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The role of gastrin in ulcer pathogenesis

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Duodenal ulcer patients are characterized by an antrum-predominant, body-sparing, non-atrophic *Helicobacter pylori* (*H. pylori*) gastritis, which results in increased gastrin release and increased acid secretion. The increased gastrin release is caused by the infection impairing the acid-mediated inhibitory control of gastrin release. The elevated levels of the gastrin stimulate the healthy uninflamed, non-atrophic acid-secreting region of the stomach to secrete excess amounts of acid. The increased gastrin also exerts trophic effects on the oxyntic mucosa, causing hyperplasia of both the enterochromaffin-like cells and the parietal cells. These trophic changes in the mucosa further enhance its ability to secrete acid. The increased acid secretion results in an increased duodenal acid load, causing gastric metaplasia of the duodenal bulb and eventually the development of ulceration.

In *H. pylori*-infected subjects without duodenal ulceration, a different pattern of gastritis is seen. This includes atrophy of the antrum, which reduces the number of G-cells and thus the degree of hypergastrinaemia induced by the antral infection. There are usually also varying degrees of inflammation and atrophy of the acid-secreting mucosa, which impair its ability to secrete acid in response to gastrin stimulation. The combined effects of the atrophy of the antrum and the inflammation of the antrum of the body mucosa therefore prevent *H. pylori*-induced acid hypersecretion and may result in varying degrees of hypochlorhydria.

The particular pattern of gastritis that a subject develops in response to *H. pylori* infection and their likelihood of developing a duodenal ulcer is likely to be determinded by host genetic factors plus dietary factors.

Key words: gastrin; acid; ulcer.

GASTRIN AND ITS ROLE IN GASTRIC FUNCTION

Gastrin is an important hormone that plays a central role in the regulation of gastric acid secretion. This is demonstrated by the marked reduction in acid secretion produced by administering gastrin receptor antagonists.[1] The hormone is produced by the G-cells, which are situated within the glands present in the antral region of the

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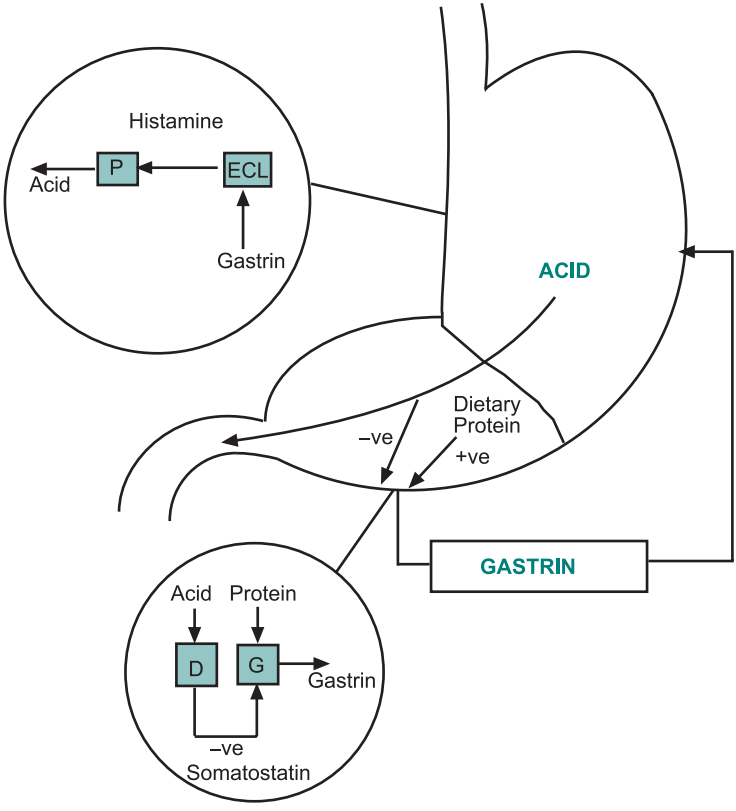

Figure 1. Role of gastrin in the regulation of acid secretion. Protein components of food stimulate the G-cells in antral mucosa to release gastrin. The hormone circulates and stimulates the body region of the stomach to secrete acid. This occurs via gastrin stimulating the release of histamine from the entero-chromaffin-like (ECL) cells, the histamine then activating the histamine-2 receptors on the acid-producing parietal cells (P). The over-production of acid is prevented by a low antral pH inhibiting gastrin release. This inhibitory control is mediated via the release of somatostatin from D-cells situated in close proximity to the G-cells.

stomach (Figure 1). These cells have microvilli on their luminal surface, allowing them to sense luminal conditions. Protein ingested in the diet stimulates the G-cells to release gastrin into the system circulation. The hormone then stimulates the proximal body region of the stomach to secrete acid.

