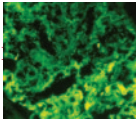




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 Division of Gastroenterology,
 Hepatology and Nutrition

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 Arnold Wald, MD
 Toby O. Graham, MD
 Daniel Chung, MD
 Joy Jenko Merusi, MA



As the fifth installment of a multi-part series, the **Pitt Quarterly Digest** features the UPMC Neurogastroenterology and Motility Center this spring. We hope you will enjoy reading about the comprehensive clinical and research innovations of this group.

NEUROGASTROENTEROLOGY AND MOTILITY CENTER

by **Arnold Wald, MD**

The UPMC Neurogastroenterology and Motility Center combines clinical expertise for the evaluation and management of a wide variety of functional gastrointestinal disorders with innovative research in visceral pain syndromes as well as disorders of gastrointestinal motility. The activities of the Center's physicians and scientists reflect the gradually evolving concept that functional GI disorders are not due solely to motility disturbances but rather are associated with altered brain-gut interactions, visceral hypersensitivity and, in some cases, disturbances of GI function mediated by mucosal immunological events. The spectrum of functional GI disorders ranges from those associated with characteristic motility patterns such as achalasia, gastroparesis and intestinal pseudo-obstruction to conditions such as irritable bowel syndrome, functional dyspepsia and functional noncardiac chest pain which are not explainable by motility disturbances but rather are characterized by a biopsychosocial model. The latter disorders are best evaluated by pathophysiologic investigations which are not restricted to motility.

The GI Motility Laboratory at UPMC continues to be an important core facility supporting



Neurogastroenterology & Motility Center Clinical Team (left to right): Klaus Bielefeldt, MD, PhD, Arnold Wald, MD, Pamela Meyer, RN, Michael Pezzone, MD, PhD and Steven Abo, MD. Missing from this photo: Belmont Cookshott.

clinical activities of the center. Under Klaus Bielefeldt, MD, PhD who succeeded me as director of the Motility Laboratory, this facility performs numerous diagnostic studies including esophageal, anorectal and gastroduodenal manometry, ambulatory esophageal pH studies using tubeless capsule technology, colon transit and breath H₂ studies. These tests are supplemented by those in other departments including gastric and gallbladder emptying (Nuclear Medicine), pelvic floor neurophysiology (Rehabilitation Medicine) and pelvic floor MRI and anal sonography (Radiology at Magee-Womens Hospital).

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Division Highlights

Significant advancements in research, education and comprehensive patient care have established the Division of Gastroenterology, Hepatology and Nutrition's Neurogastroenterology & Motility Center as one of the country's most progressive programs. The Center's translational research programs are possible because of a large and diverse patient base and the research infrastructure at the University of Pittsburgh.

In this issue, clinical advancements in GI motility are highlighted by **Dr. Arnold Wald**, while the diverse research goals and accomplishments of the neurogastroenterology group are described by **Drs. Klaus Bielefeldt** and **Michael Pezzone**. Complementing the Division's neurogastroenterology research are the postoperative ileus work of **Dr. Anthony Bauer** (Spring 2003 Pitt Quarterly *Digest*), **Dr. Kathryn Albers'** sensory neuron function research (Summer 2003 issue) and **Dr. Brian Davis'** continuing research in the pathophysiologic basis of visceral pain (Winter 2004 issue). *Previous issues of these newsletters may be found at the our Division's website: <http://gi.medicine.pitt.edu>.*

We are proud to highlight in this issue the outstanding accomplishments of two graduating fellows, **Dr. Neeraj Kaushik** and **Dr. Georgios Papachristou**. This newsletter will continue its focus on our gastroenterology fellowship program providing news of current and graduating fellows in future issues.

Please join us in Pittsburgh on July 28 & 29, 2005 for an outstanding physicians' conference, *ERCP and EUS in Pancreaticobiliary Diseases & GI Clinical Advancements from DDW*. This program will welcome some of the world's leading pancreas specialists and will provide optional entertainment options for spouses and families. For program details and registration information, please contact Chantel Snodgrass at (412) 647-8232.



