# Trends-in-Medicine

**June 2005**
*by D. Woods*

**SUMMARY**

Digestive Disease Week focused on the latest scientific developments in gastroenterology, endoscopy, and GI surgery. Highlights included the newest endoscopic techniques and devices, including capsule endoscopy, clips, disposable endoscopes, minimally invasive treatments for gastroesophageal reflux disease, new tests for gastrointestinal cancer detection, and trial results for new drugs for Crohn's disease, ulcerative colitis, and hepatitis C.



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## DIGESTIVE DISEASE WEEK (DDW)

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Chicago

There were far fewer presentations at DDW about device innovations than device techniques. Doctors said that there is plenty of research, but most of it is still in the early stages, and human trials are needed.

A colorectal cancer panel moderator pointed to these technologies as promising:

- Ways to increase sensitivity and specificity in detecting lesions, including confocal endoscopy, optical coherence tomography, fluorescence imaging, and narrow band high definition imaging.
- Miniaturization, including Given Imaging's PillCam and endomicroscopy.

### Double-balloon endoscopy (DBE)

There was quite a bit of interest in DBE. A speaker said these devices allow, for the first time, access to the small bowel. He said they differ from capsule endoscopies in that they are not only diagnostic but also therapeutic. Some doctors think DBE will replace capsule endoscopy, but others think patients would get the capsule first, then DBE.

Doctors expressed concern at the length of time the procedure takes (up to 1.5 hours) and the fact that some patients need to be explored from both the mouth and the rectum. An inventor said, "Patients were more comfortable getting the anal route compared to the oral, which is not very comfortable. With the anal route, you can make a good concentric circle and it's easy to advance, but when the endoscope makes an S-shape, it becomes difficult.

Several companies have DBEs in development, including Fujinon and Olympus. A DBE is usually a 2 mm push scope with an overtube that can be passed on the left orally or on the right transrectally and can allow small bowel interaction. The enteroscope and the overtube both have balloons. Using the balloons, the enteroscope and overtube leap-frog down the intestine. The Fujinon instrument is 8 mm and has its own set of accessories. A nine-center trial is ongoing in the U.S., and another multicenter trial is underway in Europe. A doctor said, "Olympus has been having trouble with its double-balloon enteroscope, but I think they'll have their troubles fixed shortly."

**Three-balloon systems** are also on the drawing board. A University of Chicago scientist (and Fujinon investigator) is working on a three-balloon system, but most sources had not yet heard of three-balloon systems. The inventor of the two-balloon system said that he had considered using a catheter balloon but decided against it.

He said, "I examined both using a balloon on the catheter and another on the endoscope; the other balloon is on the overtube. I didn't use the catheter balloon, but it works well too and is a good idea to use it." However, he said that it was a more primitive technique and more difficult to use.

### Endoscopic submucosal dissection (ESD)

This is a type of EMR (endoscopic mucosal resection) used for treatment of mucosal cancer and premalignant lesions of the gastrointestinal tract. Current methods include submucosal fluid injection followed by electrocautery excision, or cap-assisted EMR using endoscopic suction to achieve mucosal lifting.

### Fluorescent endoscopy

Fluorescent endoscopy used as an imaging adjutant to white light endoscopy can improve the detection of small lesions in the colon and allows the endoscopist to decide whether a small lesion that is detected is neoplastic or hyperplastic (innocent and not needing to be removed). The product sources were most excited about in this area was **XILLIX TECHNOLOGY'S Onco-LIFE** (Light-Induced Fluorescent Endoscopy), and Xillix is currently organizing a multicenter trial of Onco-LIFE.

A University of Toronto investigator said that removal of polyps with Onco-LIFE reduced the incidence of colon cancer by 75% in one study and 90% in another study. Onco-LIFE uses blue light combined with fluorescence and reflectant cameras to illuminate and obtain real-time color images during colonoscopy procedures. The light reflected in the colon is different when tumors are present. He said that, while colonoscopy remains the best way to detect colon cancer, fluorescent endoscopy is a useful tool for achieving greater accuracy.

This researcher described a prospective, single-arm, single-center study of patients undergoing colonoscopy for colorectal cancer screening or monitoring. The researchers examined the colon using white light (WL) followed by fluorescence light (FL). Of the 285 evaluable biopsies, 123 lesions were found in 44 patients (120 adenomas, two carcinomas, and one carcinoid tumor). FL examination identified 19 adenomas, including diminutive and flat adenomas that were missed at WL examination, suggesting an increased detection rate of 18.3% (19 of 104 adenomas). Accuracy of endoscopic diagnosis for atypical lesions improved from 57% to 83% and hyperplastic lesions from 59% to 70% with the use of both WL and FL. The investigator said:

- "We wanted to assess whether it improved the ability of the endoscopist to detect more lesions and also have the ability to differentiate the nature of the lesions. We studied some 70-odd patients coming in either for screening or patients who had previous polyps and a family history and some patients with ulcerative colitis, and the modality was that all patients underwent total colonoscopy."
- "We went to the cecum using conventional white light and endoscopy, and then on withdrawal we went to the cecum, observed, then withdrew in segments of 10-15 cm. So we would go in, withdraw, go in 15 cm more and record the lesions we saw, then go back over that distance and look at the same area using the fluorescent mode of the endoscope. This endoscope allows one to switch automatically between so-called white light by switch or foot pedal."
- "The endoscopist using white light was able to guess and detect 58%, and with the addition of the fluorescence was able to improve the discrimination to 82%. Hyperplastic polyps, as far as we know, have little malignant potential. Using white light, the endoscopist is able to identify correctly 59%, and the addition of fluorescence improves diagnostic accuracy to 97%. Essentially, what this means is that the addition of fluorescent endoscopy resulted in a 39% increase in the detection of small carcinomas."
- "An important feature of the use of fluorescent endoscopy is that although one increased the number of false positives, more importantly, one decreased the number of false negatives. We ended up taking more samples because we saw more, but we missed fewer patients."
- "Our study was done safely with no side effects or problems with the study overall."
- "Our conclusion was that the addition of fluorescence to white light endoscopy improved detection of small adenomas which might, in the long term, have an impact on the eventual development of cancer of the colon, and allow the endoscopist to differentiate better than his eye as to whether small lesions are adenomas or have the potential to become malignant, or where hyperplastic, which you might say you could ignore."

