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WORLD GASTROENTEROLOGY NEWS

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Modern Management of **Echinococcosis**

Does the **COX-1/COX-2 Concept** Still **Hold?**

GI Medicine on the **Frontiers: Iran**

WGO/OMGE-OMED **Training Centers**

PULL OUT

WGO/OMGE Position Statement:
Colorectal Cancer Screening and **Surveillance**

Global Guidelines for the **21st Century**

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

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Message from the Editor-in-Chief

Jerry Waye

The major European Conference for Gastroenterology, UEGW, is right around the corner. It will be held in Prague, Czech Republic from 25 to 29 September, 2004. The topics and presentations are outstanding, and you will miss out on a great educational opportunity if you do not attend. Start preparing now for the quadrennial meeting of the World Congress of Gastroenterology which will be held in Montreal next year from September 10–14, 2005. Be sure to make time in your schedule to include this exceptional international conference. Mark your calendars, make hotel arrangements, and secure the air flights since thousands of doctors will flock to this gem of a city in affordable Canada to learn, to meet friends, to be updated, to socialize, and to have all of the progress in the entire field of gastroenterology over the past 4 years detailed by the world's leading experts. There will be unprecedented hours of live endoscopy broadcast daily to the convention facility.

Since this issue precedes UEGW, we have highlighted several of the presentations at the combined EAGE, ISDS, EDS and EAES Postgraduate Course to be held on September 25 and 26, 2004.

OMGE/WGO and OMED are continuing their international leadership in all fields of gastroenterology, and especially in training and education. New learning centers are being established and certified. IDCA continues its focus on worldwide digestive cancers, and the OMED cancer screening committee continues its multidisciplinary activities. Our special insert in this issue is concerned with colorectal cancer screening as a part of the Digestive Cancer Awareness Campaign. There is a special report on mucosal neoplastic nomenclature.

In this age of information explosion, our resident librarian presents special pointers on extracting information from Pub-Med. This issue also inaugurates a new series of articles on "Gastroenterology on the Frontier". The first article in this series is from Iran, where special problems and cancers are encountered. I request anyone who knows of "frontier-style" gastroenterology be in touch with WGN so that we may track down the broad variety of gastroenterology that is being practiced outside of the mainstream of medicine.

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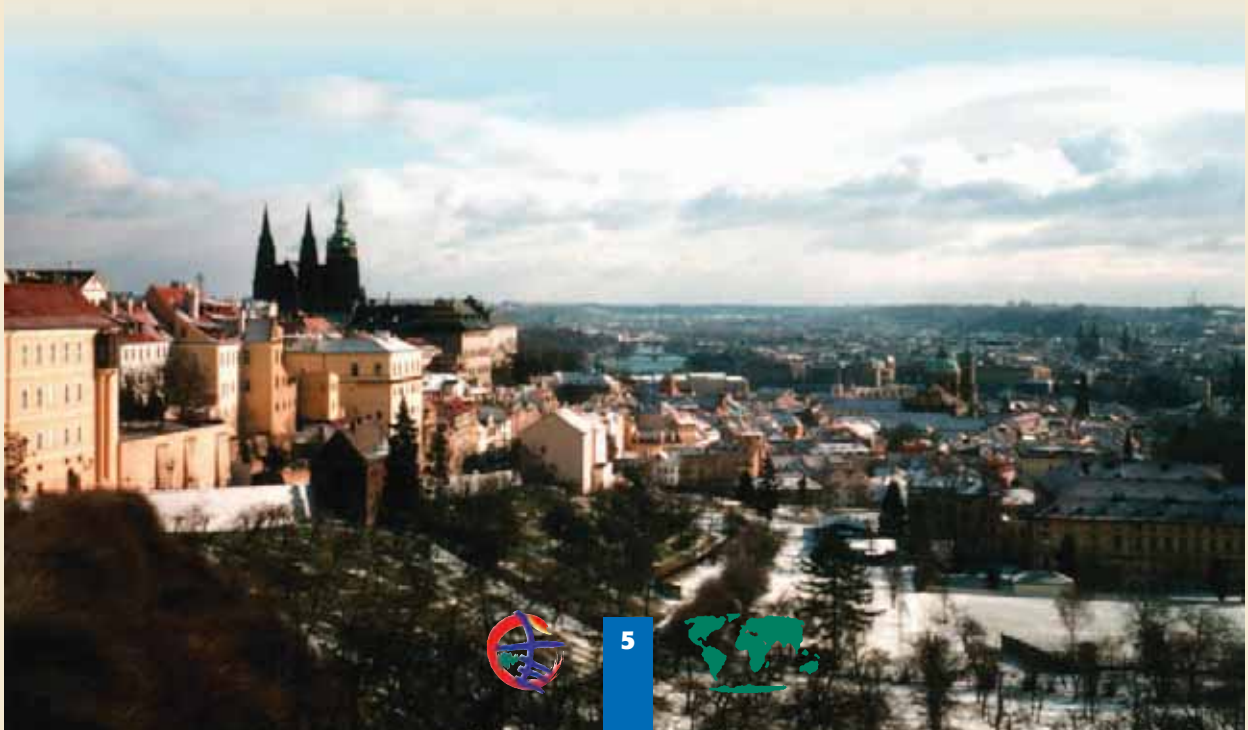
The city of Prague, venue of UEGW 2004.



Message from the Senior Editor

Impact on Surgery of Screening and Early Detection of Gastrointestinal Cancer

Alberto Montori

In the last two decades, gastroenterologists have been focusing their efforts on the screening and early detection of gastrointestinal cancers, with considerable success. Discussions at the meetings of the Combined Screening Committee of the Organisation Mondiale d'Endoscopie Digestive (OMED) and the International Digestive Cancer Alliance (IDCA) have been making a valuable contribution to answering the following questions:

- Which areas of screening require quality assurance?
- What methodology should be used?
- What further action is required?
- What impact have the screening campaigns had on surgeons' performance and on the outcome for patients?

The work of the OMED Screening Committee, chaired by Paul Rozen, in collaboration with the International Digestive Cancer Alliance (IDCA) chaired by Meinhard Classen and Sidney Winawer, is sure to be helpful in defining appropriate current indications for oncologic surgery. Surgeons today need to be directly involved in the screening process, accepting that in the future, their role in decision-making for the patient will extend well beyond the operating room. Surgeons need to be aware of current developments in their own and other fields, maintaining their enthusiasm and commitment and fully participating in every aspect of patient care. As teachers, they should prepare students for the profession in the best possible way, and as surgeons they should try to cure patients by prevention and early detection, as well as by radical intervention when necessary. All of this can be achieved with combined efforts based on a multidisciplinary approach.

I conclude with the old maxim: the competent surgeon knows *how* to operate; the good surgeon knows *when* to operate; and the best surgeon knows *when not* to operate.

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VISIT our stand at UEGW Prague to enjoy pancakes and maple syrup

A TASTE OF CANADA: OUR UNIQUE MAPLE SYRUP

In Canadian forests, the maple is considered a valuable tree. It is harvested for its hard, resilient wood and, mainly in Quebec, for its sap from which a delicious syrup is obtained.

The collection of the sap, followed by its transformation into syrup by boiling, is a very old custom inherited from native Indians who were the first to recognize it as a source of energy and nutrition. In early spring, they would pierce the tree trunk with a tomahawk, placing a wood chip under the hole to channel the maple water into a bark receptacle.

2005 WORLD CONGRESS OF GASTROENTEROLOGY

MONTRÉAL CANADA

SEPTEMBER 10-14, 2005

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Your meeting place in 2005

A Memorable Experience Awaits You At the 2005 WCOG, Montreal!

Hugh Chaun, *Co-chair, Press & Congress News Canadian Organizing Committee, 2005 WCOG*

The meeting in Montreal 10–14 September, 2005 promises to be a milestone in the history of the World Congress of Gastroenterology. It will embrace a unique program that will address the expanding horizons of global goals in Gastroenterology in the 21st century. 2005 WCOG will be an event not to be missed, and Canada eagerly anticipates welcoming all gastroenterologists, hepatologists, pediatric gastroenterologists, and gastrointestinal surgeons, pathologists, basic scientists, and GI nurse assistants and research assistants world-wide to Montreal. Of the many outstanding aspects of the program in Montreal that will enrich your educational and personal experiences, the following are just a few highlights.

THREE FULL DAYS OF LIVE ENDOSCOPY transmits directly from Toronto and Hong Kong that will demonstrate state-of-the-art techniques in diagnostic and therapeutic endoscopy by experts from around the world.

The **SCIENTIFIC PROGRAM** which will deliver **CURRENT EVIDENCE** and **CUTTING-EDGE RESEARCH** applicable to clinical practice by world-renowned speakers, on all important topics of gastroenterology and hepatology world-wide. These days will include **CANCER OF THE GI TRACT**, its global epidemiology, genetic environmental issues; **ABDOMINAL PAIN**, its international perspective, mechanisms of pain generation, and new drug therapies; **HEPATOLOGY**, with presentation of new concepts in pathogenesis and approaches to treatment; **INFECTION AND THE GI TRACT** will include a global perspective of the GI complications of AIDS.

The **GASTROINTESTINAL SURGICAL PROGRAM** will discuss controversies in the management of inflammatory bowel disease, recent advances in anorectal disorders, oesophageal surgery, surgery for obesity, and frontiers of transplantation.

You can also attend **POSTGRADUATE COURSES** of your choice over the week-end prior to the main scientific congress. These will include the AGA Course on **EVIDENCE-BASED GASTROENTEROLOGY**: Translating the Evidence into Practice; **INTERACTIVE COURSE ON UPPER AND LOWER INTESTINAL DISEASE AND LIVER DISEASE**, organized by the Sociedad Interamericana de Endoscopia Digestiva and the Interamerican Society of Gastroenterology; **EMERGING TECHNOLOGIES AND CURRENT PRACTICE IN DIGESTIVE ENDOSCOPY**, presentation en français, organized jointly by the Association de Gastroenterologie et d'Endoscopie du Quebec and the Société Française d'Endoscopie Digestive; **FRONTIERS IN MINIMALLY INVASIVE THERAPIES FOR DIGESTIVE DISEASES: EVIDENCE AND TECHNIQUES**, organized by the Canadian Surgeon Forum; and **INTESTINAL FAILURE, FUNCTION FOODS AND GI DISEASE AND HEALTH**, organized by the Canadian Society for Clinical Nutrition. In addition, there will be a post-meeting conference on **CONTROVERSIES IN THE DIAGNOSIS AND THERAPY OF INFLAMMATORY BOWEL DISEASE**, organized by Yale University, to be held in Stowe, Vermont, U.S.A.

The meeting will offer an excellent opportunity to enjoy the splendours of **MONTREAL**, a unique North-American city with a rich European heritage, vibrant, contemporary, multicultural, safe, easily accessible, and most affordable. Its many restaurants are recognized as some of the best in this continent, and September is the ideal month weather-wise to be in Montreal.

Montreal is the home of the **OSLER LIBRARY**, Canada's national library for the history of medicine. McGill University was the alma mater of **SIR WILLIAM OSLER** (1848–1919), Canada's most illustrious physician, often regarded as the greatest physician of the past century. He wrote more than 1500 papers and books, many on gastrointestinal disorders. He referred to **DYSPEPSIA** as "the besetting malady". He postulated that "more people are killed by over-eating and drinking than by the sword…" Although the sword is history, not much has changed in this regard in the last hundred years!

As a further invitation to all our colleagues in every continent to come and share an unforgettable experience in Montreal in September, 2005, it is appropriate to reflect on one of William Osler's sayings – "Medicine is the only world-wide profession, following everywhere the same methods, actuated by the same ambitions and pursuing the same ends."

THE BEST OF DDW 2004... ON CD ROM

Digestive Disease Week (DDW®) is the premier forum for research, clinical education and networking in the field of digestive diseases. The four sponsoring societies of DDW—AASLD, AGA, ASGE and SSAT—provide a diverse and comprehensive program of educational offerings designed for the clinician and researcher alike.

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- Hilar Cholangiocarcinoma;
- Management of GI Obstruction below the Esophagus;
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DDW 2004

WGN

Role of Genetic Factors in the Pathogenesis of Alcoholic Liver Disease

J. Petrasek, M. Jirsa, J. Sperl, F. Stickel, D. Schuppan, J. Spicak

Note: This paper will be presented at the core meeting of the UEGW in Prague, September 2004.

Background

Excessive alcohol intake leads to liver disease, which can range from simple steatosis to steatohepatitis, fibrosis, and/or cirrhosis. While steatosis develops in most regular drinkers, the vast majority do not develop more severe liver damage; the reasons for this are largely unknown, but may include both environmental and genetic factors.

Earlier data from retrospective epidemiological studies are conflicting, raising doubts over the relationship between alcohol consumption and the risk of liver disease. In contrast, recent prospective studies provide evidence for both a threshold effect and a dose–response relationship, suggesting that the minimum alcohol quantity that confers a measurable risk of developing alcoholic cirrhosis is 30 g ethanol per day and that the cumulative lifetime alcohol intake leading to cirrhosis is 100 kg of pure ethanol. In addition, men and women who consume more than 80 g/d of ethanol have an equal risk for cirrhosis. According to these data, less than 5% of heavy drinkers develop cirrhosis, which contrasts with the previously published incidence rate of 20%.

Evidence for a Genetic Predisposition to Advanced Forms of Alcoholic Liver Disease

The most compelling evidence for a genetic predisposition to alcoholic liver disease comes from two large studies, by Hrubec et al. and Reed et al., showing that genetic factors contribute about 50% of all the risk variables for development of end-organ damage.

The epidemiological data have stimulated investigations based on a "candidate gene" strategy to search for genes and polymorphisms involved in a predisposition to alcohol-induced liver damage. The projects are based on the principle of allelic association studies, comparing relative distributions of genotypes between patients with alcoholic liver disease and drinkers (control individuals) without liver disease. Unfortunately, associations between single gene variants and alcohol-induced liver damage need to be judged with caution, due to the polygenic background of alcoholic liver disease.

Julius Spicak

Jan Petrasek

Candidate Genes for a Predisposition to Alcoholic Liver Disease

Genes encoding enzymes in ethanol metabolism. Differences in ethanol metabolism and elimination are, in part, genetically determined. Two major degradation systems catalyze ethanol elimination. Low blood levels of ethanol are degraded by alcohol dehydrogenase (ADH) and subsequently by aldehyde dehydrogenase (ALDH), producing acetaldehyde and acetate, respectively. Chronic ingestion of larger amounts of ethanol induces the microsomal cytochrome P450 2E1 (CYP2E1) system, which converts ethanol to acetaldehyde. CYP2E1 activity may increase up to 10-fold, thereby increasing the amount of toxic acetaldehyde and reactive oxygen species. Both ADH and ALDH reduce the beta oxidation rate and induce lipid accumulation. The resulting hepatic steatosis increases the risk of lipid peroxidation, which is an independent risk factor for the development of severe forms of alcoholic liver disease.

Numerous functional polymorphisms in genes encoding ALD, ALDH and CYP2E1 have been studied. According to in-vitro studies, the presence of the ADH1B*2 and ALD1C*1 allele increases the catalytic activity of alcohol dehydrogenase, resulting in higher acetaldehyde production, but these findings could not be reproduced in subsequent studies. ALDH2*2 polymorphism, present in 50% of the Asian population, reduces the rate of acetaldehyde breakdown

by aldehyde dehydrogenase and elevates the serum level of acetaldehyde, causing flushing, tremor, and sweating and thus discouraging individuals from further alcohol drinking.

Genes affecting endotoxin-derived inflammation in alcoholic liver disease. According to both in-vitro and in-vivo studies, it is postulated that ethanol activates Kupffer cells by promoting leakage of bacterial lipopolysaccharide (endotoxin) from the intestine into the portal circulation. Activated Kupffer cells produce large amounts of tumor necrosis factor-alpha (TNF-α) and other proinflammatory cytokines such as interleukin-1 (IL-1) and IL-6. Key organelles in inducing hepatocyte necrosis and apoptosis are the mitochondria. Chronic ethanol exposure promotes mitochondrial oxidative stress, decreases adenosine triphosphate (ATP) synthesis, and initiates apoptosis. Numerous allelic variants of the TNF-α gene have a direct impact on TNF-α expression and on the tissue concentration of TNF-α. Single nucleotide polymorphisms at positions -308, -238 result in increased TNF-α synthesis, while polymorphism -863 decreases TNF-α gene expression. Despite the importance of these experimentally proved findings, none of these polymorphisms convincingly influence the risk of alcoholic liver disease.

Genes involved in hepatic fibrogenesis. Activation of stellate cells is the crucial event initiating hepatic fibrogenesis. Activation of these cells is induced by several mechanisms, the most important being transforming growth factor-beta (TGF-β), which is secreted by numerous cell types. Activated stellate cells transform into contractile myofibroblasts, which synthesize excess collagen. According to experimental studies, polymorphisms within the TGF-β gene could have an impact on TGF-β expression and thus influence the risk of alcoholic liver disease. However, no association with liver fibrosis has been proved in alcoholic liver disease.

