

Circadian pattern of intragastric acidity in duodenal ulcer patients: a study of variations in relation to ulcer activity

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Abstract

The relation between intragastric acidity and duodenal ulcer activity was studied prospectively in 21 patients with endoscopically proved duodenal ulcers. The 24 hour intragastric acidity was measured on four separate occasions by continuous recording using combined glass electrodes: (a) in the presence of an ulcer crater without treatment; (b) during active ulceration being treated with ranitidine; (c) during early healing after a six week course of ranitidine; (d) during late healing six months after acute ulceration. Intragastric acidity was also monitored in 20 healthy subjects. At all stages of ulcer activity and during all pre-defined time periods, duodenal ulcer patients had significantly higher gastric acidity than healthy control subjects. Duodenal ulcer patients showed a similar circadian pattern of intragastric acidity during exacerbation of ulcer disease and in remission during the early and late ulcer healing periods. These results argue against a direct relation between the activity of duodenal ulcer disease and gastric acidity. It is concluded that the chronic recurrent course of duodenal ulcer disease does not result from a fluctuation in intragastric acidity.

It has been shown in several studies that duodenal ulcer patients, as a group, secrete more acid than normal subjects.¹⁻⁸ Nonetheless, the precise role of gastric acid secretion in the pathogenesis of peptic ulcers is poorly defined. Duodenal ulcer disease is characterised by a chronic recurrent course. Whether intragastric acidity fluctuates in relation to the activity of the ulcer disease remains controversial. Some studies have shown little variation in relation to ulcer activity,^{9,10} while others show a fall in acid secretion during remission.¹¹⁻¹³ To elucidate further the relation between gastric acidity and duodenal ulcer activity more investigations are needed.

A new technique for continuous intragastric pH measurement that allows in vivo assessment of gastric acidity has recently been introduced.^{14,15} This method is highly reproducible and is able to detect consistent changes in pH of >0.1 units. The circadian pattern of gastric acidity has not previously been evaluated in the same patient during exacerbation and remission of duodenal ulcer disease. We have, therefore, studied the variations in intragastric acidity over 24 hour periods in duodenal ulcer patients during active and inactive disease. The pH profiles were compared with those of healthy

subjects. In addition the response to anti-secretory treatment was evaluated.

Methods

PATIENTS AND SUBJECTS

Informed written consent was obtained from each patient and control subject participating in this study, which was approved by the hospital ethics committee. Twenty five duodenal ulcer patients with endoscopically confirmed acute ulceration (ulcer size >5 mm in diameter) were entered into a prospective study of 24 hour gastric acidity. Four patients were lost during follow up, leaving 21 patients for final analysis. A patient number of at least 15 was calculated to allow a detection of consistent pH changes of >0.15 for predefined time periods.¹⁵ The characteristics of the patients are shown on Table I. None of the patients had had previous gastric surgery or had taken any medication during the previous two weeks. All duodenal ulcer patients had at least one ulcer relapse.

Intragastric pH was monitored on four separate occasions: (a) in the presence of an ulcer crater without treatment (within 48 hours of endoscopic confirmation); (b) during active ulceration being treated with 300 mg ranitidine, administered as a single dose at 6 pm for six weeks (five to seven days after beginning of therapy); (c) during early healing (one week after stopping therapy); (d) during late healing (six months after acute ulceration). Upper gastrointestinal endoscopy (Olympus GIF Q 20, Olympus Corp) was performed at the beginning of the study and again six weeks and six months later.

In four patients, ulcer healing was incomplete after a six week course of ranitidine. Three of these patients had large ulcers (>1 cm) and all were *Helicobacter pylori* positive. These patients were excluded from the third pH study (early

TABLE I Characteristics of duodenal ulcer patients and of healthy subjects

	Duodenal ulcer	Control
No	21	20
Men/women	14/7	13/7
Age (yrs), (mean (SD))	45 (10)	39 (11)
Body weight (kg), (mean (SD))	70 (8)	72 (10)
Smokers	14	12
Duration of disease (yrs), (mean (SD))	10.5 (11)	—
No of relapses (mean (SD))	3.4±(2.9)	—
Ulcer size (diameter, mm), (mean (SD))	8.9 (2.9)	—
<i>Helicobacter pylori</i> positive	19	*
Gastrin (pg/ml), (mean (SD))	36 (8)	*

*Not determined.

