

# NEW YORK-PRESBYTERIAN Digestive Diseases

Affiliated with COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS & SURGEONS and WEILL MEDICAL COLLEGE OF CORNELL UNIVERSITY

## At the Forefront: Upper Gastro MIS Procedures

A team of surgeons at New York Weill Cornell Medical Center—led by Dennis L. Fowler, MD—is pioneering the use of the minimally invasive laparoscopic technique in upper gastrointestinal procedures, such as esophagectomy, removal of gastrointestinal stromal tumors, myotomy for achalasia, and distal pancreatectomy. Commonly used in cholecystectomy or antireflux surgery, the laparoscopic technique's advantages include reduced patient discomfort and recovery time.

"None of the indications involves large numbers of patients, but together they substantially increase the proportion of upper gastrointestinal surgical procedures that can be performed with minimal invasion," reported Dr. Fowler.

The advantages are enormous. For gastrointestinal stromal tumors of the

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## Laparoscopic Colorectal Surgery Promising in Outpatient Setting

Minimally invasive laparoscopic colorectal surgery is one of the fastest growing fields worldwide," Richard Whelan, MD, observed. One of the major centers of this growth is at New York-Presbyterian Hospital.

### THERAPEUTIC INNOVATIONS

Researchers at Columbia University College of Physicians & Surgeons and Weill Medical College of Cornell University, the 2 medical schools affiliated with New York-Presbyterian Hospital, are investigating several lines of research, including the feasibility of outpatient laparoscopic colorectal surgery, particularly on patients with either colorectal cancer or inflammatory bowel disease (IBD). Researchers are also investigating the immunologic and oncologic effects of conducting surgery via traditional large-incision methods versus minimally invasive laparoscopic techniques. Research being pursued at New York Weill Cornell Medical Center includes the efficacy of laparoscopic surgery in IBD patients and cancer patients.



Researchers are investigating the feasibility of outpatient laparoscopic colorectal surgery in patients with colorectal cancer or inflammatory bowel disease (IBD).

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## 'Unexplored Territory' Yields Progress In Advanced Pancreatic Cancer

An unprecedented number of patients with advanced pancreatic cancer are achieving clinical response with a new combination chemotherapy regimen currently under investigation at the Herbert Irving Comprehensive Cancer Center at Columbia Presbyterian Medical Center.

In a recent trial of the regimen, tumor shrinkage was seen in nearly half the patients, who had either metastatic or advanced inoperable pancreatic cancer. That compares to response rates in the single digits, or just above, for current chemotherapy regimens.

"We are not curing people yet, but we are certainly improving responses and quality of life, with the ultimate goal, hopefully soon, of getting patients to live a lot longer with this disease," said Robert L. Fine, MD, who heads an experimental therapeutics laboratory devoted to developing new and novel therapies for pancreatic cancer, melanoma, brain cancer, and breast cancer.

*"A correct analysis of the past 30 to 40 years of [pancreatic cancer] is that there has been very little progress... We are not curing people yet, but we are certainly improving responses and quality of life, with the ultimate goal, hopefully soon, of getting patients to live a lot longer with this disease."*

—Robert L. Fine, MD

Prospects for treatment and cure are usually dismal in pancreatic cancer, one of the most virulent and fastest-growing malignancies that can occur in humans. Median survival is approximately 3 to 4 months for patients who present with disease metastatic to the liver, which

GTX Regimen in Pancreatic Cancer Metastatic to Liver: Response at 3 Cycles

Patients (n)	Partial Response (%)	Stable Disease or Minor Response (%)	No Response (%)	Clinical Benefit (PR+SD)
All (32)	15* (47%)	10 (31%)	7 (22%)	25 (78%)

Subset of patients who previously failed:

CPT-11/ Gemzar (4)	2 (50%)	2** (50%)	0	4 (100%)
Gemzar alone (6)	2 (33%)	2 (33%)	2 (33%)	4 (66%)

\*Three of these patients had a clinical complete response of all metastatic disease by cycle 8.

\*\*Includes 1 minor response (tumor shrinkage of less than 50%).

comprises about 50% of all new cases of pancreatic cancer.

