

Helicobacter pylori

FAP: another indication to treat *H pylori*

B Leggett

Does infection of familial adenomatous polyposis (FAP) patients with *Helicobacter pylori* lead to chronic atrophic gastritis and an increased risk of gastric adenoma?

The report in this issue of *Gut* on the impact of *Helicobacter pylori* infection and mucosal atrophy on gastric lesions in patients with familial adenomatous polyposis (FAP)¹ highlights the complex interplay between genetic and environmental factors in the genesis of malignancy and has therapeutic implications for the management of these patients [see page 485]. A similar interplay has been observed in hereditary non-polyposis colorectal cancer where gastric cancer was quite common in earlier generations but has become less common recently, a change paralleling that seen in the general Western population.²

In Western patients with FAP the incidence of gastric adenoma is of the order of 2–6%. The incidence of gastric cancer is little if at all elevated above the general population³ and the major concern with these patients is the high risk of duodenal and periampullary cancer. However, in Japan the risk of gastric cancer in these patients is significantly elevated and a high incidence of gastric adenomas has been recognised for some time.⁴ The incidence of 39% reported in the present study is slightly less than the 50% reported by Iida and colleagues.⁴

The spectrum of *APC* gene mutations which cause FAP is not different between Japanese and Western populations so it seems that the observed differences in prevalence of gastric neoplasia are most likely related to the same factors which make sporadic gastric cancer much more common in Japan. One of these factors is the high prevalence of *Helicobacter pylori* which has been linked to sporadic gastric adenomas in addition to carcinoma.⁵ The relative risk of gastric cancer conferred by *Helicobacter* infection is greatest at a young age and is mainly confined to the distal stomach,⁶ the same location that gastric adenomas occur in FAP patients. Evidence suggests that *Helicobacter* predisposes to cancer by causing chronic atrophic gastritis and intestinal metaplasia.

These observations lead naturally to the hypothesis that infection of FAP patients with *Helicobacter* leads to chronic

atrophic gastritis and an increased risk of gastric adenoma. The present study tests this hypothesis in one of the few practical ways: the occurrence of gastric adenomas in FAP patients is correlated with the presence of *Helicobacter* infection and gastric mucosal atrophy in a Japanese population where substantial numbers of patients have gastric adenomas and *Helicobacter*. The results support the hypothesis, as subjects with gastric adenomas alone had the highest incidence of *Helicobacter* and mucosal atrophy, subjects with fundic gland polyps alone had no *Helicobacter*, and subjects with mixed lesions or no lesions were intermediate. Previous studies have already shown that fundic gland polyps, which are common in Western FAP patients but have little malignant potential, rarely occur in patients infected with *Helicobacter* and this is also true for patients with sporadic fundic gland polyps.

Another way of testing the hypothesis is to use a mouse model and indeed the results of this study were published by Fox *et al* in 1997.⁷ Transgenic mice with a mutation in the *APC* at codon 1638 developed gastric tumours in old age. These were mainly adenomas in the pyloric region and fundic gland polyps did not occur. Infection of these mice with *Helicobacter felis* caused gastritis and metaplasia but did not increase the incidence of gastric adenoma. Furthermore, and quite unexpectedly, the *APC* 1638 mice demonstrated a decreased immune and inflammatory response to *Helicobacter* compared with control mice. However, the results must be interpreted with caution as there may be subtle phenotypic differences in the effect of genetic mutations on mice and humans and the time course of infection is limited by the mouse life span and death from colonic carcinoma.

In addition to the effect of *Helicobacter*, the present study suggests that gastric adenomas are more common in patients with easily detectable truncating *APC* mutations in the central portion of the gene. Germline mutations in this region have previously been associated with severe gastroduodenal disease.⁸ Further

support for this association comes from the demonstration that somatic mutations in the remaining normal *APC* allele preferentially occur in the distal central portion of the gene between codons 1450 and 1556 in duodenal and gastric adenomas.⁹ This suggests that subtle differences in the function of mutant *APC* proteins may selectively promote tumorigenesis in the upper gastrointestinal tract. Interestingly, few somatic mutations have been observed in fundic gland polyps suggesting that they seldom lose *APC* function entirely and this may explain their low malignant potential. The few somatic mutations which have been observed may relate to foci of microadenoma within the fundic gland polyps.¹⁰

A unifying hypothesis which would explain the results of the present study is that all patients with FAP are predisposed to fundic gland polyps, perhaps related to increased proliferation and/or decreased apoptosis within the gastric mucosa. Acquisition of *Helicobacter* infection protects against the development of fundic gland polyps. Some patients with mutations in the central portion of *APC* are particularly predisposed to the development of gastric adenoma and carcinoma as well as duodenal neoplasia. However, this requires an environmental trigger. In the case of the duodenum this is bile which is always present. In the stomach this is *Helicobacter* which is now more common in Japanese than Western populations. How these environmental agents trigger carcinogenesis more efficiently in mucosa bearing a germline *APC* mutation is unknown but may relate to failure of apoptosis, the normal mucosal response following environmental damage. Such apoptosis deletes damaged cells possibly bearing additional genetic mutations.

