Sir

We would question the method of tumour load assessment in this paper. The intraperitoneal tumour load was scored by counting the number of tumour nodules but there is no mention about the size of the nodules. We have found that the only way to determine tumour load accurately is by semiquantitative scoring and taking the varying diameters of the nodules into account\(^1\). We feel that this is a serious shortcoming of the methodology employed by Tan \textit{et al.} making their \textit{in vivo} results questionable.

The authors did not refer to a publication\(^2\) in which we addressed the same concern about the use of sodium hyaluronate, using a similar experimental approach. In that publication we reported the effect of sodium hyaluronate on intraperitoneal growth of a rat colon carcinoma. In contrast to Tan \textit{et al.}, in two different experiments we could not demonstrate a significant effect on tumour growth, defined by an appropriate scoring of tumour load. The final plea that ‘this matter deserves careful investigation’ has already been carried out.

R. L. Marquet 
M. P. van den Tol 
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Letter 1

\textit{Sir}

The authors argue that ‘an acute-phase protein response at 3 months after operation does not have the prognostic significance reported by earlier studies\(^1\). In this study, however, C-reactive protein (CRP) was estimated postoperatively in only 88 of 202 patients. The indications for the measurement of CRP in this group of patients are not given. The measurements may have been carried out because of a suspected infection (or inflammation) postoperatively. If this were the case then high values of CRP would obviously not be associated with tumour recurrence. This illustrates the disadvantages of such a retrospective study; although practically difficult, the prognostic value of a variable is best studied in a prospective manner. The other study which showed a correlation between high postoperative CRP levels and tumour recurrence was conducted prospectively\(^1\).


The determination of the significance of the difference in tumour recurrence rates between the two groups with and without an elevated CRP by the $\chi^2$ test is probably not appropriate (as one of the frequencies is less than 5).

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Letter 2

Sir

We read with interest that a bulky colonic carcinoma is more likely than a small tumour to elicit an acute-phase protein response (APPR). We have previously shown that there is a positive correlation between the volume of colorectal liver metastases and the serum level of interleukin 6 that stimulates hepatic production of C-reactive protein (CRP). However, whether the APPR reflects the tumour’s behavioural pattern or an epiphenomenon may be partly addressed by measuring the quality of life indices that are more predictive of survival in patients with colorectal liver metastases than tumour size. The impairment in quality of life is significantly associated with increased serum levels of interleukin 2 soluble receptor $\alpha$ that is a marker for T lymphocyte activation thought to be responsible for inducing an APPR. Furthermore, increased serum levels of CRP and of interleukin 2 soluble receptor $\alpha$ also predict weight loss in patients with metastases that is detrimental to survival. Therefore tumour-related APPR and lymphocytic activation may influence survival by inducing weight loss and quality of life impairment in patients with liver metastases. The latter may be related to the depletion of serum tryptophan by immunological activation that results in an imbalance of the neurotransmitter serotonin.

A. Huang
G. Tsavellas
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London SW10 9NH
UK


Authors’ reply

Sir

Measurements of C-reactive protein were performed retrospectively on samples collected for carcinoembryonic antigen measurement as part of follow-up and were certainly not taken because of evidence of infection. Furthermore, the concern of Balasubramanian and Dalavaye regarding the validity of using contingency table analysis ($\chi^2$ test) to compare tumour recurrence rates between two groups is misplaced. It is generally accepted that the $\chi^2$ test is valid if at least 80 per cent of the expected frequencies are greater than 5 and all expected frequencies are greater than 1. The magnitude of observed frequencies is largely irrelevant. This rule is clearly satisfied by the analysis under question. The observations by Huang and Tsavellas are interesting and add weight to our hypothesis that there is an association between tumour behaviour, a systemic host response and outcome in patients with colorectal cancer.