The drug 5-fluorouracil (5-FU), when used alone, does palliate such patients but does not improve survival; in trials,

tumor responses were seen in only about 8% of subjects. A more recent drug for these patients is gemcitabine (Gemzar); alone, this agent has produced response rates of 10% to 12% in advanced pancreatic cancer, and increased median survival, but only by about 5 weeks.

"A correct analysis of the past 30 to 40 years of this disease is that there has been very little progress," said Dr. Fine, who trained as a molecular pharmacologist at the National Cancer Institute.

Now under way are investigations of "GTX" (Gemzar, Taxotere, and Xeloda [gemcitabine, docetaxel, capecitabine, respectively]), a combination regimen developed to circumvent pancreatic cancer cell drug resistance mechanisms by exploiting biochemical synergies within the GTX combination that have been observed in the laboratory by Dr. Fine and his colleagues.

Patients in the current study, many of whom had failed prior chemotherapy, received the GTX regimen in 2-week cycles. The regimen included 2 oral doses of Xeloda daily, plus intravenous Gemzar and low-dose intravenous Taxotere on days 4 and 11 of the cycle. Response was evaluated after 3 cycles.

Of 44 patients studied, 32 had pancreatic cancer metastatic to the liver. Partial

tumor response (defined as reduction in tumor of at least 50%) occurred in 15 of 32 patients (47%), while another 10 patients (31%) had a minor response (less than 50% reduction) or stable disease. By cycle 8, 3 patients (9%) were completely free of all metastatic disease.

The other 12 patients in this study had surgically inoperable pancreatic cancer with no liver metastases; they had 3 cycles of GTX, followed by radiation and Gemzar, and then a Whipple procedure. Of the group, 8 patients (67%) had negative margins and successful Whipple surgery.

The regimen is well tolerated. Major toxicities included grade 3 diarrhea and hand-foot syndrome in 20% of patients and grade 3 neutropenia in 25%, although no febrile neutropenia or deaths occurred. Grade 2 asthenia occurred in 20% of patients.

“We have not reached median survival, but we believe that we will extend it out further,” Dr. Fine said. “Some of these patients with metastatic disease are living as long as 2 years, as compared to the 3- to 4-month survival with standard therapy.”

There is still hope for patients who fail the GTX regimen. More recently, Dr. Fine and colleagues have discovered in his laboratory that a new regimen, which includes the same drugs given in an alternative fashion, may circumvent cell-cycle drug resistance and produce responses in 30% of GTX failures and stable disease in another 20%.

Investigators caution that a carefully designed Phase III randomized trial must be undertaken to confirm the apparent benefits of GTX. Whatever the results, this chemotherapy regimen is just one step in a long journey forward. In the future, this team hopes to shed light on treatment approaches beyond GTX, such as intermittent chemotherapy regimens or tumor vaccines.

“This is all uninvestigated territory,” Dr. Fine said. “We are learning what to do as we go along. So far, it has been very gratifying to see our work in the laboratory translate into a human benefit clinically.”

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**Robert L. Fine, MD**, is Director of the Experimental Therapeutics Program, NewYork-Presbyterian Hospital, the Herbert Irving Comprehensive Cancer Center at Columbia Presbyterian Medical Center, and Herbert Irving Associate Professor of Medicine, Columbia University College of Physicians & Surgeons. E-mail is rlf20@columbia.edu.

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## **NewYork-Presbyterian Digestive Diseases Editorial Board:**

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Chief, Division of General Surgery  
Medical Director, Operating Rooms  
NewYork-Presbyterian Hospital  
Associate Professor of Surgery  
Columbia University College of  
Physicians & Surgeons  
jac4@columbia.edu

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Columbia University College of  
Physicians & Surgeons  
Adjunct Professor of Clinical Surgery  
Weill Medical College of Cornell University  
kaf2@columbia.edu

### *Dennis Fowler, MD*

Director of the Minimal Access  
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NewYork-Presbyterian Hospital  
Leon C. Hirsch Professor of  
Clinical Surgery  
Weill Medical College of Cornell University  
Professor of Clinical Surgery  
Columbia University College of  
Physicians & Surgeons  
dlf2001@med.cornell.edu

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NewYork-Presbyterian Hospital  
Chief, Division of Gastroenterology  
and Hepatology  
Vincent Astor Professor of  
Clinical Medicine  
Weill Medical College of Cornell University  
inj2001@mail.med.cornell.edu

