PostScript

LETTERS

Short segment reflux: acid but no pocket?

I read the paper by Fletcher and colleagues with interest. (*Gut* 2004;**53**:168–73.)

In their earlier study,[1] the group reported the existence of an unbuffered acid pocket in 60% of study subjects which extended for approximately 2 cm (median length) in the postprandial period. Furthermore, when pre and postprandial pH step up distances were measured and correlated with clips fixed to the oesophagus, this acid pocket was localised to a region ''just above'' the squamocolumnar junction. It would be fair to infer then, that if a pH sensor was firmly implanted just above the squamocolumnar junction, it would record a prolonged acid reflux event in the postprandial state as the probe would be continuously bathed in acid from this reservoir. This is distinct from intermittent acid reflux events due to transient lower oesophageal sphincter relaxations or straining.

In their more recent paper,[2] greater acid exposure at the squamocolumnar junction was found compared with a site located 5 cm proximally (standardised recording point), which intuitively is not unexpected. This is especially so if DeMeesters hypothesis (which was alluded to in the manuscript) were to be accepted which proposes that the lower oesophageal sphincter, incorporating the squamocolumnar junction, opens up and becomes part of the stomach in the postprandial period. However, the authors have stated that there was no significant difference in the mean length of acid reflux episodes when both sites were compared. This appears to be at odds with the first study as one would have expected to observe a prolonged acid reflux event at the distal oesophageal recording site (that is, just above the squamocolumnar junction). However, this was not the case. In addition, presentation of data in the results section of the current study show a distinct lack of emphasis regarding the ''acid pocket theory'' which would lead one to assume that this was not observed. How do the authors reconcile these observations from their two studies?

S Nandurkar

Correspondence to: Dr S Nandurkar, Department of Gastroenterology, Box Hill Hospital, Box Hill, VIC 3128, Australia; sanjay.nandurkar@med.monash.edu.au

References

1 **Fletcher J**, Wirz A, Young J, *et al*. Unbuffered highly acidic gastric juice exists at the gastroesophageal junction after a meal. *Gastroenterology* 2001;**121**:775–83.
2 **Fletcher J**, Wirz A, Henry E, *et al*. Studies of acid exposure immediately above the gastro-oesophageal junction: evidence of short segment reflux. *Gut* 2004;**53**:168–73.

Authors' reply

We thank Dr Nandurkar for his interest in our recent papers regarding luminal acidity at the gastro-oesophageal junction following meals.

In our first study, we observed a postprandial region of high acidity in the cardia region and extending across the Z-line.[1] The presence of this postprandial acid pocket at the cardia has been confirmed by two other groups[2 3]

In our more recent study (*Gut* 2004;**53**:168–73), we observed a high degree of acid exposure when a pH electrode was clipped to the squamous mucosa which is proximal to the Z-line.

Dr Nandurkar wondered why we did not observe more prolonged acid exposure in the second study if the postprandial acid pocket extends into the distal oesophagus. There are several reasons for the apparent differences in the two studies. The first is that the design and methodology of the two studies were different. The first study involved slowly withdrawing a pH probe at 1 cm increments every minute from the distal stomach into the oesophagus and was performed after a large fatty meal with the patient in a semirecumbent position. In contrast, the second study employed a static probe fixed to the distal oesophagus and which recorded both fasting and postprandial pH over a 24 hour ambulatory period. The difference in duration of the recording of pH in the distal oesophagus between the two studies and the differences in the relationship to food intake and in posture and mobility make it difficult to directly compare the two studies. In our second study, we did observe that the acid exposure of the most distal oesophagus was more during the postprandial period, consistent with the observations of the first study. However, we acknowledge that the duration of acid exposure of the most distal oesophagus during the postprandial period with the fixed probe was not as great as that observed in our earlier study when the probe was slowly withdrawn from the stomach into the oesophagus.

It is possible that the methodology employed in the first study could exaggerate the degree of proximal extension of the unbuffered acid pocket into the distal oesophagus. This might be due to the pH probe carrying over some acidic juice from the cardia acid pocket into the oesophagus and this taking time to be fully cleared/neutralised. It is always difficult to know the extent to which the technique used to measure physiology may be altering events.

