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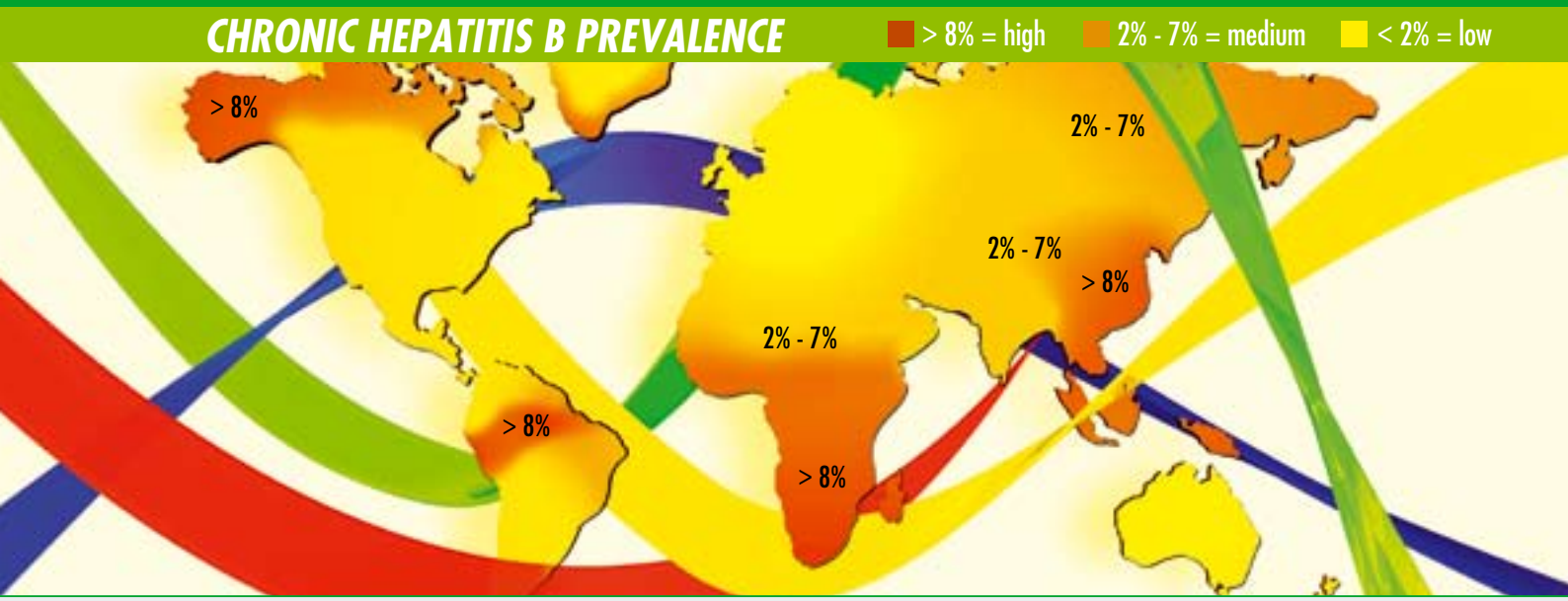
WGN
WORLD GASTROENTEROLOGY NEWS

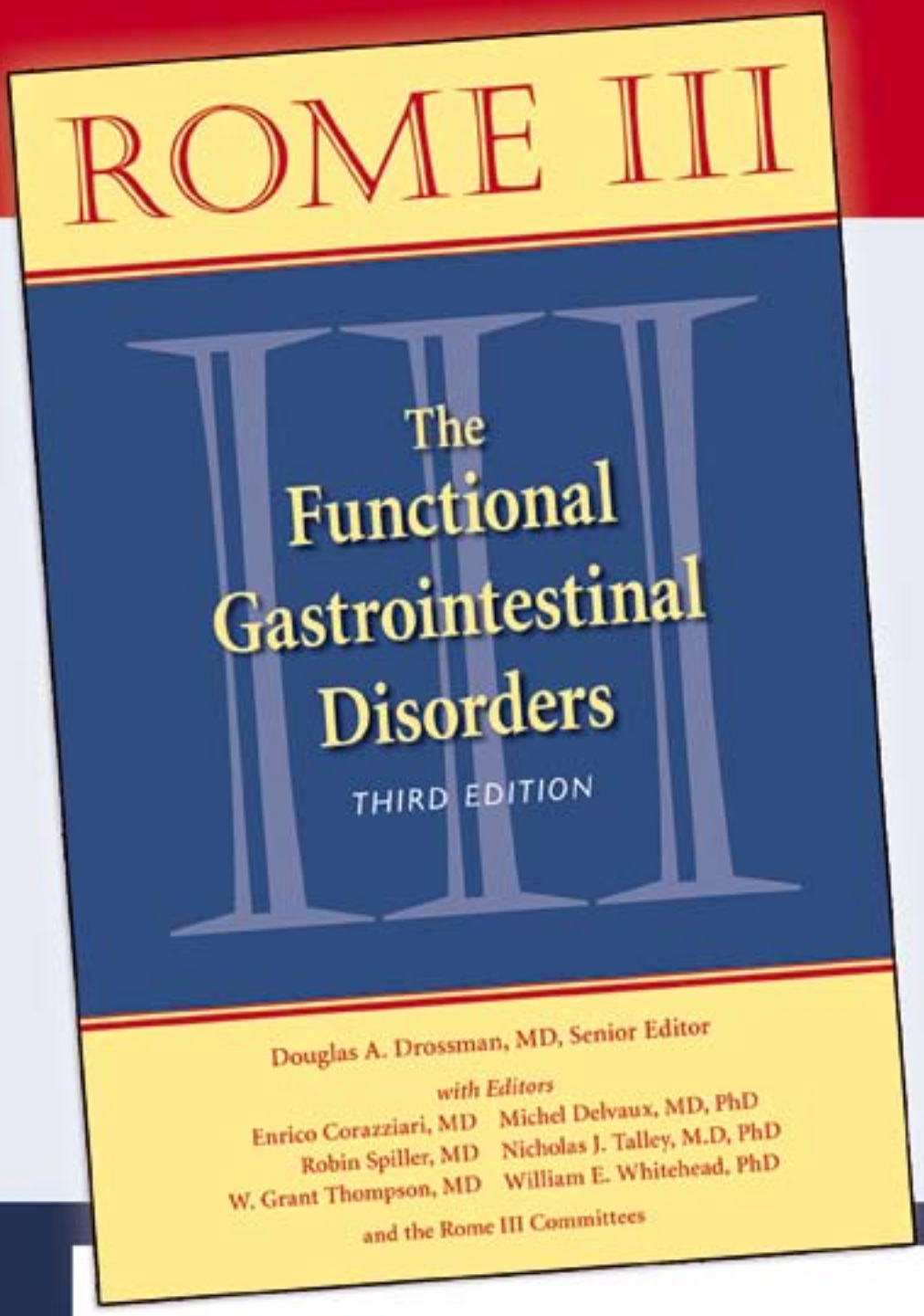


Official Newsletter of the World Gastroenterology Organisation
and the World Organisation of Digestive Endoscopy

FOCUS: Liver Diseases
Hepatitis C Therapy
NAFLD Detection & Treatment
Hepatitis Epidemiology
World Digestive Health Day "Hepatitis": May 29, 2007

GI on the Frontiers: Sudan, Chile
An Interview with One of the World's Best Gastroenterologists
WGO & UEGW present GASTRO 2009: London

ISSN 1567 7753



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Douglas A. Drossman, MD, Senior Editor

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"Red flag" questions to aid the clinician in identifying symptoms and signs that would suggest further evaluation to exclude other diagnoses or when needed to make a mental health referral.

A table is included that compares the Rome II and new Rome III diagnostic criteria.

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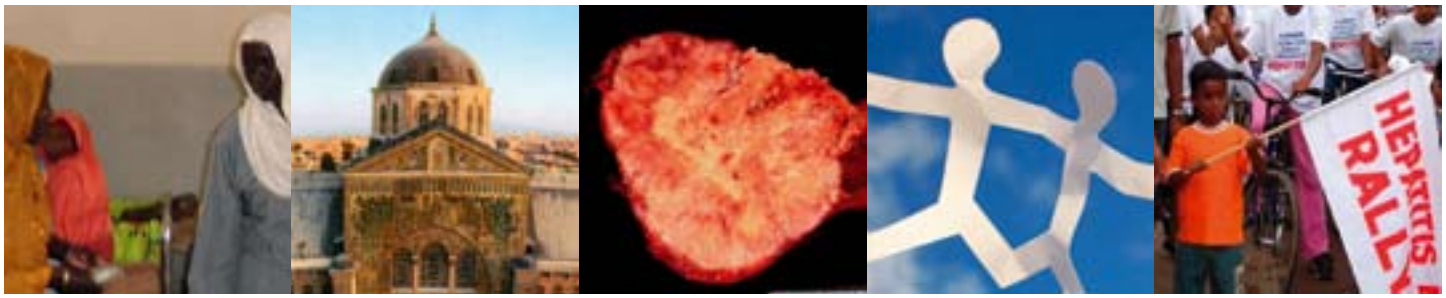

Contents

In honour of World Digestive Health Day 2007, the graph on the cover illustrates chronic hepatitis B prevalence rates across the globe.

Farewell from Jerry Waye

World Gastroenterology News (WGN) has a unique role, serving as the face and voice of the international world organizations in the field, WGO and OMED—and for many people, it is the only item that provides information about the organizations. In the past, each organization had its own newsletter, and mailings were sent out to almost the same list of gastroenterologists and endoscopists across the globe. Because of financial constraints, the two organizations merged their newsletters into one, and *World Gastroenterology News* then represented both WGO and OMED. The original editors of the combined newsletter were Prof. Meinhard Classen and Prof. Alberto Montori, now Editors Emeriti of *WGN*.

It has been fun to be the editor of *WGN* over the past few years. We have brought news of the gastroenterology community and have profiled important people in the field in our "Personality Corner." In this issue, Dr. Michael Farthing, one of the greatest gastroenterologists in the world, is interviewed about his life and his outlook on the future. We have run series such as "Women in Gastroenterology" and "Medicine on the Frontier." We have provided scientific information on a wide variety of topics and reports from meetings throughout the world. Our librarian, Justus Krabshuis, writes on different topics and presents tips on how to work with the Internet. Guidelines on several issues in gastroenterology have been published in a collectable format, and the guidelines have attracted very positive international attention, as noted in this issue.

Over the years, the newsletter has grown, but the work and effort that have gone into making this a welcome newsletter have not been mine alone. While my steering may have been successful, the motor that drives each issue is in the Medconnect office in Munich under the direction of Ms. Bridget Barbieri. My right-hand Medconnect assistant has been Molly Donohue, who makes sure we have the proper balance of articles, that timelines are adhered to, that follow-up letters are sent when authors are tardy with submission of their manuscripts, and that our series of topic-oriented articles are on schedule. In addition, she gives me advice, suggestions, and encouragement. The Medconnect staff are the backbone of this newsletter and are the ones with whom I am pleased to share the credit for its success.

In addition to the articles in this issue mentioned above, we have sollicited a report from one of the world's hotspots, Darfur in the Sudan, and we have several papers on liver disease. Hepatitis B therapy (M. Shiffman) and the refractory GERD patient (J. Richter) are among the highlights, and the cover illustrates the worldwide incidence of hepatitis B. The erudite Dr. René Lambert informs us once again about an oncology topic of international interest, and the International Digestive Cancer Alliance (IDCA) continues to report on its ongoing campaign.

With this issue of *WGN*, WGO takes over full responsibility for the newsletter. My friend and colleague, Dr. John Baillie, has been appointed as the new Editor, and I wish him well. I shall be kept busy as President-Elect of OMED, as a member of the Scientific Advisory Committee for the next World Congress of Gastroenterology (Gastro 2009), as a full-time practitioner of gastroenterology and endoscopy, and as Chief of the Gastrointestinal Endoscopy Unit at the Mount Sinai Hospital in New York.

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WGO President's column

Eamonn Quigley

Looking forward to fifty!

In 2008, the World Organization of Gastroenterology will be marking its silver jubilee, and over the next 12 months we will be keeping in touch with you in regard to special activities to mark this milestone. Watch this space! I truly believe that the organization's founders would be pleased with the progress we have made and would take as much pride as we do in its current state.

The past year has seen further expansion in our activities, with the launch of the Bangkok training center, new guidelines, and ever-increasing demand for the Train-the-Trainers program. WGO was honored to be able to take part in the wonderful Pan-American meeting in Cancun, Mexico, where Professor Alan Hofmann presented an outstanding Third WGO Lecture. Our close relations with the Inter-American Association of Gastroenterology are deeply appreciated.

The coming year, 2007, will see further growth. In response to demand, we will be holding an unprecedented total of three Train-the-Trainer programs, each in collaboration with a national society: with the Portuguese Society of Gastroenterology in Porto, in April; with the American Society for Gastrointestinal Endoscopy in Chicago, in September; and in Angra dos Reis with the Brazilian Federation of Gastroenterology, in November. It is evident that WGO has become the world leader in bringing modern educational methods to gastroenterology training, and we look forward to future collaborations with other national societies in the coming years. This year will also witness the inauguration of two further Advanced Training Centers, in La Plata, Argentina, and in Perth, Australia—providing even more opportunities for young gastroenterologists from across the globe to acquire further skills with the experts. We would like to express our sincere gratitude to all, both in the training centers and in the national societies, who are continuing to work so hard with us to ensure that our mutual mission of promoting the highest standards in training and education in gastroenterology across the world continues to be realized.

Look out also for this year's World Digestive Health Day on May 29—this year, the focus will be on a truly global issue: hepatitis. We have already heard from many of you on your plans to mark this event and attract attention to this vital health issue; we welcome your input. This is an opportunity for all of us to highlight digestive disease.

The year 2009 will also be a banner year for the society: GASTRO 2009, to be held in association with the United European Gastroenterology Federation and with input from the British Society of Gastroenterology, will take place in London, and I am delighted to report that plans for this landmark event are well in hand.