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Interim Chief, Gastrointestinal Division  
NewYork-Presbyterian Hospital  
Clinical Professor of Medicine  
Columbia University College of  
Physicians & Surgeons  
amm3@columbia.edu

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Professor of Surgery, Colon and Rectal  
Surgery Section  
Weill Medical College of Cornell University  
jwm2001@med.cornell.edu

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Attending Physician  
NewYork-Presbyterian Hospital  
Clinical Professor of Medicine,  
Division of Gastroenterology and  
Hepatology  
Weill Medical College of Cornell University  
paulmiskovitz@pol.net

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Gastrointestinal Health  
NewYork-Presbyterian Hospital  
Director, GI Endoscopy, Division of  
Gastroenterology and Hepatology  
Associate Professor of Clinical Medicine  
Weill Medical College of Cornell University  
mbpocha@mail.med.cornell.edu

### *Lewis Schneider, MD*

Assistant Attending Physician  
NewYork-Presbyterian Hospital  
Assistant Professor of Clinical Medicine  
Columbia University College of  
Physicians & Surgeons  
schneid@cpmail-nz.cis.columbia.edu

### *Peter Stevens, MD*

Director, Gastrointestinal Endoscopy  
Department  
Clinical Director, Division of Digestive and  
Liver Diseases  
NewYork-Presbyterian Hospital  
Assistant Professor, Clinical Medicine  
Columbia University College of  
Physicians & Surgeons  
pds5@columbia.edu

### *Richard Whelan, MD*

Site Director,  
Minimal Access Surgery Center  
NewYork-Presbyterian Hospital  
Associate Professor of Surgery  
Columbia University College of  
Physicians & Surgeons.  
rlw3@columbia.edu

[www.nyp.org](http://www.nyp.org)

## New Treatments Bring Rates of Viral Eradication In Hepatitis C Higher

Substantial progress has been made in the treatment of hepatitis C since the clinical trials program at NewYork Weill Cornell Medical Center was first established approximately 17 years ago.

It is estimated that up to 1.5% of the United States population is infected with hepatitis C. In those who develop chronic disease, symptomatic diseases may not develop for decades, but a substantial proportion of these individuals face serious complications, including death. Current therapies are producing viral eradication in approximately 55% of patients, while novel drugs have the potential to further boost success rates, helping to protect patients from liver failure, malignancy, and other long-term complications.

relatively treatment-refractory hepatitis C subtype.

“We are now testing several new therapies that we hope will increase eradication rates, particularly in the more treatment-resistant genotypes,” Dr. Jacobson reported. “Among areas where we hope to move forward soon are therapies targeted at viral enzymes important to replication, such as protease.”

According to Dr. Jacobson, the ongoing clinical trials program is integrated into a focused treatment center that includes a staff of physicians and support personnel, including nurse practitioners and physician assistants, largely dedicated to management of this infection. This dedication has set the stage for the clinical studies designed to identify optimal therapies, but there are also important



Ira Jacobson, MD, is seeing increasing viral eradication rates in hepatitis C patients thanks to improved therapies and new medications.

*“Among areas where we hope to move forward soon are therapies targeted at viral enzymes important to replication, such as protease.”*

*—Ira Jacobson, MD*

“This is a very exciting time in the management of hepatitis C both for the progress that has already been made in developing effective therapies and the potential for further advances,” reported Ira Jacobson, MD.

Dr. Jacobson and his co-investigators have led or participated in several of the key clinical studies that have advanced management of hepatitis C, including the trials that defined the current standard. That standard, the combination of pegylated interferon plus ribavirin, is producing substantial rates of eradication even in genotype 1, a common but

liaisons to basic research as well as to endstage management, particularly liver transplantation.

“In the form of our Collaborative Center for the Study of Hepatitis C, we have a close interaction with researchers at The Rockefeller University, which has been performing important work toward defining the molecular genetics of the hepatitis C virus as well as the interaction of the virus with liver cells. This should prove to be a fertile relationship in the effort to translate basic research into clinical advances,” Dr. Jacobson reported. The Rockefeller

group is headed by Charles Rice, PhD, a leading virologist.

