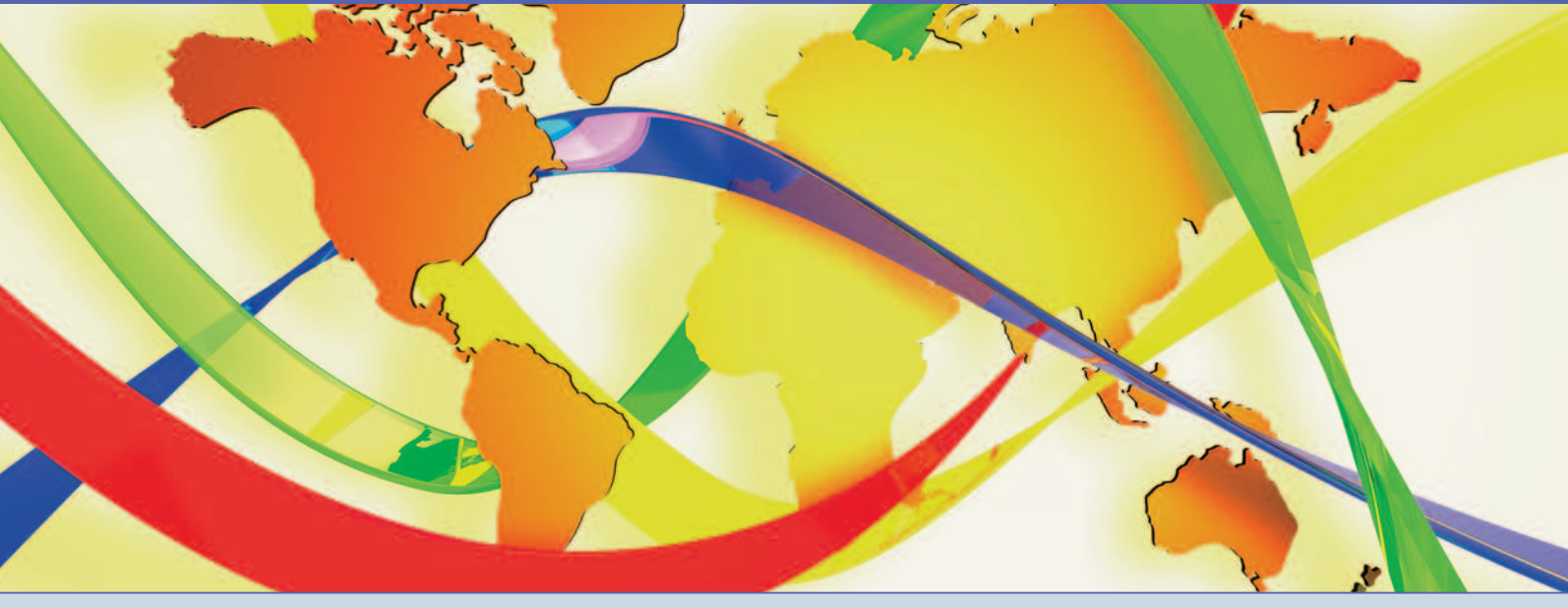
Vol.11
Issue 2 / Autumn 2006

WGN
WORLD GASTROENTEROLOGY NEWS



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

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H. pylori *Guideline Highlights & Esophageal Cancer Update*

ISSN 1567 7753

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

Marathon International
Printed in the Netherlands

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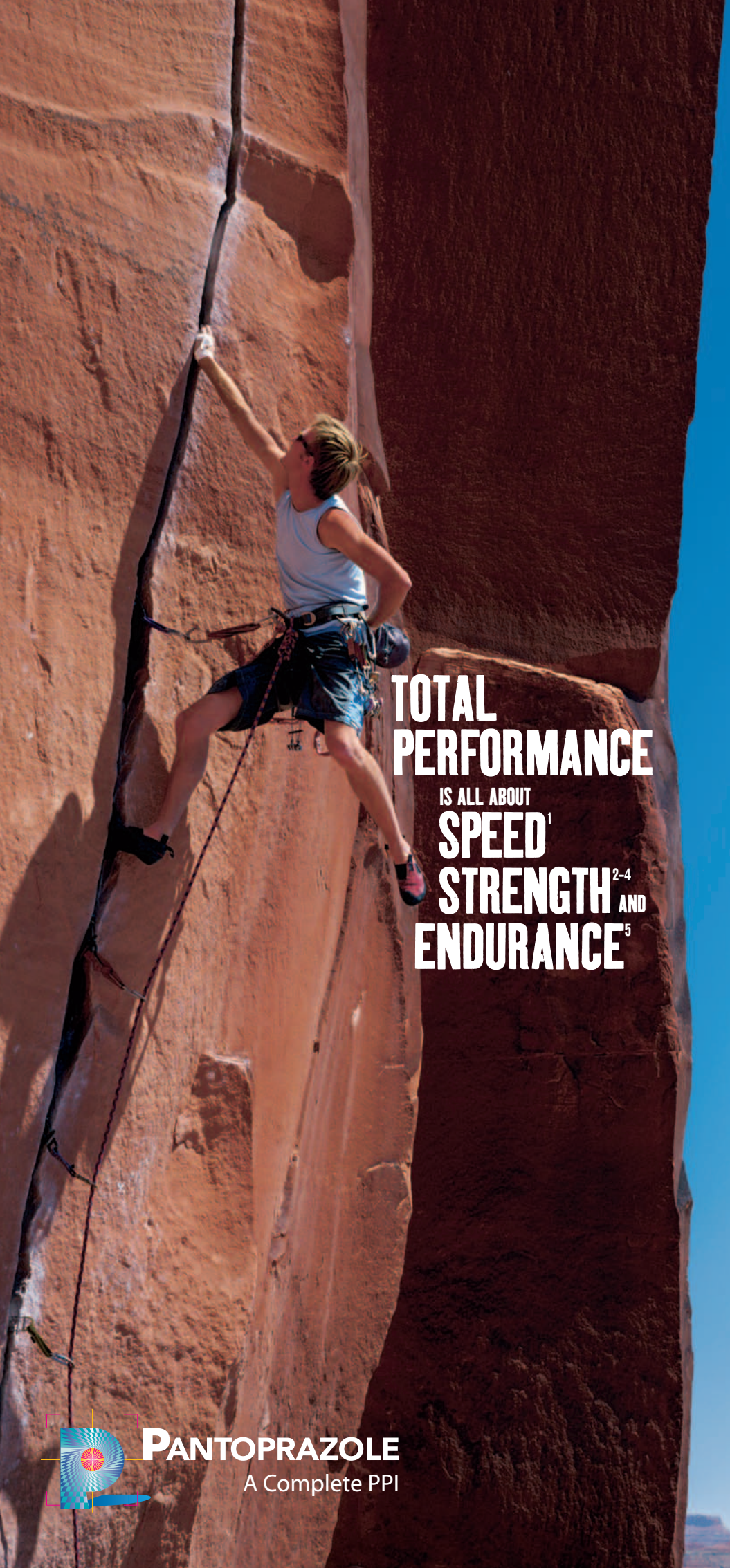

TOTAL PERFORMANCE IS ALL ABOUT SPEED[1] STRENGTH[2-4] AND ENDURANCE[5]

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® 40 mg 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, γ-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. **Last updated:** 2 February 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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Message from the Editor

Jerome D. Waye, MD

Pack your bags for an extraordinary conference at the United European Gastroenterology Week (UEGW) in Berlin on 21–25 October. Attendees will get to see and hear a superb scientific program, with lots of original research and new approaches to common and uncommon diseases. The endoscopy part of the conference will be run by the European Society for Gastrointestinal Endoscopy (ESGE) and promises to be a good show, as the best endoscopists in the world will be carrying out live procedures during the week.

This issue of *WGN* includes another guideline on a very appropriate topic, *Helicobacter pylori.* The guideline is large, and is the most complete and up to date compendium on this subject. Since mailing it to everybody across the world would be exceedingly expensive, we have printed in this issue a precis of the full article, and the entire guideline is available on the WGN web site. A group of international experts, headed by Dr. Richard Hunt, have spent innumerable hours drafting, distilling, and pondering this topic to bring the latest news on current thinking about *H. pylori.*

The section on scientific news provides short articles about Barrett's and dysplasia, carcinoid tumors, chromoendoscopy, small-bowel bacterial overgrowth, and inflammatory bowel disease in Africa. Dr. Drossman brings us up to date on the latest considerations on functional gastrointestinal disorders from the point of view of the Rome III study group. A special treat is the description of the Digital Atlas of Video Education (DAVE) web site, where a great many high-quality videos on various types of endoscopic procedure, as well as treatment videos, are available free—not only for viewing, but for downloading for teaching purposes. This superb teaching web site is brought to you by Dr. Kelsey and Dr. Bounds of the Massachusetts General Hospital in Boston.

There is news from WGO-OMGE and OMED, and our resident librarian, Justus Krabshuis, has written a delightful overview giving his views about guidelines in general. We also bring you news from members of the editorial board, informing us about the progress of gastroenterology in their countries. The Gastroenterology on the Frontier column focuses on the Sudan.

Once again, Professor René Lambert has written a superb treatise updating us on esophageal cancer.

Of particular interest is a profile by Prof. K.L. Goh of Dr. Kees Huibregtse from Amsterdam—regarded throughout the world as "Mr. ERCP." Although Kees retired because of illness, he is currently in great health, thanks to his wife. Reinvigorated, he has begun to build a new career. We wish him well and much happiness.

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New funding needed for the future

WGO-OMGE Treasurer's report, 2005

Douglas R. LaBrecque, MD

September 2005 marked a milestone for WGO-OMGE. After 15 years of dedicated service meticulously shepherding the finances of our organization, Dr. Joseph Geenen retired from the position of Treasurer, and I am honored to be able take his place at a time when the organization has never been more active or effective in striving to fulfill its mission of enhancing worldwide education and training in gastroenterology and hepatology, especially in the more medically disadvantaged areas of the world.

Our flagship program, Train the Trainers, is now in its sixth year. Dr. James Toouli and the Education and Training Committee are seeking creative ways of expanding the program so that it can be presented two and even three times each year in different regions. In order to do so, we are attempting to develop partnerships with national societies to help defray the increased costs of presenting this important program more than once a year. The South African Gastroenterological Society (SAGES) is serving in this capacity for the 2006 program in South Africa, for which we are grateful.

Our Training Centers are continuing to flourish, and Dr. Amrani's program in Rabat, Morocco, was broadcast to neighboring countries via telemedicine in January 2006. The sixth Training Center opened in Bangkok in March 2006, and the second Advanced Training Center opened in Rome in May 2006.

Although WGO-OMGE's investments did well in 2005, the World Congress will not provide the large infusion of funds we have come to expect from past World Congresses, despite the outstanding success of the meeting held in Montreal in September 2005. At the same time, the pharmaceutical companies and instrument manufacturers, our other major source of revenue, are reducing their support for meetings, training, and education. This appears to represent a paradigm shift in their approach to medical organizations. As of 1 July 2006, only seven of the 11 members of the Concordat (industry supporters) in 2005 have continued their membership for 2006. In addition, four members have not renewed their support for *World Gastroenterology News* for 2006. If new supporters cannot be identified, our flagship publication will, for the first time, be published at a deficit.

These challenges mean we will need to find new sources of funding in the future. In the short term, we will be forced into deficit spending, estimated at approximately US$ 500,000 for 2006, despite significant efforts to cut expenses, including the elimination of the annual meeting of the Executive Committee previously held during UEGW. To address the problem, we have hired a consultant who is investigating the current funding sources and looking at all possible alternatives. We will need to expand our efforts with industry, while also approaching philanthropic organizations as well as individuals who share our mission to improve world health. In this effort, we will rely on all of our member organizations and their members to assist us in identifying potential supporters as we approach this critical endeavor and devise new mechanisms of fundraising.

I am grateful to the new members of the Finance Committee who were elected at WCOG 2005 and have agreed to serve with me for the next 4 years: G. Choudhuri (India), J. Geenen (USA), W. Fleig (Germany), P. Latham (USA), D. Patel (Canada), W. Hogan (USA), H. Schneider (South Africa), and K. Fujiwara (Japan). I welcome suggestions from the membership.

The Concordat membership for 2005 consisted of: AstraZeneca, Boston Scientific, Altana, Fujinon, Janssen, Olympus, Pentax, Takeda, Novartis, Axcan, and Schering/Berlax.

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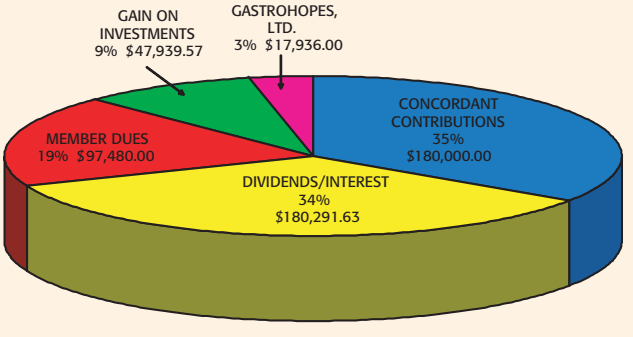
Budget report for 2005

WGO-OMGE's total revenue for 2005 was US$ 523,647.20. Revenue included members' dues of US$ 97,480; Concordat contributions (from the biomedical industry) of US$180,000; interest and dividends of US$ 180,291.23; gain on investments of US$ 47,939.57; and miscellaneous sums amounting to US$ 17,936.

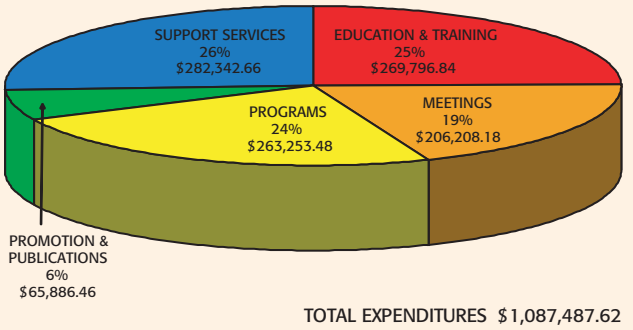
WGO-OMGE 2005 – Revenue.



TOTAL REVENUE $523,647.20

Total expenses for 2005 were US$ 1,087,487.62. Expenses were divided into the following categories: education and training, US$ 269,796.84; meetings, US$ 206,208.18 (reduced by US$ 155,678.97 from 2004); programs US$ 263,253.48; promotion and Publications US$ 65,886.46; and support services US$ 282,342.66. The total of expenses over revenue was US$ 563,840.42.

WGO-OMGE 2005 – Total expenditures.



TOTAL EXPENDITURES $1,087,487.62

OMED web site: www.omed.org

The web site has been markedly changed and updated to reflect the new thrust of the World Organization for Digestive Endoscopy (*Organisation Mondiale d'Endoscopie Digestive*, OMED), with a renewed dedication to improving the status of gastrointestinal endoscopy throughout the world. The web site presents news about OMED activities, society news, links to all of the constituent societies, and past issues of *World Gastroenterology News.* The aim of the web site is now to provide a one-stop meeting-place for all issues in gastrointestinal endoscopy: www.omed.org

Research reports

Dr. Jonathan Cohen from New York, with a group of reporters, has posted a detailed report on every research paper delivered at Digestive Disease Week (DDW) in Los Angeles during its May meeting in 2006. Both the latest research news and future trends are described in full in this detailed report.

Endoscopy directors' workshop

On 22 October 2006, at the United European Gastroenterology Week (UEGW) in Berlin, OMED will be presenting—in conjunction with the European Society for Gastrointestinal Endoscopy (ESGE)—the first in a series of workshops for endoscopy directors, directed toward clinicians who manage endoscopy units. The format will include lectures, tutorials, and interactive sessions. Various topics will be covered, including personnel management, endoscopy unit design, quality indicators and improvement programs, endoscopy disinfection, data management, and equipment purchase and maintenance. OMED and the ESGE believe that the workshops will enable participants to improve the quality and safety of endoscopy and reduce costs in the endoscopy unit. The numbers of participants in the workshops are limited, and early registration is recommended.

Ethics in gastrointestinal endoscopy

The second European symposium on ethics in gastroenterology and digestive endoscopy was held in Kos in July 2006. A full report will be presented on the OMED web site. This fascinating symposium touched on issues relating to palliative care, patient satisfaction, endoscopy and its interface with industry, endoscopy and surgery in gastroesophageal reflux disease, and several other topics.

OMED statutes

New statutes have been approved by OMED's governing council. These are intended to streamline OMED's activities and allow the organization to maintain its leadership role in the 21st century. The revised statutes are available on the OMED web site. OMED has made a concerted effort to maintain the integrity of the zonal representations, so that all areas of the world are represented at all levels of OMED.

OMED projects

Several OMED projects were listed in the last issue of *WGN,* and information about them can also be accessed on the web site. OMED is aiming to enhance its impact on world gastrointestinal endoscopy and is currently meeting with biomedical industry leaders to invite them to join in the effort to provide information, news, and support for gastrointestinal endoscopy. Several projects led by the various committee chairpersons are already underway.

Email news bulletin for individual members

WGN, published twice yearly with news about OMED and WGO-OMGE, is sent to approximately 40,000 people throughout the world. OMED is also intending to send interim news bulletins to individual members via email. To make this possible, the affiliated societies are being asked to send members' email addresses to the Executive Secretariat.

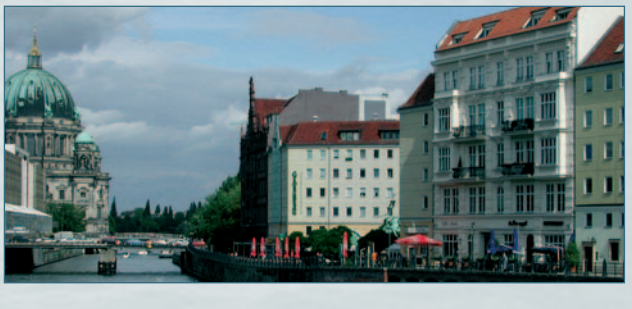
OMED Executive Secretariat
Medconnect GmbH,
Bruennsteinstrasse 10,
81541 Munich, Germany
Email: jenny.rasmussen@medc.de

UEGW in the heart of Europe

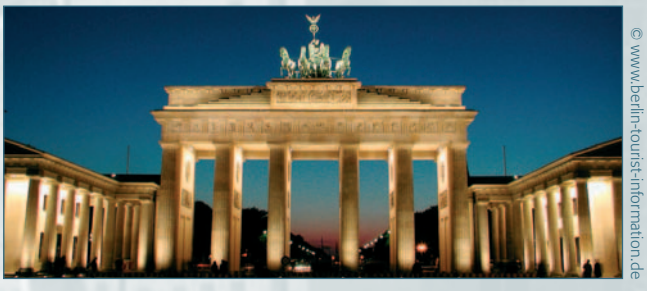
The United European Gastroenterology Week (UEGW) meeting is being held this year in Berlin on 21–25 October. The number of abstracts received this year was 2510, an increase over the previous year. This has allowed the scientific committee to raise the rejection rate, which now stands at about 35%, with a commensurate increase in scientific quality. The result is that there will be 335 oral presentations and 1256 poster presentations, supported by a balanced invited program. At least 50% of the program will consist of original research communications.

The program will include a broad range of topics, with particular emphasis on interdisciplinary symposia exploring the interface between different therapeutic modalities. For example, there will be a session on the management of common bile duct stones, including radiological, surgical, and endoscopic aspects. There will be a similar interdisciplinary symposium on acute upper gastrointestinal bleeding, which will again explore medical, surgical, endoscopic, and radiological interventions.

More original research and high-quality presentations



Colorectal cancer will also be an important theme, spearheaded by a plenary session providing both patient and clinician perspectives. There will be a symposium on colorectal polyps, putting the various pathologies into their clinical perspective. Another symposium will explore new preventive approaches to colorectal cancer, and yet another will cover the genetic implications of the disease. There will be updates on sex and the liver, drug-induced liver injury, and the management of viral hepatitis. New strategies for preventing liver fibrosis will also be discussed.



