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A study of the pathogenesis of *Helicobacter pylori* negative chronic duodenal ulceration

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Abstract

In the past five years 12 patients have been identified presenting with chronic duodenal ulcer (DU) disease and with no evidence of current or recent *Helicobacter pylori* (*H pylori*) infection. Four of them were taking regular non-steroidal anti inflammatory agents, one was subsequently found to have Crohn's disease of the duodenum, and one to have the Zollinger-Ellison syndrome. The remaining six patients with idiopathic DU disease were remarkable for their absence of the A_1 blood antigen gene. Detailed studies of gastric function were performed in these six patients and compared with *H pylori* positive patients with DU and with healthy volunteers. The median integrated gastrin response in the patients with idiopathic DU (2810 (range 750–8750) ng/l min) was similar to that of the *H pylori* positive patients with DU (3355 (550–8725)) and higher than that of the *H pylori* negative healthy volunteers (560 (225–1125)). The median peak acid output in the patients with idiopathic DU (37 mmol/h, range 17–52) was similar to that of the *H pylori* positive patients with DU (40 (15–57)) and higher than that of the non-ulcer controls (22 (16–29)). The median percentage of a liquid meal retained in the stomach at 60 minutes was less in the patients with idiopathic DU (23 (15–33)) than in *H pylori* negative healthy volunteers (34 (30–53) $p<0.01$). The median percentage of a solid meal retained at 60 minutes was less in the patients with idiopathic DU (54 (9–83)) than in either *H pylori* negative healthy volunteers (87 (49–95) $p<0.01$) or *H pylori* positive patients with DU (79 (51–100) $p<0.01$). In conclusion, three abnormalities of gastric function are prevalent in patients with *H pylori* negative idiopathic DU disease – hypergastrinaemia, increased acid secretion, and the one feature distinguishing them from *H pylori* positive patients with DU – rapid gastric emptying of both liquids and solids. Each of these abnormalities will increase the exposure of the duodenal mucosa to acid and thus explain its ulceration. The absence of the blood group A_1 antigen gene is consistent with a genetic basis for the disturbed gastric function linked to the ABO blood group antigen genes.

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More than 95% of patients with chronic duodenal ulcer (DU) disease have *Helicobacter pylori* (*H pylori*) infection and accompanying antral gastritis.[1 2] This infection is thought to play an important part in the pathogenesis of the ulcer disease as eradicating it dramatically lowers the ulcer relapse rate.[3 4] The mechanism by which *H pylori* infection predisposes to duodenal ulceration remains unclear.

Due to the high prevalence of *H pylori* infection in DU disease the numerous previous studies of the pathogenesis of DU have consisted almost entirely of patients with *H pylori* related DU. Consequently, little is known about the pathogenesis of chronic DU disease in patients without *H pylori* infection. Studies of such patients may be particularly valuable in allowing a clearer insight into the disturbances of gastric function predisposing to DU. Also, any genetic component of DU disease should be more prominent and thus more readily detected in *H pylori* negative patients with DU who have developed the disorder in the absence of this important acquired factor. Another problem with the vast number of previous publications on disturbed gastric function patients with DU is that a high proportion of the so called normal controls will have had disturbed gastric function due to unrecognised *H pylori* infection.

We have examined patients identified in our gastrointestinal unit over the past five years with chronic DU disease unassociated with current or recent *H pylori* infection. In the subgroup of these *H pylori* negative patients with DU in whom no cause for their ulcer disease was identified, detailed studies of gastric function have been performed and compared with those in patients with DU with *H pylori* infection as well as with healthy volunteers.

Patients and methods

During the past five years we have identified a total of 12 patients with endoscopically confirmed chronic DU disease unassociated with current or recent *H pylori* infection (Table 1). These patients were negative for *H pylori* infection by each of four tests: histological examination of antral biopsy for *H pylori* like organisms, ^{14}C-urea breath test, serum anti-*H pylori* IgG (Helico-G test, Porton, Cambridge, UK), and the urease slide test (CLO test, Delta West Ltd, Bentley, Western Australia) of antral biopsy. Over the same period we have seen 423 patients with DU associated with *H pylori* infection.

