Capsule Endoscopy Studies Seek New View of Small Intestine

The small intestine, long hidden from physicians' prying eyes because of its scope-defying location, is finally being visualized in studies and clinical exams conducted at NewYork-Presbyterian Hospital.

Using the technologic magic of capsule endoscopy—in which a miniature camera, a transmitter, and 4 light-emitting diodes are tucked within a capsule-sized device and swallowed by the patient—researchers are detecting previously unseen polyps, hernias, atrophy, strictures, and inflammation.

At Columbia Presbyterian Medical Center, researchers have recently begun using the capsule to investigate why some of their patients with celiac disease haven't responded to standard treatments. Researchers at NewYork Weill Cornell Medical Center are currently using this technology to study patients with familial adenomatous polyposis.

“It's incredibly useful,” said Felice Schnoll-Sussman, MD, primary investigator on a study of patients with familial adenomatous polyposis, an inherited disease in which hundreds to thousands of polyps develop in the colon (and, often, in the small intestine as well). For patients, she said, one of the benefits of the capsule endoscopy exam is that it is noninvasive. They need only fast from the evening...
The body is very well adapted to overcome most viruses,” said Gerond Lake-Bakaar, MD. “With hepatitis C virus, for whatever reason, 85% of those who get it don’t get rid of it. Clearly, there are some ways the virus has learned to overcome the body’s immune system. What we’re looking at is the interaction between the virus and the host. That is what’s going to provide the clues to how the virus manages to subvert the whole immune system.”

Basic research into the mechanisms through which the chameleon-like hepatitis C virus avoids being eliminated by the host’s immune system is being carried out through the Center for the Study of Hepatitis C, which is a cooperative endeavor of Rockefeller University, Weill Medical College of Cornell University and NewYork-Presbyterian Hospital.

Mathematic modeling of the dynamics of hepatitis C virus has shown that the virus makes about 1 trillion copies every day. “That suggests that one way the virus overcomes the host’s defense is by swamping it,” said Dr. Lake-Bakaar. If the virus remained unchanged, he continued, the body would produce more and more antibodies and, in time, eliminate it.

The fact that it doesn’t remain unchanged, in most cases, indicates that the virus is morphing in response to the attack mounted by the host’s immune system, according to Dr. Lake-Bakaar. What he and his colleagues are doing now is looking at how quickly the viral load comes down and how the virus changes over time in response to high-dose interferon treatment. “That’s where the chameleon thing comes in,” he said.

In the past, Dr. Lake-Bakaar said, investigators looked at the virus before starting treatment and then again at, say, a year afterward. “If you’re making a trillion copies every day, that’s a lot of trillions in 365 days,” he said. “We’re finding that the virus begins to change within about 12 hours of starting treatment. We’re looking at this very rapid evolution at very short intervals. That’s what we’re doing that people haven’t done before.”

They’re also hoping to learn what parts of the whole viral genome change in response to interferon’s selective pressure. Ribonucleic acid viruses like hepatitis C virus “don’t have a proofreading capacity,” Dr. Lake-Bakaar said. “Their ability to mutate is very high, so what we think we’ll be able to do is find what parts of the virus change in response to interferon.”

A third piece of the puzzle is why some individuals do not respond as well to treatment as others—a clear indication there are differences among hosts that are important as well. “We know, for example, that African-Americans don’t respond as well to interferon, and their rate of cure from hepatitis is much lower,” said Dr. Lake-Bakaar. “We also know that the response of patients with hepatitis C genotype-1 is much lower.”
“It could be that the virus that you were exposed to is different from the virus that someone else was exposed to. If the virus isn’t able to change as rapidly in me, my immune system will get rid of it. In the other person, it may not.”
—Gerond Lake-Bakaar, MD

He noted that there are features of the virus that make it harder to get rid of, but there are some features of the host that obviously make it harder as well. “Why some people get rid of it and not others is a thread that’s running through all of this,” he said. “One way to look at that is through host-gene expression in response to interferon. We give interferon and look at the gene expression in the peripheral blood nuclear cells and compare patients who respond to those who don’t.” The differences, he added, provide clues as to why some patients clear the virus while others don’t.

“It could be that the virus that you were exposed to is different from the virus that someone else was exposed to,” Dr. Lake-Bakaar explained. “So if the virus isn’t able to change as rapidly in me, my immune system will get rid of it. In the other person, it may not.”

Dr. Lake-Bakaar worked under the late Dame Sheila Sherlock, the renowned hepatologist, at Royal Free Hospital in London. He has been working on the hepatitis C puzzle since the mid-1990s. “It’s a slow process, but we’re getting there,” he said. “It’s beginning to look as if we should be able to both appreciate how much the subversion [of the host’s defenses] is due to the fact that the virus can change quickly and how much of it is due to the host.”