Conclusions and Perspectives

In summary, genetic factors may explain the broad spectrum of interindividual responses to chronic ethanol exposure. In the previous 15 years, it has been suggested that numerous candidate genes and polymorphisms may act as genetic factors capable of predisposing ethanol-exposed individuals to chronic forms of alcoholic liver disease. In-vitro studies of the candidate genes proved that some of these polymorphisms involve functional differences that could possibly lead to biological effects. However, so far, most of the polymorphisms tested have not been shown to have any significance in human studies.

Future studies should aim to identify a panel of candidate genetic variations. Identifying these would make it possible to clarify the pathogenic pathways of chronic liver disease and contribute to new approaches to prevention and treatment strategies.

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Modern Management of Echinococcosis

Hans G. Schipper

Introduction

Echinococcosis is a zoonotic infection transmitted by dogs in livestock-raising areas that incidentally affects humans. Worldwide, infection with the larval stage of the dog tapeworm *Echinococcus granulosus* is the one that occurs most frequently. This relatively benign parasitic disease is characterized by slowly growing cysts, most commonly in the liver and less frequently in lungs and rarely elsewhere in the body. Developing countries with poor hygiene in which sheep and cattle are raised are high-risk areas for acquiring cystic echinococcosis.

Infection with the larvae of the fox tapeworm *Echinococcus multilocularis* occurs in fewer areas. *Echinococcus multilocularis* causes a slowly progressive liver necrosis that tends to metastasize and behave like a malignant disease. Colder climates and mountain and forest areas inhabited by foxes are the primary risk areas for acquiring alveolar echinococcosis. Infection with *Echinococcus vogeli* (the jaguar tapeworm) and *Echinococcus oligarthrus* (the puma tapeworm) is rare and occurs only in South America.

This paper will focus on cystic echinococcosis of the liver, the

most relevant type of echinococcosis in the world.

Pathogenesis and Etiology

Dogs are the definitive host of *Echinococcus granulosus* and harbor the tapeworm in the small intestine. Sheep and cattle are intermediate hosts and become feco-orally infected by *Echinococcus* eggs shed into the environment in the feces of infected dogs. *Echinococcus* eggs hatch in the intestinal mucosa of the intermediate host and transform into oncospheres, which penetrate the bowel wall. Via the portal circulation, the liver is reached, in which slowly expanding cysts develop. The intermediate host responds to the presence of the parasitic cyst by surrounding it with fibrous tissue. This complex of parasitic cyst plus fibrous capsule is called an *Echinococcus* cyst or hydatid cyst. The parasite's life-cycle is closed when dogs are infected by viable cyst-containing organs from slaughtered livestock. In the intestine of the dog, protoscoleces develop into adult tapeworms.

Humans are dead-end hosts who become infected by *Echinococcus* eggs feco-orally. Children playing with infected dogs may become infected early in life.

Epidemiology

Echinococcosis is prevalent throughout the world. High prevalence rates are found in parts of southern and eastern Europe, the former USSR, Middle East, northern and eastern Africa, north-western Kenya (Turkana), southern Sudan, Ethiopia, Eritrea, north-western and eastern China, and South America. Sporadic infections occur in North America, the south-western United States, Central America, northern South America, South Africa, Australia, New Zealand, and northern Europe.

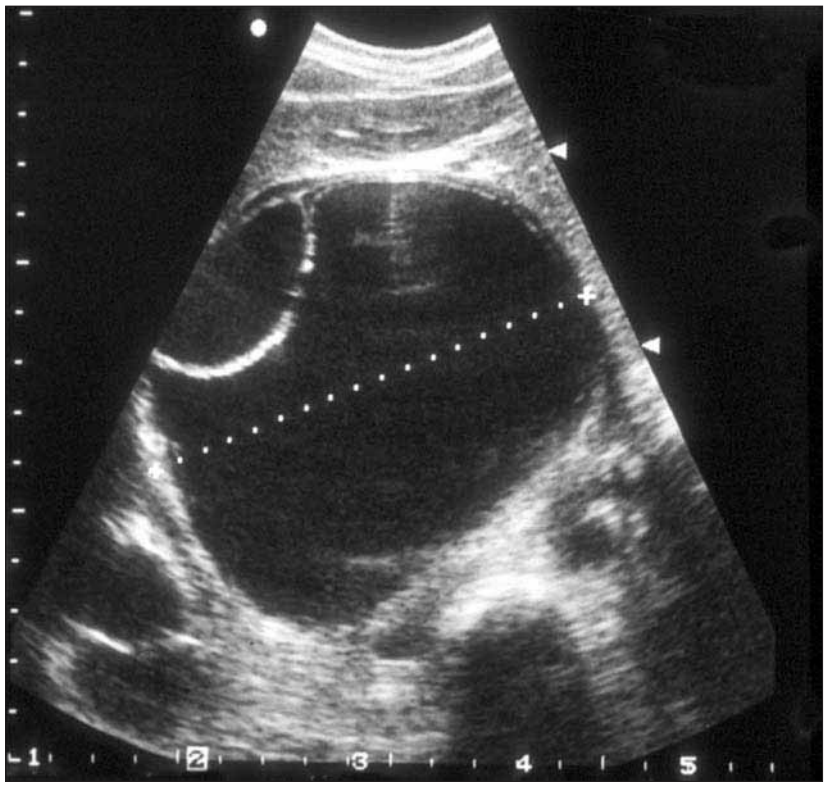

Figure 1. *Ultrasound showing a univesicular cyst with a "double membrane" and one daughter cyst.*

Diagnosis

The diagnosis is based on (1) history and geography; (2) imaging; and (3) serology. Parasitology of cystic contents confirms the diagnosis. Most cysts occur in the liver (52–77%), and they are found less frequently in the lungs (8.5–44%) or elsewhere in the body (15–19%).

Complications

Anaphylactic shock, cyst infection, and rupture into the biliary tree are the most severe complications.

Anaphylactic shock due to spontaneous or traumatic cyst rupture, or during surgery, is a rare and severe complication. Seeding of cyst contents into the peritoneal cavity is a serious secondary complication of cyst rupture. Cysts may become infected following bacteremia or via communicating bile ducts, especially when endoscopic retrograde cholangiopancreatography (ERCP) has been performed. Rupture into the biliary tree typically occurs in larger cysts containing multiple daughter cysts. Less threatening complications are related to the mass effect of the cyst, and include compression of the bile ducts and portal or hepatic veins. This may result in obstructive jaundice, postobstructive cholangitis, and impaired blood flow in the portal and hepatic veins. Treatment is primarily directed at resolving the mass effect, by percutaneous or surgical intervention.

Imaging

Ultrasonography is the preferred diagnostic tool for hepatic hydatid cysts. It is easily available, cost-effective, and is used to classify cysts and assess their viability (Figure 1).

Computed tomography (CT) is usually the next step after an ultra-

sound diagnosis has been made. The main purpose is to visualize the relation between the hydatid cyst and the surrounding liver tissue, bile ducts, and portal and hepatic veins, and to identify its segmental location.

Serology

Enzyme-linked immunosorbent assay (ELISA) is used as a screening test and immunoelectrophoresis as a confirmation test. Serology may be negative in 10–15% of cases, especially in well encapsulated cysts and pulmonary cysts.

Treatment

The ultimate goal of treatment is to eliminate the germinal layer, although the hydatid cyst itself and its mass effect on the surrounding liver tissue are the eye-catchers. Currently, three treatment options are available: (1) surgery; (2) medical treatment; and (3) percutaneous treatment. Since the early 1990s, a new method of percutaneous intervention has been used to treat uncomplicated hydatid cysts with drainable contents. The technique is known as puncture–aspiration–injection–reaspiration (PAIR). PAIR-derived techniques were later also introduced to treat complicated hydatid cysts and cysts containing nondrainable material.

Surgery. The core principles of hydatid surgery are firstly, total removing all infectious parts of a cyst; and secondly, avoiding intra-abdominal spillage of the cyst contents. Radical surgical resection (liver resection, pericystectomy, and cystectomy) is the best way of preventing intra-abdominal spillage. The hydatid cyst is entirely removed and opening the hydatid cyst is avoided. Complication and recurrence rates are low.

Recent developments. Laparoscopic (peri-)cystectomy or drainage of anteriorly located cysts has been introduced as a new surgical technique. This technique is limited to laparoscopically accessible cysts, mainly those located anteriorly in the liver.

Medical treatment. Benzimidazole carbamates (mebendazole and albendazole) are anthelmintic drugs that kill the parasite by impairing its glucose uptake. Albendazole is the drug of choice, due to its better absorption and better clinical results. Continuous daily treatment for a 3-month period is usually prescribed, with a 74% success rate; relapses may be seen in 25% of patients, usually within 2 years of treatment.

In clinical practice, albendazole should be administered at a dosage of 10 mg/kg, twice daily, combined with a meal (breakfast and dinner) and preferably not co-administered with drugs that reduce gastric acidity.

Percutaneous treatment. In PAIR, the cyst is punctured under ultrasound guidance; the cyst fluid is subtotally aspirated; 95% alcohol or hypertonic saline is injected; and scolecidal agents are reaspirated after 10 min. After intracystic injection of scolecidal agents, both the germinal layer and the protoscoleces become instantaneously nonviable. Success with PAIR is defined as detachment of the endocyst, rupture of daughter cysts, and no evidence of viable proto-scoleces on microscopy of the cyst fluid.

New developments. A simplified method of PAIR using a mixture of 95% alcohol and 1% polidocanol (lauromacrogol 400, aethoxysclerol) has also proved to be safe and effective. Polidocanol was chosen as the sclerosing agent to destroy the germinal layer of the cyst and to enhance the sclerosing effect of alcohol.

Which treatment is best? Compared with surgery, PAIR plus chemotherapy is associated with greater clinical and parasitologic efficacy; lower rates of morbidity, mortality, and disease recurrence; and shorter hospital stays.

Conclusion

Modern management of echinococcosis requires the availability of all three treatment options – medical treatment, percutaneous treatment, and surgery. Surgery is no longer the treatment of first choice for hepatic echinococcosis. In patients with univesicular cysts, albendazole monotherapy is the first choice. PAIR is indicated when pain is intractable or albendazole fails. Percutaneous treatment with a combination of alcohol and polidocanol may be used, but not in cases associated with cystobiliary fistulas. Surgery is the first choice only when: (1) expertise in percutaneous treatment is not available; (2) percutaneous treatment cannot be safely undertaken; and (3) significant extrahepatic extension of the cyst is associated with a high risk of perforation or precludes adequate percutaneous treatment; and (4) in case of a rupture into the peritoneal cavity.

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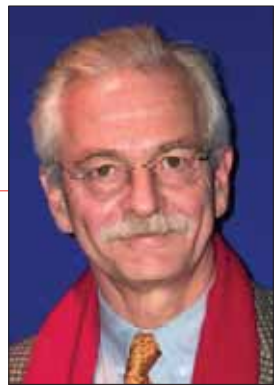
Note: This paper will be presented at the EAGE Postgraduate Course during the forthcoming UEGW in Prague, September 2004.
The full-length version including references is available in the online version of *World Gastroenterology News* (www.worldgastroenterology.org).

Critical Appraisal of Laparoscopic Bile Duct Exploration



Bertrand Millat

Laparoscopic exploration of the common bile duct (CBD) is carried out for the diagnosis or the treatment of CBD stones. CBD stones demonstrated by laparoscopic intraoperative cholangiography (IOC) or laparoscopic ultrasonography (LUS) are extracted either through the cystic duct or through choledochotomy. An alternative for the treatment of CBD stones is to perform an endoscopic sphincterotomy either before, during, or after laparoscopic cholecystectomy. The aim of this review is to evaluate these different techniques.

Intraoperative Cholangiography (IOC)

Two prospective randomized studies have assessed the value of routine IOC during laparoscopic cholecystectomy. In the first prospective trial, by Soper and Dunnigan [1], relevant information was obtained in eight of 56 patients, and it altered the intraoperative management in four. In the second trial, by Nies et al. [2], IOC was unsuccessful in 27 patients (19.6%), most often because of failure to intubate the cystic duct. Unsuspected cystic or CBD stones were diagnosed by IOC in three of 138 patients.

Cystic duct cholangiography is clearly better than cholecystocholangiography, and fluoroscopic imaging should be the standard for IOC. Until now, no specific clinically significant complications directly attributable to laparoscopic IOC have been reported. Expected success rates for laparoscopic IOC are in the range of 90–100%. Inability to cannulate a narrow cystic duct is the main cause of failure. The success rate is higher in a group with selective indications for IOC in comparison with a group without such indications – 98% versus 93%, respectively.

In addition to screening for potential asymptomatic CBD stones, the second important attribute of IOC is that it provides adequate definition of the ductal anatomy. The disastrous consequences and enormous costs of bile duct injuries have to be taken into account when evaluating the cost-effectiveness of IOC. The rate of bile duct injuries associated with laparoscopic cholecystectomy is approximately 0.6%, and this can be reduced with IOC. In all cases associated with an increased risk of CBD injury, and particularly during a physician's first 20–30 cases of laparoscopic cholecystectomy, IOC should be mandatory. Ability to perform an IOC, not just removing the gallbladder, should be one of the requirements for adequate training in laparoscopic biliary surgery.

Table 1. *Criteria for routine intraoperative cholangiography*

Preoperative factors
Endoscopic retrograde cholangiography ± sphincterotomy
Ultrasound findings
Common bile duct size over 6 mm
Choledocholithiasis
History of jaundice or pancreatitis
Elevated bilirubin, alkaline phosphatase, transaminases
Intraoperative factors
Unclear anatomy
Conversion to open cholecystectomy
Dilated cystic duct over 4 mm

Laparoscopic Ultrasonography (LUS)

Several studies of LUS have been published suggesting that LUS is superior to IOC. LUS is performed with a higher success rate, in a shorter time, and with better specificity, but with less precision with regard to the delineation of the biliary tree anatomy. LUS is of little, if any, help in diagnosing or preventing bile duct injuries, whereas IOC is better than LUS for delineating the entire biliary tree, from the intrahepatic tree to the pancreatic portion of the CBD.

LUS is operator-dependent, and there is evidently a learning curve – 20–40 examinations, which may be difficult to obtain in small-volume centers in which the 10% prevalence of CBD stones means that the learning curve may take 1–2 years to complete.

Laparoscopic Extraction of Common Bile Duct Stones

Once stones have been detected during laparoscopic IOC, laparoscopic extraction of them is a logical extension of the procedure. Laparoscopic exploration of the CBD can be performed either through the cystic duct or by laparoscopic choledochotomy, and both procedures are feasible and safe. Endoscopic sphincterotomy (ES) is commonly offered preoperatively as the alternative to surgery for CBD stones. ES is indicated in patients with severe cholangitis for urgent drainage of infected bile, and in patients with retained stones after cholecystectomy. In open conventional surgery, controlled studies have not shown that ES, performed either prior to surgery or in patients with gallbladder in situ, was superior to single-step surgical management. The conclusions reached in these randomized trials have not been extrapolated to laparoscopic biliary surgery.

Data gathered from randomized trials have demonstrated that ES, as an additional procedure to surgery, does not improve the clinical results in patients who are fit for primary single-stage surgical treatment, whether performed laparoscopically or not. Severe cholangitis is an unquestionable indication for urgent endoscopic drainage, regardless of whether or not the CBD can be cleared of associated stones.

All surgeons undertaking laparoscopic cholecystectomy must be able to perform an IOC. When IOC demonstrates CBD stones, appropriate treatment is decided on according to the available equipment and skills. Transcystic clearance of CBD stones may be successful. In the case of large stones (more than 20 mm in diameter) or other potential difficulties as regards postoperative ES, such as a periampullary diverticulum, conversion to open surgery is indicated when the stone cannot be removed during laparoscopy. In other cases, the available data do not allow any formal conclusions regarding the choice between advanced laparoscopic biliary explorations and postoperative ES. In a decision analysis by Erickson and Carlson [3], assessing different approaches to using endoscopic retrograde cholangiography (ERC) in patients undergoing laparoscopic cholecystectomy, postoperative ERC was associated with lower costs and less morbidity, but laparoscopic CBD exploration was not included in the study design. Finally before embarking on a more invasive laparoscopic CBD exploration policy for small stones that cannot be retrieved using the transcystic approach, surgeons must remember that asymptomatic migration does exist, even if the definitive fate of small CBD stones is not at present known. The potential safety afforded by temporary biliary drainage still has to be balanced with its unavoidable morbidity.

Does the COX-1/COX-2 Concept Still Hold?