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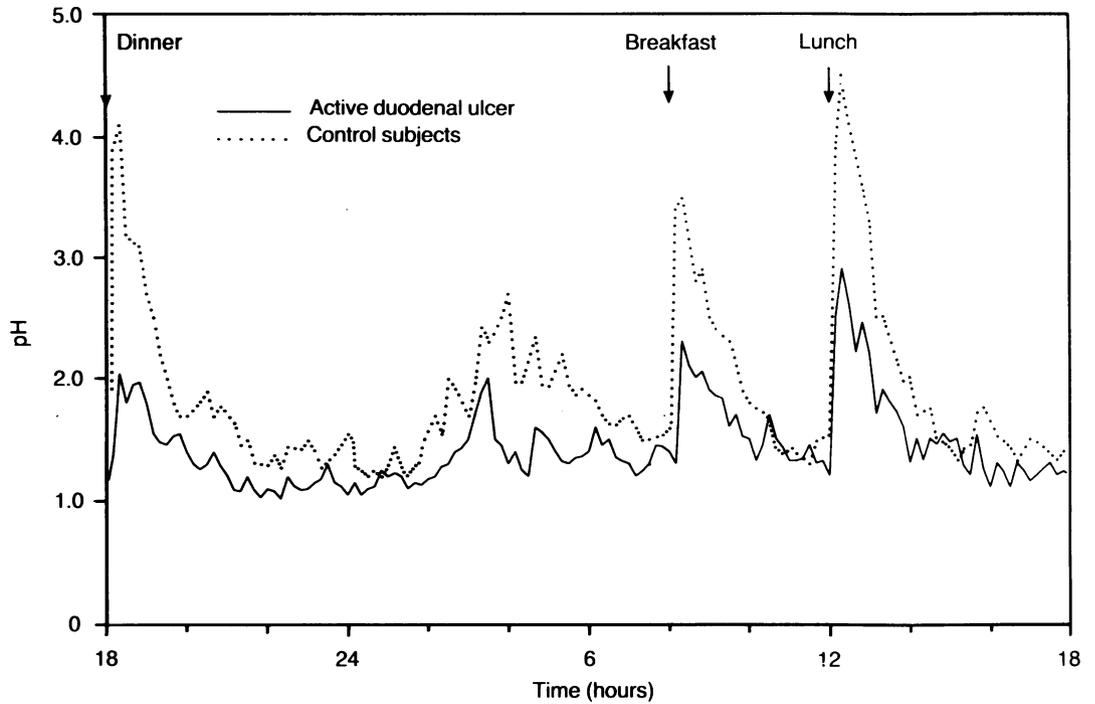


Figure 1: Median 24 hour pH profiles of duodenal ulcer patients (acute ulceration) and healthy controls.

healing) and were treated for another six weeks, after which time ulcer healing was endoscopically proved in all but one. Five patients showed an ulcer relapse at endoscopy after six months. All were *H pylori* positive, but they did not differ in age, sex, or smoking habits from those who remained in remission. Two of the slow healing ulcers relapsed at six months. The five patients with ulcer recurrence were excluded from the final pH study. At six months the drinking and smoking habits in the duodenal ulcer patients had remained unchanged.

Intragastric pH was also measured in a group of 20 asymptomatic volunteers (Table I) consisting of healthy students and hospital staff. None of the subjects had a history of gastrointestinal diseases or was taking any medication. Routine physical examination was normal in all cases.

pH MONITORING

Intragastric pH was measured with a combined glass electrode (Ingold type 440 M4, Ingold AG, Urdorf Switzerland) connected to a portable