### Narrow band imaging (NBI)

NBI is a new method of endoscopic imaging which allows more detailed magnification of mucosal images without staining. NBI improves detection and delineation of certain lesions in Barrett's esophagus (BE) by enhancing their abnormal surfaces and small vessel patterns relative to standard white light endoscopy. One study looked at 100 lesions of early gastric cancer treated by EMR with both a conventional magnifying endoscope (Olympus Gif-Q240Z) and an Olympus NBI system. A soft plastic hood with a depth of 2 mm was attached to the distal end of the endoscope tip to maintain the appropriate distance from the target mucosa. Investigators found that magnified-NBI enables more accurate endoscopic diagnosis of early gastric cancer than conventional endoscopy.

In another study, the Olympus CFQ-240ZL colonoscope was used in 48 patients. Colonoscopy was incomplete in six

patients. Forty-six percent of patients completing the procedure had polyps, with a total of 42 polyps found. There was no significant difference between NBI and standard light on either the first or second pass, and no segmental differences in polyp detection were seen. The study concluded that NBI does ***not*** appear to have a higher sensitivity for polyps than standard light, but there were only 12 adenomas total, and the polyps were small. The study also concluded that a larger study using a standard colonoscope with randomization of patients to either standard imaging or NBI should be performed in a cohort with a higher baseline adenoma prevalence to compare intention-to-treat adenoma detection rates.

A third study looked at a new, high definition (HD) endoscopic system (50x magnification) that uses NBI, with the capability of converting from conventional endoscopy to NBI with a simple switch. The aim was to assess clinical utility of this system in 16 patients with BE. Researchers reported "a striking contrast" between the squamous and columnar mucosa with this system. They concluded that the HD system allows for a detailed analysis of the mucosal and capillary patterns in BE patients and that NBI imaging can be of clinical utility in the management of BE patients.

### Confocal laser endoscopy

Doctors were interested in this device, which allows high quality endoscopy combined with confocal imaging. An investigator said, "You have to use stain, but the quality is exceptional." He added that the future of imaging will include using HDTV/electronic magnification and will combine surface imaging with functional imaging. A doctor who is interested in this form of imaging said, "A micro endoscope uses a tip device like a microscope. It allows you to look down 250 microns and get images that are an optical biopsy. It allows you to see as a pathologist does. Pentax is working in this area."

## Capsule Endoscopy (CE)

New advances in capsules include real-time access to images. A source said, "Right now you swallow and wait for the battery to die, but the new capsules will have real-time access to images, and the images will be crisper."

### Given Imaging

This small Israeli company has the only FDA-approved imaging capsule: PillCam SB and the new PillCam ESO, which was given FDA clearance in January 2005. Both of these are marketed by Johnson & Johnson's InScope (a division of Ethicon Endo-Surgery).

There is no reimbursement for PillCam yet, and use remains limited. An investigator said, "CE is more sensitive for assessing mucosal lesions than any other small bowel imaging technique. It is useful in patients with suspected Crohn's Disease because it sees things not seen by other imaging modalities. It can also be of potential value in the evaluation of indeterminate colitis as well as in the evaluation of unexplained symptoms of patients with known IBD (irritable bowel syndrome)…and Celiac Disease."

Capsule retention can be a problem in 1%-5% of all patients, a source estimated. He said, "More often than not it's a good thing when it gets stuck, and I haven't had one patient in the last 12 months who said they didn't like the risk…because where it gets stuck, there's a good chance that's where the lesion is." As for patients with Barrett's esophagus, he said that CE may be better than endoscopy, "What we learned is that because the capsule sits in the G junction a little longer, you may see small areas of Barrett's that you won't see in endoscopy."

Given also is in clinical trials in the U.S. with its Patency capsule, which dissolves, leaving only a filament. An investigator said the capsule is widely used in Europe. A J&J source said that there are no plans for his company to market it, but he didn't know why. An investigator for Given, asked if Patency will replace PillCam ESO, said, "I don't think that it (Patency) is replacing anything…I believe that if the results pan out, along what we saw in the pilot study, I think it might be a viable alternative or possible first-line for esophageal adenocarcinoma or Barrett's. What we think will happen is that it will expand the field of people who need at least an upper GI evaluation. There are a lot of patients who never get checked for Barrett's. Whether it will replace endoscopy? Perhaps for one-time screening, but it shouldn't be used in persons with upper GI symptoms not attributed to reflux because you can't see the lining of the stomach…Because the majority of patients you screen for Barrett's…won't have it. It's a non-invasive way to say, 'You're fine. Come back in a few years. It took 10 minutes, and I didn't have to sedate you.' (The next Patency study will be read by) someone blind to endoscopy, and it will be read before the endoscopist takes out his scope. If the capsule sees something the endoscopist didn't see, the endoscopist will look further. One of the difficulties in comparing capsule to endoscopy is that there are a lot of variations now in endoscopy, and we don't all agree on what's Barrett's and what's not, for example…I look at the capsule as an adjunctive addition to endoscopy used non-invasively and safely."

PillCam ESO, the esophageal capsule, is 11 mm tall, 26 mm wide, and weighs 3.7 g. It is twin-headed and has a smaller battery than the PillCam SB. It has limited recording time of about 20 minutes, but it operates at 14 frames per second. The capsule has a camera on both ends and it is the same size as a small bowel capsule. An investigator said, "Has anyone here done ESO? They are ridiculously easy to do. There are three leads that go into a patient's chest. The patient comes to the office after a 2-3 hour fast, lies flat, and puts the capsule in his mouth. He's given simethicone and a 10 cc syringe of water. He lies flat for two minutes, and we get spectacular images of

the esophageal gastric (EG) junction. It will be able to see suspected Barrett's, but won't make the diagnosis."

The investigator described a study of the PillCam ESO in 103 patients, 93 of whom had gastroesophageal reflux disease (GERD). He said:

- In side one you can see the esophageal junction 64% of the time.
- In both sides you can see the esophageal junction 92% of the time.
- Sensitivity is 100%.
- Specificity is 80%.