There will also be two new formats in Berlin, designed to stimulate debate during the meeting. The first focuses on clinical issues by way of case studies, particularly when diagnostic and therapeutic problems fall outside standard clinical guidelines. The other is a reintroduction of "poster rounds," to stimulate interaction between poster authors and delegates.

The city of Berlin offers a wide array of cultures and attractions, and has a long (and often troubled) history that is worth exploring. If you have time away from the congress, bear in mind that the city has no definite center, with pockets of attractions dotted all over. The densest array of sights lies to the east of the Brandenburg Gate, on either side of Unter den Linden. West Berlin has its attractions too, the most prominent of which is the Kaiser Wilhelm Gedächtniskirche, which was bombed out in 1943 and serves as a memorial to the Second World War. The nearby zoo and aquarium are also a major attraction for tourists. More information is available from the UEGW web site (www.uegw2006.de).

The current approach to Barrett's esophagus and dysplasia

Prateek Sharma, MD

Introduction

Barrett's esophagus (BE) is a metaplastic change in the esophagus that results in the replacement of the normal squamous-lined epithelium by intestinal metaplasia. The incidence of esophageal adenocarcinoma has rapidly increased in recent years, and BE has been found to be present as a precursor lesion in many of these cases. Patients with BE are thought to have an annual risk of developing esophageal cancer of 0.5% per year, substantially higher than that the general population, but the absolute risk of developing cancer in any individual BE patient is low.

New techniques for detecting dysplastic and cancerous tissue

Diagnosis of BE

The definition of BE has evolved over time. At a recent workshop sponsored by the American Gastroenterological Association in February 2003 (The BE Chicago Workshop), BE was defined as "a displacement of the squamocolumnar junction proximal to the gastroesophageal junction, with the presence of intestinal metaplasia." Endoscopic assessment of the extent of Barrett's esophagus (endoscopically visible esophageal columnar mucosa) depends on correctly locating esophageal landmarks such as the gastroesophageal junction (GEJ).

The Prague C and M criteria

An international Barrett's esophagus working group was recently convened in order to standardize the endoscopic measurement of Barrett's esophagus. The working group developed criteria for assessing the circumferential extent and maximum length of esophageal columnar tissue—the Prague C and M criteria. Using these criteria, circumferential Barrett's esophagus extending to 3 cm above the GEJ, with a tongue extending 5 cm above the GEJ, would be described as C3M5, while a tongue extending 3 cm above the GEJ with no circumferential extension would be designated C0M3.

For the detection of dysplasia in patients with BE, four-quadrant biopsies should be obtained for every 1–2 cm of the endoscopically recognized area of BE. Given that these biopsies are random in nature and sample only a small surface area of the BE segment, a number of new techniques (e.g., magnification endoscopy, spectroscopy, optical coherence tomography, etc.) are being evaluated as methods of increasing the yield for detecting dysplastic and cancerous tissue. Although these techniques are not yet ready for routine clinical use, they will dramatically change surveillance practices in BE patients in the future.

Treatment

Reasonable initial steps in the treatment of BE are to eliminate reflux symptoms and heal the esophagitis. The importance of reflux control was established by studies demonstrating that acid reflux predisposes to proliferation, and some studies have even shown that gastroesophageal reflux leads to the activation of protein kinase–regulated pathways, resulting in decreased apoptosis in cell lines exposed to acid. Although treatment with proton-pump inhibitors can heal and treat GERD in patients with BE, acid-suppression therapy has not yet clearly been associated with a reduction in the cancer risk. The option of surgery can be considered in some individuals with BE for treatment of their underlying gastroesophageal reflux disease. A recent meta-analysis concluded that the risk of adenocarcinoma in individuals with BE was not significantly reduced by antireflux surgical procedures.

Endoscopic treatments for BE have been developed more recently. Although the majority of the area of BE can be replaced by neo-squamous mucosa, persistent metaplastic tissue is often detected underneath the regenerated squamous tissue. Given the low risk of cancer in patients

with nondysplastic BE, or even with low-grade dysplasia, endoscopic ablation treatments cannot be recommended outside of study protocols in these patients. In patients with high-grade dysplasia, however, the risk of progression to cancer can be as high as 25–37%. In these patients, aggressive surveillance, early surgical resection, or endoscopic ablation may be considered. Endoscopic therapies, including mucosal resection and photodynamic ablation, hold promise, given that the alternative is esophagectomy. However, long-term data are lacking in this field, and only a small number of patients have been treated endoscopically. A recent report of endoscopic treatment with 5-year follow-up data on Barrett's esophagus with high-grade dysplasia and early carcinoma showed excellent complete remission rates (86%) after the 5-year follow-up period. The 5-year survival rate was 89%, with an overall complication rate of 15%. Recurrences, as well as metachronous lesions, were observed in 20% of the patients, indicating that close follow-up after endoscopic treatment is still required in these patients. Similarly, the results from a large multicenter randomized trial showed a significant decrease in cancer progression in HGD patients treated with photodynamic therapy (PDT). Such patients should probably be referred to high-volume and expert endoscopy centers in order to minimize the morbidity associated with endoscopic resection and ablation.

This paper is an excerpt from a paper presented during the Symposium of the International Digestive Cancer Alliance held in May 2006 during Digestive Disease Week in Los Angeles (the full paper can be viewed online at: www.worldgastroenterology.org).

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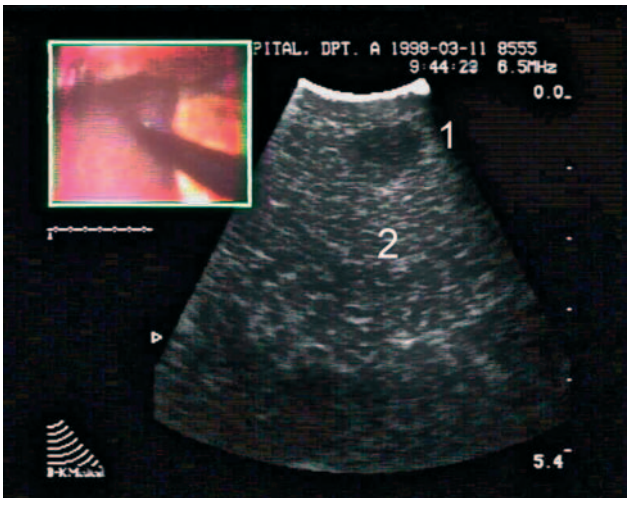
Dr. Gabriel Nagy, who was President of the Ninth World Congresses of Gastroenterology, held in Sydney in 1990, passed away at his home in Sydney on 18 July 2006 at the age of 87.

Born in Hungary, Dr. Nagy emigrated to Australia before the Second World War. He became a leader in the field of gastroenterology and endoscopy and had friends and colleagues throughout the world. His contributions to the World Congresses are remembered and greatly appreciated. He was regarded with great affection as a colleague and will be missed by all in the gastroenterology and endoscopy community.

Carcinoid tumors: management of hepatic metastases and carcinoid syndrome

Sharon M. Weber, MD



The liver is scanned from the anterior surface with 6 Mhz in frequency. The metastases are often hypoechoic with an irregular margin. Often a hypoechoic center and a hypoechoic halo can be seen. 1: 10 mm. Hepatic metastases, 2: Normal liver parenchyma

Although carcinoid tumors are indolent neoplasms, approximately 75% of patients present with metastatic disease. Because the metastases are primarily in the liver, a large proportion of patients will have carcinoid syndrome, due to the release of vasoactive mediators, including serotonin and tachykinins, into the systemic circulation. Carcinoid syndrome consists of flushing, diarrhea, bronchoconstriction, and valvular heart disease. These symptoms can result in severe limitations in the patient's quality of life. The goal of treatment for patients with metastatic carcinoid tumors is therefore twofold—palliation and prolongation of survival.

Surgical treatment

Curative intent. Surgical resection is the only potentially curative treatment option. Although various series have included both carcinoid and islet-cell tumors, many studies have suggested that there is no difference in the outcome between the two types of histology. There does appear to be a consensus that there is prolonged survival in patients who undergo hepatic resection, in comparison with other forms of therapy. In patients with resectable hepatic carcinoid tumors, complete surgical resection is therefore the treatment of choice.

Unfortunately, many of the surgical series are limited by relatively short follow-up periods. In one series with an extensive follow-up (median 81 months), the recurrence rate was 84% at 5 years and 94% at 10 years—demonstrating the need to develop effective forms of adjuvant therapy.

In addition to resection, another surgical option includes ablation—either radiofrequency ablation (RFA) or cryoablation. Either open or percutaneous ablation is possible. Large tumors (> 5 cm) and tumors in difficult locations (near the bile ducts) are not suitable for ablation treatment, even with open ablation.

The final surgical option is liver transplantation. Unfortunately, the 5-year disease-free survival rate is poor, at

less than 20%. Because of the high recurrence rate, the paucity of donor livers, and the morbidity associated with both the procedure and the immunosuppressants required after transplantation, liver transplantation should rarely, if ever, be considered for patients with metastatic carcinoid tumors.

Two key issues—palliation and prolongation of survival

Palliative intent. Generally, resection for palliative purposes can be achieved if > 90% of the tumor burden can be removed. Debulking of liver metastases by hepatic resection with or without ablation is associated both with symptomatic improvement in up to 80% of patients and with improved performance status.

Nonsurgical treatment

The intent in nonsurgical therapies is to achieve palliation of the symptoms.

Hepatic artery embolization (HAE) is an option for the treatment of carcinoid tumors, because of the hypervascular nature of these tumors. The procedure involves obtaining percutaneous access to the hepatic artery, with infusion of occlusive or chemotherapeutic agents into the vessels that feed the tumor. Up to 70% of patients have a reduction in tumor size and/or palliation of symptoms.

Medical treatment. *Chemotherapy.* In general, the response rates to conventional chemotherapy are poor in well-differentiated or moderately differentiated neuroendocrine tumors.

Octreotide. Somatostatin is a gastrointestinal hormone that inhibits neuroendocrine cell growth and hormone production by binding to somatostatin receptors on the tumor cell surface. Both short-acting and long-acting somatostatin analogs (octreotide and lanreotide, respectively) have been shown to be effective in controlling symptoms in up to 70% of patients, through a direct inhibitory effect on hormone production. Somatostatin analogs have been associated with stabilization of tumors for periods of up to 2 years. Unfortunately, the majority of neuroendocrine tumors eventually become refractory to treatment with somatostatin analogs, after a median interval of 12 months for carcinoid tumors and 3 months for islet-cell tumors.

Tumor-targeted radioactive therapy. Up to 70% of patients with carcinoid tumors have positive scans for metaiodobenzylguanidine (MIBG, a radioactive scan for neuroendocrine tumors), while an even larger number have positive octreotide scans. Radiolabeled MIBG and octreotide have therefore both been evaluated for the treatment of metastatic carcinoid tumors, with symptomatic improvement in 60% of patients after ^{131}I-MIBG and 80% of patients after ^{90}Y-octreotide.

Conclusion

Clinicians treating patients with metastatic hepatic carcinoid tumors have to address two key issues—palliation and prolongation of survival. In general, patients with resectable lesions should undergo surgical resection and/or ablation. If complete resection is not possible, palliative options include debulking surgery, hepatic artery embolization, chemotherapy, and treatment with somatostatin analogs.

This paper is an excerpt from a paper presented during postgraduate course held by the Society for Surgery of the Alimentary Tract in May 2006 during Digestive Disease Week in Los Angeles (the full paper can be viewed online at: www.worldgastroenterology.org).

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Chromoendoscopy

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Introduction

Chromoendoscopy involves the adjunctive use of chemical agents during gastrointestinal endoscopy, either to identify specific epithelia, to contrast or highlight subtle mucosal irregularities, or to tattoo a specific mucosal site. The agents have been classified as absorptive (vital) stains, reactive stains, and contrast (chromoscopy) stains.

Vital stains identify specific types of epithelium that have an absorptive capacity. Intestinal-type mucosa, such as intestinal metaplasia in the stomach or esophagus (Barrett's esophagus), absorbs some dyes, whereas the surrounding normal gastric columnar or esophageal squamous epithelium does not. When methylene blue is applied directly to these tissues, it is absorbed, allowing visual identification of an otherwise unrecognizable tissue type during endoscopy.

Reactive stains use a compound's capacity to change color, depending on the pH or other chemical characteristics of the environment. Congo red turns blue-black in the presence of acid, allowing endoscopic recognition of either acid-producing or acid-lacking areas of the gastric mucosa.

Contrast stains coat the surface of the gastrointestinal mucosa, highlighting the mucosal topography. Indigo carmine has been used in this way to identify and differentiate small polyps and inflammatory processes in the colonic mucosa.

Tattoos are permanent or semipermanent gastrointestinal mucosal stains that are injected into the mucosa in order to ensure precise repeat localization of a lesion at a subsequent endoscopic examination.

The most commonly used chromoendoscopy techniques are briefly described here—Lugol's staining of the esophagus, methylene blue staining of the esophagus and stomach and colonic chromoscopy with indigo carmine.

Lugol's staining of squamous esophageal mucosa

Lugol's solution (named after the Paris physician Jean Guillaume Auguste Lugol, 1786–1851) is a compound consisting of iodine and potassium iodide. The normal, nonkeratinized, squamous mucosa of the esophagus contains glycogen, which has an affinity for iodine-based compounds. The normal esophageal mucosa therefore avidly acquires iodine from Lugol's solution, producing a distinctive brown color. Lugol's solution has been used to accentuate the squamocolumnar border in order to identify Barrett's esophagus or to identify neoplastic squamous mucosa, which does not stain due to its reduced glycogen content.

Lugol's solution is usually applied as a 1–3% undiluted solution directly onto the esophageal mucosa, at a volume of 10–50 mL. The use of a "spraying" catheter greatly facilitates the application of Lugol's solution. One such spraying device is the Olympus washing pipe (Olympus PW-5L-1; Olympus America, Inc., Center Valley, Pennsylvania, USA). Staining is immediate, but lasts only from a few minutes up to an hour.

Methylene blue staining in nonabsorptive epithelium indicates metaplasia

Lugol's staining has been shown to improve recognition of the extent of Barrett's esophagus, as well as of dysplastic/neoplastic squamous epithelium.

Methylene blue staining of intestinal metaplasia in the esophagus and stomach

Methylene blue (methylthionine chloride) is a blue stain that is taken up into the cytoplasm of absorptive epithelium such as that in the small bowel and colon. The presence of staining in the normally nonabsorptive epithelium

of the stomach or esophagus indicates a metaplastic absorptive epithelium—i.e., intestinal. An absence of staining in the duodenal bulb indicates metaplastic nonabsorptive epithelium—i.e., gastric metaplasia.

As the stomach and small bowel are normally protected by a mucous layer, the mucus first has to be disrupted in order for the stain to be successfully applied. Mucus is a complex glycoprotein gel structure, dependent in part on disulfide bridges. The free sulfhydryl groups contained in *N*-acetylcysteine (Mucomyst) breaks down these disulfide bridges, leading to degradation of the "mucoid" cap. Once the mucus layer has been disrupted by the application of *N*-acetylcysteine, methylene blue can be applied and absorbed by actively absorbing epithelium.

Mucomyst is administered as a 10% solution, sprayed by a washing catheter at volumes of approximately 20 mL directly onto the mucosa. Mucomyst can also be given orally, but the larger volume required and the sulfurous odor and taste of the agent make this a less acceptable method of delivery for the patient.

A 0.5% solution of methylene blue is used, and approximately 20 mL is required. As residual mucus retains the stain, vigorous washing with 100–300 mL water is required to avoid artifactual staining. Staining is immediate; the stain starts to fade within 15–20 min, but may persist for up to 24 h.

Methylene blue is absorbed and excreted in the urine, causing a green-blue discoloration about which patients should be informed. No toxicity has been demonstrated for either agent when they are used in the fashion described above.

Indigo carmine contrast staining in the colon

Indigo carmine is a blue dye derived from the blue plant dye, indigo, and a red coloring agent formed from cochineal and alum. Indigo carmine is not absorbed and stays on the surface of the epithelium, acting as a contrast agent. The stain collects in surface grooves, sulci, and depressions, highlighting the surface. A 0.1–0.8% solution of indigo carmine at volumes of 20–200 mL is usually sprayed directly onto the colonic mucosa via a catheter. Indigo carmine is nontoxic and well tolerated.

This paper is an excerpt from a paper presented at a postgraduate course of the American College of Gastroenterology in 2005 (the full paper can be viewed online at www.worldgastroenterology.org).

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Bacterial overgrowth

Jack A. Di Palma, MD

Bacterial overgrowth is defined by an increased number of bacteria in areas of the gastrointestinal tract that usually do not provide an environment suitable for the colonization and proliferation of bacteria. The types of species that colonize the small intestine are altered in bacterial overgrowth. In healthy individuals, the small-bowel bacteria resemble the oropharyngeal flora, with Gram-positive aerobic organisms. In overgrowth, bacteria are mostly Gram-negative, including *Escherichia coli*; anaerobic bacteria, including *Clostridia* and *Bacteroides* species, also predominate.

Factors that influence small-intestinal bacterial proliferation include:

- Structural lesions
- Excessive bacterial load
- Motility
- Deficiency in host defenses

Obstruction to the outflow of luminal contents can occur at the sites of surgical anastomoses or with webs, adhesions, or strictures. Surgical diversions and blind loops or neoreservoirs, as in a continent ileostomy, predispose to the development of small-intestinal bacterial overgrowth. The jejunoileal bypass, once a widely used surgical procedure for patients with morbid obesity, created a long segment of diverted bowel and was often complicated by overgrowth. Diverticula and duplications are frequently colonized with colonic-type bacteria, leading to overgrowth.

Delayed transit of intestinal contents results in stasis. Overgrowth complicates intestinal pseudo-obstruction syndromes. The intestinal "housekeeper" migratory motor complex, when disrupted, is associated with bacterial overgrowth. Paralytic ileus also results in bacterial proliferation.

Important types of impairment of host defenses include:

- Acid suppression due to surgery or medication
- Hypochlorhydric disorders, such as pernicious anemia
- Immune deficiencies, particularly absence of secretory immunoglobulin A (IgA)
- Undernutrition, which can decrease gastric acidity and immune function

Conditions associated with small-intestinal bacterial overgrowth include:

- *Reduced gastric acid:*
  - Pernicious anemia
  - Atrophic gastritis
  - Gastric surgery
  - Medication (H_2-receptor antagonists, proton-pump inhibitors)
  - Neoreservoirs
- *Structural abnormalities:*
  - Small-bowel diverticula
  - Adhesions
  - Surgical anastomoses and diversions
  - Fistulas (coloenteric, gastrocolic)
  - Strictures
  - Absent or incompetent ileocecal valves
  - Webs
  - Neoreservoirs
- *Dysmotility syndromes:*
  - Diabetes
  - Acute enteric infection
  - Scleroderma
  - Intestinal pseudo-obstruction syndromes

Clinical presentations

The clinical manifestations vary. Diarrhea, anorexia, nausea, weight loss, and anemia are cardinal symptoms, but the nature of the small-bowel abnormality influences the presentation. Patients obstructed by stricture may have bloating and pain. Overgrowth in small-intestinal diverticula may present insidiously with metabolic derangements. The eventual clinical consequence of overgrowth, regardless of cause, is steatorrhea, leading to weight loss.

Malabsorption results in hypocalcemic disorders, night blindness, vitamin K deficiency, and osteomalacia. Cobalamin deficiency is common, with severe overgrowth causing megaloblastic and macrocytic anemia. Anaerobic bacteria compete for the uptake of cobalamin–intrinsic factor complex. Whereas luminal bacteria consume cobalamin, folic acid is a product of bacterial substrate fermentation. An important clinical observation in small-intestinal bacterial overgrowth is therefore the finding of low B_{12} and high folate levels.

