Interactions between *H. pylori* infection, gastric acid secretion and anti-secretory therapy

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There is evidence of a two-way interaction between gastric acid secretion and *H. pylori*-associated gastritis. Gastric acid secretion influences the density of *H. pylori* colonisation, its distribution within the stomach and the severity of the mucosal inflammatory response to the infection. In addition, *H. pylori* gastritis alters gastric acid secretion. In subjects with a predominant antral gastritis, it increases acid secretion predisposing to duodenal ulcer, whereas in others with predominant body gastritis, acid secretion is impaired and the subjects have an increased risk of gastric cancer. The two-way interaction between acid secretion and *H. pylori* gastritis is observed when *H. pylori*-positive subjects are treated with proton pump inhibitor agents. The inhibition of acid secretion induces a body gastritis and this inflammation of the body mucosa inhibits acid secretion thus augmenting the anti-secretory effect of the drug. In this article, we discuss the interaction between gastric acid secretion and *H. pylori* gastritis and its importance in determining disease outcome.

The secretion of acid is an important function of the human stomach. The acid kills the great majority of bacteria which are ingested and thus provides a first line defence against enteric infection. The acid also converts pepsinogen to pepsin and thus initiates the digestion of protein. In man, acid is secreted by the stomach constantly, though the rate of secretion varies. During periods of fasting, the rate of acid secretion is low but sufficient to maintain intragastric pH below two. Eating stimulates an increased rate of acid secretion. The sight, smell or taste of food stimulates the acid secreting parietal cells in the body of the stomach via the vagus nerve. When food enters the stomach, the protein component stimulates G cells situated in the distal antral region of the stomach to release the hormone gastrin which circulates and again stimulates the parietal cells in the body region to secrete acid. As the acidity of the stomach and duodenum increases, protective feedback pathways are activated to inhibit further acid secretion. One important acid-mediated inhibitory control involves the release of somatostatin by D cells within the antral

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mucosa. This hormone exerts paracrine inhibitory control on gastrin release by the antral G cells (Fig. 1). *H. pylori* infection can interfere with these physiological control processes, resulting in disturbances in gastric acid secretion.

Effect of *H. pylori* gastritis on gastric acid secretion

H. pylori infection is believed to be contracted mainly in childhood and then to persist as a chronic infection throughout life. There is little known about the acute infection in childhood or its effects on gastric acid secretion. However, experimental infection of adults has been observed to result in markedly reduced acid secretion which usually resolves within several months[1–5]. The acute infection causes marked inflammation of the antrum and body of the stomach and the hypochlorhydria is assumed to be due to the bacterium and/or accompanying inflammation inhibiting parietal cell function[2]. Following the initial acute episode, the infection enters a chronic phase. Much more is known about the effect of chronic *H. pylori* infection on acid secretion as discussed below.

The effect of chronic *H. pylori* gastritis on gastric acid secretion depends upon the relative extent to which the gastritis involves the antral or body mucosa. It also depends upon whether the infection is only producing inflammation of the mucosa or has resulted in the development of atrophy with loss of glands.

Effect of antral predominant gastritis on gastrin and acid secretion

H. pylori gastritis, which is confined to the antrum and unaccompanied by atrophy, results in hypersecretion of acid. This is the pattern of gastritis seen in subjects with duodenal ulceration[6]. The increased acid secretion in subjects with antral predominant non-atrophic gastritis is mainly due to the *H. pylori* gastritis stimulating increased release of the hormone gastrin which circulates and stimulates the body of the stomach to secrete acid[7,8].

Subjects with *H. pylori* antral gastritis have increased basal, meal stimulated and gastrin releasing peptide (GRP) stimulated serum gastrin concentrations[7–14]. The hypergastrinaemia fully resolves within 2–14 days of commencing *H. pylori* eradicating therapy indicating that it is caused by the infection[15,16]. The increased circulating gastrin associated with *H. pylori* is mainly due to an increase in Gastrin-17[17]. This form of gastrin originates mainly from the antral mucosa and its selective increase is consistent with the infection predominantly affecting this

