partly in helping individual units construct patient information and consent forms. It will be useful in creating audit standards for units, for individual trainees and established endoscopists. I would like the report to be used in a highly constructive manner to help improve the quality assurance of endoscopy. The JAG has quality assured >250 endoscopy units for training and this has been credible as JAG represents all the relevant stakeholders (the Royal Colleges, Specialist Societies, nurses, etc). It is now appropriate to widen the JAG remit beyond training standards to one of quality assurance for the endoscopy service. This has already effectively happened for units undertaking colon cancer screening colonoscopy in England where a successful JAG accreditation visit is a mandatory requirement. The JAG is in the ideal quality assurance body for all endoscopy units, irrespective of whether or not they contribute to the screening programme. Quality assurance needs auditable standards and ''complications of endoscopy'' is an excellent text from which to develop safety standards. Working party reports like this one, are powerful tools in our quest to maintain and improve quality, we should use them to their greatest potential.

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Oesophageal cancer

Helicobacter pylori and oesophageal cancer—not always protective

Kenneth E L McColl

The mechanism of the positive association between atrophic gastritis and oesophageal squamous cell carcinoma

Helicobacter pylori infection is now widely accepted to be an important risk factor for a number of gastric and duodenal disorders. It is the major aetiological factor for gastric and duodenal ulcers unrelated to NSAID or aspirin-usage. In addition, it plays an essential role in the aetiology of most cases of non-cardia gastric cancer as well as low-grade gastric MALTomas. Such is the importance of *H pylori* infection in disorders of the stomach and duodenum that pathology distal to the gastro-oesophageal junction is rarely encountered when endoscoping *H pylori* naive subjects.

Over the past few years, interest in *H pylori* has extended from its role in the aetiology of diseases of the stomach and duodenum to its possible role in the aetiology of diseases of the oesophagus. This has focused largely on the possibility that *H pylori* infection may protect against the development of gastro-oesophageal reflux disease and its complications of Barrett's oesophagus and oesophageal adenocarcinoma.

Most epidemiological studies have demonstrated a negative association between *H pylori* infection and gastro-oesophageal reflux disease or its complications. The prevalence of *H pylori* infection is lower in reflux patients than in controls.[1–3] There is also some evidence that reflux disease in *H. pylori*-negative patients tends to be more severe than in *H. pylori*-positive patients.[4] In addition, more virulent, cytotoxin-associated gene A (cag A)-positive strains of *H pylori* are associated with less severe reflux disease.[5 6] Numerous studies have now reported a strong negative association between *H pylori* infection and risk of adenocarcinoma of the oesophagus or gastro-oesophageal junction.[7–11] The strength of the negative association between *H pylori* infection and reflux disease or its complications appears to be related to the countries in which the association has been studied, being more marked in the East than the West.[12]

The negative association observed in epidemiological studies raises the possibility of a protective effect of the infection on reflux disease but does not establish it. Such association could be explained by confounding factors, which are influencing both the prevalence of infection and prevalence of oesophageal disease. Interventional studies examining the effect of treating the infection on oesophageal disease have examined the nature of the association. Such studies have produced conflicting results, showing that treating the infection may increase, decrease or have no effect on reflux disease.[13 14] Just as an East-West divide is apparent with respect to the epidemiological relationship between *H pylori* and reflux disease, a similar East-West divide is apparent with respect to the effect of treating the infection on reflux disease. In the East, treating *H pylori* aggravates GERD, but not in the West.[15–18]

Is there a biological explanation for the complex association between *H pylori* and reflux disease and the variations in the association between different regions of the world? A plausible explanation lies in the complex effects which *H pylori* infection exerts on gastric acid secretion, which is the most damaging factor in the development of reflux disease and its complications. *H pylori* infection may increase, decrease or have no overall effect on acid secretion, and its effect depends upon the pattern of gastritis induced by the infection.[19] In some patients, the infection produces an antral-predominant, non-atrophic gastritis and this increases the level of gastric acid secretion. This pattern of gastritis is seen in subjects who develop duodenal

ulceration. In other patients, the infection produces an atrophic gastritis involving the entire stomach and causing a marked reduction, or complete absence, of acid secretion. This pattern of gastritis is associated with an increased risk of non-cardia gastric cancer. In patients with gastric ulcers, the pattern of gastritis is between these two extremes or more towards the atrophic gastritis end of the spectrum.[20–25] Eradicating *H pylori* infection returns the levels of acid secretion towards normal, though full restoration of normal secretion is not achieved when there is severe atrophy.[26] It can therefore be seen that *H pylori* infection should not be regarded as a single entity with respect to its effects on acid secretion, and thus also with regard to effects on oesophageal reflux disease and its complications.[27]

