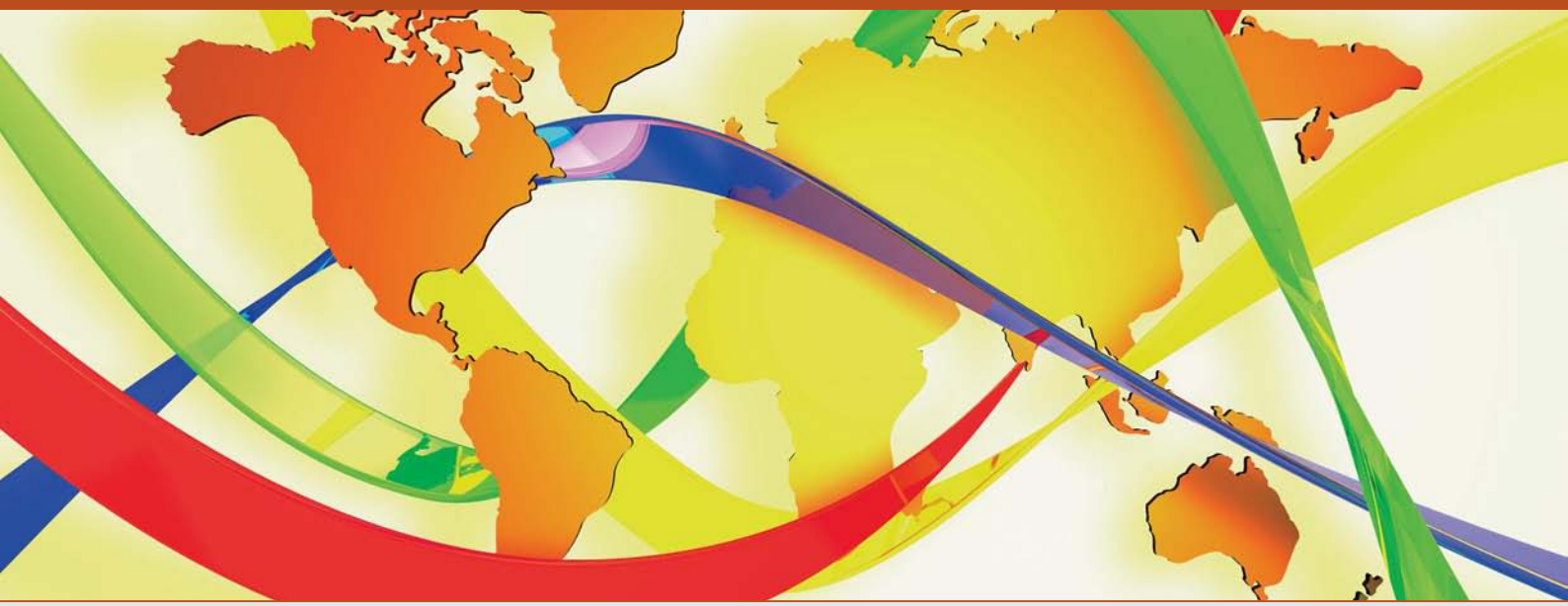
Issue 1 / Spring 2006
Vol.11

WGN
WORLD GASTROENTEROLOGY NEWS



Official Newsletter of the World Gastroenterology Organisation (WGO-OMGE) and the World Organisation of Digestive Endoscopy (OMED)

ISSN 1567 7753

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CONTENTS

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The World Gastroenterology Newsletter is published by Marathon International B.V. in association with WGO-OMGE and OMED.

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Bridging the Worlds of Gastroenterology and Endoscopy For You

GLOBAL GUIDELINES

18 Guidelines are available in 5 languages on the website.
The new Endoscope Disinfection Guideline is available in pocket format at DDW from the WGO-OMGE/ OMED Booth.

WORLD DIGESTIVE HEALTH DAY

May 29. Focus: *Helicobacter pylori:* a bacteria that infects half of the world's population and causes gastric cancer. WGO-OMGE urges all members to utilize May 29 to publicize good gastroenterological health in your community. Share your experiences on our website or e-newsletter–tell the world what you are doing to combat Hp infection.

TRAINING CENTERS

March & May 2006: Opening of WGO-OMGE and OMED's 7th and 8th Training Centers in Rome and Bangkok. For Course information see the websites.

OUTREACH PROGRAM

The Yalgado Ouedraogo Univ. Medical Center was recognized as the WGO-OMGE 2005 Outreach Center. A donation of much needed equipment from Olympus Ltd will drastically improve the health of the 1 million patients who visit this hospital every year.

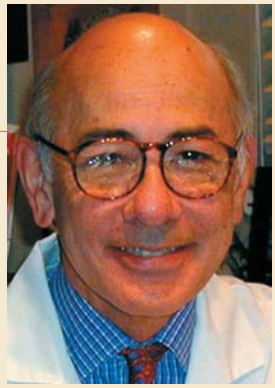
TRAIN THE TRAINERS

Completely Booked Out! Train the Trainers 2006 South Africa received an unprecedented number of applicants. Check the website for details about courses in 2007.

Visit the WGO-OMGE & OMED Booth in the Exhibition Hall at DDW

www.worldgastroenterology.org
www.omed.org

Message from the Editor-in-Chief



Jerome D. Waye

The World Congress of Gastroenterology in Montreal was a great success. The scientific sessions were superb and the social functions delightful—congratulations to the Canadian organizers for a wonderful Congress. The ability to meet old friends from around the world and make new acquaintances provides a human-interest highlight for this quadrennial educational event.

Since the last issue of *WGN,* there has been a changing of the executive hierarchy of both WGO-OMGE and OMED. I welcome all of these hardworking gastroenterologists to their new positions. We all owe the executives and governing council members a standing ovation for the countless hours of meetings, traveling, planning, and decision-making that they do without remuneration—and they do it all for you, the world of medical, surgical and pediatric gastroenterologists, endoscopists, hepatologists, and gastrointestinal pathologists.

This issue brings news from some of the members of the newly appointed *WGN* editorial board, and two articles on the theme of "gastroenterology on the frontiers." I know our readers will find them interesting. The scientific news in this issue is varied and ranges from esophageal carcinoma and esophageal motility to the surgical approach to hepatocellular carcinoma and biologic therapy of Crohn's disease. Current thoughts on radiotherapy and rectal cancer are discussed, and new fecal occult blood tests are explored. The International Digestive Cancer Alliance (IDCA) continues its series of articles on cancer with one on screening. The Secretary-General of OMED has written a witty and pleasurable treatise on a foreigner's view of Japanese endoscopy meetings, having attended many over the years. We have an interesting and uplifting report from the gastrointestinal training center in Rabat, Morocco.

The insert in this issue concerns a topic of importance for all gastroenterologists throughout the world: endoscopic disinfection. This is a subject that affects all of us, and international guidelines are included.

Our in-house librarian and academician presents viewpoints on evidence-based medicine (EBM), a topic of growing interest over the past decade. In spite of EBM, the Nobel Prize in medicine was awarded to two gastroenterologists who used "seat-of-the-pants" medicine, perseverance, and self-administration of *Helicobacter pylori* to show that ulcers are not caused by acid, aggravation, temper, or frustration. The Nobel Prize has never been awarded to gastroenterologists before, and we are proud to congratulate Dr. Barry Marshall and Dr. J. Robin Warren, a pathologist, for their seminal work that changed the whole field of gastric pathophysiology.

I just met with a group from the Massachusetts General Hospital and want everybody to know that there is a superb website for free endoscopic videos, and it will carry several therapeutic videos in the next month: www.daveproject.org.

We will see you all at Digestive Disease Week in Los Angeles. You can register and obtain housing applications by searching for "Digestive Disease Week" on the Web.

WGO-OMGE President's Column: the 4-year outlook

Eamonn Quigley

The World Congress in Montreal will linger long in all of our memories. The outstanding scientific and social program mounted by our Canadian colleagues and friends was not only a singular success in its own right, but also served as a perfect and timely illustration of why World Congresses are different and, indeed, unique. The Montreal Congress will serve as a template for many World Congresses to come.

For the World Gastroenterology Organization (WGO-OMGE), Montreal also provided several other important milestones. At the General Assembly, the decision to hold the next World Congress in London and as a joint venture with the United European Gastroenterology Federation

(UEGF) was unanimously ratified. Discussions with UEGF and with the conference center in London are already well underway and we are confident that Gastro 2009 will be a major event.

The symposium on global guidelines was a major success. Experts from diverse backgrounds supported the validity of a global approach to guidelines, but emphasized the importance of inclusion and flexibility, especially in relation to available resources—all testimony in favor of the approach to guideline development taken by Michael Fried and his committee.

At a symposium attended by several "Train the Trainers" (TTT) alumni, the value of the Train-the-Trainers program was affirmed and several valuable suggestions were made for future programs. The TTT concept is obviously catching on—the details of the next TTT meeting in South Africa in August 2006 have been set, and proposals for programs in Brazil and Portugal in 2007 are currently under review.

As I look forward as your new President to the next four years, I believe that we should pay special attention to the consolidation and integration of our training centers. We eagerly anticipate the inauguration of the latest center, in Bangkok, early in 2006 and to further programs at existing centers in Soweto, Rabat, Cairo, La Paz, and Karachi. These are complemented by the advanced training center in Santiago, Chile, which will be followed by other advanced training sites that are currently under consideration. We look forward to the day when an integrated network of training centers, both basic and advanced, will ensure access to the highest-quality training in gastroenterology for trainees across the globe.

The next four years will witness an ever-closer relationship between WGO-OMGE and its longtime partner, the *Organisation Mondiale d'Endoscopie Digestive*/World Organization of Digestive Endoscopy (OMED). The successes of the TTT program and the training centers are testimony to the hard work of the two organizations' Joint Education Committee. We also applaud the outreach program, which has already provided endoscopic equipment to the Eva Perón Hospital in Santa Fe Province, Argentina, and is now embarking on a similar exercise in Burkina Faso.

WGO-OMGE has enjoyed considerable success in recent years and has expanded its horizons well beyond the four-yearly Congress. The challenge for us now is to sustain and nurture these programs and to work with all our partners—be they national, regional, or international—to promote gastroenterology and digestive health throughout the world.

Finally, may I remind all of you of the opportunity presented by World Digestive Health Day on May 29; use this occasion to publicize issues in gastroenterology in your area!

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OMED President's Column: turning a new page

Anthony Axon

Change of management

It is my privilege to be President of *Organisation Mondiale d'Endoscopie Digestive*/World Organization of Digestive Endoscopy (OMED) for the next 4 years. Our new Secretary-General is Jean-François Rey (France), the Treasurer is Bob Bailey (Canada), and the President-Elect is Jerry Waye (United States). We are well supported by an experienced Council, and have had an infusion of new talent to chair our standing committees.

The World Congress, Montreal

The World Congress in Montreal was a wonderful occasion for endoscopy. One of the major rooms at the Congress was set aside for endoscopy, and the program ran continuously for the whole week. Live endoscopy was demonstrated by an international faculty led by Norman Marcon in Toronto. There was also an exciting live demonstration from Hong Kong. In addition, there were video presentations. Our thanks go to our Canadian colleagues who organized the event with such professionalism and skill.

The next four years

The quadrennial World Congress has previously provided us with much of our income. In the future, we recognize that financial sup-

port will be more closely linked to the success of the activities we undertake from year to year. This provides an exciting challenge.

Endoscopy is the workhorse of gastroenterology. Few gastroenterologists are able to practice without the skills achieved through training in endoscopy. OMED intends to play a leading role in widening the popularity of endoscopy whilst at the same time ensuring that it is done to the highest possible standard. With this in mind, we have identified a series of projects that we believe will be attractive to our partners in industry. We have expanded the number of standing committees responsible for taking these projects forward—the potential projects are listed in the box at the right.

OMED Project Proposals, 2005–2009

Project 1	"How I do it" documents
Project 2	Endoscopy directors' workshops
Project 3	Identification of quality indicators in endoscopy
Project 4	Application of quality standards in endoscopy to credentialing and re-credentialing
Project 5	Barrett's esophagus: workshop on surveillance and treatment
Project 6	The role of endoscopy in the diagnosis and treatment of early gastric cancer
Project 7	Workshop on screening of gastric cancer
Project 8	Core curriculum for training in endoscopy
Project 9	Hands-on instruction at meetings
Project 10	OMED teaching fellows
Project 11	OMED Training Centers activities
Project 12	Manual of training materials
Project 13	Outreach program
Project 14	Endoscope equipment updates
Project 15	Meeting reports
Project 16	Research reviews
Project 17	Cost-effectiveness of endoscopy
Project 18	Atlas of endoscopic images
Project 19	Documentation of image standards
Project 20	Standardized reporting of endoscopy
Project 21	OMED web site
Project 22	Compendium of endoscopy products
Project 23	Annual OMED colorectal cancer screening and surveillance conference
Project 24	Regional colorectal cancer symposia
Project 25	Position papers: colorectal cancer screening and surveillance
Project 26	An international survey of colorectal cancer screening practice
Project 27	Panel of international speakers: colorectal cancer screening and surveillance

Closer relationship with our members

We believe that OMED's success will depend on cooperation with our friends and colleagues, the most important of whom are our members in the national endoscopy societies. We intend to keep our membership more aware of our activities, and to do this we have appointed a professional secretariat—Medconnect, under the leadership of Bridget Barbieri—that will retain close contact with the national OMED societies through newsletters, e-mail, *World Gastroenterology News,* and a new and reinvigorated web site.

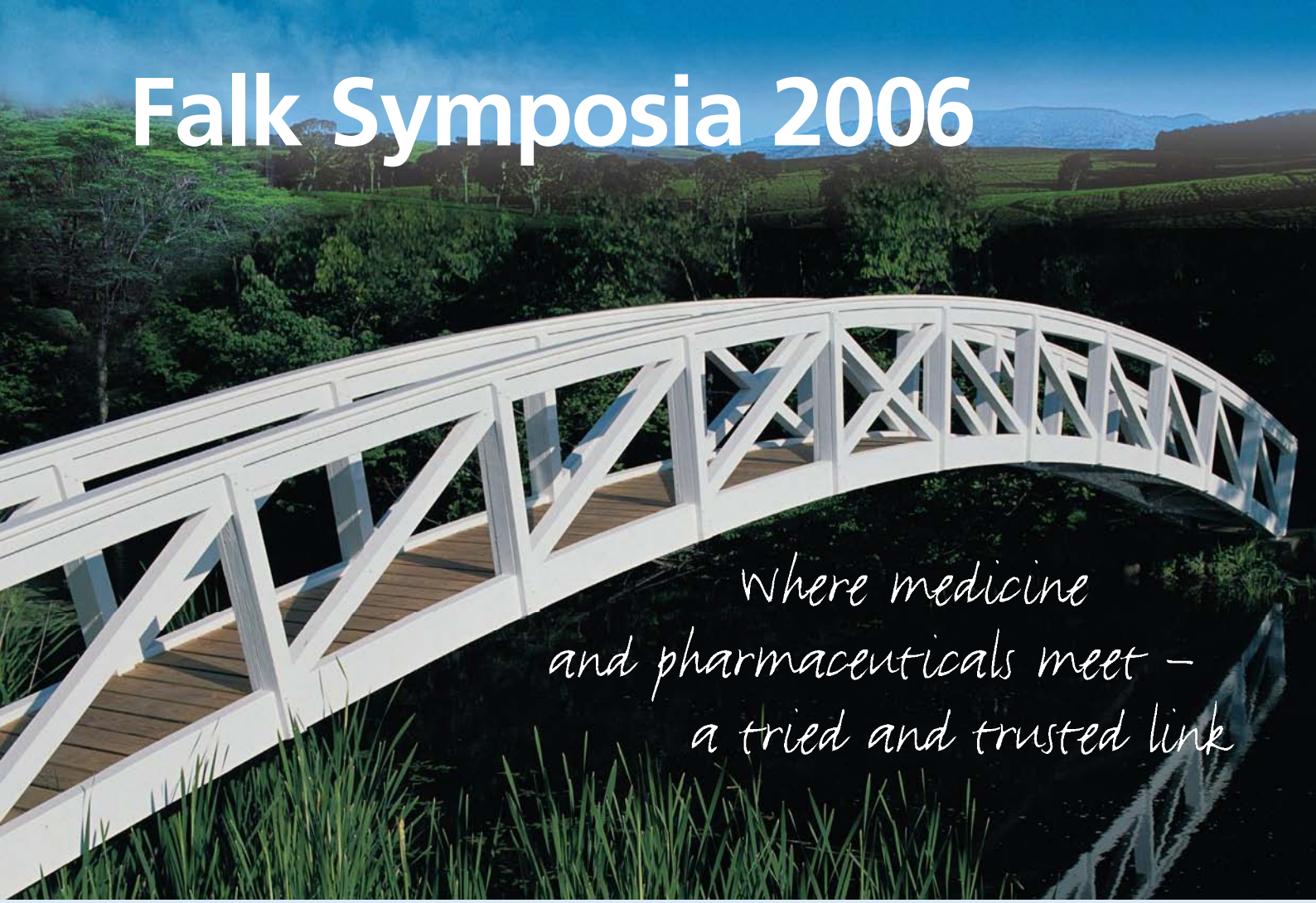
Partnership with WGO-OMGE

A second group of colleagues we work closely with is the World Gastroenterology Organization (WGO-OMGE). We believe that OMED should remain an independent world endoscopy organization, and we are negotiating with WGO-OMGE to set up a formal working partnership so that future strategic decisions will be made together. We believe that by working together, we will strengthen both organizations and enhance our financial security.

Relationship with industry

The biomedical industry is also interested in expanding the range of endoscopy, including new techniques and equipment, workshops, research, and teaching, and improving the quality and visibility of endoscopy. We have therefore taken steps to set up a consortium with the major endoscopic companies and have also invited other members of the biomedical industry to join us.

Falk Symposia 2006



Falk Research Workshop
Liver Regeneration, Stem Cells and Transdifferentiation
Leipzig, Germany
January 19 – 20, 2006

Falk Symposium 151
Emerging Issues in Inflammatory Bowel Diseases
Sydney, Australia
March 24 – 25, 2006

Intestinal Disease Meeting
Berlin, Germany
May 4 – 7, 2006

Falk Symposium 152
Endoscopy 2006 – Update and Live Demonstration
May 4 – 5, 2006

Falk Symposium 153
Immunoregulation in Inflammatory Bowel Disease – Current Understanding and Innovation
May 6 – 7, 2006

Falk Symposium 154
Inflammatory Bowel Disease – Diagnostic and Therapeutic Strategies
Moscow, Russia
June 9 – 10, 2006

XIII Falk Liver Week 2006
Freiburg, Germany
October 6 – 11, 2006

Falk Symposium 155
XIX International Bile Acid Meeting
Bile Acids: Biological Actions and Clinical Relevance
October 6 – 7, 2006

Falk Symposium 156
Genetics in Liver Diseases
October 8 – 9, 2006

Falk Symposium 157
Chronic Hepatitis: Metabolic, Toxic, Viral and Autoimmune
October 10 – 11, 2006

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"Turning Science into Medicine" in the City of Angels

Los Angeles (otherwise known as the City of Angels) is home to this year's Digestive Disease Week (DDW), the premier gastroenterology congress, at the LA Convention Center on 20–25 May. The theme of the meeting is "Turning Science into Medicine" —a reflection of the keen interest that the participating societies have in ensuring that the work of important scientific discovery is translated into meaningful clinical care.

Gastroenterology may no longer be one of the driving forces behind the pharmaceutical industry as in other disciplines, but there is no doubt that DDW continues to illustrate the dynamic nature of all the subspecialties involved. As ever, the umbrella that is DDW will cover gastroenterology, hepatology, endoscopy, surgery, and much more. The number of abstracts submitted to the meeting is continuing to grow, although more slowly than before, and now stands at just over 7000. Of these, 70% have been accepted for presentation and will form the basis of the oral and poster sessions.

For the first time, the American Gastroenterological Association (AGA) will be offering free simultaneous Spanish interpretation in the general sessions of the postgraduate courses, as well as at a number of the AGA plenary sessions to be held on the Monday and Tuesday. The AGA courses are continuing to attract participants who want to improve their understanding of the treatment of gastrointestinal diseases by studying actual clinical examples.

As ever, the American Society for Gastrointestinal Endoscopy (ASGE) Learning Center is offering interactive educational resources and hands-on demonstrations of endoscopic procedures.

