

## LETTERS TO THE EDITOR

### Is needle biopsy of the liver necessary to diagnose HCC?

EDITOR.—Schotman and colleagues (*Gut* 1999;45:626-7) reported a patient with subcutaneous seeding of hepatocellular carcinoma (HCC) after percutaneous needle biopsy together with a review of 14 similar cases and correctly outlined the necessity for a critical evaluation of the role of needle biopsy in resectable HCC.<sup>1-4</sup>

We agree with their conclusion, namely that: (i) a needle biopsy may be indicated only if it is not possible to diagnose HCC by other means (namely increased  $\alpha$  fetoprotein (AFP) concentrations, spiral computed tomography (CT), magnetic resonance imaging); in these cases, a single pass with a large needle (18 gauge) may be preferable to multiple passes with smaller calibre needles; (ii) needle biopsies are not indicated to confirm HCC in patients suitable for liver transplantation; and (iii) the entire needle tract should be resected at surgery for the primary tumour. This has been important in other skin recurrences, namely those after laparoscopic cholecystectomy for undiagnosed gall bladder carcinoma.<sup>5,6</sup>

However, we have some questions and comments concerning the reported case. Firstly, why did the authors perform tumour biopsy in a 30 year old woman with hepatitis B liver cirrhosis and raised serum AFP, showing a 2 cm diameter subcapsular nodule in segment V and two additional satellite lesions in the same segment? Adequate imaging procedures were already available four years ago. In fact, the patient had percutaneous liver biopsy together with an informative diagnostic procedure such as spiral CT. In addition, subcapsular liver lesions are known to give a high rate of both subcutaneous recurrence and intraperitoneal subdiaphragmatic seeding.<sup>1</sup> Therefore, in contrast with recurrence after laparoscopic surgery which mostly cluster around abdominal port tracts,<sup>5,6</sup> simple removal of the needle tract could not be sufficient to prevent the side effects of percutaneous liver biopsy. Secondly, why did they perform right hemihepatectomy in a cirrhotic liver rather than segment V segmentectomy? The latter could be a similarly adequate procedure while preserving better residual liver function.

The authors should be congratulated for focusing once again on a very important question (to biopsy or not to biopsy liver nodules in suspected HCC in the present era of highly effective imaging) and for their collection of 15 cases, which is obviously an underestimation of what occurs in practice and is currently observed in many transplantation centres. However, their message for the reader should be clearer as there is an apparent contradiction between what they state and what they actually did.

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- 1 Takamori R, Wong LL, Dang C, *et al*. Needle-tract implantation from hepatocellular cancer: is needle biopsy of the liver always necessary? *Liver Transpl* 2000;6:67-72.
- 2 Smith EH. Complications of percutaneous abdominal fine-needle biopsy. *Radiology* 1991; 178:253-8.
- 3 Andersson R, Andrén-Sandberg A, Lundstedt C, *et al*. Implantation metastases from gastrointestinal cancer after percutaneous puncture or biliary drainage. *Eur J Surg* 1996;162:551-4.
- 4 Cedrone A, Rapaccini GL, Pompili M, *et al*. Neoplastic seeding complicating percutaneous ethanol injection for treatment of hepatocellular carcinoma. *Radiology* 1992;183:787-8.
- 5 Baldi C, Zuckermann M, Montalto G, *et al*. Factors influencing seeding of tumoral cells and recurrence at trocar sites after laparoscopic cholecystectomy for unexpected carcinoma of the gallbladder. *Hepatogastroenterology* 1998; 45(suppl2):240.
- 6 Cetta F, Montalto G, Pacchiarotti MC, *et al*. Abdominal wall recurrence after laparoscopic cholecystectomy for unsuspected carcinoma. Is it partly preventable? *Gastroenterology* 1997; 112:A500.

### Reply

EDITOR.—We read with interest the letter of Cetta *et al* in which they discussed our case (*Gut* 1999;45:626-7) of subcutaneous seeding of a hepatocellular carcinoma (HCC) after percutaneous needle biopsy.

