

Researchers Discover **Death and Rebirth** of the Gut Brain

Last spring, Johns Hopkins researchers published new evidence refuting the longheld scientific belief that the gut nerve cells we're born with are the same ones we die with.

In a report published in the journal *Proceedings of the National Academy of Sciences*, the investigators say the finding has profound implications for the understanding and treatment of disorders and diseases that affect the digestive system.

Pankaj Jay Pasricha, director of the Johns Hopkins Center for Neurogastroenterology, and gastroenterology researcher **Subhash Kulkarni** led a team that discovered the birth-and-death cycle of the neurons that form the network of millions of nerve cells throughout the digestive tract.

Previous studies have suggested that a healthy adult gut generates few or no new neurons. According to Pasricha, the Johns Hopkins study demonstrates that a healthy adult small intestine loses and regenerates about five percent of its nerve cells every day, or a third of them every week.

"Scientific dogma believed that gut neurons don't regenerate and that this 'brain,' known as the enteric nervous system, remained relatively static shortly after birth," Pasricha says. "We now have proof that, not only do they regenerate, but the whole network turns completely over every few weeks in adult animals."

The enteric nervous system controls and regulates vital gastrointestinal functions such

as digestion, immunity and inflammation. After the brain, the digestive tract contains the largest nervous system in the human body.

"The yin and the yang of neuronal loss and birth keeps us going," Kulkarni says.

Pasricha, Kulkarni and their team confined their research to the small intestines of healthy adult mice. Using a variety of techniques, they found proteins associated with neural cell death and were able to observe the loss of neurons. Their work provided irrefutable evidence of ongoing neuronal death due to apoptosis in the adult gut.

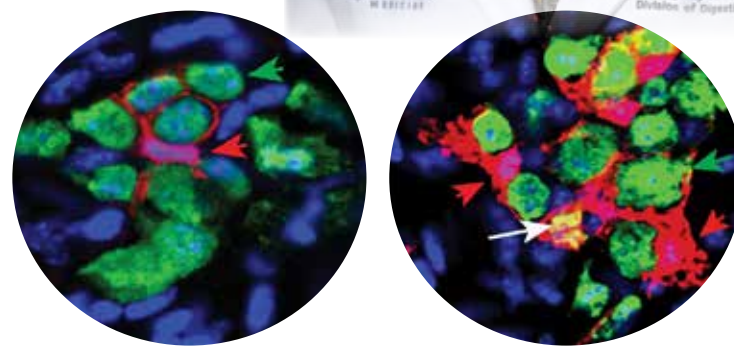
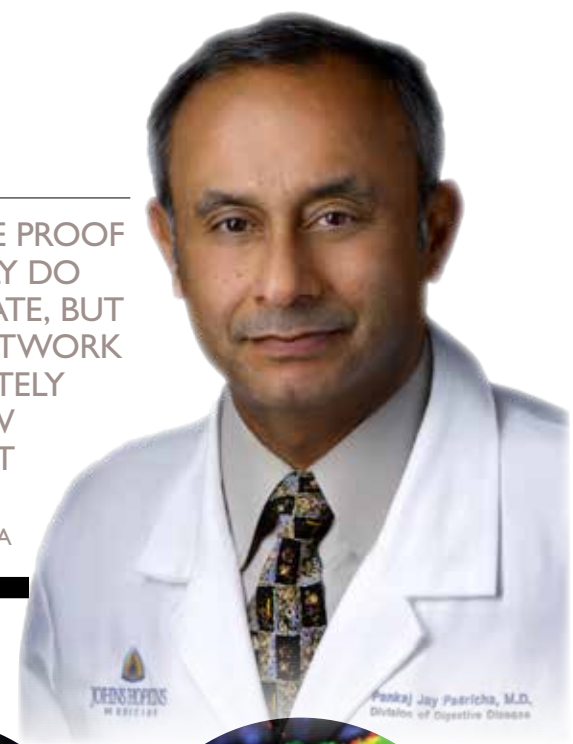
This significant rate of nerve cell loss left the research team with the question of how the gut maintains its relatively constant number of neurons.