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Value and cost of follow-up after adjuvant treatment of patients with Dukes' C colonic cancer (Br J Surg 2001; 88: 101–6)

Sir

Patients who underwent salvage surgery in this study had a 5-year survival rate of 40 per cent and a median survival rate of 38 months, compared with a 5-year survival rate of 3 per cent and a median survival rate of 9 months for those unsuitable for salvage surgery. These findings are in contrast to those of a meta-analysis by Bruinvels et al. who assessed seven randomized controlled studies. These authors found more asymptomatic recurrences, metachronous tumours, salvage operations and curative resections, with no improvement in overall or cancer-specific survival.

Similarly, four randomized controlled trials examining the same problem have failed to demonstrate any increase in overall survival, despite detecting more recurrences and thereby offering more salvage resections (references 5, 21 and 27 in the study being discussed). This is relevant considering that the


present study included only Dukes’ C lesions, compared to all stages of colorectal cancer in the other trials; one would have expected a better outcome in Dukes’ C disease. Perhaps the dramatic improvement in survival in these patients is due to an alteration in metastatic potential of tumours following chemotherapy? One also wonders whether stage migration is a factor? It should not be forgotten that routine follow-up and reassurance provides psychological support to patients and allows the surgeon an opportunity for audit. The role of general practitioners is relevant in this regard.

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Authors’ reply

Sir
We are not aware of evidence that adjuvant chemotherapy has a beneficial effect on tumour behaviour after relapse. These data are available for analysis in trials with an untreated control group. Stage migration might be important in earlier series not using sensitive liver visualization. Our series of patients with Dukes’ C colon tumours will have harboured fewer patients with cryptometastatic disease. On the other hand, incorporating significant numbers of patients with early colon cancer in the meta-analysis should have improved the chance of survival after salvage surgery in those studies. Two factors may be crucial in explaining the differences in the results: long-term survival is observed in our patients undergoing liver or colon surgery. The chance for cure from secondary surgery in the rectum is very small and studies of patients with rectal cancer will show worse survival from salvage surgery. The quality of surgery has improved compared to the time of the meta-analysis and the rate of rectal relapse and failed liver surgery will be higher in those studies. The question of optimal follow-up after colon cancer surgery is complex. The balance between reassurance for ‘good news’, the agony of false positives and the uncertainty after true relapse is not easy to find.

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Author’s reply

Sir
It is exactly for the reason raised in this letter that we chose to report opening times per square centimetre and not per wound as this enabled exclusion of wound area as a confounding factor. In our hospital and other units in Ireland there is no epidural service available on the wards. We feel the benefits to the patients of reduced pain and reduced opiate requirements are a significant advantage of diathermy incision. Since this study the senior author has used diathermy exclusively to make abdominal incisions. We feel that this technique is safe and provides a rapid, haemostatic incision that is less painful for the patient.

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Randomized clinical trial of diathermy versus scalpel incision in elective midline laparotomy (Br J Surg 2001; 88: 41–4)

Sir
The authors concluded that there is a significant advantage from the exclusive use of electrocautery in creating a midline abdominal incision, expressed in terms of incision time, blood loss and pain score. They found no significant difference in wound or peroperative complication rates. However, the significant reduction in incision time was based on an analysis that depended on wound area, a factor that would have been equivalent in both groups given adequate sample size and randomization. No significant difference in time to enter the abdomen was found between groups, both being around 8 min. With regard to pain relief we were interested to note the absence of epidural analgesia. The authors point out that the most important issue when using diathermy incision is wound complications. Unfortunately, the sample size of the study was too small to examine this issue adequately. The power is such that it would only identify a minimum infection rate of 27 per cent versus their departmental rate of 5 per cent, given a power of 80 per cent and significance level of 0.05. Alternatively, to detect a minimum infection rate of 10 per cent (twice normal) they would have needed 435 patients in each arm. The only valid conclusion to be drawn from this study is that there is a small amount of decreased blood loss from the wound when using diathermy incision. This may be grossly outweighed by a complication rate as yet unknown.