Gerond Lake-Bakaar, MD, is Assistant Attending Physician, NewYork-Presbyterian Hospital at NewYork Weill Cornell Medical Center, and is Assistant Professor of Medicine at Weill Medical College of Cornell University. E-mail: gvl2002@med.cornell.edu

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NewYork-Presbyterian Digestive Diseases Editorial Board

John Chabot, MD
Chief, Division of General Surgery
Medical Director, Operating Rooms, NewYork-Presbyterian Hospital at Columbia Presbyterian Medical Center
Associate Professor of Surgery, Columbia University College of Physicians & Surgeons
dl2001@med.cornell.edu

Kenneth Ford, MD
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Adjunct Professor of Clinical Surgery, Weill Medical College of Cornell University
da2@columbia.edu

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Director of the Minimal Access Surgery Program, 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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irm2001@mail.med.cornell.edu

Arthur Magun, MD
Interim Chief, Division of Digestive and Liver Diseases, NewYork-Presbyterian Hospital at Columbia Presbyterian Medical Center
Clinical Professor of Medicine, Columbia University College of Physicians & Surgeons
amn3@columbia.edu

Jeff Milsom, MD
Chief, Division of Colorectal Surgery, NewYork-Presbyterian Hospital at NewYork Weill Cornell Medical Center
Professor of Surgery, Colon and Rectal Surgery Section, Weill Medical College of Cornell University
jwm2001@med.cornell.edu

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

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

Lewis Schneider, MD
Assistant Attending Physician, NewYork-Presbyterian Hospital at Columbia Presbyterian Medical Center
Assistant Professor of Clinical Medicine, Columbia University College of Physicians & Surgeons
(212) 326-8426

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

Richard L. Whelan, MD
Site Director, Minimal Access Surgery Center, and Chief, Section of Colon and Rectal Surgery, NewYork-Presbyterian Hospital at Columbia Presbyterian Medical Center
Associate Professor of Surgery, Columbia University College of Physicians & Surgeons
rw3@columbia.edu

www.nypdigestive.org

The University Hospitals of Columbia and Cornell
before and take a mild laxative. After ingesting the capsule, they wear a data recorder around their waist, along with a battery. After 8 hours, the data recorder is removed, and the capsule is later excreted normally.

For researchers, though, the main benefit of the technique is that it allows them to get beyond the unsatisfactory results achieved with a small intestinal X-ray series or CAT scan.

“You could not visually examine the small intestine until now,” said Moshe Rubin, MD. “The only method available was a very specialized long scope that would require almost a full day to pass through to the small intestine. It was very cumbersome and poorly tolerated.”

Dr. Rubin is one of the physicians investigating celiac disease patients using the technology. Celiac disease is an inflammation of the small intestine occurring in genetically susceptible people in the presence of gluten. Normally, symptoms of diarrhea and abdominal pain clear up once the patient is put on a gluten-free diet. But between 5% and 10% of patients continue to have symptoms even after going on the diet.

“Celiac disease is one of the most common inherited disorders that physicians are going to see,” said Peter H.R. Green, MD. But until the advent of capsule endoscopy, he added, “there hadn’t been any sensitive way of examining the small intestine” in patients whose disease was refractory to standard treatment.

That is precisely what was done in a study of 20 refractory celiac patients. As reported at the American College of Gastroenterology’s 68th annual scientific meeting this year, the researchers detected unexpected findings in 12 of the 20 patients, including a stricture not seen on prior small bowel series in 1 patient; ulceration of the jejunum, ileum, or both in 10 patients; and a polyoid mass lesion in 1 patient. Researchers want to use capsule endoscopy as a screening tool in celiac patients, because they have a higher risk of small bowel malignancies.

Although no malignancies were found in the study, the findings did lead to the prescription of steroids and anti-inflammatory medications for patients with ulcers. But in the course of examining more than 80 other patients for additional disorders, including Crohn’s disease and unexplained bleeding, Dr. Rubin said, “I have found some tumors in the small intestine. I have also found very large ulcers that were bleeding and needed to be operated on.”

Although Medicare and most insurers cover capsule endoscopy only in the presence of otherwise unexplained occult bleeding, “I suspect in the near future it will be approved for patients with Crohn’s disease to screen them for cancer and evaluate the disease,” Dr. Green said. “And for celiac disease, once studies like ours get published, it will also be covered. This is by far the best way to look at the small bowel. Nothing else comes close.”

