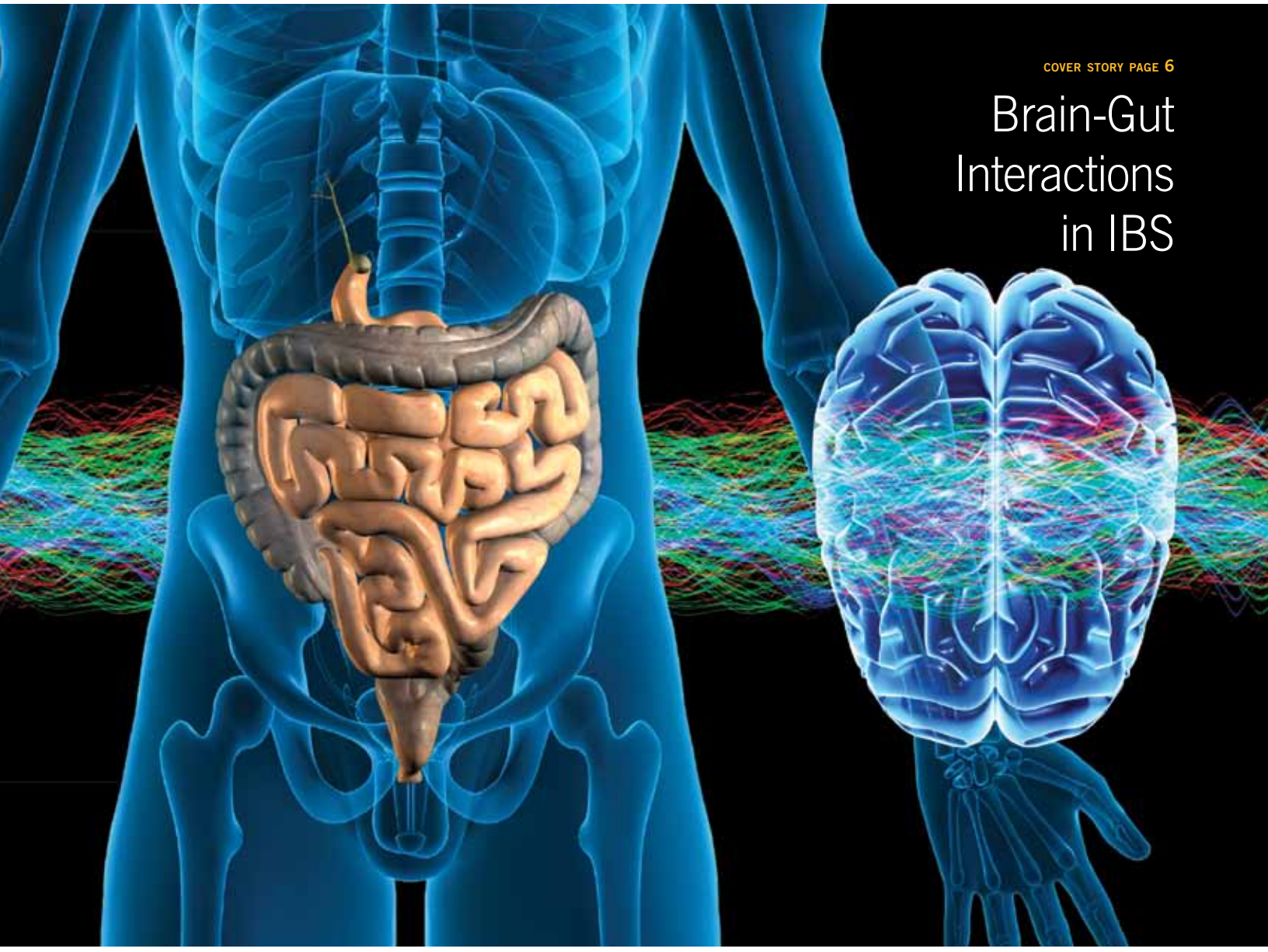
UCLA Health System

Beyond the Scope

A REPORT OF THE UCLA DIVISION OF DIGESTIVE DISEASES



COVER STORY PAGE 6

Brain-Gut Interactions in IBS

SPRING 2012

Gary Gitnick, MD

Going **Beyond** the Scope

As we start the year, we are looking forward to some exciting developments — from prominent faculty additions and program expansions to research projects and the launch of this very publication, *Beyond the Scope.*

Beyond the Scope is a new way of communicating with our colleagues the groundbreaking work taking place at the UCLA Division of Digestive Diseases. From the latest clinical and research studies to utilizing the most advanced and compassionate approaches in patient care, we are proud to be among the few top research and treatment centers for gastroenterology in the country.

It is all about going *Beyond the Scope* — beyond the conventional — exploring and discovering new and better ways to treat the full spectrum of digestive diseases. This drive to offer patients the most comprehensive care has led to program expansions and significant additions to our already renowned faculty.

Our recent recruiting efforts have yielded a robust group of top national and international faculty to lead these exciting endeavors. Learn about V. Raman Muthusamy, MD, interventional endoscopist (pg. 8) who is planning our significant endoscopy expansions in both Westwood and Santa Monica. Gregory Harmon, MD, also joined as director of the Celiac Disease Center, the first of its kind in Los Angeles (pg. 10). Bruce Runyon, MD, is joining our division as director of Hepatology at UCLA Medical Center, Santa Monica and will help develop a program in non-transplant hepatology (pg. 1). An international recruit, Daniel Hommes, MD, PhD, is establishing our new Center for Inflammatory Bowel Diseases (pg. 2).

Because of the combination of passionate faculty throughout the division, amazing talent clinically that drives the group practice, competitiveness for research funding and ongoing efforts in cultivating philanthropy, we continue to grow and expand our reach. Our goal is simple: To help patients suffering from digestive diseases live long, healthy lives. Our accomplishments this year are already substantial. As we look to the future, we are enthused at the prospect of going *Beyond the Scope* in treatment for digestive diseases.