In good health,

David C. Whitcomb, MD, PhD
*Professor of Medicine, Cell Biology & Physiology and Human Genetics
Chief, Division of Gastroenterology, Hepatology and Nutrition*

GRADUATING FELLOWS



► Neeraj Kaushik, MD

Neeraj Kaushik, MD, graduated at the top of his medical school class at the University of Delhi in India. After completing his internal medicine residency at SUNY-Downstate Medical Center in Brooklyn, Dr. Kaushik worked as an internist and medical director at a

community health center in Uniontown, PA. Since beginning his University of Pittsburgh gastroenterology fellowship in 2002, he has published several peer-reviewed papers and has enjoyed teaching medical students and internal medicine residents. Dr. Kaushik began his two-year tenure as Chief GI Fellow in July 2003.

Dr. Kaushik's clinical interests focus on advanced endoscopy, including endoscopic ultrasound (EUS), pancreatic pathophysiology and clinical applications of EUS. Under the supervision of Dr. Stephen O'Keefe, he has been co-investigator for clinical studies of healthy human subjects and patients with acute pancreatitis. These studies investigated pancreatic enzyme synthesis and secretion in response to enteral and parenteral feeding. Preliminary results have been presented at prestigious national and local meetings, and Dr. Kaushik was also awarded the 2004 UPMC Department of Medicine Research Day Award for this work. Additional studies with Dr. O'Keefe have examined endocrine regulation of the exocrine pancreas in response to different types of enteral feeding, and these findings will be presented at the upcoming May 2005 Digestive Disease Week (DDW). Dr. Kaushik was awarded a \$15,000 pilot/feasibility grant by the UPMC Obesity and Nutrition Research Center (ONRC) for his related research project, *Enteral Feeding and Pancreatic Rest*.

The staging of esophageal cancer staging using EUS and laparoscopic methods is another research interest for Dr. Kaushik. He presented this work at the 2004 DDW meeting and will present the results of EUS-guided paracentesis yield for the diagnosis of malignant ascites at DDW 2005. This research has also been accepted for presentation at the ASGE Young Investigators Conference this spring. He is currently training in EUS and advanced endoscopy under the supervision of Dr. Kevin McGrath.

Upon completion of his fellowship in June 2005, Dr. Kaushik will join the faculty of the University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition and will pursue clinical EUS work and research related to EUS and pancreatic pathophysiology.

continued on page four

A Case of Abdominal Pain and Rash

by Allen Banegura, MD

Fellow, Division of Gastroenterology, Hepatology and Nutrition

Case Presentation

A 23-year-old male presented with a one-week history of severe diffuse abdominal pain and hematochezia. He later admitted to recent intranasal cocaine and methamphetamine use but denied fevers, chills, weight loss, diarrhea, hematuria or prior history of inflammatory bowel disease (IBD).

The patient was in distress, afebrile with moderate tachycardia; abdominal exam revealed diffuse tenderness and hypoactive bowel sounds, but no rebound or guarding. He had bilateral joint swelling involving wrists, elbows and ankles and a petechial rash on all extremities. Rectal examination showed maroon stool. Pertinent laboratory evaluation revealed a white cell count of 17,000 /cu mm (nl 3,800-10,600/cu mm), normal differential and hemoglobin of 16.6 g/dL (nl 12.9-16.9 g/dL). Liver enzymes, electrolytes, amylase and lipase were normal. A urinalysis revealed mild hematuria but no proteinuria. Urine drug screen was positive for amphetamines. An abdominal CT scan (*Figure 1*) demonstrated circumferential thickening of distal duodenum, proximal jejunum and a long segment of terminal ileum.



Figure 1 Circumferential small bowel wall thickening

What is the differential diagnosis?

In this patient with acute abdominal pain, migratory arthritis, rash, small bowel wall thickening and recent drug abuse the differential diagnosis includes vasculitis (e.g. Henoch-Schönlein purpura, drug-induced vasculitis, infection-induced immune complex vasculitis or cryoglobulinemia), acute ischemia secondary to cocaine and/or methamphetamine use, and IBD.

Evaluation and Management

ANA, rheumatoid factor and cryoglobulins were negative, and serum complement levels and sedimentation rate were normal. Enteroscopy and colonoscopy revealed patchy ulcerations in the distal duodenum and cobblestoning in the terminal ileum. Biopsies revealed acute focal ischemia with preserved architecture. Skin biopsy was non-diagnostic. The patient was treated with intravenous corticosteroid, and, within three days, his abdominal pain, rash, arthritis and hematochezia began to resolve.

