- 12 Periti M, Salvaggio A, Quaglia G, Marizio LD. Coffee consumption and blood pressure: an Italian study. *Clin Sci* 1987;72:443-7.
- 13 Salvaggio A, Periti M, Miano L, Zambelli C. Association between habitual coffee consumption and blood pressure. *J Hypertens* 1990;8:585-90.
- 14 Bertrand CA, Pomper I, Hillman G, Duffy JC, Michell I. No relation between coffee and blood pressure. *N Engl J Med* 1978;299:315-6.
- 15 Klatzky AL, Friedman GD, Armstrong MA. The relationship between alcoholic beverage use and other traits to blood pressure: a new Kaiser Permanente study. *Circulation* 1986;73:628-36.
- 16 Dusseldorp M, Smits P, Thein T, Katan M. Effect of decaffeinated versus regular coffee on blood pressure: a 12 week double-blind trial. *Hypertension* 1989;14:563-9.
- 17 Bak AAA, Grobbee DE. A randomized study on coffee and blood pressure. *J Hum Hypertens* 1990;4:259-64.
- 18 Robertson D, Hollister AS, Kincaid D, Workman R, Goldberg MR, Tung C, et al. Caffeine and hypertension. *Am J Med* 1984;77:54-60.
- 19 O'Brien E, Mee F, Atkins N, O'Malley K. Accuracy of the Spacelabs 90207 determined by the British Hypertension Society protocol. *J Hypertens* 1991;9:573-4.
- 20 Coates A, Conway J, Somers V, Isea J, Sleight P. Ambulatory blood pressure monitoring in the assessment of antihypertensive therapy. *Cardiovascular Drugs and Therapy* 1989;3:303-11.
- 21 O'Brien E, Mee F, Atkins N, O'Malley K. Inaccuracy of the Hawksley random zero sphygmomanometer. *Lancet* 1990;336:1465-8.
- 22 Lelo A, Miners JO, Robson R, Birkett DJ. Assessment of caffeine exposure: caffeine content of beverages, caffeine intake and plasma concentrations of methylxanthines. *Clinical Pharmacology and Therapeutics* 1986;39:54-9.
- 23 Armitage P. *Statistical methods in medical research*. Oxford: Blackwell, 1971.
- 24 Conway J, Coates A. Values of ambulatory blood pressure monitoring in clinical pharmacology. *J Hypertens* 1989;7(suppl 3):29-32S.
- 25 Bonati M, Latini R, Galletti F, Young JF, Tognoni G, Garattini S. Caffeine disposition after oral doses. *Clinical Pharmacology and Therapeutics* 1982;32:98-106.
- 26 Grobbee DE, Rimm EB, Giovannucci E, Colditz G, Stampfer M, Willett W. Coffee, caffeine and cardiovascular disease in men. *N Engl J Med* 1990;323:1026-32.

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Eradicating *Helicobacter pylori* and symptoms of non-ulcer dyspepsia

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Abstract

Objective—To examine the effect of eradication of *Helicobacter pylori* on symptoms of non-ulcer dyspepsia.

Design—Four week prospective study.

Setting—One hospital outpatient and endoscopy department.

Patients—90 adults with persistent symptoms typical of non-ulcer dyspepsia but no clinical or endoscopic evidence of other peptic, biliary, pancreatic, or malignant disease; all had histological and microbiological evidence of infection with *H pylori*. 83 patients completed the treatment regimen.

Intervention—Colloidal bismuth subcitrate 120 mg four times a day for four weeks (27 patients); metronidazole 400 mg and amoxycillin 500 mg each three times a day for one week (27); and bismuth subcitrate 120 mg four times a day for four weeks, metronidazole 400 mg three times a day for one week, plus amoxycillin 500 mg three times a day for the first week (29).

Main outcome measures—Change in symptom scores determined with questionnaire; histological evidence of gastritis and microbiological evidence of presence of *H pylori* in biopsy specimens.

