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Review article

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ROLE OF HELICOBACTER PYLORI INFECTION IN GASTRO-DUODENAL SECRETION AND IN PATHOGENESIS OF PEPTIC ULCER AND GASTRITIS

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Etiologic role for HP appears to be best established in histologically proven gastritis. The major factors mediating gastritis induced by the colonization of the „gastric type" mucosa with HP are probably cytotoxins, cytokines and free radicals activated by this organisms. The deficiency of negative feedback in somatostatin-gastrin link in antral gastritis may result in an excessive gastrin release and increased gastric acid secretion with increased duodenal acid load under basal state and after meal. Recent NIH consensus 1994 proposes that: (1) ulcer patients with HP require treatment with antimicrobial agents whether on first presentation or on recurrence; (2) the value of treatment of HP infection in non-ulcer dyspepsia remains to be determined and (3) the asymptomatic subjects with HP infection do not require treatment with antimicrobial agents.

Key words: *Helicobacter pylori, infection, gastritis, gastrin, somatostatin.*

INTRODUCTION

The description of Helicobacter pylori (HP) in 1983 (1, 2) spawned a new body of gastroenterologic studies designed to elucidate the role of this microorganism in gastric pathology. Colonization of human gastric mucosa by spirochetes was described at the beginning of this century (3), but it was considered to result from the postmortem process (4) rather than from the active infection. Warren (1) and Marshall (2) were the first to characterize HP in human gastric mucosa and to propose its close association with histological gastritis and peptic ulcer disease.

Bacteriology and transmission

Although originally classified as a Campylobacter species, HP has distinct, morphological and biochemical characteristics (5) leading to its classification into the genius Helicobacter (6). HP is a curve or S-shaped gram negative rod, $0{,}5 \times 3$ μm in size, usually with 4—6 sheathed flagella at one pole (*Fig. 1*).

Helicobacter Pylori Infects the Mucus Layer of the Human Stomach

- **Spiral**
- **Unipolar**
- **Multiflagellate — (4–6)**
- **Blunt round ends**
- **Gram negative**
- **Stained by silver stains (e.g. Warthin-Starry)**

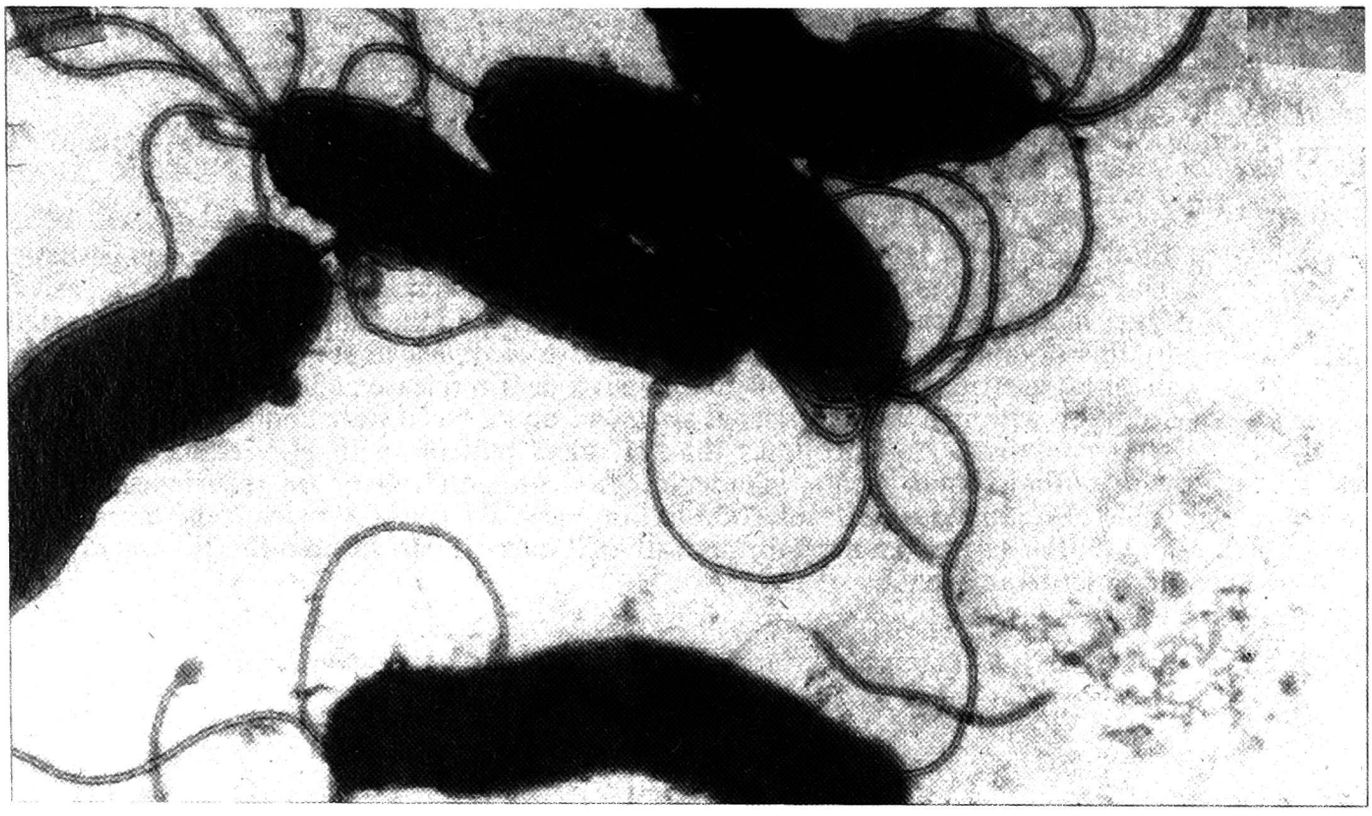

Fig. 1. Helicobacter pylori infects the mucus layer of the human stomach. It is a spiral, unipolar, multiflagellate, gram-negative organism stained by silver stains (e.g. Warthin-Starry).

The most distinctive feature is the production of highly active urease (7). The urease reaction is the basis for direct assay of gastric biopsy samples (CLO-test) and the $^{14}C/^{13}C$-urea breath tests (8—10). In the CLO-test, the biopsy sample is placed on the solution or gel containing urea and phenol red (a pH indicator). If urease is present from HP in the biopsy specimen, urea is

hydrolyzed to release NH_3 increases the pH giving a pink color. The tests are read after 2—3 h and then again 24 h later. The CLO-test is commercially available and has sensitivity in the range of 80—90% at 2—3 h and about two third of patients develop positive test in less than 30 min (8—10) (*Table 1*). The ^{13}C- or ^{14}C-labelled urea breath tests are noninvasive diagnostic method without endoscopy and mucosal biopsy. Sensitivity and specificity of these methods are in the 90%—100% range but the method requires special material and equipment (11, 12).

