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Gastro-entero-hepatology in the next millennium

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Abstract

The scope of gastroenterology and hepatology now and its development into the next century are great and expanding. Only some of the many exciting improvements which are expected during the next few years can be discussed here. Progress in the microbial aetiology and novel targeted treatments for inflammatory bowel disease (IBD) will be paralleled by better understanding of functional upper and lower gut disorders, their neural control and neuropharmacological treatment. Technical developments in the pipeline include improvements in endoscopic and endosonographic equipment and techniques, including MR- or CT-based 'virtual colonoscopy' to obviate many invasive diagnostic colonoscopies, and the remarkable self-propelled endoscope, which will worm its way to regions of interest in the bowel. In hepatology, transplantation, and vaccination for hepatitides will increase, and improved treatment of acute liver failure may involve bioreactors or cryopreserved human hepatocytes. Gastrointestinal oncology will progress through more extensive surgery, gene therapy and techniques such as mucosal resection. A target force of about 150 trained gastroenterologist/hepatologists will be needed in the Netherlands – one for every 100 000 of the population. © 1997 Elsevier Science B.V.

Keywords: Gastroenterology; IBD; Functional dyspepsia; Irritable bowel syndrome; Neuropharmacology; Endoscopy; Endosonography; Oncology

1. Introduction

In this paper I offer my own personal and optimistic view of developments in gastroenterology and hepatology in the Netherlands and world-wide into the next century. The global prospects for gastroenterology are excellent. The subspecialty involves the largest area of body surface, the largest endocrine organ, the largest neuronal organ (with 200 million neurones), and the largest immune organ (with 50% of all lymphocytes); it includes by far the largest number of diseases, many still unexplored, and the largest oncological patient load. Gastroenterology/hepatology lies at the cross-roads between in-

ternal medical and surgical specialties, and I predict an increase in medical/surgical units, which will benefit from collaboration between physician and surgeon in such areas as hepatobiliary disorders, inflammatory bowel disease (IBD), transplantation, and many more. This paper cannot hope to cover all aspects of progress in gastroenterology, and so some divisions are selected in which major improvements are expected during the next few years.

2. Inflammatory bowel disease

2.1. Introduction

The prevalence of IBD will rise as hygiene improves in the developing world; its possible aetiology

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ical factors (*Mycobacterium paratuberculosis*, measles virus, or other infectious agents) will be further investigated, as will the associated immune changes. IBD, whether ulcerative colitis or Crohn's disease (CD), is essentially a failure of downregulation of the inflammatory immune response. The increasing role of knockout animals is of particular importance here; interleukin (IL)-2-, IL-10-, TCR- and CD45RB-SCID mice are examples of more than 30 knockout models now available. The presence of bacterial flora is crucial in all these models, since inflammation will not develop in the absence of bacterial antigens. *Bacteroides* currently seems the most important bacterium in this respect. The genetic predisposition profile will also be further characterised; the list of known genes is extending daily and currently includes HLA Class I and II, IL-2, TAP2, ICAM-1 and anti-tumour necrosis factor (anti-TNF) genes.

2.2. Targeted therapy for IBD

There will be a great increase in the volume of research on more appropriately targeted therapy such as modulators of the cytokine network (e.g., anti-TNF- α , anti-platelet activating factor (anti-PAF)), less toxic immunosuppressive drugs, and stimulation of mucosal regeneration and growth with various growth factors (e.g., trefoil peptides, EGF, TGF, FGF). It has been most encouraging to experience recently [1] how the inflamed mucosae in intractable CD resistant to corticosteroids and azathioprine can be healed by one single infusion of anti-TNF monoclonal antibody (MoAb) and kept in remission by 3-monthly infusions. However, the treatment of the future for IBD will probably not be such MoAbs but rather modification at the genetic level of the expression of pro-inflammatory cytokines to moderate the inflammation.