Dr. Schnoll-Sussman agreed that the studies now under way should lengthen the list of accepted indications for capsule endoscopy. “Hopefully, insurance agencies will realize how useful it is and expand their list of indications,” she said. Her trial of familial adenomatous polyposis will seek to enroll 20 patients in a prospective, double-blind trial. All patients will receive a small bowel X-ray series, and they will also receive a capsule endoscopy (unless the X-ray indicates a stricture in the small bowel). The results of the 2 methods will be independently reviewed and compared. “The goal is to see whether capsule endoscopy is helpful in identifying additional polyps out of reach of an endoscope,” she said.

Physicians are hoping they might eventually be able to control the movement of the capsules, said Lewis Schneider, MD. “The difficulty now is that movement in the large intestine is not as fast or as regular as in the small intestine, so the capsule can sit there theoretically for days before it comes out,” he said. By powering the capsule with a controllable propulsion system, physicians could examine whichever surface they want.

For now, Dr. Rubin agreed, one of the drawbacks to the technology is that the capsule’s movement can’t be controlled. “It can move very quickly past an important spot, and you may get only a glimpse of an abnormality,” he said. “Sometimes there is fluid in the system, blocking your view.” But for him, the benefits are clear. “For the first time,” Dr. Rubin said, “you can open your eyes within the small intestine.”

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

Moshe Rubin, MD, is Associate Attending Physician, New York-Presbyterian Hospital at Columbia Presbyterian Medical Center, and is Associate Clinical Professor of Medicine at Columbia University College of Physicians & Surgeons. E-mail: mr43@columbia.edu.

Lewis Schneider, MD, is Assistant Attending Physician, New York-Presbyterian Hospital at Columbia Presbyterian Medical Center, and is Assistant Professor of Clinical Medicine at Columbia University College of Physicians & Surgeons. Phone: (212) 326-8426.

Felice Schnoll-Sussman, MD, is Assistant Attending Physician, New York-Presbyterian Hospital at New York Weill Cornell Medical Center, and is Assistant Clinical Professor of Medicine at Weill Medical College of Cornell University. E-mail: fhs2001@med.cornell.edu
Gastric bypass has proven remarkably effective in treating obesity, with up to 90% of patients achieving significant weight loss. At 12 to 18 months after surgery, an average loss of 70% of excess weight is expected.

The procedure has proven less successful, however, in patients with a body mass index (BMI) over 50, or roughly 200 pounds overweight. In these patients, weight loss is less substantial—an average loss of 50% of excess weight is expected at follow-up. Now, surgeons at NewYork-Presbyterian Hospital are investigating a dual procedure called banded gastric bypass, which may offer improved outcomes in these very obese patients.

Banded gastric bypass combines the standard gastric bypass with a nonadjustable gastric band. Surgeons use the bypass procedure to create a small pouch in the stomach. A small opening in the pouch attaches to a limb of the small intestine, bypassing a portion of the digestive tract. The band is then implanted around the stomach to restrict food intake.

Banded gastric bypass combines the standard gastric bypass with a nonadjustable gastric band. Surgeons use the bypass procedure to create a small pouch in the stomach. A small opening in the pouch attaches to a limb of the small intestine, bypassing a portion of the digestive tract. The band is then implanted around the stomach to restrict food intake.

Before and after: Banded gastric bypass combines the standard gastric bypass with a nonadjustable gastric band. Surgeons use the bypass procedure to create a small pouch in the stomach. A small opening in the pouch attaches to a limb of the small intestine, bypassing a portion of the digestive tract. The band is then implanted around the stomach to restrict food intake.

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—Marc Bessler, MD

Two compelling sideline projects have emerged from Dr. Bessler’s investigations into banded bypass procedures. First, patients who have had less than optimal weight loss after gastric bypass are being offered an adjustable band on top of the existing bypass. When the band is tightened, many patients go on to lose significant amounts of weight.

In addition, patients who have failed Lap-Band alone are being offered a gastric bypass underneath the existing banding. Usually, patients who do not lose weight with a banding system have it removed before going on to gastric bypass; it is hoped that supplementing banding with a bypass will improve the opportunity for weight loss over the long term.

“Our motto is ‘Weight Loss for Life,’ and we don’t mean only losing weight and keeping it off for life, but weight loss for improved quality and hopefully length of life,” Dr. Bessler said. “We hope to use the combination of band and bypass to improve weight loss for patients who historically don’t lose weight as well with gastric bypass, and in the meantime, we are offering revisional surgeries to patients who have had less than optimal success with either procedure alone.”

