Gastric metaplasia and *Helicobacter pylori* infection

L A Noach, T M Rolf, N B Bosma, M P Schwartz, J Oosting, E A J Rauws, G N J Tytgat

Abstract

Duodenal and antral mucosal biopsy specimens were obtained from 139 patients with dyspeptic complaints to study the prevalence and extent of gastric metaplasia in the duodenal bulb in relation to *Helicobacter pylori* (*H pylori*) infection and duodenal ulcer disease. On logistic regression, the presence and extent of gastric metaplasia was not significantly associated with *H pylori* infection. The prevalence of gastric metaplasia, however, was found to be higher in patients with current or past evidence of duodenal ulcer disease in comparison with subjects with functional dyspepsia ($p=0.01$). A follow up study on 22 patients before and at least one year after eradication of *H pylori* showed that the mean extent of gastric metaplasia did not change significantly after eradication and did not differ when compared with 21 patients with persisting infection. It is concluded that the unchanged gastric acid output after eradication of *H pylori* is a more important factor in the development of gastric metaplasia than the *H pylori* related inflammatory process.

(Gut 1993; 34: 1510-1514)

Gastric metaplasia or the appearance of patches of gastric type mucous cells interspersed between the duodenal epithelial cells, is a common finding in biopsy specimens from patients with duodenitis and duodenal ulcer disease.¹⁻³ It may also be seen in healthy subjects, but usually to a more limited extent.⁴ Gastric metaplasia is considered to be an acquired change of the surface epithelium. In contrast, gastric heterotopia represents a presumably congenital misplacement of fully developed gastric mucosa, including chief cells and parietal cells. Heterotopia is less common than gastric metaplasia and not associated with duodenal inflammation or ulceration.¹⁵

It is assumed that gastric metaplasia arises from the necks of Brunner's glands and is the result of a persistently high concentration of acidity in the duodenal bulb. As such, it can be seen as an adaptive defence response to adverse conditions. Experimental and human studies support this hypothesis.¹⁶⁻¹⁰ But gastric metaplasia may also develop as a non-specific response to mucosal injury not associated with acid peptic damage.¹¹

Wyatt *et al* found gastric metaplasia to be more extensive in patients with *Helicobacter pylori* (*H pylori*) associated gastritis than in patients without *H pylori* infection.¹¹ As *H pylori* colonisation is restricted to gastric type epithelium, the presence of gastric metaplasia in the duodenum would allow *H pylori* to colonise the duodenum and to produce active inflammation. As a result, the inflamed duodenal mucosa may then become

susceptible to acid and this may ultimately lead to ulceration. Thus both *H pylori* infection and acid induced gastric metaplasia are considered to be prerequisites for the development of duodenitis with polymorphonuclear activity and duodenal ulcer.¹²

It has previously been shown that the prevalence of gastric metaplasia in *H pylori* positive duodenal ulcer patients is significantly lower after highly selective vagotomy than in patients with duodenal ulcer before operation.¹ It has also been found that duodenal ulcer patients on continuous pharmacological acid suppression exhibit a lower prevalence of gastric metaplasia in comparison with intermittently treated patients.¹³ These findings suggest that gastric metaplasia is potentially a reversible disorder.

Eradication of *H pylori* is accompanied by a rapid disappearance of signs of acute gastritis and a gradual resolution of chronic inflammatory changes.^{14 15} Furthermore, many studies have shown that the naturally occurring relapse rate of duodenal ulcers is considerably reduced after eradication.¹⁶⁻¹⁸ There is also evidence that gastrin release returns to normal after successful treatment of *H pylori* infection.¹⁹⁻²¹ It is as yet unknown, however, whether eradication of the organism influences the presence and extent of gastric metaplastic tissue in the duodenal bulb.

This study was designed to investigate the prevalence and distribution of gastric metaplasia in relation to *H pylori* infection and duodenal ulceration and to examine whether a reduction in the extent and prevalence of gastric metaplasia occurs after eradication of *H pylori*.

