

## LETTERS TO THE EDITOR

### Cancer in an ileoanal reservoir

SIR,—Dr Appelman (*Gut* 1990; 31: 1161) has asked how we determined that the carcinoma within the rectal cuff surrounding an ileoanal reservoir that we described in our article<sup>1</sup> was a primary one and not a metastatic tumour. If one were only to assess the histology presented then the question would be extremely difficult to answer, as he has pointed out. In standard clinical practice, however, difficult diagnoses such as this are generally made by the clinician and pathologist in concert, considering both clinical and pathological features. Thus, if we do so in this case we believe we can defend the argument that we have put forward.

To establish a diagnosis of metastatic cancer we would have to accept that the original cancer which was resected in 1977 metastasised 10 years later in 1987. Moreover, the pattern of metastases would have been a selective trans-coelomic spread to predominate within the cuff of the new pouch with no evidence of other metastases to the true pelvis or to the remainder of the abdominal cavity. Although this is technically possible, the combination of events would be extraordinarily unlikely.

In favour of a new primary cancer the following evidence can be considered. The tumour predominated grossly within the cuff. Secondly, the original indication for the pouch procedure was for severe dysplasia in the remaining rectal stump.

Although it is not possible to clearly distinguish the two diagnoses on microscopy alone, the weight of evidence is sufficiently compelling in favour of a primary tumour developing in the mucosal fragments of the rectal cuff that we feel justified in the submission of the title of this article and its substance.

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1 Stern H, Walfisch S, Mullen B, McLeod R, Cohen Z. Cancer in an ileoanal reservoir: a new late complication? *Gut* 1990; 31: 473–5.

### Interleukin 1 in ulcerative colitis

SIR,—We read with interest the recent article by Ligmusky *et al*<sup>1</sup> in which the authors reported a significantly higher interleukin 1 (IL 1) content and release from colonic mucosa of patients with untreated active inflammatory bowel disease, compared with that of control subjects.

We have recently conducted a similar study determining the IL 1 production from fresh and cultured biopsy specimens and its serum concentrations in 15 patients with active ulcerative colitis, 16 with ulcerative colitis in remission, and 13 normal control subjects. The disease activity was assessed clinically, sigmoidoscopically, and histologically, by using the criteria of Truelove and Richards.<sup>2</sup>

IL 1B was measured using ELISA (Cytrotron Biotechnology). Mucosal biopsy specimens, obtained at colonoscopy, were weighed (average weight 10 mg), washed vigorously in 1 ml of 9% sodium chloride solution, and then cultured for 24 hours in 10% fetal calf serum/RPMI.

IL 1B activity was determined in the 1 ml of washing solution and in the medium after the culture.

Only slight IL 1 activity was detected in three plasma samples, all from patients with active disease, confirming IL 1 production is only rarely found in plasma, even in active disease.<sup>3</sup>

Fresh and cultured colonic mucosa obtained from patients with ulcerative colitis in remission produced significantly higher values of IL 1 compared with control mucosa ( $p < 0.01$ ). Furthermore, specimens from patients with active disease produced significantly more IL 1 than those from patients with disease in remission ( $p < 0.01$ ).

In conclusion, our findings are very much in agreement with those of Ligmusky *et al*. We also found a significantly higher IL 1 production in active patients than in those with ulcerative colitis in remission. The determination of IL 1 production from fresh colonic mucosa in the washing solution seems to represent a reliable method.

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### Non-steroidal anti-inflammatory drug induced enteropathy

SIR,—We read with interest the article by Bjarnason *et al* on treatment of non-steroidal anti-inflammatory drug (NSAID) induced enteropathy.<sup>1</sup> We wish to comment on some aspects of their study.

Although the authors set out to study the effect of sulphasalazine on the intestine in arthritic patients on NSAIDs, they have failed to design adequately the study to test their hypothesis. Such a drug study should have been done as a randomised double blind study. Particularly since the main outcome measure was estimation of faecal excretion of <sup>111</sup>indium labelled leucocytes. Inaccurate collection represents a potential major source of bias.