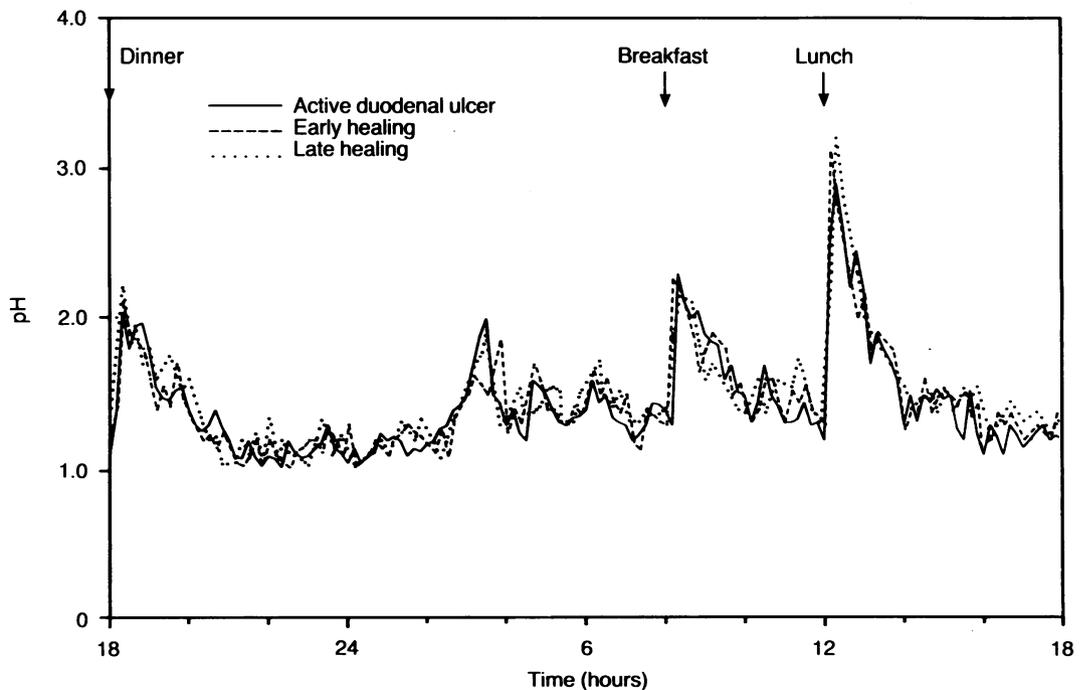


Figure 2: Median 24 hour pH profiles of duodenal ulcer patients during acute ulceration, early healing (7 weeks later), and late healing (6 months later).

TABLE II Median pH and interquartile ranges for different time periods in duodenal ulcer (DU) patients and healthy subjects. Influence of disease activity and response to treatment

	24 hour (6 pm–6 pm)	Evening (6 pm–10 pm)	Night (10 pm–6 am)	Morning (6 am–12 am)	Afternoon (12 am–6 pm)
Control* (n=20)	1.70 (1.47–2.00)	1.94 (1.62–3.10)	1.55 (1.39–1.98)	1.69 (1.53–1.94)	1.71 (1.48–2.00)
Active DU (n=21)	1.33 (1.20–1.53)	1.39 (1.21–1.55)	1.22 (1.13–1.40)	1.45 (1.32–1.65)	1.46 (1.24–1.66)
Early healing† (n=17)	1.42 (1.27–1.60)	1.50 (1.20–1.68)	1.30 (1.16–1.46)	1.53 (1.40–1.71)	1.53 (1.37–1.68)
Late healing‡ (n=16)	1.39 (1.20–1.58)	1.37 (1.18–1.58)	1.25 (1.12–1.40)	1.50 (1.40–1.60)	1.44 (1.30–1.65)
Active DU ranitidine (n=21)	2.65 (1.49–4.20)	3.60 (3.30–3.85)	5.55 (4.20–5.97)	1.65 (1.47–2.40)	1.42 (1.29–1.70)

* $p < 0.001$ or less, control *v* all DU groups for any time period.

†Not significant, early healing *v* active DU and late healing; of 21 patients 4 ulcers failed to heal, these patients were excluded resulting in 17 pH measurements.