Table 1. Methods of Diagnosis of Helicobacter pylori

Type of method	Sensivity	Specificity
I. **Invasive** (endoscopic biopsy required)		
A. Rapid diagnosis		
1. Gram stain of biopsy touch preparation	60%	70%
2. Urease test [broth, gel (CLO-test)]	80%	90%
3. ^{13}C or ^{14}C-urea breath test	95%	95%
B. Delayed diagnosis		
1. Histology (Hematoxylin and eosin, Warthin-Starry, Giemsa, acridine orange, immunohistochemistry	80%	90%
2. Bacterial culture	90%	95%
II. **Noninvasive**		
A. Urea breath test (^{13}C or ^{14}C)	95%	95%
B. Serologic testing for antibodies to HP		
1. ELISA	90%	90%
2. Others (immunoblot, component fixation, passive hemaglutination	80%	90%

In routine diagnosis and large epidemiologic studies, the most acceptable method includes serological testing such as enzyme-linked immunosorbent assay (ELISA) that serves to detect antibody to HP (13).

The histological examination of the biopsy specimen of gastric mucosa provides an excellent mean of diagnosis. Gram stain of mucosal biopsy smear is a rapid but less sensitive method. The standard hematoxylin and eosin staining or preferably, the Warthin-Starry silver or Giemsa stain are the best invasive tests for HP diagnosis (14—16). Immunohistological methods of HP diagnosis have also been used in HP testing. Proper microbiological technique, especially immediate culture of mucosal specimen, is required under microaerophilic conditions.

The transmission of HP is not clear but the increased prevalence in family members of HP positive patients (17, 18) and in institutionalized patients (19) or in chronic care facility (20) suggests the possibility of person-to-person transmission or the exposure to the same environmental source. Self-inoculation studies (21, 22) show that HP causes a transient, acute clinical

illness with upper abdominal pain, nausea and vomiting lasting for few days and resulting in transient gastric hypochlorhydria (22, 23). Chronic infection has been shown to be associated with histologic gastritis and little or no specific symptoms (24).

Helicobacter pylori infection and gastroduodenal diseases

Helicobacter pylori was first described is association with the type B chronic gastritis and the antral mucosa was considered to be the primary residence of this microorganisms. HP resides in the gastric mucus layer adjacent to the epithelial cell surface (25), in the junction between cells (26) and infrequently inside the epithelial or parietal cells (27). It is now well established that HP is, at least, as common in the antrum and body as in the fundus of the stomach in over 80% of DU patients (28, 29).

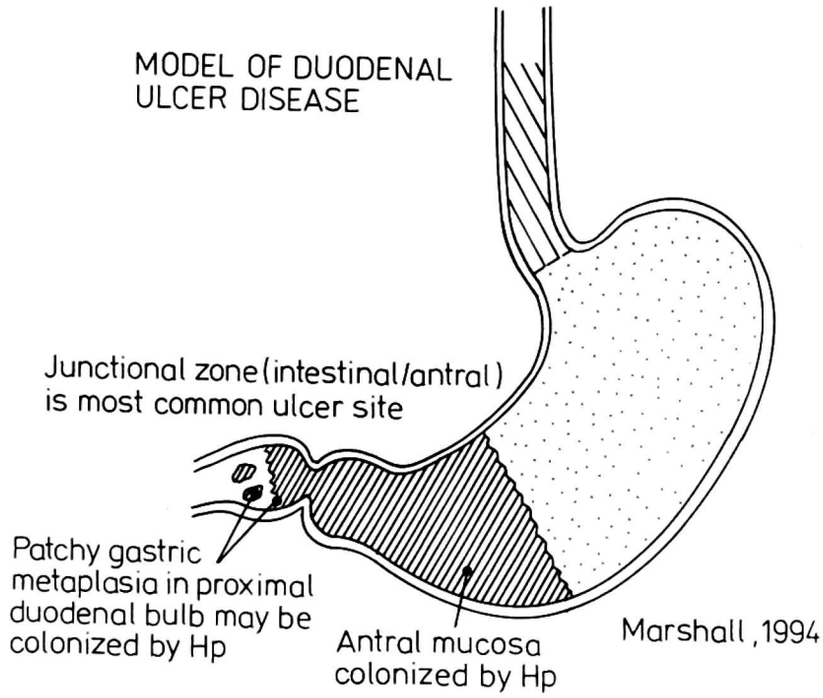

Fig. 2. The most common place for the development of peptic ulcer is a junctional zone (antral-intestinal), especially in the patchy gastric metaplasia in proximal bulb colonized by bacteria.

HP may also be identified outside the stomach, particularly in the upper duodenum, on the areas of gastric metaplasia. The organism appears to colonize only the „gastric type" mucosa and this is always accompanied by high scores for the infiltration of both mononuclear cells and neutrophils. This might explain the occurrence of peptic ulcer in the duodenum, especially in the upper part of the duodenal bulb in HP positive patients with active chronic antral gastritis (*Fig. 2*).

In fact active duodenitis is found in majority of DU patients. Because HP is found only on the gastric type epithelia in the duodenum, the relation between

gastric metaplasia of the duodenum and HP infection has been explored. It appears that gastric metaplasia is a patchy multifocal process present in 22—64% healthy volunteers and it is more common in patients with active duodenitis or DU (34). The mechanism of this metaplasia is not clear but it may be related to excessive gastrin production and increased gastric acid secretion and duodenal acid load which are more extreme in HP positive patients with duodenitis (35). Organisms may then spread from the gastric antrum into areas of gastric metaplasia in the duodenal bulb, leading to the areas of chronic duodenitis and ultimately frank ulceration. Other factors such as genetic predisposition, smoking, stress and drugs, all may contribute to the development of ulcer disease (*Fig. 3*).

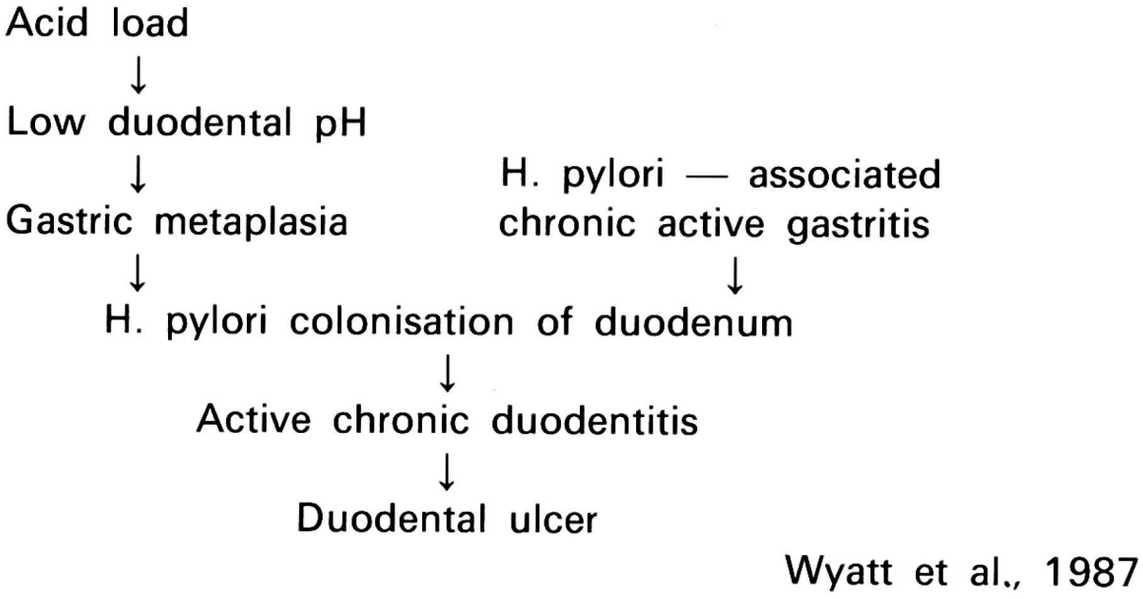

Fig. 3. Proposed pathogenic role of H. pylori in duodenal ulcer disease.