Firstly, they state that a needle biopsy was not indicated in the case presented. It must be stated that the biopsy was performed elsewhere before the patient was admitted to our hospital. Secondly, they suggest that a smaller partial hepatectomy might have been sufficient to treat the HCC in this 30 year old woman with hepatitis B liver cirrhosis.

In the case presented there was no deterioration in liver function or impaired functional reserve after resection. The postoperative course was uneventful.

In general, we agree with the opinion to limit resection as far as possible and presently we would perform a segmentectomy.

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### Management of gastric fundal varices associated with a gastrorenal shunt

EDITOR.—We read with great interest the article by Jalan and colleagues (*Gut* 2000;46:578-81) on the clinical position of transjugular intrahepatic portosystemic stent-shunt (TIPSS). This procedure is a useful method of reducing portal pressure by creating a portosystemic shunt in the liver. They suggested that TIPSS can be a successful treatment for bleeding gastric fundal varices (FV) unresponsive to pharmacological and endoscopic therapy. However, Sanyal *et al* reported that TIPSS was ineffective for FV associated with a large gastrorenal shunt, even when the hepatic venous pressure gradient falls below the critical bleeding threshold of 12 mm Hg.<sup>1</sup>

The behaviour of varices at different sites seems to differ.<sup>2</sup> Therefore, FV should be treated on the basis of their haemodynamics.

FV arise from the dilation of short or posterior gastric veins and are frequently associated with a large gastrorenal shunt that decompresses the portal system.<sup>3</sup> Balloon occluded retrograde transvenous obliteration (B-RTO) is a novel radiological treatment for FV that was developed by Kanagawa and colleagues.<sup>4</sup> This procedure involves insertion of a balloon catheter into a gastrorenal shunt via the femoral or internal jugular vein. It is similar to TIPSS but less invasive. The therapeutic effect of B-RTO is excellent without major complications, even for patients with poor liver function.<sup>4,5</sup> However, there have been few controlled trials of this technique.<sup>6</sup>

Patients with bleeding from FV have a high risk of dying from an episode of variceal bleeding or from liver failure, even when TIPSS is successful in stopping acute bleeding.<sup>7</sup> Hence patients with high risk FV should preferably undergo prophylactic treatment. Although the risk factors for the first episode of bleeding from FV are still not clear, Kim *et al* determined the one year probability of bleeding as a function of all possible combinations of two endoscopic variables (variceal size and the presence of red spots) for patients in Child's class A, B, or C.<sup>8</sup> According to their classification, FV with a one year probability of bleeding (16%) can be considered as high risk varices.

As TIPSS seems to be ineffective for FV associated with a gastrorenal shunt,  $\beta$  blockers or nitrates (which are widely used to treat high risk oesophageal varices) may also be ineffective for primary prophylaxis of bleeding from FV. Accordingly, prophylactic B-RTO may be justifiable due to its simplicity and safety.

Because the gastrorenal shunt tends to be occluded after B-RTO,<sup>4,5</sup> however, the long term effect of this procedure on portal haemodynamics needs to be evaluated.

Although a prospective randomised study comparing B-RTO with TIPSS for the prevention of bleeding or rebleeding from FV is still needed, we hope that B-RTO will become a firstline treatment for high risk FV associated with a gastrorenal shunt in the near future.

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- 1 Sanyal AJ, Freedman AM, Luketic VA, *et al*. The natural history of portal hypertension after transjugular intrahepatic portosystemic shunts. *Gastroenterology* 1997;112:889-98.
- 2 Sarin SK, Kumar A. Gastric varices: profile, classification, and management. *Am J Gastroenterol* 1989;84:1244-9.
- 3 Watanabe K, Kimura K, Matsutani S, *et al*. Portal hemodynamics in patients with gastric varices. A study in 230 patients with esophageal and/or gastric varices using portal vein catheterization. *Gastroenterology* 1988;95:434-40.
- 4 Kanagawa H, Mima S, Kouyama H, *et al*. Treatment of gastric fundal varices by balloon-occluded retrograde transvenous obliteration. *J Gastroenterol Hepatol* 1996;11:51-8.
- 5 Matsumoto A, Hamamoto N, Nomura T, *et al*. Balloon-occluded retrograde transvenous obliteration of high risk gastric fundal varices. *Am J Gastroenterol* 1999;94:643-9.