There is also collaboration with other sites at NewYork-Presbyterian Hospital, including Columbia Presbyterian Medical Center, which has developed an important liver transplantation program. Hepatitis C is the leading indication for liver transplantation, and there have been collaborative efforts to define why some patients with chronic infection progress to liver failure while others do not.

“There has been substantial cross-fertilization between our clinical trials program and parallel research efforts to better understand the nature of hepatitis C and its pathogenic role,” Dr. Jacobson observed. “This may be very useful as we attempt to determine how newer therapies should be integrated into our existing options.”

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**Ira Jacobson, MD**, is Chief, Division of Gastroenterology and Hepatology, NewYork-Presbyterian Hospital at NewYork Weill Cornell Medical Center, and Vincent Astor Professor of Clinical Medicine, Weill Medical College of Cornell University. E-mail is [imj2001@med.cornell.edu](mailto:imj2001@med.cornell.edu).

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## Upper GI

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stomach, the average reduction in recovery time is an estimated 75%, returning patients to productive activities in weeks rather than months. A similar reduction in recovery time has been associated with esophagectomy for which there is now experience to support the procedure's safety and efficacy.

"Many other institutions are now looking at laparoscopy for these indications, but these procedures are already becoming a standard of care for us," Dr. Fowler reported. "When follow-up is sufficient to demonstrate that a similar or better outcome of the treatment of the underlying disease can be achieved with laparoscopy relative to open procedures, the advantages of minimally invasive surgery are compelling."

The need for esophagectomy, indicated for high-grade dysplasia or carcinoma, is increasing due to heightened rates of esophageal adenocarcinoma secondary to rising rates of gastro-esophageal reflux disease (GERD). Laparoscopic dissection, sometimes performed with



Led by Dennis L. Fowler, MD, more and more surgeons are using minimally invasive surgery techniques—including laparoscopic surgery—for many upper GI procedures.

thoracoscopy to complete resection of the middle portion of the esophagus, has permitted large reductions in both hospital stay and the time required to return to normal activity.

*"For procedures that are not performed as frequently, there is a hurdle in gaining sufficient experience when trying to introduce a newer approach, but we now have a very large experience showing that the laparoscopic approach is feasible in a broad array of foregut surgical procedures."*

—Dennis L. Fowler, MD

In gastric surgeries, including resection of gastrointestinal stromal tumors and partial gastrectomies for malignancy, hospital stay has been reduced to 3 days when a laparoscopic approach is used. Complete recovery can be achieved in as little as 2 weeks. Most patients require a nasogastric tube for no more than 1 day.

Another area in which minimal access surgery is now used is distal pancreatectomy, even when sparing of the spleen is desired. This is advantageous when the indication for resection is benign or when the lesion might be a cystadenocarcinoma. Although dissection of the tail of the pancreas without violating the splenic artery and vein was once thought too challenging, surgeons at NewYork-Presbyterian Hospital now have a series of cases in which the spleen has been spared during laparoscopic removal of the distal pancreas.

"The difficulty of sparing the splenic artery and vein was so great that laparoscopic distal pancreatectomy generally led to spleen removal. Although removal of the spleen may be desirable when the resection is for cancer, I think preservation of the spleen while still performing surgery laparoscopically is a substantial advantage for patients with certain types of lesions of the body and tail of the

pancreas," Dr. Fowler said.

The long-term results with laparoscopic myotomy for achalasia provide support for the premise that outcomes are at least as good following minimally inva-

sive surgical procedures than after open procedures. The laparoscopic approach, widely used at NewYork-Presbyterian Hospital, is now becoming the procedure of choice at many institutions due to evidence that immediate relief of achalasia is equally as successful following minimally invasive surgical technique as the open approach.

"For procedures that are not performed as frequently, there is a hurdle in gaining sufficient experience when trying to introduce a newer approach, but we now have a very large experience showing that the laparoscopic approach is feasible in a broad array of foregut surgical procedures," Dr. Fowler commented. "As has been the case for other indications where laparoscopy has been effective, the advantages for the patient can be quite substantial."

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**Dennis L. Fowler, MD**, is Director of the Minimal Access Surgery Program, NewYork-Presbyterian Hospital, and the Leon C. Hirsch Professor of Clinical Surgery at Weill Medical College of Cornell University as well as Professor of Clinical Surgery at Columbia University College of Physicians & Surgeons. E-mail is [dlf2001@med.cornell.edu](mailto:dlf2001@med.cornell.edu).