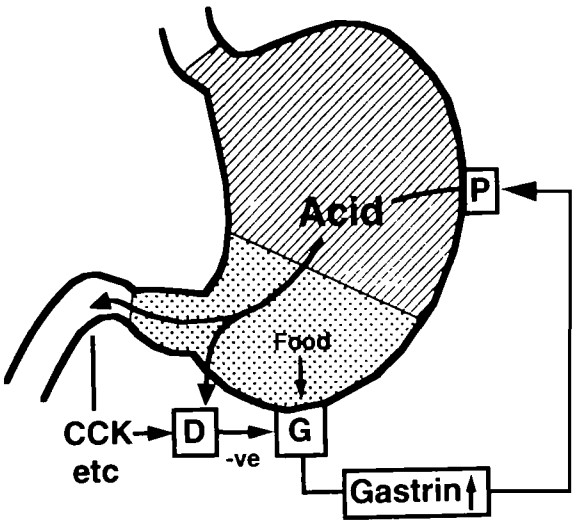

Fig. 1 Physiological regulation of gastrin release by antral mucosa. CCK = cholecystokinin, P = parietal cell, D = somatostatin producing cell, G = gastrin producing cell.

region. Gastrin-17 is also the main form of the hormone which rises in response to eating and this is consistent with *H. pylori*-associated hypergastrinaemia being most pronounced postprandially.

There have been significant advances in our understanding of the mechanism by which *H. pylori*-associated antral gastritis causes hypergastrinaemia. The release of gastrin by the antral mucosa is under physiological inhibitory control in order to prevent excessive gastric acid secretion (Fig. 1). Gastrin release is suppressed when antral luminal pH falls below 3. In addition, there is inhibitory control exerted on gastrin release by cholecystokinin and other enterogastrones released from the small intestine. The inhibition of gastrin release exerted by both gastric acid and cholecystokinin is mediated mainly via the release of somatostatin by D cells within the antral mucosa. These D cells lie in close proximity to the G cells and the somatostatin they release exerts paracrine inhibitory control on both gastrin synthesis and release. Several studies have now demonstrated lowered concentrations of somatostatin within the antral mucosa of subjects with *H. pylori* antral gastritis[16,18–21]. In addition, somatostatin mRNA concentrations are lowered, indicating a reduced synthesis of this inhibitory hormone[19,21]. These findings are consistent with *H. pylori* antral gastritis increasing gastrin by producing deficiency of antral somatostatin and thus of the normal inhibitory influence this hormone exerts on gastrin release.

Studies of gastric function have also provided evidence that *H. pylori* antral gastritis disrupts the inhibitory control of gastrin release. Tarnasky *et al* measured gastrin release and acid secretion in response to meals of varying pH[22]. In asymptomatic volunteers with *H. pylori* infection, they found impaired inhibition of gastrin release and acid

secretion at low pH. Further evidence of impaired inhibitory control of gastrin is provided by the studies of Konturek *et al* employing the cholecystokinin A receptor antagonist loxiglumide[23,24]. Cholecystokinin exerts tonic inhibitory control on gastrin release. This is mediated by the hormone activating CCK A receptors on antral D cells and, thereby, stimulating somatostatin release which inhibits gastrin release. Konturek *et al* found that the CCK A antagonist increased the gastrin and acid response to a test meal in healthy controls but not in duodenal ulcer patients[23]. In a separate study, they found that eradication of *H. pylori* infection restored the physiological response to CCK A blockade in duodenal ulcer patients[24]. These findings are again consistent with *H. pylori* antral gastritis impairing somatostatin mediated inhibitory control of gastrin release.

There is now, therefore, substantial morphological and physiological evidence that the increased release of gastrin caused by *H. pylori* antral gastritis is secondary to the infection depleting antral somatostatin. The mechanism by which *H. pylori* results in depletion of antral somatostatin has still to be elucidated, but there are at least three potential mechanisms. The first proposed by Calam's group is that *H. pylori* raises mucosal surface pH by virtue of its high urease activity and ammonia synthesis[11]. Low antral pH is an important physiological stimulus to the synthesis and release of antral somatostatin. Studies have been performed to see whether altering the rate of *H. pylori* ammonia production affects gastrin release. However, neither increasing *H. pylori* ammonia production by the intragastric infusion of urea[25] or inhibiting it by acetohydroxamic acid[26] or completely suppressing it with 24 h of triple antibacterial therapy[15] was found to alter serum gastrin. However, this lack of effect of acute alterations in ammonia production on serum gastrin does not exclude a role of long-term *H. pylori* ammonia production in disrupting the regulation of gastrin release. It has been shown that pH induced adaptive changes in antral D cells occurs at a slow rate[27]. It is possible that elevation of antral surface pH by ammonia leads to atrophy of antral D cells by blocking the chronic trophic stimulus exerted by gastric acid.