Other micronutrient deficiencies include deficiencies of water-soluble vitamins (thiamine and nicotinamide) and decreased absorption of fat-soluble vitamins (vitamins A, D, E, and K).

Diagnosis

Small-intestinal bacterial overgrowth is confirmed by the demonstration of elevated numbers of small-bowel bacteria colonies and the replacement of oropharyngeal with predominantly colonic organisms. Because small-bowel intubation and aspiration for microbial analysis are cumbersome, overgrowth is considered in patients with predisposing factors and an appropriate history. Indirect testing may help substantiate the diagnosis.

Indirect testing helps substantiate the diagnosis

- *History:* prior surgery, medical conditions such as osteomalacia, night blindness, easy bruising, tetany.
- *Examination:* systemic disease—weight loss and malabsorption.
- *Laboratory:* hemoglobin (decreased), mean corpuscular volume (increased), vitamin B_{12} (decreased), folic acid (increased), fecal fat (increased).
- *Tests:* Schilling test with intrinsic factor (decreased), ^{14}C-glycocholic acid (increased), ^{14}C-D-xylose (decreased), hydrogen testing with glucose or lactulose, and jejunal aspirate for bacterial colony counts and strain identification.

Jejunal intubation for aspiration with bacterial colony counts can provide a definitive diagnosis by showing counts $> 10^5$/mL with colonic organisms. Jejunal intubation can be carried out endoscopically, and protected catheters can be used to obtain reliable aspirates.

Radiolabeled breath tests using glycocholic acid or xylose have been used to diagnose overgrowth. Glycocholic acid is released by bacterial deconjugation of radiolabeled bile acids. Xylose is catabolized by Gram-negative aerobes and is absorbed in the proximal small bowel.

Scintigraphic and hydrogen breath tests are attractive alternatives to intubation tests for bacterial overgrowth. Hydrogen testing—although it is simple, inexpensive, and nonradioactive—does not have sufficient sensitivity or specificity.

Treatment for bacterial overgrowth includes surgery to correct an abnormality or prokinetic agents. Patients need guidance in aggregate nutrition and supplements. Antibiotics are usually given. Surgery is often impractical, and the standard stimulatory agents are not very effective. The long-acting somatostatin analog, octreotide, has been shown to stimulate motility in normal individuals, and it reduces overgrowth and improves symptoms in scleroderma.

The optimal choice of antibiotic and dosage regimen has not been determined. Some investigators prefer broad-spectrum antibiotics such as cephalosporins, tetracyclines, or chloramphenicol. Others recommend narrower-spectrum drugs that are active against anaerobes, such as metronidazole, or against aerobes, such as fluoroquinolones. A recent study showed efficacy with either norfloxacin or amoxicillin–clavulanic acid.

A single 7–10-day course is usually sufficient, but recurrences are frequent. Some patients require repeat treatment over weeks or months; others need continuous therapy.

Probiotics

Saccharomyces boulardii is a probiotic used in the treatment of pseudomembranous colitis that is effective in the treatment of bacterial overgrowth in children. Because antibiotics have potential side effects, probiotic therapy is attractive. A recent study in adults, however, showed no efficacy of *Saccharomyces boulardii* in the treatment of overgrowth.

This paper is an excerpt from a paper presented during a postgraduate course held by the American College of Gastroenterology in 2005 (the full paper can be viewed online at: www.worldgastroenterology.org).

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The DAVE Project: a web-based digital atlas of video education

Brenna C. Bounds, MD and Peter B. Kelsey, MD

Introduction

Endoscopy is a visual science, and in contrast to static images, video more accurately captures the qualities of shape, texture, and three-dimensional configuration. In May 2001, we first explored the possibility of creating an Internet-accessible digital atlas of video endoscopy. Our initial goal was to help design a system that could efficiently capture and edit large pieces of video data. The software program, developed in cooperation with Pentax Medical, is now marketed as MPS (Motion Picture Studio™).

Initially, the members of the Gastrointestinal Unit at Massachusetts General Hospital generated more than 500 high-quality teaching video clips, highlighting endoscopic findings and interventional maneuvers. Our first collected EUS videos were compiled as a DVD, which was awarded the 2002 Audiovisual Award of the American Society for Gastrointestinal Endoscopy (ASGE). The collected teaching videos on endoscopic retrograde cholangiopancreatography (ERCP) and duodenoscope-assisted cholangiopancreatoscopy (DACP) were similarly compiled as a DVD, which received the 2003 ASGE Audio Visual Award.

The DAVE Project

The Digital Atlas of Video Education (DAVE) was then formally established as the DAVE Project. The web site is designed for access free of charge. The visitor can not only play selected clips, but can also copy and download the clips free of charge for educational use. A cataloging system has been implemented to classify each video endoscopic clip by procedure, diagnosis, anatomical location, and therapeutic maneuver. An index has been set up to provide a search facility using more than a thousand keyword terms, classified according to maneuver, location, finding, and histology, or alternatively allowing selection of an organ system and viewing of all the video clips associated with it.

Each video clip is classified by procedure, diagnosis, anatomical location, and therapeutic maneuver

As video clips contain a spectrum of special information, icons have been developed to indicate which clips contain various types of educational material. For example, a movie camera indicates the presence of a video clip, while a microscope and X-ray box indicate the presence of pathology and radiology images.

As the project grew, advisory panels were developed to provide a formal peer-review process for each submission. Video clips were reviewed for video and audio quality, as well as clarity, accuracy, and educational value. Clinical lecture series were added in the form of "Clinical Journal Clubs" and "Clinical Grand Rounds," along with a "What's New?" section highlighting the most recent additions to the site. Outside contributions increased, and a new section devoted to gastrointestinal pathology was added.

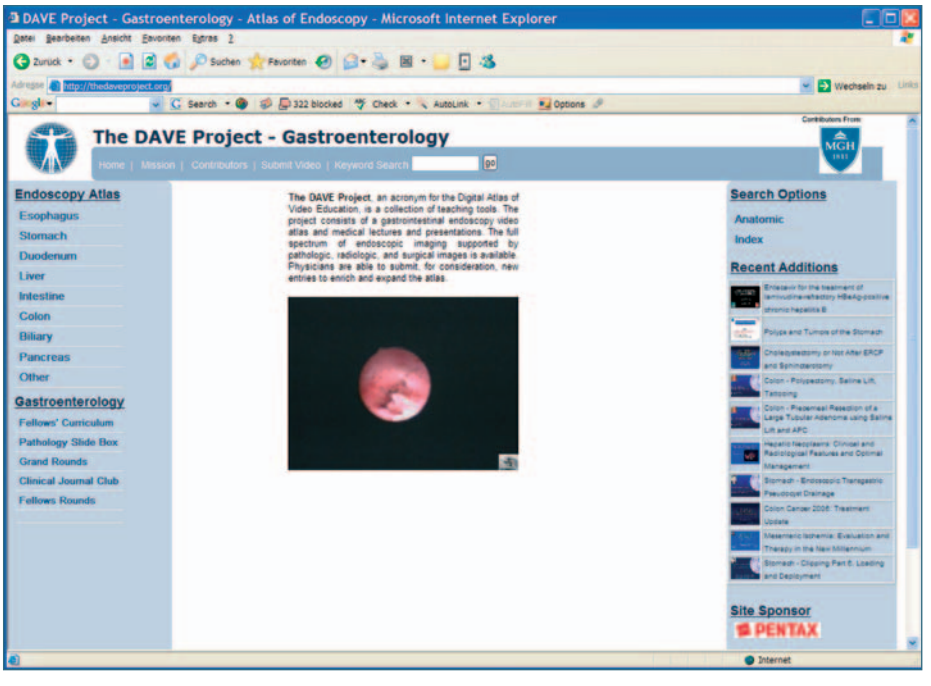
The DAVE Project traveled the globe to encourage the use of this free educational repository and further contributions to it. At present, more than half of the content has been received from over 20 medical centers around the world. We have added a section on "Techniques in Endoscopy," featuring contributions from world leaders in interventional endoscopy. In addition, a core endoscopy curriculum is now in place. The core curriculum, written by the four major gastroenterology societies in the United States—the ASGE, the American Association for the Study of Liver Diseases (AASLD), the Society of American Gastrointestinal Endoscopic Surgeons (SAGES), and the American Gastroenterological Association (AGA)—has been distilled into an outline form and includes Grand Rounds and Clinical Journal Club lectures.

Conclusion

The DAVE Project is a free-access, nonprofit educational resource that represents the first online educational atlas of medicine, integrating digital endoscopic imaging with

relevant surgical, pathologic, and radiologic data, as well as clinical grand rounds and journal clubs. Internet-submitted, peer-reviewed contributions have significantly expanded the size and depth of the DAVE Project. As the Project approaches the end of its second year, traffic on the site is vigorous and is continuing to grow. Viewers are successfully downloading images and video clips to use for teaching purposes. The Internet interface is seamless, and the video clip resolution is excellent. The DAVE Project is now a valuable educational tool for the physician, fellow, and student.

- http://thedaveproject.org



Disclosure

The DAVE Project is sponsored in part by an unrestricted educational grant from Pentax Medical.

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Epidemiology of inflammatory bowel disease in Africa and the Middle East

Hatim M.Y. Mudawi, MD

Introduction

Inflammatory bowel disease (IBD) includes ulcerative colitis and Crohn's disease—both chronic inflammatory disorders of the gastrointestinal tract. Treatment does not completely eliminate the substantial morbidity associated with the condition. This is of importance to us in the developing world, as the disease develops in patients at a young age, has a considerable impact on their health status, and may affect their earning capacity and the socioeconomic status of the patients and their families. Until recently, it was considered a disease of industrially developed countries and was thought to be rare in developing countries, and even more so among black Africans. Currently, however, the incidence in the developed countries has stabilized, while it is increasing in the developing world.

A European collaborative study on IBD by S. Shivananda and J. Lennard Jones found that 63% of cases of IBD consisted of ulcerative colitis, 32% of Crohn's disease, and 5% of indeterminate colitis. This article briefly outlines the epidemiology of IBD in Africa and the Middle East.

Studying the epidemiology of IBD in our area is difficult because of a lack of medical personnel, a lack of specialized diagnostic facilities, inadequate medical records, and the high prevalence of infectious causes of diarrhea with blood. A comprehensive literature search was carried out using electronic databases—Medline, Embase, and African Index Medicus. A total of 67 publications were identified; of these indexed studies, only 41 addressed the epidemiology of the disease, while the rest were mostly case reports. The majority of these epidemiological reports were retrospective hospital-based studies, which generally underestimate the incidence and prevalence of the disease while overestimating disease severity and mortality rates, as patients with mild disease may not reach specialized centers.

Ulcerative colitis

One of the earliest studies on the prevalence of ulcerative colitis, conducted in South Africa in 1980, identified 13 cases of South African blacks with ulcerative colitis during the period 1976–79. Most of the patients were urbanized, educated, and upper social class women who were consuming a Westernized diet. It was thought that the rarity of the disease in this population was due to genetic factors and the type of food consumed. Several studies from South Africa, Kuwait, and Oman have indicated that the incidence is similar to that in southern European countries. The disease occurs more often in the second and third decades of life, and tends to be more prevalent among females. Some countries have reported a high incidence of extraintestinal manifestations, reaching more than 30%. The incidence of colorectal cancer and the mortality are generally low (Table **1**).

Crohn's disease

The earliest data on Crohn's disease are from Groote Schurr Hospital, Cape Town, South Africa. It is interesting

Table 1. Incidence and mortality of colorectal cancer

Country	Ulcerative colitis			Crohn's disease		
	Incidence/ 100 000	M : F ratio	Colon cancer	Incidence/ 100 000	M : F ratio	Colon cancer
South Africa	0.6–5.0	1 : 1.6	0.5%	0.3–2.6	1 : 2.2	–
Saudi Arabia	–	1 : 1.1	–	0.94	1 : 1.3	–
Iran	–	1 : 1.3	–	–	1.3 : 1	–
Kuwait	2.8	1.1 : 1	–	0.45	1.8 : 1	–
Oman	1.35	1 : 1.6	–			
Sudan	–	1.6 : 1	3%	–	1.4 : 1	8%
Qatar				–	1.5 : 1	–

to note that there was an increase in the number of cases from 45 patients during the period 1970–74 to 134 patients during the period 1980–84. This rise in incidence was also observed in studies in Saudi Arabia, where the incidence of the disease rose from 0.32/10^5 in the 1980s to 1.66/10^5 in the 1990s. The disease was more prevalent in males in most countries, and involved the ileocolonic region in 78% of cases. Surgical intervention was needed in more than 60% of patients in some countries. The colorectal cancer and mortality rates were relatively low.

Crohn's disease: similarity to intestinal tuberculosis creates diagnostic dilemma

Several studies in South Africa, Saudi Arabia, Kuwait and Sudan addressed the issue of similarity between Crohn's disease and intestinal tuberculosis; many of these studies describe patients presenting with diarrhea and radiographic features of terminal ileal disease who failed to respond to antituberculous therapy and were later diagnosed as having Crohn's disease. Tuberculosis has a predilection for the ileocecal area, which is rich in lymphatic tissue; the endoscopic appearance of colonic tuberculosis is indistinguishable from that of Crohn's disease, with ulcers surrounded by normal mucosa, strictures, and skip lesions. The presence of a caseating granuloma on tissue histology in tuberculosis is one of the factors differentiating between the two diseases. The similarity between Crohn's disease and intestinal tuberculosis creates a great diagnostic dilemma, especially in Africa, with the current rise in HIV/AIDS cases, as there is a high incidence of tuberculosis in these patients.

Conclusion

Ulcerative colitis is the cause of the disease in the majority of patients with IBD, ranging from 57% in South Africa to 88% in Iran; it is more common in females, while Crohn's disease is more common in males. The peak age of onset is similar to that in Europe. The low incidence of colorectal cancer in patients with IBD may be explained by the reduced life expectancy in developing countries and the relatively limited period of follow-up in the studies that have examined the topic.

In conclusion, the studies available are few and information is incomplete, as seen above. There is a need for a multicenter prospective study to determine the real incidence and outcome of IBD in our region in comparison with other regions.

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WGO-OMGE practice guideline highlights: *Helicobacter pylori* in developing countries

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Summary and methodology

Summary. *Helicobacter* is a genus of Gram-negative, microaerophilic bacteria of the family Spirillaceae, consisting of motile, spiral organisms with multiple-sheathed flagella. *H. pylori* (Hp) is common and infects about half the world's population; the prevalence is high in developing countries and lower, but with considerable variability, in the developed world.

In developing countries, Hp infection is a public-health issue. The high prevalence of the infection requires the development of public-health interventions. Vaccination with a treatment vaccine is probably the only strategy that would make a decisive difference in the prevalence and incidence worldwide. However, such a vaccine is still not available, and one short-term approach would therefore be to follow the same strategies as for developed countries.

Provided that resources allow it, a test-and-treat strategy is preferable for those at risk for peptic ulcer disease or gastric cancer or for those with serious symptoms of dyspepsia and indigestion.

Hp eradication treatment uses either triple therapy, with a proton-pump inhibitor (PPI) and two antibiotics, or quadruple therapy (PPI + two antibiotics + bismuth) in countries in which bismuth is available. For both quadruple therapy and triple therapy, cheap generic antibiotics can be used; both forms of treatment are similarly effective and both give very high eradication rates.

The duration of treatment is still somewhat controversial, as no large differences in the outcome are observed between 14, 10, and 7 days' therapy, while the cost differences may be substantial.

Antibiotic resistance is high in developing countries, where high-quality generics may be forced out of the market by cheap fake medicines.

Methodology. This guideline is based on both consensus and evidence. Extensive searches of the published literature for systematic reviews, meta-analyses, consensus statements, and evidence-based guidelines were carried out in Medline, Embase, Cinahl, the Cochrane Library, DARE, and the National Guidelines Clearing House. The results were filtered by a review team of experts and adjusted when necessary to take account of local circumstances and patient values.

WGO-OMGE always tries to take into account the resource constraints that are often found in developing countries. Cascades—different diagnostic and management options—are used to take account of local resource constraints.

Epidemiology

Key points:

- The global prevalence of Hp is more than 50%.
- The prevalence of Hp in developed countries is declining.
- The prevalence of Hp in developing countries is increasing.
- The prevalence of Hp may vary significantly within and between countries.

Global variation (Tables **1**, **2**). Globally, different Hp strains are associated with differences in virulence, and these play a key role in the development of disease, along with host and environmental factors. This interplay between recognized risk factors subsequently leads to differences in the expression of disease.

Age, ethnicity, sex, geography and socio-economic status are all important factors that influence the incidence and prevalence of Hp infection. The overall prevalence is low in developed countries and high in developing countries, where socioeconomic deprivation contributes to the infection of children early in life. Within countries, there may be wide variation in the prevalence between more affluent populations and deprived and overcrowded populations.

The transmission of Hp is largely by the oral–oral or fecal–oral routes. The lack of proper sanitation, safe drinking water, basic hygiene, and poor diets and overcrowd-

ing all play a role in determining the overall prevalence of infection.

Table 1. *H. pylori* infection throughout the world

Mexico, Central/ South America	70–90%
Africa	70–90%
Asia	70–80%
Eastern Europe	70%
Western Europe	30–50%
United States and Canada	30%
Australia	20%

Diagnosis of *H. pylori*

- ^{13}C (preferred) and ^{14}C (less so) urea breath tests (UBTs) are recommended for the diagnosis of Hp before treatment.
- Serology is less accurate and does not identify active infection.
- UBT is the preferred test to confirm eradication.
- UBTs should not be performed within 2 weeks of PPI therapy or within 4 weeks of antibiotic therapy.
- The stool antigen test is an excellent alternative, but is not often used.
- Finger stick tests are rarely used and are not recommended for clinical application in practice, because of poor accuracy.

Table 2. Prevalence of *H. pylori* in developing countries

Country/region	Adults (> 21)	Children
Africa		
Ethiopia	> 95%	48% (2–4 years) to 80% (6 years)
Gambia	> 95%	95% (5 years)
Nigeria	91%	82% (5–9 years)
South Africa	83%	n/a
Asia		
Bangladesh	> 90%	58% (0–4 years) to 82% (8–9 years)
China	86%	68% (3–12 years)
India	88%	22% (0–4 years) to 87% (10–19 years)
Siberia	85%	30% (5 years) to 63% (15–20 years)
Sri Lanka	72%	67% (6–19 years)
Middle East		
Egypt	90%	50% (3 years)
Jordan	82%	
Libya	94%	50% (1–9 years) to 84% (10–19 years)
Saudi Arabia	80%	40% (5–9 years)
Turkey	80%	64% (6–17 years)
Central America		
Guatemala	65%	51% (5–10 years)
Mexico		43% (5–9 years)
South America		
Bolivia		54% (5 years)
Brazil	82%	30% (6–8 years) to 78% (10–19 years)
Chile	72%	36% (3–9 years)
Peru		52% (3 years)

What are the principal diagnostic tools for identifying Hp? How cost-effective are they in a low resource setting? What would an acceptable choice of options be to achieve broadly similar diagnostic ends?

Diagnostic testing for Hp is usually undertaken at the time of endoscopy, when biopsies can be taken, or by tests not requiring endoscopy.

The techniques may be *direct* (culture, microscopic demonstration of the organism) or *indirect* (using urease activity or an antibody response as a marker of disease). The choice of test depends on issues such as cost, availability, clinical situation, population prevalence of infection, the pre-test probability of infection, and current treatments such as proton-pump inhibitors and antibiotics, which may influence the test results.

Serological tests (sensitivity 92%, specificity 83%) perform less well than urea breath tests (sensitivity 95%, specificity 96%) and stool antigen tests (sensitivity 95%, specificity 94%). The resultant lower positive predictive value (64% vs. 88% or 84%, respectively) leads to concerns about the potentially unnecessary use of antibiotics when serology testing is used and gives a false-positive result.

