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Digestive Diseases

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Spring 2005

Lap-Assisted Endoscopic Resection: Latest MIS Innovation

Surgeons and gastroenterologists at NewYork-Presbyterian Hospital/Weill Cornell Medical Center are working with a new procedure that combines carbon dioxide (CO_2) colonoscopy with laparoscopy to treat benign colon conditions and avoid the use of riskier bowel resections.

"It's really exciting. We're trying to expand the horizons of minimally invasive surgery," said Jeffrey Milsom, MD, who helped to pioneer the technique more than a year ago.

"I've always thought that endoscopy and laparoscopy would be useful in combination," agreed Mark Pochapin, MD. "The procedures complement each other well in challenging cases of colon polyps and other colon disease."

In the combined procedure, the gastroenterologist and laparoscopic surgeon work as a team to treat benign colon conditions, such as polyps, when colonoscopy alone would pose an increased risk to the patient because of the size or location of a polyp. Using CO_2 rather than room air to insufflate the colon makes it possible to perform the 2 procedures together because CO_2 is absorbed rapidly and does not distend the abdomen the way air does, according to Dr. Milsom.

The laparoscopic surgeon provides assistance and serves as a kind of insurance policy for the gastroenterologist performing the colonoscopy. Say,

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Hospital Takes Leading Role in Groundbreaking NIH Study

NewYork-Presbyterian Hospital researchers are leading the way in investigating bariatric surgery, an important management approach to the growing problem of obesity in the United States. The Hospital is one of a consortium of 6 centers across the country that have been selected by the National Institutes of Health (NIH) to take part in the groundbreaking 5-year Longitudinal Assessment of Bariatric Surgery (LABS) study.

NewYork-Presbyterian Hospital physicians are leading the way in national research efforts to curb the troubling obesity pandemic in the United States.

"At least two thirds of the adult population of the U.S. is currently overweight, and there are projections that by 2025 a similar proportion will be overtly obese," said Paul Berk, MD. The NIH is providing $2 million to the Hospital to develop protocols designed to set standards for the kind of results that can be achieved "when bariatric surgery is done by very experienced surgeons in optimal settings," said Dr. Berk.

After a year of working collaboratively with the other centers to develop the protocols, according to Dr. Berk, "we're about to start entering the first patients into these protocols within the next couple of months."

Many of these patients will be in the weight category known as morbid obesity—

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NewYork-Presbyterian
The University Hospital of Columbia and Cornell

Celiac Disease: Less Baffling, Still Surprising

Long believed to be a rare childhood sensitivity to wheat protein, today celiac disease is understood to be a chameleon-like, multisystem disorder with a strong genetic component. It may be diagnosed at any age and, in severe cases, can be life-threatening. As a small-bowel enteropathy provoking a variety of gastrointestinal complaints, celiac disease is also associated with a large number of extraintestinal conditions, ranging from bone disease to type 1 diabetes, liver disease, neurologic disorders, and cancer.

"It is actually one of the most common inherited disorders that physicians are going to see, occurring in about 1% of the population," said Peter Green, MD. The complexities of celiac disease and its previously unrecognized incidence, together with prospects for discovering drug treatments and unraveling the disorder's genetic basis, have sparked international interest and research in refining the diagnosis of the disease.

Dr. Green directs the Celiac Disease Center at NewYork-Presbyterian Hospital/Columbia University Medical Center, which coordinates both clinical and research initiatives involving the disorder. Founded in 2001, the Center receives referrals, provides patients with comprehensive and coordinated care and management, and offers education to both patients and physicians. In addition, the Center is engaged in a variety of research projects aimed at better understanding this multiform disease.

Epidemiology and ever more sensitive diagnostic tools have in recent years clarified the surprising prevalence of celiac disease. Symptomatic patients may present with diarrhea, and the clinical picture can include malabsorption or irritable bowel syndrome. But other patients are asymptomatic, and the silent and insidious forms of the disease may lead to its extraintestinal manifestations. In all cases, the diagnosis is confirmed by endoscopy and biopsy.

