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WHAT'S NEW IN GASTROENTEROLOGY?: REPORT OF A SYMPOSIUM HELD IN THE COLLEGE ON 8TH MARCH 1996*

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The symposium provided practical clinical advice for generalists as well as state of the art updates on the molecular biology and pathogenesis of a range of conditions: *Helicobacter pylori*; hepatitis C virus; colorectal cancer; and inflammatory bowel disease.

HELICOBACTER PYLORI

Pathophysiology and clinical associations

In the UK approximately 50–60% of people over the age 50 are infected with *Helicobacter pylori* (HP) but few develop disease as a consequence. An understanding of the pathogenesis and pathophysiology of HP infection should clarify how most of us remain healthy despite HP colonisation.

Helicobacter pylori colonise only gastric-type epithelium predominantly in the antrum, and are only found in the duodenum in areas of gastric metaplasia. Infection and inflammation of the antrum results in duodenal ulceration. It is thought that inflammation depletes antral D-cell stores of somatostatin, thus removing the normal inhibitory control of gastrin release from neighbouring G-cells. The ensuing hypergastrinaemia stimulates acid hypersecretion from parietal cells with subsequent damage and ulceration of the duodenal mucosa. HP-positive healthy volunteers have levels of gastrin and acid secretion three fold higher than HP-negative people. Ulcer patients have similar degrees of hypergastrinaemia but even greater acid secretion and thus appear to be more sensitive to the hypergastrinaemia; the reasons for this remain speculative.

The majority of patients complaining of dyspepsia do not have either a gastric ulcer in their stomach (GU) or a duodenum (DU) one, and are labelled as non-ulcer dyspepsia (NUD). The importance of HP in this large group of patients is controversial. From current evidence, HP eradication benefits only a minority of NUD sufferers and at present cannot be widely recommended. The challenge is to find ways of defining which subgroup may benefit from such treatment.

Epidemiological studies estimate an odds ratio of 2.7–6 for gastric cancer patients who are HP positive and, if this association is causal, 60–70% of all gastric cancers could be attributable in some way to HP. How the same organism can cause both DU and gastric cancer is unclear, but it seems that a small minority of people with chronic HP infection may become hypochlorhydric with the raised intragastric pH, thus predisposing to colonisation with other bacteria and subsequent *in situ* formation of carcinogenic nitrosoamines from food components. Chronic inflammation stimulates epithelial proliferation, generates reactive oxygen radicals and impairs gastric secretion of the antioxidant ascorbic acid. This may set the scene for DNA damage with the development of an atrophic gastritis and the gradual progression to intestinal metaplasia, dysplasia and neoplasia.

*A list of speakers and the titles of their papers presented at this symposium is recorded in *Proceedings* Vol. 26 p 347.

Diagnosis and treatment

Culture of HP remains the gold standard for diagnosis but is laborious and not available in some laboratories. The rapid urease (CLO) test, in which endoscopic biopsies are placed in a well containing urea and a pH indicator, is cheap, highly specific, rapid and if carried out properly, has a sensitivity of 75–90%. Antral histology using standard stains has a sensitivity and specificity of 85–100%.

The urea breath test has high sensitivity and specificity with little (^{14}C) or no (^{13}C) radiation hazard, and is the best non-invasive means of diagnosing HP infection. Rapid office based serological kits for HP are now cheap and attractive to those in general practice; their simplicity and speed are offset by uncertain accuracy and lack of validation. Laboratory-based ELISA testing is superior but antibody titres do not fall in a proportion of patients whose colonisation has been successfully eradicated; serology cannot therefore distinguish present from past infection.

Eradication is essential first-line therapy for all HP associated duodenal and gastric ulcers. Treatment of patients with NSAID-associated ulcers who are also infected with HP is more complex but probably justified, whereas HP eradication is of no benefit in gastro-oesophageal reflex disease (GORD) or NUD. It is tempting to offer treatment to all HP positive dyspeptic patients but, to put this in perspective, it is estimated that of 100 dyspeptic patients only 20 have a peptic ulcer while another 15–30 with NUD might benefit; the remaining 50–65 patients would be treated unnecessarily and exposed to the risks associated with treatment.

