Effect of *Helicobacter pylori* eradication on gastric metaplasia of the duodenum

S Khulusi, M A Mendall, S Badve, P Patel, C Finlayson, T C Northfield

Abstract

Helicobacter pylori associated duodenal ulcers occur in patches of gastric metaplasia. The pathogenesis of gastric metaplasia is unclear, but it has been produced in experimental animals by acute injury and has been shown to be present to a greater extent of *H pylori* positive subjects. This study aimed to discover if gastric metaplasia regressed with eradication of *H pylori* or healing of duodenal ulcers, or both. Thirty two duodenal ulcer patients with *H pylori* infection confirmed by biopsy urease test and by antral histological examination were studied. Patients were treated with triple therapy (deNol 240 mg twice daily, amoxycillin 500 mg three times daily, and metronidazole 400 mg three times daily) for two weeks after the first endoscopy and were subsequently re-endoscoped. Three duodenal bulb biopsy specimens were obtained per patient at each endoscopy. Biopsy sections were stained with haematoxylin and eosin to determine the severity of duodenitis, and with diastase periodic acid-Schiff/alcan blue to assess the extent of gastric metaplasia. Slides were assessed by two histopathologists unaware of treatment status. *H pylori* was eradicated in 63% of subjects and all ulcers were healed at follow up. The median extent of gastric metaplasia at the start of treatment and 6-18 months (median 10) after treatment was compared in the two groups. Gastric metaplasia declined in eradicators from 16% to 8% ($p < 0.05$) while in non-eradicators there was no significant change (25% initially and at follow up). A positive relation between extent of gastric metaplasia and duodenal inflammation score was present before treatment ($r_s = 0.74$, $p < 0.001$) and was unchanged after treatment in the non-erasicator group ($r_s = 0.89$, $p < 0.001$). In the eradicator group, however, the inflammation score had significantly declined ($p < 0.02$) and the close relation with gastric metaplasia was no longer present. These results suggest that *H pylori* itself is at least in part responsible for producing gastric metaplasia of the duodenum. (Gut 1995; 36: 193-197)

Keywords: *Helicobacter pylori*, gastric metaplasia, duodenum.

Since the initial identification and isolation of *Helicobacter pylori* in the early 1980s,¹ the

importance of this organism in the pathogenesis of duodenal ulceration has become increasingly clear.²⁻³ *H pylori* is found in the antrum of more than 95% of patients with duodenal ulcer⁴ and eradication reduces the relapse rate in an otherwise frequently relapsing condition.⁵⁻⁷

Gastric metaplasia of the duodenum, defined as the presence of groups of gastric mucosal cells within normal duodenal epithelium, is an almost constant feature of duodenal ulcer.^{8,9} It is also present at the margin of intestinal ulcers in inflammatory bowel diseases¹⁰ and is believed to be a non-specific response to injury.¹¹ Gastric metaplasia is, however, also present in the proximal duodenum of up to two thirds of non-ulcer dyspepsia patients,^{12,13} occurring with equal prevalence in *H pylori* positive and negative subjects^{11,12} but having a greater extent in those who are positive.¹¹ In animal studies, gastric metaplasia induced by mucosal injury is of rapid onset and resolves over a period of a few months,¹⁴ showing at least in animal models that it is reversible.

H pylori only colonises gastric epithelium. It is not found in areas of intestinal metaplasia in the stomach¹⁵ and does not colonise normal duodenal mucosa.^{9,16} Gastric metaplasia is susceptible to colonisation by *H pylori* however, resulting in chronic active inflammation, which is believed to be important in the pathogenesis of duodenal ulcer.^{9,11,16} Both healing of duodenal ulcer and resolution of active duodenitis follow eradication of *H pylori*.^{5,7,17} The effect of eradicating *H pylori* on the extent of gastric metaplasia has not been determined.

We aimed to discover if *H pylori* itself may be responsible for the production of gastric metaplasia of the duodenum by observing whether it regresses after eradication of *H pylori* in duodenal ulcer patients.

Subjects and methods

SUBJECTS

Thirty two consecutive subjects with *H pylori* positive duodenal ulcer undergoing endoscopy for dyspepsia were studied; 24 were male and eight female (median age 48, range 27-79). Patients receiving non-steroidal anti-inflammatory drugs (NSAIDs) or who had taken antibiotics or acid suppression treatment in the previous month or those with previous gastric surgery were excluded. The study was approved by the St George's Hospital ethics committee and informed consent was obtained from all patients.