Physicians should consider screening for celiac disease as the underlying disorder in a number of conditions seen in both children and adults (Table). With 11 years on average between symptom onset and diagnosis, a chief goal of the Celiac Disease Center, according to Dr. Green, is to raise awareness of the disease and reduce this lag time.

The complexities of celiac disease, together with prospects for discovering drug treatments and unraveling the disorder's genetic basis, have sparked international interest and research.

Often classified as an autoimmune disorder, celiac disease nonetheless has a known environmental trigger—gluten, the protein component of wheat, barley, and rye—and may be viewed as an inflammatory condition provoked by a T-cell–mediated immune response. The genetic component is very strong, with the disease affecting 70% of identical twins; 2 of the histocompatibility genes (HLA-D2 and -D8) are clearly implicated. However, this picture remains incomplete. Non-HLA genetic linkages and environmental factors other than gluten, likely to be

Associated Conditions/ Indications for Screening for Celiac Disease

- Failure to thrive
- Short stature
- Down syndrome
- First-degree relatives of patients with celiac disease
- Chronic fatigue
- Diabetes mellitus (type 1)
- Gastrointestinal complaints
  - Dyspepsia, esophageal reflux
  - Diarrhea, constipation
  - Abdominal pain
- Reduced bone density
  - Osteopenia, osteoporosis
- Hypocalcemia
- Secondary hyperparathyroidism
- Neurologic problems
  - Ataxia, peripheral neuropathy
  - Epilepsy (with and without occipital calcifications)
- Anemia
  - Iron, folate, or vitamin B_{12} deficiency
- Dermatitis herpetiformis
- Aphthous stomatitis
- Dental enamel defects
- Gynecologic problems
  - Delayed menarche, premature menopause
  - Infertility, spontaneous abortion
- Liver disease
  - Primary biliary cirrhosis
  - Autoimmune hepatitis
  - Elevated transaminases
- Sjögren's syndrome

Source: Celiac Disease Center at Columbia University

discovered in the future, should help clarify the onset and course of the disease.

The treatment for the intestinal manifestations of celiac disease is the elimination of gluten from the diet. This solution works with intestinal symptoms and also leads to reversal or abatement of some, though not all, of its systemic manifestations. With bone disease, for example, a gluten-free diet improves bone mineral density; it also reduces the risk for malignancies, such as non-Hodgkin's lymphoma. In practice, however, gluten is difficult to avoid in the average American diet. The Center employs nutritionist Anne Lee to provide nutritional guidance, and offers patients a variety of support modalities.

NewYork-Presbyterian/Columbia's proximity to an ethnically diverse population—thanks to its location in upper Manhattan—has been an asset for epidemiologic work. In 2001, Dr. Green and colleagues reported on the long duration of symptoms before diagnosis (*Am J Gastroenterol* 2001;96:126-131). In addition, that paper reported a high percentage of patients (18%) also suffering from thyroid disease, an association that Center investigators continue to study, in collaboration with the Columbia University Mailman School of Public Health. Although female patients with celiac disease outnumber male patients (2:1 or 3:1), in a study published this year (*Scand J Gastroenterol*. 2005;40:183-187), Dr. Green developed evidence showing that men suffer more severe manifestations of malabsorption, indicated by reduced bone density and lower serum cholesterol. Moreover, surprisingly, men with celiac disease are as likely as women to develop autoimmune disease, closing the usual gender gap.

Overall, the Center participates in a wide range of ongoing clinical and laboratory studies. From basic bench research, according to Dr. Green, researchers "hope to discover the pathophysiologic mechanisms of disease with a view to finding information that will help in drug discovery."

Peter H.R. Green, MD, is Director, Celiac Disease Center at NewYork-Presbyterian Hospital/Columbia University Medical Center, and is Professor of Clinical Medicine at Columbia University College of Physicians and Surgeons. E-mail: pg11@columbia.edu.

NewYork-Presbyterian Digestive Diseases

is a publication of the Digestive Diseases Center of NewYork-Presbyterian Hospital. The Digestive Diseases Center is at the forefront of research and practice in the areas of gastroenterology; GI surgery; and liver, bile duct, and pancreatic disorders. NewYork-Presbyterian Hospital/Columbia University Medical Center and NewYork-Presbyterian Hospital/Weill Cornell Medical Center are respectively affiliated with Columbia University College of Physicians and Surgeons and the Weill Medical College of Cornell University.