The major question is whether HP is an etiologic agent for gastritis and duodenitis and subsequently for the peptic ulceration or whether it merely resides in the areas of inflammation caused by some other factors. There are several lines of evidence suggesting that HP is a cause rather than result of mucosal inflammation; (1) self-inoculation studies showing histologic acute gastritis associated with abdominal symptoms induced by acute infection and hypochlorhydria; (2) chronic gastritis is almost always present in peptic ulcer patients and the eradication of HP by appropriate therapy results in a significant decrease or the resolution of the gastritis and duodenitis (36) and (3) HP strains that possess cytokine-associated gene („cagA") elicit a greater proinflammatory expression of cytokines e.g. interleukin-1α (IL-1α), tumor necrosis factor α (TNFα) and transforming growth factor β (TGFβ) in humans gastric mucosa (37). All DU patients infected with HP have this „cagA" that acts as cytotoxin to induce inflammatory reaction in the gastric mucosa also in the area of gastric metaplasia in duodenum colonized by HP.

Among diseases associated with HP infection are not only duodenal ulcer (DU) but also gastric ulcer (GU), non-ulcer dyspepsia (NUD) and gastric carcinoma (*Fig. 4*). About 92% of DU have HP infection (38—41) and the HP-negative DUs represent only about 8% of these patients with peptic ulcer induced by non-steroidal anti-inflammatory agents (NSAID),

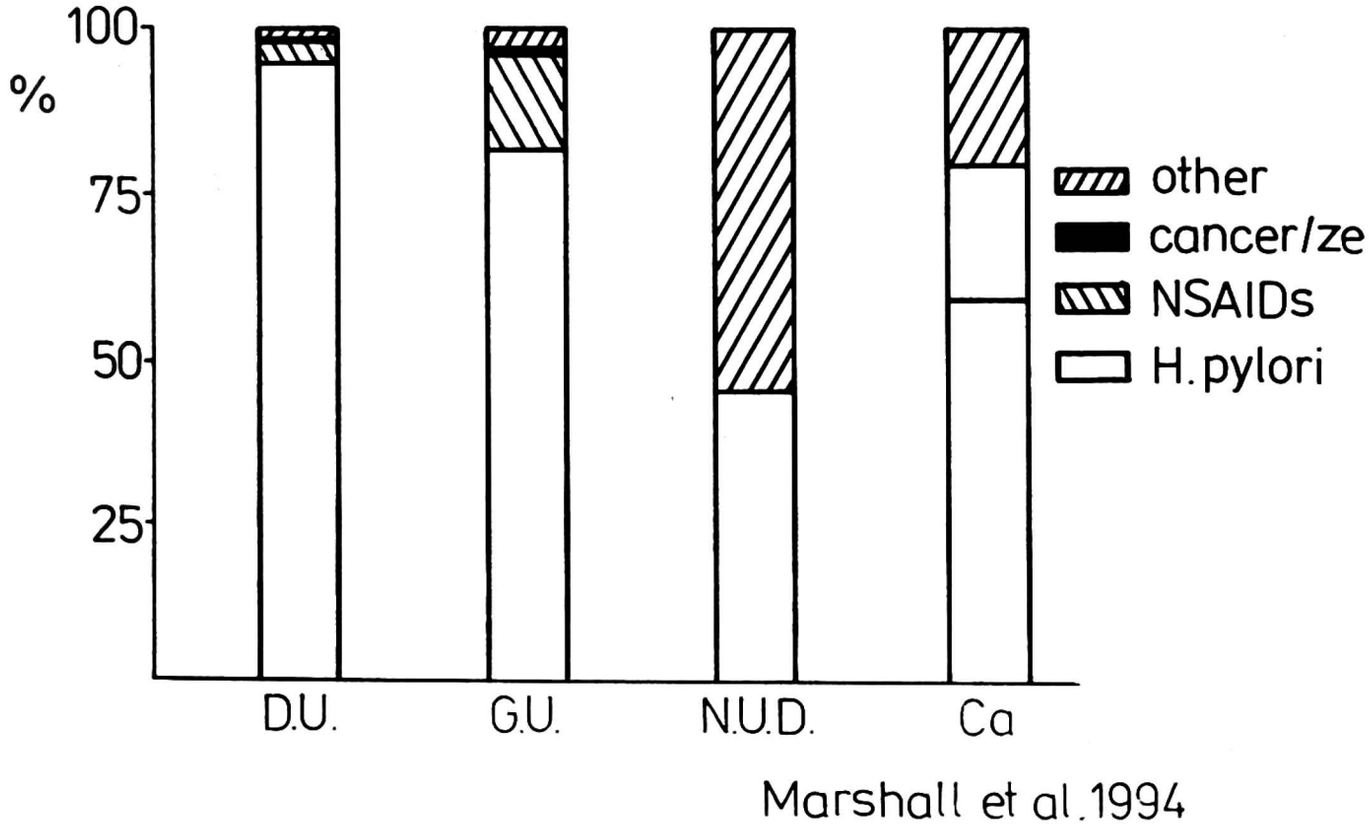

Fig. 4. The percent incidence of Helicobacter infection and other changes (cancer or Zollinger-Ellison syndrome, NSAID and others) in duodenal ulcer disease, gastric ulcer disease, non-ulcer dyspepsia and gastric cancer.

Zollinger-Ellison syndrome and other serious causes. GU patients are infected by HP in about 75% (32, 42, 43) with relatively larger percentage of patients having ulcer due to NSAID, gastric cancer and other diseases. About 40% of patients with NUD and 75% of patients with gastric cancer (3, 44) exhibit HP infection. Thus, the infection by HP represents the highest risk of development of DU disease. Other risk factors, besides HP infection, that are important in the pathogenesis of DU include genetic predisposition, pathophysiologic gastro-duodenal secretory and motor abnormalities, blood group, cigarette smoking, stress and physiological factors and certain diseases such as chronic pulmonary diseases, liver cirrhosis, chronic renal failure and others (45). In patients without past history of peptic ulcer, HP does not appear to confer an increased risk. This concerns patients using NSAID, which actually show lower prevalence of HP infection even in the presence of drug-induced gastric ulcers (46). HP is also less frequent in patients with ulcer due to profound gastric acid secretion such as Zollinger-Ellison syndrome (47). Ulcers that occur in

HP-negative patients taking NSAIDs or with Zollinger-Ellison syndrome prove that although HP may be a contributing factor in pathogenesis of peptic ulcer, it cannot be considered as the sole or even major cause of the ulcer disease.

