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Primary Prevention of **Digestive Cancer**

Gastrointestinal Medicine on the **Frontiers: Esophageal Cancer** in **North Central China**

PULL OUT: **Guideline**: Management of **Strongyloidiasis**

WCOG 2005 – Montréal, September 10–14

WGO-OMGE

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Message from the Editor-in-Chief

Jerome D. Waye

This issue provides scientific information from recognized experts in various fields. The articles touch on the latest considerations for the management of acute pancreatitis; current thoughts on the management of hepatitis C; the problem of fecal incontinence; and endoscopic therapy for esophageal reflux disease. The whole world is watching developments in "virtual colonoscopy" (or colonography), and the current status of this method is also discussed.

We continue the series on "Gastrointestinal Medicine on the Frontiers" with an article concerning the high risk of esophageal cancer in the Linxian area of China. The conditions in which epidemiological research is conducted there call for congratulations from all of us for the great work that has been accomplished and that is continuing.

The International Digestive Cancer Alliance (IDCA), inspired by the *Organisation Mondiale de Gastro-Entérologie*/World Gastroenterology Organization (OMGE/WGO), is continuing to pull together international aspects of gastrointestinal cancer, and is having an impact throughout the world. Professor René Lambert presents an article on the primary prevention of gastrointestinal cancer. This is a high-level assessment and deserves the attention of everyone interested in gastroenterology.

The "Train The Trainers" program is continuing to develop under its co-chairmen, Dr. Jim Toouli and Dr. Mel Schapiro of the combined Education Committees of WGO-OMGE and OMED. We acknowledge the endorsement by WGO-OMGE and OMED of the Center for Advanced Training in Endoscopy in Santiago, Chile. I visited this facility in December, and found it to be an invaluable addition to the diagnosis and treatment of gastrointestinal diseases throughout Chile. Dr. Navarette and Dr. Sáenz are to be congratulated for their foresight in developing this endoscopy center.

A report by Dr. Anthony Axon, President Elect of OMED, details the development of the European Society of Gastrointestinal Endoscopy (ESGE), one of OMED's three zones. It has been interesting to watch the growth and increasingly strong presence of ESGE over the past few years. A nucleus of hard-working energetic and altruistic doctors have been able to harness the potential in Europe to create an unparalleled force for teaching and development in endoscopy.

I blush at the biographic article written by my great friend and colleague, Dr. Christopher Williams, and thank him for his embellishment of everything that I have done.

The guidelines included in this issue focus on strongyloidiasis, a parasitic disease that has a tremendous impact on the global community. The guidelines have been developed by the WGO-OMGE's guidelines committee, with the primary author being Professor Farthing. The accompanying article on accessing further information on strongyloidiasis from the Internet is a great explanation of how to use the Web for medical information purposes, and the principles outlined can be adapted to any subject.

Upcoming Conferences

There are three major meetings of interest to gastroenterologists taking place this year:

- Digestive Disease Week (DDW) in Chicago, 14–19 May 2005.
- The World Congress of Gastroenterology (WCOG) will be taking place in Montreal on 10–14 September. This meeting is always a wonderful venue for meeting colleagues from all corners of the world and renewing friendships while being exposed to the entire range of gastroenterology, including surgery, hepatology, pediatrics, pathology, radiology, research and practice with several sessions devoted to updates in every field. There will be special programs for young clinicians and many satellite symposia. A highlight will be daily live endoscopic transmissions from Hong Kong and Toronto. The city of Montreal is a gem and has unbelievable cultural, recreational, and culinary facilities.
- The annual United European Gastroenterology Week (UEGW) meeting will be held in Copenhagen on 15–20 October.

Set aside the time to attend these outstanding gastroenterology events, which will keep you up to date with all aspects of our gastroenterological specialty.

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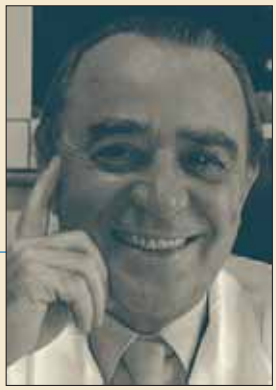
Message from the Emeritus Editor

Laparoscopic Surgery: Technical and Economic Considerations in Developing Countries



Alberto Montori

In a world which is fast growing smaller with ease of travel and speed of communication, it is imperative that the advancing edge of surgical progress should be made available to all people in all places. Being poor is neither a stigma nor a reason for despair; it is a state of existence at a particular moment in a country's history.

— T.E. Udwadia

My views on this particular topic come from various sources:

- Direct experience in visiting and teaching in several developing countries. Officially there is a total of 86 developing countries (43 in Africa, 24 in Asia, nine in the Americas, seven in Oceania, and three in Europe).
- Direct person-to-person contact with many colleagues in those countries.
- An educational program established by "La Sapienza" University in Rome and some developing countries (especially in North Africa) through financial support from the Italian government.
- Responsibility for the training young doctors from these countries in my own department.
- Information from literature in this field.

The countries concerned are all different—each with its own identity, varying financial constraints and socioeconomic realities—and the problems they face vary widely.

Colleagues in many of these countries often show a surprisingly high level of knowledge regarding endoscopy and the benefits of endoscopic procedures. It is noticeable that surgeons in many developing countries—such as India, rural Thailand, Georgia, Uzbekistan, Tanzania, Nigeria, and Bolivia—have always been interested in flexible endoscopy and emergency laparoscopy. It is an understandable approach, since these countries often lack the financial resources for diagnostic facilities such as ultrasonography, computed tomography, and magnetic resonance imaging. Exploratory laparotomy is a frequently used diagnostic tool, and the introduction of minimally invasive surgery has reduced the need for large incisions. Small wounds are better, since environmental problems in hospitals that are often very old and have precarious hygiene conditions and a lack of antibiotics, etc., do not ensure sterile conditions for wound care.

Many younger surgeons, as well as some senior ones, appear to be actively interested in laparoscopic surgery as a minimally invasive procedure. Many of them have been attending laparoscopic surgery courses in training centers, and the numbers of such procedures being performed have increased considerably in recent years.

Endoscopy has changed the practice of gastroenterology and abdominal surgery. Flexible endoscopy became established as an essential diagnostic tool in the 1970s; in the 1980s, endoscopy triumphed with the development of therapeutic endoscopy. The 1990s were characterized by an explosive growth in minimally invasive surgery, mainly involving cholecystectomy. The advantages of minimally invasive surgery are obvious to both the patient and the surgeon: minimal postoperative discomfort, shorter hospital stays, shorter convalescence periods, and faster recovery. However, there is a striking contrast between the new high-technology methods of surgery available in the industrialized countries and the realities in developing countries.

I am convinced that minimally invasive surgery would be even more useful in the developing countries than in other parts of the world. Whenever open surgical interventions can be replaced by keyhole incisions, it will reduce the risk of cross-infection of wounds and allow fast diagnosis and safe surgery. An educational program aimed at teaching modern surgical endoscopy techniques in the developing countries requires funding for organization, teaching, and equipment costs. Modern endoscopy uses video images, which can be transmitted to a conference hall or indeed across continents via satellite. Computer simulators are also available. At present, the cost of these facilities precludes their widespread use, and practical training is therefore only available to a very lucky few.

Because the technique is relatively new and the numbers of trained experts in it are limited, expertise in teaching minimally invasive surgery simply does not exist among the senior teaching staff in areas in which therapeutic endoscopy is not available. The traditional apprentice system of observation, tutelage, and practice under supervision by a mentor is not possible. Surgical endoscopy requires complex cognitive and manual skills that can only be acquired after a long period of training.

A novel method of teaching surgical endoscopy is the "master class" approach, suggested by Professor Sydney Chung (formerly of Hong Kong, now in New Guinea), borrowed from the methods used in musical training. A group of advanced trainees perform one after the other in the presence of a maestro. The maestro then gives a critique of each trainee's technique. This format creates an intensive learning atmosphere, and the trainees are able to learn from each other as well as from the teacher. A series of master classes of this type in surgery, conducted by different experts, were very well received in China and in North Africa.

The governments of the world's most industrialized countries, together with industry, should evaluate and fund educational and practical programs of this type under the supervision of the local scientific associations and societies. I am sure that, with the fast pace of economic developments in these regions, the next decade will witness an exponential growth in the availability of surgical endoscopy in the developing countries.

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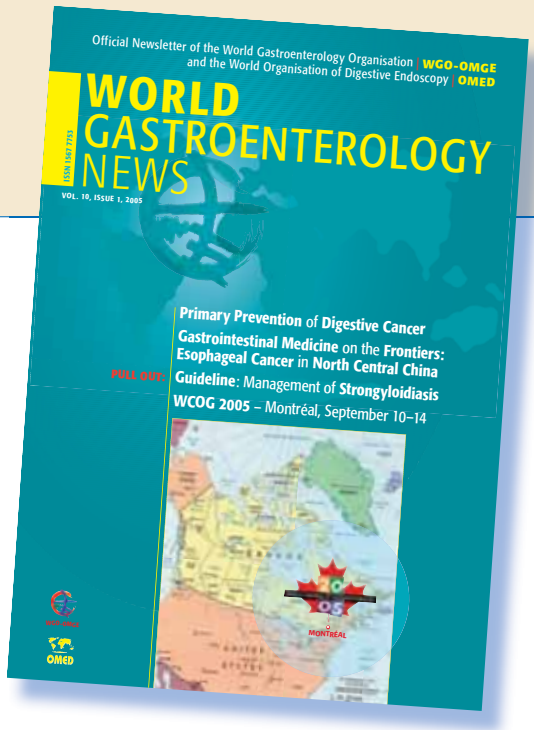

Digestive Disease Week 2005, Chicago, 14–19 May

My Kind of Town

Not surprisingly, the song *My Kind of Town* is one of the most frequently requested in Chicago. It may not be an official city anthem, but by virtue of its enormous popularity over the years, the song sums up what the people of Chicago think of their city. This year, DDW (Digestive Disease Week) is taking its stall to Chicago with hopes that this same enthusiasm will be a catalyst for another fruitful annual meeting.

The meeting will take place (14–19th May) at the enormous McCormick Center, home to most of Chicago's major events and one of the largest venues in the world – and due to get bigger still in 2008. McCormick is centrally located and within easy reach of most city hotels.

DDW is retaining the same trusted formula as in previous years. There will be the four major tracks governed by the participating societies, the AGA, AASLD, ASGE and SSAT. Each of these associations takes the lead in driving the latest developments in their area of speciality. Although there are no significant changes over last year, here are some highlights:

American Gastroenterological Association (AGA) – The Spring Postgraduate course starts the meeting off on Saturday, May 14th; a two day multi-topic course that examines the science underlying common, yet difficult, issues in gastroenterology. In the Presidential Plenaries, highlights include major developments in GI basic science and clinical research and there will be a panel discussion on the national focus on quality care and recommendations for response.

American Association for the Study of Liver Disease (AASLD) – The AASLD's focus plenary sessions are on the Sunday and Monday of the meeting, with the best scientific papers in the areas of clinical hepatology and viral hepatitis. There will also be what the organisers call 'standing room only' State of the Art Lectures on a variety of topics that include Drug induced liver disease, iron overload syndrome, and Hepatitis C therapy.

Society for Surgery of the Alimentary Tract (SSAT) – There are two new sessions this year, one together with the AHPBA (American Hepato-biliary Association) on Advances in liver resection for metastasis; the other from the SSAT education panel on Acquiring and maintaining new skills in an era of external standards.

American Society for Gastroentintestinal Endoscopy (ASGE) – In keeping with the hands on nature of endoscopy, there will be a special Advanced Endoscopy Skills Session that will take place at the ASGE's own center in Westmont, since Chicago is home to the ASGE. This is a three-hour rotating station program where the individual stations are divided into four upper and lower GI tract training models. DDW wraps up with the ASGE Postgraduate Course, which continues to deliver valuable information to practicing gastroenterologists.

Chicago may not be top of the list of most cities that people want to visit, but once you are there it can be quite surprising. Unlike other US cities, this is one of the most walkable. Chicago is on the southern tip of the vast Lake Michigan and the lake front and city are very close, with walking opportunities from most hotels. You can take in the lakeside itself, the zoo, the Navy pier, and of course the two towers that make the Chicago skyline famous – the John Hancock Building and the Sears Tower. In short, Chicago has an abundance of things to do and see, but that is all periphery to the main event – Digestive Disease Week.

World Congress of Gastroenterology 2005
A Date with Montreal!

***Hugh Chaun**, Co-Chair, Press & Congress News, Canadian Organizing Committee*

Canada proudly invites all our colleagues in every continent to join us in Montreal for the next World Congress of Gastroenterology on 10–14 September 2005. There is an outstanding program, and the meeting will rank with the best of the decade and enrich your educational and personal experiences. The world of gastroenterology has advanced immeasurably since Dr. Henry Bockus presided over the first World Congress in Washington in 1958. Each succeeding World Congress has been testimony to continuing progress—Munich 1962, Tokyo 1966, Copenhagen 1970, Mexico City 1974, Madrid 1978, Stockholm 1982, San Paulo 1986, Sydney 1990, Los Angeles 1994, Vienna 1998, and Bangkok 2002. The upcoming meeting in Montreal will be a unique milestone in the history of the World Congress of Gastroenterology.

The Endoscopy Program

Three full days of endoscopy will include live transmissions from Hong Kong and Toronto, with international panelists in Montreal to link discussion with the endoscopists and coordinate audience participation. Planned topics include the treatment of early gastric cancer; the best method of palliation for cancer of the esophagus; management of stenoses in the gastrointestinal tract; gastric lesions for the endoscopist; mapping of the mucosa: detection and selection; the role of endoscopy in chronic pancreatitis; the colon—finding the lesions that count; gastrointestinal bleeding—the benefits of early scoping; and endoscopic treatment of esophageal dysplasia and cancer. World-renowned endoscopists from Hong Kong, India, Japan, Korea, Brazil, Chile, Belgium, France, Germany, Italy, United Kingdom, United States, and Canada will be demonstrating their expertise in this innovative and live endoscopy program.

In the Moutier Lecture, Professor Anthony Axon (UK) will address the practical issue of "How can I improve endoscopy in my unit?" In the Schindler Lecture, Dr. Nestor Chopita (Argentina) will speak on "Endoscopic treatment of advanced esophageal cancer". The Tasaka Lecture will be delivered by Dr. Rikiya Fujita (Japan).

The Scientific Program

There will be parallel sessions over the 3 days of the main meeting that will discuss global issues in every important area of gastroenterology and hepatology. Highlighted topics include gastrointestinal disease—epidemiology and the environment; inflammation and gastrointestinal cancer; diagnostic advances in colorectal cancer; *Helicobacter pylori*, gastritis, and gastric cancer; global epidemiology and mechanisms of obesity; obesity and gastrointestinal disease; nonalcoholic steatohepatitis (NASH); management of obesity; global perspectives on functional gastrointestinal disorders; diarrhea in different geographical regions; host–flora interactions; the therapeutic potential of gut commensals; the future of gastroenterology; gastroenterology and oncology; practical therapeutics; gastrointestinal manifestations of AIDS—a global perspective; evaluation of risk and risk reduction—role of anti-inflammatory drugs; NSAIDs, coxibs, acetylsalicylic acid and *H. pylori* infection—what is the potential for prevention?; *H. pylori* resistance and management strategies; basic aspects of drug development; drug evaluation; recent developments in pancreatic disease; dyspepsia in the developing world; abdominal pain—clinical issues and underlying mechanisms; pain and the brain; therapeutic approaches to pain; advances in imaging of the gastrointestinal tract—from molecule to magnet; mucosal barrier function—the first line of defense; infective diarrhea; chronic infection of the intestine; the hygiene hypothesis and gastrointestinal disease; socioeconomic implications and screening for gastrointestinal cancer; carcinoids and stromal tumors; abnormal liver function tests; *H. pylori* and upper gastrointestinal symptoms; assessment of esophageal function; esophageal problems—case presentations and discussion; how I do it? (on failed PPI treatment; noncardiac chest pain); Barrett's esophagus; new concepts of gastrointestinal inflammation—lessons from animal models of inflammatory bowel disease (IBD); new biologics in the diagnosis and treatment of IBD; dilemmas in IBD management; strictures in IBD: mechanisms and management; from dysmotility to motility failure; managing the difficult functional patient—case-based; pelvic floor disorders; and swallowing disorders in the elderly.

Global Goals

Topics here include: update on the Rome III diagnostic criteria for functional gastrointestinal disorders; towards an integrative clinical molecular and serological classification of IBD; guidelines for the 21st century; are global guidelines desirable or feasible?; are minimal guidelines ethical and necessary?; can global guidelines change health policy?; industry—in or out?; is the "evidence-based" approach always desirable or feasible?; emerging leaders; a global evaluation of the TNM endoscopic staging for Barrett's; *Asociación Interamericana de Gastroenterologia* (AIGE) program; global burden of hepatitis C; Train the Trainers—a program for developing excellence in training across the world; classification system for cirrhotic cardiomyopathy; and women in gastroenterology.

Hepatology

Topics here include extrahepatic complications of cirrhosis—other organs also fail; presentation of interesting cases; hepatocellular carcinoma (HCC); tropical/parasitic liver diseases; alcoholic hepatitis; portal hypertension; hepatitis C; autoimmune liver disease; and hepatitis B.

Dr. Bernard Levin (USA) will be the Bockus Lecturer. Dr. Dana Philpott (France) will discuss "How pathogenic bacteria talk to the gut: the NOD receptor system" in the NASPHAN Presidents' and Kopelman Lecture. Announcements for the McKenna Lecture and the Solly Marks Lecture are pending. Dr. Michael V. Sivak, Jr. will be the Brohee Lecturer on "Endoscopy: past and future". There will be state-of-the-art lectures on "Nutrition and inflammatory disorders" by Professor Colm O'Morain (Ireland); "Celiac disease" by Dr. Alessio Fasano (USA); "Urbanization and gastrointestinal disease" by Dr. A. Sonnenberg (USA); Barrett's—"The battlefield of the cardia" by Professor Kenneth McColl (UK); "What do genetic abnormalities tell us about the pathogenesis of IBD?" by Dr. Charles Elson (USA); and "Bloating: fact and fiction" by Professor P. Whorwell (UK).

Speakers for the scientific program have been invited from 39 countries, representing every continent.

The Gastrointestinal Surgical Program

An excellent program has been prepared that will interest all participants at the World Congress. Highlighted topics will include esophageal surgery; management of Barrett's; pancreatitis; frontiers in transplantation; management of HCC; controversies in the management of IBD; recent advances in the management of anorectal disease; management of familial adenomatous polyposis (FAP). State-of-the-art lectures will be given on the "Management of pancreatic cancer" will be presented by Professor Markus Wolfgang Buechler (Germany), "Liver transplantation" by Professor Jacques Belghitti (France), and "What is the role of genetic testing in colon cancer?" by Dr. Steve Gallinger (Canada).

Postgraduate Courses and Other Programs

The meeting will provide an extra opportunity to attend the postgraduate courses of your choice during the weekend before the main scientific congress. These include the American Gastroenterological Association course; an interactive course organized by the *Sociedad Interamericana de Endoscopia Digestiva/Asociación Interamericana de Gastroenterologia* (SIED/AIGE); a digestive endoscopy course presentation in French, organized jointly by the *Association de Gastroenterologie et d'Endoscopie du Quebec* and the *Société Française d'Endoscopie Digestive*; minimally invasive therapies, organized by the Canadian Surgical Forum; and a nutrition course organized by the Canadian Society for Clinical Nutrition. The World Congress will also host the Young Clinicians Program and the 9th International Educational meeting of the Society of International Gastroenterological Nurses and Endoscopy Associates (SIGNEA).

At the conclusion of the important inaugural meeting in Washington in 1958, the following comment was written: "The greatest single contribution made by this World Congress was the gathering of men and women of every creed and custom from all corners of the world, all with a single purpose—to improve our measures for preserving and restoring health" (Wood et al., *Gastroenterology* 1958). Please come to celebrate the next World Congress in Montreal in September 2005, only a few months from now, to reach for the highest level of endeavor in continuing this process.

For more information about WCOG 2005, please see: www.wcog2005.org

Endoscopic Therapy for GERD: Becoming an Attractive Option?

David A. Johnson

Introduction

To date, there have been basically three approaches to endoluminal therapy for gastroesophageal reflux disease (GERD):

- Radiofrequency ablation delivered to the lower esophageal sphincter (LES).
- Endoscopic gastroplasty plication of the gastric folds immediately distal to the esophagogastric junction.
- Endoscopic implantation of a bulking agent or polymer in the region of the LES.

Radiofrequency Ablation

Radiofrequency ablation (RFA) has been used in other medical fields; it mainly works by neurolysis or tissue injury and subsequent scarring. The Stretta device (Curon Medical, Inc., Fremont, California, USA) is a temperature-controlled device that delivers RFA to the gastroesophageal junction as a treatment for GERD.

Mechanism of action. The exact mechanism of action by which RFA works in the treatment of GERD is not known, although it is most likely (as with the application of RFA in other fields) to result from scarring or neurolysis in the region of the LES. A scarring effect with collagen deposition could conceivably lead to tightening of the LES.

Procedure. A guide wire is inserted into the stomach via the endoscope. The Stretta device is then passed over this guide wire, and staged delivery of RFA is administered with a series of 14 repositioning and reapplication maneuvers. The average time required for the procedure was 69 min in the trials reported to date.

Study populations. The patients included in the trials had chronic symptoms and required daily medication. Eighty-seven percent of the patients were taking proton-pump inhibitors (PPIs) and 13% were taking a histamine2-receptor antagonist (H2RA). All of the patients had an abnormal 24-h pH-metry time of more than 4% or a DeMeester score of more than 14.7. Exclusion criteria included: Barrett's esophagus, severe erosive esophagitis higher than grade 2, and a hiatal hernia size larger than 2 cm.

Study design. The initial studies of the method were prospective but not randomized, controlled, or blinded. However, this is the only technique for which a sham-controlled study has now been published subsequent to the pivotal trial reports.

Effectiveness. Significant improvements were seen in heartburn and quality-of-life scores after 6 and 12 months in comparison with the baseline findings in patients not receiving antisecretory medication. No improvement in LES sphincter pressure was seen. The sham-controlled study showed a reduction in heartburn in patients receiving active treatment in comparison with the control group, although PPI use was reduced equally in both groups.

Safety. The post-marketing surveillance data from the web site of the Food and Drug Administration (FDA) in the United States (http://www.fda.gov/cdrh/maude.html) lists 15 major complications, including six perforations, seven cases of major hemorrhage, and two deaths.