The enormous complexity of therapies for IBD that will be explored in years to come includes cytokines and anti-cytokines, tachykinin-receptor antagonists, protein tyrosine kinase and complement blockers; NF-KB will turn out to be very important for modulating the expression of the inflammatory cytokines. Future therapy for IBD will be an individualised, fine-tuned and custom-made combination of mesalazine, topical steroids, antioxidants and im-

munomodulators, with antibiotics added when the mucosal barrier is breached.

3. Functional disorders of the upper and lower gut

3.1. Visceral hypersensitivity

Upper and lower gut functional disorders, including functional dyspepsia and irritable bowel syndrome respectively, are still poorly understood. There will be an explosive growth in the presentation of these disorders, because most patients currently do not seek medical help. In addition, knowledge of their complex pathophysiology and neuromuscular co-ordination will increase. A key concept in these disorders will be 'visceral hypersensitivity', and it may be possible to detect selectively the cerebral projection of the various visceral sensations generated in the abdomen. There will be large-scale evaluation of motility- and perception-modulating drugs (e.g., new prokinetic agents, serotonergics and neuropharmacological agents). This will become possible through new long-term monitoring technology allowing correlation of symptoms with disturbed motor function, and leading to gastric and intestinal pacing.

3.2. Functional dyspepsia

For example, such investigations into functional dyspepsia will show whether this condition represents an abnormal stimulation of normal gastrointestinal (GI) receptors, an abnormal response to normal stimuli, abnormal upper GI motility, abnormal cerebral projection of normal GI afferent signals, or abnormal central stimulation of the upper GI tract via efferent pathways.

3.3. Irritable bowel syndrome

Symptoms of irritable bowel syndrome can predominantly involve constipation, diarrhoea, or pain with bloating. Table 1 suggests how current agents may give way to new approaches in these categories of lower gut functional disturbance. The 5HT₃ antagonists will be particularly important in years to come

Table 1
Current and emerging therapies for functional lower GI disorders

Therapies	Predominant symptoms		
	Constipation	Diarrhoea	Pain/bloating
Current therapy	bulking agents osmotic laxatives	loperamide cholestyramine	spasmolytics adsorbents
Emerging therapies	motilides loxiglumide 5HT ₄ agonists α_2 -antagonists	octreotide 5HT ₃ antagonists α_2 -agonists	leuprolide octreotide fedotozine * loxiglumide 5HT ₃ antagonists tachykinins/bradykinins?

* κ -opioid agonist.

for modulating visceral sensitivity and relaxing the bowel.

4. Liver disease

Developments in liver disease will include an increase in transplantation in the Netherlands from about 7 to 9 per million population per year, to come into line with the rate in other European countries. Combined therapy of chronic and acute viral hepatitis will include interferon, nucleoside analogues, antiproteases (e.g., the cyclovirs), and immunomodulators. Vaccination programmes will be more rigorously pursued, particularly in developing countries. Treatment of acute liver failure urgently needs to be improved, perhaps by using bioreactors or cryopreserved human hepatocytes until a donor liver is available. New and better long-term immunosuppressive drugs will become available for primary biliary and sclerosing cholangitis, along with better treatment for hepatic pruritus and fatigue.

5. Pharmacological developments

Prospects are good for the development of drug carriers to target specific cell types (e.g., hepatocytes, epithelial cells, smooth muscle cells). Immunomodulators and motility and perception modulators will also be developed, with particular impact on transient lower oesophageal sphincter relaxations (TLESRs); correcting TLESRs would potentially

eradicate reflux disease. In addition, GI neuropharmacology is a most rapidly developing research area because any digestive function – or malfunction – is ultimately centrally co-ordinated and can potentially be targeted by a neuropharmacological agent.

6. Technological developments

Developments in microminiaturisation will allow ultrathin pernasal endoscopes, including cholangiopancreatoscopes, to be made and lead to smaller picture elements (pixels), so that their resolution will approach that of the human eye. Mucosal resection is an endoscopic technique that will be used more in the future; a region of mucosa bearing a lesion is separated and raised by submucosal saline injection and then snared and removed. Endosonography is also developing rapidly, and higher ultrasound frequencies will permit better image resolution. MR cholangiopancreatography (MRCP) is already providing high-quality images.