Patients and methods

One hundred and thirty nine adult patients with dyspeptic complaints had upper gastrointestinal endoscopy with multiple biopsies performed at defined sites in the gastric antrum and duodenal bulb. Oral informed consent was granted for all biopsies. Antral biopsy specimens were taken from the lesser and greater curvature, approximately 2 cm from the pylorus. Two specimens were placed in 2 ml of saline for bacteriological examination and two specimens were fixed in 10% neutral formalin for histopathological examination. To determine the extent of gastric metaplasia, multiple biopsy specimens were collected from standardised sites of the duodenal bulb. In patients without focal abnormalities, specimens were taken from the roof, the floor, the anterior, and the posterior wall of the bulb. In patients with an ulcer crater, erosion or scar, two specimens were taken approximately 1 cm from the edge of the lesion and two from the opposite wall or an area clear of any macroscopically recognisable abnormality. The specimens were fixed in McDowell or Karnovsky's solution.

Departments of
Gastroenterology and
Medical Statistics,
Academic Medical
Centre, Amsterdam,
The Netherlands

L A Noach
T M Rolf
N B Bosma
M P Schwartz
J Oosting
E A J Rauws
G N J Tytgat

Correspondence to:
Dr L A Noach, Department of
Gastroenterology, Academic
Medical Centre, Meibergdreef
9, 1105 AZ Amsterdam,
The Netherlands.

Accepted for publication
22 April 1993

Follow up endoscopies were performed during at least one year in a subgroup of 43 patients. These patients received treatment for *H pylori* infection and returned for endoscopy to investigate either the result of treatment or for the purpose of this study. Treatment consisted of combinations of colloidal bismuth subcitrate, metronidazole, or amoxicillin, or all three.

The mean extent of gastric metaplasia in all biopsy specimens collected before eradication was compared with the extent of gastric metaplasia at least one year after eradication (group 1). In patients with persisting *H pylori* infection (group 2) the mean extent of gastric metaplasia during the first 12 months of follow up was compared with the extent during the second year or later.

HISTOLOGICAL ANALYSIS

All antral biopsy specimens were stained with haematoxylin and eosin to detect the presence and severity of gastric inflammation and to identify *H pylori*.

Duodenal biopsy specimens were stained with periodic acid Schiff (PAS) for the detection of metaplastic gastric epithelium. The presence and degree of duodenal inflammation were graded according to Wyatt's classification.¹

Gastric metaplasia was defined as the occurrence of foci of gastric epithelial cells containing apical PAS positive neutral mucin together with the absence of a brush border. The extent of gastric metaplasia was estimated independently by two investigators as nil, <5%, 5–20%, 20–50%, 50–75%, or >75% of the epithelial surface of each biopsy specimen. After grading gastric metaplasia and counting the number of villi in each specimen, the mean extent of gastric metaplasia for all specimens taken at each session was calculated in relation to the number of villi in each specimen.

STATISTICS

Statistical analysis was performed using logistic regression analysis, two tailed χ^2 test, the Wilcoxon signed rank sum test and the Kruskal-Wallis test. κ statistics were used to determine interobserver agreement.

Results

A total of 927 duodenal biopsy specimens from 139 patients were studied (89 men, 50 women, aged 20 to 79 years, mean age 48.2). *H pylori* infection was proved by positive cultures or histological identification, or both in antral specimens from 113 patients. Gastric metaplasia was found in 88 of 113 (78%) *H pylori* positive and 22 of 26 (85%) *H pylori* negative patients.

TABLE I Prevalence of gastric metaplasia in relation to age, sex, and H pylori state

Age (y)	Prevalence				Total
	Hp +ve male	Hp +ve female	Hp -ve male	Hp -ve female	
20–39	23/26	8/8	4/5	1/2	36/41 (88%)
40–59	25/31	16/23	6/6	2/3	49/63 (78%)
>60	13/17	5/8	3/4	6/6	27/35 (77%)
Total	61/74 (82%)	29/39 (74%)	13/15 (87%)	9/11 (82%)

Figure 1: Duodenal biopsy specimen showing small foci of gastric metaplasia at the surface duodenal villus (arrows).