- 6 Oho K, Iwao T, Sakai T, *et al.* Randomized prospective trial for bleeding fundal varices: endoscopic sclerotherapy vs. transvenous obliteration. *Gastroenterology* 1997;112:A1351.
- 7 Chau TN, Patch D, Chan YW, *et al.* "Salvage" transjugular intrahepatic portosystemic shunts: gastric fundal compared with esophageal variceal bleeding. *Gastroenterology* 1998;114:981-7.
- 8 Kim T, Shijo H, Kokawa H, *et al.* Risk factors for hemorrhage from gastric fundal varices. *Hepatology* 1997;25:307-12.

### Reply

EDITOR.—We thank Matsumoto and colleagues for their interest in our paper. They suggest that transjugular intrahepatic portosystemic stent-shunt (TIPSS) is ineffective for the management of bleeding from fundal varices and given the haemodynamic characteristics of fundal varices, the appropriate treatment for bleeding from them is balloon occluded retrograde transvenous obliteration (B-RTO). They quote Sanyal's paper<sup>1</sup> as evidence in support of their suggestion that TIPSS is unlikely to be useful in the setting of fundal varices. Sanyal *et al* reported their experience of TIPSS in 12 patients who underwent this procedure for gastric varices and in six patients these varices did not disappear on follow up. The aim of treatment of bleeding varices is firstly to control bleeding and secondly to prevent rebleeding. In the paper by Sanyal *et al*, no data were provided about how many patients bled from gastric varices in the follow up period compared with those who rebled with oesophageal varices.<sup>1</sup> However, our previous study<sup>2</sup> and that of Chau and colleagues<sup>3</sup> clearly show that post-TIPSS bleeding from either oesophageal or gastric varices is a function of portal pressure and has little to do with whether bleeding is from oesophageal or gastric varices. Both Stanley and colleagues<sup>2</sup> and Chau and colleagues<sup>3</sup> compared the outcome of TIPSS insertion for variceal bleeding from oesophageal or gastric varices. In the study by Stanley *et al*, 106 patients (oesophageal varices 74; gastric varices 32) underwent TIPSS for variceal bleeding and during follow up the rates for variceal rebleeding were similar in both groups and there was no difference in survival. In the study by Chau *et al*, 112 patients (oesophageal varices 84; gastric varices 28) with variceal bleeding underwent TIPSS for uncontrolled variceal bleeding. Bleeding was controlled in all patients after TIPSS except for one in each group. Twenty four per cent of patients in the oesophageal varices group and 29% in the gastric varices group rebled during follow up. Most early rebleeding (within seven days after TIPSS) was related to oesophageal ulceration secondary to previous sclerotherapy. Rates of mortality were similar in both groups. These results suggest that emergency TIPSS is equally effective in the control of gastric fundal variceal bleeding compared with oesophageal variceal bleeding.

Matsumoto *et al* also suggest that there is likely to be a place for B-RTO in the primary prophylaxis of bleeding from fundal varices and that pharmacological agents have no place in their management. Again, the data for their suggestion do not exist in the literature. We think that it is extremely difficult to suggest failure of pharmacological therapy for primary prophylaxis of fundal varices based on the assumption that portal pressure changes are unlikely to be important in the management of fundal varices.

The data in the literature do not support either of the points that have been suggested by Matsumoto *et al.* Although data on the use of B-RTO for the treatment of fundal varices are exciting, we look forward to randomised controlled clinical trials comparing TIPSS with B-RTO.

