find such a good correlation between motility and ulcer pain[8 9] and although in our own studies the use of an anti-spasmodic did not affect the development of acid induced duodenal ulcer pain,[6] we feel that duodenal wall tension or dysmotility deserve further study as a possible cause of duodenal ulcer pain and a possible explanation for the imperfect correlation between the pH around the ulcer crater and development of ulcer pain in patients with symptomatic duodenal ulcer.

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1 Kang JY, Yap I, Guan R, Tay HH. Acid perfusion of duodenal ulcer craters and ulcer pain: a controlled double-blind study. *Gut* 1986; **27:** 942–5.
2 Peterson WL, Sturdevant RAL, Frankl HD, *et al.* Healing of duodenal ulcer with an antacid regime. *N Engl J Med* 1977; **297:** 341–5.
3 Bank S, Barbezat GO, Novis BH, *et al.* Histamine H-2 receptor antagonists in the treatment of duodenal ulcer. *S Afr Med J* 1976; **50:** 1781–4.
4 Macdonald AJ, Peden NR, Hayton R, Mallinson CN, Roberts D, Wormsley KG. Symptoms relief and the placebo effect in the trial of an anti-peptic drug. *Gut* 1980; **21:** 323–6.
5 Bardhan KD, Saul DM, Edwards JL, *et al.* Comparison of two doses of cimetidine and placebo in the treatment of duodenal ulcer; a multi-centre trial. *Gut* 1979; **20:** 68–74.
6 Kang JY, Yap I, Guan R, Tay HH, Math MV. Acid induced duodenal ulcer pain: the influence of symptoms status and the effect of an anti-spasmodic. *Gut* 1989; **30:** 166–70.
7 Texter EC, Vantrappen GR, Lazar HP, Puletti EJ, Barborka CJ. Further observation of the mechanism of ulcer pain. *Ann Intern Med* 1969; **51:** 1275–94.
8 Palmer WL. The mechanism of pain in gastric and duodenal ulcer. III the role of peristalsis and spasm. *Arch Intern Med* 1927; **39:** 109–33.
9 Smith AWM. The pain of peptic ulceration. *Q J Med* 1954; **24:** 392–407.

Reply

EDITOR,—We would like to thank Professor Kang for his constructive comments on our article. He suggests that the pain commonly experienced by patients with healed duodenal ulcers may be explained by erosive duodenitis producing small breaches in the mucosa. It does seem possible that such breaches may occur in severely inflamed duodenal mucosa and that they would be too small to be seen during endoscopic examination. Indeed, small and scattered breaches in the mucosa could also be missed with microscopic examination of endoscopic biopsy specimens because of the very small area of mucosa examined in this way. These small breaches would permit acidic gastric juice to penetrate the underlying inflamed mucosa and thus possibly lead to the pain. Such a process could occur both in severely inflamed gastric, as well as duodenal, mucosa and hence our suggestion that pain could result from the interaction of inflammation and acid at either site.

Microscopic breaches in the mucosa would be more likely in severely inflamed mucosa and thus the occurrence of pain may relate to the severity of mucosal inflammation as well as the degree of hyperacidity.

We agree also that spasm or dysmotility may play a part in duodenal ulcer pain. Such disturbed motility probably arises from neuronal stimuli triggered by the interaction of acid with the inflamed mucosa and would thus be a secondary, rather than primary, event. We agree, however, that the pain could originate from either events at the mucosal level or from disturbed muscle function secondary to these mucosal events.

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Malabsorption and motor dysfunction in patients with small bowel amyloidosis

EDITOR,—It was with great interest that we read the article by Tada *et al* (*Gut* 1993; **34:** 1412–7). The authors confirm our findings that it is not only familial forms of amyloidosis that cause intestinal motor dysfunction. In their fairly large series of patients they showed that amyloidosis causes either myopathy or neuropathy and that chemical types of amyloid, AL and AH, and AA respectively may determine which of the two factors will predominate the pathological findings and thus have repercussions on the clinical signs.

