

Reflections on the future of gastroenterology – unmet needs

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Introduction

To state that the future of gastroenterology (GE) is bright is readily understandable because this speciality is indeed the largest in the internal medical arena. The discipline entails the largest organ with appendices such as liver and pancreas, contains the largest number of endocrine, immune, smooth muscle and nerve cells, carries the largest cancer load, and acute and chronic inflammatory conditions and is marred with the largest number of pathologic conditions, many still to be fully characterized. Yet this statement is currently in my view in need of some qualification as progress in GE seems occasionally slower and more incomplete than originally anticipated. This overview will therefore also draw attention to some unmet needs to stimulate professional enthusiasm for the challenges ahead, realising that it is easy to be an armchair critic and that predictions about the future are fraught with error.

Key words: ulcer disease, GERD, dyspepsia, IBS, IBD, gastrointestinal oncology, endoscopy, EUS.

Ulcer disease

The greatest impact of *H. pylori* (re)discovery and cure is obviously the surprisingly rapid decrease, if not disappearance of *H. pylori*-associated peptic ulcer disease, not only in the developed, but also in the emerging world. In contrast with this phenomenon is the continuation if not rise in drug-induced

(aspirin/NSAID-induced) ulcer formation. Indeed, the expectations are that drug-induced injury will remain a major health problem, particularly now that widespread use of COX-2 selective inhibitors remains uncertain. Prophylaxis, especially with proton pump inhibitors (PPIs) against the deleterious effects of non-selective COX-antagonists is at best mediocre, if prophylaxis is given at all. In view of the high complication rate, such injury signifies a major unmet need and urgently requires further pharmacological improvement and novel prophylactic approaches.

Gastroesophageal reflux disease (GERD)

The prevalence of GERD will continue to rise also in the emerging world. Overweight/obesity, sedentary lifestyle, dietary habits, *H. pylori* disappearance etc. all contribute to this increase. More attention will also be given to the extra-esophageal manifestations of the disease (*Fig. 1*). PPIs will continue to be the standard of therapy. The problem of the discrepancy between the excellent symptom relief and healing in controlled trials and the rising patient dissatisfaction (especially in the USA) in practice needs to be solved. Also the problem of nocturnal reflux and interference with sleep quality needs to be solved. We need to learn when and how so-called rescue or adjuvant medication is to be used, particularly alginate/antacids, which partition in the acid pocket of the cardia. How to interfere with weakly acid, non-acid (biliary) reflux remains puzzling. The results of GABA-B agonists or metabotropic glutamate antagonists are eagerly awaited.

Functional disorders – dyspepsia

Despite all the recent research and trials, there remains a large unmet need in our understanding of the pathophysiology of (functional/idiopathic) dyspepsia. The real causes of fundic

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Figure 1. The MONTREAL definition and classification of GERD [Vakil et al., Am J Gastroenterol, 2006]