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- 1 Sanyal AJ, Freedman AM, Luketic VA, *et al.* The natural history of portal hypertension after transjugular intrahepatic portosystemic shunts. *Gastroenterology* 1997;112:889-98.
- 2 Stanley AJ, Jalan R, Ireland HM, *et al.* A comparison between gastric and oesophageal variceal haemorrhage treated with transjugular intrahepatic portosystemic stent shunt (TIPSS). *Aliment Pharmacol Ther* 1997;11:171-6.
- 3 Chau TN, Patch D, Chan YW, *et al.* "Salvage" transjugular intrahepatic portosystemic shunts: gastric fundal compared with esophageal variceal bleeding. *Gastroenterology* 1998;114:981-7.

### The science, economics, and effectiveness of combination therapy for hepatitis C

EDITOR.—No one affected by hepatitis C virus (HCV) will question Professor Dusheiko's insistence on the importance of effective therapy standards for HCV and the funding to meet them (*Gut* 2000;47:159-61). With research and clinical evidence pointing to a prevalence of HCV infection far in excess of human immunodeficiency virus (HIV),<sup>1</sup> the issue has now become urgent. Patients and clinicians alike will await the forthcoming NICE appraisal in the hope it recommends in favour of allocating sufficient resources to cover treatment costs for those most in need and best able to benefit.

However, while a positive response will be welcome it will also uncover issues that have still to be fully addressed. These centre on who will/should be selected for treatment and the effects of the treatment itself.

Regarding the first issue there remains a debate around who will benefit most from treatment. The tendency is to assess outcome in terms of genotyping, age, duration of viraemia, extent of liver damage, and other complicating factors, such as continued drug and alcohol abuse. While there may be some validity to such categorisations, they are not at all absolute and can demoralise patients. Nevertheless, and leaving such considerations aside, if HCV infection is as widespread as some clinicians anticipate, it would be unrealistic to assume that funding will be available to treat everyone. This means that some form of treatment selection will need to be adopted. Should this occur, the question remains as to how clinicians will make choices and what criteria they will use. Furthermore, will protocols be in place to govern these criteria to ensure they are standardised nationwide?

Although Dusheiko *et al* cite the potential priority given by the NHS to combination treatment as the salient issue, this needs to be addressed in conjunction with the equally important matter of who should receive this treatment. Whether patients are offered standard combination therapy, combination

therapy with pegylated interferon (PEG IFN), or PEG IFN alone is in some ways secondary to the issue of who is actually going to be given treatment. Will it be based on disease progression or expected response to treatment, or both?

Before considering this further, a factor that needs to be implicated in discussions around HCV, but which clinicians tend to underestimate, is patient tolerance and possible lingering effects of therapy. Although there seems to be a fairly clear cut case in favour of the greater efficacy of combination treatment, it is harder for patients to tolerate than monotherapy with IFN, particularly when taken over 48 weeks. Dusheiko *et al* state that the 20% (approximately) of patients who discontinue therapy before 48 weeks usually do so because of "insomnia, depression, irritability, or anaemia". This would seem to be a minimising of the extent and intensity of side effects from combination therapy, which can be equally as debilitating for some patients as those of chemotherapy. In addition, the sequelae of treatment can sometimes linger for months following its cessation.

Given the potential severity of side effects, many patients with mild HCV have resisted conventional treatment methods and opted instead to try to minimise disease progression by recourse to alternative therapies. A recent nationwide trial offered to patients with mild HCV failed to recruit anywhere near its target numbers. This would seem to imply that those with less risk of progressive disease, and therefore less motivation to seek a cure, are more resistant to therapeutic intervention.

Notwithstanding the obvious factor of the greater and more urgent need of treatment for patients with progressive disease following HCV infection, perhaps this trend in mild HCV sufferers might offer some insight as to how patients sometimes choose for themselves, suggesting to those involved with the healthcare of HCV patients an indicator of how best to prioritise treatment should such selection prove necessary.

