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-