Guardian of Digestive Health.
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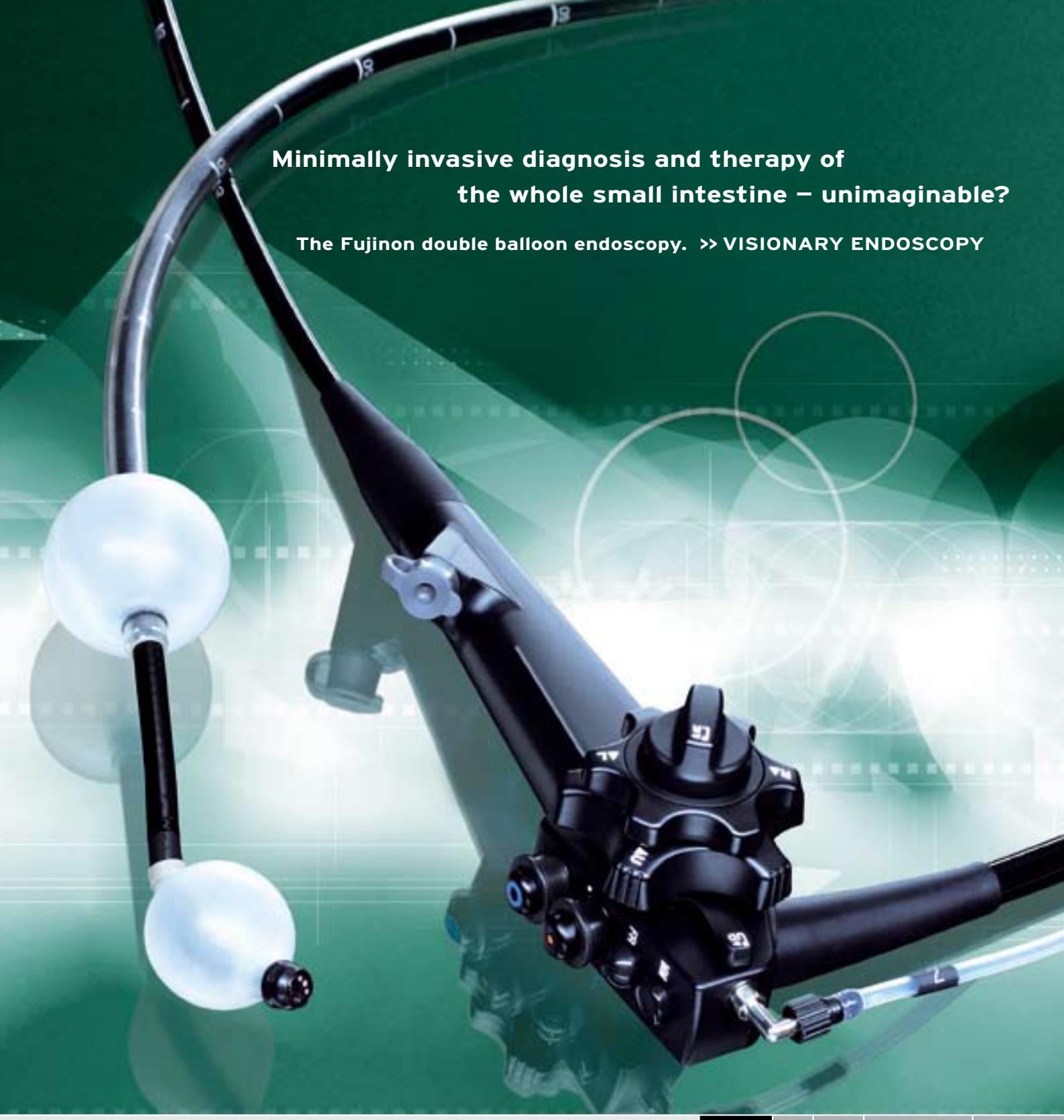
WGO and OMED

At its foundation almost 50 years ago, the World Gastroenterology Organization (OMGE, as it was then known) was the single global voice of gastroenterology. Subsequently, a world organization of digestive endoscopy—the *Organisation Mondiale d'Endoscopie Digestive,* OMED—was founded to represent the endoscopic aspects of the discipline, and OMGE and OMED collaborated in organizing the World Congresses of Gastroenterology for several decades. Following the World Congress in Vienna in 1998, the two organizations moved closer together, with the formation of joint committees on training and education and research. Collaboration between the two organizations in the area of training and education led to the now highly successful Train-the-Trainers programs and the inauguration of several training centers around the world.

Over the past 12–18 months, WGO and OMED have looked at the possibility of an even closer alliance, involving—as proposed by WGO—integration of the two societies with a shared budget, governance, and strategy and with a single treasurership, that of the WGO Treasurer. Although it was clear that there was considerable agreement and that the goals and ambitions of the two societies have much in common, it became clear that a move towards integration was premature. To allow both organizations to pursue their individual agendas, the two organizations will continue as before to be independent in governance, finances, and strategic planning, but will continue to collaborate on the World Congress and to maintain close links in promoting excellence in gastroenterology throughout the world. Programs that were previously presented as joint efforts, such as Train-the-Trainers and the Training Centers, will now be under the sole purview of the WGO, which will endeavor to work with all who represent the interests of gastroenterology and gastroenterologists across the globe and to promote standards in training and education in gastroenterology, in all of its manifestations. We, in WGO, wish OMED well for the future and we look forward to mutual success in our future programs.

www.worldgastroenterology.org



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OMED: the future

Anthony Axon (President, World Organization for Digestive Endoscopy)

OMED's mission is the worldwide promotion of the study and advancement of digestive endoscopy for the diagnosis and treatment of gastrointestinal diseases.

The organization was set up as an independent international society in 1962. At that time, a number of eminent endoscopists believed there was a need for a world organization that would focus solely on the endoscopic examination of the gastrointestinal tract. During the years that have passed since then, endoscopy has advanced far beyond anything that could have been imagined. The development of fiberoptics and chip technology now enables us to see the whole of the gastrointestinal tract minutely and in real time. We are able to obtain histology, provide therapy, and contribute to research in a manner that has revolutionized the understanding and practice of gastroenterology.

The ability to perform endoscopy is the skill that sets gastroenterologists apart from other medical specialists, and its acquisition has become the most important area of gastroenterological training. The advances in endoscopic technology are such that it is no longer possible for anyone to be expert in all of its modalities. Increasingly, gastroenterologists are appointed on the basis of the specialized endoscopic skills they possess and the specific services they are able to provide.

Many times during the past 40 years, people believed that endoscopy had finally reached its limit—only for this to be disproved almost immediately. The last five years have seen the introduction of amazing new equipment that provides a veritable Aladdin's cave of magical tools. There has never been a time in the history of endoscopy more appropriate for a specialist endoscopy organization to thrive. The huge success of the live endoscopy sessions screened by our colleagues in Toronto at the Montreal World Congress attest to the interest that delegates of all ages and nationalities have in endoscopy—the vast auditorium in which live endoscopy was projected each day during the conference was virtually full for the whole meeting, attracting more than half of the delegates at any time.

Over the past 12 months, OMED has established a new web site at www.omed.org, and we have begun a series of Endoscopy Directors' Training Workshops, the first of which was held at the United European Gastroenterology Week in Berlin. We have contributed to meetings on colon cancer screening, and in conjunction with the Asian–Pacific Society of Digestive Endoscopy, we have set up a Joint Working Party to develop guidelines for gastric cancer screening. A series of "How I do it" articles describing the practical details of challenging techniques will be published on the web site in the near future.

In conjunction with the European Society of Gastrointestinal Endoscopy (ESGE), we organized a symposium on Ethics and Gastroenterology and Digestive Endoscopy in Kos last year, a report of which will be published shortly. Our Research Committee has commissioned a series of meeting reports summarizing the endoscopic research presented at major international meetings (DDW 2006 is on our web site).

We are designing an equipment compendium that will provide a global online listing of all available endoscopic equipment. We plan to undertake research into the cost-effectiveness of high-tech endoscopy in the developing world. A number of other projects are ongoing or planned.

Following a period of close cooperation with our friends in the World Gastroenterology Organization (WGO), the two organizations have reached a parting of the ways. We will, however, work together to ensure the success of GASTRO 2009 in London, where the World Congress of Gastroenterology will be held in conjunction with the UEGW, but otherwise we will work independently.

OMED has an exciting, varied, and well-planned program for the years ahead—so with the financial support of our industrial colleagues and the practical and intellectual input of world endoscopists, we are looking forward to a bright future. Digestive endoscopy is the most powerful diagnostic tool at the gastroenterologist's disposal and it has a vital role to play in treatment and disease prevention. We will therefore press forward with dedication and determination.

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The refractory GERD patient

Joel E. Richter

Initial treatment and diagnostic approach

Patients with symptoms of gastroesophageal reflux disease (GERD) are frequently given a 4–8-week trial of a proton-pump inhibitor (PPI) in the morning. Failure to respond occurs in 25–42% of patients, thus placing them in a more difficult-to-manage classification. At this point, the physician should ensure patient compliance and review timing of the PPI dose (30–60 min before eating). One recent study found that nearly 70% of primary physicians and 20% of gastroenterologists gave the PPI dose at bedtime or did not believe the relationship to meals was important. Most physicians increase to twice-daily dosing (before breakfast and dinner), with up to 25% of patients responding. Patients who do not experience improvement fall into the "refractory GERD" category and are the subject of this discussion (Figure 1).

The first study that should be carried out in the refractory GERD patient, if it has not been done earlier, is an upper endoscopy. In my experience, the "refractory GERD" patient with a normal endoscopy is relatively common. Esophageal and gastric pH testing during b.i.d. PPI therapy is my next study of choice. However, our experience at the Cleveland Clinic showed that only 7% of patients with classic heartburn symptoms and 1% of subjects with atypical reflux symptoms still have abnormal amounts of acid reflux. Although it is currently popular today to suggest that these patients have non-acid gastroesophageal reflux, other alternatives need to be considered, and may be more common. For example, these patients could have "missed" acid reflux that was not picked up on a single-day study (25% of cases in the Bravo capsule experience), or the pH probe might be missing distal acid reflux that is confined to just above the esophagogastric junction.

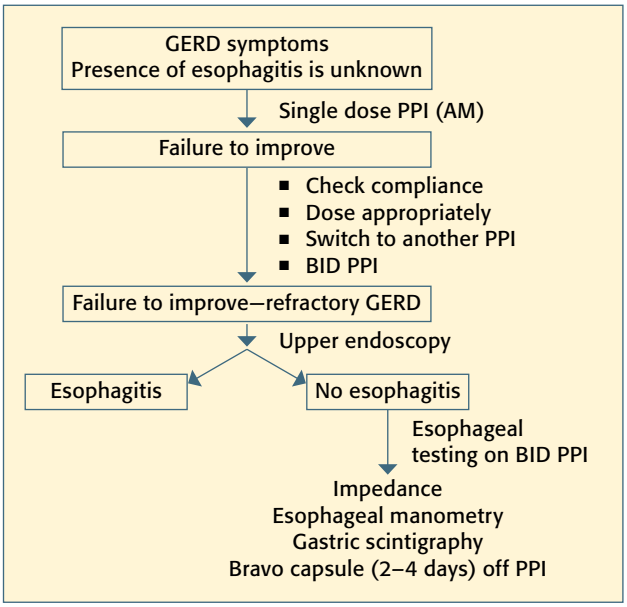

Fig. 1 Algorithm for GERD diagnosis and therapy.

Patients receiving PPIs b.i.d. rarely have significant esophagitis unless noncompliance is an issue or they have a hypersecretory state, such as Zollinger–Ellison syndrome. If esophagitis is present, diagnoses to consider include:

- *Pill-induced esophagitis.* Pills may be a complicating factor in young patients or in the elderly. In younger patients, symptoms are acute and often associated with odynophagia, chest pain, and dysphagia. In the elderly, complaints may be more chronic and may complicate an underlying esophageal motility disorder or subtle stricture. Common drugs include doxycycline and tetracycline (especially in young people), alendronate, naproxen, potassium chloride, ascorbic acid, quinidine and ferrous sulfate. In a recent large series, one-third of the cases were due to aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs). The majority of patients improve within 1 week after the offending agent has been withdrawn and treatment with PPIs and/or sucralfate is administered.
- *Skin diseases.* A variety of dermatologic diseases are associated with esophageal involvement. Those most likely to cause an intractable esophagitis syndrome include epidermolysis bullosa acquisita, pemphigus vulgaris, cicatricial pemphigoid, and lichen planus. These are generally considered uncommon autoimmune diseases. Endoscopy reveals diffuse erythema, blistering of superficial mucosa that easily peels away from the submucosa, whitish nodules/plaques, and proximal stric-

ture disease. Some patients require frequent esophageal dilation for their stricture disease; intralesional corticosteroid injection may also be helpful.

- *Acid hypersecretors.* The hypersecretion of acid may impair the efficacy of PPIs, but acid hypersecretion is uncommon in GERD patients. Patients with Zollinger–Ellison syndrome have endoscopically visible esophagitis in 30–45% of cases, some with difficult-to-manage esophageal strictures.
- *Genotypic differences.* PPIs are mainly metabolized by the hepatic cytochrome P-450 2C enzymes, and although pharmacokinetic interactions at this level are uncommon, there is considerable genetic variation in enzyme capacity. Recent reports reveal that plasma concentrations and acid-inhibitory effects on omeprazole and lansoprazole depend on the CYP2C19 genotype. Rapid metabolizers show a lower effect of PPIs on gastric acidity and esophagitis healing than slow or intermediate metabolizers. This genetic propensity to be a rapid metabolizer of PPIs is most common in the Asian population (12–20%) and infrequent in Caucasians (3–6%).
- *Eosinophilic esophagitis.* Patients with eosinophilic esophagitis, an increasingly common diagnosis, are usually young and male, and they present with dysphagia, often with a history of food impaction. The diagnosis is suggested by endoscopic findings of multiple rings, longitudinal furrows, or pinpoint white exudates. Peripheral eosinophilia is uncommon. The pathogenesis of eosinophilic esophagitis is unknown. Eosinophils and symptoms will improve with inhaled steroids (fluticasone propionate b.i.d., before breakfast and dinner) for 6 weeks.

Refractory GERD patients without esophagitis

The most common endoscopic finding in patients with "refractory GERD" is a normal esophagus, often without a hiatal hernia or at most with a small hernia. Here the issue is much more problematic and less likely to lead to a satisfactory outcome. In our experience, these patients on PPIs b.i.d. have a less than 10% chance of having an abnormal esophageal reflux profile for acid, and non-acid gastroesophageal reflux and "missed" gastroesophageal reflux therefore need to be considered. Other potential etiologies such as achalasia and gastroparesis should always be evaluated and excluded.