"There could be only one answer," says Kulkarni. "The high turnover of neurons in the gut could only be reconciled by birth of newborn neurons, or neurogenesis."

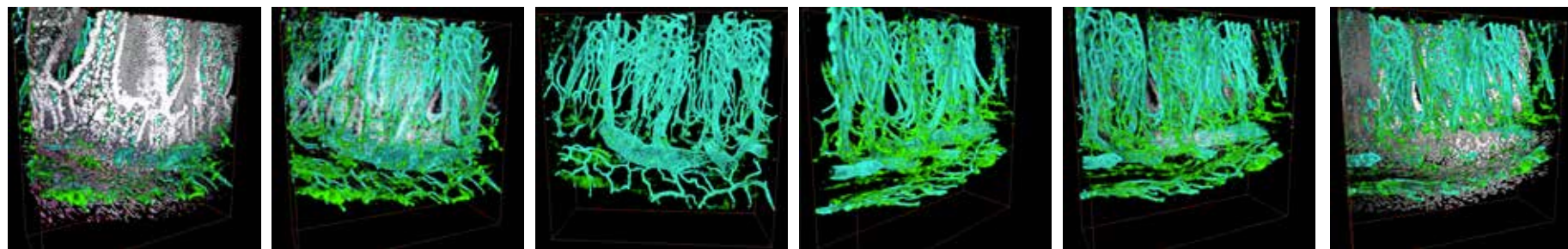
Despite years of research, proof of neurogenesis in the healthy digestive system has been elusive. Scientists knew that the numbers of enteric neurons in a healthy small intestine remain remarkably constant for most of the adult life. While previous studies have shown that the adult gut contains cells that can generate neurons in lab settings outside of living organisms, finding whether such cells truly give birth to neurons in healthy adult animals eluded scientists for years. ■

"WE NOW HAVE PROOF THAT, NOT ONLY DO THEY REGENERATE, BUT THE WHOLE NETWORK TURNS COMPLETELY OVER EVERY FEW WEEKS IN ADULT ANIMALS"

—PANKAJ JAY PASRICHA



In the first-ever images of the death and birth of intestinal nerve cells, the first photograph depicts the loss of adult mouse enteric nerve cells. The red shapes are dead neurons. Neurons that are stained with a green nuclear dye are marked for programmed cell death. The green shapes are new neurons emerging from their precursor cells, highlighted in red.



In this sample taken from a mouse small intestine, a network of neural precursor cells is highlighted in green. Johns Hopkins researchers have discovered that these stem-like precursors constantly generate nerve cells. The gut's blood vessels are highlighted in blue and the cell nuclei are gray. Every day, the researchers say, the gut loses and regenerates about five percent of its nerve cells. Over the course of a few weeks, the whole enteric nerve system turns over.



Far-Reaching Discoveries

This issue of *Inside Tract* reminds me of the remarkable breadth of clinical and scientific innovation in the Division of Gastroenterology and Hepatology—a testament to the extraordinary dedication of our faculty.

Hepatologist **Tinsay Woreta**, for example, is asking a question that, just a few years ago, we never thought we'd ask: What should we do with patients after their hepatitis C is cured? It's important to assess people who no longer harbor the virus but who have sustained liver damage. Dr. Woreta's work with transient elastography to measure liver fibrosis will help inform the way we diagnose and monitor liver fibrosis, post-HCV.

Noobia Chaudhry, a gastroenterologist who specializes in obesity medicine, is working with patients to help them not only lose weight, but also to change behaviors. Without behavior change, Dr. Chaudhry points out, weight loss is not sustainable. She and her colleagues in our Gastric Weight Loss Center offer a wide range of options for patients who are ready to take the first steps to weight loss.

Anne Marie O'Broin-Lennon's work focuses on solving the puzzle of pancreatic cysts, with the ultimate goal of knowing if and when to intervene. Her work on a "blood test biopsy" that detects early-stage pancreatic cancer by sifting through a blood sample for both mutated DNA and specific proteins could yield lifesaving discoveries.

