Pitt Digest

Spring 2007

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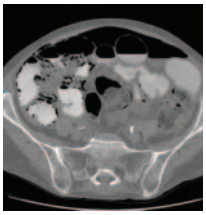

What Is This?

Centers of Excellence:

- Pancreas & Biliary Diseases
- Inflammatory Bowel Disease
- Liver Diseases
- Neurogastroenterology and Motility Diseases
- Intestinal Health & Nutrition Support
- Gastrointestinal Cancer Prevention & Treatment
- Women's Digestive Health

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

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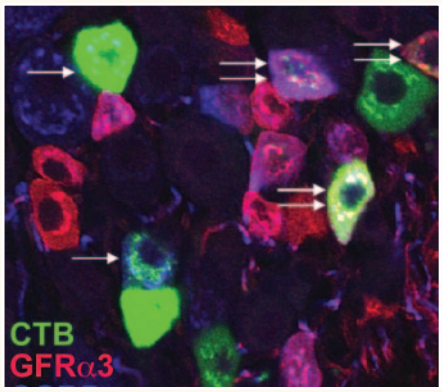
New at Pitt: **Pittsburgh Center for Pain Research**

by Gerald F. Gebhart, PhD

Newly formed in 2006, the Pittsburgh Center for Pain Research (PCPR) is a novel collaboration of pain investigators from the University of Pittsburgh's Departments of Anesthesiology and Neurobiology and the Division of Gastroenterology, Hepatology and Nutrition.

My recruitment to Pitt in May 2006 was a natural fit, as core researchers in the Division of Gastroenterology, Hepatology and Nutrition enjoyed established research programs in visceral pain and motility. My lab addresses mechanisms of visceral hypersensitivity, focusing on sensory neuron contributions to altered sensations (i.e., discomfort and pain) associated with functional gastroenterology disorders. We have developed models of gastric and colon hypersensitivity which have allowed us to examine how these organ insults affect the function of the nerves innervating these organs.

My lab's study of visceral sensory neurons is complemented by other Center investigators. Inside this issue are updates on the research of my successful colleagues: Drs. Albers, Bauer, Bielefeldt, Davis, Gold, Molliver and Pezzone. Other PCPR faculty include William Lariviere, PhD with the University of Pittsburgh Department of Anesthesiology, Richard Koerber, PhD with Neurobiology and Mitchell Max, MD, soon to join the Department of Anesthesiology with a joint appointment in GI. Dr. Lariviere's research focuses on the genetic bases of pain; Dr. Koerber's interests include cutaneous nociceptors and spinal regeneration; and Dr. Max's research addresses human genomic correlations with pain states, such as pancreatitis, irritable bowel syndrome and post-surgical pain.



Colon cell staining *(see arrows)* reveals sensitivity to inflammatory neurotrophic factor

While our principal PCPR faculty are basic researchers, translational studies focused on improving our understanding of pain mechanisms and management of clinical pain remain the impetus behind Center projects. In fact, the recent recruitment of Dr. Max, a prominent clinical investigator, will add vital clinical research components to the Center's portfolio. A major PCPR objective is to provide basic and clinical research opportunities for clinical fellows interested in pursuing academic careers.

PCPR faculty have been busy already. Our group has organized a graduate course entitled *Mechanisms and Clinical Presentation of Pain*, a monthly program of external speakers and a journal club. Additionally, bi-weekly 'work-in-progress' sessions are presented by graduate students and post-doctoral fellows working in faculty labs. To complement and expand the skills and research interests of the Center, the PCPR is actively recruiting new research faculty.

Dr. Gebhart is a Professor of Anesthesiology, Neurobiology, Pharmacology and Medicine with the University of Pittsburgh and directs the Pittsburgh Center for Pain Research.

The VIP is here! Our Division's *Visceral Inflammation and Pain* (VIP) group, that is.