The investigator said, "You can actually see the EG junction well. The point of using it to screen for Barrett's is because the incidence of reflux disease is ridiculously high in that space, so the potential population that could or should be screened is large. A million people in the U.S. are estimated to have Barrett's, and 10,000 of them will go on to have adeno-carcinoma. No one has been able to screen patients on a population base up to now. Adenocarcinoma is a lethal disease, and GERD is a firmly established risk factor for this disease." However, he went on to explain some objections to using the capsule for this kind of screening. He said, "The number of adenocarcinoma is still very small, while the cases of breast, prostate cancer, and others are much higher. So it may be hard to implement. Another argument against it is that fewer than 7% of patients with adenocarcinoma have known BE. People complained that the capsule can't take a biopsy; it just suspects BE and you'd have to take an endoscopy to confirm."

The investigator described a computer model using a high-risk population of 50-year-old white males with GERD, with symptoms followed to age 80. The results:

- Capsule endoscopy as a first strategy is nearly as effective and less expensive than conventional endoscopy as a first strategy.
- Both strategies are significantly less than $50,000 per quality-adjusted life year (QALY).
- Conventional endoscopy becomes the dominant strategy if sensitivity is more than 95%. The investigator said that sensitivity and specificity are "remarkably good."

He said that the capsule will probably also be used for screening for varices. He said the advanced cirrhosis patient population (10 million Americans) could benefit from a non-invasive diagnostic test that doesn't require sedation.

As for screening Barrett's, the investigator said that the PillCam capsule endoscopy may be the only way screening for BE could be implemented cost-effectively and on a wide-scale basis. He said he expects it to be coded 3Q or 4Q this year, with reimbursement to come sometime next year.

A PillCam investigator described the Patency capsule as cellophane coated with a lactose body, a radio tag inside, and made of 10% barium. He said the capsule disintegrates at 120 hours (five days). It is 2.12 mm in diameter and 10 mm long. The capsule is mailed to the patient, who swallows it. The capsule is passed in 95% of normals in three days. The abdomen is then scanned at 96 hours (4 days) to determine if the capsule was retained. However, several problems can occur:

- By day four, the capsule is still in some patients' colon, and they may have to get an X-ray to see if it is in the colon or small intestine.
- It can also be trapped in an area of gas.
- It can partially dissolve, become small, and then cause a small obstruction.

In a French study of 20 patients, three developed acute small bowel syndrome and two had to have an operation. The investigator said that the capsule was pulled, redesigned, and is now back in IBD trials.

The investigator said that Given Imaging has added something called Lifetime Imaging to its PillCam system, by which the devices plug into a recording device with a USB cable. The patient swallows the capsule, sits in the waiting room for a half hour or hour, then plugs into the Lifetime Imaging to see if the capsule is still in the stomach. If it is, the patient is given something to help it along.

One capsule investigator said that pharmaceutical companies are interested in CE, and he mentioned a study comparing Pfizer's Celebrex (celecoxib) to naproxen in conjunction with CE.

**The future:** Several sources said that the next step in PillCams is one designed for the colon. Some also said progress is being made in the endeavor to retrieve tissue with a wireless capsule.

Dr. Paul Swain of London described his kitchen table experiments to make a wireless capsule. Described by some doctors at the conference as a genius, he showed how he created a battery-operated, two-capsule device. He was his own guinea pig, and showed how the device went down his esophagus and through his digestive system. The radio-controlled device can be moved backwards and forwards, stopped, and started. He said, "The combination double-sausage capsule combo proved fairly easy to swallow…The device was observed functioning in the esophagus, stomach, and duodenum using both conventional endoscopes and attached wireless device. A command radio-control module allowed independent testing of the LEDs, and you could switch the electrostimulation from forward to backward and deliver single test pulses to tissue."

In one presentation, he speculated about using such a device to actually retrieve tissue, using brush cytology, tissue fluid

aspiration, and biopsy. He also demonstrated the idea of a coagulation capsule, using calcium oxide and water to form calcium hydroxide and heat.

### OLYMPUS

Olympus is working on an imaging capsule that is expected to be ready for launch within the year.

### NORIKA

This Japanese company may also be working on a capsule. A gastroenterologist said, "It's very small – so small that it tumbles around and around as it goes." Another source said the Japanese version is "nowhere near ready."

## CLIPS

A dog study compared various clips. Seven adult dogs with prehaptic portal hypertension had gastric ulcers (GUs) created by rubber band ligation. One week later, 10 chronic-appearing ulcers in pairs were randomized to control or to four different treatments – Olympus's QuickClip2, Wilson Cook's TriClip, Boston Scientific's Resolution Clip, or multipolar electrocoagulation (MPEC). The success rate of clip placement also was quantitated. Animals were treated with daily proton pump inhibitors (PPIs) and monitored for GI bleeding, obstruction, or perforation. At weekly endoscopies, stigmata, clip retention, and ulcer sizes were quantitated. Researchers concluded:

- For the 3 clip devices, similar experience and time were required for successful clipping of chronic GUs.
- Success rates of deployment varied from 100% with the Boston Scientific device to 80.6% with the Olympus clip.
- Clip retention rates were significantly higher with Boston Scientific clips than with Olympus or Wilson Cook clip at Week 1 and Week 2.
- Retained clips closing ulcers appeared to accelerate rather than to delay GU healing, compared to MPEC.
- There were no major complications of retained or excreted hemoclips.

### OLYMPUS'S Super Long Clip

Olympus has developed a Super Long Clip, which investigators said is needed for hemostasis/ligating after large polyp resection or EMR of large lesions. Olympus already makes the Short Clip, with a full aperture of 9 mm for hemostasis and marking and the 12 mm Long Clip for large lesions. The Super Long Clip, with a full aperture of 18 mm, is twice as large as conventional types, and it makes it possible for the endoscopic management of larger lesions. However, the larger the clip is, the greater the stress placed on it.

Researchers compared the three clips, finding the minimum required force for detachment at each point of action was almost the same. The three clips were nearly the same in terms of rigidity, and the researcher concluded that it is highly probable that the clasp size and the external force needed to detach each clip are not related. The larger the clip, the more reaction power from the lesion, which is the prime reason for self-detachment.

Investigators said that the Super Long Clip appears to be especially useful for management of relatively soft lesions, such as large, artificial, ulcerated lesions resulting from polypectomy of large pedunculated polyps, for which closure by a short or long clip is ineffective. In contrast, the clip is not considered good for the management of relatively hard lesions (i.e., giant peptic ulcers). Investigators said that this is unique. They added that the use of Super Long Clips can suture bigger wounds after polypectomy compared to other clips, and that the full aperture of the Super Long Clip is sufficiently long so that it can be easily rotated and adjusted to the proper angle.