New Surgical Chief Brings Innovative GI Procedure to Hospital

Stricturoplasty techniques are an important surgical innovation in the treatment of Crohn's disease because they alleviate obstructive symptoms without the need for intestinal resection. Preservation of bowel is a critical advantage in Crohn's disease because of its recurrent nature. However, until a new procedure called side-to-side isoperistaltic stricturoplasty (SSIS) was developed by Fabrizio Michelassi, MD, this approach was limited to small-bowel strictures no longer than 15 cm.

The SSIS, which has been quickly adopted by centers of excellence for the surgical treatment of Crohn's disease around the world, has proved to be highly effective for avoiding extensive small-bowel resections in patients with disease of the jejunum and ileum, or with recurrent neoterminal ileitis. Dr. Michelassi has brought his expertise in this procedure, as well as in other treatments of gastrointestinal disorders, to NewYork-Presbyterian Hospital/Weill Cornell Medical Center as Chairman and Surgeon-in-Chief for Surgery.

"Stricturoplasties have been highly effective for preserving bowel and have been adapted for use throughout the intestine, but the initial procedures were not well suited to lengthy strictures in the small bowel," said Dr. Michelassi. "The SSIS extended the concept of the bowel-conserving procedure to patients with extensive disease, a group that may be in greatest need of bowel sparing."

In the procedure, the mesentery of the diseased portion of the bowel is divided. Then the proximal intestinal loop is moved over so that it is side to side with the distal loop. Seromuscular nonabsorbable sutures are placed to join the 2 loops. The surgeon then performs a longitudinal enterotomy on both loops, spatulating the intestinal ends to avoid blind stumps. The surgery is completed with an internal row of absorbable sutures and an outer layer of seromuscular interrupted, nonabsorbable sutures (Figure).

"We have more than 12 years of experience with this new technique, and the results obtained are very encouraging," noted Dr. Michelassi. "We are now gathering data for publication from centers around the world with experience with this procedure and have been very encouraged by reports of very low morbidity and acceptable recurrence rates in the hands of different surgical teams. We were initially concerned that applying an anastomotic suture line in diseased intestine would lead to a high complication and recurrence rate. Fortunately, our concerns have not been confirmed in what is now a large clinical experience."

At centers that have adopted this procedure, the surgical methodology has remained consistent with that originally described by Dr. Michelassi. In addition, attesting to the safety of the procedure, there has not been any significant variation in overall complication rates. The most commonly reported serious complications have been gastrointestinal

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> "A decade after the original description of the procedure, the side-to-side isoperistaltic stricturoplasty has gained a rightful place among bowel-sparing procedures for Crohn's disease. Its implementation offers a conservative solution."
>
> — *Fabrizio Michelassi, MD*

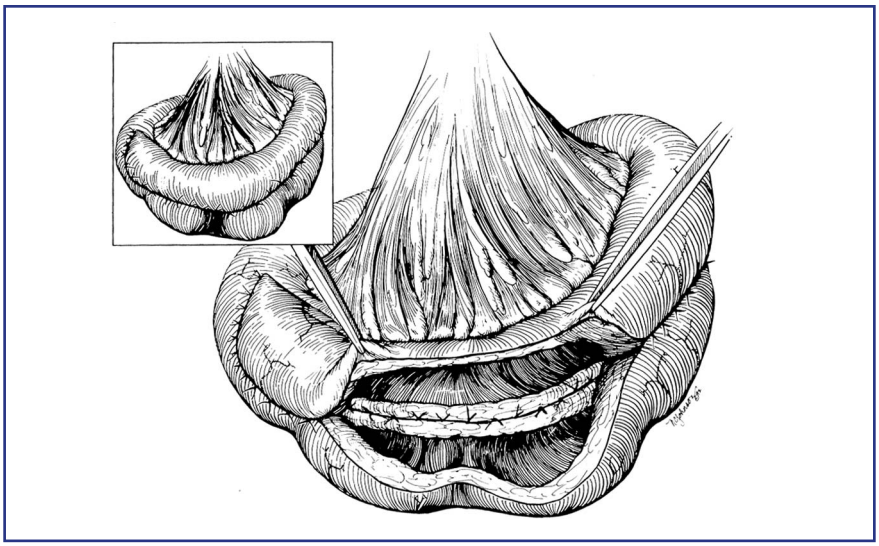

Figure. Illustration of the colon following side-to-side isoperistaltic stricturoplasty (SSIS), a procedure developed by Fabrizio Michelassi, MD. Note that the outer and inner suture lines are continued and finished anteriorly.