Study criticisms. Although the reports state that intention-to-treat analyses were used, it is not clear what happened to some missing data, particularly the 24-h pH data in 98 of 117 patients in one study. There was an unexpectedly high rate of responders to the sham intervention, and the power calculations in this study are therefore questionable, with a formidable potential for type 2 error. Finally, although a secondary objective was improvement in the 24-h pH-metry findings, this was evident only by analyzing patients regarded as responders to therapy. This type of post-hoc analysis of data in relation to an objective that was not stated a priori is statistically questionable. Accordingly, these results must be considered as subject to a higher potential for type 2 error.

Current status. The Stretta device was approved as a moderate-risk device by the FDA in April 2000. This approval was based on the initial study of 47 patients. The FDA summary statement concluded, "The risk–benefit profile of Stretta is substantially equivalent to that of fundoplication surgery." In sharp opposition to this FDA statement, however, the recent (and only) systematic review of the literature on Stretta concluded that "clear indications for Stretta treatment are nil because of the paucity of controlled data available,

patients, and the confusing nature of the data that are available".

Endoscopic Suturing

Three endoscopic suturing devices are currently available: EndoCinch (C.R. Bard, Inc., Murray Hill, New Jersey, USA); Sew-Right (Wilson-Cook Medical, Inc., Winston-Salem, North Carolina, USA); and the Plicator system (NDO Surgical, Inc., Mansfield, Massachusetts, USA). Prospective clinical trial data have not yet been published for the Sew-Right device.

Mechanism of action. The concept is that the proximal gastric folds can be plicated, potentially enhancing the barrier function of the gastroesophageal junction. In principle, this should serve to impede the ascent of gastric refluxate into the esophagus.

Procedure. *EndoCinch*. Standard endoscopy is carried out and an overtube is placed. A suture capsule system is attached to an endoscope, and this is advanced via the overtube into the distal esophagus. The plication site is identified (1–2 cm below the esophagogastric junction) and suction is applied to draw the tissue into a chamber, allowing deployment of a needle-directed suture through the wall. The entire suturing system is removed, the suture is reloaded, and the device is then reinserted through the overtube. A second plication is then done 1 cm away. The free ends of the sutures are tied. The suture is then cut, and more plications are placed. The optimal number of plications is still not clear, but typically three plications are placed (requiring passage of the endoscope approximately eight times (twice for suture placement, five times for knot tying, and one for knot cutting). The reported mean duration of the procedure is 68 min.

Plicator. The NDO Plicator procedure is also carried out on an outpatient basis, and does not require the use of an overtube. The reusable instrument has controls on the instrument handle for maneuvering the distal end of the device. The Plicator instrument contains two working channels—one for passage of the endoscope and the other for insertion of the tissue retractor. The endoscope is advanced into the stomach and then retroflexed to visualize the gastric cardia and diaphragmatic hiatus. A tissue retractor with a screw tip is inserted to within 1 cm of the gastroesophageal junction and advanced up to the level of the serosa. The full thickness of the gastric wall is then retracted into the instrument's jaws. This is followed by deployment of the implant, creating a full-thickness plication that is secured by a polypropylene suture and biocompatible suture bolsters.

Study population. Patients included in the clinical trials published to date have had symptomatic GERD, controlled by medical therapy. The majority of the patients were taking PPIs (86%). Exclusion criteria were similar to those in the Stretta trial: Barrett's esophagus, hiatal hernia larger than 2 cm, severe esophagitis higher than grade 2 (Savary–Miller), or a body mass index over 40 kg/m2. The studies were prospective, but not randomized or controlled. A sham-controlled study has not yet been conducted.

Effectiveness. A significant reduction in symptoms (heartburn, regurgitation) and quality-of-life scores was evident in all of the published studies (with follow-up periods of 3–12 months). The use of PPIs was reduced from 100% to 36% at 6 and 12 months. There were no changes in the 24-h pH-metry time < 4 or LES pressure. Repeat endoscopy at 3 months demonstrated loss of at least one suture in five patients. In addition, only 22–25% of patients were able to remain without antisecretory medication. In the only comparative trial so far conducted for any of the endoscopic therapies for GERD, the clinical outcomes for patients with surgical fundoplication were superior to those with EndoCinch.

Safety. One perforation (managed conservatively) occurred in the EndoCinch trials. In the European trial, two patients had significant bleeding; one required a transfusion and one had a gastric mucosal tear that did not require intervention. The Plicator trial reported free air in four of 64 patients, although a clinical perforation was suspected in only one of these cases and was managed without surgical intervention.

Study criticisms. In the EndoCinch studies, the primary and secondary objectives are not clearly defined in any of the published trials or abstracts. In addition, none of the trials has provided a justification of the sample size used in order to establish that there was adequate statistical power to support the hypothesis. Furthermore, the lack of an intention-to-treat analysis severely compromises the scientific validity of the statistics. For example, in the 6-month pivotal study, 13 of the 64 treated patients either withdrew or were not accounted for.

One report suggests that only 28% of the plications remained intact at the 1-year follow-up. In the report from the Mayo Clinic (one of the training centers for this procedure), no improvement in heartburn, regurgitation, or medication use was evident in 56%, 63%, and 50% of the patients, respectively.

Current status. Over 3000 suturing procedures have been carried out in the United States, and a sham-controlled study is currently in progress. New techniques are also being developed, including helical placement of the plications and the use of supplemental cautery. However, a recent comprehensive and systematic review of the literature suggests that at present, "only an indeterminate recommendation for endoscopic suturing treatment for GERD can be given."

Endoscopic Injection

An abstract describing an approach using submucosal injection of a hydrogel prosthesis (Gatekeeper; Medtronic, Minneapolis, Minnesota, USA) suggested modest efficacy, but only 75% of the prostheses remained in place at 6 months. Most of the clinical data on injection therapy for GERD involve the use of an ethylene vinyl alcohol copolymer (Enteryx; Boston Scientific, Natick, Massachusetts, USA) directed into the intramuscular layer of the distal esophagus.

Mechanism of action. The exact mechanism of action for the clinical effect of Enteryx is not known. No significant changes in LES pressures have been identified in clinical trials involving either the Enteryx or Gatekeeper methods. An increase in gastric yield pressures (the intragastric pressure needed to equalize gastric and esophageal pressure) was demonstrated with Enteryx in animals. This is probably the effect through which transient lower esophageal sphincter relaxations are reduced.

Procedure. The Enteryx procedure is carried out on an outpatient basis using standard moderate sedation. Standard upper gastrointestinal endoscopy is performed in an endoscopy suite with fluoroscopy. A 23-gauge 4-mm sclerotherapy-type needle is flushed with dimethyl sulfoxide (DMSO) solvent and then filled with the Enteryx polymer. The needle is directed to the LES. A total of 6–8 mL of implant material is delivered into the deep muscle layer of the esophagus. Each injection is carried out with fluoroscopic guidance to ensure accurate deep mural placement of the implant. This technique has been shown to be highly accurate for placement in the esophageal wall. The mean time required for the procedure in the principal trial was 33 min.

Gatekeeper implantation is also carried out on an outpatient basis with the patient under moderate sedation, and involves the use of an overtube. Three hydrogel prostheses are injected submucosally above the Z-line. The success rate for placement of the prosthesis has been reported to be in the 90–95% range, with a 6-month retention rate of approximately 75%. The mean time required of the procedure was approximately 22 min. The dried prosthesis is injected through a needle trocar into the submucosa. These hydrogel implants then fully expand over the following 24 h. Typically, three prostheses are injected. This is the only technique that allows removal of the device.

Study design. The published studies on Enteryx are multicenter prospective nonrandomized trials including patients with GERD receiving PPI therapy. Most of the treatment responders were able to discontinue PPI use completely. Sequential radiographic check-ups showed that the implant was stable, with no changes after 3 months and no evidence of migration. There was no improvement in LES pressure. Esophagitis improved or was unchanged in 74% of the patients and worsened in 26%.

Only preliminary reports are available for the Gatekeeper procedure.

Safety. There have been no major adverse events that were considered serious or life-threatening (hemorrhage, perforation) with Enteryx. There are limited data on the preliminary use of Gatekeeper. However, at least two major adverse events have been reported: one pharyngeal perforation caused by the overtube, and a case of protracted nausea and vomiting that resolved after removal of the implants.

Challenges for Endoscopic Therapy

Effective endoscopic techniques for treating GERD have developed sufficiently for them now to be regarded as viable options. The scientific designs used in virtually all of the published trials are open to criticism, although some have used greater scientific rigor in the design of the trials and analysis of the data. It is important that clinicians considering these technologies should be aware of the strengths and criticisms for each of the interventions. Several issues clearly need to be evaluated when these interventions are assessed prospectively:

- Placebo-controlled and sham-controlled studies are needed.
- The short-term and long-term efficacy (durability) of the procedures needs to studied.
- Cost-effectiveness issues need to be evaluated.
- The safety profile for each of these techniques needs to be defined.
- The role of these therapies in patients who do not have the same clinical profiles as those used in the inclusion criteria for the published studies will need to be defined.

Recommendations

These procedures should at present be regarded as options in patients with GERD who are responsive to proton-pump inhibitors (PPI). In the same way that a response to PPI treatment can be regarded as the best predictor of a favorable response to surgery, this can also be used as the guiding principle for selecting patients for endoscopic GERD therapy. At present, there are no data to suggest that these procedures may be successful in patients who do not respond to medical therapy.

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Management of Acute Pancreatitis

Peter A. Banks

Ten major considerations need to be taken into account when attempting to improve the treatment of acute pancreatitis:

1. **Look for risk factors of severity at admission**. Hemoconcentration at admission is an important risk factor for necrotizing pancreatitis. Failure to reverse hemoconcentration at admission, thereby allowing hematocrit to rise even further in the first 24 h, almost always leads to pancreatic necrosis.

2. **Determine severity**. The natural history of acute pancreatitis is to a large extent determined by the two most important determinants of severity: organ failure and pancreatic necrosis. Organ failure includes the following four parameters: shock, pulmonary insufficiency, renal failure, and gastrointestinal bleeding. Transient organ failure does not appear to increase the mortality. However, persisting multisystem organ failure in necrotizing pancreatitis is associated with a mortality rate of 40–50%. Pancreatic necrosis can be identified by dynamic contrast-enhanced computed tomography (CT). In interstitial pancreatitis, the microcirculation is intact, and there is uniform enhancement of the pancreatic parenchyma. In necrotizing pancreatitis, there is destruction of the microcirculation, resulting in nonenhancement of pancreatic parenchyma. While it remains unclear whether patients with pancreatic necrosis of more than 50% have a poorer prognosis than those with lesser amounts of necrosis, there appears to be general agreement that small areas of apparent necrosis on an initial CT scan may well represent loculated fluid that disappears on follow-up CT scans.

3. **Diagnosis necrotizing pancreatitis by CT scan**. Approximately 10–20% of patients with acute pancreatitis develop pancreatic necrosis, with a mortality rate of 10–20%. Half of the deaths in necrotizing pancreatitis occur within the first 7–14 days and are caused primarily by multiple organ failure. The remaining patients die at a later stage as a result of complications of pancreatic necrosis, particularly infected necrosis. Organ failure occurs in 50–60% of patients with necrotizing pancreatitis.

Patients with multiple fluid collections (including pleural effusions) have a more serious prognosis than those without such fluid collections.

The Balthazar Ranson CT criteria of severity combine the appearance of the unenhanced CT scan, ranging from a CT grade of A (normal appearance) to E (multiple fluid collections), with the amount of necrosis, ranging from none to over 50%. A CT severity index is helpful in comparing the results for patients from various institutions.

4. **Treat hemoconcentration aggressively**. We have found that a hematocrit greater than 44% at admission is a strong predictor of pancreatic necrosis and of organ failure. Similarly, a hematocrit of less than 44% at admission that is not decreased within the first 24 h is also a strong predictor of necrosis and to a lesser extent of organ failure.

5. **Consider enteral feeding in severe pancreatitis**. Patients with severe pancreatitis are not likely to receive oral alimentation for at least 5–7 days. Traditionally, these patients are placed on total parenteral nutrition (TPN) within a few days of admission. More recently, enteral feeding has been shown to be well tolerated; it is safer than TPN with regard to side effects such as sepsis, and possibly even prevents the development of infected necrosis by preventing bacterial translocation from the gut. However, enteral feeding has not

been shown to reduce the severity of acute pancreatitis (i.e., it has not been shown to reduce organ failure, the development of necrosis, time in the intensive-care unit, or mortality rate).

6. **Consider biliary sphincterotomy**. The role of early endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy for patients with severe pancreatitis thought to be due to gallstones remains controversial. The present guidelines are that such patients should undergo an ERCP within the first 24–36 h of hospitalization. This approach has been shown to be safe even if biliary stones are not found. If common bile duct stones are found and removed, the approach would be beneficial in treating symptoms that might have been caused by biliary sepsis.

Concern regarding post-ERCP pancreatitis remains high in the United States. Among the agents that have been used to prevent post-ERCP pancreatitis, gabexate mesylate has been most effective, but is not available in the USA.

7. **Consider antibiotics in necrotizing pancreatitis**. The value of antibiotics in necrotizing pancreatitis remains unclear. In several placebo-controlled randomized and prospective (but not double-blinded) studies, the use of potent antibiotics has been shown to reduce the incidence of infected necrosis. However, several additional studies have pointed out that the use of potent antibiotics also has led to the development of superimposed fungal infections, with a high mortality rate. There is no worldwide consensus regarding the use of potent antibiotics. Some centers routinely use antibiotics for 7–14 days in all patients with necrotizing pancreatitis. Other centers use antibiotics only in patients with necrotizing pancreatitis with organ failure. Still other centers never use antibiotics unless an infection can be proven. In a recent study, ciprofloxacin and metronidazole were found to be ineffective in preventing infection and in preventing mortality in severe necrotizing pancreatitis.

8. **Carry out aspiration to diagnose infected necrosis**. Guided percutaneous aspiration with Gram staining and culture has been shown to be a safe and accurate method of diagnosing infected necrosis. Gram stains should be obtained, and these invariably show the presence of bacteria if present. Cultures should always be performed in addition to the Gram stain to confirm the presence of bacteria.

9. **Treat sterile pancreatic necrosis medically**. Patients with sterile necrosis are generally managed medically for the first several weeks, even in the presence of organ failure. There is increased acceptance of the view that aggressive medical therapy in an intensive-care unit may be preferable to surgical debridement within the first 2 weeks. However, after 2–3 weeks, when the inflammatory response has subsided and the necrotic tissue appears better organized and at times even encapsulated (an appearance that has been termed "organized necrosis"), there is a role for intervention for refractory pain that prevents oral alimentation. The most commonly performed intervention is surgical debridement with an anastomosis of the capsule of the organized material, either to the stomach or to a Roux-en-Y loop of jejunum. In selected cases, there may also be a role for endoscopic or percutaneous radiologic drainage.

10. **Treat infected pancreatic necrosis surgically**. Approximately 30–35% of patients with necrotizing pancreatitis develop infected necrosis. This is usually documented during the second or third week of illness. Pancreatic infection can be safely and reliably diagnosed by CT-guided percutaneous aspiration with Gram stain and culture. The treatment of choice for infected necrosis is surgical debridement. On occasion, when a patient is critically ill and cannot undergo surgical debridement, there is a role for radiologic drainage using one or more percutaneously placed catheters.

Improvements have clearly been achieved in the treatment of acute pancreatitis. Ultimately, the goal is to inhibit early events in pancreatitis, prevent organ failure, prevent pancreatic necrosis, and prevent pancreatic infection. Efforts in the future should be directed toward decreasing the severity of acute pancreatitis using a number of new therapies. These include inhibition of proinflammatory mediators (such as cytokines, nitric oxide, and adhesion molecules) and possibly the use of anti-inflammatory mediators (such as IL-10). In this regard, there is increased interest in the importance of gut barrier failure in facilitating infected necrosis and organ failure.

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Hepatitis Update

Louis A. Balart

Hepatitis C

Cirrhosis secondary to chronic hepatitis C is the single most common indication for liver transplantations performed in the United States. Over the next decade, the number of patients with chronic hepatitis C reaching the end stage, developing complications, developing hepatocellular carcinoma, requiring liver transplantation, and dying will rise dramatically.

Patterns of infection and natural history. The reasons why someone develops cirrhosis are difficult to determine. Based on retrospective studies, untreated hepatitis C could result in cirrhosis in as many as 25–30% of patients after 20 years of infection. Some studies point to a much lower incidence of cirrhosis. For instance, in young Irish women who acquired hepatitis C virus (HCV) infection from contaminated anti-D globulin, the cirrhosis rate was only 2% after 17 years of follow-up.

Once cirrhosis develops, the 5-year and 10-year survival rates in one European study were 91% and 79%, respectively. The development of hepatocellular carcinoma in this group of compensated cirrhotics was 7% at 5 years and 12% at 10 years. Once decompensation occurs, survival at 5 years dramatically drops to approximately 50%. Thus, patients with cirrhosis from HCV are the group in most urgent need of treatment. Several large ongoing trials testing the efficacy of long-term maintenance treatment with pegylated interferon should provide valuable information on how to treat these patients.

HCV testing and screening. HCV antibody may fail to develop in immunosuppressed hosts, such as in patients on hemodialysis or in transplanted patients. If HCV is suspected, these patients should be checked with HCV RNA. A number of qualitative HCV RNA assays are generally available. Qualitative assays based on polymerase chain reaction testing, such as transcription-mediated analysis (TMA), can detect 10 IU/mL.

Genotype determination is clinically important and now easily available to most practitioners. Six main types are known. There appear to be no significant differences between the genotype and mode of infection or degree of severity. However, genotype is the most important factor predictive of a sustained viral response (SVR) to treatment. In addition, genotype is important in determining the length of treatment and the amount of ribavirin necessary to achieve SVR. Patients with genotype 2 or 3 infection can be treated for 6 months and need only receive 800 mg of ribavirin daily, thus significantly improving the side effect profile. Furthermore, the high SVR rates achieved in genotype 2 and 3 patients are leading to reconsideration of the need for pretreatment liver biopsy; my view is that these patients do not need a liver biopsy before treatment. This has recently been recognized by the National Institutes of Health consensus panel.

Goals of treatment in HCV. Since the inception of the first randomized trials of treatment, the goal has been to eradicate the virus, thus preventing disease progression and related morbidity and mortality. More recently, there has been a new emphasis on viral suppression, which could in turn lead to slowing of disease progression and improvements in the morbidity and mortality. Unfortunately, there are no prospective data available to show that antiviral treatment of chronic HCV prolongs survival. Several retrospective studies in Japan and the United States suggest that treated patients live longer than untreated ones.

Treatment. Combination therapy with pegylated interferon and ribavirin is the standard of care in the majority of patients.

A review of published studies of the two approved forms of pegylated interferon (PEG Intron and Pegasys) shows the similarities and differences between these two compounds: pegylated interferon alfa-2b (PEG Intron, Schering Plough) is a smaller, 12-kDa molecule that is cleared by the kidneys and has a sustained level in circulation for 96 h. Pegylated interferon alfa-2a (Pegasys, Roche) is a larger, 40-kDa molecule that is not renally cleared and has sustained levels for 120 h. Despite pharmacokinetic and pharmacodynamic differences, both formulations have been shown to achieve significantly higher SVR rates in comparison with standard interferon and are not associated with an increased risk of significant side effects.

The two approved pegylated interferons, in combination with weight-based ribavirin, offer similar results, but it is clear that these products are pharmacologically different. One is a weight-based product offering potential advantages for heavier patients, while the other appears to have fairly equal efficacy across most weights. These differences should be taken into account when selecting treatment for a specific patient.

Early viral response. It appears that at 12 weeks after the start of therapy, patients whose viral load has not dropped by at least 2 logs or become undetectable will have a very small chance (3%) of achieving SVR (with a negative predictive value of 97%). This applies to both pegylated interferon formulations in combination with ribavirin, but does not apply to genotype 2 and 3 patients, since virtually all of these patients achieve an early viral response and therefore do not need to be tested at 12 weeks.

Relapse. Relapse is defined as the reappearance of HCV during follow-up. This generally occurs within the first 6 months. In fact, long-term observation of small groups of patients beyond 6 months shows that the durability of SVR is in the range of 95–98%, so that late relapse is rare but not impossible.

The available data show that over 85% of relapsers will respond in a similar fashion to the second round of treatment; the real question is how many of these patients will achieve a sustained response.

Nonresponders. In my opinion, histology is possibly the most important factor in deciding whether to offer repeat treatment and whether to offer maintenance therapy. Patients with advanced fibrosis or cirrhosis (stage 3 or 4) are the most deserving of repeat treatment. At present, data from multiple trials show that the best that can be expected from repeat treatment of nonresponders is 10–15%.

Chronic Hepatitis B

Chronic hepatitis B affects 350 million people throughout the world. Patients with chronic hepatitis B are at risk for developing cirrhosis, hepatocellular carcinoma, and liver failure, leading to death.

Following acute infection, approximately 5% of adults and over 95% of infants fail to clear the infection and become chronically infected. The many available serologic markers and confusing patterns in chronic hepatitis B have led to a lack of uniformity and even confusion in addressing the need for monitoring and treatment in this disease.

Adults with chronic hepatitis B have marked disease activity with elevated alanine aminotransferase (ALT) early in the course of the disease. HBeAg seroconversion (defined as HBV DNA $<10^5$ copies/mL, loss of HBeAg, and gain of HBeAb) can occur in these patients and is usually preceded by a drop in HBV DNA levels. Eventually, ALT normalizes and the patients pass to an inactive carrier state in which there is little if any evidence of hepatitis. If HBsAg disappears, patients have then resolved the infection and are considered cured.

Some patients who undergo HBeAg seroconversion may experience a reappearance of high HBV DNA levels and persistent or fluctuating ALT elevation, but do not develop HBeAg. These patients represent the other major form of the disease, HBeAg-negative chronic hepatitis B. Periodic, spontaneous flares of activity can occur in chronic hepatitis B, and it is thought that this may lead to progression of fibrosis and eventually cirrhosis. The presence of HBeAg and HBV DNA is associated with a higher risk for hepatocellular carcinoma; a recent study calculated relative risks of 60 for individuals who were HBsAg-positive and HBeAg-positive and of 8.6 for individuals who were HbsAg-positive alone.

Genotypes. There are eight genotypes (A through H), with varying geographic distribution. Genotype A is most common in the United States and Europe, whereas genotypes B and C are more common in Asia. HBeAg-negative chronic hepatitis is more commonly seen in patients infected with genotypes B, C, and D, thus explaining why this type of infection is more common in Asia. Preliminary data suggest more severe liver disease and hepatocellular carcinoma in Asians infected with genotype C. Other studies suggest that genotype A and B respond better to interferon therapy.