- *Nocturnal gastric acid breakthrough (NAB).* Persistent gastric acidity at night despite b.i.d. PPI therapy is common (60–80% of patients). However, this natural phenomenon allows the potential for breakthrough acid reflux at night, when the esophagus is least likely to protect itself. Studies in healthy volunteers showed that NAB was nearly eliminated with the addition of histamine$_2$-receptor antagonists (H_2RAs; ranitidine 150 mg or 300 mg at bedtime) to omeprazole 20 mg twice daily. Although it has not been formally tested, intermittent H_2RA use when the patient is exposed to a refluxogenic stimulus (e.g., after a large fatty meal or a night of cocktails) may possibly be the optimal approach to minimizing the chance of developing drug tolerance.
- *Non-acid gastroesophageal reflux.* New technology makes it possible to measure non-acidic reflux with the patient in an ambulatory state. Most often, the reflux represents previously ingested food and least frequently reflux of duodenal contents (i.e., bile reflux). Several studies on b.i.d. PPI therapy suggest that 20–40% of patients have non-acid reflux, often containing bile, which may be contributing to their symptoms. The role of antireflux surgery in patients with non-acid reflux has not been carefully studied, except for those with clear symptoms of regurgitation.
- *Missed gastroesophageal reflux.* Acid gastroesophageal reflux may be missed by traditional tube catheters because the phenomenon does not occur every day, because the pH probe has been positioned too proximally in the esophagus, or because the noxious effect of the nasal catheter limits eating and activity, leading to a false-negative test. Wireless pH monitoring (with the Bravo capsule) allows measurement of acid reflux for at least 2 days; initial studies have shown that at least 25% of patients do not have reflux on two consecutive days. The Bravo capsule allows pH monitoring in unusual situations (heavy exercise, swimming) and can

potentially continue collecting pH data until the capsule dislodges (usually after 5–7 days).

- *Wrong diagnosis.* Achalasia with a minimally dilated esophagus may occasionally mimic GERD. This can easily be diagnosed with esophageal manometry. Patients with epigastric pain, early satiety, postprandial abdominal bloating, nausea, and vomiting may have delayed gastric emptying that is contributing to or worsening their reflux disease.

Conclusions

- Patients with refractory GERD—defined as symptoms unresponsive to PPIs b.i.d. after 4–8 weeks of treatment—should first undergo upper endoscopy to exclude ulcer disease and cancer and to identify the presence of esophagitis.
- Refractory esophagitis suggests a pill injury, a skin disease with associated esophageal involvement, or the syndrome of eosinophilic esophagitis. Less likely are a hypersecretory syndrome (Zollinger–Ellison) or genotypic differences in PPI metabolism.
- Refractory reflux syndrome with a normal endoscopic examination are more problematic and require further testing, including measurement of non-acid reflux, prolonged pH monitoring over 48 h or more, esophageal manometry, and gastric function tests. Although the diagnosis of non-acid reflux is popular today, the appropriate medical and surgical treatments are poorly defined. Atypical presentation of achalasia and gastroparesis should not be overlooked.

This article is an excerpt from an original paper that was presented during the 2006 American College of Gastroenterology course held in Las Vegas. The full paper can be viewed online at www.worldgastroenterology.org.

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TELL US YOUR STORY

A call to all TTT and Training Center Participants

We would like your feedback on WGO sponsored training programs. If you have taken part in a Train the Trainer Workshop or have visited one of the 10 WGO Global Training Centers, WGO asks you to share your experience. What lasting effects have the program had on you as a doctor and/or educator? What kind of impact has your training had in your region? Any thoughts, comments or input on the effects of the WGO training programs are greatly appreciated.

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Nonalcoholic liver disease: detection and treatment

Zobair M. Younossi

Nonalcoholic steatohepatitis (NASH) is a liver disease that is morphologically indistinguishable from alcoholic hepatitis, but in which the patients have no history of excessive alcohol intake. It is now recognized that NASH forms part of a larger spectrum of nonalcoholic fatty liver diseases (NAFLDs). Clinical and postmortem analyses have been used to estimate the prevalence of NAFLD (20%) and NASH (2–3%) in the general population. Conditions associated with NAFLD include type 2 diabetes mellitus, obesity, and dyslipidemia, all of which are related to metabolic syndrome. The prevalence of NAFLD increases to about 50% in diabetics, 74% in the obese, and over 90% in the morbidly obese. The prevalence of NASH is 25% in morbidly obese individuals. NAFLD affects both adults and children, affecting 2.6% of children and 23–53% of obese children. Endothelial dysfunction in patients with NAFLD is suggested by their reduced vasodilator response to ischemia. In addition, increased intima media thickness suggests an increased risk for carotid artherosclerosis. A study of 2103 diabetics showed that NAFLD is an independent risk factor for cardiovascular mortality (OR 1.53; 95% CI, 1.1 to 1.7). These data indicate an interaction between NAFLD and another complication of metabolic syndrome, atherosclerosis.

Some 10–20% of patients with NASH progress to cirrhosis or end-stage liver disease within a decade or more. Risk factors for progressive disease are age, an aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio > 1, and the presence of diabetes, obesity, or metabolic syndrome. In addition, the survival of patients with NAFLD is lower than that in the general population, with mortality increasing with age, impaired fasting glucose, and cirrhosis.

There is indirect evidence relating NASH to cryptogenic cirrhosis and hepatocellular carcinoma (HCC). NASH may recur after liver transplantation, due to cryptogenic cirrhosis.

The pathophysiology of NAFLD is complex, potentially involving multiple tissues including the liver, adipose tissue (mostly central), and other peripheral tissues such as muscle. Insulin resistance plays a pivotal role in the pathogenesis of NAFLD. White adipose tissue stores and mobilizes lipids, and in the presence of caloric excess—i.e., overeating and visceral obesity—adipose stores respond pathologically. An increased release of free fatty acids from adipose tissue into the circulation influences the accumulation of lipids in the liver and striated muscle. The free fatty acids in the liver stimulates *de novo* lipogenesis and fatty acid esterification. This is accompanied by impaired apolipoprotein B-100 and the formation of very low density lipoprotein (VLDL). Together, these factors trigger lipid accumulation and oxidation in the liver, oxidative stress, inflammatory cytokines release, and possibly hepatic stellate cell activation.

The accumulation of hepatic steatosis is considered to be the first "hit" in this complex setting—a prerequisite for development of NAFLD. Additional "hits" (such as oxidative

stress, and proinflammatory cytokines) are required for progressive liver disease. There is now increasing evidence that adipokines released from white adipose tissue seem to mediate "second hits" involved in the pathogenesis of NAFLD. Adiponectin is an adipokine with anti-inflammatory properties. Low levels of adiponectin are strongly associated with visceral adiposity, hyperlipidemia, and insulin resistance. Leptin, another adipokine, is proinflammatory and may enhance hepatic fibrogenesis by increasing the expression of transforming growth factor-β and hepatic stellate cell activation. In spite of progress, the actual sequence of events in NAFLD pathogenesis remains unclear.

NAFLD should be considered in any patient with abnormal liver enzymes, hepatomegaly, or a "bright" liver on ultrasound. It is important to exclude other causes of chronic liver disease, especially alcoholic liver disease and hepatitis C virus infection. Liver enzymes are not always sensitive markers for NAFLD, because some patients (especially those undergoing bariatric surgery) can present with normal liver enzymes in the presence of significant liver disease. Most hepatic imaging modalities can detect steatosis, but they are unable to distinguish between simple steatosis and NASH and cannot detect significant fibrosis.

The role of liver biopsy for the diagnosis of NAFLD has not been fully established for routine clinical practice. A biopsy can confirm the diagnosis of NAFLD and is the only technique that can differentiate between simple steatosis and NASH, a distinction with prognostic importance. In one study of NASH predictors, obesity, older age, and the presence of diabetes were associated with advanced fibrosis. A raised ALT or an AST : ALT ratio > 1 has also been associated with advanced fibrosis. A reasonable approach for a patient who might have NAFLD is to consider a liver biopsy for: a) those with evidence of metabolic syndrome; and b) those with persistently elevated liver enzymes despite optimal management of associated metabolic conditions such as obesity, diabetes, or hyperlipidemia.

Several proposed treatments for NASH have been used. These include modifying the clinical conditions associated with NASH (particularly the components of metabolic syndrome) with weight reduction, diet, exercise, treatment for type 2 diabetes mellitus, and treatment for hyperlipidemia. In addition to lifestyle modifications, it is important to discontinue medications that can cause NASH, including: corticosteroids, synthetic estrogens, amiodarone, perhexiline, nifedipine, and salicylates. Another option is surgical intervention for morbid obesity. Pharmacologic interventions for NASH include vitamin E, *N*-acetylcysteine, betaine, thiazolidinediones, metformin, lipid-lowering agents, anti-tumor necrosis factor, and ursodeoxycholic acid. However, no single agent improves the histological end points and long-term outcomes.

This article is an excerpt from an original paper that was presented during the 2006 American College of Gastroenterology course held in Las Vegas. The full paper can be viewed online at www.worldgastroenterology.org.

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Latin-American consensus on chronic constipation

Max Schmulson and Carlos Francisconi

The Latin-American Consensus Group on Chronic Constipation met several times in 2006, with coordinators from Latin America and with Dr. Kevin Olden from Arkansas serving as honorary coordinator. The group's aim is to define guidelines for the correct recognition, diagnosis, and treatment of chronic constipation in Latin America, on the basis of a systematic review of the literature published during the last 10 years and of treatments available in the region. Efforts to establish the consensus have been supported by the Inter-American Association of Gastroenterology (*Asociación Interamericana de Gastroenterologia,* AIGE), and meetings have included 17 representatives of the local gastroenterology associations in Argentina, Brazil, Colombia, Chile, Ecuador, Guatemala, Honduras, Mexico, Panama, Peru, Uruguay, and Venezuela. The process lasted a full year, with the main meeting being held in Los Angeles, California, in May 2006, and the conclusions were presented at the 30th Pan-American Congress of Gastroenterology in Cancun, Mexico, on 15 November 2006.

Chronic constipation is a disorder with an estimated prevalence of 7–21% in the region, with a female-to-male ratio of 3 : 1 and a significant economic impact, as 75% of patients with the disorder in Latin America use some kind of medication, including a high frequency of laxatives, with more than 50% using home remedies.

The Consensus Group recommended a diagnosis based on the Rome Criteria and diagnostic tests only in patients over 50 years of age or with any alarm symptoms. The use of a barium enema was recommended as an initial investigation only in countries with a high prevalence of idiopathic megacolon, such as Argentina and Chile.

With regard to treatment, an increase in dietary fiber up to 25–30 g/day was recommended, and no evidence was found to indicate other general measures such as exercise, increased water intake, or frequent visits to the toilet. Fiber supplements such as *Psyllium* received a grade B recommendation. Tegaserod, a 5-HT_4 agonist, and polyethylene glycol (PEG), an osmotic laxative, were both grade A recommendations. Although there was not enough evidence to recommend the use of lactulose, the consensus findings did not disapprove of its use when necessary, especially in areas of the region in which no other treatments were available.

Complementary investigations such as colonic transit followed by anorectal manometry and defecography were only recommended in patients who do not respond to the treatments mentioned above, and in areas in which these studies were available (grade C), to rule out colonic inertia and functional outlet obstruction. In patients with pelvic dyssynergia, biofeedback was recommended (grade B).

The final document from the consensus meetings is scheduled for publication in early 2007.

Latin-American consensus on gastroesophageal reflux disease

Henry Cohen, Joaquim P.P. Moraes-Filho, Giselle Tomasso, M. Luisa Cafferata, Graciela Salis, and the Latin American Consensus Group

Introduction

In a Latin-American consensus process concerning the diagnosis and treatment of GERD, experts from Latin American gastroenterology societies representing 16 countries (one vote per country) were invited by the Inter-American Association of Gastroenterology (*Asociación Interamericana de Gastroenterologia,* AIGE) and the Inter-American Society of Digestive Endoscopy (*Sociedad Interamericana de Endoscopia Digestiva,* SIED) to participate in a meeting held in Cancun, Mexico, in September 2004.

Main recommendations

Diagnosis

A methodological analysis of the evidence available on the various diagnostic tests for gastroesophageal reflux disease (GERD) shows that none of the tests can be regarded as highly effective; there is no "gold standard." The expert opinions were:

- *Endoscopy*. The following were considered to represent criteria justifying an endoscopic examination:
  - Initially in patients > 45 years of age with typical symptoms.
  - In patients < 45 years with typical symptoms who fail to respond to trial therapy with proton-pump inhibitors (PPIs) (as a therapeutic diagnostic test).
  - In patients with alarm symptoms (dysphagia, odynophagia, anemia, weight loss, hemorrhage).
  - In patients with long-standing symptoms (> 5 years).
- *24-h pH monitoring.* The indications below were suggested for prolonged pH monitoring:
  - Patients with no response to PPIs (pH monitoring should be conducted without discontinuing medication).
  - Nonerosive disease with no response to therapy (pH monitoring should be carried out with no medication).
  - Atypical GERD signs (respiratory; ear, nose, and throat; chest pain).
  - Recurrent symptoms after antireflux surgery and in the absence of lesions in the mucosa.
- *Diagnostic and therapeutic testing with PPI*. The Consensus suggested the following indications:
  - A trial of PPI should be carried out in patients under 45 years of age with typical symptoms.
  - Since there was no agreement on dose or duration, professionals are left free to choose the dosage, the term during which the test should be performed, and the criteria used to interpret the patient's response.

Treatment

- *Behavioral approach*. Dietary and lifestyle changes should be decided by each physician on a case-by-case basis.
- *Antacids, alginates, and sucralfate*. Their use can be considered to provide transient relief of symptoms.
- *Pharmacological therapy*.
  Short-course treatment:
  - There is good evidence supporting the use of PPIs instead of histamine$_2$-receptor antagonists (H_2RAs) or pharmacokinetic agents for the initial management of patients with erosive and nonerosive GERD.
  - PPIs should be the initial therapy of choice (4–8 weeks).
  - Histamine$_2$ blockers and pharmacokinetic agents are regarded as second-line therapy.

  Maintenance therapy:
  - There is good evidence supporting the use of PPIs instead of H_2RAs and pharmacokinetic agents in the maintenance treatment of patients with GERD (with or without esophagitis; grade A recommendation).
- *Pharmacological* versus *surgical therapy*. Surgical intervention is an alternative approach that is comparable with pharmacological therapy in terms of efficacy.
- *Surgical treatment: indications*. Patients who respond to medical therapy (but cannot or are not willing to continue it) are good candidates for surgery.
- *Surgical treatment: open surgery* versus *laparoscopy*. Laparoscopy is recommended.
- *Treatment of* Helicobacter pylori *infection*. Once a diagnosis of *H. pylori* infection has been made, the bacterium should be eradicated (78.5%).
- *Endoscopic treatment*. This is still considered to be experimental.