## MINIMALLY INVASIVE PROCEDURES FOR GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Numerous devices have been introduced that seek to replace invasive surgery for GERD with a less invasive approach, while also saving procedure time. A source said, "Using the Syntheon ARD Plicator, we've taken a 45 or 60 minute procedure down to a two-minute procedure." Among the devices available are:

- **BARD'S EndoCinch**
- **BOSTON SCIENTIFIC'S Entyrex device**
- **CURON MEDICAL'S Stretta device**
- **MEDTRONIC'S Gatekeeper**
- **NDO SURGICAL'S Full-Thickness Plicator**
- **OLYMPUS'S His-Wiz device (Prototype Version 8).** This endoscopic cardioplicator for GERD has four components: a control handle used to fire the unit, a scope insertion port, an overtube, and a distal tip. The distal tip has a plication window, allowing for suction of tissue, and two needles that penetrate through tissue. The suture unit consists of two titanium alloy bars connected to 3.0 nylon sutures, held together by a silicone stopper. There also are two reversal sutures and a pledget. At maximal suction, the needles are fired into the tissue and pledget in a single step, and the silicone stopper is advanced to create the plication. After the suture is cut, plicated tissue is released, leaving a robust plication.

  The first six patients in a 13-patient trial underwent single plication, and the next seven received double plication. A researcher reported that there were no mortalities, and

side effects were mild. Based on three- and six-month follow-up data, he said, "What we found was significant improvement in heartburn scores in both single and double plication. There was also significant percent time pH <4 in the double plication, which is rather unique…The His-Wiz is safe, effective, and simple."

In animal studies, by three months all the suture plication units had migrated out, but the effects remained. A researcher said, "This gives us the idea perhaps that not only is the plication unit acting as a buttress, but it also prevents gastric distention."

- **OPTIMUM TECHNOLOGIES' Endoscopic Full-Thickness Plicator**
- **SYNTHEON'S ARD Plicator**
- **WILSON COOK MEDICAL'S Sew-Right**

## DISPOSABLE ENDOSCOPES

Disposable endoscopic devices have proven difficult to develop cost-effectively. A source who has worked with USGI Medical's ShapeLock device *(see page 10)* said, "Only the sheath of the ShapeLock is disposable. The more expensive part is the stainless steel part…Boston Scientific is working on one. However, the question is not technology; it's price point. It all comes down to price point." Few doctors questioned could name any companies working on disposable endoscopes.

### GI VIEW'S Aer-O-Scope

This small Israeli company has developed a colonoscopy product called Aer-O-Scope, which it calls a self-propelling, self-navigating disposable device. It is made of two components: a PC-based working station that helps operate the motion of the device and allows a picture to be taken from inside the colon, and a special disposable balloon which contains a 1.5 cm diameter electrical capsule. A distal tip protrudes from the front of the balloon, which is driven forward by $CO_2$. The device is introduced from the rectum. The balloon moves forward, pulling cable which supplies the device with electricity, air suction, and water. The investigator said, "There is no pressure on the wall of the colon. The capsule contains a sophisticated optical system which provides only directional viewing." He described a study of the device on ten anaesthetized pigs. The device advanced 60% of the cases on its own, and, in 10% of the cases it traveled farther than the standard colon scope. He said, "There were no clinically significant abnormalities. We concluded that the system is functional, safe in pig model, and safety and efficacy has been proven."

Other companies thought to be working on disposable endoscopes include:

- Boston Scientific.
- Endosheath, which reportedly is working on a disposable sheathed flexible gastroscope.
- ImagIn, another Israeli company, is working on a disposable colonoscope.
- Invendo.
- Medtronics' MurphyScope endoscopes.
- Olympus.
- Paradigm Optics, which may be working on fiber optic-based technology for disposable endoscopes.
- SightLine.
- U.S. Endoscopy, a privately held company, also has a disposable overtube.
- Vision-Sciences' Vision System.

## ENDOSCOPIC INNOVATIONS AND NEXT-GENERATION TECHNOLOGIES

Further in the future are devices such as:

- Implantable pacemakers.
- Injection of Genzyme's Synvisc to stimulate new tissue.
- Injectable gene therapies that manipulate hormonal stimulation.
- EMR (endoscopic mucosal resection) / endoscopic stapled diverticulostomy tissue resection.
- Mucosal ablation using balloon electrodes.

***Specific devices in development worth watching include:***

### ALVEOLI'S Endoventions division

This company is developing removable metal esophageal and biliary stents, as well as guidewires. The endoscope goes through the device itself, and the stent eliminates the need for fluoroscopy.

### BOSTON SCIENTIFIC/ADVANCED BIONICS' Bion

This endoscopically implantable on-demand stimulator is powered by an internal battery. It is rechargeable and is activated by remote control. The aim of the device is to stimulate the LES (lower esophageal sphincter). In pigs there was little difference at 3, 5, and 7 mA, but there was significant elevation of LES when the amplitude of stimulation was 9.6 mA - 26.5 mA. The investigator said, "This novel, minimally invasive technique has the potential to be an effective new treatment for GERD and other GI motility disorders."

### CITHARA ENDOSCOPY

This company's resector device is an esophageal wide-excision EMR that peels the esophagus lining like a potato-peeler.

### COOK IRELAND'S Duette

This multi-band mucosectomy device, already used in Europe, was recently approved in the U.S. (April 2005). According to a speaker, it facilitates EMR in Barrett's esophagus, "Up to now, the most common practice for EMR has been the suck and cut technique. However, there are several problems. The endoscope has to be withdrawn and reintroduced several times, making the procedure time-consuming. The braid snare that is used in the cap technique can be used for a single resection. There is a need for improved techniques, so the extensive EMR may be more convenient to use. We modified the six-shooter device from Cook company, which now allows sequential banding and snare resection…The key modification is the enlargement of the threading channel of the cranking device from 2 mm to 3.2 mm. This allows for introduction of a 7 Fr snare and other accessories. During suction and ligation, the snare may be retracted into the working channel of the scope and resection may be performed immediately. The modified device also has a widened catheter and a hexagonal polyectomy snare. The snare can be retracted into the end of the scope during suction and ligation. After suction and ligation, the snare will be placed around the pseudo-polyp and dissection is performed."