It is important to emphasize here that breath testing identifies active infection, while serology tests detect only a "footprint" and not an active infection.

Good practice point:

- Ensure that patients undergoing a breath test, stool antigen test, or endoscopy are free from treatment with either a PPI or histamine2-receptor antagonist (H2RA) for a minimum of 2 weeks before testing.

In low-prevalence areas, serology works less well, so that a negative test has more value than a positive test. In high-prevalence areas, a positive serology test may be acceptable.

Good practice point:

- Dyspeptic patients should be considered for early endoscopy on the basis of the local incidence of gastric cancer, the presence of alarm features such as weight loss, bleeding, and anemia, and the patient's age of presentation. The decision for early endoscopy will depend on the age-specific incidence of gastric cancer in the particular country/region.

Key symptoms:

- Epigastric pain
- Bloating
- Early satiety
- Bleeding
- Nausea
- Vomiting
- Appetite loss

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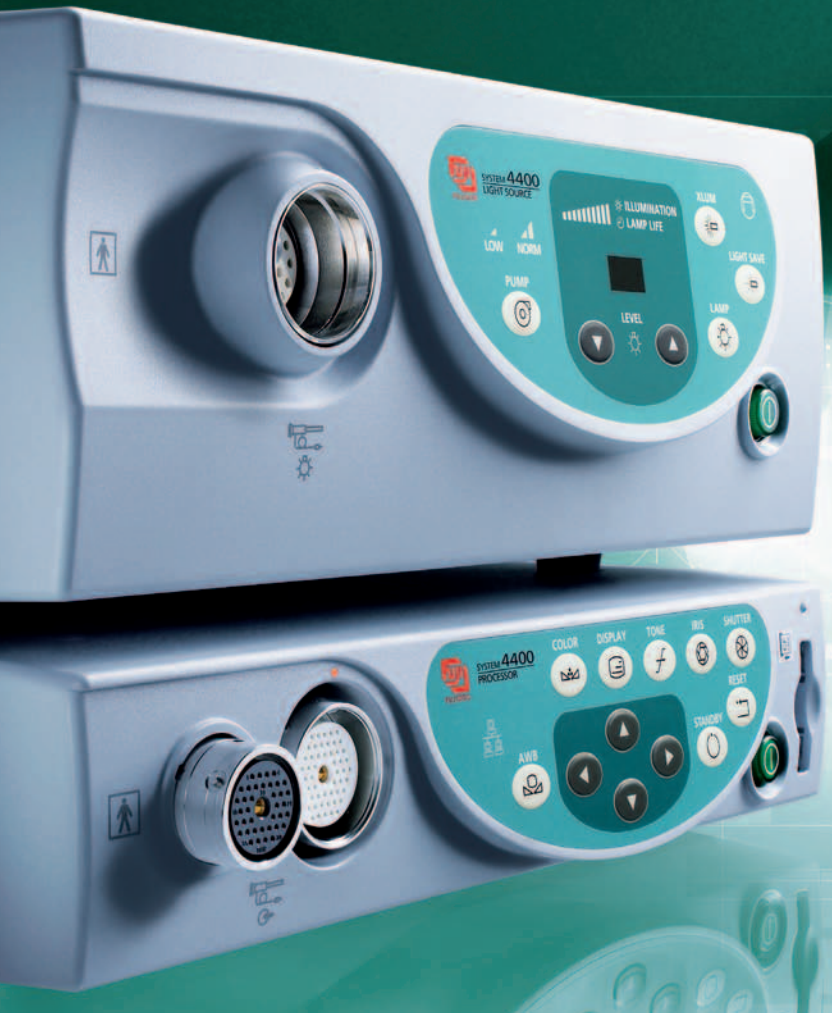

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Common ulcer symptoms include gnawing or burning pain in the epigastrium when the stomach is empty, between meals and in the early morning hours, but symptoms can also occur at other times. Pain may last from minutes to hours and may be relieved by eating or by taking antacids. Less common ulcer symptoms include nausea, vomiting, and loss of appetite. Bleeding can also occur; prolonged subclinical bleeding may cause anemia with weakness and fatigue, and frank hematemesis and or melena may also occur.

One problem with diagnosing Hp is that there are several conditions with similar symptoms that may result from the infection. A rigorous process of identification and exclusion is required. In developed countries, the use of the test-and-treat strategy for younger patients presenting with dyspepsia is declining, since fewer younger patients are infected with Hp. A 20% infection prevalence appears to be the critical threshold below which testing with this strategy is not cost-effective.

Starting an anti-secretory drug, usually a PPI, is preferred. For those aged 50–55 years of age and older, endoscopy and testing for Hp infection is still a logical approach.

In developing countries in which peptic ulcer rates or cancer rates are high, an empirical test-and-treat approach or endoscopy is more appropriate than starting treatment with a PPI.

Diagnostic tests for Hp. *Key points:*

- Endoscopy with rapid urease testing (RUT) or culture are key standards.
- There is no single gold standard.
- Breath tests with ^{13}C and ^{14}C are effective; ^{13}C is preferable.
- Serology does not determine active infection.
- Serology or finger stick tests may be a cheap option in low-resource settings, but are not always accurate enough for clinical application in developed countries.
- Stool antigen tests are comparable to breath tests, but are less often used.

The gold standard is endoscopy with RUT, but it is not practical to carry out endoscopy in all patients, and endoscopy is not readily available in some less developed countries. Cost-effectiveness considerations play a major role in all settings. In low-resource settings, precision and sensitivity considerations may sometimes be traded against the cost and availability of resources.

Maastricht III diagnostic options. A large group of 50 specialists from 26 countries, the European *Helicobacter pylori* Study Group (EHSG), met in Florence in 2005. The meeting was named the Maastricht III meeting, after the town in the Netherlands in which the first EHSG meeting had been held in 1996. At this consensus meeting, it was agreed that the UBT and stool antigen tests were the preferred noninvasive diagnostic tests. It was agreed that certain serological tests with a high accuracy can also be used, although testing for active Hp infection should use either the stool antigen test or a UBT.

Cascade of diagnostic options for Hp in developing countries:

- Endoscopy with RUT or culture.
- ^{13}C UBT (preferred) or ^{14}C UBT (not in children).
- Stool antigen testing (effective but not used much outside France).
- Serology (does not distinguish between past and present infection).
- In very high-prevalence low-resource areas, do nothing and assume infection.

Differential diagnosis. Dyspeptic symptoms may be due to a number of causes other than Hp infection. In different parts of the world, Hp is associated with different conditions. For example, giardiasis (a parasitosis) can produce similar symptoms.

Management of *H. pylori* infection (Table 3)

Key points:

- Both quadruple and triple therapies give very high eradication rates.
- Generic antibiotics can be used for both quadruple therapy (PPIs + antibiotics + bismuth) and triple therapy.
- Metronidazole and clarithromycin resistance reduce eradication rates.
- Time should be taken to explain the regimen to the patient, including what adverse events to expect, suggesting that the patient should choose a 14-day period in which he or she can take the treatment without it interfering with other important things in life (such as birthdays, weddings). This will improve compliance and the success of eradication treatment.

Good practice point:

- Treat all patients who test positive, but do not test a patient if you do not intend to treat.

Table 3. Indications for the eradication of *H. pylori* in Hp-positive patients.

▶ Dyspepsia
▶ Duodenal ulcer
▶ Gastric ulcer
▶ Complicated peptic ulcer disease
▶ Gastric MALToma (MALT lymphoma)
▶ Atrophic gastritis
▶ Post gastric cancer resection
▶ Patients with first-degree relatives with gastric cancer
▶ Patient's request

An Hp eradication regimen should achieve at least an 80% eradication rate. Current eradication treatments can be de-

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fined as one of the following regimens, given for at least 1 week:

- PPI triple therapy (PPI plus two of the following; amoxicillin, clarithromycin, metronidazole).
- Triple therapy based on H_2-receptor antagonists (H2RAs; H2RA plus two of the following; amoxicillin, clarithromycin, metronidazole).
- Bismuth triple therapy (Bismuth salt and a nitroimidazole with either amoxicillin or tetracycline).
- Bismuth quadruple therapy (as bismuth triple therapy, but with a PPI in addition).

The aim of Hp eradication is to reduce the lifetime risk of peptic ulcer disease and, possibly, gastric cancer. Patients with active gastric or duodenal ulcer or a documented history of ulcer should be tested for Hp infection and treated if found to be infected. This is especially true for those taking nonsteroidal anti-inflammatory drugs (NSAIDs) or who require long-term NSAID treatment. First-degree relatives of those with a history of gastric cancer should also be tested. Testing for and treatment of Hp infection are recommended for patients with low-grade gastric MALT lymphoma and in patients who have undergone resection of early gastric cancer.

Repeat testing after treatment to confirm eradication may be prudent for patients with bleeding or otherwise complicated peptic ulcer disease and those taking NSAIDs. Pediatric patients who require extensive diagnostic workup for abdominal symptoms should be evaluated by a specialist, who might consider testing for Hp infection. However, there is no place for routine Hp testing in children with recurrent abdominal pain of childhood.

It is uncertain at what stage in the natural history of the infection eradication of Hp can prevent gastric cancer. There may be a point of no return before which eradication is successful in preventing later development of gastric cancer. The appearance of mucosal precursor lesions such as intestinal metaplasia (IM) and dysplasia may prove to be this "point of no return." Once these precursor lesions have appeared, Hp eradication may no longer prevent progression to gastric cancer.

The management of Hp infection in areas with a high prevalence of infection should be similar to that in low-prevalence areas. In high-prevalence areas with limited resources, however, a trial of Hp eradication may be used in an appropriate clinical setting. Due to the high cost of medications, alternatives to PPI triple therapy combinations using generics such as furazolidone may have a place.

Maastricht III and other options. Overall, the Maastricht III treatment options are preferable. However, a number of other treatment options have been recommended by different consensus groups around the world. These can be considered as alternative or complementary approaches. There are many factors that need to be taken into account when considering a particular treatment, and these factors may vary in different regions of the world—for example, the availability of bismuth, the prevalence of Hp infection, the prevalence of gastric cancer, resistance to antibiotics, and the availability of endoscopy.

Quadruple versus triple therapy. Bismuth availability is a key factor. Maastricht III shows that eradication rates and confidence intervals for bismuth-based quadruple therapy and standard triple therapy are broadly similar; cheap generic antibiotics may be used. However, quadruple therapy is more difficult to take than triple therapy, and compliance may pose a problem.

Availability of bismuth. Bismuth is not available in all countries. Bismuth has been used for years as a medicine (tripotassium dicitratobismuthate), often in combination with antibiotics. It can also be found as bismuth oxide in hemorrhoid creams and in ointments, as bismuth subgallate. In the USA and several other parts of the world, oral bismuth is available as bismuth subsalicylate (Pepto-Bismol) and is available without prescription.

Availability of generics. PPI brand names are expensive, and good-quality generics can be used. However, in developing countries especially, high-quality generics may be forced out of the market by cheap fake medicines.

Risks of NSAIDs. Maastricht III cautions that the risk with Hp infection and NSAIDs in peptic ulcer disease is complex: Hp and NSAIDs independently and significantly increase the relative risk of peptic ulcer to 1.79 and 4.86, respectively; the relative risk of ulcer bleeding increases to 6.13 when both factors are present.

The results of Hp eradication in NSAID users are conflicting. It may depend on when Hp eradication therapy is given before or after NSAID use and on whether or not NSAID use is chronic. Patients receiving long-term aspirin administration who have ulcer disease and a history of bleeding should be tested for Hp infection, and if positive should be given eradication therapy.

Compliance. Taking a combination of three or four different drugs two to four times a day for up to 14 days—sometimes with a likelihood of side effects such as malaise, nausea, and diarrhea—requires determination, and it is advisable to take time to counsel the patient and explain the treatment, in order to ensure appropriate expectations and achieve the best compliance and outcome. The results of the treatment may well be proportional to the amount of time a physician takes to talk to the patient and explain the treatment approach.

Good practice point:

- One should take time to counsel the patient and explain the treatment, and appropriate expectations should be established when prescribing complicated drug regimens such as quadruple therapy. This will improve the compliance and outcome.

Treatment approaches.

Good practice point:

- Always emphasize that successful eradication depends on good compliance with the treatment regimen.

Maastricht III Florence consensus report, March 2005 (Table **4**). Efficient Hp eradication is necessary for good clinical management of Hp infection. Quadruple and triple therapies are the preferable first-line therapies. The choice of a first-line therapy is based on the availability of bismuth and on the prevalence of metronidazole and clarithromycin resistance.

Table 4. The Maastricht III consensus report recommendations

Treatment options	
Quadruple therapy	PPI + bismuth + two antibiotics
Triple therapy	PPI + clarithromycin + amoxicillin (or metronidazole)
Rescue therapy	To be based on antimicrobial susceptibility testing

Antimicrobial resistance continues to be the main reason for treatment failures. Treatments given for 14 days show a 12% advantage over 7-day therapy. However, cost considerations and compliance issues have tended to favor a 7-day period of therapy.

Antibiotic resistance is high in developing countries.

Triple therapy is given twice daily in populations with a clarithromycin resistance < 20%. An alternative triple therapy consisting of a PPI with clarithromycin and metronidazole can be given in populations with a metronidazole resistance < 40%.

The Maastricht III meeting agreed that Hp eradication does not cause gastroesophageal reflux disease (GERD). Maastricht III also recognized that the burden of gastric cancer is increasing, particularly in developing countries as populations live longer, and that eradication of Hp infection has the potential to reduce the risk of gastric cancer.

Summary of treatment approaches by different (consensus) groups. Worldwide, many Hp consensus groups have produced or are updating guidelines for the management of Hp infection. A review of the principal publications shows that:

- All groups recommend triple therapy with one of a PPI + two antibiotics (usually clarithromycin + amoxicillin) as the preferred approach.
- Quadruple bismuth-based therapies are similarly effective.
- Antibiotics must be chosen on the basis of known antibiotic resistance.
- Suggestions for the treatment duration vary from 7 to 14 days, and this issue is still controversial and unresolved.

There is a bewildering range of alternative antibiotic combinations. A choice should be based on available evidence and resources and on local preferences, costs, and values.

Antibiotic resistance throughout the world:

- Clarithromycin: 5–25%
- Metronidazole: 50–80% in developing countries
- Tetracycline: 0–5%
- Amoxicillin: 0–1%

Good practice point:

- In the case of treatment failure, drug sensitivity testing is advised in order to avoid the use of antibiotics to which Hp is resistant.

Triple therapy with a PPI and amoxicillin plus clarithromycin may fail due to resistance to clarithromycin. Resistance to metronidazole is also significant, although to a lesser extent. Resistance to tetracycline, fluoroquinolones, and rifamycins is also an emerging issue.

Figure **1** presents a western European perspective.

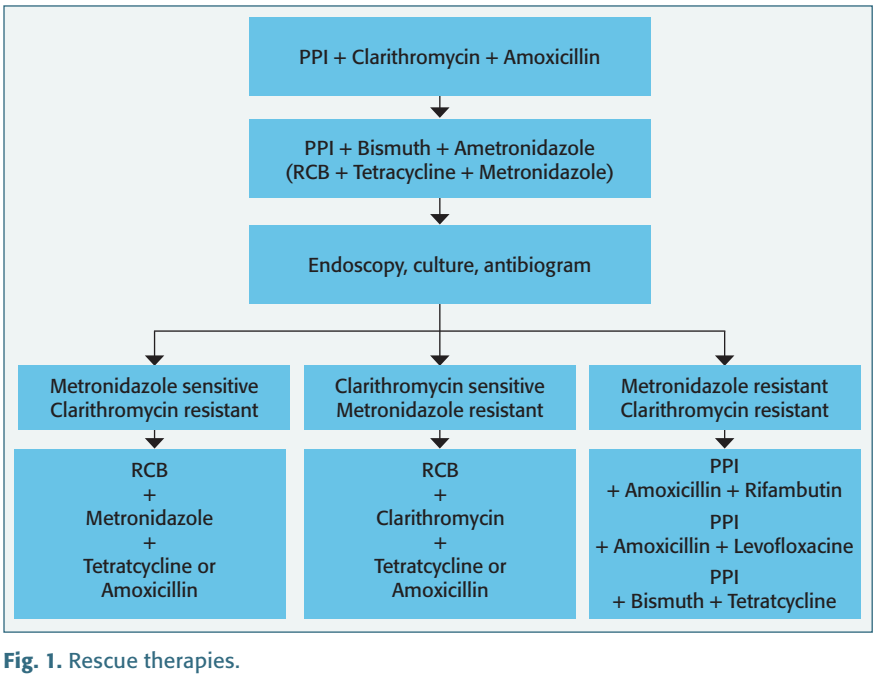

Fig. 1. Rescue therapies.

Prevention. Currently, a vaccine is not available. Since the exact source of Hp infection is not yet known, it is difficult to make recommendations for avoiding the infection. In general, however, it is always wise to wash hands thoroughly, to eat food that has been properly prepared, and to drink water from a safe, clean source; in children, overcrowding should be avoided and children should not share a bed.

Screening for *H. pylori* infection

Key points:

- The debate about screening for Hp infection as part of a periodic health examination is growing in importance in some developed countries.
- The potential for a screening program is of particular interest and importance in countries with a high incidence of gastric cancer.

The question of whether Hp infection should be sought out and eradicated in people who do not present with symptoms is an important one. Detection when there are no symptoms is especially important in developing countries in which there is a high incidence of gastric cancer. Most consensus statements, guidelines, and reviews have focused on the treatment of patients who present with a clinical problem. But is this cost-effective?

Should consideration be given to searching for and detecting infection in the context of a public-health program? There is certainly no evidence that Hp eradication is justified in Africa in asymptomatic individuals with a high prevalence but low risk.

The discovery of Hp infection and the observation that it is responsible for the development of chronic gastritis with atrophy and intestinal metaplasia has raised the possibility that this organism is a necessary contributor to the carcinogenic process in most cases of gastric cancer. Early nested epidemiological studies confirmed that infected individuals had a three to six times greater risk of developing gastric cancer than uninfected control individuals. More recent studies suggest that the link is much higher than this, at 10–120-fold.

There are biologically plausible mechanisms that may explain the association between Hp infection and gastric cancer. The infection leads to a hyperproliferative state, intragastric concentrations of ascorbic acid are reduced, and the levels of mucosal reactive oxygen metabolites capable of inducing DNA damage are increased. The eradication of *H. pylori* infection normalizes gastric cell turnover, luminal ascorbic acid concentrations, and the levels of reactive oxygen species in the mucosa.

A systematic review identified 12 nested prospective case–control studies and meta-analyses, which suggested that *H. pylori* is associated with an increase in the odds ratio of developing non-cardia gastric cancer of 5.9 (95% CI, 3.4 to 10.3) These are not interventional studies, and it is not known with confidence whether eradication of Hp infection reduces the risk of gastric cancer.

There is circumstantial evidence that a policy of screening populations for Hp infection and treatment of those infected may lead to a reduction in the incidence of gastric cancer. More research is needed to evaluate the efficacy of Hp eradication in preventing gastric neoplasia (gastric adenocarcinoma and MALT lymphoma) in the general population before decisions can be taken on whether or not screening for Hp in countries with a high incidence of gastric cancer will be cost-effective.

Community screening and eradication of Hp infection is feasible in the general population and can lead to significant reductions in the numbers of patients who consult for dyspepsia with symptoms 2 years after treatment. However, these benefits have to be balanced against the costs of eradication treatment, so that a targeted eradication strategy in dyspeptic patients may be preferable.

Acknowledgments

We are grateful to Prof. Hunt for facilitating access to the Canadian *Helicobacter* Study Group meeting in September 2005 and to Prof. Peter Malfertheiner for early access to a draft of the Maastricht III report.