Gary Gitnick, MD

Fran and Ray Stark Foundation Chair
Professor of Medicine
Chief, Division of Digestive Diseases
David Geffen School of Medicine at UCLA

World-Renowned Liver Specialist Joins UCLA Medical Center, Santa Monica

Bruce Runyon, MD

Hepatologist Bruce Runyon, MD, recently joined the UCLA Division of Digestive Diseases, bringing his world-renowned expertise in liver disease to this burgeoning program. As the number of patients with liver disease continues to rise in the United States, there is an increased need for research and specialized treatment.

Dr. Runyon, named director of Hepatology at UCLA Medical Center, Santa Monica, is looking forward to establishing a strong program that works cohesively not only within the Division of Digestive Diseases, but with referring physicians, hospitalists and the liver transplant team.

Dr. Runyon was on the faculty of University of Southern California at its 86-bed Liver Unit for eight years, including four years as chief. He spent a decade in transplantation and wrote all three iterations of the US national practice guideline on ascites.

UpToDate is an online and DVD-based source of information for physicians. It has become the foremost source of up-to-date information. Dr. Runyon has been an author of multiple liver topics for *UpToDate* since 1996 and the editor for *Complications of Cirrhosis* since 2006. In 2010, Dr. Runyon's authored topics were "hit" 537,937 times.

There are many hepatologists in Southern California. Dr. Runyon says that most focus on liver transplantation. His expertise brings "a general hepatology focus of a senior nature" to UCLA.

"It is critical to provide liver patients with the highest quality of care," he says. "UCLA has outstanding gastroenterologists and hepatologists with their own expertise. With my experience in liver disease and liver failure, I can help diagnose patients with obscure liver problems and help direct optimal treatment of patients with all forms of liver disease. I will be able to provide another level of consultation that will be especially beneficial for the patients who are not in need of transplantation or are not candidates for transplantation due to advanced age or other issues."

Dr. Runyon's clinical expertise is equally matched with his research experience. Over his long career, he has collected 20,000 microtubes of ascitic fluid and serum from patients with and without liver disease.

"I've used this bank for the last 31 years," notes Dr. Runyon, who will be bringing the bank with him to UCLA. "I started in 1981 and have used this fluid to do a number of studies, including biomarkers that help with diagnosis. The next study will be of another biomarker that is elevated in patients with bacterial infection." Biomarkers help with differential diagnosis, allowing patients to be diagnosed more quickly.

"My bank offers the potential for development and validation of new biomarkers," says Dr. Runyon, who will also play a significant role in the department's fellowship program where he plans to help enhance liver training.

Value Redefined

Left-right; Ellen Kane, RN; Leticia Gutierrez, Administrative Assistant; Daniel Hommes, MD, PhD, Clinical Director; Jennifer Choi, MD, Associate Clinical Director; Elizabeth Inserra, RN

UCLA's new Center for Inflammatory Bowel Diseases (IBD) is implementing a new approach to chronic disease management — focused on the concepts of value-based healthcare. The emphasis lies on the aspects of healthcare that matter most to individual patients over a full cycle of life: 1) burden of disease, 2) quality of life, and 3) work productivity. The model is one in which stakeholders ranging from patients, healthcare professionals and researchers to payers, industry and government are active participants, with all standing to gain from co-creating and improving health outcomes, as well as lowering costs.

"The US healthcare system has grown into a short-term cost reduction system," says Daniel Hommes, MD, PhD, a leading IBD clinician and researcher in the Netherlands for more than two decades before being recruited to UCLA's Division of Digestive Diseases to head the new center. "If we want to reach affordable and sustainable success in achieving full disease control, we need to redefine and re-create actual value for individual patients and all other healthcare participants."

Playing off the concepts of intelligence quotient (IQ) and emotional intelligence quotient (EQ), the center is tracking patients' value quotient (VQ), quantified using a disease-specific data model that incorporates three measures: the annual burden of the patient's disease including factors such as disease activity, complications, medication side effects, and hospitalizations; quality of life, including mental health, well-being, and the patient's ability to enjoy social situations; and work productivity.

"These are the things that matter the most to patients with inflammatory bowel diseases," says Jennifer Choi, MD, the center's associate director. "Each year, we will aim to increase each patient's VQ. By doing so, we expect to decrease patients' associated annual healthcare costs for Crohn's disease and ulcerative colitis."

The center's efforts to raise patients' VQs are based on what it calls a tight control (TC) infrastructure integrating state-of-the-art healthcare

delivery with translational research. The TC system for IBD care consists of well-defined care scenarios and clinical management based on the most up-to-date IBD practice guidelines. “This aims to make IBD care proactive rather than reactive,” explains Dr. Choi. As part of the process, the center will educate nurse specialists and other providers in delivering high-quality IBD care.

The TC infrastructure for translational research — what Dr. Hommes refers to as the engine of the center’s work — includes biobanks, data warehouses and a platform for systems biology. All patients are asked for consent to participate in building the biobank infrastructure. Biomaterials from consenting patients will then be used to extract information on IBD through the systems biology platform, which will improve our understanding and clinical practice of IBD. The data warehouse will capture massive amounts of clinical information on patients and integrate it with molecular data for decision support. By implementing such “intelligent databases” on individual patients, Dr. Hommes will build upon his previous work in an effort to tailor therapy to each patient.

