

Pugh's grading in the classification of liver decompensation

EDITOR.—As a houseman on the Liver Unit at King's College Hospital, London, I benefited from a unique experience of acute medical care during the heady years of the emerging unit, from an absorbing exposure to active clinical research, and from the career motivation of early publication.¹ It was the practice of the unit director to engage the houseman in the collection of clinical data, under the supervision of the registrar or senior registrar.

The series of patients with bleeding oesophageal varices, which represented my particular assignment, interested me since the morbidity and mortality data did not conform that well to Child's classification of A, B, and C.² In particular, this system did not consider any bleeding tendency. An alternative classification that included reference to the prothrombin time was proposed in the report of these patients and an attempt was made to devise a numerical scoring system. It is apparent that this alternative system has stood the test of time, because of two major advantages: (a) it does not artificially place patients into a category of abnormality; (b) it results in a total score which provides a better index for statistical analysis.³

Now, as a clinical epidemiologist working in an academic environment, I find it slightly amusing to reflect that a strictly scientific method was not adopted in formulating an alternative classification of liver decompensation. Rather, it was the adoption of a pragmatic response to a *gut* feeling that something more flexible was required to categorise these patients!

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Proliferation of human gastrointestinal epithelium

EDITOR.—The altered pattern of epithelial proliferation in familial adenomatous polyposis (FAP) noted by Potten *et al*¹ must be interpreted carefully. In studying the upward shift of the proliferative compartment using the monoclonal antibody Ki-67, I have satisfied myself that this phenomenon occurs only within the context of adenomatous change, whether this is a macroscopically visible adenoma, a microadenoma, or an unicyptal adenoma (unpublished observations). This interpretation is not completely straightforward, because early adenomatous change in FAP may deviate minimally from the normal. It is, however, important to establish whether the unicyptal adenoma is the first manifestation of the disease or whether there are 'field changes' detectable through cell kinetic disturbances or other functional alterations. For example, some workers have described mucin or lectin histochemical changes in the normal appearing mucosa in FAP that we have been unable to confirm in a carefully controlled study.² The concept of 'preneoplastic field

change' has been accepted widely but uncritically in relation to gastrointestinal epithelium.³

The observations of Potten *et al* are based on a very elegant series of experiments.^{1,4} Their demonstration of a negative correlation between cell kinetic indices and likelihood of malignancy will hopefully lead to a full reappraisal of the place of cell kinetics in our understanding of colorectal neoplasia.

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Cholestatic hepatitis associated with clavulanic acid

EDITOR.—We read with great interest the report by Larrey and colleagues regarding hepatitis associated with the combination of amoxicillin-clavulanic acid in *Gut*.¹ With others, we have reported a series of similar cases in Melbourne, Australia,² as well as a single case of prolonged cholestasis following treatment with ticarcillin-clavulanic acid.³

Larrey and coauthors, as well as others,⁴ contend that a hypersensitivity reaction is the likely cause with which we agree; in most of the cases reported by us, however, the patients were simultaneously taking oral corticosteroids, and so the manifestations of an immunological reaction might have been masked. Interestingly, three of the 15 patients reported by Larrey and coauthors were also taking oral corticosteroids; none of them exhibited skin rashes, hypereosinophilia, or positive tests for autoantibodies.

In part, the relatively larger proportion of our reported cases receiving concurrent steroid treatment (6/8 with the amoxicillin-clavulanic acid group, 1/1 with ticarcillin-clavulanic acid) may reflect different prescribing practices; in Australia, amoxicillin-clavulanic acid is most often given to patients suffering from the infectious complications of chronic obstructive airways disease, because of its efficacy in treating infection with the common respiratory pathogen, *Haemophilus parainfluenzae* (usually resistant to amoxicillin alone). These patients typically have severe airways disease and are often receiving corticosteroids at the same time. Other supposed predisposing factors, such as increasing age and prolonged duration of treatment, may also relate to this older group of patients, who are most likely to be prescribed the amoxicillin-clavulanic acid combination for longer than usual.