Markers

- HbsAg– appears first, and if it persists for more than 6 months, the patient is chronically infected.
- HbsAb– implies recovery or immunity to HBV, either naturally occurring or after vaccination.
- HBeAg– indicates active infection/replication of HBV, but absence cannot be taken as implying an absence of viral replication (i.e., precore mutant).
- Anti-Hbe– presence indicates seroconversion, but can also be found in active disease in patients with HBeAg-negative chronic hepatitis.
- HBV-DNA– detectable in serum is a measure of the level of viral replication. Several different assays with varying sensitivities and ranges are available.

Treatment

HBeAg-positive. The goal of treatment in chronic hepatitis B is the elimination or suppression of HBV replication in order to prevent the progression of liver disease to cirrhosis, liver failure, hepatocellular carcinoma, and death.

Standard interferon, lamivudine, and adefovir are all approved for first-line therapy in patients with chronic hepatitis B. Most clinical trials have defined response as loss of eAg and acquisition of eAb, loss

or reduction of HBV-DNA, and normalization of ALT. A more important end point—improvement in liver histology—has also been used in many of the available clinical trials.

Interferon given subcutaneously has been studied extensively, with a meta-analysis of 15 clinical trials showing HBsAg loss in 5–10% of European patients within 1 year of therapy and 11–25% after 5 years of follow-up. In Asians, the results are much more disappointing, reflecting the fact that many Asian patients have normal ALT despite having high HBV DNA levels. The two best predictors of a response to interferon treatment are an elevated ALT and a low level of HBV DNA. Adverse effects include flu-like symptoms, fatigue, anorexia, depression, and leukopenia.

Lamivudine therapy for 1 year will result in HBV DNA loss in 44% and HBeAg seroconversion in 16–18% of patients. After 5 years of therapy, this goes up to 50%. The majority of patients achieve normalized ALT, and histologic improvement is observed in 69% after 5 years of therapy. If therapy is stopped prior to HBeAg seroconversion, viral replication returns, and long-term therapy (> 5 years) may therefore be required in many patients. As patients are treated longer, the rate of HBeAg seroconversion increases, such that after 5 years it reaches 50%. Unfortunately, the emergence of a mutant strain, the YMDD mutant, also increases with the duration of treatment, and after 5 years, approximately 70% of patients have developed this mutation. In these patients, ALT and HBV DNA levels return to pretreatment levels, and some patients have been shown to experience reversal of histologic improvements. Lamivudine is very well tolerated and has an excellent safety profile.

Adefovir 10 mg daily for 1 year results in reduced HBV-DNA levels, improved ALT, and HBeAg seroconversion in a significant number of patients. After 72 weeks of therapy, approximately 50% of patients have undetectable HBV DNA by the most sensitive assays, 75% have a normalized ALT value, and 44% have lost HBeAg. The emergence of mutant strains is rare with adefovir, occurring in less than 5% after 4 years of treatment. This very important fact makes adefovir the drug of choice for patients requiring long-term therapy. Adefovir shows an excellent safety profile, similar to that in the placebo group.

Predictors of response. For interferon and also for the two oral drugs, the best predictors of response are a high pretreatment ALT and a low pretreatment HBV DNA level.

HBeAg-negative. In this group of patients, HBV DNA suppression and ALT normalization are the main goals. The sustained response to interferon in this group has been low, averaging 15–25%, and patients need to be treated for over 12 months to achieve the best results. Lamivudine therapy, on the other hand, can achieve a biochemical and virologic response in about two-thirds of patients treated for 12 months. Most patients relapse after therapy is stopped or if the YMDD mutation develops. Adefovir 10 mg for 1 year resulted in histological improvement in 64% of the patients treated. There was a marked reduction in serum HBV DNA levels and normalization of ALT in 72%. Again, because of the low rate of mutations when using adefovir, this drug can be continued for years and should probably be continued indefinitely in this patient group.

Cirrhotics. Cirrhosis due to chronic hepatitis B represents a unique opportunity to treat an advanced disease, with a huge potential for improvement. Before the advent of antiviral therapy, the 5-year survival in this group was 84% for compensated patients and between 25% and 35% for decompensated ones. There is no place for interferon therapy, given the number of side effects, difficulties with cytopenia, and the occurrence of bacterial infections, as well as exacerbation of hepatitis. Lamivudine and adefovir are very well tolerated by patients with more advanced disease and are both very effective in rescuing patients with liver failure and an imminent need for transplantation. The emergence of the YMDD mutation poses a serious problem, leading to rapid deterioration in some patients.

Adefovir is also very effective in this group of patients. A large compassionate-use study showed that after 48 weeks of therapy, the HBV DNA level had decreased by significant amounts in patients both before and after transplantation. In fact, this reduction was maintained up to 96 weeks and in 81% of pretransplant patients HBV DNA was reduced to less than 400 copies/mL. ALT levels normalized in 76%, and 38% of the patients were able to be removed from the transplantation list. As in other studies, no resistance to adefovir was encountered. This makes adefovir, in my opinion, the treatment of choice for this group of patients.

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Virtual Colonoscopy vs. Colonoscopy: Competing or Complementary?

John H. Bond

Virtual Colonoscopy

Virtual colonoscopy uses data obtained from rapid helical CT scanning of the abdomen to create computer-reformatted two-dimensional and three-dimensional images of the colon. These images can be rotated for different views and even combined to provide a complete three-dimensional view of the colon that then can be rapidly "flown through", thus simulating conventional optical colonoscopy. At present, a thorough purging bowel-cleansing preparation is required before the procedure. Immediately before obtaining the CT scans, a rectal tube is inserted and the colon is insufflated with room air to the maximum level tolerated by the patient. Gas distension of the bowel is essential, because interpretation is not possible when the bowel is spastic or collapsed. Scans then are obtained in both the supine and prone positions during a breath-hold in order to redistribute the air into all parts of the colon, and to help distinguish retained fluid (which shifts its location) from fixed filling defects.

Some centers now use new special software that allows an initial rapid fly-through of the reformatted three-dimensional reconstruction of the colon, with any endoluminal findings being confirmed using the corresponding two-dimensional images.

Advantages and Disadvantages of Virtual and Conventional Colonoscopy

Virtual colonoscopy has several proven and potential advantages over conventional colonoscopy. The examination time is substantially shorter and there is no need for preprocedural sedation. There are few, if any, complications. To date, no serious morbidity or mortality has been reported with virtual colonoscopy, while diagnostic conventional colonoscopy results in perforation of the colon in about 0.05% of reported cases. Lesions can be precisely located with virtual colonoscopy. Both sides of the bowel wall and bowel folds can be scrutinized during virtual colonoscopy. The radiologist can examine and reexamine segments of the colon long after a scan has been performed. Lastly, virtual colonoscopy can be used to examine the proximal colon when an obstructing left-sided cancer prevents passage of a colonoscope, or it can complete a large-bowel examination when colonoscopy is incomplete.

The current limitations of virtual colonoscopy in comparison with conventional colonoscopy include the need for very thorough bowel-cleansing preparation and for the somewhat uncomfortable preprocedural gas distension of the colon. Colonic spasm or retained fecal debris or liquid may severely interfere with the accuracy of readings. Each case may require 20–30 min of expensive reading time. In most reported studies, accuracy is poor for smaller polyps and for flat lesions that are flush with the colorectal mucosal contour. If scans need to be repeated at relatively short intervals, radiation exposure also may be a concern. Lastly, as is also the case with barium enemas, the procedure is only diagnostic. A positive scan usually has to be followed by conventional colonoscopy in a different session, with additional bowel preparation.

Clinical Studies of Virtual Colonoscopy

Studies have demonstrated a good level of sensitivity for detecting polyps ≥1 cm in diameter and for finding any polyps in patients who have synchronous polyps of this size (patient sensitivity). However, even in the best of these series, the sensitivity and specificity for detecting smaller polyps falls off rapidly. The sensitivity for detecting medium-sized polyps (6–9 mm) in these studies was in the range of 47–82%. Nevertheless, these studies generally show that virtual colonoscopy already is substantially more accurate than double-contrast barium enema, that it compares favorably with conventional colonoscopy for the detection of larger polyps, and that it therefore may be an effective screening test for colorectal neoplasia.

A recent large study by Pickhardt et al. including 1233 asymptomatic adults may represent an important breakthrough in the development of virtual colonoscopy, and the results appear to predict a positive future for this new modality. In this large comparison of virtual and conventional colonoscopy, the patients underwent a standard 24-h colonic preparation and then also consumed 500 mL of barium for solid-stool tagging and 120 mL

of diatrizoate solution for opacification of retained luminal fluid. This preparation allowed the computer program to differentiate between retained stool and polypoid defects and allowed electronic fluid cleansing. Colonoscopy was complete to the cecum in 99.4% of the participants, as assessed by endoscopists blinded to the results of the virtual examination.

Remarkably, the sensitivity of virtual colonoscopy in this study was 93.8% for adenomatous polyps at least 1 cm in diameter, 93.9% for polyps at least 8 mm in diameter, and 88.7% for polyps at least 6 mm in diameter. The sensitivity of optical colonoscopy for polyps of these sizes was 87.5%, 91.5%, and 92.3%, respectively. Of two malignant polyps detected by virtual colonoscopy, one was missed by conventional colonoscopy. Virtual colonoscopy specificity for these three sizes of polyps also was high (96%, 92.2%, and 79.6%, respectively). The negative predictive value for polyps with a diameter of at least 8 mm was more than 99%. The authors concluded that CT virtual colonoscopy, using the more advanced methodology employed in this study, is as accurate as conventional colonoscopy for detecting clinically important colorectal polyps (≥ 6 mm) in asymptomatic, average-risk adults.

Unresolved Issues

Most gastroenterologists now agree that missing diminutive polyps (≤ 5 mm) has very little clinical importance. Currently, however, the controversial area has to do with adenomas of intermediate size (6–9 mm). Although such polyps pose a low immediate cancer risk, most clinicians and many patients may not be willing to have such lesions regularly missed unless they know that repeat screening will be carried out within 3–5 years. Increasing the frequency of screening virtual colonoscopy, of course, greatly increases the cost of this procedure as a screening option, and may not allow it to compete with the option of carrying out direct colonoscopy screening every 10 years, as is now recommended by the guidelines. Frequent CT scanning also raises concerns about cumulative radiation exposure.

Like conventional colonoscopy, virtual colonoscopy is expensive. However, if the indication for an examination is screening, additional colonoscopies will be needed in at least 10–20% of patients to assess findings or resect polyps. In these cases, a more cost-effective approach may be just to do an initial colonoscopy that is both diagnostic and therapeutic in a single sitting, with a single bowel preparation. Expected advances in automated reading of virtual colonoscopy scans performed with super-rapid CT scanners, together with other economies of scale and efficiency, may bring the cost down to a level that would allow it to compete with the other established screening options.

In studies of back-to-back comparisons of virtual and conventional colonoscopy, there

Update on the Testing and Treatment of Fecal Incontinence

Satish S.C. Rao

Introduction

Fecal incontinence is defined as the recurrent uncontrolled passage of fecal material for a period of at least 1 month. The prevalence estimates vary from 2.2% to 18.4%. Clinically, there are three subtypes:

- Passive incontinence—the involuntary discharge of stool or gas without awareness.
- Urge incontinence—the discharge of fecal matter in spite of active attempts to retain bowel contents.
- Fecal seepage—the leakage of a small amount of stool without awareness, or staining of undergarments following an otherwise normal evacuation.

The ability to maintain continence requires structural and functional integrity of the anal sphincters, pelvic floor musculature, pudendal nerve function, rectal compliance, and rectal sensation. When one or more of these mechanisms of continence are disrupted to an extent that others are unable to compensate, incontinence ensues.

Diagnosis

The first step in the evaluation of fecal incontinence is to establish a rapport with the patient. Thereafter, an assessment of the timing and duration of the incontinence, its nature (i.e., incontinence of flatus, liquid, or solid stool), and its impact on the quality of life is important. The use of pads or other devices and the ability to distinguish between formed or unformed stool and gas should be documented. A detailed inquiry of

have been at least six surveys of patient preferences. In three of these, patients preferred virtual colonoscopy and in three they preferred conventional colonoscopy. However, when later asked which test they would want for repeat screening, virtual colonoscopy was selected as a preference in five of the six surveys. The preference for virtual colonoscopy would probably increase further if better-tolerated methods of bowel cleansing and gas distension were developed. If current efforts to find a way to do virtual colonoscopy without the need for a cathartic preparation—by tagging stool with oral contrast, so that the computer can accurately differentiate between retained luminal contents and abnormal tissue ("virtual preparation")—are successful, virtual colonoscopy would probably become the preferred screening option for many more people.

Summary and Conclusions

Virtual colonoscopy screening appears to have a promising future and should help improve overall screening compliance and have a favorable impact on colorectal cancer control. In my opinion, endoscopists need not worry that the more widespread use of virtual colonoscopy will negatively affect their practices. On the contrary, virtual colonoscopy, by identifying more of those who harbor clinically significant polyps, is likely to increase the demand for colonoscopy and polypectomy.

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any obstetric history and coexisting problems and a prospective stool diary may be helpful.

A digital rectal examination should assess the resting sphincter tone, length of the anal canal, the integrity of the puborectalis sling, the acuteness of the anorectal angle, and the strength of the anal muscle and elevation of the perineum during voluntary squeeze. The sensitivity, specificity, and positive predictive value of a digital rectal examination as an objective test for evaluating anal sphincter function are very low.

Testing for Fecal Incontinence

Several specific tests are available for defining the underlying mechanisms of fecal incontinence. The selection of diagnostic tests will depend on probable etiologic factors, symptom severity, impact on quality of life, and the patient's age. These tests are often complementary. A flexible sigmoidoscopy or colonoscopy is usually desirable in most patients to exclude mucosal disease or colon cancer. However, in patients with long-standing fecal incontinence without diarrhea, these tests may not be necessary.

Anorectal manometry. Anorectal manometry provides an objective assessment of anal sphincter pressures and rectoanal reflexes. Currently, several types of probe and pressure-recording devices are available to measure anorectal pressures. Each system has distinct advantages and drawbacks. Typically, a manometry probe, with multiple pressure sensors and a balloon, is placed in the rectum and anal canal and the resting and squeeze sphincter pressures are assessed.

Anorectal manometry is also useful in evaluating the responses to biofeedback training, as well as assessing objective improvement following drug therapy or surgery. The American and European motility societies have initiated a collaborative effort to develop standards for manometry testing, and a consensus document was recently published.

Sensory testing. Rectal sensation and compliance are commonly measured by incremental balloon distension. Often, three types of threshold for rectal sensation can be detected: 1) first detectable sensation; 2) urge to defecate; and 3) maximum tolerable volume. In patients with fecal incontinence, both hypersensitivity and hyposensitivity can be seen. In some patients, rectal sensory thresholds may be altered because of changes in the compliance of the rectal wall, and alterations in sensory data should therefore be interpreted along with measurement of rectal compliance.

Imaging the Anal Canal

Anal endosonography. Anal endosonography is performed using either a 7-MHz rotating transducer or a 10–15 MHz transducer. It provides an assessment of the thickness and structural integrity of the external and internal anal sphincter muscle and can detect the presence of scarring, thinning of sphincter, loss of muscle tissue, and other local pathology. Although endosonography can distinguish between internal and external

sphincter injury, the finding of a sphincter defect does not necessarily mean that it is the cause of fecal incontinence. Anal endosonography is a simple and inexpensive method of imaging the anal sphincters and is currently the preferred technique for examining the morphology of the anal sphincter.

Defecography. In this radiographic test, approximately 150 mL of contrast material is placed in the rectum and the patient is asked to squeeze, cough, or expel the contrast. The test is used to assess several parameters, such as the anorectal angle, pelvic floor descent, length of the anal canal, presence of rectocele, rectal prolapse, or mucosal intussusception. There is poor agreement between observers when measuring the anorectal angle. Many investigators have also questioned the rationale for performing defecography in patients with incontinence, as it adds very little additional information to that obtained from manometry.

Magnetic resonance imaging (MRI). MRI is the only imaging modality that can visualize the anal sphincters and the global pelvic floor motion in real time without radiation exposure. Endoanal MRI has been shown to provide superior imaging, with better spatial resolution in the external anal sphincter. The addition of dynamic pelvic MRI, using fast imaging sequences, or MRI colpocystography, which involves filling the rectum with ultrasound gel as a contact agent and having the patient evacuate this while lying inside the magnet, may allow more precise definition of the anorectal structures. With the availability of open-magnet units, dynamic MR imaging can be performed in a more physiological position, with the patient sitting up. MRI and endosonography have been compared for the evaluation of anal sphincters. The internal anal sphincter is seen more clearly on anal endosonography, whereas the external sphincter is seen more clearly on MRI.

Pudendal nerve terminal latency (PNTL). The pudendal nerve terminal motor latency measures the functional integrity of the terminal portion of pudendal nerve. Measurement of the nerve latency can help to distinguish whether a weak sphincter muscle is due to muscle or nerve injury. A prolonged nerve latency time suggests pudendal neuropathy. A normal PNTL does not exclude pudendal neuropathy. The American Gastroenterology Association technical review did not recommend PNTL for the evaluation of patients with fecal incontinence, because it correlated poorly with clinical symptoms and histology findings, it did not discriminate muscle weakness caused by nerve or muscle injury, it had poor sensitivity and specificity, was operator-dependent, and did not predict the surgical outcome. However, two recent reviews of eight uncontrolled studies suggest that patients with pudendal neuropathy generally have a poor surgical outcome in comparison with those without neuropathy.

Clinical utility of tests for fecal incontinence. Few studies have evaluated the utility of anorectal physiologic tests in fecal incontinence. In the study by Wexner and Jorge, history and physical examination alone could detect an underlying cause in only nine of 80 patients (11%) with fecal incontinence, whereas anorectal physiological tests revealed an abnormality in 66% of patients. In another prospective study, anorectal manometry with sensory testing confirmed the clinical impression of fecal incontinence, and the management was altered by it in 76% of patients. A recent prospective study showed that a clinical diagnosis was confirmed in 51% of the patients and a new diagnosis was established in the remaining patients by combining anorectal physiological testing with imaging.

Treatment of Fecal Incontinence

The goal of treatment for patients with fecal incontinence is to restore continence and to improve the quality of life. Several strategies that include supportive and specific measures may be useful.

Supportive measures. The underlying predisposing condition or conditions, such as fecal impaction, dementia, neurological problems, inflammatory bowel disease, or dietary factors (carbohydrate intolerance) should be treated. Other supportive measures can include dietary modifications such as reducing caffeine or fiber intake.

Specific treatment. Specific treatment of fecal incontinence may be considered under the following categories: pharmacologic therapy; biofeedback therapy; plugs, sphincter bulkers, and ancillary therapy; and surgery.

Pharmacologic therapy. Several drugs, each with a different mechanism of action, have been proposed to improve fecal incontinence. Antidiarrheal drugs such as loperamide hydrochloride or diphenoxylate/atropine sulphate are commonly used. A placebo-controlled study showed that loperamide 4 mg t.i.d. reduced the stool frequency and urgency, increased colonic transit time, reduced stool weight, and increased anal resting sphincter pressure. Clinical improvement was also reported with diphenoxylate/atropine (Lomotil), but objective improvement was lacking. Topical phenylephrine, an alpha1-adrenergic agonist applied to the anal canal,

increased the anal resting pressure by 33% in healthy controls and in incontinent patients. However, phenylephrine did not improve incontinence scores or resting anal sphincter pressure in a randomized placebo-controlled cross-over study.

Biofeedback therapy. Behavioral therapy using "operant conditioning" techniques has been shown to improve bowel function and incontinence. The goals of biofeedback therapy in a patient with fecal incontinence are: 1) to improve the strength of the anal sphincter muscles; 2) to improve the coordination between the abdominal, gluteal, and anal sphincter muscles during voluntary squeeze and following rectal perception; and 3) to enhance the anorectal sensory perception. Biofeedback training is often carried out using visual, auditory, or verbal feedback techniques. The instrument used to provide feedback can either be a manometry probe or an electromyography electrode that is inserted into the anorectum. In the literature, the terms "improvement", "success", and "cure" have been used interchangeably, and the definitions of the terms used have been inconsistent. In uncontrolled studies, subjective improvement has been reported in 40–85% of patients. A recent randomized controlled trial compared biofeedback with conservative standard care or standard care with Kegel exercises. Both the biofeedback treatment and specialist nurse including advice on diet, fluids, technique for improving evacuation, and bowel training produced a 50% or more improvement in patients with fecal incontinence, and there was no difference between the treatments. In another recent prospective long-term study of 94 patients, subjective and objective parameters of anorectal function improved, with 60% of the patients reporting no episodes of incontinence.

Surgery. Surgical treatment for fecal incontinence should be considered in patients who do not respond to medical treatment or have a well-documented sphincter defect. In 80% of patients with obstetric damage, anterior overlap repair of the external anal sphincter resolves the symptoms. In patients with incontinence due to a weak but intact anal sphincter, postanal repair has been tried. The success of sphincter repair appears to wear off over time, and less than one-third of the patients are continent to liquid or solid feces after 5 years.

Sacral nerve stimulation. This new therapeutic approach is less invasive and has the advantage that a temporary procedure can be carried out before the final operation to make a reliable estimate of its outcome. This technique is well established in the treatment of urinary incontinence. Temporary electrodes are placed percutaneously through the sacral foramina. If the test period of 2–3 weeks shows satisfactory continence, the permanent electrode is placed and a neurostimulator is implanted. In one study that assessed the short-term effects, continence was restored in eight of nine patients. Another study analyzed the medium-term results of permanent sacral nerve stimulation in 15 patients and reported improvement in continence in all patients up to 5 years.

Other procedures. The Malone or antegrade continent enema procedure consists of fashioning a cecostomy button or appendicostomy, which allows antegrade wash-out of the colon and may be suitable for children and patients with neurological lesions. In the longer term, fibrosis of the stoma site may lead to a loss of response, but an overall success rate of 61% has been reported at a mean follow-up of 3.25 years. If none of these techniques are suitable, or if they fail, a colostomy is a safe option, although aesthetically less preferable.

Conclusion

Fecal incontinence is primarily a subjective symptom, with a complex etiology and pathogenesis. A detailed history and examination, including digital rectal examination, will help diagnose and exclude common disorders causing it. All patients should be offered conservative management, and if this fails, further investigations should be undertaken. Anorectal physiological tests help evaluate functional abnormalities, and anal endosonography is helpful for assessing anatomical sphincter defects. The results of these tests may guide further management of fecal incontinence. However, abnormal findings with these procedures do not predict the severity of incontinence or the response to treatment. Behavioral therapy is successful in most patients. Surgical treatment of fecal incontinence improves the symptoms but does not cure them, and the outcome deteriorates with time. Several experimental approaches, including bulking of the anal sphincter, sacral nerve stimulation, and the delivery of radiofrequency energy to the anal canal are currently being investigated.