Hepatitis C therapy

Mitchell L. Shiffman

Preparing the patient for therapy

Before treatment for hepatitis C virus (HCV) infection is initiated, several laboratory tests and a thorough discussion with the patient regarding treatment should be carried out.

HCV genotype. HCV exists as a family of six different genotypes and numerous subtypes. The most common genotype in the USA is type 1. This is found in 70% of patients overall, but in 97% of African-American patients. Genotypes 2 and 3 account for most of the remaining 30% of patients. Genotype 4 is the most common genotype in Egypt and many Middle-Eastern countries. Genotype 5 is most commonly found in South Africa, and genotype 6 in South-East Asia.

There is no relationship between genotype and the severity of chronic HCV or the risk of developing cirrhosis. However, both the likelihood of responding to peginterferon and ribavirin and the optimal dose of ribavirin recommended for treatment are dependent on the genotype. Overall, patients with genotype 1 have a sustained virologic response (SVR) of 40–45% after 48 weeks of treatment; patients with genotypes 2 and 3 have a 75–80% SVR with just 24 weeks of treatment.

Serum HCV RNA level. It is important to establish the baseline level of HCV RNA before initiating treatment. Patients with high levels of HCV RNA have a lower SVR after peginterferon and ribavirin therapy in comparison with patients with a low viral load. There is no relationship between viral load and the severity of liver disease. Similarly, patients with high viral loads do not have an increased risk of developing fibrosis and progression to cirrhosis, in comparison with patients with lower viral loads. Viral load does not change over time, but remains constant even in patients who develop progressive liver disease.

It is very important to define the baseline viral load in all patients before initiating peginterferon and ribavirin therapy. Only those patients who have a marked decline in serum HCV RNA within the first several weeks to months after peginterferon and ribavirin are initiated are capable of having HCV RNA becoming undetectable with therapy and achieving a sustained virologic response.

It is frequently helpful, but not essential, to take a liver biopsy before initiating HCV therapy.

The great majority of patients with chronic HCV who receive peginterferon and ribavirin actually respond to treatment. Recognizing virologic response patterns is therefore essential for the proper management of patients receiving HCV therapy.

- *A rapid virologic response* (RVR) is defined as HCV RNA becoming undetectable within 4 weeks of the start of peginterferon and ribavirin therapy. Patients with an RVR have a 90% chance of achieving a sustained virologic response (SVR), regardless of genotype. Approximately 10–15% of patients with HCV genotype 1 and 66% of patients with genotype 2 and 3 achieve RVR.
- *An early virologic response* (EVR) is defined as a 2 log (100-fold) decline in HCV RNA from the pre-treatment baseline. Only those patients who achieve EVR are also capable of going on to achieve SVR.
- *A virologic response* (VR) is defined as HCV RNA becoming undetectable within 24 weeks of the start of treatment. It is exceptionally rare for HCV RNA to become undetectable and for patients to achieve a VR if this has not occurred within the initial 24 weeks of therapy.
- *Relapse.* Relapse is defined as becoming HCV RNA–positive after treatment has been discontinued in a patient in whom HCV RNA was undetectable at the end of treatment. Relapse occurs in about 30–40% of patients, in whom HCV RNA is undetectable at the end of treatment with peginterferon and ribavirin. The rate of relapse is markedly increased in patients who frequently miss doses of ribavirin.

Can the dose of peginterferon and/or ribavirin be reduced without affecting SVR?

The first study to evaluate the impact of dose reduction on SVR demonstrated that patients who took ≥ 80% of the prescribed dose of peginterferon and ribavirin for ≥ 80% of the planned duration of therapy (36 weeks) had a significantly higher SVR in comparison with patients who took less than this amount of medication (an SVR of 64% compared to 34%). A more careful analysis in two large recent clinical trials has recently demonstrated that dose reduction of ribavirin in patients who remain on full-dose peginterferon does not reduce SVR and that small reductions in both peginterferon and ribavirin can be tolerated without affecting SVR. However, temporarily discontinuing therapy for more than 7–14 days during the first 24 weeks of therapy leads to a marked reduction in SVR, because the patient either fails to achieve a VR or relapses after treatment is discontinued.

The standard duration of therapy for patients with chronic HCV is 48 weeks for patients with genotypes 1, 4, 5, and 6; and 24 weeks for patients with genotypes 2 and 3. The ability to achieve SVR depends on the time at which HCV RNA becomes undetectable in a patient, regardless of genotype. Identifying this time point allows treatment to be adjusted (individualized). This means that HCV RNA needs to be monitored at regular and frequent intervals to allow these treatment decisions to be made.

Patients who achieve an RVR have an SVR of 90%, regardless of genotype. The recommended duration of therapy for patients with genotypes 2 and 3 who achieve RVR should remain at 24 weeks. Similarly, the treatment duration for genotype 1 patients with RVR should remain at 48 weeks.

A recent study has demonstrated that the later during treatment that HCV RNA becomes undetectable in a patient, the lower is the likelihood of SVR.

The overall SVR in patients with genotypes 2 and 3 is 75–80%. However, it has recently been recognized that genotype 2 patients who do not achieve RVR have an SVR of only 49%. This suggests that the duration of therapy should be prolonged in these patients, possibly to 48 weeks. Although this appears to be intuitively correct, there are currently no data available to support this recommendation.

This article is an excerpt from an original paper that was presented during the 2006 American College of Gastroenterology course held in Las Vegas. The full paper can be viewed online at www.worldgastroenterology.org.

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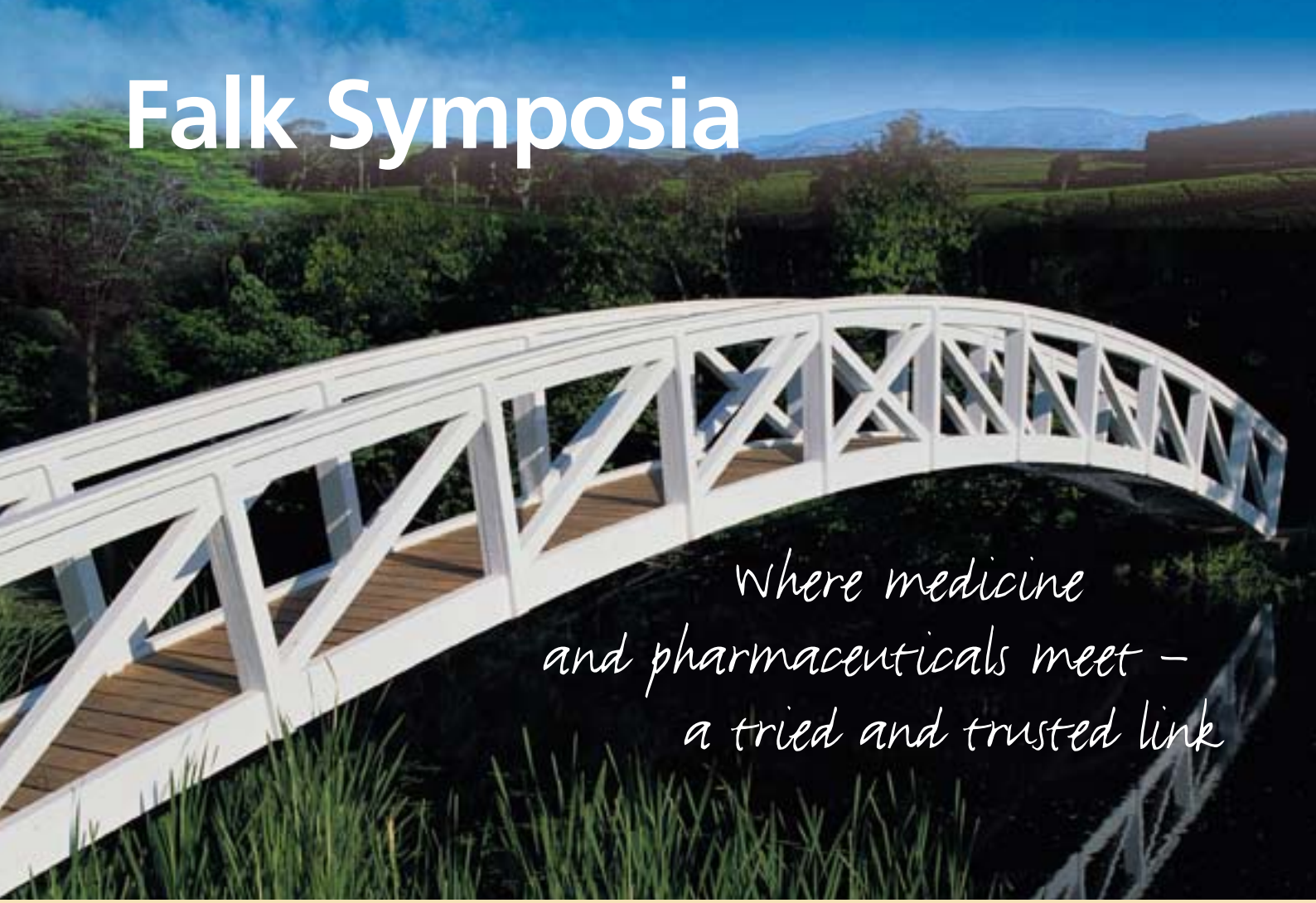
Falk Symposia



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Sevilla, Spain
March 23 – 24, 2007

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

Stomach cancer: epidemiology, precursor conditions, and detection

René Lambert and Martyn Plummer

René Lambert

The global burden of stomach cancer

Gastric adenocarcinoma is the second most common cancer in the world. In 2002, the numbers of incident new cases and deaths were estimated at 933,000 and 699,000, respectively, in the IARC Globocan 2002 database. The areas of highest risk are in eastern Asia; in eight population-based registries from Japan, stomach cancer accounted for 31% of all cancer incident cases in men and 22% in women during the period 1985–89. Other high-risk areas include eastern Europe and the Andes in South America. Geographical comparisons between regions or countries are shown in Tables 1 and 2. The incidence in men is about twice that in women in both high-risk and low-risk countries. A distinction should be made between adenocarcinoma of the proximal stomach, located within 2 cm of the esophagogastric junction, which is termed cancer of the cardia; and adenocarcinoma of the distal stomach, which is termed noncardia stomach cancer. Cancer is more frequent in the distal stomach (around 80% of cases) than in the proximal stomach. The proportion of distal stomach cancer is higher in women than in men, and higher in developing countries.

Declining incidence of cancer in the stomach

The incidence of stomach cancer is declining throughout the world at the rate of 2–3% per year. The cumulative

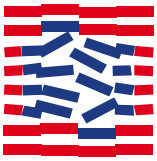
Table 1 The burden of stomach cancer in world populations as estimated in 2002. The crude incidence per 100,000 represents the actual risk occurring in the country. The age-standardized rate (ASR) per 100,000 adjusted to the world population makes it possible to compare the risk in populations with different age pyramids. The estimated number of incident cases occurring in 2002 (from IARC Globocan database, 2002).

	Men			Women		
	Incidence		Cases (n)	Incidence		Cases (n)
	Crude	ASR		Crude	ASR	
World	19.3	22.0	603000	10.7	10.3	330000
More developed countries	33.7	22.3	196000	18.8	10.0	115400
Less developed countries	15.9	21.5	405000	8.7	10.4	214000

Table 2 The burden of gastric cancer in selected high-risk countries, as estimated in 2002 (from IARC Globocan database, 2002).

	Men			Women		
	Incidence		Cases (n)	Incidence		Cases (n)
	Crude	ASR		Crude	ASR	
Japan	118.6	62.1	73800	55.4	26.1	36000
China	39.9	41.4	264000	20.5	19.2	128500
Republic of Korea	66.9	69.6	15900	32.9	26.8	7700
Portugal	43.4	27.6	2100	25.8	13.6	1300
Chile	41.6	46.1	3200	20.1	17.7	1600

ASR: age-standardized rate.



effect of this decline has been a substantial decline in the age-standardized rate (ASR) in recent decades, suggesting that the decline is associated with changing lifestyle and environmental factors. This is confirmed by the study of populations migrating from high-risk to low-risk countries. The ASR incidence in Japanese migrants to Hawaii, California, Washington State, and New York City decreases sharply in the second generation; the high rate still observed in the first generation suggests that environmental factors play a role in early infancy. In Japan, the ASR is also declining, but the crude incidence rate is still high because of the increasing proportion of aged persons in the population. In America and Europe, the declining risk of adenocarcinoma in the distal stomach contrasts with a stable risk in the proximal stomach (cardia) and an increased risk of adenocarcinoma in the distal esophagus. In Japan, early diagnosis may also play a role in the declining incidence.

Sequence of gastric carcinogenesis

As a rule, gastric carcinogenesis follows the sequence described by Correa: atrophic chronic gastritis — intestinal metaplasia — dysplasia. Atrophic gastritis, attributed to *Helicobacter pylori* infection, increases the intraluminal pH with transformation of nitrites (NO_2) into NO under the influence of inducible nitrite oxide synthetase (i-NOS). This chain reaction towards nitrosation results in the endoluminal formation of carcinogens, and it is inhibited by antioxidants; this explains the preventive action of ascorbic acid. A meta-analysis of the literature has suggested that the rate of transformation from low-grade dysplasia to cancer is low, in contrast to high-grade dysplasia, which progresses to cancer in 80% of cases after 6 months. On the other hand, the speed of progression from early to advanced cancer is variable, and some early tumors may remain without clinical relevance during the individual's life.

The development of neoplastic lesions in the gastric epithelium is an effect of proinflammatory stress and follows the known sequence of events leading from inflammation to cancer. Intestinal metaplasia, a central event in gastric carcinogenesis, may result from reversible events. The most common "irreversible" event is mutation of the tumor suppressor gene *TP53.* The sequence of mutations in the transition from benign precursors to cancer includes altered oncogenes (K-*ras,* β-catenin), suppressor or regulatory genes (*APC, TP53*), and mismatch repair genes (*hMLH1*). A somatic mutation in the regulatory gene (16q) for the transcription of E-cadherin plays a major role in *de novo* carcinoma.

Premalignant gastric lesions

Premalignant neoplastic lesions develop in circumscribed areas of the gastric mucosa modified by chronic inflammation in *H. pylori* infection. The risk of malignant progression is high when there is high-grade dysplasia. Benign polypoid neoplastic lesions are termed "adenoma"; nonpolypoid lesions are called "dysplasia" in Western countries and "flat or depressed adenomas" in Asian countries. Adenomatous polyps account for only 10% of gastric polyps; they are sessile, with a tubular or villous architecture, and have malignant foci in less than 10% of cases. Flat or depressed adenomas are less frequent, but have a higher risk of malignant transformation.