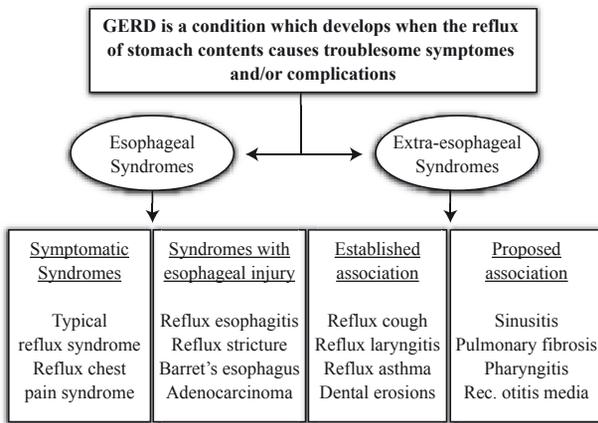


Figure 2. Dyspepsia therapy

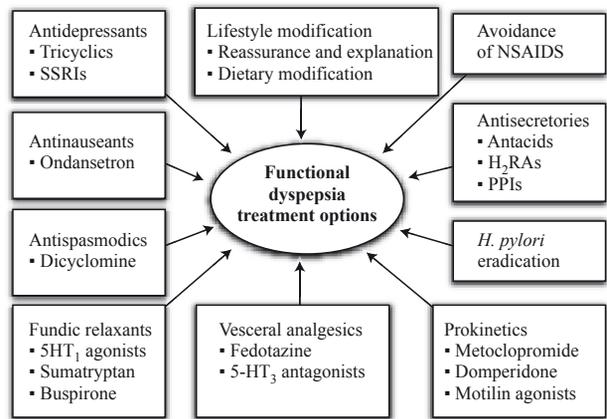


Figure 3. IBS therapy

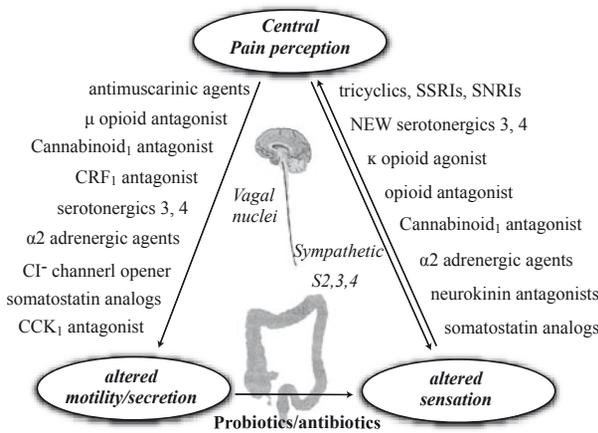
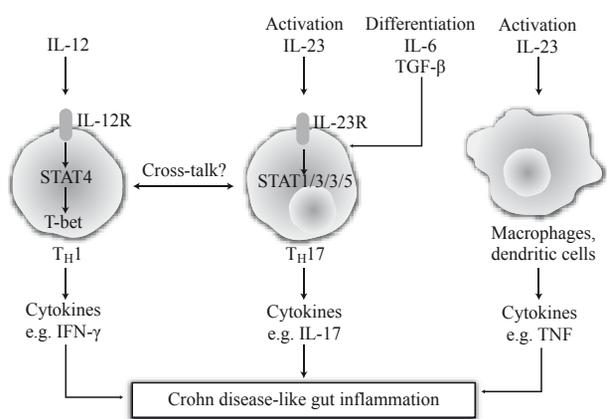


Figure 4. CD pathogenesis



dysaccommodation, visceral hypersensitivity, dysmotility and emptying abnormalities etc. remain enigmatic. Equally disappointing is the lack of efficacious pharmacotherapy to truly and reproducibly correct the functional aberrations. The plethora of current therapeutic possibilities (Fig. 2) is misleading as the efficacy of all avenues is low/mediocre at best, if present at all. New eager and bright researchers, with genuine interest in GE functional disorders, should tackle these challenging problems with a fresh open mind, willing to explore new paths and avenues, using uncontaminated well selected patient material, and applying the most advanced sophisticated technology.

Irritable bowel syndrome (IBS)

Progress in our understanding of the pathophysiology and therapy of IBS, the most common aberration in Gastroenterology has been disappointingly slow. All current attention is focused on so-called post-infectious IBS but to what extent this will really enhance our understanding remains uncertain. We ultimately need to know what the dominant pathophysiologic abnormalities are, where they are located along the circuit from bowel, afferent nerve, spinal cord, ascending and descending

nerve tract. Moreover, we need to find out the proper therapy for these patients. Again, the plethora of drugs being considered (Fig. 3) is somewhat misleading as current pharmacotherapeutic possibilities are mediocre at best.

Inflammatory bowel disease – Crohn disease (CD) – ulcerative colitis (UC)

Inflammatory bowel disease (IBD) should definitively remain the territory of the interested and experienced gastroenterologist in view of the complexity and difficulty of this condition. Vast experience is mandatory for optimal coaching and counselling such patients. The pathophysiologic paradigms are constantly changing and switching and that will probably remain so in the years to come. Currently the leading hypothesis focuses on an overly reactive immune system, responsible for driving the lymphocytes in a T_H1 direction in CD and (perhaps) in a somewhat modified T_H2 phenotype in UC but the emphasis is switching from IL-12 to IL-23 as the dominant cytokine driving pathway in CD (Fig. 4). We should, however, be aware that other investigators feel that the opposite viewpoint is more relevant, claiming a failing inflammatory/immune response as

the cause of CD as the consequence of inadequate clearing of the bowel from antigenic/bacterial influx.