And gastroenterologists **Jay Pasricha** and **Subhash Kulkarni** dispelled a myth that the intestinal neurons that we're born with stay with us for life. Dr. Pasricha provides us with the first-ever images of the death-and-rebirth cycle of the enteric nervous system.

When I consider the wide-ranging work of my colleagues to solve medical problems across a host of conditions, I am both humbled and proud.

As always, we welcome your thoughts, and we invite you to call on us if we can contribute to your practices.

Tony Kalloo, Director

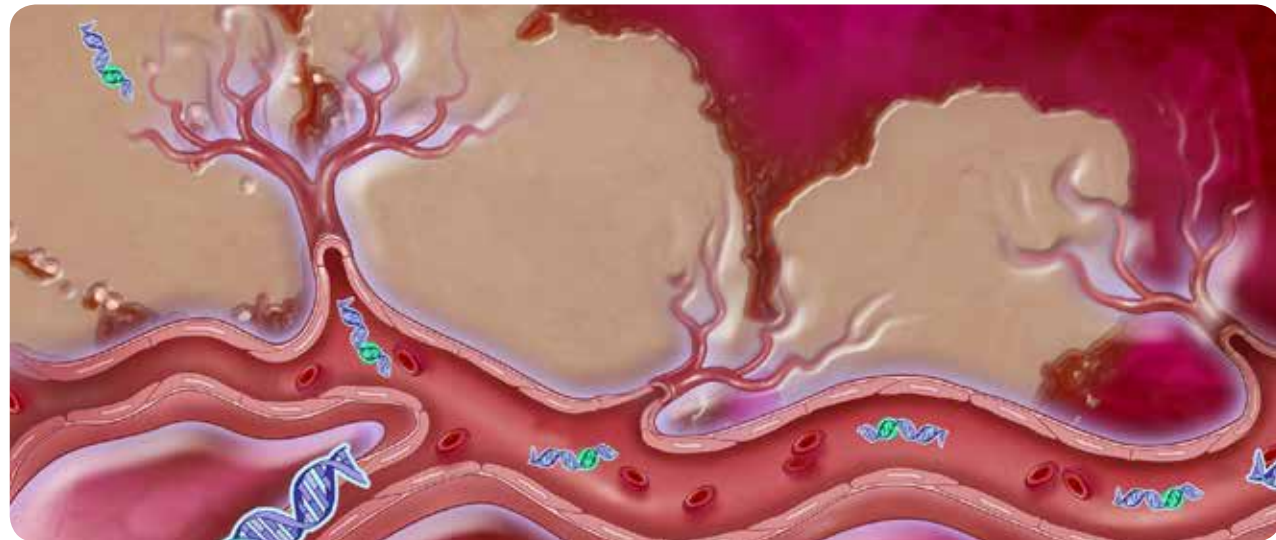
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DNA and Protein "Liquid Biopsy" Finds Tumors Faster



Testing blood for protein biomarkers as well as tumor-specific mutated DNA yielded more accurate detection of early-stage pancreatic cancer than searching for DNA alone.

Johns Hopkins scientists have developed a blood test that identifies early-stage pancreatic cancer sooner using a combination of tumor-specific DNA and protein biomarkers.

The "liquid biopsy" identified the markers in the blood of 221 early-stage pancreatic cancer patients. The researchers' results, described in a 2017 issue of the *Proceedings of the National Academy of Sciences*, show that detection of markers from DNA and its protein products was twice as accurate at identifying the disease as detection of DNA alone.

Such tests aim to fish out DNA molecules specific for cancer amid a wide sea of normal DNA circulating in the blood. Tumors tend to shed their mutated DNA into the bloodstream, enabling scientists to use genomic sequencing tools to sift through the blood and find such cancer-linked DNA.

"But a single marker on its own won't identify early cancers in most people," says gastroenterologist **Anne Marie Lennon**, director of the Johns Hopkins Multidisciplinary Pancreatic Cyst Program. "This study shows that it may be possible to use multiple markers to

nail down the detection of early pancreatic cancer with a blood test and to treat those patients earlier and better."

Early-stage pancreatic cancer is often unaccompanied by symptoms and many patients are unaware of the disease until it has advanced.