In six of these 12 patients a cause for their DU was readily identified (Table 1). Four of them had been taking non-steroidal anti inflammatory drugs (NSAIDs) for a mean period of 10 (range one to 18) months for arthritis and remarkably one of these had DU in spite of having pentagastrin fast achlorhydria due to pernicious anaemia. A further patient was found to have the Zollinger-Ellison syndrome. Another patient had severe inflammation and numerous granu-

TABLE I *Details of patients with* Helicobacter pylori *negative chronic duodenal ulcer disease*

Patient No	*Age*	*Sex*	*Family history*	*Cigarettes/ day*	*Alcohol (units/week)*	*NSAIDs*	*Other disease*
1	45	M	−	0	<2	Ketoprofen	Rheumatoid arthritis
2	62	F	−	0	<2	Indomethacin	Rheumatoid arthritis
3	64	F	−	0	<2	Indomethacin	Osteoarthritis
4	57	M	−	0	10	Ibuprofen	Osteoarthritis
5	19	F	+	0	<2	No	Crohn's disease
6	49	M	−	0	<2	No	Zollinger-Ellison syndrome
7	40	M	−	20	<2	No	None
8	28	F	−	0	5	No	None
9	34	F	+	20	<2	No	None
10	51	M	−	5	20	No	None
11	45	M	−	20	<2	No	None
12	64	M	−	20	<2	No	None

NSAIDs=non-steroidal anti-inflammatory drugs.

lomata on histological examination of duodenal biopsies indicating Crohn's disease of the duodenum.

Six patients remained in whom there was no apparent explanation for their DU disease and we have chosen for convenience to refer to these patients as having idiopathic DU. Four were men and their median age was 42 (28–64) years (Table 1). Five were smokers but only one drank more than five units of alcohol a week and only one patient had a family history of ulcer disease. The median age of onset of their DU disease was 34 (18–56) years. The median interval between the initial endoscopic diagnosis of their DU disease and entry into this study was eight (one to 12) years and each patient had suffered recurrent dyspepsia requiring medical treatment over this time.

Five of these six idiopathic DU patients had been difficult to control on acid inhibitory treatment. In four there was persistence of symptoms and endoscopic evidence of failure of ulcer healing despite three months of treatment with 300 mg ranitidine a day. Two of these patients who were refractory to H_2 antagonist treatment required treatment with omeprazole and one of them (No 7) eventually needed a highly selective vagotomy. Two of the five patients who were difficult to control on acid inhibitory treatment had complications from their DU; one having an acute bleed requiring transfusion of three units of blood while on full dose H_2 antagonist treatment and one experiencing two separate acute bleeds each requiring blood transfusion.

METHODS

In these six patients with idiopathic DU, further investigations were performed as described later. The results of these tests were compared with those in age and sex matched patients with DU and with *H pylori* infection. In most of the tests it was also possible to compare the results with those in age and sex matched healthy volunteers with and without *H pylori*. The control data were obtained from patients and healthy volunteers who had undergone identical tests as the patients with idiopathic DU and over the same period either specifically for the present study or as part of another study. These control subjects did not all undergo all the tests that were performed on the patients with idiopathic DU and, therefore, the number of control subjects for the different tests varies. Detailed studies of gastric function were not performed in the *H pylori* negative patients with DU in whom an explanation for their ulcer disease was apparent (NSAIDs use, Crohn's disease, or Zollinger-Ellison syndrome).