However, HP closely correlates with the histologic finding of chronic gastritis accompanied by a neutrophil infiltration and may be a cause of this gastritis. HP prevalence is lower in atrophic gastritis associated with pernicious anemia (48) or postgastrectomy gastritis (49).

The mechanisms of the damage of gastroduodenal mucosa by HP have not been well elucidated. Ammonia produced by HP was shown to be deleterious to the gastric mucosa in experimental animals (50,51), but it is not clear whether prolonged exposure to this noxious substance in humans is responsible for the gastritis or duodenitis. HP organism elaborates also proteases, lipase and phospholipase (52—54) that might increase the permeability of mucus to hydrogen ions and damage the mucosal cell membrane to impair the gastric mucosa defense system (55).

Recently, the mucosal damage by HP has been linked with the production by organism of cytotoxins that can directly induce cytopathic effects on mammalian cells *in vitro* such as cytotonic-like, cytotoxic and vacuolating effect (56). As mentioned previously certain strains of HP produce an unique protein with molecular weight of 87 kD (57), which may be harmful for the gastric epithelial cells. In addition, cytotoxic strains also express a polypeptide with larger weight (about 127 kD). This protein is highly immunogenic but does not have toxic activity. However, the gene encoding for this peptide has been cloned and found to be present in cytotoxin strains of HP. This is the reason why the gene has been named „cagA" (cytotoxin-associated gene A) (58).

Another factor related to injurious action of HP on gastro-duodenal mucosa could be increased production of free radicals and lipid peroxidation products in the stomach infected by HP (59). Indeed, it was shown (59) that HP-positive patients show higher tissue levels of malondialdehyde, a secondary byproduct of lipid peroxidation, and tissue level of this product was closely correlated with severity of tissue damage. Mucosal content of reduced--glutathione has been proposed to serve as free radical scavenger and detoxificating substance of various ulcerogens and carcinogens. Thus, activation of lipid peroxidation and reduced-glutathione synthesis in patients with chronic gastritis and HP infection may contribute to the enhanced production of free radicals in the gastric mucosa and the tissue damage.

Helicobacter pylori and changes in gastrin-stomatostatin link

Before the discovery of HP, the etiology of duodenal ulcer disease was linked with abnormalities of gastric acid secretion. DU patients were shown to secrete more acid in response to maximal histamine or pentagastrin

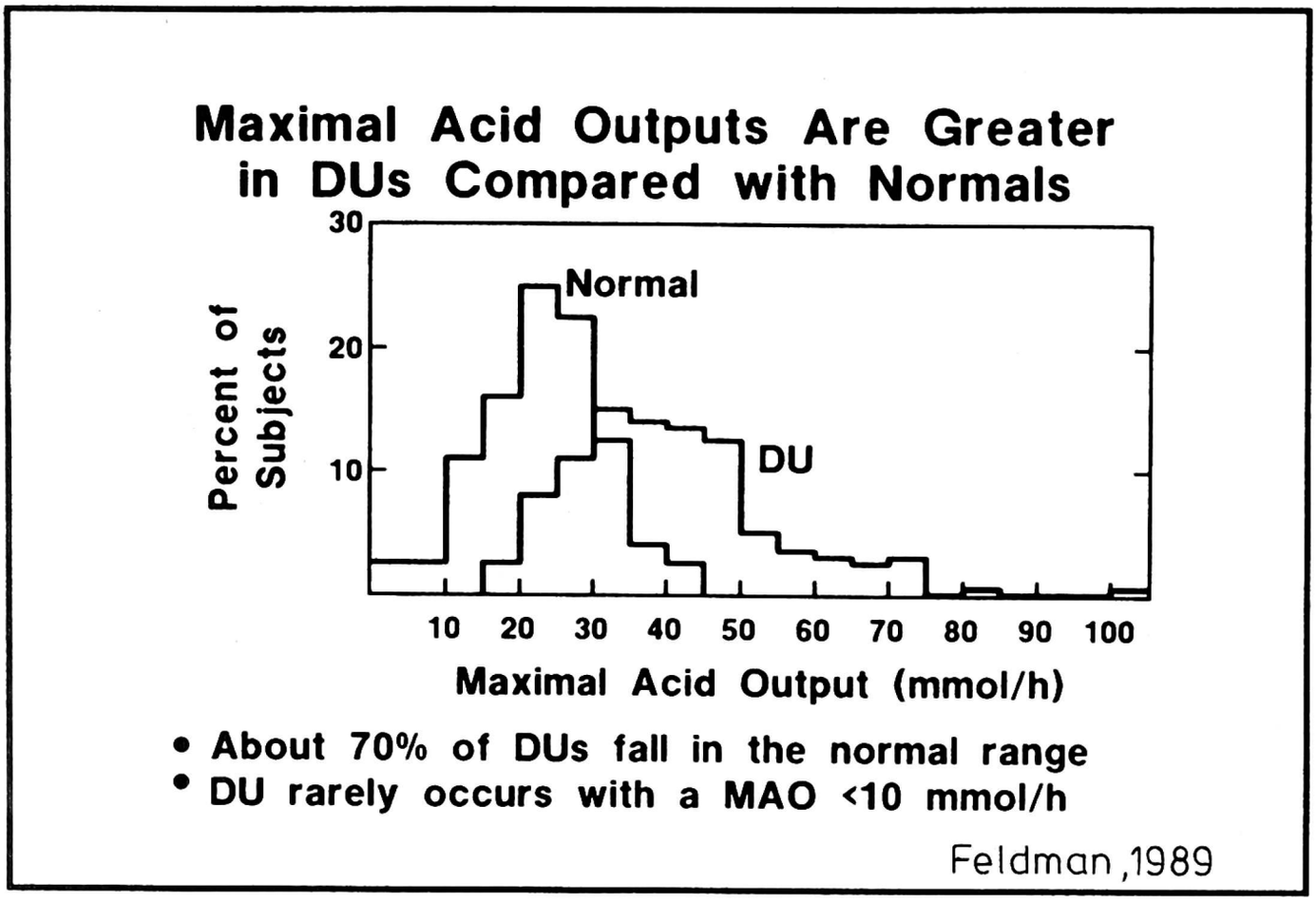

Fig. 5. Maximal acid outputs are greater in DU compared with normals (60).

stimulation (60) indicating a greater-parietal cell mass (*Fig. 5*). Studies of physiological control in DU patients revealed a failure to inhibit gastrin release and gastric acid secretion in response to meal (61). Acid secretion and serum gastrin responses to protein meal were reported to decrease progressively as intragastric pH falls below pH 3.5. Impaired inhibition in DU patients has been found at pH 2.5 when relatively low concentrations of amino acid were used to stimulate acid secretion (*Fig. 6*).

Recent studies suggested that the abnormal pH inhibition of gastrin release may be a feature of HP infection rather than specific abnormality of DU disease as proposed before (61). Levi et al. (62) found that HP-positive DU patients have higher postprandial gastrin levels compared to HP-negative DU patients. They postulated that urea-splitting HP in the gastric mucosa and the formation of ammonia may raise the pH within the mucus layer where the organisms are located. This leads to impaired feedback inhibition of gastrin release. Other studies have demonstrated that eradication of HP results in the reduction in plasma gastrin responses in DU patients (63, 64). Tarnasky et al. (65) demonstrated that chronic infection of HP results in an impaired inihibition of gastrin release and gastric acid secretion at low intragastric similar to that described by these authors in DU disease. These defects may not be related to the pathogenesis of acid-peptic disorder since they occurred also in asymptomatic subjects infected with HP (*Fig. 7*).