Under fasting conditions, the concentration of gastrin in the serum is approximately 25 pmol/l. Following the ingestion of the protein-containing meal, the serum gastrin level rises 2–3-fold within 15–30 minutes of starting the meal and remains elevated for 1 or 2 hours. There are two main forms of gastrin present in the serum, the 17 amino acid peptide referred to as gastrin-17 (G-17) and the 34 amino acid peptide, gastrin-34 (G-34). Under fasting conditions, G-34 is the predominant form present in the serum. However, following a meal, the increased gastrin released is mainly G-17, and this becomes the predominant form in serum post-prandially.[2]

The acid-secreting cell of the stomach is the parietal cell, which is found in the gastric glands or pits of the body region of the stomach (Figure 1). The G-cells and the

parietal cells are therefore found in different regions of the stomach, the parietal cells being confined to the proximal body region of the stomach and the G-cells to the distal antral region. Gastrin stimulates acid secretion not by acting directly on the parietal cells but by acting on the enterochromaffin-like (ECL) cells, which are situated in close proximity to the parietal cells. These ECL cells have gastrin receptors that cause the cell to release histamine when activated by gastrin. The histamine released in this way then acts on histamine-2 receptors on the adjacent parietal cells causing them to secrete acid.

In addition to stimulating acid secretion in the above way, gastrin also exerts trophic effects on the acid-secreting mucosa of the body of the stomach. The trophic effect of gastrin is most evident on the ECL cells of the oxyntic mucosa. Producing animal models void of gastrin or gastrin receptors results in marked depletion and hypoplasia of the ECL cells.[3,4] The administration of gastrin receptor antagonists produces a similar effect.[5,6] In contrast, the exogenous administration of gastrin to rats results in hyperplasia and hyperfunction of the ECL cells.[7,8] Similarly, chronic hypergastrinaemia induced by proton pump inhibitor therapy in humans or animals results in hyperplasia of these same cells.[9–13] The trophic effect of gastrin is not confined to the ECL cells but also affects the parietal cells and surface epithelial cells of the oxyntic mucosa.[14] However, the trophic effect exerted by gastrin on some cells may be indirect as they do not all have gastrin receptors. Recent studies suggest that ECL or parietal cells may release heparin-binding epidermal growth factor-like growth factor when their gastrin receptor is activated, and this growth factor may mediate trophic effects on the epithelial progenitor cells.[14]

The release of gastrin by the G-cells in the antral mucosa is inhibited by low antral luminal pH.[15,16] This serves as an important negative feedback control of gastric acid secretion. The role of intraliminal acidity in controlling gastrin release is clearly demonstrated by the exaggerated gastrin response seen during proton pump inhibitor therapy.[17] These powerful acid inhibitory drugs elevate intragastric pH and thus remove the acid-mediated inhibition of gastrin release.

The acid inhibition of gastrin release is mainly mediated by the release of somatostatin from D-cells situated close to the antral G-cells[18–23] (see Figure 1 above). These D-cells are of the open type and have microvilli enabling them to sense luminal pH.[24] Low intragastric pH stimulates the D-cells to release somatostatin, which then exerts a paracrine inhibitory influence on the adjacent G-cells.

Two effects of the protein component of a meal, therefore, exert a concerted effect on the antral G-cells to release gastrin. The first is the direct effect of the protein on the G-cells. The second is the fact that protein is a powerful buffer and therefore raises the intragastric pH. This elevation of pH reduces somatostatin release for the antral D-cells and thus removes this inhibitory control of gastrin release. The rise in gastrin stimulates the proximal body region of the stomach to secrete acid, which eventually overcomes the buffering effect of the meal and thus lowers intragastric pH. The low pH stimulates the D-cells to secrete somatostatin again, thus lowering the gastrin level and preventing excess acid secretion.