What is clear from both of our studies and the two other groups which have undertaken similar studies is that during the postprandial period, (a) there is a region of relatively unbuffered high acidity in the proximal cardia region of the stomach and (b) this acid frequently encroaches on the distal oesophageal mucosa.[1–3]

K E L McColl
Department of Gastroenterology, University of Glasgow, Glasgow, UK

J Fletcher
Department of Gastroenterology, Borders District General Hospital, UK

Correspondence to: Professor K E L McColl, Section of Medicine, Western Infirmary, 44 Church St, Glasgow G11 6NT, UK; k.e.l.mccoll@clinmed.gla.ac.uk

References

1 **Fletcher J**, Wirz A, Young J, *et al*. Unbuffered highly acidic gastric juice exists at the gastroesophageal junction after a meal. *Gastroenterology* 2001;**121**:775–83.
2 **Hila A**, Xue S, Knuff D, *et al*. Post-prandial gastric acid layer is not only localised below the EG junction. *Gastroenterology* 2003;**124**(suppl 1): A410.
3 **Iwakiri K**, Nind G, Wu Zou D, *et al*. Regional variations in postprandial gastric pH and their relationship to acid reflux in healthy volunteers. *Gastroenterology* 2003;**124**(suppl 1):A412.

The role of age in the protection of appendicectomy against ulcerative colitis

We read with great interest the article by Hallas and colleagues (*Gut* 2004;**53**:351–4) investigating the protective role of appendicectomy in reducing hospital admission rates in patients with ulcerative colitis.

The population studied consisted of a cohort of 202 cases who underwent appendicectomy after their first admission for ulcerative colitis. A population of patients affected by ulcerative colitis who had not an appendicectomy was used as a reference cohort. The authors suggested that appendicectomy had no significant beneficial effect on hospital admission rates in patients with ulcerative colitis as no differences were found between the study and the reference cohort in the decline in hospitalisations. Mean age of the study population was 38.6 years and no stratification of data for any age was performed. Several papers[1 2] on the supposed protective role of appendicectomy against ulcerative colitis concluded that appendicectomy is associated with a low risk of subsequent ulcerative colitis only for patients who had surgery before the age of 20 years old. Hence we wondered if the results of Hallas *et al* might be different if the study population were analysed after stratification for patients younger and older than 20 years.

G L Adani, U Baccarani, A Risaliti
Department of Surgery, University Hospital Udine, Italy

Correspondence to: Dr G L Adani, Department of Surgery, University Hospital Udine, Italy; adanigl@hotmail.com

References

1 **Andersson RE**, Olaison G, Tysk C, *et al*. Appendectomy and protection against ulcerative colitis. *N Engl J Med* 2001;**344**:808–14.
2 **Kurina LM**, Goldacre MJ, Yeates D, *et al*. Appendicectomy, tonsillectomy, and inflammatory bowel disease: a case-control record linkage study. *J Epidemiol Community Health* 2002;**56**:551–4.

Author's reply

Dr Adani and colleagues pose a very interesting question. Some studies have suggested that appendicectomy only confers a prophylactic effect against ulcerative colitis (UC) if

performed before the age of 20 years. Thus it would be conceivable that the therapeutic effect (that is, ability to reduce admissions for those who already have UC) might be confined to this age group also.

Unfortunately, we cannot provide a precise answer to their question. Only 11 subjects in our cohort had their appendicectomy performed before the age of 20 years, which is far too few patients to allow a meaningful analysis. Our lack of very young subjects is probably a selection phenomenon; we required patients to have their onset of UC before their appendicectomy. As it is unlikely that a person would experience both the onset of UC and an appendicectomy (in that order) before the age of 20 years, eligible subjects become very scarce.

If we raise the limit and examine those who had their appendicectomy before the age of 30 years, we can identify 59 index subjects and 236 reference subjects. By a method similar to the main analysis in our article, we find an adjusted incidence rate ratio of 1.20 (95% confidence interval 0.71–2.01), implying that the incidence of hospital admissions is 20% higher than expected after appendicectomy, albeit with very wide confidence intervals that do not rule out a small therapeutic effect.

In conclusion, our data to support the notion that appendicectomy would be useful against UC in young subjects.