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The full length version of this text, including references, is available online: www.worldgastroenterology.org

Guo-Qing Wang and You-Lin Qiao at the Cancer Institute of the Chinese Academy of Medical Sciences field station in Linxian.

Esophageal Cancer in North Central China

You-Lin Qiao, Guo-Qing Wang, Sanford M. Dawsey

Background

High rates of esophageal cancer, locally known as "hard swallowing disease" (噎嗝病, yē gé bìng) have been recognized in the Taihang mountain region of north central China since the time of the Han Dynasty (206 BC–220 AD) (Fig. 1). In this area, esophageal cancer has always been defined by its clinical course—difficulty in swallowing, followed by wasting and death—and has included both squamous-cell carcinoma of the esophagus and adenocarcinoma of the gastric cardia. In this population, reflux symptoms are uncommon, Barrett's esophagus has not yet been documented, and adenocarcinoma of the esophagus is extremely rare.

Starting in 1959, scientists from Fu-Wai Hospital of the Chinese Academy of Medical Sciences in Beijing and from the medical colleges of Henan, Hebei, Shanxi, and Shandong provinces began a series of studies in the Taihang mountain region to try to uncover the etiology and reduce the morbidity and mortality from this geographically localized disease.

Cancer Registration

One of the first scientific efforts, in 1959, was the establishment of a cancer registry in Linxian, a county in northern Henan that was known to have especially high rates of esophageal cancer. In Linxian, the age-adjusted mortality rates were 161 per 10^5 for men and 103 per 10^5 for women, the highest rates in China. The data from this national survey illustrated the wide variation in esophageal cancer rates across China and increased interest in epidemiologic studies of this disease (Fig. 2).

Etiological Studies

For centuries, the economy of Linxian and the surrounding areas has been based on subsistence farming. Early studies documented a monotonous diet of corn, wheat, and tea, with few fruits and vegetables and little meat, which led to deficiencies or near-deficiencies of many vitamins and minerals. Early studies also implicated *N*-nitroso compounds as possible etiological agents. Ecological studies conducted in the 1970s by Dr. S.X. Lu and Dr. M.X. Li of the Cancer Institute of the Chinese Academy of Medical Sciences (CICAMS) found much higher levels of nitrosamines and their precursors (nitrates, nitrites, and amines) in food, drinking water, saliva, gastric juice, and urine in high-risk areas than in low-risk areas.

By 1980, the leading etiological hypotheses were dietary deficiencies of vitamins and minerals and dietary exposure to potential

Fig. 1*. Map of China, showing the Taihang mountain region.*

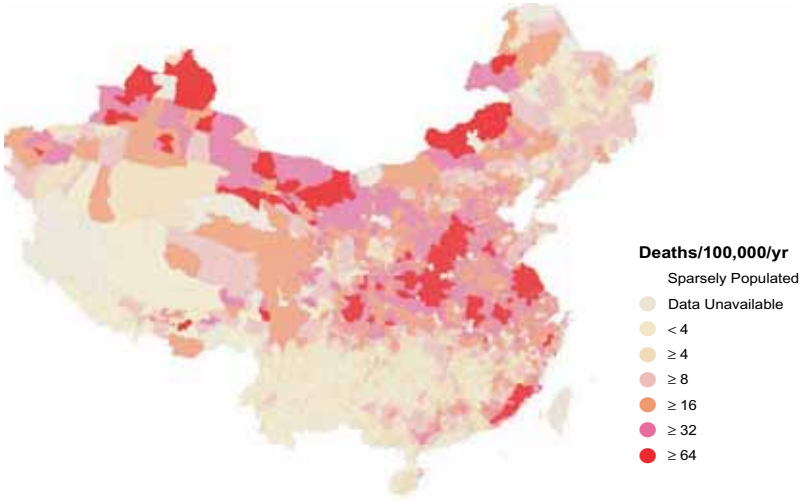

***Fig. 2**. Esophageal cancer: age-adjusted mortality for males by county in China (1973–1975).*

carcinogens (nitrosamines and fungal toxins) found in pickled vegetables and moldy food. To test the hypothesis that supplementation with vitamins and minerals would reduce the mortality from esophageal and other cancers in this population, scientists from CICAMS and the U.S. National Cancer Institute (NCI) designed and carried out two randomized, placebo-controlled nutrition intervention trials in Linxian (Fig. 3). The dysplasia trial enrolled 3318 individuals with cytological evidence of dysplasia who received either supplementation with 26 vitamins and minerals or a placebo for 6 years, while the general population trial enrolled 29 584 persons who received supplementation in a factorial design with either one or more of four vitamin/mineral combinations or a placebo for a period of 5 years and 3 months. The results showed that a combination of selenium, vitamin E, and β-carotene significantly reduced all-cause mortality (9%), total cancer mortality (13%), the incidence of gastric cancer (16%), and the mortality rate (21%) in the larger trial drawn from the general population.

Since the end of the intervention study in 1991, all living participants in these trials have been followed up as cohorts, and prospective etiological studies have been conducted to compare baseline characteristics with the later development of cancer. These nested case–control, case–cohort, and cohort studies have found that:

- Baseline serum selenium levels were inversely associated with the incidence of esophageal squamous-cell carcinoma and gastric cardia adenocarcinoma (GCA).
- Baseline serum vitamin E (α-tocopherol) levels were inversely associated with the incidence of esophageal squamous-cell carcinoma.
- Baseline serum retinol, β-carotene, β-cryptoxanthin, and lutein/zeaxanthin levels were not associated with a significant change in the esophageal or gastric cancer risk.
- Zinc concentrations in esophageal biopsies from the dysplasia trial were inversely associated with the incidence of esophageal squamous-cell carcinoma (a significant 79% risk reduction for persons in the highest vs. lowest quartiles for tissue zinc values).
- Baseline tooth loss (greater than the age-specific median number of teeth lost) was significantly associated with increased mortality from all causes (13%), upper gastrointestinal cancer (35%), heart disease (28%), and stroke (12%), and these associations were not limited to tobacco smokers. The association with upper gastrointestinal cancer may be related to alterations in oral bacterial flora and a subsequent increase in endogenous production of carcinogenic nitrosamines.
- Baseline levels of serum sphingolipids, which are potential but not proven biomarkers of fumonisin fungal toxin exposure, were not associated with the risk of esophageal squamous-cell carcinoma.
- Baseline seropositivity for *Helicobacter pylori* was significantly associated with similar increased risks for cardia and noncardia gastric adenocarcinoma.
- Polymorphic variants of the interleukin-8 gene were associated with a twofold to fourfold increased risk of gastric cardia adenocarcinoma, but no increased risk of esophageal squamous-cell carcinoma.
- Food and urine measurements have documented high levels of exposure to polycyclic aromatic hydrocarbons in this population, probably due to the use of soft coal in unvented stoves for heating and cooking.

Esophageal Balloon Cytology Studies

Most patients with esophageal cancer come to medical attention with incurable late-stage disease. One of the first and most innovative efforts to reduce the mortality due to esophageal cancer in Linx-

ian was the development and use of esophageal balloon cytology (EBC; 拉网, lā wǎng) to identify individuals with precursor lesions or early, curable cancers .

In the EBC technique, the patient swallows a deflated balloon covered with an abrasive cloth or plastic mesh. When the balloon reaches the stomach, it is inflated and brought back up the esophagus, collecting exfoliated and scraped surface cells. At the upper esophageal sphincter, the balloon is deflated and removed, and the cells are smeared onto slides and processed and read like cervical Pap smears.

The first balloon samplers were designed and used by Dr. Qiong Shen of Henan Medical University in the 1960s. During the following three decades, nearly 300 000 adults were screened by EBC in Linxian and the surrounding counties, and 1500 early cancers were diagnosed and treated with esophagectomy. In a recent study of 432 asymptomatic Linxian adults who were examined with both EBC and endoscopy with mucosal iodine staining, EBC had a sensitivity of 47% and a specificity of 81% for identifying biopsy-proven squamous dysplasia or early esophageal squamous-cell cancer (ESCC). This limited ability to detect the individuals who are the targets of screening has reduced the appeal of traditional EBC as a screening test.

Endoscopic Studies

Rigid endoscopy was introduced to Linxian in 1965 by Dr. G.Q. Wang and was replaced by flexible fiber-optic endoscopes in 1972 and by video endoscopes in 1989.

In 1980–81, in a collaborative effort between Dr. M. Crespi and Dr. N. Muñoz from the International Agency for Research on Cancer (IARC) and endoscopists from CICAMS, endoscopic surveys were carried out in high-risk (Linxian) and low-risk (Jiaoxian) Chinese populations; higher prevalences of histological esophagitis, atrophy, and dysplasia were found in the high-risk group. These findings led the investigators to propose that these conditions are precursors of esophageal cancer, which develops via the following steps: chronic esophagitis → atrophy → dysplasia → cancer. In 1983, Dr. G.R. Yang and Dr. S.L. Qiu of Henan Medical University carried out similar endoscopic surveys in nearby high-risk (Huixian) and low-risk (Fanxian) counties. They found equivalent prevalences of esophagitis and atrophy in these populations, but higher prevalences of basal-cell hyperplasia and dysplasia in the high-risk group, leading them to believe that dysplasia is the key precursor of this cancer.

More recently, scientists from CICAMS and NCI have collaborated with several American gastroenterologists, including Dr. David E. Fleischer, Dr. Wilfred M. Weinstein and Dr. Paul J. Limburg, to conduct additional studies on the identification, localization, focal therapy, and chemoprevention of precursor lesions of esophageal squamous-cell cancer:

- A 13-year follow-up of 682 patients who had undergone endoscopy showed that squamous dysplasia was the only histological lesion significantly associated with the development of esophageal squamous-cell carcinoma (Table 1). Increasing grades of dysplasia were associated with dramatically increasing levels of risk.
- A cross-sectional study of 225 patients who had undergone endoscopy showed that iodine staining significantly improved the detection and delineation of moderate and severe squamous dysplasia and early invasive esophageal squamous-cell carcinoma (Fig. 4). The sensitivity/specificity rates for visually identifying these lesions were 62%/79% before staining and 96%/63% after staining, and 88% of the lesions were larger or more clearly defined after staining.
- Since 1995, we have carried out 323 focal therapy procedures in 234 Linxian patients with

***Fig. 3**. The Cancer Institute of the Chinese Academy of Medical Sciences (CICAMS) research field station in Linxian.*

***Table 1**. Incidence and relative risk of esophageal squamous-cell carcinoma during 1987–2001, relative to the initial histological diagnosis.*

1987 diagnosis	Patients (*n*)	ESCC cases (*n*)	Cumulative incidence of ESCC	RR (95% CI) of ESCC incidence
Normal	375	31	8.3%	1.0 (reference)
Acanthosis	77	6	7.8%	0.9 (0.4–2.2)
Esophagitis	33	2	6.1%	0.8 (0.2–3.2)
Basal-cell hyperplasia	40	6	15.0%	1.9 (0.8–4.5)
Mild dysplasia	76	18	23.7%	2.9 (1.6–5.2)
Moderate dysplasia	30	15	50.0%	9.8 (5.3–18.3)
Severe dysplasia	39	29	74.4%	30.8 (15.3–52.3)
Dysplasia NOS	12	7	58.3%	12.7 (5.5–29.6)
Total	682	114	16.7%	

ESCC, esophageal squamous-cell carcinoma; NOS, not otherwise specified; RR, relative risk.

moderate or severe dysplasia or early esophageal squamous-cell carcinoma, using excisional and ablative methods. Outcome analysis is ongoing, but it is clear that these procedures are feasible, safe, acceptable to patients, and usually curative in this population.

- We recently completed a randomized, placebo-controlled chemoprevention trial in Linxian among patients with mild or moderate squamous dysplasia who were randomly assigned to treatment with selenomethionine (200 µg per day) and/or celecoxib (200 mg twice per day) or a placebo in a 2 × 2 factorial design. Patients underwent endoscopy before and after 10 months of treatment, and 238 completed the trial. Patients who took selenomethionine experienced approximately one-third more regression and one-quarter less progression than those who did not take this agent, and among patients who began the trial with mild dysplasia, these beneficial effects were nearly doubled. Celecoxib treatment did not change the dysplasia grade. These findings may be most relevant to populations with low selenium levels such as that in Linxian.

Ongoing Research

Ongoing projects to further understand the causes and reduce the impact of esophageal cancer in the Taihang mountain region include: additional etiologic studies of nitrosamines and polycyclic aromatic hydrocarbons; new efforts to improve primary screening for precursor lesions of esophageal squamous-cell carcinomas and early cancers (developing better esophageal cell samplers and looking for molecular markers that can improve or replace conventional cytology); a study to evaluate the feasibility and effect of endoscopic screening and therapy of early lesions in larger population groups; and consideration of a study of selenium fortification of staple foods.

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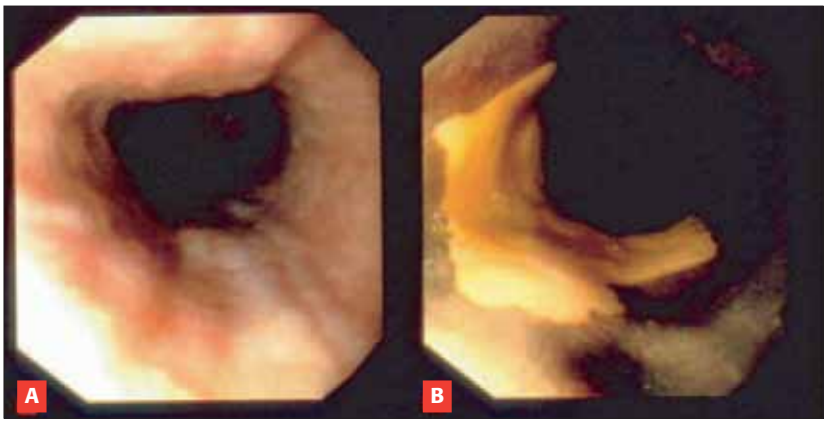

***Fig. 4**. Mucosal iodine staining. (A) Before staining. (B) After staining. The histopathological findings in this case showed severe dysplasia.*

WGO-OMGE and OMED Endorse Advanced Endoscopic Training Center in Latin America

Richard A. Kozarek, James A. DiSario, Roque Sáenz

The first WGO-OMGE/OMED Advanced Endoscopy Training Center was formally endorsed and inaugurated at Clinica Alemana in Santiago, Chile, on 23 July 2004. The Center, supported by Olympus, Wilson-Cook, and Boston Scientific, has been offering hands-on training in advanced endoscopic techniques with the academic support of the University of Chile and the Universidad del Desarrollo since 1997. Under the leadership of Claudio Navarrete, Chair, and Roque Sáenz, Vice-Chair, over 200 practicing gastroenterologists and surgeons have spent periods of 3–12 months learning advanced therapeutic techniques in endoscopy, colonoscopy, endoscopic ultrasonography, and ERCP. Trainees are charged no fee, and housing is provided at no cost, courtesy of Wilson-Cook.

The trainees are primarily from countries in South and Central America, but the Center has also trained individuals from France, Australia, the United States, Thailand, and Saudi Arabia. Private patients partly support the Training Center economically, although over two-thirds of the patients are transported from one of approximately 50 public hospitals in the greater Santiago area or from nearby cities and undergo their procedures at no charge. Attending gastroenterologists, surgeons, pediatricians, and anesthesiologists donate up to one day a week to teach at the Training Center, which also has an extensive video library and computerized phantom simulator. Virtually all of the equipment used at the Center has been donated. The benefit to industry is the testing and of new devices and promotion of them to the trainees.

The Center's inauguration as an WGO-OMGE/OMED Training Center also included a one-day course on therapeutic endoscopy, held on the same day. Dr. Richard Kozarek and Dr. James D. DiSario participated in this course, representing WGO-OMGE and OMED, respectively, along with Dr. Navarette and Dr. Sáenz and other members of the Training Center faculty. Attracting approximately 150 gastroenterologists, the course was also transmitted by satellite to Clinica Alemana in Temuco, 800 km south of Santiago. Covering endotherapy for sclerosing cholangitis, the endoscopic approach to Barrett's, gastrointestinal bleeding and pancreatic cancer, as well as the future of therapeutic endoscopy, the course also outlined the rationale and history of this relatively unique training center. There was also a presentation regarding WGO-OMGE/OMED cooperation in Latin America and on the other training centers supported by WGO-OMGE/OMED in Soweto, South Africa; Cairo, Egypt; Rabat, Morocco; Karachi, Pakistan; and plans for an upcoming center in Bangkok, Thailand.

In addition to reserving three trainee positions yearly for physicians recommended by WGO-OMGE/OMED, the Santiago Center will participate in electronic learning by making complex cases available on the WGO-OMGE web site, and will participate in a future satellite "Train the Trainers" course to be held at the Pan-American Congress of Gastroenterology in Viña del Mar in 2008. In addition, the Fourth Biannual Live Endoscopy Course will be held in May 2005 with the International Endoscopy Team: Drs. J. Ponsky, M. Giovanini and H. Neuhaus.

This affiliation between WGO-OMGE/OMED and Clinica Alemana de Santiago ensures that the Latin American Advanced Endoscopy Training Center receives well-deserved recognition as one of the premier endoscopic training units. WGO-OMGE/OMED applicants require a letter of support by their national organization and should send résumés and letters of support to the address below.

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(Top to bottom) Dr. C. Navarrete, Chair (left) and Dr. Roque Sáenz, Vice Chair (right); Dr. C. Navarrete (left), Dr. R. Kozarek (center) and Dr. J. DiSario (right); Trainees and Guests at the Opening of the Center.

Outreach Program: One Year Old and Thriving

James DiSario

The OMED/WGO-OMGE Outreach Program was designed to allow endoscopic equipment to be donated to areas of need and to provide on-site education and training to the recipients, on the basis of submitted proposals. The Olympus Corporation donated the endoscopic equipment and supplies to OMED, and they were directed to the Eva Perón Teaching Hospital in Rosario, the province of Santa Fe, Argentina, and formally presented to the hospital in a public ceremony on 26 September 2004.

Dr. DiSario, Dr. Sáenz (Santiago, Chile) and Dr. Murature (the local proposer) provided the hospital's medical staff, regional physicians and surgeons, and trainees with an on-site educational program, including didactic and practical training. This was the first educational program of this type organized at the hospital in many years (see the report in WGN volume 9, issue 1, 2004).

Since that time, Dr. Murature has been providing us with quarterly reports on the use of the endoscopic facilities. A total of 745 procedures have been carried out, representing an increase of more than 80% over the previous year. Thirty-three percent of the procedures were therapeutic, some of which included treatment for variceal and nonvariceal upper gastrointestinal bleeding, gastric and colonic polypectomy, gastrostomy placement, and biliary sphincterotomy, stone extraction, stricture dilation, stenting, and pseudocyst drainage. This was in contrast to the preceding year, in which no endoscopic treatment procedures were performed. The proportions of colonic examinations shifted from 74% sigmoidoscopy and 26% colonoscopy in the year before to 16% sigmoidoscopy and 84% colonoscopy after donation of the equipment. In addition, the cecal intubation rate increased from 50% to over 90% due to the new equipment and training.

In March 2004, Dr. Sáenz inspected the facility, reviewed its operations, and rated the site as excellent in a report to OMED/WGO-OMGE. Other activities have included the introduction of a computerized program for endoscopy reports, purchase of additional monitoring equipment, and acquisition of a digital editing program for endoscopic videos for training purposes. Scientific publications are forthcoming, and there are plans to hold the first endoscopic workshop at the Eva Perón Hospital. The goals of the Outreach Program at the Eva Perón Teaching Hospital in Argentina have been achieved and sustained over the whole year.

The Combined Education and Training Committee is now finalizing arrangements for a donation site in sub-Saharan Africa and looking to establish a new site in south-east Asia, which encompasses the recent tsunami-ravaged areas. A request for proposals for a south-east Asian site will be posted in the near future when the transportation and communications infrastructure has been restored in the disaster areas.

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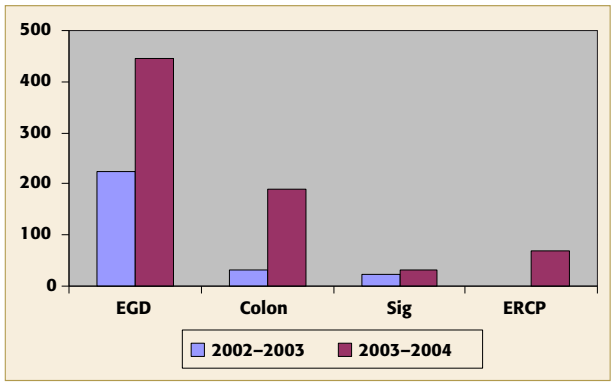

***Fig. 1**. Endoscopic procedures at the Eva Perón Teaching Hospital in Rosario, in the province of Santa Fe, Argentina, from the fourth quarter of 2002 through the third quarter of 2003, in comparison with the fourth quarter of 2003 through the third quarter of 2004. EGD, esophagogastroduodenoscopy; Sig, sigmoidoscopy, ERCP, endoscopic retrograde cholangiopancreatography.*

(Left to right): Dr. D Murature and Staff, Delegates at Medical Congress March 2004, Drs DiSario and Murature at the Eva Peron Teaching Hospital.

IDCA
The International Digestive Cancer Alliance

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

Primary Prevention of Digestive Cancer

René Lambert

Primary and Secondary Prevention

Cancer in the esophagus, stomach, colon, liver, and pancreas caused 2.2 million deaths in the year 2000. Environmental causes of cancer include radiation, chemical agents, infectious agents, and nutritional factors; digestive cancer has a strong nutritional component involving many different aspects of the diet are concerned. The progression of carcinogenesis is described has involving four steps: *initiation* (first mutation); *promotion* (premalignancy); *progression* (confirmed malignancy); and *evolution*, with metastases. The aim in primary prevention is to reduce the incidence of cancer by intervening during the initiation phase, but also in the promotion or even progression phases. Secondary prevention aims to detect disease at a curable stage through screening, and only improves the survival period. In theory, primary prevention should have a greater impact than secondary prevention.

Focusing on Gastrointestinal Cancer

The mucosa of the gastrointestinal tract is exposed to mutagens. In the digestive-tract lumen (external compartment), carcinogens may contaminate nutrients (fruit, vegetables, meat, and fish) before preparation, during cooking, or on contact with the intestinal flora. Dietary excess may result in hyperglycemia, hyperinsulinemia, insulin resistance, and synthesis of IGF-1 by the liver—representing proliferative stimuli for the receptors of epithelial cells.