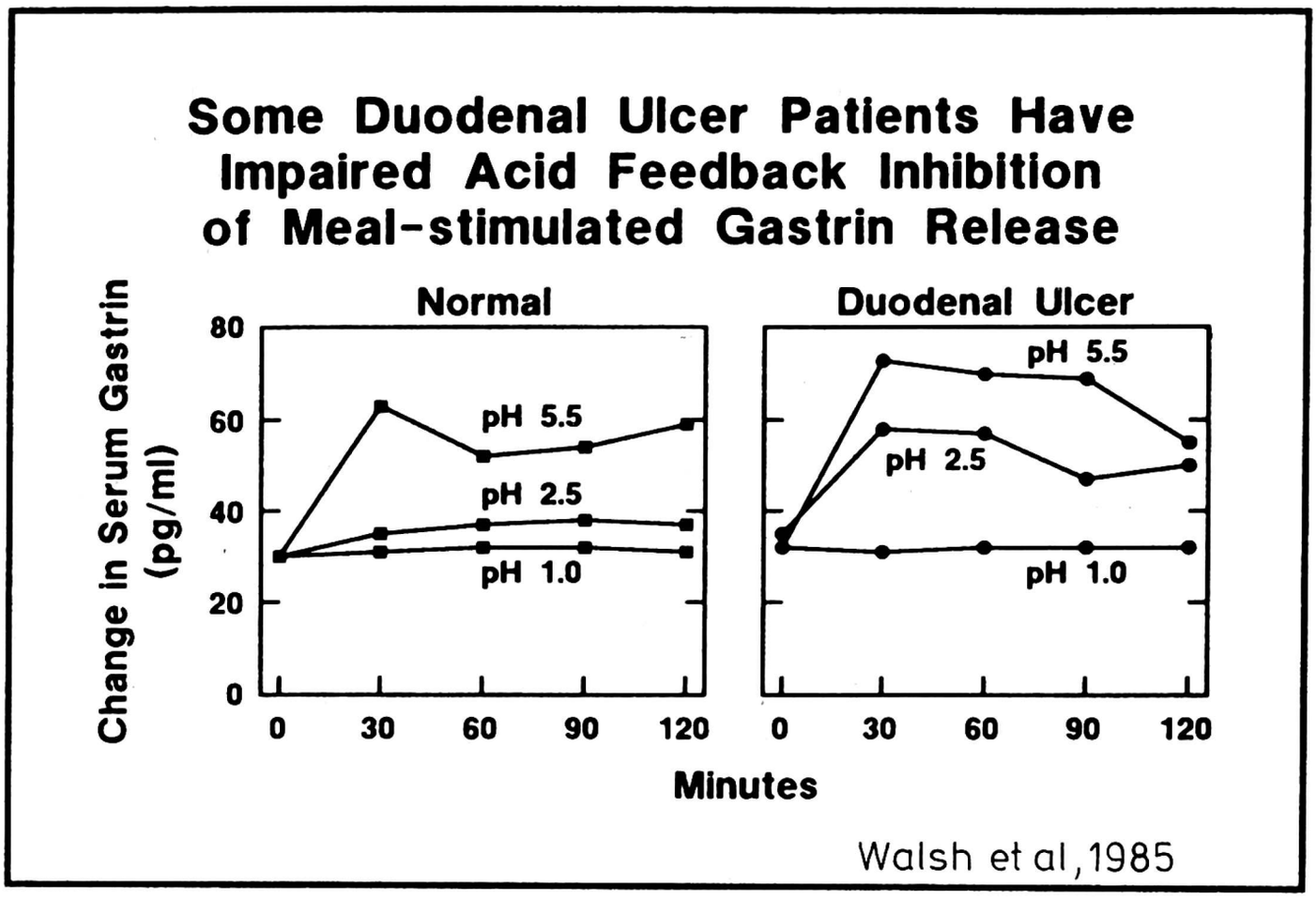

Fig. 6. Some duodenal ulcer patients have impaired feedback inhibition of meal-stimulated gastrin release and at lower pH of gastric meal, such 2.5, release more acid than healthy subjects at the same conditions. This abnormal pH may be a feature of Helicobacter infection rather than specific for peptic ulcer disease. (61, 65).

There may be several possible explanations for impaired inhibition of meal-stimulated gastrin at low pH. Ammonia derived from HP could lead to a local increase of pH and either neutralize directly the G-cells to release excessive amounts of gastrin or to impair the D-cells that normally inhibit gastrin release at low intraluminal pH. The concept of impaired feedback inhibition of gastric secretion involving reduced release of somatostatin and excessive production of gastrin is under active investigations (*Fig. 8*) but it is unlikely that ammonia formation by HP directly regulates gastrin release because intragastric infusion of urea, a substrate for HP-derived urease, in HP-positive subjects did not elevate plasma gastrin (66). Furthermore, in patients with renal failure and HP infection, the luminal concentration of ammonia was about 4 times higher than in HP-positive patients without renal failure (67). Despite the much higher ammonia production in the HP positive uremic patients, the nature and severity of their gastritis was not different from those observed in HP-positive non-uremic patients. The fasting plasma gastrin concentration was markedly increased in uremic patients as compared to non-uremic patients but were similar in patients with or without HP infection. These findings confirm that gastritis and hypergastrinemia associated with HP