Results—Overall, *H pylori* was eradicated in 41 (49%) patients. Although gastritis scores improved significantly in only patients in whom *H pylori* had been eradicated (from 1.56 to 0.61, $p < 0.01$ v from 1.83 to 1.07, $p = 0.52$) mean symptom scores after treatment were similar in patients in whom *H pylori* had or had not been eradicated (3.0 v 2.3, NS). Similarly the mean symptom score improved whether or not gastritis improved (2.8 v 3.1 respectively, $p = 0.72$). The observations were similar for treatment groups analysed individually.

Conclusion—Antral infection with the organism does not seem to have an important aetiological role in non-ulcer dyspepsia short term.

Introduction

The discovery of *Helicobacter pylori* and its close association with chronic active gastritis^{1,2} and peptic ulcer disease^{3,4} had led to speculation that it may have a role in causing symptoms of non-ulcer dyspepsia. In Europe non-ulcer dyspepsia accounts for almost a third of all gastroenterological referrals⁵ and up to a quarter of all general practice consultations.⁶ The definition of the non-ulcer dyspepsia syndrome varies widely, making comparison of studies of non-ulcer dyspepsia difficult. In 1988 an international working party defined

non-ulcer dyspepsia as "upper abdominal or epigastric pain, discomfort, heartburn, nausea, vomiting, or other symptoms considered to be referable to the upper gastrointestinal tract, and lasting for more than four weeks, unrelated to exercise and for which no focal lesion or systemic disease can be found responsible."⁷ Clearly, patients with the syndrome constitute a heterogeneous group for whom no effective treatment is available at present. The higher prevalence of *H pylori* in patients with non-ulcer dyspepsia compared with age matched blood donors supports the theory that *H pylori* has an important role in the aetiology of non-ulcer dyspepsia.⁸ *H pylori*, however, is also common in the asymptomatic population,⁹ and its prevalence varies with age and ethnic group.¹⁰ Therefore, in an attempt to show whether *H pylori* plays an important part in the pathogenesis of non-ulcer dyspepsia we carried out a prospective study to examine the effect of eradication of *H pylori* on symptoms and histological appearance of the gastric antrum in patients with non-ulcer dyspepsia in whom *H pylori* was cultured.

Patients and methods

All patients referred to our endoscopy department over six months for investigation of persistent symptoms consistent with non-ulcer dyspepsia were considered suitable for the study. The study was approved by the medical ethics committee of the Meath and Adelaide Hospitals, and informed consent was obtained from all patients. Only patients with histological and microbiological evidence of infection with *H pylori* and with persistent symptoms of at least two months' duration were included in the study. Patients with evidence of active or previous peptic ulcer disease, gall bladder disease, oesophagitis, malignancy, or previous abdominal surgery were excluded, as were patients receiving non-steroidal anti-inflammatory agents or those who had taken antibiotics up to four weeks before the start of the study. Pregnant women were also excluded. All patients were examined by endoscopy at entry and again at four weeks after completion of treatment to check for eradication of *H pylori*. Endoscopy was performed with an Olympus Q10 gastroscope and on each occasion two biopsy specimens were taken from the gastric antrum for histological and microbiological examinations. In total, 90 patients were enrolled during the study period, and each was sequentially allocated one of three treatment regimens: (a) colloidal bismuth subcitrate 120 mg four times a day for four weeks; (b) metronidazole 400 mg and amoxycillin 500 mg each three times a day for one

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week; and (c) colloidal bismuth subcitrate 120 mg four times a day for four weeks and metronidazole 400 mg three times a day for one week, plus amoxycillin 500 mg three times a day for the first week. *H pylori* was considered to have been eradicated if antral biopsy specimens showed negative results histologically and microbiologically four weeks after treatment was completed.

Assessment of symptoms—Patients' symptoms were evaluated before the start of treatment and again immediately before repeat endoscopy. Evaluation consisted of a previously validated questionnaire in which the presence and severity of six symptoms of dyspepsia (night pain, day pain, bloating, flatulence, heartburn, nausea, and vomiting) were assessed. Each symptom was scored numerically from 0 to 4, where 0 indicated absence of the symptom and 4 severe and incapacitating symptoms. All assessments were performed by the same person (SB), who was unaware of the treatment received or of the *H pylori* status after treatment.