Source: Reproduced from Michelassi F. Side-to-side isoperistaltic strictureplasty for multiple Crohn's strictures. *Dis Colon Rectum* 1996;39:345-349.

New GI Chief's Research Links Cancer and Infection

An unexpected link between chronic gastrointestinal infection and cancer has been suggested by a study that has implicated bone marrow stem cells in malignant transformation. The circulating cells are initially recruited for epithelial repair of inflamed tissue but eventually progress to cancer.

This study has challenged some fundamental assumptions about how gastric cancer develops, according to Timothy C. Wang, MD, Chief, Division of Digestive and Liver Diseases at NewYork-Presbyterian Hospital/Columbia University Medical Center. It was outlined late last year in *Science* (2004;306:1568-1571), and it may be relevant to other malignancies linked to infections. This area promises to be a focus of ongoing research at the Hospital.

"This is still in the basic science stage of investigation, but the clinical value of identifying the origins of cancer includes earlier detection and intervention when the processes are easier to reverse," explained Dr. Wang. "We think our model may explain a great deal about how some cancers develop."

The study was conducted in animals infected with *Helicobacter felis*, a bacterium closely related to *Helicobacter pylori*, a common cause of infection in humans that is associated with increased risk for gastric cancer. In the animal model, inflammation associated with chronic *H. felis* infection led to repopulation of the damaged epithelium with bone marrow stem cells. These cells were then followed through progression to metaplasia, dysplasia, and intraepithelial cancer. None of these steps toward malignancy, including initial recruitment of the bone marrow stem cells, were observed when the gastric epithelium of the animal models was subjected to injury or acute inflammation (Figure).

"The bone marrow stem cells began to engraft in the stomach lining after about 20 weeks of infection. While these cells did start to differentiate to take on some of the characteristics of stomach epithelium, they quickly showed abnormalities similar to cancer cells, including distorted shapes and rapid growth," Dr. Wang said. Although he believes that the cells were recruited for healing, he speculated that it is the chronic inflammation induced by the *H. felis* infection that inhibits normal development and leads to malignant transformation.

In humans, chronic *H. pylori* infection is thought to be acquired in childhood and persist through adulthood. The prevalence of *H. pylori* infection in the United States is estimated to be between 20% and 30%, but it is much higher in other parts of the world. In most individuals, *H. pylori* infection does not appear to have any clinical consequences, but it appears to place a subpopulation at increased risk for gastric cancer. It has long been theorized that in individuals with *H. pylori* infection who develop gastric malignancy, the chronic gastritis caused by this bacterium eventually leads to the malignant transformation of normal epithelial cells. New studies indicate that if the animal models infected with *H. felis* are relevant, stem cells migrating to the epithelium, rather than resident epithelial cells, play the key role in producing cancer.

"There are many examples in which inflammation due to an infection is implicated in development of malignancies. It is estimated that up to 15% of cancers are related to infection and that more than 50% are related to inflammation," noted Dr. Wang in outlining one of the reasons why this study has attracted interest. "The involvement of bone marrow stem cells has not been observed previously and may provide new insight into how cancers related to inflammation develop."