J Hallas
Department of Internal Medicine, and Department of Medical Gastroenterology, Odense University Hospital, Denmark

D Gaist
Department of Epidemiology, Institute of Public Health, University of Southern Denmark, Denmark

W Vach
Department of Statistics and Demography, University of Southern Denmark, Denmark

H T Sørensen
Department of Clinical Epidemiology, Aarhus University Hospital and Aalborg Hospital, Denmark

Correspondence to: Dr J Hallas, Odense University Hospital, Medical Department C, Odense C DK 5000, Denmark; j.hallas@dadlnet.dk

Influence of antisecretory drugs on *Helicobacter pylori* eradication rates

We read with great interest the article by Sherwood and colleagues (*Gut* 2002;**51**:490–5) evaluating the role of acid secretion and gastric luminal pH on the gastric transfer rate of amoxycillin, clarithromycin, and metronidazole. The study showed that metronidazole and clarithromycin but not amoxicillin transfer was increased by acid secretion. Gastric acid suppression, induced by the use of omeprazole, produced the fall in clarithromycin and metronidazole transfer.

These data may help to clarify preliminary results of our study on *Helicobacter pylori* eradication in a population of 120 *H pylori* infected dyspeptic patients (63 males and 57 females; mean age 53.2 (12.31) years).[1] None of the patients received prior antibiotic treatment with nitroimidazoles or macrolides, or *H pylori* eradication therapy, nor was there a history of gastrointestinal surgery, alcohol use, or smoking.

Our population was divided in two groups of 60 patients who underwent two different 14 day triple eradicating regimens based on either ranitidine 300 mg twice daily and clarithromycin and metronidazole 500 mg twice daily (RCM group) or omeprazole 20 mg twice daily and clarithromycin and metronidazole 500 mg twice daily (OCM group).

A higher *H pylori* eradication rate was obtained in the RCM group. In fact, 54 of 60 patients had *H pylori* eradicated in the first group compared with 42 patients in the OCM group ($p<0.025$), suggesting an important impact of the antisecretory drug on the therapeutic result. Incomplete gastric acid suppression, caused by H_2 receptor antagonists, may be responsible for the difference.

While omeprazole inhibits gastric acid secretion with irreversible block of the parietal cell H^+/K^+ ATPase, the pump responsible for HCl secretion, ranitidine does not abolish gastric secretory activity completely. Ranitidine affects only the pathway mediated by activation of H_2 parietal cell receptors, thus the ''acid trapping'' mechanism and active secretion of clarithromycin and metronidazole to the gastric lumen are maintained.[2 3]

In fact, metronidazole, which is a weak base, may passively diffuse from gastric capillaries into the acid compartments (tubulovescicles and canaliculi) of parietal cells and into the gastric lumen, in accordance with the pH partition hypothesis.[4] In the acidic environment, this antibiotic becomes ionised and as such is trapped and concentrated both in the acidic compartments of the parietal cells and in the gastric lumen. Therefore, metronidazole may both passively diffuse across the gastric mucosa and be secreted to the gastric lumen with gastric acid, performing its topical anti-*H pylori* activity.

Sherwood *et al* reported that clarithromycin may also be secreted with HCl. The lower acid inhibition mediated by H_2 receptor antagonists not only maintains clarithromycin secretion with gastric acid but also contributes to the molecular stability of this antibiotic.[5]

Despite the fact that proton pump inhibitors are usually preferred as adjuvants for antibiotic therapy against *H pylori*, because of their greater effectiveness on acid suppression and the additional antibacterial effect, recent meta-analytical papers have shown no difference between proton pump inhibitors and H_2 receptor antagonists in improving *Helicobacter* eradication rates.[6]

In conclusion, our clinical results support the hypothesis that inhibition of gastric acid decreases gastric clearance of metronidazole and clarithromycin, reducing the therapeutic effectiveness of triple eradicating regimens.