Serum gastrin and pepsinogen I

The patients reported at 0900 after an overnight fast and having discontinued their acid inhibitory treatment two weeks previously. Three venous blood samples were taken at 15 minute intervals. They then drank a peptone meal over five minutes consisting of two beef cubes (OXO Ltd, Croydon, UK) dissolved in 200 ml water at 50°C. A further blood sample was obtained 10 minutes after starting the drink and thereafter at 10 minute intervals for 90 minutes. The blood samples were allowed to clot over 15 minutes and then the serum was separated by centrifugation and stored at −20°C. Serum gastrin concentration was measured by radioimmunoassay with antibody R98 as previously described.[5] This detects both gastrin 17 and 34 and uses G17 as standard. The mean of the three fasting samples was used as the basal gastrin concentration. The integrated response to the meal was assessed by the area under the gastrin concentration time curve by the trapezoid method. Serum pepsinogen I was measured in the sample taken immediately before starting the meal by the commercial radioimmunoassay kit manufactured by Incstar Ltd (Berkshire, UK). Serum pepsinogen I shows little response to eating.[6]

Gastric acid and pepsin secretion

The patients reported at 0900 after an overnight fast and having discontinued acid inhibitory drugs two weeks earlier. A 16F dual lumen tube (Andersen Inc, New York, USA) with side vent open to the atmosphere was passed orogastrically and the residual gastric contents aspirated and discarded. The position of the tube was confirmed by the water recovery test. Three 15 minute collections of fasting gastric juice were taken. The patients then received either a single injection of 6 μg/kg pentagastrin (peptavlon, ICI Pharmaceuticals, UK) subcutaneously or an intravenous infusion of 0·6 μg/kg/h over one hour. Four 15 minute collections were taken over the hour. The volume of each collection was recorded and its hydrogen ion concentration determined by titration with 0·1 N sodium hydroxide to pH 7 with an autotitrator (Radiometer ETS 822). A 1·0 ml sample from each collection of gastric juice was mixed with 0·3 ml glycerol/HCL (10 mmol/l v/v) and stored at −80°C before measurement of pepsin activity by the method of Gray and Billings.[7] Preliminary studies confirmed that pepsin was stable when stored in this way for up to seven months. The second and third 15 minute basal collections were used to determine the basal output. Peak acid output was calculated from the two highest stimulated 15 minute outputs.

Gastric emptying of liquids and solids

The patients reported on fasted at 0900 having not taken any drugs which affect gastric secretion or motility over the previous 10 days. They then con-

TABLE II *Individual details of gastric function studies in patients with idiopathic duodenal ulcer*

Patient No	Serum pepsinogen I (ng/ml)	Basal gastrin (ng/l)	Integrated gastrin response (ng/l.min)	Basal acid output (mmol/h)	Peak acid output (mmol/h)	Peak pepsin output (units/h)	Liquid emptying $t_{1/2}$ (min)	Solid emptying $t_{1/2}$ (min)
7	198	110	8750	20	52	-	38	221
8	40	15	1820	1	17	25·6	37	11
9	64	85	8150	5·6	25	50	22	11
10	84	39	750	6·2	34	45	29	69
11	249	17	3820	11	48	59	28	106
12	88	37	275	2·4	39	58	24	66

sumed a peptone meal over five minutes consisting of two beef cubes (OXO Ltd, Croydon, UK) dissolved in 200 ml water at 50°C, 75 ml of semi-skimmed milk, and 20 g cornflakes (Kellogg's). The liquid phase was labelled with ^{133m}In and the solid phase with ^{99m}Tc albumin colloid.[8] The solid marker was impregnated on blotting paper and then coated with cellulose. This was then cut into 0·5 cm squares and mixed into the cornflakes. Images of each nuclide were taken in anterior and posterior projections every 15 minutes for two hours, with the patient standing. The patient sat between measurements. The gastric outline was defined on the early images of both nuclides in anterior and posterior projections and applied to all images of the study, after moving as necessary into correct registration. Total gastric counts were evaluated on each image. For each nuclide at each time the geometric mean of anterior and posterior counts was calculated, to compensate for the anteroposterior movement of the gastric contents during emptying. The mean counts were each corrected for nuclide decay and the results plotted against time on a semi-logarithmic plot. The liquid emptying plots were all straight lines and were fitted to a single exponential function by an iterative least squares method. The liquid emptying half life and percentage retentions at 60 minutes were calculated from these fits. The solid emptying plots started with a straight line section but often suffered an abrupt increase in slope at between 45 and 90 minutes. In two cases, however, the emptying rate decreased. The solid emptying half life and percentage retentions at 60 minutes were calculated by exponential interpolation with as many surrounding points as appropriate.