On hospital day eleven the patient developed hypertension, acute renal failure, hematuria and nephrotic syndrome. A renal biopsy revealed IgA-predominant mesangial proliferation and exudative glomerulonephritis, without crescent formation consistent with Henoch-Schönlein purpura (HSP), findings confirmed by immunofluorescence microscopy (*Figure 2*).

Discussion

HSP is a systemic vasculitis characterized by deposition of IgA predominant immune complexes in small vessels. Typically occurring in children between ages 3 and 15 years, HSP in adults may have a more severe clinical course and higher frequency of renal involvement. The classic tetrad of rash, arthralgias, abdominal pain and renal disease is often preceded by an upper respiratory infection. Other gastrointestinal symptoms include nausea, vomiting, diarrhea, constipation and, in 25 to 50 percent of cases, self-limited bleeding. The most common GI complications include intussusception (14%), acute appendicitis (7%), massive hemorrhage (5%), and, less commonly, ulcerations, cholecystitis, acute pancreatitis, bowel ischemia and perforation.

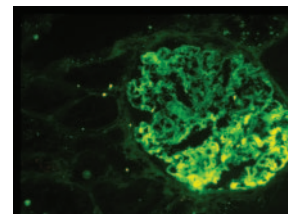


Figure 2 IgA-predominant mesangial deposits on immunofluorescence microscopy

Renal involvement is common in HSP, with 30 to 70 percent of patients having clinically overt symptoms. Whereas most patients have mild disease characterized by asymptomatic hematuria, proteinuria and slight elevation of serum creatinine, some develop severe renal involvement. Studies have demonstrated a correlation between the clinical course and the percentage of glomeruli with crescent formation. When more than 50 percent of the glomeruli have crescents, patients are likely to develop chronic kidney disease.

The prognosis overall is good. One study demonstrated complete recovery in 94 percent of children and 89 percent of adults. Corticosteroids enhance resolution of the arthritis, abdominal pain and bleeding, and patients with severe disease (i.e., crescent nephritis) may benefit from pulse dose steroids, immunosuppressive drugs and plasmapheresis.

Our patient responded initially to corticosteroids with improved renal function, but he presented three weeks later with renal failure requiring hemodialysis.

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GRADUATING FELLOWS *continued from page two*



► **Georgios Papachristou, MD**

Georgios Papachristou, MD attended medical school in Patras, Greece where he graduated first in his class. After completing his internal medicine training at Albany Medical Center in New York and serving as the chief resident during his senior year, he

joined the University of Pittsburgh's gastroenterology fellowship program in the summer of 2002. His clinical interests focus on advanced endoscopy, and his research interests on pancreatic diseases. Dr. Papachristou is enrolled in the Clinical Research Training Program (CRTP) at the University of Pittsburgh, which will result in a Masters of Science degree. CRTP provides young investigators with formal training to design and perform clinical trials.

The Severity of Acute Pancreatitis Study (SAPS-1) was initiated at the University of Pittsburgh in the summer of 2003 and is managed primarily by Dr. Papachristou under the direction of David Whitcomb, MD, PhD and Adam Slivka, MD, PhD. SAPS-1 is a pilot study, which seeks to understand the genetic and immunologic basis of severe acute pancreatitis. Thus far, more than 100 patients have been enrolled and studies and preliminary results have been presented at several national meetings.

The concept of using serum proteomic patterns to predict severity in acute pancreatitis was introduced by Dr. Papachristou and colleagues, who later presented this work in 2004 at the American Cancer Association's Annual Meeting and Digestive Disease Week. Dr. Papachristou and colleagues also presented work demonstrating a novel association between a polymorphism in the monocyte chemotactic protein (MCP-1) and severity in acute pancreatitis. Dr. Papachristou has co-authored multiple review articles on these subjects. Using key advances in genetics and immunology, Dr. Papachristou and his colleagues aim to achieve a better understanding of pancreatic diseases and to initiate clinical trials with disease-specific therapeutic agents in the near future.

This summer, Dr. Papachristou will travel to the Mayo Clinic in Rochester, MN for a one-year advanced fellowship in endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS). His future plans include an academic career in advanced endoscopy combined with translational research in pancreatic diseases.