The paper by Bahmanyar *et al*[27] in this issue of *Gut* (***see page 464***) investigates indirectly the influence of the pattern of gastritis induced by *H pylori* infection on the association between the infection and oesophageal adenocarcinoma. This has been done by examining the incidence of oesophageal adenocarcinoma developing in patients with a history of duodenal ulceration, gastric ulceration and controls. The duodenal ulcer patients represent a group with *H pylori* antral-predominant, non-atrophic gastritis and high acid secretion, and the gastric ulcer patients, a group with more atrophic gastritis and normal or low acid secretion.[20–25] They found that the *H. pylori*-infected duodenal ulcer subjects had an increased risk of oesophageal adenocarcinoma, whereas there was no association between gastric ulcer and oesophgeal adenocarcinoma.

This observation supports the hypothesis that it is not *H pylori* itself which may influence reflux disease and its complications but the effects of the infection on acid secretion. Consequently, *H pylori* infection may be associated with an increased risk of oesophageal adenocarcinoma in patients in whom it causes high acid secretion secondary to an antral-predominant, non-atrophic gastritis.

The pattern of gastritis induced by *H pylori* infection being the determinant of the effects of the infection on reflux disease fits comfortably with the different findings in the East versus West. In the East, *H pylori* infection tends to be associated with a high incidence of atrophic gastritis and low acid secretion, which is likely to protect against reflux disease.[28] In contrast, in the West, the infection is more often associated with antral-predominant, non-atrophic gastritis, which may aggravate reflux disease.

The history of *H pylori* infection is that as soon as the mechanism of its association with one disease becomes clarified, its association with yet another disease becomes apparent. When the role of *H pylori* infection in gastric and duodenal disorders became established, its negative association with oesophageal reflux disease and oesophageal adenocarcinoma became apparent. No sooner has the mechanism of its role in these latter diseases become clear, than its association with oesophageal squamous cell carcinoma has become apparent.

Ye *et al* first reported that oesophageal squamous cell carcinoma was positively associated with both serological evidence of atrophic gastritis and with *H pylori* CagA-positive infection in the Swedish population.[10] A similar association has recently been observed in Japan.[29] The current paper by Bahmanyar in this issue of *Gut* provides further evidence of an association between *H pylori* atrophic pattern of gastritis and oesophageal squamous carcinoma by finding that gastric ulcer patients have an 80% increased risk of the cancer.

The new challenge facing us is to clarify the mechanism of the positive association between atrophic gastritis and oesophageal squamous cell carcinoma. Is it due to confounding factors that predispose to both oesophageal squamous cell carcinoma and gastric atrophy? The study by Ye *et al* largely excludes confounding due to smoking or alcohol.[10] Is there an underlying genetic predisposition to both diseases? Or is there a mechanism by which atrophy increases the risk of oesophageal squamous carcinoma, such as bacterial overgrowth leading to *N*-nitroso compound generation or a nutritional effect? Each of these possible mechanisms now need to be investigated.

The extent and complexity of the association between *H pylori* and upper GI disease is now quite staggering. It is an important risk factor for ulcers of the stomach and duodenum, for gastric cancer and also for low-grade MALToma. It is associated with a reduced risk of oesophageal adenocarcinoma when it induces gastric atrophy but an increased risk when it induces a non-atrophic antral-predominant gastritis. It is now also associated with squamous cell carcinoma when it induces atrophic gastritis.

One concern about eradicating *H pylori* in the general population has been the possible adverse effects this might have on the incidence of reflux disease and oesophageal adenocarcinoma. However, the observation that *H. pylori*-positive subjects with an antral-predominant, non-atrophic gastritis have an increased risk of oesophageal adenocarcinoma and that *H pylori* atrophic gastritis is associated with an increased risk of oesophageal squamous cell carcinoma indicate that *H pylori* is not always protective with respect to serious oesophageal disease.