Virtual colonoscopy is the technology of the future for colon cancer screening. It uses computer-processed data collected by rapid spiral CT or from MR images to produce an image of the bowel that can then be 'explored'. This technique will, potentially, drastically cut the number of diagnostic colonoscopies needed. Other approaching technological revolutions are stereo-endoscopy, infrared endoscopy in conjunction with appropriate intravascular contrast agents, combined visual and ultrasound endoscopy, intravenous endoscopy, and scope posi-

tion mapping. The self-propelling endoscope will move like a worm through the gut to regions of interest.

7. Changes in workload patterns

Therapy to combat *Helicobacter pylori* in the primary care setting will decrease the endoscopic workload, and only symptomatic cases will be referred for endoscopic examination. In addition, detailed MR-based analysis will compete with endosonography, MRCP will eliminate diagnostic ERCP, and spiral-CT or MR-based virtual colonoscopy will substantially decrease the need for diagnostic colonoscopy.

Thus, the need for diagnostic endoscopic manpower may be substantially reduced in future, although the demand for expert therapeutic endoscopy will remain and increase. Already 'sub-specialties' are being considered, each involving training to a high level of expertise in one very advanced therapeutic technology.

8. Oncology

Oncology will continue to be an extremely important aspect of gastroenterology. Table 2 summarises

some of the main areas of development in GI oncology in the future.

Because the pancreas drains into the GI tract, faecal early pancreatic mutations can increasingly be detected. The art of correct staging will be to select the most appropriate therapy, and photodynamic therapy will become increasingly important as new photosensitising agents become available.

There has been little recent improvement in the therapy of solid tumours, but in the future, surgery – including lymph node dissection – will be much more extensive, and gene transfer will be used to prevent cancer growth, to re-release chemotherapeutic agents, or to induce apoptosis in cancer cells. Mutations associated with oesophageal, gastric and pancreatic cancer mirror mutations seen in other malignancies, and understanding the uniform mechanisms leading to genetic aberration will allow more appropriate intervention. The techniques of mucosal resection can already remove nearly the whole oesophageal mucosa if necessary, with subsequent re-epithelialisation.

(Barrett's) oesophageal/intestinal metaplasia (EIM) is the commonest premalignant lesion known and screening for it is no more costly than screening for breast cancer. In one recent study [2], costs for each cancer detected were US\$ 31 500 for EIM and US\$ 54 000 for breast cancer; and the costs of each year of life saved were about \$ 5000 and \$ 4600 respectively.

Table 2
Future developments in the GI oncology

Improved parameter	Means of improvement
Multistep mutations leading to cancer	Further characterisation
Screening for cancer	Faecal detection of mutations (e.g., p53, Ki-ras, cErb, DAF)
Staging of cancer	Endosonography, endoscopic MRI, spiral CT, MRI, etc.
Early detection of dysplasia/cancer	Tissue autofluorescence
Selective removal/destruction of mucosal dysplasia/cancer	Mucosal resection, photodynamic therapy, argon plasma photocoagulation
Therapy for advanced solid tumours	Large-scale adjuvant/radiotherapy, gene transfer, multimodal protocols, more radical surgery, passive monoclonal immunotherapy, recombinant cytokines
Detection of oesophageal/cardial cancer	Surveillance of (Barrett's) oesophagus and cardia intestinal metaplasia
Detection of gastric cancer	Population screening for eradication of <i>H. pylori</i>
Detection of colorectal cancer	Population screening (50–55 years) with single or 10-yearly colonoscopy
Detection of biliohepatic cancer	Ultrasound/ α -fetoprotein screening
Detection of pancreatic cancer	Screening for faecal onco-markers

9. Training for the future

Finally, there is a need for more trained gastroenterologists/hepatologists in the Netherlands. In the future, a new professional training environment will be created in which pharmaceutical companies will be closely involved. The period of training must be no longer than 6 years, so as to leave the maximum possible productive life remaining, and the target will be to establish 150 such trained personnel in the Netherlands – one for every 100 000 of the population.

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