DISTURBANCES OF GASTRIN PHYSIOLOGY IN DUODENAL ULCER DISEASE

More than 30 years ago, several disturbances of gastric function were recognized as being present in duodenal ulcer patients and were thought to be important in the

aetiology of the disease. Such patients were seen to secrete excessive amounts of acid in fasting conditions and also to have an exaggerated acid response to a meal.[25,26] In addition, duodenal ulcer patients were shown to have a larger capacity to secrete acid under maximal stimulation by gastrin, this being caused by their having an increased number of parietal cells.[26] Further studies were performed by Walsh and colleagues to investigate the mechanism of the increased acid output characteristic of the duodenal ulcer patients. These indicated that the increased basal acid output and meal-stimulated acid output, characteristic of the duodenal ulcer patients, was caused by an impaired acid-mediated inhibitory control of gastrin release.[16,27,28] These observations were confirmed by Jensen et al.[29] At that time, the reasons for the disturbances in gastrin control on acid secretion were unclear.

HELICOBACTER PYLORI AND DISTURBANCES OF GASTRIN AND ACID SECRETION IN DUODENAL ULCER PATIENTS

The discovery of *Helicobacter pylori* (*H. pylori*) infection of the gastric mucosa by Marshall and Warren led to a major breakthrough in our understanding of the aetiology of duodenal ulcer disease. The prevalence of the infection was markedly increased in duodenal ulcer patients, and, more importantly, eradicating the infection resulted in cure of the ulcer disease in the great majority of subjects. Discovery of the role of *H. pylori* infection in duodenal ulcer disease was also to transform our understanding of the pathophysiology of this common disorder.

H. pylori infection can result in a wide spectrum of morphological changes to the gastric mucosa. However, in duodenal ulcer patients the infection is associated with a specific pattern of gastritis. In such patients the infection is found in both the antral and body regions of the stomach, but the inflammation induced by the infection is more marked in the antral region of the stomach, with relatively little inflammation of the body region of the stomach.[30–32] In addition, in duodenal ulcer patients the infection does not result in significant atrophy of the mucosa of either the antrum or the body of the stomach. Duodenal ulcer patients therefore have an antrum-predominant, body-sparing, non-atrophic gastritis. It is now recognized that this pattern of gastritis results in increased antral gastrin release and increased acid secretion, and that this is a key mechanism by which the infection induces the ulcer disease.

This non-atrophic, antrum-confined *H. pylori* gastritis stimulates an increased release of gastrin from the antral mucosa. The fasting serum gastrin level is slightly increased in such subjects, and that following stimulation with a meal or with gastrin-releasing peptide is increased several-fold.[33–40] The increased circulating gastrin is mainly caused by a rise in gastrin-17, which is the form of the hormone that increases following antral stimulation with food. The increased circulating gastrin concentration resolves within 2–14 days of commencing *H. pylori* eradication therapy, indicating that it is caused by the infection.[41,42]

A considerable number of studies have investigated the mechanism by which *H. pylori* infection or the accompanying gastritis of the antral mucosa stimulates increased gastrin release. Interestingly, the main mechanism appears to be an impairment of the acid-mediated inhibitory control of gastrin release. As discussed above, this inhibitory control is mediated via the release of somatostatin from D-cells situated close to the antral G-cells. Several studies have demonstrated a lower concentration of somatostatin within the antral mucosa of *H. pylori*-infected subjects.[42–46] In addition,

the somatostatin mRNA concentration is lowered, indicating a reduced synthesis of this inhibitory hormone.[44,46]

Functional studies have also shown evidence of an impaired acid-mediated inhibitory control of gastrin release in *H. pylori*-infected subjects. Tarnasky et al measured gastrin release and acid secretion response to meals of varying pH.[47] In asymptomatic volunteers with *H. pylori* infection, they found an impaired inhibition of gastrin release at low pH. Further evidence of an impaired inhibitory control of gastrin is provided by the studies of Konturek et al, employing the cholecystokinin A (CCK A) receptor antagonist, loxiglumide.[48,49] Cholecystokinin exerts a 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 gastric acid response to a test meal in healthy control but not in duodenal ulcer patients.[48] In a separate study, they found that eradicating the *H. pylori* infection restored the physiological response to CCK A blockade in duodenal ulcer patients.[49] All of these findings are therefore consistent with *H. pylori* antral gastritis impairing the somatostatin-mediated inhibitory control of gastrin release.