Histological examination—One of the two gastric biopsy specimens was fixed in 10% buffered formalin, embedded in paraffin, and sectioned. The sections were subsequently stained with haematoxylin and eosin to detect *H pylori* and histological evidence of gastritis. The Warren Marshall classification for gastritis was used to grade the severity of gastritis (0 normal, 1 mild round cell infiltrate, 2 massive round cell infiltrate with or without polymorphonuclear leucocyte infiltrate but without epithelial migration or destruction, 3 polymorphonuclear leucocyte infiltration of the epithelial layer with or without glandular destruction).

TABLE 1—Characteristics of patients with non-ulcer dyspepsia completing study

	Treatment			Total
	Bismuth	Metronidazole and amoxycillin	Bismuth and metronidazole plus amoxycillin	
No of patients	27	27	29	83
Mean (range) age (years)	59.1 (24-77)	54.3 (23-68)	56.4 (22-69)	56.3 (22-77)
No of men/women	7/22	8/19	8/19	23/60
Mean duration of symptoms (months)	4.1	3.1	3.5	3.6

TABLE 2—Eradication rates of *H pylori* infection after treatment

Treatment	Patients negative for <i>H pylori</i>	Patients positive for <i>H pylori</i>	Eradication rate (%)
Bismuth (n=27)	10	17	37
Metronidazole and ampicillin (n=27)	15	12	56
Bismuth and metronidazole plus amoxycillin (n=29)	16	13	55
Total	41	42	49

TABLE 3—Mean symptom scores for non-ulcer dyspepsia before and after treatment, by each treatment

	Treatment			Total
	Bismuth	Metronidazole and amoxycillin	Bismuth and metronidazole plus amoxycillin	
Before treatment	8.44	5.67	6.31	6.80
After treatment	3.14	2.67	1.83	2.61

TABLE 4—Mean symptom scores for non-ulcer dyspepsia before and after treatment according to histological results and presence of *H pylori* after treatment

	Positive for <i>H pylori</i> (n=42)	Negative for <i>H pylori</i> (n=41)	Gastritis unchanged (n=28)	Gastritis improved (n=55)
Before treatment	6.69*	6.95†	6.91	7.1
After treatment	3.0*	2.3†	3.1	2.8

*p=0.015. †p=0.01.

Microbiological examination—The second biopsy specimen was placed immediately in nutrient broth transport medium and sent to the microbiology department for culture. A smear of the specimen was examined for *H pylori* and the remainder of the sample was inoculated on to chocolate agar and incubated at 37°C in a microaerophilic environment for five days. The growth of small translucent colonies positive for urease (on incubation in Chrisensen's urea medium) was taken as evidence of *H pylori*.

Statistical analysis—The effect of treatment on gastritis scores and symptom scores was analysed with Student's *t* test. *p* Values of <0.05 were taken as significant in all analyses.

Results

Eighty three patients completed the treatment regimen (23 men and 60 women, mean age 56.3 years, range 22 to 77 years). Seven patients failed to complete the study: five showed a subjective improvement and were thus unwilling to undergo repeat endoscopy (three receiving bismuth and two receiving metronidazole and amoxycillin) and two had intercurrent illness (one patient receiving metronidazole and amoxycillin had a road traffic accident and one receiving bismuth and metronidazole and amoxycillin had a malignancy). All three groups were similar with regard to sex, mean age, and mean duration of symptoms (table I).

A total of 41 (49%) patients showed eradication of *H pylori* infection with treatment; table II shows the eradication rates for the individual treatment groups.

An improvement of gastritis was observed histologically in all three treatment groups. Overall the mean gastritis scores fell from 1.70 (SD 0.21) to 0.84 (0.08) (*p*<0.05). The improvement, however, correlated significantly with eradication of *H pylori*. In patients in whom the infection was eradicated the mean gastritis score fell significantly from 1.56 to 0.61 (*p*<0.01), and in those who remained infected it fell from 1.83 to 1.07 (*p*=0.52). This observation was similar when all three treatment groups were analysed individually.