Histology of antral mucosa

During routine upper gastrointestinal endoscopy one biopsy was taken for histological examination from the antral mucosa 2 cm from the pylorus and one from the first part of the duodenum on the opposite wall to the area of ulceration. The biopsies were fixed in formalin and stained with haematoxylin and eosin. The severity of the antral gastritis was assessed with the scoring system described by Rauws *et al*, which gave a possible total cumulative score of 10.[9]

Blood groups and secretory state

ABO blood group state was found by standard haemagglutination techniques with monoclonal reagents and red cell suspensions prepared by the Scottish National Blood Transfusion Service.[10] The lectin from *Dolichos biflorus* was used to distinguish A1 from A2 antigens. Secretor state was assessed on saliva samples taken fasting and treated with centrifugation and heat inactivation. Standard haemagglutination inhibition techniques with diluted human anti-A, anti-B, and anti-H (extracted from the lectin *Ulex europaeus*) were applied with saliva at dilutions up to one in 16.

Statistical analysis

Statistical significance was assessed by the Mann-Whitney U test.

The study was approved by the Western Infirmary ethics committee and each patient gave informed written consent.

Results

Antral histology was normal in five of the six patients with idiopathic DU, with their cumulative antral gastritis scores being either 0 or 1. In the other patient (No 7) there was evidence of chronic and acute inflammatory cell infiltration and the cumulative gastritis score was 6. In three of the patients, the duodenal biopsies were normal and in the others there was a chronic and acute inflammatory cell infiltrate and evidence of gastric metaplasia.

The median serum pepsinogen I concentration (ng/ml) in the patients with idiopathic DU was 86 (range 40–249). This was not significantly different from that in the *H pylori* positive DU patients (97 (53–130)), *H pylori* negative healthy volunteers (73 (46–101)), or *H pylori* positive healthy volunteers (81 (43–115)). Two of the patients with idiopathic DU had, however, serum pepsinogen I values that were more than 50% higher than the highest value of all the other groups studied (Table II).

The blood group antigen A_1 was not found in any of the six patients with idiopathic DU. By comparison it was present in 38% of the *H pylori* positive patients with DU and 56% of the non-ulcer controls (Table III). Four of the six patients with idiopathic DU were blood group 0. Only one of the six patients with idiopathic DU was a non-secretor of blood group antigens compared with 46% of the *H pylori* positive patients with DU and 32% of the healthy volunteers.

The basal serum gastrin concentrations (ng/l) were increased in the *H pylori* positive patients with DU (median 57 (range 13–103)) compared with the *H pylori* negative healthy volunteers (20

TABLE III *Blood group antigens and secretor state of patients with idiopathic DU. Prevalence values in* H pylori *positive patients with DU and non-ulcer controls are provided for comparison*

	Patients with idiopathic DU (identified by number)						Prevalence (%) in H pylori + patients with DU (n=24)	Prevalence (%) in non-ulcer controls (n=25)
	7	8	9	10	11	12		
A_1							38	56
A_2					+		8	4
B			+		+		12	4
O	+	+		+		+	42	36
Non-secretor				+			46	32
Secretor	+	+	+		+	+	54	68

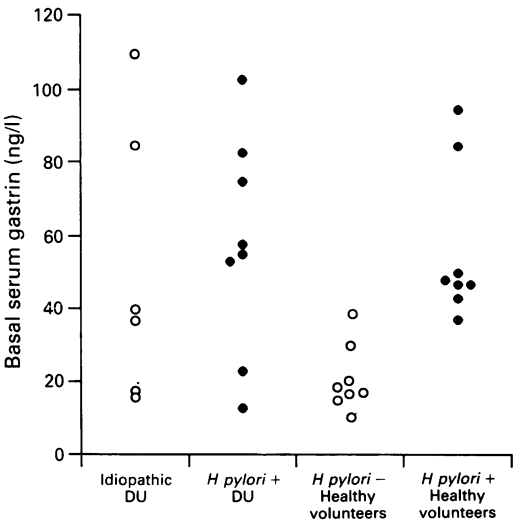

Figure 1: Basal serum gastrin concentrations in patients with idiopathic DU, patients with H pylori *(HP) +ve DU, and healthy volunteers with (+) and without (−)* H pylori.