The mucosa in the digestive tract is affected by micronutrients in preserved foods (salt, nitrites) and phosphates, which increase permeability to endoluminal mutagens. Protective elements include calcium, which decreases the permeability of the mucosa, and antioxidants (vitamin C, carotenoids), minerals (selenium) and anticarcinogens in plants (phytoestrogens, flavonoids, polyphenols in tea). There is still debate on whether the protection afforded by dietary fibers is quantitative or related to specific components. Dietary fibers alter the fermentation process in the large bowel (resulting in production of short-chain fatty acids such as butyrate, an apoptosis inhibitor), and increase fecal bulk (thereby physically diluting the presence of carcinogens in the large bowel).

Information Sources

The primary source is found in *ecological studies* comparing the risk of cancer and environmental factors in different countries. One strength of ecologic studies is that they avoid individual dietary measurements. A limitation is potential confounding factors (countries that differ in dietary patterns also differ in many other lifestyle and even biological factors). *Human metabolic studies* on diet may be conducted in volunteers living in metabolic suites (e.g., the Dunn Human Nutrition Unit in the United Kingdom), where all food and drinks are provided. Biomarkers may be useful in validating the assessment tools: 24-h collection of urine samples (*recovery biomarker*) measures the urinary loss of N and is a good proxy for dietary protein intake. *Animal studies* test carcinogen compounds and prove that nutritional changes can modulate carcinogenesis, even for genetically determined neoplasms.

Observational Studies

In *case-control studies*, the causal factor is compared in cases (patients with cancer) and controls (individuals with no cancer). A limitation of such studies is recall bias (especially for dietary factors) and selection bias. Prospective *cohort studies* may be conducted to study infectious (*Helicobacter pylori*) or dietary factors. Most cohort studies assess dietary intake with a food frequency questionnaire. The role of diet in cancer has been analyzed within several cohorts around the world. Of note are the 88 764

females in the Nurse Health study and 47 325 males in the Health Professionals study in the USA; and the European Prospective Investigation of Cancer (EPIC) cohort (n = 523 000, both sexes). Disparities in diet between northern and southern European countries are a major advantage with the EPIC cohort.

Interventional Studies

Chemoprevention aims to prevent or reverse carcinogenesis with micronutrients or pharmaceutical agents. A strength of intervention studies (randomized controlled trials) is that randomization avoids confounding factors. A limitation of some interventional studies (for example, polyp trials) is the use of surrogate end points rather than cancer itself. The prolonged administration of aspirin, nonsteroidal anti-inflammatory drugs or cyclo-oxygenase-2 (COX-2) inhibitors decreases the occurrence or growth of colonic polyps, but it has not yet been proved that these agents can prevent colorectal cancer.

Causal Factors in Digestive Cancer

Alcohol and tobacco. Worldwide, 30% of incident cancers are attributed to cigarette smoking or smokeless tobacco (snuff and chewing tobacco). Carcinogens in tobacco vary with the product. In spite of being a source of calories, alcohol is a potential carcinogen, often associated with tobacco. Cigarette smoking and alcohol consumption cause 90% of cases of esophageal squamous-cell cancer. Smoking is a risk for esophageal and pancreatic cancer. Alcohol is a risk for hepatocellular carcinoma in Western countries.

Dietary factors. Assessment of exposure to dietary factors is less precise than assessment of tobacco consumption; nevertheless, dietary change can be a major tool in primary prevention. Nutrients for which there is some evidence of protection against cancer include dietary fibers, polyunsaturated fatty acids of vegetable origin, and unsaturated fatty acids from wild fish. The protection against colorectal cancer provided by dietary fiber has recently been confirmed in the EPIC cohort, in which the relative risk for colorectal cancer was reduced (RR 0.58) by daily consumption of 35 g of fiber in comparison with a daily consumption of 15 g. With regard to meat, an increased risk for colorectal cancer (RR 1.7) was observed in the group with the highest consumption of processed meat. Poultry consumption is less protective (RR 0.75) than fish consumption (RR 0.35).

Food contaminants. Food may contain natural carcinogens or residual pesticides. Nitrosamines, bracken fern, and mycotoxins in maize (*Geotrichum candidum*, *Fusarium* species) are risk factors for esophageal cancer. Intraluminal nitrosamines synthesized from amines and nitrates/nitrites may play a role in gastric cancer, via the premalignant condition of gastric atrophy. Aflatoxin-1 (a mycotoxin present in traditional diets) is a risk factor for hepatocellular carcinoma in sub-Saharan Africa, south-east Asia, and South America.

Food preparation. Scalding hot beverages (maté tea in South America, for example) are a risk factor for esophageal cancer. Red meat cooked at a high temperature (broiling or barbecuing) contains mutagenic polycyclic aromatic hydrocarbons and is a risk for colon cancer.

Excess weight. A high body mass index (BMI) is a risk factor for cancer of the endometrium, breast, kidney, colon, and esophagus (adenocarcinoma). In the male Health Professionals cohort, the relative risk for colon cancer was found to be increased in the group with a high BMI.

Physical activity. Physical activity (at work and during leisure time)—an important determinant of body weight—appears to be a preventive factor for cancer of the breast, lung, and colon. Physical activity inversely relates to the risk of colon cancer: in the male Health Professionals cohort, the relative risk for colorectal cancer was found to be reduced by exercise activity. Similar results were found in the female Nurse Health cohort.

Infectious agents. In the distal stomach, *H. pylori* infection with gastric atrophy is a premalignant condition. The prevalence of the infection in adults is around 50% throughout the world, but most infected persons never develop gastric cancer in the absence of promoting dietary factors—a high intake of irritants (salt and nitrates) and a low intake of antioxidants (fruit and vegetables). The relative risk for gastric cancer in *H. pylori* infection is estimated at 5.9 in prospective studies with a long follow-up period. The number of cases attributable to *H. pylori* infection worldwide (556 000 in 2000) has been calculated from the prevalence of *H. pylori* infection and the number of new cases of gastric cancer (excluding cancer at the cardia).

In the liver, 80% of cases of hepatocellular carcinoma occur in developing countries and two-thirds of the cases are caused by hepatitis B virus infection (HBV). In Japan and the USA, hepatitis C virus infection is the prevalent infectious factor.

Specific Strategies for Digestive-Tract Cancer

Controlling smoking and excess alcohol consumption could pre-

***Table 1**. Level of evidence for a relationship between diet and physical exercise and digestive-tract cancer (data from the World Cancer Research Fund, 1997, and the World Health Organization, 2002)*

Level of evidence	Reduced risk	Increased risk
Convincing	Physical activity: colorectum	Excess weight, obesity: esophagus, colorectum Alcohol: esophagus, liver Smoking: esophagus, colorectum, pancreas Aflatoxin: liver HBV and HBC: liver *H. pylori*: stomach
Probable	Fruit and vegetables: esophagus, stomach, colorectum	Preserved meat: colorectum Salt-preserved foods: stomach Very hot drinks: esophagus
Possible or insufficient	Fiber, soya , fish, omega-3 fatty acids, carotenoids, vitamins; zinc ,selenium, allium, flavonoids, lignans: all digestive-tract cancers	Animal fats, heterocyclic amines, polycyclic aromatic hydrocarbons, nitrosamines: all digestive-tract cancers

HBV, hepatitis B virus; HCV, hepatitis C virus.

vent most cases of squamous-cell esophageal cancer. Specific recommendations have been adapted for various regions of the world: excessively hot beverages in South America; the chewing of toxic vegetable products (pickled vegetables or opioids) in Asia; and possibly drinking, if the patient has a positive flushing test with alcohol (inefficient aldehyde dehydrogenase-2 enzyme).

Screening is still the priority for colon cancer, but there is an urgent need to for this to be combined with primary prevention based on increased physical activity, control of excess weight, and a fiber-rich diet.

Vaccination against HBV infection is the priority for hepatocellular carcinoma. In Asia, HBV transmission is vertical (from mother to child at birth); neonates require vaccination, and early development of hepatocellular carcinoma in children is the early end point for assessing prevention. Following the vaccination campaign in Taiwan, the incidence of cancer in children declined from 4.5 to 1.9 per 100 000. In Gambia, a collaborative study conducted with the cooperation of the International Agency for Research on Cancer and the British Medical Research Council confirmed the efficacy of HBV vaccination against infection and chronic carrier status.

Public Health Recommendations

Recommendations by health authorities are legitimate if there is convincing evidence (Tables 1, 2). While screening can be offered to individuals in the appropriate age groups, primary prevention can be aimed at younger persons and children. In the developed countries, ethnic background and conditions of privation and poverty can also have an impact on cancer mortality, as confirmed by cancer statistics in the USA for cancer of the breast, lung, prostate, and colon. Overall, it is bad to have cancer, worse if you are either black or poor, and still worse if you are black and poor. Early cases of cancer detected by endoscopy have a good prognosis, and screening campaigns are complementary to primary prevention. Guidelines for healthy lifestyles need to focus on increasing physical activity, improving diet, and controlling smoking and excess alcohol consumption. These basic prescriptions can form the basis for a multifactorial approach to primary prevention.

***Table 2**. General dietary recommendations on food sources (data from the World Cancer Research Fund, 1997)*

Food sources and eating	Choose predominantly plant-based diets and minimally processed starchy staple foods
Maintaining body weight	Avoid being underweight or overweight. Limit weight gain during adulthood to less than 5 kg
Maintaining physical activity	Take an hour's brisk walk every day and exercise vigorously for a total of at least 1 hour a week
Alcohol	Limit alcoholic drinks to two drinks a day for men and one drink for women
Tobacco	Do not smoke or chew tobacco
Dietary supplements	Dietary supplements are probably unhelpful for reducing the cancer risk in those who follow the above recommendations

Conclusions

Controlling both dietary changes and toxic and/or infectious agents increases the efficacy of preventive measures. It is estimated that 80% of esophageal cancers and hepatocellular carcinomas could be avoided by controlling toxic and/or infectious factors. The proportion of cancers avoidable with dietary change is estimated at 50–80% for colorectal cancer, 10–50% for pancreatic cancer, and 30–70% for gastric cancer.

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Gastric Cancer Awareness Campaign in Asia

Sidney Winawer, Meinhard Classen

Introduction

The IDCA co-sponsored a symposium on gastric cancer, held on 6 October 2004 during an Asia–Pacific Digestive Week (APDW) meeting in Beijing in collaboration with our Chinese partners in the working group. Beginning in early 2004, the IDCA formed a working relationship with colleagues in China to address the problem of gastric cancer, which has the highest worldwide mortality among the digestive cancers and is the leading digestive cancer in the Asia–Pacific area. A video conference and meetings were held in early 2004 to plan the symposium and a meeting of the working group. The purpose of the symposium was to review the current status of gastric cancer worldwide, with special emphasis on the Asia–Pacific area. The working group was to discuss plans for a randomized pilot study on *Helicobacter pylori* eradication and a larger population-based randomized trial to reduce the incidence and mortality of gastric cancer in China. This was also to serve as a model for other countries, as well as providing the basis for a widespread campaign in China.

Symposium

The APDW symposium was chaired by Shu Dong Xiao, President of the APDW, and Meinhard Classen and Sidney Winawer, co-chairs of the IDCA. Professor Xiao emphasized the importance of the problem of gastric cancer in China and the Asia–Pacific area. Professor Classen discussed the opportunity for prevention and the importance of a gastric cancer campaign in China.

Professor Winawer, from Memorial Sloan-Kettering Cancer Center in New York, spoke on the worldwide epidemiology of gastric cancer. He indicated that in the year 2002, there were 10 million new cases of cancer and 6.2 million people died of cancer throughout the world. Digestive cancers account for the highest incidence and mortality of cancer worldwide, with 3 million new cases and 2.2 million deaths annually (colorectal, esophageal and stomach, liver and pancreas). Among the digestive cancers, gastric cancer is the leading cause of mortality, with more than 600 000 deaths each year. Regionally, gastric cancer is the most common cancer in eastern Asia, and the third most common cancer in South America and in eastern and southern Europe. Although the age-adjusted incidence is continuing to fall worldwide, the crude unadjusted rate is rising. The number of new cases will rise significantly throughout the world in the next 20 years. Screening and primary prevention directed toward lifestyle, nutrition, and eradication of *H. pylori* are all important preventive strategies. The success of any prevention program begins with awareness on the part of health-care providers and the public and must involve multidisciplinary approval, including policy-makers, specialists, primary-care providers, and community leaders.

Professor Weishen You of the School of Oncology at Beijing University Hospital and Beijing Institute for Cancer Research then presented a paper on the etiology and prevention of gastric cancer in Linqu County, Shandong Province, in China. A series of studies has been carried out in Linqu County, a high-risk area for gastric cancer in China. Between 1984 and 1986, a population-based case–control study of 564 gastric cancer cases and 1132 controls was initiated. From 1989 to 1994, an investigation was carried out on the prevalence of gastric lesions, their determinants, and rates of transi-

tion among 3400 adults in the high-risk area. In 1995, a randomized multifactorial intervention trial was initiated to determine whether supplementation with vitamins and minerals, garlic, and treatment for *H. pylori* infection can retard the progression of precancerous gastric lesions. A follow-up study showed that the relative risk of developing gastric cancer was associated with dietary factors and *H. pylori* infection. These findings strongly support the concept that gastric cancer is determined by environmental factors and develops in a multistep progression from precancerous lesions.

Professor M. Stolte of the Institute of Pathology, Bayreuth, Germany, provided an overview of the histopathology of gastric carcinogenesis. He indicated that *H. pylori* infection of the gastric mucosa is a precancerous condition. Nevertheless, only one in about 1000 patients with *H. pylori* infection actually develops cancer of the stomach. For this reason, general eradication of *H. pylori* to prevent a gastric carcinoma does not make good economic sense. His studies attempted to identify patients with a precancerous "risk gastritis". These studies show that patients with corpus-dominant *H. pylori* gastritis have an elevated risk of developing gastric carcinoma, and this is the patient group that should be studied.

Professor Sanren Lin of the Department of Gastroenterology, Third Hospital, and Beijing University presented an eight-year follow-up study on the morbidity of gastric cancer after *H. pylori* eradication. One thousand and six adults were randomly selected from the general population in the Yantai area, Shandong Province. All of the *H. pylori*–positive 552 individuals were randomly assigned either to a treatment group or a placebo group. The treatment group received triple therapy with omeprazole, amoxicillin, and clarithromycin (OAC) for 1 week. One month after the completion of treatment, *H. pylori* status was reassessed using the ^{13}C urea breath test. The *H. pylori* eradication rate in the treatment group was 89%. Follow-up in the eighth year (in 2004) revealed that there was one case of gastric cancer in the treatment group and six cases in the placebo group (statistically significant). *H. pylori* infection increased the morbidity of gastric cancer, while eradication reduced it. *H. pylori* eradication results in resolution of intestinal metaplasia in the antrum.

Professor S.K. Lam of the Department of Medicine, University of Hong Kong, and Queen Mary Hospital, Hong Kong, presented the results of experience with *H. pylori* eradication treatment and gastric cancer in Fujian Province, China. Any chemotherapeutic intervention should use the resolution of chronic gastritis as an initial objective. If the resolution of chronic gastritis—for example, following *H. pylori* eradication treatment—can be shown to prevent gastric cancer, then all individuals with *H. pylori*–related chronic gastritis should receive eradication treatment. A 7-year population-based ($n = 1632$) study concluded that the progression of atrophic gastritis could be delayed after *H. pylori* eradication. The crucial question remains of whether *H. pylori* eradication can prevent cancer. This study showed that early eradication of *H. pylori* prevented the development of gastric cancer. In patients who already had precancerous lesions, the incidence of gastric cancer was not reduced after 7 years of follow-up.

A paper on endoscopic submucosal resection for early gastric cancer was presented by Hiroyuki Ono from the Endoscopy and Gastrointestinal Oncology Division of Shizuoka Cancer Center Hospital, Shizuoka, Japan. Endoscopic mucosal resection (EMR) has been accepted for treatment of early gastric cancer for appropriate patients with a low probability of lymph-node metastases. The number of EMR procedures carried out to treat early gastric cancer has been increasing, as the quality of life after EMR for patients is superior to that after surgical gastrectomy. Dr. Ono developed a special endoscopic accessory by applying a ceramic insulation tip to a needle-knife. With the insulated tip in the submucosa, the electrical device can cut safely and remove a lesion completely. Ninety-six percent of the tumors (471 of 488) removed were resected in one piece using this procedure. This method is termed "endoscopic submucosal dissection". There were 47 perforations in 906 patients treated, all of which were successfully treated with endoscopic clipping, nasogastric tube placement, and antibiotics. One-piece resection allows a correct prognosis and recommendations for patients with early gastric cancer.

The presentations were followed by a lively discussion on the relationship between *H. pylori*, strategies for eradication, and the need to demonstrate the effect of eradication treatment on the incidence and mortality of gastric cancer convincingly.

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2005 Worldwide Survey of Colonoscopy Performance

Massimo Crespi, Jean Escourrou

The increasing use of colonoscopy for diagnosis and treatment, as well as for screening for colorectal cancer, requires high technical and professional standards. This is especially true when a colonic bill of health is to be given to an asymptomatic individual or to a patient with a positive fecal occult blood test. Even with modern colonoscopes, experienced endoscopists encounter anatomic variations, unsatisfactory bowel preparation, and anatomy altered by previous abdominal surgery, among other factors, which make it difficult to carry out a complete colonoscopic examination.

Discrepancies in the reported rates of cecal intubation and complications in different studies, as well as variations in the use of sedation and/or anesthesia, have prompted the OMED/OMGE Research Committee to organize a multinational, multicenter prospective inquiry to evaluate the performance of diagnostic colonoscopy among endoscopists with various levels of experience in countries throughout the world.

The idea for this survey originated with M. Schapiro, co-chair of the OMED/OMGE Education Committee, and it was further elaborated by J. Escourrou, co-chair of the combined Research Committee, with crucial further input from J. Waye, an undisputed authority in colonoscopy, M. Crespi, A. Grassi (OMED webmaster) and D. Lisi, an expert in computerized questionnaires.

The survey was sent to OMED's affiliated societies, who were to nominate four centers in each country for participation, potentially including:

- One university hospital or teaching center.
- One regional or provincial hospital.
- One endoscopy unit in a local hospital.
- One private clinic or office (if applicable).

A precoded questionnaire, available in both electronic and paper versions, will prospectively record 25 colonoscopies together with a series of questions related to the problems encountered when performing the procedures. The data and origin of each questionnaire will be kept strictly confidential, and the data will be tabulated anonymously. Every member of the team at each participating center is requested to complete a separate questionnaire. The data will be evaluated by a team of experts at the OMED Technical Secretariat (M. Crespi, A. Grassi, D. Lisi). It is intended to report the results of the survey at the forthcoming World Congress of Gastroenterology in Montreal.

Jean Escourrou

Massimo Crespi

We would ask each of the affiliated societies and their chosen endoscopy centers to respond immediately, if they have not done so already, so that all the data can be included in the final report.

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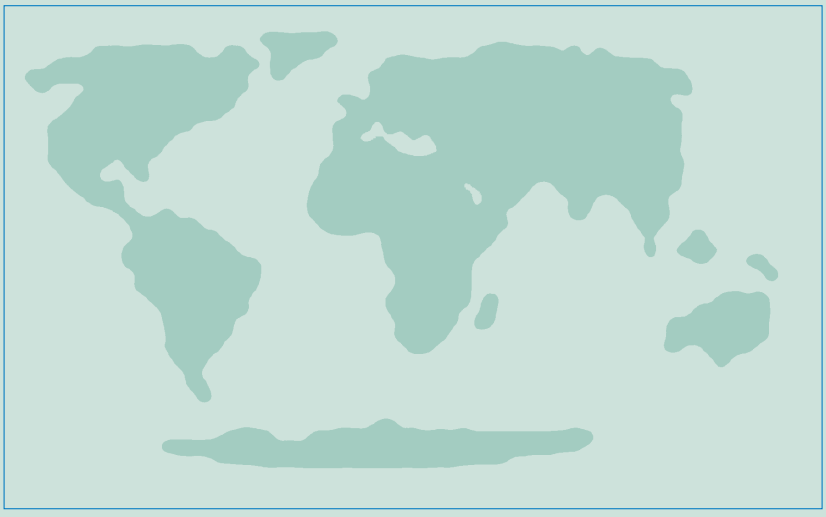

The European Society of Gastrointestinal Endoscopy: A Story of Success

Anthony Axon *(Past President of the ESGE, President Elect, OMED)*

Introduction

The European Society of Gastrointestinal Endoscopy (ESGE) is one of the most active international gastroenterology organizations in the world. Founded in 1960 before flexible endoscopy had become a reality, it has grown in size and influence with the increasing importance and popularity of endoscopy as a diagnostic and therapeutic tool.

What Is It?

The ESGE includes all of the national digestive endoscopy societies in Europe and the Mediterranean who seek membership—44 countries at present. The Society represents the European zone within the World Organization of Digestive Endoscopy (OMED). It is one of the seven founding members of the United European Gastroenterology Federation (UEGF).

How Does It Work?

A general assembly, held each year at the United European Gastroenterology Week (UEGW), is in ultimate control of the Society. A governing board is elected by the single transferable vote system from nominations made by individual member societies. The governing board is responsible for the activities and for the general running of the Society. Councilors serve for a limited term and only one member from any country may be appointed. The governing board recommends its own officers from those elected and its choice is ratified at the general assembly. The board and the Society are chaired by the President, who has a 2-year term of office.

The ESGE technical secretariat, based in Munich, is responsible for the smooth running of the Society and the management of the ESGE web site. The Society's official journal is *Endoscopy.*

What Does It Do?

Training and education. The ESGE is extremely active in education. Its main scientific input is to the UEGW, where it is largely responsible for the endoscopic part of the scientific program, which usually makes up one-third of the core meeting. A major live endoscopy teaching symposium is held at the UEGW and is the direct responsibility of the ESGE. The Society also organizes the endoscopy training center, which is active during the whole of the meeting.

The main function of the ESGE is to encourage the development of high-quality endoscopy in Europe and the Mediterranean countries. A major part of its activities during the year includes the organization and running of live and video training courses, mainly in eastern Europe and the Mediterranean. The ESGE also approves and participates in live endoscopy courses that are run by other individuals and organizations. Approval for these courses is based on guidelines laid down by the Society to ensure that these are run in an ethical manner and with appropriate educational input.

The Society also provides personal training grants for endoscopists, mainly from Eastern Europe and the Mediterranean, to spend time in large, specialized European centers, enabling them to obtain teaching and high-level experience in endoscopy. Up to ten grants are awarded each year for this purpose.