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Author’s reply

Sir
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Extensive surgical cytoreduction and intraoperative hyperthermic intraperitoneal chemotherapy in patients with pseudomyxoma peritonei (Br J Surg 2001; 88: 458–63)

Sir

While congratulating the authors and completely agreeing with the indications for such an aggressive approach I wonder if adjuvant chemotherapy in these patients is really necessary. Since more than 70 treated patients did not benefit from systemic chemotherapy given prior to surgery, why should they benefit after cytoreductive surgery? Endoluminal recurrences at the resection sites are not a major problem and hyperthermic intraperitoneal chemotherapy often results in small and large bowel oedema. What is the rationale for bowel anastomoses after intraperitoneal chemotherapy? Could the rate of enteral fistula be due, at least in part, to the operative techniques? Despite these concerns, the data clearly emphasize that patients with pseudomyxoma peritonei need adequate treatment in specialized centres to avoid inappropriate laparotomy by surgeons less experienced in the treatment of this disease.

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Authors’ reply

Sir

Dr Jähne is correct when he emphasizes the lack of reliable data on the effects of 5-fluorouracil-based systemic chemotherapy in the treatment of pseudomyxoma peritonei. The effects in colon cancer are well established. It is sometimes difficult to distinguish clearly between pseudomyxoma peritonei and well differentiated mucinous adenocarcinoma. We therefore add 5-fluorouracil/Leucovorin to our treatment schedule if our pathologists find malignant foci in the resection specimen. We frequently observe pseudomyxoma peritonei recurrence in bowel suture lines of previous operations. We therefore take the precaution to delay suture lines until after the perfusion. Whether this prevents suture line recurrence is difficult to prove. We are currently studying this question in an animal model. Our rate of suture line breakdown was low and seems not to have been influenced by the sequence chosen. Our main problem remains leakage from pinpoint holes in small bowel due to serosal damage after cytoreduction and adhesiolysis especially in reoperative surgery.

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Sir

Reporting from a database of 2176 patients, the authors focus on a group of 1023 who survived 12 months after endovascular graft insertion. They exclude all complications within the first month of the original procedure. Thereafter, only the ‘most extensive’ of multiple interventions are included. Their analysis is not therefore made ‘on the intention-to-treat principle’ as claimed. Their mean follow-up is only 20 months. How can they justify a results sections on late deaths in this report? The size of aneurysms treated also merits comment. What is the justification for treating patients with aneurysms with diameters of 28–55 mm?

With a 10 per cent reintervention rate, even in this idealized study group, they demonstrate that the current generation of endovascular devices are not robust enough for clinical use. Are the EUROSTAR participants going to stop all further attempts at endovascular aneurysm control in patients? Almost 50 per cent of their patients are classified as American Society of Anesthesiologists grades I and II and should now be offered open aneurysm surgery. Would the authors agree that, at best, the current use of endovascular devices should be confined to developmental research?

Finally, the term endovascular aneurysm repair, although in common usage, is unfortunate. Endovascular interventions never restore vascular integrity to an extent that allows patients to forget about their former life-threatening condition. Endovascular aneurysm control can never be guaranteed for life, as unacceptable reintervention and rupture risks always remain. Perhaps endovascular aneurysm control should be adopted for future use.

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Authors’ reply

Sir

Patients’ results were included prospectively (for 73 per cent of the patients, as reported), which is after preoperative notification of the planned treatment to the Data Registry Centre. We do not see that selecting the most extensive of redo procedures as an endpoint compromises the intention-to-treat principle and such patients were included in the registry. The mean annual death rate after aneurysm repair was approximately 4 per cent in the reported series, which is in agreement with other reported series. After 3 years the cohort in follow-up still included 286 patients (standard error smaller than 10 per cent),
which is a sufficiently large group for a meaningful analysis of the death rate and causes of death within this period.

It was the purpose of the present report to emphasize the relatively frequent need for late revision. We agree that the first and second generation of devices, which constituted the major part of this series, were susceptible to material fatigue and disconnection of different device components. Details of device failure were described extensively in the discussion. It is of note that the majority of revisions were by catheter technique, and only 23 of the 1023 patients required a transabdominal secondary intervention.

