A Dynamic and Challenging Time for Medicine

Even with uncertainty, we are clear on several fundamental realities:

- *Digestive diseases remain a major health problem in the United States.*
- *Academic medical centers with true translational research programs are receiving mandates to improve patient care.*

At the University of Pittsburgh, we remain fully committed to these goals, recognizing that centers such as ours are significant national resources.

UPMC Digest provides a snapshot of activities within the Division of Gastroenterology, Hepatology, and Nutrition’s seven Centers of Excellence. A *New England Journal of Medicine* study by Robert Schoen, MD, MPH, and colleagues clarifies the role of CRC screening. True translational research, as published by Vijay P. Singh, MD, in *Science Translational Medicine*, demonstrates the role of lipids in severe acute pancreatitis, specifically related to unsaturated free fatty acids. Other recent publications in *Nature* (IBD faculty) and *Nature Genetics* (pancreas faculty) also highlight “big science” advances. Our dedication to strengthening and expanding the successful translational research model at UPMC is reflected in the work of our new faculty member Alison Jazwinski, MD, MHS.

UPMC’s highly competitive gastroenterology fellowship program also enters a new era this year as Kenneth Fasanella, MD, previously associate director, accepts the program director reins from Miguel Regueiro, MD. In this issue, several of our talented fellows describe unusual case studies with important teaching points.

We trust that this accredited issue of UPMC Digest will lead to better options in caring for your patients. Thank you for your time and interest.

David C. Whitcomb, MD, PhD

*Giant Eagle Foundation Professor of Cancer Genetics
Professor of Medicine, Cell Biology & Physiology and Human Genetics
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Oils That Fuel the Dragon of Acute Pancreatitis

By Vijay P. Singh, MD
Assistant Professor of Medicine

Acute pancreatitis (AP) is a complex, acute, non-infectious inflammatory disorder. Despite decades of in-depth clinical and basic research, this disease has eluded early-risk stratification and targeted therapies.

AP has an unpredictable onset and clinical course with outcomes ranging from spontaneous resolution to death. This unpredictability makes disease complications a possibility hovering over the horizon like a scary mirage. When these strike, they are a constant source of frustration to the researcher or clinician striving to develop the magic bullet to subdue this multidisease-headed dragon. Standard approaches that are successful in other scientific disciplines, such as inhibiting a single crucial mechanistic step, as is the basis of antibiotic use for a bacterial infection, have faced repeated clinical failures.

Recently, our multidisciplinary team approach, with surgeons, pathologists, radiologists, epidemiologists, cell biologists, biochemists, and pancreatitis experts, gathered new clinical, autopsy, radiologic, animal, cellular, and biochemical evidence in a single comprehensive study,1 and has provided a newfound hope by depleting the dragon of AP of the fuel that energizes it: unsaturated fatty acids (UFAs).

UFAs in AP are derived predominantly from adipocytes in visceral fat. For more than a century, several studies have alluded to fat as a player in pancreatitis, starting with Chari2 in 1906. More recently, epidemiological studies have implicated obesity as a risk factor for severe outcomes. It is the distinction between obesity being an initiator of the disease versus an outcome modifier that demands attention, since the majority of obese people will pass through life without ever experiencing AP. The accumulation of adipocytes enriched in UFAs within deposits of visceral fat, including those within the pancreas in obesity, become a reservoir of fuel to be ignited, and therefore an adverse AP outcome determinant.

My lab has shown that, normally, there is no communication between the cells of the pancreas, which contain digestive enzymes, and the neighboring adipocytes, which are increased in obesity. During pancreatitis, however, digestive lipases leak from the pancreatic cells into the adipocyte compartment. This causes the stored fat in adipocytes to be cleaved into fatty acids, predominantly UFAs. With high local concentrations, these UFAs kill even more of the pancreatic cells, resulting in a vicious cycle of heightened damage, both locally and to vital organs, such as the lungs and kidneys, which receive the UFAs through circulation. Lipase inhibition results in decreased damage to pancreatic cells, prevention of lung and kidney injury, reduced inflammation, and improved survival.

Interestingly, food nutrition labels in a typical grocery store will show that UFAs form 70% of our recommended daily allowance. These UFAs comprise the same proportion of stored fat in obesity. Evidence supports that stored UFAs come from our diets. Linoleic acid, for example, is an essential fatty acid that cannot be synthesized by us, so dietary intake is its sole source. Linoleic acid forms one third of the UFAs in the surgically removed pancreatic fluid from obese patients with severe AP. Therefore, it is not the saturated fats, such as those found in butter and lard, that play a role in heart attacks and strokes. Instead it is the UFAs from oils, such as corn oil, canola, olive oil, and fish oil, which are enriched in adipocytes during obesity and fuel the dragon of pancreatitis. Alas, excess of anything is bad!

