Gastroenterology

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Introduction

Sex began in 1963[1] and was followed shortly after by the birth of gastroenterology as a mainstream medical specialty (give or take a little for poetic licence), assisted by the advent of commercially available fibreoptic gastroscopes. Until the 1970s gastroenterology was usually the province of the general surgeon. This was not inappropriate since many of the gastroenterological conditions were, until then at least, commonly treated by surgery – ulcers, polyps, cancers, gallstones. Inflammatory bowel disease (IBD) was a partial exception, its prognosis having been substantially improved by the advent of sulfasalazine in the 1940s and cortisone in the 1950s. The surgeons were not quite so good at treating irritable bowel syndrome (IBS) and idiopathic constipation – but they tried! Some key discoveries and developments in the 1970s and 1980s changed gastroenterology for ever and put it firmly within the remit of the specialist physician, albeit one who often did minor endoscopic surgery and was sometimes regarded suspiciously as an aspirant surgeon. Critical early changes were the advent and development of fibre-optic (and later video-) endoscopy and the development of effective anti-ulcer drugs – firstly the histamine H2 receptor antagonists and later the proton pump inhibitors (PPIs).[2–6] Without these developments the associations between *Helicobacter pylori* and peptic ulceration, stomach cancer and gastritis would have been hard to establish.[7] The identification of *H. pylori* as the major cause of peptic ulceration and stomach cancer justly won a Nobel prize for its principal discoverers – a most unusual achievement for active clinicians in the modern era and of course led to the almost total disappearance of surgery for recurrent duodenal ulceration.

Therapeutic endoscopy has transformed the management of polyps and other pre-cancerous lesions and of common bile duct stones. Advances in scanning – ultrasound, computed tomography, magnetic resonance imaging and, most recently positron emission tomography, have of course had major impacts on diagnosis as elsewhere in internal medicine. Other developments have been more subtle. There is a better understanding of pathogenic mechanisms behind IBD but these have not yet translated into dramatic changes in therapy with the exception of the serendipitous 'borrowing' of anti-tumour necrosis factor (TNF) therapies from the rheumatologists who got there first. Functional bowel disorders are also better understood and more appropriately investigated and managed but as yet without any dramatic therapeutic breakthroughs.

Endoscopy

Although earlier pioneers had made some progress with multiple lens systems that allowed limited flexibility of endoscopes, the major advance was the development of 'coherent' bundles of optical fibres that were made from a glass of one refractive index surrounded by glass with a different refractive index.[2] This allowed total internal reflection 'trapping' the relevant 'pixel' of the image within each flexible fibre allowing the endoscopist to see around corners. Basil Hirschowitz was the first to see the potential application of this to gastroenterology and arguably invented modern gastroenterology in the process.[3,4] Developments in computerisation and the video-endoscope digital imaging system have allowed further step-by-step improvements. The more recent development of endoscopic confocal microscopy is a fascinating quantum leap that allows visualisation of individual epithelial cells and bacteria in vivo and has yet to be fully exploited.[8]

How did endoscopy change things? It allowed a much better understanding of oesophagitis, its relationship or otherwise to symptoms and to hiatus hernia. It allowed oesophageal stenting although that could also be done radiologically or with the use of a rigid oesophagoscope under general anaesthetic. It expedited the development of injection therapy and, later, banding for effective treatment of oesophageal varices. It greatly improved diagnosis for gastric ulceration, in particular the distinction between benign and malignant ulcers. Duodenal ulcers were reasonably accurately diagnosable by barium meal but the subsequent ability to diagnose *H. pylori*, initially by gastric biopsy, transformed the approach to treatment.