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## Minimally Invasive Alternative to Esophagectomy Shows Promise in Barrett's Esophagus Patients

**F**or patients with Barrett's esophagus who develop mucosal carcinoma or focal lesions of high-grade dysplasia, a minimally invasive approach under investigation at Columbia Presbyterian Medical Center is emerging as a safe and effective alternative to esophagectomy.

with endoscopic mucosal resection (EMR) is emerging from selected medical centers, including Columbia Presbyterian Medical Center.

Experience to date suggests that this esophagec-

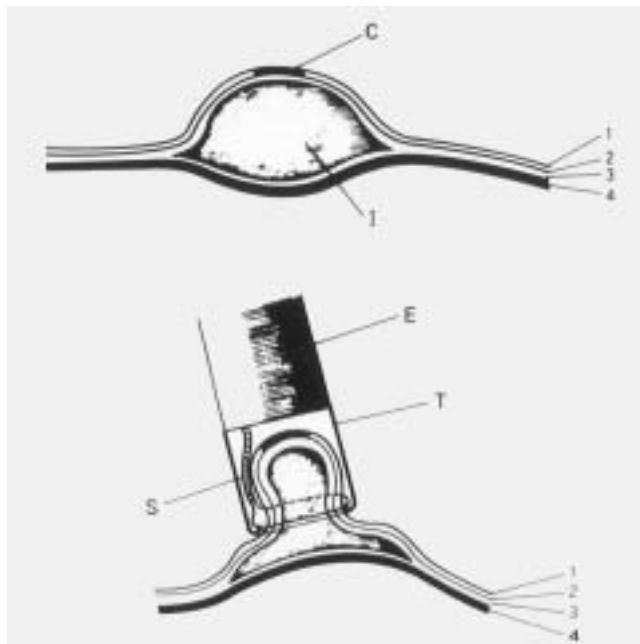
*Unlike endoscopic ablation, EMR allows for the retrieval of large pathologic specimens through which the completeness of the resection can be evaluated.*

"This looks like a very promising treatment, particularly useful in patients who are elderly and have other illnesses that make them high surgical risks," said Charles Lightdale, MD. "It's also a very effective method for staging, because it provides definitive evidence on pathology of how deep the tumor has invaded."

While esophagectomy has been the standard of care for Barrett's patients with high-grade dysplasia, such procedures are associated with morbidity and, occasionally, mortality. Now, experience

tomy-sparing procedure is a promising alternative. Unlike endoscopic ablation—another experimental technique that has sparked a great deal of interest lately—EMR allows for the retrieval of large pathologic specimens through which the completeness of the resection can be evaluated.

Pathologists viewing the deep and lateral resection margins under a light



The illustration above shows the key aspects of endoscopic mucosal resection (EMR) using the cap-assisted method. The numbers illustrate the layers of the esophageal wall from the inside out. Layers 1 and 2 represent the superficial and deep mucosa; layer 3 is the submucosa; and layer 4 is the muscularis propria, the esophageal muscle that is the outside layer of the esophagus. These layers are easily seen using high-frequency endoscopic ultrasound (EUS) probes, and EUS is usually performed before EMR to make sure that the lesion (C) to be removed is confined to the first two layers.

microscope observe "a very similar result to that obtained by esophagectomy, but without sacrificing the entire organ," Dr. Lightdale said.

### Endoscopic Mucosal Resection (EMR)

**E**ndoscopic Mucosal Resection (EMR) is performed through the endoscope and involves lifting up the Barrett's lining to be removed by injecting a solution under it or applying suction to it and then cutting it off, much like colon polyp removal. The lining containing the early cancer or high-grade dysplasia is taken out through the endoscope and sent for histologic analysis (analysis under the microscope) to check if the margins are free of cancer or high-grade dysplasia. This procedure, unlike surgery, cannot remove all of the Barrett's lining but can be used to remove a small cancer or remove a localized area of high-grade dysplasia, especially in those patients who are not good surgical candidates. If EMR is used to treat an early cancer, another procedure called endoscopic ultrasound is performed beforehand to make certain that the cancer involves only the very top layer of cells and is, therefore, an intramucosal cancer. Complications include bleeding or perforation.