The speaker said, "We have performed 471 resections on 29 patients and minor bleeding occurred in only six of them. There was one perforation, and 66% of patients developed a stricture….The high stricture rate was due to our aggressive approach rather than the device…The number of bouginage (a procedure using dilators to enlarge the esophagus) sessions was five. Five patients underwent surgery – one with the perforation – and in two patients we found T1sm (a tumor linked to the submucosa) was involved. In one patient non-compliant tissue was due to reflux, and in one patient we had a deep tear post-bouginage…With the MBL-EMR device, extensive EMR is simpler to perform within a shorter period of time. All remaining ridges of BE may be removed using a monofilament snare. Patients with SSBE (short-segment Barrett's esophagus) may be treated with only one MBL-EMR kit in a single treatment session. Strictures in SSBE after EMR are short and well-manageable. To prevent long stricture formulation in LSBE (long-segment Barrett's esophagus) circumferential, EMR should not be performed in a single session. This novel MBL-EMR technique is safe and effective, facilitating and simplifying extensive and circumferential removal."

### ECHOSENS' FibroScan

This test to measure liver stiffness is in clinical trials. A speaker said, "FibroScan is a very interesting device. It is the echocardiogram of liver disease. It has a transducer which emits and receives ultrasound, and the vibrator induces a sheer elastic wave through the liver. The software gives an image of the liver, and you can get a measure of the liver's stiffness."

### FUJINON'S EC450-ZH

This magnifying colonoscope uses a CCD (charged couple device) with 410,000 pixels and optical zoom magnification up to 100x on a 14 inch monitor. The colonoscope provides clear magnification. One study showed that magnified colonoscopic observation of microvessels was helpful for diagnosing colorectal tumors, especially small to massive invasive cancers that showed a greater degree of malignancy.

### JOHNSON & JOHNSON/ETHICON

➢ **Optical dilator.** Stricture dilation is often performed in a blind manner, with the gastroenterologist having to estimate stricture size and making dilation imprecise. The ability to directly visualize and progressively dilate a stricture would potentially improve the process by allowing greater control. J&J has an optical dilator designed to improve this. It is a flexible, transparent vinyl bougie with three dilating segments permitting sequential dilations under direct visualization. The dilator fits over a standard upper endoscope.

Investigators at Northwestern University and the University of Louisville reported on their study of J&J's new optical dilator, concluding it provides safe and effective dilation of esophageal strictures and rings as well as offering a high degree of control and visualization.

Using this device in consecutive patients with solid/liquid dysphagia who were found to have either a peptic esophageal stricture or ring during endoscopy, which was performed using a videoendoscope with either 27 or 29 Fr diameters. Based on the stricture appearance, one of 3 dilator sizes was chosen:

- OD14 (14-15-16 mm dilating segments)
- OD16 (16-17-18 mm dilating segments)
- OD18 (18-19-20 mm dilating segments)

Prior to dilation, 26 patients rated dysphagia on a 7-point Likert scale (0=no dysphagia to 7=unable to handle secretions). Patients also rated procedure tolerance on a 5-point scale (0=no recollection, 5=worst experience of my life) both immediately after the procedure and 21 days after endoscopy. At that time they also rated dysphagia improvement on a 4-point Likert scale (0=no change, 4= complete relief). Peptic stricture was found in 17 of the 21 patients, and Schartzki's ring in 9. There were no complications. The mean pre-procedure dysphagia score was 4 (difficulties with solids at every meal). Most patients (18) reported either significant or complete relief of dysphagia at two-week follow-up. Patients rated the dilation

experience as largely "not at all unpleasant" immediately after endoscopy and had no recollection at three weeks follow-up.

➢ **EndoRail.** This device is used to simplify endoscopic placement of feeding tubes through the pylorus into the small intestine. Without EndoRail, this procedure is technically difficult; when pulled down along the side of the endoscope, retrograde migration out of the small intestine proximally into the stomach or esophagus is frequently observed. Researchers reported EndoRail allows for quick and successful transpyloric placement of feeding tubes into the small intestine, and further optimization of the design will improve the success rate and ease of use.

EndoRail consists of a thin plastic sheath and a plastic rail. The scope is inserted through the sheath, allowing the rail to serve as an exterior channel along which accessories may be passed. Investigators use 140 cm length 10 Fr Dobb-Hoff-type feeding tubes with a compatible rail to allow insertion along the EndoRail affixed to a pediatric colonoscope. The colonoscope was inserted perorally, deeply intubated into the small intestine, and the feeding tube was then slid along the EndoRail to the tip of the scope. The tube was left in place by backing the scope out while advancing the tube along the rail.

A study in four dogs compared the EndoRail technique to the standard technique of using a polypectomy snare to drag a similar tube through the pylorus and deeply into the small intestine. In all cases, deep intubation of the small intestine was achieved (130-140 cm) from the incisors. Successful placement was achieved in 75% of attempts with the EndoRail but only 8% of attempts with the snare (p=.001). Failures with the snare were all due to proximal tube migration during scope withdrawal. The three EndoRail failures occurred in three different dogs and appeared to be due to difficulty in passing the feeding tube over the rail and through the pylorus.

### NIPPON SHERWOOD MEDICAL INDUSTRIES' Dennis Colorectal Tube

This device uses a balloon and guidewire catheter. The presenter said a study was done with 29 patients, "The placement of the DCT (discrete cosine transform) was technically successful in all 29 patients, suggesting this may eventually be used as a primary method before surgery.

### NEOGUIDE'S Navigator endoscopy system

An investigator for the devices called it a new, partially automated, potentially sedationless colonoscopy system. He said, "Looping as a phenomenon happens. When we push the endoscope into the colon, push it against the wall and pull it up, it puts a lot of stress on the supporting tissue and causes pain." The device is made of hinges which run the entire length of the scope rather than just the distal tip. Each hinge is connected to four pull wires which are controlled by a computer. The distal tip pulls the hinges, and the scope is moved through the colon without coming into contact with the lateral wall. The investigator said, "This isn't a computer-advancing scope. Tip deflection, insertion, and withdrawal are completely within endoscopist control…This technique can reduce force applied to the colon and adjacent structures and has the potential to reduce sedation and analgesia. Clinical experience will provide definitive validation." He added that it would be realistic to expect reaching cecum in less than five minutes.

