The level of prolongation of the prothrombin time at which a contemplated percutaneous biopsy should be abandoned in favour of a transjugular or plugged procedure has likewise not been defined. It would be helpful if future audits or reviews aimed to clarify this point. A prospective study of the efficacy and duration of action of fresh frozen plasma is underway at the Queen Elizabeth Hospital.

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Reply

EDITOR,—As Dr Jolobe will be aware from the design of the study, we are reporting on current practice over a wide range of hospitals in England and Wales, and, as he points out, suspected malignancy was the indication in about half of those patients over 65 years of age who had a percutaneous liver biopsy. As the data were drawn from the last 10 biopsies done in each hospital, they do not tell us how many patients with suspected hepatic malignancy were treated without histological confirmation, but it is likely that there were many. The frequency with which clinicians found the result helpful, however, emphasises that they found the confirmation useful in discussions with the patient and relatives and in establishing a management plan in a condition that has such a poor prognosis. Clinicians will be only too aware of the harm that can be done by the occasional mistaken diagnosis of a terminal condition. The relative roles of biochemistry, imaging, and liver biopsy in the diagnosis of hepatic malignancy in this study is the subject of a separate communication,¹ but in this study the specificity of ultrasonography was only 86% and sensitivity 82%. Furthermore, in a small number of cases a non-malignant diagnosis was positively established at liver biopsy when malignancy had been suspected on ultrasound examination.

Like Dr Fisher, we believe the data supporting the relation between coagulopathy and haemorrhagic complications are important in view of previous negative reports. Bleeding can occur, however, with normal clotting. The precise indications for alternative techniques such as plugged or transjugular biopsy techniques (used very rarely in this study) remain empirical, but they are an attractive alternative to the expensive and precious resource of human fresh frozen plasma.

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Increased CA 125 in tuberculous peritonitis

EDITOR,—O'Riordan *et al* reported the case of a patient with tuberculous peritonitis, ascites, and pleural effusion who also had a remarkably increased concentration of serum CA 125 (*Gut* 1995; **36**: 303–5). Because of the increase in this tumour marker an ovarian cancer was suspected and a laparotomy was performed with negative results for cancer. The authors consider the increased values of CA 125 the most interesting aspect of the case, and review other published reports on increased CA 125 values in patients with tuberculous ascites.

I believe, however, that the only interesting and noticeable aspect of the case would have been if the patient had had a normal value of CA 125. This tumour marker, commonly used in the diagnosis and follow up of ovarian cancer, increases in a variety of processes involving pleura, pericardium, and peritoneum including endometriosis, peritonitis, pelvic inflammatory disease, and surgical trauma.^{1–3} The increase in CA 125 is not unexpected because this antigen has been detected on mesothelial cells in pleura, pericardium, and peritoneum, particularly in areas of inflammation.⁴

Benign serous effusions, particularly ascites, are associated with increased serum concentrations of CA 125 with values up to 100 times the upper normal limit in some cases.^{1–6} CA 125 has proved to be an excellent marker for ascites in patients with benign liver diseases (sensitivity 98.4%, specificity 95.9%, efficiency 96.9%).⁶ This marker is also very sensitive to minimal amounts of ascites and correlates very well with the amount of ascitic fluid.⁶ Thus, the specificity of CA 125 for ovarian cancer is very low in the presence of ascites of whatever origin.

In addition, the return of CA 125 to normal after anti-tuberculous treatment in the patient of O'Riordan *et al* is not unexpected. CA 125 decreases to normal values when the ascites is removed in cirrhotic patients and increases again when ascites recur.^{6–7}

The authors conclude that 'tuberculosis needs to be considered in the differential diagnosis of ascites with increased tumour markers'. It is well known, however, that CA 125 is an unspecific marker of ascites of whatever aetiology, and tuberculosis, a disease that only uncommonly produces peritoneal effusions, represents only one of the many aetiologies of ascites. Finally, I believe that a laparotomy should not have been performed in this case because both computed tomography and cytological study of ascitic fluid were negative for ovarian cancer and the very high concentration of CA 125 could have been easily explained by the existence of both ascites and pleural fluid.

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Reply

EDITOR,—Dr Collazos' points concerning CA 125 are valid. He is, however, an expert in the area and has published widely on CA 125. We felt this case to be of interest to a general audience because they might not have been familiar with the wide range of differentials for increased serum CA 125. The concentrations of CA 125 are high in many conditions as outlined in Dr Collazos's letter. We mentioned all of these and more in our discussion. Dr Collazos does not mention how he would have made the diagnosis. He might have legitimately requested laparoscopy in place of laparotomy. He suggests neither. We believe he overstates the value of negative computed tomography and non-diagnostic ascitic fluid cytology in excluding intra-abdominal tumour, however. Such measures can only reduce the relative risk that a tumour is present.

One additional point of some interest is that despite our considerable experience with immunocytochemistry and CA 125 in cytological preparations, we were unable to identify positive staining in the mesothelial cell population in the ascitic fluid specimen in retrospect. Had the immuno-panel been performed during the case this too would have urged us towards more invasive investigations.