My lab is now working to identify and inhibit the specific lipases involved in cleaving the stored fat of the adipocytes to UFAs. Hopefully, after having its fuel depleted, the dragon of pancreatitis and other acute non-infectious illnesses will slither away into oblivion.

References:


Future Promise Through Liver Genetics

By Alison B. Jazwinski, MD, MHS
Assistant Professor of Medicine

The field of medicine is changing at a rapid pace as technologies improve. It is now possible to study the genetic composition of patients to better understand pathways of disease development and responses to therapeutic interventions. In the past, scientists had to make an “educated guess” regarding which pathways were involved in disease and then try to study the implicated pathway by assessing the effect of manipulating genes.

Now we are able to study the genome in ways that are unbiased and non-hypothesis driven, using genome-wide association studies (GWAS). GWAS allow for the discovery of new and unexpected genetic determinants of disease development, progression, and treatment responses. Many believe that we will be practicing “personalized medicine” within the next several decades.

Personalized medicine combines a patient’s genetic information with other clinical factors to accurately determine their likelihood of acquiring a disease, developing progressive disease, and responding to a particular therapy.

Most liver diseases are considered to be complex diseases, resulting from the interface of multiple genes interacting with one another and the environment, and we are in the beginning stages of understanding the genetic contributions to these diseases. Some very exciting findings have occurred since the advent of GWAS, such as the discovery of a single nucleotide polymorphism (SNP) near the IL28B gene that is better at predicting whether a patient will respond to hepatitis C therapy than previously utilized clinical information.

Soon after this discovery, a diagnostic test was developed and is now used in clinical practice, enabling physicians to incorporate genetic information into clinical decision making. A second important discovery was the SNP in the PNPLA3 gene related to the development of fatty liver disease. This SNP also may be associated with the severity of non-alcoholic fatty liver disease and to progressive fibrosis development in patients with liver disease from heavy alcohol use and chronic hepatitis C infection.

Other SNPs seem to be related to fibrosis development in patients with chronic hepatitis C, but these polymorphisms have not been replicated yet, and we are still uncertain about how this information will enable us to provide enhanced prognostic information to our patients. Furthermore, this study of the genome often cannot determine the specific causal SNP, and studies are ongoing to determine how these polymorphisms result in their effects.

Newer genomic technology called “next generation sequencing” may allow us to assess which variant is causing an effect more accurately.

The University of Pittsburgh is poised to be a leader in this new era of medicine. We have collected DNA from a large number of patients who have sought care at UPMC’s Center for Liver Diseases, and researchers are working to characterize this genetic information and build associations with clinical outcomes. We aim to validate other investigators’ findings through our patients, discover previously unknown genetic variants, and create predictive models to incorporate genetic information.

Advancements using models can offer superior prognostic information to our patients and may determine which patients will respond to a particular intervention. To complement these liver studies, UPMC has large quantities of related patient epidemiological and basic science data associated with other chronic inflammatory and fibrotic diseases, such as chronic pancreatitis and inflammatory bowel disease. This additional data will enable us to make comparisons among diseases and determine common pathways of inflammation and fibrosis. Additionally, new internal system technologies allow for electronic collection of information directly from the patients’ medical records to quickly and accurately phenotype these patients for further study.

Will a patient’s genetic code be incorporated into future medical records? Probably so. To utilize these advancements, physicians will need to understand the meaning of specific variants and provide diagnostic and prognostic information to their patients. Our lab plans to translate this complex genetic information into clinically useful models to more accurately predict a patient’s disease course and to help make this information meaningful to front-line clinicians.

Dr. Jazwinski is an assistant professor of medicine with the University of Pittsburgh Division of Gastroenterology, Hepatology, and Nutrition. She cares for hepatology patients at the UPMC Center for Liver Diseases (CLD), and her research interests focus on liver genetics.
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By Nicholas Mahoney, MD
Gastroenterology Fellow

The differential for a liver mass in a non-cirrhotic patient is limited. None of the lesions are associated with end-stage liver disease complications, including encephalopathy. In this case, a non-cirrhotic patient with a newly diagnosed liver lesion presented with altered mental status related to metabolic encephalopathy.