The majority of gastric polyps are nonneoplastic. Cystic polyps located in the gastric fundus occur sporadically or through a germline *APC* mutation in familial adenomatous polyposis (FAP). Hamartomatous polyps rarely progress to cancer in the stomach.

Superficial, early, *de novo,* localized cancer

Although it is the gold standard procedure, there is still a considerable miss rate for early cancer with endoscopy—even in Japan, where a miss rate of 19% has been reported. High-resolution video endoscopy has shown that a simple discolored area or an alteration in the microvascular pattern are significant markers for a flat neoplastic lesion.

Neoplastic digestive lesions are called "superficial" when their morphology suggests that they are limited to the mucosa or submucosa (m or sm). This applies to premalignant lesions and to cancer. These lesions are classified into subtypes of type 0 in the Paris consensus classification: polypoid (0-Ip or 0-Is); nonpolypoid, slightly

elevated (0-IIa); flat (0-IIb); slightly depressed (0-IIc); and excavated (0-III). In the stomach, 95% of superficial neoplastic lesions belong to type 0-II, most belonging to the depressed type 0-IIc. "Early gastric cancer" is a superficial (m or sm) tumor with confirmed malignancy, in which curative treatment is expected to be possible: the depth of invasion is superficial and the presence of positive regional lymph nodes is accepted in the definition. The term "*de novo* cancer," often used in Japan, describes small and flat carcinomas (not larger than 5 mm), surrounded by nonneoplastic gastric mucosa. This suggests that they do not arise from a precursor. In cancer registries, the "localized" stage includes superficial cancer and advanced cancer limited to the gastric wall. The two other stages are "regional" and "distant." The high overall 5-year survival rate in patients with gastric cancer in Japan (over 40%) is an effect of the country's screening policy, which leads to the detection of a high proportion of localized tumors.

Histopathologic classification of stomach cancer

Intramucosal neoplastic lesions with high-grade cell atypia and no invasion of the lamina propria are termed "intramucosal carcinoma" (malignant) in Japan and "high-grade dysplasia" (premalignant) in Western countries. The recent Vienna classification consensus makes a distinction between low-grade and high-grade intraepithelial neoplasia. High-grade premalignant lesions without invasion of the lamina propria and intramucosal carcinoma with invasion of the lamina propria are now placed in the same category.

Gastric cancer is classified by the World Health Organization (WHO) into tubular, papillary, mucinous, and signet-ring cell adenocarcinoma. The Lauren classification is often used in epidemiological studies. In the *intestinal* type, or differentiated carcinoma, precursor lesions (protruding or nonprotruding adenomas) play a role, and *H. pylori* infection is the first step in the carcinogenesis sequence. In the *diffuse* type, or undifferentiated carcinoma, there are no precursors, and the tumor is known as *de novo* carcinoma; recent observations suggest that *H. pylori* infection is also a causal factor in undifferentiated carcinoma.

Genetic susceptibility to stomach cancer

Familial stomach cancer occurs in less than 10% of cases. Hereditary gastric cancer (the diffuse type in the Lauren classification), which has been reported in New Zealand, is caused by a germline mutation in a gene encoding the cell adhesion protein E-cadherin. A similar, but somatic, mutation occurs in sporadic diffuse cancer. Stomach cancer may also occur in the hereditary nonpolyposis colon cancer syndrome and in patients with gastrointestinal polyposis, including FAP.

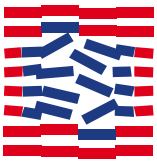
Gene polymorphisms both in the host and in the bacterial agent may play a role in sporadic stomach cancer. Cytokines (interleukins) are produced by the epithelial cells of the host in the immune response to the bacterial agent. The multiple recombinant genotypes of *H. pylori* explain the adaptation of distinct strains to distinct populations. *H. pylori* expresses the same surface antigens as the host cells. The association of the blood group A phenotype with gastric cancer is explained by greater adhesion of the bacteria to the gastric epithelium in individuals with the Lewis^b antigen.

Stomach cancer and environmental factors

In chronic atrophic gastritis, the increased intraluminal pH stimulates the growth of anaerobic bacteria that reduce nitrate to nitrite, potentially forming *N*-nitroso mutagens. The consumption of salt increases the risk of cancer; cohort studies conducted in Japan have shown that the risk of progression of atrophic gastritis to cancer was lower in individuals who had a reduced intake of salted food. There is a consistent association of cancer of the stomach with cigarette smoking in both men and women. Antioxidants such as beta-carotene, alpha-tocopherol (vitamin E), and ascorbic acid (vitamin C) prevent the formation of mutagens and carcinogens in the stomach. This explains the protection afforded by a high intake of fruit and vegetables.

Gastric cancer and *H. pylori* infection

H. pylori infection is acknowledged as the principal causal factor in noncardia gastric cancer (80% of cases), but not in cancer of the cardia. The prevalence of *H. pylori* infection in humans is estimated at 74% in developing



countries and 58% in developed countries. It is estimated that in 2002 some 590,000 cases of gastric cancer were attributable to *H. pylori* infection (5.5% of cancers worldwide), and gastric cancer is the most frequent among infection-associated cancers (slightly ahead of cancers attributed to human papillomavirus). In humans, the cycle of infection is through oral contamination in childhood, increased contamination with age, possible seroconversion after eradication, and possible reinfestation. Variations in the prevalence of the infection among populations result from interaction with environmental factors.

Atrophic gastritis is attributable to *H. pylori* infection. Cohort studies have reported an increased risk of gastric cancer in individuals in whom anti-*H. pylori* antibodies were identifiable in serum samples stored 10 or more years before the diagnosis. The WHO classification of *H. pylori* as carcinogenic in humans has been questioned in relation to the presence of gastric carcinogens generated by increased endoluminal pH. However, recent research on the sequence of oxidative stress occurring in mucosa infected by *H. pylori* has confirmed the early presence of i-NOS in the mucosa as a cause of DNA damage, consequently justifying the acceptance of the view that *H. pylori* is carcinogenic.

The recent determination of the complete DNA sequence of the genome of *H. pylori* has shown that specific islands are common to various strains. However, some strains may be more oncogenic than others. The genetic polymorphism involves the CagA island (35/40 kb), which improves the connection of the bacterial agent to the cell with the Lewis^b antigen, and increases tissue damage. Injected by the bacterial agent into the cell, the CagA protein generates inflammation and is associated with the VacA protein, which produces vacuoles. Human subjects infected with CagA-positive strains have a higher prevalence of atrophic gastritis and higher levels of IgG anti-*H. pylori* antibodies than those with CagA-negative infections.

Screening for gastric cancer

Mass screening for cancer is based on the ability to detect treatable early cancer or premalignant lesions in asymptomatic individuals. In organized population-based screening for gastric cancer, endoscopy is only offered to individuals who have positive results on a filter test. In Japan, mass screening for gastric cancer began in 1963 using gastrophotofluorography as a filter test. Despite a certain amount of bias in many studies, randomized trials, cohort and case–control studies have shown a reduction in the risk of gastric cancer in individuals participating in this type of screening. More recently, the pepsinogen filter test has become available in Japan. Outside Japan, it has been suggested that *H. pylori* serology could be used as a filter test, identifying aggressive strains such as the CagA antibody. However, this is not a cost-effective strategy. There are various tumor antigens, which can occur either in serum (CEA, CA-19-9, CA-50) or in gastric juice (fetal sulfoglycoprotein antigen).

Individual (opportunistic) screening is carried out in individuals who contact their own physician for early detection of cancer; endoscopy is then the primary diagnostic procedure. Organized and individual screening have a concurrent impact on the early detection of cancer. In Japan, organized screening detects only a fraction of the incident cases of early cancer occurring in the country. The low yield results from the limitations of compliance with the filter test and with endoscopy. The increasing trend toward early detection in Japan suggests that individual screening also plays a role. In the 10 cancer registries in Japan, the proportion of localized gastric cancer identified is higher (54% in 2000) than in the nine Surveillance, Epidemiology, and End Results (SEER) registries in the USA (24% in 1995–2001). This explains the high 5-year relative survival after gastric cancer at all stages observed in seven population-based registries in Japan (58% in 1993–96).

Limitations to the beneficial effects of early detection and treatment of gastric cancer involve compliance with the filter test and with recall for diagnosis and treatment in individuals with a positive test.

Primary prevention

The Westernized lifestyle that is being adopted everywhere by younger generations involves multifactorial changes in diet and in the control of hygiene, with a reduc-

tion of *H. pylori* infection. In Japan, there is declining consumption of salted and pickled foods and increasing consumption of fruits and vegetables. These lifestyle changes, occurring since childhood, explain the declining incidence of gastric cancer throughout the world.

Chemoprevention through the addition of antioxidants (beta-carotene, vitamin C, and alpha-tocopherol) to the diet has been suggested. Two dietary studies have been conducted in Europe, as well as two prevention trials in South America (in Columbia and Venezuela). The disappointing results of these trials suggest that multiple factors play a role in combination with *H. pylori* infection.

Eradication of *H. pylori* may be a valuable prevention strategy in countries with a high incidence of cancer. However, the cost-effectiveness of this approach is probably poor. Protocols based on eradicating the infection using antibiotics involve preliminary identification of the infected individuals who are to be treated. The limited experience in Venezuela was a failure, with a very low level of eradication (due to treatment resistance rather than reinfection); a higher level of eradication was observed in the trial conducted in Colombia. Two vaccines against *H. pylori* have been developed, one using recombinant urease produced in genetically engineered *E. coli*, the other with the VacA toxin. As yet, there is no evidence that a large-scale vaccination program would be cost-effective.

Strategies for the prevention of gastric cancer

There are still large numbers of cases among the older generations in countries with a high risk for gastric cancer, but lifestyle changes that reduce this risk in younger generations are occurring throughout the world. An active program of prevention, supported by health authorities, is justified only in countries in which the risk of stomach cancer is very high. It is generally considered that concentrating on primary prevention is appropriate, even though there may be debate about whether the best approach is through dietary change or eradication of *H. pylori.* In Japan, where the screening strategy should be continued, the photofluorography filter test could be replaced by the less costly pepsinogen test and the age groups undergoing screening (age 40 and over) could also be revised (to age 50 and over). In developed countries in the Western world, screening for gastric cancer does not require a specific public health policy. More emphasis should be given to quality assurance in gastroscopy, since the persistent and nonnegligible mortality rate from gastric cancer is associated with a poor quality of endoscopic detection outside Japan.

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A total of 400 million people are chronically infected with hepatitis B, and about half that number are chronically infected with hepatitis C. Together, these diseases are responsible for the majority of hepatocellular carcinoma cases, the third leading cause of cancer death worldwide. WGO calls upon all members to raise awareness about hepatitis on May 29, 2007.

WGO: World Digestive Health Day - May 29, 2007

HEPATITIS

High School students rally on the steps of the U.S. Capital

WORLDWIDE IMPACT OF VIRAL HEPATITIS

Hepatitis A	1,500,000 cases annually
Hepatitis B	over 2 billion people alive have been infected during their lifetime with over 350,000,000 chronic carriers
Hepatitis C	3% of world's population has been infected; over 170,000,000 chronic carriers
Hepatitis D	requires co-infection with Hepatitis B; co-infection greatly increases severity of hepatitis B infection
Hepatitis E	epidemics related to fecal contamination of drinking water, especially in developing countries; particularly dangerous in pregnant women

- The state of Amazonas, in the north Amazon region of Brazil, had one of the highest rates of hepatitis B in the world: 60% of children infected by age 10; 7.4% of deaths due to hepatitis. After 10 years of a broad vaccination campaign, carrier rates were reduced from 16.7% to 5.8%.

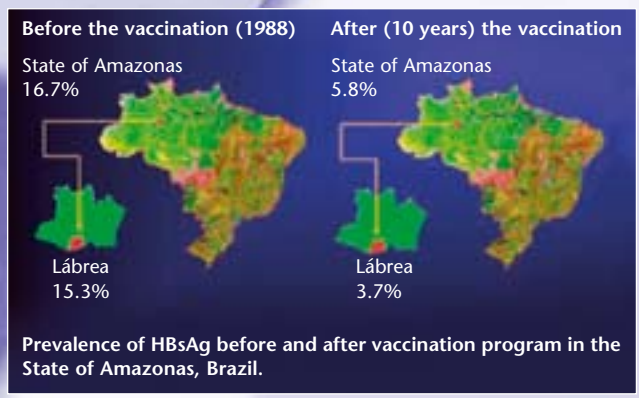
- Universal newborn vaccination against Hepatitis B could eliminate this disease because there is no animal reservoir for hepatitis B; however, many countries still don't have a universal vaccination policy or it is not uniformly applied.

- Consequences of hepatitis B and C include hepatocellular carcinoma, cirrhosis and portal hypertension with variceal bleeding, ascites and hepatic encephalopathy.

- Treatments for hepatitis B and C are effective but not widely available because of cost.

- Hepatitis B and C are transmitted by blood products and although most countries routinely test blood products for hepatitis B, many still do not test for hepatitis C.

- Hepatitis is also transmitted in hospitals and clinics due to the reuse of needles and syringes which have not been adequately sterilized between patients.



Prevalence of HBsAg before and after vaccination program in the State of Amazonas, Brazil.

Hepatitis B Bicycle Rally, India

HEPATITIS IN THE UNITED STATES

The disease burden of chronic hepatitis C among Americans is three to five times that of HIV/AIDS. An estimated 75% of Americans with hepatitis C have yet to be diagnosed.

In May 2007, WGO will provide a free WDHD tool-kit to members on the website:

- Ground breaking White Paper on Global Viral Hepatitis (Dr. D. LaBrecque, Univ. of Iowa)
- Hepatitis B guideline, written by a team of international experts, led by Dr. J. Heathcote
- Compendium of state of the art, freely accessible, "must read" articles about hepatitis
- articles from a special WDHD DDW newspaper, focusing on problems in individual countries and efforts to solve them

WWW.WORLDGASTROENTEROLORGY.ORG

WGO: The world is watching

Michael Fried, Michael Farthing, Justus Krabshuis, and Eamonn Quigley,
on behalf of the WGO Global Guidelines Task Force Division of Gastroenterology and Hepatology

The need to make clinical practice guidelines relevant to the target population remains a major challenge for clinicians and policy developers worldwide. Examples include WHO's approach to antiretroviral treatment in resource-limited settings, which shows how local adaptions of medical practice to overcome resource deficits can work, and the American College of Chest Physicians' guidelines for cough, which address the appropriate use of evidence in guideline development.