Whatever the explanation, the present observations have therapeutic implications. There is some evidence that eradication of *Helicobacter* reduces the risk of sporadic gastric cancer and it certainly reduces the incidence of gastric atrophy and intestinal metaplasia. Therefore, it seems logical to suggest that *Helicobacter* infection should be sought and treated in patients with FAP, especially in communities where it is common. However, it is not at all certain that treatment stops an established adenoma from progressing to cancer¹¹ and indeed in cases where there is advanced gastric atrophy due to *Helicobacter*, the organism can spontaneously die out but the cancer still progresses. Therefore, it would seem prudent to recommend that patients with FAP be screened early in life for *Helicobacter* if maximum benefit is to be gained from this strategy.

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Author's affiliation

B Leggett, Department of Gastroenterology, Royal Brisbane Hospital, Herston 4029, Brisbane, Australia; barbara-leggett@health.qld.gov.au

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Motility and visceral sensation

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Functional dyspepsia: bye-bye to PPIs

O Nyrén

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Absence of therapeutic benefit of proton pump inhibitor therapy among Chinese patients with functional dyspepsia

When specifically asked, a significant proportion of the adult population reports dyspepsia—that is, pain or discomfort in the upper abdomen. The prevalence reported in the literature varies from 25% to 30%. Although only one in four patients with dyspepsia in the UK and USA sees a doctor for their symptoms^{1–4} dyspepsia accounts for up to 5% of consultations in family practice.⁵ When appropriately investigated, less than half have an underlying structural explanation for symptoms such as peptic ulcer or reflux oesophagitis. The remainder are classified as having functional dyspepsia. The vast number of patients with functional dyspepsia, and the usually chronic or recurrent nature of this ailment, creates an enormous market for the drug industry. In spite of the obvious difficulties in delimiting the patient population, and the absence of hard end points, a fair number of—mostly industry initiated—controlled trials have been conducted. However, regardless of whether the target has been gastric acid, gastrointestinal dysmotility, or *Helicobacter pylori*, the treatment effects have generally been unimpressive, and similar to the usually strong effects observed with placebo alone.

Although meta-analyses^{6–8} seem to indicate an approximately 20–30% advantage for acid suppression therapy (H_2 receptor antagonists or proton pump inhibitors (PPIs)) over placebo in functional dyspepsia, the value of these secondary publications may be limited

due to possible publication bias and various imperfections in the studies included. The main concern is the admixture of patients with non-erosive gastro-oesophageal reflux disease (GORD), which is known to respond to acid suppressive treatment.⁹ As large studies are unlikely to remain unpublished even in the event of a negative result, it appears well advised to focus on such studies. It also seems adequate to concentrate on studies involving PPI treatment. Such treatment is expected to maximise the chances of a positive result if gastric acid plays any role in the production of symptoms in functional dyspepsia. Conversely, negative results are likely to be more informative in a study with PPI treatment than in a study with drugs of less antisecretory potency. In the past four years, two large and carefully planned studies of PPI therapy in adequately investigated patients with functional dyspepsia have appeared in the peer reviewed literature.^{10,11} In this issue of *Gut*, Wong and colleagues¹² report the results from a third large high quality study conducted in Hong Kong [see page 502]. Under double blind conditions, 453 endoscoped patients with functional dyspepsia according to the Rome II criteria were randomised to receive high (30 mg) or low (15 mg) dose lansoprazole, or placebo for four weeks. Irrespective of the outcome measures (proportion of patients with complete symptom relief, change in dyspepsia score, change in SF-36 quality of life score), and regardless of the substrata

(subtype of functional dyspepsia, *H pylori* positive, *H pylori* negative, moderate/severe dyspepsia, mild dyspepsia), patients who received lansoprazole did not fare better than those who received placebo. The absence of any trend towards an advantage for lansoprazole allays concerns about a possible type II error.