The realisation that coeliac disease could be as readily diagnosed by multiple endoscopic duodenal biopsy as by use of the Crosby capsule was a huge relief for junior doctors and patients alike.[9] The Crosby capsule that was widely used from the 1960s to the early 1980s consisted of a rotating knife blade inside a cylinder with a hole in one side to admit the mucosa when suction was applied via the connecting tube. The knife was spring loaded, requiring the

skills of a watchmaker to 'prime' it. The capsule was attached to a length of tubing, one end of which remained outside the patient's mouth while the capsule was swallowed. When in the jejunum (after a variable number of trips to the X-ray department to monitor what was often agonisingly slow progress through the pylorus and duodenum) the knife was fired by applying rapid suction to the tube and the capsule pulled out and opened. This ceremony was accomplished using an Allen key to unscrew the cylinder and accompanied by elation or despair for both relevant parties depending on the contents of the capsule which would often have fired prematurely or not at all. Worse still, the capsule would sometimes come unscrewed or fall away from the tubing and the patient and nursing staff would then be pleaded with to hunt through subsequent stool samples to recover the valuable capsule.

Colonoscopy has probably had even more impact than upper gastrointestinal (GI) endoscopy by allowing easy removal of polyps that would previously either have been missed or would have required open surgery. It has also allowed much more reliable diagnosis of lower intestinal bleeding – previously a source of worrying guesswork sometimes leading to 'blind' hemicolectomy in the hope that the bleeding point was contained within the resected colon. This gradually lead to the realisation that occult colonic bleeding more often came from the proximal than the distal colon although identification of the usual explanation for this (angiodysplasia) required the advent of colonoscopy. It has also allowed a better understanding of colon cancer development, particularly of the dysplasia-cancer sequence although this has yet to lead to clear changes in management or prevention.[10] Some will argue heatedly that routine colonoscopy for all would of course help to prevent colon cancer but this is expensive when applied to the normal risk population; given that only 3% of Western populations are destined to die of colorectal cancer at an average age of over 65 it follows that prevention of all deaths from colorectal cancer would only prolong life by about four months (3% of 10 years, assuming 10 years life lost for each colorectal cancer death) and it would take a huge number of colonoscopies to achieve such total prevention.

Acid-suppressing drugs

Another gastroenterological Nobel prize was awarded to Sir James Black for his invention of histamine H2 receptor antagonists (admittedly he invented beta blockers as well).[5] These at last allowed reliable healing of duodenal and gastric ulcers. This led to evidence that duodenal ulcer healing could be achieved with relatively modest suppression of acid production, particularly if nocturnal secretion was suppressed, whereas oesophagitis was more effectively treated using the more powerful acid suppression of the proton pump inhibitors that followed later.[11,12] Drugs were finally available that worked and had clearly identifiable mechanisms. An effective treatment for duodenal ulcers had existed for many years – bismuth subcitrate solution (Denol®), but it tasted odd, was bright red in colour, turned the stools black and had so little known about its mode of action (subsequently found to be killing of *H. pylori*) that its use seemed to verge on sorcery and its sales were modest, particularly after the introduction of H2 antagonists. Antacids only produced sufficient acid suppression to heal ulcers if they were used in very large doses. The advent of PPIs had only a modest additional impact on ulcer healing which was already very good with H2 antagonists but a more significant impact on the treatment of oesophagitis because of the need for greater acid suppression, presumably to bring the pH above 4.0, ie above the effective range of action for pepsin.[13] Initial anxieties about the induction of gastric carcinoid tumours by PPI administration in experimental animals were raised in a heated commercial battle between the H2 antagonist and the PPI manufacturers but the lack of any short- or medium-term evidence of worrying side effects in humans gradually dispelled anxiety and the choice of preparation became resolved by more subtle differences in dosing regimen, drug interaction (eg with warfarin and anti-convulsants) and competitive pricing. Since the global market for acid-suppressing medications now runs at over $24bn these were not trivial issues. With the increasing prevalence of reflux oesophagitis in association with obesity this has now led to very long-term and widespread use of PPIs, with some persisting uncertainties about very long-term safety although data so far are reassuring.[14]