*In 4 cases, the pathologist found positive margins on the EMR specimen, indicating that cancer had gone beyond the mucosa into the wall of the esophagus. These 4 patients underwent esophagectomy; in 3, cancer had invaded the submucosa, and, in the fourth, there was no residual disease, presumably because the electrocautery burn destroyed the cancer during the EMR.*

The procedure starts with a submucosal injection of dilute epinephrine, lifting mucosa from the muscularis propria of the esophagus. The endoscopist then grasps the mucosa in a polypectomy snare and resects it.

Dr. Lightdale and colleagues are taking advantage of a recent advance in EMR technology—a clear plastic cap on the endoscope tip, which has a rim that allows a snare to be placed. Using the cap technique, the entire procedure can be conducted with a single pass of the endoscope.

The group's initial experience with EMR using this cap technique includes 34 Barrett's esophagus patients with nodular lesions. Adequate pathology specimens were retrieved from every patient without complications. "The major risk of EMR is bleeding, but this is usually minor," said Dr. Lightdale.

None of the 30 patients with negative margins have developed recurrent cancer in a mean follow-up period of 18 months. Some have had endoscopic treatments to remove residual areas of Barrett's mucosa, and others have entered experimental trials using chemopreventive medication.

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"What that tells me is that EMR is really an excellent diagnostic staging method as well as a definitive treatment for some patients," Dr. Lightdale said. "If the disease is superficial—just in the mucosa—then they have been successfully treated, whereas if the disease is deeper, then you know that the treatment has not been sufficient, and they can go on to have the surgical procedure."

The EMR procedure is patient-

friendly. It is completed in 1 hour or less and is typically performed as an outpatient procedure; after a brief recovery period, the patient goes home. The main side effect is mild esophageal soreness, which can last for a few days.

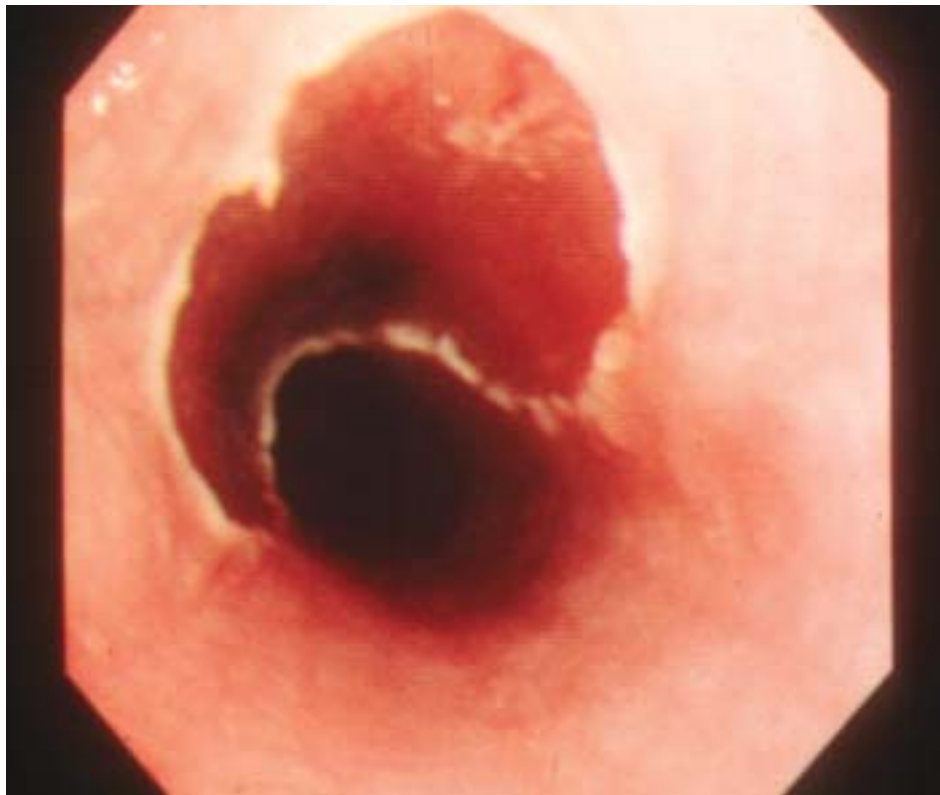
"This is a great minimally invasive technique that is safe and effective," Dr. Lightdale said. "It's really not very invasive and doesn't

interfere with the patient's life, as opposed to an esophagectomy, which is a major invasion and is associated with some deaths and a lot of side effects."