The mechanism by which the *H. pylori* infection or accompanying gastritis of the antral mucosa depletes antral somatostatin levels and thus impairs the acid-mediated inhibitory control of gastrin release is not fully understood. It was proposed by Calam et al that the high concentrations of ammonia produced by *H. pylori* urease activity would raise antral surface pH and thus prevent the antral D-cells from sensing the low pH of the antral lumen.[37] Several studies have investigated the effects of acutely changing the rate of ammonia production of gastrin release in *H. pylori*-infected subjects, but these have not shown any early change in gastrin release.[41,50,51] However, this lack of effect of an acute alteration of ammonia production does not exclude the role of long-term *H. pylori* infection in depleting antral somatostatin levels. It has been shown that pH-induced adaptive changes in antral D-cells occur at a slow rate.[52] Recent studies have demonstrated that several weeks' treatment with omeprazole induces changes in gastrin-releasing peptide-stimulated gastrin release that are identical to those observed with *H. pylori* infection. These findings would, therefore, support the theory that the loss of acid-mediated inhibitory control is caused by *H. pylori* elevating the antral surface pH by its ammonia production.

It is possible that *H. pylori* antral gastritis might affect G- and D-cell function by stimulating the production of cytokines.[53,54] Recent in vitro studies have shown that certain cytokines affect gastrin somatostatin release, although it is difficult to know whether this can be extrapolated to the in vivo situation.[55]

There is thus now substantial evidence that the previously observed impaired acid-mediated inhibitory control of gastrin release characteristic of duodenal ulcer patients is a consequence of *H. pylori* infection of the antral mucosa.

EFFECT OF *HELICOBACTER PYLORI*-INDUCED HYPERGASTRINAEMIA ON ACID SECRETION IN DUODENAL ULCER PATIENTS

In duodenal ulcer patients, the increased gastrin stimulated by *H. pylori* infection is accompanied by an increased acid secretion. The increased basal acid output characteristic of these patients can be largely attributed to the *H. pylori* infection as it falls following eradication therapy.[33,34,55,56] The acid response to stimulation with gastrin-releasing peptide is also markedly increased in *H. pylori*-infected duodenal ulcer

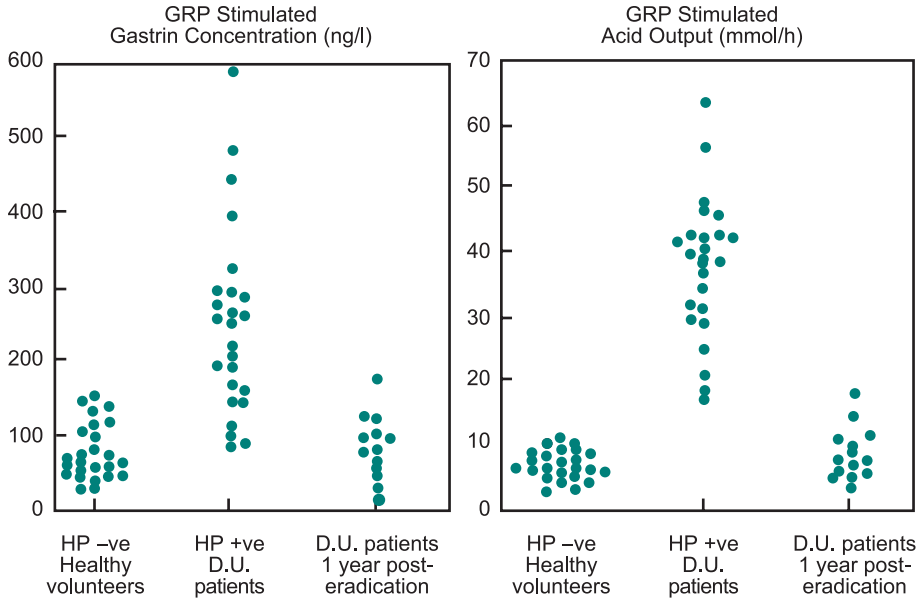

Figure 2. Gastrin and acid response to stimulation with gastrin-releasing peptide in *H. pylori* (HP) negative volunteers and duodenal ulcer patients before and after eradication of the infection. In the ulcer patients, *H. pylori* infection stimulates increased gastrin release, and this is accompanied by increased acid secretion.