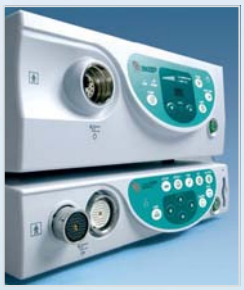
For hepatologists, the American Association for the Study of Liver Diseases (AASLD) will be holding a number of state-of-the art lectures that will address cutting-edge developments in liver disease, such as new developments in the treatment of hepatitis C virus and the treatment of portal hypertension.

The Society for Surgery of the Alimentary Tract (SSAT) will be holding its usual postgraduate course on the Sunday before the start of the meeting, discussing how to optimize outcomes in a number of pancreatic and biliary tract conditions through a multidisciplinary management approach.

Many visitors to conventions in Los Angeles are probably more used to meetings being held at the Anaheim Convention Center near Disneyland. No, just to avoid any confusion of venues—DDW is not being held in Anaheim, though Mickey and friends are not far away. The LA Convention Center is a large and modern downtown facility that will host DDW, just as it did the World Congress of Gastroenterology in 1994. Hotels will be served by shuttles and the local public transport systems, and we will all be able to share in the daily experience that is the notorious and hectic California commute.

Most of the important deadlines will have passed by the time this issue of *WGN* is received, but all the up-to-date information can still be found at www.ddw.org, including online housing and travel details, file downloads, and much more.

Outstanding teamwork.



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Dr Herbie Schneider

5th AMAGE Conference, Sharjah, United Arab Emirates

The 5th AMAGE conference was held from 24–26 February 2006 with over 800 delegates from many African, mid-East and Asian countries. Speakers from the AMAGE region were joined by a strong international faculty including Alberto Montori and Massimo Crespi from Italy, Firas al Kawas (USA), Lucas Greiner (Germany), Chris Fraser and Dr Kumar (UK) and Terry Bolin (Australia). The postgraduate course consisted of various practical aspects of interventional endoscopy. Symposia covered topics including hepatitis, oncology, GERD and Inflammatory bowel disease.

The presence and participation by prominent WGO-OMGE executive members, both present and past included Profs. E. Quigley, H. Cohen, M. Farthing and M. Classen.

The organising committee under the direction of Asaad Dajani are to be congratulated for the well-organised meeting. The general council meeting honoured the outgoing president of AMAGE Prof Ziad Shariah and bestowed the honorary title of "Founding President".

A very sad tribute was paid to our dear departed friend and colleague Fouad Thakeb, who died tragically in 2005. His wife and family were present, and many delegates were able to express their condolences. The council has approved an annual eponymous lecture to be known as the Fouad Thakeb Memorial Lecture.

amage
African-Middle East Association of GastroEnterology

The meeting was held under the generous patronage of the ruler of Sharjah His Highness Sheikh Dr Sultan bin Mohammed Al Qassimi. He attended the opening ceremony, and hosted the gala dinner. He has offered significant assistance to WGO-OMGE through Prof. Quigley.

We should be under no illusion that a daunting task lies ahead to succeed in our mission: to improve the health of the people in Africa and the Middle East, and to advance the role of Gastroenterology in the region.

Dr Herbie Schneider
President, AMAGE

Sharjah, panorama.

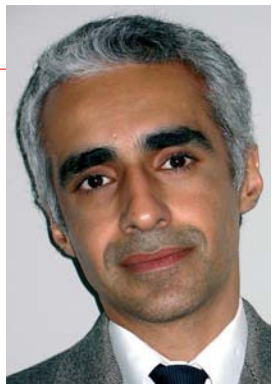
Liver Resection and Transplantation for Hepatocellular Carcinoma

Sasan Roayaie, MD and Myron Schwartz, MD

Liver resection for hepatocellular carcinoma

Introduction. Apart from limiting resectability, cirrhosis also causes hepatocellular carcinoma (HCC). It is therefore not surprising that, over time, new tumors develop after resection (estimated at 75–90% within 5 years in hepatitis C-related HCC). Nonsurgical methods of destroying HCCs, including percutaneous ethanol injection and radiofrequency ablation, have been reported to yield survival rates similar to those with resection. While these procedures are not as reliable in completely eliminating the tumor, the associated morbidity and mortality are lower. The ultimate result of either resection or percutaneous treatment is highly dependent on careful follow-up and treatment of new tumors. What, then, is the role of resection?

Sasan Roayaie



Myron Schwartz

Selection criteria. Most patients with cirrhosis have diminished liver function at presentation; such patients are not good candidates for resection. While a variety of different liver function tests (e.g., indocyanine green clearance) have been used to assess suitability for resection, none has proved more useful than the Child–Pugh–Turcotte classification. Patients with Child's A cirrhosis in general have sufficient functional reserve to tolerate limited hepatic resection. The degree of portal hypertension also correlates with the outcome; a platelet count under 100,000/mm^3 and a hepatic venous pressure gradient > 10 mmHg are indicators that significant portal hypertension is present. Even in patients with Child's A cirrhosis and no significant portal hypertension, resection of a large proportion of the functioning liver (e.g., right lobectomy for a small, centrally located tumor) carries substantial risk.

The size, number, and location of tumors and presence of vascular invasion are assessed preoperatively using helical computed tomography or magnetic resonance imaging. The criteria used vary considerably among centers, with some advocating resection only for patients with small, (< 5 cm) solitary tumors and others, such as our own center, offering resection to patients with single tumors irrespective of size. Resection may technically be possible in patients with multiple tumors, but the likelihood of undetected small nodules is increased in these patients, limiting the benefit. Patients with macroscopic vascular invasion, including main portal vein involvement, have a high rate of recurrence after resection, but survival in well-selected cases can be far greater than the median 2–3 months achieved by current medical therapy.

When resection of substantial functioning liver tissue is required, preoperative portal vein embolization can reduce the likelihood of postoperative liver failure. This procedure, performed percutaneously in the portion of the liver to be resected, induces compensatory hypertrophy in the opposite lobe within 3–4 weeks.

Results. The reported survival after resection for HCC is in the range of 80–92% at 1 year, 61–86% at 3 years, and 41–74% at 5 years. The short-term results depend on the severity of the underlying liver disease and on the class, degree of hepatic fibrosis, total bilirubin level, presence of clinically relevant portal hypertension, and platelet count.

The long-term survival is most closely related to tumor recurrence, which occurs in approximately 20% of patients at 1 year, 50% at 3 years, and 75% at 5 years. Predictive factors for recurrence include tumor grade, microscopic and macroscopic vascular invasion, tumor size, number of tumors, presence of satellites, alpha-fetoprotein (AFP) level, and positive surgical margins.

Adjuvant treatment. The most common site of metastasis after resection for HCC is the remaining liver. Treatment of the remaining liver with iodine-131 Lipiodol via the hepatic artery, with the intention of de-

stroying micrometastases, has been shown to reduce recurrences and prolong the survival period. As ^{131}I Lipiodol is not universally available, alternative transarterially administered agents including yttrium-90 microspheres and Ethiodol chemoembolization are used at many centers as an alternative therapy.

Interferon-based treatment of hepatitis C has been shown to decrease the incidence of *de novo* tumors, both primarily and after resection. Polyprenoic acid may prevent *de novo* HCC in patients who have undergone resection.

Liver transplantation for HCC

Introduction. In the early days of transplantation, most patients with HCC had advanced tumors, and the majority developed recurrences; more recently, improved diagnosis has allowed some HCC patients to enjoy outcomes that are as good as those for patients who undergo transplantation for nontumor indications. The major challenge facing transplant centers is finding donor organs.

Selection of candidates for transplantation. Recognizing the favorable transplant outcomes in well-selected patients, the organ allocation system in the United States gives such patients priority. The current criteria for priority (one tumor 2–5 cm in size; two or three tumors all ≤ 3 cm) were established on the basis of a study conducted in Milan. Although there is some regional variation, patients meeting these criteria generally receive a deceased-donor liver within a 6–12 month period. Patients with tumors that do not meet the criteria are not excluded from candidacy, but without priority they are unlikely to be assigned a deceased donor liver; living-donor transplantation has emerged as an alternative in such cases.

A number of centers have advocated extending the Milan criteria. At Mount Sinai School of Medicine in New York, a multimodality protocol has been established for transplanting patients with HCCs ≥ 5 cm.

Results. When patients are selected for transplantation according to the Milan criteria, the 5-year survival and disease-free survival are in the range of 70–80%. With more advanced HCCs, tumor recurrence begins to affect survival. At Mount Sinai, the survival period for patients with tumors 5–7 cm in size is similar to that of patients who met the Milan criteria.

A number of studies have examined factors capable of predicting post-transplantation recurrence of HCC. A multivariate analysis showed that tumor size (≤ 2 cm vs. > 2 cm), number (single or multiple), unilobar or bilobar involvement, vascular invasion (none, microscopic, or macroscopic), and absence or presence of lymph-node metastases were independently associated with poorer survival.

Living-donor transplantation and HCC. Living-donor transplantation (LDT) is an option that is particularly applicable to patients with HCC, as it allows the transplant to proceed without the need to wait and the patients can readily tolerate receiving a small graft, as they usually do not have advanced liver failure. Since there is no standard allocation policy, LDT makes transplantation possible for patients with HCC who do not meet the Milan criteria. At Mount Sinai, HCC has been the indication for nearly 40% of the LDTs performed at the center. The majority of the patients have had tumors exceeding the Milan criteria; nevertheless, the survival and recurrence rates have been comparable to those in transplant patients who met the Milan criteria. We believe that HCC is an excellent indication for LDT.

This paper was originally presented at the American Society of Clinical Oncology (ASCO) meeting in Orlando in May 2005. The research is supported by National Institutes of Health NIH K24 award no. DK 60498-03.

This is a summary of the original text, which is available in full at: www.worldgastroenterology.org

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Dysphagia and Esophageal Motility Disorders

Peter J. Kahrilas, MD

Dysphagia is the fundamental symptom experienced by patients with esophageal disorders. However, because dysphagia can be caused by difficulty in the passage of food anywhere from the mouth to the stomach, a thoughtfully taken history is critical for evaluating the condition. In esophageal dysphagia, the patient's own identification of the location of the obstruction is of limited accuracy. For example, a distal esophageal obstruction caused by an esophageal ring or an esophageal motility disorder may often be sensed as dysphagia at the level of the neck, so that patients are correct in identifying the location of the dysfunction only 60% of the time. A thoughtful diagnostic approach to the patient depends on the array of symptoms elicited.

Causes of esophageal dysphagia

Esophageal dysphagia can result from a failed propulsive mechanism, a structural problem impairing the bolus flow, or an abnormal sensation of bolus transit during swallowing.

Structural lesions. Structural abnormalities may partially or completely compromise the esophageal lumen, and the resulting propulsive failure may be intermittent or constant. Esophageal webs, rings, and strictures result in limited esophageal opening, which can potentially impede bolus transit. This problem typically occurs while swallowing solid food, especially meat, and is frequently intermittent. Esophageal webs or strictures can be congenital, malignant, or may result from benign processes, most commonly reflux esophagitis. Recently, it has been recognized that many cases of esophageal rings—especially multiple rings that may have previously been attributed to gastroesophageal reflux disease—are in fact attributable to eosinophilic esophagitis. For this reason, it is now recommended to obtain mucosal biopsies from individuals with undiagnosed dysphagia, even when there is a seemingly normal endoscopic appearance.

A number of dermatological disorders, such as bullous pemphigoid and pemphigus vulgaris, are associated with esophageal involvement.

Esophageal motility disorders. A working—although restrictive—definition of an esophageal motility disorder is: *an esophageal disease attributable to neuromuscular dysfunction causing esophageal symptoms, most commonly dysphagia, chest pain, or heartburn.* Using this definition, there are only a few esophageal motility disorders, and they can be categorized as primary if the esophagus is uniquely afflicted or secondary if the condition is an esophageal manifestation of a more general disease (Table 1).

Table 1. *Esophageal motility disorders (EMDs) **

Primary EMD
Achalasia
Diffuse esophageal spasm*
Gastroesophageal reflux disease
Secondary EMD
Pseudoachalasia
Chagas' disease
Scleroderma esophagus
Parkinson's disease
Infiltrative disorders
Manometric variants, not EMDs
Nutcracker esophagus
Hypertensive lower esophageal sphincter
Ineffective esophageal motility
Nonspecific EMD

* With the restrictive definition given above.

Achalasia

Epidemiology. The incidence of achalasia is about one in 100,000 of the population, affecting both sexes equally and usually presenting between the ages of 25 and 60. Because achalasia is a chronic condition, its prevalence greatly exceeds its incidence; prevalence estimates range from 7.1 to 13.4 per 100,000.

Pathogenesis. The neuroanatomic change responsible for achalasia is loss of ganglion cells within the myenteric plexus. The key physiological abnormalities in achalasia are impaired lower esophageal (LES) relaxation and aperistalsis. With regard to the esophagus itself, long-standing achalasia is characterized by progressive dilation and sigmoidization of the esophageal body, with hypertrophy of the LES.

Clinical presentation. Clinical manifestations of achalasia may include dysphagia, regurgitation, chest pain, weight loss, and aspiration pneumonia. Strangely, despite the severe dysphagia, significant weight loss is unusual.

Regurgitation occurs when food, fluid, and secretions are retained in the dilated esophagus. An estimated 10% of achalasia patients have bronchopulmonary complications (bronchitis, pneumonia, or lung abscess) due to chronic regurgitation and aspiration.

Differential diagnosis. The only distinction between vigorous achalasia and diffuse esophageal spasm is the demonstration of incomplete LES relaxation in vigorous achalasia, making diffuse esophageal spasm a key element in the differential diagnosis. Also included in the differential diagnosis are Chagas' disease and pseudoachalasia. These disorders may resemble achalasia so closely that conventional diagnostic tests are misleading.

Tumor infiltration (especially carcinoma in the gastric fundus) can completely mimic the functional impairment seen with idiopathic achalasia. The resultant "pseudoachalasia" accounts for up to 5% of the suspected cases and is more likely with advanced age, an abrupt onset of symptoms (< 1 year), and weight loss of more than 7 kg. Endoscopy should therefore be part of the initial evaluation of achalasia.

Diagnostic methods. With long-standing achalasia, the esophagus may develop a sigmoid configuration, and in some instances an air–fluid level, mediastinal widening, and an outline of the dilated esophageal wall are even evident on a plain chest film. The characteristic radiographic findings depend on esophageal dilation, but as this is not always present, radiography only has limited sensitivity.

The defining manometric features of achalasia, present in over 90% of patients, are aperistalsis and incomplete LES relaxation. Impaired LES relaxation by itself (to a nadir value greater than 12 mmHg) has a 92% sensitivity and 94% specificity for detecting achalasia. Atypical cases require the manometric findings to be combined with additional clinical data. Some patients have higher-amplitude (> 60 mmHg) simultaneous repetitive contractions in response to swallows, which define a variant known as vigorous achalasia.

Endoscopy is relatively insensitive for detecting achalasia except in advanced disease, in which the findings are obvious. The achalasic LES has a pinpoint appearance and does not open with air insufflation. However, the instrument should pass with minimal pressure.

Treatment. As the ultimate cause of achalasia is unknown, treatment is directed at compensating for the functional abnormalities. There is no known way of preventing the disease. The main functional abnormality in achalasia—poor esophageal emptying—is treated by reducing LES pressure so that gravity promotes the passage of food. Peristalsis rarely, if ever, returns. LES pressure can be reduced by pharmacological therapy, forceful dilation, or surgical myotomy. The optimal approach is still a matter of debate, as there is a lack of high-quality randomized and controlled trials.

Nitrates or calcium-channel blockers, administered orally or sublingually 30–45 min before eating, can relieve dysphagia in achalasia patients by reducing the LES pressure. Sildenafil has been reported to be beneficial.

Botulinum toxin, a potent inhibitor of acetylcholine release from nerve endings, has been used successfully in achalasia. The technique involves injecting 80–100 units of botulinum toxin into the four quadrants of the LES with a sclerotherapy catheter. However, the effect of botulinum toxin is eventually reversed by axonal regeneration. Studies have confirmed that although most patients initially experience good results, there is minimal continued efficacy after 1 year.

The basic element of an achalasia dilator is a noncompliant cylindrical balloon that can be positioned fluoroscopically or endoscopically across the LES and then inflated to a diameter of at least 3 cm with a hand-held manometer.

The technique of pneumatic dilation varies, but the procedure is usually done in an outpatient setting using moderate sedation. Patients should be advised to advance their diet gradually over a period of 2–3 days. The reported clinical efficacy of dilation ranges from 32% to 98%. Patients with a poor initial result or rapid recurrence of symptoms are unlikely to respond to additional dilations, but the subsequent response to myotomy is not influenced.

The major complication of pneumatic dilation is esophageal perforation, with a reported incidence ranging from 1% to 5%. If a perforation appears to be small and confined, conservative management is appropriate. If a substantial perforation occurs, surgical repair should be carried out quickly. Patients with perforation due to pneumatic dilation that is recognized and treated surgically within 6–8 hours have outcomes comparable to those in patients undergoing elective Heller myotomy.

Currently, the most common open surgical procedure for achalasia is an anterior myotomy from the

CME-certified Symposium

Save The Date

Monday, May 22, 2006
Sheraton Hotel LA
711 South Hope Street
California Ballroom
Los Angeles, California

Registration and Breakfast: 5:00 AM - 6:00 AM
Scientific Session: 6:00 AM - 7:45 AM

Decoding **Crohn's Disease** Cross-Talk: Pathology, Pathways and Emerging Paradigms

This activity has been approved for AMA PRA Category 1 Credit

5:00 AM - 6:00 AM	**Registration and Breakfast**
6:00 AM - 6:15 AM	**Welcome and Introduction** Maria Abreu, MD New York, NY
6:15 AM - 6:40 AM	**Innate Immunity in Crohn's Disease: New Concepts and Therapeutic Targets** Maria Abreu, MD New York, NY
6:40 AM - 7:05 AM	**Medical Management of Crohn's Disease: Current Therapy and Recent Advances** Stephen Bickston, MD Charlottesville, VA
7:05 AM - 7:30 AM	**Bridging Innate and Adaptive Immunity: The Emerging Role of Innate Immunity Activators** Brian K. Dieckgraefe, MD, PhD St. Louis, MO
7:30 AM - 7:45 AM	**Questions and Answers**

Objectives

At the conclusion of this symposium, participants should be able to:

- Describe the emerging evidence and implications that Crohn's disease may be due to a primary defect in innate immunity
- Assess the efficacy and safety of currently accepted maintenance medications and treatment strategies for Crohn's disease
- Discuss the efficacy and safety of promising agents currently in development for the treatment of Crohn's disease

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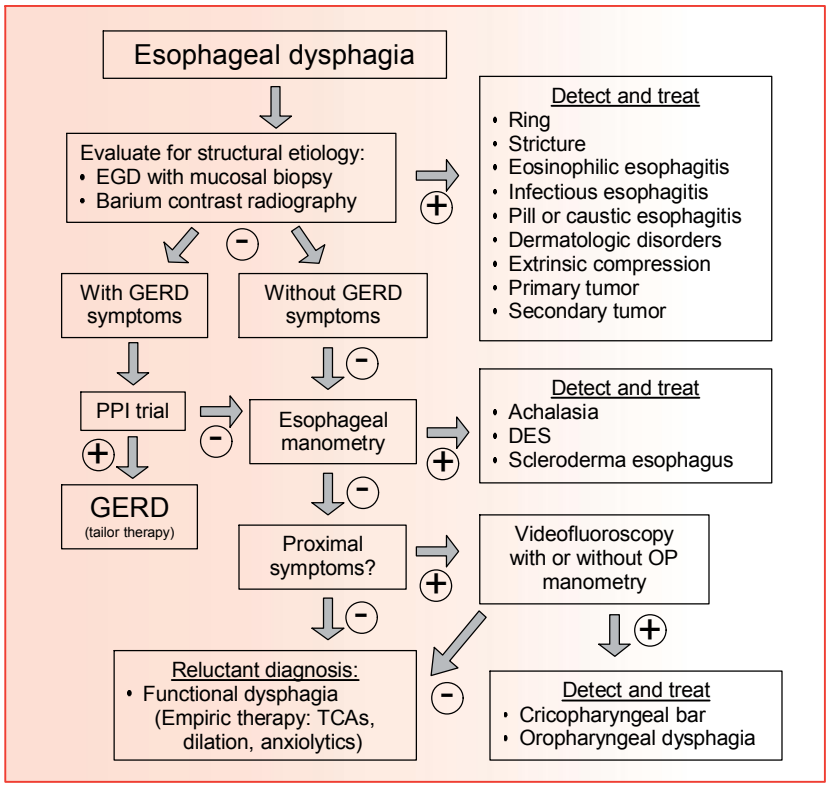

Fig. 1. *Differential diagnosis of esophageal dysphagia. DES, diffuse esophageal spasm; EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; OP, outpatient; TCA, tricyclic antidepressant.*

distal esophagus to the proximal stomach through a thoracotomy. Some surgeons routinely carry out an antireflux procedure (partial fundoplication) at the same time as the myotomy, while others reserve this for patients with an associated hiatal hernia.