Please visit the WGO-OMGE website to view this guideline in full, and to download additional guidelines, free of charge, in English, French, Spanish, Mandarin and Russian.
www.worldgastroenterology.org

Functional gastrointestinal disorders

Douglas A. Drossman, MD

Gastroenterologists often see patients with complaints that do not have an identifiable basis. Some of these may have a severe impact on the quality of life. When physicians fail to discover a structural cause for these complaints, they are frequently labeled as "functional," and as such the patient and the complaint are given a nebulous diagnosis in which the symptoms are enigmatic and less amenable to explanation or effective treatment than structural diseases of the gastrointestinal tract. Often, physicians lack an understanding of the true genesis of the symptoms of functional gastrointestinal disorders (FGID), and they often do not have a rational basis for diagnosing and treating them. Because functional gastrointestinal disorders have been so poorly understood, they have been relegated to a less important category of diagnosis and treatment.

At an International Congress of Gastroenterology held in Rome in 1988, Professor Aldo Torsoli entrusted a working group with producing a consensus paper on FGID. The work was carried out by a dedicated group of workers in the field, and the criteria they established were eventually published as the Rome I Criteria (Drossman DA et al., eds., *The Functional Gastrointestinal Disorders,* McLean, VA: Degnon Associates, 1994). Rome II followed (Drossman DA et al., eds., *Rome II. The Functional Gastrointestinal Disorders,* 2nd ed., McLean, VA: Degnon Associates, 2000), and Rome III is now the most recent version of the criteria for adult and pediatric FGID (http://www.romecriteria.org/romeIII.html).

Rome III criteria are now the most recent version for adult and pediatric FGID

As a reflection of the significant progress made in this field, the April 2006 issue of *Gastroenterology* is dedicated to functional gastrointestinal disorders and the Rome III process, with the present author serving as the guest editor. Rome III conceptualizes these functional disorders within a biopsychosocial context. During the several years' work carried out by the Rome FGID study group, these previously poorly understood illnesses and the term "functional gastrointestinal disorders" have become clinically legitimate. Recent scientific studies have linked the mind with the part of the system in which dysregulation can produce illness and disease. Currently, there is no doubt that a person's psychosocial development determines, to a great extent, his or her susceptibility to life's stresses, as well as susceptibility to gut dysfunction, with abnormal motility or visceral hypersensitivity. An FGID is a clinical product of an altered gut physiology via the brain–gut axis, which is in turn modified by psychosocial factors.

Over the past two decades, considerable progress has been made in investigative methods that make it possible to quantify both motor and sensory abnormalities and the role of peptides, mucosal immunology, inflammation, and alterations of bacterial flora that can affect the brain–gut axis. In addition, pharmacological agents have been developed to treat FGIDs, including 5-HT agonists and antagonists and a variety of drugs for functional constipation and diarrhea. The Rome III document provides a basis for understanding the pathophysiological, diagnostic, and treatment aspects of FGIDs. A detailed review of this field will be published in the forthcoming Rome III textbook.

The Rome III classification system is based on the premise that for each functional disorder, there are symptom clusters that remain consistent across clinical and population groups. Thus, this new classification system is a symptom-based diagnostic schema. Many symptom-based criteria are accompanied by abnormal motility, but motility is not the only consideration in the diagnostic schema, which includes visceral hypersensitivity and brain–gut dysfunction. Symptom-based criteria are used in other medical specialties such as psychiatry and rheumatology and are becoming increasingly accepted within gastroenterology.

Several changes have been made between Rome II and Rome III, and these reflect new data and new ideas

that have developed over the past 4 years. One of the changes has been the decrease in the time necessary for the symptom complex to become expressed. There are other changes in several classification categories. Functional abdominal pain has become a separate category from functional bowel disorders, as there is growing evidence that this syndrome relates more to CNS amplification of normal regulatory visceral signals, rather than functional abnormalities of the gastrointestinal tract. Two new pediatric categories have been established, and there have been criteria changes for functional dyspepsia. More restrictive criteria have been proposed for functional disorders of the gallbladder and sphincter of Oddi, which may help prevent unnecessary invasive biliary and pancreatic investigations.

The Rome III text is the result of a 5-year effort on the part of 87 internationally recognized investigators, representing 18 countries. It provides a comprehensive overview of FGIDs and is regarded as a work in progress. The Rome process is a dynamic one, and we look forward to future activities to help improve our understanding of the scientific basis of FGIDs and provide better patient care.

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Confocal endomicroscopy: real-time in vivo histology and molecular imaging

Useful for surveillance of Barrett's esophagus and GERD

Confocal endomicroscopy (Pentax) is a patented technological advance that provides in vivo subsurface optical histological information with a high degree of sensitivity in real time during ongoing endoscopy. It appears to be particularly promising for the diagnosis of early gastrointestinal cancer in flat lesions. Published data suggest that the method has a clinical performance comparable to that of conventional histology for distinguishing between intraepithelial neoplasia and nonneoplastic mucosa (*Gastroenterology* 2004;127:706–13).

International clinical results presented in abstracts, lectures, and symposia at the Digestive Disease Week (DDW) meeting in 2006 again confirmed the initially positive data for a growing range of indications. The adjunctive procedure will not replace pathological tissue diagnosis, but is likely to have a significant impact on endoscopic diagnostic and therapeutic algorithms—for example, potentially making it possible to take only targeted biopsies in the future, or facilitating rapid diagnostic decision-making for endoscopic mucosal resection. Confocal endomicroscopy is also regarded as having the potential to allow molecular imaging in gastrointestinal endoscopy, through the use of fluorescence-labeled markers in vivo.

In a prospective study including 42 patients, for example, confocal endomicroscopy was carried out in patients with long-lasting reflux symptoms or Barrett's esophagus and in patients with suspected Barrett's-associated neoplasias (Kiesslich et al., *Clinical Gastroenterology and Hepatology* 2006, in press). Using a confocal Barrett's classification, confocal in vivo histology images were compared with the biopsied histological specimens by blinded investigators. Barrett's-associated neoplasias were predictable with a sensitivity of 92.9% and an accuracy of 97.4%. The mean kappa interobserver agreement for predicting the histopathological diagnosis was considered excellent (0.843).

It has been suggested that confocal endomicroscopy may be a useful tool for the surveillance of patients with Barrett's esophagus and in selected patients with gastroesophageal reflux disease (GERD). Pathologists such as Michael Vieth (Bayreuth, Germany) have stated that confocal endomicroscopy is a highly accurate tool for imaging goblet-cell metaplasia in vivo and that it allows targeted biopsy procedures. It may enhance the detection of areas suspicious for neoplasia.

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Qi-lian Zhang

5000 physicians in China are now practicing gastrointestinal endoscopy

The present status of gastroenterology and digestive endoscopy in China

Guo-ming Xu, MD and Qi-lian Zhang, MD

Gastroenterology

The Chinese Society of Gastroenterology was founded in 1980. It is affiliated to the Chinese Medical Association, which is a quasi-official academic and administrative body in the country. The everyday management of the Society is run by a 15-member standing committee, which is elected every 3–4 years. Working groups in more specialized fields such as intestinal hormones, *Helicobacter pylori,* gastrointestinal motility, pancreatopathy, gastrointestinal tumors, and inflammatory bowel disease (IBD) convene national meetings about once every 2 years, at which official guidelines are developed and issued. The first guideline on the treatment of IBD was published in 2002 after a conference in Chengdu, and publication of the guideline was followed by an increased number of published studies on the topic.

Dyspepsia is common in China, and studies have shown that the rates of gastroesophageal reflux disease (GERD) and reflux esophagitis are 5.8% and 1.9%, respectively.

The prevalence of symptoms may vary in different places. In Tianjin, a northern city, the prevalence of chronic constipation is 11.6% (13.4% in women and 9.7% in men), while the figure is only 4.0% in Guangdong province in the south; in both regions, the prevalence appears to be higher among women.

A 3-year follow-up study on the prevalence of *H. pylori* infection, covering 39 centers in 19 different provinces, concluded that there are substantial variations in the prevalence, ranging from 42% to 90% in different regions. Guangdong province has the lowest infection rate at 42%, while lamas in Tibet have the highest rate, at 90%. The study found that the prevalence of *H. pylori* infection in China is quite high, with an average rate of 59%.

Digestive endoscopy

The Chinese Society of Digestive Endoscopy (CSDE) was founded in 1991, affiliated to the Chinese Medical Association. The CSDE has established local branches in China's twenty-odd provinces and municipalities. Diagnostic and therapeutic endoscopy can now be conducted in every major hospital in the country. The annual number of cases handled by the main hospitals in Beijing, for example, is roughly estimated at 200 000. At least 5000 doctors in China are currently using the endoscope to diagnose and treat gastrointestinal diseases.

The CSDE has established a wide network of international academic relationships. Since it was founded in 1991, the CSDE has enjoyed very good collaboration with both the Hong Kong Society of Digestive Endoscopy and the Japanese Society of Gastroenterological Endoscopy. The biennial International Workshop on Therapeutic Endoscopy has so far been held seven times since 1991, in cooperation with the Hong Kong Society of Digestive Endoscopy. The First Sino–Japan Symposium on Digestive Endoscopy was held in Shenyang, China, in 1999; the second was held in Kobe in Japan; the third was held in the beautiful city of Guilin in China in 2004; and the fourth was held in Tokyo in 2005. The CSDE became a member of the Asia–Pacific Society of Digestive Endoscopy (APSDE) in 2000, at the same time automatically becoming a member of OMED. In addition, in collaboration with the Chinese Society of Gas-

Prof. Kenjiro Yasuda supervising young Chinese doctors carrying out EUS at Peking University's First Hospital.

Professor Guo-ming Xu delivering a lecture at the 5th Workshop on EUS in China in Nanjing in 2000.

troenterology and the Chinese Society of Hepatology, the CSDE in October 1997 organized the First Digestive Disease Week (DDW) China Congress, including a session of the OMGE Symposium on gastrointestinal oncology, in Beijing; the Second DDW China Congress in Shanghai in November 2001; and the Asia–Pacific Digestive Week 2004 in Beijing.

The CSDE is thus strongly committed to establishing and maintaining relationships with international bodies in the field of digestive endoscopy, and it will continue to promote and develop digestive endoscopy for China and the world.

Diagnosis and treatment of early esophageal cancer

Esophageal carcinoma is a type of cancer most commonly found in the north and north-west of China, particularly in the region of Tai Hang Mountain. Lin county (in Henan province) is located in the region. As the results of a mass screening campaign conducted from 1959 to 1981 showed, the age-adjusted annual incidence of esophageal cancer in individuals aged 40–69 in Lin county was $470/10^5$, and in one specific area the figure was as high as $760/10^5$. In Lin county, the earliest use of rigid gastroscopy was in 1965, followed by subsequent use of fiber gastroscopy in 1972, video gastroscopy in 1989, and endoscopic ultrasonography in the 1990s. As a result of the endoscopic mass screening, a high prevalence of esophagitis, atrophy, and dysplasia was detected in Lin county. The screening work was assisted by collaboration with international endoscopists (including Dr. T. Lok Tio, Dr. David Fleischer, and Dr. Crespi, to name a few).

From 1995 to 2000, Chinese colleagues carried out endoscopic screening of esophageal cancer with iodine staining among 3022 people aged 40–69 in these high-risk areas. Biopsy diagnosis identified 111 cases of superficial esophageal cancer and 659 cases of moderate and severe dysplasia. The rates of identification of superficial esophageal cancer before and after iodine staining were 1.9% (57 cases) and 3.7% (111 cases), respectively, whereas the rate of moderate and severe dysplasia was 5.0% (154 cases) and 21.8% (659 cases), showing some significant statistical differences.

In 1995, Dr. G.Q. Wang at the Cancer Hospital of the Chinese Academy of Medical Science began to carry out endoscopic mucosectomy in patients with superficial esophageal cancer and precancerous lesions. His work lasted until 2002, with a 100% success rate in 154 cases (including 187 lesions cases suitable for endoscopic mucosal resection). The hemorrhage rate was 11.7%, the perforation rate was 1.3%, and all of the affected patients were cured uneventfully.

Colon and small intestine

Colonoscopy is widely used in the diagnosis and treatment of colonic diseases in China. Magnifying colonoscopy with mucosal staining has recently been introduced for the diagnosis of laterally spreading tumors in the colon.

Double-balloon enteroscopy was first used in China in 2003. The M2A capsule endoscope (Given Imaging Ltd., Yoqneam, Israel) was introduced into China in 2002. The Chinese-manufactured OMOM capsule endoscope was first produced in 2005.

Endoscopic ultrasound in China

The first EUS instrument, the Olympus GF-UMB2, was introduced in China in 1987. It is estimated that by August 2005, a total of 54 radial-scanning ultrasound endoscope sets were available for EUS diagnosis, as well as 26 sets of convex linear-scanning EUS scopes for fine-needle aspiration (FNA) and fine-needle tattooing (FNT), and 223 probes for intraductal ultrasonography. The devices are distributed among 90 hospitals in 25 provinces and municipalities throughout the country (mostly in Beijing, Shanghai, and Guangdong province). According to recent statistics released by the CSDE's EUS group, 62 884 diagnostic EUS procedures (including 50 347 upper gastrointestinal procedures, 2610 colonic procedures, and 9927 pancreatic and biliary procedures) had been conducted in the hospitals concerned by August 2005. In addition, 2081 therapeutic EUS procedures (including 1749 FNAs, 190 FNTs and 142 celiac plexus neurolyses) and 3557 IDUS procedures were carried out. As EUS was introduced in 1987, it can be seen that the EUS technique has not been promoted as widely in China as it should have been—largely due to the inadequate supply of such instruments relative to the demand represented by the country's huge population. To tackle the problem, we have placed great importance on education and training. Workshops and seminars on EUS are organized almost every year, at which international EUS experts are invited to act as keynote speakers (speakers have included Dr. T.L. Tio, Dr. Kenjiro Yasuda, Dr. Thomas Rösch, Dr. Mitsuhiro Kida, and Dr. Kenneth Chang).

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Changing trends in gastrointestinal disease in the Asian–Pacific region

Khean-Lee Goh, MD

CRC will be the major form of gastrointestinal cancer in Asia in the coming years

More than half the world's population, or approximately 4 billion people, live in Asia. Changes in disease trends in Asia therefore have a significant impact on the global heath burden. With respect to gastrointestinal diseases, major changes have been observed in gastric cancer and colorectal cancer (CRC), as well as with acid-peptic diseases, including peptic ulcer disease and gastroesophageal reflux disease (GERD).

Gastric cancer

Gastric cancer is still one of the most common cancers in the Asian–Pacific region. In 2002, Korea and Japan recorded the highest incidence of gastric cancer in both males and females. In absolute numbers, for the same year, close to 1 million new cases of gastric cancer were diagnosed, and more than half the cases were in East Asia—41% in China and 11% in Japan. The age-standardized incidence rates in India, Thailand, and the Philippines are amongst the lowest in the world at 10–15 per 100 000 per year. Ecological comparison studies in the Asian population have shown a close association between *Helicobacter pylori* infection and gastric cancer. Although the Indian population has a high prevalence of *H. pylori,* it has a relatively low incidence of cancer.

While the burden of gastric cancer remains high in the Asian–Pacific region, age-standardized incidence rates (ASR) have started to show a decline. This is in keeping with observed trends noted in Western countries, where gastric cancer has been observed to have declined since the 1940s.

Colorectal cancer

CRC has long been considered a Western disease. However, there has been clear evidence that CRC incidence rates have been increasing among Asians. In the recent Globocan figures from 2002, CRC age-standardized rates have increased markedly in Japan and among Singapore Chinese, and are reported to be amongst the highest in the world. In several Asian countries, the age-standardized rate of colon and rectal cancer has now surpassed that of gastric cancer.

The reasons for this are likely to be similar to those experienced in the West previously. Increasing affluence, with an increase in obesity and a decrease in physical activity, have been implicated in CRC. The adoption of a Westernized diet with higher protein and fat content has also been implicated as a cause of the rising incidence of CRC. CRC will be the major form of gastrointestinal cancer in Asia in the coming years.

Peptic ulcer disease

A decrease in the prevalence of peptic ulcer disease has been documented in several Asian studies. While the overwhelming majority of patients in Asia are diagnosed as having ulcers associated with *H. pylori* infection, one study in the Philippines has noted a steady decline in the prevalence of *H. pylori*–associated ulcers.

Gastroesophageal reflux disease

GERD was previously thought to be a rare disease in the East. The situation has changed dramatically. More and better studies are now available, which have shown prevalence rates of esophagitis approaching 20% and prevalence rates of reflux symptoms of 10–15%. Barrett's esophagus is still uncommon, but one study in Malaysia has reported an overall prevalence of Barrett's esophagus of close to 6%. If this is confirmed by other studies in the region, it is a development that will certainly give rise to great concern.

Helicobacter pylori infection

H. pylori infection underlies several gastrointestinal disorders, including gastric cancer and peptic ulcer disease. Reports from Asia have shown a steady decline in *H. pylori* infection over the years, in keeping with socio-economic development and an improved standard of living.

Discussion

Dramatic changes in disease epidemiology have taken place in the Asian–Pacific region in the new millennium. Many of these changes mirror Western experience 40–50 years previously. Socio-economic development has brought about marked improvements in living conditions. At the same time, lifestyle changes, with an increase in body weight and a more sedentary lifestyle, have resulted not just in an increase in metabolic diseases but also in an increase in CRC.

Asia is a diverse continent, and changes do not affect all geographical locations or population groups. With regard to gastric cancer and CRC, low incidences continue to be reported for Indians, Filipinos, and Thais. Such reports suggest differences in host genetic factors or common environmental factors that may confer some protection in these populations, and it may be important to identify the protective factors involved.

This article is adapted from a State of the Art Lecture presented at the Asian–Pacific Digestive Week 2005, held in Seoul, Korea, 25–28 September 2005.

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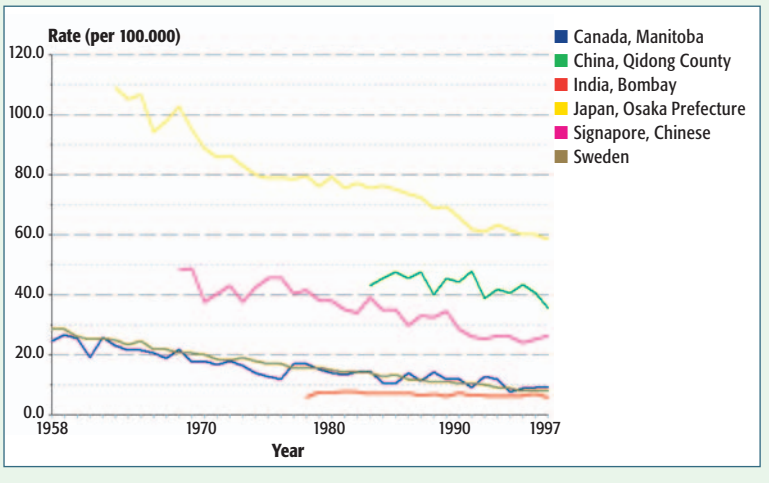


Fig. 1. Time trends ASR of gastric cancer of males from Western and Asian cancer registries showing declining incidence rates. WHO/IARC database.

