LETTERS TO THE EDITOR

Conjugation of phenols in human colonocytes

SIR,—The role of altered colonic detoxification mechanisms in various pathophysiological conditions including ulcerative colitis and carcinogenesis cannot be overemphasised.[1 2] We have thus read with great interest the recent report of Ramakrishna *et al* about sulphation as a mechanism of phenolic compound inactivation in human colonocytes (*Gut* 1991; **32**: 46–9). Though the work provides valuable new information, we feel obliged to make a few critical comments. Firstly, the title and parts of the text may be misunderstood: in fact, paracetamol (acetaminophen) and not phenol sulphation has been investigated. Secondly, the mention that 'studies, on phenolic compound inactivation, using colonocytes from resected colon specimens have not been undertaken' is not entirely correct. Indeed, we have reported preliminary results about the conjugation of 1-naphthol, another phenolic compound, in human isolated colonic cell preparations.[3] 1-Naphthol was extensively conjugated in human colonic crypts, mainly by sulphation (75%), but also by glucuronidation (24%). These results were in agreement with those of Cohen *et al* in cultured human colonic mucosa,[4] where normal colon predominantly sulphated 1-naphthol; in contrast, cancer tissue showed a glucuronidation predominant pattern. In the study of Ramakrishna *et al* paracetamol was poorly glucuronidated in normal colonocytes. This finding is not representative of the metabolic activity of human colonocytes for all phenolic compounds, since 1-naphthol was efficiently glucuronidated.[3] Moreover, this discrepancy may also come from the higher substrate concentration used by Ramakrishna *et al*, as it has been observed in animal species that glucuronidation is more readily saturable than sulphation.[5]

In dialysates of patients with ulcerative colitis, a known preneoplastic condition, Ramakrishna *et al* found no increase of paracetamol glucuronide concentrations and a reduction of sulphated conjugates, which they interpret as an impairment of the capacity of the mucosa to sulphate phenols. However, the reduced recovery of sulphate in dialysate may alternatively be interpreted as increased paracetamol sulphate absorption.[6] Moreover, reduced sulphation activity in colonocytes from ulcerative colitis patients would be at variance with other reports of enhanced biotransformation reactions.[7] These discrepancies between different compounds and experimental models, and the strong pathophysiological relevance of colonic biotransformation activities, emphasise the need for further studies in this field.

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Reply

SIR,—We are pleased to respond to the comments by Dr Dechelotte and Professor Schwenk. Paracetamol, also known as p-acetamidophenol, was used as an example of a phenol because much is known about the metabolism of paracetamol and because it is implicated in causing exacerbations of ulcerative colitis.[1]

The evaluation of colonocyte metabolism by rectal dialysis does have limitations, in particular, underestimation of metabolite formation due to rectal absorption. This point was discussed in detail in a previous paper[2] and has also been addressed by Sund and Lauterbach.[3] The latter study indicated that the dialysis technique may underestimate detoxification mechanisms by at least 50%. Given these limitations, we found that glucuronidation was absent in a large number of healthy control subjects.[2] We accept that colonocytes can detoxify phenols by glucuronidation. However, using rectal dialysis in subjects with ulcerative colitis paracetamol glucuronide was undetectable in most cases and consequently we did not discuss this finding in detail.

The reduced recovery of sulphated paracetamol in ulcerative colitis is in part a phenomenon of reduced sulphation by colonic epithelial cells, an observation to be published shortly.[4] In acute and chronic ulcerative colitis absorption processes, in particular sodium absorption, are diminished and the low recovery rate of sulphated phenol in dialysate may not necessarily be due to an accelerated absorption process. To prove or disprove either point of view further experimentation would be needed.

We thank Dr Dechelotte and Professor Schwenk for drawing our attention to glucuronidation processes in colonic epithelial cells.