While the test is not ready to be used outside of research settings, mutated DNA of the type shed from tumors and found in blood is "exquisitely specific" for cancer, says **Bert Vogelstein**, co-director of the Ludwig Center at the Johns Hopkins Kimmel Cancer Center. "If cancer-linked DNA can be found in the blood of an individual, it is very likely that person has cancer," he says.

In the study, blood and tumor tissue samples were collected from 221 men and women with stages I and II pancreatic cancer and who underwent pancreatic surgery. Another 182 people with no known history of cancer, autoimmune diseases or chronic kidney disease donated blood samples for the study.

(continued on back cover)

OBESITY

Weight-Loss Team Aims to Change the Way Patients Think About Eating



If promoting weight loss in patients was as easy as telling them to eat fewer calories and exercise more often, **Zoobia Chaudhry's** job would be very different.

"It's easy to tell people what to do," says the Johns Hopkins Digestive Weight Loss Center obesity medicine specialist. "It's not so easy to tell them how to do it."

In addition to various endoscopic outpatient procedures that mimic the effects of bariatric surgery, the weight loss center

offers programs aimed at helping patients change the way they think about food and nutrition.

Chaudhry cites lifestyle change as the cornerstone of weight-loss management.

"It's not simply what you eat and how much you exercise," she says. "This is about a fundamentally different approach to think about the role of food in our lives."

Chaudhry works with patients both individually and in groups. She tailors weight-loss programs

After The Cure: What comes next for patients with post-HCV liver fibrosis?

Direct-acting antiviral treatment of patients with the hepatitis C virus is indisputably one of the most important medical advances of the 21st century. In only a few years, the therapy has saved untold lives in the US and around the world.

But Johns Hopkins hepatologist **Tinsay Woreta** wonders what comes next for patients who, while cured of HCV, suffered liver damage while they still harbored the virus.

“It’s a new era,” she says. “But there are still plenty of questions.”

Woreta is studying the progression of liver fibrosis in patients who have been cleared of the hepatitis C infection. In the short history of combating the infection with direct-acting antiviral (DAA) therapy, studies have described changes in liver fibrosis in the context of interferon-based therapies or have examined the effects only during DAA therapy and through three months of post-treatment.

By the end of this one-year study, which ends in March, 2018, Woreta says she expects to understand more about the treatment of the condition and how long to monitor patients after successful DAA therapy.

“There is real concern that patients who achieve cure are still at risk for cirrhosis and liver cancer,”

Woreta says, “particularly those with advanced fibrosis.”

The study looks at cases where physicians have used transient elastography (TE) to evaluate liver stiffness at various follow-up points after DAA therapy.

“TE is a noninvasive way to determine the degree of fibrosis,” says Woreta, noting that liver biopsy, long the gold standard, is imperfect, expensive and comes with significant patient risk. “This is a much better, more efficient way to learn what we need to know.”

Woreta and her co-principle investigator Carla Rodriguez of the Kaiser Permanente Research Institute are using data from electronic health records of hepatitis B and C patients who had TE at Johns Hopkins or Kaiser’s Mid-Atlantic facilities. They’re measuring long-term changes in a diverse cohort, looking at factors such as fibrosis stage, sex, race, age BMI and therapy status.

“We hope this research contributes to the way clinicians assess risk for liver cancer and other serious diseases,” says Woreta. “Looking at the rate of progression—or even regression—after therapy should teach us more about how and when to treat patients and should tell us about the need and the frequency of follow-up TE.” ■

Transient elastography uses ultrasound waves to determine the severity of liver fibrosis.



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—TINSAY WORETA

individually for each patient, based on that patient’s history and life situations.

A common mistake in weight loss, Chaudhry says, is too much ambition too soon. A patient accustomed to consuming large portions of food high in calories slams on the brakes, making radical cuts in calories and eating foods that are unfamiliar and, often, unappealing. Chaudhry calls that a recipe for failure.

“You don’t completely take away things from people,” she says. “Because you are making people deprived. And they’re going to get frustrated and they’re going to give up. It’s just not achievable.”

