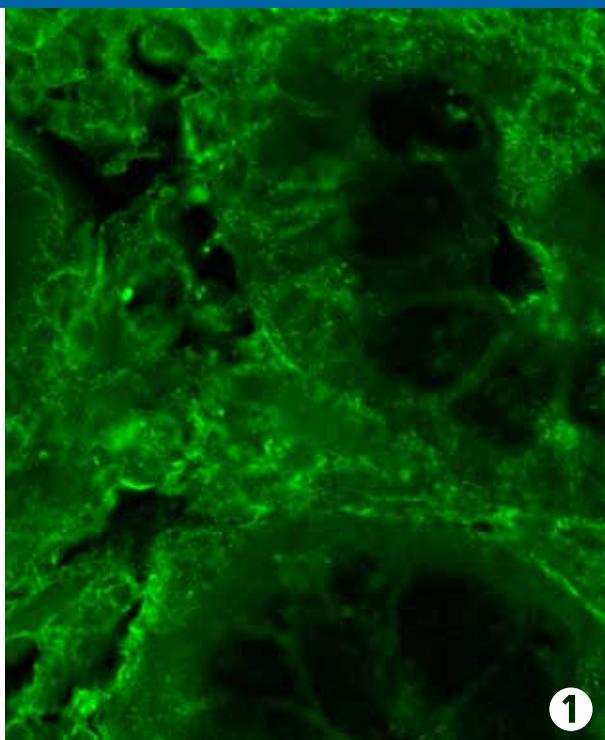


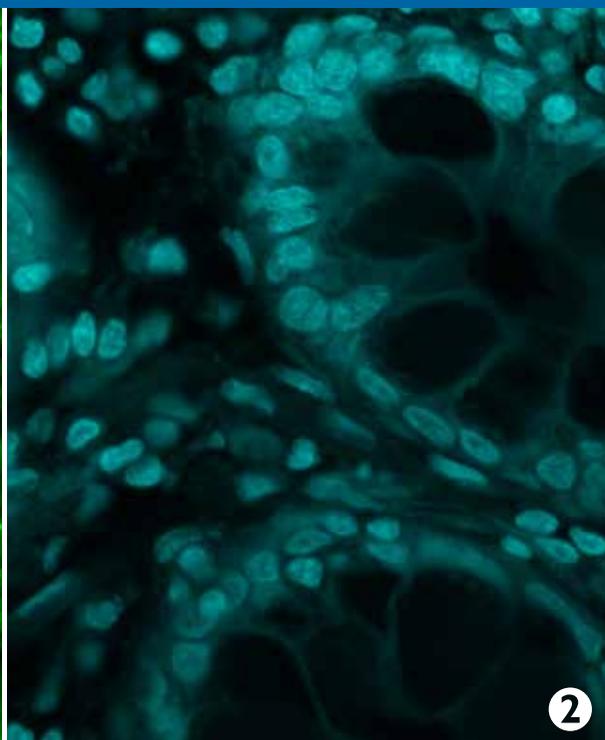
JOHNS HOPKINS InsideTract

SPRING 2017

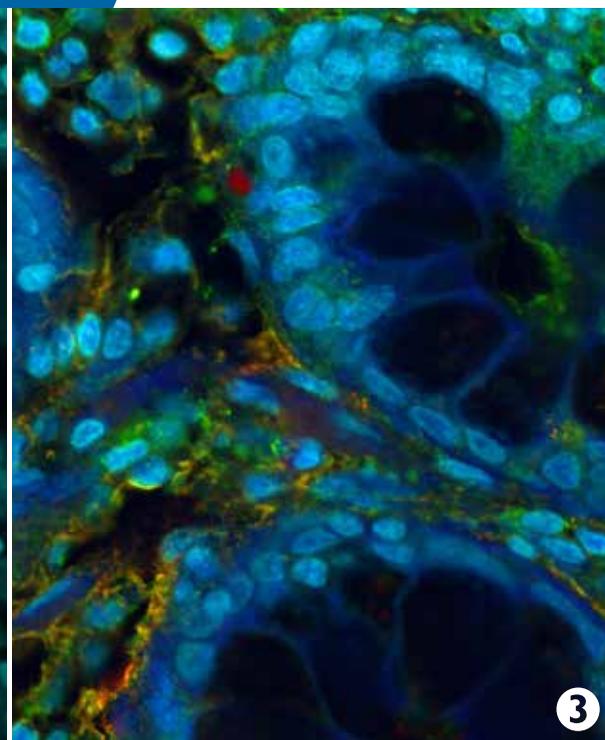
NEWS FROM THE JOHNS HOPKINS
DIVISION OF GASTROENTEROLOGY AND HEPATOLOGY



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In this colocalization of a specimen taken from a patient with ileal Crohn's disease, a green stain in image 1 illuminates zinc transporter genes within the intestinal crypt cells. Image 2 shows the cells' teal-stained nuclei. Image 3 overlays the other two images and highlights in red a special type of crypt cell. "This tells us that the zinc transporter is present in some of the immune cells in the epithelia of both the terminal ileum and the small bowel," says researcher Joanna Melia, "and that there is even more of it in the presence of inflammation."

Unlocking the Genetic Mysteries of IBD

Joanna Melia's patients with inflammatory bowel disease all ask her the same thing. "Every single one of them wants to know what they should and shouldn't eat," she says. "Which seems reasonable, right? But there's very little information on dietary recommendations for patients" with Crohn's disease and ulcerative colitis.

Her research is driven by a desire to give those patients some answers.

Melia, a gastroenterologist and researcher, says some patients tell her that certain foods trigger episodes while others report diet has no effect on their symptoms.

For example, for a long time, IBD patients were encouraged to avoid foods containing fiber. "Now the pendulum is swinging the other way," she says. "Newer studies say that fiber is good. So it's really a moving target."

To better understand one aspect of diet and IBD, Melia is researching a zinc transporting gene that has a mutation associated with increased risk of Crohn's disease. The mutation has also turned up in research of several other diseases, including obesity and schizophrenia, and it might hold clues to how micronutrients in the gut affect disease.

"We still don't understand what happens when this gene is mutated," she says. "But we know zinc is very important to immunity and gut health."

Melia says that it may produce either too much

"WE STILL DON'T UNDERSTAND WHAT HAPPENS WHEN THIS GENE IS MUTATED, BUT WE KNOW ZINC IS VERY IMPORTANT TO IMMUNITY AND GUT HEALTH."

—JOANNA MELIA



or too little immune response in patients with IBD. Either can lead to intestinal inflammation.

"Historically, we have divided up inflammatory bowel disease into only two disease conditions, Crohn's disease and ulcerative colitis," says Melia. "But there are likely many subtypes driven by many different processes."