More than 2.1 million people in the U.S. suffer from recurrent acute or chronic abdominal pain. With few effective treatments available, visceral pain and functional disorders of the digestive system account for 119,000 hospitalizations, 2.2 million prescriptions and 46,000 patients on disability per year. Physicians struggle to identify a cause for their patients' pain. The reasons for extreme variations in pain generation, perception and tolerance are poorly understood. How can we solve this highly complex problem of visceral pain? How can we identify new and specific targets for effective treatment?

The solution is *translational research*, the interactive bed-to-bench, bench-to-bedside process, through which basic science and clinic-based researchers collaborate. Ranked 7th nationally in 2005 NIH funding with $431 million in biomedical research spending, the University of Pittsburgh Medical Center (UPMC) is a comprehensive network comprised of 19 hospitals serving a 29-county tri-state area having more than 4,000 licensed beds, 165,000 inpatient admissions, three million outpatient visits, 115,000 surgeries, and one million home care visits. The University and UPMC provide both the solid research base and large patient populations necessary to conduct translational research studies.

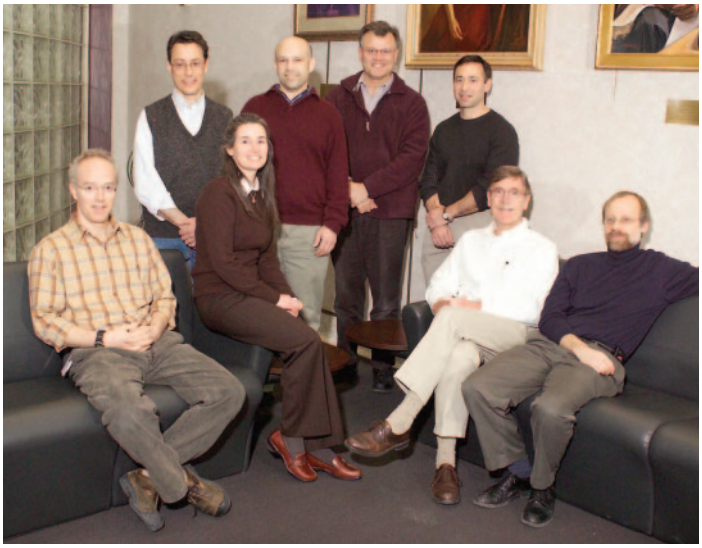
The Division of Gastroenterology, Hepatology and Nutrition has risen once again to this challenge with its continued expansion and recruitment of basic science and clinical researchers focused on Visceral Inflammation and Pain (VIP). In this issue, we feature Dr. Gebhart (cover story) and our own basic science faculty who, in collaboration with clinical and basic science researchers from the Departments of Anesthesiology and Neurobiology, have launched the Pittsburgh Center for Pain Research.

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

Pitt GI Pain Research: Brain-Gut Connections and the Study of Pain



Gastroenterology Researchers with the Pittsburgh Center for Pain Research: (left to right) Michael Gold, PhD, Brian Davis, PhD, Kathryn Albers, PhD, Derek Molliver, PhD, Anthony Bauer, PhD, Michael Pezzone, MD, PhD, Gerald Gebhart, PhD and Klaus Bielefeldt, MD, PhD.

Our program is proud to feature the ground-breaking work of the following internationally recognized GI researchers. For more information about these Division of Gastroenterology, Hepatology and Nutrition faculty members and their visceral pain research, visit ***http://www.dom.pitt.edu/gi***

Anthony J. Bauer, PhD
Professor of Medicine

Postoperative ileus is a common and almost obligatory sequel to abdominal surgery and is accompanied by a significant increase in morbidity and substantial hospitalization costs, estimated at more than one billion dollars per year in the U.S. Neurogenic activity, medications (narcotics) and local enteric inflammation, as identified by my laboratory, cause postoperative ileus.

In the acute postoperative period, spinal and supra-spinal adrenergic and non-adrenergic pathways are activated. Prior studies, performed within hours after surgery, identified neuronal mechanisms as playing a significant role. These studies focused on proximal bowel motility and defined the duration of ileus dependent on the return of colonic motility. Since postoperative ileus can last several days, we hypothesized that there were other contributing factors.