(10–40) p<0·01) but were similar to those in the *H pylori* positive healthy volunteers (48 (37–95)) (Fig 1). The basal serum gastrin concentrations in the patients with idiopathic DU (38 (15–110)) were more similar to those of the *H pylori* positive patients with DU or *H pylori* positive healthy volunteers than to those of the *H pylori* negative healthy volunteers.

The integrated gastrin response (IGR) (ng/l. min) was exaggerated in the *H pylori* positive patients with DU (3375 (550–8725)) compared with the *H pylori* negative healthy volunteers (560 (225–1125), p<0·002) but was similar to that in the *H pylori* positive healthy volunteers (4150 (900–8500)) (Fig 2). The integrated gastrin response in the patients with idiopathic DU (2810 (750–8750)) was similar to that of the *H pylori* positive patients with DU and *H pylori* positive volunteers, with four of the six patients with idiopathic DU having values above the range of the *H pylori* negative healthy volunteers.

Basal acid output (mmol/h) was higher in the *H pylori* positive patients with DU (7 (1–9)) compared with the healthy volunteers (1·8 (0·3–5), p<0·05) (Fig 3). The values in the patients with

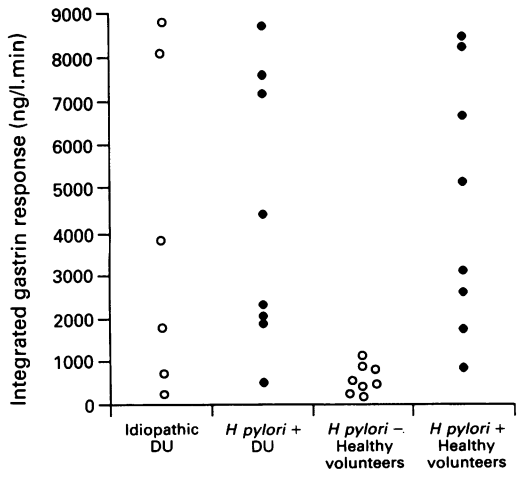

Figure 2: Integrated gastrin response to peptone meal in patients with idiopathic DU, H pylori *positive patients with DU, and healthy volunteers with and without* H pylori.

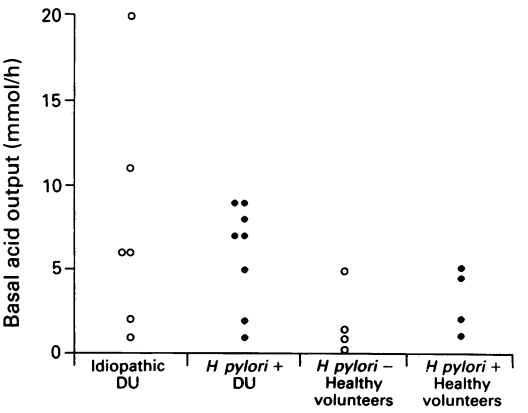

Figure 3: Basal acid output in patients with idiopathic DU, H pylori *positive patients with DU, and healthy volunteers with and without* H pylori.

idiopathic DU (5·9 (1–20)) were similar to the *H pylori* positive patients with DU. Four of the six patients with idiopathic DU had basal acid output values above the range in the healthy volunteers although due to the small numbers of the former the difference between these groups did not reach statistical significance (p=0·06).