Departments of
Medicine
S Khulusi
M A Mendall
P Patel
T C Northfield

and Histopathology,
St George's Hospital,
London
S Badve
C Finlayson

Correspondence to:
Professor T C Northfield,
Department of Medicine,
St George's Hospital
Medical School, Cranmer
Terrace, London
SW17 0RE.

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Figure 1: Section of a duodenal biopsy specimen stained with diastase PAS/alcian blue showing an area of gastric metaplasia at the apex of the villus marked with an arrow.

CLINICAL METHODS

At initial endoscopy, three gastric antral biopsy specimens were obtained 2 cm from the pylorus, one for rapid urease test and two for histological examination to confirm *H pylori* infection. Three duodenal bulb biopsy specimens per patient were obtained from the anterior, inferior, and superior walls, at least 1 cm away from any ulcer margin and from the pylorus. Specimens were placed in buffered formal saline and processed for histological examination.

All patients were treated with antibiotics (amoxycillin 500 mg three times daily and metronidazole 400 mg three times daily) and colloidal bismuth subcitrate (deNol 240 mg twice daily) for two weeks after the first endoscopy and all were re-endoscoped from 6–18 months (median 10) after treatment; antral and duodenal biopsy specimens were repeated from similar topographical sites. Eradication of *H pylori* was diagnosed by a negative biopsy urease test and negative results on histological examination.

Ten patients required an additional endoscopy less than six months after treatment

Figure 2: Section of a duodenal biopsy specimen stained with diastase PAS/alcian blue showing extensive gastric metaplasia and inflammatory cell infiltration of the mucosa.

because of recurring symptoms. In four no ulcer was detected and antral *H pylori* was absent on histological testing and on urease test, but in six a persisting ulcer was seen and antral *H pylori* detected. All six patients were treated with ranitidine 150 mg twice daily for six weeks.

HISTOLOGICAL METHODS

Sections from duodenal biopsy specimens were stained with diastase periodic acid Schiff/alcian blue and examined for gastric metaplasia and duodenitis (Figs 1 and 2), while antral sections were stained with haematoxylin and eosin to detect *H pylori*. Histological material was examined by two histopathologists unaware of the clinical details. The severity of duodenitis was graded on a scale of 0–3, corresponding to nil, mild, moderate, and severe mucosal inflammation.¹⁸ The extent of gastric type epithelium in the duodenal biopsy specimens (gastric metaplasia) was subjectively scored on a scale of 0–10 (representing 0–100% of the total epithelial surface present¹⁹). For both severity of duodenitis and extent of gastric metaplasia, the mean score of the three specimens obtained from the same subject were used.

STATISTICAL METHODS

The extent of gastric metaplasia and duodenal inflammation score for the eradicator and non-eradicator groups were calculated as medians. Differences between initial and follow up values were compared within groups by the Wilcoxon signed rank test, and between groups by the Mann-Whitney U test. The relation between gastric metaplasia and duodenitis was determined by Spearman's rank correlation coefficient.

Results

ERADICATION AND ULCER HEALING RATE

H pylori was eradicated in 20 patients and persisted in 12. There was no significant difference between eradicators and non-eradicators with respect to age, sex, length of follow up, smoking or a family history of peptic ulceration (Table). At the time of re-biopsy no active ulcers were seen, however, in patients who had failed to eradicate *H pylori* endoscopic evidence of duodenitis was seen in eight of 12 patients and duodenal cap deformities of previous ulceration in six of 12. Ranitidine was required for six patients in the non-eradicator group. There was no significant difference in

Patient characteristics		
	Eradicators (n=20)	Non-eradicators (n=12)
Median age (range)	56 (27–78)	48 (34–79)
Male/female	14/6	10/2
Smokers	12	5
Family history of duodenal ulcer	11	5
Length of follow up (month)	10 (6–18)	10 (6–18)

Figure 3: Effect of *H pylori* eradication on median gastric metaplasia.

the mean extent of gastric metaplasia between these subjects and non-eradicators not receiving H_2 receptor antagonists, showing that this treatment is unlikely to have influenced the results of our non-eradicator group.

