented through markedly abnormal fecal elastase testing.

The patient's frequency of hospital admission increased due to recurrent attacks. Narcotics were required to control severe pain, but these drugs interfered with his ability to concentrate in school, and he was falling behind in all areas of his life.

The patient was referred to the Multidisciplinary Pancreas Clinic team at UPMC. After a careful evaluation and review of his clinical history the patient and his family were informed of the possibility of total pancreatectomy and auto-islet cell transplantation. He was evaluated by a multidisciplinary team comprised of gastroenterologists, pancreatic surgeons, transplant coordinators and endocrinologists. He was found to be a good candidate by the team, and auto-islet cell transplantation surgery was performed. He received an infusion of 7,000 pancreatic islets/kg BW that were harvested from his own pancreas. The postoperative period was uneventful, and he was able to eat after four days. He was treated with IV insulin and IV pain medications which were soon changed to oral and subcutaneous regimens, respectively.

At the two month post-operative follow-up clinic visit, the patient was taking no pain medications. He progressed well on a regimen of a small amount of insulin (he was a diabetic prior to the surgery), pancreatic enzyme supplementation, pregabalin and a proton pump inhibitor. And, he returned to school.

Four months later, he was reported as doing great. He even joined a community soccer team. His parents stated that their biggest regret is that they did not have this procedure done earlier.

Pancreatitis Advances *continued from page 1*

After surgery, pain is markedly decreased and is often controlled completely with non-narcotic approaches.

Many patients are initially insulin independent. Over time, however, islet cell function tends to decline, and patients must be aware of diabetes risk years after surgery.

For more information about auto islet cell transplantation and advanced approaches to pancreas disease care at UPMC, contact 412-623-3108.

Dr. Gelrud is an Associate Professor of Medicine with the University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition. He is the Medical Director for Total Pancreatectomy/Islet Auto-transplantation and directs Therapeutic Endoscopy for the Division, caring for patients primarily at UPMC Shadyside.

UPMC

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Acute Pancreatitis (SNAP) *continued from page 2*

explaining the similar outcomes in both randomized groups. Mortality rates were unusually high in both studies (i.e., 25-50%), raising doubt about efficacy.

Our team designed the Study of Nutrition in AP (SNAP) to randomize patients with predictors of severe disease to gastric vs. jejunal feeding >40cm past the ligament of Treitz. Early feeding is believed to prevent organ failure, so entry will be restricted to patients in whom tube feeding may be initiated within 96 hours of abdominal pain onset. The primary endpoint will be the relative feeding efficacy determined by feeding tolerance of the 136 study patients. Secondary endpoints will measure inflammatory responses, complication rates, hospital outcome and mortality. The following national centers will collaborate on SNAP: University of Pittsburgh, Harvard University, University of Florida, Mayo Clinic Rochester, University of Louisville, Medical University of South Carolina and UCLA. SNAP results will reveal critical information about SAP pathobiology and responses to interventional feeding, and should improve our current management leading to reduced morbidity and mortality.

Dr. O'Keefe is a Professor of Medicine with the University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition. He leads the Division's Center for Intestinal Health and Nutrition Support.

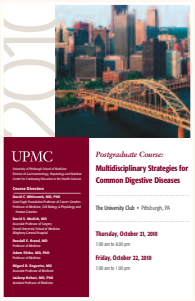
Annual Physician Education Opportunities

PancreasFest 2010: July 29, 30 & 31, 2010

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 2010**. Education programs are interspersed with investigative research meetings to further the multidisciplinary understanding and treatment of pancreas diseases. Visit **www.pancreasfest.org**.

Multidisciplinary Strategies for Common Digestive Diseases

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 **October 21 & 22, 2010**.



Both programs will be held in Pittsburgh, Pennsylvania. For more information about either program please contact Joy Jenko Merusi at **joj2@pitt.edu.**