Christopher Hawkey

Recognition that nonsteroidal anti-inflammatory drugs (NSAIDs) were inhibitors of prostaglandin synthesis was critical to understanding both their therapeutic activity and gastrointestinal pathology. In the stomach and duodenum, inhibition of prostaglandin synthesis undermines defensive mechanisms such as mucosal blood flow and mucus and bicarbonate secretion, and leads to the development of microerosions that ultimately deepen to become ulcers as a consequence of acid peptic attack. Subsequently, it has become clear that prostaglandin synthesis derives from two distinct but similar cyclooxygenase enzymes. The constitutive cyclooxygenase – cyclooxygenase-1 (COX-1) – is expressed in many tissues, including the gastrointestinal tract. The inducible cyclooxygenase – cyclooxygenase-2 (COX-2) –becomes highly expressed under the influence of many factors such as cytokines and growth factors in tissue injury, inflammation, and malignant transformation.

The COX-1/COX-2 hypothesis was that drugs that inhibit COX-2 would have the same therapeutic activity as NSAIDs, but without their adverse effects.

Therapeutic Activity

Numerous clinical trials have shown that COX-2 inhibitors relieve pain and inflammation in arthritis in a dose-dependent fashion, with maximum effects that are usually not significantly different from those of NSAIDs. Thus, although some have suggested – contrary to the COX-1/COX-2 hypothesis – that COX-1 may contribute to

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symptoms in arthritis, this effect does not appear to be sufficiently great to have a measurable clinical impact.

Toxicity of COX-2 Inhibitors and NSAIDs

Remarkably, acute studies have shown that even at very high doses (up to ten times the therapeutic dosage), COX-2 inhibitors cause no demonstrable mucosal injury in healthy volunteers. Medium-term endoscopy studies in patients show substantial reductions in ulceration in comparison with NSAIDs. In some, but not all, studies, the levels of ulceration have been similar to those observed with a placebo. In outcome studies, the incidence of clinically significant ulcers or ulcer complications is reduced in comparison with NSAIDs. In most studies, the reduction has been between 50% and 60% rather than the 75–85% that might be inferred from the fourfold to fivefold increase in ulcer complications caused by NSAIDs.

Dyspepsia

The original COX-1/COX-2 hypothesis did not relate to dyspepsia. Nevertheless, high levels of dyspepsia with NSAIDs are sufficiently general that this may be a class-based (and therefore mechanism-based) effect. This argument is reinforced by data from COX-2 inhibitors, which quite consistently appear to be associated with levels of dyspepsia that are greater than those with a placebo but lower than those with NSAIDs.

Thrombotic Events

When patients present with NSAID-associated ulcer bleeding, it may be because the NSAID causes ulcer formation or impairs hemostasis, leading to bleeding. Equally, since vascular prostacyclin is recognized to be largely derived from the COX-2 enzyme, it is possible that COX-2 inhibitors could induce thrombosis. This issue came to a head in the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, in which patients receiving naproxen were reported to have fewer thrombotic cardiovascular events than those receiving rofecoxib. This could be attributed either to a harmful effect of rofecoxib or of naproxen. Recent data suggest that the latter is the dominant factor, although the former may not be absent.

Cancer

Since COX-2 is induced in gastrointestinal cancers, a development of the COX-1/COX-2 hypothesis predicts that COX-2 inhibitors may prevent or reverse gastrointestinal malignancy without harmful effects on normal mucosa. This has been shown in animal studies and in genetic models in humans. However, aspirin is also effective, but is a COX-1 inhibitor. Understanding the way in which aspirin prevents or reverses premalignant and malignant processes in the gastrointestinal tract will contribute to our understanding of oncogenesis.

Practical Prescribing

The COX-1/COX-2 hypothesis does not discount the influence of additional factors, and in fact acknowledges that NSAID ulcers have prostaglandin-dependent and acid peptic-dependent components. This would lead one to hypothesize that acid suppression and COX-2 inhibitor substitution might be complementary strategies in preventing ulcer disease. Recent data show that acid suppression very effectively reduces ulcer development and dyspepsia in patients receiving COX-2 inhibitors who are at high risk of these two gastrointestinal problems.

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PENTAX

Molecular Biology for the Gastroenterologist

Peter Ferenci

An increasing number of diseases of the digestive organs are being recognized as having a genetic background (Table 1). The era of genetics began with the observations by Gregor Mendel that changes in the color of flowers and the shape of their seeds followed a clear pattern over the years. The fundamental rules of inheritance that he established were thus based on easily recognizable signs. His work preceded the discovery that DNA is the carrier of genetic information.

An observed trait is referred to as a *phenotype*; the genetic information defining the phenotype is called the *genotype*. As advances were made in understanding the functioning of DNA, phenotypic genetics was replaced by molecular genetics. In contrast to phenotypic genetics, which assumes that gene products are either fully functional or devoid of function as a result of a mutation, molecular genetics describes variations in the base sequence of the genes. These changes are not always associated with impaired functions of the gene product, and do not necessarily imply the presence of phenotypic disease. It is these fundamental differences from phenotype-based genetics that define the role of molecular genetics in clinical medicine.

Definitions

A few basic definitions are needed to clarify the implications of molecular genetics.

What constitutes a normal gene? A normal gene is defined by the base sequence that is observed in the majority of healthy individuals in a given population, and it is known as the *wild type*. Base variations in the wild-type gene in healthy individuals are termed *DNA polymorphisms*. These alternative forms of a gene or a genetic marker are referred to as *alleles*. In other instances, allelic variants may reflect mutations in a gene that clearly alter its function.

What is a mutation? A mutation is a base sequence that differs from the wild type in a patient who presents with a phenotypic disorder. The sequence is never observed in healthy individuals.

The functional consequences of a mutation are manifold. Mutations can be broadly classified as either gain-of-function mutations or loss-of-function mutations. Gain-of-function mutations are typically dominant. Inactivating mutations are usually recessive, and an affected individual is homozygous or compound heterozygous (i.e., carrying two different mutant alleles) for the disease-causing mutations. Mutations may result in the complete absence of gene products ("null" mutations), or in proteins devoid of any function. Such mutations are associated with severe diseases occurring at birth or in early childhood. Other mutations result in less pronounced functional consequences and milder disease that presents later in life. A change in a single amino acid may affect the tertiary structure, the assembly, inactivation, secretion, or conformational stability of the gene product.

Table 1. *Selected genetic diseases in gastroenterology and hepatology.*

Diseases	Gene symbol
Cholestatic liver diseases	
Byler disease, Summerskill–Walshe syndrome	*FIC1* (now *ATP8B1*)
Progressive familial intrahepatic cholestasis 2	ABCB11
Progressive familial intrahepatic cholestasis -3	ABCB4
Dubin–Johnson syndrome	*ABCB2* (now *TAP1*)
Hepatic storage diseases	
Wilson's disease	ATP7B
Hemochromatosis	HFE
Colon cancer	
Familial polyposis coli	APC
Hereditary nonpolyposis colon cancer	MSH2, MLH1
Peutz–Jeghers syndrome	STK11
Idiopathic pancreatitis	
Cystic fibrosis	CFTR
Hereditary pancreatitis	Trypsinogen, *SPINK*
Crohn's disease	*NOD2* (now *CARD15*)

Tools for Molecular-Genetic Analysis

Molecular genetics requires the visualization of differences in the DNA sequence. DNA polymor-

phisms in coding regions (exons) or noncoding regions of the genes are inherited in accordance with the Mendelian rules. The value of highly variable DNA sequences as genetic markers rests on straightforward principles. Every person carries two copies of each chromosome, except for the sex chromosomes. To be useful for analyzing the transmission of the two chromosomes in a family, the DNA copies at the polymorphic site in the person under study have be different in the two chromosomes. The chromosomal sites at which the DNA sequences can have many alternative forms are thus ideal sites for genetic markers. In the human genome, the sites that have the properties most favorable for such extensive variation include a repetition of the same short DNA sequence a variable number of times (known as tandem-repeat sequences or microsatellites).

There are several methods of assessing variations in the DNA sequence. *Restriction fragment length polymorphism (RFLP) analysis* detects variations in the size of DNA fragments obtained after digestion with restriction enzymes.

Direct mutation analysis. *Direct sequencing.* New technologies allow automated sequence analysis of large portions of a gene to detect point mutations, deletions, inversions, and other changes in the nucleotide sequence. However, direct sequencing of the whole sequence does not yet play a role in clinical medicine.

Polymerase chain reaction (PCR)-based detection of known mutations. The simplest approach takes advantage of the base-sequence specificity of restriction endonucleases. A mutation will prevent the enzyme from cutting at that point in the sequence; conversely, a mutation may result in the creation of a new enzyme-recognition site and lead to cutting where it normally should not occur. The pattern of digestion is indicative of the presence or absence of a particular mutation. The specificity of the PCR reaction itself allows direct detection of mutations.

Interpretation of Test Results

Molecular-genetic analysis can yield three possible findings: the individual being tested can be a homozygous carrier of the mutation, a heterozygous carrier of it, or does not carry the mutation at all.

Homozygous mutation carrier. Genotypic diagnosis in a healthy individual raises the question of whether person being tested will ever develop the disease. In most hereditary diseases, the penetrance of a disease is not complete.

Heterozygous mutation carrier. *Compound heterozygotes* carry two different disease-causing genes. In most inherited diseases, multiple different mutations of the affected gene are present (more than 800 in cystic fibrosis, for example). The problem is to differentiate a "true" heterozygote (carrying a wild-type allele) from a compound heterozygote. The most important question is whether the individual being tested is (and will remain) free of a disease or not. According to Mendelian rules, individuals carrying a wild-type and a disease-causing gene with autosomal-recessive inheritance (true heterozygotes) are healthy. This statement is only valid if the other gene not carrying the mutation is also functionally intact. The gene that does not have an established mutation may have a different (disease-causing) one. Unfortunately, this is not an exception, but a general rule.

Haploinsufficiency. Mutation in a single allele can result in a situation in which one normal allele is not sufficient for a normal phenotype. This phenomenon applies, for example, to the expression of rate-limiting enzymes in heme synthesis that cause the porphyrias. Mutation in a single allele can also result in loss of function due to a dominant-negative effect.

Loss of heterozygosity. Individuals with a normal and an abnormal gene without any apparent disease may undergo somatic mutations of the normal gene later in life. Such events may result in overt dysfunction of the gene product in the affected cells. This loss of heterozygosity is assumed to be an important event in carcinogenesis.

Individuals not carrying the mutation. A negative finding does not exclude phenotypic disease, since other mutations of the gene may be present. In addition, gene defects may be due to mutation of other genes.

Target Populations for Molecular-Genetic Testing

Patients with symptomatic phenotypic disease. In patients with hereditary diseases, DNA analysis strengthens the final diagnosis. In diseases that have only a few mutations (such as *HFE*-associated hemochromatosis), mutation analysis can replace invasive diagnostic tests. In patients with a transferrin saturation index > 45%, testing for common *HFE* mutations allows a direct diagnosis of hereditary hemochromatosis.

Mutation analysis is important for differentiating between various genetic diseases with similar phenotypic symptoms, as in patients with primary findings of iron overloading. At least four independent genetic diseases are now known to result in the accumulation of iron in various organs.

Family screening. Mutation analysis is the state-of-the-art approach for screening the family of index patients and can replace other diagnostic tests to identify individuals at risk of developing the disease. A negative test result in a relative of a patient with a disease-related mutation indicates a low risk of the disease.

Population screening. Mutation analysis has not yet been tested for detecting presymptomatic disease in the general population. Apart from the difficulties in interpreting test results mentioned, there are also several factors that limit the use of genetic tests for population screening. Firstly, screening is only appropriate if a validated treatment is available for asymptomatic individuals. Secondly, other screening strategies may be more cost-effective or straightforward than mutation analysis. For colorectal screening, DNA-based mutation analysis is not capable of replacing endoscopy, as a colonoscopy examination is needed whether or not a mutation is present. In addition, the development of cancer can be prevented by endoscopic polypectomy. Endoscopy combined with testing for fecal occult blood will therefore continue to be the standard approach for the foreseeable future.

Disease association studies. The rapid growth of human genetics is creating countless opportunities for studies of disease association. Given the number of potentially identifiable genetic markers and the multitude of clinical outcomes to which these may be linked, the testing and validation of statistical hypotheses in genetic epidemiology is a challenge on an unprecedented scale.

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Upper Gastrointestinal Cancer in Iran

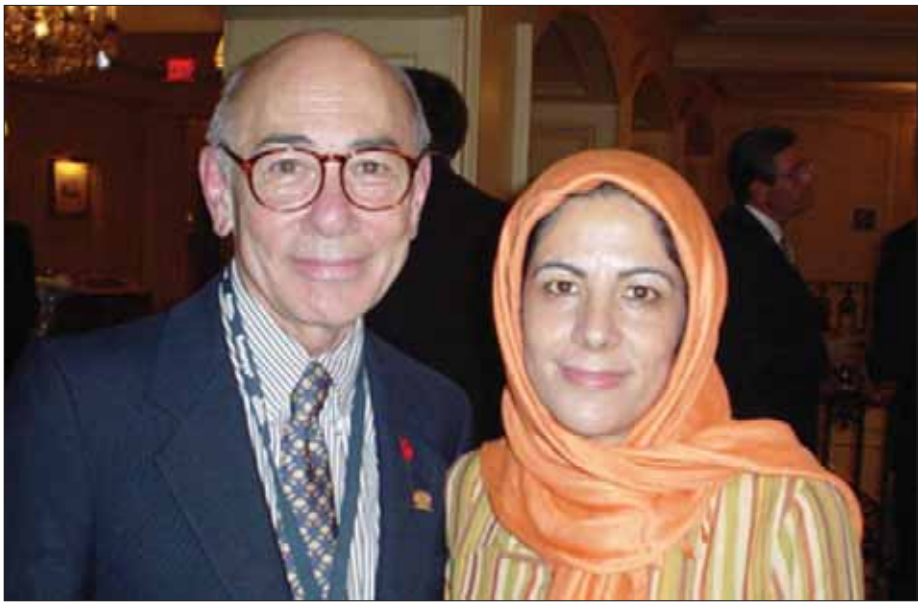
A. Pourshams, R. Malekzadeh

Background

After cardiovascular disease and accidents, cancer is the third most frequent cause of death in Iran, with its population of 69 million. Iran is bounded by the Persian Gulf in the south and Turkey and Iraq on the west. The Caspian Sea, Armenia and Turkmenistan lie on the northern border, and on the east are Afghanistan and Pakistan (Figure 1).

There are major regional variations within Iran in the incidence of different types of cancer, related to differences in ethnicity, lifestyle, environment, climate, and living conditions. Because of the high risk of esophageal and gastric cancer in northern Iran, several studies have been carried out to evaluate the population at risk.

Carrying out research in the western part of the Caspian Sea area is much easier than in the east. The people who live in the western part are ethnically Turkish, and are more educated and better off than the residents in the eastern part of the area. About 40% of Iranians are Turks who have both the power and resources needed for development (large cities, multiple universities and businesses). There was no problem in finding physicians and paramedical personnel to work for the Ardabil studies, since almost everybody in Ardabil is Turkish and also speaks Farsi, the official Iranian language, in addition to their mother tongue.



A. Pourshams (right) and J.D. Waye (Editor-in-Chief WGN).

***Figure 1**. Map of Iran*

Acceptance of medical research among the general population has always been high in Ardabil. In 1968, the first cancer registry program was launched on the basis of a collaborative agreement between the Health Institutes of the University of Tehran and the International Agency for Research on Cancer (IARC) in order to study esophageal cancer in the area of the Caspian littoral, from Ardabil province in the west to Golestan province in the east. Studies conducted at that time calculated the annual age-adjusted incidence rate of esophageal cancer (mainly esophageal squamous-cell cancer) to be over 100 per 100 000 in the Gonbad district in Golestan province – among the highest rates in the world. A subsequent collaborative case–control study revealed a pattern of very low consumption of fresh fruit and vegetables in north-eastern Iran.

The situation in the north-east part of the country, near Turkmenistan, is considerably different from that in the west (Ardabil). Most Turkmen live in northern Golestan province, and they constitute less than 2% of the population of Iran. In their appearance (especially their eyes), ethnicity, and social habits, they are different from Persians (who make up 50–55% of Iranians). The main traditional occupation of Turkmen has been in animal husbandry. They traditionally lived in temporary houses and tents in the hills, mountains, and plains in the border region between Iran and Turkmenistan, and they had several disputes with the central governments before taking up obligatory permanent residence in north-eastern Iran about 70 years ago. Because of the differences in cultures, Turkmen have not had strong relationships with the Persians (intermarriage, for example) until the last few years.

There were many problems in conducting the studies in the north-eastern Turkman area, including:

a) The fact that more than 90% of women and about 50% of men over 40 years of age in the villages are illiterate and cannot speak Farsi, so that gathering data is possible only through face-to-face interviews together with Turkmen interpreters.
b) Finding enough educated Turkmen able to assist in the studies is a major problem; Persians cannot speak the Turkmen language and are not a suitable substitute.
c) Most Turkmen are aware that survival in those with esophageal cancer is poor, and did not initially accept any intervention for people with the signs and symptoms of esophageal cancer; however, acceptance is improving.
d) Gonbad does not have units for chemotherapy or radiotherapy, and does not have specialist cancer surgery units, so that cancer patients need to travel to other provinces. Unfortunately, there are no flights or fast trains between Gonbad and Tehran or other provinces that do have cancer care facilities.
e) Some of the roads are unpaved in the Gonbad district.
f) The weather is not tolerable during the summer in the Gonbad district (very hot and humid), and there is a risk of huge floods every spring.