M Pellegrini
Division of Gastroenterology and Digestive Endoscope, University of Siena, Italy

R Urso, G Giorgi, D Cerretani
''G Segre'' Department of Pharmacology, University of Siena, Italy

Correspondence to: Dr M Pellegrini, Division of Gastroenterology and Digestive Endoscopy, University of Siena, Italy; gastro.unisi@email.it

References

1 **Pellegrini M**, Cerretani D, Lisi L, *et al*. Influence of antisecretory drugs on metronidazole pharmacokinetics and therapeutic efficacy in Helicobacter pylori eradication. *Dig Liver Dis* 2003;**35**(suppl 4):S58.
2 **Goddard AF**, Jessa MJ, Barrett DA, *et al*. Effect of omeprazole on the distribution of metronidazole, amoxycillin and clarithromycin in human gastric juice. *Gastroenterology* 1996;**111**:358–67.
3 **Goddard AF**, Spiller RC. In vitro assessment of gastric mucosal transfer of anti-Helicobacter therapeutic agents. *Antimicrob Agents Chemother* 1997;**41**:1246–9.
4 **Shore PA**, Brodie BB, Hogben CAM. The gastric secretion of drugs: a pH partition hypothesis. *J Pharm Exp Ther* 1956;**119**:361–9.
5 **Erah PO**, Goddard AF, Barrett DA, *et al*. The stability of amoxycillin, clarithromicyn and metronidazole in gastric juice: relevance to the treatment of Helicobacter pylori infection. *J Antimicrob Chemother* 1997;**39**:5–12.
6 **Graham DY**, Hammoud F, El-Zimaity HMT, *et al*. Meta-analysis: proton pump inhibitor or H2-receptor antagonist for Helicobacter pylori eradication. *Aliment Pharmacol Ther* 2003;**17**:1229–36.

Authors' reply

We thank Dr Pellegrini *et al* for their interest in our article (*Gut* 2002;**51**:490–5).

As they correctly point out, the very effective inhibition of acid secretion may interfere with acid trapping and thus decrease antibiotic transfer into the gastric juice. However, the final antibiotic concentration in gastric juice depends on both the rate of secretion and the rate of degradation. Although metronidazole and amoxycillin are stable in gastric juice, clarithromycin is not,[1] hence more effective inhibition of acid secretion will tend overall to increase the concentration of undegraded clarithromycin. The acid degradation product has some antibacterial effect which also needs to be considered.

As can be seen, there are so many variables that we feel there is no substitute for actually measuring antibiotic concentrations in gastric juice on ranitidine and omeprazole, and comparing them in patients before any definite conclusions can be drawn on their relative pharmacological merits.

It is interesting that there have been relatively few clinical trials of proton pump inhibitors versus H_2 receptor antagonists for *Helicobacter* eradication, with conflicting results from the two meta-analyses.[2 3] One conclusion could be that the convention for using proton pump inhibitors has more to do with the large number of trials of proton pump inhibitor based regimens in the 1990s and the perhaps erroneous assumption that more reliable ulcer healing equates to better antibiotic drug delivery, rather than adequate evidence that proton pump inhibitors are superior.

R C Spiller, P Sherwood
University of Nottingham, Nottingham, UK

Correspondence to: Professor R C Spiller, Division of Gastroenterology, University of Nottingham, Nottingham NG7 2UH, UK; robin.spiller@nottingham.ac.uk

References

1 **Erah PO**, Goddard AF, Barrett DA, *et al*. The stability of amoxycillin, clarithromycin and metronidazole in gastric juice: relevance to the treatment of Helicobacter pylori infection. *J Antimicrob Chemother* 1997;**39**:5–12.
2 **Gisbert JP**, Khorrami S, Calvet X, *et al*. Meta-analysis: proton pump inhibitors vs. H2-receptor antagonists—their efficacy with antibiotics in Helicobacter pylori eradication. *Aliment Pharmacol Ther* 2003;**18**:757–66.
3 **Graham DY**, Hammoud F, El-Zimaity HM, *et al*. Meta-analysis: proton pump inhibitor or H2-receptor antagonist for Helicobacter pylori eradication. *Aliment Pharmacol Ther* 2003;**17**:1229–36.

Cytokines in portopulmonary hypertension

I wish to raise some questions regarding the paper of Benjaminov *et al* on portopulmonary hypertension in decompensated cirrhosis with refractory ascites (*Gut* 2003;**52**:1355–62).