Difficult questions still unanswered but which are areas of active study are the following. What should be done about a dyspeptic patient in whom non-invasive tests show HP positivity? Should they be referred for endoscopy or empirically treated? Should therapy for HP be offered to relatives of those with gastric cancer or to patients who have read about gastric cancer and request testing for HP and eradication therapy?

Choice of eradication regimen

Triple therapy regimens (acid inhibitor plus two antibiotics) have been shown to be more successful than dual therapy. Currently the most widely used regimen includes omeprazole and two antibiotics, commonly amoxycillin and metronidazole (OAM). Lansoprazole-based regimens are also highly effective. Many factors, notably local rates of metronidazole resistance, may influence success rates but patient compliance is of critical importance. Ulcer recurrence after successful treatment of HP infection is rare and usually associated with reinfection (1–2% per year).

HEPATITIS C INFECTION

The papers presented for the most part covered the same ground as the recent workshop in the College. A verbatim account of this has been published in *Proceedings* (1995; **25:** 583–622).

COLORECTAL CANCER

Molecular genetics

Approximately 30,000 new cases are diagnosed and 19,000 deaths occur annually from colorectal cancer in the UK. Overall 5 year survival remains low (30–40%)

with little improvement over the last 30 years, largely because the majority of patients present with advanced disease.

The large number of genes implicated in the development of colonic neoplasia fall into two broad classes, dominantly acting oncogenes, for which a mutation in only one allele is required (e.g. *Ki-ras, c-myc, src*), and recessive tumour suppressor genes, for which a functional loss of both alleles is necessary for acquisition of oncological potential (e.g. p53, APC, hMSH2). For neoplasia to develop the presence of several genetic abnormalities is required, and different and discreet processes are involved sequentially at different stages of the development of an adenocarcinoma.

Mutations in APC which are present in 60% of all colonic cancers occur during the transition of normal epithelium to an adenoma. Specific activating-point mutations in codon 12 of the *Ki-ras* gene are found in 50–60% of colorectal carcinomas and in a similar percentage of benign adenomas. It is now possible to detect *ras* mutations in stool samples from patients with colonic cancer, thus opening up the possibility of non-invasive screening.

p53 protein, expressed following DNA damage, prevents DNA damaged cells from proliferating, either by arresting them at the G1/S 'check-point' in the cell cycle or by inducing apoptosis. Loss or inactivation of p53 occurs relatively late in the neoplastic process and is found in 75% of colon cancers. Thus determination of p53 status may be of more than academic value; some studies suggest that tumours containing this mutation are associated with a worse prognosis.

The DNA mismatch repair family consists of a set of genes (hMSH2, hMLH1, hPMS1 and hPMS2) which maintains DNA fidelity. Protein products of these genes are critical for the repair of errors in DNA replication; germline mutations in these genes underlie the autotosomal disorder hereditary non-polyposis colon cancer (HNPCC) which accounts for 5–10% of all colorectal malignancy. Whether detecting these genetic abnormalities is of clinical value in diagnosis, screening and management of the majority of patients with 'sporadic' colonic malignancy is yet to be established.

Screening

Currently the only way to secure cures in colonic cancer is by removal of pre-malignant lesions or early cancers at a curable stage. The gradual adenoma-carcinoma sequence offers an ideal opportunity to do this, but there are pertinent questions about screening for colorectal cancer.

Does screening reduce colorectal cancer incidence and mortality? Case control studies have demonstrated that effective methods do exist for reducing incidence and mortality of colorectal carcinomas. In the US National Polyp Study, colonoscopy with polypectomy was associated with a 76–90% reduction in subsequent tumour incidence. Other studies and randomised trials have reported substantial benefits of screening by faecal occult blood (FOB) testing (25–33% mortality reduction) and flexible sigmoidoscopy (59–80%).