To develop guidelines, national specialty and subspecialty societies, whether driven by a genuine concern for public health, a desire to improve standards, or the need to reduce the costs of medical care, face serious challenges over and above the demands of evidence-based medicine. A society with a global focus, such as the World Gastroenterology Organization (WGO), which seeks to create guidelines also applicable in the developing world, faces further difficulties. Should all recommendations be supported by up-to-date systematic reviews of the evidence? If so, how does level 1 evidence from one country relate to level 3 evidence from another? Is a global guideline on a digestive disorder possible and worthwhile, in view of the substantial variations in disease incidence, prevalence, and presentation, as well as in resources or access to health care, throughout the world? Most policy-makers have failed to address these issues. Faced with these questions, the WGO Guidelines Committee established a task force to report on two questions: are global guidelines desirable and feasible? Is the evidence-based approach always the right one?

For the first question, global guidelines are desirable because they serve at least four useful functions: advocacy, setting standards, encouraging critical scrutiny of published work, and providing a platform on which the quality and clinical implications of evidence can be debated. However,

Symposium Faculty. From left to right: M. Fried, R. Horton, R. Hunt, D. Bjorkman, J.R. Hampton, M. Fishman, J.P. Kassirer, S. Fedail, R.W. Green-Thompson. Absent: B. Anderson, M. Farthing, L. Laine, E. Quigley, G.N.J. Tytgat

these guidelines have additional problems, such as topic selection. A global agenda should not serve merely to develop a compendium of opinions from the many extant guidelines in the developed world on their most prevalent disorders, but should strive to address problems that afflict the developing world. Similarly, guideline-development panels should represent and include those who care for affected individuals in the respective countries. The final steps, dissemination and implementation of such guidelines, could be the most daunting. How can these obstacles be surmounted?

The most practical way could be to establish several smaller panels that develop recommendations for different communities under the auspices of a central sponsoring group. Once an appropriate topic is identified, a systematic review could be done centrally. Every panel would then transform the evidence from the systematic review into recommendations appropriate for their communities and thus help to promote acceptance in different geographical areas. Furthermore, the translation of guidelines into different non-English versions (e.g., Mandarin, Spanish, French) could help to promote their recognition in many countries.

Is the evidence-based approach always the right one? The answer is "yes, but…": the implementation of the best approach could prove impossible in under-resourced societies. This problem does not advocate inappropriate or substandard approaches, but could promote alternatives that are not the best but are adequate and locally achievable. Thus, if possible and appropriate, WGO has developed a series of options in its guidelines that range from the best approaches for resource-rich environments, to alternatives that are effective but less ideal for resource-poor areas. The approach to variceal hemorrhage is a good example: evidence from controlled trials indicates greater efficacy for banding than for sclerotherapy; however, banding is more expensive, rendering sclerotherapy a valuable alternative in a resource-poor country. The second limitation is that evidence is scarce or nonexistent for many digestive disorders that are common in the developing world. In this respect, expert opinion should be used, because the lack of grade 1 evidence should not preclude the provision of guidelines of these conditions.

Finally, with other guideline-development panels, we believe that the current proliferation and duplication of guidelines is wasteful; every specialty group should produce a central repository of evidence that is updated regularly to be used as a central resource for the development of regional guidelines. We should not relinquish the maxim that "authors must not lose sight of the fact that guidelines are not an end in themselves but a means to improving clinical care."

This comment article, under the title "Global guidelines: is gastroenterology leading the way?" was published in The Lancet *2006;368:2041–2.*

Michael Fried,[1] Michael Farthing,[2] Justus Krabshuis,[3] Eamonn Quigley,[4] on behalf of the WGO Global Guidelines Task Force Division of Gastroenterology and Hepatology
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[1] Zurich University Hospital, Zurich, Switzerland; [2] St. George's Hospital, University of London, London, UK; [3] Highland Data, Tourtoirac, France; and [4] Dept. of Gastroenterology, Cork University Hospital, Cork, Ireland.

Other members of the Task Force include: Richard Hunt (McMaster University), David Bjorkman (University of Utah School of Medicine), Suleiman Fedail (Sudanese Society of Gastroenterology), Benjamin Anderson (University of Washington), Ronald Green-Thompson (KwaZulu–Natal Department of Health), Gordon Guyatt (McMaster University), John Hampton (University Hospital Nottingham), and Loren Laine (University of Southern California, Los Angeles). Justus Krabshuis is employed by WGO as its guidelines project manager. Highland Data is a library consultancy. The other authors have declared that they have no conflict of interest.

IDCA: Chilean postgraduate course

Sidney Winawer, Meinhard Classen, and Pedro Llorens

On 24 November 2006, a postgraduate course on digestive oncology was held in Viña del Mar, Chile, organized by the International Digestive Cancer Alliance (IDCA), the World Gastroenterology Organization (WGO), and the Chilean Society of Gastroenterology. This full-day course, attended by approximately 300 people, mostly gastroenterologists, was the first such course to be held in Latin America and was incorporated into the annual national 3-day Congress of the Chilean Society of Gastroenterology, Endoscopy, and Hepatology.

The course was initiated as a direct result of the new IDCA/WGO approach to rapid changes in the field of gastroenterology. With the introduction of new noninvasive imaging methods (such as computed-tomographic colonography) and biological techniques (fecal and blood testing), as well as new endoscopic technology that requires less intensive involvement by the physician (such as wireless capsule endoscopy and self-propelling colonoscopes), the gastroenterologist needs to become more knowledgeable and more actively involved in the broad range of benign and malignant gastrointestinal disorders. This concept was well formulated in a recent paper published by the Future Trends Committee of the American Gastroenterology Association in the October 2006 issue of *Gastroenterology*.

The initial mission when the IDCA was first organized in Rome in 2002 was directed toward prevention, but this has now been modified to include prevention and management, reflecting developments in the field of gastroenterology and the importance of gastroenterologists' broader interests, which is now recognized. Accordingly, IDCA/WGO's symposia and postgraduate courses now focus on what the gastroenterologist needs to know about digestive oncology.

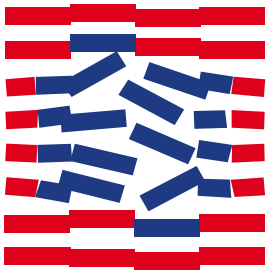
There will be 3 million new cases of digestive cancer throughout the world this year, with 2.2 million deaths. These numbers are projected to increase over the next 20 years with the growth and aging of populations in both the developed and developing countries. The risk of cancer varies in different countries. Chile is a country with a very highrisk for gastric cancer and an intermediate but increasing risk for colorectal cancer, and it has a unique and extraordinarily high risk for gallbladder cancer, relating to a very high prevalence of gallstones.

Faculty, Postgraduate course.

The postgraduate course was therefore divided into three sections—gastric, colorectal, and gallbladder cancer—preceded by an overview of cancer epidemiology and genetics. Each section used a multidisciplinary approach, including: risk factors, primary and secondary prevention as appropriate, endoscopic diagnosis and treatment, surgery, chemotherapy, radiotherapy where appropriate, and follow-up surveillance.

The faculty members included gastroenterologists, basic scientists, surgeons, medical oncologists, and radiation oncologists from Chile, the United States, Argentina, France, Holland, and Germany. The course closed with presentations of the IDCA/WGO's vision and plans for a global campaign for the prevention of digestive cancers and a summary of the course. It was clear from the course that many disciplines are necessary in order to achieve a complete approach to digestive cancers—from a basic biological and genetic understanding, to prevention, diagnosis, treatment, and follow-up. The overwhelming consensus was that we have a lot to learn from each other and that working together as a multidisciplinary team, we can bring greater benefits to patients with digestive cancer.

Chilean Society of Gastroenterology: www.socgastro.cl



IDCA: Charles Moertel would surely be delighted

Meinhard Classen and Sidney Winawer

If he had read the report of the American Gastroenterology Association's Future Trends Committee (*Gastroenterology* 2006; 131:1287–1312), Charles Moertel would surely have been delighted. In what is a highly readable description of scientific and technological progress in gastroenterology during the past few years, the Committee predicts that "significant challenges facing health care in general and GI practice specifically are poised to place significant demands on the field … In recent years, the procedures (i.e., endoscopy) that skilled endoscopists provide have, to a large degree, defined the field … screening colonoscopy accounts for a large portion of the total revenue of many GI practices. Clearly, obsolescence of this technology or emergence of imaging procedures that obviate the role of the gastroenterologist would change the practice and business of gastroenterology."

The available funds for public health projects are diminishing in connection with different demographic trends—the aging of the population in the industrialized world, on the one hand, and the rise in population figures in the less developed countries, on the other. The situation in the U.S. and some European countries is aggravated by impending moves to replace screening colonoscopy, at least in some instances, with alternative endoscopic methods and less intrusive techniques that do not require a gastroenterologist, such as nonendoscopic imaging (computed-tomographic colonography, magnetic resonance imaging) or stool screening.

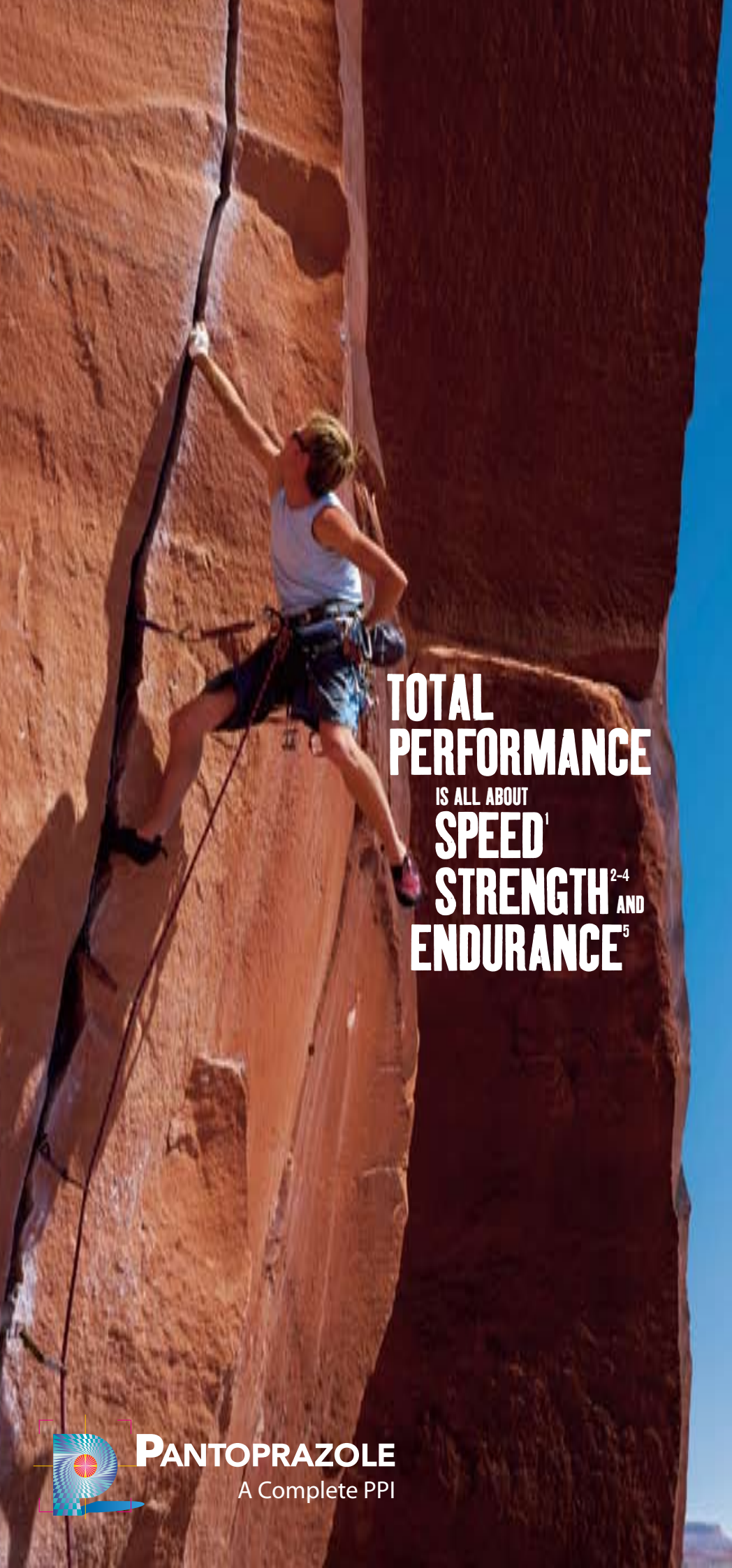
The International Digestive Cancer Alliance shares the view of the Committee that gastroenterologists should become actively involved in the development and improvement of new endoscopic and nonendoscopic techniques, as well as in clinical implementation studies.

Furthermore, we expressly welcome the Committee's recommendation that the scope of cognitive practice should be extended specifically in the field of digestive oncology. The statistical figures demand stronger involvement by gastroenterologists. The incidence of gastrointestinal carcinomas has risen worldwide to 3 million, with a global mortality of 2.2 million, while recent developments appear to suggest that further increases are impending. We join the Committee in recommending that interested gastroenterologists should become involved in the management of cancer disease in the gastrointestinal tract through intensive and ongoing training—not, however, as a part-time "sideline."

In some European countries—i.e., Belgium, France, and Germany—gastroenterologists are already receiving intensive training in digestive oncology and are also treating tumors from our area of specialization using chemotherapy and biological agents. Dr. Winawer, Chairman of a WGO Working Party, recently established that 31% of respondents from a survey of 47 countries had dealt "frequently" with chemotherapy.

We advocate interdisciplinary tumor management—including, as a matter of course, medical oncologists, surgeons, pathologists, and radiologists, as well as gastroenterologists. The best results in the fight against the illness appear to come from tumor centers in which interdisciplinary boards analyze the specific disease patterns of each individual patient and collaborate in developing the most promising therapeutic strategies.

Charles Moertel (1928–1994), a gastroenterologist from the Mayo Clinic who described chemotherapy for advanced carcinoma of the large intestine as early as 1962, would have been pleased to read that gastroenterologists in the U.S. and other countries are following in his footsteps.



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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.

NYCOMED

Gastroenterology in Syria

Daccak Munzer

The Syrian Society of Gastroenterology celebrated its 30th anniversary this year, in the city of Aleppo. The Society has 357 members, and holds an annual 4-day conference and a yearly workshop in various cities throughout Syria.