Although the role of endothelin-1 in portopulmonary hypertension has been suggested by many clinicians and is timely, as well as clinically important, issues remain concerning the limited number of patients (n = 10 portopulmonary patients) presented in this study. Furthermore, it is very difficult to demonstrate or hypothesise a role of endothelin-1 in portopulmonary hypertension without measuring gradients of endothelin-1 over the pulmonary and portal vascular beds. Without these data, how do they know where the increased levels of endothelin-1 came from?

Furthermore, why did the authors not analyse the role of circulating cytokines, such as interleukin 6 and interleukin 1β which are implicated in the pathogenesis of pulmonary hypertension? We found high plasma concentrations of endothelin-1 and in particular interleukin-6 in 15 patients affected by portopulmonary hypertension and in a group of 20 patients with primary pulmonary hypertension (endothelin-1, 5.26 (3.5) *v* 5.69 (1.4) pg/ml; interleukin 6, 9.1 (3.1) *v* 6.6 (4.4) pg/ml, respectively) compared with a group of 30 cirrhotics with ascites (endothelin-1, 1.79 (0.8); interleukin 6, 3.43 (2.7)). Our data suggest that endothelin-1 and in particular interleukin 6 show similar plasma concentrations in portopulmonary hypertension and primary pulmonary hypertension and could play a part in the pathogenesis of these diseases.[1]

A M Pellicelli

Correspondence to: Dr A M Pellicelli, Department of Hepatology, San Camillo-Forlanini Hospital, Rome, Italy; a.pellicelli@libero.it

Reference

1 **Pellicelli AM**, Guarascio P, Cerasari G, *et al*. Role of plasmatic cytokines in portopulmonary hypertension. *Hepatology* 2002;**36**:523.

Infallibility of a normal platelet count/spleen diameter ratio in ruling out oesophageal varices?

We read with interest that an abnormal platelet count/spleen diameter ratio predicts the presence of oesophageal varices (*Gut* 2003;**52**:1200–5). This otherwise excellent article contained a statistical error that we would like to bring to your attention.

The authors reported 100% sensitivity for the diagnostic test (platelet count/spleen diameter ratio at a cut off value of 909) in ruling out the diagnosis of oesophageal varices: all patients with varices had an abnormal ratio. The reported 95% confidence interval (CI) for the sensitivity was 100–100%. This is simply incorrect, and is was probably calculated using a statistical formula that can be only used when:

(1) the sample size is large and

(2) the proportion in question is not equal to 0% or 100%.

The formula

$SE(p) = \mathrm{sqrt}[p(1-p)/n]$

where SE = standard error, p = proportion, and n = sample size, gives a value for the standard error of a proportion. However, when the proportion is 0% or 100%, the standard error becomes 0, and this formula is void.

Imagine a diagnostic test that is performed on 10 patients, two of whom have the disease in question. Let us say that the test is positive in both patients with the disease and in two of the eight patients without the disease. The calculated sensitivity is 100% and specificity is 75%. Would any respectable journal editor be convinced that the true sensitivity of this diagnostic test lies somewhere between 100% and 100%—that if a validation cohort underwent this diagnostic test we could be confident that all patients with the disease should test positive? Of course not. But the above formula would also give a standard error of 0 in this case.

The bottom line is that it is never acceptable to give a confidence interval in medicine that is a point estimate. If a computer program or statistical textbook formula gives a point estimate instead of an interval, then the wrong formula was used. This particular statistical error (expressing a confidence interval as a point estimate) is easily identified without any statistical training or calculations.

In the case of the platelet count/spleen diameter ratio, an appropriate statistical test is the score confidence interval (Agresti-Coull) method. Using this method (in JMP 5.1, SAS Institute, Cary, North Carolina, USA), the sensitivity of the platelet count/spleen diameter ratio in the derivation cohort should have been:

- 89 of 89 patients with varices correctly identified = 100% (95% confidence interval 95.9–100%)

and for the validation cohort:

- 71 of 71 patients = 100% (95% confidence interval 94.9–100%).

Combining the validation and derivation cohorts:

- 160 of 160 patients = 100% (95% confidence interval 97.7–100%).

This is not nit-picky as many clinicians will read this article and believe that a normal platelet count/spleen size ratio rules out oesophageal varices with 100% certainty. But surely someone, somewhere, will find an exception to this useful (and remarkably accurate) diagnostic rule.