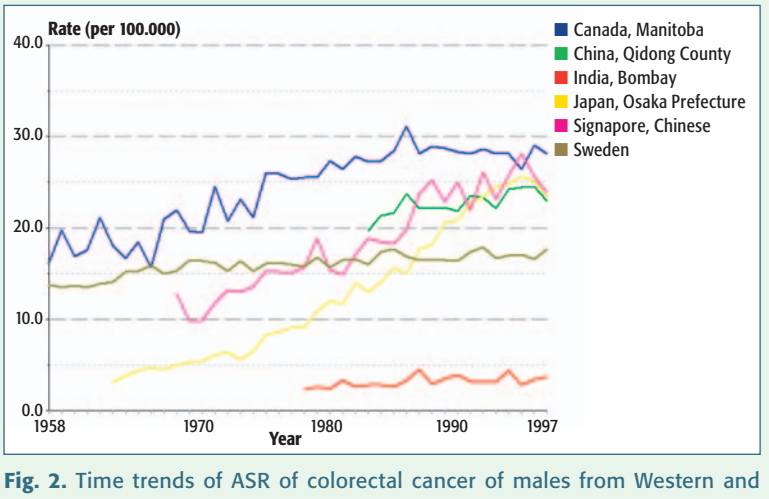
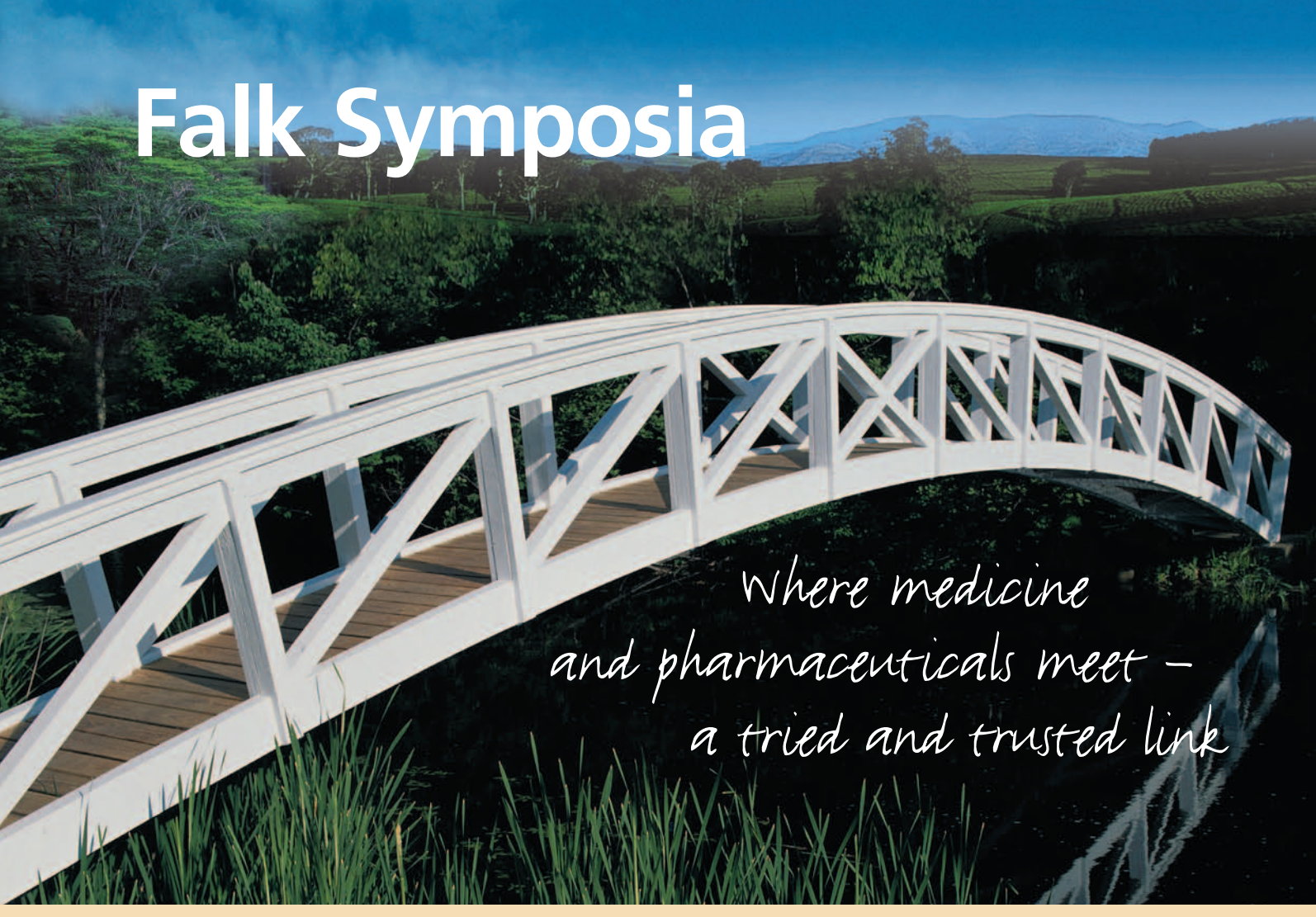


Fig. 2. Time trends of ASR of colorectal cancer of males from Western and Asian cancer registries showing increasing rates. WHO/IARC database.

Falk Symposia



Falk Research Workshop
Morphogenesis and Cancerogenesis of the Liver
Göttingen, Germany
January 25 – 26, 2007

Falk Symposium 158
Intestinal Inflammation and Colorectal Cancer
Sevilla, Spain
March 23 – 24, 2007

Falk Symposium 159
IBD 2007 – Achievements in Research and Clinical Practice
Istanbul, Turkey
May 4 – 5, 2007

Falk Symposium 160
Pathogenesis and Clinical Practice in Gastroenterology
Portorož, Slovenia
June 15 – 16, 2007

II Falk Gastro-Conference
Dresden, Germany, October 10 – 14, 2007

Falk Workshop
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IDCA

Digestive Cancer Series (series editors: Meinhard Classen, MD, Sidney Winawer, MD)

René Lambert

Esophageal cancer

René Lambert, MD and Pierre Hainaut, MD

Esophageal squamous-cell carcinoma (SCC) develops from the normal squamous-cell epithelium. Adenocarcinoma develops from a metaplastic, specialized columnar-lined epithelium, also known as Barrett's esophagus, which arises in the distal esophagus when it is exposed to a hostile endoluminal environment (low pH and bile acids).

The global burden of esophageal cancer

It is estimated that 462 000 new cases of esophageal cancer occurred in the world in 2002, and there were 386 000 deaths (Globocan 2002). Most cases were in developing countries, particularly in Asia (362 000 new cases and 293 000 deaths). The age-standardized rate per 100 000 persons in China in 1993–97 was extremely high in the Cixian registry—183 in men and 123 in women, contrasting with low figures in the Beijing registry (10.2 and 4.0). Adenocarcinoma is less frequent than SCC, but the proportions vary in relation to ethnic and geographic origin (Fig. **1**).

Columnar-lined esophagus and adenocarcinoma

The columnar-lined esophagus (CLE) shows a patchwork of epithelial types: cardiac, oxyntic, and incomplete intestinal metaplasia (types II or III). This "specialized epithelium" differs from the complete intestinal metaplasia (type I) found in the stomach; the specialized epithelium is a specific histological criterion for CLE. Several prospective studies have shown an increased risk of cancer in patients with CLE, and the presence of genetic and molecular biomarkers of neoplastic progression has been described.

Esophageal carcinogenesis

In the squamous epithelium. The progression of SCC is accompanied by sequential accumulation of molecular alterations. Mutation of *TP53* is an early event, sometimes detectable in the uninvolved mucosa adjacent to cancer.

In high-incidence areas in northern Italy and western France (Normandy), mutations of *TP53* are frequent and occur at A:T base pairs in about 40% of cases. This type of mutation, induced in vitro by acetaldehyde, is compatible with alcohol, in synergy with tobacco, being a causal factor.

In the "Asian esophageal cancer belt," which reaches from the eastern shores of the Caspian Sea to central China, *TP53* mutations are also frequent, but mutations at A:T base pairs are rare. The main type of mutations occur at G:C to A:T transitions, compatible with a role for chronic inflammation as a risk factor.

In columnar metaplasia. The molecular changes that underlie the progression to neoplasia are very similar to those involved in the transformation of the squamous epithelium. However, the spectrum of *TP53* mutations is more homogeneous, without obvious geographic variations. Most mutations are G:C to A:T transitions occurring at methylated cytosines, a type of mutation compatible

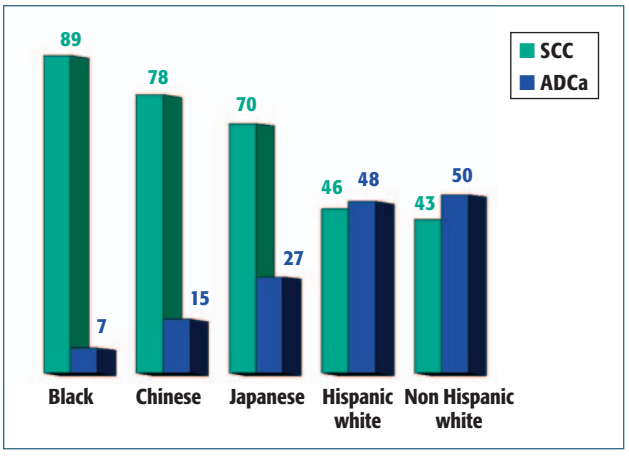
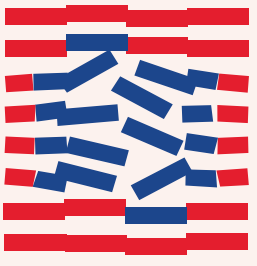


Fig. 1. Relative frequency (as percentages of all esophageal carcinomas) of squamous-cell carcinoma and adenocarcinoma relative to racial origin, in the USA (Los Angeles Registry, both sexes, 1993–97). Carcinoma of unspecified histology is not reported here. (Reproduced with permission from Cancer incidence in Five Continents, Lyons: IARC Press, 2002.)



with the role of chronic inflammation caused by reflux in the transformation of columnar metaplasia to neoplasia.

Classification of superficial esophageal tumors

When the endoscopic appearance of a lesion suggests that invasion is limited to the mucosa or the submucosa, the lesion is called superficial or type 0, in contrast to more advanced tumors (types 1 to 5). Superficial neoplastic lesions are benign or malignant, and invasion of the lamina propria characterizes intramucosal or submucosal malignancy. In addition to qualitative indices (tumor grade, images of vascular invasion, tumor budding), invasion into the submucosa is critical for the risk of nodal metastases, and a micrometric measure of the depth of invasion from the lower limit of the muscularis mucosae is recommended. Endoscopic mucosectomy is safe when invasion of the submucosa is less than 200 µm in the squamous mucosa and 500 µm in the columnar mucosa.

For superficial lesions, pathologists use the Vienna classification into 5 categories:

- 1 and 2 for preneoplastic conditions
- 3 and 4 for noninvasive or invasive intramucosal neoplasia
- 5 for submucosal carcinoma

The TNM staging system is designed for cases of confirmed malignancy and combines selected categories for T (tumor), N (lymph nodes), and M (metastases) into stages 0, I, II, III, and IV. When the classification is assigned postoperatively it is called pTNM; when the tumor is staged clinically, each component has to be defined as clinical or pathological. Superficial malignant lesions are classified as T1m or T1sm.

Epidemiology of squamous-cell cancer

Western countries. In most Western countries, the incidence of esophageal SCC is low (less than three per 100 000 in men and one per 100 000 in women). Higher figures have been observed in some regions of Europe such as Normandy and Scotland, in relation to consumption of alcohol and tobacco. An endoscopic survey in Normandy has shown chronic erosive esophagitis in 63% of individuals with regular alcohol consumption. In the same region, the high incidence of SCC in men (22.6 per 100 000) is now decreasing in relation to the reduction in the consumption of homemade alcohols. In Scotland, the incidence is increasing in women, with a combined influence of alcohol and tobacco.

Primary prevention involves changing drinking and smoking habits and practicing a healthy lifestyle

Africa and South America. The risk of SCC has increased in the Transkei region; the trend is attributed to a shift in the basic diet from sorghum to maize contaminated with the mycotoxin fumonisin. In South America, a high incidence observed in Uruguay is attributed to the habit of drinking hot beverages (mate tea), as well as alcohol and tobacco.

Asia. There is a high incidence of SCC in regions with a low socio-economic conditions, and incidence rates are high in men and women. Recent surveys in China indicate that the incidence and mortality are now decreasing, perhaps in connection with improved socio-economic conditions. With regard to causal factors in Asia, carcinogens can be absorbed with nutrients such as smoked meat, vegetables containing toxic alkaloids (alternariol) or fumonisin, a mycotoxin of *Fusarium verticillioides* that contaminates maize. Water may contain nitrites, nitrates, and nitrosamines. Other possible factors include deficiencies in oligoelements (riboflavin, vitamin A, zinc), poor oral status, thermal trauma occurring when drinking hot beverages, potential inhalation of polycyclic aromatic hydrocarbons when cooking without ventilation in thatched houses,

close contact with horses, and infectious agents such as papillomavirus types 16 and 18.

Nonerosive esophagitis as a preneoplastic condition in Asia. The prevalence of chronic esophagitis is high (40–80%) in regions of Asia at high risk for cancer, but a causal relationship with cancer is unproven. There is still no evidence that esophagitis is a significant step toward neoplastic transformation.

Epidemiology of adenocarcinoma

Adenocarcinoma and gastroesophageal reflux. Adenocarcinoma is not a major contributor to the worldwide burden of esophageal cancer, and is not a frequent tumor, even in Western countries such as the USA and northern Europe. However, the incidence steadily increased during the last quarter of the 20th century. There is evidence for a correlation between gastroesophageal reflux (GERD), CLE, and adenocarcinoma in the esophagus.

Columnar metaplasia as a preneoplastic condition. The prevalence of CLE is difficult to evaluate, since as many as 80% of patients may remain undiagnosed. CLE is a preneoplastic condition, but not all patients are exposed to the same risk for adenocarcinoma in the esophagus. Factors increasing the risk include Caucasian ethnicity, male sex, older age, alcohol consumption, continuous smoking, dietary deficiency in fruit and vegetables, and a long history of reflux symptoms. Currently, a reasonable estimate of the risk of cancer in persons with CLE is one case per 200 patients followed during 1 year. The risk of cancer increases with the length of the CLE segment, but the difference is small, and short segments deserve as much attention, as they are more common than longer segments.

Early endoscopic detection

Endoscopic diagnosis is a two-step procedure:

- Firstly, a suspect area is identified by a change in color and by an abnormal pattern of superficial microvessels.
- Secondly, the suspect area is characterized with the help of chromoscopy and image-processing, including the techniques of narrow-band imaging and magnification endoscopy. Staging with endosonography and computed tomography supplement the endoscopic techniques.

In the squamous stratified epithelium. In nonerosive chronic esophagitis, erythema and edema are less precise criteria than elongation of intrapapillary capillary loops observed with magnification. Precancerous and superficial malignant neoplastic lesions appear as abnormal areas that are friable, focally red, erosive or nodular, and stain negative with iodine–potassium iodide (1.5–2% solution). Most of these lesions are nonprotruding, as a multicenter analysis in Japan showed. There may be multiple neoplastic areas with different degrees of progression in the same patient—a finding that is compatible with the concept of "field carcinogenesis."

In the columnar-lined esophagus. In the distal esophagus, a segment of CLE is easily diagnosed if it is more than 1 cm long. Detecting very short segments of columnar metaplasia requires very careful analysis of landmarks at the esophagogastric junction. The use of methylene blue chromoscopy to detect intestinal metaplasia has been described. When magnification and the NBI technique are used, any abrupt change in the average size of the epithelial crests, or areas with an amorphous surface and corkscrew microvessels, are suggestive of intraepithelial neoplasia.

Primary prevention

Primary prevention of SCC in Western countries involves altering drinking and smoking habits. Prohibiting the use of alcohol is recommended in patients with inefficient ALDH-2 enzyme isoforms, which can be detected by the facial flushing questionnaire developed in Japan. Primary prevention of adenocarcinoma involves preventing GERD by practicing a healthy lifestyle and controlling excess body weight in young persons. In persons with CLE, primary prevention of cancer through pharmacological or surgical control of the reflux is not effective. Anti-inflammatory medication (COX-2 inhibitors) may be more effective, but the side effects may outweigh the benefit.

Screening and surveillance for esophageal cancer

The aim of secondary prevention is to achieve early detection of cancer and precancerous lesions in asymptomatic individuals. In Western countries, opportunistic endoscopic screening for SCC can be offered to persons with a high consumption of alcohol and tobacco. In areas of high risk for SCC in Asia, screening campaigns based on cytology smears have been conducted. For patients with CLE, factors justifying surveillance are male sex, a prolonged symptomatic history of GERD, continuous smoking, presence of a peptic stricture, or ulcer at endoscopy.

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OMED: About the ESGE

The European Society of Gastrointestinal Endoscopy (ESGE) represents the European zone of OMED, and is an umbrella society consisting of 45 gastrointestinal societies from Europe and neighboring countries. The diversity of the countries involved provides a fascinating view of different health systems, organizational and financial differences, and even clinical variations. One of the main objectives of the ESGE is to achieve widespread improvement in endoscopic practice in the European zone by publishing guidelines, organizing a selection of multicenter studies, and especially through active teaching events, such as:

- *UEGW postgraduate activities*. In addition to its postgraduate course, the ESGE organizes a number of teaching activities throughout the week: hands-on training on simulators and biological models, meet-the-expert small-scale topic discussions, a DVD self-study library, and a marathon video session.
- *ESGE live demonstrations and video workshops*. These meetings are organized twice a year, mostly in Eastern Europe. A combined local and international faculty offers a combination of transmitted live cases with panel discussions and keynote lectures on relevant topics.
- *ESGE postgraduate grants*. A minimum of 10 grants are offered each year to postgraduate fellows for 2 months of training at a selection of 15 expert centers throughout Europe.
- *Traveling tutors*. This is a newly developed activity in which an expert endoscopist and nurse spend a week visiting several units in an area, working within the local context with regard to equipment, competence, and patients. We hope to see a lasting regional impact with this type of teaching, as an addition to large-scale meetings.

Further information is available on the ESGE web site (www.esge.com).

ESGE at UEGW

At the forthcoming United European Gastroenterology Week (UEGW) in Berlin in October, OMED will be joining forces with the European Society of Gastrointestinal Endoscopy (ESGE) to present the first in a series of Endoscopy Director's Workshops, aimed at clinicians managing endoscopy units. The session takes place on Sunday 22 October and will focus on needs in the European context, featuring lectures, tutorials, and interactive sessions.

The ESGE will also be offering other highly educational events at the UEGW meeting. At the ESGE Postgraduate Course on Saturday 21 October, satellite transmissions from expert centers in Amsterdam and Berlin will demonstrate basic techniques, as well as the cutting edge of novel methods. Live transmissions will alternate with review talks on core topics in current and future gastrointestinal endoscopy practice.

Those attending the meeting should also visit the ESGE Learning Area, open to all delegates from Sunday to Wednesday. Various activities will be offered here, including hands-on training on simulators and biological models, meet-the-expert small-scale topic discussions, plus a DVD Learning Center where teaching videos, mainly based on the ESGE Teaching Encyclopedia, can be viewed at 18 workstations.

More detailed information on these and other ESGE activities is available on the web site (www.esge.com). Online registration for the ESGE Postgraduate Course is available on the UEGW web site (www.uegw2006.de).

Upper GI Screening

An international conference on Cancer Prevention and Early Detection was jointly organized by OMED with Beijing Oncology Hospital, European Cancer Prevention Organization (ECP), Asian Pacific Society of Digestive Endoscopy (APSDE), Cancer Research and Prevention Foundation (CRPF) and American Cancer Society (ACS) in Beijing on 22-24 March 2006. In this conference, a one-day symposium was dedicated to Upper GI Cancer Screening co-chaired by Joseph Sung and Colm O'Morain. Latest data covering the epidemiology, pathogenesis, screening and prevention of gastric and esophageal cancer have been presented by experts in the field.

The Upper GI Screening Committee is planning to work together with APSDE on a joint project on "The Role of Endoscopy in Early Detection and Treatment of Gastric Cancer." A working group involving around 10 countries in the Asia Pacific will be established. The first meeting will be held in Cebu, Philippines (during the APDW 2006). The working group will aim to discuss the following topics:

1 Epidemiology of gastric cancer
2 New endoscopy technology in detecting early gastric cancer
3 New endoscopic treatment for early gastric cancer
4 Screen-and-treat or screen-and-scope for dyspepsia

Joseph Sung
Chair, Upper GI Screening

WGO-OMGE/OMED: Train the Trainers

If care for patients with digestive diseases is to improve throughout the world, standards in training and education of the physicians must also improve. Since 2001, the Train the Trainers (TTT) program run by WGO-OMGE/OMED has trained more than 250 physicians from 70 countries.