For the 83 patients who completed the study the mean symptom score was significantly reduced four weeks after completion of treatment. (Mean score before treatment 6.80, after treatment 2.61, *p*<0.01). In addition, all three treatment regimens achieved a similar reduction in symptoms (table III). When patients were divided according to the presence of *H pylori* after treatment, however, a significant reduction in mean symptom scores was seen in both groups (table IV). Thus improvement of symptoms was independent of eradication of *H pylori*. In addition, the mean treatment scores after treatment were not significantly different among the individual regimens (*p*=0.3). Improvement in symptoms was also independent of improvement in gastritis histologically. Thus the mean symptom score after treatment was not significantly different in patients whose gastritis improved histologically and those whose gastritis remained unchanged (2.8 *v* 3.1, *p*=0.72).

Discussion

Currently there is little doubt that *H pylori* has an important role in the development of chronic active gastritis and that it is also associated with duodenal ulcer. There is also substantial evidence that acute *H pylori* infection can produce self limiting symptoms in some people.^{2,11} The relation between chronic *H pylori* infection and symptoms of dyspepsia, however, remains to be clarified. Several investigators have reported that the eradication of *H pylori* leads to

improvement in gastritis histologically,¹²⁻¹⁴ which has been confirmed in this study. Moreover, recent reports suggest that treating patients with non-ulcer dyspepsia associated with *H pylori* with agents known to be active against the organism leads to appreciable improvement in symptoms.^{15,16} None of these studies, however, have concentrated on the effect of eradication of *H pylori* on symptoms of dyspepsia, and thus they cannot adequately explain the role of *H pylori* in the disorder.

In this study only patients found to have *H pylori* on culture and histological examination were analysed, and eradication of *H pylori* or otherwise was recorded four weeks after completion of treatment. This allows the effect of eradication of *H pylori* alone on symptoms of dyspepsia to be compared directly in a large group of patients from a single institution.

H pylori infection was eradicated after treatment in 41 of 83 patients, and, as might be expected from other treatment studies, a significant improvement in symptom score was noted. However, a similar proportion of patients (51%) remained infected after treatment and also experienced significant improvement in symptoms. Clearly, colonisation of the gastric antrum by *H pylori* is unlikely to be responsible for the symptoms experienced by this group of patients, and our findings strongly suggest that the improvement occurred by some other mechanism. It is also unlikely that this response occurred owing to a local effort of bismuth on the gastric mucosa as the antibiotics alone proved to be equally effective in reducing symptom scores. A placebo effect is thus likely, but this cannot be proved in the setting of this study.

As expected, eradication of *H pylori* and improvement in gastritis histologically were significantly correlated. However, improvement in symptoms proved to be independent of improvement of gastritis. Patients whose gastritis remained unchanged with treatment showed an improvement in symptoms similar to that of those whose gastritis improved. Thus the presence of chronic active gastritis, although strongly related to the presence of *H pylori* infection does not seem to bear a significant relation to the presence of symptoms.

In conclusion, we confirmed the close association of

H pylori infection with chronic active gastritis and that eradication of *H pylori* leads to improvement of this gastritis histologically. There seems to be no relation, however, between eradication of *H pylori* or such improvement of gastritis and improvement of symptoms of non-ulcer dyspepsia. Thus, although *H pylori* may have an important role in the pathogenesis of peptic ulcer disease, this short term study suggests that it is unlikely to do so in non-ulcer dyspepsia. Clearly, long term follow up of these patients is indicated to identify whether any future benefit of eradication of *H pylori* becomes apparent.