patients, and again this markedly falls following eradication of the infection[33,34] (Figure 2). The increased duodenal acid load also falls after eradication of *H. pylori*.[57] Some, but not all, studies have shown that eradicating *H. pylori* infection also results in a fall in the maximal acid output in duodenal ulcer patients.[34,55,56] Although the fall in serum gastrin occurs within a few days of eradicating *H. pylori* infection, the fall in acid secretion occurs more slowly, being most evident 6 months after eradication therapy.[34]

The fact that the rate of resolution of the acid hypersecretion is slower than that of the resolution of the hypergastrinaemia indicates that the increased acid secretion is not entirely explained by the increased gastrin directly stimulated rise in acid secretion. The delay in resolution of the increased acid secretion is consistent with the resolution of trophic effects of the *H. pylori*-induced hypergastrinaemia on the acid-secreting mucosa. As discussed earlier, gastrin exerts trophic effects on both the ECL cells and the parietal cells of the acid-secreting mucosa. These effects are most pronounced on the ECL cells. Hyperplasia of these cells induced by increased circulating concentrations of gastrin will result in increased basal acid output because of their increased histamine release in response to a variety of stimuli. Similarly, trophic effects of gastrin on both the ECL cells and the parietal cells will increase the maximal acid output. Although resolution of the hypergastrinaemia will be associated with an early reduction in gastrin-stimulated acid secretion, resolution of the atrophic changes induced by the increased gastrin on the acid-secreting mucosa will take weeks or months, and thus considerable time is needed for a complete resolution of some of the changes induced over the many years of the infection.

HELICOBACTER PYLORI INFECTION AND THE PATHOPHYSIOLOGY OF DUODENAL ULCER DISEASE

It can be seen, therefore, that many of the previously recognized abnormalities of gastric function characteristic of duodenal ulcer patients can now be explained by the effects of *H. pylori* infection. These include the impaired acid-mediated inhibitory control of gastrin release, the increased basal and stimulated acid output and the increased duodenal acid load. The original studies examining pathophysiology in duodenal ulcer patients were handicapped by the fact that many of the so-called normal controls themselves had *H. pylori* infection and disturbed physiology. As discussed below, the infection produces some disturbances of physiology as well as ulcers, and this would have obscured the physiological abnormalities in the ulcer patients.

The role of *H. pylori* infection in the pathophysiology of duodenal ulcer disease is summarized in Figure 3. The non-atrophic antral confined gastritis disrupts the acid-mediated inhibitory control of gastrin release. The increased gastrin results in the healthy body region of the stomach secreting excess amounts of acid. This in turn leads to an increased duodenal acid load. The increased duodenal acid load progressively damages the duodenal mucosa, resulting in the development of gastric metaplasia within the duodenal bulb. *H. pylori* infection is then able to colonize the patches of gastric metaplasia within the duodenal bulb. The combination of the increased acid load, the local damaging effect of the infection and the associated inflammation results in progressive damage to the duodenal mucosa, eventually causing ulceration. Eradicating the infection reduces the acid load on the mucosa and removes any local