Therapy has obviously progressed over the past decade and many are bewildered by the occasional rapid mucosal healing with biological therapy to the point that a top-down therapeutic approach is advocated instead of the traditional step-up approach. The enthusiasm of other investigators is more restraint or they realize that ultimately less than half the patients are in true remission at the end of one year, whichever biological scheme has been applied. Moreover, safety concerns are rising as infections and malignancy become non-negligible. Future progress again demands novel thinking, outside the traditional box, in order to advance the field. Whichever hypothesis is generated, it has to explain all features of these diseases, including the patchiness of CD and the segmental distribution of UC. The ultimate dream is to really find the cause of IBD with the possibility of permanent cure.

Oncology

GE is worldwide responsible for the largest cancer load. The gastroenterologist should become the central player in the multidisciplinary approach to digestive cancer, responsible for all aspects of diagnosis, therapy and care. He should be the permanent direct contact person for the patient, fully capable of per-endoscopic or endosonographically-guided interventions and standard chemotherapy. He should, for example, be well trained in endoscopic resection of early cancer, endosonographically-guided injection of oncolytic viruses, autologous transfected dendritic cells or other modalities for immune therapy, celiac plexus neurolysis etc.

We need to understand the intriguing rise of esophageal adenocarcinoma, whether it is reflux-, obesity- or therapy-related, or explained by the nitrate-nitrite-NO and nitrosating species pathway, responsible for DNA mutation and damage in the columnar metaplastic mucosa. We need to refine the population at true risk for neoplasia to bring the screening/surveillance cost-benefit ratio in balance in parallel with intensified attempts at chemoprophylaxis.

Gastric cancer is largely *H. pylori*-related in its early phases of development. Particularly for high incidence areas, *H. pylori* eradication should be considered but antimicrobial therapy should be carried out early in the evolution before advanced atrophy, achlorhydria and intestinal metaplasia has developed. The results of large scale, well-designed trials are eagerly awaited. If positive plans need to be developed for mass vaccination or early eradication in high gastric cancer areas. For the time being opportunistic screening and screening of individuals with a family history seems sensible in low incidence areas.

Pancreatic cancer will remain the most difficult and dismal cancer. Detection of early malignancy, amenable to cure is rare. Symptomatic cancer usually signifies incurability. Screening, preferably with endosonography should be offered to genetic/familial conditions with increased risk. Otherwise the development of sensitive and specific proteomics marker has to be awaited.

Colorectal cancer is dominating in many areas of the world and is rising in the far east. Population screening for precancerous polyps and (early curable) cancer should be designed and set-up in all countries. The screening modality (FOBT, virtual CT/MR, sigmoidoscopy, colonoscopy) will be largely determined by local resources and facilities. Colonoscopy, if chosen, should be of highest quality and patient acceptability with minimum missed lesions and minimum miss rate in detection of (flat)polyps and cancer: Improved technology and intense teaching will be necessary to reach that goal. Wherever screening modality is ultimately chosen, it will not only cost-effective but also cost-saving in view of the rapidly rising costs for chemotherapy for advanced metastasized colorectal cancer (Fig. 5).

Figure 5.

DIGESTETIVE ONCOLOGY

- Multimodality therapy of advanced cancer
 - organ preserving surgery (largely minimally invasive and robotic)
 - superselectively targeted conformational radiotherapy
 - in vitro selected chemotherapeutic cocktail (mutational microarrays)
 - intense and prolonged application of biologicals addressing all aspects of cancer growth

Figure 6.

Possibilities to improve resolution and analysis of surface microarchitecture and vascularity

- high resolution, high magnification CCD-endoscopy
- chromoscopy
- accentuation of vascular pattern (filters, index, hemoglobin)
- narrow band imaging

Figure 7.