Larrey and coauthors have contributed to the growing number of cases of cholestatic hepatitis associated with clavulanic acid combinations, and we hope that this will help to raise the practising clinician's awareness of these agents as the cause of uncomfortable, often prolonged cholestasis. We recommend the reporting of suspected or confirmed cases to the

appropriate national adverse drug reaction committee, to enable more accurate data regarding incidence to be gathered. Finally, we wish to emphasise that consideration of the diagnosis of amoxicillin-clavulanic acid associated jaundice can save the patient from potentially hazardous investigations such as endoscopic retrograde cholangiopancreatography and liver biopsy.

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Superior mesenteric blood flow

EDITOR.—We read with interest the paper by Sieber *et al* in *Gut*.¹ We cannot agree with their findings of a smaller postprandial increase in superior mesenteric artery (SMA) blood flow with a carbohydrate meal rather than with a meal of fat or protein. These results are at odds with the findings of the late Dr Mohammed Qamar and others,^{2,3} and we cannot agree that these results are flawed by the lack of any consideration of gastric emptying. Qamar devoted an entire chapter of his PhD thesis to the role of gastric emptying in postprandial hyperaemia.⁴ In unpublished work, using simultaneous transcutaneous Doppler ultrasound to measure SMA blood flow and gamma-camera scanning to measure the passage of a radiolabelled meal from the stomach into the duodenum in 12 healthy young subjects, he found no consistent difference between SMA blood flow rates following liquid and solid meals. He concluded that gastric emptying was of no physiological significance in regulating SMA blood flow. We believe the addition of polyethylene glycol (PEG) to the duodenal perfusate explains this unexpected result.

The absorption of glucose by the upper small intestine is reduced significantly by the addition of complex, non-absorbed polysaccharides such as guar gum and pectin^{5,6} and the resultant reduction in postprandial hyperglycaemia has an application in the management of diabetes.⁷ The precise mechanism by which this occurs is obscure but it seems likely that the addition of PEG - which is also a complex, non-absorbed carbohydrate - will reduce glucose absorption in a similar way. It therefore seems that the original observations^{2,3} - made without test meal additives - are correct.

We do not dispute the fact that meal composition is the chief determinant of postprandial hyperaemia; the precise mechanism by which this occurs is, however, still unknown, although our own unpublished data are in agreement with those of Sieber *et al* and others^{8,9} who have suggested that gut hormones have no role.

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Reply

EDITOR, — We appreciate the interest of Professor Read's team in our recent article in *Gut*.¹ Nevertheless, we would like to comment why we think our conclusions are valid, and also do not contradict the ones mentioned by Read *et al.*^{2,3}

Divergent rates of gastric emptying of different food components and their subsequent hyperaemic responses are well established.⁴ Indeed, in the cited paper by Moneta *et al.*,³ the hyperaemic effect of oral carbohydrates was the fastest one, whereas fat induced the most pronounced response in agreement with our hypothesis. These findings are not a contradiction to the unpublished studies by Qamar, where he tested the hyperaemic response to both liquid and solid oral meals. Indeed, in our own publication,¹ the response to oral liquid and solid food was tested and shown in Figure 1, giving similar amounts of responses with the exception that the maximal response was observed 15 minutes later for the solid meal, probably owing to slower gastric emptying. The aim of our studies, however, was to gain further insight into how different food components elicit different degrees of intestinal hyperaemia. To do so, we examined the major food components in an isocaloric and isosmotic manner by perfusing them into the duodenum to overcome the confounding effects of divergent rates of gastric emptying.

We cannot accept the hypothesis that differences between our results and those of Qamar *et al.*² were due to the addition of the water soluble non-absorbable marker polyethylene glycol (PEG). Non-absorbable polysaccharides such as pectin may delay gastric emptying and glucose absorption.⁵ Nevertheless, the concentrations given were higher than our PEG4000 concentration of 2 g/l. Interestingly, the authors of the cited study² used PEG4000 at a concentration of 5 g/l as an inert marker to examine the role of pectin.

Finally, animal studies have shown that PEG

at high osmolarities (3000 mosm/l) by itself increases splanchnic blood flow.⁴ Concentrations below 1500 mmol/l had no effect. In fact, postprandial osmolarities are much lower and in the range we tested with the 560 mM saline solution, where we found no change in superior mesenteric artery blood flow. As we added PEG at the same concentration in all our intraduodenal perfusion experiments, differences in hyperaemic responses to different food components cannot be caused by PEG.

We are unable to comment upon unpublished data and therefore hope that these studies will be published soon to help fruitful discussions.

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