Should endovascular technique for aneurysm treatment in general be abandoned because of inferior results? Probably not. Improved device construction, and increased experience of vascular surgeons and interventional radiologists will help overcome the flaws of the technique during the initial years of use. Continued patient and device surveillance after endovascular abdominal aortic aneurysm repair (or control) remains mandatory. Registries, such as EUROSTAR, appear to be useful in identifying adverse events of novel treatment.

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Endoscopic ultrasonography in the evaluation of idiopathic acute pancreatitis (Br J Surg 2000; 87: 1650–5)

Sir

The authors should be commended for their contribution to the rather complex management issues in patients with idiopathic pancreatitis. The article further highlights the limitation of ultrasonographic examination of the gallbladder; 11 of 44 patients had gallbladder stones which were missed on more than one examination. It also draws attention to the issue of biliary sludge/microliathiasis. A previous study concluded that intervention (cholecystectomy/endoscopic retrograde cholangiopancreatography (ERCP)) significantly reduces the incidence of recurrent attacks of pancreatitis. The results of this study fail to show this. Of the 11 patients with microliathiasis, even the five in whom no intervention was carried out did not experience any further attacks of pancreatitis. It would be helpful to know if the authors have more information of further follow-up on this group.

Questions regarding the need for intervention and the most appropriate one in the presence of microliathiasis remain to be answered. In the presence of microliathiasis, do the authors recommend intervention only if the pancreatitis recurs, or even after the primary attack? It is evident that since the advent of laparoscopic cholecystectomy the numbers of cholecystectomies performed have increased. There is still not enough evidence that this group of patients benefit from surgery as there are still a few patients who experience further attacks of pancreatitis even after cholecystectomy. These patients probably belong to a group in whom the microliathiasis is related to stasis secondary to sphincter of Oddi dysfunction. On the other hand, ERCP as the sole therapeutic modality does not seem to be justified as biliary sludge on follow-up scans has been shown to develop into gallbladder stones.

K. Moorthy
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UK


Authors’ reply

Sir

As stated in the original article, one patient with untreated microliathiasis suffered a second attack of pancreatitis 8 weeks after the first. We feel clear evidence of microliathiasis (after feeding has been restarted to reduce biliary stasis) should prompt definitive treatment within 4 weeks of the initial attack as per British Society of Gastroenterology recommendations for gallstone pancreatitis. We disagree that endoscopic retrograde cholangiopancreatography (ERCP) (presumably with sphincterotomy) does not seem justified as the sole treatment modality. In elderly patients in whom the risk of developing symptomatic gallstones is low, it may suffice. In younger patients in whom there is concern regarding long-term sequelae of sphincterotomy and in whom gallbladder stones may develop in the future, laparoscopic cholecystectomy is our preferred treatment.

We believe the hypothesis that recurrent pancreatitis after cholecystectomy is due to sphincter of Oddi dysfunction should be tested only in patients in whom a clear bile duct at the time of surgery has been proven by on-table cholangiography and not preoperative ERCP. It should be remembered that tiny stones may be missed by cholangiography and this remains a difficult problem to solve.
Follow-up of 20 patients revealed a significant reduction in frequency of attacks of acute pancreatitis among those treated for pathology found using endoscopic ultrasonography compared to those in whom no treatment was warranted. The overall morbidity of this approach was only 0.5 per cent. As such, we believe endoscopic ultrasonography is a valuable investigation in idiopathic pancreatitis.