What is the optimum method of screening? FOB testing, flexible sigmoidoscopy and colonoscopy all have their proponents. Most controversy surrounds FOB testing; epidemiological studies have shown repeatedly an increased detection of Dukes A cancers and a reduced incidence of liver metastasis at diagnosis. However, only one study has shown significant impact on cancer mortality. Against this has been set the low sensitivity and specificity of FOB testing, the costs of colonoscopy if offered to all those with positive tests, and the dislike of FOB testing by some members of the public which results in poor uptake of the test. It has been estimated that widespread FOB testing would cost around £3,000 for every cancer detected.

At the other extreme, total colonoscopy is unarguably the optimal diagnostic test but it is expensive and invasive; it is unlikely that medical services in the UK could cope with such an increased endoscopic burden. As a compromise once-only colonoscopy for those aged over 60 has been advocated and is currently being assessed.

Flexible sigmoidoscopy is relatively cheap, highly sensitive and specific, safe and easy to perform. Several trials have demonstrated its efficacy in reducing incidence (45–80%) and mortality (85%) from cancer arising in the segment of colon examined. Cost-benefit analyses estimate an approximate cost of £5,500 per cancer prevented and £8,500 per cancer death prevented. The implications for endoscopy workload, however, are sobering; nationwide adoption of such a policy might mean up to 50 extra flexible sigmoidoscopies per week for each British gastroenterologist. Delegating this task to trained nurse endoscopists is one approach to this problem and early trials in the USA are promising.

Is it possible to select those who are at high risk of malignancy? The importance of a thorough family history cannot be overstated. Familial adenomatous polyposis (FAP) and HNPCC account for 6–15% of all cases of colon cancer and many so called sporadic tumours may also have a familial basis. The lifetime risk of colonic cancer in people with one affected first degree relative is around 1 in 17 this rises to 1 in 12 if the relative is under 45 at diagnosis, and to an alarming 1 in 6 if two first degree relatives have colorectal cancer. Members of these families require life-long surveillance by colonoscopy as the tumours often develop in the proximal colon and are not detected by flexible sigmoidoscopies.

The risk of colorectal carcinoma in patients with long-standing extensive ulcerative colitis or Crohn's colitis is also high with estimates of 7% at 20 years and 16.5% after 30 years although the impact of colonoscopic surveillance or early diagnosis even in these patients is questionable.

What can be said of current UK screening guidelines? No guidelines currently exist in this country and the optimum schedule for screening and surveillance is yet to be determined. Reluctance expressed by both politicians and doctors is based on the cost and the additional endoscopic workload. These issues need to be addressed, not least because the case for cost-effective colon cancer screening is possibly even stronger than that for either breast or cervical cancer; it is no longer a question of whether colon cancer screening is effective, but whether society deems the cost worthwhile.

INFLAMMATORY BOWEL DISEASE (IBD)

Mechanisms of IBD

The aetiology of IBD remains elusive, and both environmental factors (intestinal microflora, diet, smoking, possibly the oral contraceptive pill) and genetic factors are likely to be involved.

Increased familial prevalence of IBD may be present in 10–35% of cases and

close concordance exists between parents and affected offspring with respect to disease type and extent, but not with age of onset; affected offspring often develop disease at a younger age. The mechanism of this genetic anticipation is unknown. Varying prevalence rates in ethnic groups, studies in migrants and an increased concordance in monozygotic twins also support the importance of genetic factors in determining predisposition to IBD.

Currently genetic markers are being investigated and MHC Class II genes have attracted attention. The presence of HLA-DR2 has been strongly associated with IBD in Japan but not in the UK. Recently HLA DRB1*0103 was found twice as frequently in IBD patients as in controls and this gene may modify disease behaviour and predict clinical outcome. Up to 60% of the genetic susceptibility to ulcerative colitis can be attributed to genes of the MHC Class II region, but this does not hold true for Crohn's disease where non-HLA genes may be more important.