Logistic regression analysis showed no statistically significant differences in the prevalence of gastric metaplasia in different age groups, between sexes, and *H pylori* state (Table I). The metaplastic cells usually presented in patches and did stand out clearly because of the presence of abundant PAS positive mucin in their cytoplasm. In some cases gastric metaplasia was only seen at the tips of (stunted) villi (Fig 1). In other cases the surface epithelium was more affected (Fig 2). The average extent of gastric metaplasia was calculated to be 19% in *H pylori* positive patients and 16.2% in *H pylori* negative patients. No relation between the extent of gastric metaplasia and the presence or absence of *H pylori* could be shown (Mann-Whitney U test, $p=0.2$) (Fig 3).

Gastric metaplasia was present in 55 of 61 (90%) *H pylori* positive patients with current or past evidence of duodenal ulceration and 31 of 44 (70%) of patients with functional dyspepsia (χ^2 test, $p=0.01$).

In 38 patients endoscopy showed focal abnormalities or signs of diffuse inflammation of the duodenal bulb. Samples taken from the edges of ulcer craters in 15 of these patients or scars in six patients contained more extensive gastric metaplasia (mean extent 19%) in comparison with specimens from the opposite, macroscopically normal looking wall (mean extent 10%). This difference, however, did not reach statistical significance with the signed rank sum Wilcoxon test ($p=0.13$). In 17 patients with an endoscopic picture of diffuse duodenitis the average extent of gastric metaplasia was 15%.

Histological examination of the biopsy specimens from macroscopically abnormal tissue showed a picture of chronic duodenitis in 18 (47%) and active duodenitis in eight (21%) patients. Only four patients (11%) with endo-

Figure 2: Duodenal biopsy specimen showing extensive area of gastric metaplasia (arrows).

Figure 3: Distribution of different grades of gastric metaplasia in *H. pylori* positive (Hp +ve) and negative (Hp -ve) patients.

scopic abnormalities had a normal duodenal histology.

Fourteen patients had a distorted bulb without focal abnormalities. The other patients ($n=87$) had a normal endoscopic appearance of the bulb. Microscopic examination of specimens from the second group of patients showed active duodenitis in nine patients (10%), whereas a mononuclear infiltrate without intraepithelial neutrophils was found in 32 (37%). Thirty five (40%) of these patients had normal duodenal histology. Gastric metaplasia seemed to be significantly more extensive in patients with microscopic evidence of chronic or active duodenitis (23%) in comparison with histologically normal mucosa (13%) ($p=0.02$).

A follow up study of at least 12 months was

Figure 4: Mean percentage of gastric metaplasia before eradication (A1) and at least 12 months after eradication (B1) of *H. pylori* in patients of group 1 and during the first 12 months of follow up (A2) and at least 12 months later (B2) in patients of group 2.

TABLE II Characteristics of patients in follow up study. Group 1: patients that have become *H. pylori* negative; group 2: patients with persisting *H. pylori* infection

	Group 1 ($n=22$)	Group 2 ($n=21$)
Mean age	45	49
Male/female	14/8	12/9
Duodenal ulcer disease	11	10

performed in 43 patients. In 22 of these patients *H. pylori* was successfully eradicated (group 1) and follow up biopsy specimens were obtained 13–60 months (median 18 months) after eradication. In the remaining 21 patients *H. pylori* was not eradicated (group 2) and these patients were followed up for 12–54 months (median 24 months). There were no significant differences with regard to age, sex, and number of patients with a history of duodenal ulcer disease between both groups (Table II).

At the start of follow up, the mean extent of gastric metaplasia was 25% (range 0 to 88%) in group 1 and 12% (range 0 to 63%) in group 2. This difference, however, did not reach statistical significance (Mann-Whitney test, $p=0.08$). During the period of follow up, no significant decrease of the median extent of gastric metaplasia occurred in both groups (Wilcoxon rank sum test for paired data, $p=0.08$ for group 1 and $p>0.5$ for group 2). Comparison of the changes in gastric metaplasia of group 1 with group 2 showed no significant difference between both groups (Mann-Whitney U test, $p=0.3$) (Fig 4).

Eight patients of group 1 and seven patients of group 2 were followed up for a period of >3 years (mean follow up 47 (range 37–60) months for both groups). Again, the Mann-Whitney U test showed no significant change in the mean extent of gastric metaplasia in both groups ($p=0.31$ for both groups).