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**Charles J. Lightdale, MD**, is Attending Gastroenterologist, NewYork-Presbyterian Hospital at Columbia Presbyterian Medical Center, and Professor of Clinical Medicine, Columbia University College of Physicians & Surgeons. E-mail is [cjl18@columbia.edu](mailto:cjl18@columbia.edu).

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An endoscopic view following 3 cap applications to remove an area of high-grade dysplasia in Barrett's esophagus. The mucosa and submucosa have been removed, leaving the esophageal muscle exposed. This defect will heal in about 6 weeks.

## 'Treatment Individualization' Approach Produces Critical Progress in IBD

A newly developed tissue bank is the most recent addition to a campaign at NewYork Weill Cornell Medical Center to tailor therapies for inflammatory bowel disease (IBD). The heterogeneity of disease expression and its response to treatment is one of the greatest challenges to maintaining remission in IBD patients. The tissue bank intensifies the focus on how individuals differ and may provide an opportunity to more rapidly translate laboratory advances to improved care for the specific needs of each patient.

"About one third of patients do not respond to current therapies. If we can correlate differences in specific cell signaling between those patients who respond and those who do not, we may be able to better understand the pathobiology of IBD on a molecular basis," reported Ellen Scherl, MD.

Understanding the molecular mechanics of IBD pathobiology has the potential to permit current drugs to be employed more rationally.

Individualized medicine is captured in the concept of pharmacogenomics, which teaches that different patients respond to medications differently. This concept is especially relevant to IBD. Although IBD is generally divided into 2 main disease categories—ulcerative colitis and Crohn's disease—the spectrum of disease activity and symptoms has led to suspicion that IBD is the end result of a variety of pathways, only some of which are relevant to any given individual.

*Although IBD is generally divided into 2 main disease categories—ulcerative colitis and Crohn's disease—the spectrum of disease activity and symptoms has led to suspicion that IBD is the end result of a variety of pathways, only some of which are relevant to any given individual.*

"There is considerable controversy about the 2-disease model of IBD. Some have suggested that there is an

array of distinct pathologies. Better information about the molecular pathobiology behind disease expression could help sort this out, but, more importantly, it might allow us to better target treatment," suggested Dr. Scherl, who has written an article on the importance of individualized IBD care for *The Pharmacogenomics Journal* (in press).

"By being active in the clinical trials, we are in a good position to evaluate and implement algorithms for patient care," Dr. Scherl reported. Again, the goal is

not only to be familiar with the risks and benefits of specific therapies but to be able to develop a reasonable expectation of the risk-to-benefit ratio of therapy in a given patient. Many of the most potent therapies also pose a risk of significant toxicities, underlining the importance of treatment individualization.

The efforts at NewYork Weill Cornell Medical Center have included patient advocacy and continuing medical education, both of which have kept Dr. Scherl and her colleagues at the center of progress in optimal care, where they have helped to define the state of the art in IBD management. Dr. Scherl recently participated in refining wording of the IBD Act, a comprehensive bill in front of the US Congress to expand research on IBD and increase access of IBD patients to insurance

## Inflammatory Bowel Disease Facts

An estimated 2 million Americans suffer from ulcerative colitis or Crohn's disease. In about 10% of cases, the similarity between the two Inflammatory Bowel Diseases (IBDs) makes precise diagnosis impossible. Ulcerative colitis and Crohn's disease have many similar clinical and pathological features, but the pathogenesis of IBD is complex and not fully known. Current research indicates the condition may be the result of a combination of factors, including patients' genetic predisposition, changes in their mucosal immune system, and exposure to unknown exogenous factors—including intestinal microbes, toxins, and certain food substances. Commonly used medications include: 5-aminosalicylic acid (5-ASA) preparations, corticosteroids, antibiotics, and immune modifiers. Further complicating the diagnosis and treatment of IBD is the disease's similarity to other conditions, including celiac disease and irritable bowel syndrome (IBS), the latter being the most common functional disorder of the gastrointestinal tract. Their comparable symptoms and clinical presentation often lead to delayed diagnosis and treatment.