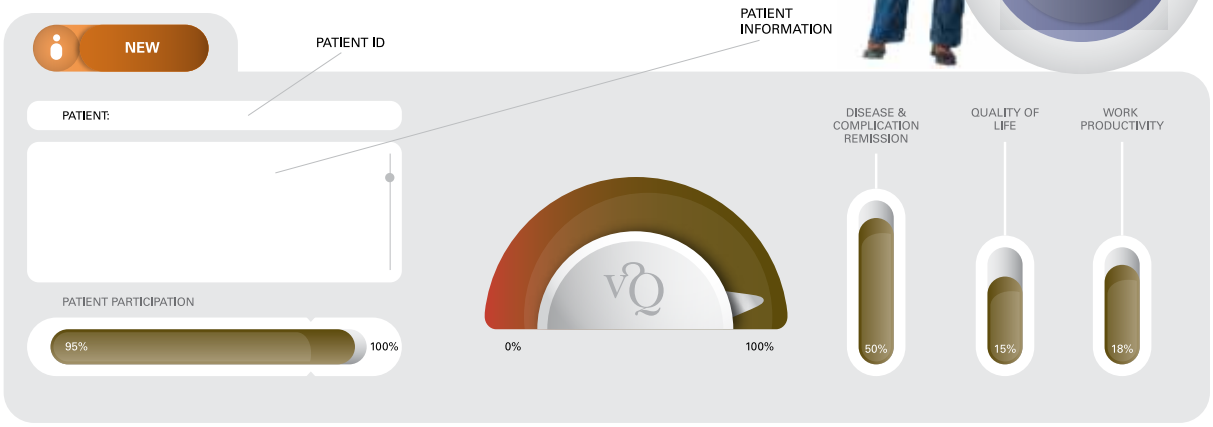
Patients who fail to respond to standard treatments can participate in state-of-the-art research in IBD through a clinical trials program and a stem-cell treatment program. Dr. Hommes has been a leader in both autologous hematopoietic stem-cell transplantation, which uses patients’ own stem cells from blood, and mesenchymal stem cell therapy, which uses cells with the capability of differentiating into a variety of cell types. These cutting-edge therapies represent new strategies for controlling inflammation in IBD.

A cornerstone of the strategy for raising patients’ VQ via tight control care is the active participation of the patients themselves through online education. The center’s e-Learning program empowers patients

by educating them on the disease, treatments, home care, and individual care pathways. “This is an exciting concept that will give patients more ownership in and understanding of their disease management,” says Dr. Choi. The e-Learning approach is also being used to keep healthcare professionals and providers up to date on the latest IBD knowledge.

The center is also developing home care devices, including biochips for clinical testing and tablet PCs that patients can use to enter values as a way of further optimizing tight control care and improving their VQ. Approximately every eight weeks, patients are invited to transmit information on disease activity, quality of life, and work productivity, as well as laboratory data, ensuring close monitoring of their disease.

Dr. Hommes believes that if the new center’s approach proves successful, it can serve as a model for other chronic conditions. “Traditionally, the focus in IBD has been on individual care delivery processes, and changing those processes hasn’t led to a reduction in cost or improvement in quality of care,” he says. “By focusing instead on value to individual patients in a way that can be measured, we are introducing a form of competition that’s been lacking in healthcare, where everyone tends to focus on different things. We believe this is the right direction for the future.”



Metabolic Syndrome Lab

The obesity epidemic in the United States has generated growing concern about metabolic syndrome — a cluster of conditions including excess body fat, hyperglycemia, dyslipidemia and hypertension — that foreshadows such leading killers as diabetes, heart disease and stroke.

Given the liver's role as the workhorse organ for metabolism, it's no surprise that fatty liver is the hepatic manifestation of the metabolic syndrome. How fatty liver leads to chronic liver disease and cirrhosis is an area of great research interest, and several molecular pathways have been identified, including direct toxicity of fats on liver cells, chronic inflammation, insulin resistance and oxidative damage to the tissue. All of these processes lead to chronic scarring of the liver, fibrosis, that can become cirrhosis after several years. Roughly one in three Americans have abnormal liver function tests — most commonly as a result of fatty liver — placing them at risk for fibrosis and, ultimately, progression to end-stage liver disease. There are no drugs that effectively treat fatty liver over the long term or the fibrosis that fatty liver can trigger.

Simon W. Beaven, MD, PhD, a member of the UCLA Division of Digestive Diseases faculty, studies the process by which fibrosis occurs in the hope of finding a way to intervene. Using a powerful mouse model of liver fibrosis, Dr. Beaven and colleagues have begun to hone in on potential drug targets that might change the trajectory of this ominous trend.

Dr. Beaven's group is performing a large-scale screen to identify genetic factors influencing liver fibrosis in the Hybrid Mouse Diversity Panel (HMDP), a collection of over 100 different strains of mice. This panel was initially developed by Dr. Beaven's collaborator, A. Jake Lusis, PhD, to identify genetic contributions to atherosclerosis, but now Dr. Beaven is using this tool to parse out the genetic contributions to liver fibrosis in a chronic liver injury model. The HMDP consists of the 29 classically inbred (CI) strains of mice, commonly available through breeding facilities and research institutions. The mapping power of the panel is greatly enhanced by adding in many other genetically distinct substrains, called recombinant inbred, or RI, strains. The genomic sequences are known for all the strains of mice and are functionally indexed by a comprehensive map of up to four million unique single nucleotide polymorphisms (SNPs).

"With 100 strains of mice, we have a 50 percent chance of detecting a genetic variation that contributes as little as five percent to fibrosis," Dr. Beaven explains. "This provides a very high degree of mapping resolution such that we may only need to study a small number of candidate genes (e.g. four to five) when we find a genetic locus that significantly affects fibrosis. This is in contrast to typical human genomewide association studies (GWAS) in which a region of interest may contain 50-100 candidate genes."

Inducing liver injury through the administration of carbon tetrachloride, a chemical once used in cleaning products and fire extinguishers, Dr. Beaven's group hopes to identify genetic elements that influence the behavior of the principal wound healing cell of the liver, the hepatic stellate cell. Stellate cells make up only five percent of the liver mass, but during any form of chronic liver injury (e.g. chemical injury from carbon tetrachloride, fatty liver, alcohol or viral hepatitis), these cells respond in a stereotyped way to generate the scar tissue that leads to chronic fibrosis and cirrhosis.