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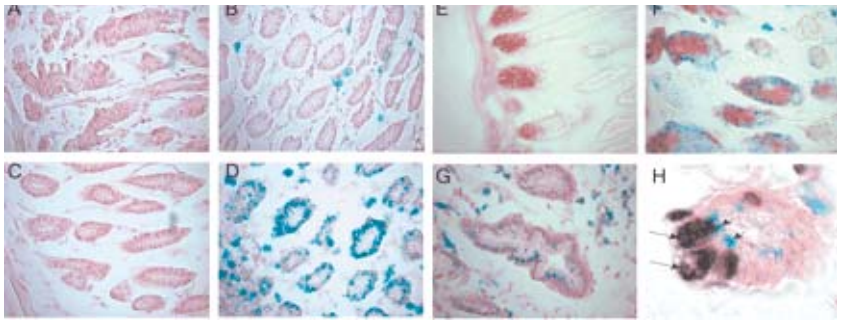

Figure. A and C: X-gal staining (blue) of C57BL/6 mouse transplanted with wild-type marrow and (A) mock infected or (C) infected with *H. felis* for 30 weeks. **B and D:** C57BL/6 mouse transplanted with ROSA26 marrow and (B) mock infected or (D) infected with *H. felis* for 30 weeks. **E:** Wild-type mouse with chronic *H. felis* infection shows TFF2 (red) staining and is X-gal negative (blue). **F:** In the infected ROSA26-transplanted mouse, BMDCs are positive for both ß-galactosidase (blue) and TFF2 (red). **G:** Dysplastic glands in the infected ROSA26 mouse express abundant ß-galactosidase activity. **H:** Mitotic activity in BMD epithelial cells demonstrated by coexpression of cytoplasmic ß-galactosidase activity (short arrows; blue) and chromosomal BrdU incorporation (long arrows; brown). 10-µm frozen sections. Reprinted from *Science*.

Crohn's

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hemorrhage and anastomotic dehiscence (in fewer than 2% of patients). In addition, the long-term results with the SSIS are reassuring in demonstrating a low risk for immediate or long-term surgical complications.

Small-bowel obstruction is a result of inflammation and bowel wall thickening or chronic scarring that results in fixed strictures. Although there has been progress in medical therapies with the development of monoclonal antibodies that turn off the inflammatory response, surgery is still essential when therapies fail and obstruction develops. Although surgery is highly effective for relieving acute symptoms and restoring bowel function, conservative surgery is essential to avert the risk for recurrences requiring additional resections.

"It has been estimated that no more than half to two thirds of the bowel can be resected before absorption of nutrients is dramatically altered," said Dr. Michelassi. "Short-gut syndrome due to multiple resections is an uncommon occurrence, but conservative surgery plays a critical role in keeping this risk low." It is estimated that about one third of patients require a second resection within 10 years after their index procedure, and 50% have undergone at least one additional surgery when follow-up is extended to 20 years.

"A decade after the original description of the procedure, the side-to-side isoperistaltic stricturoplasty has gained a rightful place among bowel-sparing procedures for Crohn's disease," added Dr. Michelassi. "Its implementation offers a conservative solution to extensive Crohn's disease of the small bowel. Further follow-up is necessary to evaluate the long-term recurrence rate at each site and to assess its potential for neoplastic transformation."

Fabrizio Michelassi, MD, is Chairman and Surgeon-in-Chief for Surgery, at NewYork-Presbyterian Hospital/Weill Cornell Medical Center, and is Lewis Atterbury Stimson Professor and Chairman of the GI Surgery Department at Weill Medical College of Cornell University. E-mail: fam2006@med.cornell.edu.

Infection

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Confirming that the animal model is relevant to human gastric cancer will be difficult because there is no current methodology for demonstrating that cells in a malignancy were initially recruited from the bone marrow. In the animal studies, bone marrow was transplanted containing cells with a genetic marker so that they could be distinguished from resident epithelial cells. However, the observations in this animal model are credited with opening a whole new area of investigation.

"It is not fair to say that these studies really have any clinical correlations at this point, but the model has produced some potentially important new directions in basic science that could have very important implications in clinical medicine down the road," Dr. Wang explained. "Clearly, the more we understand about the pathogenesis of cancer, the more opportunities we are likely to identify for intervening effectively."

Timothy C. Wang, MD, is Chief, Division of Digestive and Liver Diseases at NewYork-Presbyterian Hospital/Columbia University Medical Center, and is Dorothy L. and Daniel H. Silberberg Professor of Medicine at Columbia University College of Physicians and Surgeons. E-mail: tcw21@columbia.edu.