EFFECT OF ERADICATION ON GASTRIC METAPLASIA

The median extent of gastric metaplasia after eradication of *H pylori* declined from 16% (range 0–80) to 8% (range 0–39) over the period of follow up (Wilcoxon signed rank test $p<0.05$) but no significant change was seen in

non-eradicators (25%, range 0–93; v 25%, range 0–100) (Fig 3). No significant difference in the extent of gastric metaplasia was found between the two groups initially, however a lower extent of gastric metaplasia was detected in eradicators at follow up (Mann-Whitney U test, $p<0.02$).

RELATION BETWEEN GASTRIC METAPLASIA AND DUODENITIS

Figure 4 shows the duodenal inflammation scores initially and at follow up in the eradicator and non-eradicator groups. There was a significant reduction in duodenal inflammation after *H pylori* eradication (Wilcoxon signed rank test, $p<0.02$).

Figure 5 shows the relation between duodenal inflammation score and the extent of gastric metaplasia. A positive relation was present before treatment ($r_s=0.74$, $p<0.001$) (Fig 5A) and at follow up in the non-eradicator group ($r_s=0.89$, $p<0.01$) (Fig 5B). In the eradicator group, however, the same close relation between duodenal inflammation and gastric metaplasia was no longer present at follow up (Fig 5C).

Discussion

This study shows that the extent of gastric metaplasia in the duodenum is reduced after *H pylori* eradication but not after duodenal ulcer healing alone. This suggests that *H pylori* infection may increase the extent of pre-existing gastric metaplasia. Other studies that have investigated whether non-acid suppressant treatment reverses gastric metaplasia have given conflicting results. Moshal *et al*²⁰ showed that duodenal ulcer healing after six weeks of colloidal bismuth was associated with reversal of gastric metaplasia while duodenal ulcer healing with H_2 receptor antagonist was not. This difference could be explained by an inhibitory effect of bismuth on *H pylori* although *H pylori* status after treatment was not reported. A recent study by Noach *et al*,²¹ of a similar size to this study, showed a trend towards reduction in gastric metaplasia after *H pylori* eradication. The reduction did not achieve statistical significance, and the authors concluded that *H pylori* eradication had no effect on gastric metaplasia, although their

Figure 4: Effect of *H pylori* eradication on median duodenal inflammation scores.

Figure 5: There was a significant relation between gastric metaplasia and duodenal inflammation score in *H pylori* infected subjects.

negative result may be caused by insufficient statistical power.

A study of a highly variable feature such as gastric metaplasia can be associated with sampling error. Biopsy of an inflamed part of the duodenal bulb may result in increased detection of gastric metaplasia compared with an adjacent less inflamed area.¹² To reduce bias in this study, the endoscopist was unaware of the eradication status of the patients and biopsies were targeted to similar topographical sites. Gastric metaplasia has a patchy distribution in the duodenal bulb and a single anterior duodenal biopsy has been shown to detect 63% of the gastric metaplasia detected by multiple biopsies.¹¹ Three duodenal bulb biopsy specimens, including one from the anterior wall, were used in this study to provide adequate sampling of the extent of gastric metaplasia. A longer period of follow up in our study, might have shown more complete resolution of gastric metaplasia. Animal studies suggest, however, that 10 months of follow up would be expected to be adequate to show maximum resolution.^{14 22}

In humans even in the absence of duodenal ulceration, the extent of gastric metaplasia is related to gastric acid output¹¹ suggesting that acid itself could lead to the formation of gastric metaplasia. It is possible that gastric metaplasia affords some protection against an acidic, gastric environment within the duodenal cap. This is supported by the finding that the incidence of gastric metaplasia is rare beyond the first part of the duodenum.¹¹ Other factors such as cigarette smoking, NSAIDs, and male sex are not related to the extent of gastric metaplasia independently of acid output.^{11 12} Duodenal ulcer patients have significantly raised gastric acid production as well as more extensive gastric metaplasia compared with subjects without duodenal ulcer.^{23 24} Studies have attempted to assess the effect of decreasing acid production on gastric metaplasia with conflicting results. Wyatt *et al*²⁵ showed that two years after vagotomy, patients had a lesser extent of gastric metaplasia than a control group about to undergo vagotomy. In contrast, Jönsson *et al*²⁶ found no reversal of gastric metaplasia two to three years after parietal cell vagotomy. The same study failed to show any effect after the same period of treatment with cimetidine. Similarly, Noach *et al*²¹ found no significant difference in the mean extent of gastric metaplasia between patients taking H₂ receptor antagonists for more than a year and subjects not taking these drugs. In our study ranitidine was used in six non-eradicators with persisting duodenal ulcer. No significant difference in the extent of gastric metaplasia was detected between these subjects and non-eradicators who had not received ranitidine. It is possible that the degree of acid suppression produced by H₂ antagonists, at the doses given in these studies, was insufficient to affect gastric metaplasia.