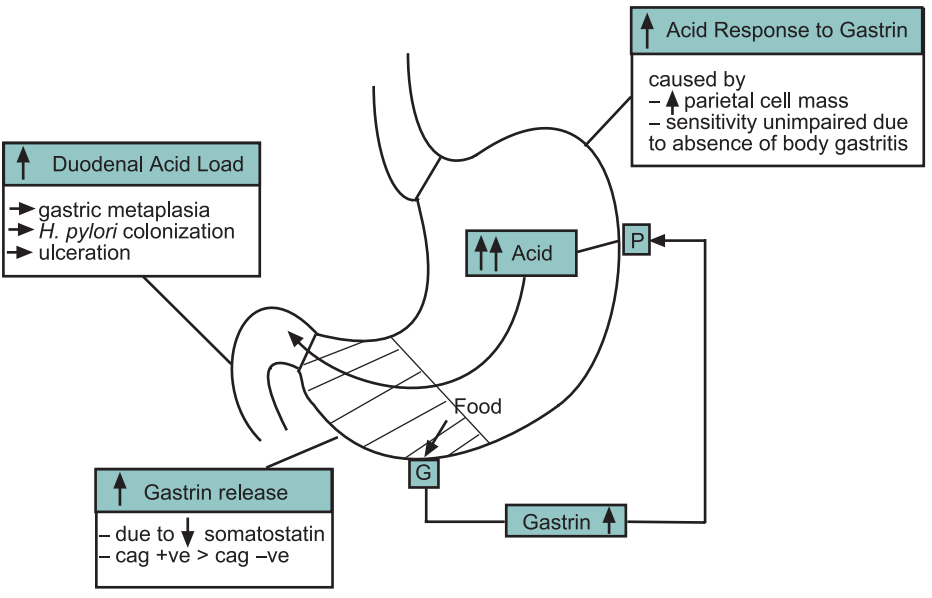

Figure 3. Duodenal ulcer patients have a non-atrophic, antrum-predominant *H. pylori* gastritis. This stimulates the antral G-cells to secrete excess gastrin, which circulates and stimualtes the healthy body region of the stomach to secrete excess acid. The resulting increase in duodenal acid load eventually leads to duodenal ulceration.

effects of the bacterium. Consequently, eradicating the infection results in a long-term cure of the ulcer disease.

WHY DO ONLY A SUBGROUP OF *HELICOBACTER PYLORI*-INFECTED SUBJECTS DEVELOP DUODENAL ULCER DISEASE?

It is important to recognize that disturbances in gastrin release and gastric acid secretion induced by *H. pylori* infection in duodenal ulcer patients do not occur in all *H. pylori*-infected subjects. The physiological disturbances seen in duodenal ulcer patients are the result of the antrum-predominant, body-sparing, non-atrophic gastritis produced by *H. pylori* infection in duodenal ulcer patients. The morphological changes induced by the infection in non-duodenal patients are different. In most other patients, the inflammation induced by the infection extends to varying degrees into the acid-secreting body region of the stomach. In addition, in many non-duodenal ulcer patients, the infection results in atrophy of the antral and body mucosa. The inflammation of the body mucosa and the atrophy of the antrum and body mucosa seen in non-duodenal ulcer patients modify the changes in gastric physiology, as discussed below.

INFLUENCE OF ANTRAL ATROPHY ON GASTRIC PHYSIOLOGY IN *HELICOBACTER PYLORI* INFECTION

Atrophy of the antral mucosa develops in a substantial proportion of *H. pylori*-infected non-duodenal ulcer subjects and modifies the *H. pylori*-induced changes in gastrin release. It results in depletion of gastrin-producing G-cells and thereby reduces the degree of hypergastrinaemia induced by the infection.

We have recently examined serum gastrin levels in *H. pylori*-infected subjects with and without evidence of atrophy of the antral mucosa. In those with antral atrophy, the gastrin level was consistently lower than in those without atrophy when corrected for intragastric acidity (Figure 4).[58] In addition, the ability of the gastrin concentrations to rise in response to decreasing intragastric acidity was impaired.

It has for many years been recognized that, in subjects with achlorhydria caused by atrophic gastritis, gastrin level rises as a result of the lack of the acid-mediated inhibition of gastrin release.[59] However, it has also been shown that the degree of increase in gastrin level depends upon the pattern of atrophic gastritis. In those in whom the atrophy affects the antrum, the degree of increase in gastrin level is much less than that seen in subjects with the autoimmune type of atrophy confined to the body mucosa.[60] This again highlights the importance of atrophy of the antral mucosa with regard to the degree of increase in serum gastrin level. Consequently, the presence or absence of *H. pylori*-induced atrophy of the antral mucosa considerably modifies the degree of increase in gastrin level induced by *H. pylori* infection.