D J Brotman
Department of General Internal Medicine, Cleveland Clinic Foundation, Cleveland, Ohio, USA

R G O'Brien
Department of Biostatistics and Epidemiology, Cleveland Clinic Foundation, Cleveland, Ohio, USA

Correspondence to: D J Brotman, Department of General Internal Medicine, Cleveland Clinic Foundation, Cleveland, Ohio, USA; brotmad@ccf.org

Sporadic fundic gland polyps: what happened before?

We read with great interest the article by Watanabe *et al* (*Gut* 2002;**51**:742–5) on regression or complete disappearance of sporadic fundic gland polyps (FGPs) in two patients following acquisition of *Helicobacter pylori* infection. This very interesting article raised a very basic question: "What happened before (and after) the first diagnosis of FGPs?"

We know from previous studies[1–3] and personal experience[4 5] that the association between FGPs and actual *H pylori* gastritis is rare, but what remains unanswered is are patients with sporadic FGPs really protected (by some presently unknown mechanism) against *H pylori* colonisation (that is, *H pylori* colonisation is really rare in these patients) or are patients with sporadic FGPs prone to *H pylori* colonisation in a similar manner as the general population, and perhaps the association between *H pylori* and FGPs seems rare because FGPs disappear when a patient acquires *H pylori* (and reappear after eradication). So our second question is: "How often do patients with sporadic FGPs acquire *H pylori*? Is it a rare or common, if unnoticed, event?

From October 1997 to March 2004, we prospectively collected all endoscopic and histological data from 162 patients (mean follow up 34 months) with sporadic FGPs. All of the original slides were reviewed by one of the authors (PD) assessing location, presence, and type of gastritis, intestinal metaplasia, and *H pylori* colonisation. Furthermore, all preceding and successive gastroenterological examinations were taken into account. The vast majority of our patients (126 of 162 (77.7%)) had no evidence of past or present gastritis, and remained free from *H pylori* during the observation period. Of these, 74 had also antral biopsies which were all *H pylori* negative. In 16 patients (9.8%) we found histological evidence of past active antral gastritis with *H pylori* colonisation years before the first diagnosis of FGPs but only one patient acquired *H pylori* after the first diagnosis of FGPs, with complete disappearance of polyps. Finally, 19 patients (11.7%) had inactive gastritis with intestinal metaplasia, without *H pylori* colonisation at the time of the first FGP diagnosis, and in the following period. Therefore, in our experience, the large majority of patients with FGPs appear to be (and remain) free from *H pylori* colonisation. In only one patient could we document acquisition of *H pylori* with disappearance of FGPs.

In conclusion, it seems that patients with sporadic FGPs are largely protected from *H pylori* colonisation and that these patients rarely acquire the infection with disappearance of polyps.

P Declich, E Tavani, S Bellone, M Porcellati, L Pastori
Service of Pathology, Rho Hospital, Italy

B Omazzi, C Gozzini, A Bortoli, A Prada
Division of Gastroenterolgy, Rho Hospital, Italy

Correspondence to: Dr P Declich, Service of Pathology, Rho Hospital, Corso Europa n 250 I-20017 Rho, Italy; paolo.declich@libero.it

References

1 **Bonilla Palacios JJ**, Miyazaki Y, Kanayuma S, *et al*. Serum gastrin, pepsinogens, parietal cell and Helicobacter pylori antibodies in patients with gastric polyps. *Acta Gastroenterol Latinoam* 1994;**24**:77–82.
2 **Dickey W**, Kenny BD, McConnell JB. Prevalence of fundic gland polyps in a western European population. *J Clin Gastroenterol* 1996;**23**:73–5.
3 **Stachura J**, Galazka K, Pirog K. Gastric fundic gland polyps (Elster's polyps) and Helicobacter pylori-induced gastritis. *Pol J Pathol* 1997;**48**:159–61.
4 **Declich P**, Isimbaldi G, Sironi M, *et al*. Sporadic fundic gland polyps: an immunohistochemical study of their antigenic profile. *Path Res Pract* 1996;**192**:808–15.
5 **Declich P**, Ambrosiani A, Bellone S, *et al*. Helicobacter pylori prevalence in fundic gland polyps. *Pol J Pathol* 1999;**50**:221–2.