The mean extent of gastric metaplasia in 39 patients who were treated continuously (>1 year) with H_2 receptor antagonists was 19% (range 0–88%) and 15% (range 0–88%) in 53 patients who did not take these drugs. In 38 patients who were treated intermittently (<4 months/year) with these drugs the mean extent was 21% (range 0–72%). The Kruskal-Wallis test did not show a significant correlation between the extent of gastric metaplasia and the use of H_2 receptor antagonists. In six patients, however, who were receiving omeprazole treatment the extent of gastric metaplasia was significantly lower than in patients using no acid reducing drugs or H_2 receptor antagonist (mean 1%, range 0–7%) ($p=0.035$). A limited extent of gastric metaplasia (of 1% in two and 16% in one patient respectively) was also found in three patients who had had highly selective vagotomy in the past. During follow up 13 patients in group 2 continued anti-secretory treatment. In these patients the extent of gastric metaplasia hardly changed (from 9 to 8%).

INTEROBSERVER AGREEMENT

The two investigators agreed over the presence or absence of gastric metaplasia in 92% of all biopsy specimens (κ value=0.83). In 79% of the biopsy specimens there was concurrence over the grading of the extent of gastric metaplasia. Only in two cases was a difference of more than one grade in the extent of gastric metaplasia found. This gave a κ value of 0.72, which shows a very high level of agreement over the six categories.

Discussion

Duodenal ulcer disease has traditionally been

TABLE III Prevalence of gastric metaplasia in asymptomatic subjects (AS), functional dyspeptic (FD), and duodenal ulcer patients (DU)

Author	Prevalence		
	AS	FD	DU
James 1964 ²⁴			90%
Patrick <i>et al</i> 1974 ²⁶			75%
Kreuning <i>et al</i> 1978 ⁴	64%		
Greenlaw <i>et al</i> 1980 ²⁵		30%	60%
Shousha <i>et al</i> 1984 ³⁰			39%
Wyatt <i>et al</i> 1987 ¹		28%	65%
Fitzgibbons <i>et al</i> 1988 ²⁹	22%		
Carrick <i>et al</i> 1989 ²		32%	92%
Tucci <i>et al</i> 1990 ¹³	30%		40–90%
Offerhaus <i>et al</i> 1990 ²⁷			88%
Noach <i>et al</i> 1992		70%	90%

associated with excess secretion of gastric acid. The correlation, however, is incomplete implying the existence of other pathogenic factors.²² It is now widely accepted that *H. pylori* is one of the most important factors in the pathogenesis of duodenal ulcer disease.^{15, 23}

Only a minority of patients infected with *H. pylori* will eventually develop a duodenal ulcer. According to previous studies, gastric metaplasia is an almost constant finding in patients with duodenal ulceration.^{1, 2, 13, 24–27} It is considered to be an acquired condition, as it seems to be comparatively rare in children without a history of duodenal ulceration.^{11, 28}

An important problem in the detection of gastric metaplasia is its patchy distribution. Wyatt *et al* calculated that a single anterior biopsy detected only 63% of patients with gastric metaplasia proved by multiple biopsy.¹¹ This may partly explain the lower prevalence rate found in several previous studies in comparison with our results.^{1, 11, 25} In addition, underestimation of gastric metaplasia may occur if biopsy specimens have been collected from the distal bulb.²⁹

Overestimation is possible in studies where biopsy specimens from the pyloroduodenal transition zone have been included.^{1, 4, 29} To limit sampling error, we took multiple biopsy specimens at standardised sites. Other factors may also have contributed to the large variability in prevalence rate of gastric metaplasia as mentioned in published works. These include differences in the prevalence of duodenal ulcer disease, consumption of alcohol, and the use of anti-secretory drugs in different populations.^{13, 30}

In this study, the extent of gastric metaplasia was estimated independently by two investigators to limit interobserver variability. We found good agreement between the two different investigators.