Despite the key role of trainers in the development of future gastroenterologists, it is still the case that only a few of them receive formal instruction or training as educators. The TTT program attempts to meet this need. By bringing together trainers from across the globe in intensive and interactive sessions lasting 3–4 days, and dedicated to the development of teaching and training skills, WGO-OMGE/OMED has developed a forum for interaction between world leaders in education, for the sharing of experience and the discussion of common problems.

TTT course modules include: trial design, evidence-based medicine, publication and presentations, inter personal skills and teamwork, teaching procedural skills, and credentialing.

The Train the Trainers program for 2007 will be held from 16–19 April in Porto, Portugal. Those interested in applying for TTT 2007 should contact their national societies, which are now accepting applications. Unfortunately, WGO-OMGE/OMED is unable to accept direct applications.

Further information about Train the Trainers is available on the web site www.worldgastroenterology.org

The TTT program has trained more than 250 physicians from 70 countries

Comments from participants

"It is very useful for improving the gastroenterology services in our hospital in Balikpapan, East Borneo, Indonesia. As we are far from Indonesia's capital city, we have to try to develop our skills and our instruments with more effort."
— Dr. Lukman Hatta Sunaryo, Balikpapan, Indonesia

"When I first received the invitation to attend the course, I was skeptical regarding its usefulness. I always thought teaching is an art, an inborn talent—either you have it or you do not. What can this type of workshop teach us? But this turned out to be one of the best conferences I have ever attended."
— Dr. Ajay Kumar, India

"Following the course, I was more confident in providing feedback to advanced trainees in gastroenterology. The general consensus among them was that they were previously not accustomed to feedback sessions, and they were generally positive about this procedure. I therefore wondered why this course is not more widely publicized or even compulsory for any potential departmental heads, directors of endoscopy, or anyone with similar interests. I am also most interested in upcoming moves toward introducing simulators as part of training for gastroenterology trainees. I appreciated the full 4 days of the course, and it was one of the best-organized workshops I have ever attended."
— Dr. Rupert Leong, Australia

WGO-OMGE/OMED: World Digestive Health Day

In 1979, Dr. Robin Warren, a pathologist, reported the presence of an unusual bacterium in gastritis patients. Warren continued his studies of the bacterium and joined forces with Dr. Barry Marshall, a gastroenterologist, who in the 1980s famously conducted an experiment on himself that would undeniably link *Helicobacter pylori* to inflammation of the stomach. Today, almost 25 years after the first sighting of *H. pylori,* it is now scientifically accepted that the bacterium is the cause of 60% of the global cases of gastric cancer and 80% of the global cases of peptic ulcer. The Nobel Foundation recognized the researchers' achievements—including perseverance—by awarding them the 2005 Prize in Physiology or Medicine.

Accelerated effort. WGO-OMGE/OMED honored the work of Marshall and Warren by focusing World Digestive Health Day 2006 on *H. pylori*. On 29 May, WGO-OMGE/OMED urged member societies to undertake local activities to highlight this public-health issue, with a particular focus on developing countries. We are grateful to all who responded to this call and contributed to the increased awareness of the impact of *H. pylori* on digestive disease.

Consensus on national guidelines reached in Lahore, Pakistan

Prof. Ghias Un Nabi Tayyab, Vice-President, Pakistan Society of Gastroenterology

The Pakistan Society of Gastroenterology and Gastrointestinal Endoscopy hosted a consensus meeting on 13 and 14 May 2006 to formulate national guidelines for the management of *H. pylori* infection against the background of the local situation. The meeting included lectures and committee deliberations on epidemiology, disease pattern, and prevention and management in adults as well as in children. Guidelines are now being written.

UAE commemorates World Digestive Health Day with special CME program in Abu Dhabi

Wael Al Mahmeed, MD (Meeting Organization, Abu Dhabi) and Makki Fayadh, MD (President of the Iraqi Society of Gastroenterology and Hepatology)

The Emirates Medical Association, in collaboration with the UAE Gastroenterology Society and the General Authority for Health Services for the Emirate of Abu Dhabi, hosted a special Council on Medical Education (CME) program on 3 June 2006, which was attended by approximately 300 participants from the region. Topics included the history of *H. pylori,* diagnosis of *H. pylori* infection, treatment methods, and "updates and non-responders."

Support from the Uruguayan Society of Gastroenterology

Cristina Dacoll, MD and **Susana Kohen, MD** (President and Secretary-General, Sociedad de Gastroenterología del Uruguay)

The Uruguayan Gastroenterology Society officially recognized and supported the call from the World Gastroenterology Organization and congratulated WGO-OMGE/OMED

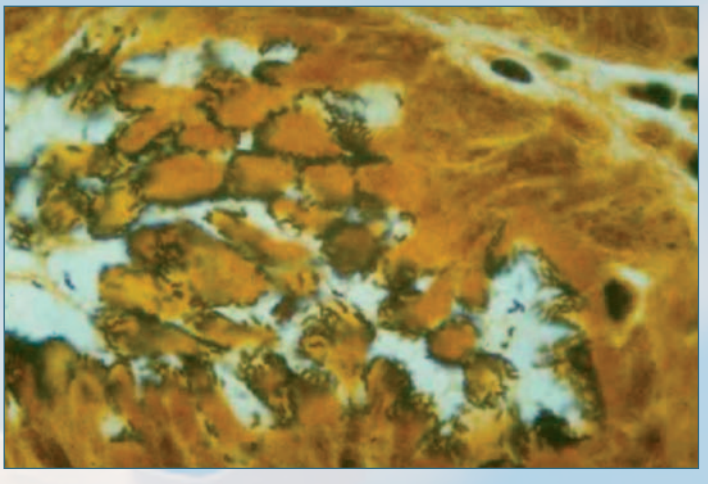
World Digestive Health Day 2006 focused on *H. pylori*

on initiating this activity. Together with its sister societies, the Uruguayan Society of Digestive Endoscopy (*Sociedad Uruguaya de Endoscopía Digestiva,* SUED) and the Uruguayan Society of Pathology (*Sociedad Uruguaya de Patología,* SUP), the Society organized a special scientific program on *H. pylori* to commemorate the event.

Belgian gastroenterologists respond to the call for action

Vincent Lamy, MD (President, Belgian *Helicobacter pylori* Study Group)

The Belgian *Helicobacter pylori* Study Group (BHpSG) distributed informative materials to its members, patients, and the press in both French and Dutch about *H. pylori* and its importance as a risk factor for non-cardia gastric cancer.



World Digestive Health Day, 29 May, is observed each year to raise awareness about digestive diseases. This year the focus was on *Helicobacter pylori* infection. The photo shows a sample of *H. pylori* as viewed by Robin Warren in 1979.

H. pylori guideline

As a service to members and with the aim of improving global gastric health, WGO-OMGE/OMED set up a working group, led by Prof. Richard Hunt of McMaster University in Canada, and developed an *H. pylori* guideline which is globally applicable and available free of charge from the web site (www.worldgastroenterology.org). Highlights from the guideline are also available in this issue of *WGN* (pp. 22–29).

World Digestive Health Day 2007: viral hepatitis

A total of 400 million people are chronically infected with hepatitis B, and about half of that number are chronically infected with hepatitis C. Together, these diseases are among the two or three major causes of cancer in the world. The World Gastroenterology Organization has set up a working group, headed by Dr. Douglas LaBrecque (University of Iowa, USA) to coordinate activities on viral hepatitis for World Digestive Health Day 2007. Information on planned activities and support materials will be provided in the coming months. WGO-OMGE/OMED urges all member societies to draw attention to this health problem and invites any member to apply for inclusion in the working group by filling out the application form that is available on the web site and sending it to info@worldgastroenterology.org. The final selection of group members will be made by November 2006.

www.worldgastroenterology.org

"The best ERCP endoscopist in the world"

Kees Huibregtse—the man and the legend

K.L. Goh

Kees and Annemarie Huibregtse at home in Bussum, Netherlands, September 2005.

One of the most unforgettable professional sights for Malaysian endoscopists is that of a hefty blond doctor cannulating the bile duct during an endoscopy workshop. Quietly confident and always imperturbable, Kornelis (Kees) Huibregtse was the "champion of all champions," in the words of the ERCP pioneer, Peter Cotton. It is no accident that Kees acquired this reputation. His sublime endoscopy skills, characterized by a minimum of movements, were "designed" to be maximally effective—he had a strong and stable left arm, and his calm outward demeanor belied an unflappable concentration and a deft touch.

Kees Huibregtse was born in a small village close to the Hague during the Second World War, in May 1941. He recalled vaguely the hard times in those early days, when food was scarce and people had to eat tulip bulbs for food during the winter of 1944. In his own words (tongue-in-cheek), "I have compensated for this during the rest of my life." Kees loved Malaysian food and was always excellent company during the many dinners he had with our local doctors.

Kees's father was a teacher and later headmaster of the *Gymnasium* school in Haarlem, to which the family moved in 1946. His mother was a full-time pediatrician, but still managed to find enough time to bring up two boys. The school system in the Netherlands at that time consisted of 6 years' primary school, starting at the age of six, followed by six years' secondary school, leading to a university entrance qualification.

Music has always played an important role in Kees's life. He started playing the piano at the age of eight, and the flute at age ten. He played the flute in the school orchestra during secondary school. He was greatly encouraged by his father to pursue and develop his musical interests and talent. In his own words, "My father, as headmaster of the *Gymnasium*, allowed me not to attend gymnastics on condition that I should spend the same time playing music. Neither of us could ever understand why some people like physical exercises and like to hit a ball instead of leaving the ball alone."

After graduation from high school, he entered the University of Leiden to study medicine. Kees was not exactly a "nerdy" student — "I knew that the time at university would be my last opportunity to do other things than medicine. So I spent a lot of time playing the flute in the Dutch Student Orchestra and other amateur bands of musicians, learning Italian, traveling to Italy and working in an art gallery, and buying and selling paintings."

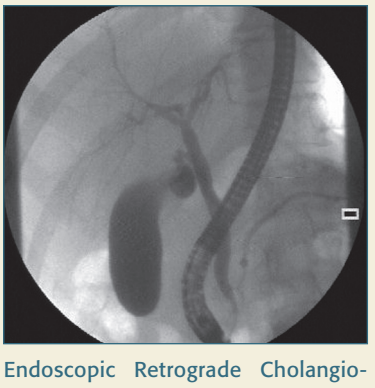
He qualified as a doctor, and after a year's training in internal medicine and surgery, Kees entered military service, which was compulsory at that time. He was appointed the chief physician for a squadron consisting of a cruiser and six destroyers. Those were halcyon days: "A whole year of

a 30-minute consulting hour (per day) and the rest of the day to spend for myself. The cruiser was very old and broke down close to lovely harbors like Edinburgh and Cadiz to be repaired. Ladies' clubs organized the most spectacular trips and parties for us, to while away the time."

In 1973, in his own words again, "the more serious part of my life started." He met and married the love of his life, Annemarie. Annemarie and Kees are blessed with two children, and the family has remained the cornerstone of Kees's life.

He obtained a position as fellow in training for internal medicine in the Wilhelmina Gasthuis in Amsterdam in 1973. He had an early interest in hematology, and had spent a period training in London under the late Professor David Mollin, hematologist at St. Bartholomew's Hospital. "His main interest at that time was folic acid absorption and metabolism, and he roused an enthusiasm for the subject in me." However, this interest was "extinguished" by the professor in Amsterdam on his return. It was fortuitous that in 1971, a young Belgian gastroenterologist, Guido Tytgat, had become the chief of gastroenterology at the Wilhelmina Gasthuis. "His great enthusiasm and his great commitment were catching for me, and I decided to specialize in gastroenterology. During my training, I found that the technical aspects of endoscopy attracted me. Guido did the first diagnostic ERCP and the first endoscopic sphincterotomy, and I soon followed." Together with Guido Tytgat, Kees formed the nucleus of a great gastroenterology department, which subsequently moved to beautifully purpose-built premises at the Academic Medical Center in polder land on the outskirts of Amsterdam.

The 1970s and 1980s were exciting times in therapeutic gastrointestinal endoscopy, with constant advances involving the introduction of new scopes, accessories, and methods. ERCP had first been reported by William McCune in 1968 and by Oi et al. in Japan in 1970. With the expansion of the department at the AMC in 1978, Guido Tytgat, recognizing Kees's special skills, decided that he should concentrate on ERCPs full time. The rest is history. "Since that time, our department has published many papers on the subject. The first straight biliary endoprosthesis, with a diameter of 10 French and with side flaps, was inserted endoscopically in an elderly lady with a gallbladder carcinoma on 3 August 1980. The controversial needle-knife technique was developed by me. My Ph.D. thesis on *Endoscopic Biliary and Pancreatic Drainage* was published in 1988." In November 1997, after so many years of top-class pioneering work in ERCP, his efforts were recognized by the University of Amsterdam through the establishment of a personal chair, and Kees was appointed Professor of Gastroenterology. By that time, the Amsterdam unit had reported on almost every aspect of therapeutic ERCPs, with up to 20 Ph.D. theses emanating from the AMC on the subject.



Endoscopic Retrograde Cholangio-Pancreatogram (ERCP).

From the mid-1980s, the gastrointestinal unit at the AMC started to accept foreign trainees, mainly to train in ERCP and therapeutic endoscopy. Initially, they were all Americans, but trainees subsequently came from all over the world, including Asia and Malaysia. The unit's reputation was further enhanced when these trainees returned to their home countries and continued to practice ERCP in the "Huibregtse" style. Kees's personal reputation also spread, and he was a constant feature in many therapeutic endoscopy workshops in Europe, North America, and Asia. Professor Sydney Chung of Hong Kong, long-time course director for such workshops, often remarked that "Kees Huibregtse is the best ERCP endoscopist in the world." The Malaysian Society of Gastroenterology and Hepatology has had the pleasure and honor of inviting Kees to conduct workshops a total of four times, and in 1999, he delivered the University of Malaya Distinguished Lecture on "The History and Development of Biliary Endoprostheses."

His enduring legacy in endoscopy will always be the large number of endoscopists he has trained. They will all remember the "Master" and continue to practice ERCP in his tradition. They all have fond memories of Amsterdam and the AMC. Kees Huibregtse will forever be remembered as the redoubtable Dutchman who made ERCP into a fine yet simple art.

Epilogue. Kees Huibregtse retired from the University of Amsterdam in February 2004. He was suffering from chronic renal insufficiency and was on dialysis. In August 2004, he underwent renal transplantation with his wife Annemarie as the donor. Following a "hiccup" postoperatively for Annemarie, both Kees and Anne Marie are now in excellent health and have started a new life "away from medicine!" They have lived during most of their married life in the village of Bussum, near Amsterdam. Annemarie is continuing her lifelong interest in art and organizing art exhibitions. Kees Huibregtse is now an "art detective" and spends many hours in the numerous art museums in Holland tracking down and cataloguing pieces of Dutch and foreign art. Their sons are now both qualified doctors. May we wish the Huibregtses happiness and good health in the many more years yet to come.

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Schistosoma mansoni prevalence can reach up to 70% and periportal fibroses up to 18%

Gastroenterology in Sudan

Hatim M.Y. Mudawi, MD

Northern Africa.

Sudan is the largest country in Africa, with an area of 1 million square miles (ca. 2590 square kilometers) and populated by 35 million people with various ethnic and religious backgrounds. The country has a heavy burden of intestinal schistosomiasis and hepatitis B virus infection, both of which lead to portal hypertension and esophageal varices. Both diseases have considerable impact on health status and affect the earning capacity and socioeconomic status of patients and their families, straining the country's resources. The prevalence of infection with *Schistosoma mansoni* may reach up to 70% and periportal fibroses up to 18% in areas not covered by control programs; more than 50% of patients with periportal fibroses have esophageal varices, and 3–4% develop hematemesis, causing significant morbidity and mortality. More than 10% of the population has chronic HBV infection, while HCV has a much lower seroprevalence of 2–3%. There are many cases of gastrointestinal malignancy, mainly involving colonic, esophageal, and hepatocellular cancer.

The introduction of gastrointestinal endoscopy in the late 1950s was an important landmark in the advancement of gastroenterology in Sudan. Dr. Ibrahim El-Maghraby used a rigid gastroscope for the first time in Wad Medani Hospital in central Sudan in the late 1950s; in 1970, the first fiberoptic gastroscope was used in Khartoum's teaching hospital by Dr. Bashir Arbab and Prof. Mohamed Ahmed Hassan. The first full endoscopy service was established in Soba University hospital (SUH) in Khartoum. The first ERCP procedure was performed in 1979 and the first endoscopic sclerotherapy was done in 1980 at SUH. In 1985, a specialized hospital for gastrointestinal and liver disorders was established. This was donated to us by the

The endoscopy staff at Soba University Hospital. Standing, from the right: Dr. Mudawi, Dr. Shakir Zein, Dr. Suliman, Ragabia, Ahmed, Nagla, and Dr. El Tahir. Seated are Nagwa, Awad, Fatma, and Inam.

Japanese, and is now the National Center for Gastrointestinal and Liver Disease (NCGLD). The Sudanese Society of Gastroenterology (SSG) was founded in 1976 and is now an active member of OMGE, the African–Middle East Association for Gastrointestinal Endoscopy (AMAGE), and the Pan-Arab Association of Gastroenterology.

The Society has held regular monthly meetings for the past 30 years, as well as regular symposia on various aspects of gastrointestinal and liver disorders. The Society also organizes two yearly workshops on therapeutic endoscopy and ultrasonography, both attended by international experts in the field. The SSG has always been involved in education and training in endoscopy. Under its current president, Prof. Suleiman Fedail, it has continued to do so, and has trained many physicians, surgeons, and nursing staff both in Sudan and abroad through the help of one of the good friends of the SSG, Prof. Meinhard Classen. We are currently seeking to train our colleagues from southern Sudan in order to help establish a service in that part of the country.

Despite these efforts by the society, Sudan remains a poor country with difficult economic conditions and low living standards. Many of our patients are unable to pay for the services which we can provide; we are forced to reuse disposable equipment, mainly ERCP accessories, after sterilization; we use locally produced ethanolamine oleate for injecting esophageal varices because the ready-made solutions are very expensive, and we also make our own urease test for detecting *Helicobacter pylori* infection, as the commercial CLO test is too expensive for our country.

Despite these difficulties, the specialty is flourishing, and endoscopic ultrasonography and motility studies have now been introduced at the NCGLD. The President of the Society, Prof. Fedail, convinced a Sudanese businessman, Mohamed Salih Idris, to build a fully equipped center for the treatment of gastrointestinal bleeding costing over US$ 1 million, which now provides free emergency services for patients with bleeding esophageal varices. Within the next 2 years, we hope to be able to establish a 2-year gastroenterology training program for physicians, thanks to the help provided by the "Train the Trainers" program sponsored by the WGO-OMGE/OMED.

The Fourth Pan-Arab Congress in Khartoum, 2001. The Vice-President is seen in the center, wearing the national dress. To his left are Prof. Classen, Prof. Fedail (President of the SSG), the late Prof. Eltayeb (President of the Sudanese Medical Association). To his right are Prof. Ziad Shariaha (President of AMAGE), the Minister of Health, Prof. Zaki Eldin, and Prof. Alrasheed.

Sudan has a bright future, and now with oil production and with peace in the South and Darfur, our dreams and ambitions have no limits.