‡Not significant, late healing *v* active DU and early healing; 5 patients had an ulcer relapse, these patients were excluded resulting in 16 pH recordings.

solid state recorder (Ditrappor 6200 MII, Synectics Medical, Stockholm, Sweden). The pH measuring unit was calibrated at 37°C using standard buffer solutions of pH 6.70 and 1.11 (Synectics Medical). After each run, calibration was repeated for assessment of the drift of the electrode. One of the total of 95 pH studies was repeated because of inaccuracy of the electrode.

All study subjects were admitted to our gastrointestinal unit at 5 pm having fasted since 3 pm. The electrode was placed fluoroscopically in the gastric corpus (8–10 cm below the cardia). The distance between the tip and the nostrils was recorded and kept constant for repeated studies in each subject. Measurement began at 6 pm and lasted for 24 hours. All subjects were ambulatory. The conditions were standardised as to meal timing and composition (dinner at 6 pm: 100 g bread, 40 g ham, 40 g ham, 40 g cheese, 20 g butter, 150 g yoghurt; breakfast at 8 am: 2 rolls, 20 g butter, 30 g jam, 2 cups of coffee with cream, 150 g yoghurt; lunch at noon: 100 g bread, 20 g butter, 40 g ham, 40 g cheese, 200 g pudding (total energy content: 8275 kJ)). Water and unsweetened tea were allowed during meals, but no food or liquids were allowed between meals. Normal daily activities were unrestricted. All study subjects marked their

TABLE III Area under the curve of the 24 hour pH profiles of healthy subjects and of duodenal ulcer (DU) patients with active and inactive ulcer disease

	Control	Active DU	Early healing	Late healing	Active DU, ranitidine
Mean	1386*	1036†	1070†	1044†	2285*
SD	277	282	321	268	450

* $p < 0.05$, control *v* all DU groups; active DU plus ranitidine *v* all DU groups.

†Not significant, active DU *v* early healing and late healing.

activities, meals, and special events in a diary card.

DATA PROCESSING AND STATISTICS

The pH measurements were stored every four seconds (21 600 readings) and the collected data were transferred to an IBM computer (AT 286). The recorded data were analysed for predefined time periods (total 24 hours: 6 pm–6 pm, evening: 6 pm–10 pm, night: 10 pm–6 am, morning: 6 am–12 am, afternoon: 12 am–6 pm) using a commercial computer program (Oesophogram Ver 5.40 and StatpHac Ver 2.14, Synectics Medical). Median pH and median hydrogen ion activity and interquartile ranges were calculated for individuals and groups. For graphic presentation, the medians of pH values averaged over 10 minute periods were used. In the duodenal ulcer patients all time periods during the different study days were compared using the matched pairs Wilcoxon signed rank test. Differences between the different time periods of duodenal ulcer patients and healthy control subjects were assessed by Wilcoxon's rank sum test. In addition, the integrated area under the curve (AUC) for each 24 hour pH profile was calculated using the trapezoidal rule. AUCs were compared using the Wilcoxon matched pairs signed rank test within the duodenal ulcer group and the rank sum test for comparison of control subjects and duodenal ulcer patients. Probability values $p < 0.05$ were considered significant.