Possible etiologies for hyperammonemia in a non-cirrhotic patient include Reye’s syndrome, inborn errors of urea synthesis, medication-induced injury (5-fluorouracil or valproate), and malignancies. The urea cycle involves transformation of nitrogen into urea for excretion, and disorder may be caused by a deficiency of any enzyme that leads to the buildup of excess nitrogen waste or ammonia.

An 18-year-old female with depression was transferred to UPMC from an outside hospital after presenting from home with altered mental status. The family reported that the patient was in her usual state of health until two days earlier, when she became confused and developed nausea and vomiting. No recent travel or new medications were reported.

At the outside hospital, the patient was noted to be lethargic, disoriented, and febrile. Initial workup included a negative lumbar puncture and a normal head CT. A CT of the abdomen showed a liver mass. Her labs were significant for mild leukocytosis and elevated transaminases (AST 140, ALT 158) with a normal total bilirubin (0.5). Ammonia level was elevated to 342. Monoscreen, acetaminophen level, urine tox screen, and serum alcohol level were all negative. The patient’s mental status continued to worsen, prompting intubation and transfer.

Upon arrival at UPMC, the patient was intubated and sedated, and her physical examination was benign. Review of the patient’s medical history included the use of an oral contraceptive pill. She had no history of alcohol, drug, or tobacco use. Family history was unremarkable.

CT of the chest and abdomen showed a large right hepatic lobe mass with probable right portal vein thrombosis and portocaval adenopathy (Figure 1). In addition, a left lower lobe 8mm lesion was identified in the lung, concerning for metastasis. Biopsy of the liver lesion noted polygonal large hepatocytes with eosinophilic granular cytoplasm containing pale bodies, vesicular nuclei, and prominent eosinophilic nucleoli. Those findings were consistent with a fibrolamellar variant of hepatocellular carcinoma (FLHCC).

A possible urea cycle disorder was investigated by checking serum amino acid and urine organic acid levels. A trace serum citrulline level, and, elevated urine orotic acid level (704, normal < 1.2) were consistent with an ornithine transcarbamylase (OTC) deficiency.

OTC deficiency is the most common urea cycle disorder in adults. It is an X-linked disorder, typically presenting in male infants. Females have a carrier ratio of 1:70. Female heterozygotes can have random inactivation (lyonization) of the X-chromosome leading to phenotypic variation. Through lyonization, females may present with symptoms later in childhood or adulthood.

In partial urea cycle enzyme deficiency, hyperammonemia may be chronic or may occur during metabolic decompensation associated with catabolic stress. Common symptoms include vomiting, headache, and psychiatric illness. Avoiding protein in the diet can alleviate symptoms. In severe cases, hyperammonemia can lead to cerebral edema. There is reported evidence of urea cycle disorders being complicated by hepatic dysfunction, involving elevated liver enzymes, coagulopathy and findings of glycogenosis. No current medical literature data links FLHCC with a urea cycle disorder.

Initially, the patient worsened clinically and developed posturing, raising concern for cerebral edema. She was treated with mannitol and mechanical hyperventilation to lower the intracranial pressures. The elevated ammonia and encephalopathy were treated with lactulose, rifaximin, hemodialysis, and Ammonul®. Once a diagnosis of OTC deficiency was identified, low protein TPN with additional arginine supplementation was administered, and her ammonia level and mental status improved. She subsequently underwent band embolization of the right hepatic artery followed by a right liver lobectomy and excision of the left lower lung nodule.

References:
Gallbladder Perforation with Hemoperitoneum in the Setting of Cirrhosis

By Heitham Abdul-Baki, MD
Gastroenterology Fellow

A 55-year-old man with cirrhosis secondary to NASH was admitted with progressive confusion. His disease was complicated by esophageal variceal bleeding, requiring endoscopic band ligation. His ascites was controlled with frequent therapeutic paracentesis. Chronic iron deficiency anemia was attributed to gastric vascular ectasia treated with endoscopic coagulotherapy. Despite lactulose, he had a decrease in stool frequency (one stool in two days). He denied abdominal pain and bleeding.

At the time of admission, he was afebrile and hemodynamically stable. Evaluation showed no infection, medication, or gastrointestinal bleeding to cause the worsened confusion. Physical exam revealed a distended, tense, non-tender abdomen with normal bowel sounds and a fluid wave. Asterixis also was present on exam. Analysis of the ascites showed 30 WBC and 30 RBC, and was not compatible with peritonitis. Labs were significant for a dropping hemoglobin, from 8.1 g/dL to 6.7 g/dL in three days. This was initially attributed to his history of gastric ectasia and hemodilution.