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- 1 Figures released by the Communicable Disease Report of 26 May 2000 (Vol 10, No 21) cite 41 174 cases of HIV infection in the UK—that is, less than 0.07% of the population (UK data from the PHLS AIDS and STD Division, Scottish Centre for Infection and Environmental Health; Institute of Child Health; London and Oxford Haemophilia Centre—on behalf of UK Haemophilia Centre Directors Organisation). HCV infection is currently anticipated to be around 10 times higher, an estimate that would seem to be underscored by the recent study carried out at St Mary's Hospital (Ward C, Tudor-Williams G, Cotzias T, *et al.* Prevalence of hepatitis C among pregnant women attending an inner London obstetric department: uptake and acceptability of named antenatal testing. *Gut* 2000;47:277-80), which reported a prevalence of HCV infection in 0.8% of women who took part, of whom 0.6% were viraemic. In the US, HCV infection is reported to be possibly four times higher than HIV with 3.5 million affected and 30 000 new cases each year (Turkington C. *Hepatitis C: the silent killer*. Chicago: Contemporary Books, 1998:xvii).

### Screening for genetic haemochromatosis in blood samples with raised alanine aminotransferase

EDITOR.—Bhavnani *et al* (*Gut* 2000;46:707-10) claim to have identified 12 patients

homozygous for C282Y or with compound heterozygosity at a cost of only £117 per patient identified. This astonishingly low total of £1400 allowed them to:

- Select out of 35 065 blood samples 4.2% (1490) with an elevated alanine aminotransferase.
- Undertake measurement of 1490 serum irons, transferrins, and ferritin concentrations.
- Give information on haemochromatosis and offer genetic screening to the 56 patients found to have a transferrin saturation >60%, and to re-contact those not responding.
- Obtain informed consent from the 33 patients who did respond, and undertake genetic testing for HFE mutations.
- Offer appropriate management to the 12 patients with C282Y homozygosity or compound heterozygosity.

We have some difficulty in accepting that all this can be achieved for only £1400, and would be intrigued to know how the authors arrived at their costings.

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### Reply

EDITOR.—Our preliminary study set out to examine the clinical usefulness of screening a targeted population for genetic haemochromatosis. The costing given in our paper was as stated, based solely on laboratory costs, a summary of which is given below. Costs of the clinician, nursing, and clerical time were not included in the paper, and are detailed below.

Laboratory costs:

- Screening for blood samples with elevated ALT incurred no additional costs as these samples were processed routinely as part of the normal hospital and GP biochemistry requests.
- The marginal costs for the measurement of 1490 serum irons and transferrins, £1085; 33 serum ferritins, £51; and genetic testing: £264 (total £1400).
- Although serum ferritins were performed on all 1490 specimens as part of the study, at a cost of £1788, we felt that they did not help in the screening process.

Thus we advocated "In those patients found to have a raised ALT, the cost of screening with iron saturation and follow up when appropriate with ferritin and gene testing would be £1400".

Other costs:

We were awarded a research grant of £5000 from the Health Authority, and the rest of the money was used for employing a medical laboratory assistant, (8 h/week) who picked out the relevant specimens and batched them for future testing. Information on haemochromatosis, plus offering genetic screening to the 56 patients found to have a transferrin saturation >60% and recontacting the non-responders was done by means of a standard letter to the clinicians who had requested the original liver function tests. Consent for genetic testing was obtained by these clinicians. Management of the 12 patients (homozygotes and compound heterozygotes) was undertaken (with no extra funding) by one of the authors (MB) as part of the routine Clinical Haematology service.

Since then, the Health Authority has awarded us continuing revenue for this targeted screening, and included in these monies are the clinical, clerical, and nursing costs incurred in providing this service as a routine for patients in our District.