The second mechanism by which *H. pylori* antral gastritis might alter G and D cell function is via the local production of specific cytokines. *H. pylori* infection results in severe antral gastritis with infiltration of the mucosa with acute and chronic inflammatory cells. There is also up-regulation of local production of various cytokines[28,29]. Recent *in vitro* studies have shown that certain cytokines affect gastrin and somatostatin release though it is difficult to know whether this can be extrapolated to the *in vivo* situation[30]. The third mechanism by which *H. pylori* might suppress antral somatostatin is related to its recently reported production of N alpha-methyl histamine which is a potent H_3

receptor agonist[31]. Such receptors have been demonstrated on human antral D cells and their activation inhibits somatostatin release and, consequently, increases gastrin release[32,33].

In subjects in whom *H. pylori* gastritis is confined to the antral mucosa and is non-atrophic in type, the increased gastrin release produced is accompanied by increased acid secretion[7,8,34,35]. This pattern of gastritis and acid response is seen in duodenal ulcer patients. When compared to true normal controls (i.e. *H. pylori* negative healthy volunteers) *H. pylori*-positive duodenal ulcer patients have increased basal acid secretion and increased acid response to stimulation with gastrin releasing peptide. The basal acid output is increased 3-fold and GRP stimulated acid output increased 6-fold. Following eradication of *H. pylori* infection, there is resolution of both the increased gastrin release and accompanying increased acid secretion[7,8,34,35].

Role of H. pylori-*induced acid hypersecretion in the pathophysiology of duodenal ulcer disease*

This gastrin-mediated increased acid secretion induced by antral predominant *H. pylori* gastritis is likely to play a key role in the pathophysiology of duodenal ulcer disease (Fig. 2). As shown by Hamlet and Olbe, the increased acid secretion results in an increased duodenal acid load[36]. *H. pylori* has also been shown to reduce duodenal bicarbonate secretion which will reduce its resistance to the increased acid load[37]. This results in damage to the duodenal mucosa and the

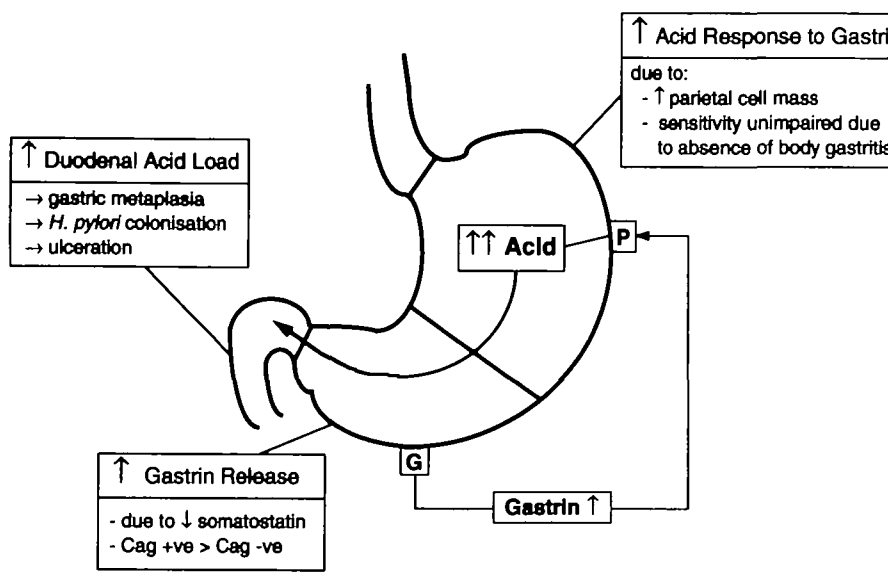

Fig. 2 Sequence of events by which *H. pylori*-infection of antral mucosa leads to duodenal ulceration in some subjects. G = gastrin producing cell, p = parietal cell.

development of gastric metaplasia within the duodenal bulb[38]. The presence of gastric type mucosa within the duodenum enables *H. pylori* to colonise this region and the local mucosal damaging effect of bacterial cytotoxins add to the acid induced damage. The integrity of the duodenal mucosa is impaired and erosive duodenitis and ulceration develop. It can thus be seen that the *H. pylori*-induced disturbance of the antral regulation of gastric acid secretion is a key factor in the development of duodenal ulcer disease. Eradicating the infection restores the normal control of acid secretion with induced secretion and duodenal acid load and thus cure of the ulcer disease.