Peak acid output (mmol/h) was increased in the *H pylori* positive patients with DU (40 (15–57)) compared with the healthy volunteers (22 (16–29), p<0·05) (Fig 4). The patients with idiopathic DU had peak acid output values (37 (17–52)) that were similar to those of the *H pylori* positive patients with DU. Four of the six patients with idiopathic DU had peak acid output values above the range of the healthy volunteers but again due to the small number of the first the difference between these groups did not reach statistical significance (p=0·08). The *H pylori* negative and positive healthy volunteers were similar for both basal and peak acid output. The pentagastrin stimulated pepsin output in the *H pylori* negative patients with DU (median 50 units/h (range 26–59)) was similar to that in the *H pylori* positive patients with DU (42 (15–168)) (Table II).

The liquid emptying rate in the patients with idiopathic DU was significantly faster than in the *H pylori* negative healthy volunteers (median 60 minute percentage retentions 23 (range 15–33) and 34 (30–53) respectively (p<0·01) (Fig 5)). The liquid emptying half time was correspond-

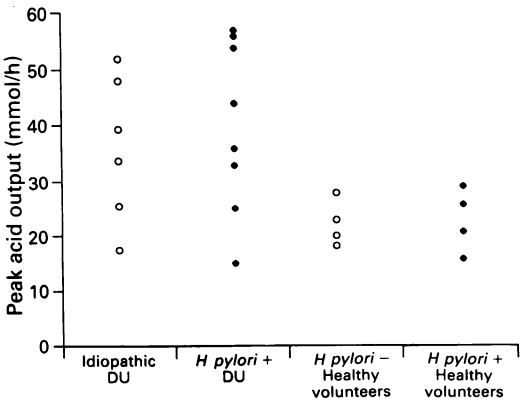

Figure 4: Peak acid output in patients with idiopathic DU, H pylori *positive patients with DU, and healthy volunteers with and without* H pylori.

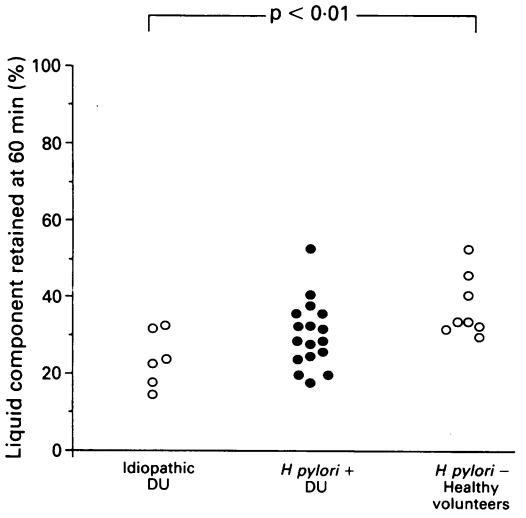

Figure 5: Gastric emptying of liquids in patients with idiopathic DU, H pylori *positive patients with DU, and* H pylori *negative healthy volunteers.*

ingly shorter in the patients with idiopathic DU (median 28 min (range 22–38)) than in the *H pylori* negative healthy volunteers (39 (35–66), $p<0·001$). There was no significant difference in liquid emptying rate between the patients with idiopathic DU and *H pylori* positive patients with DU or between the *H pylori* positive patients with DU and *H pylori* negative healthy volunteers (Fig 5).

The solid emptying rate as measured by the percentage retention at 60 minutes was faster in the patients with idiopathic DU (median 54 (range 9–83)) than in the *H pylori* positive patients with DU (79 (51–100), ($p<0·01$) or *H pylori* negative healthy volunteers (87 (49–95), $p<0·01$) (Fig 6). The solid emptying half time was correspondingly shorter in the patients with idiopathic DU (median 67 min (range 11–221)) compared with the *H pylori* positive patients with DU (180 (62–1500, $p<0·01$) and *H pylori* negative healthy volunteers (431 (58–838), $p<0·01$). The *H pylori* positive patients with DU were similar to the *H pylori* negative healthy volunteers with respect to both solid emptying

