References

- 1 Pearson RC, McCloy RF. Blowing hot and cold on peptic disorders. *Br J Surg* 1987; **74**: 1160.
- 2 Pearson RC, McCloy RF, Cutler WC, Levitt JR, Richards B, Vickery JC. Multichannel digital recording of intraluminal temperature in the upper gastro-intestinal tract of man: techniques and analyses. *Clin Phys Physiol Meas* 1988 (In press).
- 3 Respass JC, Ingelfinger FJ, Kramer P, Hendrix TR. Effect of cold on esophageal motor function. *Am J Med* 1956; **20**: 955.
- 4 Winship DH, Viegas De Andrade SR, Zboralske FF. Influence of bolus temperature on human esophageal motor function. *J Clin Invest* 1970; **49**: 243-50.
- 5 Ritschel WA, Erni W. The influence of temperature of ingested fluid on stomach emptying time. *Int J Clin Pharmacol* 1977; **15**: 172-5.

Reply

SIR,—We read with interest the comments made by Pearson and McCloy on our paper studying the effect of meal temperature on gastric emptying (*Gut* 1988; **29**: 302-5). We agree that intraluminal temperature in the upper gastrointestinal tract during normal daily life may sometimes be higher than the maximum temperature used in our study. We, however, chose to select a maximum temperature that was acceptable to all our volunteers, thus ensuring that none of our volunteers were unduly stressed, which itself may inhibit gastric motility and delay gastric emptying.

We do not agree with their assumption that because intraduodenal temperature remains below 35°C for nearly six minutes after a cold drink, that cold liquids must empty from the stomach faster than warm ones. We have shown that up to 10 minutes after ingestion, when cold (4°C) liquids are emptying more slowly than liquids at body temperature, intra-gastric temperature is below 35°C. Consequently, liquids entering the duodenum over this period of time would have a temperature of less than 35°C, and the intraduodenal temperature could well stay below 35°C. Furthermore, our data have shown that intra-gastric temperature is well below 35°C (between 21 and 30°C) for the first six minutes after ingestion of a cold drink.

Their use of Ritschel and Erni's paper (*Int J Clin Pharmacol* 1977; **15**: 172-5) in support of cold liquids emptying faster than warm ones is also inaccurate. Ritschel and Erni investigated the effect of the temperature of ingested water on the emptying time of a telemetric pH capsule. The emptying time of the water was not studied and it is not known whether the capsule left the stomach before or after all the water had emptied from the stomach.

Finally, we agree that it would be preferential for investigators to report the temperature of test

meals used to study upper gastrointestinal motility, especially when using fatty meals with higher thermal inertia.

L A HOUGHTON AND W M SUN

Sub-Department of Human Gastrointestinal Physiology and Nutrition, University of Sheffield, Sheffield S10 2JF.

Cimetidine, carbenoxolone and gastric mucus

SIR,—Reading the paper by Ene *et al*¹ I was rather surprised to find that someone took the trouble to try to reproduce my eight to 10 year old studies on the effects of cimetidine and carbenoxolone on gastric mucus, a topic which seems a little outdated in 1988. Nevertheless, having been quoted and criticised so much by these authors, I cannot refrain from replying to some of their issues.

First, perusing Glass' papers I did not have the impression, as Ene and colleagues seem to think, that he considered acid mucoproteins as the component of mucus responsible for mucosal protection. Of course this great pioneer in mucus researches is beyond the possibility of entering the debate. In my opinion, however, the viscous and protective properties of mucus are more related to neutral than to acid mucoproteins.² This should be apparent by some of my papers quoted by Ene *et al*, where in fact I was using as a parameter of mucosal protection the ratio of neutral to total mucoproteins (so-called Mucoprotective Index).^{2,4} What we actually found at that time was that cimetidine treatment increases acid mucosubstances and induces a marked, significant decrease of neutral mucoproteins.^{3,4} Carbenoxolone, in contrast, promotes a rise of both mucin components, the effect being more dramatic on neutral mucoproteins, with a consequent increase in the values of Mucoprotective Index.⁴ The key point is that we undertook our studies in peptic ulcer patients treated for four weeks with either cimetidine 1 g daily or carbenoxolone 150 mg daily (300 mg the first week). Ene's experiment included normal subjects who received either drug for only two weeks and in lower doses. Thus it is hard to compare Ene's results with ours.

Furthermore I am not quite sure that the method used by the authors, sophisticated as it may be from a biochemical point of view, provides a better insight of the effects of drugs on mucus secretion. On the other hand the adverse influence of cimetidine on gastric mucus has been also observed by others.⁵ As for the mucogenic activity of carbenoxolone, this was reported, by means of various techniques, by different investigators⁶⁻⁹ before and after the appearance of my

papers. Therefore it is unfair to give me all the credit (or the blame) for this finding.

Our attempt to explain ulcer recurrences after cimetidine only on the basis of changes in the composition of gastric mucus³ may appear naïve 10 years later, yet in the case of cimetidine and carbenoxolone this relationship has been confirmed.¹⁰ Moreover, ulcer relapses in cimetidine healed patients were found to be more frequent than after ranitidine^{11,12} or after other anti-ulcer drugs¹³⁻¹⁶ which, according to our method, either exert no effect, or actually stimulate mucus secretion.²

Thus, despite 'the simplicity of these ideas', we were not so wrong.