Chaudhry recalls a recent patient who reported that fried chicken and ice cream were among the high-calorie

foods he ate most frequently.

“We can’t cut those foods out entirely, though it may be more acceptable to him if I suggest that he eats these high-calorie foods once or twice a week or in smaller portion sizes” she says. “Without behavioral change, which is gradual and is based on patients being motivated by the results they see, that patient will not succeed.”

She adds that when patients are not successful in weight loss, they too often become discouraged and resigned to unhealthy habits.

“We set goals that are realistic and achievable,” says Chaudhry.

Both Chaudhry and her colleague **Kimberly Gudzone** have published oft-cited research on

the effectiveness and scientific basis for various commercial diets. They found that very few of the popular commercial programs on the market produced sustained weight loss. The two physicians are leading a new meal-replacement program at the Digestive Weight Loss Center that, in coordination with other strategies, can help certain patients lose extra pounds.

“It’s not for everyone,” says Chaudhry. “But for some people, it will be exactly right.”

The meal replacements simplify weight loss by decreasing the guesswork in nutrition. Patients are expected to consume meal replacement products, but continue to eat one meal per day with family and friends. As part of the twice-a-month program, patients

attend physician-led group sessions and receive education on key principles and skills for weight management.

“This really is about comprehensive lifestyle intervention and finding the right combination of what works,” she says. “So that neither unhealthy behaviors nor the weight come back.” ■

Watch a Video: Endoscopic Sleeve Gastroplasty for Weight Loss

Vivek Kumbhari, director of bariatric endoscopy for Johns Hopkins, answers questions about endoscopic sleeve gastroplasty, including what it involves and how it differs from weight loss surgery. Please visit: bit.ly/EndoscopicSleeveGastroplasty



DNA and Protein “Liquid Biopsy” Finds Tumors Faster *(continued from page 3)*



“A SINGLE MARKER ON ITS OWN WON’T IDENTIFY EARLY CANCERS IN MOST PEOPLE.”

—ANNE MARIE LENNON

In the first part of the experiment, the researchers used only the DNA to sift for mutations of a specific gene linked to pancreatic cancer. They identified early-stage cancers in 66 of the 221 patients.

Next, they turned to five specific protein biomarkers circulating in the blood. Such circulation protein markers are used to detect and monitor diseases like diabetes, as well as to monitor patients with a prior history of cancers. When the scientists looked only for the protein biomarkers in their study participants, they found them in 109 of the 221 patients, or 49 percent.

However, when they combined detection of DNA alongside the

protein biomarkers, the scientists correctly identified pancreatic cancer in 141 of the 221 patients (64 percent).

“A screening test needs to be highly reliable to spare people the worry and side effects of procedures following a positive test for cancer,” says **Kenneth Kinzler**, co-director of the Ludwig Center at Johns Hopkins.

Studies have shown that DNA can be identified in the blood of more than 85 percent of patients who have advanced cancers. This study is the first to show that it is feasible to identify tiny amounts of cancer DNA in the blood of patients with early cancer. ■

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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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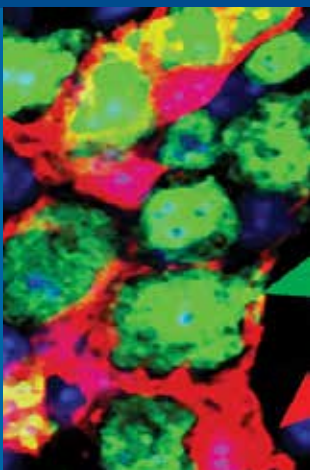
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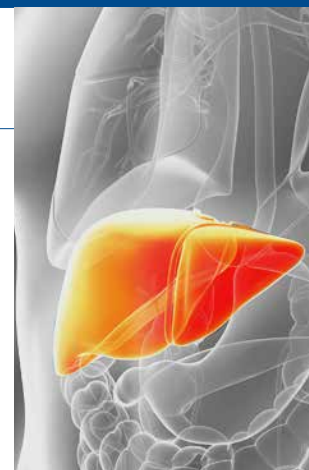
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