PostScript

LETTERS

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Non-variceal upper gastrointestinal haemorrhage

I enjoyed reading the guidelines on non-variceal upper gastrointestinal haemorrhage (*Gut* 2002;**51**(suppl 4):V1–6) and would like to congratulate the British Society of Gastroenterology (BSG) on their production, and hope they will form the basis for continued improvements in the management of this condition. However, several areas of the guidelines require further comment and exploration before they can be accepted as a national "gold standard" by which the management of non-variceal haemorrhage should be judged.

The guidelines give a grade A recommendation for the use of endoscopic therapy to treat adherent clots. This is despite failure of individual randomised controlled trials of endoscopic versus no endoscopic therapy to demonstrate a benefit in this subgroup.[1–4] The guidelines indicate the rationale for recommending endoscopic therapy is a meta-analysis of trials[5]; this is an incorrect interpretation of those results. The quoted meta-analysis showed that endoscopic therapy was of significant benefit in patients with active bleeding or a visible vessel but not in patients with adherent clots or flat spots.[5] If this analysis is the sole basis on which endoscopic therapy is recommended in this situation, it might be reasonable to reconsider the grade A status.

While the use of endoscopic therapy for adherent clots remains unproved, it may be beneficial in certain circumstances, but the widespread applicability remains to be determined. For instance, Jensen *et al* used a specific technique of adrenaline infiltration around the clot, followed by progressive guillotining through the clot with a snare without electrocautery, followed by bipolar cautery to the clot remnant or underlying stigmata (not the technique suggested in the BSG guidelines). In a randomised controlled trial against active medical therapy, this approach was significantly better at reducing rebleeding (0/15 *v* 6/17).[6] However, the two groups were not particularly well matched, with more patients having their index bleed while already an inpatient being enrolled in the medical arm, possibly tipping the benefit towards the endoscopic therapy arm. The rebleeding rate in the treatment arm was zero, which is rather lower than that seen in most other trials of endoscopic therapy and even one single rebleed in the endoscopic arm would have abolished the statistical significance of the result.

Difficulties in deciding on a treatment policy may also arise following different approaches to removal of the adherent clot. The rebleeding rate probably depends on the definition of adherence, and a clot that withstands prolonged forcible attempts at washing is likely to carry a different risk from one seen still to be adherent after only a couple of squirts with a syringe. Laine *et al* used irrigation of adherent clots for five minutes with a bipolar probe, and adherent clot remained in 57% of cases. The rebleeding rate in this group was only 8%.[7] Endoscopic therapy has not been shown to be effective in this subgroup of tightly adherent clots. Thus the approach to adherent clots is not as clear and unequivocal as implied in the BSG guidelines and further discussion of the recommendations on the use of washing and specific endoscopic therapies should be considered.

The guidelines also strongly endorse the use of high dose continuous intravenous proton pump inhibitor (PPI) therapy after endoscopic therapy. This opinion has clearly been swayed by the trial from Hong Kong by Lau and colleagues.[8] While the design and outcomes of this exemplary work are not in question, it would be wise to consider the applicability to a UK population before widely endorsing the extra costs involved in the wholesale adoption of this therapy. The omeprazole treated group were younger than those treated in the UK for acute non-variceal bleeding and had significantly lower numbers of patients taking non-steroidal anti-inflammatory drugs (NSAIDs) (32.5% *v* 68%) and with important comorbidity (25% *v* 60%).[9] In addition, there are pharmacokinetic and pharmacodynamic issues that suggest there might be a difference in responses between this trial group and a standard UK bleeding population. Asians and Orientals have a lower parietal cell mass than Europeans[10] and PPI therapy would be expected to be more effective. Omeprazole is predominantly metabolised and inactivated by cytochrome P450 2C19 (CYP2C19). The activity of this enzyme is genetically determined and those with low activity variants (poor metabolisers) have a fivefold increased exposure to omeprazole and consequently significantly greater acid inhibition compared with wild-type variants (extensive metabolisers). Poor metabolisers are uncommon in Northwest European White populations (3%) but much more common in Orientals (up to 23%).[11–13] Thus the impressive results may not directly translate to a major benefit in the UK.

Perhaps the most convincing argument for avoiding blanket use of high dose PPI was provided by Udd *et al*'s randomised controlled study of omeprazole 20 mg once daily compared with the endorsed high dose continuous regimen. Sample size was comparable with that of Lau *et al* and powered to detect equivalence. The study enrolled Europeans with apparently similar demographics to UK patients (57% on NSAIDs, comorbidity in 74–79%). Rates of rebleeding, surgery, and mortality were equivalent in the two treatment groups.[14]

The publication and dissemination of the BSG guidelines should enhance practice but it is important that all of the recommendations are not accepted and implemented uncritically and further discussion and refinement are encouraged.

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To perform or not to perform liver biopsy: an alternative view

Roger Chapman (*Gut* 2002;**51**:9–10) commenting on the recent important study from Nottingham[1] concluded that there is a strong case for liver biopsy in most asymptomatic patients with persistently abnormal liver tests, even when diagnostic serology is negative. This conclusion is reasonable, particularly if diagnostic accuracy is paramount. However, accuracy is not the only consideration and other equally valid conclusions can be made from different viewpoints.

Unfortunately, liver biopsy is often painful,[2] requires bed rest for at least six hours,[3] and is associated with a small but definite mortality.[4] We need to appraise our patients of these factors and the likely benefits so that they can make an informed choice. Standard methods of evidence based medicine can greatly assist us in doing this.