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Randomized clinical trial of laparoscopic versus open appendicectomy (Br J Surg 2001; 88: 200–5)

Letter 1

Sir
The authors must be congratulated for successfully recruiting 828 patients in just 19 months. From this study, and others quoted in it, minimal access appendicectomy appears to carry a lower incidence of wound infection and would, logically, be preferable in obese patients presenting with diagnostic uncertainty. Indeed, several authors1–3 have reported a direct correlation between obesity and increased risk of wound infection. However, it was disappointing to read that the wound complications presented in this study were not correlated with body mass index. In terms of cosmesis, it is hardly surprising that patients preferred the minimal access procedure. It is unfortunate, however, that no data were presented in relation to the actual length of the horizontal incision in the ‘open’ group. While an apparently normal appendix was removed at open operation, it was left in situ in the laparoscopic group. The rationale for this practice seems rather unclear. Regarding the patient who developed a caecal leak, was the base of the appendix gangrenous leading to the sloughing of a ligature? How was this patient subsequently managed?

D. Banerjee
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UK


Letter 2

Sir
We were intrigued by this trial showing significantly more intraperitoneal abscesses in patients randomized to laparoscopy (4.6 versus 1.0 per cent). They believed the most important reason was the chance inclusion of a greater proportion of patients with more severely inflamed appendices in the laparoscopic group. A simple calculation showed that the difference was merely between 46 and 33 per cent. A subgroup analysis focusing only on patients with gangrenous/perforated appendicitis revealed a threefold increase in the incidence of intraperitoneal abscess in the laparoscopic group (3.0 versus 9.2 per cent). Surgical technique was therefore a more important factor than uneven randomization.

The authors alluded to, among other technical points, the possibility of irrigation spreading infected material. We have previously highlighted the risk of energetic irrigation which may disseminate infection to hernial sacs, resulting in scrotal abscess or infected hydrocele1,2. We have now abandoned irrigation and, after thorough suction, the peritoneal cavity is meticulously mopped (as in open appendicectomy) with 4 × 4 cm gauze swabs introduced through a 5/10-mm reducing sheath. The added advantage includes confinement of the infected site by several gauze packs during dissection and suction on a gauze obviates blockage of the sucker. Our updated audit showing four intraperitoneal abscesses in 432 laparoscopic appendicectomies (1.1 per cent) compared favourably with that of open appendicectomy3.

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Y. T. Wong
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3 Lee YK, Sze YS, Yeung HC, Ng WT. Laparoscopic appendicectomy in a community hospital. Clinical meeting of the Hong Kong Society of Minimal Access Surgery, Panyun, China, 2 December 2000.
by our observation that no prospective randomized controlled trial comparing parathyroidectomy with conservative management for patients with mild or asymptomatic disease has been published.

N. Roche
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UK


**Evaluation of the necessity for gastrectomy with lymph node dissection for patients with submucosal invasive gastric cancer (Br J Surg 2001; 88: 444–9)**

Sir

This article describes the association of a number of parameters with the presence of lymph node metastasis in patients over a period of almost 20 years. We are not told how the presence or absence of lymph nodal metastasis was determined. Was it recorded from the records or were the sections studied again? This is important because of the possible variation in the method and intensity of the search for lymph node metastases over this time period. It would be important to look for micrometastases in patients with negative nodes before negating the benefits of lymphadenectomy, especially as these patients would not receive adjuvant treatment.

S. P. Balasubramanian
Department of Surgical Oncology
Royal Hallamshire Hospital
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UK


Sir

We are familiar with Dr Silverberg’s study\(^1\) and wish to record that it was not a randomized trial. Patients were simply advised whether or not to undergo surgery on the basis of the guidelines adopted by the National Institutes of Health Consensus Conference\(^2\). The value of the study was further impaired because 35 of the 121 patients studied opted for a different treatment to that indicated by the protocol. We therefore stand by our observation that no prospective randomized controlled trial comparing parathyroidectomy with conservative management for patients with mild or asymptomatic disease has been published.