Preliminary data from the experiments are encouraging. Dr. Beaven and colleagues have found that genetic variation in one particular gene is strongly and significantly correlated on a genome-wide level with the development of fibrosis. As it turns out, the same gene has recently been associated with liver fibrosis in humans but its function is unknown. "We're getting early validation that our chemical injury model in mice will identify genetic influences on fibrosis that are applicable to humans," says Dr. Beaven. "Furthermore, by the very nature of how we identify regions of interest in this genetic association study, we know what general pathways to pursue, so we can quickly identify the relevant cell types and molecular mechanisms by which the effects of the genetic variation are mediated."

Simon W. Beaven, MD, PhD

Dr. Beaven's team is particularly interested in identifying "druggable targets," such as enzymes, kinases, phosphatases or receptors, that are ripe targets for the development of new drugs, or the application of already existing drugs, to slow fibrosis. "Researchers have been trying to develop treatments for fatty liver for over 40 years, and nothing has worked particularly well," Dr. Beaven says. "It's been a very hard problem." In recent years, he notes, vitamin E and the class of anti-diabetic drugs called glitazones appear to be promising in the treatment of fatty liver disease from metabolic syndrome. But the positive effects are only known in short-term studies up to 24 months and presumably these drugs might have to be taken indefinitely for fatty liver, just as antihypertensives or aspirin therapy can be lifelong for heart disease. Unfortunately, glitazones are associated with an increased risk of cardiovascular complications and are not currently indicated for patients without diabetes. Additionally, vitamin E has been associated with increased stroke and prostate cancer risk in people taking the supplement for more than 10 years. Thus the long-term outcomes of glitazones and vitamin E on liver fibrosis in patients with metabolic syndrome are unknown and may involve significant long-term risks in other organs.

But the urgency to find an effective treatment has risen from a drumbeat to a deafening roar. Cirrhosis from fatty liver is the only cause of end-stage liver disease that is rising (cf. Charlton MR, et al. *Gastroenterology*, 141:1249-53, 2011). "There is a lot of controversy about how many people are going to wind up with cirrhosis from fatty liver and metabolic syndrome," Dr. Beaven notes. "About 6,000 Americans got a liver transplant in 2011, half of them for hepatitis C cirrhosis and only about 600 for fatty liver," Dr. Beaven says. "Even by the most conservative estimates, within 20 years we will have 30,000-50,000 people who need a liver transplant because of fatty liver and metabolic syndrome alone. That number dwarfs our current capacity and suggests that even if we transplanted only for fatty liver, we will still need 10 times as many donor organs. That's just not feasible. To make matters worse, people with cirrhosis from fatty liver are often obese and make poor surgical candidates. Those who don't get a transplant will still need chronic medical management and use a large share of hospital and Medicare resources. Clearly, we need to come up with better prevention and effective medical treatments for fatty liver. If not, many people will die prematurely from liver disease as our healthcare system is crippled by the unsustainable costs of obesity."

A Growing Body of Evidence is Proving Chronic Be Rooted in Disruptions in the Communication

Lin Chang, MD and Kirstin Tillisch, MD

"CNS aims to enhance the understanding of how stress, pain and emotion interact in health and disease — particularly in the digestive system."

Lin Chang, MD

Functional gastrointestinal (GI) and motility disorders affect a substantial portion of the US population — irritable bowel syndrome (IBS) alone is estimated to affect up to 15 percent of Americans — and for some, the conditions can be quite severe and even debilitating. While pharmaceutical approaches to treating these disorders have produced mixed results, the success in some studies of so-called mindful treatments such as hypnosis, meditation, relaxation breathing and cognitive behavioral therapy support a growing body of evidence that these disorders are rooted in disruptions in the communication between the brain and the gut.

UCLA's Oppenheimer Family Center for Neurobiology of Stress (CNS), based in the Division of Digestive Diseases, has charted a course as a leader in approaching these disorders through a paradigm in which the brain-gut axis is central to diagnosis and treatment. The only National Institutes of Health-funded research and clinical center of its kind, CNS aims to enhance the understanding of how stress, pain and emotion interact in health and disease — particularly in the digestive system — by using cutting-edge technologies such as brain imaging, molecular biology and genetic approaches to learn more about the neurobiological underpinnings of mind/brain/body interactions. Center investigators also focus on sex-related differences in the pathophysiology and treatment response of these disorders, which affect women at higher rates than men.

Clinically, that involves assessing the patient's illness experience in a holistic manner and evaluating the contribution of stress and other psychological factors in their symptoms, then providing integrative care that combines the best pharmacological treatments with selected complementary treatments, including mind-body approaches. "Traditionally, doctors believed that the mind and the brain had very little role in or impact on chronic medical disorders, including those of the digestive system," says Emeran Mayer, MD, CNS director and a professor in UCLA's Division of Digestive Diseases. This is rapidly changing with new insights gained from cutting-edge research into brain gut interactions."

Dr. Mayer and his group have played a major role in this growth by publishing seminal research on the role of brain-gut interactions in the pathophysiology of symptoms in IBS and other chronic GI diseases. For example, he recently headed a group that published in the journal *Gastroenterology* its findings that IBS patients have alterations in their brain structure, characterized by a remodeling of the connections among different brain regions that play a role in pain modulation. These findings for the first time have demonstrated organic, structural changes in IBS patients. Dr. Mayer and his CNS colleagues have also helped to unravel the biological mechanisms mediating the effects of early life stressful events on GI symptoms, and have provided preliminary evidence to show the possible role of gut microbiota modulating brain activity. He has recently published a review article in the prestigious *Nature Reviews in Neuroscience* of the emerging neurobiology of gut feelings, bidirectional brain gut interactions, and the possible role of intestinal microbiota in these interactions.

Consistent with their research findings, the CNS follows a bio-psychosocial model in evaluating and managing patients, most of whom are referred with moderate to severe disease. "Typically these patients have a complex set of symptoms that are multi-factorial," says Lin Chang, MD, co-director of the CNS

Medical Disorders May
Between the Brain and the Gut

and professor in the Division of Digestive Diseases. "Because of that, it's important not to look just at their specific GI symptoms."

