LETTERS TO THE EDITOR

Cancer risk in patients treated surgically for duodenal ulcer

EDITOR,—Macintyre and O'Brien (*Gut* 1994; **35:** 451–4), although discussing our paper[1] in some detail, seem to have misunderstood it.

They claim that Caygill *et al* reported an 'increased risk of cancers of the colon, rectum, biliary tract and female breast', in contrast with their own results in duodenal ulcer patients. In fact, firstly we did not separate colon and rectum but, like them we reported a decreased risk (relative risk 0·8) in duodenal ulcer patients of colorectal cancer (see our Table I).

We did report an excess risk of biliary tract cancer in duodenal ulcer patients but it was not significant. The excess risk of female breast cancer that we reported was seen only after a 20 year latency. Elsewhere in the paper they claim that we reported an excess risk of oesophageal cancer, again in contrast with their own results. But like them we found no significant excess of oesophageal cancer in duodenal ulcer patients (see our Table I).

We did report significant excess risks at these sites in gastric ulcer patients or in our whole cohort of peptic ulcer patients.

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1 Caygill CPJ, Hill MJ, Hall CN, Kirkham JS, Northfield TC. Increased risk of cancer at multiple sites after gastric surgery for peptic ulcer. *Gut* 1985; **28:** 924–8.

Reply

EDITOR,—We are grateful to Drs Caygill and Hill for their response to our paper. Confusion over deaths from cancer of the colon and rectum has probably arisen because while they did not separate these in their Table I they did so in Table III. There has, however, been no misunderstanding on our part about their conclusions. They state in their summary '. . . from 20 years after operation there was a significant excess risk not only of cancer of the stomach but also of the large bowel, bronchus, pancreas, biliary tract, oesophagus, bladder, breast, and cancer of all sites. These findings are consistent with the production in the operated upon stomach of circulating carcinogens with a 20 year latency period'. The evidence from our study and from others does not support their suggestion of a circulating carcinogen being produced in the operated stomach. Furthermore we take issue with their statement that cancers in such patients 'are unrelated to a common predisposition such as smoking'. We believe that the evidence of our study, and the others that we quoted in our paper, suggests that cigarette smoking is indeed the most important risk factor in carcinogenesis in such patients.

While Drs Caygill and Hill did find differences in subsequent cancer mortality between patients operated on for duodenal ulcer and gastric ulcer, they did not draw attention to this in subsequent discussion or summary.

As the debate draws to a close with the disappearance of elective surgical treatment for peptic ulcer, it is appropriate that the conclusions from this area should be clarified. We believe that these are as follows: that patients operated on for gastric ulcer are at significantly higher risk of developing gastric cancer 20 years postoperatively: that there is a significant increase in smoking related cancers as a result of the excess of cigarette smokers in this group, and finally that there is no evidence to support production of circulating carcinogens by the operated stomach.

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Intestinal permeability in patients with Crohn's disease

EDITOR,—We read with great interest the article by Munkholm *et al* (*Gut* 1994; **35:** 68–72). While this is very interesting work we feel that several important facts must be pointed out.

An important conclusion reached by the authors is that these data do not support the hypothesis that asymptomatic first degree relatives of patients with Crohn's disease have increased intestinal permeability. Furthermore, they state that as a large number of participants were included in their study, it had minimal risk of a type 2 error. We would like to point out that in another study, similar in design to this one, we have examined a comparably sized group and by combining data from two separate studies we have in fact studied almost twice as many relatives of patients with Crohn's disease as reported here.[1] Most importantly, our interpretation of the data differs dramatically from that presented in this paper. We described in our paper a fundamental flaw in the analysis of this type of data that has potentially contributed to much of the confusion in published works concerning these issues. We are disappointed to see the same flaw repeated in this work.

Not all relatives of patients with Crohn's disease ultimately develop the disease. In fact it has been estimated that only 10% of this group will develop disease during their lifetime.[2] Therefore, even if increased intestinal permeability is a prerequisite for disease and, furthermore, is manifested lifelong only 10% of the relative group would be expected to show increased intestinal permeability. In the study by Munkholm *et al* only 39 relatives of patients with Crohn's disease were studied, therefore, given these assumptions only four subjects should have increased permeability. It is almost inconceivable that such a small fraction would significantly change the mean of the entire group. We discuss this more fully in our paper. The point that must be made is that this type of data analysis cannot disprove the hypothesis that relatives of patients with Crohn's disease have increased intestinal permeability.

The most effective means to analyse the data obtained in this study is to construct a normal range of permeabilities and to ask whether a subgroup of relatives exists with increased permeability and disregard group statistics. These points were clearly made in our paper and we are disappointed that they have been ignored. From our perspective, unless the study by Munkholm *et al* deals with these issues it is merely a repetition of numerous previous studies that have completely missed the point. With only 10% of relatives having abnormal permeability the approach used in this paper will be unlikely to even show a statistical difference between control and relative groups. Thus, we believe the conclusions reached by the authors are unwarranted as the statistical analysis fails to consider the question that the authors intended to ask.