Our results confirm that a basal level of gastric metaplasia is present, which is independent of *H. pylori*; this is consistent with previous reports implicating possible genetic factors¹³ or

gastric acid secretion¹⁹ in the formation of gastric metaplasia. There are two possible mechanisms by which *H. pylori* itself could increase this basal level of gastric metaplasia. Firstly, *H. pylori* infection has been shown to increase gastric acid production in duodenal ulcer patients leading to greater duodenal acidity.²⁷ The second possibility is that infection of gastric metaplasia with *H. pylori* leads to duodenal inflammation, provoking extension of gastric type epithelium as a response to injury. Results from our study support this possibility, as they show a close association between severity of duodenal inflammation and extent of gastric metaplasia, and reduction in both after *H. pylori* eradication. Recent studies, including our own,^{28 29} have shown that infection density is greater in the antrum of *H. pylori* positive patients who have duodenal ulcer than those who do not. It is therefore possible that subjects with a sufficiently high infection density in the gastric antrum are more likely to develop colonisation of gastric metaplasia of the duodenum, which in turn leads to duodenal inflammation generating more extensive gastric metaplasia. This could result in greater colonisation and more severe inflammation of the duodenum, eventually leading to ulceration.

This study has been presented to the British Society of Gastroenterology, September 1993 and has been published in abstract form in *Gut* 1993; 34 (suppl 4): S50.

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key topics' category. It should be judged in these terms, of course, as it is not a textbook of paediatric gastroenterology. The authors of the chapters are well recognised names in the community of paediatric gastroenterologists, from North America and from the United Kingdom, with one representative from continental Europe. Predictably, all have undertaken their task competently and successfully.

The success of the publication must depend on the choice of topics included. This is good in the main, but at times somewhat specialist. The generalist who sees children with gastrointestinal problems will find the chapters on oral rehydration solution, constipation, food allergy, inflammatory bowel disease, gastro-oesophageal reflux, recurrent abdominal pain, and gastrointestinal bleeding, of great interest and educational value. The chapter on 'when to transplant the liver in children' fits uncomfortably; it is a very interesting question for the paediatric hepatologist or specialist gastroenterologist but of little relevance to the probable readership of the publication. The chapters on the role of gastrointestinal motility studies and of home parenteral nutrition fall in between, probably. The relevance of the book to a reader will depend on the number of children with these problems they see, and I suspect that the book will be most useful to the general paediatrician and not the general gastroenterologist.

In keeping with the ethos of counting credits, I would rate this book as being worth three credits (assuming that most generalists would probably read six chapters, and perhaps spend half an hour on each). By doing this, they are probably learning more than by earning six credits by listening to the same authors giving lectures on the same topics, and in addition they have the book on their shelves afterwards. Paediatricians should put it on their reading list for next term, as should any general gastroenterologist who sees children.

S P DEVANE

NOTES

Wilson's disease and Menkes' disease

The 7th International Symposium on Wilson's disease and Menkes' disease will be held in Vienna, Austria on 25–27 August 1995. Further information from: Prof Dr Peter Ferenci, Department of Internal Medicine IV, Gastroenterology and Hepatology, Währinger Gürtel 18–20, A-1090 Vienna, Austria. Tel: (43 1) 40 400 47 41; fax: (43 1) 40 400 47 350.

Neurogastroenterology

An International Symposium on Neurogastroenterology will be held on 10–11 November 1995 in Rome, Italy. Further information from: Dr Enrico Corazzari, Cattedra di Gastroenterologia I, Clinica

Medica II, Policlinico Umberto I, V.le del Policlinico, 00161, Rome, Italy. Tel/fax: 39 6-4469965.