The negative results of this carefully conducted and adequately analysed study are at odds with the two other large and comparable studies of PPIs in properly defined functional dyspepsia.^{10,11} The German FROSCH study, published two years ago in this journal,¹¹ comparing omeprazole 10 mg and 20 mg with ranitidine 150 mg or placebo, used a slightly different main outcome criterion (disappearance of dyspeptic symptoms requiring further treatment). Overall, the frequency of this outcome did not differ significantly between the omeprazole and placebo treated patients.¹³ However, complete disappearance of dyspeptic symptoms—a secondary response variable in this study—was observed more often among patients treated with the highest omeprazole dose. In the full paper, the authors explained their results according to *H pylori* status.¹¹ The bottom line message was an alleged effect modification by *H pylori* with a positive effect of omeprazole confined to infected patients. However, it appears that this stratified analysis was done ad hoc. This might have increased the risk of chance findings. Moreover, the investigators may have had an incentive for categorising *H pylori* positive subjects as non-responders.¹⁴ Although a non-significant tendency towards a higher response rate was observed by Wong *et al* among *H pylori* positive subjects treated with the highest lansoprazole dose—without a dose-response trend—the absence of any statistically significant therapeutic gain among *H pylori* positive subjects in two of three high quality studies seems to tentatively refute the idea that acid suppressive therapy is particularly indicated in these patients.

The other large high quality study published previously is the Bond/Opera trial of omeprazole 10 mg and 20 mg versus placebo in functional dyspepsia.¹⁰ In this study, omeprazole was noted to be modestly superior to placebo but only among patients with ulcer-like and reflux-like dyspepsia. Case definition, inclusion and exclusion criteria, study design, and outcome measures were almost identical to those in the Wong *et al* study,¹² with a few small exceptions: while the Bond/Opera trial required symptoms during the three day period immediately prior to randomisation, symptoms exceeding a certain severity score during the preceding two weeks was sufficient for inclusion in the Wong *et al* study. The Bond/Opera study had a short run in period during which antacid treatment was allowed whereas no such period was prescribed in the Wong *et al* study, and no antacid treatment was allowed. It may be important to note that all three high quality studies included patients with heartburn or acid regurgitation as long as these reflux symptoms were accompanied by other dyspeptic symptoms.

How did the very similar Bond/Opera and Wong *et al* studies arrive at such different conclusions? A closer look at the Bond/Opera study may provide a clue. Interestingly, this study consisted of two combined studies, of which one—the Opera study conducted mainly at specialist departments—was negative. Overall, differences in symptom abolition rates between active treatment and placebo were considerably larger among patients who were enrolled by general practitioners than among those recruited by specialists. This was due mainly to a higher placebo response among the latter patients. The authors speculated that these patients may have felt more reassured than patients primarily managed in general practice. However, if this explains the absence of pharmacological effects in the specialist patients, it means that reassurance and acid inhibition are likely to compete for the same mechanism for symptom relief and that reassurance may be as potent as omeprazole 20 mg daily for four weeks. A more probable explanation is that specialists and general practitioners select different study populations. It seems a reasonable

hypothesis that gastroenterology specialists are more apt at distinguishing between “genuine” functional dyspepsia and other syndromes or organic diseases than general practitioners, and that the study populations selected by the specialists are “cleaner”, notably less contaminated with GORD patients. This makes the negative results in the Wong *et al* study more understandable.¹² In this study, specialists selected the eligible patients. Thus Wong’s study corresponds more to the Opera study. Possibly more importantly, the study was performed among Chinese patients. For reasons that are only partly known, GORD is very rare among Asians.¹⁵ Hence the admixture of GORD patients is likely to have been negligible.

The rarity of GORD in the studied population is one of the attractions of the study of Wong and colleagues¹² and makes it an important contribution to the dyspepsia literature. It adds support to the notion that if patients with GORD related dyspepsia can be removed from the study population, the remainder will have true functional dyspepsia, which may have causes other than hypersensitivity to naturally occurring gastric acid. In the other high quality studies, attempts were made to distinguish between genuine GORD and reflux-like dyspepsia, but the criterion used (presence or absence of other dyspeptic symptoms in addition to heartburn and acid regurgitation) may have been inadequate. The assertions in the FROSC and Wong *et al* studies that patients with and without heartburn showed similar responses to PPI treatment may indicate that the demarcation line between GORD and functional dyspepsia does not coincide with the presence or absence of this symptom. However, the indirect indications that gastroenterology specialists and general practitioners may differ in their ability to distinguish between GORD and functional dyspepsia suggest that there may be other pieces of information in the patient history that add to the discriminative power. Identification and evaluation of more accurate criteria for classification of dyspeptic patients should perhaps be given high priority, despite previous setbacks. An individualised pharmacological approach, with acid suppressive therapy

tentatively reserved for GORD related dyspepsia, might have the potential for considerably improved cost effectiveness in the management of dyspepsia in general practice.

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Author's affiliation

O Nyrén, Department of Medical Epidemiology, Karolinska Institutet, Box 281, S-171 77 Stockholm, Sweden; olof.nyren@mep.ki.se

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