The evidence of small intestinal inflammation and subsequent improvement was provided by the above test. However, this test is unable to distinguish between leakage of leucocytes from large or small bowel.<sup>2</sup> There is increasing evidence that NSAIDs produce inflammation in large as well as small intestine.<sup>3</sup>

The authors' finding that patients on gold therapy did not show deterioration in leucocyte excretion is interesting. This seems to contradict current evidence which suggests that gold can be acutely toxic to buccal, gastric, and colonic mucosa.<sup>4</sup> Do these findings in fact suggest that (as with NSAID treatment) initial mucous membrane damage heals in spite of continuing therapy with development of tolerance?

Further well designed studies should be done to confirm these important findings by Bjarnason *et al* before sulphasalazine can be considered as the preferred second line therapy in arthritic patients on indefinite NSAID therapy.

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### Reply

SIR,—It is not possible to construct a double blind trial without preliminary studies to show rates and magnitude of change.

Your correspondents fail to grasp the advantage of the <sup>111</sup>indium leucocyte technique. The four day faecal excretion of <sup>111</sup>indium is an objective and not a subjective measure of intestinal inflammation. Inaccurate faecal collections do not apply to our studies that are carried out in a purpose built metabolic research ward, where there is no access to an open lavatory. All that the patient passes is collected (or spilt and therefore recovered).

Saverymattu *et al*<sup>1</sup> are misquoted by your correspondents when they suggest that the <sup>111</sup>indium leucocyte technique cannot distinguish between small and large bowel inflammation. The article specifically comments on the accuracy of the technique for localising colonic disease but it may slightly underestimate the extent of small bowel disease.

While we agree that there is increasing evidence that non-steroidal anti-inflammatory drugs (NSAIDs) produce inflammation in the large bowel, the reference to this in a letter describing two patients on a number of drugs capable of damaging the large bowel is hardly appropriate and the association is refuted in a simultaneously published letter.<sup>2</sup> There are two recent comprehensive reviews on the effect of NSAIDs on the large bowel.<sup>3,4</sup> We scanned all 60 patients in our study and found no evidence of colonic inflammation. Neither did De Vos *et al* during colonoscopy in more than 200 patients on NSAIDs.<sup>5</sup>

The mucocutaneous reactions to sodium aurothiomalate cited are very rare and tend to be idiosyncratic. No such patients were included.

We never suggested that sulphasalazine should be the preferred second line therapy in rheumatoid arthritis, nor would we contemplate its use in arthritic patients on indefinite NSAID therapy.<sup>6</sup>

There is no evidence whatsoever that the small intestinal mucosa develops tolerance to NSAIDs.

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### Duodenal ulcer and carbohydrate

SIR,—We have read with interest the results of the study from Nottingham by Katschinski *et al* (*Gut* 1990; 31: 993-6) concerning the association between duodenal ulceration and fibre and refined carbohydrate intake. The findings suggested that relative risks were reduced by a high vegetable fibre and low refined sugar intake but not a high intake of cereal fibre.

We have continued to gather information about the geographical distribution of duodenal ulceration and the staple diets of high and low incidence areas, and we find no correlation between duodenal ulcer incidence and fibre intake alone. There are high incidence areas in Ethiopia, Rwanda, and Burundi and in sorghum eating areas of India where the fibre intake is high.

The overall picture suggests that areas where polished rice, yams, or cassava are the staple foods the duodenal ulcer incidence is high. Where unrefined wheat, soya, some pulses or millets, or certain green vegetables form a large part of the staple diet the incidence is low.<sup>1,2</sup>

Experimental work on several animal models of peptic ulceration shows that the food substances mentioned above from low incidence areas contain a protective fraction which is liposoluble. The fraction is present in wheat bran but to a less degree in wheat germ.<sup>3</sup> We think that it is a protective factor present in certain high fibre foods and not the fibre itself that protects against duodenal ulceration.

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### Gastric acid and urinary acid excretion

SIR,—Johnson *et al* (*Gut* 1990; 31: 826-6) could not find a significant rise of urinary pH two hours after the start of a standard meal in normal subjects (despite a reduction in urine acid output) nor in patients after vagotomy. They concluded that changes in the rate of urinary acid output after a meal could not be detected by measuring pH because of the presence of buffers in normal urine. Their findings may reflect the inferiority of a standard meal to pentagastrin for maximal stimulation of gastric acid secretion.