Research from my lab has shown that the prolonged phase of postoperative ileus is caused by an enteric molecular inflammatory response. Leukocytes are recruited into the muscularis of the intestinal segments manipulated during surgery. This inflammatory response impairs gastrointestinal transit, decreases local neuromuscular function and activates neurogenic inhibitory pathways which suppress motility along the entire gastrointestinal tract.

Currently, we are investigating the mechanisms which trigger this inflammatory response within the muscularis of the intestinal wall and seek to understand the endogenous anti-inflammatory pathways which return the inflamed postoperative intestine to its control state.

Kathryn M. Albers, PhD
Associate Professor of Medicine

The expression of **neurotrophic growth factor proteins** is essential for the development and function of sensory neurons that innervate the skin, muscle and visceral organs. These proteins can change the chemical and physiologic properties of sensory neurons and can increase their sensitivity to thermal and mechanical stimuli. Such changes can lead to a persistent pain state that is accompanied by altered expressions of growth factor receptor proteins, neurotransmitters and ion channel proteins.

My lab is using cell culture models and genetically modified lines of mice which either over-express these growth factors or lack them to determine how this sensitization process develops. Young and aged animals are also being studied to determine how aging affects growth factor expression and behavioral sensitivity to noxious thermal and mechanical stimuli.

We are interested as well in transcriptional regulator proteins that are expressed in sensory neurons and how the expression of these proteins changes following neuropathic or inflammation associated injury. Nerve injury and inflammatory changes are associated with changes in gene expression which are thought to underlie the development and maintenance of a state of sensitization. By understanding how changes in gene expression are regulated, we hope to improve our understanding of injury- and pain-related changes in gene expression and identify new approaches for effective treatment.

Klaus Bielefeldt, MD, PhD
Associate Professor of Medicine

Functional disorders of the gastrointestinal tract are very common, leading to more than 12 million clinic visits in the United States each year. I direct the neurogastroenterology clinic at UPMC Presbyterian Hospital, which focuses on a challenging group of patients with **motility disorders**. My academic interests are extensions of my medical practice, and my research focuses on the complex mechanisms regulating normal neuromuscular function in the gut. We are seeking to understand how acid is sensed in the esophagus and stomach, a relevant question for the many individuals affected by heartburn and non-cardiac chest pain. In addition, my laboratory and clinic are pursuing studies on the pathogenesis and treatment of chronic intestinal pseudoobstruction affecting individuals with systemic sclerosis.

Brian M. Davis, PhD
Associate Professor of Medicine

The number one reason for doctor visits in the U.S. is ongoing visceral pain in the thorax, abdomen and pelvis. These pain sensations originate in the organ and are carried to the central nervous system via sensory neurons whose cell bodies are located in clusters called spinal or dorsal root ganglia. Sensory ganglia are located at each vertebral level along the entire length of the vertebral column, and each organ is innervated by sensory neurons located at specific vertebral levels. **Sensory neurons innervating thoracic, abdominal and pelvic organs** are heterogeneous with respect to the type of sensation they detect, their anatomical properties and their role in generating pain signals. Pain sensations that are transmitted by these cells are typically initiated by a pathological process. We need to be able to perceive pain to alert us to potentially damaging processes which might be occurring in our bodies. However, once the threat to proper function is detected, pain becomes a counterproductive sensation. In many cases, the pain persists even after the underlying cause has been resolved. This type of pathological pain is often due to changes in the sensory neurons themselves. Such pathological changes are thought to contribute to chronic pain associated with IBS, pancreatitis, GERD and visceral cancers. In addition to producing debilitating pain sensations, hyperactive sensory neurons can release bioactive peptides which further exacerbate disease. Recent studies suggest that dysfunctional sensory neurons may be underlying causes of Type I diabetes and pancreatitis.