The device has a part that is located next to the anus and measures how deep the tip of the scope is inside the body. The system records the shape of the tip at any given depth and remembers it. With those two pieces of information – depth and position – the device builds a 3D map of the colon. The device is built out of segments controlled by wires. The investigator said, "The technology enables the scope to navigate through the colon without hurting the wall."

### OLYMPUS:

➢ **M-Scope, or XGIF 2T240M**, with double 3.2 mm channels and a second bend.

➢ **V-Scope**, a duodenoscope elevator. This was described as "nothing special," just a way to facilitate ERCP (endoscopic retrograde cholangiopancreatography). It is a modification of the standard TJF-160 duodenoscope, in which the elevator level is configured to include a V-shaped groove and an increased angle of articulation. These modifications combine to enable fixation of the guidewire by the elevator lever.

Multiple exchanges of accessories over guidewires are common during therapeutic ERCP. Catheter/guidewire exchange during ERCP requires the coordinated effort of the endoscopist and the endoscopy assistant. Mishaps during catheter/guidewire exchange are common and result in loss of access and/or a need for repositioning of the guidewire. Highly flexible, hydrophilic-coated guidewires increase the need for adjustments during exchange.

Olympus XT JF-140V2F with a dedicated short (270 cm length) guidewire was compared to a conventional duodenoscope and guidewire combination in a multicenter

**V-Scope Study**

| Measurement | Standard scope | V-Scope | p-value |
|---|---|---|---|
| Number of cases | 22 | 27 | --- |
| Case length | 14.3 minutes | 12.5 minutes | .4214 |
| Fluoroscopy time | 3.46 minutes | 3.49 minutes | .7107 |
| Median exchange time | 31.7 seconds | 19.4 seconds | <.001 |
| Guidewire repositioning | 35.7% | 9.4% | .0005 |
| Loss of guidewire access | 10% | 20.8% | .4280 |

trial. The study found the 140V2F duodenoscope performed better than the TJF-160 during ERCP, decreasing the exchange time and decreasing the number of times that the guidewire needed repositioning. There was a decrease in the overall case time, but this result was not statistically significant. The V-scope effectively locked the guidewire in 64 of 72 exchanges (89%).

➢ **R-Scope.** This was specifically designed for improvement of EMR, and a pig study indicated it is promising. It provides a second bending section for an improved positioning cap and two instrumentation channels – one with an elevator for lifting of the targeted mucosal area with rat tooth forceps and a second one for horizontal swinging of knives to cut the submucosal layer without moving the R-Scope.

Investigators said that conventional EMR techniques are inappropriate for en-block resection (EBSD) of early neoplastic lesions larger than 2 cm in diameter. Even smaller lesions are frequently resected without sufficient safety measures. Piecemeal resectioning of larger lesions doesn't allow histologic confirmation of tumor-free margins of the specimen and is associated with higher recurrence rates. Submucosal dissection can achieve EBSD of large mucosal lesions but is technically difficult, time consuming, and hazardous, in part because of limited visual control of the cutting area.

A study of the R-Scope was performed in eight 30-40 kg anesthetized pigs. Seventeen areas with diameters of 4 cm were pre-determined with coagulation markers in various parts of the stomach. Researchers concluded the R-Scope is a significant improvement in EBSD of large gastric areas in live animal testing, facilitating control of cutting with four different knives (IT-knife, hook-knife, triangle-knife, and flex-knife), which were selected depending on the anatomical situation and operator preference. However, the procedure was technically demanding and time consuming. The risk of perforation was thought to be relative to insufficient submucosal injection and a short learning curve.

➢ **Eagle Claw**, a prototype suturing device. A control arm is used to open and close the jaws of this device, and a mounting bracket allows for mounting a standard upper endoscope. The distal end houses the mechanism for this suture application. There are two jaws: one to fix the tissue and a second curve needle which allows for delivery through the tissue itself. The two components are the suture unit and the Eagle Claw. The suture unit connects the suture unit cartridge and the penetrating needle tip. It is retracted into the Claw and the detachable tip is mounted onto the curved needle itself. The presenter described using the Eagle Claw on pigs to attempt full thickness repair. He said, "All the animals recovered well, with successful closure. We think the claw may be used for acute perforations in humans." The presenter admitted that "Clearly, refinement of this device needs to be done; we have limited mobility now because the apparatus attaches to the distal tip and therefore limits mobility. Increasing mobility will allow you to go in further." Asked how the Claw compares to clips, which are getting larger, the presenter said, "Clips are able to close some of these colonic perforations, but one thing they can't do is produce these full thickness sutures. Our study was done in 2 cm perforations; we can go to 2.5, but I envision with more training and more aggressive techniques, we may be able to close larger perforations which may not be able to be bridged by clips."

➢ **XGIF-N160Y1,** a prototype video endoscope for transnasal gastroscopy. In a pilot study of feasibility and toleration, Italian researchers found that unsedated transnasal gastroscopy using this device was feasible and well-tolerated by patients.

The Olympus XGIF-N160Y1 has an outer diameter of 4.9 mm, a total length of 1,410 mm, and a working length of 1,100 mm, allowing only "up-down" movement. It has a metallic distal tip, and a deflection capability of 210 degrees up and 180 degrees down. In the Italian study of 50 patients examined using this device without sedation, every patient was able to be scoped without complications. Procedure time was ~5 minutes, and only one patient reported pain at instrument insertion or during endoscopy. The researchers reported:

- No significant change in oxygen saturation and blood pressure during the exam.
- A significant increase in heart rate and rate-pressure product during the endoscopy ($p<.01$), which returned to baseline at the end of the exam.
- No ST changes or serious arrhythmias.
- Biopsies obtained in all patients.
- Patient satisfaction questionnaires indicated no anxiety, and only one patient would have preferred conscious sedation.

### PENTAX'S Mucosectome

This prototype device has insulated tip-knives for ESD. It is made with flexible plastic shaft and cutting wire. By handle operation, the top of the device turns freely so that it assists with cutting wire and faces the proper direction. To use it, the doctor:

- Marks around the lesion with a needle knife.
- Injects solution with indigo carmine into the submucosa.
- Cuts mucosa outside marks with the IT-knife.
- Dissects submucosa of the lesion with the Muscosectome.
- Takes the specimen out and has it examined pathologically.