Colon

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for example, the colonoscopist discovers a large polyp that is too dangerous to remove endoscopically because of the risk for bowel perforation. Normally, a separate surgical procedure would be scheduled to remove the polyp by resecting the bowel. The surgery probably would be performed laparoscopically.

However, by combining laparoscopy with colonoscopy, the gastroenterologist can proceed more aggressively to remove the polyp. If the colonoscopist damages or burns the colon wall, "All you do is just put a couple of stitches in it laparoscopically and repair it immediately," said Dr. Milsom. "There is minimal risk to the patient from a perforation or infection."

The surgeon can also facilitate colonoscopic removal of a large polyp that is partly obscured by a bend or fold in the colon wall by straightening the colon wall or invaginating it to allow the colonoscopist an unobstructed view of the site. Dr. Pochapin calls the combined procedure "laparoscopically assisted endoscopic resection."

Patients who undergo laparoscopically assisted endoscopic resection, Dr. Milsom said, can "go home the next day, instead of being in the hospital for 3 to 5 days or a week, having lost a section of their intestine." He said the combined procedure with the use of CO_2 insufflation has been performed more than 10

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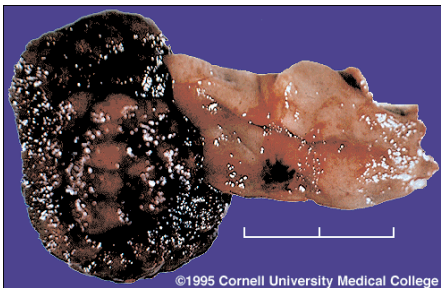

A colon polyp. A new procedure combines carbon dioxide (CO_2) colonoscopy with laparoscopy to treat benign colon conditions such as polyps when traditional colonoscopy might be risky.

Bariatric

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that is, with a body mass index (BMI) of 40 or more—and as many as half of the patients will have BMIs of 50 or more, which is twice what is considered normal. "This is not simply a cosmetic issue," Dr. Berk said.

Medical regimens have been able to produce significant short-term weight loss in some obese individuals, but they generally have not been effective in maintaining these outcomes long term, Dr. Berk said. Surgical interventions, "produce the best results, with long-term persistence of weight loss and alleviation of some of the comorbidities, including improvements in diabetes."

As a result, the number of patients undergoing bariatric surgery in this country has grown significantly, going from fewer than 20,000 procedures a year in the early 1990s to some 140,000 last year. This rapid increase has left some unresolved issues in its wake. Among these is determining the optimal choice of available operative procedures for the individual patient.

Michel Gagner, MD, said the protocols will be seeking answers to "a lot of questions about bariatric surgery that people don't know the answers to: Is it safe and beneficial? What are the complications and the outcomes? Does it really cure diabetes?"

Four surgeon-investigators at NewYork Presbyterian Hospital are expected to perform bariatric procedures on about 2,000 of the 12,000 patients enrolled nationally in LABS. In addition to Dr. Gagner, they are Marc Bessler, MD; William B. Inabnet, MD; and Alfons Pomp, MD. All 4 doctors are highly experienced in the various forms of bariatric surgery. "Among the 4 of us, we've done thousands of these surgeries," said Dr. Pomp.

Research Director Gladys Sprain, PhD, who helped to write the NIH proposal, said that "all new patients that come into NewYork-Presbyterian Hospital for weight loss surgery, regardless of the type that they elect, will be recruited to participate in the study."

LABS is divided into 3 parts. LABS I, involving the entire cohort of 12,000 patients, will be "straightforward and simple," according to Dr. Inabnet, and will gather basic intraoperative data and 30-day mortality figures. In LABS II, a subset of approximately 240 cases per year at each center will be designated for more intensive physiologic and psychological assessments, ranging from changes in mood states to changes in the thickness of the cardiac walls. The effect of the operation on comorbidities such as diabetes, hypertension, and sleep apnea will also be studied. LABS III will entail even more detailed analyses.

The protocol will also seek to determine the safest and most effective types of bariatric surgery for various levels of obesity. For those with the very highest levels of obesity, Dr. Gagner developed a 2-stage procedure in September 2000.