The understanding that *H. pylori* infection induces duodenal ulcer disease by stimulating increased acid secretion provides a unifying hypothesis for the efficacy of the full range of duodenal ulcer healing drugs. Previously, ulcer healing drugs were classified as those which inhibit acid secretion and those which exert a mucosal protective effect, namely bismuth preparations and sucralfate. However, we now know that bismuth preparations suppress *H. pylori* infection and consequently *H. pylori*-induced acid hypersecretion. In addition, we have recently shown that sucralfate also suppresses *H. pylori* infection and the associated acid hypersecretion[39]. The fact that each drug which is effective in healing duodenal ulcers inhibits acid secretion either directly or indirectly strongly supports the role of acid hypersecretion in the pathophysiology of this condition.

It is interesting to compare gastric function in *H. pylori*-infected duodenal ulcer patients and *H. pylori*-infected healthy volunteers (Fig. 3). It is worth remembering that *H. pylori*-infection is very common in the community and that only about 25% of infected subjects develop

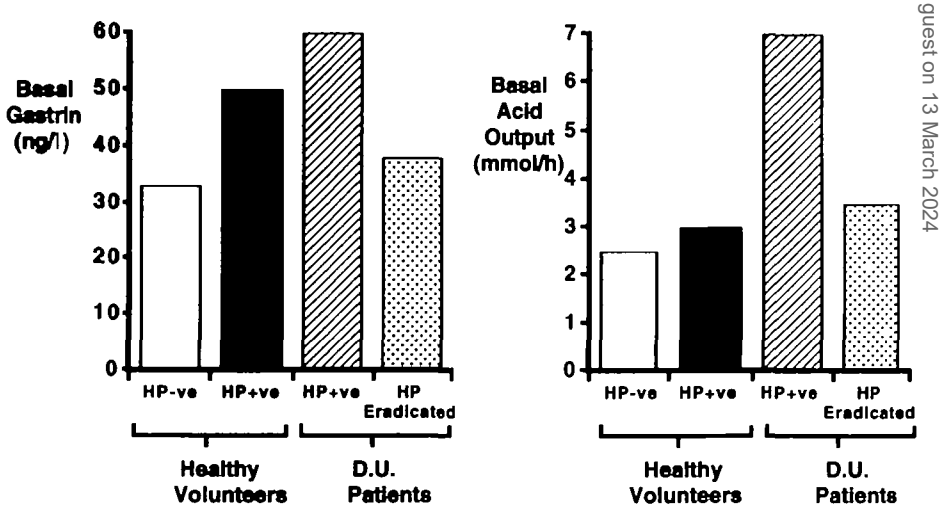

Fig. 3 Effect of *H. pylori* infection on basal gastrin and acid secretion in subjects with and without duodenal ulceration.

duodenal ulcer disease. *H. pylori* infection increases serum gastrin levels in *H. pylori*-infected healthy volunteers as well as in duodenal ulcer patients and the degree of increase in gastrin is similar in both groups. However, the increased serum gastrin concentration is not associated with significantly increased acid secretion in the non-ulcer subjects. The reason for the elevated serum gastrin being associated with increased acid secretion in the infected ulcer patients but not in the infected non-ulcer subjects appears to be two-fold. Firstly, the ulcer patients have a greater parietal cell mass reflected in a higher maximal acid output[40]. This may be a genetic factor predisposing them to duodenal ulcer disease. In addition, it may be partly due to the trophic effects of the *H. pylori*-induced hypergastrinaemia on their oxyntic mucosa. In addition to this, the sensitivity of the parietal cells to gastrin stimulation is considerably less in the infected non-ulcer subjects than in the duodenal ulcer patients[40]. Sensitivity to gastrin is measured by performing a gastrin dose response study and calculating the concentration of gastrin required to achieve 50% of the maximal acid output. The difference in sensitivity between these two groups is mainly due to the fact that the infected non-ulcer subjects have a reduced sensitivity to gastrin compared to true normal subjects (*H. pylori*-negative healthy volunteers). This reduced sensitivity may be partly genetic in origin but, in addition, is partly related to the varying degrees of body gastritis impairing the parietal cell function and their ability to respond to gastrin stimulation. The effect of body gastritis on acid secretion is discussed in the following section.

Effect of body gastritis on acid secretion

In some subjects, *H. pylori*-induced gastritis involves the body mucosa. These subjects may also have gastritis of the antral mucosa or the gastritis may be confined to the body mucosa. In subjects with significant body gastritis, there is usually evidence of atrophy of the mucosa as well as inflammation.