Possibilities for molecular characterisation of tissue (bio-endoscopy)

- use of fluorescent monoclonal antibodies
- application of molecular beacons
- detection of cellular chromosomal changes/mutations with FISH

Figure 8.

Therapeutic EUS-indications

- Tissue sampling
 - mass lesions
 - lymph nodes
- Injection therapy
 - celiac plexus block
 - (gene therapy)
- Interventional therapy
- EUS guided (pseudo)cyst drainage

Figure 9.

NOTES

- Retroperitoneal
 - pseudocyst drainage
 - necrosectomy of pancreatic necrosis
- Intra-peritoneal
 - surgical procedures
 - gynaecological procedures
 - others...

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Diagnostic – therapeutic endoscopy – endosonography

Technology for both diagnostic and therapeutic endoscopy and endosonography will continue to expand and improve (Fig. 6-9). High-resolution-high-magnification endoscopy, chromoscopy, autofluorescence endoscopy, narrow-band imaging will become the standard for diagnostic investigation, although competition will increase from standard radiology, CT and

Figure 10.**Future Threats**

- GI-specialisation in Primary Care
 - GERD-IBD – Functional Disorders
 - transnasal endoscopy-screening
 - proctology
- (Eur. Soc. Prim. Care Gastroent.)
- Nurse-practitioners; Nurse-endoscopist
 - colorectal cancer screening
 - home follow-up malignancy etc.

MRI. Especially the therapeutic dimension of endoscopy and endosonography will remain the territory of the well-trained gastroenterologist. Hemostasis, polypectomy, sphincterotomy, endoscopic resection, pseudocyst/abscess drainage and necrosectomy, NOTES (natural orifice transluminal endoscopic surgery) etc. is and will remain in the hands of the experienced talented therapeutic endoscopist.

Potential future threats

Gastroenterologists should be aware of potential future threats. Specialisation is starting at the primary care level (*Fig. 10*). Indeed, the primary care-gastroenterologist is on the horizon, claiming competence in the treatment of GERD, IBD, proctology, transnasal endoscopic screening etc. Also nurse practitioners, nurse assistants are on the rise, involved in colonoscopic screening, home care of cancer patients etc etc. Integration of all such developments in our discipline will demand substantial creative thinking.

However, the most important threat to our specialty is the lack of pharmacotherapeutic success. For over a decade no blockbuster has been developed and nothing is in the pipeline for the foreseeable future. This ultimately translates in loss of attractiveness of the discipline and shrinkage of financial resources for research and training!

Figure 11.**Optimal GI-Training**

- 2 years of general internal medicine training (including general ward care, intensive care, cardiology, pulmonology)
- 4 years specific GI-Training
- 3 years basic GI-Training including endoscopy & preferably (endo)ultrasound
- 1 year advanced GI-specialisation advanced therapeutic endoscopy, hepatology, oncology etc.

Figure 12.**THE WAY FORWARD**

- RAISING ENTHUSIASM AND NURTURE GLOBAL TALENT FOR G-E
- RAISING BUDGETS FOR G-E BASIC AND CLINICAL RESEARCH
- WGO-SUMMIT WITH BMI – AND GI-LEADERSHIP TO ANALYSE FAILURES
- STREAMLINE RESEARCH PRIORITIES, BASIC, CLINICAL, TECHNOLOGIC

The way forward

The future of gastroenterology will largely depend upon the quality of its specialists. A proposal for a uniform training program is given in *Fig. 11*. Only optimal diagnostic and therapeutic competence and experience of the GE membership will guarantee progress and expansion. For that we need to enhance enthusiasm and to mobilize and nurture top global talent (*Fig. 12*). Budgets and financial resources need to increase to facilitate training and to activate basic and clinical research. Streamlining research priorities is mandatory for optimal effectiveness and minimal waste of resources. The World Gastroenterology Organisation/WGO should take the lead in bringing the scientific leadership of the Biomedical Industry and the GE profession together to analyse the cause of failure in the past, to discuss in depth the unmet needs, to design priorities and to create a platform for future evaluation and interaction. Hopefully, if all this can be realised, we will truly foster the development of our specialty, to the benefit of the patients we care for.