M GUSLANDI

*Institute of Internal Medicine,
University of Milan, Italy.*

References

- 1 Ene MD, Clamp JR, Roberts CJC. Effects of cimetidine and carbenoxolone on gastric mucus. *Gut* 1988; **29**: 636-41.
- 2 Guslandi M. Evaluation of gastric mucus in man by means of the 'mucoprotective index'. A review of a five-year experience with this method. *Meth Find Exptl Clin Pharmacol* 1983; **5**: 735-9.
- 3 Guslandi M, Tittobello A, Evangelista A, Fesce E, Cambielli M. Cimetidine and protective effect of mucus in gastric ulcer. *Br Med J* 1978; **i**: 1486.
- 4 Guslandi M, Cambielli M, Bierti L, Tittobello A. Effect of carbenoxolone and cimetidine on gastric mucin. *Clin Ther* 1980; **3**: 40-2.
- 5 Watanabe Y, Kobayashi R, Yoshigoe F, *et al.* Effect of pirenzepine on gastric mucus secretion. In: *Gastrozepin/Bisvanil: new aspects in research and therapy*. Asia Pacific Congress Series No 40. Amsterdam: Excerpta Medica, 1985: 24-32.
- 6 Domschke W, Domschke S, Classen M, Demling L. Some properties of mucus in patients with gastric ulcer. Effect of treatment with carbenoxolone sodium. *Scand J Gastroenterol* 1972; **7**: 647-51.
- 7 Parke DV. Some recent advances in the pharmacology of carbenoxolone. In: Avery Jones F, Langman MJS, Mann RD, eds. *Peptic ulcer healing: recent studies on carbenoxolone*. Lancaster: MTP Press, 1978: 1-8.
- 8 Bickel M, Kauffman GL. Gastric gel mucus thickness: effect of distention, 16,16-dimethyl prostaglandin E₂ and carbenoxolone. *Gastroenterology* 1981; **80**: 770-5.
- 9 Green AP, Lander JE, Turner DH. The effect of stress and indomethacin, carbenoxolone, salbutamol, metiamide, zolimidine and CF19415 on rat gastric mucus. *J Pharm Pharmacol* 1981; **33**: 348-52.
- 10 Guslandi M, Cambielli M, Tittobello A. Carbenoxolone maintenance in cimetidine-healed patients. *Scand J Gastroenterol* 1980; **15**: 369-71.
- 11 Gough KR, Bardhan KD, Crowe JP *et al.* Ranitidine and cimetidine in prevention of duodenal ulcer relapse. A double-blind, randomised multicentre comparative trial. *Lancet* 1984; **ii**: 659-62.
- 12 Silvis SE. Final report on the United States multicenter trial comparing ranitidine to cimetidine as maintenance therapy following healing of duodenal ulcer. *J Clin Gastroenterol* 1985; **7**: 482-7.
- 13 Guslandi M. Importance of defensive factors in the prevention of peptic ulcer recurrence. *Acta Gastroenterol Belgica* 1983; **46**: 411-8.
- 14 McLean AJ, Byrne AJ, Harrison PM, McCarthy P, Ioannides-Demos L, Dudley FJ. The choice of ulcer healing agent influences duodenal ulcer relapse rate and long-term clinical outcome. *Aust NZ J Med* 1985; **15**: 367-74.
- 15 Miller JP, Faragher EB. Relapse of duodenal ulcer: does it matter which drug is used in the initial treatment? *Brit Med J* 1986; **293**: 1117-8.
- 16 Dobrilla G, Vallaperta P, Amplatz S. Influence of ulcer healing agents on ulcer relapse after discontinuation of acute treatment: a pooled estimate of controlled clinical trials. *Gut* 1988; **29**: 181-7.

Reply

SIR,—There is little in common between the paper by Ene *et al.*¹ and those by Guslandi and so our paper can hardly be called a reproduction of his work. Indeed there have been few biochemical studies of the type described by Ene *et al.*¹ on the effects of carbenoxolone and H₂ antagonists on gastric mucus.

The paper by Jerzy Glass² was a review of his pioneering work on gastric mucus carried out in the 1950s and early 1960s. He was too good a scientist to have resented the fact that the field had moved on in the intervening period. The use of Jerzy Glass' fractions is, however, not the point. The ratio of neutral to total 'mucoproteins' has been termed by Guslandi the 'Mucoprotective Index.' This concept was first introduced by Guslandi in an unrefereed letter in the *British Medical Journal*.³ I know of no paper which presents scientific evidence to justify the use of such an index.

J R CLAMP

*Department of Medicine,
University of Bristol,
Bristol Royal Infirmary,
Bristol
BS2 8HW.*

References

- 1 Ene MD, Clamp JR, Roberts CJC. Effects of cimetidine and carbenoxolone on gastric mucus. *Gut* 1988; **29**: 636-41.
- 2 Jerzy Glass GB. Current status of the glandular mucoprotein and mucoprotease fractions of the gastric mucin: a review of 15 years' progress in this area. *Ann NY Acad Sci* 1967; **140**: 804-34.
- 3 Guslandi M, Tittobello A, Evangelista A, Fesce E, Cambielli M. Cimetidine and protective effect of mucus in gastric ulcer. *Br Med J* 1978; **i**: 1486.