The initial collaborative studies stopped at the time of the political changes that took place in Iran in 1978. Recently, The Digestive Disease Research Center (DDRC) at Tehran's University of Medical Sciences, the IARC, and the United States National Cancer Institute have started studying upper gastrointestinal cancers in the northern Iranian plain again. The Turkmen were resistant to endoscopy when the case–control study started in 2002. To motivate them to participate in the studies, the DDRC established a very well-equipped endoscopy unit in Gonbad 3 years ago (with the latest video endoscopes from Olympus and Pentax), along with a gastrointestinal pathology laboratory, providing free diagnosis, treatment, and management of all patients with upper gastrointestinal cancer. This included payment for surgery, chemoradiotherapy, dilation procedures, and stenting. Once the results were seen, acceptance of the treatment improved rapidly.

Recent Studies on Upper Gastrointestinal Cancers in Northern Iran

North-west. Gastric adenocarcinoma is the most common gastrointestinal malignancy in Iran. Ardabil has the highest incidence of gastric adenocarcinoma. According to an active cancer surveillance program conducted in Ardabil (1996–1999), gastric adenocarcinoma represents 31% of all malignancies in the region, with incidences of 49.1 and 25.4 per 100 000 per year for men and women, respectively. Half of these gastric cancers are located in the cardia. In 2000, upper endoscopic screening was carried out in 1011 randomly selected rural and urban residents of Ardabil, with mean age of 53 years. Urease testing or histology for *Helicobacter pylori* was positive in 89% of those tested, and 95% had chronic gastritis. *H. pylori,* which is known to contribute to the development of gastric adenocarcinoma, is common in Ardabil. No dysplasia or esophageal cancer was found in a recent population-based study with chromoendoscopy screening program in 504 asymptomatic randomly selected adults in Ardabil.

North-east. *Case–control study.* A referral clinic for upper gastrointestinal diseases was established by the DDRC in Golestan province in August 2001. Among the initial 682 patients seen at the clinic, 370 were confirmed histologically as having cancer, including 60% with esophageal squamous-cell cancer, 6% with esophageal adenocarcinoma, 16% with gastric cardia adenocarcinoma, and 16% with non-cardia gastric adenocarcinoma. The proportional occurrence of these four main upper gastrointestinal cancers was similar to that seen in Linxian, China, another area with a high incidence of esophageal squamous-cell cancer, and was markedly different from the current proportions in Western countries. Negligible alcohol consumption and cigarette smoking in these patients suggest that the high rates

of esophageal squamous-cell cancer seen in north-eastern Iran are associated with other risk factors.

Cohort study. In 2002, a cohort study was initiated in Gonbad district to evaluate the genetic and environmental risk factors of upper gastrointestinal cancers, mainly esophageal carcinoma. A total of 1359 (704 rural, 645 urban) inhabitants aged between 35 and 80 were selected randomly and invited to participate in the study. An active follow-up examination was carried out after 12 months. Cigarette smoking and opium and alcohol use were reported by13.8%, 10.3%, and 3.7%, respectively. The mean temperature of ingested tea was 57.4ºC. Two subjects developed esophageal squamous-cell cancer. The data show that the incidence of esophageal carcinoma is still high in the region, but that the pattern of causes of death is similar to that in other parts of Iran.

Active surveillance. Although Iran's National Cancer Registry program is still in its initial stages, the DDRC carried out active surveillance for cancers in the Caspian littoral and Kerman province (in the center of the country) in 1999 (Table 1). The data show that the cancer burden relative to each organ is similar in all areas of the Caspian littoral, but quite different from that found in the central part of Iran.

Ecological studies. A study was carried out to assess the hypothesis that the high rates of esophageal carcinoma in Golestan and the high rates of gastric cancer in Ardabil may be partly attributable to selenium deficiency. The findings suggest that selenium deficiency is not a major contributor to the high incidence of esophageal cancer seen in north-eastern Iran, although it may play a role in the high incidence of gastric cancer in Ardabil province.

Genetic studies. The frequencies of polymorphisms in 10 genes that have been hypothesized to have a role in the risk of esophageal carcinoma were compared among three Iranian ethnic groups with highly varying rates of the disease. These three groups included high-risk Turkmen, medium-risk Turks, and low-risk Zoroastrian Persians. Compared to Zoroastrians, Turkmen had a higher frequency of four alleles that are thought to favor carcinogenesis (*CYP1A1 m1, CYP1A1 m2, CYP2A6*9,* and *ADH2*1*); these results were consistent with an influence of these allele variants on the population risk of esophageal carcinoma. However, none of these four alleles had a high enough prevalence in Turkmen to explain the high rates of the disease in that group. Three of the four alleles were less frequent among Turkmen than in some Asian populations with lower risks of esophageal cancer. The authors concluded that it is unlikely that variations in these polymorphic genes are major contributors to the high incidence of esophageal carcinoma among Turkmen in Iran.

Because P53 mutations are the most frequent mutations in cancer, and may provide clues on the etiological mechanisms of esophageal squamous-cell cancer, P53 was analyzed in pathology samples from 98 Iranians with esophageal squamous-cell cancer, and mutations in 50% of the patients were found. The P53 mutation pattern in Iran was significantly different from that observed in esophageal squamous-cell cancer in high-incidence areas of China and Western Europe. These results are consistent with the hypothesis that several factors are involved in P53 mutagenesis in Iran, including a background of chronic inflammatory stress, as was shown by Crespi and colleagues in the 1970s.

Table 1. *The relative frequency of cancers by province (1999–2002).*

Ardabil	Gilan	Mazandaran	Golestan	Kerman
Stomach 31.4%	Stomach 19.0%	Stomach 16.3%	Esophagus 31.0%	Breast 10.2%
Esophagus 13.1%	Breast 9.9%	Esophagus 12.9%	Stomach 16.8%	Stomach 8.8%
Colorectal 4.8%	Colorectal 9.2%	Breast 9.6%	Breast 8.8%	Colorectal 6.7%
Lung 4.7%	Esophagus 8.7%	Colorectal 7.1%	Colorectal 5.3%	Blood 5.6%
Blood 4.4%	Bladder 7.9%	Blood 5.3%	Bladder 3.4%	Lung 5.0%
Other cancers 41.6%	Other cancers 45.3%	Other cancers 48.8%	Other cancers 44.7%	Other cancers 63.7%

Ongoing Studies

Case studies on esophageal and gastric cancers are ongoing in Ardabil and Golestan provinces. A cancer registry in the northern plain has been initiated by the DDRC, and reports will soon be forthcoming.

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Spread of WGO/OMGE-OMED endorsed Training Centers around the world. (● Center for advanced endoscopic training.)

WGO/OMGE-OMED Training Centers

Jim Toouli *(Co-Chairman, Joint Education and Training Committee)*

The Organisation Mondiale de Gastro-Entérologie/World Gastroenterology Organization (OMGE/WGO), along with its partner organization, the Organisation Mondiale d'Endoscopie Digestive/World Organization of Digestive Endoscopy (OMED), has developed training centers in different regions of the world with the aim of delivering education and training in all aspects of gastroenterology. These centers have been developed over the last few years, bringing together the ideas of numerous people who have served on the executive and/or education committees of the organizations and our colleagues in many parts of the world. They reflect the major mission of the organizations, which is to foster the progress of our profession through education and training with a global perspective.

There are two types of training center. The first type, of which there are five, are situated in the vicinity of developing countries, and their major aim is to train gastroenterologists in the developing world. The second type, of which there is only one at this stage, is aimed at providing more advanced training in gastroenterology.

The centers have evolved gradually, with most of the activity happening in the last 2–5 years. The first center was inaugurated in Soweto, South Africa, and was supported initially by the Munich Gastroenterology Foundation through Professor Meinhard Classen. The center was the "brainchild" of Professors Issy Segal and Classen, and the former also became its first Director. The World Organization of Gastroenterology became associated with the Soweto center as a result of Professor Classen's involvement. Professor Segal brought his ideas regarding the training center concept to the early meetings of the newly formed combined Education and Training Committee. These ideas merged with those being developed by the chairs and committee members through other contacts, and as a result the committee took on the task of enlarging and expanding the training center concept. The WGO/OMGE executive embraced the ideas with enthusiasm and there then evolved guidelines for setting up centers in areas of the world where it was felt a need existed, where trusted colleagues would be our local representatives, and where we would be welcomed, but also where our limited budget might provide a nidus for attracting further funds that would make the centers viable in the long term. An underlying principle has been the development of centers in association with the local government authorities and relevant gastroenterology groups (e.g., the local gastroenterology society). In addition, each of the centers has a designated member of the WGO/OMGE executive assigned to oversee negotiations with the relevant authorities, as well as two members of the Education and Training Committee who plan its activities. (One of these two is usually the director of the center, who is co-opted on to the education committee as a full member.)

Five centers have now developed, including Soweto. They are all different, but have the common aim of bringing education and training in gastroenterology to our colleagues in the developing world. Apart from Soweto, the other four centers are situated in Rabat (Morocco), Karachi (Pakistan), Cairo (Egypt), and La Paz (Bolivia). The centers in Morocco, Pakistan,

and Egypt are functioning and have taught a number of trainees on a variety of topics. The La Paz center will be inaugurated early in 2005. Each of the centers has developed differently from the others and their initial activities have been quite diverse.

In Soweto, trainees come from the surrounding countries and include gastroenterology nurses, family practitioners receiving basic training, and physicians obtaining specialist training in gastroenterology. Soweto aims to reach out to the developing countries in sub-Saharan Africa, where there is a large need for training in gastroenterology. The activities of the Soweto center have been embraced by the South African Gastroenterology Society, and as a result, much-needed support is provided for the center's educational activities by our South African colleagues.

The Rabat Center has evolved to address the needs of Francophone Africa. In conjunction with the Moroccan Ministry of Health, the center has been placed in a renovated ward of the main teaching hospital in Rabat. An ambitious program has evolved, and already a number of workshops have taken place. In addition to our own involvement, our colleagues from ASNEMGE (the European/Mediterranean Gastroenterology Association – Association des Sociétés Nationales Européennes et Mediterranéennes de Gastroentérologie) have provided financial support. It is planned that trainees from the French-speaking countries of Africa will be trained at this center by our colleagues from Rabat, along with international colleagues who will visit periodically to provide a global perspective.

The Karachi center has developed in partnership with the Aga Khan University and its department of gastroenterology. The department and university are highly developed institutions with programs at the cutting edge of medicine. The aims here are to develop an electronic web-based teaching program that may be deliverable to more remote regions of the world (e.g., Afghanistan). The center in Karachi can serve as the medium for disseminating valuable programs from any of our other centers or any departments in the world that may wish to contribute to the overall program. A curriculum is being established, and we believe that the future potential of this resource will be enormous.

The Cairo center is the most recent to be inaugurated and is a joint venture with the Egyptian Ministries of Higher Education and Health and the Theodor Bilharz Institute in Cairo. In addition, the involvement of the African and Middle East Association of Gastroenterology (AMAGE) has been important in setting up this facility. The opening ceremony and the opening meeting were highlighted in the last issue of *WGN*. With aims similar to those of the other centers, this center is targeting the training needs of our colleagues in the Middle East and in particular the Arab world. The first training program appropriately focused on the assessment and management of portal hypertension and

View of Baragwanath hospital (the largest in the southern hemisphere) in Soweto, South Africa.

attracted trainees from the Middle East and throughout Africa.

It is the aim of the education committee, which oversees the centers' activities, that – while always recognizing the diversity of the various centers – a common basic philosophy should evolve for all of the centers. A subcommittee has therefore been charged with developing this philosophy and the necessary guidelines for implementing it. Our vision for these training centers is that they will become centers of major influence in the training of colleagues in the developing world. As finances permit, we would hope to expand the numbers to other regions of the world.

The second type of center aims to address areas of excellence in gastroenterology and will be recognized for providing training at the cutting edge of our specialty. However, in keeping with the philosophy of an internationally recognized center of excellence, these centers need to be able to offer hands-on experience for trainees from all countries.

The first of these centers to be recognized is a center of excellence in delivering of endoscopic training and is to be designated The WGO/OMGE-OMED Advanced Center in Endoscopy Training. The first center recognized is in Santiago, Chile, and will be inaugurated in August. It is hoped that other centers, not only in endoscopy but also in the other areas of gastroenterology (e.g., hepatology, luminal gastroenterology, gastrointestinal surgery, liver transplantation, minimal-access surgery) will be recognized. We invite colleagues to consider whether their center may qualify for this prestigious designation.

The team at the Soweto Center with representatives of WGO/OMGE and AMAGE.

The members of the executives of the WGO/OMGE and OMED, as well as the committee members of the combined education and training committee, have great aspirations for the potential of the various training centers. We anticipate that they will become the focus of many of the activities of our societies and have a significant impact in leading the training and maintenance of standards in gastroenterology on a global basis. On behalf of the organizations, I invite input from the wider gastroenterology community on how best to advance our vision for these centers. In so doing, I also wish to acknowledge the support provided to the organizations by our industry partners, without whom none of this activity would be possible. Whilst there is no direct financial support from the biomedical industry for any of the centers, it is the income that is derived from the industry's support for the World Congresses that is used to underpin these important educational endeavors. With the anticipated success of the next World Congress in Montreal next year, we hope to not only expand the activities at the existing centers but also to expand the number of centers around the world.

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The European Endoscopy Training Center in Rome

Guido Costamagna

Prof. Costamagna teaching EETC trainees

The European Endoscopy Training Center (EETC; **www.eetc.it**) – a comprehensive center exclusively devoted to education and training in gastrointestinal endoscopy, based at the Catholic University School of Medicine in Rome, Italy – has now completed its first year. The EETC is at present the only permanent establishment of its kind in Europe. The idea of creating a center in Rome for teaching gastrointestinal endoscopy developed out of long-term experience in training activities over the past 15–20 years at the well-established Digestive Endoscopy Unit in Rome's Gemelli University Hospital. Between 1987 and 2003, nearly 200 endoscopists (111 from Italy, 16 from other European countries, and 52 from outside Europe) attended training courses ranging from a month (observation) to a year (hands-on) at the unit. The EETC project was successfully implemented thanks to collaboration between the Catholic University in Rome and five leading industrial companies involved in gastrointestinal endoscopy: Bard, Boston Scientific, Erbe Elektromedizin, Olympus, and Wilson-Cook.

The EETC is located in the center of the university campus, close to the animal laboratory, in a fully renovated building (Figure 1) on two floors, with an area of approximately 500 square meters. The heart of the EETC is on the basement level, where there is an operating room (Figure 2) with five workstations fully equipped with state-of-the-art Olympus video endoscopes and Erbe electrosurgical generators with argon plasma coagulation (APC), where trainees can carry out a variety of therapeutic endoscopic procedures on animal models, with appropriate guidance from tutors. Various endoscopic procedures can be carried out in the isolated swine upper or lower gastrointestinal tract using the Erlangen model – including polypectomy, mucosectomy, hemostatic procedures, APC treatments, self-expandable metal stent insertion, antireflux procedures, and sphincterotomy. The EETC is also fully certified and authorized to use live animals under general anesthesia for special procedures. The presence of a veterinary doctor specialized in animal care ensures that all ethical requirements are fully respected. The development of other models for teaching gastrointestinal endoscopy is also being currently investigated at the EETC.

On the first floor, there is an auditorium for 20–25 people, with up-to-date audiovisual equipment and a permanent link to an endoscopy suite at Gemelli University hospital to allow live display of endoscopic procedures conducted by local staff or by invited guest teachers. The center includes a small library and meeting room and another room equipped with four personal computer workstations for electronic interactive teaching, as well as a Simbionix electronic simulator for upper and lower gastrointestinal endoscopy and ERCP (Figure 3). Uniquely, the EETC includes facilities in which every step in the teaching process that should precede hands-on experience with patients can be replicated.

Other facilities associated with the center include a low-cost hotel on campus and a nearby apartment that can accommodate foreign trainees free of charge for periods of up to a year, thanks to a Wilson-Cook educational grant.

The EETC started its activities in July 2003. During the past year, there have been 34 courses lasting 2–4 days, including hands-on sessions, with more than 500 participating physicians. A further six courses for nurses at the hospital, on preoperative and postoperative assessment of patients undergoing therapeutic gastrointestinal endos-

copy, were also given by the unit's endoscopy nurses. New courses being prepared include capsule endoscopy, esophageal endotherapy, and treatment of acute and chronic pancreatitis.

The EETC has been already recognized as an official training center for the European Society of Gastrointestinal Endoscopy (ESGE) and is currently applying for similar recognition by the OMED-WGO/OMGE Education and Training Committee and by the gastroenterology branch of the Union Européenne des Médecins Spécialistes/European Union of Medical Specialists (UEMS). All of the staff at the EETC are looking forward to expanding the center's activities further and welcoming physicians from all over the world.