Using enteroids grown from intestinal tissue samples, Melia and other Johns Hopkins researchers study intestinal transporters.

She says that many of her Johns Hopkins colleagues have produced important work in IBD genetics and in the area of dietary trace minerals, such as copper, iron and zinc. Melia sees herself working in that tradition.

Melia's research also focuses on how micronutrients, required by both humans and the microorganisms present in the gut, shape

the microbiome.

"There seems to be some competition among the host and organisms in the gut for these micronutrients in IBD," she says. "For instance, we and our collaborators have found that the microorganisms in the intestines of patients with Crohn's disease have more zinc transporters than the ones in healthy people."

The role of diet in shaping the microbiome is undeniable, Melia says. But exactly what effects various foods produce remains elusive. Still, she believes there is hope to unlocking the puzzles of IBD, diet and the microbiome.

"We really want to learn how we can harness micronutrients to improve gut health. I think we have new laboratory tools to begin to study these questions in new ways, and it is my hope we can provide more answers for patients," she says. ■



Innovating for Others

We're proud of—and humbled by—our reputation for world-class research at the Johns Hopkins University School of Medicine. For 127 years, our institution has led advancements in the science of medicine.

But underlying our relentless pursuit of medical knowledge is a fundamental drive: to help alleviate human suffering through the treatment of illness and disease.

This edition of *Inside Tract* showcases just a few of the ways that we do what we've dedicated our lives to—blending rigorous science with the compassionate care of patients.

The conditions you'll read about in this issue are among today's most widespread and pernicious: inflammatory bowel disease, gastroparesis, diabetes, obesity and, of course, cancer. Though the conditions are common, our teams' approaches are often anything but.

Saowanee Ngamruengphong, for example, spent last summer in Tokyo, studying advanced therapeutic endoscopy techniques for gastric cancer. There, she learned from some of the world's foremost experts in the field, and she brings this expertise, scarcely available in the U.S., to our patients most in need.

Mouen Khashab continues to advance surgery-sparing, endoscopic solutions for conditions of the GI tract. In this issue, we delve into his efforts centered on the ubiquitous condition refractory gastroparesis.