To dye or not to dye? That is beyond question! Optimising surveillance colonoscopy is indispensable for detecting dysplasia in ulcerative colitis

We read the article by Rutter *et al* (*Gut* 2004;**53**:256–60) with great interest. They demonstrated that a dye spraying method with indigo carmine successfully detected dysplastic lesions in surveillance colonoscopy for ulcerative colitis (UC), and proved by back to back colonoscopy that such a method is effective. Since 1979, we have carried out a surveillance colonoscopy programme for UC associated cancer in which we successfully detected colitic cancer at an early stage.[1] We have routinely used the dye spraying method with indigo carmine, which enables us to recognise subtle mucosal irregularities. Furthermore, we recently introduced magnifying colonoscopy and pit pattern diagnosis for surveillance colonoscopy for UC.[2]

We agree with Rutter *et al* that dye spraying can visualise flat dysplastic lesions. By using this method in our series, we also found a flat dysplastic lesion with low grade dysplasia in a patient with a 10 year history of UC. At first, it was impossible to recognise this lesion at pre-dye spray colonoscopy (fig 1A) but after spraying with indigo carmine, the lesion became evident (fig 1B). Magnifying colonoscopy revealed that the lesion had a type IV pit pattern according to Kudo's classification,[3] which corresponded to the neoplastic pattern of Kiesslich's classification (fig 1B inset).[4] Biopsy specimens revealed low grade dysplasia. In this case, magnifying colonoscopy, used together with the dye spraying method, was very effective in detecting flat dysplasia.

As Kiesslich and Neurath remarked in their accompanying commentary (*Gut* 2004;**53**: 165–7), the difference in dyes used for chromoendoscopy is also of interest. Dye spraying methods can be divided into two types: contrast method and staining method, according to the dyes used. We consider it wise to understand the differences between the two methods. In the contrast method, dyes such as indigo carmine do not stain colonic mucosa but just form pools at grooves, highlighting the contrast of subtle mucosal irregularities. Dyes used in the staining method, however, such as methylene blue or crystal violet, stain the circumferential convex portions, but not grooves. Therefore, images in the contrast and staining methods are quite different, just like those of negative and positive films in photography. In addition, several differences can be noted between these two methods. Firstly, it takes a few minutes for colonic mucosa to be stained in the staining method whereas colonic mucosa can be seen soon after the dye is sprayed in the contrast method. Secondly, the dye can be diluted by colonic fluid or lavage in the contrast method while this is not the case in the staining method. Hence it is easy to intentionally remove dye in the contrast method while it is difficult to do so in the staining method. Therefore, the contrast method should be first tried, and then, if both methods are required, the staining method should follow. Lastly and most importantly, the contrast method offers better contrast (fig 1C) while the staining method provides a better view of glandular openings or pits (fig 1D).

Together with the article by Rutter *et al*, we would like to reassure readers that the dye spraying method is an indispensable tool in detecting dysplasia in surveillance colonoscopy in UC.

K Hata, T Watanabe, M Shinozaki, T Kojima, H Nagawa
Department of Surgical Oncology, University of Tokyo, Tokyo, Japan

Correspondence to: Dr K Hata, Department of Surgical Oncology, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan; khata-tky@umin.ac.jp