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Ranitidine and non-steroidal anti-inflammatory drug (NSAID) associated gastric and duodenal ulcers

SIR,—We read with interest the recent article by Lancaster-Smith *et al* (*Gut* 1991; **32**: 252–5). They showed in a prospective clinical trial that ranitidine was effective in treating gastric and duodenal ulcers related to NSAID use whether or not the NSAIDs were continued and even more effective in patients in whom the NSAIDs were discontinued. Thus gastric ulcers had healed at eight weeks in 63% of those still taking NSAIDs compared with 95% of those who had stopped NSAID treatment. Duodenal ulcers healed in 100% in those who stopped NSAIDs at eight weeks compared with 84% of the group who continued NSAIDs, but the healing rates were slower.

The question remains of whether NSAID induced ulcers behave differently. Do ulcers that seem to have been induced by taking NSAIDs have different rates of healing or recurrence with or without H_2 antagonists or any other treatment? Our own prospective studies evaluating the efficacy of famotidine in NSAID induced duodenal and gastric ulcers as well as ulcers unrelated to the use of NSAIDs did show differences in healing rates at eight weeks in patients in whom the ulcers were temporally related to NSAID use and those in whom there was no relation to the use of NSAIDs. Thus of 160 patients with duodenal ulcers, 40 (25%) were entered into the trial with a history of recent or prolonged NSAID use who had NSAID/aspirin just before presenting with their ulcer. All (100%) healed in eight weeks with famotidine when the NSAIDs were stopped at the beginning of the trial. This contrasts with the group of patients who were non-NSAID users where only 88% were endoscopically healed at the end of eight weeks. Furthermore, of the 110 who went onto six month maintenance treatment with famotidine, all those previously related to NSAID use remained healed at six months (100%) against 74% of patients with ulcers not related to NSAID use.[1] Among the 66 patients with gastric ulcers, 50% had taken NSAIDs just before presenting with gastric ulcer; 88% had complete healing with famotidine when NSAIDs were discontinued within eight weeks compared with the non-NSAID users who had a healing rate of 75% (unpublished data). These studies suggest that NSAID/aspirin induced duodenal and gastric ulcers not only have a different pathogenesis to de novo ulcers but may also have a different natural history than non-NSAID ulcers. The questions from these studies are: Do ulcers that are induced by NSAIDs really need the intensive treatment once the inducing agents (NSAIDs) have been stopped? In fact, what would the healing rate be just by stopping the NSAIDs without any treatment? Once healed, do these ulcers have the same tendency to recur as de novo ulcers and, thus, will patients who are able to stop NSAIDs be required to take maintenance treatment or will the recurrence rate be low even after discontinuing treatment? It seems that maintenance treatment will be extremely effective in this group if it is used. Do all past and future studies on peptic ulcer disease need to be stratified to examine the difference in the healing rates of NSAID induced ulcers com-

pared with non-NSAID ulcers? The results of our study seem to indicate that this aspect of clinical trials would have to be addressed in future publications on ulcer treatment.

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1 Bank S, Greenberg RE, Magier D. The efficacy and tolerability of famotidine and ranitidine on the healing of active duodenal ulcer and during six-month maintenance treatment, with special reference to NSAID/aspirin-related ulcers. *Clin Ther* 1991; **13**: 304–18.

Reply

SIR,—Bank *et al* report healing rates for NSAID associated gastric and duodenal ulcers while taking a histamine receptor antagonist (HRA) after stopping NSAID treatment strictly comparable to those published recently on behalf of a United Kingdom multicentre study group. It seems probable from their comparative studies that an H_2RA heals NSAID associated ulcers even more readily than non-NSAID associated ulcers providing the NSAID is stopped. A similar comparison cannot be made from our study because all patients were taking NSAIDs at the time of referral. Bank *et al* ask whether NSAID associated ulcers heal successfully with placebo treatment if the NSAID is stopped. Neither their or our study answers this question. With respect to gastric ulcer, however, Loludice *et al*[1] found that with antacid alone only 25% of patients healed within six weeks despite having stopped NSAIDs compared with 66% with antacids plus cimetidine.