Subjects with body gastritis have abnormally low gastric acid secretion (Table 1)[41,42]. This may vary from mildly reduced acid secretion to complete achlorhydria. Eradicating the infection in these subjects results in various degrees of recovery of gastric acid secretion[41,42]. The recovery of acid secretion coincides with the disappearance of the infection and resolution of the accompanying inflammation of the mucosa. This indicates that the reduced acid secretion is a consequence of the bacterium or the inflammation it induces, impairing the function of the acid secreting body mucosa. The degrees of recovery of acid secretion following eradication of *H. pylori* is less in subjects with atrophy as there is no early resolution of atrophy of the glands. Eradication of *H.*

Table 1 Features of *H. pylori* associated chronic hypochlorhydria

- Severe hypochlorhydria or achlorhydria.
- Body predominant gastritis with varying degree of atrophy.
- Density of *H. pylori* colonisation usually low.
- Hypochlorhydria due to the inflammation impairing the function of the parietal cells and atrophy reducing their number.
- Usually no antibodies to parietal cell or intrinsic factor.
- Eradicating *H. pylori* produces resolution of inflammation and varying degrees of return of acid secretion.
- Association with increased risk of gastric cancer.

pylori thus produces resolution of the functional impairment of acid secretion caused by the inflammation of the acid secretion but does not correct any impairment due to actual loss of acid secreting cells (i.e. atrophy) (Fig. 4).

In subjects with *H. pylori*-related body gastritis and profound hypochlorhydria, the density of *H. pylori* colonisation is often very sparse and may be missed if only one of two mucosal biopsies are examined[41]. In addition, the mucosal urease slide tests and urea breath test may also be negative. This is due to the fact that the bacterium has difficulty surviving in the achlorhydric stomach. In the presence of chronic achlorhydria and the development of marked atrophy the infection may indeed be spontaneously cleared from the stomach.

Subjects with markedly reduced acid secretion due to *H. pylori* body gastritis also have increased serum gastrin concentrations which fall following eradication of the infection[41,42]. The mechanism of the increased

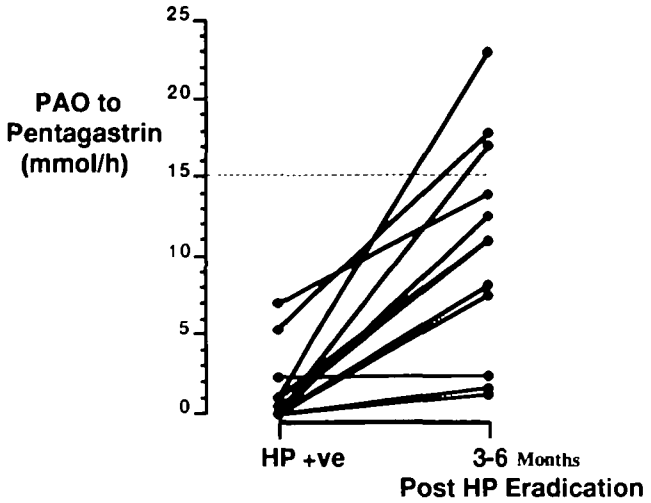

Fig. 4 Effect of eradication of *H. pylori* infection on pentagastrin stimulated peak acid output in subjects with hypochlorhydria. The broken line indicates lower limit of normal.

gastrin in subjects with body gastritis is different from that in subjects with antral gastritis, being secondary to the achlorhydria removing the normal inhibition of gastrin release exerted by gastric acid. For this reason, the degree of hypergastrinaemia may be more marked in these subjects. In some subjects with *H. pylori*, body gastritis and hypochlorhydria gastrin levels are normal and low and this may be explained by atrophy of antral mucosa with loss of the gastrin producing G cells.

The mechanism by which *H. pylori* infection can cause functional inhibition of gastric acid secretion by the body mucosa is unclear. It may be explained by a bacterial product as suggested by the studies of Cave *et al*[43]. Alternatively, it may be related to the inflammation induced by the organism. There is evidence that the organism stimulates increased production of interleukin 1β[44] and this cytokine is the most potent inhibitor of acid secretion yet identified[45]. Recent studies have also shown that antibodies raised against *H. pylori* may cross-react with the acid secreting proton pump of the parietal cell[46]. This antigenic mimicry might result in impairment of parietal cell function.

Role of H. pylori*-induced hypochlorhydria in gastric cancer and other human diseases*

The ability of *H. pylori* infection to produce chronic hypochlorhydria has implications for human disease. The main function of gastric acid is to provide protection from enteric infection. The chronic suppression of gastric acid secretion by *H. pylori* in some subjects may increase their susceptibility to enteric infection. This would be particularly important in the developing world where enteric infections are more common and pose a major threat to life. It may be a particularly important problem in children in the developing world. At present, very little is known about the effect of *H. pylori* infection on gastric secretory function in childhood or in the developing world.

