

ADVANCES IN GASTROENTEROLOGY AND GI SURGERY



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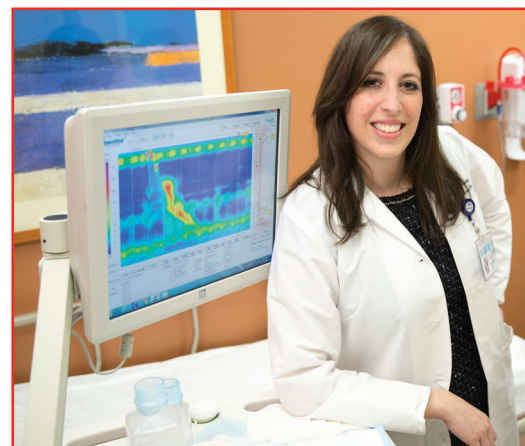
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Motility Disorders: A Comprehensive Management Approach

Disorders related to gastrointestinal motility and gastric acid production are among the most common problems in the field of gastroenterology and represent an enormous burden to patients, adversely affecting the quality of life of millions of Americans. At the Center for Gastrointestinal Motility and Physiology in the Division of Digestive and Liver Diseases at NewYork-Presbyterian/Columbia University Medical Center, specialists in the field bring decades of clinical and research expertise and experience to manage these often complex disorders.

Daniela Jodorkovsky, MD, Director of the Center, first became interested in gastroenterology during her residency in internal medicine at Mount Sinai Hospital, and went on to complete a general GI fellowship at Johns Hopkins Hospital, where she developed an interest in motility while receiving specialty training in motility and functional disorders. Dr. Jodorkovsky continued in the field at New York Medical College/Westchester Medical Center before joining Columbia in 2016.



Dr. Daniela Jodorkovsky

“Patients with motility disorders can be diagnostically challenging and challenging to manage,” says Dr. Jodorkovsky, who also serves as Director of the Gastroenterology Fellowship Program at Columbia.

(continued on page 2)

NAFLD Research: Making Progress on Many Fronts

When **David E. Cohen, MD, PhD**, Chief of the Division of Gastroenterology and Hepatology at NewYork-Presbyterian/Weill Cornell Medical Center, began research on nonalcoholic fatty liver disease (NAFLD) some 20 years ago, the condition was still coming into its own – so to speak. “Until about 30 years ago, doctors assumed too much liver fat was the result of immoderate alcohol consumption,” notes Dr. Cohen. “But in the 1980s, we really started to appreciate that those who had only modest alcohol intake had this condition anyway. And so the term nonalcoholic fatty liver disease was adopted. In the last 20 years, it has become one of the major issues in hepatology in the United States, tracking alongside the epidemic of obesity.”

According to a number of studies, an estimated 20 to 30 percent of people in the U.S. and other Western countries have too much fat in their liver. Of those, about 15 percent have some form of serious

liver disease. “In this country, the most common cause of liver disease is attributed to being overweight,” Dr. Cohen explains. Treatment answers are, however, more complex than changing habits.

“When you look at how can we manage NAFLD, there are a few approaches we might consider,” notes Dr. Cohen. “The first thing we always try is to get people to lose weight, but for the most part, weight loss through lifestyle and dietary changes is not a therapy that achieves the desired results. Weight loss surgeries are effective to treat obesity but are not indicated for the treatment of NAFLD. So we are looking for strategies to address the complications in liver processes – inflammation, fibrosis, and scarring – and there are therapies directed at those processes. But our main concern on an investigative level is how to stop the fat from accumulating in the first place. The assumption is that if there were no fat there’d be no inflammation and scarring.”

(continued on page 3)



Motility Disorders: A Comprehensive Management Approach *(continued from page 1)*

“Functional GI disorders make up about a quarter of general gastrointestinal patients,” says Dr. Jodorkovsky. “Motility disorders can span the entire GI tract from the esophagus to the anus. They can include problems related to the motor or neurological function of the gastrointestinal tract, such as achalasia, diffuse esophageal spasm, functional dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction, constipation, and fecal incontinence. Acid-related disorders, such as acid reflux and esophagitis, also come under this umbrella. And overlying many of these conditions are systemic disorders, such as scleroderma or other connective tissue diseases that can affect the GI tract.”