MARK YOUR CALENDAR:

Thursday, July 28 and Friday, July 29, 2005



ERCP and EUS in Pancreaticobiliary Diseases and GI Clinical Advances from Digestive Disease Week

For more information contact:

CCEHS@upmc.edu or (412) 647-8232

Images and explanation provided by Niraj Jani, MD, Fellow, Division of Gastroenterology, Hepatology and Nutrition.

neonates and in adults in the 40 to 50 age range. In neonates, it can cause an incomplete obstruction and may be associated with other congenital diseases such as trisomy 21, duodenal atresia and TE fistula. In adults, patients may present with upper abdominal pain, nausea, vomiting, duodenal stenosis, peptic ulceration, or chronic pancreatitis. The characteristic findings on abdominal X-Ray include a double-bubble sign or small amount of gas distal to the high-grade stenosis. Surgical bypass is indicated if patients are symptomatic secondary to gastric or duodenal outlet obstruction.

Annular pancreas represents a band of normal pancreatic tissue that encircles the second portion of the duodenum (Figure 1, on page 6). The incidence is 1:20,000 with a bimodal presentation, occurring in neonates and in adults in the 40 to 50 age range. In neonates, it can cause an incomplete obstruction and may be associated with other congenital diseases such as trisomy 21, duodenal atresia and TE fistula. In adults, patients may present with upper abdominal pain, nausea, vomiting, duodenal stenosis, peptic ulceration, or chronic pancreatitis. The characteristic findings on abdominal X-Ray include a double-bubble sign or small amount of gas distal to the high-grade stenosis. Surgical bypass is indicated if patients are symptomatic secondary to gastric or duodenal outlet obstruction.

Answer to What Is This photo on page six:

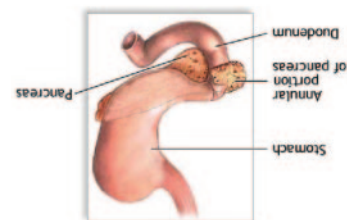


Figure 2. Pancreatic tissue encircling the second portion of the duodenum.



Cross-Sensitization of Pelvic Viscera: Implications for the Overlap of Chronic Pelvic Pain Disorders

by Michael A. Pezzone, MD, PhD

Irritable bowel syndrome (IBS) and interstitial cystitis (IC) are two common forms of chronic pelvic pain (CPP), defined as lower abdominal pain of at least six months duration and not associated with pregnancy, menses or sexual intercourse. CPP has a prevalence of 15 percent and primarily affects women of reproductive age, although a male counterpart, chronic prostatitis, is becoming increasingly recognized.

IBS, characterized by chronic or recurrent lower abdominal pain or discomfort associated with altered stool consistency and frequency, is the most common gastrointestinal cause of CPP, affecting 50 percent of such women presenting to gynecologic clinics. IC or painful bladder syndrome, a CPP disorder that almost exclusively afflicts women, is characterized by unpleasant urinary symptoms such as urinary frequency, urgency, nocturia and, most notably, pain related to bladder filling in the absence of active infection or organic disease. As many as 40 to 60 percent of patients diagnosed with IBS also exhibit symptoms and fulfill diagnostic criteria for IC. Correspondingly, 38 percent of patients diagnosed with IC also have symptoms and fulfill diagnostic criteria for IBS. Although the etiologies of both IBS and IC have been studied extensively, a common underlying mechanism responsible for the development and the overlap of these and other causes of CPP remain unidentified.

I have received NIH funding to study these bowel-bladder interactions. Members of my research team, Elena E. Eustino-Gutkin, PhD, and Ruomei Liang, MD, are studying neurogenic pathways mediating cross-sensitization of the urinary bladder and distal colorectum in animal models. We have found that acute urinary bladder irritation leads to increased sensitivity to colonic distension. Likewise, acute and chronic colonic irritation leads to acute and chronic bladder sensitivity. Through shared sensory nerves or afferent reflexes, cross-sensitization of the pelvic viscera may occur. Chronic organ irritation can lead to long-term changes in sensory and motor function of the other pelvic organs. Ongoing studies are attempting to elucidate these pathways in greater detail and may shed more light on CPP disorders.