In agreement with previous studies, we found that gastric metaplasia was significantly more prevalent in patients with duodenal ulcer disease than in patients with functional dyspepsia (Table III). In contrast with some of these studies, we also found a comparatively high prevalence of gastric metaplasia in the second group of patients. This discrepancy may be explained by a more sensitive method of collecting biopsy specimens and is in agreement with the results of Kreuning *et al* who also investigated multiple biopsy specimens from the proximal duodenum.⁴

Marshall *et al* detected gastric metaplasia at the margin of ulcers in 92% *v* 63% elsewhere in the bulb.³ In accordance with Wyatt *et al* we found a significant association between the extent of gastric metaplasia and microscopic signs of duodenitis.¹ We could not show a significant difference between the extent of gastric metaplasia at sites around ulcer craters or scars and macroscopically normal appearing mucosa. Sampling error because of an insufficient number of biopsy specimens may have been responsible for the fact that this difference did not reach significance.

It has been suggested that gastric metaplasia develops as a result of high intragastric acidity or rapid gastric emptying, or both.^{12, 22} This, in association with *H. pylori* infection, allows *H. pylori* to colonise the duodenum. Duodenitis follows and this inflammation impairs mucosal defences, ultimately leading to ulceration.

That gastric metaplasia develops in response to acid hypersecretion has been found both experimentally and in human studies.^{2, 6, 11, 30} Additional support for an acid induced mechanism comes from the finding that gastric metaplasia is quite extensive in patients with Zollinger-Ellison syndrome.²⁴

In contrast with one previous report, we found no evidence that the chronic use of H₂ receptor antagonists influenced the extent of gastric metaplasia.¹³ In a limited number of patients, however, who were treated continuously with omeprazole, we found an appreciably reduced extent of gastric metaplasia.

Gastric metaplasia is probably a non-specific response to injury. Heavy alcohol consumption may also cause gastric metaplasia in humans and a similar phenomenon may occur in Crohn's disease anywhere in the gastrointestinal tract.^{30, 31} It has recently been suggested that chronic inflammation in patients with Crohn's disease as well as peptic ulceration induces buds at the bottom of gastrointestinal crypts in the mucosa adjacent to ulcers. These buds are composed of columnar cells. They produce neutral mucin and develop into a new small gland. Further studies indicate that these cells are derived of a novel cell lineage. If this theory is correct, the term 'metaplasia' is a misnomer: metaplasia implies a change from one differentiated cell type to another and not the induction of a novel cell lineage.³¹ After eradication of *H. pylori*, duodenal ulcers do not usually recur and the associated chronic gastritis gradually disappears.^{14, 16–18} Several investigators have found ablation of the exaggerated gastrin release after eradication of *H. pylori*.^{19–21} Gastric acid output, however, is not changed by treatment of the infection.^{19, 21, 32} The question has been raised whether these changes result in restoration of the duodenal mucosa and disappearance of gastric epithelium from the duodenal bulb.

Although the extent of gastric metaplasia decreased during follow up of group 1, this difference did not reach statistical significance (*p*=0.08). Even among subjects examined at least three years after successful treatment of *H. pylori* infection, the extent of gastric metaplasia did not change significantly. In our opinion, a more appropriate comparison con-

cerns the changes seen during follow up in group 1 *v* the changes in group 2. As stated before, these changes were statistically indistinguishable between the groups ($p=0.3$). We do realise that the large variability when estimating the extent of gastric metaplasia is one of the important limitations of any endoscopic study. It may well be that because of this large variation and the comparatively small numbers of patients in this study a possible correlation between the presence of *H. pylori* and the development of gastric metaplasia could not be shown. The lack of regression of gastric metaplasia in the bulb, however, is biologically compatible with the current data on the evolution of acid secretion after eradication of *H. pylori*.^{19,21,32} Almost all studies show that acid secretion remains at the same rate. This would show that acid secretion is of superior importance compared with *H. pylori*.

So far, no prospective study has been performed to investigate the natural history of gastric metaplasia. Only in one report was it suggested that 'fundic gland metaplasia' was a transient lesion, which tended to disappear spontaneously within a few months.³³ This paper, however, describes heterotopia and, although the number of biopsy specimens taken at endoscopy are not mentioned, the transient character of heterotopia may be a result of sampling error.