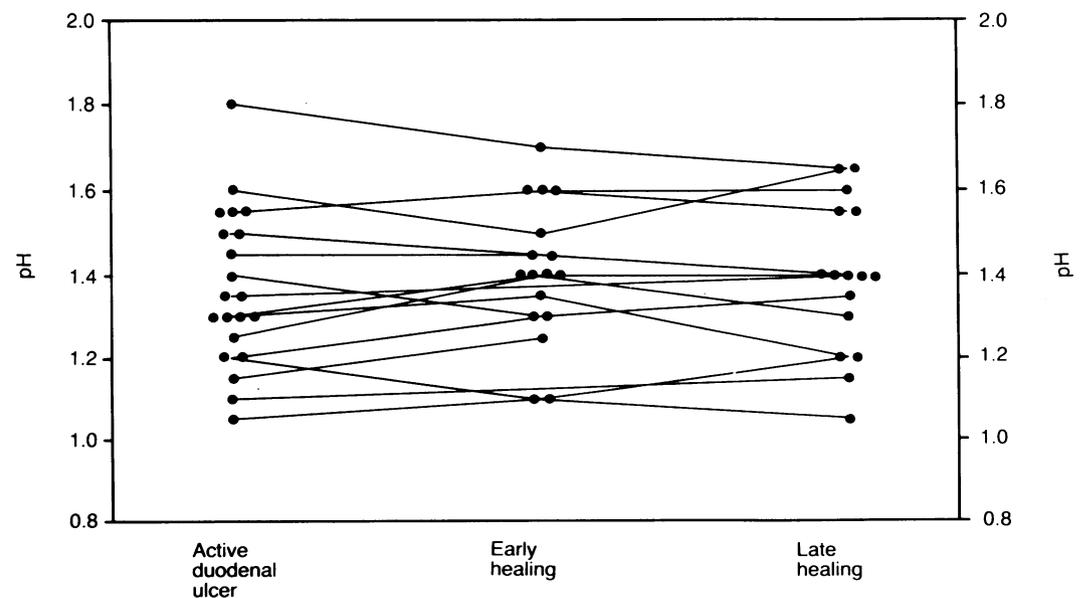


Figure 3: Median 24 hour pH values for all duodenal ulcer patients during active and inactive disease.

GASTRIN ASSAY AND *H pylori* STATUS

A fasting blood sample was obtained from the duodenal ulcer patients before treatment for measurement of serum gastrin by a commercial radioimmunoassay (Becton Dickinson, Heidelberg, West Germany). *H pylori* status was assessed by bacterial culture, a modified Giemsa stain, and a urease test (CLO-test, Delta West, Bentley, Australia) using antral biopsy specimens.¹⁶ Of five antral biopsy specimens, two were taken for histology, two for bacterial culture, and one for the urease test.

Results

Twenty four hour acidity was analysed in 21 duodenal ulcer patients and 20 healthy control subjects. Both groups were reasonably comparable, although mean age was somewhat lower in the control group (Table I). Nineteen of the 21 duodenal ulcer patients showed colonisation of gastric mucosa with *H pylori*. Basal gastrin values were in the normal range. The 24 hour profiles of median pH of both groups are shown in Figure 1. The profile of duodenal ulcer patients resembled that of healthy subjects. In contrast to controls, however, duodenal ulcer patients showed only a small postprandial rise in gastric pH. During the fasting nocturnal period, gastric pH was constantly lower in the duodenal ulcer group. Both groups showed a rise in gastric pH late at night. A quantitative analysis of the pH profiles showed that intragastric pH was significantly lower in duodenal ulcer patients during all predefined time periods (Tables II and III). However, 35% of the duodenal ulcer patients were in the interquartile range of the normal group (data not shown). Median 24 hour hydrogen ion activity (interquartile range) was 20 (10.0–33.9) mmol/l in control subjects and 47 (29.5–63.1) mmol/l, 38 (25.1–53.7) mmol/l, and 41 (26.3–63.1) mmol/l

in duodenal ulcer patients with active disease and early and late healing respectively.

Figure 2 shows the pH profiles of duodenal ulcer patients during different stages of ulcer disease. Gastric acidity was not significantly different in the presence or absence of an ulcer crater (Table II). Moreover, gastric pH was essentially the same shortly after healing of a crater and six months later. The integrated AUCs of the 24 hour pH profiles of the duodenal ulcer patients were similar in all stages of ulcer disease, but were significantly lower than those of the healthy controls (Table III). The individual median 24 hour pH values of all duodenal ulcer patients are shown in Figure 3.

Figure 4 illustrates the response to anti-secretory treatment in duodenal ulcer patients. In the presence of ranitidine, an appreciable decline in nocturnal acidity was observed. The profile showed a biphasic curve, with a more accentuated rise in pH after midnight. The antisecretory effect disappeared in the morning hours. Quantitative analysis of the response to treatment is shown in Table II for different time periods.