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***Figure 1**. Newly renovated premises of the EETC.*

***Figure 2**. The operating room features five fully equipped endoscopic workstations.*

***Figure 3**. Trainees have the opportunity to work on personal computer workstations for electronic interactive teaching as well as a computer simulator.*

IDCA
The International Digestive Cancer Alliance

Digestive Cancer Series (Co-Editors: Sidney Winawer and Meinhard Classen)

Taxonomy for Neoplastic Lesions of the Digestive Mucosa

René Lambert

Taxonomy: "the systematic distinguishing, ordering, and naming of type groups within a subject field" (*Merriam–Webster 3rd Unabridged Dictionary*, 2003).

Superficial versus Advanced Neoplastic Lesions

In digestive endoscopy neoplastic lesions are called **superficial** when their appearance suggests that the depth is restricted to the mucosa of the submucosa or **advanced** when involvement of the muscularis propria is suspected. The classification as superficial or advanced will be confirmed (or eventually unconfirmed) by the pathologist.

The Relevance of Classifications

The secondary prevention of gastrointestinal cancer relies on detecting superficial neoplasia at a presymptomatic stage. At this stage, the probability of a complete cure is very high. Endoscopy is the gold standard for detection: protruding or excavated lesions are easily found, because they alter the surface contours. Nonprotruding lesions may be suspected on the basis of changes in color or in the network of superficial capillaries.

The endoscopic appearance or morphology of superficial lesions affects the choice of treatment between three options: doing nothing, for a nonneoplastic lesion; carrying out endoscopic mucosectomy; or referring the patient for radical surgery.

Table 1*. Macroscopic classification of neoplasia in the gastrointestinal mucosa (Paris Consensus Classification).*

Superficial cancer	
Type 0	Superficial protruding or nonprotruding lesions
Advanced cancer	
Type 1	Protruding carcinoma, attached with a wide base
Type 2	Ulcerated carcinoma with sharp and raised margins
Type 3	Ulcerated carcinoma without definite limits
Type 4	Nonulcerated, diffusely infiltrating carcinoma
Type 5	Unclassifiable advanced carcinoma

The Paris Classification of Gross Morphology

In 1926, Borrmann classified the gross morphology of gastric cancer into types 1, 2, 3, and 4 relative to protrusion, excavation, or infiltration. The same categories were later adopted in Japan for the esophagus and the large intestine, and a type 5 was added for unclassifiable advanced cancer. The Japanese experts also added type 0 for the endoscopic description of superficial lesions – i.e., the precursors of advanced cancer (Table 1). Based on these descriptions, a consensus Paris classification was published in December 2003.

Large neoplasms are readily identified by endoscopy, but the most important aspect of cancer prevention is the observation and classification of superficial lesions.

Endoscopy can discover "superficial" neoplastic lesions by identifying a slight elevation or depression, discolored areas, or irregularities in the vascular network. Various dyes can be applied to the lesions to enhance their surface characteristics, and endoscopic magnification is opening up new perspectives for analyzing the surface (e.g., the pit pattern in the large intestine) and the capillary network, as seen through the translucent unstained epithelium.

The endoscopic description of "superficial" neoplastic lesions (type 0) is based

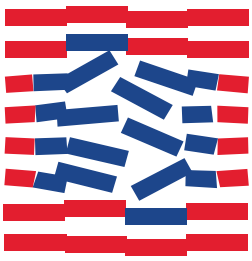

Table 2. *Subtypes of type 0 superficial neoplastic lesions (Paris Consensus Classification).*

Protruding	
Pedunculated	Ip
Sessile	Is
Nonprotruding	
Slightly elevated	IIa
Completely flat	IIb
Slightly depressed	IIc
Elevated and depressed	IIa + IIc
	IIc + IIa
Excavated	
Ulcer	III

on three criteria: size; morphology (Table 2); and location in the gastrointestinal tract. Type 0 is divided into categories: protruding lesions are termed 0-I and divided into two subtypes, pedunculated (Ip) or sessile (Is). Nonprotruding and nonexcavated lesions are termed 0-II, and these are divided into three subtypes: slightly elevated (IIa), completely flat (IIb), or slightly depressed (IIc). The distinction between small sessile protruding lesions (Is) and slightly elevated nonprotruding lesions (IIa) can be made more easily by placing a closed forceps biopsy device (2.5 mm in diameter) next to the lesion and using it as a calibrating gauge. The lesion is called IIa when its elevation is less than the diameter of the forceps (< 2.5 mm) and Is when it is more elevated than the forceps. Excavated lesions (ulcers) are classified as 0-III.

The morphologic classification of superficial lesions has a prognostic value at all sites, and the risk of invasion into the submucosa varies with the subtype. Depressed 0-IIc lesions deserve special attention, because the risk of invasion is greater and is relatively independent of the size. A suspicion of deep invasion can be further confirmed if the lesion fails to lift after injection of saline into the submucosa. Types that combine the IIa and IIc patterns share the same prognosis as depressed lesions.

There are wide variations along the gastrointestinal tract in the relative proportions of each subtype of superficial neoplastic lesion that are observed. Overall, the nonprotruding subtypes are more frequent, reaching 84% in the esophagus (squamous epithelium), 97% in the distal stomach, and 50% in the large intestine. Depressed (IIc) lesions are frequent in the squamous epithelium of the esophagus (45%), but relatively rare in Barrett's esophagus or at the esophagogastric junction, and are very frequent (78%) in the distal stomach. In the large intestine, most nonprotruding lesions are slightly elevated (IIa), with a very low risk of progression to cancer. On the other hand, depressed (IIc) lesions are significant precursors of advanced cancer, in spite of being rare (no more than 5% of all superficial neoplastic lesions).

The Vienna Histopathological Classification

There is worldwide agreement among pathologists in the interpretation (diagnosis, histological pattern, grading of differentiation) of invasive gastrointestinal cancer. On the other hand, there has been wide variation in the classification of superficial neoplastic lesions: in Western countries, a polypoid neoplastic lesion of the columnar epithelium in the gastrointestinal tract is called "adenoma," and a flat neoplastic area is called "dysplasia." In Asian countries, these lesions are referred to as polypoid, flat, and depressed adenomas. Similarly, noninvasive lesions with

Table 3*. Histological classification of superficial neoplastic lesions in the esophagus, stomach, and large intestine (revised Vienna Classification).*

Group 1	Negative for intramucosal (or intraepithelial) neoplasia
Group 2	Indefinite for intramucosal (or intraepithelial) neoplasia
Group 3	Low-grade intramucosal (or intraepithelial) neoplasia (this is equivalent to adenoma or dysplasia)
Group 4	High-grade intramucosal neoplasia
4-1	Adenoma/dysplasia
4-2	Noninvasive carcinoma
4-3	Suspicious for invasive carcinoma
4-4	Intramucosal carcinoma with invasion of the lamina propria
Group 5	Submucosal carcinoma

Table 4*. Staging of superficial tumors in the TNM classification.*

Esophagus	Stage 0	Tis N0 M0
Squamous-cell cancer	Stage I	T1 N0 M0
Adenocarcinoma	Stage IIb	T1 N1 M0
Stomach	Stage 0	Tis N0 M0
Carcinoma	Stage IA	T1 N0 M0
	Stage IB	T1 N1 M0
Colon and rectum	Stage 0	Tis N0 M0
Carcinoma	Stage I	T1 N0 M0

high-grade intraepithelial neoplasia have been called intramucosal carcinoma in Japan, but high-grade dysplasia in Western countries.

Most of the divergence in semantics has now disappeared with the adoption of the Vienna consensus classification, which applies to both squamous and columnar epithelium. In the Vienna classification (Table 3), the term "intraepithelial neoplasia" replaces both of the terms "adenoma" and "dysplasia." Noninvasive neoplastic lesions are classified as low-grade or high-grade intraepithelial neoplasia. Noninvasive intramucosal carcinoma, also called "carcinoma in situ," is in group 4-2; invasive intramucosal carcinoma is in group 4-4. Lesions termed "intramucosal carcinoma" in the East and "high-grade dysplasia" in the West have therefore now become subdivisions of the same group. Carcinoma invading the submucosa is in group 5 of the classification. Confirmed superficial neoplastic lesions are therefore classified into groups 3, 4, or 5.

The TNM Classification

Tumor staging for cancer registries uses the TNM classification (Table 4). The TNM applies only to cases that have been microscopically confirmed as malignant and combines categories selected in the T (tumor), N (nodes), and M (metastases) components in all stages.

Advanced carcinomas are classified as T2 (invasion of the muscularis propria), T3 (invasion of the serosa), or T4 (invasion into adjacent structures). Superficial malignant lesions are classified as T1m or T1sm. For carcinomas, an "in situ" category (Tis) is used for high-grade intramucosal neoplasia when there is no invasion of the basal membrane – i.e., no invasion into the lamina propria. In the esophagus and stomach, intramucosal lesions are Tis (noninvasive) or T1m (invasive). In the large intestine, all intramucosal lesions (invasive or noninvasive) are Tis, because there is no risk of lymphatic propagation.

Superficial malignant lesions are classified into stages I or II, but Tis lesions are always classified as stage 0. Advanced tumors are classified into stages I to IV. When the tumor is staged clinically, each component has to be defined as clinical or pathological. For example, after an endoscopic mucosectomy, pT1, cN0, cM0 means that the primary tumor is confirmed at histology and that positive lymph nodes and metastases were absent clinically. When the classification is based on postoperative findings, it is called pTNM. The TNM classification used in cancer registries is also used for clinical trials in cancer treatment.

The WHO Classification of Neoplastic Lesions

The WHO International Classification of Diseases (ICD) includes a specific classification for oncology (ICD-0). The double coding system, for topography and morphology, is also used in tumor registries, and it describes premalignant and malignant lesions.

The coding for topography is based on four alphanumeric symbols – the first three refer to the viscera (C15, esophagus; C16, stomach; C18, colon; C20, rectum), and the fourth is for the subsite. An adenocarcinoma is coded C15.5 in the lower third of esophagus, C16.3 in the gastric antrum, and C18.7 in the sigmoid, with the fourth digit indicating the visceral sector.

The coding for histology has six numbers – the first five for the type of carcinoma, and the sixth for the behavior of the tumor (2 for benign, 3 for malignant). An adenocarcinoma in the esophagus, stomach, or large intestine would be classified with the code 81140/3.

An Inseparable Couple: the Clinician and the Pathologist

Assessment of invasion into the submucosa based on surgical specimens is easy, as the full thickness of the gastrointestinal wall is available for examination. A semiquantitative evaluation into superficial invasion (sm1) or deep invasion (sm2) is frequently used. In specimens from endoscopic mucosectomy, the submucosa is not complete, and a quantitative micrometric measure of the depth of invasion from the lower limit of the muscularis mucosae is preferred. Japanese pathologists have established empirical cut-off limits for the legitimacy of endoscope treatment: 200 μ in the esophagus, 500 μ in the stomach and 1000 μ in the large bowel. This micrometric measure actually deserves generalization for comparing outcomes after either surgical or endoscopic treatment. Assessment of the completeness of a resection often requires input from the clinician, which can be combined with the microscopic view from the pathologist.

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International Digestive Cancer Alliance Meeting during Digestive Disease Week 2004

Sidney J. Winawer, Meinhard Classen, Paul Rozen

In the four years since the launching of the International Digestive Cancer Alliance (IDCA) in Rome in May 2000, many meetings have been held around the world and others are being planned. A tradition has been established of holding an annual meeting during the Digestive Disease Week (DDW) conference in the United States, taking advantage of the presence of many American and international members. The IDCA meeting held during Digestive Disease Week (DDW) in New Orleans (Sunday 16 May 2004) was opened by a brief review of the evolution of IDCA and its mission and activities since inception. The meeting was especially exciting; being attended by 97 invited IDCA members from 36 countries and representation of Industry.

National Colorectal Cancer Screening Programs: Successful Strategies for Unique Challenges and Barriers – Key Lessons

The aims of the meeting were: firstly, to present successful strategies and key lessons from several national programs; secondly, to communicate information to members about expertise, outcome models, and the resources available to assist national screening programs; thirdly, to review the relative benefits of primary and secondary colorectal cancer (CRC) prevention; and fourthly, to initiate a discussion on gastric cancer, its epidemiology and potential for prevention.

Presentations of various pilot and screening programs on CRC already established were made by professors Finlay Macrae (Australia); Benjamin Wong (Hong Kong); Robert J.C. Steele (United Kingdom); Julius Spicak (Czech Republic); Dai Ming Fan (China); Roque Sáenz (Chile); and Urs Marbet (Switzerland). CRC is on the rise in Australia, where pilot programs using immunochemical tests have been initiated. To date, 38 228 people have taken part in these, and 95% of those with positive findings (8.7–12.5% of those screened), have been referred for colonoscopy. In Hong Kong, CRC is also on the increase, but so far the government has not been willing to initiate a screening program. The IDCA has agreed to help develop a prevention model with outcomes that will help make a positive case for prevention to the health authorities there. Large-scale pilot studies have already been started in the United Kingdom, using guaiac-based fecal occult blood testing (FOBT) to detect early-stage cancer, but several issues still need to be clarified in connection with compliance, improvements in the test, pathology, and surgery. Eastern Europe has many programs in progress, almost all using FOBT, except for Poland, where a large colonoscopy screening trial is in progress involving approximately 40 centers throughout the country. China has been studying various approaches to CRC screening, including guaiac-based FOBT immunochemical testing and exfoliative cytology. The incidence of CRC has been rising very rapidly in Chile, doubling in the last 5 years and rising 83% in the last 20 years. There are many problems there in attempting to initiate a screening program, including costs and colonoscopy capacity. There is currently no national screening program in Switzerland, although they are studying population preferences for flexible sigmoidoscopy, FOBT, and colonoscopy, as well as the quality of the examinations, acceptance, and the outcome of each examination.

International Assistance to National Screening Programs: Expertise, Outcome Models, Resources

The second phase of the meeting provided a forum for presenting the resources available through international organizations involved in the prevention of

colorectal cancer. Presentations were made by Professors René Lambert (International Agency for Research on Cancer), Ann Zauber (IDCA), Carolyn Aldigé (Cancer Research and Prevention Foundation), Robert Smith (Union Internationale Contre le Cancer/American Cancer Society), Marion Nadel (Centers for Disease Control, USA), Anthony Axon (European Society of Gastrointestinal Endoscopy), Christa Maar (Burda Foundation), Colm O'Morain (United European Gastroenterology Federation Public Affairs Committee), and Mark Pochapin (Weill Medical College, Cornell University, Monahan Center, New York). It was clear that considerable resources are available internationally that can be helpful to the national programs. The International Agency for Research on Cancer (IARC), with its new Director, Professor Peter Boyle, has a strong interest in cancer prevention worldwide. The IARC has substantial resource materials available, including the Globocan program (**http://www-dep.iarc.fr/globocan/globocan.html**), which provides the latest data on cancer incidence, mortality, and other statistics worldwide.

The IDCA model is to use the Globocan data in its mathematical model, as well as country-specific additional data to help IDCA members in each country make the case for cancer prevention to health ministers, and then help organize awareness meetings, followed by pilot campaigns. The Cancer Research and Prevention Foundation (CRPF) has developed a number of creative methods of increasing CRC awareness, including the "Dialogue for Action" meeting that was replicated recently in Berlin, "remember to be screened" bracelets, the Colossal Colon model tour in U.S. cities, developing partner groups to promote screening, and having the U.S. Congress designate March as CRC Awareness Month. The American Cancer Society (ACS) has developed a round table that brings together many disciplines from the professional and lay community to work together on CRC prevention, and is working closely with the Union Internationale Contre le Cancer (UICC). A world congress on cancer prevention is being planned. The Centers for Disease Control (CDC) have initiated several campaigns in the USA, including "Screen for Life" (**http://www.cdc.gov/cancer/screenforlife**) and "Call to Action" (**http://www.cdc.gov/cancer/colorctl/calltoaction**) and has recently supported, along with the ACS, an International Colorectal Cancer Screening Network that will focus on universal outcome measures and quality indicators for screening programs. An inaugural meeting was held in London in 2004.

The European Society of Gastrointestinal Endoscopy (ESGE) has mounted several initiatives, including meetings, journals, and training programs, and together with the United European Gastroenterology Federation (UEGF) it has recently published a review of CRC screening (*Endoscopy* 2004; 36: 348–66). The UEGF Public Affairs Committee has recently completed a European survey of colorectal cancer prevention practices. It was quite clear that both in Europe and the United States, the media and role models are critical for achieving increased public awareness. Many barriers to screening perceived by the public can be broken down through active involvement by the media, and screening awareness and screening activities can be increased.