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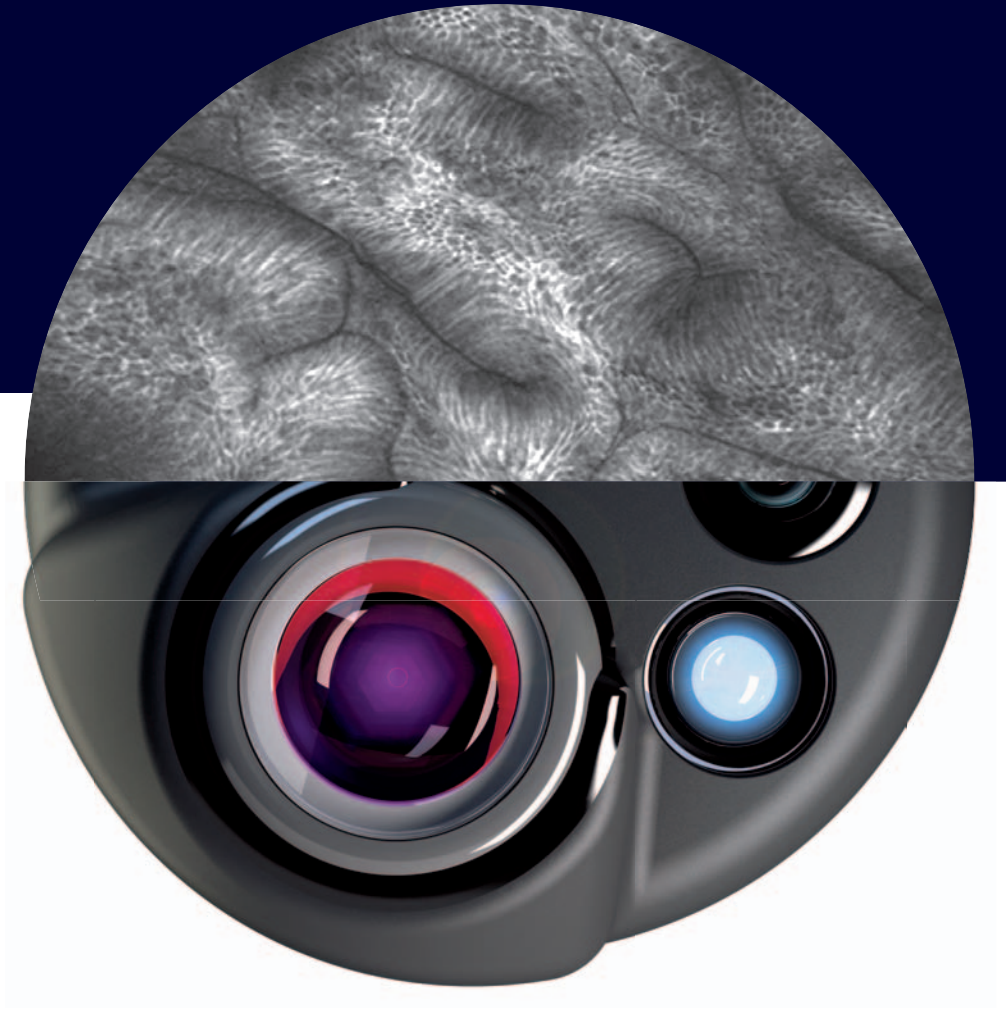

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Gastroenterology guidelines—time for a change!

Justus Krabshuis

Brace yourself, reader: this is going to be a hard ride—a rough journey with interview stops at the American Gastroenterological Association (AGA), the American College of Gastroenterology (ACG), the American Society for Gastrointestinal Endoscopy (ASGE), its European counterpart (ESGE), the European Digestive Motility Center (EDMC), the British Society for Gastroenterology (BSG), and a few more.

At each stop we will look at what guidelines are on offer, how old they are, and whether they have been updated. Are they re-inventing wheels already made by others? Consider the bizarre 2005 AGA and ACG guidelines on Management of Dyspepsia—both by the same group of authors. If that is not overlap, what is? And are guidelines evidence-based? Can they be?

Most guidelines are not evidence-based—that is to say, they are not based on a comprehensive and systematic analysis of the medical literature. At best, there is a quick look at PubMed/Medline, and perhaps the references from some of the key articles are scanned for further relevant literature. Maybe too there is a look at the Cochrane Library for systematic reviews and randomized controlled trials, but that is *it*. This rather limited approach does not come anywhere near the methodological purity required to justify the claim that a guideline is "evidence-based." Strictly speaking, one could argue that it is not possible to achieve that anyway. After all, you can blow holes in any Embase or Medline search strategy, even when it has been done by true experts in the field, by asking questions such as: what were the selection and assignment policies for journals not indexed cover-to-cover in the period searched? And: the thesaurus terms you are using—how were articles indexed prior to the introduction of that term into the MeSH and EMTREE thesauri?

Only the WGO-OMGE guidelines are published in all major languages and include cascades of options

And so, as all the sticklers for principle rush on towards ever-vanishing end points, never actually achieving 100% sensitivity with perfect confidence intervals—would it not be better to go back to the experts who have published extensively in the field? These are experts who publish in the top gastroenterology journals, not in the *Remotania Journal of Gastroenterology.* One of my interviewees used the expression "evidence-based paralysis"!

A systematic analysis of the published literature on *Helicobacter pylori* eradication—for example, on the question of triple versus quadruple bismuth-based therapy, or whether or not to choose 7-day treatment or 10- or 14-day treatment—involves large issues with serious cost implications. Such questions can never be answered solely by literature searches, however systematic they may be.

Here are some further difficulties worth reflecting on:

- It costs a great deal of time and expertise, and the corresponding resources are only available for the really powerful gastroenterology associations. Preparing guidelines is a kind of "macho" publishing. There is little evidence of the need for it and there is little evidence of its impact and usefulness.
- All guidelines need updating, at least every 3 years, and if you decide not to update, it can only be done on the basis of a full analysis of the literature published in the previous 3 years, which in itself is major undertaking not lightly entered into, even by the august AGA. And so—nobody updates guidelines.
- There is little agreement on what constitutes a guideline. Does it include the concepts of a "position statement," a "technical review," and "algorithm," and a "technology assessment," for example?

So, what are the Americans societies doing (Table **1**)?

The Europeans are unable to keep up with the powerful publishing program being pursued by their U.S. colleagues (Table **2**).

Possibly because the American societies are ahead, they also have been the first to see the problems looming ahead—they appear to be having more difficulty in updating their guidelines. However, this may also be because their guidelines tend to be more solid, more evidence-based, and more like systematic reviews—some of them, at least (Table **3**).

In conclusion, therefore, here are some notes for reflection (with apologies for my serious WGO-OMGE bias):

- Gastroenterology guidelines are not based on a systematic review of the available evidence.
- Most gastroenterology guidelines are out of date or will be soon.
- There is very considerable overlap between published gastroenterology guidelines, even when published by the same society.
- Only the WGO-OMGE guidelines (www.omge.org) are published in all the world's major languages.
- Only the WGO-OMGE guidelines include cascades—different guideline options that take into account the resources available.
- Guidelines ought to be ongoing, iterative documents—never finished!
- Multiple-society central guidelines may be better than single-society guidelines.

Table 1. Guidelines produced in the last 3 years (2003–2006) by three large societies in the USA, with the most recent ones first[1]

ASGE (total is 134) [2] http://www.asge.org/ nspages/practice/patientcare/sop/index.cfm	**AGA (total is 38)** [3] http://www.gastro.org/ wmspage.cfm?parm1=160	**ACG (total is 21)** http://www.acg.gi.org/ physicians/resources.asp#guidelines
• Quality of endoscopy • Colorectal cancer screening and surveillance • Inflammatory bowel disease • Endoscopy in the elderly • Surveillance of premalignant conditions in the upper gastrointestinal tract • Risk management • Acute non-variceal upper gastrointestinal hemorrhage • Low molecular weight heparin and non-aspirin antiplatelet agents • Capsule endoscopy • Use of propofol in gastrointestinal endoscopy • Endoscope disinfection • Antibiotic prophylaxis • Conscious sedation and monitoring • Preparation of patients • EUS evaluation of mediastinal adenopathy • Obscure gastrointestinal bleeding • Esophageal cancer • Colonoscopy complications • ERCP complications • Argon plasma coagulation • Tissue sampling and analysis • Safety and infection prevention • Endoscopy during pregnancy and lactation	• Drugs in IBD (corticosteroids, immunomodulators, infliximab) • Hepatitis C • Quality in practice • Dyspepsia evaluation • Esophageal carcinoma • Esophageal manometry • Gastroparesis • Hemorrhoids • Sedation • Colorectal cancer screening • Anal fissure • Osteoporosis and gastrointestinal diseases • Osteoporosis and hepatic disorders • Perianal Crohn's disease • Short bowel syndrome and transplantation	• Dyspepsia • Ulcerative colitis • Fecal incontinence • Gastroesophageal reflux disease

ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; ASGE, American Society for Gastrointestinal Endoscopy.

[1] Quality is not taken into account. All three are of poor quality from the point of view of evidence-based medicine; there is no evidence of a systematic review of the literature in a strict "Cochrane" sense. Most appear to be based on Medline searches only. Hence it is not possible to compare simply the total number of guidelines published.

[2] The ASGE uses a very broad definition of "guideline," including many technology assessments. The ASGE column does not include biliary and pancreatic endoscopy guidelines, nor their extensive collection of "technology assessments."

[3] The AGA guidelines combine technical reviews with position statements. These are the best we have to date, but they too are inadequate from a methodological point of view. The evidence base for their guidelines is not always clear.

All in all, the available guidelines represent a magnificent publishing program from the top gastroenterology societies. All of the societies have told me they are looking to the future to make sure that new developments are published as soon as possible. These guidelines work hard to narrow the gap between knowing and doing. One promising example of the way forward can be found at http://www.acg.gi.org/media/asgejoint/QualityinEndoscopyBjorkmanPopp.pdf, where one can see the results of excellent cooperation between two of the big players—the ACG and ASGE—with a jointly developed and researched publishing program on quality indicators for endoscopy.

Acknowledgment

My thanks go to Professor A. Gangl in Vienna for providing me with information about the German-language gastroenterology guideline sites.

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Table 2. Gastroenterology guidelines produced by large European organizations in the last 3 years, with the most recent ones first

EDMC (total is 24) [1] http://www.digestive-motility.org/ediciones/JAN2006-21/medical.htm	**BSG (total is 27)** [2] http://www.bsg.org.uk/bsgdisp1.php?id=48c1b0bcae9daa89d36a&h=1&m=0144	**DGVS (total is 10)** [3] http://dgvs.de/322.php	**ESGE (total is 12)** http://www.esge.com/index.php?page=guidelines
• Botulinum toxin in chronic anal fissure, gastroparesis, achalasia, and in non-achalasia esophageal motility disorders • Enteral nutrition • Heller myotomy in achalasia • Parenteral nutrition • Pneumatic dilation and achalasia • Dysphagia • Recurrent vomiting • Intestinal pseudo-obstruction • Chronic constipation • 24-h esophageal pH-metry • Anorectal manometry • Colonic transit time scintigraphy • Electrogastropathy • Gastric barostat/ tensostat • Gastric emptying—scintigraphy • Gastrointestinal manometry • Hydrogen breath test • Intestinal gas transit • Esophageal manometry • Esophageal transit scintigraphy • Esophageal sensory testing • Orocecal transit time testing • Oropharyngeal video fluoroscopy • Sphincter of Oddi manometry	• Hepatitis B • Nutritional support • Endoscope disinfection • Barrett's esophagus • Nonmedical endoscopists • Iron-deficiency anemia • Referral for suspected cancer • Gastroentero-pancreatic neuroendocrine tumors • Pancreatic cancer • Acute pancreatitis • Liver biopsy • Dyspepsia • Colorectal cancer • Inflammatory bowel disease • Esophageal dilation • Enteral feeding • Sedation for endoscopy • Hepatitis C • Chronic diarrhea and malabsorption • Hepatocellular carcinoma (HCC)	• Esophageal reflux • Colorectal carcinoma • Crohn's disease • Chronic hepatitis • Virus hepatitis C • Virus hepatitis B/D	• Video capsule endoscopy • Endoscope service and repair; quality control • Endoscope disinfection

Table 3. Currency of gastroenterology guidelines

Society	Guidelines produced in 2003–2006 (n); total in brackets	% over 3 years old
AGA	18 (38)	53%
ACG	4 (21)	81%
OMGE	12 (17)	29%
EDMC	53 (53)	0%
ASGE	23 (134)	83%
ESGE	3 (12)	75%
BSG	18 (27)	33%
DGVS	5 (10)	50%

BSG, British Society for Gastroenterology; DGVS, Deutsche Gesellschaft für Verdauungs- und Stoffwechselkrankheiten (German Society for Digestive and Metabolic Diseases); EDMC, European Digestive Motility Center; ESGE, European Society of Gastrointestinal Endoscopy.

[1] The EDMC guideline total includes standardized guidelines, technical protocols, management protocols and flowcharts, plus extensive drug profiles for the 30 most commonly used drugs in motility disorders. They are very good indeed; strictly speaking of course, they are not guidelines at all. Their approach is different. But who is aware that they exist? They need more publishing expertise, urgently—another year down the line and everything will need to be updated again.

[2] Of the three BSG 2006 guidelines, two are simply links to guidelines from the National Institute of Clinical Excellence (NICE).

[3] The DGVS guidelines are in German. There are a number of endoscopy guidelines and recommendations from the DGVS endoscopy section, but these are all pre-2003. Additional German-language guidelines are available from the Austrian Society for Gastroenterology (www.oeggh.at) and the Swiss Society (http://www.sggssg.ch/)

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The task of documenting the success of GERD therapy is complicated by the fact that the extent of mucosal damage stands in no relation to the severity of symptoms.[1] Until now, GERD assessment has relied primarily on the measure of esophageal healing. However, 70% of all patients with GERD symptoms have endoscopy-negative GERD.[2,3]

Symptom assessment is critical to the successful management of a patient. In recent years, research has suggested that the symptom complex experienced by GERD patients is much wider than previously appreciated. Besides heartburn, acid eructation and pain on swallowing a variety of other GERD-related symptoms are experienced including nausea, diarrhoea, sleep disturbance, and other complaints, such as respiratory symptoms.

Patients may find it difficult to describe accurately all the symptoms of GERD they are experiencing. Consequently, the physician may not gain a full picture of a patient's symptoms and the patient 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.

To address this medical need, ALTANA Pharma has developed ReQuest™, 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.

The short version of ReQuest™ is solely focused on the seven dimensions and can be completed in less than 5 minutes, while the full version, which takes approximately 20 minutes, asks additionally for the occurrence of symptom descriptions typical to the corresponding dimension. Both tests have undergone extensive clinical trial evaluation and statistical analysis confirming their internal consistency, test-retest reliability, construct validity and responsiveness to changes during treatment.[4,5,6] Furthermore, ReQuest™ fulfils 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.

Combining symptom assessment with esophageal healing

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

A recent randomised, double-blind study using ReQuest™ has established pantoprazole as non-inferior to esomeprazole (both 40 mg/day) over 12 weeks with regard to complete remission in 581 patients with erosive GERD. Pantoprazole was superior to esomeprazole with respect to endoscopically confirmed healing.[7] A second randomised, double-blind ReQuest™ study, demonstrated parity between pantoprazole and esomeprazole (both 40 mg/day) in terms of symptom relief scores over four weeks' treatment (n = 561), 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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Nexium®
esomeprazole

ABBREVIATED PRESCRIBING INFORMATION: Nexium® (esomeprazole magnesium). See local prescribing information for full details. **PHARMACODYNAMIC PROPERTIES:** Nexium® reduces gastric acid secretion through a highly targeted mechanism of action by being a specific inhibitor of the acid pump in the parietal cell. **INDICATIONS AND DOSAGE: Treatment of erosive reflux esophagitis:** Nexium® 40 mg once daily for 4–8 weeks. **Long-term management of patients with healed esophagitis to prevent relapse:** Nexium® 20 mg once daily. **Symptomatic treatment of gastro-esophageal reflux disease:** Nexium® 20 mg once daily in patients without esophagitis. Once symptoms have resolved, an on demand regimen of 20 mg once daily can be used when needed, to control subsequent symptoms. ***Helicobacter pylori*-associated peptic ulcer disease:** Healing of *H pylori*-associated duodenal ulcer, prevention of relapse of peptic ulcers in patients with *H pylori*-associated ulcers: Nexium® 20 mg, amoxicillin 1 g and clarithromycin 500 mg, all bid for 1 week. USA – Nexium® 40 mg once daily, amoxicillin 1 g and clarithromycin 500 mg twice daily, all for 10 days **CONTRAINDICATIONS:** Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation. **WARNINGS AND PRECAUTIONS:** In the presence of any alarm symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melena) and when gastric ulcer is suspected or present, the possibility of gastric malignancy should be excluded before treatment is initiated. **INTERACTIONS:** Due to the decreased intragastric acidity, the absorption of ketoconazole and itraconazole can decrease during esomeprazole treatment. Concomitant administration of esomeprazole resulted in a 45% decrease in clearance of diazepam. Concomitant administration of esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients; but dose adjustments were not required in this study. In healthy volunteers, combined therapy with esomeprazole and cisapride resulted in a 32% increase in AUC and a 31% prolongation of elimination half-life but no significant increase in peak plasma levels of cisapride. Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, as with all patients receiving warfarin, monitoring is recommended during concomitant treatment with esomeprazole. **PREGNANCY AND LACTATION:** Caution should be exercised when prescribing Nexium® to pregnant women. Nexium® should not be used during breast-feeding. **UNDESIRABLE EFFECTS:** The following adverse drug reactions have been identified or suspected in the clinical trials programme. None was found to be dose related. Common: Nausea/vomiting, diarrhoea, constipation, abdominal pain, flatulence and headache. Uncommon: Dermatitis, pruritus, urticaria, dizziness and dry mouth. From marketed use, there have been rare reports of increased liver enzymes and of hypersensitivity reactions e.g. angioedema, anaphylactic reaction. For further information please contact AstraZeneca, SE-431 83 Mölndal or the local AstraZeneca subsidiary.

Nexium® is a registered trademark of the AstraZeneca group of companies.

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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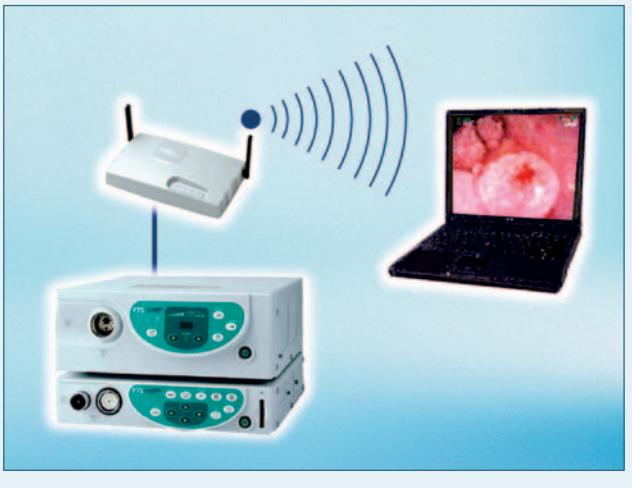
DICOM & Image Gateway (DIG), the imaging software for the EPX-4400 video processor from Fujinon



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BREAKFAST MEETING

Innate Immunity Activation:
A New Approach to the Treatment of Crohn's Disease

Chair: Stefan Schreiber, MD

7:00-7:10
Introduction: The Need for New Treatment Approaches
Stefan Schreiber, MD

7:10-7:30
Innate Immunity: A New Target for Treating Crohn's Disease
Richard Flavell, PhD

7:30-7:50
Sargramostim, an Innate Immunity Activator for the Treatment of Crohn's Disease: From Theory to Clinical Practice
Alastair Forbes, MD

7:50-8:00
Question and Answer Session

Tuesday, October 24th 2006
7:00-8:00 AM, Room Oslo
International Congress Centrum (ICC)
Berlin, Germany

Visit us at Booth #6, Hall 12
and enjoy a drink at the Innate Immunity Bar