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.

J N BLACKWELL AND D O CASTELL

*University Department of Therapeutics
and Clinical Pharmacology,
Royal Infirmary of Edinburgh,
Edinburgh,
and*

*Gastrointestinal Section,
Bowman Gray School of Medicine,
Wake Forest University,
Winston-Salem, North Carolina, USA.*

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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.

S L GRAINGER,

J H MARIGOLD, AND R P H THOMPSON

*Gastrointestinal Laboratory,
The Rayne Institute,
St Thomas' Hospital,
London, SE1.*

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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.