On the fifth day of hospitalization, he had an episode of hematemesis, prompting an upper gastrointestinal endoscopy. The gastric antrum contained moderate amounts of fresh blood and clots covering vascular ectasia and a suspected Dieulafoy lesion that was treated with injection and clipping. A hint of blood trailed into the duodenum through the pylorus. After intubating the duodenum and lavaging the mucosa, no identifiable source of bleeding was found (Figure 1). His hemoglobin levels dropped further to 3.9 g/dL, requiring a six-unit packed red blood cell transfusion. His small volume of melena, negative nasogastric lavage, and endoscopic findings did not correlate with the significant drop in hemoglobin, so a computed tomography (CT) scan was ordered. The CT revealed a spontaneous perforation of the gallbladder with secondary hemoperitoneum. Gallstones were seen dispersed in the abdomen (arrows in Figure 2). The arrowhead in Figure 2 points to the perforated gallbladder and hematoma. The patient underwent an emergent exploratory laparotomy and cholecystectomy. Postoperative bleeding was controlled, but the patient remained deconditioned, due to decompensated liver cirrhosis requiring frequent therapeutic abdominal paracentesis and physical rehabilitation.

Perforation is a rare complication of gallbladder disease. It is reportedly associated with calculous and acalculous cholecystitis, as well as conditions that compromise the structural or vascular integrity of the gallbladder wall, such as trauma, cancer, and iatrogenic surgical injury.1,2 Perioperative mortality of gallbladder perforation can be as high as 45%.1 Identification of the perforation by history or physical exam can be difficult, since signs and symptoms may be nonspecific. Most cases are discovered intraoperatively.1,3 The highest sensitivity reported for ultrasound detection is 70%.3 CT scanning is the most sensitive noninvasive test for gallbladder perforation.4

Niemier (1934) first classified gallbladder perforations into three types based on acuity: Type I (acute), Type II (subacute), and Type III (chronic).1 Patients with Type I or II are predominantly male and are younger than 50 with comorbid atherosclerosis, diabetes, cirrhosis, malignancy, or immunosuppression. Patients with Type III are mostly elderly, female, and have chronic gallstone or obstructive biliary disease. Antibacterial and antifungal treatments are proposed for adjuvant management of gallbladder perforation, but surgical resection and debridement are definitive treatments.4,5

References:

The Proof: CRC Screening Works

By Robert E. Schoen, MD, MPH
Professor of Medicine and Epidemiology
Principal Investigator, Colorectal portion of the National Institutes of Health PLCO Trial

The results of the colorectal portion of the randomized National Cancer Institute’s Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial were published in the New England Journal of Medicine in June 2012. This trial examined the effects of colorectal cancer (CRC) screening with flexible sigmoidoscopy on CRC incidence and mortality.

Participants in the intervention arm were offered flexible sigmoidoscopy at baseline and again after three or five years, whereas participants in the usual care arm received whatever screening they were offered within the context of their usual medical care. More than 86% of participants in the intervention group received at least one flexible sigmoidoscopy exam, attesting to the fact that subjects were willing to partake in screening.

The second screening exam also demonstrated benefit, since there was a 25% increase in detection of advanced adenomas among women and a 33% increase among male subjects who had a second sigmoidoscopy exam. About 22% of subjects went on to have a colonoscopy as a result of an abnormal sigmoidoscopy. After an average of twelve years, deaths from colorectal cancer were reduced by 26% in persons randomized to receive sigmoidoscopy screening, and there was a 21% reduction in CRC incidence in the screening group.

Flexible sigmoidoscopy screening reduced distal colorectal cancer by 29% and deaths from distal cancer by 50%. Screening was less effective in the proximal colon, reducing cancer incidence by 14%, but deaths from proximal cancer were not reduced. Why the difference? We are not sure, but proximal colorectal cancer precursors may be more challenging to detect. There is a renewed emphasis on improving adenoma detection in the proximal colon, where sessile serrated adenomas are easy to miss and may be more prone to evolve into colorectal cancer.

This trial confirms CRC screening benefits. Screening can detect colorectal cancers at an earlier stage, resulting in less advanced cancers and fewer deaths due to cancer. Through the identification and facilitation of adenomatous polyp removal, screening also can significantly reduce cancer incidence. With colorectal screening, one can actually realize the adage, “The best cancer is the one you don’t get.”