Most of these activities are organized through the ESGE Education Committee, whose chairman is one of the officers of the Governing Council.

Quality and guidelines. The ESGE attaches great importance to the quality of endoscopy within Europe. In conjunction with the European Society of Gastroenterology and Endoscopy Nurses and Associates (ESGENA), the ESGE Guidelines Committee has made recommendations on topics including the cleaning and disinfection of equipment, antibiotic prophylaxis, capsule endoscopy, endoscopic ultrasound, and other issues.

An important project started some years ago was the development of the Minimal Standard Terminology (MST). The intention was to establish an internationally accepted nomenclature for endoscopic appearances. This project has been completed in English and has been translated into a variety of other languages. Using suitable software, it will in the future be

possible to write an endoscopy report that can be read in any of the participating languages. In view of its international importance, this project has now been transferred to the World Organization of Digestive Endoscopy (OMED).

The ESGE has developed a quality assurance project, which is currently undergoing assessment. When completed, it will enable the Society to recommend standards applicable throughout Europe in a system in which individuals and independent units will be able to assess the quality of their outcomes and compare them with other endoscopy departments. A potential benefit of this system will be to establish objective credentialing for trainees.

The ESGE has taken on a new initiative by setting up a Networked European Endoscopy Database (NEED). The goal is to create a data collection network and a central database for European digestive endoscopy. It is likely that the quality assurance project, based on the MST, will be incorporated into this project.

Workshops. Over the years, the ESGE has organized a number of focused workshops. A highly successful one was held on "Ethics in Gastroenterology and Digestive Endoscopy" in 2002. It took place appropriately in Kos, the birthplace of Hippocrates, and covered a wide range of topics including live demonstrations, teaching, informed consent, endoscopic screening, and insertion of percutaneous endoscopic gastrostomy (PEG) tubes. The meeting included lectures, debates, working groups and an "ethics court". The proceedings have been published 1,2]. Views about ethical matters change with time, and new challenges present themselves. A second ethics symposium is planned for June 2006.

A more recent workshop was held in Oslo in 2003, on "Colonoscopic Screening for Cancer". Separate working groups reported on methods of screening and health economics; implementation of colorectal cancer screening; public awareness and lobbying; and legal and ethical considerations. The proceedings were published in 2004.

How Is It Funded?

The ESGE is funded by fees paid by the member societies, and a proportion of the profits from UEGW; however, the Society receives significant income from a consortium of biomedical companies, who provide an unrestricted grant negotiated on an annual basis. The Society wishes to record its thanks to the companies that form the consortium: Takeda Europe R&D Center, Ltd.; Cook Ireland, Ltd.; Boston Scientific, Ltd.; Given Imaging, Ltd.; CBC Germany, Ltd.; Fujinon Europe, Ltd.; Altana Pharma, Inc.; Steris, Ltd.; Olympus Europe, Ltd.; Pentax Europe, Ltd.

The Secrets of Success

The ESGE is a strong and active Society that has made a considerable impact on European endoscopy and gastroenterology over many years. It also provides strong support for OMED, in which the European zone represents one-third of the membership. Its success has been achieved because of its democratic constitution and the election of energetic and motivated endoscopists to the governing board, which also encourages input from young and enthusiastic endoscopists within Europe.

No organization of this kind can survive without a secure and guaranteed income. The European Society has benefited from the strong liaison it has with the biomedical industry, which has been promoted in an ethical manner. Regular, unrestricted funding is given for the Society's activities, and additional financial support is raised for specific projects such as endoscopic teaching meetings and workshops. A society of this nature, however, cannot hope for success without the full-hearted support of its members. The European Society has been fortunate in receiving enormous encouragement from the various national endoscopy societies in Europe, which themselves are extremely active and are run by highly motivated and forward-looking endoscopists.

Web Site

The ESGE web site, www.esge.com, provides helpful up-to-date information about the Society and its activities.

Member Countries

Bold type indicates countries that have hosted ESGE video/live demonstrations.

- Austria
- **Belgium**
- Bosnia and Herzegovina
- Bulgaria
- **Croatia**
- Cyprus
- **Czech Republic**
- Denmark
- **Egypt**
- **Estonia**
- Finland
- **France**
- **Germany**

Greece
Hungary
Iceland
Iraq
Ireland
Israel
Italy
Jordan
Latvia
Lebanon
Lithuania
Luxembourg
Macedonia
Morocco
Netherlands
Poland
Portugal
Romania
Russia
Scandinavia
Slovakia
Slovenia
Spain
Sweden
Switzerland
Syria
Tunisia
Turkey
Ukraine
United Kingdom
Yugoslavia

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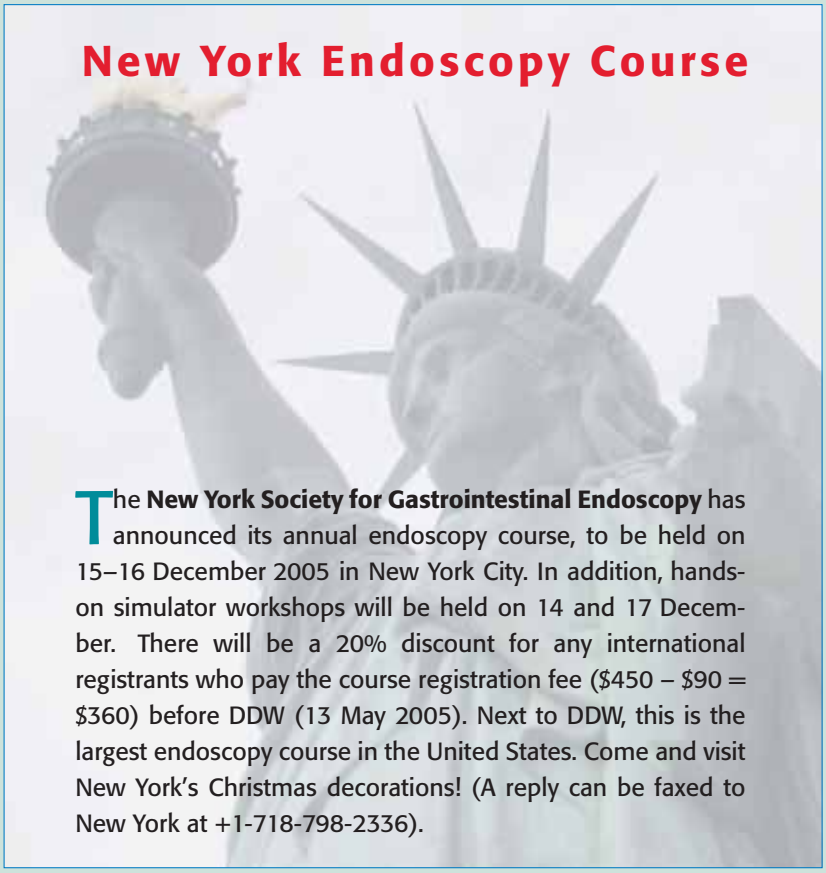
New York Endoscopy Course



The **New York Society for Gastrointestinal Endoscopy** has announced its annual endoscopy course, to be held on 15–16 December 2005 in New York City. In addition, hands-on simulator workshops will be held on 14 and 17 December. There will be a 20% discount for any international registrants who pay the course registration fee ($450 – $90 = $360) before DDW (13 May 2005). Next to DDW, this is the largest endoscopy course in the United States. Come and visit New York's Christmas decorations! (A reply can be faxed to New York at +1-718-798-2336).

Special Initiative:

Can Guidelines Span the Globe?

Michael Fried

A multidisciplinary International Consensus Conference on Global Guidelines will be held during the forthcoming World Congress of Gastroenterology in Montreal, Canada (Monday, 12 September 2005, 12.30–16.00). Special invitations to attend the conference will be extended to the member societies of the World Gastroenterology Organization and all collaborating organizations.

With its global responsibility to 93 national societies and associations involved in the field of gastroenterology, WGO-OMGE wishes to investigate ways in which the production of global guidelines can take account of the large variations in gastroenterology practice worldwide while simultaneously meeting the demands of evidence-based medicine.

- Are global guidelines desirable, feasible, and necessary?
- Is an "evidence-based" approach always right?
- Industry: in or out?
- Can global guidelines change health policy?

A questionnaire has been sent to 77 societies in both gastroenterology and other fields in order to ascertain the current approach to global guidelines in specialist medical societies. All of the societies who have responded have confirmed that there is a need to create guidelines that address the issues faced by colleagues in resource-deficient regions of the world.

WGO-OMGE's global mandate poses unique challenges for guideline development. In addition to the issues experienced by all guideline developers—the complexities of methodological rigor, including a strictly "evidence-based" approach—WGO-OMGE is faced with special production, distribution, and implementation requirements. The quality of WGO-OMGE guidelines may not only be based on evidence. Often there is no evidence base—and even when there is evidence, it may require tools and technologies that are not widely or universally available.

Can guidelines take account of wide variations in practice? Should WGO-OMGE only publish full evidence-based guidelines reflecting state-of-the art technology that is not available in most parts of the world? This is the unique challenge for WGO-OMGE in this area.

A prestigious and dedicated faculty at the conference will include experts from various international organizations involved in guideline production, as well as policy-makers and publishers:

- Michael Fried (Switzerland). Chair, WGO-OMGE Guidelines and Promotion Committee and Chair of the Consensus Conference
- Guido Tytgat (Netherlands). President, WGO-OMGE
- Benjamin Anderson (USA). Director, Breast Health Center, University of Washington, Seattle
- David Bjorkman (USA). Dean, University of Utah School of Medicine, Salt Lake City, Utah
- Michael Farthing (United Kingdom). Principal of St. George's Hospital, London
- Suliman Fedail (Sudan). President of the Pan-Arab Association of Gastroenterology (PAG)
- R.W. Green-Thompson (South Africa). Superintendent-General, KwaZulu–Natal Dept. of Health, Pietermaritzburg, South Africa
- Gordon Guyatt (Canada). Professor of Clinical Epidemiology, Biostatistics and Medicine, Faculty of Health Sciences, McMaster University, Hamilton, Ontario
- John Hampton (United Kingdom). Professor of Cardiology (emeritus), University of Nottingham
- Richard Horton (United Kingdom). Editor of The Lancet
- Richard Hunt (Canada). Professor of Medicine, Faculty of Health Sciences, McMaster University, Hamilton, Ontario
- Loren Laine (USA). Chair, Council of the American Gastroenterological Association (AGA)
- Mark Fishman (Switzerland). President, Novartis Institutes for Biomedical Research (NIBR), Cambridge, Massachusetts/Basle, Switzerland
- Eamonn Quigley (Ireland). Vice-President, WGO-OMGE.

"As the Chair of the Guidelines Committee of the European Society of Cardiology, which includes several countries in Europe, I congratulate you on this brilliant initiative. Obviously the issue of how to make guidelines applicable in different medical environments is a key topic for us as well."

Silvia G. Priori, M.D., Ph.D.,
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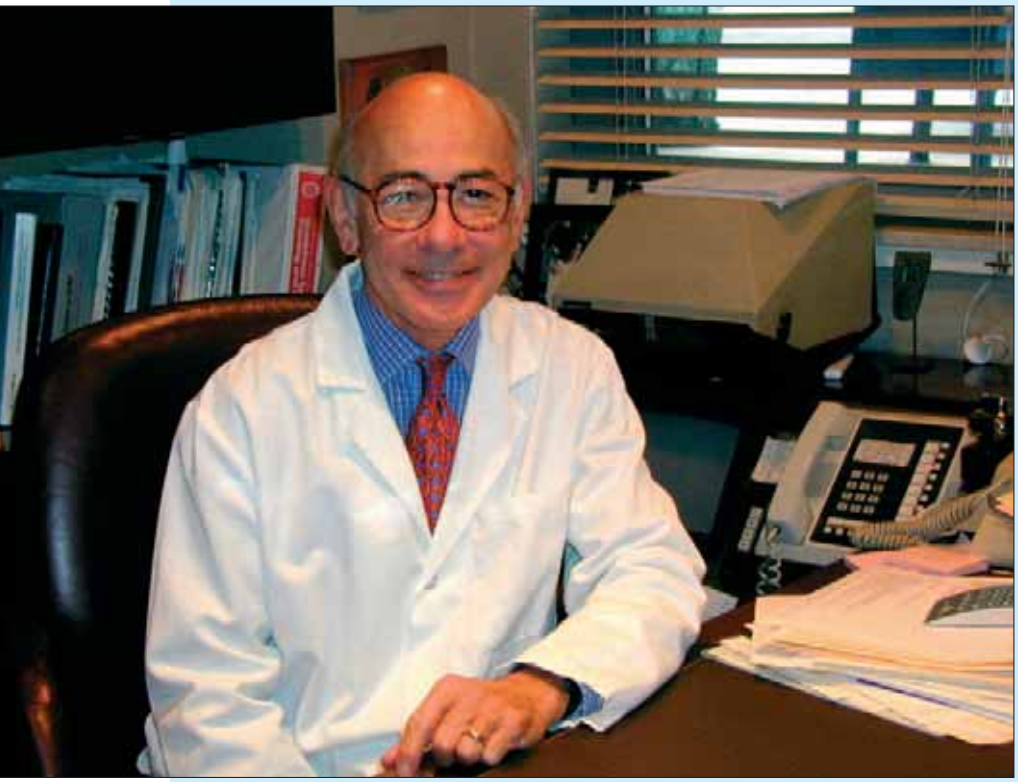


Dr. Jerome D. Waye—"the patient's view".

Jerome D. Waye—Man and Superman

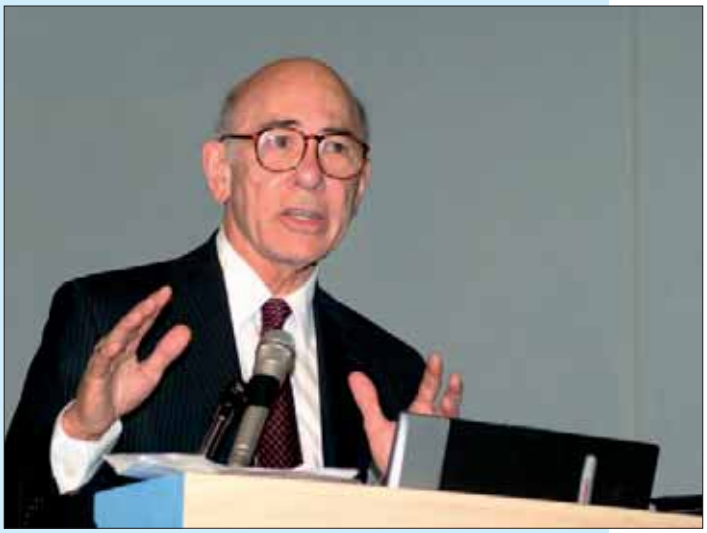
Christopher Williams

No one calls him by his full first name, Jerome. To everyone he's "Jerry", a familiar and well-loved figure but a brightly shining star in the field of gastrointestinal endoscopy, especially colonoscopy. The name of Jerome D. Waye on a program, or in an article or a book, will ensure a large audience and guarantee good value. If it's a live event, there'll be authority but also *fun*—a rare and precious commodity, especially in medicine. On any committee or journal editorial board, his administrative common sense and drive will shake things up, but always with levity and good humor. What's the secret?

Genetics may be part of it. Jerry, born of a Shanghai Chinese father and New York mother, has perhaps the special ebullience and drive of both stereotypes—"pizzazz" and "chutzpah" are amongst the words that come to mind. He's a natural driver and inspirer of others. For instance, he coxed the winning Boston rowing crew in his university days at the Massachusetts Institute of Technology, egging them on by sheer force of personality. Jerry's serious side and innate ability was already in evidence then; he studied biology before medicine, was an award-winning medical student and top fraternity member and graduated M.D. "cum laude"—with top honors—in 1958, with subsequent positions as intern, resident, and gastroenterology fellow at Mount Sinai Hospital in New York.

A bright beginning indeed—but the stereotypic energy one might expect from Jerry's origins really shows up in the galaxy of his achievements since then (expressed in a curriculum vitae extending to over 50 pages). His prodigious creative energy is demonstrated by over 400 articles, book chapters, and published abstracts over the years, and in nearly 400 lectures and televised demonstrations of endoscopic technique internationally. He is undoubtedly the most esteemed and popular presenter and teacher of colonoscopy in the world. Countless endoscopists around the world, many taught on-site in their own countries, others visiting in his remarkable Park Avenue office facility in New York, have been motivated and encouraged by him. It is easy to forget that Jerry's own excellence as a pioneer colonoscopist was based on determination and hard graft (he recalls that his first colonoscopy took 4 hours). The drive and the enthusiasm are still there unchanged, but now translated into a zeal to pass on all his "tricks of the trade" to help other endoscopists—and their patients. As Clinical Professor of Medicine and Chief of the Endoscopy Unit at the Mount Sinai Hospital and an activist in the New York Society for Gastrointestinal Endoscopy, as well in his presentations around the USA, Jerry has similarly taught or influenced huge numbers of fellow American endoscopists.

Jerry's 14 books include the recognized classics on colonoscopy and endoscopic therapy. His 2003 award-winning blockbuster, *Colonoscopy: Principles and Practice* was a particular editorial *tour de force*, involving the dragooning of 50 international contributors (still friends!) so that he could issue the book within 18 months of its first conception. On top of all this, Jerry has served U.S. national and world medicine in his membership of 30 organizing boards or work groups—he has been president of two of the three major gastroenterology organizations in the United States, the American Society for Gastrointestinal Endoscopy (ASGE) in 1980 and the American College of Gastroenterology (ACG) in 1982—and 14 editorial boards (he is international editor of *Gastrointestinal Endoscopy*). Amongst numerous well-deserved honors and citations resulting are top alumni awards from Boston University and Mount Sinai Medical Centers, the Rudolph Schindler Award of the ASGE in 1985, and honorary membership of many national endoscopy societies.



Jerome D. Waye—always a charismatic international lecturer, 2003.

What a drone, you might think! But not at all; behind all this is the man—a very human and humane one. A much-loved physician as well as a super-talented endoscopist, a devoted father and good husband, he's also a restless, noisy, teenaged bundle of fun—even though he is now approaching 70 years of age. He's unstoppable, so he seems to cope effortlessly with challenging patients and accepts a huge range of professional tasks. "No problem" is the typical Waye response to any dilemma or request, followed by immediate and appropriate action. Jerry runs every morning wherever he is in the world and, amazingly, is ready to perform as a magician—to professional standards and much acclaim—at any social occasion he attends. A natural entertainer, Jerry tends to steal any show; he did so when supposedly acting only as Master of Ceremonies to superstar entertainers at the opening ceremony of the World Congress of Gastroenterology in Los Angeles in 1994. However, his real magic is the ability to light up any occasion, of any size and whatever formality, with a unique combination of incisive comments, explosive wit and raucous New York laughter—generated by a small dynamo of a man who, remarkably, manages to remain completely sincere, kind, humble, and approachable as well.

Jerome D. Waye, M.D., F.A.C.P., esteemed Editor of *World Gastroenterology News*, is everyone's friend and admired by all. A "super-mensch" might be the New York description—truly a man of the world, in the best possible sense.

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Dr. Jerome Waye, star of the Opening Ceremony of the 1994 World Congress of Gastroenterology in Los Angeles; he was also the Congress' Secretary-General.

Searching for Strongyloidiasis, Sanitation, and Shoes with Boolean Logic and MeSH Subheadings

Justus H. Krabshuis

Bibliometric Note

Compared with the usual "blockbusters", strongyloidiasis is not a popular topic in the Western literature on gastroenterological research. Over the last 10 years, around 60 articles each year have been indexed in PubMed Medline with the Medical Subject Headings (MeSH) term "strongyloidiasis"—and research interest in the topic is not growing.

***Table 1**. Numbers of articles published on eight gastroenterology topics between 2002–2004, listed in Medline.*

Index terms	2002	2003	2004
Colorectal cancer	4496	4603	4557
Helicobacter	1913	1821	1551
Dysphagia	1574	1654	1305
GERD	862	938	1104
Peptic ulcer	1255	1087	782
Reflux disease	746	788	768
Strongyloidiasis	65	74	60

Before we go on, you might want to know how to do that:

***Table 2**. Searching for "strongylodiasis" in PubMed.*

1 Go to www.pubmed.org
2 Type "strongyloidiasis" in the query box. Now you have two options:
- Either: click on "Limits" and select each year as a separate search:
  1999–1999, 2000–2000, 2001–2001, etc.
- Or: continue in the query box with:
  AND "1999"[PDAT], AND "2000"[PDAT],
  AND "2001"[PDAT], etc.
  (This method is much quicker and easier.)

This makes it possible to find out whether there is interest in a topic and whether the interest is growing or not. By the way, you can do the same with famous authors or famous research establishments, or cities or countries—just to keep an eye on what they are saying.

- Mongolia AND "2002"[PDAT], Mongolia AND "2003"[PDAT], (etc.)
- Mayo AND "2000"[PDAT], Mayo AND "2004"[PDAT], (etc.)
- Farthing M AND "2003"[PDAT], Farthing M AND "2004"[PDAT], (etc.)
- Malagelada J AND "2001"[PDAT], Malagelada J AND "2002"[PDAT], (etc.)

Boolean Logic

As I am pondering PubMed Medline's Boolean operators AND, OR, NOT (always use capitals!) in combination with strongyloidiasis, I am beginning to realize the complexity of the issues involved.

What causes strongyloidiasis? To be sure, the infection is caused by the worm *Strongyloides stercoralis*, and everyone agrees that ivermectin (Mectizan, supplied by Merck) is the best medication. But when there are children in Africa walking barefoot on soil infected due to poor sanitation facilities in the village, then—from the health-economics point of view—what is the role of "sanitation" and would it be better to buy shoes instead of ivermectin? Which would have the greater benefit for the population? Should we forget about Merck and buy shoes instead? Is there any evidence for one view or another? Try searching on:

1. Strongyloidiasis AND ivermectin
2. Strongyloidiasis AND sanitation
3. Strongyloidiasis AND shoes
4. 1 AND 2 AND 3 (don't worry if you get zero hits!)
5. Strongyloidiasis AND (ivermectin AND sanitation AND shoes)
6. 4 OR 5
7. Strongyloidiasis AND (ivermectin OR sanitation OR shoes)
8. Hello reader—is your brain overheating?
9. Strongyloidiasis OR (ivermectin AND sanitation OR shoes)
10. (4 OR 5) AND 8

You have now entered the world of Boolean logic. Does the above make sense? No? Maybe? If you think search statements 4, 5 and 6 are the same, then you can go to "advanced mode".