The experiments in my laboratory are designed to understand the functions of visceral sensory neurons and how changes in these cells contribute to common gastrointestinal disorders. For example, we have recently discovered that neonatal mice exposed to brief, mild colonic stimulation exhibit symptoms similar to those seen in patients with IBS. We are now using this model to determine how the sensory nervous system is altered in these mice. If we can identify these changes, new therapies may be developed to counteract these perturbations and allow the colon to regain normal function. In separate studies, we have characterized sensory neurons which project to the

pancreas selectively and have unique properties which allow us to selectively destroy them without affecting other sensory neurons. This could be a potentially helpful procedure for patients with intractable pain associated with pancreatitis or pancreatic cancer, and this type of selective ablation could also be used in patients with developing Type I diabetes to halt disease progression.

Derek C. Molliver, PhD
Assistant Professor of Medicine

My lab's research focuses on signaling mechanisms that enhance the function of **pain-sensing neurons in response to injury or inflammation.** Activation of these mechanisms results in persistent painful hypersensitivity in a wide range of pathological conditions. Recently, we learned that members of a little-studied family of receptor proteins which are activated by nucleotides (referred to as P2Y receptors) are expressed by pain-sensing neurons and appear to play a key role in the development of persistent pain. In contrast, other members of this receptor family may actually have endogenous analgesic actions. Our current studies examine the contribution of these receptors to the pain of pancreatitis.

Michael S. Gold, PhD
Assistant Professor of Medicine

A number of pain syndromes such as migraine, temporomandibular joint disorder and irritable bowel syndrome are characterized by pain which is restricted largely to a single body structure or organ. The unique distribution of these syndromes suggests that it may be possible, even necessary, to treat pain associated with these structures by selectively blocking activity in nociceptive afferents which innervate them.

Much of the effort in my laboratory is dedicated to the identification of molecules associated with injury-induced increases in afferent excitability and the validation of these molecules as potential therapeutic targets. Many of these **pain syndromes** manifest in women with a higher prevalence, severity and duration than in men. This gender difference often emerges during adolescence and resolves in older adulthood. Such observations raise the possibility that gonadal hormones contribute to the sex difference in the manifestation of a number of pain syndromes. A second research focus in my lab is dedicated to the identification of mechanisms in the peripheral nervous system underlying the manifestation of sex differences in pain syndromes. The primary methods of analysis involve the physiological characterization of proteins isolated from tissue obtained from animal models of various pain syndromes.

Michael A. Pezzone, MD, PhD
Assistant Professor of Medicine and Pharmacology

Chronic pelvic pain (CPP) disorders affect 15 percent of both men and women and include well-known disorders such as irritable bowel syndrome (IBS) and interstitial cystitis/painful bladder syndrome (IC/PBS). Because pelvic organ functions such as those of the distal colorectum and lower urinary tract are interrelated, pelvic organs and structures require an integrated neural control mechanism to permit cross-organ communication or "cross talk."

While these pathways are important for carrying out normal pelvic physiologic function, my lab proposes that "cross sensitization" can develop, through which acute or chronic irritation of one pelvic organ can lead to abnormal activity, sensitivity or even neurogenic inflammation in another. We are currently looking at the role of afferent-immune interactions for such diseases as IBS and IC/PBS. We were one of the first groups to describe an animal model of pelvic organ cross-sensitization, showing that acute cystitis lowered colorectal sensory thresholds to distension and that acute colonic irritation leads to irritative micturition patterns. Follow up studies showed evidence of direct afferent sensitization both acutely and subacutely. Chronic effects were noted, and a role for mast cell-afferent nerve interactions was hypothesized. As we learn more about the pathogenesis of these disorders including their overlap and the role of neurogenic mechanisms, we may be able to treat these disorders more effectively.

Answer to ***What Is This*** *photo on page six:*

The CT scan demonstrates free intraperitoneal air, as well as multiple, loculated, gas-filled cysts within the wall of the small bowel and colon, consistent with pneumatosis cystoides intestinalis (PCI). PCI has been linked to multiple connective tissue disorders (CTD), but systemic sclerosis, or scleroderma, is the most commonly-associated CTD. Though the mechanism is unclear, it is theorized that bacterial overgrowth leads to altered mucosal integrity, allowing gas-forming organisms to form hydrogen-dense pockets in cysts within the intestinal wall. Patients may present with or without abdominal pain, bloody stools or pneumoperitoneum without peritonitis. The small bowel, especially the ileum, is involved more often than the colon. Conservative therapy, consisting of bowel decompression via nasogastric suction, bowel rest, antibiotics, high-flow oxygen and even hyperbaric oxygen is often successful. Our patient was treated with rifaximin, bowel rest with TPN and octreotide injections. She is currently transitioning to an oral, residue-restricted diet with liquid nutritional supplements. References available upon request.