The subgroup of subjects with hypochlorhydria due to *H. pylori* body gastritis is also likely to be important in the link between the infection and gastric cancer. It has been recognised for many years that subjects with chronic hypochlorhydria or achlorhydria have an increased risk of gastric cancer[47]. In addition, it is recognised that gastric cancer tends to occur against a background of a body predominant gastritis and the presence of atrophy. The important role of hypochlorhydria in the link between *H. pylori* and gastric cancer may explain why duodenal ulcer patients have a very low risk of gastric cancer despite having severe *H. pylori* gastritis[48]. The high acid secretion characteristic of the duodenal ulcer patients probably explain their protection from gastric cancer. The mechanism by which hypochlorhydria is associated with a high risk of gastric cancer is not completely understood but may be related to the

production of potentially carcinogenic nitrosoamines[49]. When intragastric pH is above 4, the gastric lumen becomes colonised with various bacteria which may catalyse the reaction of nitrite with secondary amines to form nitrosoamines. Gastric juice nitrite levels are increased in the hypochlorhydric stomach[50]. In addition, gastric juice ascorbic acid concentration is reduced in the hypochlorhydric stomach, further predisposing to nitrosoamine formation[51,52]. In less severe hypochlorhydria, nitrosoamines may be formed by chemical non-bacterial nitrosation reactions which occur optimally at pH 2–3[49].

We have recently tested the hypothesis that it is the subgroup of subjects with *H. pylori*-induced acid hyposecretion who have an increased risk of developing gastric cancer. We have done this firstly by investigating whether there is an increased prevalence of this hyposecretory response to chronic *H. pylori* infection in subjects recognised to have an increased risk of gastric cancer. We studied 100 first-degree relatives of patients with gastric cancer who are known to have an increased risk of gastric cancer. We found that 46% of *H. pylori*-positive gastric cancer relatives had achlorhydria or hypochlorhydria[53]. In the spouses of the first-degree relatives, the prevalence of hypochlorhdyria in those who were *H. pylori*-positive was only 4%. In addition, we found that first-degree relatives without *H. pylori* infection had normal acid secretion. This study, therefore, strongly supports the association between *H. pylori*-induced hypochlorhydria and increased risk of gastric cancer.

In a further study conducted in collaboration with Dr Hansen from the Norwegian Cancer Institute, we measured serum gastrin as a surrogate marker of hypochlorhydria in a cohort of patients whose serum had been stored 10–15 years ago[54]. This study confirmed the previous observations that those who were seropositive for *H. pylori* infection had a 3-fold increased risk of gastric cancer compared to those who were seronegative. However, we were also able to show that the risk of gastric cancer in those who were seropositive for the infection was strongly associated with the serum gastrin concentration. Those in the highest tertile for serum gastrin had a 7-fold higher risk of developing gastric cancer than those in the lowest tertile. This provides further support for hyposecretion being a marker of those who carry the highest risk of gastric cancer.

In addition to the potential hazards associated with *H. pylori* induced hypochlorhydria, the absence of acid may also have some beneficial effects in protecting subjects from acid-related upper gastrointestinal disorders. It is of interest that the fall in prevalence of *H. pylori* in the Western world is associated with a rise in prevalence of gastro-oesophageal reflux disease and of the cancer associated with it. It is possible that the rising prevalence of those acid-related disorders is due to the eradication of *H. pylori* from the Western world and the associated maintenance of high levels of acid secretion throughout life.

Table 2 *H. pylori* induce disturbances in gastric acid secretion

- Effect on acid secretion depends upon relative involvement of antrum and body mucosa by *H. pylori* gastritis.
- Antral-predominant, body-sparing gastritis stimulates increased gastrin release and increased acid secretion with high risk of duodenal ulcer disease.
- Body-predominant gastritis impairs parietal cell function and produces marked hypochlorhydria and increased risk of gastric cancer.
- Involvement of both body and antrum mucosa is the most frequent pattern and produces no significant overall change in acid secretion.