For Dr. Chang and the center's other clinicians that means also considering genetic, psychosocial and environmental factors that contribute to the onset and exacerbation of symptoms — from early adverse life events and current emotional stressors to issues such as infection and food intolerance. It also means assessing how patients cope with their symptoms. "For some patients, you might not be able to completely relieve their chronic abdominal pain, but you can try to reduce the pain with treatment and help them learn ways to more effectively manage their symptoms," says Kirsten Tillisch, MD, assistant professor.

For patients with moderate to severe functional GI and motility disorders, treatment is largely driven by symptoms and how the patient functions with them. "These are disorders that are currently not reliably defined by a biologic abnormality," says Dr. Chang. "There is no blood test or conventional imaging test that can diagnose IBS. A lot of what we can do is to provide education, reassurance and treatment and resources that can help them get better — but this is a process and can take time, as opposed to being a magic bullet."

CNS is different from many others in its openness to incorporating both Eastern and Western approaches, Dr. Chang adds. Management strategies include gut-directed therapies as well as a range of adjuvant mind-based treatments, many of which are provided through community referrals. The center is also developing innovative interactive Web-based tools that patients can use to enhance their practice of mind-based techniques.

The focus on IBS and related functional GI disorders has broadened in recent years. "Because the brain and gut are so closely interconnected, we believe that in most chronic gastrointestinal disorders — including not only IBS but also inflammatory bowel disease, celiac disease and adult cyclic vomiting syndrome — alterations in the brain-gut axis are involved," Dr. Mayer explains. "So we have expanded into looking at structural, as well as functional, changes in the brains of people with these conditions. It's not just a psychological phenomenon; we believe if the gut is chronically disturbed, it will manifest at the brain level, with or without psychological components." The expanded focus received a major boost last year with a major gift from the Gerald Oppenheimer Family Foundation, along with the opening of a new 5,500-square-foot research and clinical facility on the UCLA campus.

A better understanding of brain-gut connections could help improve the effectiveness of mind-body therapies, Dr. Mayer says. Among other things, CNS investigators are studying whether improving symptoms through mind-based approaches results in changes that "normalize" structural and functional brain changes.

The center also works with industry in the development of novel treatments for IBS, participating in both laboratory experiments and human clinical trials. But even in drug development, Dr. Mayer says, the brain is as much a target as the gut. "We don't separate psychology from biology when it comes to these disorders," he explains. "We look at mind-based and drug-based therapies in very similar biological terms."

Current Practices in Treating Barrett's Esophagus and Esophageal Strictures

V. Raman Muthusamy, MD

In treating Barrett's esophagus, "the key is to accurately determine the level and extent of disease, in order to choose the appropriate care," explains V. Raman Muthusamy, MD, director of UCLA's Interventional Endoscopy Program. UCLA physicians use high-definition endoscopes to carefully assess the lining of the esophagus and to take biopsies as needed. Endoscopic ultrasound allows them to look through the esophageal wall for adjacent lymph nodes and they can perform needle biopsies through the esophageal wall to detect the spread of cancer. In collaboration with expert pathologists who are highly experienced in interpreting esophageal biopsies, UCLA interventional endoscopists are able to provide accurate diagnoses of Barrett's esophagus, low- and high-grade dysplasia and esophageal cancer.

Chronic acid exposure from gastroesophageal reflux disease (GERD) leads to changes in the lining of the esophagus that increase the risk for esophageal cancer. Though uncertainty remains regarding the amount of the increase in risk, current estimates put the chance that Barrett's with high-grade dysplasia will progress to esophageal cancer at about six to seven percent per year. "Most physicians, when confronted with a condition that has a 30 percent five-year risk of progressing to cancer are going to act on that," asserts Dr. Muthusamy. "We now typically treat high-grade dysplasia."

The treatment used depends in part on the appearance of the tissue. High-grade dysplastic tissue can appear either bumpy or flat. At UCLA, interventional endoscopists perform endoscopic mucosal resection (EMR) to remove nodular sections, removing the area of concern and also allowing them to have the tissue analyzed. About eight weeks after EMR, they will go back and ablate the remaining flat high-grade dysplastic tissue. Ablation can be done with cryotherapy or radiofrequency ablation (RFA), which is the best-studied ablative modality. RFA is associated with high rates of Barrett's eradication with few complications and excellent durability. For patients with Barrett's with low-grade dysplasia (LGD), current guidelines call for surveillance biopsies every six months. The best current estimates of the risk of low-grade dysplasia progressing to cancer are about one and one-half to two percent per year, though the numbers have varied widely. The issue is complicated by the fact that non-dysplastic Barrett's tissue often exhibits inflammation when exposed to stomach acid in the esophagus. The inflamed non-dysplastic tissue strongly resembles Barrett's with low-grade dysplasia.

This may explain why some studies have found that the risk of progression to cancer is nearly identical for non-dysplastic Barrett's and for Barrett's with low-grade dysplasia — it may be that the two groups are not being accurately distinguished. Some studies have indicated that as many as five of every six patients diagnosed with low-grade dysplasia actually have non-dysplastic Barrett's with inflammation. Recent data suggest that among patients accurately diagnosed with low-grade dysplasia, the risk of progression to either high-grade dysplasia

"Removable stents can offer patients with esophageal strictures an attractive alternative to repeated frequent dilations." V. Raman Muthusamy, MD

or cancer may be as high as 12 to 14 percent per year. For patients with confirmed LGD, ablation may be an alternative to continued surveillance biopsies.

"There is an increasing change in thought supported by new American Gastroenterological Association (AGA) guidelines that for patients with confirmed low-grade dysplasia — where two expert pathologists agree on the diagnosis — ablation should be an option," reports Dr. Muthusamy.