The appeal of myotomy is that it is more predictable than pneumatic dilation. Surgical series report good to excellent results in 62–100% of achalasia patients. In a recent report, relief of dysphagia was obtained in 93% of those who underwent laparoscopic myotomy and 85% of those treated with thoracoscopic myotomy. Laparoscopic Heller myotomy has therefore become the preferred surgical procedure for achalasia.

Diffuse (distal) esophageal spasm

Epidemiology. The prevalence of diffuse esophageal spasm (DES) is similar to that of achalasia, while the prevalence of the manometric variants listed is up to ten times greater.

Pathogenesis. Physiological evidence again implicates neuronal dysfunction in the myenteric plexus. The most striking reported pathological change is diffuse muscular hypertrophy or hyperplasia, with thickening of up to 2 cm in the distal two-thirds of the esophagus.

Clinical presentation. The major symptoms of DES are dysphagia and chest pain. Weight loss is rare. Dysphagia is usually intermittent.

Diagnostic methods. Spastic disorders of the esophagus are defined by manometry or barium radiography, but the abnormal motility events are usually intermittent, and there are no uniform definitions. The LES typically functions normally. Radiographically, a "corkscrew esophagus," "rosary-bead esophagus," pseudodiverticula, or curling are indicative of DES. Although DES has no pathognomonic endoscopic features, endoscopy is nonetheless useful for identifying structural lesions and inflammation.

Treatment. Although the prevailing view is that treatment should be administered with smooth-muscle relaxants, there are few controlled data regarding pharmacological treatment for DES. The only controlled trial showing efficacy was anxiolytic treatment, suggesting that reassurance and control of anxiety are important therapeutic goals. Consistent with this conclusion, success has also been reported using behavioral modification and biofeedback.

This is an excerpt of a paper presented at the 70th American College of Gastroenterology Annual Scientific Meeting and Postgraduate Course, October 28–November 2, 2005 in Honolulu, Hawaii, USA.

This is a summary of the original text, which is available in full at: www.worldgastroenterology.org

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Update on Biological Therapy for Crohn's Disease

Gary R. Lichtenstein, MD

Introduction

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract. The disease can be quite severe, resulting in hospitalization and requiring long-term treatment with a variety of medications and frequent surgery. Infliximab is a chimeric monoclonal antibody directed against tumor necrosis factor (TNF). Controlled studies have shown significant improvement in both clinical and endoscopic luminal and fistulizing Crohn's disease with infliximab treatment. The clinical efficacy of and indications for infliximab treatment are reviewed here, in addition to other potential future treatments for patients with luminal Crohn's disease.

Tumor necrosis factor-α in inflammatory bowel disease

TNF is a proinflammatory cytokine produced by T cells, monocytes, and macrophages. It has a central role in initiating and promoting the inflammatory cascade, and is known to be a key mediator in several disease states.

Infliximab

Infliximab is a chimeric monoclonal antibody that is 75% human and 25% murine. Marketed as Remicade (Centocor Inc., Malvern, Pennsylvania, USA), infliximab targets TNF. The name denotes its structure and use: "-mab" stands for monoclonal antibody; "-xi-" indicates that it is chimeric in nature; and "infli-" refers to its target in the inflammatory cascade.

Pharmacokinetics and metabolism. When given as a single infusion of 5 mg/kg body weight, infliximab has a half-life of approximately 8–10 days, with detectable levels being present for up to 8–12 weeks.

Clinical efficacy. Two open-label studies and a placebo-controlled trial initially evaluated infliximab for inducing remission in active steroid-resistant Crohn's disease. Ten patients with steroid-refractory Crohn's disease were evaluated. Eight patients were given a single intravenous infusion of 10 mg/kg body weight infliximab, and two patients received a single intravenous infusion of 20 mg/kg body weight infliximab. Eight of nine patients had symptomatic improvement by the first week and were in remission by the second week.

The use of repeated infusions to maintain remission in CD has also been examined. Among the patients receiving repeated infliximab infusions, 53% maintained their remission in comparison with 20% of those in the placebo group.

The "*A* Crohn's Disease *C*linical Trial *E*valuating Infliximab in a *N*ew Long-Term *T*reatment Regimen" (ACCENT) study was a large, multicenter, international, randomized, long-term trial that assessed whether maintenance therapy with infliximab induced and maintained better remission and response rates in Crohn's patients who initially responded to a single infusion of infliximab. The group concluded that repeat treatment with infliximab every 8 weeks in initial responders was more effective than a single infusion for maintaining remission in patients with Crohn's disease.

Approximately 20–40% of patients with Crohn's disease develop fistulas during their lifetime, often requiring antibiotics, hospitalization, and surgery. Infliximab has been found to lead to significantly higher rates of fistula improvement (with a reduction in the number of draining fistulas) and fistula remission (no draining fistulas), with 36% of the infliximab-treated group maintaining remission at week 54 in comparison with 19% in the placebo group.

Other agents that inhibit TNF-α

It is clear that tumor necrosis factor-α is an important proinflammatory mediator in Crohn's disease. It has been shown that TNF-α is involved in apoptosis, metabolism, inflammation, thrombosis, and fibrinolysis. In addition to infliximab, several other agents directed against TNF-α are at various stages of development: adalimumab (D_2E_7), CDP-571, CDP-870 (certolizumab), RDP58, etanercept, onercept, and thalidomide.

Adalimumab (Humira). Adalimumab is a fully human IgG_1 monoclonal antibody to TNF-α that is administered subcutaneously. One controlled trial has demonstrated that adalimumab is effective for inducing a clinical response and remission in patients with active inflammatory Crohn's disease.

CDP-571. CDP-571 is a humanized (2–5% murine components) IgG_4 monoclonal antibody directed

against TNF-α. CDP-571 is administered intravenously. Controlled trials have demonstrated that CDP-571 is effective for inducing a clinical response in patients with active inflammatory Crohn's disease, but it is no more effective than a placebo for maintaining the clinical response after CDP-571 induction therapy.

CDP-870. CDP-870 is a humanized TNF-α antigen-binding monoclonal antibody fragment (Fab) linked to polyethylene glycol (PEG) that is administered subcutaneously. It is linked to PEG in order to reduce the frequency of administration and prolong the half-life of the medication. The agent is generally well tolerated, and in an exploratory study significantly increased the proportion of Crohn's patients with a remission at 2 weeks in comparison with a placebo. However, in a 28-week double-blind, randomized, placebo-controlled trial, CDP-870 (10 mg/kg every 8 weeks) showed benefits that were significant at 2 weeks but were no longer significant at the 28-week time point.

Etanercept (Enbrel). Etanercept is a fully human fusion protein composed of two soluble p75 components of the TNF receptor linked to an IgG_1 crystallizable monoclonal antibody fragment (Fc). This medication is administered subcutaneously. One randomized, double-blind, placebo-controlled trial demonstrated that etanercept was no more effective than a placebo for inducing a clinical response or remission in patients with active inflammatory Crohn's disease.

Onercept. Onercept is a fully human recombinant soluble TNF p55 receptor that is administered subcutaneously. A randomized, placebo-controlled trial demonstrated that onercept is not effective for inducing a clinical response or remission in patients with active inflammatory Crohn's disease at week 8.

Thalidomide. Thalidomide's immunomodulatory properties are complex and include inhibition of TNF-α synthesis and enhancement of the production of interleukin-4 and interleukin-5 (IL-4, IL-5). Recent small, open-label trials including 11 and 10 patients, respectively, have suggested that thalidomide is an effective short-term treatment for inflammatory bowel disease (IBD). The rate of response was 67–70%, and remission was achieved in 40% of the patients. Preliminary reports also suggest that thalidomide can be an effective treatment for maintenance after remission has been induced with infliximab. Teratogenicity is a well-known risk of thalidomide treatment.

MAP kinase. Tumor necrosis factor effects can also be prevented by inhibition of mitogen-activated protein kinases (MAPKs), enzymes that regulate gene expression and cell proliferation. CNI-1493, a small-molecule cytokine inhibitor and MAPK blocker, inhibits the production of several proinflammatory cytokines. In a small study, a clinical response was observed in 67% of patients with severe Crohn's disease after 4 weeks and in 58% of the patients after 8 weeks.

Modulation of the innate immune system

The initial phase of antigen processing and presentation can also be influenced by direct stimulation of the immune system or modulation of intestinal cells with growth factors. Several factors that modulate the innate immune system have therefore been investigated. In a study of patients with clinically inactive Crohn's disease, treatment with recombinant human granulocyte colony-stimulating factor (G-CSF) resulted in complete mucosal healing in two of five patients in a pilot study. In another open-label trial (n = 20), the Crohn's Disease Activity Index (CDAI) was reduced by at least 70 points in 11 patients (55%) and five patients (25%) achieved a sustained remission after treatment with G-CSF. A case study of a patient with Crohn's disease also demonstrated that G-CSF achieved a response after all standard treatments had failed. Finally, in an open-label trial including 15 patients, 12 (80%) had a decrease in CDAI of more than 100 points, and eight (53%) achieved clinical remission after treatment with sargramostim, a granulocyte-macrophage colony-stimulating factor (GM-CSF).

IBD biological therapies that inhibit T-cell activation and proliferation. The CD40 ligand, expressed on T lymphocytes after their interaction with antigen-presenting cells, is an important co-stimulatory molecule involved in T-cell activation. A humanized monoclonal antibody to this ligand, IDEC-131, was developed and tested in patients with CD. However, the phase II trial was halted because of reports of thromboembolism. T-helper cells ($CD4^+$ T cells) play a central role in regulating the immune response. Several anti-CD4 antibodies have been developed, including cM-T412, MAX.16H5, and B-F5. These antibodies produced variable response rates in IBD patients and were associated with significant decreases in $CD4^+$ cells.

Interleukin-2 is produced by T helper subset 1 cells, interacts with receptors on T lymphocytes, and induces the clonal expansion of T-effector cells. Antibodies to IL-2R, including daclizumab and basiliximab, have been developed to inhibit T-cell proliferation. In an open-label pilot study in patients with refractory ulcerative colitis, daclizumab was well tolerated and was associated with decreased clinical activity and endoscopic scores and a significant increase in the quality of life. Interleukin-2 may also play a role in inducing steroid resistance in T cells. Basiliximab was therefore

studied in an open-label, single-arm study in patients with steroid-resistant ulcerative colitis. Basiliximab induced clinical remission in nine of 10 patients (90%) within 8 weeks of treatment.

IBD therapies that reduce leukocyte recruitment, migration, and adhesion. Natalizumab, an anti-α_4 integrin monoclonal antibody, blocks $\alpha_4\beta_1$ integrin-mediated leukocyte migration. A phase II study of natalizumab demonstrated increased rates of clinical remission and response in patients with moderate to severe Crohn's disease at multiple time points. However, the remission rate was not significantly increased in comparison with placebo at 6 weeks (the primary end point).

This is an excerpt of a paper presented during the American College of Gastroenterology Course in Hawaii, October 2005.

This is a summary of the original text, which is available in full at: www.worldgastroenterology.org

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Preoperative versus Postoperative Radiotherapy in Rectal Cancer

Lars Påhlman MD

Introduction

Although surgery is the most important element in the treatment of patients with rectal cancer, the additional use of radiotherapy has changed treatment policy dramatically during the last 30 years. The indications for radiotherapy in the treatment of rectal cancer can be classified under four main headings:

- To lower the local failure rate and improve the survival in patients with resectable rectal cancer.
- To allow surgery in patients with unresectable rectal cancer.
- To facilitate sphincter-preserving procedures in patients with low-lying rectal cancer.
- To achieve a totally curative procedure without major surgery.

Resectable rectal cancer

In this setting, it is optional to use radiotherapy preoperatively (neoadjuvant) or postoperatively (adjuvant). However, radiotherapy is more dose-effective in relation to reducing local recurrence rates if it is given preoperatively.

Adding preoperative chemotherapy to radiotherapy was found to be beneficial in T4 tumors, and this treatment approach has slowly been introduced with T3 tumors as well. The advantages are a reduction in toxicity and a good tumor response due to well-oxygenated tissues. The main disadvantage is the staging process, in which patients who have tumors with a very low risk of local recurrence—i.e., patients with T1 and T2 tumors—still receive radiotherapy. There has been a major debate about this problem, and not only surgeons but also radiotherapists and medical oncologists have proposed that postoperative radiotherapy should be reserved only for those who really need it. With modern preoperative staging, it is possible to identify patients who have a high risk of local recurrence. In patients with a larger tumor that is more or less tethered or fixed, preoperative magnetic resonance imaging is being used more frequently to evaluate the local growth in relation to the rectal fascia. Patients who have a tumor close to the surgical circumferential margin—i.e., the rectal fascia—should be treated with radiotherapy, which is preferably administered preoperatively on the basis of the current state of knowledge.

Radiotherapy and sphincter preservation

It has been claimed from numerous phase II trials that preoperative radiotherapy, preferably chemoradiotherapy, is capable of downsizing the tumor to such an extent that the sphincter can be preserved more often. It is important to realize that the philosophy for rectal cancer treatment has changed during the past 40 years. It is now accepted that a much smaller distal

margin (5–10 mm) can represent a curative procedure.

In one trial, patients with T2 and T3 tumors received preoperative radiotherapy and were randomly assigned either to immediate surgery or to surgery 5 weeks after irradiation. Sphincter preservation was possible in a slightly larger number of the patients in whom surgery was delayed.

In another trial, patients randomly assigned to preoperative chemoradiotherapy had tumors at a more favorable stage. In a subgroup analysis of 183 patients with low rectal cancer, 18% had their sphincter preserved if postoperative chemoradiotherapy was administered, in comparison with 35% after preoperative radiotherapy. However, the overall number of preserved sphincters was the same in both treatment arms.

Patients in another trial were randomly assigned either to a short course of radiotherapy with immediate surgery or to a long course of chemoradiotherapy and delayed surgery. The inclusion criteria in this trial were a tumor palpable on digital examination, no sphincter infiltration, and clinical stage T3 or a resectable T4 tumor. The primary end point was the sphincter preservation rate. Among the 300 patients included, 61% had preserved sphincters after short-course radiotherapy with immediate surgery, in comparison with 59% after prolonged chemoradiotherapy and delayed surgery.

Conclusion

There are very strong data to support the view that preoperative radiotherapy, as an additional treatment to surgery in patients with resectable rectal cancer, is superior to postoperative treatment with regard to dose-effectiveness and toxicity.

This is an excerpt of a paper presented during the joint postgraduate course organized by the European Society of Gastrointestinal Endoscopy (ESGE), European Digestive Surgery (EDS), International Society for Digestive Surgery (ISDS), and European Association for Endoscopic Surgery (EAES) and held during the United European Gastroenterology Week in Copenhagen, Denmark, 15–19 October 2005.

This is a summary of the original text, which is available in full at: www.worldgastroenterology.org

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Is Esophageal Adenocarcinoma a Preventable Disease?

Rudolf Arnold, MD

Prevalence of adenocarcinoma of the distal esophagus. Several studies have shown that the age-standardized incidence rates of esophageal adenocarcinoma increased by up to eightfold during the last 20 years, mostly in Western countries. Esophageal adenocarcinoma represents approximately 40% of all esophageal cancers. The incidence of esophageal adenocarcinoma is increasing more rapidly than that of any other type of gastrointestinal cancer.

Are all patients being detected? The presence of Barrett's metaplasia in the esophagus is a premalignant condition. Barrett's esophagus is only found in a minority of patients with adenocarcinoma of the distal esophagus. It has therefore been suggested that many cases of Barrett's esophagus occur in asymptomatic adults with no symptoms of gastroesophageal reflux disease (GERD) requiring medical treatment. However, the incidence of diagnosed Barrett's esophagus is increasing, independently of the total number of upper gastrointestinal endoscopies conducted in the general population.

When does Barrett's esophagus arise? As several studies have shown, the prevalence of Barrett's increases with age, reaching a plateau in the seventh decade of life. The length of the columnar epithelial lining of the distal esophagus, however, does not increase with age. In addition, no significant changes in length were found in 22 GERD patients and 32 patients with cured GERD between the first endoscopic examination and a follow-up endoscopy after a median of 7.5 years. These data are consistent with a rapid development of BE to its full length, with little subsequent change. Accordingly, there are no data that show any new development of Barrett's in GERD patients in whom BE was not detected in earlier endoscopies. Patients without

Barrett's esophagus at the first endoscopy are free of Barrett's during subsequent endoscopies. This has important implications for surveillance strategies, and only GERD patients with Barrett's esophagus need to be included.

Barrett's esophagus in patients with adenocarcinoma of the distal esophagus. The published data on patients with BE known before operation for adenocarcinoma of the distal esophagus have not changed over 30 years. The overall percentage of patients undergoing resection who had prior diagnosis of BE was 4,7% and dependent on the number of operated patients per study.

Incidence of esophageal adenocarcinoma in patients with Barrett's esophagus. The incidence of Barrett's esophagus per patient-year is in the range of one in 52 to one in 208, and the incidence rates per year are between 0.5% and 1.9%. However, the incidence rates increase considerably if dysplasia is present—highlighting the importance of surveillance in patients with known Barrett's.

Mortality in patients with Barrett's esophagus and esophageal adenocarcinoma. Several studies have investigated survival in patients with Barrett's esophagus. In a retrospective study of 155 patients in whom Barrett's was diagnosed over a 12-year period, only four patients developed cancer. The survival did not differ from that in an age-matched and sex-matched control population. Similar results were also obtained by others, who reported that even patients with esophageal adenocarcinoma rarely died from cancer and mostly from other concomitant diseases.

Is esophageal adenocarcinoma a preventable disease? Unfortunately, the answer is no. Most cancers arise in patients with unknown preexisting Barrett's esophagus. The risk of esophageal adenocarcinoma can only be reduced in a minority of patients—those with GERD symptoms who request medication and those who undergo screening for the presence of Barrett's and are included in surveillance programs.

This is an excerpt of a paper presented during the joint postgraduate course organized by the European Society of Gastrointestinal Endoscopy (ESGE), European Digestive Surgery (EDS), International Society for Digestive Surgery (ISDS), and European Association for Endoscopic Surgery (EAES) and held during the United European Gastroenterology Week in Copenhagen, Denmark, 15–19 October 2005.

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Fecal Immunochemical Tests (FITs) for Hemoglobin: a paradigm shift in noninvasive fecal screening tests for colorectal cancer

Graeme P. Young, MD and Paul Rozen, MD

Introduction

Screening is by its very nature a process that aims to improve the likelihood that affected people receive effective treatment for colorectal cancer (CRC) while their disease is at a curable stage. The screening test is a critical part of this process. Screening can be provided in two main ways:

- **One-step testing:** colonoscopy is offered as the diagnostic test. Selection is based solely on age, and many individuals undergoing colonoscopy will be found to have no clinically significant neoplasia (CRC or "advanced" adenomatous polyps).
- **Two-step testing:** a simpler and cheaper noninvasive test (such as some form of fecal test) is offered, and then those with a positive result proceed to colonoscopy. Applying the simpler test to asymptomatic people classifies them as being likely or unlikely to have the disease at that point in time. Inherent in this approach is the intention that the test should be repeated at intervals in order to detect newly emergent or missed neoplasia.

Recent commentaries have critically explored a number of reasons why two-step screening, starting with a noninvasive method, is still a useful strategy:

- The evidence base showing a reduction in deaths from CRC comes from randomized trials of two-step

screening using guaiac-based fecal occult blood tests (G-FOBTs).
- Sufficient colonoscopic and economic resources are not usually available for widespread one-step colonoscopic screening.
- Even in high-risk countries, only 4–7% of people will develop CRC during their lifetime, so if colonoscopy is the primary screening test, millions will undergo colonoscopy without benefit, but with the attendant morbidity.
- The balance of risk against benefit is unclear with colonoscopic screening.
- People are reluctant to undergo colonoscopy because it is an invasive and inconvenient procedure, so participation rates are poor.