A Paradigm Shift in the Making

by Carmen B. Meier, MD
Gastroenterology Fellow

Case Presentation

A 59-year-old woman without family history of colorectal cancer (CRC) presented for her first screening colonoscopy. The patient had no complaints, and a physical exam did not reveal abnormalities. At colonoscopy, a diminutive polyp in the sigmoid colon and several flat polyps at the splenic flexure were found. Thickened folds were noted in the transverse colon, and biopsies were taken from each area. The biopsies were read as sessile serrated adenomas (SSA) *(see Figure 2)*.

Discussion: Rapid accumulation of epithelial cells within the limited crypt surface area causes cells to pile up and internally enfold, histologically appearing "serrated." SSAs are often defined as polyps demonstrating features of both hyperplastic and adenomatous transformation.

The actual prevalence of SSAs is difficult to estimate, since they may be missed given their typical flat morphology and pale appearance *(see Figure 1)*. Retrospective reviews have estimated that this lesion represents about two percent of all polyps removed at colonoscopy. In a recent prospective study of 190 patients with either warning symptoms or a personal or family history of colon cancer, magnifying chromoendoscopy found a nine percent prevalence of SSAs.

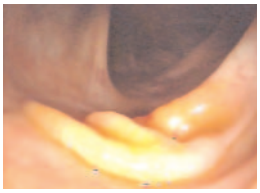


Figure 1 – Serrated adenoma.

The SSA lesion is a relatively new and poorly studied entity, partially due to disagreements in the literature about exact nomenclature. Currently, most pathologists describe two different serrated polyps. The **traditional serrated adenoma** has cytological dysplasia, while the **sessile serrated adenoma** does not have dysplasia. Thirty-seven percent of serrated colonic polyps show dysplasia, while ten percent show intramucosal carcinoma.

The risk of transformation of SSAs to colon cancer may be significant. The SSA has particular importance for the DNA microsatellite-instabile (MSI) subtype of CRC, which represents about 15 percent of all sporadic CRC. For example, one retrospective review of MSI colon cancers showed the presence of SSAs at the same site as the neoplasms on earlier colonoscopy. Other researchers analyzed polyps found in colectomy specimens containing either microsatellite-stable or instable carcinomas and noted marked predominance of what would now be classified as SSA in the MSI group. Furthermore, SSAs and MSI colorectal cancers show similar molecular characteristics, such as *BRAF* oncogene mutations. These mutations are found in up to 75 percent of MSI colon cancers, up to 82 percent of SSAs, but in only two to 12 percent of microsatellite-stable colorectal carcinomas.

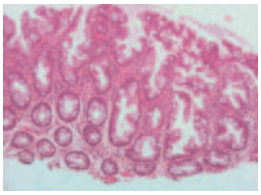


Figure 2 – Sessile serrated adenoma (SSA).

Unfortunately, there is minimal clinical data concerning subsequent risk of developing CRC after having an SSA. One study addressing outcomes after excision of colonic polyps suggested that subsequent CRC risk is about the same as for conventional adenomas. Yet unpublished, retrospective data recently presented at the ACG Annual Scientific Meeting and Postgraduate Course suggested that patients with SSAs have a significantly higher risk of developing successive adenomatous polyps than a control group.

No universal guidelines for SSA management exist, but complete resection accompanied by surveillance (i.e., at least as frequently as for adenomatous polyps) remain prudent treatment options.