- 1 Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1984;i:1311-4.
- 2 Marshall B, Armstrong J, McGreiche D, Glancy R. Attempts to fulfil Koch's postulates for pyloric campylobacter. *Med J Aust* 1985;142:436-9.
- 3 Goodwin C, Armstrong J, Marshall B. Campylobacter pyloridis gastritis and peptic ulceration. *J Clin Pathol* 1986;7:206.
- 4 Coghlan JG, Gilligan D, Humphries H, McKenna D, Dooley C, Sweeney E, et al. Campylobacter pylori and recurrence of duodenal ulcers: a 12 month follow up study. *Lancet* 1987;ii:1109-11.
- 5 Adami HO, Aghasizadeh I, Gustavsson S, Lööf L, Nyberg A, Nyrén O, et al. The clinical diagnosis of "gastritis." *Scand J Gastroenterol* 1984;19:216-9.
- 6 Heatley RV, Rathbone BJ. Dyspepsia: a dilemma for doctors. *Lancet* 1987;ii:779-82.
- 7 Management of dyspepsia: report of a working party. *Lancet* 1988;i:576-9.
- 8 Marshall BJ. Campylobacter pylori: addressing the controversies. In Menge H, Gregor M, Tytgat GNJ, eds. *Campylobacter pylori*. Berlin: Springer-Verlag, 1988:235-45.
- 9 Barthel JS, Westblom TU, Havey AD, Gonzales F, Everett DE. Gastritis and campylobacter pylori in healthy asymptomatic volunteers. *Arch Intern Med* 1988;148:1149-51.
- 10 Morris A, Nicholson G, Lloyd G, Haines D, Rogers A, Taylor D. Seroprevalence of campylobacter pyloridis. *N Z Med J* 1986;99:657-9.
- 11 Morris A, Nicholson G. Ingestion of campylobacter pyloridis causes gastritis and a raised fasting pH. *Am J Gastroenterol* 1987;82:192-9.
- 12 Loffeld RJLF, Potters HVJP, Strobberingh E, Flendrig JA, van Spreenwel JP, Arends JW. Campylobacter associated gastritis in patients with non-ulcer dyspepsia: a double blind placebo controlled trial with colloidal bismuth subcitrate. *Gut* 1989;30:1206-12.
- 13 Rokkas T, Pursey C, Uzoehina E, Dorrington L, Simmons NA, Filipe MI, et al. Non ulcer dyspepsia and short term De-Nol therapy: a placebo controlled trial with particular reference to the role of campylobacter pylori. *Gut* 1988;29:1386-91.
- 14 Raus EAJ, Langenberg W, Houthoff HJ, Zanen HC, Tytgat GN. Campylobacter pyloridis associated chronic active antral gastritis. *Gastroenterology* 1988;94:33-40.
- 15 Borody T, Hennessy W, Daskalopoulos G, Carrick J, Hazell S. Double blind trial of De-Nol in non ulcer dyspepsia associated with campylobacter pyloridis gastritis [abstract 919]. *Gastroenterology* 1987;92 (suppl):1324.
- 16 Lambert JR, Dunn K, Borromeo M, Korman MC, Hanskey J. Campylobacter pylori: a role in non-ulcer dyspepsia. *Scand J Gastroenterol* 1989;160 (suppl):7-13.

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Relation between Glasgow coma scale and the gag reflex

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The airway is the foremost concern of those who treat acutely ill or traumatised patients. Avoiding hypoxia due to airway obstruction and the aspiration of vomitus are always priorities, especially in the accident and emergency department. Airway patency is normally maintained by a variety of protective and regulatory reflexes.

In the comatose patient (defined as a Glasgow coma score ≤ 8) these vital mechanisms may be compromised. The situation at higher levels of consciousness is unreported. In this prospective study we aimed to clarify the relation between the Glasgow coma scale and the gag reflex, which is the most easily and commonly tested airway reflex and the absence of which is recognised as one of the criteria for brain stem death.^{1,2}

Patients, methods, and results

The Glasgow coma score, gag reflex, and clinical details were collected for 111 patients (treated con-

secutively by the authors) requiring neurological observation in the accident and emergency department. The gag reflex was tested by pharyngeal stimulation and the response was recorded as being normal (light touch), attenuated (more vigorous stimulation required), or absent.

The table compares the Glasgow coma score and gag reflex in patients whose presentation was related to exposure to various pharmacological substances and in patients with a non-pharmacological cause for cerebral depression, usually head injuries. Both groups might have taken alcohol.

The gag reflex may be significantly attenuated, or absent, at all levels of the Glasgow coma scale. In the comatose patient (score ≤ 8) it is unlikely that the gag reflex will be normal. In more conscious patients (score > 8) the gag reflex was depressed in 64% (32/50) of patients who had been exposed to drugs but in only 8% (2/24) of head injured patients ($p < 0.05$, χ^2 test).

Comment

The Glasgow coma scale is widely accepted as an easily and accurately reproducible method of assessing conscious level. Many patients have a depressed conscious level of mixed origin, and separation of the individual components is impossible.³ A Glasgow coma score of 15 does not, however, distinguish between the