Additional reasons for including two-step screening in national guidelines include test simplicity, acceptability, and initial cost.

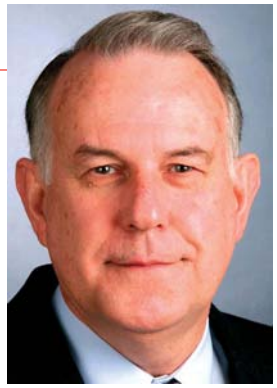
Guaiac FOBTs

Although they are effective, guaiac-based fecal occult blood tests (G-FOBT) have some shortcomings, which can be summarized as follows:
- Restriction of heme-rich or peroxidase-rich foods and drugs that induce bleeding are needed to optimize the specificity of the tests, especially with the more sensitive types of G-FOBT.
- The sensitivity for cancer is 35–50% for one-time testing with less sensitive G-FOBTs. The sensitivity for advanced adenomas is significantly lower than this. Randomized and controlled population trials show that G-FOBTs are only modestly effective with regard to reducing the mortality due to colorectal cancer.
- G-FOBTs with higher sensitivity levels are subject to unpredictably high false-positive rates.
- G-FOBTs that are dependent on the peroxidase activity of the intact heme molecule, which is relatively stable during digestion, are not selective for colorectal bleeding.
- The end point for G-FOBTs can be difficult to read and is transient.
- G-FOBTs are not suitable for automated instrument development or for automatic reading of the results.

Immunochemical FOBTs (FITs)

Fecal immunochemical tests (FITs) for hemoglobin provide a number of important advances that affect screening in terms of technical issues involving testing, test performance, and the behavior of the screening population. FITs for hemoglobin (Hb) are increasingly being considered in place of G-FOBT.

Graeme P. Young



Paul Rozen

Specificity of FITs. The chemistry is specific. Detection is based on antibodies that are specific for human Hb. FITs are not subject to interference by diet or drugs, and adequate specificity does not depend on proscribing certain foods or drugs before fecal sampling. The lack of interference of dietary factors on FITs is a major advantage in regions in which the diet contains a high level of peroxides, as in China or Japan, where the specificity of FITs is superior to that of sensitive guaiac tests.

FITs are selective for colorectal bleeding. FITs are much more selective for occult bleeding of colorectal origin than are G-FOBTs.

The sensitivity for neoplasia is improved with FITs. The Immudia®HemSp test, manufactured by Fujirebio (Tokyo, Japan) has been extensively studied and in screening studies has been found to detect significantly more neoplasms than the original Hemoccult test.

More importantly, it has been shown that some FITs are comparable to a high-sensitivity G-FOBT but without the disadvantage of unacceptable specificity. In a study controlled with colonoscopy examinations, the OC-Sensor test (Eiken, Japan) achieved the same sensitivity as the Hemoccult Sensa test (USA), but led to far fewer false-negative colonoscopies. Interim results from an ongoing comparison of a brush-sampling FIT with the G-FOBT Hemoccult Sensa have been published (Table 1, see next page). The results show that this FIT has better sensitivity than the most sensitive G-FOBT, but with comparable specificity.

In some studies, better sensitivity has allowed successful population screening on the basis of sampling just one or two rather than three stools, the recommended number for G-FOBT. This must be due to the test's analytical sensitivity for Hb.

Table 1. *Results of a paired comparison of the brush-sampling InSure fecal immunochemical test (FIT) with the guaiac-based Hemoccult Sensa fecal occult blood test (FOBT) in 18 patients with colorectal cancer who underwent both tests. The 95% confidence interval for the difference of 39% is 16–61%, indicating that InSure is significantly more sensitive for cancer than the Hemoccult test.*

	Hemoccult Sensa		
	Positive	Negative	
InSure			
Positive	9	7	16 (89%)
Negative	0	2	2
Total	9 (50%)	9	18

Novel sampling methods have been introduced with FITs. Fecal sampling processes have undergone further development with the introduction of FITs. The wooden spatula supplied with early G-FOBTs required multiple sampling. FITs have incorporated newer approaches. Some require a probe to be inserted into the stool, while others sample toilet bowl water from around the immersed stool.

The brush-sampling method has been shown to be preferable to the stick-sampling method used with Hemoccult, with an increased participation rate of between 66% and 90%.

Mass processing is possible. G-FOBTs are designed for small-scale in-office use, while population screening requires rapid processing and development of many samples. Some of the new FITs provide a facility for mass processing with automated reading, which provides economies of scale and allows rapid throughput of large numbers of samples.

Quantifiable FITs

Several types of FIT, including the Magstream 1000 (Fujirebio, Tokyo), InSure, and OC-Sensor, are quantifiable. The specificity/sensitivity ratio no longer has to be controlled by the test manufacturer but can be selected by the end-user in accordance with local conditions (Figure 1).

Fecal Hb levels are predictive for neoplasia, with higher levels being more likely in patients with advanced adenomas and cancer. Other studies have shown that for higher fecal Hb concentrations, sensitivities for cancer in the range of 68–85% (and perhaps higher) are achievable. This facilitates the assessment of optimal test positivity rates (and hence colonoscopy rates) in a given population in order to maximize the detection of CRC and advanced adenomas.

Conclusions

FITs represent a paradigm shift in FOBT technology. While not all manufactured tests have all the features of the class, as a class they provide the following benefits:

- The whole sampling process is simplified for the individual, in that the need for dietary restrictions is removed and fecal sampling is made more acceptable.
- Performance is better than with G-FOBTs, as FITs have a better sensitivity/specificity balance.
- Mass processing and automated reading are possible.
- FITs do not detect occult gastric bleeding.
- Some FITs are quantifiable, thus removing the constraints of qualitative tests that have an inflexible sensitivity/specificity relationship.

FITs should replace G-FOBTs as the noninvasive fecal test for two-step population-based screening.

This is a summary of the original text, which is available in full at: www.worldgastroenterology.org

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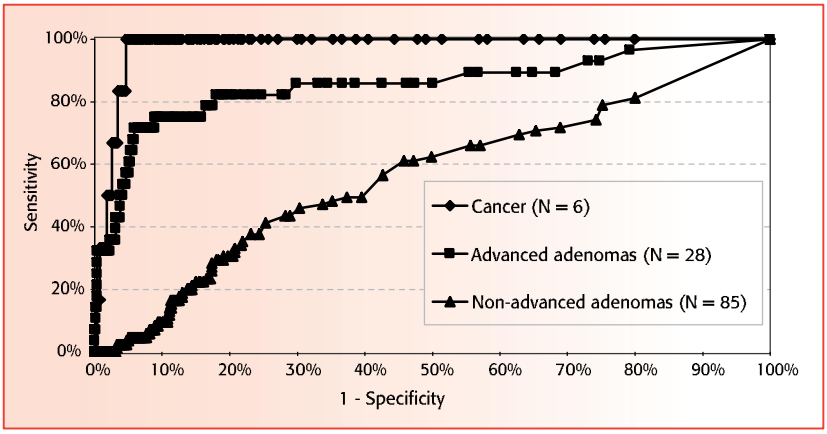

Fig. 1. *Receiver operator characteristic (ROC) curves using the OC-Sensor test, showing a high sensitivity level for colorectal cancer with high specificity. Most advanced adenomas (72%) were identified with a specificity of 95%, with good separation from nonadvanced adenomas.*

Gastroenterology in Spain

Miguel Muñoz-Navas, MD

Gastroenterology in Spain is booming! The country's leading gastroenterologists work in a national network of tertiary hospitals, carrying out highly specialized activities in patient care, education, and research. But we also have an extensive and well-trained body of gastroenterologists in clinical practice who ensure that the specialty is practiced to high standards.

Spain has a training system that we can be proud of. After a period of 6 years in medical school, graduates progress to 4-year training programs, entrance to which is regulated by a national competition. The candidates who obtain the highest scores are given first choice among the training positions (around 90 per year) offered by approved centers around the country (normally gastroenterology departments in major hospitals). Many training centers provide opportunities for research, either during training or afterwards to achieve a PhD degree.

With academic expertise available in all the subdivisions of the field, gastroenterology in Spain is a highly specialized discipline.

The gastroenterology societies that have been established in Spain reflect the mixture of interests within the gastroenterological community. The *Sociedad Española de Patología Digestiva* (the national gastroenterology society) has a 75-year history, with 2400 members, and organizes the annual national congress. The endoscopy-oriented gastroenterological community is represented by the *Sociedad Española de Endoscopía Digestiva,* with more than 500 members, and is very active in providing continuing education, information about methodological innovations, and research opportunities for its members. The two societies organize annual courses in collaboration with the American Gastroenterological Association and American Society for Gastrointestinal Endoscopy, respectively. The *Asociación de Ecografía Digestiva* represents a smaller but very active group of gastroenterologists with a special interest in ultrasonography. In Granada in June 2006, the *Sociedad Española de Patología Digestiva,* together with the other two societies mentioned above, will be holding the first Spanish Digestive Diseases Week meeting.

Many training centers provide opportunities for research, either during training or afterwards to achieve a PhD degree.

Another professional society of substantial importance in Spain is the *Asociación Española para Enfermedades de Hígado,* which represents the hepatology sector. As in many other countries, the hepatology society constitutes a powerful force in research and education, and it sets the standards for good practice in the management of liver disease. A newer organization, the *Asociación Española de Gastroenterología,* includes many academically oriented gastroenterologists and has organized a network of research groups conducting collaborative studies, as well as a high-quality annual meeting.

Spanish gastroenterology is in good health, busy, and enthusiastic.

Pamplona, Pont de Magdalena.

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Gastroenterology in Malaysia

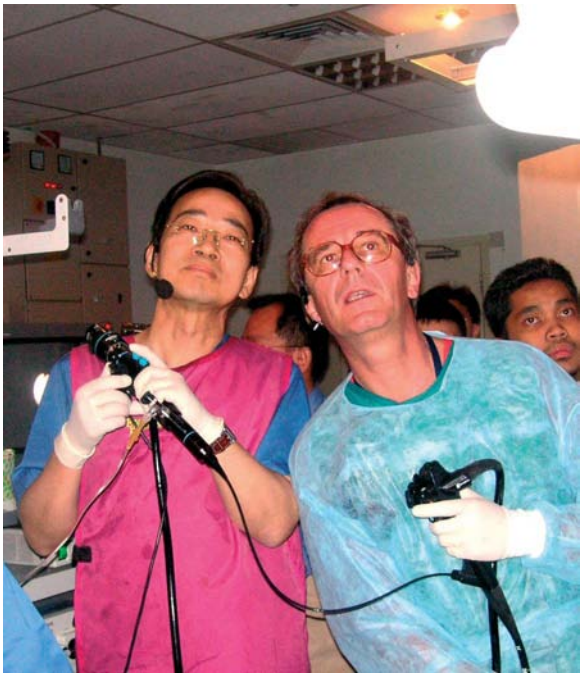
Khean-Lee Goh, MD

As a specialized discipline, gastroenterology has developed slowly in Malaysia. In keeping with the British system of training, physicians who have obtained the Member of the Royal Colleges of Physicians (MRCP) diploma who have an interest in gastroenterology and hepatology acquire clinical experience and, in some instances, spend training periods abroad in centers specializing in gastroenterology, hepatology, and endoscopy. Training in gastroenterology as a post-specialization course is provided by the Malaysian Ministry of Health, which offers a 3-year fellowship program in gastroenterology leading to the certification of physicians as gastroenterologists in government service. Plans for credentialing of gastroenterologists under the auspices of the College of Physicians and Academy of Medicine in Malaysia are under consideration.

The Malaysian Society of Gastroenterology and Hepatology started off humbly in 1982 when a small group of general surgeons and physicians with an interest in gastroenterology and liver diseases was set up. The founding President was Dr. M. Balasegaram, who was the eminent hepatic surgeon in the country at that time. Dr. Panir Chelvam, the pioneer gastroenterologist in Malaysia, was the society's secretary and subsequently president, and was the driving force behind the society in its early years. The Malaysian society has since then grown in strength year by year. The first international conference organized by the society was "Stomach 1996," held in Kuala Lumpur under the chairmanship of Dr. P. Kandasami and focusing on all aspects of gastric diseases. In 1997, the society organized another international meeting in Penang, in collaboration with the British Society of Gastroenterology and Hepatology, under the chairmanship of Dr. Robert Ding. In 1998, the Malaysian Society of Gastroenterology and Hepatology (MSGH) hosted the second Western Pacific *Helicobacter* Congress, under the chairmanship of Professor K.L.

Gastroenterology is continuing to grow in strength in Malaysia.

Course Faculty.



International experts at a live course in Malaysia.

Goh, in Kota Kinabalu in the state of Sabah. Since then, the society has held annual scientific meetings in various parts of the country, with broad participation by members of the society as well the medical fraternity in the country. Every year, 7–10 international faculty members are invited. In 2001, the MSGH annual scientific meeting was held in Kota Kinabalu, in collaboration with the American Gastroenterological Association, under the presidency of Dr. Jayaram Menon. The MSGH Lecture was initiated in the same year to honor members of the gastroenterology fraternity who have contributed significantly to the field both locally and internationally. To date, lecturers have included Dr. P. Kandasami, Dr. Barry Marshall, Prof. G.N.J. Tytgat, Prof. S. K. Lam, Prof. Meinhard Classen, Dr. Ismail Mercian, and Prof. Peter Malfertheiner.

Live endoscopy workshops have always been popular with the gastroenterology fraternity in Malaysia. The society has been involved with these workshops since 1993, and since 2000—at the insistence and on the initiative of the then president of the Society, Dr. Mazlam Zawawi—the society has organized regular annual workshops. The workshops are held at the Faculty of Medicine in the University of Malaya, with live transmission from the endoscopy unit at the University of Malaya Medical Center. Annual courses for gastroenterology assistants are also held, and these workshops provide a useful meeting point for all involved. In recent years, several faculty members from abroad have also been invited.

Gastroenterology is continuing to grow in strength in Malaysia. Under the stewardship of the MSGH, the Malaysian gastroenterology community has started to make forays into the international scene. The MSGH committee has taken the decision to bid for the 2010 Asian–Pacific Digestive Week, and if the application is successful, the MSGH will spare no effort to make the conference a truly memorable international meeting.

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References: 1. Richter JE et al. Am J Gastroenterol 2001;96:656–65. **2.** Kahrilas PJ et al. Aliment Pharmacol Ther 2000;14:1249–58. **3.** Castell DO et al. Am J Gastroenterol 2002;97:575-83 **4.** Labenz J et al. Aliment Pharmacol Therap 2005;21:739–746 **5.** Miner P et al. Am J Gastroenterol 2003;98:2616-20.

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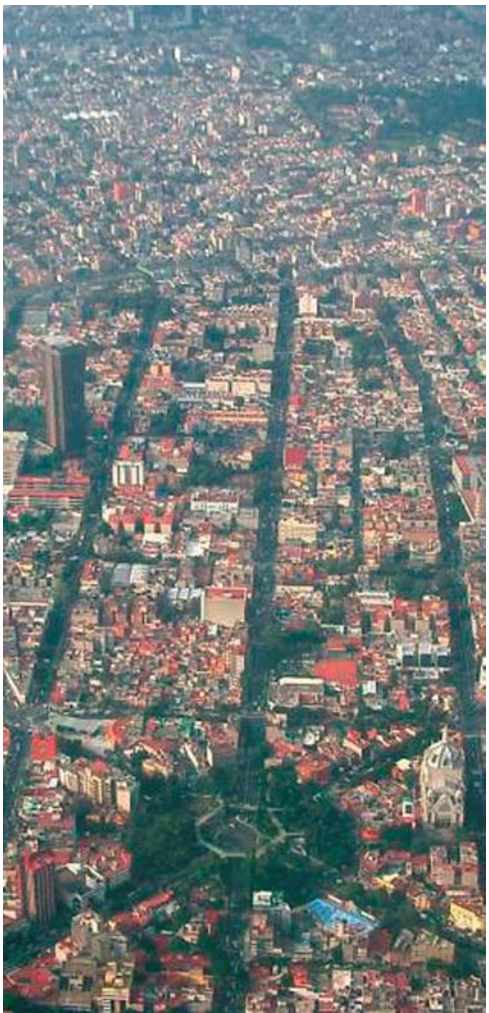
Gastroenterology in Mexico

Max Schmulson, MD

Gastroenterology in Mexico dates back to 1920—only a few years after the foundation of the General Hospital of Mexico. In 1925, the first department dedicated to gastroenterology was opened by Dr. Abraham Ayala Gonzales, the physician regarded as the father of Mexican gastroenterology. The *Asociación Mexicana de Gastroenterología* (AMG, Mexican Association of Gastroenterology) was founded in 1935; it celebrated its 70th anniversary in 2005, and currently has more than 1350 members. The *Revista de Gastroenterologia de Mexico* (Mexican Journal of Gastroenterology) started publication shortly after the AMG was established.

Mexico City.



Between 1935 and 1958, gastroenterology was a clinical–surgical discipline in Mexico. The oldest subspeciality is digestive endoscopy, which was initially introduced in the mid-1930s. The first postgraduate courses began in 1936, and the first pan-American gastroenterology conference and the first national gastroenterology meeting were held in Mexico City. Following the foundation of the World Gastroenterology Organization (WGO-OMGE) in 1954, the AMG requested membership, and the World Congress of Gastroenterology was held in Mexico in 1974. Since then, the National Gastroenterology Week has been held each year and is regarded as the most important event for the specialty. The ECOS Internacionales course—at which all of the advances and investigations presented at international meetings such as Digestive Disease Week and the Liver Meeting are discussed—has also been held every year since 1995. I should mention here that the Pan-American Congress of Gastroenterology will be held next year in Cancun, with a first-rate scientific program.

Gastroenterology in Mexico is a high-quality specialty in every area—both in academic research and in private practice.

There are currently several national training programs in gastroenterology that have university recognition. In 1979, the Mexican Board of Gastroenterology was founded to take charge of certification and re-certification of all gastroenterologists and training programs, including specialists in gastroenterology, surgery of the alimentary tract, digestive endoscopy, and pediatric gastroenterology. In accordance with the guidelines, every specialist has to be re-certified every 5 years by taking courses or a test.

Research in the field of gastroenterology is regarded as being sufficiently important that the Faculty of Medicine at the *Universidad Nacional Autónoma de Mexico* (National Independent University of Mexico) last year opened its first department exclusively dedicated to research—the Liver, Pancreas, and Motility Laboratory (HIPAM) in the Department of Experimental Medicine, which combines aspects of clinical and basic research.

Gastroenterology in Mexico is a high-quality specialty in every area—both in academic research and in private practice. Mexican researchers have made important advances in the field and are continuing to conduct research activities with international collaboration.

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Endoscopy in Serbia and Montenegro

Milutin M. Bulajic, MD

The Yugoslav Association of Gastroenterologists (YUGA) was founded in 1964 and is an active member of WGO-OMGE, OMED, the European Society of Gastrointestinal Endoscopy (ESGE), the *Association des Sociétés Nationales Européennes et Mediterranéennes de Gastroentérologie* (ASNEMGE), and the European Association for the Study of the Liver (EASL). After the disintegration of Yugoslavia in 1991, the Yugoslav Association of Gastroenterologists continued its expert work and activities within the newly formed Federal Republic of Yugoslavia (which in 2003 changed its name to Serbia and Montenegro). The first Yugoslav gastroenterology week was held in Centinje (Montenegro) in 1993, and the event has been repeated every year since.

It is difficult to describe the present conditions in our health-care system in a few sentences. Many events have occurred in our country in the past 20 years—wars, economic sanctions, and isolation, all of which led to the complete destruction of the health-care system. Before all these unhappy events, the expertise of the Medical Faculty in Belgrade was well known all round the world. Our medical diploma was recognized everywhere abroad, and we had strong relationships with other European medical schools. Nowadays we are trying to restore the standards of the past, to recover our international reputation and rebuild the old image. However, faced with the very difficult economic situation and low working and living standards, most people here, including doctors, have to think first of all about how to survive and earn enough for their families. Trying to introduce standards in endoscopy here is therefore a difficult goal—but at the same time, it's the only right one.