Dr. Pezzone is an assistant professor of medicine and pharmacology with the Division of Gastroenterology, Hepatology and Nutrition at the University of Pittsburgh.



Neurogastroenterology & Motility Center Research Team (left to right): Kathryn Albers, PhD, Klaus Bielefeldt, MD, PhD, Brian Davis, PhD, Michael Pezzone, MD, PhD and Derek Molliver, PhD. Missing from this photo: Anthony Bauer, PhD.

Peripheral Mechanisms of Visceral Pain

by Klaus Bielefeldt, MD, PhD

A 35-year-old woman complains of epigastric pain associated with food intake and occasional episodes of nausea. Her symptoms started with a brief flu-like illness about ten months ago and have persisted despite various therapies and an extensive diagnostic evaluation.

This case exemplifies a common clinical problem. Nearly half of all patients with chronic abdominal pain demonstrate no structural or biochemical abnormalities. Many patients recall a new onset of abdominal pain and associated problems after an acute GI infection. This important finding provides the context for many interesting investigations. Why and how does the physiologically important experience of pain become a disorder itself?

Can GI inflammation affect visceral sensory nerves? Using animal models of gastritis and peptic ulcer disease, my lab has demonstrated significant changes in nerves innervating the stomach. While normally silent, these nerves spontaneously send signals (i.e. generate action potentials) and are more readily excited by a variety of different stimuli in the presence of inflammation. Is this also true for humans? Recent results obtained in collaboration with gastroenterology research fellow, Yasser Bhat, MD, show increased nerve fiber density in patients with non-cardiac chest pain.

continued on page six

Center physicians have regionally and nationally recognized expertise in disorders of colonic and anorectal function such as severe constipation, fecal incontinence, chronic proctalgia syndromes, esophageal motility disorders, gastroparesis and intestinal motility disorders. The Center also serves as a tertiary referral center for patients with refractory irritable bowel syndrome, chronic visceral pain syndromes and chronic intestinal failure. Center physicians are located currently at UPMC Presbyterian and Magee-Womens Hospitals. To consult with a physician or to schedule patients, call the UPMC Digestive Disorders Center, toll-free, at 1-866-4GASTRO (1-866-442-7876).

Dr. Wald is a professor of medicine with the University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition, where he also directs the Division's Gastroenterology Fellowship Program and is a Pitt Quarterly Digest editor.



Several reports have suggested the importance of childhood abuse in the pathogenesis of functional bowel diseases. Brian Davis, PhD is studying the unique nature of the nervous system during this early period of life. His experiments with Julie Christianson, PhD show that colitis in early postnatal life triggers increased responses to graded colorectal distension in experimental animals. Associated changes in the expression of ion channels and other molecules point to an important role of peripheral nerves in the development of visceral hyperalgesia.

If peripheral nerves are important in visceral pain, can we develop drugs that will selectively target them? Selectivity will be critical, as visceral nerves share many properties with other excitable cells, such as brain and myocardial cells. Studies by members of the UPMC neurogastroenterology group and others have clearly shown that visceral sensory neurons have unique properties, meaning that they may express unique molecules that could function as drug targets. Derek Molliver, PhD, Sacha Malin, PhD and Dr. Davis have shown that by turning on or off a seemingly harmless signaling protein on the membrane of nerve cells, sensory neurons are affected to a degree normally seen with opioids. While it will take many more steps to move these findings from the bench to the bedside, these and the other projects will hopefully provide us with novel future treatment strategies for chronic visceral pain.

Dr. Bielefeldt is an associate professor of medicine with the University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition.

What Is This?

A 57-year-old white female with history of breast and ovarian cancer was referred for an abdominal CT scan. She complained of occasional fullness, distension and abdominal pain. She denied having nausea, vomiting, early satiety, fever, or change in her bowel habits. The CT scan at right was obtained (*Figure 1*). Compare your answer to Dr. Jani's answer on page four.

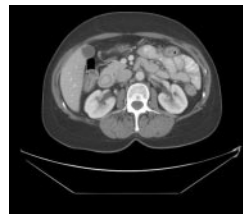


Figure 1 CT image depicting rounded area of soft tissue infiltration in the omentum adjacent to the left lobe of the liver representing area of omental infarction.

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