Helicobacter pylori

The combined availability of H2 antagonists and endoscopy led to the discovery that duodenal ulcers usually recurred within a year if H2 antagonists were stopped after ulcer healing.[15] In 1984, Marshall and Warren showed that most patients with duodenal ulcers had bacteria in their gastric antrums – a curved rod initially named *Campylobacter* ('bent rod') *pylori* and subsequently relabelled *Helicobacter pylori* once it was recognised that it was genetically distinct from other *Campylobacter spp*.[7] Marshall and Warren were not the first to find these bacteria. Others had done so but had generally regarded them as being rather common (which they were in the 1960s and before, probably affecting about 80% of the global population) and probably a harmless commensal.[16]

When I was a senior registrar we had a near miss on this, as had others before us.[17,18] I had performed an endoscopy on a patient with persistent vomiting who had multiple duodenal erosions. Suspecting possible hookworm infestation, I took duodenal biopsies and aspirate and was surprised when the report came back showing spiral bacteria plus spermatozoa. We never did track down the source of the spermatozoa (direct questioning of the patient proved dangerous and unrewarding) but an astute colleague (TR) performed silver staining on a large number of archival pathology specimens (no ethics permission required in those days) and found that similar bacteria were commonly present in patients with gastritis. Then came the two sad inadvertent errors that cost us our Nobel prize. First, our study depended heavily on archival tissue much of which was from surgical gastrectomy specimens and we failed to find a significant association between *H. pylori* and duodenal ulcer – it was subsequently recognised that ulcers which presented as

acute surgical emergencies due to bleeding or perforation were less likely to be *H. pylori* associated. The second problem was that we failed to culture the bacteria despite numerous attempts. The Australians cultured their bacteria by fortuitously leaving the culture plates for an extra-long incubation over a bank holiday weekend. This of course then allowed Barry Marshall to perform his famous self-infection experiment and show that histological gastritis was induced. Our modest paper, sadly misleading in view of the lack of correlation with duodenal ulcer, was in press when the Australians published their letter in the *Lancet* reporting the association of spiral bacteria with peptic ulceration.

At first there was much scepticism that bacteria could cause ulcers – we all knew ulcers were due to acid moreover the bacteria were found in the stomach and only rarely in the duodenum (if gastric metaplasia is present). Proof that the association was real awaited results of controlled trials of eradication therapy. The first agents to be used were bismuth salts, encouraged by the discovery that relapse rates for recurrent ulceration were much lower after ulcers had been healed with oral bismuth than after healing by H2 antagonists.[19] The bacteria proved difficult to eradicate with monotherapy and it was only after the realisation that concurrent use of proton pump inhibitors greatly enhanced the efficacy of antibiotics that eradication rates rose above 80%. Quadruple combination therapy, including a bismuth preparation, is still used in intransigent cases.[20]

The association between *H. pylori* and gastric cancer was harder to prove, particularly since there was a known negative association between duodenal ulceration and gastric cancer. This only started to make sense when it was realised that *H. pylori* could affect different parts of the stomach in different individuals. Antral infection and its subsequent antral gastritis would give rise to hypergastrinaemia, since the G cells are sited in the gastric antrum, and consequent hyperacidity and increased risk for peptic ulceration. Infection of the gastric body by *H. pylori* would, however, cause atrophic gastritis, hypochlorhydria, contamination by other bacteria, and an increased risk for gastric cancer.[21,22] This was confirmed in animal models and supported by parallel changes in worldwide *H. pylori* prevalence and gastric cancer rates. Sadly though, as the rates for gastric cancer have been falling, the rates for adenocarcinoma of the lower oesophagus have been rising – but that is another story.

Inflammatory bowel disease

This is a particular interest of mine but one where progress objectively has been rather slow. It still awaits its '*H. pylori* moment'. The new genetics have allowed the identification of a gene, NOD2/CARD15, abnormalities of which are associated in Western population with an increased risk for Crohn's disease.[23–25] This and subsequently identified genetic associations have thrown some light on likely pathogenic mechanisms all of which revolve around an abnormal immunological response to bacteria, but with considerable remaining uncertainty about the detailed mechanisms. Smoking has been identified as a risk factor for Crohn's disease but curiously, and strongly, protective against ulcerative colitis but with the mechanisms for neither relationship properly understood. The vast literature on the immunological changes in IBD, while intellectually fascinating, has so far proved of little practical help. Even the undoubted improvement in treatment that has resulted from anti-TNF antibodies is somewhat fortuitous since the recombinant TNF-alpha receptors that are so effective in rheumatoid arthritis do not work in Crohn's disease.[26] It looks as though the useful effect of the anti-TNF antibodies is mediated via induction of apoptosis of T cell and monocyte subsets that bear transmembrane TNF-alpha. Had the recombinant TNF-alpha receptor therapies been tried first we might easily have abandoned anti-TNF therapy in Crohn's disease.