Equally innovative, Joanna Melia's research into the genetics of IBD mines the origins of Crohn's disease and ulcerative colitis—teasing out clues that may one day lead to advanced treatments.

And Ashish Nimgaonkar and colleagues are engineering a pill—based on prior research focused on weight loss—that may eliminate diabetes symptoms in patients who take it before meals.

It is truly an honor to work with such colleagues—physicians and scientists who strive every day to improve the health and lives of our patients and people throughout the world. Should you have questions for me, anyone in this issue, or other members of our division, please don't hesitate to contact us.

Tony Kalloo, Director

Division of Gastroenterology and Hepatology
Johns Hopkins University School of Medicine

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Myotomy Offers Relief for Some Gastroparesis Patients

The National Institutes of Health estimates that as many as 5 million Americans live with gastroparesis. Johns Hopkins gastroenterologist **Mouen Khashab** cites a 2008 *American Journal of Gastroenterology* study stating that diagnoses of gastroparesis have increased by more than 150 percent in the past 20 years.

"It's becoming more common," he says. "We don't know why it's on such a steep rise."

What's more, Khashab says there's no reliable medication or treatment for the condition, in which the stomach cannot empty properly, causing abdominal pain, nausea and vomiting. Ultimately, patients with persistent or chronic gastroparesis can suffer dehydration and malnutrition.

"No one has found a specific cause," explains Khashab, "and the only medication for it has a black-box warning for significant side effects."

Khashab has developed an endoscopic procedure that snips the pyloric sphincter to treat certain sufferers of gastroparesis. He is encouraged by the early results.

In 2012, he and several Johns Hopkins colleagues began testing a metallic mesh stent to treat patients with severe, refractory gastroparesis.

"These were patients whose condition was debilitating," Khashab says.

The endoscopist slides a stent past the stomach and deploys it into the pyloric valve, holding the valve open and allowing nutrition to begin its journey through the intestines. Khashab says the stent was successful more often than not, but that he never meant it as a permanent solution.

"Stents migrate," he says. "Mucosa grows over them. There are all sorts of reasons why it wasn't permanent."

Meanwhile, Khashab and other Johns Hopkins endoscopists were frequently performing another procedure for patients with achalasia. That procedure, called peroral endoscopic myotomy (POEM), involves cutting the lower esophageal sphincter muscle to relieve spasms that prevent it from opening and closing properly. Patients with

spastic lower esophageal sphincter muscles have difficulty swallowing, and food stays undigested in the esophagus. A myotomy of that muscle brought many patients relief, prompting Khashab to wonder if gastroparesis patients might enjoy similar benefits.

"It's a sphincter muscle in a different place," he says. "Instead of at the bottom of the esophagus, it's at the bottom of the stomach. I thought it might work."

Khashab did a study on the procedure and found that, in many cases, myotomy did indeed relieve gastroparesis symptoms. He notes

(continued on back cover)



Mouen Khashab says that about two thirds of his patients who have had pyloric myotomy report no more gastroparesis symptoms.

"IT'S A SPHINCTER MUSCLE IN A DIFFERENT PLACE. I THOUGHT IT MIGHT WORK.."

—MOUEN KHASHAB

The Cutting Edge of Endoscopic Resection

Johns Hopkins among the few U.S. centers to offer innovative procedure

Looking at results from high-definition scopes, enhanced imaging, endoscopic ultrasound and other advanced diagnostic tools, Johns Hopkins' multidisciplinary teams work together on personalized care plans for patients with gastric cancer. Most times, when resection is necessary, common endoscopic mucosal resection (EMR) is sufficient.

But when patients require something more complex, gastroenterologist **Saowanee Ngamruengphong** and colleagues offer other options.

For 10 weeks last summer, she studied advanced endoscopic early-cancer removal techniques at the place where they perform the procedures several times a day: Tokyo's National Cancer Center, the world's

foremost facility for innovative endoscopic removal of gastric cancers.

Gastric cancer is far less common in North America than in Eastern Asia, which sees 50 percent of all new cases worldwide each year. The Japanese center's faculty teaches the latest endoscopic resection techniques annually to only a few physicians from around the world.

Ngamruengphong spent her time there learning endoscopic submucosal dissection (ESD), as well as detection, evaluation and treatment of all kinds of early luminal cancers and precancers.

She says that EMR, the most common approach in the U.S., is not always the appropriate one for complex,

Bypassing Bypass Surgery

Polymer-pill for weight loss may hold promise for patients with diabetes

A Johns Hopkins gastroenterologist is on his way to reproducing a serendipitous byproduct of a gastric bypass using neither surgery nor endoscopy.