This study suggests that both acid induced injury and *H. pylori* infection may play a part in the pathogenesis of duodenal ulcer disease. Both factors may be part of a complex cascade of events that ultimately leads to the development of duodenal ulceration. Gastric metaplasia and *H. pylori* infection are prerequisites, but evidence exists that mucosal production of cytokines, *H. pylori* specific toxins and other, still unknown factors may all play a part in possible ulcer formation in the duodenum.³⁴⁻³⁶ As the acid secretory capacity does not change after *H. pylori* eradication, it would seem that the former is the more important determinant factor in the development of gastric metaplasia and the *H. pylori* related inflammatory process is of less importance.

- Wyatt JL, Rathbone BJ, Dixon MF, Heatley RV. Campylobacter pyloridis and acid-induced gastric metaplasia in the pathogenesis of duodenitis. *J Clin Pathol* 1987; 40: 841-8.
- Carrick J, Lee A, Hazell S, Ralston M, Daskalopoulos G. Campylobacter pylori, duodenal ulcer, and gastric metaplasia: possible role of functional heterotopic tissue in ulcerogenesis. *Gut* 1989; 30: 790-7.
- Marshall BJ, Goodwin CS, Warren JR, Murray R, Blincow ED, Blackbourn SJ, et al. Prospective double-blind trial of duodenal ulcer relapse after eradication of Campylobacter pylori. *Lancet* 1988; ii: 1437-42.
- Kreuning J, Bosman FT, Kuiper G, vd Wal AM, Lindeman J. Gastric and duodenal mucosa in 'healthy' individuals. *J Clin Pathol* 1978; 31: 69-77.
- Shousha S, Spiller RC, Parkins RA. The endoscopically abnormal duodenum in patients with dyspepsia: biopsy findings in 60 cases. *Histopathology* 1983; 7: 23-34.
- Rhodes J. Experimental production of gastric epithelium in the duodenum. *Gut* 1964; 5: 454-8.
- Dixon MF. Helicobacter pylori and peptic ulceration: histopathological aspects. *J Gastroenterol Hepatol* 1991; 6: 125-30.
- Wyatt JL. Campylobacter pylori, duodenitis and duodenal ulceration. In: Rathbone BJ, Heatley RV, eds. *Campylobacter pylori and gastroduodenal disease*. Oxford: Blackwell Scientific, 1989.
- Leung FW, Andrews RD, Miller JC, Paulsen G, Guth PH. Brunner's glands protect the overlying mucosa against acid induced injury. *Gastroenterology* 1987; 92: A1502.
- Joffe SN, Lee FD, Blumgart LH. Duodenitis. *Clin Gastroenterol* 1978; 7: 635-50.
- Wyatt JL, Rathbone BJ, Sobala GM, Shallcross T, Heatley RV, Axon ATR, et al. Gastric epithelium in the duodenum: its association with Helicobacter pylori and inflammation. *J Clin Pathol* 1990; 43: 981-6.
- Wyatt JL, Rathbone BJ, Dixon MF, Heatley RV, Axon ATR. Campylobacter pylori and development of duodenal ulcer [Letter]. *Lancet* 1988; i: 118-9.
- Tucci A, Susi D, Bovani I. Effect of chronic acid inhibition on duodenal gastric metaplasia. *Gastroenterology* 1990; 98: A141.
- Valle J, Seppala K, Sipponen P, Kosunen T. Disappearance of gastritis after eradication of Helicobacter pylori. *Scand J Gastroenterol* 1991; 26: 1057-65.
- Rauws EAJ, Langenberg W, Houthoff HJ, Zanen HC, Tytgat GNJ. Campylobacter pyloridis-associated chronic active antral gastritis: a prospective study of its prevalence and the effects of antibacterial and anti-ulcer treatment. *Gastroenterology* 1988; 94: 33-40.
- Rauws EAJ, Tytgat GNJ. Eradication of Helicobacter pylori cures duodenal ulcer. *Lancet* 1990; i: 1233-5.
- George LL, Borody TJ, Andrews P, Devine M, Moore-Jones D, Walton M, et al. Cure of duodenal ulcer after eradication of Helicobacter pylori. *Med J Aust* 1990; 153: 145-9.