The Society started in 1976 with only seven members, five of whom were gastroenterologists, with one surgeon and one pathologist. Professor M. Malki is regarded as the father of the specialty of gastroenterology in Syria, and was President of the Society for the first 10 years. The organization initially held monthly meetings in various teaching hospitals in Damascus. In 1982, the first 2-day workshop in gastroenterology was held in the main university hospital. The meeting was attended by 100 gastroenterology physicians and was devoted to all aspects of digestive endoscopy. Since then, an annual meeting has been held in the last week of April every year, and in 2007 it will again be in Damascus. Some 10–20 international faculty members are invited to this conference. We also organize an annual 2-day seminar in a city outside Damascus in the first week of November each year.

Our gastroenterological community is endoscopy-oriented. The endoscopy section has more than 111 members and provides continuous quality education during two workshops each year. We also have an affiliated hepatic section, which is heavily involved in research on viral hepatitis.

The gastroenterology training system in Syria involves a national competition, with the highest-scoring candidates given first choice among the training positions. After 6 years in medical school, there is an obligatory 5-year training course in internal medicine, following which the gastroenterology competition is held. Each of the largest cities in Syria (Damascus, Aleppo, Latakia, and Homs) has a medical school, with endoscopy units in the regional hospital centers.

The Syrian Society of Gastroenterology was the pioneer in establishing the Pan-Arab Association of Gastroenterology, which includes all of the gastrointestinal societies in the Arab world from Morocco to Iraq. The Pan-Arab Association of Gastroenterology has held six meetings all over the Middle East. The latest one was held in Beirut, and the next will be in Morocco in 2008.

Gastroenterology in Syria is a high-quality specialty in every area, both in terms of academic research and private practice.

Damascus Mosque.

Daccak Munzer, MD, FACP, FACG
Professor of Medicine, Chief-Division of Gastroenterology, Damascus University
Damascus, Syria

One of the world's best gastroenterologists

Interview with Michael Farthing

World Gastroenterology News: **What are you doing to fill in all the free time that you have since you retired as editor of the prestigious journal, *Gut*?**

Michael Farthing: When I stepped down as Editor of *Gut,* I felt a huge sense of bereavement. Over the years, *Gut* became an increasingly important part of my working life. I serve on a number of editorial boards and have continued to work in the field of research integrity and research misconduct.

WGN: **What do you think the role of professional organizations, such as the World Gastroenterology Organization (WGO), will be in the future?**

MF: WGO is setting standards for clinical practice through the publication of clinical practice guidelines. These have the potential to influence health policy-makers in different regions of the world. WGO will continue to establish training centers in the developing world. WGO should assist in building research capacity in the developing world, because in the future this will become increasingly important in the development of relevant local health policies.

WGN: **If given the opportunity, what single piece of advice would you give young doctors who are just starting out?**

MF: The most important consideration when starting a career in medicine is to be absolutely sure that it is something that you really want to do. It should be a genuine personal wish, not an attempt to satisfy the aspirations of others.

WGN: **If you weren't a doctor, what would you be?**

MF: When I was at school, medicine was always my first choice. However, if for any reason I was unable to practice medicine now, I might consider interior design or landscape gardening!

***WGN:* You skillfully juggle many different roles on a daily basis—Principal of St. George's, President-Elect of WGO, Chair of the Scientific Committee of the next World Congress of Gastroenterology (WCOG). What keeps you sane and where do you get your energy from?**

MF: I thrive on change, and with change comes new energy. I really enjoy working with good teams—other people and their ideas are a great source of energy. For me, physical fitness is very much a part of mental fitness. Another source of energy! I take exercise, I don't smoke, I try not to drink too much and I keep an eye on my BMI!

***WGN:* What journals or periodicals do you read on a weekly/monthly basis?**

MF: On a weekly basis I read the *BMJ, Lancet,* and the *New England Journal of Medicine.* I try to read them on the weekend after they arrive and I tear out the articles which I think will be useful in the future.

***WGN:* At the time of the next WCOG, which is to be held in your home town, you will become President of WGO. What goals do you have for the organization?**

MF: I would like to see the number of training centers increase—possibly in Turkey, central Asia, and India. I would also like to develop a more prominent research agenda for WGO. In the future, I believe WGO will be working increasingly closely with the regional societies. The joint meeting with the UEGF in 2009 will be a new venture for WGO, but may well be a model for the future. I have no doubt that the meeting will be a great success.

***WGN:* In these days of tight finances, how will WGO be affected by reduced income from the biomedical industry?**

MF: WGO is a strong organization with a very clear mission and some excellent "products," many of which are highly innovative and some of which are unique. The organization bridges a gap that is currently not filled by other organizations. I believe there will always be buyers for the products that we have, both for altruistic and for more commercial reasons.

***WGN:* In your travels across the globe, what experience has affected you the most?**

MF: Two special experiences spring to mind that were, I believe, highly influential and resulted in lasting memories. Both took place when I was a medical student.

In the middle of the medical course at University College, London, before entering the clinical years, I worked in a very small mission hospital in rural South India. After 2 weeks, I was invited to assist the hospital superintendent in the operating theater. I operated morning and afternoon for six or seven days a week, and ended up with my own operating list—tubal sterilizations under local anesthetic, amongst others! What was important about this visit, however, was not just the extraordinary exposure to clinical medicine but an intense experience of life in village India. This early influence, I believe, was one of the factors which directed my career progression and research interests.

The second was a student elective in a hospital in Warsaw. It was 1968, in the middle of the Cold War. It was a time when Poles were experiencing huge restrictions of personal freedom. Certainly nobody spoke freely in public places. I remember sitting in the surgeon's room on the morning of 21 August 1968 listening to the radio as the Russians rolled their tanks into Prague to regain control after attempts by Alexander Dubcek to liberalize what was then Czechoslovakia. They translated snippets so that I knew what was going on, but were wondering of course whether Warsaw would be next. I suddenly realized what liberty and human rights were all about. My affection and interest in the former Eastern European countries has continued to this day.

***WGN:* What do you do for relaxation?**

MF: I have always been interested in photography, particularly black and white photography, and have a rather impressive personal photographic archive, which goes back to my school days. I try to keep fit and enjoy exercise. One of my great loves is writing (nonmedical)—I have written a couple of plays and have others on the stocks. My really big challenge is the novel! I am working on it!

***WGN:* Do you have children, and if so, what career paths have they chosen?**

MF: I have two fantastic boys. Tom, aged 24, went to the Ruskin School of Drawing at the University of Oxford and wants to be a painter. Jack is 21, still at the University of Oxford, studying art history, although he spends most of his spare time in the theater. He wants to be an actor and is planning on going to drama school next year. Where did I go wrong? Or maybe they've got it right!

***WGN:* What advice do you have for young people of college age as far as career choices are concerned?**

MF: Don't decide too early… but don't leave it too late. The most important thing is to do something that really interests you and to which you can make a real commitment.

***WGN:* You are one of the most outstanding gastroenterologists in the world. Do you have time to do any clinical medicine? Do you do endoscopy? Do you see patients on a regular basis and take care of them?**

MF: Yes, yes, and yes! I am part of the gastroenterology team at St. George's and do a regular outpatient clinic, and see ward consults. I still see the full range of gastrointestinal and liver patients. I still do diagnostic endoscopy, but refer on any interventional procedures, as now I simply do not do enough procedures to remain effective and safe.

> Interviewed by Dr. J. Waye, Editor of *WGN*

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Did you know... WGO postgraduate Train the Trainers (TTT) will increase from one per annum to three per annum in 2007? Yet the demand for these workshops is 120% above capacity!

Did you know... 50% of TTT participants come from developing countries, while the other 50% come from developed countries?

Did you know... WGO supports 10 Global Training Centers? Over 300 participants have attended educational courses.

Did you know... 53% of WGO Global Guideline website visits in 2006 went to the non-English versions in French, Spanish, Portuguese, Mandarin and Russian?

Did you know... why the WGO sponsors World Digestive Health Day annually on the 29th of May? The WGO was founded on May 29th 1958 and will celebrate its 50th Anniversary next year!

Did you know... that you become de facto a member of WGO due to your national society's affiliation to WGO? There are 50.000 members in WGO.

Did you know... your membership fee to WGO is US $ 1 per year?

WGO's global programs are a mixture of philanthropic, educational and informational opportunities:

- WGO Train the Trainer Workshops – a postgraduate pedagogic course for educators and educators-to-be in gastroenterology.
- WGO Global Training Centers – these 10 centers offer "in residence" training for 3-6 months under the Center Director's personal supervision.
- WGO Global Guidelines – the 18 Global Guidelines to date provide a "cascade" of treatment options adapted for local equipment resources and expertise.

To enhance gastroenterology standards throughout the world, the WGO assists and sponsors colleagues from developing countries to participate in our programs. With your support, WGO can continue to fulfill its vital role as "Global Guardian of Digestive Health. Serving the World."

HOW CAN YOU HELP?

- Make a personal donation to WGO
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Hepatitis B: bibliometric landscape, disease burden, and a reassurance about vaccination

Justus Krabshuis

- Which are the top hepatology journals?
- What is the burden of hepatitis B virus (HBV) disease worldwide?
- What about HBV vaccination?
- How safe is HBV vaccination?
- Key web sites for HBV information.

Which are the top hepatology journals?

Let's say you want to track the top 10 hepatology journals for HBV. OK, but which are they? Well, if I look at the top 50 gastroenterology and hepatology journals from ISI's 2005 *Journal Citation Report,* 11 of the 50 journals focus on hepatology (Table 1).

By the way: just put the International Standard Serial Number (ISSN) into the PubMed query box; for example, typing in 0270-9139 gives you all articles published in *Hepatology* that are available on PubMed—and the most recent ones always come first, of course (Fig. 1).

What is the burden of HBV disease worldwide?

Much research has been done since Baruch Blumberg received the Nobel prize in 1976 for the discovery of HBV and the introduction of the HBV vaccine (PMID 12467696). I expect you are familiar with the World Health Organization's acronyms for the African, American, eastern Mediterranean, European, south-east Asian and western Pacific region? OK, I admit I had to look it up myself at:

http://www.who.int/choice/demography/regions/en/index.html

Oh, and you can click this if you want to find out which region your country belongs to:

http://www.who.int/choice/demography/by_country/en/index.html

Globally then, it is a very gloomy picture indeed (Table 2 and Fig. 2):

- HBV accounts for 60–80% of primary liver cancer globally.
- More than 2 billion people have serologic evidence of HBV infection.
- About 360 million people are chronically infected and at risk of death from liver cancer and cirrhosis.
- Up to 90% of those infected as infants and 50% of those infected as young children may become chronic carriers of the virus, and they are at high risk for liver disease later in life.
- Some 500,000–700,000 people die each year from HBV-related liver disease.

Table 1 Top 11 hepatology journals, based on JCR 2005 impact factors, with ranking among the top 50 gastroenterology journals in brackets.

Ranking	*Index Medicus* title abbreviation	ISSN	Impact factor
1 (2)	Hepatology	0270-9139	9.792
2 (5)	J Hepatol	0168-8278	4.931
3 (6)	Liver Transplant	1527-6465	4.447
4 (9)	Semin Liver Dis	0272-8087	3.752
5 (15)	J Viral Hepat	1352-0504	2.550
6 (23)	Dig Liver Dis	1590-8658	1.818
7 (25)	Liver Int	1478-3223	1.766
8 (28)	J Gastroenterol Hepatol	0815-9319	1.718
9 (29)	Eur J Gastroenterol Hepatol	0954-691X	1.690
10 (32)	Hepatol Res	1386-6346	1.474
11 (44)	Hepatogastroenterology	0172-6390	0.699

Fig. 1 Searching PubMed for all 9608 (!) articles published in *Hepatology* using its ISSN, 0270-9139.

Table 2 Current hepatitis B disease burden

Region	Total deaths	Deaths from chronic infection
AFRO	69000	90%
AMRO	12000	92%
EMRO	21000	90%
EURO	51000	94%
SEARO	143000	92%
WPRO	325000	95%
Global	621000	94%

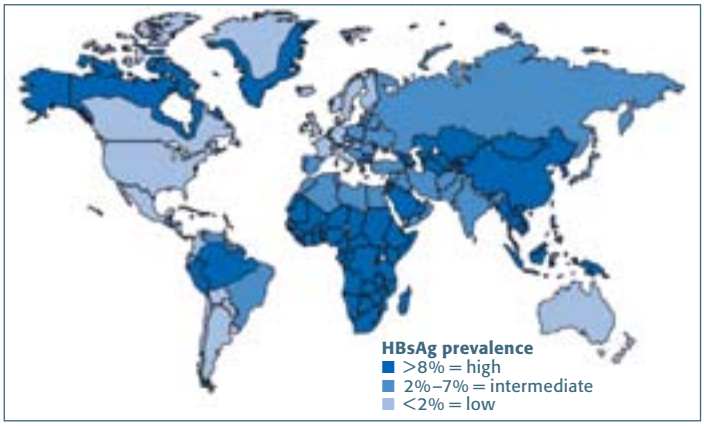


Fig. 2 Geographic distribution of chronic HBV throughout the world (source: Centers for Disease Control, Morbidity and Mortality Weekly Report).

What about HBV vaccination?

Vaccination is the most effective measure for preventing hepatitis B virus infection and its consequences, including cirrhosis of the liver, liver cancer, liver failure, and death. In adults, ongoing HBV transmission occurs primarily among unvaccinated persons with behavioral risks for HBV transmission (e.g., heterosexuals with multiple sex partners, injection-drug users, men who have sex with men, among household contacts, and sex partners of persons with chronic HBV infection.

The above data are from the best (and most recent) report on HBV vaccination in adults from the Centers for Disease Control (CDC) Morbidity and Mortality Weekly Report (MMWR) for 8 December 2006 entitled *A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States – Part 2 – Immunization of Adults*. The full report is available from:

http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5516a1.htm?s_cid=rr5516a1_e

Part I of the report, dealing with the immunization of infants, children, and adolescents was published on 23 December 2005; the full report for part 1 is available from:

http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5416a1.htm

The WHO has also stated that the prevention of chronic HBV infection has become a high priority in the global community. Immunization with hepatitis B vaccine is the most effective means of preventing HBV infection and its consequences:

http://www.who.int/csr/disease/hepatitis/whocdscsrlyo20022/en/index5.html

So—everyone agrees it should be done. What about the "how"? The CDC recommendations are shown in Table 3.

All you need now is a strategy with buy-in from all stakeholders, a very large budget and especially "political will." Finally—and I admit it is a bit late in the day to ask this, it should have been addressed earlier in this article—is HBV vaccination safe?