Discussion

This study confirms the finding of increased intragastric acidity in duodenal ulcer patients compared with healthy controls.^{1,2,5,6,8,17,18} In agreement with previous studies,^{5,17-19} both healthy subjects and duodenal ulcer patients showed a circadian rhythm in gastric acidity, with high acidity concentrations in the late evening and in the first half of the night and reduced acidity in the second half of the night. The reason for the decline in acidity late at night is unknown and could result from either a reduced acid secretion rate or increased duodenogastric reflux of alkaline duodenal juice.¹⁴

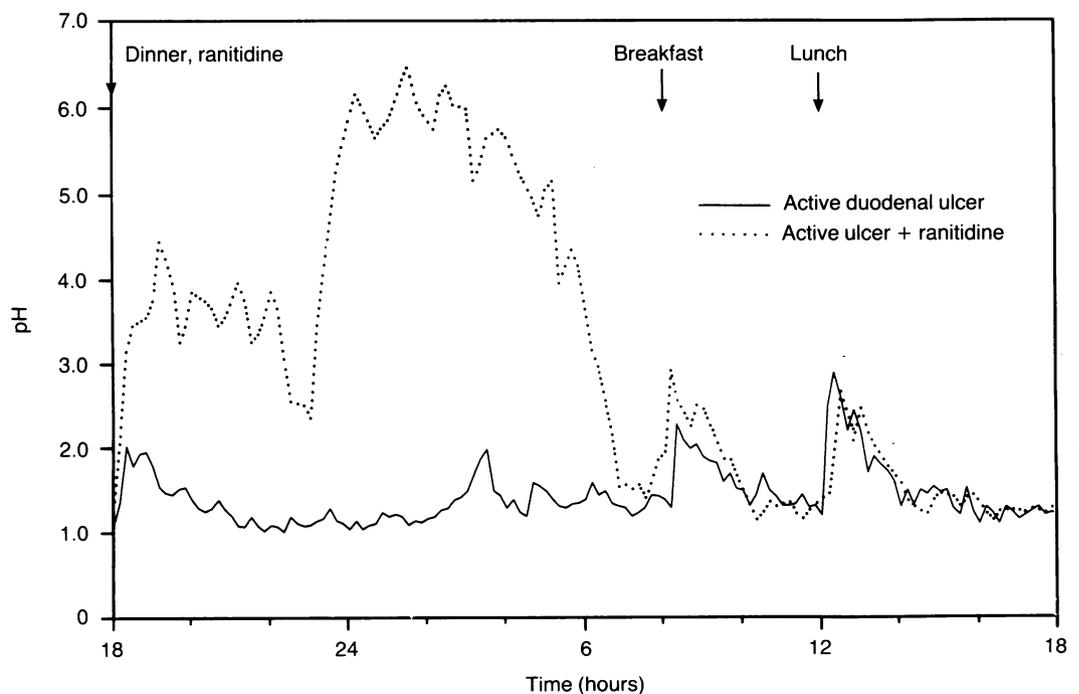


Figure 4: Median 24 hour pH profiles of duodenal ulcer patients with acute ulceration. Response to treatment with 300 mg ranitidine.

Significant differences between the acidity of duodenal ulcer and normal subjects were found during all the time periods studied, but were most prominent during evening and early night. Nevertheless, there was no clear separation between the median 24 hour acidity of both groups. Some 35% of the values of duodenal ulcer patients fell in the interquartile range of the normal group values. A somewhat smaller overlap in acidity (25%) has been found in a recent study by Merki *et al* who used a similar pH measuring technique.¹⁸ By means of acid secretory tests, which take into account the volume of acid secreted, Feldman *et al* have shown that about half of their American duodenal ulcer patients have a normal acid secretion.⁷

The duodenal ulcer patients showed an attenuated postprandial rise in gastric pH. Several factors may contribute to this finding. Duodenal ulcer patients may have a larger amount of acidic gastric juice already present in the stomach resulting in a smaller buffering effect of food.¹⁸ Since our pH measuring technique monitors intragastric pH, but ignores differences in the intragastric volume and acid output, this hypothesis cannot be examined further in our study. The acid secretory response to the meal has been shown to be higher in patients with duodenal ulcer,^{3,4,20} however, contradictory results have recently been reported.⁶ Finally, gastric emptying has been shown to be accelerated in duodenal ulcer patients, resulting in a shorter buffering effect of the food.^{3,21}