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**Authors’ reply**

Sir

In response to the letter from Banerjee, although clinically significant, infectious complications and cosmesis were classified as secondary endpoints in our study. In the absence of prior calculations of sample size and power of secondary endpoints, statistical tests on secondary endpoints must be exploratory, serving to explain or support findings and to suggest further hypotheses for subsequent research. Inclusion of predictor variables such as body mass index and length of incision seems to be most appropriate in studies in which wound infection and cosmesis, respectively, are primary endpoints. There is accumulating evidence, including a pilot study in the *Danish Medical Journal*\(^4\), that a non-inflamed appendix can be safely left *in situ* at laparoscopy, even if another diagnosis is not achieved. The decision to remove a normal looking appendix at open surgery was approved by the ethical committee and primarily based on the possible confusion caused by a transverse scar in the right fossa if the appendix was not removed. The patient with a caecal leak had the first proximal endoloop placed on the elongated caecal wall resulting in necrosis. Following open suture repair and antibiotics the patient recovered uneventfully.

Ng *et al.* are to be congratulated on an intraperitoneal abscess rate of 1·1 per cent. We do agree that surgical factors such as experience or technique influence the rate of developing intraperitoneal abscess in the postoperative period. Until results from controlled trials comparing surgical techniques are available the significance of surgical technique as a risk factor remains speculative. Our study allowed us to identify variables such as body mass index and length of incision seems to be most appropriate in studies in which wound infection and cosmesis, respectively, are primary endpoints. There is accumulating evidence, including a pilot study in the *Danish Medical Journal*\(^4\), that a non-inflamed appendix can be safely left *in situ* at laparoscopy, even if another diagnosis is not achieved. The decision to remove a normal looking appendix at open surgery was approved by the ethical committee and primarily based on the possible confusion caused by a transverse scar in the right fossa if the appendix was not removed. The patient with a caecal leak had the first proximal endoloop placed on the elongated caecal wall resulting in necrosis. Following open suture repair and antibiotics the patient recovered uneventfully.

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1 Pedersen AG, Petersen OB, Wara P, Qvist N, Laurberg S.

**Authors’ reply**

Sir

The existence of nodal metastases is based on the pathology report of each patient and not re-evaluation using a new technique such as immunohistochemical staining by cytokeratin antibody. Assessment involved a single section of each node in its longest axis and stained with haematoxylin and eosin. The existence of micrometastases certainly may be a source of residual disease. The incidence of micrometastases in submucosal invasive cancer is reported as 14–23 per cent\(^1,2\). The reported risk factors for micrometastases are exactly the same as ours and the low-risk group have a limited risk.

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UK


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Sir

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UK


Sir

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N. Roche
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Department of Surgery
St Thomas’ Hospital
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**Authors’ reply**

Sir

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1 Pedersen AG, Petersen OB, Wara P, Qvist N, Laurberg S.
We accept that the presence of micrometastases may afford a small, but as yet undetermined, additional risk and agree that careful follow-up of locally resected patients is mandatory. Such risks should be explained to patients when informed consent is obtained.

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Randomized clinical trial of Helicobacter pylori from dental plaque (Br J Surg 2001; 88: 206)

Sir

Butt et al. base their study on a conclusion from the work of Desai et al.¹ which suggests that Helicobacter pylori in dental plaque is more resistant to conventional therapy as used for gastric organisms. Having shown how the oral population of H. pylori may be controlled, do the authors propose to study patients endoscoped both before and after gastric and dental treatment? This might be in the form of a randomized controlled trial, with groups assigned to those receiving or not receiving oral treatment in addition to triple therapy.

The assumption the authors made is reasonable, but does not consider environmental factors such as person-to-person transmission, as suggested by Berkowicz and Lee², or H. pylori in patients without dental plaque who may be acquiring it by other means than from the environment. The evidence perhaps needs to be stronger if the recommendation is to send patients with antral H. pylori gastritis for dental assessments.

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Author’s reply

Sir

The relevance of H. pylori in the oral cavity is still unknown. The pilot study raised several interesting questions, namely the potential source of the dental plaque for gastric re-infection following triple therapy. The proposed study by Mr Chaudhuri is of interest but our first priority is to improve the laboratory identification of the micro flora. We recognize the need to undertake a more sophisticated identification of H. pylori.

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