What determines the pattern of gastritis and associated disturbance of acid secretion induced by H. pylori *infection?*

In summary, the effect of chronic *H. pylori* infection on gastric acid secretion depends upon the relative involvement of the antrum and body of the stomach (Table 2; Fig. 5). When the *H. pylori* gastritis is confined to the antral mucosa it stimulates increased release of gastrin and this stimulates parietal cells in the healthy uninflamed body region of the stomach to secrete high levels of acid. In subjects with a large compliment of parietal cells the particularly high acid response leads to duodenal ulcer disease. When the gastritis also involves the body mucosa, then the inflammatory process impairs the ability of the parietal cells to secrete acid and, thus, the increased gastrin arising from the antral gastritis is prevented from causing excess acid secretion. This is the morphological pattern and functional response seen in the majority of infected subjects. In some subjects, there is marked body gastritis and

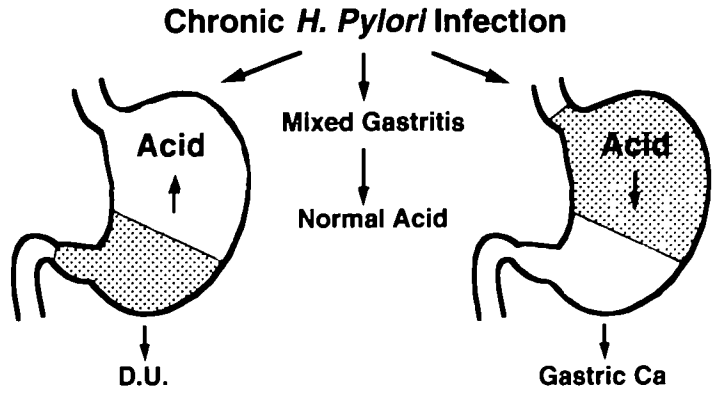

Fig. 5 Divergent responses to *H. pylori* infection and factors which may influence the response.

this markedly impairs parietal cell function leading to severe hypochlorhydria or achlorhydria. These subjects usually also have evidence of atrophy of the body mucosa and have an increased risk of developing gastric cancer (Fig. 5). It is not known whether these different responses to *H. pylori* infection represent divergent or sequential pathways. In other words, whether the pattern of gastritis and associated change in gastric function is seen soon after contracting the infection and then persists throughout life or whether subjects can change over time from an antral predominant to a body involving gastritis with related change in acid secretion.

At present, it is unclear why some people develop antral predominant gastritis with increased acid secretion and duodenal ulcer disease whereas others develop a body predominant gastritis with hypochlorhydria and increased risk of gastric cancer (Fig. 5). Differences in bacterial strains might be important. Cag positive strains are more virulent, produce a more marked gastritis and subjects with these strains have an increased risk of both duodenal ulcer disease and gastric cancer[55,56]. The fact that the Cag positive strains increase the risk of both duodenal ulcer disease associated with antral predominant gastritis and gastric cancer associated with body gastritis indicates that the strain does not determine which of these two disease pathways an individual follows. The development of body gastritis and low acid secretion in some subjects could be explained by *H. pylori* inducing an immune reaction against the proton pump of the parietal cell and, thus, causing hypochlorhydria and accompanying body gastritis. Dietary factors may also be important. A high salt intake is an important risk factor for gastric cancer and this might predispose to a body gastritis[57]. An individual's premorbid natural acid secretory status may also determine the distribution of gastritis and disease outcome as discussed below.

Effect of gastric acid secretion on *H. pylori* gastritis

As discussed above, *H. pylori* gastritis affects gastric secretory function and the overall effect is related to the distribution of the gastritis within the stomach. There is also evidence that gastric acid secretion affects *H. pylori* gastritis and its distribution within the stomach.

The recognition that gastric acid secretory status modifies *H. pylori* gastritis is largely based upon observations following inhibition of acid secretion with proton pump inhibitor drugs (Table 3). When duodenal ulcer patients with their antral predominant gastritis are commenced on powerful acid inhibitory drugs, *H. pylori*-related gastritis changes in the following ways:

Table 3 Interactions between proton pump inhibitor (PPI) therapy and *H. pylori* gastritis

- PPI therapy reduces the density of *H. pylori* colonisation and may result in false negative *H. pylori* testing.
- PPI therapy induces a body-predominant *H. pylori* gastritis.
- In *H. pylori*-positive subjects, long-term PPI therapy produces atrophy of body mucosa.
- *H. pylori* infection increases the acid-suppressing efficacy of PPI therapy due to the body gastritis impairing acid secretion and complimenting the pharmacological effects of the drug.

1 The total number of bacteria colonising the stomach is reduced[58,59]. This is thought to be due to the fact that the bacterium is best adapted to surviving in an acid environment. In a few patients, suppression of acid by PPI therapy results in complete eradication of the infection. The suppression of *H. pylori* infection by PPI therapy reduces the reliability of *H. pylori* tests in patients on such therapy.

2 The infection and accompanying inflammation changes from being antral predominant to being body predominant[58–60]. This is thought to be due to the fact that the infection is managing to survive only in the region where there is still some acid being secreted.