Gastroenterologist **Ashish Nimgaonkar** is engineering a pill that will mimic not only the weight loss effects but also the glycemic benefits of a gastric bypass procedure.

When patients first underwent gastric bypass surgery, the obvious benefit was dramatic weight loss. But patients who happened to have type 2 diabetes enjoyed an additional, unexpected outcome.

"A few days after the surgery, they were walking out of the hospital without a need for insulin or diabetes medicine," says Nimgaonkar.

Rerouting food past the duodenum during the digestion process has a tremendous and immediate effect on glycemic control," he says.

Nimgaonkar along with his colleagues gastroenterologist **Jay Pasricha** and biomedical engineer **Kevin Colbert** are developing a pill that will deploy a polymer that creates a barrier to the same part of the small intestine that is bypassed in gastric bypass surgery, producing similar weight loss and glycemic benefits as a surgical or endoscopic procedure.

"It's still at a very early stage," he says. "But we have shown that it works in animal models."

Nimgaonkar and his team won a \$500,000 prize for the pill's concept in an international competition sponsored by a large multinational drug maker. They continue to engineer the pill to optimize the dose, properties and delivery system for the polymer. They will soon embark on clinical trials.

The patient swallows the pill before a meal, and it activates upon contact with the duodenum. This allows food to pass untouched from the pylorus to the jejunum.

"That way, we're able to avoid the

duodenum altogether," says Nimgaonkar.

Because the barrier remains superficial and does not adhere to intestinal cells, the polymer dissipates within several hours; its remains are excreted by the patient. An hour or so before the next meal, the patient takes another pill.

Because of diabetes' increasing prevalence, researchers and pharmaceutical companies have long pursued drugs and devices aimed at treating the disease. But side effects and spotty results have derailed most efforts.

One such study used a plastic tube as a bypass device. The tube did its job; diabetes was no longer a problem. But because of side effects—patients reported severe nausea and some experienced systemic infection from the metal anchor that held the tube in place—as well as the device's 12-month implant duration, it was never approved in the United States. But Nimgaonkar says researchers nevertheless learned from the data the tube yielded.

"For us, it provided a great insight," he says. "The device worked. It just had some problems."

Nimgaonkar points out that both surgery and endoscopy present an added cost when patients with diabetes require frequent visits to surgeons and gastroenterologists.

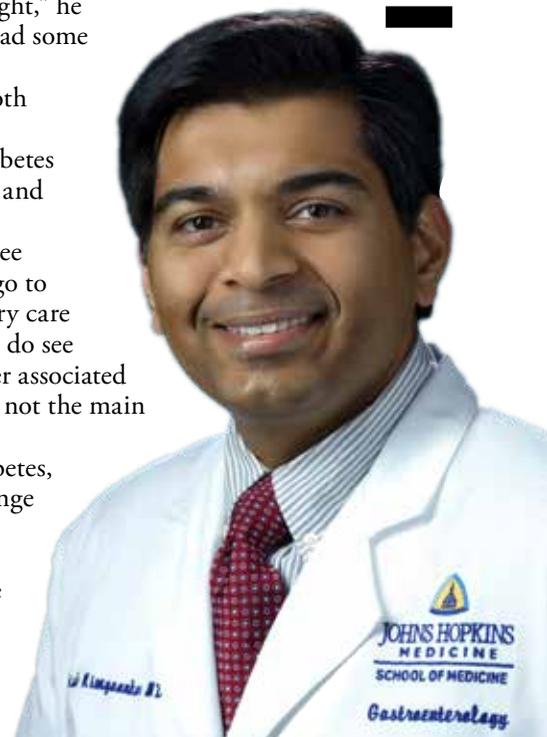
"GI physicians don't typically see diabetic patients," he says. "They go to endocrinologists or to their primary care doctors. When gastroenterologists do see patients with diabetes, it's for other associated gastrointestinal conditions but it's not the main purpose for the visit."

While the pill doesn't cure diabetes, Nimgaonkar believes it could change the way it's treated in the future.

"As long as they take the pills, patients with diabetes should have well-regulated blood sugar." ■

"REROUTING FOOD PAST THE DUODENUM DURING THE DIGESTION PROCESS HAS A TREMENDOUS AND IMMEDIATE EFFECT ON GLYCEMIC CONTROL."