Advanced Diagnostics, Innovative Interventions

Dr. Jodorkovsky emphasizes that the Center for Gastrointestinal Motility and Physiology draws patients with some of the most complex and challenging motility disorders. Many come for second or third opinions. At the Center they aim to provide comprehensive care that includes a thorough diagnostic assessment, access to medical and surgical specialists within GI as well as in multiple disciplines, and management approaches that incorporate innovative therapies and procedures.

Patients benefit from the availability of the most technologically advanced motility tests, such as high-resolution esophageal and anorectal manometry; the SmartPill, which provides a motility map of the entire GI tract; and two types of reflux testing: a wireless capsule-based 48-hour pH monitoring test and a 24-hour pH/impedance measurement that evaluate patients for both acid and non-acid reflux.

“What I like about working with individuals with motility disorders is you have to look at the whole patient,” says Dr. Jodorkovsky. “Our close collaboration with other disciplines within Columbia enables us to provide seamless access to the wide range of services often needed. For example, we work very closely with surgeons and ENT specialists for patients with esophageal motility disorders. For fecal incontinence, constipation, and rectal prolapse, we call on colleagues in the colorectal surgery group. We collaborate with specialists in rheumatology to manage acid reflux and dysphagia in patients with underlying connective tissue diseases or neurologists for patients with intestinal involvement of neurological conditions. We are also accustomed to caring for patients who have complex and multiple non-GI-related disorders, such as heart or lung conditions, or those who have undergone solid organ transplantation.”

Dr. Jodorkovsky notes that nutrition counseling is another key component of managing motility and functional gut disorders. The Center’s nutritionists discuss how the patient’s diet can impact symptoms and how to avoid any situation or substance that may cause the symptoms to worsen.

The Center’s interventional specialists offer a number of novel treatment approaches, including peroral endoscopic myotomy – POEM – a procedure that allows for a longer myotomy than the traditional surgical myotomies performed to treat achalasia, or G-POEM, a similar procedure performed for gastroparesis. “For GERD therapy, several endoscopic techniques are also available. For example, endoscopic ultrasound can be used to perform an endoscopic fundoplication, or wrap, creating a reflux barrier,” says Dr. Jodorkovsky.

“Many of our patients present with multiple motility disorders. A person with an esophageal motility disorder may also have a functional irritable bowel syndrome or fecal incontinence. Treating these patients effectively requires expertise in all of the various disorders.”

— Dr. Daniela Jodorkovsky

Under the direction of principal investigator Marc Bessler, MD, Chief of Minimal Access and Bariatric Surgery, Columbia University Medical Center, a multicenter investigation is evaluating the EndoStim® lower esophageal sphincter neuro stimulation system for the treatment of severe reflux. “This is a novel and minimally invasive approach that does not alter the anatomy of the GI tract,” says Dr. Jodorkovsky, “There are strict recruitment inclusion criteria to make it as safe as possible. However, once the system becomes FDA-approved – and we are hoping it will as the preliminary data is very promising – it can then be extended to other indications. There is some discussion about whether there might be a role for patients who have other co-morbidities and are not candidates for standard therapies, such as fundoplication.”

The Center’s motility specialists also address opioid-induced constipation, providing counseling as well as newer targeted treatments that help restore bowel function in patients who have advanced illness and receive opioids for pain relief. “There are medications now for opiate-induced constipation and we provide them when necessary,” says Dr. Jodorkovsky. “The goal for the patient who doesn’t need them is to get off of them. People are also becoming more aware of a diagnosis called narcotic bowel syndrome, which I think has been under-recognized in the community but is important to know, especially with the opioid epidemic. The cause is a paradoxical increase in pain sensitization so the patients actually require escalating doses of opiates. Their abdominal pain gets worse even as they are taking more and more pain medication. The treatment is to wean off the opiates, but that’s a slow process and one where the physician-patient therapeutic relationship is key.”

In collaboration with the Division of Colorectal Surgery, the Center also provides pelvic floor biofeedback, a unique clinical service involving retraining treatment for patients with fecal incontinence, constipation due to pelvic floor dyssynergia, or chronic rectal pain.

“We have a vast network of referring providers and partner with other physicians to treat patients referred from the New York metropolitan area as well as internationally,” says Dr. Jodorkovsky. “We want our colleagues to know that our physicians and faculty are readily available to assist them in caring for their patients with these most challenging disorders.”

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NAFLD Research: Making Progress on Many Fronts (continued from page 1)

“So how can we understand how fat accumulates in the liver and what are reasonable approaches in a setting where nutritional excess continues despite efforts to treat? Much of our research is targeted toward that question,” says Dr. Cohen.