An investigator said the result is a safer, easier, faster technique. He said, "General endoscopists may also be able to

perform ESD in a breeze…A hook-knife is a very safe device but takes a very long time."

In a Japanese study, researchers were able to achieve en-block resection in 10 of 11 patients with rectal tumors. Minor perforation occurred in one patient but was successfully managed by clipping. Peritonitis was not observed, and all patients were discharged uneventfully. ESD using the Mucosectome enabled the investigators to resect LSTs and other lesions without any severe complications, and the investigators concluded that the method is feasible.

### USGI MEDICAL'S ShapeLock endoscopic guide

This device, which the presenter called "a device everyone can use," is currently in Phase II trials. It is specifically designed for patients with tortuous or very long colons. The device is a skeleton multilink device of highly polished stainless steel, and a disposable liner with inner lining and outer sheath. The external diameter of ShapeLock is 22 mm and the inner diameter is 14 mm, so a standard or pediatric scope can be used. The length is about 60 cm. The device doesn't require an additional assistant, and it has a sponge like tip, which reduces the possibility of trauma.

Currently, small bowel enteroscopy is limited by loss of vector forces and curling of the scope within the stomach. Attempts have been made to overcome the limitations using capsule endoscopy, double-balloon endoscopy, and conventional overtubes, but each of these has its own limitations. Capsule endoscopy is limited by the inability to undertake endo-therapy, double-balloon endoscopy requires a significant capital expenditure, and conventional overtubes are difficult to get through the pylons and have been associated with inadvertent strip mycosectomy and even procedural pancrea-titis from damage to the papilla. A speaker said, "What makes ShapeLock unique and different from the tubes we're used to is that it slides over the scope as a sleeve and we can adopt whatever shape the scope has…This is quite straightforward, simple, and amazingly helpful in that small percentage of difficult colons…I haven't seen any superficial tearing with this device."

In a study of 20 previously failed colonoscopies, the total time of procedure averaged 8-10 minutes. The investigator said, "This can be used without fluoroscopy." Asked about lubricants, he said the inner lining of the disposable part is hydro filler – water is put down the inner lining – and standard lubricants are used for the other side.

In another 17-patient study, ShapeLock was able to be inserted to the terminal ileum in two patients, the mid-distal jejunum in nine patients, and the proximal-med jejunum in six patients.

An 18 mm or 16 mm diameter ShapeLock (SL), 80 or 100 cm in length, was used in conjunction with an Olympus pediatric colonoscope or SB enteroscope, respectively. After initial scope passage into the ligament to Trietz Area, ShapeLock was passed under fluoroscopic control through the pylorus and locked in place within the C loop to prevent scope looping. Subsequent scope and ShapeLock passage to definable pathology or the limits of the scope length were undertaken using push and pull maneuvers with and without unlocking and advancement of the ShapeLock.

**ShapeLock Performance**

| Measurement | Device performance *(scale 1 poor – 10 optimal)* |
|---|---|
| Ease of insertion through esophagus | 8 |
| Ease of insertion through pylorus | 6 |
| Ability to maneuver scope though locked ShapeLock | 7 |
| Ease of manipulating to manage looping in the stomach | 8 |
| Ease of manipulating to manage looping in the small bowel | 7 |
| Prevented scope looping in stomach | 9 |
| Enabled deeper penetration into the small bowel | 8 |
| Facilitated procedure completion | 7 |

### Miscellaneous

A Japanese multi-bending endoscope with elevated forceps and knife-swinging functions. This new therapeutic scope is being developed at the Jikei University School of Medicine. Although it may increase risk of perforation, it allows a better view of the submucosal layer than current devices. The scope has two separately movable instrument channels operated by one person. One provides elevation of the lesion and the other provides a swing of the knife. It has a multi-bending section to elevate the forceps and swing knife. It was used on 14 patients with 14 early stage gastric cancers; 11 were completed, two were incomplete, and there was one perforation. The investigator said that a smaller scope would make it better.

## CROHN'S DISEASE AND ULCERATIVE COLITIS

### JOHNSON & JOHNSON'S Remicade (infliximab)

Data presented at ADA from the ACT-I and ACT-II trials found Remicade, which is approved to treat Crohn's disease and rheumatoid arthritis, also is effective in ulcerative colitis (UC). The standard first- and second-line therapies – 5-ASA agents and corticosteroids – are not effective in all patients and also may cause severe side effects. In December 2004, the FDA granted fast-track status for this indication, so a decision should come soon.

Results from these two Phase III, randomized, placebo-controlled studies showed that Remicade appears to reduce signs and symptoms of ulcerative colitis, including remission, attaining mucosal healing, and allowing for reduced corti-

costeroid therapy. Remicade was relatively well tolerated. In both ACT-I and ACT-II studies, 364 patients with active ulcerative colitis were randomized for Remicade at 5 mg/kg and 10 mg/kg or placebo at Week 0, 2, 6, and then every 8 weeks for 46 weeks (ACT-I) or 22 weeks (ACT-II).). The primary endpoint was induction of clinical response, defined as a decrease in the Mayo score of ≥30% and ≥3 points, accompanied by a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding score of 0 or 1 at Week 8 and Week 30. and mucosal healing at Week 8. Clinical remission, a secondary endpoint, was defined as a Mayo score of 2, with no individual subscores >1; and mucosal healing was defined as an endoscopy sub-score of 0 or 1.

Remicade was generally well tolerated with a safety profile similar to that previously reported.

**ACT-I and ACT-II Remicade Results in Ulcerative Colitis**

| Measurement | Remicade 5 mg/kg | Remicade 10 mg/kg | Placebo | p-value |
|---|---|---|---|---|
| ***Primary endpoint:*** Clinical response at Week 8 | 64.5% | 69.2% | 29.3% | <.001 |
| ***Secondary endpoint:*** Clinical remission at Week 8 | 33.9% | 27.5% | 5.7% | <.001 |
| Clinical remission at Week 30 | 25.6% | 35.8% | 10.6% | 5 mg .003<br>10 mg <.001 |
| Mucosal healing at Week 8 | 60.3% | 61.7% | 30.9% | <.001 |
| Mucosal healing at Week 30 | 46.3% | 56.7% | 30.1% | 5 mg .009<br>10 mg .010 |

## ABBOTT'S Humira (adalimumab)

Six-month results from a one-year, 220-patient, Mayo Clinic study, CLASSIC-II, found Humira improved the condition of Crohn's patients with moderate to severely active disease. Patients were up titrated if they experienced flare-ups or were not responsive to treatment. Humira has not yet been filed with the FDA in Crohn's.