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1 May GR, Sutherland LR, Meddings JB. Is small intestinal permeability really increased in relatives of patients with Crohn's disease? *Gastroenterology* 1993; **104:** 1627–32.
2 Yang H, McElree C, Roth M-P, Shanahan F, Targan SF, Rotter JI. Familial empiric risks for inflammatory bowel disease: differences between Jews and non-Jews. *Gastroenterology* 1992; **102:** A31.

Reply

EDITOR,—We only became aware of the publication of May *et al* [1] when our article was in press.

Although the analytical methods for determination of urine concentrations used by May *et al* seem to be identical to those of our study, the results obviously differ in that we did not find any difference in permeability among Crohn's disease patients, healthy or inflammatory bowel disease (IBD) diseased relatives, ulcerative colitis patients, and controls.

The proposed method for statistical evaluation is in our opinion not acceptable because non-parametric statistics should be applied in data not normally distributed. Furthermore the correct comparison between controls and patients data seem to be a direct test.

Defining absolute normal limits for permeability based on data from 31 controls does not seem reasonable, which is further illustrated by the 'borderline' values considered abnormal by May *et al*.

The calculations of the Canadian group on the probability of relatives of Crohn's disease patients developing the disease are based on all first degree relatives. In our study we examined only relatives from 18 families with known familial IBD occurrence where the expected inheritance will be higher.[2] Furthermore the individual values of diseased relatives were not different from controls.

We thus conclude that even with the most positive and optimistic view of our permeability data we cannot see anything that points to the very interesting hypothesis suggested by the study of Hollander *et al* in 1984.[3]

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1 May GR, Sutherland LR, Meddings JB. Is small intestinal permeability really increased in relatives of patients with Crohn's disease? *Gastroenterology* 1993; **104:** 1627–32.
2 Orholm M, Munkholm P, Langholz E, Nielsen OH, Sørensen TIA, Binder V. Familial occurrence of inflammatory bowel disease. *N Engl J Med* 1991; **324:** 84–8.

3 Hollander D, Vadheim CM, Brettholz E, Petersen G, Delahunty T, Rotter J. Increased intestinal permeability in patients with Crohn's disease and their relatives. *Ann Intern Med* 1986; **105:** 883–5.

Gall stones in Crohn's disease: another hypothesis

EDITOR,—We read with interest the paper by Hutchinson *et al* (*Gut* 1994; **35:** 94–7) suggesting that in Crohn's disease postoperative gall bladder hypomotility may be the main risk factor for the development of gall stones.

There are indeed several lines of evidence showing that decreased postprandial gall bladder motility participates in gall stone formation.[1] Recent data, however, show that filling and emptying of the gall bladder are complex processes. The gall bladder cyclically contracts during fasting to up to 40% of its maximal volume, just before the occurrence of phase III of the migrating motor complex (MMC) in the antroduodenal area.[2 3] The mechanism of these cyclic contractions is not clear. Serum motilin peaks just before phase III of the MMC in the antroduodenal area.[4] Moreover, exogenous motilin, producing premature MMCs in the gut, causes an increase in gall bladder motility similar to that seen during spontaneous gall bladder cyclic activity in dogs.[3 5] It has therefore been suggested that the increment in plasma motilin concentrations may be responsible for the gall bladder contractions.[5]

We have recently studied 25 patients with uncomplicated, inactive Crohn's disease (mean Crohn's disease activity index 60·7). Gastrointestinal motility was studied during fasting (5 hours) and after a meal (1 hour) by standard perfusional manometry.[6] Data obtained were compared with those of 33 healthy controls. The incidence of phase III of MMC was considerably reduced. In 13 of 25 patients phase III was absent (*v* 0 of 33 of healthy controls $p<0·001$). In the other patients phase III was less frequent (one of 140 minutes *v* one of 99 minutes, $p<0·05$), shorter in duration (4·6 (1) minutes *v* 6·9 (1), $p<0·05$), and rarely starting from the stomach (four of 25 *v* 18 of 33, $p<0·01$). Mean motilin values were in the normal range, but lacked a clear peaking during phase III of the MMC.

The high prevalence of gall stones in Crohn's disease is well established. The accepted mechanism of disturbed enterohepatic circulation of bile salts in these patients could perhaps be enhanced if a change in gall bladder motility also occurs. Hutchinson *et al* suggest that gall bladder sludge may occur because of prolonged fasting or parenteral nutrition in the postoperative period. They found a higher incidence of gall stones in patients with previous laparotomy compared with patients who had not had any abdominal surgery (32% *v* 13%, $p<0·005$). They did not take into account, however, that the age of the patients, duration of the disease, and number of operations are dependent variables. The incidence of gall stones increases with age in Crohn's disease patients; but the incidence of surgery also increases in these patients with the duration of the disease.