Recently we reported two cases of a non-familial form of amyloidosis with malabsorption and motor dysfunction.[1] The patient diagnosed as having Waldenström disease and AL amyloidosis was investigated for chronic, watery diarrhoea while the other patient diagnosed with Bechterew's disease and AA amyloidosis suffered from untreatable ferriprive anaemia but also with difficulties of swallowing, bouts of diarrhoea, and episodes of abdominal cramps. Malabsorption tests, among others the bile acid breath tests suggested malabsorption caused by motor dysfunction or bacterial overgrowth, or both. Amyloid deposits in the small intestine were shown in the submucosal blood vessels in case one (endoscopic biopsy specimens) and in the muscularis mucosae, the myenteric plexus, and submucosal blood vessels in case two (necropsy material).

Unlike Tada *et al* we cannot, however, confirm the difference in prognosis in the advantage of the AA amyloidosis. All their AL (n=2) and AH (n=1) cases died during follow up, while 62% of the AA cases (n=8/13) survived. The follow up of our first case (four years) was long but uneventful.

In the second case the clinical situation remained fairly stable for five years. Thereafter ischaemia induced necrosis of the terminal ileum was responsible for faecal peritonitis and death of the patient.

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Reply

EDITOR,—We are grateful to Drs Ectors, Geboes, and Rutgeerts for their comments on our paper. In patients with every type of amyloidosis, the prognosis seems to depend on the extent and degree of amyloid deposits. Pathological examination of the necropsy specimens in our AL and AH cases showed extensive infiltration and replacement of the muscularis propria by amyloid deposits throughout the gastrointestinal tract. Therefore, we thought that they did not respond to any treatment and had a poor prognosis. Varying degrees of amyloid deposits in the gut, however, have been found among the patients with amyloidosis.[1] In the patients with AL or AH, as shown in a case of Fraser *et al*[2] some treatments may be effective and improve the life span until the amyloid deposits become extensive. As in the AA case of Ectors *et al*,[3] submucosal vascular deposits, which were commonly and noticeably found in our AA cases, may produce life threatening symptoms. In amyloidosis patients with clinical manifestations of intestinal pseudo-obstruction, however, life threatening organopathy seems to be more common in AL amyloidosis than in AA amyloidosis.

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1 Tada S, Iida M, Iwashita A, *et al.* Endoscopic and biopsy findings of the upper digestive tract in patients with amyloidosis. *Gastrointest Endosc* 1990; **36:** 10–4.
2 Fraser AG, Arthur JF, Hamilton I. Intestinal pseudoobstruction secondary to amyloidosis responsive to cisapride. *Dig Dis Sci* 1991; **36:** 532–5.
3 Ectors NL, Ghoos YF, Geboes KJ, Rutgeerts PJ, Ponette EP, Verbeken EK. Malabsorption and motor dysfunction in small bowel amyloidosis – a report of two cases and review of literature. *Eur J Gastroenterol Hepatol* 1992; **4:** 361–6.

Iron deficiency anaemia

EDITOR,—I enjoyed the excellent leading article by Drs Sayer and Long (*Gut* 1993; **34:** 1297–9), but differ from them when they state 'hiatus hernia alone seems unlikely to cause iron deficiency anaemia'. I showed that anaemia was 18 times more common in patients with hiatus hernias large enough to be seen on a plain chest *x* ray, than in age and sex matched controls.[1] Subsequently, Dr J A Higgins and I prospectively evaluated 109 patients with large hernias, having at least one third of the stomach above the diaphragm.[2] Endoscopy in these patients showed a correlation between anaemia and the presence of superficial linear erosions of the gastric mucosal folds where the body of the stomach was constricted by the diaphragm. We suggested that these lesions resulted from local trauma. Anaemia did not correlate with oesophagitis or peptic ulcers. We confirmed earlier findings by Holt *et al* that repair of the hernia prevented recurrence of anaemia.[3]

Having observed many subsequent cases in which no other cause for anaemia was found, my colleagues at this institution have generally accepted that large hernias can cause iron deficiency anaemia secondary to the erosions we described.

In my experience, this is a common cause of chronic blood loss anaemia in older patients.