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Adenomas and a family history of colorectal cancer

EDITOR,—The data presented by Gaglia *et al* (*Gut* 1995; **36**: 385–90) imply that adenomas in hereditary non-polyposis colorectal cancer (HNPCC) occur with increased frequency, show a predilection for the proximal bowel but are not especially large, dysplastic or likely to show villous change. It is interesting to note that these data are at complete variance with our own.¹ We have suggested that the high risk of colorectal cancer in HNPCC is explained not by increased initiation of

adenomas, but by an accelerated evolution of the adenoma-carcinoma sequence.^{1,2} Can the conflicting data be reconciled? The central issue is the identification of genuine HNPCC families. A high proportion of our findings are based on a small number of very large families, one of which is known to harbour a point mutation in *hMSH2*.³ Conversely, a high proportion of tumours originating from smaller families is now turning out to be negative for the mutator phenotype (lacking in DNA replication errors). Thus, different genetic factors must be operating in these families, if any. It is clear that HNPCC mutations may be successfully transmitted through multiple generations.⁴ Geographic regions showing a relative high frequency of HNPCC families have turned out to harbour a single, highly extended family.⁴ The frequency of HNPCC in other regions of the same country may be considerably lower. It would therefore appear that the frequency of HNPCC may be lower than 5% and that the most typical presentation of the syndrome may be within rare but relatively large, extended families. Authentic descriptions of the pathological spectrum within HNPCC must be based either on very large families or families known to carry an HNPCC gene mutation. Conversely, the main practical and logistic problems posed by familial colorectal cancer may lie outside classic HNPCC.

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Reply

EDITOR,—Professor Jass comments that our finding of an increased frequency of adenomas, particularly in the proximal colon in 127 subjects from 69 HNPCC families compared with subjects with less of a family history, is somewhat at variance with the colonoscopic findings in his study of 197 'at-risk' subjects from 29 HNPCC families.¹ His study showed no significant increase in the frequency of adenomas in subjects from HNPCC families compared with a necropsy population. His findings are at variance, however, with another publication of the results of colonoscopy examination of 161 first degree relatives of affected members from 28 HNPCC families,² in which the same group reported an increased prevalence of adenomas similar to what we observed. The increased prevalence of adenomas persisted in all ages. We did not have a control group of subjects with general population risk and it could be argued that our reference group of non-HNPCC subjects may have had an increased risk of adenomas compared with the rest of the pop-

ulation. This would tend to underestimate the increased prevalence of adenomas in our HNPCC group. In our study, however, the colonoscopies were performed mostly by the same operator and at least by the same technique. We cannot be sure in their study that they are comparing like with like – that is, in comparing findings at colonoscopy with those at postmortem examination.

We disagree with Jass that any apparent differences in findings can be reconciled by consideration of family size. All of our HNPCC families were defined by the Amsterdam criteria, as were those of Jass. These are very strict criteria and highly specific for this diagnosis. Thus our description of the pathological spectrum in subjects from relatively smaller families that fulfil the Amsterdam criteria is likely to be as accurate as that obtained from the Jass series. Indeed, to understand the true spectrum of this disease, information from members of large numbers of families in addition to large sized families is required.

We agree with Professor Jass that the jury is still out regarding the proportion of families with HNPCC among those with familial clustering of colorectal cancer, and that the HNPCC may be uncommon.

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Cholecystokinin and transient lower oesophageal sphincter relaxation

EDITOR,—The paper by Ledebor *et al* (*Gut* 1995; **36**: 39–44) clearly shows that CCK infusion does not affect the occurrence of transient lower oesophageal sphincter relaxations (TLOS) in humans. In contrast, we have recently shown that in dogs CCK infusion dramatically increases the frequency of TLOS.¹ A hasty conclusion would be that the dog is not an adequate model. There are arguments, however, suggesting that the difference between the two results is caused by the use of different forms of CCK: CCK-33 in the paper of Ledebor *et al* and CCK-8 in our work. CCK-33 is one of the major molecular forms found in the plasma² while CCK-8 can be considered as the neuronal form synthesised in nerve cell bodies and released at nerve endings.³ It can indeed be postulated that CCK-8, but not CCK-33, is able to trigger TLOS, which are known to depend on the vago-sympathetic pathway.⁴

Moreover, a comparison between the control of TLOS and satiety, which also requires vagal afferent fibres integrity,⁵ shows the difference of the two CCK forms in question. The inhibition of food intake by administration of exogenous CCK-8 is well reported. However, increase of endogenous plasmatic CCK⁶ or administration of exogenous CCK-33⁷ has been found unable to induce satiety.

In conclusion, despite the absence of effect of CCK-33, a CCKergic control of transient lower oesophageal sphincter relaxations and gastro-oesophageal reflux cannot be excluded.

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Diverticular distraction

EDITOR,—Aldoori *et al* (*Gut* 1995; **36**: 276–82) claim to show an inverse relation between physical activity and symptomatic diverticular disease. Their data do not support such a conclusion, and it is unfortunate that such flawed conclusions have been so widely broadcast (the *Times*, *BMJ* 1995; **310**: 476, *Hospital Doctor*).

Despite the paper's title, this was not truly a prospective study, but a retrospective look at a prospective study of heart disease and cancer to which diverticular questions were opportunistically appended while the main study was underway. This study's original hypotheses did not include diverticular disease, and the design did not include a rationale, or a means of systematically detecting diverticula, most of which are asymptomatic.¹

Symptomatic diverticular disease is not a meaningful term. Diverticula probably cause systems only when they bleed or perforate causing peritonitis. Do diverticuli themselves cause symptoms? We think not. When subjects found to have diverticula on barium enema were blindly compared with controls they were no more likely to have bowel symptoms, and the bowel symptoms were mainly those of the irritable bowel (IBS).^{2–4} The authors claim that there is no basis for the diagnosis of IBS, yet there are published criteria.^{5–6} IBS occurs in 10 to 20% of adults.^{7–8} Therefore the abdominal pain and changed bowel habit found in the reported patients of Aldoori *et al* are most probably due to IBS in people who happen to have been found to have diverticular disease.

The authors have not shown that exercise prevents diverticular disease, symptomatic or not. What they might have shown is that exercise prevents functional bowel symptoms, but a better designed study is needed to confirm that. We have certainly seen patients whose