We hypothesise that in some patients with Crohn's disease a reduction of cyclic phasic contractions of gall bladder occurs because of a decreased incidence of phases III of the MMC in the antroduodenal area. The lack of periodic stirring and agitation of gall bladder bile may lead to supersaturation of bile and increase propensity for precipitation of salts and formation of gall stones in these patients.[7]

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1 Grace PA, Poston GJ, Williamson RCN. Biliary motility. *Gut* 1990; **31:** 571–82.
2 Toouli J, Bushell M, Stevenson G, Dent J, Wycherley A, Iannos J. Gallbladder emptying is relative to fasting duodenal migrating motor contractions. *Aust NZ J Surg* 1986; **56:** 147–51.
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4 Vantrappen G, Peeters TL. Motilin. In: *Handbook of physiology.* Section 6. Vol II. Bethesda, MD: American Physiology Society, 1989: 545–58.
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Reply

Annese and Vantrappen state that the incidence of gall stones increases with age and duration of Crohn's disease. Our paper supports these statements (*Gut* 1994; **35:** 94–7). The multivariate analysis of our data, however, showed that previous laparotomy also predisposed to gall stones, and that this was an important risk factor independent of age and duration of disease. Furthermore, the prevalence of gall stones was positively correlated with the number of previous operations. We found that the site of disease or intestinal resection did not seem to influence the risk of gall stones. These findings called into question the accepted explanation that changes in the enterohepatic circulation of bile salts predispose to gall stones in patients with Crohn's disease. Rather, we postulated that laparotomy may predispose to gall stones by inducing gall bladder hypomotility, and that the risk of gall stone formation increases with number of operations.

We did not study the mechanism of this phenomenon in our epidemiological study, but the interesting findings by Annese and Vantrappen on the migrating motor complex and motilin concentrations in patients with Crohn's disease may provide clues to the mechanism of gall bladder hypomotility in Crohn's disease.

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Value of granulocyte scintigraphy in inflammatory bowel disease

EDITOR,—We read with great interest the article by Sciarretta *et al* (*Gut* 1993; **34:** 1364–9) on the value of technetium-99m labelled granulocyte scintigraphy in Crohn's disease. Although we agree that technetium labelled granulocyte scintigraphy is of great value in the assessment of inflammatory activity in patients with inflammatory bowel disease (IBD), in providing information on the localisation, the extent, and the severity of the inflammation, we have some reservation concerning certain aspects of this study. The differentiation between ileal and ascending colon localisation is difficult. In a prospective study,[1] granulocyte scintigraphy was compared with operative and endoscopic findings. This study shows the unsuccessful anatomical differentiation with granulocyte scintigraphy in five of eight patients with a hot spot in the right lower abdomen. Therefore, we are curious to discover the criteria of the authors to differentiate between both of the localisations when there is a hot spot in the right lower abdomen.

We are surprised by the finding of a 100% sensitivity and specificity in the detection of intestinal fistula and abscesses. To our knowledge, this is the first study to claim a 100% accuracy with these diagnoses. From Figs 1 and 2 in the article, we cannot distinguish abscess or fistula from simple skipped lesions, which are quite common in Crohn's disease. Which criteria have the authors used in differentiating between skipped lesions and fistula? From the article it is not clear how many patients received the 24 hour scintigram, which was their main criterion for diagnosing an abscess. With which techniques have the abscesses and fistulas been subsequently confirmed? Is it possible that the choice of techniques, or procedures to confirm the diagnoses, have influenced the 100% specificity finding? Furthermore, because not all of the patients have been checked for fistulas and abscesses (only those with evidence on granulocyte scintigraphy) the sensitivity might be lower than the 100% mentioned in the article. In our prospective, blinded study,[1] the detection of abscesses and fistula with granulocyte scintigraphy was disappointing. The sensitivity and specificity for abscesses was 60% and 78%, and for fistulas 40% and 78%, respectively. For detection of fistulas and abscesses in the acute phase, computed tomography was more accurate in this and other studies.[1–4] Although the study by Sciarretta *et al* has confirmed the value of ^{99m}Tc-HMPAO granulocyte scintigraphy in assessment of activity and extent of IBD, the diagnostic accuracy of granulocyte scintigraphy might be less accurate than suggested. Therefore, despite the finding of Sciarretta *et al*, we would advise clinicians who see a patient with suspected abscess or fistula, to perform computed tomography before starting corticosteroid treatment.

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1 Kolkman JJ, van Dijk DH, Bannink I, den Hollander W, Roos JC, Cuesta MCA, *et al.* CTScan and granulocyte scintigraphy enable assessment of localisation and inflammatory activity in IBD exacerbations. *Gastroenterology* 1994; **106:** A713.
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