Single dose treatment with ranitidine in the evening resulted in a sustained suppression of nocturnal acidity, as has been shown in previous studies.²²⁻²⁵ The nocturnal pH profile was characterised by a biphasic curve, with a more accentuated rise after midnight. The reason for this type of pH pattern is not clear. Similar pH curves have been obtained in previous studies with early evening administration of the H₂ antagonist,^{23,26} whereas bedtime administration was accompanied by a monophasic pH curve.^{24,26} The interaction with food may be responsible for this biphasic antisecretory effect of the H₂ blocker.^{27,28}

Because there is a controversy over the existence of fluctuation in gastric acidity with different stages of ulcer disease, we addressed this question in more detail. Intragastric pH was monitored several times in the same subject: during active ulceration, shortly after the absence of a crater (early healing), and six months later during endoscopically proved remission (late healing). Our investigations showed that there was hyperacidity during exacerbation of ulcer disease and in remission as well. There were no significant differences between the early and late ulcer periods. These findings suggest that the chronic recurrent course of duodenal ulcer disease does not result from a fluctuation in intragastric acidity. Our results are supported by a very recent study by Hölscher *et al*, who failed to detect significant differences between active and healed duodenal ulcers by acid secretory tests and ambulatory pH monitoring.²⁹

The reason for the discrepancy in published

reports relating gastric acidity to duodenal ulcer activity is not clear. Many previous reports have compared gastric acidity or acid secretion during active and inactive ulcer disease using two different duodenal ulcer populations studied at one stage of their disease only. Interpretation of these results is complicated by the large variability in acidity between individual duodenal ulcer subjects, as has been shown in this and previous studies.^{5,17} Therefore, the study design should include prospective follow up of individual duodenal ulcer patients at different stages of ulcer disease. Many of the older reports did not prove the presence of an ulcer crater by endoscopy, which is the only reliable method of determining disease activity. We have used 24 hour pH monitoring for assessment of intragastric acidity, since this method allows measurement of the circadian pattern of acidity under real life conditions.¹⁴ Although the volume of acid output is ignored by this method, the pH profile reflects periods of basal – for example, night time – and stimulated (postprandial) acid secretion. The lack of difference in acidity between active and healed ulcers in this study cannot be attributed to an inaccuracy in the measuring technique as it was possible to detect highly significant differences between ulcer patients and healthy control subjects. Moreover, Merki *et al* have recently shown that 24 hour pH monitoring has a high day to day reproducibility and is able to detect consistent changes in pH of >0.1 units.¹⁵ Therefore, it is very unlikely that a consistent difference between active and healed ulcers would have been missed by our pH measuring technique.

As fluctuation in gastric acidity does not seem to be responsible for the chronic recurrent course of duodenal ulcer disease, what other factors might cause the relapse of peptic duodenal ulcers? It is generally agreed that an ulcer crater is the result of an imbalance between aggressive digestive factors – for example acid and pepsin – and protective mucosal mechanisms – such as microcirculation, mucus and bicarbonate secretion, and epithelial regeneration. A variation in gastric pepsin secretion in relation to disease activity has been reported previously.^{13,30-32} Duodenal bicarbonate secretion is impaired in duodenal ulcer patients,³³ but a direct relation between disease activity and bicarbonate secretion has not been found.³⁴ Recently, gastric or duodenal mucosal colonisation, or both, with *H pylori* has been suggested as a factor in the pathogenesis of duodenal ulcer disease, since eradication of *H pylori* was accompanied by a significant reduction in the duodenal ulcer relapse rate.³⁵⁻³⁷ The precise pathogenic role (if any) of *H pylori* in duodenal ulcer disease has not, however, been established. Further investigations are therefore needed to clarify the factors defining the natural history of this disorder.

In conclusion, our data show that, overall, duodenal ulcer patients have higher circadian gastric acidity than healthy people. Hyperacidity is present both during exacerbation of ulcer disease and in remission, showing similar acidity in the early and late ulcer healing periods. We conclude that the chronic recurrent course of

duodenal ulcer disease does not result from a fluctuation in intragastric acidity.

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