Relative Benefits of Primary and Secondary Colorectal Cancer Prevention

The IDCA meeting concluded with a review by Professor Graeme Young (Australia) of the relative benefits of primary and secondary prevention of CRC, and a review by Professor Richard Hunt (Canada) of the epidemiology and potential for preventing gastric cancer. The IDCA considered it important to include these topics in the meeting, to emphasize both primary prevention and the importance of other cancers in addition to CRC. The IDCA has a strong interest in primary prevention as well as screening and has a broad interest in all types of digestive cancers in addition to colorectal cancer. The latter two aspects are to be included in the next IDCA campaign, concerned with reducing the burden of gastric cancer through *Helicobacter pylori* eradication in a model project in China. A workgroup, conference, and protocol are currently being planned for October 2004 in China.

The meeting closed with a brief summary of future IDCA activities, including active involvement in China, meetings in Brazil and Rome, and the World Congress in Montreal in 2005.

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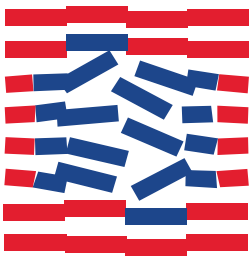

OMED Colorectal Cancer Screening Committee Meeting

Paul Rozen, Sidney J. Winawer

The annual meeting of the Colorectal Cancer Screening Committee of the Organisation Mondiale d'Endoscopie Digestive/ World Organization of Digestive Endoscopy (OMED/WGO) was held jointly with the International Digestive Cancer Alliance (IDCA) during Digestive Disease Week in New Orleans on 15 May 2004.

Session 1 (Chaired by Dr. M. Crespi, Italy, and Dr. J. Mandel, USA)

This session addressed colorectal cancer (CRC) epidemiology and screening modeling. Dr. Mandel reported a declining CRC incidence and mortality in the white population in the United States. Dr. R. Lambert (France) reviewed International Agency for Research on Cancer (IARC) data on the high and rising CRC incidence and mortality in "Westernizing" and "aging" countries. Dr. A. Zauber (USA) discussed CRC screening modeling using the MISCAN model, and reported that flexible sigmoidoscopy with fecal occult blood testing (FOBT) saved more life-years with lowest costs.

Session 2 (Chaired by Dr. P. Rozen, Israel, and Dr. J. Terdiman, USA)

This session considered nonendoscopic screening methodologies. Automated quantitative immunochemical FOBTs for fecal hemoglobin, without dietary restrictions, should provide better specificity than office-developed guaiac FOBTs. Dr. G. Castiglione (Italy) uses the latex agglutination test (OC-SENSOR). Biennial one-day testing increased screenee compliance, the overall positivity was 5%, and the predictive positive rate for significant neoplasia was 29%. Dr. H. Saito (Japan) compared HemSp with the automated MagStream Sp. The sensitivities of both tests were 90% for CRC, but MagStream's specificity was significantly lower. The automated FOBT is convenient, but its specificity needs improvement. Dr. G.P. Young (Australia) compared InSure (an automated immunochemical test) and the guaiac, office-developed HemoccultSensa test. InSure has simplified sample collection, which improved compliance; predictive positive rates and specificities for neoplasia were similar. Two-day InSure, with 96% specificity, detected 100% of CRCs and 60–70% of adenomas. Dr. D. Ahlquist (USA) reviewed fecal DNA testing; this requires collection, rapid transfer to a central laboratory, and freezing. A colonoscopy-controlled comparison showed a sensitivity of 51.6% and a specificity of 94.4% for invasive CRC, and a sensitivity of 15.1% for advanced adenomas. Dr. J.H. Bond (USA) reviewed computed-tomographic colonography; the best results were from an experienced single institution. The limitations of this method are its long learning curve, radiation exposure, costs, availability, a decreased sensitivity for lesions smaller than 1 cm, and the inability to take biopsies or carry out polypectomy.

Session 3 (Chaired by Dr. M. Classen, Germany, and Dr. M. Korman, Australia)

This session addressed endoscopic screening programs. Dr. R.S. Bresalier (USA) updated the U.S. Flexible Sigmoidoscopy PLCO screening trial. Three to 5 years after flexible sigmoidoscopy, 3.1% of the patients had distal neoplasia after a negative baseline examination. Advanced distal adenoma, male sex, and age over 70 were risk factors for advanced proximal neoplasia. Nonphysicians had performed 70% of the 56 000 examinations. Dr. W. Schmiegal (Germany) addressed the issue of quality control in Germany's national colonoscopy screening program, including 320 000 examinations. Total colonoscopy was achieved in 98.8% of the examinations, 18% of which were without sedation. Adenomas were found in 30% of cases and cancers (Dukes A and B) in 0.54%. Dr. M. Crespi (Italy) noted that Italy provides free screening colonoscopy, but there is no centralized data management and because of low uptake, a public awareness campaign has now been initiated. Dr. J. Regula (Poland) stated that Poland now has a national single-colonoscopy screening program with recruitment by general practitioners. A total of 30 000 persons participated, 77% without sedation; 90% of the examinations were completed to the cecum, and significant neoplasia was detected in 5.1% of cases. Dr. D. Lieberman (USA) observed that the Medicare program allows screening colonoscopy every 10 years; quality and resource availability is being evaluated. Interval lesions occurred 3–5 years after baseline neoplasia, cancer in 0.7–1.1% of cases, and advanced neoplasia in 6–11% – underlining the importance of high-quality examinations.

Session 4: Panel Discussions (Chaired by Dr. S.J. Winawer, USA)

The first panel session addressed the question of interval neoplasia, occurring during surveillance of the colon. Dr. D.O. Faigel (USA) noted that "new" findings could represent polyps that were missed initially due to inadequate preparation and examination. Dr. R. Lambert (France) stated that with the low sensitivity of the guaiac test, biennial FOBTs can be false-negative for CRC, especially as some CRCs start as flat adenomas. Dr. J. Mandel (USA) observed that FOBTs have to be prepared in adequate numbers and repeatedly. Dr. Y. Sano (Japan) reported that after polypectomy, 7% of patients were found to have advanced lesions at the follow-up examination; 34% were flat lesions and 5% were depressed. The panel's conclusions were that the use of sensitive FOBTs should be promoted, as well as good bowel preparation, high-quality and complete colonoscopic examinations, and follow-up adjusted to the quality of the initial examination and findings.

The second panel session focused on "population CRC screening and/or case-finding." Dr. M. Crespi (Italy) stated that many countries have no population CRC screening, and case finding should therefore be supported. Dr. R.J. Steele (UK) reported that a United Kingdom national FOBT screening program will probably be introduced, but he considered that this did not negate case-finding. Dr. B. Wong (Hong Kong) observed that there is a high incidence of CRC in Hong Kong, but that screening is not a public health priority, so that case-finding is therefore encouraged there. Dr. G.P. Young (Australia) considered that a national CRC screening program is best, but that case finding should also be available. In conclusion, it was agreed that both population screening and case-finding have their place.

Conclusions

This annual meeting allowed an international exchange of experience and ideas on how to perform and promote CRC screening. It emphasized the development and promotion of high-quality screening methodologies. Modeling will help decide on appropriate screening policies for diverse settings. Population CRC screening should be promoted and integrated into public health policy. Case-finding is acceptable and is needed when public health policy has not yet included population CRC screening.

A full report is also to be published and will be available from the authors or OMED.

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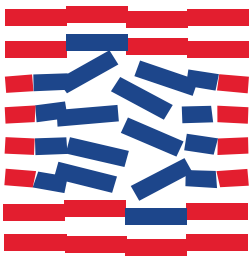
Ten Rules for Cancer Prevention

Attilio Giacosa, Massimo Crespi *(United European Gastroenterology Federation Public Affairs Committee)*

Colorectal cancer (CRC) is the leading cancer in nonsmokers (of both sexes) in North America, Australasia, and western Europe. The major risk factors for CRC are genetic and dietary. Evidence regarding genetic polymorphisms, which may influence the metabolism of nutrients, is thought to be important in the etiology of CRC and colorectal adenomatous polyps. At present, the strongest evidence of gene–nutrient interaction in relation to CRC is for folate and genetic variants associated with differences in metabolism of folate. In European studies, significant trends have been found for increased CRC risk proportional to the intake of bread and pasta, cakes and desserts, and refined sugar. Regardless of the specific food source of calories, caloric excess and its consequences can be regarded as a well-established risk factor for colorectal cancer.

Diets high in calories tend to be high in fat (especially animal fat) and refined carbohydrates, but low in fiber and vegetable intake. The consequent glycemic overload produces a compensatory increase in blood insulin and insulin-like growth factors, which in turn are thought to stimulate colorectal cell turnover and increase the susceptibility of cells to malignant transformation.

Most vegetables are inversely associated with CRC risk. A reduced risk has been particularly associated with raw, green, and cruciferous vegetables, but less so for fruit consumption. Among macronutrients, a high intake of starch and saturated fat appears to lead to an increased risk. High intakes of polyunsaturated fatty acids (chiefly



derived from olive oil and seed oils) show a marginal inverse association with CRC. While fish consumption has been thought to be inversely associated with CRC risk, the correlation with meat intake is still debated.

While excess weight is associated with increased CRC risk (more so in men than women), physical exercise is inversely correlated to colon cancer. In addition, the body mass index (BMI) is directly associated with colon adenomas (with a stronger association for larger adenomas). Analysis of the available observations shows that increasing levels of physical activity are associated with an approximately 40% reduction in the risk of colon cancer, independent of BMI.

Taking all this into consideration, the Public Affairs Committee of the United European Gastroenterology Federation (UEGF) has developed "Ten Rules" on healthy diet and lifestyle for preventing colorectal cancer. These guidelines, which have been widely distributed through the national gastroenterology societies, also apply to other types of cancer (e.g., prostate, breast) and degenerative diseases in general.

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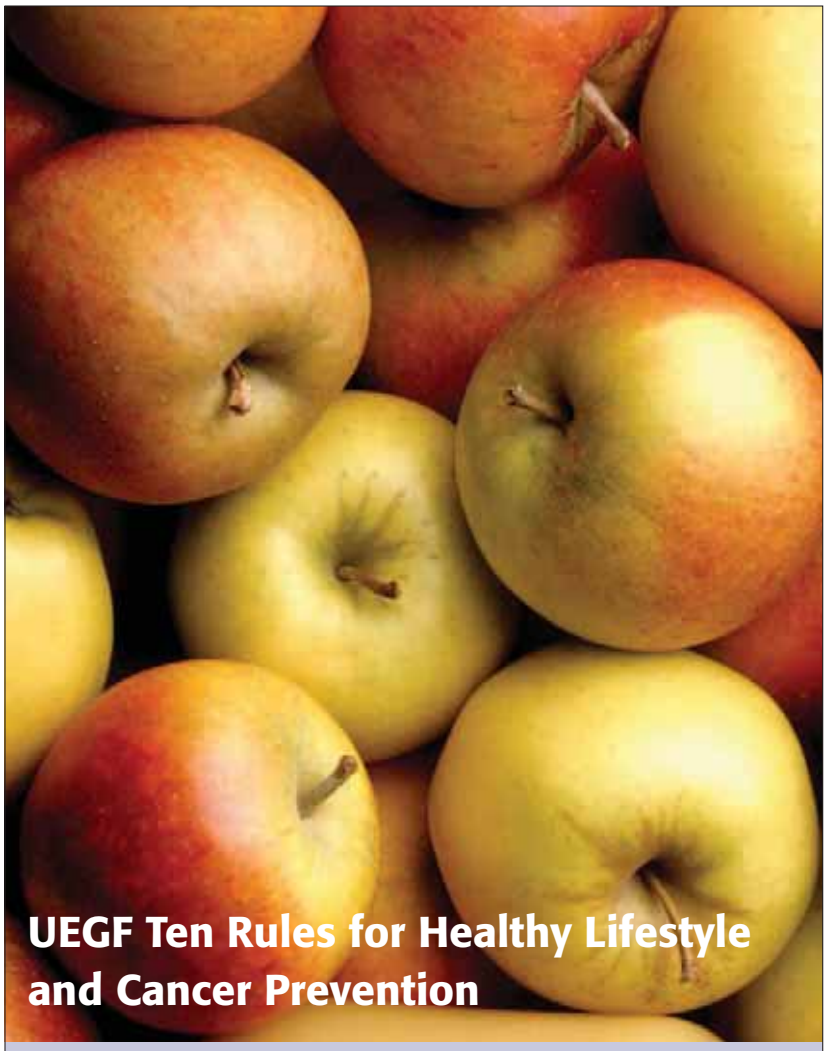

UEGF Ten Rules for Healthy Lifestyle and Cancer Prevention

- Maintain a high level of physical exercise: at least 30 minutes a day of vigorous activity are suggested (but the type of activity can vary with age).
- Avoid excess weight, preferably by increasing physical activity.
- Eat plenty of fiber-rich food and whole grains and less food containing sugars and products with white flour.
- Aim to eat at least five portions a day of fruits and vegetables.
- Moderate the intake of animal fat (i.e., dairy fat and fatty meat) by choosing light dairy products and removing visible fat from meat and skin from chicken. Fat derived from "added fat" during cooking can be replaced by vegetable oils and possibly extra-virgin olive oil.
- Remember that fish and beans are attractive alternatives to meat. Fish oil is also good for preventing some other types of cancer (such as breast cancer) and cardiovascular diseases.
- Drink plenty of water. For alcoholic beverages, have less than two glasses a day of wine or beer.
- The selection and storage of food are very important: look mainly for local and seasonal fresh or frozen food.
- Healthy cooking requires lowering the amounts of added cooking oils and fats, using low temperatures and short cooking times.
- Whatever you do, do not smoke!

Treasurer's Report

J.E. Geenen

The Organisation Mondiale de Gastro-Entérologie/World Gastroenterology Organization (OMGE/WGO) had a very busy year. We successfully launched another training center in Cairo, Egypt. With this facility, we now have four functioning centers, with another two planned to open in 2005.

The "Train the Trainers" program is continuing to be a successful endeavor for WGO/OMGE. The feedback received from the program held in New Zealand in 2003 shows that WGO/OMGE is fulfilling its aim of ensuring that endoscopists from all parts of the world are able to participate, learn, and take their new-found knowledge and skills back to their own countries.

Plans for the next World Congress of Gastroenterology (WCOG), to be held on 10–14 September 2005 in Montreal, are progressing well, and it is anticipated that the event will meet or exceed our expectations.

The above are a few examples of our accomplishments since 2003. The finances for managing these initiatives (as well as many others) are outlined below.

Total revenue for 2003 was $624,702.39. Funds received from members' dues amounted to $61,125.94; funds received from the biomedical industry, mainly from our Concordat members, amounted to $280,000. Income from interest and dividends totaled $173,616.70; refund on consulting fee amounted to $6.673,75 and gain on investments was $103,286.00.

WGO/OMGE's total expenses for 2003 were $837,411.76. The expenses have been broken down into three categories: meetings; educational activities; and supporting services. Meeting expenses totaled $295,238.02. Educational activities, which include preparing guidelines and publications, running training centers, the Train the Trainers course, and expenses for the partner societies OMED and IDCA, totaled $330,900.90. Supporting service expenses totaled $211,272.84. Supporting services include Medconnect, administrative services, professional fees, and Marathon publications.

The difference between expenses and revenue was $202,709.37.

Total expenses are continuing to increase. The 2004 budget is $1 million, and the budget for 2005 is projected as $1.1 million. Hopefully we will be able to continue to support all of our educational programs.

Concordat Contribution Update

The annual Concordat contributions have been raised to $30,000 per member company. The current members are:

- AstraZeneca
- Boston Scientific
- Altana
- Fujinon
- Janssen
- Olympus
- Pentax
- Takeda
- Novartis
- Axcan

WGO/OMGE thanks the Concordat members for their ongoing support.

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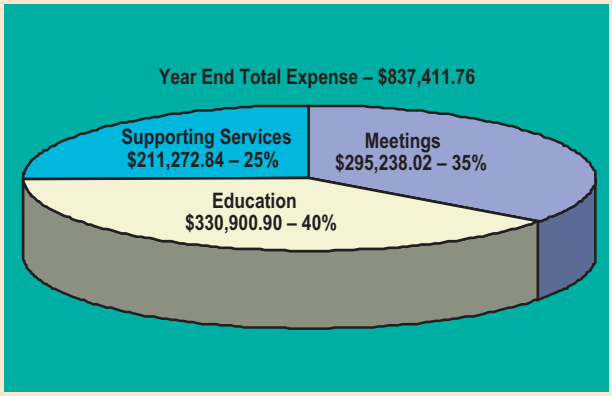

***Figure 1**. WGO/OMGE 2003 Total Expense Comparison.*

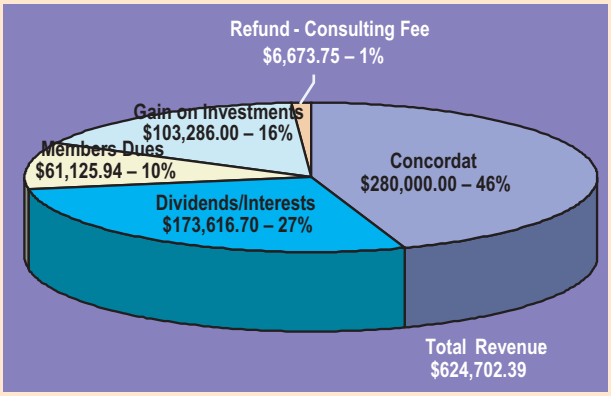

***Figure 2**. WGO/OMGE 2003 Components of Revenue.*

An Invitation to a Special Symposium

Global Guidelines for the 21st century – Focus on "Evidence" or Focus on "Need"?