**6-Month CLASSIC-II Results of Humira in Crohn's Disease**

| Measurement | Baseline | After 24 weeks of Humira 40 mg EOW |
|---|---|---|
| Clinical remission | 5.5% | 33.2% |
| Clinical response | 40.5% | 78.2% |

## ENZO BIOCHEM'S Alequel

This is an oral mixture of proteins from a patient's own colon. In a 27-week, randomized, double-blind trial in 31 patients with moderate-to-severe Crohn's disease, Alequel appeared effective and safe.

**27-Week Alequel Results in Crohn's Disease**

| Measurement | Alequel | Placebo |
|---|---|---|
| Clinical remission | 58% | 29% |
| Clinical response | 67% | 29% |
| Improvement in overall quality of life | 43% | 12% |

# HEPATITIS C (HCV)

## INTERMUNE'S Infergen (interferon alfacon-1)

Two studies showed promise for the use of daily Infergen either combined with ribavirin or as monotherapy in HCV. One trial reviewed data from 137 patients who had participated in a study to evaluate the safety and efficacy of daily Infergen combined with ribavirin for treatment of PEG-non-responders. At enrollment, none of the 137 patients had shown at least a 2 log drop in alpha-2b (1.5 µg/kg every week) and weight-based ribavirin. Patients were then retreated with 15 µg of Infergen daily plus weight-based ribavirin for 12 weeks and then with 3x week Infergen (15 µg) plus ribavirin for another 36 weeks. At the end of follow-up, 37% of patients achieved an SVR. Using a model to assess the predictive value of viral and demographic factors, the investigators found patients who achieved an SVR with daily Infergen plus ribavirin had significantly greater reductions in HCV RNA after 12 weeks of pegylated interferon alpha-2 plus ribavirin compared to the non-responder group. HCV geno-type, presence of fibrosis, viral copy number at baseline, and gender were not significant predictors of SVR.

The other study compared daily Infergen monotherapy to TIW therapy in previously untreated HCV patients. This multicenter, international Phase IV study showed promise for the daily dosing of Infergen. The trial was conducted at 24 centers in the U.S. and Germany and included 509 previously untreated chronic HCV patients who were randomized to one of three monotherapy regimens of Infergen: 9 µg daily for 48 weeks, 9 µg TIW for 48 weeks, or 9 µg TIW for 72 weeks. HCV RNA virologic responses were measured at Weeks 12, 48, and/or 72, and at 24 weeks following the end of therapy to determine SVR.

Results showed that 20% of patients taking daily Infergen monotherapy achieved an SVR compared to 11% of patients who received 48 weeks of TIW monotherapy and 12% of those who received 72 weeks of TIW monotherapy. Infergen was well-tolerated, but nearly all patients reported at least one adverse event, including headache, fatigue, and rigors. Serious adverse events such as depression, pneumonia, anemia, and convulsions were seen in 6%, 3%, and 2% of the treatment groups, respectively. Daily dosing of Infergen is also being studied in the PEG-non-responder population in the company's Phase III DIRECT trial.

## VERTEX'S VX-950

Investigators presented initial results of a Phase Ib multi-dose study of oral VX-950, a protease inhibitor, that showed the drug dramatically reduces viral levels. Part A of the study included 24 healthy subjects who were given placebo or one of three VX-950 doses – 450 mg, 750 mg, or 1250 mg – every eight hours for five days. Part B included 36 patients with

genotype 1 HCV who received 450 mg or 750 mg every 12 hours for 14 days. Researchers reported:

- VX-950 was well-tolerated by healthy subjects.
- No serious adverse events were reported, and there were no treatment discontinuations.
- There were no changes in vital signs, physical exams, or ECGs.
- The most common adverse events were all mild in severity.
- Trough levels are positively correlated with increasing dose, and interim safety reviews did not delay or prevent dose escalation.
- Steady state is reached on Day 3.
- There is good bio-availability.
- There were no elevations of ALT/AST or other relevant lab values.

A substantial decrease in HCV-RNA with VX-950 was found, with the 750 mg q8h dose showing the biggest reduction. The investigator said, "All the groups showed a steep decline in RNA levels in the first two or three days. After three days, continued decline in RNA was observed, although at a slower rate. In the 450 and 1250 mg patients, RNA levels remained more or less stable and even tended to increase again….But there was certainly superior performance with the 750 mg dose…One gets the impression that all patients had a steep decline, but after the first phase a much slower decline was noted in some patients, and there was a slow return toward baseline HCV-RNA levels after the end of dosing in subjects who achieved an HCV-RNA of <30 IU/nL."

Researchers concluded:

- Multiple dosing of VX-950 for 5-14 days was well-tolerated in healthy subjects and patients with HCV.
- More than a 4 log median reduction in HCV-RNA and undetectable HCV-RNA was achieved within 14 days of administration of VX-950.
- Rapidity of viral load decline, undetectable HCV-RNA levels and slow return of HCV-RNA post-dosing suggest that the drug should be explored as monotherapy.
- Combined therapy with other oral antiviral agents or IFN may be required.
- Treatment duration with HCV protease inhibitor therapy may be shorter than required with the current standard of care.

## OTHER AGENTS

➢ **Statins.** Cholesterol-lowering statins have been reported to reduce the risk of pancreatic and esophageal cancer by >50%. Two case-controlled studies presented at DDW looked at the correlation between statin use and pancreatic and esophageal cancer in a cohort of half a million U.S. veterans. In one study, researchers found that the use of statins such as generic fluvastatin and lovastatin was associated with a 59% reduction in the risk of pancreatic cancer. In the second study, researchers reported that statin use reduced the risk of esophageal cancer by 56%.

➢ **Antidepressants.** A 1,488-patient study of antidepressant use and GI bleeding showed that ongoing use of SSRIs is associated with a risk of GI bleeding similar to that found with regular NSAID use (1.5-fold vs. 1.4-fold increase, respectively). Researchers reviewed records of 549 hospital inpatients admitted with acute GI bleeding between June and December, 2003 and compared them to similar patients admitted during the same time period with non-bleeding diagnosis (939 patients).

♦