For Barrett's patients without dysplasia, the risk of progression to cancer is sufficiently low that ablation is usually not indicated, though the AGA guidelines state that it should be an option for high-risk Barrett's patients even in the absence of dysplasia. While there isn't widespread agreement on the definition of high-risk Barrett's, suggested standards include patient age of 50 years or less, long-segment disease, a family history of esophageal cancer and poorly controlled reflux.

Esophageal Strictures

Complex benign esophageal strictures can be difficult to manage, as they are often refractory to dilation. Because UCLA physicians treat a high volume of these patients, they "have developed comfort with aggressive dilation that some physicians may be uncomfortable performing," states Dr. Muthusamy. Mechanical dilation, also known as bougienage, is done either with a semi-rigid, tapered-shaped dilator or a balloon device and is often combined with steroid injections to reduce scarring.

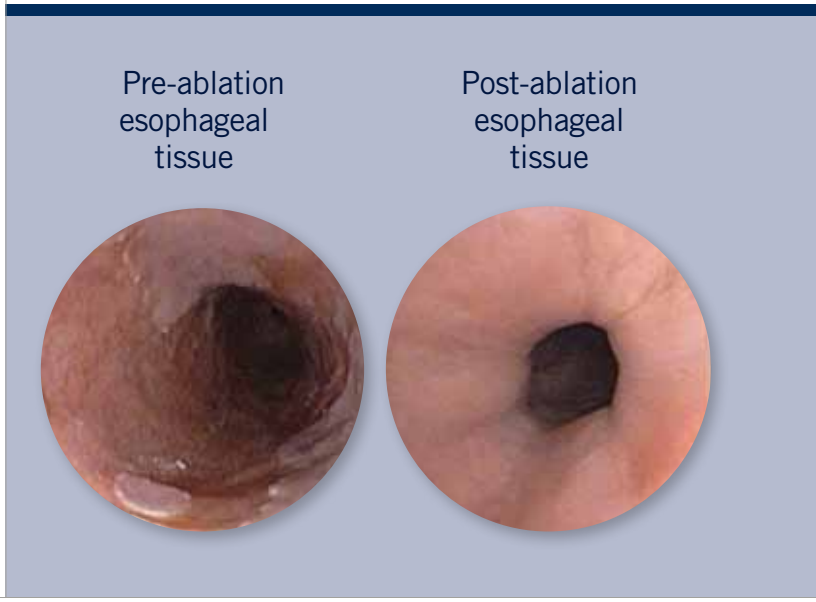
Stenting, which is often used to treat malignant strictures, has become more applicable to the treatment of benign strictures with the development of removable stents. These devices, which are fully coated to prevent tissue from growing into the stent and incorporating it into the esophageal wall, are typically left in place for about two months. Patients can experience long-term relief from symptoms for several months to even years after the stent is removed. The process can be repeated as necessary.

"Removable stents can offer patients with esophageal strictures an attractive alternative to repeated frequent dilations," states Dr. Muthusamy. "Not only are there fewer endoscopic procedures per year, but the opening made by the stent is larger, at least for the time that the stent is in place."

Research

Dr. Muthusamy has been among the leading enrollers in past studies of using ablation to treat Barrett's esophagus, and plans to work with his colleagues in the Interventional Endoscopy Program to continue to build evidence for various treatment options. "We'd like to become better able to predict which patients are good candidates for endoscopic treatment, determine which treatments are most successful in specific patients, and establish what level of follow-up care is needed after treatment," Dr. Muthusamy explains.

For esophageal strictures, Dr. Muthusamy is interested in creating models to determine the point at which stents become a cost-effective alternative to mechanical dilation based on the cost of the device and the longevity of relief.



Gregory Harmon, MD

"Patients with refractory celiac disease are at a higher risk for enteropathy-associated T-cell lymphoma and overall mortality."

Gregory Harmon, MD

Celiac Disease Center First of Its Kind in Los Angeles

Once thought to be a rare disorder in children, we now know that celiac disease affects nearly one percent of the US population. The disease manifests as an immune-mediated enteropathy characterized by villous atrophy and inflammation of the duodenum and jejunum resulting in both gastrointestinal and extra-intestinal symptoms. Gluten peptides from wheat, rye or barley trigger the immune response in genetically susceptible individuals carrying HLA-DQ2 or DQ8.

"Today we know that the prevalence of celiac disease has increased five-fold in the last 50 years," says Gregory Harmon, MD. To meet this rising demand, UCLA has recruited Dr. Harmon, one of the leading experts in the care and management of celiac disease to the new Celiac Disease Center in the Division of Digestive Diseases. Dr. Harmon previously worked with Martin Kagnoff, MD, director of the Celiac Disease Center at the University of California, San Diego prior to joining UCLA.

Most patients with celiac disease respond well to a gluten-free diet. However, learning how to handle a gluten-free diet can be difficult for new patients. "Following a gluten-free diet can have a major impact on a patient's health and quality of life, so proper dietary education is important," says Dr. Harmon. As part of the new center, the division is dedicating a dietician specifically to provide expertise in the education and evaluation of patients with celiac disease.

"For people who don't respond to the gluten-free diet, there are currently no approved medications specifically for celiac disease," explains Dr. Harmon. He describes his vision for the program, which includes developing translational research studies and protocols for managing patients with non-responsive celiac disease. Refractory celiac disease, one of the causes of non-responsive disease, is defined by a failure to respond to a strict gluten-free diet after six to 12 months. Patients with refractory celiac disease are at a higher risk for enteropathy-associated T-cell lymphoma and overall mortality. Determining what is causing non-responsive celiac disease is a major cornerstone for the celiac disease program. Dr. Harmon also indicates that several pharmaceutical companies have begun developing treatments that may benefit patients with refractory celiac disease. He is working with industry to help develop these therapies.