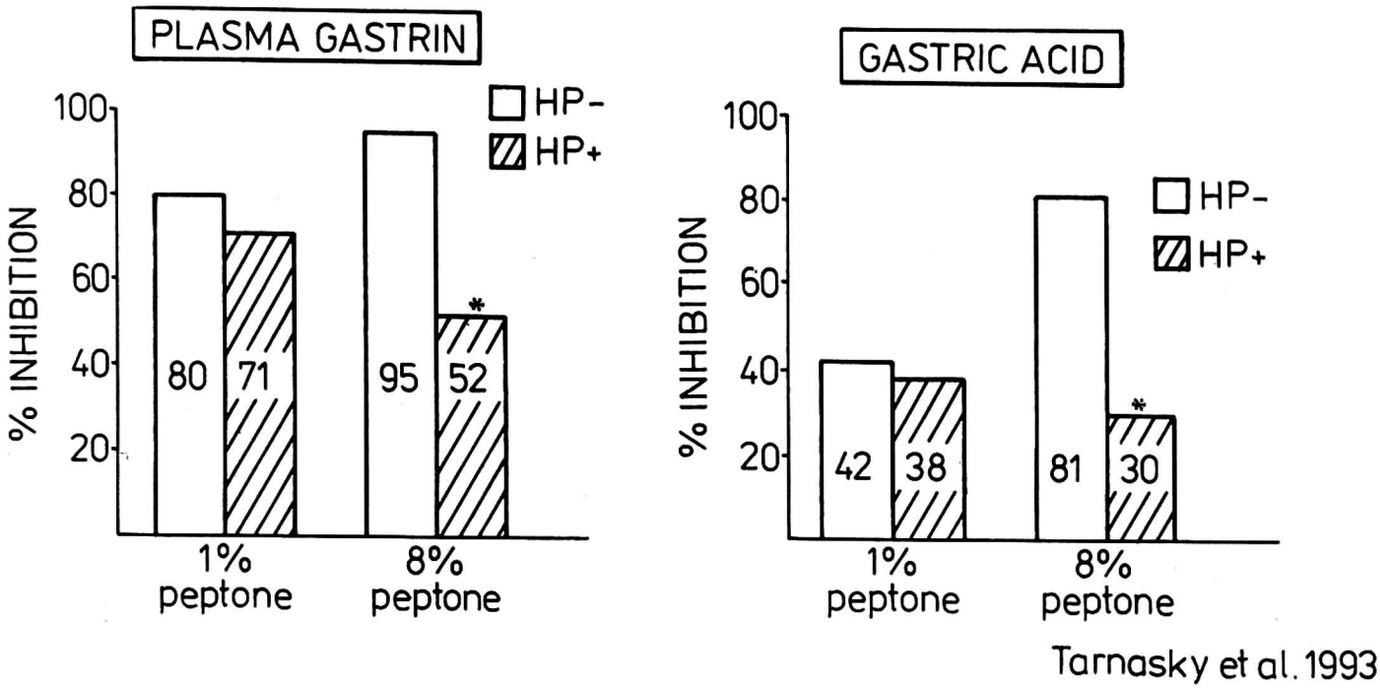

Fig. 7. Plasma gastrin and gastric acid responses to 1% or 8% amino acid meals in HP-negative and HP-positive subjects (65).

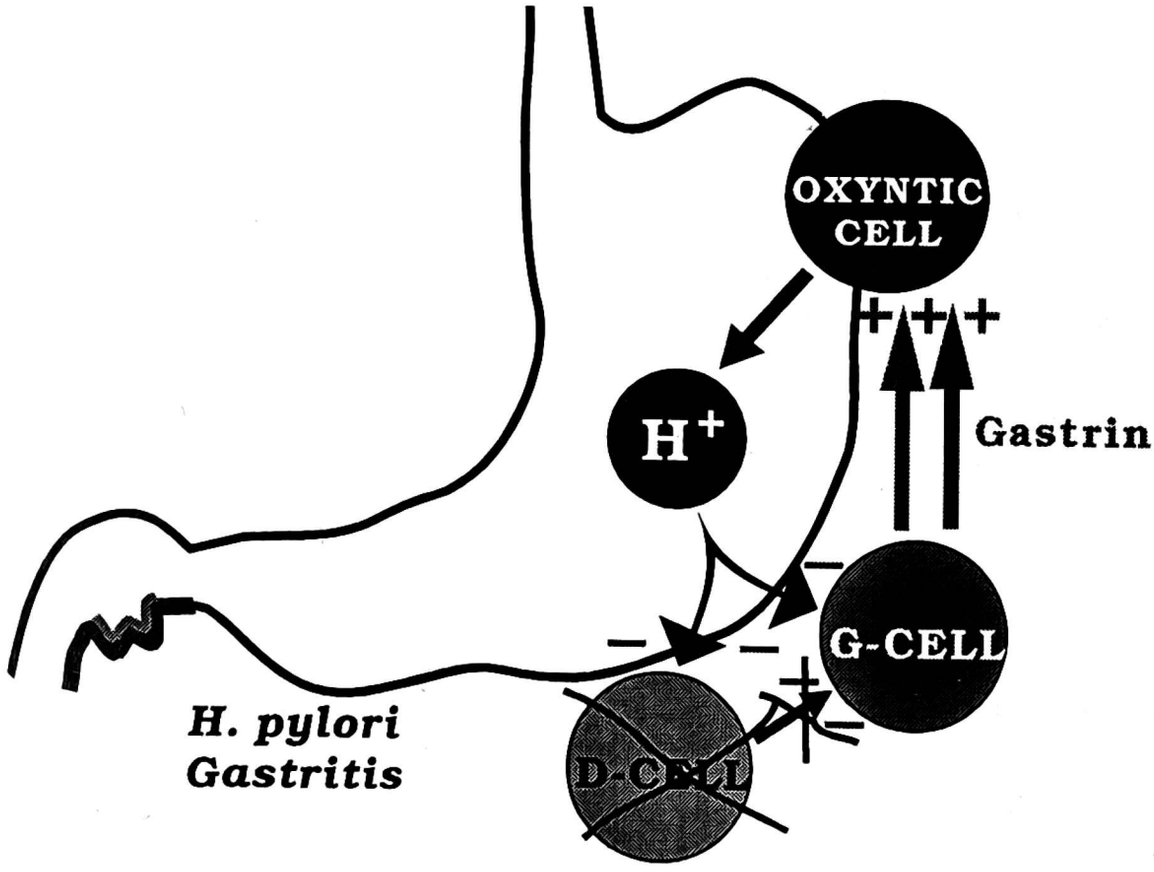

Fig. 8. Schemtatic presentation of the impaired feedback inhibition of gastric secretion caused by Helicobacter infection and involving somatostatin-gastrin link.