Bianchi Porro and Pace[2] also showed that severe gastric lesions after NSAID withdrawal healed within four weeks in 50% of patients on placebo compared with 83% on ranitidine. By contrast, of those who continued with NSAIDs and took placebo, only 25% had healed lesions. Comparable information about the behaviour of NSAID associated duodenal ulcer seems not to be available.

The better performance of HRA maintenance treatment in NSAID associated duodenal ulcer compared with non-NSAID associated ulcer reported by Bank *et al* agrees with the findings of Penston and Wormsley.[3] Nevertheless, responsiveness to maintenance treatment seems not to be accompanied by a low natural relapse rate because seven of 14 patients in Penston and Wormsley's study had recurrent ulceration despite discontinuing NSAIDs when maintenance was omitted.

It is clear that future studies should take into account these apparent differences between the natural history of NSAID associated and 'idiopathic' ulcers, but retrospective analysis of past work is likely to be of limited value as most ulcer healing and maintenance studies have specifically excluded patients on NSAID treatment.

Peptic ulcer remains a multifactorial disease but despite this these studies show that in the great majority of cases, regardless of aetiology, control is achievable with HRA treatment.

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Case of watermelon stomach successfully treated by heat probe electrocoagulation

SIR,—We read with interest the report by Tsai *et al* (*Gut* 1991; **32**: 93–4) of a patient whose gastric antral vascular ectasia was treated by laser photocoagulation. We have a similar case of a 77 year old woman to whom we applied heat probe electrocoagulation (Olympus Heat Probe Unit) with an equally satisfactory result.

The patient had a long history of iron deficiency anaemia, thought to be due to severe antral gastritis, which despite continuous oral and intravenous administration of iron was not under control. Several transfusions (at a rate of 1·4 units of blood per month) had been required since the beginning of 1990. In July when she collapsed with a haemoglobin concentration of 54 g/l, a diagnosis of 'watermelon stomach' was made endoscopically and confirmed histologically. There was no evidence of liver disease or portal hypertension. Two sessions of heat probe treatment were carried out applying 100 deliveries of 10 joules each. Subsequently there has been no need for further transfusion and the patient's haemoglobin remains above 100 g/l. However, there has been no change in the endoscopic picture.

Our patient had a history of coronary heart disease which is suggested[1] as a predisposing factor (as are liver cirrhosis and portal hypertension) to the formation of mucosal vascular malformations. Bipolar[2] and heat probe[3] electrocoagulation have been reported to be as effective as the more expensive laser photocoagulation for treatment of gastric antral vascular ectasia, and our experience confirms this.

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Reply

SIR,—I read the letter of Kamberoglou *et al* with interest. Their patient had many features similar to the case we reported, with similar pretreatment transfusion requirements and earlier misdiagnosis. Heat probe thermocoagulation has been used successfully in treatment of bleeding duodenal ulcers[1] and also has the advantage of being cost effective compared with the Nd:YAG laser photocoagulation. I am, however, a little concerned over its use in the control of bleeding in the watermelon stomach. Collateral thermal damage to gastric mucosa is likely to be greater. It would be of little consequence if the vascular ectasia occupied only a small area of the antrum. However, the vascular lesions may be extensive.[2] The safety aspect of thermocoagulation of large areas of the stomach with a heat probe has not been addressed. The authors also admit that there was no visible resolution of the lesions endoscopically. In the laser treated patient, however, the endoscopic appearances improved, suggesting regression of the vascular abnormality which may have some bearing on rates of recurrence of bleeding in treated patients.

While heat probe thermocoagulation represents a cheap and attractive treatment for the smaller lesions of watermelon stomach, I think that treatment of the more extensive lesions is likely to be better with laser photocoagulation.

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NOTES

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