Since my own area of training and interest is purely gastrointestinal endoscopy, both diagnostic and therapeutic, I will try to describe the situation in this field in my country. Endoscopy is well developed only in the largest cities in Serbia and Montenegro. The four largest cities in Serbia are Belgrade, Niš, Novi Sad, and Kragujevac, each of which has a medical school, as well as Podgorica, the capital of Montenegro. These cities have endoscopy units in their regional hospital centers. Basic endoscopy of the upper and lower gastrointestinal tract is carried out in these centers, but more complicated and expensive procedures such as endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasonography (EUS) are only available in Belgrade. This centralized system dates back to the earliest stages of the Yugoslav health-care system after the Second World War and has continued down to the present day.

The lack of widespread endoscopy units has very severe consequences. In the provinces, endoscopy is mainly carried out in private offices, which are not of the same standard as those abroad. As it is difficult to support the large endoscopy centers in Belgrade financially from the country's national health funds, the majority of endoscopes are more than 10 years old. During the last few years, we have been dependent on humanitarian donations, through which we have received various supplies and equipment, mostly from Japan and the European Union. Only a few centers in Serbia and one in Montenegro have video endoscopes; the rest are still equipped with old fiberoptic instruments. Even when repairs are needed, the process sometimes takes more than 3 months. What about endoscopic accessories? Well, despite the fact that most of them are disposable, we always try to reuse them—especially sphincterotomes, Teflon guide wires, polypectomy snares, diagnostic ERCP catheters, Dormia baskets, and extraction balloons. At present, there is only one video duodenoscope with a large channel (4.2 mm) available

Only a few centers in Serbia and one in Montenegro have video endoscopes; the rest are still equipped with old fiberoptic instruments.

for therapeutic ERCP in the whole country. The standard treatment for patients with common bile duct strictures or hilar strictures is still based on 7-Fr plastic stent placement, while biliary self-expanding metal stents have never been introduced because of their high cost. Several centers do not have facilities for performing hemostasis, except for the use of epinephrine solution. Argon plasma coagulation is only available in the two largest centers.

What possible solutions are available? I think we need to train as many young endoscopists abroad as possible. I know how important this is from my own personal experience; I have been lucky to have the opportunity to meet experts such Prof. Thomas Rösch, Prof. Jerome D. Waye, and Prof. Guido Costamagna. But this type of development is not easy, as it may give rise to resentment among older colleagues who have not had the opportunity to go abroad for further education.

Scientific research as part of endoscopic practice is very difficult, since there is a lack of necessary equipment. Despite the poor condition of our medical equipment, however, we are still among the countries in which it is quite easy to recruit volunteers for clinical studies or to obtain biopsy samples and other material for laboratory analyses.

Because of the lack of equipment, the constant need to improvise, and self-training by endoscopists, the damaged health-care system produces endoscopists who have basic potential and skills, but no opportunity to reach a more advanced level. Without advanced skills, there will be no high-quality endoscopy available to provide solid education for the next generations. The world should be reminded that generations of Yugoslav doctors before 1990 were able to improve their skills thanks to the country's good political position. Today, the situation is just the opposite. As a country in transition that is still on the margins of the EU, and which does not have a national education strategy for young doctors, the only way of obtaining meaningful training is to reach out beyond our country's borders and learn from foreign experts. The Council on Medical Education (CME) program in our country has just begun, and we need time to develop it.

There is a strong desire, especially on the part of younger colleagues, to find a way of improving the current situation. The tradition and good reputation that our medical university still has means a lot to us, and we are determined to do our best to improve it further by obtaining hands-on training in European and American centers and by creating a strong relationship with universities abroad. The world is constantly getting smaller, and thoughtful gastroenterologists in the developed countries should open their arms to welcome young doctors and provide them with the opportunity to learn first-class endoscopy and gastroenterology skills. The spirit of international cooperation is growing, but we also need the tools to bring the benefits of modern medicine to our patients.

Serbia and Montenegro is a country that is still in a phase of economic transition, and it is not realistic to expect the health-care system to recover quickly. Our young endoscopists need to meet the experts around the world in order to increase the quality of our service and reach the desired level of skill. It will take a lot of time and effort to fulfill this aim, but this is the only right way if we want to join and develop as a member of the worldwide endoscopic family.

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The Battle for the Baghdad Gastroenterology Hospital

Makki H. Fayadh, MD

The Iraqi Society of Gastroenterology and Hepatology was established in 1992 after 13 years of struggle with Iraqi government officials, which ended in the high court with a decision in favor of establishing the society. After 1992, the society's members succeeded in convincing officials to set up a gastroenterology and hepatology teaching hospital in 1995. With 100 beds, the hospital was established within a large medical complex (3000 beds) in Baghdad, on the remains of the old Jamhoree Hospital. The complex extends between two bridges on the River Tigris and consists of seven buildings, in addition to Baghdad Medical College and the Ministry of Health building and, across the bridge, the Ministry of Defense.

Many developments occurred between 1995 and 2003: the establishment of the gastroenterology board in 1996; the establishment of the surgical gastroenterology board in 1999; and the launching of the Iraqi gastroenterology journal in 2001.

During the days of the war and afterwards, I was the Director of the Hospital and was responsible for postgraduate studies, as well as serving as President of the Gastroenterology and Hepatology Society and chief editor of the Iraqi gastroenterology journal.

The hospital was supplied with many new video endoscopes, endoscopic ultrasound equipment, accessories, and a library collected through donations by the society's members. The hospital had four large operating theaters, four interventional endoscopy theaters, and four endoscopy procedure rooms. Many computers and electronic materials were collected through donations from colleagues all over the world.

As the hospital building was located near the Ministries of Defense and of Health, we evacuated the patients after the start of war to the neighboring Baghdad teaching hospital, limited our work to interventional endoscopic hemostasis for gastrointestinal bleeding, and used our medical resources for the wounded patients in the complex. The brave staff and postgraduate students in surgical and medical gastroenterology were available round the clock, despite the heavy shelling of the Ministry of Defense and the penetration of the roof by a missile. The bombing was so heavy that all of the windows shattered, doors were broken off, and the ceiling was penetrated by missiles. Sandbag fortification did little to prevent damage. Electricity was interrupted, and we had to work with generators, which eventually stopped due to lack of fuel.

…looters started entering the hospital and taking away air conditioners, refrigerators, and hospital kitchen and ward equipment.

During the entry of the allied forces into the city medical complex and the disappearance of the Iraqi police, the big surprise was that looting of government buildings started—close to the Ministry of Health to begin with, and then later in the medical college, and I saw some looters enter the gastroenterology hospital. I decided to ask for help from the American troops to protect the hospital buildings and the neighboring ministry. There were three tanks very close by, but the officer in charge refused to help and said plainly that they were fighters and not policemen—protecting the hospital was the duty of the police!

Following that, looters started entering the hospital and taking away air conditioners, refrigerators, and hospital kitchen and ward equipment. I again went to the main commander (stationed in the large conference hall in the city medical complex) and asked for

The sign for the Baghdad Hospital, swinging from the ceiling.

Missile remains collected inside the hospital.

help. This time, a detachment of four fully armed soldiers came with me. I was walking in front of them, and their fingers were on the triggers … We managed to catch all of the looters, about a dozen of them, and they were taken into custody but then released by the soldiers a few hours later.

We managed to put locks on all the doors, but the next day, the American soldiers broke into the hospital because of a suspicion of hidden weapons, and destroyed all the locks. At this point, as it was forbidden for any of the hospital staff to hold weapons, I decided to defend the hospital by any means available. I held a meeting with the available staff and decided to use formaldehyde (formalin), of which I had a good stock—so we started splashing four containers of formalin in every theater and equipment store. This succeeded dramatically in stopping the looting, as nobody entered the hospital during the subsequent weeks.

After 2 weeks, things settled down and security improved, and we immediately started repairing the window glass and doors and replaced torn curtains stolen air-conditioning. The medical equipment, books, and medical accessories were saved by formalin. Thanks to the inventor of formaldehyde—a chemical with dual uses? In the end, what happened was that we discovered the use of formalin as a chemical weapon and defended ourselves with it—but the allied forces did not discover the weapons of mass destruction they were looking for.

We are looking forward to better gastroenterology in the new democratic Iraq and hoping that all of the international and national gastroenterology/hepatology societies will stand with us to help us upgrade our gastroenterology and hepatology facilities. We hope that 2006 will bring peace to our country.

Donate Teaching Materials to Iraq

Do you have any educational cds, textbooks or journals that you no longer need? If so, please send them to the Iraq Society of Gastroenterology where they will of great assistance.

Donations can be sent to:

Miss Baydaa M Salih
Gastroenterology & Hepatology Teaching Hospital
Medical city complex, Bab al Muaddam
PO Box 61103
Baghdad, Iraq

Please only send up-to-date material.

Hospital staff and Dr. Makki Fayadh (center wearing a tie).

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Ask A Librarian: a free service to all except the Librarian – A true tale

Jerome D. Waye, MD

Justus Krabshuis

There some truly free gifts in this world, and your Editor takes pleasure in relating how one man, our Librarian, Justus Krabshuis, spent his time and efforts without recompense to help a doctor in Sudan. We track the work from first request to its successful conclusion through a series of emails. [Editor's note: almost all are here, but not every email].

The doctor sent this email requesting assistance on November 11, 2005:

Doctor (11/10/05, 2:06 pm)
Dear Justus
I am the secretary general for the Sudanese Society of Gastroenterology,
I am currently preparing a talk on the current status of inflammatory bowel disease in the Middle East and Africa.
I have been advised by Prof Suliman Fedail to get in touch with you as he thought you are the best person to contact in order to get any papers that have been published on the subject.
I am most grateful for your help,
yours,
Dr. Hatim Mudawi, MBBS, FRCP (London)

Justus (11/10/05, 7:52 pm)
I have started work on your query.
Attached are the results of two simple searches – one in Medline (results are called IBD-II) and one in Embase (called IBD-I).
In both cases the search went back only three years.
The Embase search used a very broad interpretation of IBD – basically I searched for the broad term 'enteritis' but this picks up all records indexed with the narrower terms 'under' enteritis – see the thesaurus structure below. [Editor's note: Justus sent a list of 30 items].
This search when combined with Middle East and Africa picks up 168 articles published in the last three years.
In the Medline search I used a far narrower interpretation of "Inflammatory Bowel disease". This search produced only 24 articles. This is a start.
I have some questions and notes below:

- *If you see any particular relevant articles let me know and I can try to obtain full text for you*
- *Do you want me to search the Cochrane Collaboration databases?*
- *There is an African Index Medicus database – do you have access to this or shall I search this for you?*
- *Do you want me to go back further than 3 years?*
- *What is your timeline for this? When do you need results?*
- *Have you thought of contacting the WHO regional office?*
- *What exactly do you mean with 'current status of IBD in the Middle East and Africa? Are you looking for epidemiological data? This is probably very hard to find and/or may not exist at all?*
- *Does all this mean you are not interested in the "current state of the art" in IBD diagnosis and treatment?*
- *Do you want me to try and find the latest high-quality evidence-based practice Guidelines dealing with IBD?*

I will send you further information in the next few days as I wait for your response.
Please let me know how we can start to refine this further

Doctor
[after several exchanges, the doctor requested 7 articles not found in usual Western sources]

Justus (11/22/05)
It took me a while to get back to you - apologies.
Results of my searches in the African Index Medicus (AIM) were disappointing. I did send you a few things directly from AIM. Since you want 10 years data I did go back to Medline and this time I searched 1996-2005; 64 results (instead of 24 earlier). I think this is probably useful. Results are attached in a file called IBD-III.
You may also want to have a look yourself at WWW. NGC.ORG [Editor's note: this is a site for guidelines: type in 'inflammatory bowel disease' and you will get >100 hits = guidelines. Perhaps some of that is relevant.

Justus (1/6/06)
Yes – I know – I am working on the rest - maybe we are lucky. I will report back with an update next week.

Justus (1/09/06)
I have managed to get the two articles from 'Digestion' at Glasgow University Library Yesterday - I am faxing these to you today and I will also send copies by ordinary mail. The remaining 3 articles are very difficult to get but I keep trying.
P.S. I am attaching the short version of "IBD in Saudi Arabia" because this particular version carries the references and this may still be useful for you.

Justus (1/12/06)
As regards the remaining three articles, I have ordered these from INIST - the French document delivery service from the National Institute of Science in Paris. This may take some time but I hope everything can be sent to you before the end of January.

Justus (1/13/06)
By the way - when is your presentation in February? How much time do I have?

Doctor (1/15/06)
The presentation is for the African/ Middle East Gastroenterology Society on the 24th of February in the UAE.

Justus (1/21/06)
Good news! Today I received from INIST:
1. *Inflammatory Bowel disease Saudi Arabia presentation initial management J of Gastr and Hepatol 1998; 13:119-1124*
2. *Inflammatory Bowel disease in Kuwait. The Am. J.of Gastroenterology 1984;79:191-194*

I will post these to you on Monday and I will also fax them to you on Monday. I am waiting for the final article – it is looking hopeful.

Doctor (1/21/06)
I am so grateful for all the help and assistance. The presentation is for the AMAGE meeting in Sharjah UAE end of February. Once it is ready, I will email you a copy.

Justus (2/1/06)
Good news – I have just received from INIST the remaining article we were waiting for. The rarity of ulcerative colitis in South African blacks by Segal I et al. American Journal of Gastroenterology 1980; 74: 332-336
I will fax the document this evening plus post a copy in the mail to Khartoum tomorrow.
You should now have all documents requested. Please let me know if I can be of further help and provide more library support.

Justus (2/2/06)
All articles have now been delivered both by fax and posted to you. I trust everything has arrived in time for the preparation of your lecture at the next AMAGE meeting later this month in the UAR.
Every first day of the month I run 'Electronic Alerts' for non-western gastroenterologists; I have included you for an Alert on IBD and Africa. Hopefully that may be of use to you.

Justus (2/2/06)
During this AMAGE meeting - could you please spare a moment to meet with Professor Eamonn Quigley - Professor Quigley is our new president of WGO-OMGE (I assume he will attend) and he is very interested to meet with you and find out if the WGO-OMGE 'Ask a Librarian" service is helpful and learn from you how it can be improved or expanded for you and your colleagues in the Sudan?
I know he has a special interest in Africa and like me I am sure he will be most grateful for any feedback and suggestions about my 'voluntary' WGO-OMGE "Ask a Librarian" service.

Doctor (2/28/06)
Dear Justus: I returned yesterday from Sharjah, UAE where I attended the 5th AMAGE conference. I was the 1st speaker on the postgraduate course.
The talk lasted for 15 minutes, it went very well, and a lot of the information provided was not known to many of the audience. I met Dr. Quigley & spoke to him about the great help you provided, he was impressed. Thanks again.

Justus
Congratulations with the success of your talk. Wonderful. It has been a pleasure to help. I hope you will remember the 'Ask a Librarian" service in the future. We are always pleased to help with information requests.

Justus
This query was unusual because a lot of old material not available in HINARI [Editor's note: this is Health InterNetwork Access to Research Initiative where top medical publishers make the full text of their journals

available for free in a joint initiative with WHO. This is for underdeveloped countries]. And even if it would be it is not always easy to search. Karin Fenton (SAGES), Groote Schuur Hospital, kindly supplied the SA citations. I got some citations in the Glasgow University Library as I was passing through, and the remainder I had to resort to a commercial document supplier (INIST). But this was exceptional – normally I have no costs – just time.

Editor

Justus gets about 2 requests each week, and as above, each one leads to a series of email responses and then he does the literature research. Justus supplies this information for free for doctors in underdeveloped countries. He has had 192 requests, and the topics cover such diverse issues as:

- Role of EUS in pancreatic cancer
- Actualitè sur les gastrites atrophiques et leurs traitements
- Seroprevalence of Hepatitis B in the world
- Clonazepam in functional vomiting
- Postoperative jaundice for acute abdomen with nonconclusive findings
- Use of ultrasound instead of fluoroscopy in performing ERCP.

Justus also has supported the Argentine Society of Gastroenterology in a series of literature searches to establish the topic: Minimum requirements for emergency endoscopy.

A doctor in Brazil without access to library services has requested literature support in preparing a review of Eosinophlic Esophagitis.

We honor the involvement, the efforts, and the willingness to freely donate his time and expertise to gastroenterologists in underdeveloped countries. He writes a column for World Gastroenterology News in every issue, and can be reached through the website: http://omge.org/?askalibrarian

WGO-OMGE/OMED Postgraduate Training Center in Hepatogastroenterology in Rabat

Naïma Amrani, MD

"At last we've got the high-level training center that we've always dreamed of for Francophone Africa" – C.Z.

These words were inscribed in the guest book at our Postgraduate Hepatogastroenterology Training Center by a participant in the very first course.

The establishment of the WGO-OMGE Center in Rabat was the result of an agreement reached between the Moroccan Minister of Higher Education and the World Gastroenterology Organization. The center welcomes all Francophone gastroenterologists, particularly those from Africa, who wish to improve their theoretical and practical knowledge in the field of hepatogastroenterology.

The aims established for the center are:

- To promote the highest quality standards in training.
- To promote the best guidelines for practice in gastroenterology, and particularly in endoscopy.
- To develop a training program that integrates recent advances in hepatogastroenterology and the appropriate ethical principles with local and regional needs.
- To provide the latest learning tools for young gastroenterologists who are receiving training.
- To promote contact with experts and to become a training center for trainers, with the ambitious goal of playing a leadership role for the specialty in the region and becoming a recognized center of excellence at the international level.

The center was inaugurated in January 2003 by Morocco's Minister of Higher Education, Scientific Research and Civil Service Training, at a ceremony attended by Prof. M. Classen, retiring President of WGO-OMGE and signatory of the agreement; Prof. G. Tytgat, President of WGO-OMGE; Prof. P. Ferenci, President of the *Association des Sociétés Nationales Européennes et Mediterranéennes de Gastroentérologie* (ASNEMGE); the President of the University of Mohammed V Souissi; the Dean of the Faculty of Medicine and Pharmaceutics in Rabat; and the Director of Rabat's University Hospital, as well as numerous other prominent figures in the world of hepatogastroenterology.

Location and description of the facilities

The Center, affiliated with the Mohammed V Souissi University, is based in the Faculty of Medicine and Pharmaceutics in Rabat, near the Ibn Sina University Hospital, the kingdom's largest.

The Center has its own premises, consisting of:

- A conference room
- Four rooms for workshop meetings and for assisted training on simulation models and on the computer simulator
- A media center with computer materials and a video library
- A library
- A café/restaurant for relaxation and for meet-the-expert luncheons

The Center is provided with staff to maintain the premises and ensure security. Thanks to its location, it benefits substantially from logistic and material support from the hospital and faculty.

General training program

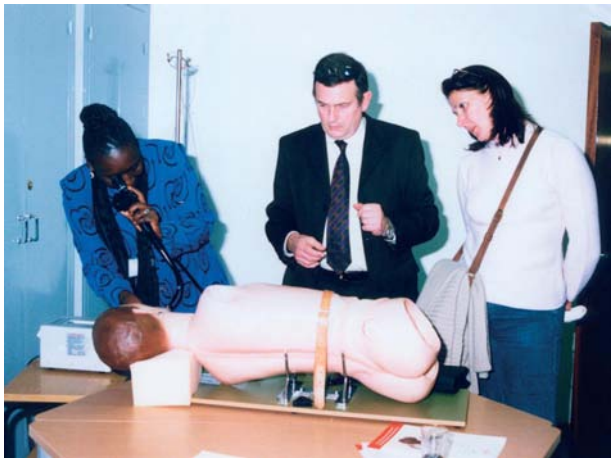
Now nearly 3 years old, the Center is running smoothly and holds 10-day training sessions, as well as providing an opportunity for African trainees to attend longer courses lasting from 6 months to 4 years.

Short-term courses. The training program consists of both theoretical courses and direct demonstrations of specific diagnostic and therapeutic procedures, particularly endoscopy and ultrasonography.

The patients in the course are recruited independently of their socio-economic status, drawn from various courses held at the University Hospital and consultations provided by our own service. They are selected on the basis of two major criteria—the provision of consent and the educational interest of the procedure for teaching purposes.

The teaching of imaging techniques and of both diagnostic and therapeutic endoscopy on the computer simulator, as well as the use of ex-vivo animal models, allow us to give greater emphasis to practical training and to avoid the potential pitfalls of direct training.

An important place is given to interactive teaching in the form of practical workshops, electronic teaching, and the presentation of clinical cases. Our media library,



An international expert demonstrating endoscopic technique on a model.

which has been constantly developing since the Center's opening, makes electronic documents available to trainees.