The celiac disease program at UCLA will be the first of its kind in Los Angeles and will offer a fully integrated program including coordination with primary care providers and other key subspecialists for patients with comorbidities such as diabetes mellitus and hypothyroidism. This new program builds on a long tradition of collaborative interaction between clinicians and a world-class program in gastrointestinal pathology. Dr. Harmon also will partner with community organizations to raise awareness of celiac disease in the local community. "Being diagnosed with celiac disease is a life-changing event. Our goal is to make sure that we treat patients the right way at the right time to avoid future complications. The timing could not be better given the other exciting developments both for patient care and cutting-edge research within the Division." In joining UCLA, Dr. Harmon brings a wealth of knowledge and expertise on a disease that people are now only beginning to understand.

Endoscopic Techniques Used to Improve Bariatric Surgery Results

More than two million people in the United States have undergone bariatric surgery for weight loss, most commonly in the form of gastric bypass procedures. The majority of these individuals begin to regain weight over time, in part because their surgically created gastric pouch starts to stretch, allowing for increased food consumption.

Rabindra R. Watson, MD, who joined the faculty of UCLA's Division of Digestive Diseases last September, is among a small group of gastroenterologists who are using endoscopic techniques to improve the results of bariatric weight-loss surgery. Dr. Watson participated in the development of these techniques at Boston's Brigham and Women's Hospital as part of an advanced endoscopy fellowship prior to being recruited to UCLA.

The first and simplest approach to endoscopic revision of previous gastric bypass is to reduce the volume of the surgically created gastric pouch through the injection of sclerosants into the gastric pouch. "Studies have shown this to be fairly effective in producing weight stabilization and weight loss over six to 12 months," Dr. Watson explains. "It can be performed using the tools available to any endoscopist, and can be repeated if the patient doesn't respond to the initial injection. Additionally, there may be pleiotropic effects beyond restriction such as alteration in paracrine and exocrine signaling."

The second type of revision involves using endoscopic suturing techniques to reduce the size of the pouch as well as the stoma. "Based on recently published data, the diameter of the stoma appears to be directly associated with weight regain on multivariate analysis," Dr. Watson says. "By reducing the stomal diameter and pouch size with endoscopic suture placement, we have been able to achieve encouraging early results while proving the procedure to be safe and effective." The suturing technique requires more expertise, but may result in a more durable reduction in the size of the pouch and stoma — and, thus, more sustained weight loss, Dr. Watson notes.

Operative revision of bariatric surgery has a high morbidity rate — above 25 percent — along with a two to three percent mortality rate. "Both surgeons and their patients are concerned about the risks," Dr. Watson says. "The endoscopic approach is faster, safer and has shorter recovery times."

Dr. Watson is also continuing to study ways to use endoscopy as a primary weight-loss procedure. He and his colleagues have seen promising results in preliminary studies of restrictive therapies to reduce the size of the stomach, as well as the use of implantable sleeves as a form of bypass. They are also looking into creating anastomoses endoscopically, which may serve as a functional form of bypass surgery. "There is a growing interest in minimally invasive techniques to effectively treat obesity," Dr. Watson says. "It's analogous to being able to do cardiac interventions beyond medical therapy but short of bypass surgery, such as performing angioplasty or cardiac stenting. That's the role endoscopy might play for obesity."

The use of endoscopy has the potential to assist patients in their initial weight-loss and diabetes-control efforts, with patients eventually being returned to their original anatomy. It could be used as a bridge to bariatric surgery or used for people who are overweight but not enough to qualify for bariatric surgery — a substantial population.

"We have the potential to reach a lot more people with endoscopy — creating a new paradigm for attacking obesity," Dr. Watson says. "The pathophysiology of obesity is obviously complex, which we are only beginning to understand. However, it's my hope that in the future we will no longer see people undergoing surgery for benign indications such as obesity, and that endoscopy will effectively treat these patients, without any incisions."

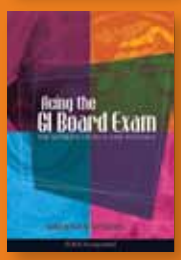
Rabindra R. Watson, MD

> "Based on recently published data, the diameter of the stoma appears to be directly associated with weight regain on multivariate analysis."
>
> Rabindra Watson, MD

NIH Awards Two Grants to Studies at UCLA Division of Digestive Diseases

Books for Healthcare Professionals

Eric Esrailian, MD, MPH
Vice-Chief
Division of Digestive Diseases



Brennan M.R. Spiegel, MD, MSHS
Director, UCLA GI Fellowship Training Program
Director, UCLA/VA Center for Outcomes Research and Education
Associate Professor of Medicine
VA Greater Los Angeles Healthcare System

FACULTY MEMBER RECEIVES PRESTIGIOUS GRANT FROM NIH

Kirsten Tillisch, MD

Kirsten Tillisch, MD, assistant professor in the UCLA Division of Digestive Diseases who specializes in IBS and other functional gastrointestinal disorders, has conducted studies suggesting that certain people's persistent abdominal discomfort has to do with their brain's response to the symptoms. She has found differences in the brains of people with and without the disorder. In recent years, mind-body approaches, such as cognitive behavioral therapy, yoga, hypnosis and meditation, have been shown to reduce subjective symptoms in several persistent pain disorders, including IBS (see story on on page 6).

Now, Dr. Tillisch has received a five-year RO1 grant from the National Institutes of Health to learn more about the biological basis for these improvements. Researchers would be able to better assess and compare the impact of various mind-body therapies, while assisting clinicians in fine-tuning the approaches and targeting specific treatments to the patients most likely to benefit.

Expanding on their previous research, Dr. Tillisch and her colleagues will develop "biomarkers," structural and functional brain alterations that can serve as objective and reliable measures of response to treatment. Once validated, these biomarkers will be used in a clinical trial with regard to Mindfulness-Based Stress Reduction (MBSR), an eight-week intensive training program that incorporates ancient healing practices, including meditation and yoga.