Marc Bessler, MD, is Surgical Director of the Center for Obesity Surgery and Director of Laparoscopic Surgery, NewYork-Presbyterian Hospital at Columbia Presbyterian Medical Center, and is Assistant Professor of Surgery at Columbia University College of Physicians & Surgeons. E-mail: mb28@columbia.edu.
Pancreatic cancer has long been associated with a poor prognosis, but cure rates have been increasing in surgical candidates because of continued progress toward perfecting the Whipple procedure. First developed at NewYork-Presbyterian Hospital, the Whipple procedure has become a standard of surgical management throughout the world.

NewYork-Presbyterian Hospital surgeons are among the most experienced in this technique, perhaps helping to explain why its mortality rates in pancreatic cancer are so much lower than the national average.

“There is probably no single thing we do differently that would explain our low complication rate. It comes from experience that ranges from preoperative planning to handling the problems, such as unexpected postoperative bleeding, when they occur,” reported John A. Chabot, MD. “The national mortality rate is high because many Whipples are done at hospitals where there is very limited experience. However, our numbers are competitive with other leaders in this area.”

At NewYork-Presbyterian Hospital, more than 100 Whipple procedures are performed each year. Many of these are performed at Columbia Presbyterian Medical Center, where Allen O. Whipple, MD, first developed the procedure. Mortality rates were recently calculated at 0.5% per year, or about 10% of the national average, as derived from data generated by the Centers for Medicare & Medicaid Services.

Pancreatic cancer is the fifth leading cause of cancer death in the United States, but prognosis improves substantially in patients whose tumor is sufficiently localized to permit the Whipple procedure. This accounts for about 15% of patients.

At Columbia Presbyterian Medical Center, a staging protocol has been developed to identify surgical candidates, in which surgeons evaluate patients based on several modalities, including computed tomography scan, endoscopic ultrasound, and laparoscopy. Once surgery is considered feasible, comprehensive surgical planning is implemented to allow the least invasive procedure to yield the greatest likelihood of an adequate resection.

Laparoscopy helps identify patients for whom surgery is feasible. A traditional incision can be avoided if, on laparoscopic examination, the tumor is found to be inoperable. “About 5% to 10% of the time, the laparoscopic exploration reveals that the patient is not suitable for a Whipple, and we do not proceed,” Dr. Chabot reported.

However, the population of patients with pancreatic cancer who are candidates for the Whipple procedure is growing as a result of efforts to identify patients earlier and get them to surgery sooner while the tumor is still resectable. Surgery is also being considered for patients with more advanced disease. The team at Columbia Presbyterian Medical Center has been an innovator in using aggressive chemotherapy and radiation to reduce the size of tumors that would otherwise be considered inoperable.

“In about two thirds of the cases in which we pretreat patients with chemotherapy and radiation, we are proceeding to surgery and getting the tumors out safely. We have about a year and a half of experience with this approach, so we do not yet have data on whether we are improving survival,” Dr. Chabot noted. “But there has been no excessive morbidity or mortality.”

Survival from pancreatic cancer was relatively rare even 15 or 20 years ago. At major centers with high standards of care, such as NewYork-Presbyterian Hospital, the cure rates in patients who are candidates for complete tumor excision are now approaching 20%. According to Dr. Chabot, the steady progress toward lower morbidity and better outcomes at NewYork-Presbyterian Hospital can be credited to a series of modest but cumulative improvements generated by broad experience at the institution where the Whipple procedure was pioneered.

John A. Chabot, MD, reviews patient computed tomography scans, part of the protocol for evaluating candidates for the Whipple procedure.
COX-2 Inhibition Holds Promise in Digestive Cancers

Research has firmly established the benefit of celecoxib in patients with familial adenomatous polyposis (FAP), an inherited type of colon cancer found in a small minority of patients.

Celecoxib, a nonsteroidal anti-inflammatory drug (NSAID) that inhibits the cyclooxygenase-2 (COX-2) enzyme, was first approved as a preventive treatment for FAP patients based on a National Institutes of Health–sponsored, placebo-controlled trial in 1998. Results showed that 6 months of treatment significantly reduced the number of colorectal polyps and the total polyp burden in patients with this aggressive, though rare, condition. An important question now, however, is whether this COX-2–specific NSAID might also have a role in preventing precancerous polyp recurrence in a much larger population of patients.

This question may soon have an answer. NewYork-Presbyterian Hospital investigators are leading a randomized, placebo-controlled trial to determine if celecoxib can prevent the recurrence of precancerous adenomatous polyps in patients at high risk of recurrence.