"In the first stage, a relatively simple sleeve gastrectomy is done laparoscopically," Dr. Berk said. "Typically, patients lose close to 100 pounds and then either plateau or start to regain weight. But in this protocol, when maximal weight loss is achieved, the patients become a much better risk for a more substantial second operative procedure."

Dr. Inabnet said there are still "a lot of nonbelievers, medical doctors who don't fully appreciate the good effects of bariatric surgery because some of the earlier procedures gave bariatric surgery a bad name." (Early procedures such as jejunoileal bypass produced mixed results.) He added that one of the purposes of LABS "is to validate the excellent outcomes that we see in most of our patients and allow that to actually improve healthcare for all patients."

Medical regimens have been able to produce significant short-term weight loss in some obese individuals, but they generally have not been effective in maintaining these outcomes long term.... As a result, the number of patients undergoing bariatric surgery in this country has grown significantly.

Paul D. Berk, MD, is Assistant Attending Physician at NewYork-Presbyterian Hospital/Columbia University Medical Center, and is Assistant Professor of Medicine at Columbia University College of Physicians and Surgeons. E-mail: pb2158@columbia.edu.

Marc Bessler, MD, is Surgical Director, Center for Obesity Surgery and Director, Laparoscopic Surgery at NewYork-Presbyterian Hospital/Columbia University Medical Center, and is Assistant Professor of Surgery at Columbia University College of Physicians and Surgeons. E-mail: mb28@columbia.edu.

Michel Gagner, MD, is Director, Bariatric Surgery Program at NewYork-Presbyterian Hospital/Weill Cornell Medical Center, and is Professor of Surgery at Weill Medical College of Cornell University. E-mail: mig2016@med.cornell.edu.

William Barlow Inabnet, III, MD, is Chief, Endocrine Surgery at NewYork-Presbyterian Hospital/Columbia University Medical Center, and is Assistant Professor of Surgery at Columbia University College of Physicians and Surgeons. E-mail: wbi2102@columbia.edu.

Alfons Pomp, MD, is Assistant Attending Physician at NewYork-Presbyterian Hospital/Weill Cornell Medical Center, and is Assistant Professor of Surgery at Weill Medical College of Cornell University. E-mail: alp2014@med.cornell.edu.

Colon

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times since the technique was developed at NewYork-Presbyterian/Weill Cornell. In a few instances, he said, a similar procedure has been used to locate and repair a site of bleeding in the colon.

The procedure can also work the other way around, according to Dr. Pochapin, with the endoscopist providing support to a laparoscopic surgeon who is performing a colectomy. "If the laparoscopist needs help in identifying a lesion to minimize the resection, the endoscopist can put the scope in there and define the margins for the laparoscopist to resect it," he said.

The procedure is not for every patient. Dr. Milsom said, "We tell all the patients, 'Look, if we get in there and it doesn't look right, you're going to get a bowel resection.' So they're prepared as they go in. We're building more and more sophisticated tools for working both inside the lumen of the intestine and laparoscopically. So down the line, we're going to have the potential to treat more and more diseases by this method, like Crohn's disease and diverticulitis."

Jeff Milsom, MD, is Chief, Division of Colorectal Surgery at NewYork-Presbyterian Hospital/Weill Cornell Medical Center, and is Professor of Surgery, Colon and Rectal Surgery Section at Weill Medical College of Cornell University. E-mail: num2002@med.cornell.edu.

Mark Pochapin, MD, is Director, Jay Monahan Center for Gastrointestinal Health at NewYork-Presbyterian Hospital/Weill Cornell Medical Center, and is Director, GI Endoscopy, Division of Gastroenterology and Hepatology and Associate Professor of Clinical Medicine at Weill Medical College of Cornell University. E-mail: mbpocha@mail.med.cornell.edu.

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NEWYORK-PRESBYTERIAN Digestive Diseases

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NewYork-Presbyterian Hospital
525 East 68th Street
New York, NY 10021

Important news from the Digestive Diseases Services Center of NewYork-Presbyterian Hospital, leading the way in treatment and research in gastrointestinal, liver and bile duct, pancreatic, and nutritional disorders.

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