Summary of Boolean Logic

- Search A = strongyloidiasis
- Search B = sanitation
- Search C = shoes

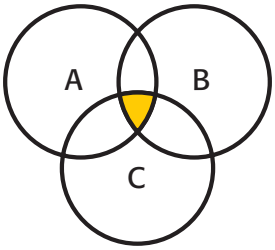


***Fig. 1**. A AND B AND C. The results include only articles in which A and B and C are discussed in the same article.*

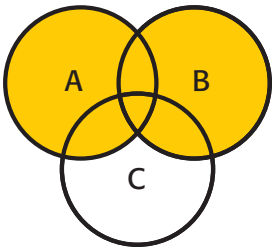


***Fig. 2**. A OR B. The results include only articles in which either A or B is discussed (although some of these articles also mention shoes).*

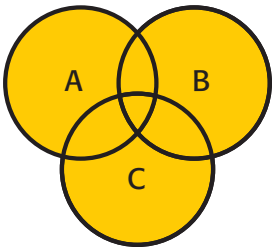


***Fig. 3**. A OR B OR C. The results include all articles in which either A or B or C is present (not a useful strategy for including articles only about shoes (this is the white area in Figure 2) or sanitation!).*

Strongyloidiasis and MeSH Subheadings

What are MeSH terms and MeSH Subheadings? We all know about MeSH terms – the main indexing terms in the MeSH thesaurus. The MeSH term for strongyloidiasis is … strongyloidiasis. Entry terms (synonyms) are:

- Strongyloidiases
- Anguilluliasis
- Anguilluliases

So if you type in "anguilluliasis", PubMed searches for all articles indexed with the MeSH term strongyloidiasis—this is clever "mapping"! You could of course type in anguillulias*—this truncated word stem would search for "anguilluliasis" and "anguilluliases", but using a wild card like * turns off the automatic mapping to the preferred MeSH term—in this case, strongyloidiasis.

However, subheadings are also available. I am consulting the PubMed Help file (in the left-hand side bar; click on "help/FAQ" under the "Entrez PubMed" heading).

- MeSH terms [MH]. The National Library of Medicine's "Medical Subject Headings" controlled vocabulary of biomedical terms that is used to describe the subject of each journal article in MEDLINE. MeSH contains more than 22 000 terms and is updated annually to reflect changes in medicine and medical terminology. MeSH terms are arranged hierarchically by subject categories, with more specific terms arranged beneath broader terms. PubMed allows you to view this hierarchy and select terms for searching in the MeSH Database.
- MeSH subheadings [SH]. MeSH subheadings are used with MeSH terms to help describe more completely a particular aspect of a subject. For example, the drug therapy of strongyloidiasis is displayed as strongyloidiasis/drug therapy; see MeSH/Subheading Combinations. The "MeSH Subheading" field allows users to "free-float" subheadings—e.g., strongyloidiasis [mh] AND toxicity [sh]. MeSH subheadings automatically include the more specific subheading terms under the term in a search. To turn off this automatic feature, use the search syntax [sh:noexp]—e.g., therapy [sh:noexp]. In addition, you can enter the Medline two-letter MeSH subheading abbreviations rather than spelling out the subheading—e.g., dh [sh] = diet therapy [sh].

Now we can design the searches. Let's have a look at the four main section headings in the *OMGE Practice Guideline: Management of Strongyloidiasis*. For each heading, we can select the relevant terms available. Go to the list of MeSH subheadings in the Help file.

***Table 3**. Searching for OMGE strongyloidiasis headings with MeSH subheadings.*

OMGE strongyloidiasis heading		Search with subheading
3	Disease burden and endemicity	Strongyloidiasis/ep
4	Risk groups	Strongyloidiasis/pc
5	Diagnosis and differential diagnosis	Strongyloidiasis/di
6	Management	Strongyloidiasis/th

The subheadings "therapy" (/TH) and "diagnosis" (/DI) are subheadings that can be "exploded". Using "therapy" as a subheading would also pick up any article in which strongyloidiasis was linked to the subheadings: diet therapy, drug therapy, prevention and control, rehabilitation, surgery, etc.

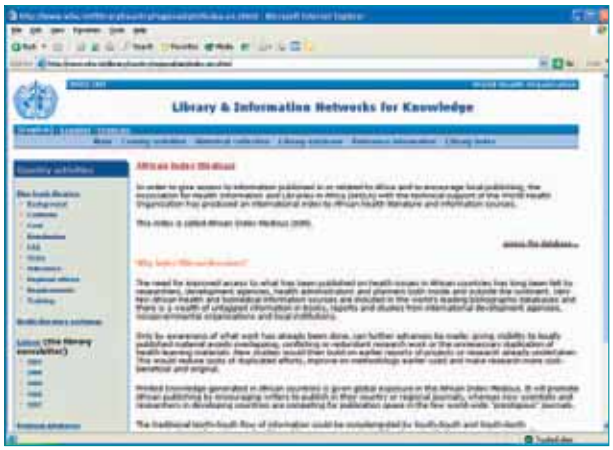
Similarly, using strongyloidiasis/diagnosis would also pick up any article in which strongyloidiasis was linked to the subheadings: pathology, radionuclide imaging, ultrasonography, etc.

***Table 4**. Clinical research tools for information on strongyloidiasis.*

Clinical tool	Web site	Cost
UpToDate	www.uptodate.com	Subscription-based (online + CD)
MDConsult	www.mdconsult.com	Subscription-based (online)
eMedicine	www.emedicine.com	Free
DoctorGuide	www.docguide.com	Free

A Few Other Useful Sources for Strongyloidiasis Information

Of course you know now about the Centers for Disease Control (CDC), the World Health Organization,



and eMedicine sites for searching for information on strongyloidiasis (see the "further reading" references in the *Guideline* itself). Here are a few more (less well known sources) that are just as reliable.

Indexes to regional journals. Start from the Health InterNetwork Access to Research Initiative (HINARI) site at http://www.healthinternetwork.org/scipub.php and choose one of the following four options:

- African Index Medicus (AIM)
- Index Medicus for the WHO Eastern Mediterranean Region (IMEMR)
- Latin American and Caribbean Center on Health Sciences Information (LILACS)
- Index Medicus for South-East Asia Region (IMSEAR)

Clinical information (Table 4). The clinical information tools today are often linked to Council on Medical Education (CME) activities. You can stay up to date wherever you are—no need to travel to Europe to keep in touch. And talking about UpToDate, its site has the added attraction that the (personal) subscription also includes a CD version (with quarterly updates)—just in case you have occasional problems with Internet access.

The eMedicine site is free and has several excellent guidelines on strongyloidiasis (see the reference list in the *OMGE Guideline*).

OMGE's "Ask a Librarian" service (http://www.omge.org/asklibrarian/ask.html). This is a free OMGE resource for non-Western gastroenterologists—not even the American Gastroenterological Association, American College of Gastroenterology, or British Society of Gastroenterology offers a personal service like this. Besides, you are a physician, not a librarian, and time is of the essence …

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NEWS FROM THE INDUSTRY

Fujinon

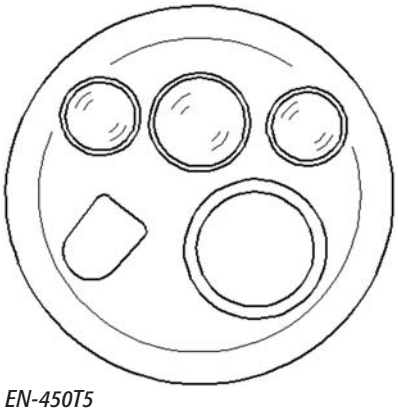
DOUBLE BALLOON ENDOSCOPY

NEW – Variety of Double Balloon Endoscopy System

The newly developed Double-Balloon-Endoscope (patent pending) from Fujinon entered the international market just over two years ago. Since then, with this unique technique it has become possible to examine the whole small intestine non invasively and to intervene at the same time.

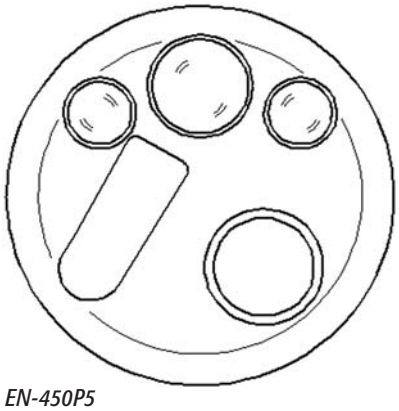
This groundbreaking innovation has been developed based on the idea of Dr. Yamamoto, MD, Department of Gastroenterology of Jichi Medical School. This technology has defined the future standard in modern diagnosis of small bowel diseases.

Following this world first Double-Balloon-Enteroscope, Fujinon has now introduced another type of Double-Balloon-Enteroscope suitable for treatment. Type EN-450T5 equipped with 2.8 mm channel allows various kinds of treatments with any accessories available for this size of channel.



EN-450T5

On the other hand, for oral intubation, type EN-450P5 makes the procedure easier and smoother with a very thin outer diameter of 8.5 mm (12.2 mm, overtube). With two types of Double-Balloon-Enteroscopes, the application field for Enteroscopes has been significantly enlarged. For both of these remarkable Enteroscopes, Fujinon offers specially developed accessories to support their professional application and to provide a full range of services. Accessories available include a capsule retriever and an APC-probe, which has been developed in cooperation with Erbe.



EN-450P5

Indications for Double-Balloon-Endoscopy:

- Unexplained digestive bleeding
- Crohn's disease
- Radiographic abnormalities of the small intestine
- Unexplained chronic diarrhoea and chronic abdominal pain
- Multiple polyps
- Difficult B2-ERCP's

For further information regarding Double-Balloon-Endoscopy please contact:

Fujinon (Europe) GmbH
Halskestrasse 4,
47877 Willich, Germany
Tel: +49(0)2154/924-0
Fax: +49(0)2154/924-290
Url: www.fujinon.de

FUJINON CORPORATION
1-324 Uetake, Kitaku,
Saitama-City, Saitama 331-9624, Japan
Tel: +81-(0)48/668/2152
Fax: +81-(0)48/651/8517
Url: www.fujinon.co.jp

FUJINON

World Gastroenterology News, Vol. 10, Issue 1, 2005, Supplement: 1–8

World Gastroenterology Organisation

Setting Global Standards in Education and Training

WGO-OMGE PRACTICE GUIDELINE

MANAGEMENT OF STRONGYLOIDIASIS

Review Team: Dr. M. Farthing (Chair, WGO-OMGE Guideline Review Team); Dr. S. Fedail (World Gastroenterology Organization); Dr. L. Savioli (World Health Organization); Dr. D.A.P. Bundy (World Bank); J.H. Krabshuis (Highland Data)

Dr. M. Farthing
(Chair, WGO-OMGE Guideline Review Team)

INTRODUCTION

Dr. T. Polderman

There are a number of reasons why it is important to draw attention to *Strongyloides* infections in this OMGE practice guideline.

The impact on public health of the common geohelminth infections has been the subject of extensive research and interventions during the last 10 years. At the population level, the effects of the high prevalence of infection with hookworms, roundworms, and whipworms appear to be more significant than had previously been thought. Careful population-based studies have shown that even the comparatively well-adapted and benign whipworms may cause significant morbidity, particularly in young children.

The new insight into the role of these geohelminths is based to a great extent on the introduction of the Kato thick smear technique as the universal diagnostic tool in population-based studies of helminth infections. Originally developed for schistosome infections, the procedure is simple and cheap. The results can be interpreted quantitatively, and the test performs very satisfactorily provided the smears are examined quickly, before hookworm eggs disintegrate. It is precisely because this stool examination procedure fails to identify *Strongyloides* infections that strongyloidiasis can rightfully be described as the forgotten (or neglected) geohelminth infection. The impact of geohelminth infections on public health became even clearer as a result of successful control based on mass treatment with highly effective broad-spectrum anthelmintics such as albendazole. Again, strongyloidiasis did not share the benefits of these achievements: the commonly used anthelmintics are less efficacious in strongyloidiasis than they are in the other intestinal nematode infections, and due to the comparatively complicated and insensitive methods of parasitological diagnosis, the effects of treatment in control programs directed at the other helminth infections remained largely unexplored. Although considerable reductions in infection rates may have been achieved by mass treatment for lymphatic filariasis or common intestinal nematode infections, little is known regarding the extent of these achievements.

Nonetheless, strongyloidiasis must be regarded as a clinically important and treacherous–potentially lethal–parasitic infection. The worm's unique ability to multiply in the human host and to cause hyperinfection in immunosuppressed patients gives it a very special position in human helminth infections. As it is a well-adapted human parasite, infections remain without significant symptoms in a great number of hosts, and infections are very easily overlooked in the chronic stage of infection. Once hyperinfection develops, however, the prognosis is very poor. In disseminated infection of this

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type, concomitant septicemia is the rule, the otherwise characteristic sign of eosinophilia disappears, and the mortality rates range from 50% to 90%. Much remains to be learned about the mechanisms involved in the association between immune deficiency and disseminated *Strongyloides* infection, but immunosuppressive therapy is already leading to significant numbers of fatal infections in nonendemic countries. With increasingly widespread use of immunosuppressive therapy, a significant increase in the numbers of disseminated *Strongyloides* infections can be expected in all regions of the world in which the condition is endemic.

Failure to recognize infection in time is not only a problem in population-based studies in poorly developed areas in which the disease is endemic; it is a similar problem in the wealthy, medically well-equipped part of the world. Diagnosis is still unsatisfactory even in the developed world, and here in particular our understanding of when hyperinfection develops and how it becomes manifest remains unsatisfactory.

Both at the population level and at the level of the individual patient in the wealthier parts of the world in which the disease is not endemic, it must be admitted that we are poorly equipped and have too little knowledge and experience to manage the infection effectively. In strongyloidiasis, more than in any other common helminth infection, the key to dealing with the infection successfully is to recognize the possibility of this type of infection in sufficient time.

Focusing on this infection in these OMGE practice guidelines is an important step towards better recognition of the importance of strongyloidiasis.

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WGO-OMGE PRACTICE GUIDELINE

MANAGEMENT OF STRONGYLOIDIASIS

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CONTENTS

1 DEFINITION

Strongyloidiasis is an infection with *Strongyloides* stercoralis, a roundworm occurring widely in tropical and subtropical areas.

The genus *Strongyloides* is classified in the order Rhabditida, and most members are soil-dwelling microbiverous nematodes. Fifty-two species of *Strongyloides* exist, but most do not infect humans. *S. stercoralis* is the most common pathogen for humans.

The adult male worm is passed in the stool after fertilizing the female worm—it is not a tissue parasite.

The adult female worm is very small and almost transparent. It measures approximately 2.2–2.5 mm in length with a diameter of 50 µm; it lives in tunnels between the enterocytes in the human small bowel.

Strongyloides stercoralis is different from all other soil-transmitted helminthic infections because the female worm can reproduce by parthogenesis within the human host. Depending on the host immune response, this can lead to autoinfection and hyperinfection.

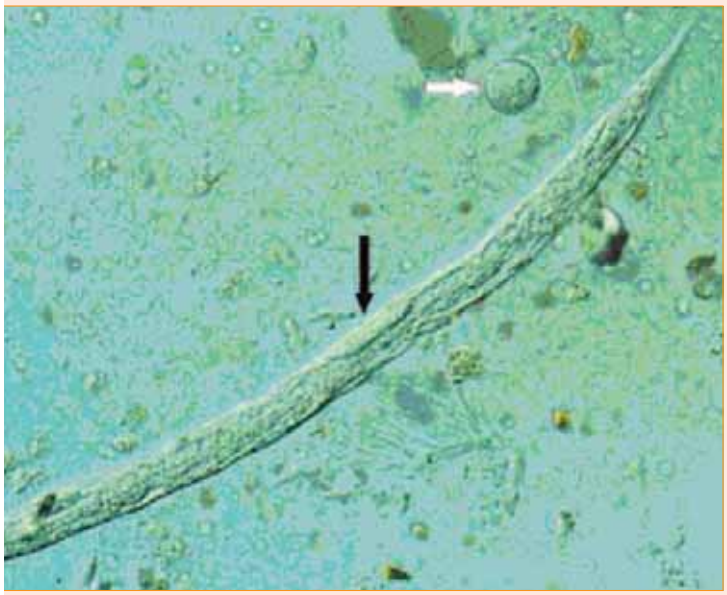

***Fig. 1**. A* Strongyloides stercoralis *first-stage larva preserved in 10% formalin. The prominent genital primordium in the mid-section of the larva (black arrow) is readily evident. Note also the* Entamoeba coli *cyst (white arrow) near the posterior end of the larva.*

Terminology:

- "Autoinfection": the process that enables the parasite to survive very long in the human host, mostly asymptomatically.
- "Hyperinfection": the process of intense autoinfection; the phase in which third-stage larvae can be found in fresh stools.
- "Disseminated infection": the outcome of hyperinfection: larvae can be found anywhere, particularly in sputum and skin.

There are two important stages in the life-cycle of the worm, the rhabditiform stage and the filariform stage.

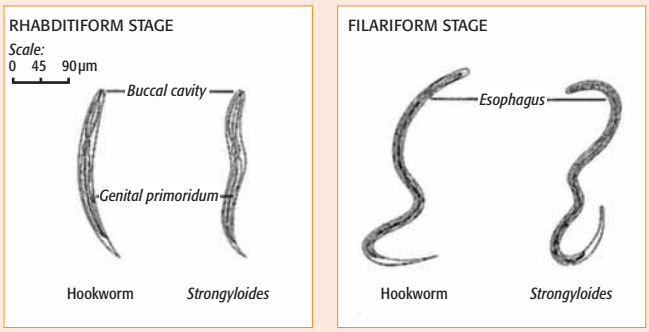

***Fig. 2**. Hookworm and* Strongyloides *larvae (adapted from Melvin, Brooke, and Sadun, 1959)*

2 INTRODUCTION AND KEY POINTS

2.1 Pathophysiology

Strongyloides stercoralis has a unique and complex life-cycle.

The drawing on the next page (Fig. 3), taken from the U.S. CDC web site, outlines the unique routes of *S. stercoralis* replication.

The *Strongyloides* life-cycle is more complex than that of most nematodes, with its alternation between free-living and parasitic cycles, and its potential for autoinfection and multiplication within the host. Two types of cycles exist:

Free-living cycle. The rhabditiform larvae passed in the stool can either molt twice and become infective filariform larvae (direct development) or molt four times and become free-living adult males and females that mate and produce eggs from which rhabditiform larvae hatch. The latter in turn can either develop into a new generation of free-living adults or into infective filariform larvae. The filariform larvae penetrate the human host skin to initiate the parasitic cycle.

Parasitic cycle. Filariform larvae in contaminated soil penetrate the human skin, and are transported to the lungs, where they penetrate the alveolar spaces; they are carried through the bronchial tree to the pharynx, are swallowed and then reach the small intestine. In the small intestine, they molt twice and become adult female worms. The females live threaded in the epithelium of the small intestine and by parthenogenesis produce eggs, which yield rhabditiform larvae. The rhabditiform larvae can either be passed in the stool (see "Free-living cycle," above), or can cause autoinfec-

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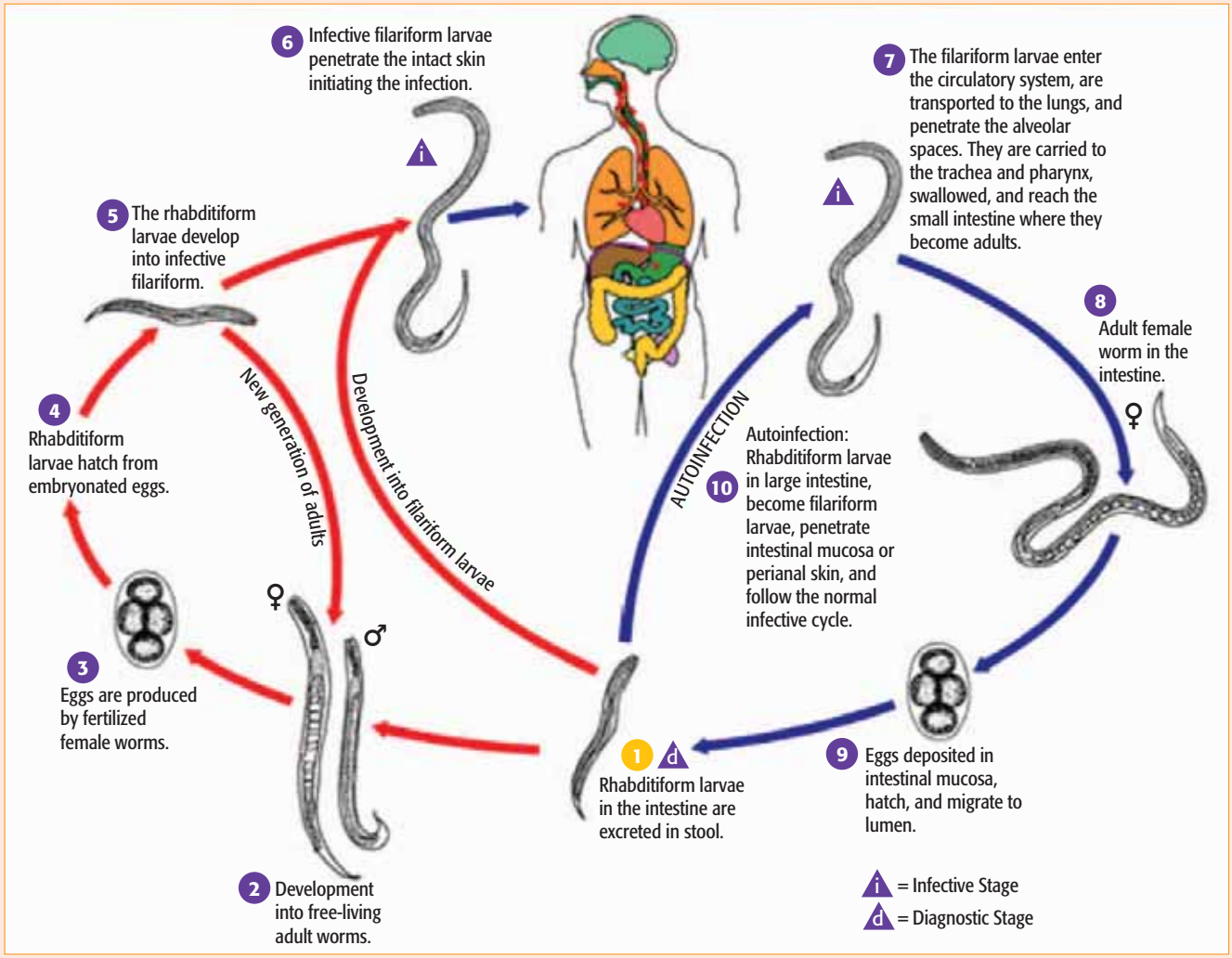

***Fig. 3**. Strongyloides stercoralis life-cycle*

tion. In autoinfection, the rhabditiform larvae become infective filariform larvae, which can penetrate either the intestinal mucosa (internal autoinfection) or the skin of the perianal area (external autoinfection); in either case, the filariform larvae may follow the previously described route, being carried successively to the lungs, the bronchial tree, the pharynx, and the small intestine, where they mature into adults; or they may disseminate widely in the body. To date, occurrence of autoinfection in humans with helminthic infections is recognized only in *Strongyloides* stercoralis and *Capillaria philippinensis* infections. In the case of *Strongyloides*, autoinfection may explain the possibility of persistent infections for many years in persons who have not been in an endemic area and of hyperinfections in immunocompromised individuals. The current record is 65 years.