Paediatric gastroenterology

The 1st International Congress of Pediatric Gastroenterology will be held in Jaipur, India on 12–16 December 1995. Further information from: Dr Balvir S Tomar, Head, Department of Pediatric Gastroenterology, 4 Govind Marg, Jaipur, 302 004, India. Tel: 91 141 604040 or 605050; fax: 91 141 563788.

Gastroenterology

A Postgraduate Gastroenterology Course will be held in Oxford on 7–10 January 1996. Further information from: Dr D P Jewell, Gastroenterology Unit, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE. Tel: 01865 224829; fax: 01865 790792.

Inflammatory bowel disease

The International Inflammatory Bowel Disease Symposium will be held in Chester on 14–16 April 1996. Further information from: Prof Jonathan M Rhodes, Department of Medicine, Liverpool University, L69 3BX. Tel: 0151 706 3558; fax: 0151 706 5802.

ABIM announcement regarding change in training requirements for certification in gastroenterology

The American Board of Internal Medicine announces a new policy requiring three years of accredited training in a gastroenterology fellowship programme.

This decision follows a lengthy review by the ABIM Subspecialty Board on Gastroenterology and has the support of the American Gastroenterological Association, the American College of Gastroenterology, the American Society of Gastrointestinal Endoscopy, the American Association for the Study of Liver Diseases, and the Gastroenterology Training Program Directors.

This new policy becomes effective for fellows entering gastroenterology fellowship training programmes in June 1996 and thereafter. Trainees who have questions about this policy should contact the American Board of Internal Medicine, 3624 Market Street, Philadelphia, Pennsylvania, 19104-2675, USA.

Falk Symposia

Details of Falk Symposia for 1995 and 1996 and the Basel Liver Week 1995 are now available. Further information from: Falk Foundation V, Leinenweberstraße 5, Postfach 65 29, D-79041 Freiburg, Germany. Fax: 0761/13034-59.

Sir Francis Avery Jones BSG Research Award 1996

Applications are invited by the Education

Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 1996 Award. Applications (**eighteen copies**) should include:

(1) A manuscript (2 A4 pages *only*) describing the work conducted.

(2) A bibliography of relevant personal publications.

(3) An outline of the proposed content of the lecture, including title.

(4) A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

Entrants must be 40 years or less on 31 December 1996 but need not be a member of the BSG. The recipient will be required to deliver a 40 minute lecture at the Spring meeting of the Society in 1996. Applications (**eighteen copies**) should be made to: The Honorary Secretary, BSG, 3 St Andrews Place, London NW1 4LB by 1 December 1995.

CORRECTIONS

The authors (Van't Hof *et al* 1995; **36**: 691–5) omitted an acknowledgement from their paper and would like to gratefully acknowledge the support of the Medical Research Council, South Africa.

An authors' error occurred in the paper by Khulusi *et al* (*Gut* 1995; **36**: 193–7). The second sentence under Clinical Methods should read 'One duodenal biopsy was obtained from the ulcer margin and two from the anterior duodenum', and on the same point the second paragraph of the Discussion should re-affirm that the three duodenal bulb biopsy specimens included 'two from the anterior wall'.

Some editorial errors occurred in the paper by Mothes *et al* (*Gut* 1995; **36**: 548–52). The tenth line of the Methods section should read 'was stopped by the addition of 10 ml acetic acid' and not 100 ml. In the legend to Fig 1: lane 2 should read 'gliadin (gli)' and not 'purified gliadin', lane 3 should read 'tryptic digested gliadin (t-gli)' and not 'gliadin'. The abscissa to Fig 3 should begin with zero and not 1. The legend to Fig 4 should read 'MHC expression by HT-29 cells – influence of gliadin (gli) (●), tryptic digested gliadin (t-gli) (○), casein (▼), tryptic digested casein (▽), and β lactoglobulin (■). Culture in the presence of interferon γ without addition of food derived peptides was 100%. Means of three or four (t-gli, four to seven) individual cultures are shown (*only two cultures performed). For sake of clarity the SEM is given in only one direction'.

Also, 'trypsin' and 'tryptic digestion' has been printed as 'tryptin' and tryptin digestion' throughout the text.