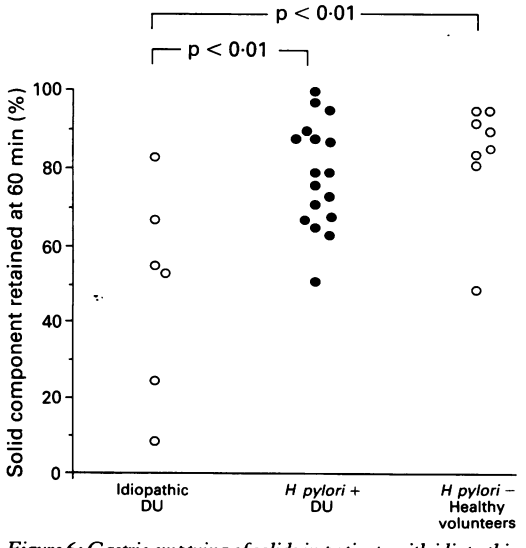

Figure 6: Gastric emptying of solids in patients with idiopathic DU, H pylori *positive patients with DU, and* H pylori *negative healthy volunteers.*

60 minute retention values ($p=0·3$) and half time ($p=0·4$).

Discussion

In this study we adopted particularly strict criteria for accepting a patient as having *H pylori* negative DU. By insisting that each patient was negative for *H pylori* by microscopy, ^{14}C-urea breath test, urease slide test, and *H pylori* IgG serology we ensured that no patient was included with current or recent infection. Although the 12 such patients were identified from more than 400 patients with DU examined, this may not represent the true prevalence of *H pylori* negative patients with DU as not all the 400 patients with DU had their *H pylori* state determined with the same stringency.

In half of the *H pylori* negative patients with DU, an explanation for the ulcer disease was readily apparent. Four of these patients were taking regular NSAIDs. Nensey *et al* recently reported that nine (75%) of their 12 *H pylori* negative patients with DU were taking NSAIDs or aspirin compared with 33% of their *H pylori* positive patients with DU.[11] Likewise, Borody *et al* found that eight (57%) of their 14 *H pylori* negative patients not on antibiotics were taking NSAIDs compared with only 5% of their *H pylori* positive patients with DU.[2] One of our patients with *H pylori* negative DU associated with NSAIDs was achlorhydric due to pernicious anaemia indicating that NSAIDs can cause ulceration in the absence of both acid and *H pylori*.

One *H pylori* negative patient with DU had the Zollinger-Ellison syndrome and this is consistent with the finding of Fich *et al* that 55% of their patients with the syndrome were negative for *H pylori* infection.[12] Another of our *H pylori* negative patients with DU had histological changes in duodenal biopsies consistent with Crohn's disease. Borody *et al* found that two of their 14 *H pylori* negative patients with DU not taking antibiotics had Crohn's disease of the duodenum.[2] In the light of these findings it is important that Crohn's disease and the Zollinger-Ellison syndrome are excluded in patients with *H pylori* negative DU who are not taking NSAIDs.

The six patients with chronic DU disease in whom there was no evidence of *H pylori* or other explanation for their ulceration are of particular interest. We have chosen to refer to these patients as having idiopathic DU. Though *H pylori* is recognised to be the most important acquired factor in the pathogenesis of DU the prevalence of the infection is more than four times that of DU. This indicates that other cofactors must play an important part. One would expect that such cofactors would be particularly apparent in patients who develop DU in the absence of the most important acquired factor. Smoking is an important cofactor in the development of DU[13] and five of the six patients with idiopathic DU were smokers. To further elucidate the mechanism of the ulceration in these patients with idiopathic DU, studies of gastric function and of claimed genetic markers for DU were performed.

Hyperpepsinogenaemia I has been claimed to be a marker for the DU diathesis.[14] More recent studies, however, have shown that *H pylori* infection raises serum pepsinogen I.[15 16] The fact that two of our patients with idiopathic DU had serum pepsinogen I concentrations that were considerably higher than those in any of the *H pylori* positive patients with DU or *H pylori* positive healthy controls suggests that there is an association between hyperpepsinogenaemia I and DU disease independent of *H pylori*.