INFLUENCE OF ATROPHY AND INFLAMMATION OF THE OXYNTIC MUCOSA ON GASTRIC FUNCTION IN *HELICOBACTER PYLORI* INFECTION

The gastritis induced by *H. pylori* infection in the body region of the stomach also markedly affects the acid response to *H. pylori*-induced hypergastrinaemia. In duodenal

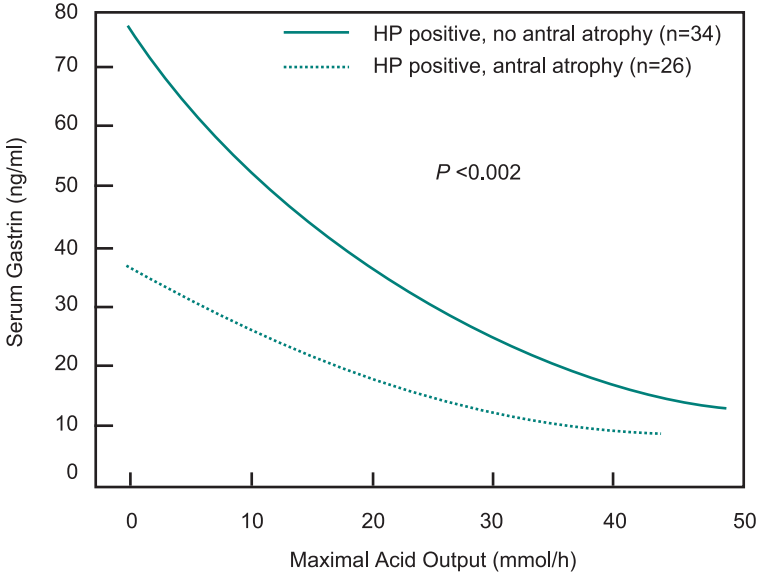

Figure 4. This shows the correlation between serum gastrin and acid output in *H. pylori*-infected subjects with and without antral atrophy. The antral atrophy lowers the gastrin level and impairs the ability of the hormone level to increase in response to falling acid output.

ulcer patients, the *H. pylori*-induced hypergastrinaemia results in increased acid secretion.[61] This is due to the fact that the acid-secreting body mucosa is healthy, with little or no inflammation and no atrophy. In addition, it is hyper-responsive because of the trophic effects of the hypergastrinaemia.

In non-duodenal ulcer patients with *H. pylori* infection, there is usually evidence of varying degrees of inflammation and sometimes atrophy of the acid-secreting body mucosa. This impairs the function of the body mucosa and its ability to secrete acid in response to gastrin stimulation.[61,62] Eradication of the infection and resolution of the inflammation of the body mucosa results in an early return of gastric acid secretion[62] (Figure 5). This demonstrates that the inflammation of the body mucosa is somehow impairing the function of the body mucosa. The precise mechanism by which *H. pylori* gastritis of the body mucosa impairs its function is unclear. It may be related to the local production of interleukin-1B, which is the most potent inhibitor of acid secretion yet identified. The combination of a loss of acid-secreting cells because of atrophy, and the impaired functioning of the remaining acid-secreting cells markedly reduces the acid response to gastrin stimulation that is seen in atrophic body gastritis.

The combination of three factors therefore explains why subjects with *H. pylori*-induced atrophic pangastritis do not have increased acid secretion. The first factor is the atrophy of the antrum, reducing the number of G-cells and therefore their ability to release excessive amounts of gastrin. Second is the inflammation of the body mucosa, impairing the functioning of the acid-secreting cells. Third, there is the loss of the acid-secreting cells themselves as a result of the atrophy of the body mucosa (Figure 5).