When the World Congress of Gastroenterology (WCOG) opens in Montreal in September 2005, the Organisation Mondiale de Gastro-Entérologie/World Gastroenterology Organization (OMGE/WGO) will be able to look back at 4 years of successful publication of guidelines. Almost twenty guidelines will have been produced by then, and the guidelines are being quickly translated into French, Spanish, Russian, Chinese, and Arabic – in line with WGO/OMGE's global commitments. But are global guidelines truly possible? Do they have to be based strictly on evidence, or should they also take local needs and available resources into account?

WGO/OMGE's unique global position makes developing guidelines a special challenge. In addition to the challenges experienced by all guideline developers – for example, the complex issues involved in methodological rigor, including a strictly evidence-based approach with graded recommendations whenever possible – WGO/OMGE is faced with unique challenges involved in production, dissemination, and implementation. No other body involved in gastroenterology has WGO/OMGE's global commitments, and no one else needs to take into account the gap between resource-poor and resource-rich regions in the same way.

For WGO/OMGE, the quality of guidelines cannot be based strictly on issues of evidence alone. Sometimes there is no evidence base, and even when there is evidence, it may require the use of equipment and technologies that are not available throughout the world. The gap between resource-poor and resource-rich regions is expanding, rather than narrowing. The increasing sophistication of medical technology saves extra lives in the highly resourced West, but the use of intermediate technology and the provision of better infrastructure could save millions of lives in the rest of the world. Should these differences in resources be taken into account when guidelines are being compiled?

As no one else has addressed these issues systematically from a medical and clinical point of view, WGO/OMGE has decided to call upon experts throughout the world to participate in a unique symposium as part of WCOG 2005 (**www.wcog2005.org**), focusing on the following five questions:

- Are global guidelines desirable and feasible?
- Most clinical guidelines do not take into account the limited resources in the developing world. Is it necessary and ethical, therefore, to recommend and implement "minimum" guidelines?
- How can we improve on the implementation of guidelines? Is it reasonable to expect that global guidelines can change health policy?
- Should the biomedical industry be involved in the guideline-making process? If so, in what ways?
- Is the evidence-based approach always desirable or feasible?

These questions will serve as the framework for the symposium, which will take the form of a half-day meeting with an invited faculty. Special invitations to attend the conference will be extended to all 93 member societies of the World Gastroenterology Organization and all the collaborating organizations.

The core team of renowned gastroenterologists who will chair the five symposium sessions is: Prof. M. Fried (Switzerland, Chair); Prof. E. Quigley (Ireland); Prof. G.N.J. Tytgat (The Netherlands); Prof. M. Farthing (United Kingdom); Prof. R. Hunt (Canada); and Prof. D. Bjorkman (United States). Each session will feature one advocate and one opponent of a motion. These chaired sessions and a subsequent round-table discussion will then form the basis for an WGO/OMGE position statement. For a full program with details of all the speakers for and against each motion, and the names of the moderators and commentators, please consult the symposium web site (www.worldgastroenterology.org).

This unique consensus conference will bring together key leaders involved in producing, disseminating, implementing clinical guidelines. Much can be learned from other medical disciplines, as well as from organizations whose task it is to monitor implementation and assess needs. With a strong belief in professional solidarity, and mindful of its global commitment to the 93 national gastroenterology societies affiliated to it, WGO/OMGE hopes to ensure it will continue to represent gastroenterologists in every part of the world.

Global Guidelines Conference Core Team
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ASNEMGE–WGO/OMGE European School of Gastroenterology Launched

In a joint venture, the Association des Sociétés Nationales Européennes et Mediterranéennes de Gastroentérologie (ASNEMGE) and Organisation Mondiale de Gastro-Entérologie/World Gastroenterology Organization (OMGE/WGO) held the first European School of Gastroenterology in Dubrovnik, Croatia, on 11–13 June 2004.

The event involved a new educational approach, combining state-of-the-art lectures (covering gastroesophageal reflux disease, malabsorption, inflammatory bowel diseases, chronic liver diseases, and colon cancer screening) in the morning with practical training in the afternoon. Each of the courses given (abdominal ultrasonography; endoscopy training with the Erlangen EASIE model; liver disease; how to write a scientific paper) was limited to a maximum of 10 participants.

With Professor G. Tytgat (WGO, Amsterdam) and Professor P. Ferenci (ASNEMGE, Vienna) as chairmen, the faculty included Professors R. Caprili (Rome), M. Carneiro de Moura (Lisbon), C. Gasche (Vienna), J. Hochberger (Hildesheim), R. Hultcrantz (Stockholm), L. Greiner (Wuppertal), K. McColl (Glasgow), F. Megraud (Bordeaux), H. Mönnikes (Berlin), R. Stockbrügger (Maastricht), B. Vucelic (Zagreb), and C. Yurdaydin (Ankara). The participants were young gastroenterologists from 12 European countries, enjoying a unique opportunity to work with faculty members at this level.

The European School of Gastroenterology will be repeated in the first half of June 2005 and will be announced both by ASNEMGE and OMGE/WGO through the national societies. Participants will be selected by ASNEMGE and OMGE/WGO.

The organizers and participants are grateful to Altana Pharma for their generous support for this high-level educational event (with six Council on Medical Education credits), and to Doris Möstl (ASNEMGE) and Heike Dietrich (ALTANA) for their organizational support and Boris Vucelic for his invaluable work as the local organizer.

Participants and faculty of the launch of the ASNEMGE–WGO/OMGE European School of Gastroenterology.

Elbio Zeballos (left) with colleague and friend Henry Cohen.

Elbio Zeballos

Henry Cohen

Professor Elbio Zeballos died of heart failure in Montevideo in April 2004 at the age of 61. The Uruguayan gastroenterology community has lost a respected leader, as well as an outstanding scholar, physician, and teacher.

Dr. Zeballos was known among his peers for his thoughtfulness and calmness, and for his friendly approach. He was always willing to express encouragement and provide valuable advice to those around him, and he never failed to express his convictions and defend his principles when necessary. He was deeply committed to the university's medical school and served for 12 years as head of the Gastroenterology Department in Montevideo's Hospital de Clínicas. His outstanding teaching and unique style were widely recognized.

He served as Secretary-General of the National Academy of Medicine and as President of the Uruguayan Society of Gastroenterology (1984 to 1986), completing his final term with an extremely successful national conference. As President of the most important association for the specialty in the Americas, the Asociación Interamericana de Gastroenterologia (AIGE) in 1999 to 2001, he led major advances for the society and for gastroenterology in the region. It was thanks to his exceptional work that Uruguay was able to organize the Pan-American Congress in October 2003, at which he was elected to act as Honorary President, allowing his pupils to chair the meeting under his guidance.

In the scientific field, he played an active role in the development of diagnostic laparoscopy. His interest in celiac disease brought him prominence as a recognized expert on the subject, and shortly before his death, the World Gastroenterology Organization acknowledged his expertise by appointing him as a coordinator for international guidelines on the condition. In addition to being a natural teacher and educator, he also published and contributed to dozens of scientific papers. His last work, *Semiología Gastroenterológica*, is already a classic in the field. As a keen scholar and historian, he was the author of several papers on the development of gastroenterology in Uruguay and South America.

In addition to his professional achievements, he was also interested in art and was himself an outstanding painter. His paintings merged aesthetic sensitivity with a fine sense of humor, delicate irony, and tremendous creativity.

His life-long companion Rosario and family were, above all, the most important focus of his life, and he was proud to see both of his children becoming successful members of the medical profession themselves.

PubMed/Medline: What Every Gastroenterologist Needs to Know

Justus Krabshuis

Earlier this year, I asked an eminent New York gastroenterologist/endoscopist a few short questions about the average U.S. gastroenterologist's awareness of PubMed/Medline. It's one man's view, admittedly – but surely his answers below are not far from the truth?

- *Do gastroenterologists use PubMed?* Yes.
- *Do gastroenterologists use MeSH?* I doubt that most use MeSH.
- *Do gastroenterologists use Boolean logic in searches?* Most know about it, but are not sure how to do it.
- *Do they use the Preview/Index features?* I don't think so.
- *Do they combine free text and indexing?* Definitely not.
- *Are they aware of the limitations of MeSH (e.g., creation date issues; indexing policies)?* Definitely not.
- *Are they aware of the limitations of Medline vis-à-vis other databases in terms of currency, scope, and coverage?* Not at all.

Let's assume the above views are true, and let's also assume that it matters.

Searching PubMed

PubMed searching is easy: just enter search terms in the query box and press the Enter key, or click Go. The Features bar directly underneath the query box provides access to additional search options. The PubMed query box and Features bar are available from every screen, so you don't need to return to the home page to enter a new search.

You can enter one or more terms (e.g., "gastro-esophageal reflux disease") in the query box, and PubMed automatically combines (ANDs) significant terms together using *automatic term mapping.* The terms are searched in various fields of the citation. If your search includes the Boolean operators AND, OR, NOT, they have to be in upper case:

Gerd OR Gord
Gerd AND children
Gerd NOT animals

Once you click Go, PubMed will display your search results. The query box displays your search terms as you entered them.

You can modify your current search by adding or eliminating terms in the query box or in Details. If you applied Limits, the check box next to Limits will be marked, and a listing of your limit selections will be displayed. To turn off the existing limits, click on the check box to remove the check before running your next search.

It is very useful to be able to limit the search to "title" and to "time."

Example:

1 Type "how to find the evidence you need" in the query box.
2 Click on "Limits" on the Features bar.
3 Select "Title" from the drop-down menu that starts with "All fields."
4 Click "Go"

The four hits together provide you with a small comprehensive vade-mecum for searching Medline.

Searching for Journals

PubMed (**www.pubmed.org**) is a service provided by the U.S. National Library of Medicine (NLM) and includes over 14 million citations for biomedical articles.

You can search by the full journal title – e.g., molecular biology of the cell; the Medline abbreviation – e.g., mol biol cell; the International Standard Serial Number (ISSN) – e.g., 1059-1524; or the variant title as it appears in the NLM catalog. See the Journals Database there for the full journal titles.

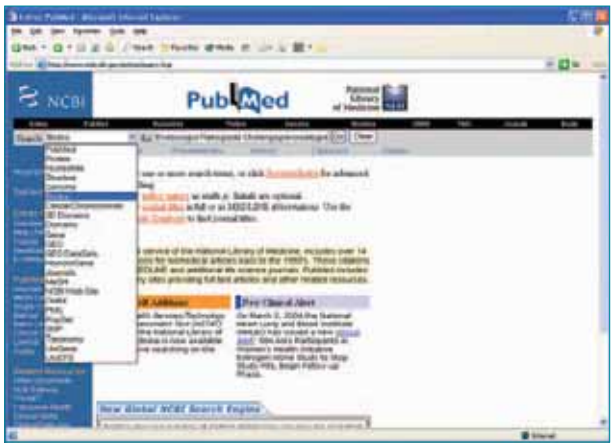
Example:

1 Click on "Journals database" in the left-hand bar.
2 Type in "gastroenterology" in the search box, and click "go"
3 From the 41 journals with titles including the word "gastroenterology," click the journal you are interested in – e.g., "China national journal of new gastroenterology = Chung-kuo hsin hsiao hua ping hsueh tsa chih."

Searching for Books

Did you know you can search 'books' in PubMed/Medline? Books on the "Bookshelf" are also linked to terms in PubMed abstracts: when viewing an abstract, select the "Books" link to see *phrases* within the abstract hyperlinked to book sections. Click on 'books'

in the drop-down menu just to the left of the search box, as illustrated below. Then type in your search – e.g. "Endoscopic Retrograde Cholangiopancreatography" and click "Go." Note the 138 items in the HSTAT book series.



Searching for Articles

Looking for an article? Use the "Single citation matcher"! Try and remember as many details of the article as possible.

Example:

Let's say you remember that Professor Jerry Waye wrote an article about colonoscopy – you can't remember the journal or the title, but you do remember that the word "painless" was in the title. This is easy … go to "Single citation matcher" in the left-hand navigation bar. Fill in as many details as you can remember – e.g., the author name, WAYE J, and fill in the word you remember, e.g. "painless"; click "Search" and voilà!

Searching for Authors

To search by an author's name, enter the name in the format of last name plus initials (with no punctuation) – e.g., Waye JD, Tytgat GN. PubMed automatically truncates the author's name to account for varying initials and designations such as "Jr." or "2nd." A name entered using this format will prompt a search in the author field. If only the author's last name is entered, PubMed searches the name in All Fields, except when the author name is found in the MeSH translation table (e.g., Yang will search as Yin-Yang [MeSH] or Yang [Text Word].) To search for an author in the author field when only the last name is available, qualify the author name with the author search field tag [au] – e.g., tytgat [au].

Note:

- Use double quotes around the author's name with the author search field tag [au] to turn off the automatic truncation, e.g., "smith j" [au].
- Use the [au] search tag if the author name is also a subject term – e.g., moran a [au]. The unqualified phrase, moran a, will search as "moran A"[Substance Name] OR moran a [Text Word].

So, you want to search for articles written by Professor J.D. Waye , the Editor of *WGN*.

Example:

1 Waye JD
2 Click "go"

Searching for a Topic – GERD or GORD?

The key problem here is how to make sure you find all relevant articles about gastro-(o)esophageal reflux disease – unless you only want key articles such as reviews, perhaps . If you search for "gord" you will not find "gerd," and vice versa. But if all articles dealing with "gerd" and "gord" are indexed with the term "GERD," then you *will* find all articles about gastroesophageal reflux disease, whatever the spelling and description used by the author, if you search for articles indexed with the indexing term "GERD."

This is the first of three reasons why you should use: indexing. The second reason has to do with what is called "explosion." If you search for "proton-pump inhibitors" (PPIs), you will only find articles where these words occur together – usually adjacent to each other in that order. But surely you want to find literature dealing with 'esomeprazole' (drugs are usually indexed with their INN generic name – so Nexium is indexed as "esomeprazole," for example – yet another reason for using indexing) and other PPIs. In other words, you need an indexing system that assigns "narrower" terms like esomeprazole to broader terms such as "proton-pump inhibitors." This indexing system is called Medical Subject Headings (MeSH). Find MeSH terms by clicking on "MeSH Database" in the left-hand side bar. Then maybe spend a few moments viewing the animated tutorial – this will pay off later.

Clinical Queries

PubMed/Medline does provide some help by offering a choice between "clinical queries" and "systematic reviews" – the two poles of the study-type evidence continuum. If you click "clinical queries" in the left-hand bar, you can choose between the options below:
Category: therapy – diagnosis – etiology – prognosis
Emphasis: sensitive search (broad) – specific search (narrow)

If you click "systematic reviews," it limits retrieval to articles indexed with the MeSH term "systematic reviews" and/or indexed with "systematic review" as a document type.

Example:

1 Click "Clinical Queries" in the left-hand bar on the home page under "PubMed Services."
2 Mark : "Systematic Reviews."
3 Type "dysphagia" in the subject search box at the bottom of the screen.
4 Click "Go"

And sure enough – the Cochrane Reviews come rolling out.

Complex Evidence-Based Searches

You are a very busy clinician; instead of mastering the intricacies of deep thesaurus- driven evidence-based multifile searches, why not invest some time instead in telling a research librarian what you want, and then get him or her to do the job. Physicians are physicians and not knowledge managers.

Finally, remember that WGO/OMGE runs a free help desk for "remote" gastroenterologists searching for clinical or research information. E-mail WGO/OMGE's "Ask a Librarian" service at **www.omge.org**.

Happy searching – and thanks to the American taxpayer for providing us all with PubMed.

References and Further Reading

1 PubMed/Medline: **www.pubmed.org**

2 Where to get help/NLM Publications on PubMed:
- PubMed Help Manual
- Tutorial
- NLM PubMed Training Manuals
- NLM Technical Bulletin- Articles about PubMed

3 Evidence-based emergency medicine. How to find evidence when you need it, part1: databases, search programs, and strategies:

Corrall CJ, Wyer PC, Zick LS, Bockrath CR. Ann Emerg Med 2002; 39: 302–6.

4 How to find evidence when you need it, part 2: a clinician's guide to Medline: the basics:

Gallagher PE, Allen TY, Wyer PC. Ann Emerg Med 2002; 39: 436–40.

5 How to find evidence when you need it, part 3: a clinician's guide to Medline: tricks and special skills.

Gallagher PE, Allen TY, Wyer PC. Ann Emerg Med 2002; 39: 547–51.

6 How to find evidence when you need it, part 4: Matching clinical questions to appropriate databases:

Wyer PC, Allen TY, Corrall CJ. Ann Emerg Med 2003; 42: 136–49.