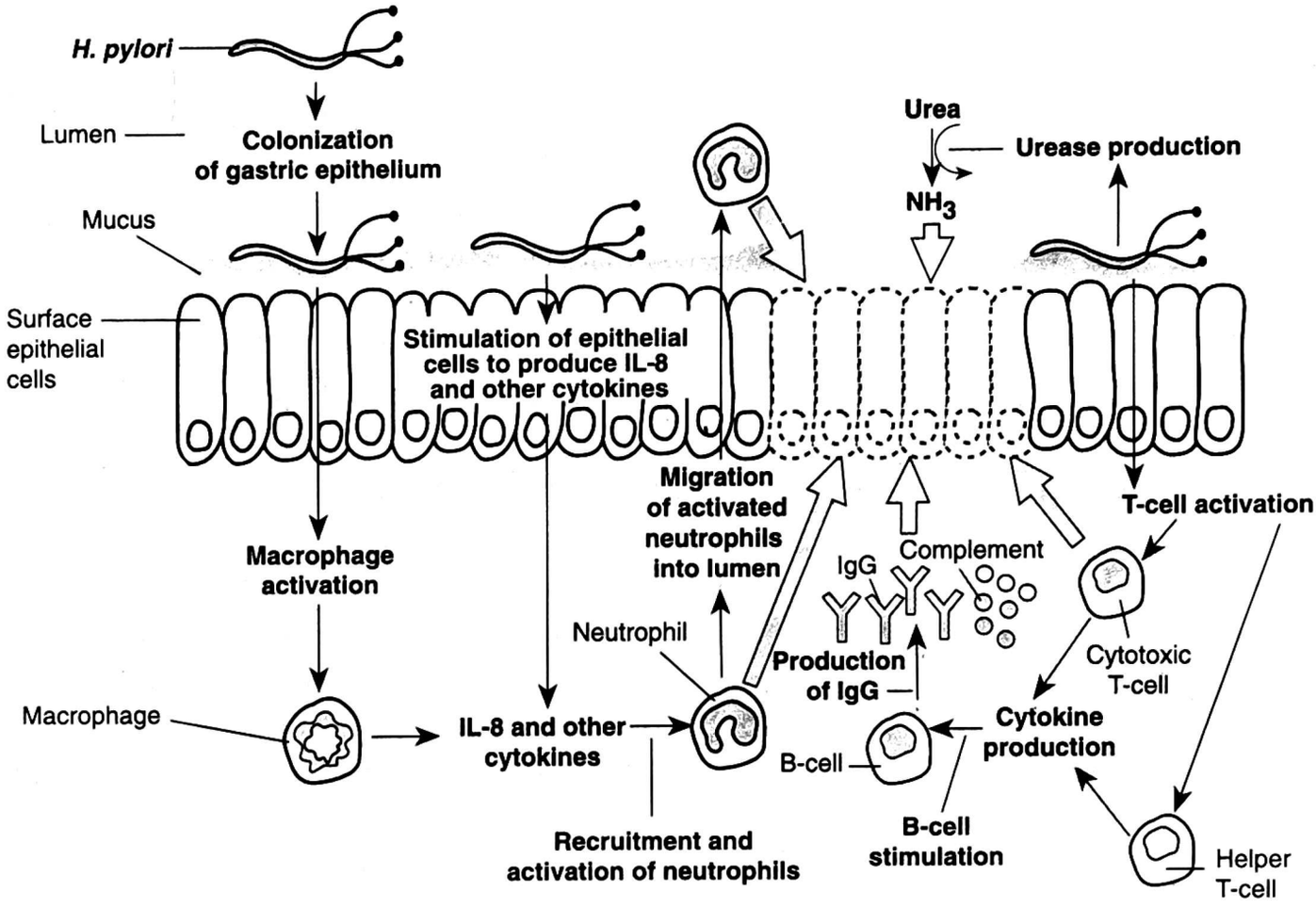

Fig. 9. Factors involved in the process leading to H. pylori-induced antral gastritis. IgG, immunoglobin G; IL-8, interleukin-8, NH_3; ammonia.

infection are not the result of mucosal damage induced by the organism's ammonia production. It is likely, however, that HP infection and chronic gastritis by itself result in some deficiency of negative feedback from the D cells to the G-cells because immediately after the eradication of HP, the elevated plasma gastrin is still observed and it takes several months after successful anti-HP therapy to normalize the disturbed somatostatin-gastrin link. Implication of these observations is that antral gastritis of any origin, not necessarily caused by HP infection, may lead to the augmentation of gastrin release and increased gastric acid secretion. Studies on the *in vitro* isolated antral G and D cells indicate that cytokines such as IL1α, interferon γ and TNFα, released in HP-associated antral gastritis may stimulate gastrin release and reduce expression of somatostatin by direct action on the G and D cells, respectively (68) (*Fig. 9*).

Studies *in vitro* on HP infected DU patients and on volunteers with or without HP infection revealed that although the eradication of HP resulted in dramatic reduction in stimulated gastrin secretion, this was not associated with the change in the number of antral G cells or D cells n DU patients (69). It was calculated that HP-associated increase in gastric secretion is related to the local factors regulating D cell function rather than to the alteration in the number of

G or D cells. In another study (70) after the HP eradication, both antral somatostatin concentration and antral D cell density increased significantly. Conversely, although the number of G cells was unchanged, gastrin content decreased. These results strongly suggest that the hypergastrinemia observed in HP-positive patients may be due to a deficiency in antral somatostatin which normally inhibits the synthesis and the release of gastrin (70). This notion is supported by the finding that after eradication of HP in DU patients, the density of D cells increased significantly and somatostatin mRNA/rRNA ratio almost doubled while the number of G-cells and quantity of gastrin mRNA remained virtually unchanged. This suggests that DU patients with HP infection, gastric secretory function is disinhibited through the suppression of mucosal somatostatin expression (71). Recent comparative studies on gastric secretory function revealed that when compared to truly normal (e. HP-negative) control subjects, the DU patients had elevated basal acid output, peak acid output and fasting and postprandial gastrin concentrations suggesting that in DU patients, the hypergastrinemia is largely related to gastric HP infection, whereas acid hypersecretion is probably due to other factors than HP infection (72).

It is of interest that excessive gastrin release in HP-positive subjects is accompanied not only by enhanced gastric acid secretion but also with a marked increase in serum concentrations of pepsinogen I and II. This hyperpepsinogenemia was similar in HP positive persons without symptoms and those with DU symptoms suggesting that it is mediated by similar mechanisms as hypergastrinemia that are secondary to HP infection (73).

Helicobacter pylori and duodenal alkaline secretion

Approximately half of gastric acid that enters the duodenum is neutralized by HCO_3^- secreted by proximal duodenal mucosa and the other half by HCO_3^- originating from the pancreatic and biliary secretions (74) (*Fig. 10*).

As shown by Isenberg and his coworkers (75), duodenal HCO_3^- secretion in DU patients both under basal conditions and after topical application of acid, appears to be several folds lower than in healthy subjects. The difference in HCO_3^- secretion between DU and normal subjects cannot be explained merely by duodenal scaring or any obvious abnormality in mucosal structure. Recent studies of Rapier et al. (76) showed that DU patients with HP infection have several times lower basal and acid stimulated secretion than the same patients with eradicated HP. In was concluded that HP infection causes decreased proximal duodenal mucosal HCO_3^- secretion, contributing to DU pathogenesis. Furthermore, eradication of HP infection was found to restore proximal duodenal mucosal HCO_3^- secretion to normal and to promote ulcer healing (76).