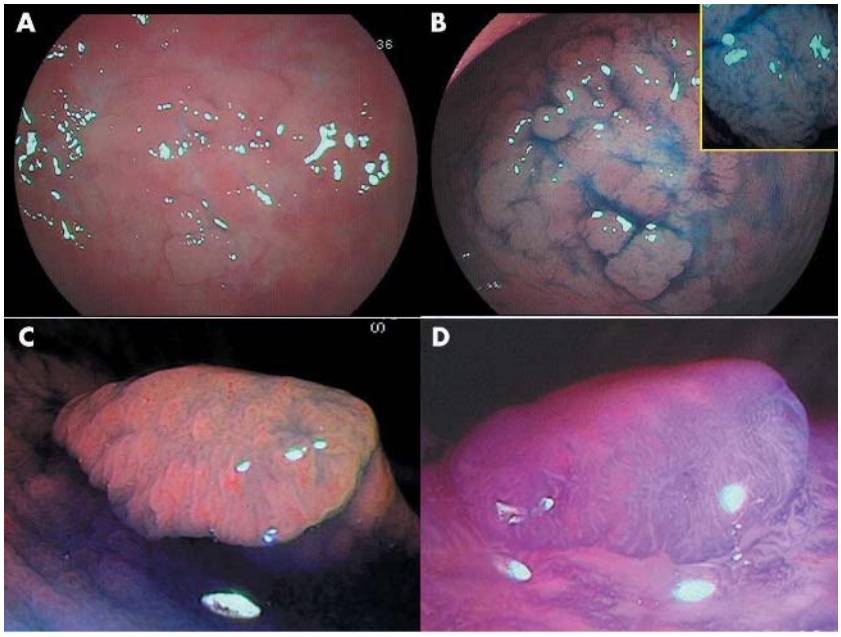

Figure 1 (A) Pre-dye spray colonoscopy failed to detect this lesion. This picture was taken after washing out indigo carmine. (B) The dye spraying method with indigo carmine was able to visualise the lesion clearly. Magnifying colonoscopy revealed that the lesion had a type IV pit or neoplastic pattern (inset). (C) A lesion with low grade dysplasia highlighted by the contrast method using indigo carmine. (D) The same lesion as shown in (C) was stained with crystal violet. Glandular openings or pits were more clearly seen.

References

1 **Hata K**, Watanabe T, Kazama S, *et al*. Earlier surveillance colonoscopy programme improves survival in patients with ulcerative colitis associated colorectal cancer: results of a 23-year surveillance programme in the Japanese population. *Br J Cancer* 2003;**89**:1232–6.
2 **Hata K**, Watanabe T, Motoi T, *et al*. Pitfalls of pit pattern diagnosis in ulcerative colitis-associated dysplasia. *Gastroenterology* 2004;**126**:374–6.
3 **Kudo S**, Tamura S, Nakajima T, *et al*. Diagnosis of colorectal tumorous lesions by magnifying endoscopy. *Gastrointest Endosc* 1996;**44**:8–14.
4 **Kiesslich R**, Fritsch J, Holtmann M, *et al*. Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. *Gastroenterology* 2003;**124**:880–8.

NOTICE

4th International Inflammatory Bowel Disease Meeting

This meeting will be held in Liverpool on 7–8 February 2005. It will include keynote lectures, case discussions, and oral and poster presentations selected from submitted abstracts (200 words, no form needed, to be received electronically by 8 November 2004). Further details and registration forms are available from Professor JM Rhodes, 4th International IBD Meeting, ref AL/JL, Resource House, 20 Denmark Street, Wokingham, Berks RG40 4BB; tel 01189 369100; fax 01189 794670; email: 4thIntIBD@tta-int.co.uk. Register by 19 November 2004 for cheap rates.

CORRECTION

The wrong section banner heading was used for five papers in the September issue. The following five papers were listed under the banner of irritable bowel disease, however, this should have read as inflammatory bowel disease:

S J Connor, N Paraskevopoulos, R Newman, *et al*. CCR2 expressing $CD4^+$ T lymphocytes are preferentially recruited to the ileum in Crohn's disease. *Gut* 2004;**53**:1287–1294. doi: 10.1136/gut.2003.028225

S Zeissig, C Bojarski, N Buergel, *et al*. Downregulation of epithelial apoptosis and barrier repair in active Crohn's disease by tumour necrosis factor antibody treatment. *Gut* 2004;**53**:1295–1302. doi: 10.1136/gut.2003.036632

K Matsuoka, N Inoue, T Sato, *et al*. T-bet upregulation and subsequent interleukin 12 stimulation are essential for induction of Th1 mediated immunopathology in Crohn's disease. *Gut* 2004;**53**:1303–1308. doi: 10.1136/gut.2003.024190

G Masala, S Bagnoli, M Ceroti, *et al*. Divergent patterns of total and cancer mortality in ulcerative colitis and Crohn's disease patients: the Florence IBD study 1978–2001. *Gut* 2004;**53**:1309–1313. doi: 10.1136/gut.2003.031476

F Bataille, F Klebl, P Rümmele, *et al*. Morphological characterisation of Crohn's disease fistulae. *Gut* 2004;**53**:1314–1321. doi: 10.1136/gut.2003.038208