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1 Cameron AJ. Incidence of iron deficiency anemia in patients with large diaphragmatic hernia. A controlled study. *Mayo Clin Proc* 1976; **51:** 757–9.
2 Higgins JA, Cameron AJ. Linear gastric erosion. A lesion associated with large diaphragmatic hernia and chronic blood loss anemia. *Gastroenterology* 1986; **91:** 338–42.
3 Holt JM, Mayet FGH, Warner GT, Callender ST, Gunning AJ. Iron absorption and blood loss in patients with hiatus hernia. *BMJ* 1968; **3:** 22–5.

Reply

EDITOR,—We are grateful to Dr Cameron for his interesting comments. The finding of a hiatus hernia is a very common one and he is commenting on patients with particularly large hernias. We believe that they have shown an association but would like to see more direct evidence for the lesions causing bleeding and thus iron deficiency anaemia. Many patients with a hiatus hernia do not have oesophagitis or gastritis within the sac. It is possible that aspirin or non-steroidal anti-inflammatory drugs may have more potential to cause local damage in hiatus hernias but the case is unproved. The presence of non-haemorrhagic gastritis or oesophagitis may not necessarily be a source of sufficient blood loss to explain anaemia. More evidence is required for us to accept hiatus hernias as a significant cause of gastrointestinal bleeding.

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Chemotherapy *v* symptomatic treatment for hepatoma

EDITOR,—It is with considerable interest that we read the paper by Madden *et al* on their randomised trial of chemotherapy *v* symptomatic treatment in hepatocellular carcinoma (HCC) (*Gut* 1993; **34:** 1598–600). This is actually the second paper reporting an unsuccessful outcome of lipiodol mediated local chemotherapy in hepatocellular carcinoma, on the basis of a randomised trial (the first being a study by a French group).[1]

As lipiodol mediated transcatheter arterial chemoembolisation (TACE) has been reported by a number of authors as a useful treatment for hepatocellular carcinoma,[2–4] it is natural to wonder about the possible explanations for such an unexpected result.

We suggest that the results presented by Madden *et al* may be explained by a number of drawbacks in the design of their study.

The authors show the number of patients joining the study as 25 for each arm, but only 18 patients were actually treated.

There may be a bias, apart from the racial one suggested by the author, as more than half of the selected patients were excluded from the study; the reasons for exclusion vary considerably, but patients living too far away, undergoing surgery or refusing to take part might well have had a better prognosis, for a variety of reasons.

The very low median survival (apparently similar to the survival rate reported by Okuda in patients with extremely advanced disease[5]) in both treated and untreated patients suggests that despite the good median Eastern Cooperative Oncology Group (ECOG) performance rating and Okuda stage reported, the patients included in the study all had extremely advanced disease, which may have been underestimated. In addition, nothing is said about liver function. On the other hand, it may be, as the authors suggest, that hepatocellular carcinoma has a worse prognosis in South Africans. But we know that, although TACE was originally proposed for all hepatocellular carcinoma patients ineligible for surgery or percutaneous ethanol injection, this treatment is only indicated in patients with a comparatively good functional state (Child-Pugh A and B). As the authors mention, this may also represent an important bias.

This possibility is further emphasised by the fact that only three patients were still eligible for a second course of treatment; moreover, it must be remembered that TACE is only useful when repeated courses are given to a patient.[6]

It has also been established that the most useful step in TACE is final embolisation, without which it is much less effective,[7] but it would seem that none of Dr Madden's patients had this procedure.

As we do not believe that a randomised trial of TACE *v* no treatment is ethically acceptable in hepatocellular carcinoma patients, our own experience is based on prospective data collection on 48 patients given an average of three courses of TACE since 1991. The Table gives the patients' age, male/female ratio, and Child-Pugh and Okuda staging. Most of our patients were in Okuda's stage I and fitted in the 0 or 1 ECOG performance rating. Their survival rates at 1 and 2 years were respectively 74% and 50%, with a median survival of 390 days and a treatment related mortality of 2%. This survival rate is actually higher than Okuda describes in stage I patients (345 days).