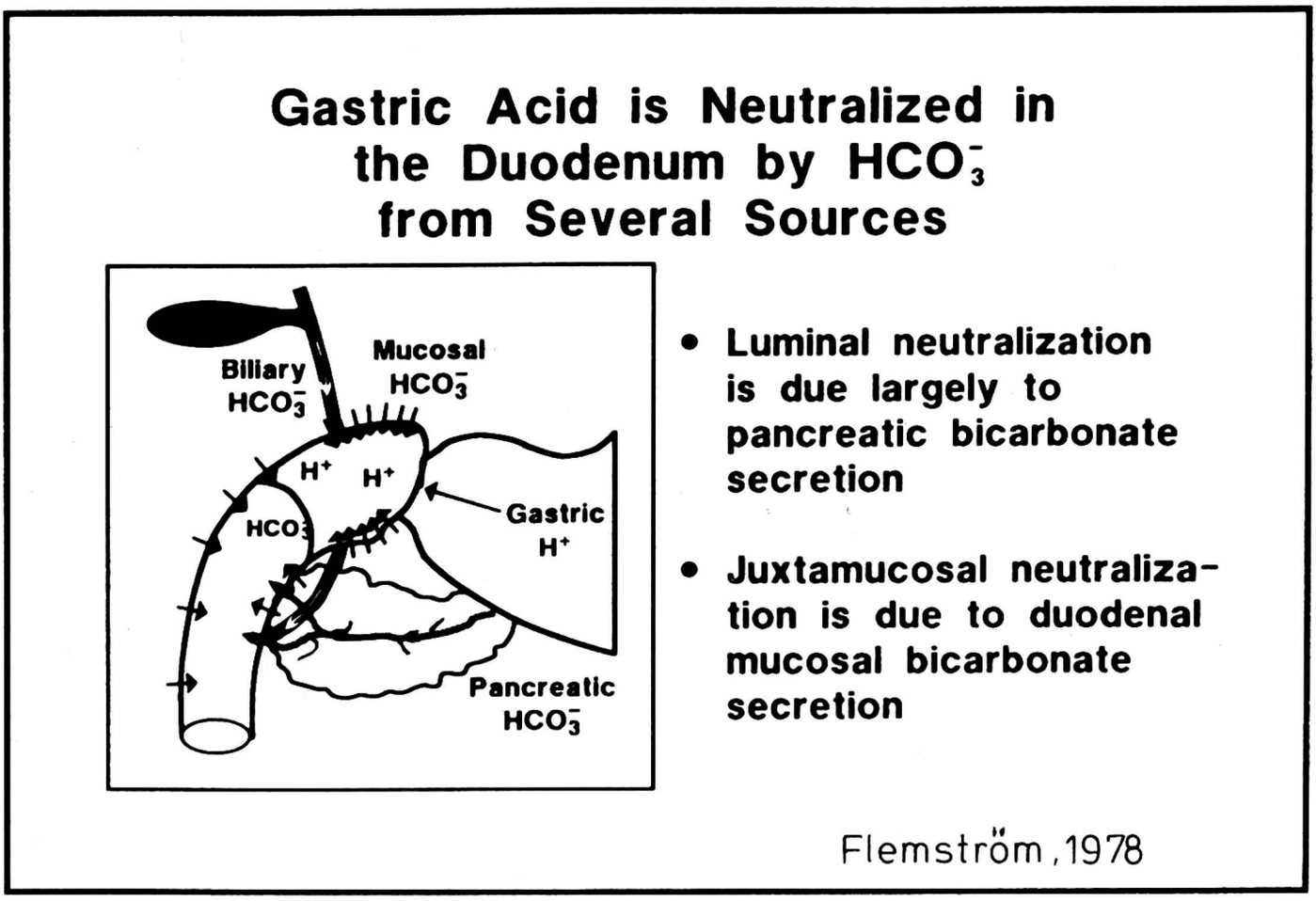

Fig. 10. Gastric acid entering the duodenal ulcer is neutralized by HCO_3^- originating in about 50% from the secretion of the duodenal mucosa and the rest from the bile-pancreatic secretion (74).

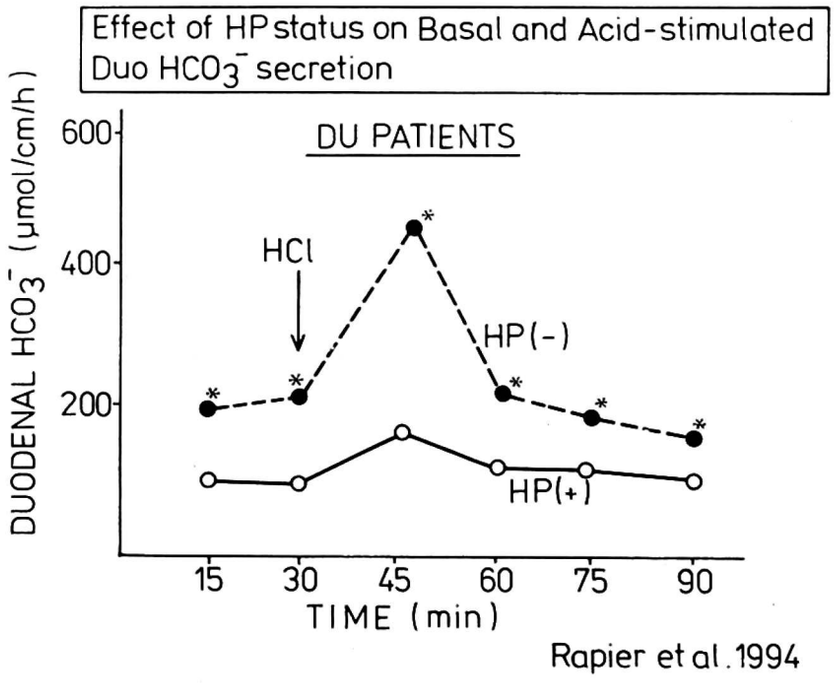

Fig. 11. Duodenal ulcer patients with HP infection have reduced basal and defective acid-stimulated duodenal alkaline secretion (76).

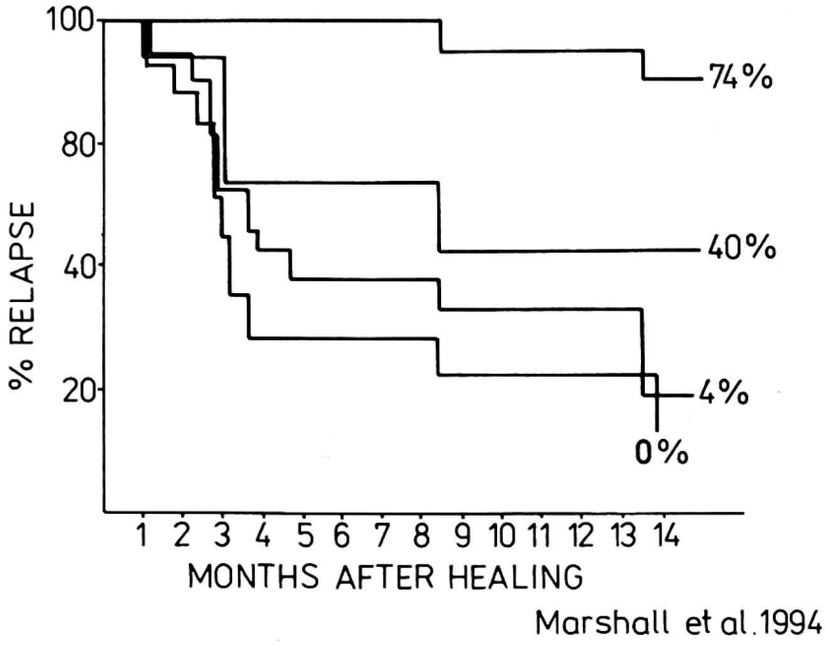

Fig. 12. DU recurrences are greater after healing with H_2-antagonists (upper line), bismuth preparations (bout 40%), antibiotics (about 4%) or the combination of antibiotics, bismuth and omeprazole (lowest line) (according to Marshall — unpublished data).

The best evidence supporting an important role of HP in pathogenesis of peptic ulcers are the results with eradication of this organism (45). Single-agent antibiotic therapy rarely leads to long-term HP eradication and bismuth compounds alone also are unsuccessful in eradicating HP in a majority of patients but the combination therapy is more successful (*Fig. 12*). Triple therapy with bismuth, metronidazole and either amoxycillin or tetracycline appears to be effective in intial clearing over 90% and eradicating HP at least 80% of cases (45).

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