7 WGO/OMGE's "Ask a Librarian" desk: **www.omge.org**; click on "global guidelines" and then on "Ask a librarian" in the left-hand navigation bar.

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NEWS FROM THE INDUSTRY

ALTANA Pharma

GERD is More than Just Heartburn

Gastroesophageal reflux disease (GERD) has a highly heterogeneous symptom profile, characterized by numerous abdominal and chest symptoms. Although heartburn and acid regurgitation are frequently defined as the most prominent symptoms, it is acknowledged that GERD is also associated with extraesophageal manifestations – respiratory complaints, as well as dyspepsia.

GERD Symptom Assessment – ReQuest™ Leads the Way

The measurement of GERD symptoms has traditionally relied on a variety of symptom scales that are not GERD-specific. In addition, there is a lack of standardization in defining and assessing the broader symptom spectrum. This limits the scope for changing to alternative treatment options that might be more suitable to treat the condition. Consequently, there is a pressing need for a tool capable of assessing symptoms accurately and evaluating the daily treatment response in patients with GERD.

ALTANA Pharma is leading the field in developing ReQuest™ – a state-of-the-art reflux questionnaire. It is a brief and reliable patient-administered symptom scale, sensitive and specific for GERD, that can precisely define symptomatic healing. ReQuest™ was recently validated in erosive GERD and in GERD patients [1–3].

Pantoprazole: Fast, Sustained Symptomatic Relief

The first study using ReQuest™ to evaluate the time to symptom relief was conducted by Mönnikes et al. in symptomatic patients with endoscopy-negative reflux disease who received either pantoprazole 20 mg or esomeprazole 20 mg for 28 days. The results showed rapid and sustained relief of a wide range of GERD symptoms, and established that pantoprazole 20 mg is at least as effective as esomeprazole 20 mg with regard to the time needed to achieve initial and sustained symptom relief [4].

Proton-Pump Inhibitors (PPIs) are Equipotent on a Milligram-for-Milligram Basis

The results of the study by Mönnikes et al. confirm those of previous studies showing that pantoprazole and esomeprazole are therapeutically equivalent at a dosage of 40 mg in patients with erosive GERD (Los Angeles grades B/C) with regard to healing of esophageal lesions (88% patients healed in each group), and that pantoprazole provides significantly faster first-time relief from daytime and night-time GERD-related symptoms than esomeprazole (approximately 2 days earlier) [5,6] In addition, pantoprazole 40 mg and esomeprazole 40 mg have an equivalent effect on intraesophageal pH in patients with symptomatic GERD [7].

Pantoprazole the PPI of Choice

In clinical studies, pantoprazole has been shown to provide fast, sustained, and excellent daytime and night-time symptom relief – which, combined with high healing rates, makes pantoprazole the ideal PPI for treating the overall spectrum of symptomatic GERD.

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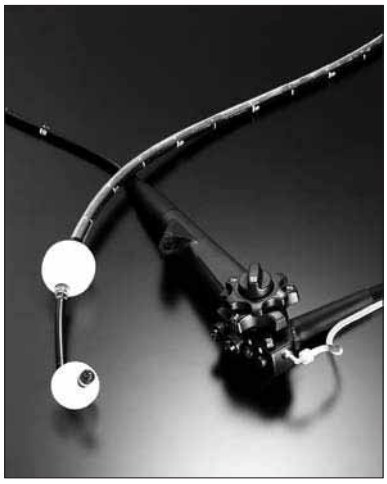
Fujinon

DOUBLE BALLOON ENDOSCOPY

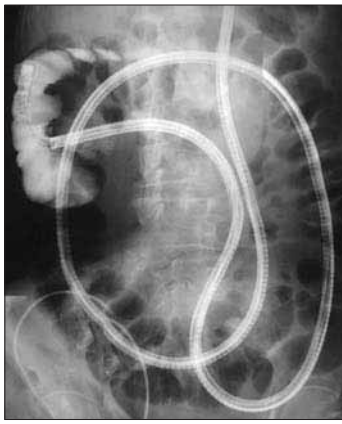


The double balloon enteroscope.

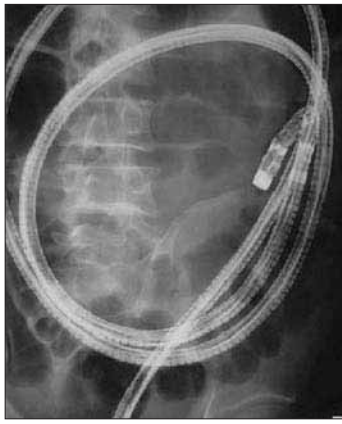
In collaboration with Dr. H. Yamamoto, Jichi Medical School, Japan, Fujinon has now developed a new double-balloon enteroscope (DBE) system that allows detailed examination and treatment throughout the whole small intestine.

The Principle

The examination procedure starts with the insertion of an enteroscope, which has a balloon attached to its tip, into a sliding overtube that has another balloon attached to the tip of the tube. The endoscope is first inserted into the stomach with both balloons deflated. When the scope reaches the stomach, the overtube is advanced along the endoscope until the tip of the overtube reaches the stomach. With the overtube being held by an assistant to prevent it from being withdrawn, the scope is then inserted further until it reaches the descending duodenum. The balloon on the endoscope is then inflated so that it maintains a stable position within the intestinal lumen. The overtube is advanced along the endoscope until the overtube tip enters the duodenum. The balloon on the overtube is then inflated to hold a stable position in the intestine. With both balloons inflated, the endoscope is gently withdrawn together with the overtube to straighten it. The balloon on the endoscope tip is then deflated, and the endoscope is advanced along the overtube, which is held by the assistant, until the distal end of the scope reaches the ligament of Treitz.

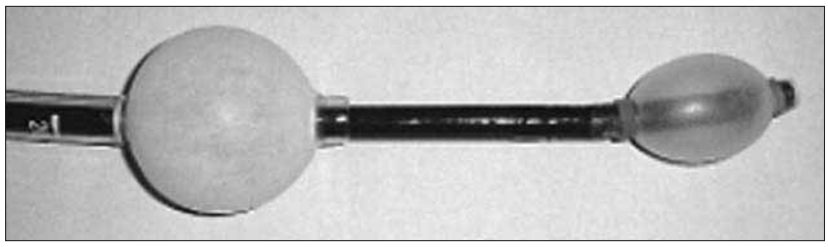


The anterograde route.



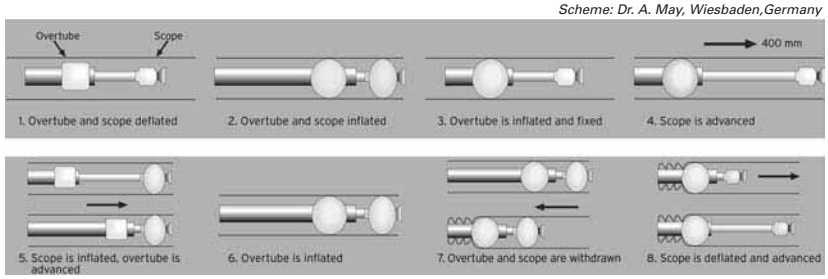
The retrograde route.

At this point, the overtube tip is fixed in a stable position in the duodenum, so that the scope can advance further without becoming looped again in the stomach. After the balloon at the tip of the scope has been inflated and fixed in a stable position in the intestine, the balloon on the overtube tip is deflated so that the overtube can be advanced again along the scope, up to the balloon at the distal end. The overtube balloon is then inflated again and fixed in a stable position in the intestine, and the scope balloon is deflated so that the scope



The two balloons (the tip of an enteroscope and an overtube).

Scheme: Dr. A. May, Wiesbaden,Germany



Double Balloon Enteroscopy Method.

can advance. These procedures are repeated so that the balloons can be advanced and alternately fixed in stable positions in deeper and deeper locations. If complex loops form, the overtube can be gently withdrawn together with the scope with both of the balloons inflated.

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Olympus

V-SYSTEM

A Revolutionary System that Simplifies and Enhances the Efficiency of Therapeutic ERCP

The Olympus V-System is a complete system that integrates endoscopes and endotherapy devices. The revolutionary design simplifies and improves the efficiency of therapeutic endoscopic retrograde cholangiopancreatography (ERCP). With an array of unique features, the Olympus V-System allows either the physician or the assistant to manipulate the guidewire. It also makes it easier to exchange catheters and enhances cannulation capability.

The Innovative OLYMPUS V-System Design Lets You Proceed with Confidence and Efficiency

When a guidewire slips out of position, it can be extremely frustrating. With the new LinearGuideV™, unwanted movement is a thing of the past. Olympus V-System scopes feature a revolutionary V-Groove in the V-Scope forceps elevator that allows LinearGuideV™ to be securely locked in place without any special attachment when extended 13 cm from the distal end of the scope. Approaching the biliary or pancreatic ducts via the papilla can be accomplished quickly and easily without worrying about the guidewire slippage.

Unique Features of Endotherapy Products in the Olympus V-System

V-Marking. This indicates when to raise and lower the V-Groove forceps elevator in the Olympus V-System ERCP Scope elevator. The exclusive V-Marking is located on the proximal side of the sheath. When this marking reaches the instrument channel port on the scope's control section, it indicates that the device tip has reached the distal end of the scope, and the Olympus V-System ERCP Scope elevator can be lowered. When withdrawing the device from the scope, the same marking indicates when to raise the elevator to lock the guidewire.

C-Hook. Now endoscopists have the option to manipulate guidewires and devices. The convenient C-Hook allows the device handle to be attached to the endoscope's control section, so that it is within easy reach for the endoscopist. With the device handle immediately to hand, the endoscopist can maneuver the guidewire, inject contrast media, and manipulate the handle – while still keeping hold of the scope control section.

V-Sheath – device control by the endoscopist or the assistant. The C-Hook gives the endoscopist

complete control of the device, but device control can also be passed to the assistant if preferred. The unique device design allows the guidewire sheath and injection sheath/handle to be separated. The V-Sheath, with a forked sheath design, allows either the endoscopist or the assistant to control the device.

Procedure for replacing devices with the Olympus V-System:

1. Confirm the position of the V-Marking on the V-System Endotherapy accessory.
2. When the V-Marking is completely visible above the instrument channel port the guidewire may be locked in the V-Groove.
3. Completely remove the device leaving the guidewire in place.

Olympus V System Product Line-Up

- V-System ERCP Scope
- LinearGuideV™ (guidewire)
- CleverCut 3V™ (triple-lumen sphincterotome)
- CleverCut 2V™ (double-lumen sphincterotome)
- FlowerBasket V™ (retrieval basket)
- TetraCatch V™ (retrieval basket)
- Multi3V™ (triple-lumen extraction balloon)
- StarTip V™ (cannulas)
- X-Press V™ (cannulas)
- Biliary Stent on QuickPlace V™ (biliary stent and insertion device)
- DoubleLayer™ Stent V on QuickPlaceV™ (biliary stent and insertion device)

– And more new products will be launched in the future.

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Takeda

Lansoprazole: Wide Range of Indications and Administration Options

Eighteen years of clinical experience and availability in 98 countries throughout the world have shown that lansoprazole is effective and well-tolerated in the management of acid-related disorders. The range of indications and modes of administration for lansoprazole are continuing to expand (approved indications vary from country to country; please refer to local prescribing information for all formulations mentioned here).

Lansoprazole Fast-Disintegrating Tablet (LFDT): First and Only Orally Disintregating PPI

LFDT is an easy-to-take tablet that has been micro-engineered so that it disintegrates quickly in the mouth, usually in less than 60 seconds, allowing a patient to take the medication with or without water. The tablet is strawberry-flavored. Patients simply place the tablet on the tongue and allow it to disintegrate until the particles can be swallowed. LFDT is bioequivalent to lansoprazole capsules and has identical indications and recommended dosages (approved indications vary from country to country). For children and elderly or other patients who have difficulty in swallowing tablets, two other ways of administering the drug – via either an oral syringe or a nasogastric tube – are available in the United States.

Now Approved for Treatment of Acid Reflux Disease in Children Aged 1–17

Lansoprazole is now available in the United States for short-term treatment of symptomatic gastroesophageal reflux disease (GERD) in children aged 1–17 years and in those with erosive esophagitis, with a variety of administration options suitable for children and teenagers. The availability of the drug to help this larger group of patients further reinforces its leadership position in the PPI market. Use of lansoprazole in patients aged 1–17 is supported by evidence from adequate and well-controlled studies of lansoprazole in adults, and additional clinical, pharmacokinetic, pharmacodynamic and safety studies have been conducted in pediatric patients (Figure 1).

New Intravenous Administration Option for Lansoprazole

Lansoprazole injection has been approved for the treatment of erosive esophagitis in hospitalized patients in the United States. When patients are unable to take oral formulations, intravenous injection of lansoprazole is indicated as an alternative for short-term treatment (up to 7 days) of all grades of ero-

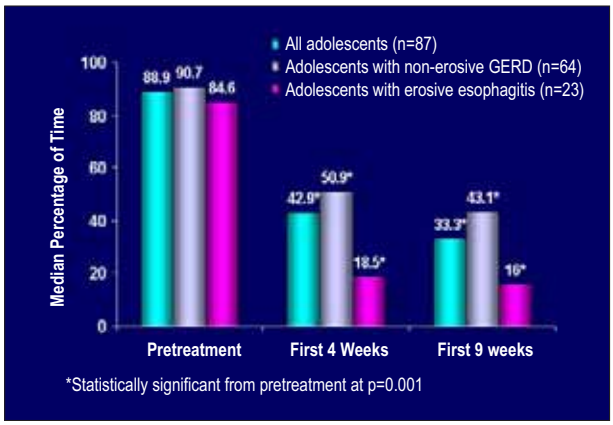

Figure 1. *Median percentage of days with symptoms of gastroesophageal reflux [1].*

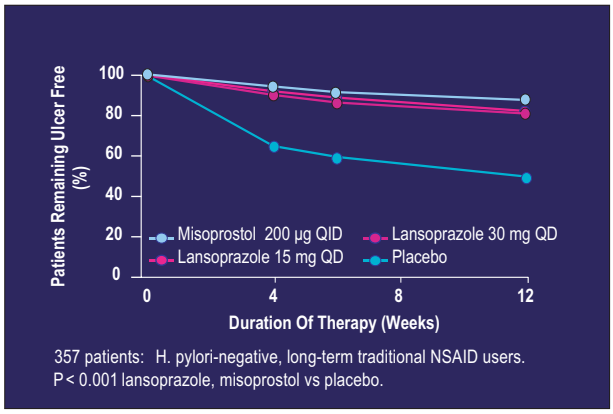

Figure 2. *Ulcer prevention in long-term users of traditional NSAIDs: comparison of lansoprazole, misoprostol, and placebo [4].*

sive esophagitis in the U.S., and it will become available worldwide (Table 1).

NSAID Ulcers

The risk of gastrointestinal events induced by nonsteroidal anti-inflammatory drugs (NSAIDs) is two to four times greater in patients with a history of ulcer disease or complications. Clinicians and carers need to balance the risks, benefits, and costs of NSAIDs, COX-2 inhibitors, and prophylactic PPIs. Clinically detailed, evidence-based, and economically sensitive guidelines can help rationalize decision-making involving different NSAID treatment strategies in patients with varying degrees of gastrointestinal and cardiovascular risk (Figure 2). (Lansoprazole is the only PPI in the United States that is indicated for healing and reducing the risk of recurrence of gastric ulcers associated with NSAIDs in chronic NSAID users, and the indications have been approved worldwide [3]).

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Takeda Satellite Symposium and Booth at the 12th United European Gastroenterology Week (UEGW), Prague, 2004:
"Experience or evidence? New Challenges in Acid-Related Disorders"
Time and date:
Tuesday 28 September 2004, 18:00 h.
Venue:
Congress Hall, Congress Center.
Panel:
Prof. James W. Freston (chairman),
Prof. Jean P. Galmiche,
Prof. Chris Hawkey,
Prof. Brendan Delaney,
Prof. Fabio Baldi.

Table 1. *Antisecretory effect of intravenous lansoprazole 30 mg and oral lansoprazole 30 mg in patients with erosive esophagitis [2].*

Parameter	Lansoprazole delayed-release capsules (oral)	Intravenous lansoprazole	Intravenous placebo
Maximal acid output (mEq/h; median, interquartile range)	7.16 (4.65, 10.05)	7.64 † (4.47, 10.29)	26.90 ** (22.02, 30.37)
Basal acid output (mEq/h; median, interquartile range)	0.77 (0.24, 1.66)	0.51 (0.09, 1.35)	3.19 * (1.87, 8.94)

* Significantly different from intravenous lansoprazole at $P = 0.005$.
** Significantly different from intravenous lansoprazole at $P < 0.001$.
† Equivalent to oral lansoprazole: significant at $P < 0.04$ for rejecting the hypothesis that intravenous lansoprazole is inferior to oral lansoprazole (Wilcoxon's signed-rank test).