Correspondence

Oesophageal chest pain

SIR, – We would like to make three comments on the leading article by Drs Blackwell and Castell in the January issue of *Gut*.¹

They point the need for studies of oesophageal motility during effort angina in patients with proven coronary artery disease: we would refer them to our publications reporting that in six such patients we found no associated evidence of significant oesophageal dysmotility from simultaneous manometric studies.^{2,3}

They note the lack of controlled trials in the treatment of this condition: we would refer them to our preliminary report of a double blind, placebo controlled trial of nifedipine⁴ (a further paper in preparation).

They comment on the dangers of ergometrine and the advantages of edrophonium. We find the ergometrine test useful^{5,6} and believe that it is safe, provided that patients are first carefully screened from the cardiological point of view and are shown not to have coronary artery disease, and that the oesophageal study is conducted with electrocardiographic monitoring and resuscitative facilities to hand, giving ergometrine in an initial dose of 0.05 mg, doubling every two to three minutes to a total of 0.5 mg over *ca* 10 minutes. We would point out that edrophonium is a cholinesterase inhibitor⁷ and that methacholine (a cholinergic agent and thus a vasoconstrictor) is capable of inducing coronary spasm in susceptible subjects^{8,9} so that the authors' suggestion that edrophonium is safer than ergometrine seems likely to represent a type II error. Because edrophonium has not yet been shown to induce coronary spasm does not mean that it does not. We would caution against accepting the view that edrophonium is safe on present evidence.

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Reply

SIR, – We were very interested to receive the observations from Dr Alban Davies and his colleagues on our leading article and we are pleased to have the opportunity to respond to them.

In order to interpret the high prevalence of oesophageal manometric abnormalities in patients with non-cardiac chest pain with more certainty, it is desirable to perform oesophageal manometry in a group of patients with known ischaemic heart disease. We were therefore interested to hear that Dr Alban Davies and his colleagues have found normal manometric results in six patients with known ischaemic heart disease. It is to be hoped that they are extending this experience in order to make meaningful statistical comparisons with this important control group. We were also interested to hear that they are preparing a paper on the results of a controlled trial of nifedipine for diffuse oesophageal spasm. We look forward to seeing the data when this paper has been published.

The third point concerns the relative safety of ergometrine and edrophonium as provocative

agents. We are pleased to be able to give preliminary results of the effect of edrophonium administered during coronary angiography. The results of this study will be published,¹ indicating that edrophonium was not associated with spasm or other abnormality of the coronary arteries. Therefore we stand by our suggestion that edrophonium is a safer provocative agent than ergometrine, which is itself used to provoke coronary artery spasm.

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Cimetidine on apparent liver blood flow

SIR, – We were interested to read the paper by Daneshmend *et al* in the February issue of *Gut* (*Gut* 1984; **25**: 125–8) on the lack of effect of cimetidine on apparent liver blood flow. The work contains two fundamental assumptions whose validity may be questioned and that may influence the interpretation of the authors' findings. In addition, there are some minor errors and omissions.

Firstly, the authors calculate indocyanine green clearance by fitting a single compartment model to the plasma disappearance of the dye. Although this is frequently done, a two compartment model is more appropriate for describing the disposition of indocyanine green¹ and sizeable errors occur in calculating clearance if the less complex model is adopted.² Secondly, the authors equate clearance of indocyanine green with apparent liver blood flow, a simplification which always underestimates real liver blood flow as the hepatic extraction of indocyanine green is less than unity. This might be acceptable in paired studies if hepatic extraction remained constant but we for instance have observed that in normal subjects cimetidine impairs hepatocellular uptake of indocyanine green by mean 13.5%, and similar results have been reported in patients with liver disease.³ Moreover, hepatic extraction of the

dye is itself altered by changes in blood flow.⁴ The changes in indocyanine green clearance reported by Daneshmend and colleagues therefore may not directly reflect changes in real liver blood flow because hepatic extraction was not measured.

The authors do not state the time of the second indocyanine green injection in relation to the last dose of cimetidine. If this interval were longer than a few hours, plasma concentrations of cimetidine would be low and a transient effect on liver blood flow might be missed. Antipyrine clearance, however, would still be affected as enzyme inhibition is unlikely to reverse so rapidly.

A less serious error occurs in Table 1. The initial volume of distribution of indocyanine green is usually little more than the plasma volume, but the mean value given is 33.36 litres, which is probably a typographical mistake. Finally, we are surprised that the 19% average increase in indocyanine green clearance did not reach statistical significance. Presumably the large inter-individual variation and the small number of subjects introduced a type II error.

There is unfortunately a conflicting literature on the possible effects of cimetidine on liver blood flow and this conflict has yet to be resolved.

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Reply

SIR, – We thank you for giving us the opportunity to comment on the letter from Drs Grainger, Marigold, and Thompson.