All of the sessions are led by national and international experts with worldwide reputations both for their medical skills and teaching ability. The experts come from various countries: Austria, Belgium, Cameroon, Canada, France, Germany, Ireland, Italy, Morocco, the Netherlands, Portugal, Senegal, Sweden, Turkey, and the United Kingdom.

Since its opening, the WGO-OMGE/OMED Training Center has organized four 10-day training sessions for groups of 40–50 young gastroenterologists, representing a current total of 180 trainees from 12 Francophone countries in Africa and the Middle East: Algeria, Burkina Faso, Cameroon, Congo–Brazzaville, Democratic Republic of Congo, Gabon, Ivory Coast, Lebanon, Mali, Morocco, Mauritania, Senegal, Togo, and Tunisia (see photographs).

The courses will soon be publicized on our web site to coincide with the fifth course, which is to be held from 26 January to 8 February 2006.

Longer-term courses. The Rabat Center also provides an opportunity to attend long-term courses for two candidates each year, lasting from 6 months to 4 years, covering the statutory period for obtaining the national diploma in the specialty. The long term trainee is employed by our service and becomes a member of the team and takes part in all the activities involved in patient care, training, and research.

For example, we welcomed a female trainee from Togo for a 1-year course lasting from January 2004 to February 2005 and a young gastroenterologist from the Ivory Coast, a native of Lebanon, for a period of 6 months from June 2004 to February 2005. We currently have a doctor from Benin who registered to stay for four years.

After the trainees have returned to their own countries, our continuing contacts with them enable us to follow up the later development of their careers. The feedback received has been very positive, particularly since the same trainees often express a wish to return for subsequent training sessions.

Our center is thriving, because this type of training meets a real need. In addition, Morocco as the sole WGO-OMGE/OMED Training Center in Francophone Africa represents a recognition of the country's privileged relationship with the entire Francophone world, both north and south. The WGO-OMGE/OMED Center in Rabat, which operates thanks to support from the Moroccan government, would be unable to flourish without support from its partners, particularly ASNEGME, the United European Gastroenterology Federation (UEGF), the *Société Nationale Française de Gastro-Entérologie* (SNFGE), the *Association Française pour l'Etude du Foie* (AFEF) and the Munich Gastroenterology Foundation.

This support allows us to enlist experts, provide modern teaching materials, and grant scholarships to African physicians—large numbers of whom have applied to take part in the course, but who are often unable to do so due to the high travel costs involved.

Conclusion

The WGO-OMGE Training Center in Rabat, dedicated to the Francophone world, has now become a reality. We are honored in many ways by the choice of Morocco for the establishment of the Center, which puts us in touch with the national, African, and international network. The firm commitment and powerful support on the part of all of the Center's partners in general, and from WGO-OMGE/OMED in particular, will ensure that the Center continues to operate well. We

Faculty of the teaching center, N. Amrani 5th from right, back row.

need to augment our equipment and facilities in order to enhance the Center's reputation and allow it to achieve its aims rapidly—including the goal of becoming a center of excellence in hepatogastroenterology accessible to our African colleagues.

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Linking the African Scientific Community – A Landmark Event

On January 30, gastroenterology communities across Africa were linked simultaneously for the first time in a unique pilot project. From Egypt, Morocco, Senegal and down to the coast line of South Africa, medical facilities were brought together in this exceptional e-learning event. Through video feed, a panel headed by Prof. Manns, Bougouma, Marcellin and Cales, presented lectures and reviewed challenging regional cases on Hepatocarcinoma and Viral Hepatitis A & B. WGO-OMGE and OMED hope that this pilot project will mark the beginning of a regular series of transmissions and educational collaboration and extend a special thank you to Prof. N. Amrani and colleagues from the participating centers for their initiative and support!

Latin-American Gastrointestinal Endoscopy Training Center: update

Claudio Navarrete, MD, Cecilia Castillo, MD, Carlos Reyes, MD, Roque Sáenz, MD, Jerome D. Waye, MD

The Latin-American Gastrointestinal Endoscopy Training Center in Santiago, Chile, was established in 1997 and was designated as an WGO-OMGE/OMED Advanced Gastrointestinal Advanced Endoscopy Training Center in 2004. More than 200 trainees from all over the world have been trained since the opening of the center, including endoscopists from Saudi Arabia, Belgium, Thailand, Australia, USA, France, Japan—and, of course, mostly from the Latin-American area and Chile (Figure 1).

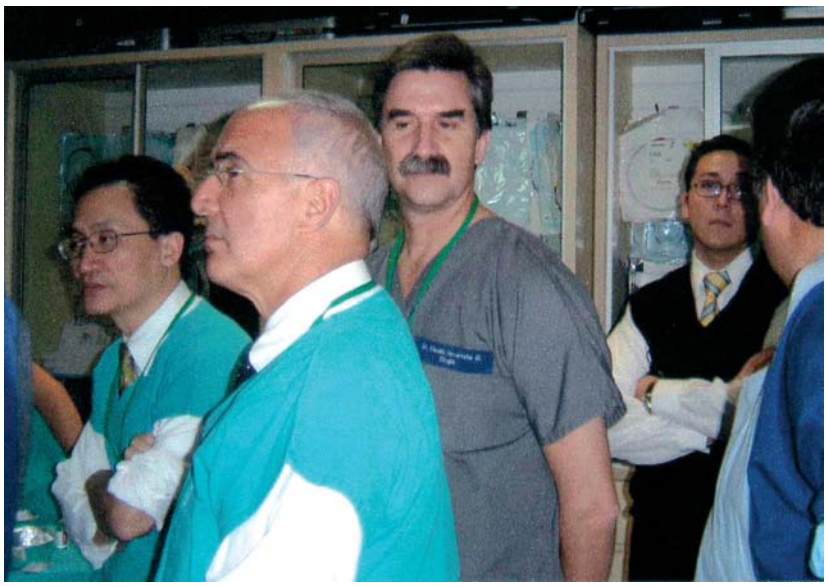

Fig. 1. *(l–r) Dr. Simon Lo, Dr. Jeffrey Ponsky and Dr. Claudio Navarrete.*

Seventy percent of the patients are referred by public hospitals and are paid for by the Ministry of Health at the lowest insurance rate, to cover minimal costs. The Ministry of Health has determined that sending patients to this center for advanced endoscopic procedures solves clinical problems, saves money, and reduces the length of hospital stays. Transferred patients travel by ambulance, usually with a resident or nurse, and have procedures performed in the Center that could not be done in their local hospital. They are sent back the same day after the procedure. Private patients pay a fee for the service or are covered by private insurance plans. The waiting list is relatively short; patients are usually seen within 1 week, and emergencies—mostly for pancreaticobiliary procedures—are often treated on the same day as the referral (e.g., for cholangitis, bleeding, or acute biliary pancreatitis).

The clinic has six endoscopy rooms, one with radiography equipment and five for other purposes. Diagnostic and therapeutic endoscopic ultrasound, capsule endoscopy, colonoscopy, and magnification and upper gastrointestinal endoscopy procedures are carried out. Up to 40 procedures can easily be performed in a day—the record is 51 procedures.

Our English is not that good, but not that bad either. We are also able to communicate with trainees from France in a kind of half-French. There are exchange programs with Dr. Sahel's group in Marseilles and with Antioquia University in Colombia.

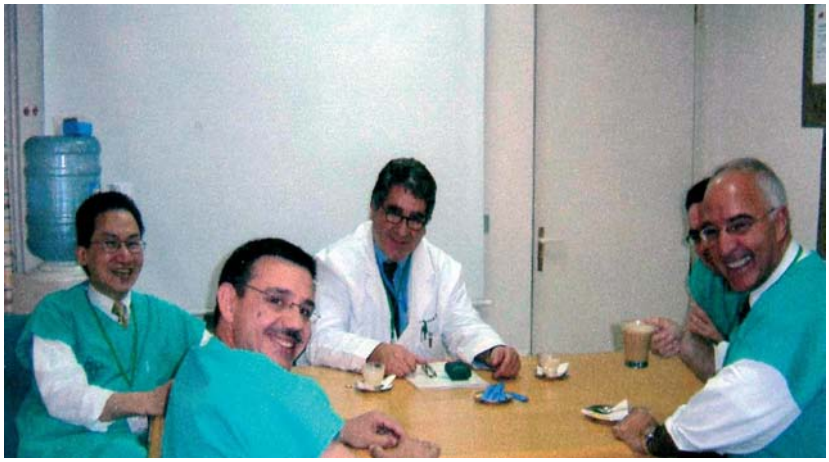

Fig. 2. *(l–r) Dr. Simon Lo, Dr. Marc Giovannini, Dr. Roque Saenz and Dr. Jeffrey Ponsky.*

The training program emphasizes therapeutic endoscopy procedures, with a "hands-on" basis. All applicants have to have at least basic training in diagnostic endoscopy. Trainees have access to the video library at the endoscopy training center, where there are over 10,000 cases on file. The program also includes training in cardiovascular emergencies and airway management, supervised by a university anesthesiologist. The anesthesiology unit devoted to endoscopy is probably unique, with staff anesthesiologists. The working group consists of 17 gastroenterologists, six surgeons, three anesthesiologists, three nurses, eight technicians, and six secretaries. The weekly academic activities include:

- A gastroenterology department conference and specific conferences on surgery, esophagus, and dysphagia, with satellite transmission to the Clinica Alemana in Temuco (700 km south).
- Slides, posters, abstracts, and talks, with critical appraisal, research, editing, and publishing activities.

The trainees are fully involved in research, editing, and publishing activities and are provided with accommodation in a modern, cost-free apartment near the Center.

The University del Desarrollo and the University of Chile provide academic support, and the staff all hold academic appointments at the university. The Olympus endoscopic equipment is purchased by the Clinic at a favorable rate, and Wilson-Cook have also provided acceptable reimbursement charges for the Clinic, supplying disposable devices, stents, guide wires, etc.

Surgical laparoscopy and bronchoscopic procedures are also carried out. Capsule endoscopy has been included in the armamentarium of advanced endoscopic techniques since 2003.

> ***The Ministry of Health has determined that sending patients to this center for advanced endoscopic procedures solves clinical problems, saves money, and reduces the length of hospital stays.***

Every other year, the center holds an advanced endoscopy course, with experts from all over the world performing live procedures (Figure 2). The waiting list for trainees is now 20 months. One of our trainees, Dr. Diego Murature, has been a beneficiary of the WGO-OMGE/OMED Outreach Program at the Eva Perón Hospital, Santa Fé, Argentina, where he has developed a new endoscopy center with enormous success.

A practical course on endoscopy tools, using animal models in order to standardize techniques such as glue injection, banding, clipping, looping, endoscopic mucosal resection, argon plasma coagulation, heater-probe treatment, BICAP treatment, chromoendoscopy, etc., is held more than once a year and is open to the local endoscopy community.

Dr. David Bjorkman and Dr. Robert Hawes from the USA, Dr. Guido Costamagna from Italy, and Dr. Guido Villa-Gómez from Bolivia are to be faculty members on the 2007 course. The recipient of the American Society for Gastrointestinal Endoscopy's Don Wilson Award in 2004, Dr. Timothy Kinney from Chicago, has decided to train with Dr. Navarrete's group in Santiago.

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IDCA
The International Digestive Cancer Alliance

Digestive Cancer Series (Series-Editors: Meinhard Classen, MD, Sidney Winawer, MD)

Screening for Digestive Cancers: from theory to practice

René Lambert, MD and Cedric Mahé, MD

Burden of gastrointestinal cancer

The International Agency for Research on Cancer (IARC) Globocan Database shows that the five most frequent gastrointestinal-tract tumors throughout the world accounted for 3.2 million new cases and 2.6 million deaths in 2002 (Table 1). In a recent analysis conducted in the 25 member states of the European Union, colorectal cancer was found to be almost as common as lung cancer.

Most cases of esophageal squamous-cell cancer, gastric cancer, and primary liver cancer occur in Asia. Cases of colorectal cancer are distributed equally between Europe, Asia, and North America. With the exception of the pancreas, the sex distribution is uneven, with the rates of esophageal and gastric cancer being lower in women. The rates are also lower for the liver, except in the Americas. The rate of colorectal cancer is similar in both sexes, with the exception of Japan, where it is twice as high in men.

The IARC Globocan Database can provide an indication of the global prognosis associated with a tumor, by comparing figures such as firstly, the number of individuals registered with cancer during the period 1997–2001, and still alive in 2002—i.e., the prevalence over 5 years; and secondly, the number of new cases occurring in 2002—i.e., the incident cases. The ratio of prevalence over 5 years to the incidence in 2002 is an index of the average survival time after detection (Table 2). In most regions, the ratio is less than 1 for esophageal, liver and pancreatic cancer; the average survival of patients is therefore less than 1 year. The average survival is just

Table 1. *Estimated numbers of new cases of gastrointestinal-tract cancer throughout the world in 2002 (both sexes). Data and regions of the world in the database of the International Agency for Research on Cancer (Globocan 2002)*

New cases in 2002	Esophagus	Stomach	Colon, rectum	Liver, primary	Pancreas
North America	15700	24900	183500	16200	34900
South America	12800	52500	46300	9600	13400
Central America	1400	12600	7500	4700	4200
Africa (5 regions)	24300	26200	23700	52700	7100
Europe (4 regions), with Russia	43000	174000	371700	53600	78000
Asia (4 regions) (Japan included)	361800	637000	369600	485500	91000
Japan alone	13700	109800	95600	39700	20000
Australia and New Zealand	1400	2500	14900	860	2200

Table 2. *Gastrointestinal cancer throughout the world in 2002 (both sexes): ratio of the numbers of surviving patients (5-year prevalence) to the number of new cases. Ratio < 1: average survival after declaration is less than 1 year. Ratio > 1: survival increases in proportion to the ratio. In Japan, at all sites, the ratio is higher than in the other countries or regions.*

Ratio of new cases to 5-year prevalence	Esophageal cancer	Gastric cancer	Colorectal cancer	Liver cancer	Pancreatic cancer
North America	1.13	1.25	3.36	0.89	0.65
South America	0.64	1.19	2.12	0.54	0.60
Central America	0.77	1.23	2.2	0.44	0.60
Africa (5 regions)	0.91	1.13	1.65	0.70	0.68
Europe (4 regions)	0.91	1.36	2.68	0.69	0.50
Asia (4 regions) (Japan included)	0.90	1.69	2.71	0.59	0.69
Japan alone	2.3	3.22	3.74	2.1	1.15
Australia and New Zealand	1.31	1.45	2.8	0.74	0.50

over 1 year (ratio between 1 and 1.5) for gastric cancer. The ratio is higher (between 2 and 2.5) for colorectal cancer, indicating better survival. There is a special situation in Japan, where there is a better prognosis for gastrointestinal-tract cancer: the ratio is higher than 1—higher than in other regions of the world and higher for all sites of gastrointestinal cancer. The most probable cause of this discrepancy is the general policy of early diagnosis in Japan, based on the widespread use of endoscopic screening for early gastrointestinal cancer (esophagus, stomach, colon) and of abdominal ultrasonography to explore the liver.

Screening for gastrointestinal cancer is justified

A large proportion of late-stage gastrointestinal tumors are still detected in symptomatic patients, resulting in the overall poor prognosis in these patients: gastrointestinal cancer accounted for 31% of the new cases of cancer at all sites in 2002, but for only 13% of the persons alive 5 years after detection. The gastrointestinal tumors (5%) occurring in family cancer syndromes can be identified using specific genetic questionnaires and linkage analyses. For cases occurring in average-risk persons (95%), screening policies aim at detecting cancer (or precancerous conditions) in asymptomatic persons when it is localized in the organ of origin and when the treatment is more effective. The Japanese example confirms the benefits of the effort to achieve early detection.

Screening needs to be associated with public information programs on ways of achieving a healthy lifestyle and needs to providing warnings about poor awareness and poor incorporation of screening programs into primary-care practice. Primary-care providers, specialists, key professional societies, the media, and industry should be all be involved.

Screening targets asymptomatic individuals and is justified when the incidence of the disease is high and resources are sufficient. Screening is based on simple tests that can classify individuals into those who probably do, and those who probably do not, have the disease. Those with positive screening tests are referred for diagnosis and treatment. For gastrointestinal cancer, screening should be offered to men and women aged 50–75. When early cancer is the sole target, the aim of screening is to reduce the specific mortality, without affecting the incidence. When premalignant lesions are included, a larger number of screened individuals are tested and there is also an impact on the incidence.

Parameters for screening tests

Firstly, a screening test needs to be simple, safe (noninvasive if possible) and acceptable. The response to the test is positive or negative, and in those with positive screening tests, a diagnostic procedure is provided. However, there is no perfect test. *False-positive tests* result in unnecessary examinations in individuals who have no cancer or precursor lesions, with a concomitant increase in cost and morbidity. *False-negative tests* result in missed cancers or precursor lesions, which in the best case are detected at the next screening or may become symptomatic (at a late stage) during the interval.

In theory, screening is performed against appropriate thresholds of *sensitivity* (the proportion of positive tests in persons with the disease) and *specificity* (the proportion of negative tests in persons with no disease). However, for the screened individual, the relevant parameter is the *positive predictive value* (PPV) of the test—i.e., the proportion of individuals with the disease among those who test positive. A high PPV reduces the number of non-useful procedures conducted in persons without the disease. However, false-positive tests may occur in a significant proportion if the prevalence of the disease is very low. The *negative predictive value* (NPV)—i.e., the proportion of persons without the disease among those who test negative—relates to the degree of confidence that the individuals screened actually do not have the disease. In screening for cancer, the NPV is always high, because most asymptomatic individuals have no cancer. However, false-negative tests may occur in a significant proportion of those with cancer.

The screening tests available for gastrointestinal cancer include imaging procedures (radiography or endoscopy) or biological reactions in blood or fecal samples. The use of DNA sequencing for genetic screening in sporadic cancer cases is still under development.

Screening tests using blood samples

Blood tests are usually well accepted. The pepsinogen (Pg) test selects individuals with complete atrophic gastritis who are at risk for *gastric cancer*. The test is based on a double threshold: less than 50 ng/mL for Pg I and less than 3 for the Pg I/II ratio. In mass screening for gastric cancer in Japan, the Pg test was able to replace—at lower cost and with better compliance—the current selection test (photofluorography). More than half of gastric cancers are attributable to *Helicobacter pylori* infection. This infection is highly prevalent in some populations, particularly in African countries. In the age range 45–64, the prevalence of *H. pylori* infection is estimated at 58% in the developed countries and 76% in developing countries. In addition, *H. pylori* does not survive in complete gastric atrophy, and false-negative tests are frequent in patients with gastric cancer. Serology for *H. pylori* infection is therefore not a good screening test. To

select persons at risk for *primary liver cancer,* and in the absence of better rests, the low-sensitivity alpha-fetoprotein (AFP) test (threshold 20 ng/mL) is available. The test is repeated at 6-month intervals and supplemented by ultrasound examinations.

Fecal screening tests

Fecal tests are simple, but compliance is lower than with blood tests. The fecal occult blood test (FOBT) is commonly used to screen for *colorectal cancer.* In randomized trials, it has been shown to reduce the mortality of the disease. Using the Hemoccult II guaiac test, about 2% of those screened are found to be positive and undergo diagnostic procedures. However, due the test's low sensitivity, interval cancers after a negative test are frequent. Using the Hemoccult II FOBT, 50% of early cancers give a false-negative response at the first round; this is why it is repeated at 1-year or 2-year intervals. After rehydration, the test has increased sensitivity, but the larger number of positive tests leads to increased numbers of diagnostic procedures and higher costs. Other fecal tests have been developed, based on immunological detection of human hemoglobin or polymerase chain reaction (PCR) analysis of DNA mutations, and these are discussed elsewhere in this issue of *WGN* (see the article by Graeme P. Young and Paul Rozen, pages 20–24).

Radiographic screening tests

Radiographic imaging tests include:

- Photofluorography, with 7–12 automatic miniature exposures, for *gastric cancer.* The efficacy of this procedure has been confirmed in Japan, where the prevalence of gastric cancer is very high.
- Ultrasonography, for *primary liver cancer.*
- Virtual colonoscopy, with a multiprobe computed-tomography scan and three-dimensional analysis. This procedure has been shown to be a viable screening tool for *colorectal cancer,* but the equipment is expense, the preparation required is the same as for colonoscopy, and a subsequent endoscopic examination is needed if there are abnormal findings.