We measured urinary pH in 14 duodenal

ulcer patients with no vagotomy (group A) and in 14 patients after vagotomy (group B), before and two hours after pentagastrin 6 µg/kg subcutaneously. Median pH of basal urine in group A was 4.9 (range 3.9-5.7). Two hours after the meal the corresponding values were 6.2 (5.2-7.0). In group B preprandial and postprandial urine pH was 5.3 (4.7-7.0) and 5.3 (4.5-7.0).

Thus the conclusion drawn by Johnson *et al* is correct for pentagastrin stimulation after vagotomy, but not for duodenal ulcer patients who have not had a vagotomy.

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### Reply

SIR,—Thank you for the opportunity to reply to these comments. Like us, Dr Niv and colleagues were unable to show a true 'alkaline' tide in the urine after gastric stimulation because their pH values were all 7 or less. Nevertheless, they showed an alkalisation of the urine, as measured by rising pH in duodenal ulcer patients after pentagastrin stimulation, and were unable to show this effect in duodenal ulcer patients after vagotomy.

It would be interesting to know whether these measurements were taken during a standard gastric secretory study, with aspiration of gastric contents. This manoeuvre will clearly render the body's acid-base balance more alkaline by the removal of the gastric acid secretion. Perhaps this explains why they were able to show a change in pH in non-vagotomised ulcer patients. We maintain, however, that pH is a much less sensitive indicator of the amount of acid excreted in the urine than is direct titration of the acid content of the urine.

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### Lipid pattern and plasma insulin in diabetics with gall stones

SIR,—We read with great interest the paper by Laakso and colleagues (*Gut* 1990; 31: 344-7) regarding the relation between serum lipids, plasma insulin, and gall stones in non-insulin dependent diabetic women. The authors suggest that diabetics with gall stone disease have higher fasting insulin concentrations and lower total and low density lipoprotein cholesterol than diabetics without gall stones.

In the introduction they state that no studies have been published comparing lipids and lipoproteins in diabetics with or without gall stones. Some years ago we reported different results on the relations between gall stones and serum lipids in non-insulin dependent diabetic patients. We studied total cholesterol, serum triglycerides, and apolipoproteins A I and B in 81 subjects with non-insulin dependent diabetes mellitus affected by gall stones and 305 diabetics without gall stone disease.<sup>1</sup> We documented increased concentrations of triglycerides and decreased values of apolipoproteins A I in diabetic women with gall stones compared with those without, while no difference was shown in men. Total cholesterol and apolipoprotein B concentrations did not differ

between groups. The observation of high concentrations of triglycerides in gall stones has been reported by most authors; our experience is in agreement with published papers and conflicts with the data reported by Laakso. Our finding of such an association only in women agrees with the observation of more severe lipid alteration in women with diabetes<sup>2</sup> and of an association of gall stones, low concentrations of high density lipoprotein cholesterol, and coronary disease found only in women.<sup>3</sup>

The serum lipid pattern in our patients might be related to increased serum insulin concentrations, as suggested by Laakso *et al* in another paper.<sup>4</sup> In this regard, in a case-control study (34 patients with gall stones and non-insulin dependent diabetes mellitus *v* 30 controls without gall stones, comparable for sex, age, body mass index, and duration and metabolic control of diabetes) we also documented increased values of C peptide in subjects with gall stones compared with controls.<sup>5</sup>

Concerning the possible mechanism by which hyperinsulinaemia could enhance gall stone formation, Laakso *et al* report that high insulin concentrations could activate low density lipoprotein receptors with an increased plasma-bile clearance of low density lipoprotein cholesterol. It, however, has also been reported that insulin is able to enhance the activity of β-hydroxy β-methylglutaryl coenzyme A reductase<sup>6</sup> and to suppress 7 alpha-hydroxylase<sup>7</sup> with consequent increased cholesterol and decreased bile acid secretion in bile. According to this finding Bennion and Grundy<sup>8</sup> showed that insulin administration in non-insulin dependent diabetics could increase cholesterol saturation of bile. In a preliminary retrospective evaluation of 386 subjects with non-insulin dependent diabetes mellitus we showed a significantly higher frequency of gall stones in patients treated with insulin compared with those being managed by diet or oral hypoglycaemic agents.<sup>9</sup> This finding seems to support the hypothesis of an increased risk of gall stones in diabetics treated with insulin, but prospective investigations on this topic are necessary.

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