Patients' characteristics

Mean age (y)		61·0 (range 37–81)
Male/female ratio		3·8/1
Child-Pugh grade	A	63%
	B	27%
	C	10%
Okuda grade	I	63%
	II	37%
	III	0%

Survival: median 390 days–1 year 74%, 2 years 50%

In conclusion, the authors correctly suggest that their data may not apply to hepatocellular carcinoma patients from other geographical areas, but we think it would also have been more suitable to emphasise that their study differs from other reports possibly in terms of the tumours treated, probably as regards patient enrolment, and certainly as concerns the lack of embolisation in the treatment protocol and the non-repetition of the TACE treatment. Despite this and the other study we quoted previously (the authors of which have recently claimed that chemoembolisation is effective in patients with Okuda I hepatocellular carcinoma[8]), unresectable patients with hepatocellular carcinoma clearly benefit from TACE and this has been shown in several studies from Japan and Europe and also in our own experience. To what extent randomised trials of TACE *v* symptomatic treatment are still ethically acceptable is open to debate.

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1 Pellettier G, Roche A, Ink O, Anciaux ML, Derhy S, Rougier P, *et al*. A randomized trial of hepatic arterial chemoembolisation in patients with unresectable hepatocellular carcinoma. *J Hepatol* 1990; **11:** 181–4.
2 Yamada R, Sato M, Kawabato M. Hepatic artery embolization in 120 patients with unresectable hepatoma. *Radiology* 1983; **148:** 397–401.
3 Kanematsu T, Furuta T, Takemata K. A 5 years experience of lipiodolization: selective regional chemotherapy for 200 patients with hepatocellular carcinoma. *Hepatology* 1989; **10:** 98–102.
4 Bismuth H, Morino M, Sherlock D, Castaing D, Miglietta C, Cauquil P, *et al*. Primary treatment of hepatocellular carcinoma by arterial chemoembolization. *Am J Surg* 1992; **163:** 387–94.
5 Okuda K, Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, Hasegawa, *et al*. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. *Cancer* 1985; **56:** 918–28.
6 Ikeda K, Kumada H, Saitoh S, Arase Y, Chayama K. Effect of repeated transcatheter arterial embolization on the survival time in patients with hepatocellular carcinoma. *Cancer* 1991; **68:** 2150–4.
7 Takaysu K, Shima Y, Muramutsu Y, Moriyama N, Yamada T. Hepatocellular carcinoma treatment with intraarterial iodized oil with or without chemotherapeutic agent. *Radiology* 1987; **162:** 345–51.
8 Rougier P, Roche A, Pellettier G, Ducreux M, Pignon JP, Etienne JP. Efficacy of chemoembolization for hepatocellular carcinomas: experience from the Gustave Roussy Institute and the Bicêtre Hospital. *J Surg Oncol Suppl* 1993; **3:** 94–6.

Reply

EDITOR,—Dr Farinati *et al* feel that our random control trial may have underestimated the value of chemotherapy with lipiodol and 5-epidoxorubicin for hepatoma. We offer the following comments on the three points that they make.

They suggest that the outcome should be analysed by treatment received, not treatment intended. We published the results according to treatment intended because in both trials and clinical practice some patients cannot receive the treatment after it has been chosen. We also analysed the results according to treatment received. This did not change the conclusions.

They propose that the patients who were ineligible for the trial may have had a better prognosis than those randomised. We think that ineligible patients probably had a worse prognosis, although we did not follow them up until death. Sixty per cent were ineligible because of conditions that confer a bad prognosis. They were bedridden (33%), aged over 70 years (13%), had extrahepatic tumour (9%) or serious heart disease (6%).

Thirdly, they suggest that final embolisation makes the treatment more effective. The study that Dr Farinati says proves this statement was not a random control trial. We are cautious about accepting its claim.

Finally, Pelletier's trial used doxorubicin but not lipiodol, so this combination has not previously been tested in a random control trial.

We share Dr Farinati's concern that our findings may not apply to all cases of hepatoma because our patients had a short median survival time. We hope that workers who treat cases with a better prognosis will also perform random control trials. It is important to know if the treatment increases morbidity (which we found) or helps such patients.

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