Beyond prevention, there is also a large research effort under way to assess the potential for using celecoxib to treat cancers that overexpress COX-2. Already, NewYork-Presbyterian Hospital investigators have presented compelling evidence—some of the first hard data to emerge—that celecoxib is active as an adjunct to preoperative chemotherapy in patients with non–small-cell lung cancer. Investigators are also participating in a multicenter clinical trial of this COX-2 inhibitor in patients with Barrett’s esophagus, a precancerous condition that often leads to esophageal cancer.

“Here we have a drug that was designed to treat arthritis and pain, made its foray into the cancer field as a prevention drug, and is now being fast-tracked into studies to assess its potential role in cancer therapy,” said Andrew J. Dannenberg, MD.

Meanwhile, investigators are looking forward to results of the precancerous polyp prevention trial. To date, no trial results have been reported, but enrollment is completed, and it is expected that data will be available in approximately 2 years. The recruitment goal of the trial is 2,000 patients who have had a premalignant polyp removed within the previous 6 months. The patients have been randomized to celecoxib—low dose 200 mg twice daily, high dose 400 mg twice daily—or placebo. Colonoscopy is performed at years 1 and 3 after enrollment to see if celecoxib reduces the number of polyps versus placebo.

“Right now, it’s estimated that between 20% and 30% of people who have colonoscopy have polyps, so we are talking about a huge cohort of patients who might benefit from this,” said Mark B. Pochapin, MD.

“If this drug proves to be effective—and we know NSAIDs are very safe—we could have an additional weapon in our armamentarium to reduce risk of cancer by preventing polyp growth,” added Carl McDougall, MD.

Andrew J. Dannenberg, MD, is Co-Director of Cancer Prevention, NewYork-Presbyterian Hospital at NewYork Weill Cornell Medical Center, and is the Henry M. Erle, MD–Roberts Family Professor of Medicine at Weill Medical College of Cornell University. E-mail: ajdannen@med.cornell.edu.

Carl McDougall, MD, is Attending Physician, NewYork-Presbyterian Hospital at NewYork Weill Cornell Medical Center, and is Associate Professor of Clinical Medicine at Weill Medical College of Cornell University. E-mail: cmcdou1036@aol.com.

Mark B. Pochapin, MD, is Director of the Jay Monahan Center for Gastrointestinal Health at NewYork-Presbyterian Hospital at NewYork Weill Cornell Medical Center and is also Associate Professor of Clinical Medicine, and Director, Gastrointestinal Endoscopy in the Division of Gastroenterology and Hepatology at Weill Medical College of Cornell University. E-mail: mbpocha@mail.med.cornell.edu.
grow, in part due to the progressive scarcity of cadaveric donors. While living donor procedures have excellent results in children, with a favorable track record of donor safety, many questions remain unanswered in adults. In particular, risk to the donor is uncertain, since a more extensive hepatectomy is required.

The safety of living donor liver transplantation has been shown in a recent survey conducted by Dr. Brown and colleagues and published in The New England Journal of Medicine (2003;348:818-825).

Of 449 procedures performed in 84 programs, there was only 1 donor death (0.2%) directly related to the procedure. Donor complications were more frequent in centers performing the fewest transplantations; many centers had done fewer than 10 procedures.

More systematic study of safety is needed. End points of the study include morbidity and mortality for both recipients and donors, as well as predictors of those outcomes; long-term donor outcomes, including quality of life; waiting list and posttransplant mortality for recipients; and regeneration of liver in living donors and recipients, among others.

Ultimately, the in-detail data that come from NewYork-Presbyterian Hospital and the 8 other active transplant centers in the A2ALL study will supplement registry data from the United Network for Organ Sharing to provide a more complete picture of living donor liver transplantation.

“There is no doubt that living donor transplantation saves lives.”
—Robert S. Brown, Jr, MD

“Though there is a risk to the donor, there is no doubt that living donor liver transplantation saves lives,” Dr. Brown said. “Figuring out how to best apply this technique will allow us to derive the maximum benefit, without taking on increased risk.”

Robert S. Brown, Jr, MD, MPH, is Medical Director of the Center for Liver Disease and Transplantation, NewYork-Presbyterian Hospital at Columbia Presbyterian Medical Center, and is Associate Professor of Clinical Medicine and Pediatrics at Columbia University College of Physicians & Surgeons. E-mail: rb464@columbia.edu.

Manikkam Suthanthiran, MD, is Chief of Nephrology and Transplant Medicine, NewYork-Presbyterian Hospital at NewYork Weill Cornell Medical Center, and is the Stanton Griffis Distinguished Professor of Medicine at Weill Medical College of Cornell University. E-mail: msuthan@med.cornell.edu.