Focusing on a Family of Genes

“A theory that many, including myself, subscribe to is that for so much of human history our genes have evolved to store energy because we’re always scrambling,” notes Dr. Cohen. “Food was a scarce commodity, and survival depended on storage and economy. The genes that are most effective at doing this have, in some literature, been characterized as ‘thrifty genes.’ They’re always trying to reduce energy expenditure and maximize the length of nutrient storage. These genes are very adaptive in a resource or nutrient scarce environment, but they become what we call maladaptive as soon as there’s a surplus.”

Dr. Cohen’s laboratory seeks to identify new molecular targets that could be leveraged in the management of obesity and its common metabolic complications, including NAFLD and type 2 diabetes. “We are particularly focused on a family of genes that seems to try to figure out how much fat there is in a liver cell, for example, and then have regulatory events based on that,” says Dr. Cohen. “There are interesting proteins that will bind to a lipid molecule and appear to provide information that allows the cells to take certain actions.”

Because the liver serves the rest of the body by providing nutrients, Dr. Cohen explains, it has a special decision-making function. “The liver must export glucose to different tissues in the body. When the organism is not eating, it exports nutrients accordingly to the brain or to the muscles. And when the organism is eating, it switches into conservation and storage mode, but then the destination is fat tissue.”

Dr. Cohen and his colleagues have been investigating the mechanisms that make the metabolic measurements and decide on how to deliver the liver’s products. Using mice, his research group “identified genes that mediate this process,” he says. “If you overfeed, you begin to see these genes contributing to overproduction of glucose. And overproduction of glucose by the liver is, for example, a characteristic finding in type 2 diabetes. If we, for example, knock out the gene in a mouse and we put it under the same nutrient stress, that mouse won’t develop diabetes. That says to us that while this may not be the only cause of diabetes, it certainly contributes. We then try to target that protein.”

Dr. Cohen and his research team have made a small molecule that inactivates this protein that seems to work in mice. “While we are considering if this should be pursued for human application, we are currently using the molecules to tease apart exactly what the mechanisms are that allow the cell to think about when it’s ready to export nutrients and how that goes awry when the environment is too nutrient rich.”

The researchers are also looking at proteins in the same gene family that are involved in energy balance in animals. For their body size, mice lose much more heat than humans and need to worry about their heat loss. “Mice have a special organ called brown fat,



Dr. David E. Cohen

which is essentially a heater,” explains Dr. Cohen. “At room temperature mice use about half their calories to stay warm. At about four degrees centigrade, they burn 80 or 90 percent of their calories to create heat.”

In particular, Dr. Cohen’s group was looking at genes expressing itself in heat production. “Our original thinking,” he says, “was that all genes must be contributing to the large amount of heat required to keep the mouse warm. But interestingly, we noticed that one of the genes in that same family was very highly turned on by cold temperature.” To better understand the observation, the researchers created a mouse without that gene, assuming that it must somehow be contributing to creating heat. To their surprise, the mouse made even more heat. “We thought we would find that a mouse that can’t burn off the heat would get much fatter as

you fed it more calories at room temperature, but it was the other way around,” says Dr. Cohen. “That mouse could eat twice as much food and not gain weight.”

Imagine being able to inactivate the off switch to promote calorie burn? That is what the researchers were able to achieve genetically in the mice. “Now we’re trying to do this chemically,” adds Dr. Cohen. “The question is do humans use this brown fat? Human beings actually do have brown fat, an interesting discovery that occurred within the last 10 years. It was a serendipitous finding revealed in PET scans of patients undergoing evaluations for cancer. The PET scan lit up areas taking up large amounts of glucose. These areas were thought to be cancers, but biopsies determined they were brown fat. We know that people who have more of the brown fat tend to be less obese. Because we can show that if we deactivate a mouse off switch for heat then we can increase the amount of food they can eat and burn off at the same time, the hope is that we could do the same thing in humans.”

Dr. Cohen’s research in these and other areas of NAFLD continues to be supported by several grant awards from the National Institute of Diabetes and Digestive and Kidney Diseases. He currently serves as principal investigator on three NIDDK projects over the next five years that enable him and his team to pursue important research in the regulation of hepatic lipid and glucose metabolism and new mechanisms for the regulation of energy homeostasis. Their goal is to provide novel insights that could lead to new therapeutic targets for the management of nonalcoholic fatty liver disease.

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