- Lamouliatte H, Bernard PH, Boulard A, Cayla R, de Mascarel A, Megraud F, et al. Helicobacter pylori eradication prevents duodenal ulcer relapse. *Gastroenterology* 1991; 100: A104.
- McColl KEL, Fullarton GM, Chittajalu R, El Nujumi AM, Macdonald AMI, Dahill SW, et al. Plasma gastrin, daytime intragastric pH, and nocturnal acid output before and at 1 and 7 months after eradication of Helicobacter pylori in duodenal ulcer subjects. *Scand J Gastroenterol* 1991; 26: 339-46.
- Graham DY, Opekun A, Lew GM, Evans DJ, Klein PD, Evans DG. Ablation of exaggerated meal-stimulated gastrin release in duodenal ulcer patients after clearance of Helicobacter (Campylobacter) pylori infection. *Am J Gastroenterol* 1990; 85: 394-8.
- Prewett EJ, Smith JTL, Nwokolo CU, Hudson M, Sawyerr AM, Pounder RE. Eradication of Helicobacter pylori abolishes 24-hour hypergastrinaemia: a prospective study in healthy subjects. *Aliment Pharmacol Therap* 1991; 5: 283-90.
- Wormsley KG. The pathophysiology of duodenal ulceration. *Gut* 1974; 15: 59-81.
- Marshall BJ, Armstrong JA, McGeachie DB, Glancy RJ. Attempt to fulfil Koch's postulates for pyloric campylobacter. *Med J Aust* 1985; 142: 436-9.
- James AH. Gastric epithelium in the duodenum. *Gut* 1964; 5: 285-94.
- Greenlaw R, Sheahan DG, DeLuca V, Miller D, Myerson D, Myerson P. Gastroduodenitis. A broader concept of peptic ulcer disease. *Dig Dis Sci* 1980; 25: 660-72.
- Patrick WJA, Denham D, Forrest APM. Mucous change in the human duodenum: a light and electron microscopic study and correlation with disease and gastric acid secretion. *Gut* 1974; 15: 767-76.
- Offerhaus GJA, Molyvas EN, Hoedemaeker PJ. Helicobacter pylori infection of gastric mucin cell metaplasia: the duodenum revisited. *J Pathol* 1990 162: 239-43.
- Shabib S, Cutz E, Drumm B, Sherman P. Helicobacter pylori infection is associated with gastric metaplasia in the duodenum. *Gastroenterology* 1992; 102: A163.
- Fitzgibbons PL, Dooley CP, Cohen H, Appleman MD. Prevalence of gastric metaplasia, inflammation, and Campylobacter pylori in the duodenum of members of a normal population. *Am J Clin Pathol* 1988; 90: 711-4.
- Shousha S, Barrison IG, El-Sayed W, Khan S, Parkins RA. A study of incidence and relationship of intestinal metaplasia on gastric antrum and gastric metaplasia of duodenum in patients with non-ulcer dyspepsia. *Dig Dis Sci* 1984; 29: 311-6.
- Wright NA, Pike C, Elia G. Induction of a novel epidermal growth factor-secreting cell lineage by mucosal ulceration in human gastrointestinal stem cells. *Nature* 1990; 343: 82-5.
- Montbriand JR, Appelman HD, Cotner EK, Nostrant TT, Elta GH. Treatment of Campylobacter pylori does not alter gastric acid secretion. *Am J Gastroenterol* 1989; 84: 1513-6.
- Terruzzi V. Gastric metaplasia of the duodenal bulb/a prospective endoscopic study [Letter]. *Endoscopy* 1987; 19: 252-3.
- Denizot Y, Sobhani I, Rambaud JC, Lewin M, Thomas Y, Benveniste J. Paf-acether synthesis by Helicobacter pylori. *Gut* 1990; 31: 1242-5.
- Crabtree JE, Shallcross TM, Heatley RV, Wyatt JL. Mucosal tumour necrosis factor α and interleukin-6 in patients with Helicobacter pylori associated gastritis. *Gut* 1991; 32: 1473-7.
- Leunk RD, Johnson PT, David BC, Kraft WG, Morgan DR. Cytotoxic activity in broth-culture filtrates of Campylobacter pylori. *J Med Microbiol* 1988; 26: 93-9.