Dr. Schoen is a professor of medicine and epidemiology with the University of Pittsburgh Division of Gastroenterology, Hepatology, and Nutrition. He is the principal investigator for the colorectal portion of the National Institutes of Health PLCO Trial.

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DIVISION UPDATES

Dr. Whitcomb and Colleagues Discover New Pancreas Genetics Link

A genetic link between alcohol consumption and chronic pancreatitis in men was recently published in *Nature Genetics*, and explains why men have chronic alcoholic pancreatitis more often than women.

A region on chromosome X, called the *CLDN2* locus, seems to cause a rapid progression from acute pancreatitis to chronic pancreatitis, instead of recovery, in persons who continue to drink alcohol after an acute pancreatitis episode. About 4% of men in the United States are at risk, since these men have both the X-factor and are drinking alcohol (>4 drinks/day). Men have the XY chromosome pair, while women have XX. Women are most often protected, since they possess these two X chromosomes with at least one X chromosome usually being normal. Only 0.6% of U.S. women are at risk.

The study also demonstrated that a genetic factor on chromosome 7 decreases the expression of trypsin and reduces the risk of recurrent acute and chronic pancreatitis. For more information, please visit the *Nature Genetics* or UPMC websites.

Dr. Duerr and Colleagues Advance IBD Genetics

In a paper published in *Nature* (November 1, 2012), the NIDDK IBD Genetics Consortium, the International IBD Genetics Consortium (IBDGC), and others reported the discovery of additional genetic variants linked to Crohn’s disease and ulcerative colitis. The study included more than 75,000 cases and controls and identified 71 new associations for a total of 163 loci that meet genome-wide significance thresholds. Richard Duerr, MD, IBD Genetics Research Chair, is a member of this consortium and has provided both samples and scientific input into these efforts with the collaboration of the nine additional faculty members of the UPMC IBD Center of Excellence.

Dr. Liu Supported by Prestigious Broad Foundation

Yang Liu, PhD, has received a research grant from The Broad Foundation for Scientific & Medical Research in support of her proposal “Rectal Spectral Markers for the Surveillance of Colorectal Cancer in Patients with Ulcerative Colitis.” Dr. Liu is an assistant professor of Medicine and Bioengineering at the University of Pittsburgh School of Medicine. Her research focuses on the emerging interdisciplinary field of biomedical optical imaging and spectroscopy, which involves electrical engineering, physics, optics, medicine, and biology.

Fellowship Update

The Division of Gastroenterology, Hepatology, and Nutrition has a large and proactive GI Fellowship program with 18 gastroenterology fellows and one transplant hepatology fellow in its accredited training programs.

After building a successful program and receiving numerous program commendations, Miguel Regueiro, MD, stepped down as the GI Fellowship program director in the summer of 2012. Our division thanks Dr. Regueiro for his dedication, and welcomes Kenneth Fasanella, MD, as the new GI program director. Dr. Fasanella is a previous GI chief fellow in this program, and he serves as an upper-GI, EUS attending.

The division’s 2012 graduating class all pursued initial academic appointments. David Levinthal, MD, PhD, and John Nasr, MD, both accepted faculty positions with our division. Dr. Levinthal pursues clinical and research study in the functional bowel subspecialty. Dr. Nasr is an upper-GI specialist at UPMC McKeesport. The additional four 2012 graduates — Bridger Clarke, MD, of the University of North Carolina; Venkata Muddana, MD, of the Cleveland Clinic; Matthew Rockacy, MD, of Dartmouth-Hitchcock; and Amit Raina, MD, of the University of Pennsylvania — are participating in fourth-year advanced endoscopy training. Dr. Rockacy plans to join UPMC as a faculty attending in 2013, upon completion of his training.

The following year-one fellows joined the division’s GI fellowship training program in 2012: Shrinivas Bishu, MD; Lia Kaufman, MD; Haq Nawaz, MD; Anthony Razzak, MD; Kavitha Thudi, MD; and Matthew Warndorf, MD. Cristina Strahotin, MD, is the division’s current one-year transplant hepatology fellow.
A 21-year-old woman presented to the hospital with crampy, right upper quadrant pain. It was moderate in severity and worsened after eating fatty foods. The pain was associated with a 12-pound weight loss, nausea, and diarrhea. An ultrasound incompletely visualized the gallbladder, so a MRCP was performed.

Compare your answer to Dr. Rogal's on page 6.