Data suggest that IBD is primarily immunologically mediated but it is not clear whether the activation of T and B lymphocytes in IBD is a specific response to a single antigenic stimulus. No convincing evidence exists for a specific defect of T lymphocyte function in IBD. Nevertheless a large number of cytokines and chemokines have been identified as crucial mediators of the inflammatory cascade in active IBD. Many have pro-inflammatory properties (IL-1, IL-6 and TNF-α), some are primarily chemotactic factors (IL-8) and still others may play important regulatory roles (IL-2, γ-interferon, IL-4 and TGF-β). Dysregulation of these inflammatory mediators may be important in the pathogenesis of IBD and may provide targets for novel approaches to therapy.

A causative role for these cytokines is supported by newly developed animal models using genetically manipulated mice. Both IL-2 and IL-10 'knockout' mice develop spontaneous colitis which improves following treatment with the relevant cytokine. In some models treatment with antibodies to the pro-inflammatory cytokine TNF-α have resulted in dramatic responses. Two reports of anti-TNF-α antibody infusions therapy in patients with active Crohn's disease are very encouraging.

Many questions about the development of IBD remain unanswered, such as which luminal factor triggers the whole process and what determines the predilection of Crohn's disease for the terminal ileum and the distal distribution of ulcerative colitis?

Management of IBD

The range of therapies available for IBD continues to expand. 5-aminosalicylates (5-ASA) and corticosteroids remain the mainstay of treatment with azathioprine as an effective second-line agent. Corticosteroids are ineffective in maintaining remission and the serious side-effects seen with long term use have prompted the search for newer, safer steroids. Much of the benefit of steroids in IBD may also be topical and so newer steroids with minimal systemic activity are attractive; one of these, budesonide, undergoes rapid and extensive first-pass metabolism but has high affinity for glucocortiocoid receptors. Two randomised trials in active ileocolonic Crohn's disease have demonstrated a similar efficacy to prednisolone but fewer steroid-related side-effects and less suppression of the pituitary-adrenal axis. Budesonide enemas are also as efficacious as prednisolone enemas in ulcerative colitis and have fewer side-effects.

Azathioprine remains an underused immunomodulatory agent. It is effective in steroid resistant/dependent patients and in patients with fistulae in whom a response rate of over 60% may be seen. The onset of its effect may be delayed for several months and side-effects lead to cessation of therapy in 10% of patients. Accumulating safety data are reassuring and, importantly, no increased risk of malignancy appears to exist with such long-term treatment in IBD.

Intravenous cyclosporin A is effective in some patients with severe active disease, but the number of patients studied has been small and toxicity is common. Unfortunately long-term oral treatment in IBD has been disappointing and enema formulations are ineffective in distal ulcertative colitis. Small studies of intramuscular methotrexate in refractory Crohn's disease have been promising with up to 72% of treated patients in remission at 3 months and an acceptable level of toxicity.

Metronidazole and ciprofloxacin have been widely used in active Crohn's disease but, while isolated impressive results have been reported, data from well designed trials is lacking. They are effective in perianal Crohn's disease or 'pouchitis' after surgery but their wider use requires further investigation.

A diverse array of new therapies exist and are currently being evaluated. Heparin may have useful anti-inflammatory properties as well as anti-thrombotic effects. Epidemiological studies correlating smoking and IBD have lead to interest in treatment with nicotine patches; flaws in study design have cast doubt on their reported benefits in active ulcerative colitis. Luminal short chain fatty acids, notably butyrate, may be deficient and trials of enemas containing them have been encouraging in distal ulcerative colitis.

Immunomodulatory therapy is now one of the most exciting areas in the management of IBD. As well as anti-TNF-α antibodies, treatment with IL-10 is being evaluated and beneficial effects with IL-1 receptor antagonists, interferon-α and anti-CD4 antibodies have also been reported. The next few years will undoubtedly see an expanding role for these novel therapies in IBD as well as in other inflammatory disorders.

CONCLUSIONS

A gastroenterologist today requires a working knowledge of epidemiology, infectious diseases, oncology, immunology and molecular biology, and this symposium was invaluable for keeping abreast with recent advances. Gastroenterology is and will continue to be an exciting and rapidly evolving speciality, attractive to many different types of doctor and scientist.