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Reply

SIR,—In their comments on our original paper, Karlstadt *et al* claim that ranitidine may have qualitatively similar effects to cimetidine on drug metabolism and also that cimetidine can have no clinically significant effect on adrenocortical function. In support of their claims they selectively cite a large number of abstracts, letters and papers only a few of which are relevant to either issue.

In respect of the first point, we referred to the work of Henry *et al*³³ to support our statement that ranitidine does not interfere with hepatic metabolism of other drugs. Karlstadt *et al* have considered extrahepatic metabolism also and include six papers in their list of 14 in which ranitidine's effects on the metabolism of other drugs has been ascribed to interference either with intestinal absorption^{3 9 10 11 14} or with the cholinergic system.⁸ Two of the letters cited^{5 13} do describe single case reports of possible interference with theophylline metabolism. Breen *et al*,⁴ however, in a formal study found that cimetidine, but not ranitidine, interfered with the clearance of theophylline and antipyrine. Similarly, the concern expressed by Iliopoulou *et al*¹² in a letter about adverse effects of ranitidine on quinidine metabolism in one of their patients has yet to be formally confirmed. The plasma clearance of nifedipine was not significantly affected by ranitidine.² The effects of ranitidine on warfarin clearance described by Desmond *et al*⁶ have not been observed by others.³⁴ It is interesting that ranitidine has been shown to interfere with the clearance of one β -blocker, metoprolol, but not with that of propranolol or atenolol^{1 35} (see also review 15). In *in vitro* studies, hepatic microsomal cytochrome P-450 has been

shown to bind ranitidine with an affinity which is 10 fold less than that of cimetidine.¹⁶ This weak affinity was noted in the introduction to our paper and may account for the *in vitro* effects of ranitidine on fentanyl metabolism.¹⁵ Clinical differences of ranitidine and cimetidine on drug metabolism are a result of not only their relative cytochrome binding affinities but also because the normal daily ranitidine dose is one-fifth that of cimetidine.

The second point that Karlstadt *et al* take exception to is our suggestion that under certain circumstances cortisol secretion may be impaired *in vivo* by cimetidine. We were careful to point out that with normal oral treatment, plasma concentrations of cimetidine and ranitidine are 100-fold and 4000-fold less than corresponding IC₅₀ values for the *in vitro* inhibition of cortisol synthesis. Even if cortisol biosynthesis were to be affected *in vivo*, it is likely that plasma concentrations would be unchanged as pituitary ACTH would compensate appropriately. *In vivo* inhibition might be apparent under conditions of stress – for example, haemorrhage, or after maximal doses of ACTH. In some of the papers cited by Karlstadt *et al* to support their argument, cortisol data are not presented.^{21 23 25 30} In others only the effects of the less potent adrenocortical inhibitor, ranitidine, are considered.^{29–32} In another, the effects of cimetidine on parenterally administered cortisol rather than cortisol production are considered.²⁸ The works of May *et al* and Coiro *et al*^{23 27} provide indirect evidence that ACTH-mediated cortisol release is unimpaired. We are grateful to Karlstadt *et al* for bringing to our attention the work of Valk *et al*²⁰ which reported a 45% reduction in urinary free cortisol excretion after six weeks of cimetidine treatment. This may, however, not be the most serious adverse consequence of cimetidine treatment. Adrenal steroids play a vital role in physiological response to haemorrhagic shock. It is therefore crucial to establish that the cortisol response to gastric bleeding is not impaired by high intravenous bolus dose of cimetidine. It is this situation, which is not uncommon, which needs to be investigated more thoroughly.

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Anastomotic recurrence of colorectal cancer

SIR,—The review of Keighley and Hall (*Gut* 1987; **28**: 786-91) is a timely reminder that this important complication of restorative resection is still incompletely understood, but one must question their conclusion that "the term 'anastomotic recurrence' is misleading". Many local recurrences after an anterior resection certainly occur in the pararectal tissues, and many reports lump all local recurrences together, but recurrence which commences within the suture line is still a serious entity.

It was very much a reality to the pioneers of anterior resection in the 1930's and 1940's^{1,2} and they were dismayed to find some suture line recurrences occurring in patients who had been placed in Dukes' grades A and B. They knew that these patients had had a radical resection, so it was natural to suspect that implantation of exfoliated cancer cells was the source of the recurrences. At the end of 1947 Lloyd-Davies and Naunton Morgan decided to counteract this hazard by thorough irrigation of the colon and rectal stump with perchloride of mercury solution. Their trial was not controlled but a rate of anastomotic recurrence of over 14% was succeeded by one of 2% after the introduction of irrigation, without other changes in technique having been made.^{3,4} Later figures from St Mark's confirmed a recurrence rate of 1-2% in over 400 radical restorative resections.⁵

Those of us trained by these pioneers were certainly convinced by these results, and continued to use their techniques, including cytotoxic irrigation. In 177 radical restorative resections,⁶ 122 of which were followed for more than five years, we directed attention particularly to any sign of anastomotic recurrence by carrying out regular sigmoidoscopies, with biopsy of any suspicious nodule: only one positive biopsy was obtained, although 14 other pelvic recurrences could be felt in the vagina or pararectal tissues. When the operative specimen shows good distal clearance of the carcinoma, recurrence commencing within the suture line is likely to be the result of either a local change in the biology of the mucosa, or implantation. Nothing can be done at present about a field change, but there is a strong suggestion that omission of rectal washout results in more suture line recurrences. In one carefully analysed series⁷ there were 16 such recurrences among 150 patients, in seven of whom the specimen was placed in Dukes' grade A or B, with a mean

margin of resection of 4-5 cm. In another report⁸ 11 of 34 patients suffered an anastomotic recurrence between three and 22 months after resection.

These results are not proof that all these recurrences are caused by implantation but they, and others showing suture material adjacent to recurrent tumour, do suggest that the concept of prophylactic irrigation is soundly based, especially in the light of recent evidence favouring the existence of free viable cancer cells in the rectal lumen.^{9,10} It may well be that it is the mechanical effect of cleansing achieved by irrigation which is the most important effect because Heald reports no suture line recurrences after 115 resections in which water alone was the irrigant.¹¹

Irrigation of the rectal stump and the end of the colon before restorative anastomosis is harmless, desirable from a hygienic point of view, and easily done with the patient in lithotomy-Trendelenburg position. In the light of present knowledge it is surely right also to regard irrigation as an essential prophylactic before performing a restorative anastomosis after anterior resection for cancer.

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