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Hirschsprung's ENS transplantation

Transplanting the enteric nervous system: a step closer to treatment for aganglionosis

Michael D Gershon

Autologous transplantation can be used to treat Hirschsprung's disease by implantation and proliferation of the crest-derived stem cells in vitro

One might think that Hirschsprung's disease (congenital megacolon) should be passé as a medical problem. After all, many genes, including *RET*, *GDNF*, *NRTN*, *EDNRB*, *EDN3*, *ECE1*, *PHOX2b*, *SOX10*, *PAX3* and *SMADIP1* (SIP1, ZBFX1B),[1–7] have successfully been linked to its pathogenesis. Knowledge of the actions and interactions of these genes and their products has enabled the processes by which the bowel is colonised to be, if not completely understood, at least comprehended in general terms.[3 8–10] Effective treatment for Hirschsprung's disease, moreover, exists in the surgical removal of the aganglionic segment of bowel.[11–13] Unfortunately, the medical problems posed by Hirschsprung's disease continue despite the lengthy list of genes implicated in its generation and the progress that has recently been made in understanding enteric nervous system (ENS) development. Unresolved medical problems continue because advances made in comprehending genes and pathogenesis have not been translated into new and improved methods of treatment; moreover, although surgical techniques are evolving and associated morbidity is decreasing,[12 13] the surgical treatment of Hirschsprung's disease essentially converts an otherwise lethal defect into a chronic condition with which many, if not most, patients must learn to cope.[14 15]

Hirschsprung's disease occurs when a variable length of terminal bowel is congenitally aganglionic. Because the reflexes and behaviours mediated by the ganglionated plexuses of the ENS are essential for propulsive motility and normal secretion,[16] aganglionosis results in a pseudoobstruction that, if left untreated, is incompatible with life. Reliable modern statistics on untreated Hirschsprung's disease are not available because failure to treat it is immoral; however, aganglionosis is lethal to animals with genetic defects that model the condition.[17–23] Because the aganglionic region of the bowel lacks the inhibitory neurotransmitter nitric oxide some authors have speculated that the aganglionic zone goes into spasm and narrows to become obstructive[24]; however, it is more likely that motor patterns simply fail to propel luminal contents through the aganglionic zone so that the ganglionated bowel proximal to the aganglionic segment dilates. Removal of the aganglionic portion of the gut is thus obviously necessary in the treatment of Hirschsprung's disease, but in many patients it is not sufficient.

The greatest problems faced by patients after the definitive surgical correction of the aganglionosis of Hirschsprung's disease include faecal soiling,[15] constipation and postoperative enterocolitis.[25] Studies vary in the reported incidence of these complications, and the type of surgery used to carry out the repair undoubtedly matters; however, soiling has been reported in as many as 76% of patients.[15] A transanal one-stage pull-through operation may be advantageous for rectosigmoid aganglionosis[13] even though it carries a high risk of postoperative enterocolitis because a single surgical procedure is preferable to two[12 25]; however, a modified Duhamel procedure has been advocated as superior to any other for total colonic aganglionosis.[26] Whatever procedure is used, faecal soiling is a serious risk, which over the long term causes surprisingly less psychiatric morbidity than would be expected, given the social stigma attached to that particular defect; nevertheless, faecal soiling gives rise to a great deal of concern in families and is highly distressing to patients.[15] The outcomes of treatment are worse for patients with total colonic aganglionosis than for those with short-segment disease, and patients with total colonic aganglionosis tend to perceive themselves as less well adjusted than their matched pairs with a shorter aganglionic region of gut.[27] Additional surgeries, including posterior myotomy/myectomy, can be undertaken to lessen the effect of persistent soiling, but these procedures are not invariably successful.[28] Clearly, no treatment that carries a high risk of faecal soiling can be considered to be perfect, and one has to examine what we know about the pathogenesis of Hirschsprung's disease and the development of the ENS to determine whether anything can be done that is better than what is now being done to treat Hirschsprung's disease.

The gut is colonised by precursors that migrate to it from the neural crest. The