Blood group O and non-secretor state are genetic traits associated with DU disease and when both are present they increase the risk of the disease by 150%.[17] In this study blood group O was positively associated with idiopathic DU, being present in four of the six patients compared with 36% of non-ulcer controls. More notable, however, was the total absence of the A_1 antigen and gene in the patients with idiopathic DU. Calculations based on the A_1 gene frequency of 0·21 in the UK population[18] and the presence of 2 ABO genes a patient indicate a random probability of this association of only 2·4%. It seems likely that the patients with idiopathic DU represent a largely genetic form of the disease and the noticeable absence of the A_1 antigen gene is consistent with the genetic basis being linked to the absence of the A_1 antigen gene. It is notable also that the *H pylori* positive patients with DU differed more from the non-ulcer controls with respect to their lower prevalence of blood group A_1 than increased prevalence of blood group O.

Hypergastrinaemia is a recognised factor in the pathogenesis of DU as exemplified by the Zollinger-Ellison syndrome and G cell hyperplasia. *H pylori* infection also causes hypergastrinaemia,[15 19] which may be relevant to its role in DU disease. As previously reported,[20] the *H pylori* positive patients with DU and the *H pylori* positive healthy controls had similarly exaggerated integrated gastrin responses to eating compared with the *H pylori* negative healthy controls. Four of the six patients with idiopathic DU had gastrin responses to eating that were similar to those of the *H pylori* positive patients with DU and *H pylori* positive volunteers. The mechanism of hypergastrinaemia associated with *H pylori* infection is not known but the accompanying antral gastritis might be involved. The reason for the hypergastrinaemia in the four idiopathic DU patients is also unclear and it is of note that only one of them had antral gastritis.

Increased basal acid output and increased peak acid output are important features in patients with DU[21 22] and in our study we found that these were both increased in the *H pylori* positive patients with DU compared with the non-ulcer healthy controls. Increased basal and peak acid output was also prevalent in the patients with idiopathic DU. In a recent study Levi *et al* reported that pentagastrin stimulated acid output was less in *H pylori* negative patients with DU than in *H pylori* positive patients with DU[23] but we could not show this in our study. The difference between the studies may be explained by the fact that we adopted more stringent criteria for assessing *H pylori* state and also assessed gastric function only in *H pylori* negative patients with DU who had no other explanation for their ulcer disease. The stringent criteria for selecting our patients meant that we had few patients and it is possible that a difference in acid secretion between the patients with idiopathic DU and *H pylori* positive patients with DU could become apparent with greater numbers. The increased peak acid output to pentagastrin in the patients with idiopathic DU and *H pylori* positive patients with DU indicates that both have an increased parietal cell mass. The cause of this is unclear but it could be due to the trophic effect of hypergastrinaemia on the oxyntic mucosa,[24] an effect of smoking,[25] an inherited characteristic, or a combination of these.

The only characteristic that clearly distinguished the patients with idiopathic DU from both *H pylori* positive patients with DU and *H pylori* negative healthy volunteers was their rapid gastric emptying of both liquids and solids. An increased rate of gastric emptying has previously been noted in some patients with DU,[26 27] and a familial form of the disease associated with rapid gastric emptying has also been described.[28] The accelerated gastric emptying of both liquids and solids in the patients with idiopathic DU may explain why their ulcer disease was more difficult to control with antisecretory agents and the use of pharmalogical agents to delay gastric emptying might be helpful.

In summary, this study shows that in about 50% of patients with *H pylori* negative DU their disease can be explained by NSAID use, underlying Zollinger-Ellison syndrome, or Crohn's disease. In the rest of the patients with idiopathic DU three disturbances of gastric function are prevalent: hypergastrinaemia, increased basal and peak acid output, and rapid gastric emptying. Each of these abnormalities of gastric function will increase the duodenal acid load, thus supporting a role for duodenal acidity in the pathogenesis of the ulceration. The cause of the disturbed gastric function in the patients with idiopathic DU is unclear but their lack of the blood group A_1 antigen is consistent with a genetic basis linked to ABO blood group antigen genes.

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