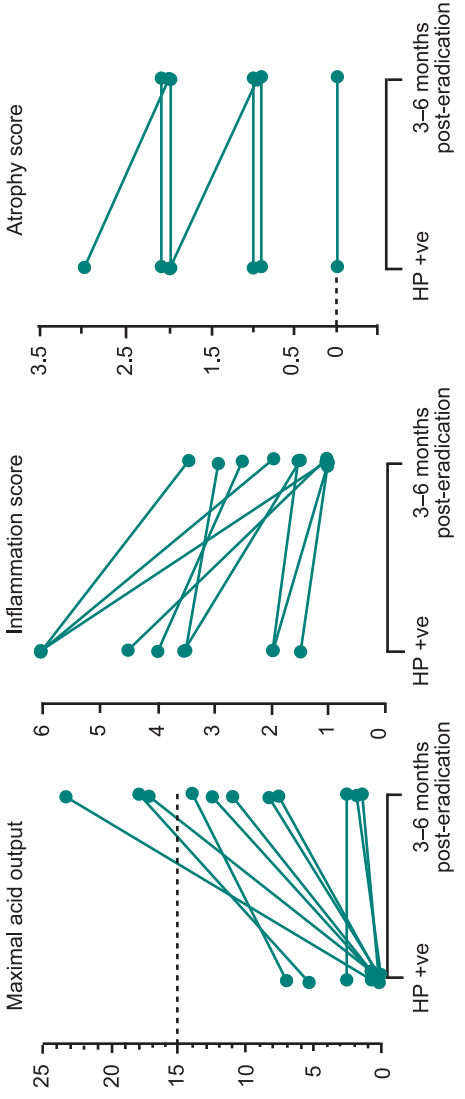

Figure 5. In subjects with *H. pylori*-induced hypochlorhydria, there is a recovery of acid secretion following eradication of the infection. The increase in acid secretion coincides with the resolution of inflammation in the oxyntic mucosa. There is little evidence of resolution of atrophy in the short term. The dotted line indicates the lower limit for normal acid secretion.

WHY DO DIFFERENT SUBJECTS HAVE DIFFERENT PATTERNS OF *HELICOBACTER PYLORI* GASTRITIS AND CONSEQUENTLY DIFFERENT DISEASE OUTCOMES?

The non-atrophic antrum-confined gastritis leads to increased gastrin release and increased acid secretion, resulting in the development of duodenal ulceration. Other patterns of gastritis result in normal or low acid secretion. There is considerable interest in the reasons determining the pattern of gastritis induced by *H. pylori* infection in different individuals and consequently the probable outcome of the disease.

A person's pre-morbid acid secretory status may be an important determinant of disease outcome. There is considerable interindividual variation in the amount of acid that normal uninfected subjects secrete, and it is now recognized that the level of acid secretion determines the distribution of gastritis between the antral and body regions of the stomach. When a duodenal ulcer patient with an antrum-predominant gastritis is treated with a proton pump inhibitor, which reduces his acid secretion, the gastritis migrates from the antral region into the body region of the stomach, resulting in a pangastritis or body-predominant gastritis.[63] In addition, one study has suggested that an inhibition of acid secretion may also predispose to the development of atrophy of the body mucosa in response to the *H. pylori* infection.[64] In the light of these observations, it can be proposed that subjects with a high pre-morbid acid secretory status will develop an antrum-predominant, body-sparing, non-atrophic gastritis and consequently progress to develop a further increase in acid secretion and therefore duodenal ulceration. In subjects with a low pre-morbid acid output, the gastritis will be able to extend into the body region of the stomach, resulting in a further fall in acid secretion and thus protecting them from duodenal ulcer disease.

The propensity for a person to develop atrophy of the antral or body mucosa is also likely to be a key factor in determining the outcome of *H. pylori* infection. In someone without atrophy, the increased antral gastrin release stimulated by the infection will increase acid secretion, and this will maintain the antral distribution of the gastritis. However, if the antral gastritis results in the development of atrophy of the antral mucosa, the loss of the G-cells will result in a diminution of the degree of hypergastrinaemia. This will lower the acid secretion, allowing the gastritis to spread into the body region of the stomach. This inflammation of the body region of the stomach will now also lead to atrophy in this region and consequently a further lowering of acid secretion. Several factors are likely to predispose to the development of atrophy. These may include host genetic factors determining the nature of the immune and inflammatory response produced in response to the infection and also the effectiveness of their anti-oxidant defences. The propensity to develop an autoimmune response against the parietal cells may also be important. The person's dietary intake of anti-oxidant vitamins is also likely to be a contributory factor, and this may explain the different patterns of gastritis seen in different parts of the world.

There has been considerable interest in the role of different strains of *H. pylori* in influencing disease outcome. However, the more pathogenic *cagA*-positive strains are more prevalent in both those who develop duodenal ulcer and those who develop gastric cancer. The strain therefore increases the likelihood of developing a serious disease but does not determine which disease.

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