This perhaps does not truly reflect the current situation. I believe that quite rapid progress is now being made in understanding the role of bacteria in IBD and thus for better medical treatments. I would be hopeful that in the next 10 years we will progress a long way beyond 'steroids for acute relapse, mesalazine for maintenance and immunosuppressives if things get desperate'.

Irritable bowel syndrome

At least one in 10 individuals have irritable bowel syndrome (IBS) which is a cause of considerable distress and loss of earnings. There are no positive diagnostic tests and medical treatments are unsatisfactory so patients need considerable traditional 'physicianly' skills to be appropriately reassured and treated. Gastroenterologists have taken rather a long time to learn how to do this but I think we are getting there and this is a practical aspect of patient care that has changed considerably during my professional lifetime. There is now a widespread recognition that it cannot be appropriate to subject one in 10 of the population (or the arbitrary sample of that one in 10 who come to clinic) to head to toe endoscopy and radiology and moreover that increasing the number of negative tests does not usually increase patient reassurance since most patients not unreasonably think the doctor must know there is something wrong with them if they are putting them through so many unpleasant tests. Diagnosis is increasingly, and appropriately, based on probabilities so that young patients (say under 40 years) with typically intermittent symptoms of IBS, no significant family history of cancer or IBD and no alarm symptoms such as weight loss or bleeding can usually be diagnosed and reassured with only a few very simple investigations. One of these investigations should be the anti-endomysial (or tissue transglutaminase) antibody test for coeliac disease. Although not totally reliable, sensitivity and specificity usually exceed 95% making this is a reasonable way of excluding coeliac disease in a low risk group of patients.[27]

Understanding of the pathogenic mechanisms behind IBS has also advanced considerably with the realisation that up to one third of cases may be a consequence of prior gastroenteritis and that very low-grade subclinical inflammation may be a significant factor in upregulating intestinal sensitivity to distension – the fundamental physiological alteration in IBS.[28] This greater understanding has, hopefully, led to the cessation of doctors telling their patients 'not to worry, it's all in the mind', a past

strategy that invariably provoked fury, a provocation of the irritable bowel, and a demand for a further opinion. Step by step we gradually progress.

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CURRENT KEY DEVELOPMENTS

Irritable bowel syndrome – the new inflammatory bowel disease?

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Irritable bowel syndrome (IBS) is currently diagnosed from symptoms which include chronic abdominal pain/discomfort associated with disturbed or altered bowel habit in the absence of structural or metabolic changes.[1] This would seem to exclude significant gut inflammation but recent studies suggest the need to rethink.[2] Progress in defining the mechanisms underlying IBS research has been limited by an inability to subdivide a very heterogeneous population. Recent research has attempted to overcome this limitation by focusing on a small subgroup of patients whose IBS developed after a bout of infectious gastroenteritis.[2]

Post-infective IBS as a model to study functional gastrointestinal diseases

Post-infective IBS (PI-IBS) is by definition the development of IBS in individuals with previously normal bowel function. Unlike other irritable bowel syndromes it has a defined start date and a known precipitant. It represents nature's experiment, infection being a random event not obviously dependent on personal choice. This provides a rare opportunity to study the mechanisms underlying the development of IBS. Numerous studies have confirmed earlier reports demonstrating an increased incidence of functional gastrointestinal (GI) diseases following GI infections (Table 1).[3,4,5] Adverse risk factors include an initial illness lasting >3 weeks, toxigenic bacteria, female gender, and age <60.[4,5,6]