Management after positive tests

A positive test requires detection and treatment decisions. Endoscopy is the gold standard diagnostic procedure for neoplastic lesions in the esophagus, stomach, and colon. The disadvantages of endoscopy are: poor compliance; a frequent need to administer deep sedation; a small, but nonnegligible risk of severe complications (such as perforation or hemorrhage); and a potential shortage of well-trained specialists. The cost of endoscopy is a major problem; professionals should be instructed to avoid unnecessary procedures and treatments and follow the guidelines regarding surveillance intervals.

The advantage of endoscopy is its high sensitivity for detecting early cancer and premalignant lesions, as well as allowing immediate tissue sampling. Endoscopic diagnosis is a two-step procedure:

- Detection of the lesion relies on slight irregularities in the surface, color, or superficial vascular network.
- Characterization of the lesion is based on subtypes of type 0 neoplastic lesions, as summarized in the Paris classification. Characterization evaluates the risk of invasion into the submucosa, and contributes to the decision on whether to offer no treatment, endoscopic resection, or surgery.

Endoscopy allows simple and effective treatment of localized neoplastic lesions in the esophagus, stomach, and colon. Resection is possible either during the dame procedure or as a second step. Mucosectomy is justified for premalignant lesions and for cancer limited to the mucosa, or when there is superficial invasion of the submucosa. A large proportion of premalignant lesions in the esophageal squamous-cell epithelium and in the stomach require treatment rather than surveillance. In the colon, the majority of the premalignant precursors (polyps) have a very low potential for malignancy, and removing them will result in many unnecessary treatments. Generalized use of colonoscopy for cancer prevention is justified if it is based on a reliable endoscopic characterization of lesions that have a low potential for progression (which should be left in place) and those lesions that have a high potential or represent confirmed carcinoma (which should be treated). The most recent video endoscopes with magnification and/or image-processing facilities should help in achieving this objective.

Sophisticated techniques of radiographic imaging and tissue sampling are needed in the diagnosis of neoplastic lesions in the liver, and there are no simple treatments capable of effectively curing a localized tumor. This is why primary prevention is more effective than organized screening. With regard to neoplastic lesions of the pancreas, both primary prevention and screening have poor efficacy.

Opportunistic and organized screening

Opportunistic screening is a case-finding strategy involving an individual contract between the patient and the physician. Because it is usually carried out with imprecise guidelines and is associated with low coverage of the target population, this approach may lead to an excessive repetition of procedures and a small benefit for the

overall population. Usually, opportunistic screening is carried out in the absence of monitoring, and the cumulative outcome of individual initiatives is not measured.

Mass screening includes large groups of the population and operates with precise guidelines. A screening campaign includes repeated rounds of screening at regular intervals. Monitoring and evaluation of the outcome is required. Mass screening is costly and requires adequate financial resources; any deviation from the established protocol impairs the expected benefit and increases the cost. A recent national survey of the FOBT test for the prevention of colorectal cancer in the USA showed that there were wide deviations from the protocol in the individual practice of primary-care physicians.

Screening can also be offered to selected groups, in a procedure lying between mass and opportunistic screening. This approach would include "voluntary" users among cancer organizations, private insurance systems, or "entitled" users, including employee groups who are offered screening.

The coverage of the population by a mass screening approach is always incomplete, and opportunistic screening can therefore be a helpful additional method. The two approaches are complementary, as they usually do not reach the same targets. The attitude of the health-care authorities to screening programs varies from country to country. In the USA, Medicare, a Federal Health Insurance program, recommends a screening strategy and establishes contracts with the health maintenance organization programs. The decision on whether to enrol in the screening program is freely taken by the individual patient. In European countries, screening is organized under the direct control of national health authorities, and individuals are directly and firmly encouraged to accept its free provision. In Japan, screening for gastric cancer freely provided by health-care institutions is supplemented by several nongovernmental screening programs offered by employers in large companies.

Coverage, compliance, and acceptability of screening

The efficacy of any mass screening intervention depends on the coverage of the population in the age classes selected as the target. If the coverage is less than 50%, the benefit is expected to be small. More important than the initial enrollment of individuals for an initial screening test is their compliance with the recommended diagnostic procedure and treatment if the test is positive. In addition, individuals who comply with the first round of screening will not necessarily comply with check-up tests.

Usually, individuals who seek screening are highly compliant with diagnostic and treatment procedures, but this opportunistic screening usually does not reach the population at higher risk (those in lower social classes and those who are less able to have a healthy lifestyle). The advantage of mass screening is that it has a better chance of identifying high-risk persons, as it covers a large proportion of the target population. However, old age, female sex, lower social class, and fear of what the test may show are still factors that lead to lower compliance rates.

Benefits and disadvantages of screening

A screening program cannot be successful without quality-assurance procedures and available infrastructure. Even if the best screening test is used, a screening program conducted haphazardly can lead to an incredible waste of resources. Screening programs should start with a stepwise approach, including pilot programs. Quality assurance requires safety, training of professionals, and recording of indicators. There are *early monitoring indicators* for compliance with screening, diagnosis, and treatment and for complication rates, and *long-term monitoring indicators* for assessing the impact on the incidence and mortality and the occurrence of interval cancers.

When the outcome of screening procedures is evaluated, negative consequences should also be assessed. Negative consequences include: anxiety in persons with no disease who have positive tests, overdetection and overtreatment, and complications of endoscopy (such as accidents involving sedation, hemorrhage, and perforation).

Conclusion

There are two pillars in the prevention of gastrointestinal cancer—primary and secondary prevention. Primary prevention is based on circulating guidelines and providing the population with information about a healthy lifestyle, including diet, physical activity, and reducing contact with exogenous carcinogenic agents (tobacco, alcohol, hepatitis virus B and C). Secondary prevention is based on early detection of neoplastic lesions. Here, mass screening and opportunistic screening are complementary, as they cover different targets. Primary and secondary prevention should interact in a synergistic way, and the importance of each is related to our knowledge of the causal factors at each site.

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OMED: A Japanese Scientific Meeting from a "Gaijin" Point of View

Jean-François Rey, MD

Japanese gastroenterology meetings are an eye-opening experience, especially in the absence of a local friend to explain cultural differences. Since 1992, I have been attending Japanese endoscopy society meetings twice a year. There are several things I had to get used to: occasional earthquakes (fortunately minor ones), typhoons (which result in the grounding of all planes at Kansai Airport), the sophisticated but crowded Shinkansen, and the everyday difficulties of the Japanese way of life (having no street signs in downtown Osaka can become a nuisance when looking for the restaurant where you have reserved a table).

The meeting itself is, of course, perfectly organized. It runs smoothly and calmly, despite having 15,000 attendees. Overall, the conferences are highly organized, according to Japanese custom. Several hostesses are waiting to greet the presenters in front of each room. Oral presentations are limited to 10 old-fashioned slides arranged ahead of time. Recently, PowerPoint technology has slightly altered this rule. There are multiple registration desks, making registration easy. Until this year, you had to bring cash (250 US dollars), as credit cards were not accepted. Cash machines are useless to foreigners, since everything is written in Japanese. The phone book is also, obviously, in Japanese, but sometimes names are also written phonetically using the Roman alphabet. However, first and last names are frequently reversed.

From the endoscopic point of view, the scientific presentations are worthwhile, even though they are almost always in Japanese, with the occasional English slide. Important topic sessions such as "pit pattern" or endoscopic mucosal dissection are chaired by well-respected scientists such as H. Niwa and S. Kudo, with 15 presentations on nearly identical topics (e.g., IIa+IIc lesions), followed by 30 minutes of general discussion in front of a large audience. Usually, 10 to 12 rooms seating between 50 and 2000 are occupied at the same time, with a strict order and timing.

> ***"…exhibits are mainly restricted to technical manufacturers, with no large booths from pharmaceutical companies."***

Foreigners particularly appreciate the video session (easy to understand) and lecturers by foreign specialists from Korea or China (which are given in English). Personally, I find that the most interesting sessions are the technical ones on new equipment and devices. I learned quite a lot from a young Japanese medical doctor and highly-specialized engineer who gave a presentation in a crowded room in 2001 on the Triangle Knife, or early narrow-band imaging technology—most of the new technology in the field is developed in Japan.

Poster sessions are important and unconventionally organized. The topics selected vary, from young doctors' clinical cases to more traditional posters on endoscopic trial series. But instead of a Western-style organization, all of the posters are presented orally, following a schedule, in front of a small audience in a session led by a senior gastroenterologist. This 5-minute talk is conducted with a portable microphone system and a pointer held by a hostess, emphasizing the importance of the poster sessions.

The luncheon seminar is another typical Japanese meeting. Pharmaceutical companies and endoscope manufacturers sometimes hold 45-minute meetings starting at 12.30. At the front door, you receive a program and a lunch box with rice, chopsticks, and orange juice. It's not easy sitting and listening to the presentation while trying to use chopsticks. In some cases, foreign lecturers are invited to speak at the seminar and provide scientific translations. During the past year, more questions have been put by young endoscopists. This is a significant change, as most Japanese doctors in their 30s and 40s do not speak English. Lecture seminars are a typical way of discussing endoscopic devices designed and manufactured outside of Japan.

Evening symposiums are held by the major endoscopic manufacturers. Usually, there is a 90–120-minute presentation on a particular topic, including a highly

detailed lecture, a video, and a final 10-minute honorary lecture. Some 2000 participants stay for these lectures, running from 6 to 8 p.m., after a long day of work. Afterwards, all the participants are invited to an evening party in a large ballroom, where a sit-down dinner is reserved only for senior guests—all the others have to remain standing. At 10 p.m. sharp, a short announcement invites all the guests to leave. If you are in an important position, you might be invited to a presidential dinner: this is, of course, very formal, with a strictly followed code and some typical form of entertainment, such as traditional Japanese songs or dances. Times are changing; the dinner used to end only when the oldest president left, surrounded by a cohort of bowing waiters.

As you may know, Japanese doctors behave very differently from their Western colleagues: exhibits are mainly restricted to technical manufacturers, with no large booths from pharmaceutical companies. Although all of the sessions are well attended, the international symposium, at which foreign lecturers and senior Japanese doctors give talks, is poorly attended—so that you find yourself speaking in front of a large but nearly empty theater.

The Japanese spring meeting and Japan Digestive Disease Week (DDW) are technically and scientifically on a par with the American DDW and European Weeks. Last but not least, the Japanese are extremely warm and friendly hosts. Their guests are treated with the utmost respect. Thanks go to Hiruhito for his lesson about sake in 1992 before a traditional Friday evening drinking party, and thanks also to Japan for its beautiful landscape and its boiling hot springs. But above all, one should remember that Japan is where endoscopy was born and developed. Come and enjoy a Japanese meeting!

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Invitation to the Second European Symposium on Ethics in Gastroenterology and Digestive Endoscopy

Kos Island, Greece, 6–8 July 2006

Organizing Societies: ESGE and OMED

The scientific program includes working group sessions, lectures, and debates on hot topics in ethics, which will help address several ethical issues in everyday clinical practice and research. The Symposium is being held on Kos, the island of Hippocrates, where the Hippocratic Oath is displayed on the ancient ruins of Asklepion. Please join us, actively contribute to this symposium, and submit abstracts and ethics cases.

Visit **www.esge.com** and Hippocrates will transfer you to our web site.

Professor Spiros Ladas
Professor Carol Stanciu
Presidents of the Symposium
Dr. Jean-François Rey
President of ESGE
Professor Anthony Axon
President of OMED

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WGO-OMGE/OMED World Digestive Health Day
May 29, 2006

FOCUS: *Helicobacter pylori* infection: the most important risk factor for non cardia gastric cancer

H. pylori infection accounts for more than 60% of the global cases of gastric cancer. WGO-OMGE and OMED urge you to make the most of World Digestive Health Day on May 29, to educate your medical colleagues, staff and community about *H. pylori* detection and treatment.

A special WGO-OMGE team of experts is currently writing a Guideline on *Helicobacter Pylori* Infection which will be available free on the internet (www.worldgastroenterology.org) in five languages in June 2006.

Highlights of topics addressed in the Helicobacter Pylori Infection Guideline:

- Quadruple vs. triple therapy
- Patient Compliance
- Differences in 14, 10, 7 day therapy

WGO-OMGE and OMED urge all members and societies to make the most of World Digestive Health Day 2006 and to share your experiences with us for posting on the website or in our e-newsletter. Tell your global colleagues about what you are doing to combat Hp infection.

Email us at: info@worldgastroenterology.org

WGO-OMGE and OMED extend a special thanks to Prof. Rene Lambert of the IARC for his invaluable assistance and consultation on this project.

H. pylori infection rates

Adults in Developed Countries	58%
Adults in Developing Countries	74%

***Helicobacter pylori* infects more than half the world's population**

Parkin DM, 2006

Estimate numbers of gastric cancer (both sexes) in 2002, occurring in developed and developing countries.

	All cases stomach cancer	Non cardia stomach cancer	Cases attributable to HP	% of all
Developed Countries	312,400	259,000	192,000	61.4%
Developing Countries	621,500	511,000	400,000	64.4%
World	933,900	770,000	592,000	**63.4%**

The estimation is based on the following assumptions:

1 – HP infection plays no role in cancer of the cardia which represents approximately 18% of all cases.
2 – The prevalence of HP infection is lower in developed countries (58%) than in developing countries (74%).
3 – The attributable fraction of stomach cancer related to HP infection, obtained by the classical formula of Cole and MacMahon is 0.74% of the numbers of non cardia stomach cancer in developed countries and 0.78% in developing countries.

Parkin DM. The global health burden of infection-associated cancers in the year 2002. Int J Cancer. 2006 Jan 10; [Epub ahead of print]

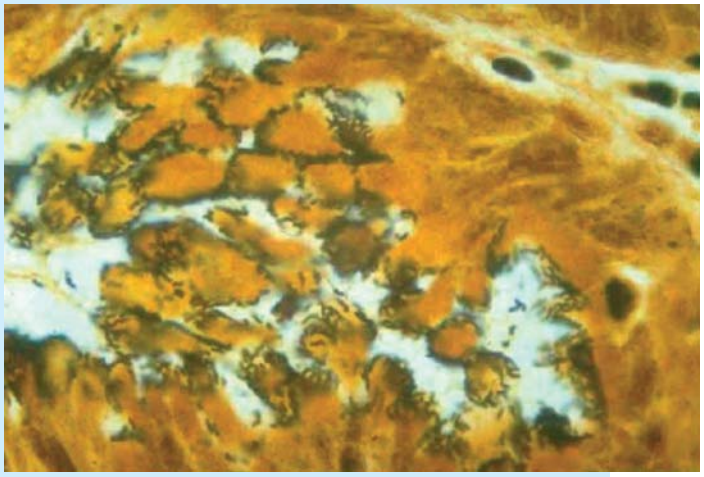
Nobel Prize in Medicine Awarded to Gastroenterology Team

Jerome D. Waye, MD

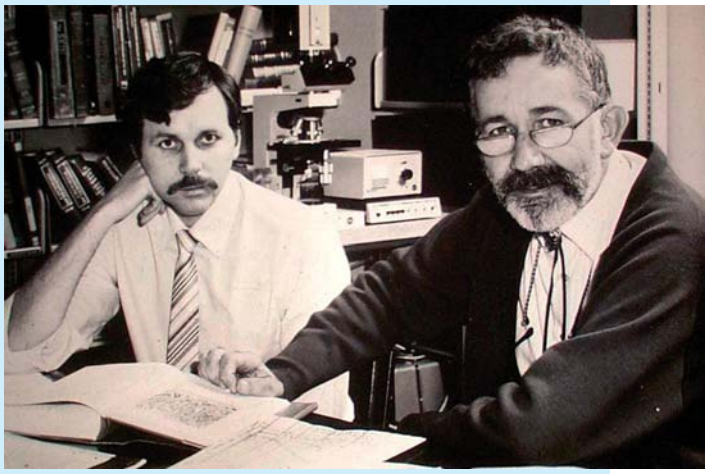
The long-held belief that ulcers were caused by acid and that and eliminating acid cured them was exploded by Dr. Barry J. Marshall (of the University of Western Australia in Nedlands, Perth) and Dr. J. Robin Warren (a pathologist at the Royal Perth Hospital), who "made an irrefutable case that the bacterium *Helicobacter pylori*" causes ulcers and other diseases (quoted from the citation by the Nobel Committee from the Karolinska Institute in Stockholm). The citation goes on to state that "it is now firmly established that *Helicobacter pylori* causes more than 90% of duodenal ulcers and up to 80% of gastric ulcers." The discovery of this basic phenomenon—that intestinal ulcers are caused by an infection—has forever changed the way gastroenterologists approach the ulcer problem.

In the early 1980s, Dr. Warren noted the spiral-shaped bacterium in the lower part of the stomach in about half of the patients who had biopsies. He made the observation that inflammation was always present in the gastric mucosa when the bacterium was present. Dr. Marshall joined Dr. Warren in studying this hitherto unknown bacterium, which they originally thought was one from the *Campylobacter* family, and named it *C. pyloridis* after Dr. Marshall succeeded in culturing it. It was later found that it was a member of the *Helicobacter* family, and it was renamed *H. pylori.*

Dr. Marshall conducted a classic experiment on himself that undeniably linked the bacterium to inflammation of the stomach and demonstrated that the inflammation resulted from an infectious process. When Dr. Marshall was in his early 30s, he had a colleague examine his stomach and take a series of biopsies. Ten days later, after waiting for the biopsy sites to heal, he swallowed a pure culture of *H. pylori.* One week later, he felt dyspeptic, full after eating, and had bad breath and general malaise. Several days later, he underwent the first of three post-ingestion gastroscopies and biopsies. The biopsies demonstrated that he had developed an acute inflammatory process in the stomach, which he successfully treated with antibiotics. When Dr. Marshall presented his first paper on his discovery of the relationship between this bacterium and gastric inflammation and ulcers, the world of gastroenterology refused to accept the findings. Gastroenterologists in general were slow to accept this



Warren's first case of H. pylori, *1979.*



Barry Marshall and Robin Warren, 1984.

> ***"Gastroenterologists in general were slow to accept this report, which was so diametrically opposite to the teaching of generations of stomach experts."***

report, which was so diametrically opposite to the teaching of generations of stomach experts. These two ordinary men were able to look at a finding that many had seen before, and "with tenacity and a prepared mind challenged prevailing dogmas," as the Nobel citation states.

Both members of this team accepted their prize with modesty. Dr. Warren pointed to the groundbreaking clinical experiment that Dr. Marshall performed on himself, while Dr. Marshall states that working in an academically obscure location aided in the discovery, as he and Dr. Warren were able to pursue their observations without interference from prevailing beliefs. Dr. Marshall stated, "If I had come up through the normal gastroenterology training schemes in the United States, I would have been so indoctrinated on the acid theory that I wouldn't have been considering anything else and might have skipped over *Helicobacter,* as everyone else had done." He also stated that "Robin is quite obsessional. Once he sees something, he is determined to see what it is. He would have found another Barry Marshall" to work with. These two scientific researchers were awarded the Nobel Prize by the King of Sweden on 10 December 2005, the anniversary of the death of Alfred Nobel, the Swedish dynamite inventor who created the prizes in his will.

The world's gastroenterology community congratulates Dr. Barry Marshall and Dr. J. Robin Warren, on being awarded the 2005 Nobel Prize for Medicine.

Portions of this article were excerpted from an article by Lawrence K. Altman published in the New York Times *on 4 October 2005.*

Marshall and Warren celebrating outside their local pub in Australia, October 2005.

Evidence-Based Medicine – Why Did it Take the World by Storm?

Justus Krabshuis

"Evidence-based medicine" (EBM) [1] requires the integration of the best research evidence with our clinical expertise and our patient's unique values and preferences." This description from the best team in the field [2] is very good, but it is also somewhat ambitious and vacuous. It is ambitious (some might even use the word "evangelistic"), because it suggests that all medical practice should adhere to this. It is vacuous, because the definition is so general that almost everyone would agree—after all, medical practice always combines the science of medicine with the art of medicine. But let's leave the critical notes to the last.