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## NOTES

### American College of Gastroenterology 2001 International GI Training Grants Programme

The ACG International GI Training (IGT) Grant Programme provides funding for clinical or clinical research training in gastroenterology and hepatology so that an individual can acquire or develop new cognitive knowledge or a technical skill. This newly acquired knowledge or skill would then be used to improve patient care in the applicant's geographic area. Physicians outside of the United States and Canada are eligible to apply. At least one fellowship with a maximum of \$10 000 per IGT fellowship will be awarded during 2001, for a training period of not less than six months. Awards will be made by a special committee of the ACG and will be based upon the applicant's credentials, the merit of the proposed training by the selected host training centre and the potential for enhancing the field of gastroenterology in the applicant's home country. Application forms can be obtained from the ACG administrative office: 4900B South 31st Street, Arlington, Virginia 22206-1656. Tel: +1 703 820 7400; fax: +1 703 931 4520; website: www.acg-gi.org. **Deadline for submission of application is 1 April 2001.**

### Redefining Priorities in Gastroenterology

This congress will be held on 11–14 April 2001 in Monte Carlo, Italy. It will be chaired by Professor Massimo Crespi (Rome, Italy) and Professor Eammon Quigley (Cork, Ireland). Further information: Maddalena Massaro, Project Leader, AISC-AIM Group, Via A Ristori 38, 00187 Rome, Italy. Tel: +39 06 809681; fax: +39 06 80968229; email: gastro2001@aisc.it.

### 3rd European Federation of Autonomic Societies (EFAS)

The third European Federation of Autonomic Societies (EFAS) meeting in conjunction with the annual meeting of the sections "Autonomic nervous system" of the German Neurological Society, "Diabetes and Nervous System" of the German Neurological Society, and "Autonomic Nervous System" at the University of Erlangen-Nuremberg, Germany, will be

held in Erlangen, Germany on 26–28 April 2001. Further information: Professor Dr M J Hilz, Department of Neurology, University of Erlangen-Nuremberg, Schwabachanlage 6, D-91054 Erlangen, Germany. Tel: +49 0131 8534444; fax: +49 9131 8534328; website: www.neurologie.med.uni-erlangen.de/oeffentliche\_Veranstaltungen.htm

### Falk Workshop

The workshop entitled Update in Inflammatory Bowel Diseases will be held in Ljubljana, Slovenia, on 5 May 2001. Further information: Prof Dr S Markovič, University Medical Center Ljubljana, Division of Internal Medicine, Japljeva 2, 1525 Ljubljana, Slovenia. Tel: +386 (1) 231 6925; fax: +386 (1) 433 4190; email: sasa.markovic@kclj.si

### EPGS Endosonography Live in Amsterdam

This European Postgraduate Gastro-Surgical School congress will take place on 31 May and 1 June 2001 in Amsterdam, the Netherlands. Further information: Mrs Helma Stockmann/Mrs Joy Goedkoop, European Postgraduate Gastro-Surgical School, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. Tel: +31 20 566 3926; fax: +31 20 566 6569; email: W.J.Stockmann@amc.uva.nl; website: www.epgs.nl.

### 33rd European Pancreatic Club

The meeting will take place on 13–16 June 2001 in Toulouse, France. A training course will be organised on 13 June on "Genomics and post genomics: developments in biomedical sciences". Further information: Dr Nicole Vaysse, Inserm U531, CHU Rangueil, 31403 Toulouse, France. Tel: +33 (0)5 61 32 24 02; fax: +33 (0)5 61 32 24 03; email: nicole.vaysse@rangueil.inserm.fr; website: www.e-p-c.org.

### Gastroenterology and Endotherapy: XIXth European Workshop

This course, to introduce the experienced gastroenterologist to the growing field of therapeutic endoscopy, will be held on 18–20 June 2001 in Brussels, Belgium. Further information: Mrs Nancy Beauprez, Gastroenterology Department, Erasme Hospital, Route de Lennik 808, B-1070 Brussels. Tel: +32 02 555 49 00; fax: +32 02 555 49 01; email: beauprez@ulb.ac.be

## CORRECTION

Abstract A277 in *Gut* 2000;47(suppl III) contained errors. The title should read "Disposable versus reusable endoscopic biopsy forceps: comparison of costs and histological quality", and the complete author list is C Lejeune, P Prost, C Michiels, J-M Phelip, L Martin, J Faivre. *Gut* would like to apologise for this error.