—ASHISH NIMGAONKAR



Radioactive dye shows how the polymer used by Ashish Nimgaonkar coats the duodenum, sealing it off from food absorption and the part of the digestive tract responsible for diabetes.



"IT'S VERY DELICATE. YOU NEED A HIGH-DEFINITION SCOPE, AND YOU USE AN ENDOSCOPIC KNIFE TO SEPARATE THE MUSCLE FROM THE SUBMUCOSA."

—SAOWANEE NGAMRUENGPONG

large or difficult-to-reach dysplasia. This technique uses the endoscopic snare to resect lesions a piece at a time.

"But with ESD, you can resect no matter the size," says Ngamruengphong. "And you can tell if it's curative, which EMR cannot do."

ESD uses endoscopy to accomplish what, not long ago, could only be achieved with open surgery. By separating the intestinal lining from the muscle

wall, taking great care against any perforations, Ngamruengphong can excise tumors that have not entered the muscle layer.

"It's very delicate," she says. "You need a high-definition scope. And you use an endoscopic knife to separate the muscle from the submucosa."

For larger, more invasive cancers, Ngamruengphong performs full thickness resection, which involves gathering up cancerous or

precancerous tissue, as well as the area around it, then using a clip to isolate it. Ngamruengphong says she usually sutures the bottom of the gathered-up tissue and cuts just above the suture. Because the excision is already closed, there is very little bleeding and patients seldom require hospital admission.

"We send the whole resected tissue to pathology, looking for clear margins," she says.

She describes a recent procedure as typical.

"The patient had a four-centimeter tumor in her colon. We removed it and sutured it," Ngamruengphong says. "The patient went home after the procedure."

Pathology found that the tissue was malignant. "But because we got the foci of cancer and the margins were clear, all she requires now is follow-up monitoring for recurrence."

(continued on back cover)

The Cutting Edge of Endoscopic Resection (continued from page 3)



Endoscopic submucosal dissection for a rectal tumor. The procedure allows Saowanee Ngamruengphong to resect the whole tumor rather than snare it in pieces.

Because she used the endoscopic knife rather than the snare, she was able to remove the whole tumor.

"In the past, that would have come out in about 20 pieces," Ngamruengphong says. "It would have been impossible for pathologists to tell us whether we got it all." ■

Myotomy Offers Relief (continued from page 2)

that patients whose symptoms abated with the temporary stent therapy were the best candidates for what he now calls G-POEM, or gastric peroral endoscopic myotomy.

"We knew that the cause of their gastroparesis was most likely a spastic pyloric sphincter because, for a while, the stents worked for them," he explains.

Khashab has performed about 30 G-POEM procedures, which he describes as slightly more technically challenging than POEM.

"It's like going from driving a car to driving a truck," he says. "It's the same principle, but it requires a little more skill."

He says the rate at which patients show significant improvement is roughly the same as the pyloric stent, about 80 percent. The difference, of course, is that G-POEM offers a better chance at permanent relief.

Khashab can't say for sure if the patients' gastroparesis is cured, since the procedure is only a few years old. But for patients who have responded to the treatment, the outlook is good.

"About two-thirds of our patients who've experienced relief have reported no more gastroparesis symptoms." ■

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JOHNS HOPKINS InsideTract

Inside Tract is one of many ways the Johns Hopkins Division of Gastroenterology and Hepatology seeks to recognize and enhance its partnership with its thousands of referring physicians. Comments, questions and thoughts on topics you would like to see covered in upcoming issues are always welcome.

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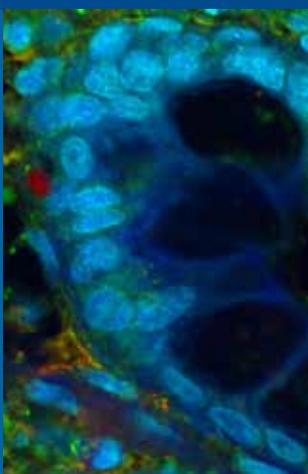
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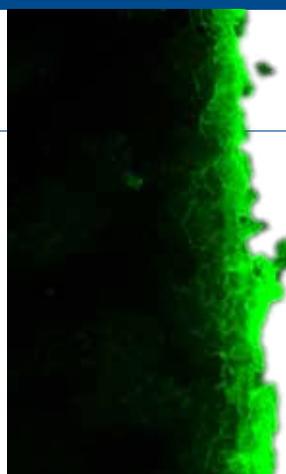
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