Selected References:

Snover DC, et al. Serrated Polyps of the Large Intestine: A Morphological and Molecular Review of an Evolving Concept. *Am J Clin Pathol* 2005;124:380-391.
Cunningham KS, et al. Serrated Mucosal Lesions of the Colorectum. *Curr Opin Gastroenterol* 2006;22:48-53.
Goldstein NS. Serrated Pathways and APC (Conventional)-Type Colorectal Polyps. *Am J Clin Pathol* 2006;125:146-153.
Glazer E, et al. Serrated Adenoma is a Risk Factor for Subsequent Adenomatous Polyps. *Abstract at 2006 ACG Meeting*.
Spring KJ, et al. High Prevalence of Sessile Serrated Adenomas with BRAF Mutations: A Prospective Study of Patients Undergoing Colonoscopy. *Gastroenterology* 2006;131:1400-1407.

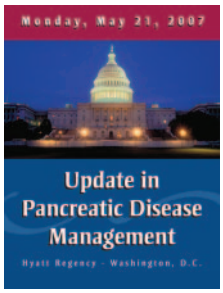
Cutting Edge Research at DDW 2007

To learn more about serrated polyps, plan to attend the following program at the AGA Digestive Disease Week meetings in Washington, DC, this spring:

Rodger C. Haggitt Gastrointestinal Pathology Society presents:
ON THE SERRATED EDGE OF POLYPS, an AGA Institute Clinical Symposium
Chair: Alyssa Krasinskas, Department of Pathology, University of Pittsburgh
Sunday - May 20, 2007 • 4:00 to 5:30 pm
Room 209, Washington Convention Center
Washington, DC

Physician Education Opportunities

To register or learn more about these courses, visit **http://ccehs.upmc.edu**. Hope to see you there.



Update in Pancreatic Diseases*
Monday – May 21, 2007
Hyatt Regency Washington
Washington, DC
University of Pittsburgh Course Director:
David C. Whitcomb, MD, PhD

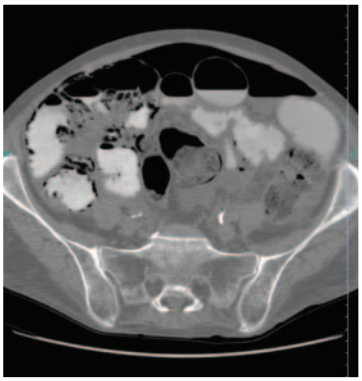
*This program is not affiliated with Digestive Disease Week.

From End-Stage Liver Disease to Liver Transplantation: State of the Art Summit
June 1 & 2, 2007
Sheraton Station Square Hotel, Pittsburgh, PA
University of Pittsburgh Course Directors:
Michael E. de Vera, MD, FACS
Kapil B. Chopra, MD, FACP

Management of Female-Predominant GI Diseases
November 15 & 16, 2007
The Duquesne Club, Pittsburgh, PA
University of Pittsburgh Course Directors:
Janet R. Harrison, MD
Kapil B. Chopra, MD, FACP
David C. Whitcomb, MD, PhD

What Is This?

Presentation: A 63-year-old woman with a history of limited scleroderma presents to the emergency room with a three-week history of progressive periumbilical abdominal pain. It was worse after meals and had a cramping, aching quality. Recently, her pain worsened and was associated with nausea. Her bowel habits changed from her usual diarrhea to no bowel movement for the two days prior to presentation. Physical exam revealed a thin woman in moderate distress with mild tachycardia but otherwise normal vital signs. Abdominal exam was notable for distension, decreased bowel sounds and diffuse tympany, but her abdomen was soft and without peritoneal signs. Laboratories confirmed a mild microcytic anemia but are otherwise normal.



Abdominal CT scan was obtained and is demonstrated above.

Image and explanation provided by Kenneth Fasanella, MD, chief gastroenterology fellow. Compare your answer to Dr. Fasanella's answer on page 4.

Information concerning **Pitt Digest** or requests for additional newsletter copies may be directed to Joy Jenko Merusi at **merusij@dom.pitt.edu** or **1-866-4-GASTRO (1-866-442-7876).** Visit our website at **http://www.dom.pitt.edu/gi**

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