NIH RENEWS FIVE-YEAR GASTROENTEROLOGY TRAINING GRANT

Dennis Jensen, MD

For more than four decades, numerous academic leaders in gastroenterology have gotten their start through the Gastroenterology Training Grant administered by the UCLA Division of Digestive Diseases with affiliated laboratories and mentors at UCLA, West Los Angeles VA Medical Center, CURE: Digestive Diseases Research Center, and Cedars-Sinai Medical Center. The program, funded by the National Institutes of Health, was recently competitively renewed for another five years, ensuring that six annual slots will continue to be filled by talented young trainees through at least 2016.

Originally devoted to the postdoctoral training of fellows in GI physiology, the program has evolved to include laboratory studies, clinical and outcomes research, as well as translational science to bring basic findings to clinical settings. The current group includes a pediatric gastroenterologist and, for the first time, a GI surgeon. The program's leadership reflects that continuum: The training grant has been directed since 2000 by Dennis Jensen, MD, professor in the Division and associate director of CURE, who is a clinical investigator and outcomes researcher. Co-directors are Peter Anton, MD, also professor in the Division and a translational researcher, and Stephen Pandol, MD, gastroenterologist at the West Los Angeles VA Medical Center who is a basic scientist.

Study Identifies New Way to Treat Common Hospital-Acquired Infection

Novel approach may offer treatment for other bacterial diseases

Researchers at the Division of Digestive Diseases, David Geffen School of Medicine at UCLA and the University of Texas Medical Branch at Galveston have discovered a molecular process by which the body can defend against the effects of *Clostridium difficile* infection (CDI), pointing to a promising new approach for treating an intestinal disease that has become more common, more severe and harder to cure in recent years.

In the US, several million people are infected each year with *Clostridium difficile*, approximately double the incidence of a decade ago, mainly due to the emergence of a new, highly virulent strain of the bacteria that produces excessive amounts of toxins that mediate symptoms for this disease. Although successful antibiotic treatment has been available since the early 80s up to 35 percent of patients experience re-infection within a few weeks and these patients are difficult to treat. This clinical issue represents a significant medical and financial challenge to healthcare systems, and has rekindled an interest in improving therapy against this infection. Moreover, there has been an urgent need to find alternative forms of therapies that preferentially target the toxins and not the pathogen since this means treating a disease caused by antibiotics with yet another antibiotic, which creates the conditions for re-infection from the same bacteria.

Clostridium difficile causes diarrhea and colitis by releasing two potent toxins into the gut lumen that bind to intestinal epithelial cells, initiating an inflammatory response. Dr. Pothoulakis and his colleagues found in laboratory studies that upon infection with *Clostridium difficile*, human cells in the gut are capable of releasing molecules that will neutralize these toxins, rendering them harmless. This study shows that *Clostridium difficile* toxins are S-nitrosylated by the infected host and that S-nitrosylation attenuates virulence by inhibiting toxin self cleavage, cell entry and toxicity. Animal studies reported in this work showed that drugs that induce this process, known as protein S-nitrosylation, neutralize the ability of *Clostridium difficile* toxins to destroy intestinal cells and cause diarrhea. Forthcoming clinical trials will test this approach in humans. The study suggests a novel therapeutic approach for treating CDI by exploiting a newly discovered defense mechanism that has evolved in humans to inactivate microbial toxins. This approach could be applied to developing new treatments for other forms of diarrhea, as well as non-diarrheal diseases caused by bacteria, since gene-sequencing analyses have shown that hundreds of microbial proteins can be regulated by nitrosylation.

Harry Pothoulakis, MD

The study was published in the August 21, 2011 issue of the journal *Nature Medicine* and was accompanied by press releases from Reuters, BBC, MSNBC, CNBC, and AGA News, as well as by a Research Article published in the *World Street Journal*, on September 6, 2011.

The study was funded by grants from the National Institutes of Health, The Eli and Edythe Broad Medical Foundation, the John S. Dunn Gulf Coast Consortium for Chemical Genomics/Robert A. Welch Collaborative Grant Program, and the Howard Hughes Medical Institute. Other institutions participating in this study include the University of Texas Medical Branch at Galveston, The Commonwealth Medical College, Tufts University, and Case Western Reserve University.

David Geffen School of Medicine

Division of Digestive Diseases
405 Hilgard Ave
BOX 956949, 2114 PVUB
Los Angeles, CA 90095-6949

NON-PROFIT
ORGANIZATION
U.S. POSTAGE
PAID
U C L A

The UCLA Division of Digestive Diseases continues to be rated "Best in the Western United States" and is ranked in the top six among digestive diseases centers in the United States by *U.S.News & World Report* in its annual survey.

UCLA DIVISION OF DIGESTIVE DISEASES

CHIEF
Gary Gitnick, MD

VICE CHIEF
Eric Esrailian, MD, MPH
eesrailian@mednet.ucla.edu

BUSINESS DEVELOPMENT
Trisha James, MBA
trishajames@mednet.ucla.edu

DEVELOPMENT
Steve Ramirez
sramirez@support.ucla.edu

FINANCE AND OPERATIONS
Adriana Centeno
acenteno@mednet.ucla.edu

CONTRIBUTING WRITERS
David Barrad
Dan Gordon
Kara Welter

DESIGN
Oglesby Design

PHOTOGRAPHY
Paul Kennedy

CONTACT INFORMATION

PHONE

UCLA Physician Referral Service
1-800-UCLA-MD1
(800-825-2631)

Digestive Disease Call Center
(310) 825-1597

WEB

Learn more about UCLA Division of Digestive Diseases: www.gastro.ucla.edu

Thank you for your interest in our division. We are honored to be a resource for you and your patients. If you would like more information beyond what is available on our expanded website, please contact me at eesrailian@mednet.ucla.edu.

Eric Esrailian, MD, MPH
Vice Chief
Assistant Clinical Professor of Medicine
Division of Digestive Diseases
David Geffen School of Medicine at UCLA

UCLA Health System

A Report of the UCLA Digestive Disease Division