3 The degree of inflammation relative to the density of bacterial colonisation in the body mucosa becomes much more marked[58–60]. Duodenal ulcer patients have *H. pylori* colonising the body mucosa but they induce little, if any, body gastritis. Inhibiting their acid secretion with PPI therapy results in the development of marked inflammation of the body mucosa despite no change, or even reduction, in *H. pylori* colonisation density. It appears that active secretion of acid somehow protects the body mucosa from *H. pylori*-induced inflammation. The mechanism of this acid protection is unclear. It could be due to the low pH maintaining ammonia produced by *H. pylori* in the ionised form and thus unable to penetrate the epithelial cells and induce toxic injury. This development of body gastritis on PPI therapy is the most likely explanation for the greater acid-suppressing efficacy of these drugs in *H. pylori*-positive subjects. The degree of elevation of intragastric pH and the degree of suppression of gastric acid secretion by PPI therapy is much more profound in subjects with *H. pylori*[61–63]. Though *H. pylori* ammonia production may contribute to this, the major influence is likely to be the body gastritis impairing parietal cell function and thus supplementing the pharmacological effects of the drug.

4 Long-term treatment with PPI therapy has been shown to result in the development of atrophy of the body mucosa in a proportion of *H. pylori* positive subjects[58,64]. This effect does not occur in *H. pylori*-negative subjects on similar therapy.

It can be seen that the pattern of *H. pylori* gastritis which develops in *H. pylori*-positive subjects treated with PPI therapy is similar to that observed in subjects with spontaneous *H. pylori* body gastritis and chronic hypochlorhydria. As already mentioned, the subjects with the latter are recognised to have an increased risk of gastric cancer and there is, therefore, concern that the administration of PPI therapy may predispose *H. pylori*-positive subjects to gastric cancer. For that reason, it has been suggested that *H. pylori* should be eradicated prior to long-term PPI therapy. One problem associated with eradicating *H. pylori* infection in patients requiring long-term proton pump inhibitor therapy is that it is likely to reduce the acid suppressant efficacy of the drug as discussed above and thus its ability to adequately control gastro-oesophageal reflux disease.

The recognition that acid secretory status affects the distribution of *H. pylori* gastritis may be a further reason why some people develop an antral predominant gastritis with increased acid secretion causing duodenal ulcer disease whereas others develop a body involving gastritis with markedly reduced acid secretion predisposing them to gastric cancer. In a subject with a genetically determined high level of acid secretion, the gastritis will be confined to the antrum. This will increase gastrin and further increase acid loading to duodenal ulcer disease. In those with a genetically determined low acid output, the infection will be able to induce a body gastritis leading to impairment of acid secretion and predisposing them to gastric cancer. In addition to genetic factors other influences (e.g. diet, smoking) are known to affect acid secretory status and thus potentially influence the distribution of gastritis and associated disease outcome.

Summary and conclusion

It is now recognised that there are complex two-way interactions between *H. pylori* gastritis and gastric acid secretion (Fig. 6). *H. pylori* gastritis affects gastric acid secretion and the nature of the effect depends upon the relative extent to which the gastritis involves the antral and body mucosa. Acid secretion also affects *H. pylori* gastritis and the extent to which it involves the body versus antral mucosa. This interaction is seen when subjects with the infection are treated with proton pump inhibitor therapy. The pharmacological suppression of acid secretion transforms the antral predominant gastritis to a body predominant gastritis and the latter further inhibits acid secretory function. This interaction between acid secretory status and *H. pylori* gastritis may explain the different response to the infection and different

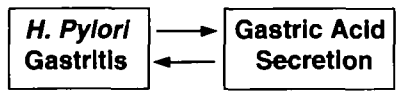

Fig. 6 Two-way interaction between *H. pylori* gastritis and gastric acid secretion.

disease outcomes. Subjects with a premorbid natural high acid secretion will develop an antral-predominant body-sparing gastritis and this form of gastritis stimulates further increase in acid secretion leading to duodenal ulcer disease. Subjects with premorbid low acid secretion will develop a body predominant gastritis and this further reduces the acid secretion leading to hyperchlorhydria and risk of gastric cancer. In the majority of subjects with normal premorbid acid secretion the gastritis will involve both the antral and body mucosa and this will result in no overall significant change in acid secretion and thus no clinical disease. Other factors such as diet, smoking, anti-secretory drugs, bacterial strains and auto-immune responses will contribute to the complex interaction and thus also influence the disease outcome.

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