How safe is HBV vaccination?

CDC data show that HBV vaccine is safe for all age groups! The most frequently reported side effects are

Table 3 HBV vaccine doses by vaccine and group.

Group	Single-antigen vaccine				Combination vaccine	
	Recombivax HB® *		Engerix-B® †		Twinnix® ‡	
	Dose (µg) §	Vol. (mL)	Dose (µg) §	Vol. (mL)	Dose (µg) §	Vol. (mL)
Adults (aged > 20)	10	1.0	20	1.0	20	1.0
Hemodialysis patients and other immuno-compromised persons aged > 20	40 #	1.0	40 ¶	2.0	n/a	n/a

* Merck & Co., Inc, Whitehouse Station, New Jersey, USA.

† GlaxoSmithKline Biologicals, Rixensart, Belgium.

‡ Combined hepatitis A and hepatitis B vaccine, recommended for persons aged > 18 who are at increased risk for both hepatitis B virus and hepatitis A virus infections.

§ Recombinant hepatitis B surface antigen protein dose.

Dialysis formulation administered on a 3-dose schedule at 0,1, and 6 months.

¶ Two 1.0-mL doses administered in one or two injections on a 4-dose schedule at 0,1, 2, and 6 months.

pain at the injection site (3–29%) and a temperature of > 99.9 °F (> 37.7 °C) (1–6%). With regard to adverse events, a causal association has been established between receiving HBV vaccine and anaphylaxis. The estimated incidence of anaphylaxis among children and adolescents receiving HBV vaccine is one case per 1.1 million vaccine doses distributed (95% confidence interval, 0.1 to 3.9).

There is no evidence of a link between Guillain–Barré syndrome (GBS) and HBV vaccination, nor is there any evidence of a link with multiple sclerosis.

Contraindications and precautions. Hepatitis B vaccination is contraindicated in individuals with a history of hypersensitivity to yeast or any vaccine component. Despite a theoretical risk of allergic reaction to vaccination in individuals with an allergy to *Saccharomyces cerevisiae* (baker's yeast), there is no evidence to document adverse reactions after vaccination of persons with a history of yeast allergy.

Individuals with a history of serious adverse events (e.g., anaphylaxis) after receiving hepatitis B vaccine should not receive additional doses. As with other vaccines, vaccination of persons with moderate or severe acute illness, with or without fever, should be deferred until the illness resolves. Vaccination is not contraindicated in individuals with a history of multiple sclerosis, GBS, autoimmune disease (e.g., systemic lupus erythematosus or rheumatoid arthritis), or other chronic diseases.

Pregnancy is not a contraindication to vaccination. Limited data suggest that developing fetuses are not at risk for adverse events when hepatitis B vaccine is administered to pregnant women. Available vaccines contain noninfectious HBsAg and should cause no risk of infection to the fetus.

If you see HBV vaccine frozen, then it is damaged. A vaccine may also have been frozen earlier and then thawed again. The shake test can be used to check whether the vaccine has been damaged by earlier freezing:

- Shake the vaccine vial.
- Leave the vaccine for 15–30 min for any sediment to settle.
- Do not use it if a sediment settles below an almost-clear liquid.

Key web sites for HBV information

Watch this space (www.worldgastroenterology.org), because in spring 2007 the World Gastroenterology Organization (WGO) will have its new HBV guideline online—a worldwide team of experts will have summarized what we know. It will include a comprehensive bibliography plus a listing of key web sites. For the moment, however, we can list the key sources on hepatitis B:

- The WHO has fact sheets for hepatitis A, B, C, D, and E at: http://www.who.int/csr/disease/hepatitis/en/
- The CDC has fact sheets for hepatitis A, B, C, D, and E at: http://www.cdc.gov/ncidod/diseases/hepatitis/
- The CDC/MMWR document on HBV vaccination in adults: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5516a1.htm?s_cid=rr5516a1_e
- WGO is working on a HBV global guideline under the supervision of Professor Heathcote; see http://www.worldgastroenterology.org/?globalguidelines
- For the best source of evidence on treatment for HBV, go to the Cochrane Hepatobiliary Group at: http://ctu.rh.dk/chbg and ask for a subscription to their excellent (free!) CHBG newsletter
- The 2007 World Digestive Health Day (WDHD) also will focus on hepatitis—have a look at: http://www.worldgastroenterology.org/?wdhd
- Or you could try WGO's "Ask a Librarian," a free service to Health InterNetwork Access to Research Initiative (HINARI) countries, at: http://www.worldgastroenterology.org/?askalibrarian

Acknowledgment

I am grateful to Prof. Anthony E. Fiori of the CDC for drawing my attention to the MMWR data.

Note: The links in this article can be accessed through the WGO website (www.worldgastroenterology.org) and clicking on the links there.

Gallbladder cancer: a Chilean challenge

Xabier de Aretxabala and Ivan Roa

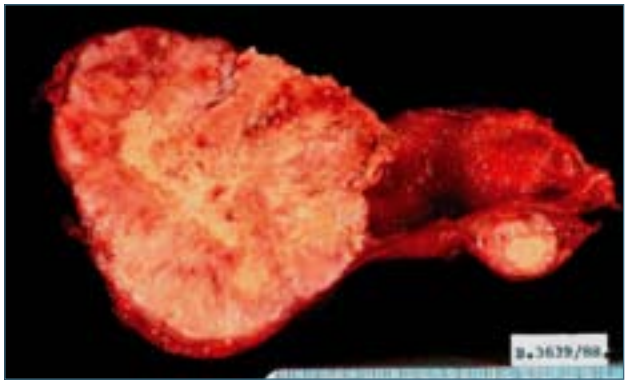
Xabier de Aretxabala

Ivan Roa

Gallbladder cancer is a common disease in Chile and is responsible for a high proportion of cancer deaths. It is the main cause of death from cancer among women in the country—more frequent even than breast and stomach cancer. The mortality rate with gallbladder cancer among women is 16.4 per 100,000 inhabitants, while the figures are 13.2 and 12.4 for breast and stomach cancer, respectively. In men, gallbladder cancer is not as frequent. Gallbladder cancer is common not only in Chile; other countries along the Pacific coast of America, such as Bolivia and Mexico, also have an increased incidence of the disease.

Gallstones are present in almost all patients with gallbladder cancer. In Chile, the prevalence of gallstones is extremely high; half of women in their fifties have gallstones. Ethnic characteristics are another important factor related to the disease, and the high prevalence of gallstones in the indigenous population may suggest a link between ethnicity and gallbladder cancer. In Chile, the indigenous population has the highest prevalence rate of gallbladder cancer in the country.

Gallbladder cancer is usually associated with late symptoms and a poor prognosis. As cholecystectomy is frequently carried out for gallbladder conditions, it is possible to detect early forms of the disease. In some hospitals in Chile, almost 25% of patients with gallbladder cancer are found to have early forms of the disease, a detection rate that is higher than that for early gastric cancer. Early forms of the disease are almost exclusively detected after pathological examination of the cholecystectomy specimen. In Chile, almost 30% of patients with gallbladder cancer remain completely asymptomatic until the acute episode that precipitates surgery. It has been observed that the prevalence of gallbladder cancer in cholecystectomy specimens is directly related to the patients' age. The rate of concomitant gallbladder cancer may be as high as 10% in 60-year-old patients with gallstones. The rate starts to increase after the age of 40, when women have a 2.8% rate of concomitant gallbladder cancer when cholecystectomy is performed.



Advanced gallbladder cancer with lymph node invasion.

By studying the average age of patients relative to different pathological stages, it is possible to calculate the progression period from an early tumor to an advanced lesion. From these observations, it takes approximately 12 years for progression from dysplasia to advanced cancer to occur. Because of the relatively slow growth of gallbladder cancer, simple therapeutic procedures such as cholecystectomy can be curative in a high proportion of patients. When the potential mortality and morbidity associated with laparoscopic cholecystectomy are compared with the possibility of developing gallbladder cancer, the results favor surgical cholecystectomy.

Imaging methods for detecting early forms of gallbladder cancer have failed due to the high proportion of flat lesions, while the changes produced by gallstones make it difficult to detect suspicious lesions on ultrasonography.

During the past year, because of the high incidence of gallbladder cancer in the Chilean population, the Chilean government has begun a new program to promote cholecystectomy in the high-risk population. The Chilean population between 35 and 49 years of age with symptomatic gallstone disease has the highest priority for undergoing cholecystectomy. The long waiting list in the majority of public hospitals in Chile is currently contributing to an increase in prevalence of the disease. By implementing the program, it is hoped that it will be possible to reach out to high-risk patients and thereby reduce the prevalence of gallbladder cancer in the country. This should be the first step in the management of the disease.

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Gastroenterology in Darfur

Badreldin A. Yousif

Background

El Fasher hospital in North Darfur was established in 1916 to offer medical service to the town's 18,000 citizens. There was a single doctor who ran all of the hospital's medical activities, which was sufficient due to the low incidence of illness and the possibility of referring patients to other facilities. However, since 2003 when the Darfur crisis started, the population in North Darfur has risen to 8,910,000, mainly consisting of internally displaced persons (IDPs), but the hospital facilities have not expanded as the population increased. IDPs continue to flow into the city due to the ongoing war between the insurgency groups and the government. Our small hospital and staff are overwhelmed by the vast number of persons whom we need to serve. In this crisis, nearly 210,000 persons have been killed and 375,000 wounded, and over 2 million have been forced to leave their homes.

The Department of Internal Medicine

The medical department has 52 beds, and the total number of the hospital beds is 188. We treat 110–150 patients daily, and 15–17 require hospital admission; most of these have gastrointestinal tract problems.

In our department, we have three MD consultants and six house officers. The mortality rate is high because of the lack of basic equipment such as: Ambu bags, suction machine, oxygen, ECG machine, defibrillator, agents to control hematemesis such as Sengstaken tubes, and intravenous proton-pump inhibitors (PPI).

Since the Darfur disaster, there have been increasing numbers of gastrointestinal cases due to poor sanitation and hygiene. In August 2006, there was an outbreak of cholera (*Vibrio cholerae* El Tor), which affected over 450 patients; thanks to the World Health Organization and other non-governmental organizations, the epidemic was controlled. All patients were isolated in large tents with latrines and cholera beds. Treatment was with oral or intravenous fluids and antibiotics. We still receive some sporadic cases. On the other hand, typhoid fever has become an endemic disease in El Fasher, reflecting poor sanitation in the town. Drinking nonchlorinated water contributes further to the spread of illness, and the inability to control the fly population leads to further dissemination of disease.

Peptic ulcer disease is a major problem, which is now being much better diagnosed and treated thanks to the establishment of the Endoscopy Center (located inside El Fasher Hospital) by Professor Suleiman Salih Fedail. He is continuing to look after the center and fund it from his patients' gifts. Before this, all patients with gastrointestinal problems used to be referred to Khartoum, over 480 km away.

In our hospital, we have performed 402 elective esophagogastroduodenoscopy (EGD) procedures over the past year. The majority of diagnoses (57%) involved inflammation of the upper gastrointestinal tract; gastric erosions were diagnosed in 18% of cases. Gastric cancer was found in 6% of cases. We carried out 37 emergency EGDs, and 18% of these were for hemorrhage due to gastric cancer. Most of the emergency cases were due to esophageal varices, but 23% of the patients were diagnosed with extensive candidiasis. We use 5% ethanolamine solution to inject varices and rarely use epinephrine to control torrential upper gastrointestinal bleeding. Band ligation is not possible for us, as it is very expensive. We adhere to international standards for instrument disinfection, and our two fiberoptic upper gastrointestinal endoscopes are cleaned and disinfected with Cidex solution for 20 min.

Female ward.

Male ward.

Quality assurance in Egypt

Ahmed Gado

Bolak El-Dakror Hospital (BDH) is a 450-bed public primary-care hospital located in Giza City, 20 kilometers from the Pyramids. It serves a population of one million people. The gastrointestinal endoscopy unit was founded on 1 March 1998 and formally opened on 1 November 1999, and I had the privilege to be the first Director of the unit. Without the support of business people, we would have not been able to build the unit we have today. Since the inauguration of the unit, we have carried out 2152 endoscopic examinations, 78% of which were upper gastrointestinal endoscopies. The fee for diagnostic upper endoscopy is about € 7.

We are grateful to the European Society of Gastrointestinal Endoscopy (ESGE), the American Society for Gastrointestinal Endoscopy (ASGE), and St. Mark's Wolfson Endoscopy Unit in London for their generous contributions to the unit, through providing us with free teaching aids in the form of videos and DVDs.

In December 2002, during an international conference held in Cairo, Professor Axon from Leeds in the UK presented a lecture on quality assurance in gastrointestinal endoscopy. On the basis of his information and citations from the literature, we instituted a quality-assurance program, with data being collected using electronic databases. This has helped us improve efficiency, the safety of the medical care provided, and patient outcomes.

In November 2003, after 4 years of preparation and training, we started managing patients with acute upper gastrointestinal bleeding. We are the only government hospital that provides this service in Giza Governorate. In September 2005, we opened a new three-bed intensive-care unit for patients with acute upper gastrointestinal bleeding. In May 2005, excision of all polyps became standard practice in the unit, and in June 2005 we instituted imaging documentation of the ileocecal valve. In November 2005, our quality-assurance program in colonoscopy was completed. In December 2005, we started using chromoendoscopy and also received funds for the development of a modern endoscopy unit, which will be constructed in accordance with designs provided by KeyMed in the UK. We have five upper intestinal endoscopes, two of which are video scopes, and two colonoscopes, one of which is video. We use international standards for disinfection.

The future plan is to continue upgrading the unit, maintaining the quality-assurance program, monitoring practices and procedures so that any suboptimal performance relative to an agreed standard can be recognized and remedied, ensuring continuous quality improvement and looking for different ways to achieve further improvement.

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Conclusion

Our patients in North Darfur have a great deal of peptic ulcer disease, but another major health problem is hepatocellular carcinoma (HCC). Of every 10 patients with an abdominal mass, four have HCC and die within a very short period of time, as they present very late, as in this part of the world people believe strongly in traditional therapy. Since the incidence of HBV infection is low, the causative agent may be Alpha toxins because people here consume a large amount of ground nut.

I would be very grateful if readers of *World Gastroenterology News* could help us with the following:

- Video endoscopes (we do not have any).
- Laser instruments.
- Heater probes.
- Colonoscopes (we do not have any).

Above all, I would ask the readers of *WGN* to try to find opportunities for us to receive further training, as this would definitely improve our ability to care for our patients and would reduce the need to refer cases to Khartoum.

19 December 2006

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