Why did it take the world by storm? Here are several reasons:

- The explosive growth of published information and the associated explosive growth in expectations and in the need to have this information available in a usable form at the point of care. Compared with 1996, for example, the number of randomized controlled trials (RCTs) published in the medical literature doubled to 15,000 in 2004.
- The use of the word "evidence-based" in the medical literature also shows this explosive growth. In 1996, the term was only used 181 times. This had risen to 6452 times by the end of 2004 (see Table). Today, it has entered mainstream thinking, and the curve will probably flatten out soon.
- Traditional resources such as textbooks are out of date almost as soon as they are published, experts are frequently proved wrong, and often these textbooks were too cumbersome anyway to function as decision support tool for delivering clinical care at the bedside.
- Lack of time—usually not more than a few seconds per patient is available for finding and assimilating evidence, and most doctors do not have more than half an hour or so per week for general reading and study. They cannot keep up with the "traditional" literature.
- And so there developed a growing gap between what is known and what is done, first identified by David Sackett—the intellectual father of the EBM "movement" (he should get a Nobel prize after a few more years have passed).

Year	"Evidence-based"
1996	181
1997	495
1998	1074
1999	1628
2000	2195
2001	3055
2002	4118
2003	5745
2004	6452

Doctors, patients, payers, and managers were becoming aware of the gap. Solutions were developing fast. Publishers, the traditional protectors of creativity, moved with the times. Medline introduced "randomized controlled trials" as a MeSH (Medical Subject Headings) indexing term, and "randomized controlled trial" as a "document type" indexing option in 1990 and 1991, respectively. This allowed investigators from 1990 onwards to search Medline for all RCTs for a particular disease or treatment option.

Enter the key player in the field … the Cochrane Collaboration had the vision and the determination to re-index Medline and to re-index Embase specifically for RCTs. The resulting records were licensed as RCT subsets from Medline and Embase and entered the Cochrane Library controlled clinical trials database, the prime source for identifying RCTs today. Evidence-based medicine was the only methodology to narrow the gap between what was known and what was done—and so the Cochrane Collaboration had found its true mission.

Many EBM publishing initiatives followed. A typical example of an early mainstream publisher initiative was the *British Medical Journal*'s Clinical Evidence publication—one of the first in the field [3]. A more recent example of a very high-quality evidence-based alerting service, free to everyone and jointly produced by the *British Medical Journal* (BMJ) and the Health Information Research Unit (HIRU) at McMaster, is called "BMJUPDATES" [4].

The HIRU team at McMaster (I realize I keep mentioning them, but the Canadians are leading players here) has recently developed the Hedges project [5]. This publishes free evidence-based searching strategies for finding evidence in Embase, Medline, and Cinahl.

Another key development was the early emphasis on "critical appraisal." Once it became possible to search online databases for all published RCTs, the next important step was of course "critical appraisal" of all the RCTs. David Sackett started critical appraisal work-

shops for doctors in the late 1980s and early 1990s at McMaster University, and this also had a great impact. Critical appraisal workshops took off, and free tools from authoritative sources such as HIRU [6] in Canada and the Centre for Evidence-Based Medicine in Oxford [7] helped spread the practice.

Finally, mindsets have changed. Today, there is a great deal of emphasis on lifelong learning and on continuing medical education (CME). Are we wiser perhaps? As the ripples spread, we realize how little we know yet—to paraphrase the 12th-century medical oath by Maimonides: "Today you can discover your errors of yesterday, and tomorrow you can obtain new light on what you think yourself sure of today." … Ponder that as you fire up your hand-held PDAs.

All these reasons converged for evidence-based medicine to take the world by storm. It helped also that EBM is therapy-oriented—this meant that resources could be found. Critics sometimes say that it is drug industry–oriented. High-quality evidence can only be produced by high-quality trials. Most trials assess only small differences in effect, which means large trials are needed, which means high costs; this in turn means that there is interest from the drug industry, as they can pay for the trials. *Voilà,* reader, we have arrived at some critical notes at last!

However, there are serious critics of the approach focusing on RCTs. John Hampton's paper on evidence-based medicine, opinion-based medicine, and real-world medicine is a good example [8]. Richard Horton, the editor of *Lancet*, recently claimed that of all trials published in top medical journals, only 50% provide adequate documentation on a number of key issues: blinding was not done properly, randomization was faulty, the systematic literature review was not complete [9]. There are doctors who claim that most of their patients would never meet the entry criteria for the trial in question. Typical real-life patients, especially elderly ones, have more than one problem and many are taking more than one drug. Such factors are difficult to control in a randomized controlled trial that needs to control all variables for variance if meaningful conclusions are to be reached.

Does EBM, in its more fundamentalist guise, appeal only to those who want to change the world? Probably not. What is certain is that the rise of EBM and its now widespread adoption in medical research and practice has created very significant change, and almost all of it for the better. Archie Cochrane's unwritten law: "all treatment must be proved to be effective" [10] still holds true. So—get involved, stay alert, and … always ask for the "evidence"!

Notes and further reading

1. The term "evidence-based medicine" was officially used for the first time in 1992 in the "seminal" article: Evidence-based Medicine Working Group. Evidence-based medicine: a new approach to teaching the practice of medicine. JAMA 1992; 268: 2420–5.
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3. Clinical Evidence. One of the first EBM publishing initiatives, from the BMJ publishing group at: http://www.clinicalevidence.com
   Free for developing countries via the Health InterNetwork Access to Research Initiative (HINARI): http://www.healthinternetwork.org
4. The McMaster/BMJ Update service is an excellent "free" alerting service jointly produced by the BMJ Group and McMaster university's HIRU unit: http://bmjupdates.mcmaster.ca/index.asp
5. The Hedges project, HIRU, McMaster University, Canada: http://hiru.mcmaster.ca/hedges/indexHIRU.htm
   The best search strategies for searching Embase, Medline and Cinahl.
6. The Health Information Research Unit (HIRU) at McMaster (Hamilton, Canada) is one of the leading EBM research institutes: http://hiru.mcmaster.ca/Overview.htm
7. The Centre for Evidence-Based Medicine (CEBM), Radcliffe Infirmary, Oxford, UK. The best toolboxes in the field: http://www.cebm.net/
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9. Richard Horton: presentation at the WGO-OMGE Montreal Global Guidelines symposium, 15 September 2005. Audio file at: http://www.omge.org/?cc_program
10. Read here how it all started: Cochrane AL, Blythe M. One man's medicine: an autobiography of Professor Archie C. Cochrane. London: BMJ, 1989. (Memoir Club series; ISBN 0727902776).

Additional reading

- The Cochrane Library. The best source for systematic reviews and randomized controlled trials: http://www.cochrane.org
  Free for developing countries via HINARI: http://www.healthinternetwork.org
- Database of Abstracts of Reviews of Effects (DARE), from the University of York, UK. The best source for structured abstracts of quality-assessed reviews: http://www.york.ac.uk/inst/crd/darehp.htm
- An excellent summary of the EBM debate is given in an open-access BioMed Central publication: Sehon SR, Stanley DE. A philosophical analysis of the evidence-based medicine debate. http://www.biomedcentral.com/1472-6963/3/14

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NEWS FROM THE INDUSTRY

ALTANA Pharma

True Measures of GERD: putting patients at the heart of assessment innovations

Until now, assessment of gastroesophageal reflux disease (GERD) has relied primarily on the assessment of esophageal healing. Documentation of GERD therapy success is a difficult task, as the extent of mucosal damage stands in no relation to the severity of symptoms[1]. In addition, 70% of patients with GERD symptoms have endoscopically negative GERD[2,3].

In the absence of a "gold standard" diagnostic test for GERD, symptom assessment is critical to successful patient management. Understanding how symptoms affect patients' quality of life can also be an aid to management. In recent years, research has suggested that the symptom complex experienced by GERD patients is much wider than previously appreciated. In addition to heartburn, acid eructation, and pain on swallowing, a variety of other GERD-related symptoms are experienced, including nausea, diarrhea, sleep disturbance, and other complaints such as respiratory symptoms.

The problem for gastroenterologists trying to obtain a full picture of a patient's symptoms is that patients may find it difficult to describe accurately all the symptoms they are experiencing, with the result that they may not be effectively treated. The broad spectrum of symptoms in GERD patients and the high prevalence of endoscopy-negative GERD highlight the need for a robust, validated approach for symptom assessment in these patients.

One such method is ReQuest™, developed by ALTANA Pharma—a simple and effective questionnaire for patients' daily self-assessment of a wide range of GERD symptoms. It was constructed following discussions with patients and physicians to identify the spectrum of symptoms reported and how they were described by GERD patients, and included evaluation of the literature and clinical trial data. ReQuest™ is divided into seven dimensions: acid complaints; upper abdominal/stomach complaints; lower abdominal/digestive complaints; nausea; sleep disturbances; general well-being; and other complaints.

A short version, which can be completed in less than 5 minutes, is solely focused on the seven dimensions, while the full version, which takes approximately 20 minutes, asks additionally for the occurrence of symptom descriptions typical for the corresponding dimension. Both tests have undergone extensive clinical trial evaluation and statistical analyses that have confirmed their internal consistency, test–retest reliability, construct validity, and responsiveness to changes during treatment[4,5,6]. In addition, ReQuest™ meets the criteria set by the regulatory authorities for a validated symptom-based system for use as the primary outcome measure in clinical trials of GERD therapy.

ReQuest™ / LA-classification

ReQuest™ / LA-classification is the first system to effectively integrate a highly sensitive patient questionnaire (ReQuest™) with an adaptation of the established Los Angeles classification. The new index therefore allows combined assessment of symptom relief and healing of esophageal lesions in GERD—a measure termed "complete remission".

A recent randomized, double-blind study using ReQuest™ has established that pantoprazole is non-inferior to esomeprazole (both 40 mg/day) over 12 weeks with regard to complete remission in 581 patients with erosive GERD. With respect to endoscopically confirmed healing, pantoprazole was superior to esomeprazole[7]. A second randomized, double-blind ReQuest™ study, this time of 4 weeks' duration (n = 561), demonstrated parity between pantoprazole and esomeprazole (both 40 mg/day) in terms of symptom relief scores, but also showed that the beneficial effects of pantoprazole were sustained for longer, with significantly fewer symptomatic relapses in the 7-day post-treatment phase[8].

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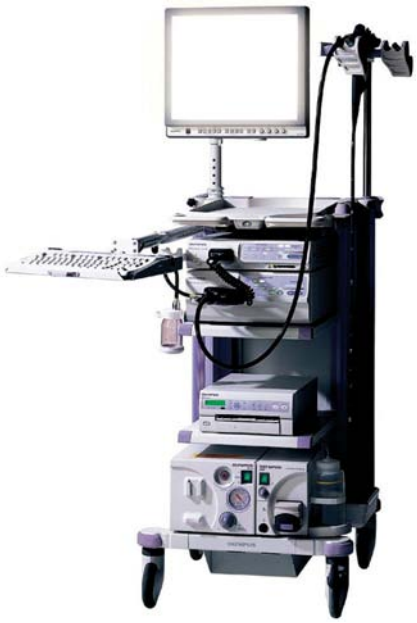
Olympus

EVIS EXERA II

Advanced performance and refined design take your endoscopic procedures to the next level

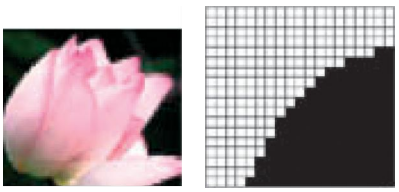
As the pioneering company in the field of endoscopy, Olympus is committed to providing physicians with the tools they need to perform the most challenging procedures with confidence. This means designing endoscopes and accessories that provide ease of operation and maneuverability, while offering the top quality and superior performance needed to achieve consistent, reliable results. You'll get all that and more with the all-new EVIS EXERA II 180 Series system.



Featuring unprecedented image quality, enhanced optics, ultra-slim design, expanded compatibility, and refined ergonomics, EVIS EXERA II sets a new standard of excellence for examination and treatment in the upper and lower gastrointestinal tract.

High-resolution HDTV images*

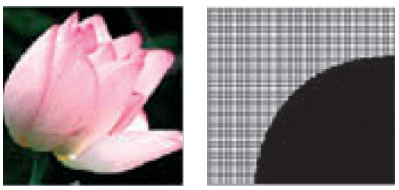
The HDTV images produced by EVIS EXERA II *(available with the GIF-H180 and CF-H180AL/I only) are composed of more than twice the number of scanning lines and horizontal pixels used in conventional video systems. With HDTV, it is now possible to observe capillaries and subtle mucosal tissue in greater detail throughout the screen area



Conventional TV image

Narrow-Band Imaging (NBI)

EVIS EXERA II's NBI is an optical image enhancement technology that enhances the visibility of vessels and other structures on the mucosal surface. The improved visibility made possible by NBI may improve examination efficiency by helping to decrease examination time and reduce unnecessary biopsies.

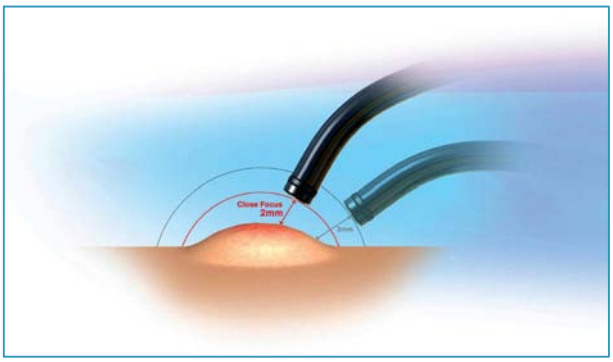


HDTV Image

Compatibility with other systems. In addition to gastrointestinal endoscopy, the EVIS EXERA II 180 Series system can be used with other specialties such as endosurgery and bronchoscopy. It also has backward compatibility with the EVIS 130, 140 and 160 series scopes.

Digital output. A practical digital solution, EVIS EXERA II features a built-in PC card slot that allows you to store still images on removable media. An SDI connection is provided for easy, long-distance cabling. Digital images can be stored via DV interface (iLINK) by connecting a DV/DV CAM type VCR and DV-compatible PC.

Close focus for detailed observation. The GIF-H180 and CF-H180AL/I's HDTV-compatible CCD combined with the optical system's extended depth of field achieves the same effect as with electronic magnification simply by bringing the scope tip as close as 2 mm to the observation area.



170° Wide-angle

Wide angle 170° field of view. The fields of view of the CF-H180AL/I and CF-Q180AL/I have been increased to 170° from the 140° available with the preceding models. By making it possible to view the surfaces behind the folds of the colon with minimal angulation of the scope tip, this wide-angle capability may help reduce examination times.

OLYMPUS
Your Vision, Our Future

TOTAL PERFORMANCE IS ALL ABOUT SPEED[1] STRENGTH[2-4] AND ENDURANCE[5]

PANTOPRAZOLE
A Complete PPI

Abbreviated Prescribing Information. Since indications and prescribing information may vary from country to country, please consult your local prescribing information for detailed information on the product. **PANTOPRAZOLE® 40 mg: Indications and dosage:** *Combination therapy for eradication of H. pylori in patients with peptic ulcer disease:* twice daily for one week with two appropriate antibiotics. Duodenal ulcer: 40 mg pantoprazole once daily for 2–4 weeks. *Gastric ulcer and moderate and severe reflux esophagitis:* 40 mg pantoprazole once daily for 4–8 weeks is recommended. If needed in individual cases, the dose can be increased to 80 mg. *Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions:* For the long-term management patients should start treatment with a daily dose of 80 mg. Thereafter, the dosage can be titrated to individual needs, guided by gastric acid secretion measurements. With doses above 80 mg daily, the dose should be divided and given twice daily. In patients with severe liver impairment, the dose has to be reduced to 1 tablet (40 mg pantoprazole) every other day. The daily dose of 40 mg pantoprazole should not be exceeded in elderly patients or in those with impaired renal function. An exception is combination therapy for eradication of H. pylori, where also elderly patients should receive the usual pantoprazole dose (2 x 40 mg/day) during 1-week treatment. **Contra-indications:** Pantoprazole® 40 mg should generally not be used in cases of known hypersensitivity to one of the constituents of pantoprazole or of the combination partners. Due to lack of clinical data, do not use Pantoprazole® 40 mg in combination with antibiotics for H. pylori eradication in patients with moderate to severe hepatic or renal dysfunction. **Special precautions for use:** Prior to treatment, the possibility of malignancy of gastric ulcer or a malignant disease of the esophagus should be excluded as the treatment with pantoprazole may alleviate the symptoms of malignant ulcers and can thus delay diagnosis. *Pregnancy and lactation:* Clinical experience in pregnant women is limited. There is no information on the excretion of pantoprazole into human breast milk. Pantoprazole tablets should only be used when the benefit to the mother is considered greater than the potential risk to the fetus/baby. To date there has been no experience with treatment in children. **Interactions:** Interactions with other drugs metabolized by the Cytochrome-P-450-System cannot be excluded. In a series of studies specific with such drugs (amoxicillin, antacid, caffeine, carbamazepine, clarithromycin, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, metronidazole, nifedipine, phenytoin, theophylline, and an oral contraceptive), no interactions were observed. Alteration of absorption of substances with pH-dependent absorption should be considered. **Undesirable effects:** Treatment with Pantoprazole® 40mg can occasionally lead to headache, gastrointestinal complaints such as upper abdominal pain, diarrhea, constipation or flatulence, and allergic reactions such as pruritus, skin rash (in isolated cases also urticaria, angioedema or anaphylactic reactions including anaphylactic shock). There have been rare reports of nausea, dizziness or disturbances in vision (blurred vision). Peripheral edema, fever, depression or myalgia subsiding after termination of therapy were reported in individual cases. There have been very rare reports of severe hepatocellular damage leading to jaundice with or without hepatic failure. In individual cases, increased liver values (transaminases, g-GT) and elevated triglyceride levels were reported as well as isolated cases of severe skin reactions such as Stevens-Johnson-Syndrome, Erythema multiforme, Lyell-Syndrome, and Photosensitivity. **Presentation:** Pantoprazole® 40 mg gastro-resistant coated tablets, each containing 45.1 mg Pantoprazole-Sodium-Sesquihydrate. **PANTOPRAZOLE® 20 mg: Indications and dosage:** *Treatment of mild reflux disease and associated symptoms* (e.g. heartburn, acid regurgitation, pain on swallowing): 20 mg pantoprazole per day. Symptom relief is generally accomplished within 2–4 weeks, and a 4-week treatment period is usually required for healing of associated esophagitis. If this is not sufficient, healing will normally be achieved within a further 4 weeks. When symptom relief has been achieved, reoccurring symptoms can be controlled using an on-demand regimen of 20 mg once daily, when required. A switch to continuous therapy may be considered in case satisfactory symptom control cannot be maintained with on-demand treatment. *Long-term management and prevention of relapse in reflux esophagitis:* 20 mg pantoprazole per day, increasing to 40 mg pantoprazole per day if a relapse occurs. Pantoprazole® 40 mg is available for this case. After healing of the relapse, the dosage can be reduced again to 20 mg pantoprazole. In long-term treatment, a treatment period of 1 year should be exceeded only after careful consideration of the benefit/risk ratio, as drug safety over several years is not sufficiently established. *Prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs):* 20 mg pantoprazole per day. Note: A daily dose of 20 mg pantoprazole should not be exceeded in patients with severe liver impairment. **Contra-indications:** Pantoprazole® 20 mg should not be used in cases of known hypersensitivity to the active ingredient or/and any of the other constituents. **Special precautions for use:** The use as a preventive of gastroduodenal ulcers induced by NSAIDS should be restricted to patients who require continued NSAID treatment and have an increased risk to develop gastrointestinal complications. In patients with severe liver impairment the liver enzymes should be monitored regularly during treatment with pantoprazole, particularly on long-term use. In the case of a rise of the liver enzymes, Pantoprazole® 20 mg should be discontinued. See also section Pantoprazole® 40 mg. *Pregnancy and lactation/Undesirable effects:* See section Pantoprazole® 40 mg. **Presentation:** Pantoprazole® 20 mg tablets each containing 22.6 mg Pantoprazole-Sodium-Sesquihydrate. For further information please contact **ALTANA Pharma AG**, Byk-Gulden-Str. 2, 78467 Konstanz, Germany, or the local subsidiary. (02/2005) **References:**

1. Yacyshyn BR and Thomson ABR. Digestion 2002; 66: 67-78. **2.** Gillessen A *et al*, J Clin Gastroenterol Volume 38, Number 4, April 2004. **3.** Richter JE. Aliment Pharmacol Ther 2004; 20: 567-575. **4.** Bardhan KD. Data on file 2005. **5.** Avner D. Clinical Therapeutics 2000; 22: 1169-1185.

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Adverse events should be reported to your local ALTANA Pharma office. For UK, please call ALTANA Pharma Pharmacovigilance Freephone 0808 141 0047. Information about adverse event reporting can also be found at www.yellowcard.gov.uk.

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