Alternative theories have been suggested, for example the simple idea that larvae may migrate directly from the skin to the duodenum through the connective tissues; however, no direct evidence to support such hypotheses is available to date.

2.2 Relationship with HIV/AIDS

HIV/AIDS facilitates strongyloidiasis.

Strongyloidiasis is not an important opportunistic infection associated with AIDS, but it is an opportunistic infection associated with the human T-lymphocyte virus.

The literature cited in Table 1 reviews evidence of interaction. The key issue for a clinician is to be very careful indeed, as immunosuppression may facilitate strongyloidiasis becoming hyperinfective/disseminating.

General comment: strong evidence of immunological interaction during co-infection by the soil-transmitted helminth *S. stercoralis* and a retrovirus that causes leukemia, as well as immune disorder diseases, in humans (human T-cell lymphotropic virus type-1 [HTLV-1]), has been reported from Brazil, Jamaica, Japan and Peru (Robinson et al. 1994, Hayashi et al. 1997, Neva et al. 1998, Gotuzzo et al. 1999, and Porto et al. 2001). These findings support the possibility that a similar situation may occur during co-infection by helminths and HIV-1, which is also an immunosuppressive retrovirus.

Strongyloidiasis and immunosuppressed people. There are many patients with rheumatoid arthritis and bronchial asthma in the tropics who are on long term steroids (leading to immune suppression). Patients can purchase steroids directly from pharmacies—often these are much cheaper than NSAIDS .

2.3 Mortality and Morbidity

Acute strongyloidiasis is often asymptomatic and can remain hidden for decades. Immunocompetent patients often have asymptomatic chronic infections causing negligible morbidity. Clinically apparent strongyloidiasis can lead to cutaneous, gastrointestinal and pulmonary symptoms. Severe disseminated strongyloidiasis has a high mortality rate of up to 87%.

3 DISEASE BURDEN AND ENDEMICITY

Strongyloides stercoralis is endemic in the tropical and subtropical regions and infects up to 100 million people. It is widespread also in Eastern Europe and in the Mediterranean region.

***Table 1**. Strongyloidiasis in relation to HIV/AIDS. Strongyloidiasis in immunosuppressed people can lead to hyperinfection.*

Reference	Main conclusions of the study and review comments
Pampiglione and Riccardi 1972	In parts of Africa, the prevalence of *Strongyloides fuelleborni* infestation reaches 50%. The characteristics of the immune response are not defined. *Comment:* HIV/AIDS is now the leading cause of death in sub-Saharan Africa. The two diseases are co-endemic
Pelletier 1984	Autoinfection by *S. stercoralis* ensures long-term or indefinite infestation, which indicates immune evasion or suppression by undefined means. *Comment:* the global endemicity overlaps that of HIV/AIDS (see Conway et al. 1995, below)
Conway et al. 1995	*S. stercoralis* is endemic throughout the tropical and warm temperate regions of the world. Infestation by *S. stercoralis* can persist for decades by means of autoinfection, and there is familial aggregation. *Comment:* the global distribution overlaps the regions of the highest prevalence of HIV/AIDS (Bundy et al. 2000, UNAIDS 2001). Heterosexual HIV/AIDS is also inevitably familial, to some extent
Mahmoud 1996	Seroprevalence rates of *S. stercoralis* are high in several communities where this helminth is endemic. Diagnosis by serology is much more sensitive than microscopy. In Brazil, seroprevalence can reach 82%. *Comment:* HIV/AIDS and strongyloidiasis are co-endemic in some Brazilian communities, and the possibility of immunological interaction certainly exists
Karp and Neva 1999	Prevalence of *S. stercoralis* infection in adults ranges between 20% and 50% in Kinshasa and infestation can persist for 50 years because of autoinfection (Pelletier 1984, Conway et al. 1995, Mahmoud 1996). *Comment:* the prevalence of HIV/AIDS in Kinshasa is also high (UNAIDS 2001). Chronic immune activation and eventual anergy could increase the risk of infection by HIV and contribute to more rapid progression to AIDS and impairment of immunoprophylaxis

An interesting table is produced by Siddiqui.

***Table 2**. Recent data on* Strongyloides stercoralis *prevalence in some developing nations.*

Location	Specimens examined (n)	Specimens positive for *S. stercoralis* (%)
Abidjan	1001	1.4
Argentina	36	83.3
Argentina	207	2.0
Brazil	200	2.5
Brazil	900	13.0
Ethiopia	1239	13.0
Guinea	800	6.4
Honduras	266	2.6
Israel	106	0.9
Kenya	230	4.0
Laos	669	19.0
Mexico	100	2.0
Nigeria	2008	25.1
Romania	231	6.9
Sierra Leone	1164	3.8
Sudan	275	3.3
Thailand	491	11.2

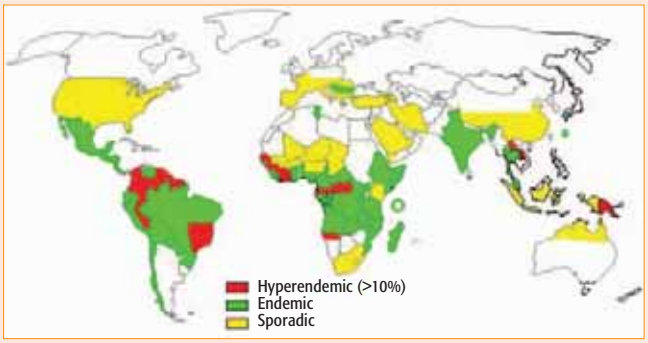

***Fig. 4**. Geographic distribution of strongyloidiasis. S. stercoralis is endemic in the tropics and subtropics and infects as many as 100 million people. It is endemic in South-East Asia, Latin America, sub-Saharan Africa, and in the south-eastern United States.*

4 RISK GROUPS

Patients with AIDS and HIV and those on immunosuppressive drugs are at increased risk. Risk factors for severe strongyloidiasis:

- Immunosuppressive medications (especially corticosteroids, also tacrolimus and chemotherapeutic agents)
- Patients with altered cellular immunity
- Human T-cell leukemia virus type 1 infection
- Neoplasms, particularly hematologic malignancies (lymphoma, leukemia)
- Organ transplantation (kidney allograft recipients)
- Collagen vascular disease
- Malabsorption and malnutrition states
- End-stage renal disease
- Diabetes mellitus
- Advanced age
- HIV-1 infection
- Travelers to and from endemic areas
- Prisoners
- Local factors, diverticular and blind loops (persistent *Strongyloides* stercoralis in a blind loop of the intestine)

5 DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

5.1 Physical Signs and Symptoms (Table 3)

The key to diagnosing strongyloidiasis is to have an index of suspicion—a diagnosis of strongyloidiasis can only be made for certain when the worm is identified in stool. Because of a low worm burden and because of its ability to replicate within the host, it is often impossible to diagnose the worm in one analysis only. Serial analysis over a number of days is necessary. A white blood count (WBC) is important, as is eosinophilia (high in 50% of patients).

The issue of eosinophilia is confusing: it is a most helpful sign in simple uncomplicated infections and mostly absent in disseminated strongyloidiasis.

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***Table 3**. Strongyloidiasis: physical signs and symptoms.*

Acute	• Larva currens (most characteristic sign) * • Itch (usually on feet) • Wheezing/cough/low grade fever • Epigastric tenderness • Diarrhea/nausea/vomiting
Chronic (usually the result of autoinfection)	• Larva currens (most characteristic sign) • Epigastric tenderness • Asymptomatic/vague abdominal complaints • Intermittent diarrhea (alternating with constipation) • Occasional nausea and vomiting • Weight loss (if heavier infestation) • Recurrent skin rashes (chronic urticaria)
Severe (usually as a result of hyper or disseminated infection)	• Insidious onset • Diarrhea (occasionally bloody) • Severe abdominal pain, nausea and vomiting • Cough, wheezing, respiratory distress • Stiff neck, headache, confusion (meningismus) • Skin rash (petechiae, purpura) • Fever, chills

** Larva currens, or creeping infection, is a form of cutaneous larva migrans specific to Strongyloides infection; it is a result of autoinfection. The eruption begins in the perianal region and rapidly spreads, causing intense pruritus. Episodes usually last several hours, and patients can remain free of symptoms for weeks or months between episodes. Evidence of larva currens may appear soon after infection with Strongyloides organisms, or it may first appear many years (often decades) later. Because of autoinfection, episodes may continue for many years.*

5.2 Diagnostic Techniques (Fig. 5)

There are a number of diagnostic procedures:

- String tests
- Duodenal aspiration
- Immunodiagnostic tests (IFA, IHA, EIA,ELISA)
- Repeated examination of stool

All have some advantages (see http://www.journals.uchicago.edu/CID/journal/issues/v33n7/010345/010345.html), but overall the repeated examination of stool is the best method.

There are several techniques to identify larvae in stool.

- Baermann funnel technique (still regarded as the gold standard)
- Directly (dissection microscopy)
- Direct smear of feces in saline–Lugol iodine stain
- After concentration (formalin-ethyl acetate)
- After culture by the Harada–Mori filter paper technique
- Nutrient agar plate cultures (not for case-management/limited to epidemiological studies)

The use of these tests in addition to direct microscopy of fecal smears will depend on local availability of resources and expertise.

The most important test for demonstrating *S. stercoralis* remains the repeated examination of stool over a number of consecutive days.

Stool analysis for *Strongyloides* using the Baermann funnel technique is the best way to diagnose strongyloidiasis.

Baermann funnel technique. The basic Baermann funnel technique, which has a large number of modifications, utilizes a glass funnel with a wire

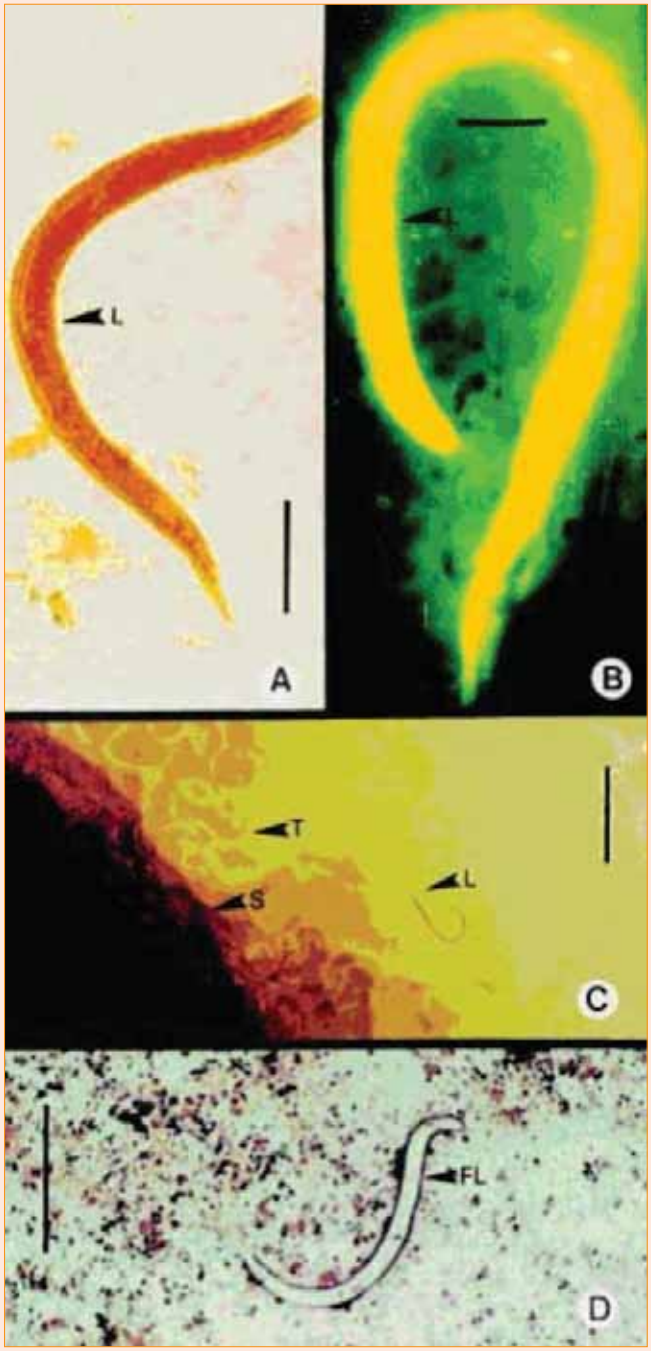

***Fig. 5**. Different diagnostic staining and culture techniques for* Strongyloides stercoralis.
A. *Lugol iodine staining of the rhabditiform larva in stool. This is the most commonly used procedure in clinical microbiology laboratories. A single stool examination detects larvae in only 30% of cases of infection. Scale bar = 25 µm.*
B. *Human fecal smear stained with auramine O, showing orange-yellow fluorescence of the rhabditiform larva under ultraviolet light. Routine acid-fast staining of sputum, other respiratory tract secretions (e.g., bronchial washings), and stool may also serve as a useful screening procedure. Scale bar = 25 µm.*
C. *Agar plate culture method. Motile rhabditiform larvae and characteristic tracks or furrows, which are made by larvae on the agar around the stool sample. This diagnostic method is laborious and time-consuming (2–3 days) but is more sensitive than other procedures (e.g., wet mount analysis) for the detection of larvae in feces. Tracks are marked (arrows and* T*). S, stool sample on agar plate;* L*, larva or larvae. Scale bar = 250 µm.*
D. *Gram stain demonstrating* S. stercoralis *filariform larvae (FL). Gram staining of a sputum sample is an excellent tool for diagnosing pulmonary strongyloidiasis. Scale bar = 250 µm.*

mesh basket nested on top. A piece of rubber tubing is slipped over the stem and sealed with a clamp. The funnel is filled with water to a level that will cover soil or plant tissue to be placed in the basket at the top of the funnel. A piece of tissue is used to line the basket and minimize the amount of soil that passes through. Nematodes leave the soil or plant tissue, pass through the tissue liner, and accumulate at the constriction of the tube created by the clamp. After a period of time, the clamp is loosened slightly to allow a few milliliters of solution to pass into a container, leaving a fairly clean solution to view under a microscope. Laboratories have developed variations for every component of this technique.

Materials

- Paper toweling
- Fine mesh screen (metal)
- Small wire basket (or plastic food basket)
- Funnel
- Tubing (that fits the base at the bottom of the funnel)
- Clamp
- Microscope, slides, cover slips and petroleum jelly (for observing specimens)

Procedure

1. Separate the soil in each sample by passing it through the fine mesh screen.
2. Once the larger chunks have been broken down, spread the sample on a paper tissue. The soil should form a layer about 1 cm thick.
3. Wrap up the soil within this tissue and place it within the wire basket or plastic fruit basket.
4. Slip a hose with a clamp onto the neck of a large funnel. Position the basket and soil in the funnel (see Figure 6).

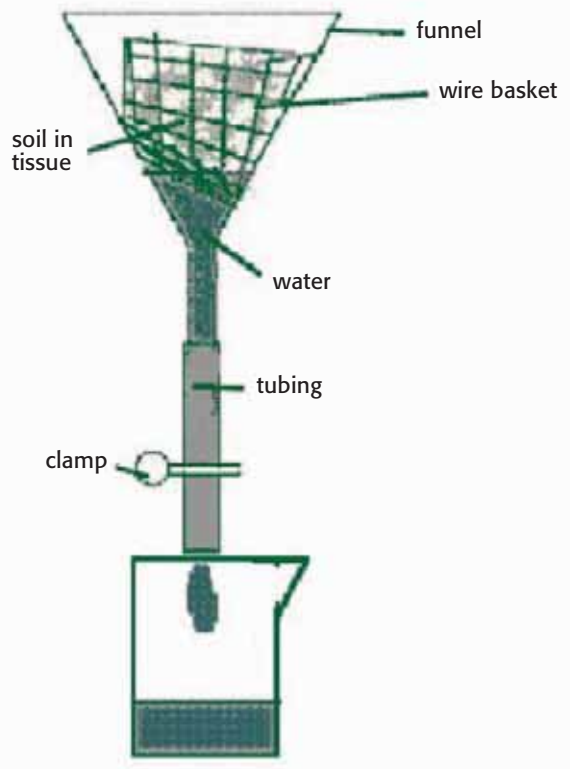

***Fig. 6**. The Baermann funnel.*

5. Make sure that the clamp is set on the hose. Fill the funnel with enough water so that the bottom of the soil is positioned beneath the surface of the water.
6. Leave undisturbed for 2–3 days. You may have to refill the funnel to replace water lost to evaporation.
7. During this time, active nematodes will move out of the soil and into the water. They'll fall to the bottom of the funnel and collect in the tube. To retrieve these specimens, release the clamp allowing water to flow through the hose into a collection beaker.

Agar plate cultures are performed as follows:

- Place stool on agar plate
- Seal plate to avoid accidental infection
- Store plate for 2 days at room temperature
- Larvae crawl over surface and carry bacteria with them, creating visible tracks
- Examine plates to confirm larvae
- Wash with 10% formalin and collect larvae by sedimentation

Repeat this procedure up to 6 or 7 consecutive days because of low parasite load and irregular output of larvae in many patients. Tests have shown the agar plate method is superior over a) direct smear, b) formalin–ether sedimentation technique, c) filter paper method. The agar plate method is not however available globally–sometimes only in the large town and teaching hospitals.

Endoscopy shows signs characteristic of inflammation of the duodenal mucosa. A strict observation of endoscope disinfection procedures is important as unprocessed endoscopes can transmit the worm.

5.3 Differential Diagnosis

There are many conditions producing similar symptoms–consider:

- Intestinal infections (amebiasis, bacterial colitis, Shigella, Campylobacter, Yersinia, Clostridium difficile)
- Inflammatory bowel disease
- Irritable bowel syndrome
- Functional abdominal disorders
- Drugs (NSAIDS, gold)

The key diagnostic element is to identify the parasite. This is not easy because the worm load is usually low and a number of stool tests need to be done to arrive at a conclusive diagnosis.

The chances of finding the worm are proportionate to the number of occasions in which the feces is examined.

6 MANAGEMENT OF STRONGYLOIDIASIS

6.1 Uncomplicated Strongyloidiasis (Table 4)

The treatment of strongyloidiasis is difficult because in contrast with other helminthic infections the *Strongyloides* worm burden must be eradicated completely. Complete eradication is difficult to ascertain because of the low worm load and irregular larval output. A true cure cannot be pronounced on the basis of negative follow-up stool examination alone.

A single stool analysis for *Strongyloides* stercoralis was found to be negative in up to 70% of known cases with *Strongyloides* infection.

Use a single dose of ivermectin 200 µg/kg to treat strongyloidiasis. A single dose of ivermectin at 200 µg/kg body weight is the drug of choice for the treatment of uncomplicated strongyloidiasis, although there is little evidence to support its use in children. Currently, dosing in children is estimated by height rather than weight using a centimeter-marked pole.

Ivermectin is available in 3 mg and 6 mg tablets.

A follow-up stool examination after therapy can confirm results. In chronic cases ivermectin can be given every 3 months until stools are negative in at least three subsequent tests.

Albendazole can also be used as an alternative.

***Table 4**. Preferred medication for strongyloidiasis (from http://www.emedicine.com/med/topic2189.htm)*

Drug name	Ivermectin (Stromectol, Mectizan) – drug of choice (DOC) for acute and chronic strongyloidiasis. Binds selectively with glutamate-gated chloride ion channels in invertebrate nerve and muscle cells, causing cell death. Half-life is 16 h; metabolized in liver
Adult dose	200 µg/kg /d p.o. for 2 days; may repeat course in 14 days
Pediatric dose	Administer as in adults if > 2 years. If < 2 years: 200 µg/d p.o. for 3 days
Contraindications	Documented hypersensitivity; do not use in first trimester of pregnancy and avoid use until after delivery, if possible
Interactions	None reported
Pregnancy	Safety for use during pregnancy has not been established
Precautions	Treat mothers who intend to breast-feed only when risk of delayed treatment outweighs possible risks to newborn caused by ivermectin excretion in milk Repeat courses of therapy may be required in patients who are immunocompromised May cause nausea, vomiting, mild CNS depression, and drowsiness

6.2 Hyperinfection or Disseminated Infection

The terms are used interchangeably and refer to a very high and rapid spread of the infection—usually in immunosuppressed patients and often associated with corticosteroid treatment.

Hyperinfection carries a high risk of Gram-negative septicemia and thus broad-spectrum antibiotics are usually given, especially to prevent bacterial meningitis.

6.3 Prevention

Infection is prevented by avoiding direct skin contact with soil containing infective larvae. People at risk—especially children—should wear footwear when walking on areas with infected soil. Identify patients at risk and perform appropriate diagnostic tests before they begin immunosuppressive therapy.

Persons in household contact with patients are not at risk for infection. The proper disposal of human excreta reduces the prevalence of strongyloidiasis substantially.

No accepted prophylactic regimen exists and no vaccine is available.

6.4 Prognosis

Acute and chronic strongyloidiasis have a good prognosis. However, untreated infection can persist for the remainder of the patient's life because of the autoinfection cycle. A patient's prolonged absence from an endemic area is no guarantee of freedom from infection.

Severe disseminated infection is commonly a fatal event, and it is often unresponsive to therapy.

7 LITERATURE REFERENCES

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8 USEFUL WEB SITES

- The U.S. CDC publishes a free information sheet on strongyloidiasis at: http://www.dpd.cdc.gov/dpdx/HTML/Strongyloidiasis.htm
- The American Society of Tropical Medicine and Hygiene: http://www.astmh.org/index2.html
- Royal Society of Tropical Medicine and Hygiene: http://www. rstmh.org
- eMedicine on strongyloidiasis: http://www.emedicine.com/derm/topic838.htm http://www.emedicine.com/ped/topic2161.htm http://www.emedicine.com/med/topic2189.htm
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