As the predominant finding on biopsy is non-alcoholic fatty liver disease (NAFLD), the first question is: can any other test reliably predict fatty liver in this situation? There are three imaging techniques which can detect fatty liver—ultrasound, computerised tomography, and magnetic resonance imaging. Ultrasound is the most patient friendly, cheapest, safest, and most readily available. Furthermore, it is the only imaging technique for which we have sensitivities and specificities for fatty liver.[5–8] The most recent study[8] gives a sensitivity of 89% and a specificity of 93%.

However, to obtain the predictive value of a positive or negative test one needs to know not just sensitivity and specificity but the prevalence (the pretest probability) of the condition being tested for in the population being studied. The Nottingham study provides precisely that and we now know that in England the prevalence of fatty liver in "well" patients with abnormal liver tests and negative serology is 66%. The easiest way of obtaining the post test probability of a positive or negative ultrasound scan (the positive and negative predictive values, respectively) is to calculate the likelihood ratios and apply them to the nomogram devised by Fagan.[9]

The likelihood ratio for a positive test (LR+) is sensitivity/100–specificity which, using the latest data,[8] is 12. The likelihood ratio for a negative test (LR–) is 100–sensitivity/specificity, which is 0.12. From the nomogram[9] it can be shown that a positive scan for fatty liver has a positive predictive value of 96%. Many would consider this degree of certainty sufficient to diagnose fatty liver and not biopsy. If the scan is negative it can be shown that there is still a 20% probability of fatty liver and one would therefore be more likely to favour biopsy. However, the patient might well want to know what the biopsy might reveal. We can readily provide them with this information by recalculating the percentage of patients having the various liver conditions when the number expected to have a positive scan is subtracted.

Column 2 of table 1 shows the prevalence of the various liver conditions found in the Nottingham study. Column 3 shows the likely prevalence of the various conditions in those with a negative scan. This clearly informs the patient's and our decision making. Initially, we can consider how important it is to detect these various conditions and how they might be managed.

To take account of the remaining 19% patients with fatty liver (that is, those not detected by ultrasound and shown in column 3 of table 1) one might simply rely on diet and exercise for all those with a raised body mass index, and good control in diabetics. Currently, what else can be done for such patients outside clinical trials? Bearing in mind the likelihood of unsuspected drug damage and alcohol excess, taking a more careful history may be appropriate. One wonders whether knowledge of cryptogenic hepatitis, granuloma, sarcoid, amyloid, and glycogen storage disease would significantly change management. One might be happy to miss the diagnosis of primary biliary cirrhosis and primary sclerosing cholangitis until jaundice or other symptoms supervenes. Perhaps the only two conditions it would be important not to miss are haemochromatosis and autoimmune hepatitis. Therefore, it would be possible to appraise patients with a normal scan that there is a 6.6% chance of missing a condition which may benefit from treatment (prednisolone or venesection). That is, 15 patients would need to be subjected to biopsy to detect one requiring important treatment. Such patients could be said to have informed choice.

Imaging has no place in staging NAFLD.[10] Currently, there is no established treatment for NAFLD apart from weight reduction and good diabetic control, and there is good reason for recommending this in all such patients. However, for patients entering clinical trials, staging biopsy is likely to be necessary.

In conclusion, we do not believe that most "well" patients with abnormal liver tests and normal serology need biopsy, but we are now able to give patients an informed choice by applying simple evidence based medicine to the findings of the Nottingham study.

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Table 1 Prevalence of various liver conditions in the Nottingham study and, based on this, the prevalence expected if those likely to have a scan suggesting fatty liver are excluded

Various liver conditions	Prevalence (%) in Nottingham study	Projected prevalence (%) in those expected to have a negative scan for fat
NAFLD or NASH	66	19
Drug related damage	8	19
Cryptogenic hepatitis	9	21
Alcoholic damage	3	7
AIH	1.9	4.5
Granuloma/sarcoid	1.7	4
PBC	1.4	3.3
PSC	1.1	2.6
Haemochromatosis	0.9	2.1
Secondary biliary cirrhosis	0.6	1.4
Amyloid	0.3	0.7
Glycogen storage disease	0.3	0.7
Normal	6	14

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

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Penetrance of haemochromatosis

Ryan and colleagues (*Gut* 2002;**51**:108–12) note that the expected homozygote frequency of 1 in 83 for the *HFE* C282Y mutation is not reflected in the number of patients with haemochromatosis seen in a clinical setting. Accordingly, they have studied family members of patients with haemochromatosis as a surrogate for population screening. As they point out, there are probably genes other than *HFE* that affect the expression of hereditary haemochromatosis, and such genes are likely to be overrepresented in the families of index cases. Thus the choice of relatives would tend to overestimate the prevalence of clinical manifestations of haemochromatosis. Yet their studies confirm others published within the past year[1–5] that suggest that the clinical penetrance of the homozygous state is so low that it cannot be detected, even in very large samples. Interestingly, Ryan *et al* seemed not to reach this conclusion, rather attributing symptoms such as fatigue, arthropathy, and impotence to the disease. But these are very common symptoms, and not only do they

need to be ascertained from the target population before they have been told of their diagnosis, but also they must be compared with the prevalence of the same symptoms in those who are not homozygous for the C282Y mutation. It is notable in this respect, for example, that while Ryan *et al* found that 42.9% of "the expressing female cohort" complained of fatigue, a NHANES III study found that 43.4% of 14 235 women complained of extreme fatigue[6]; we found that 31.7% of women with wild-type *HFE* and 32.4% of women homozygous for the C282Y mutation complained of severe fatigue.[1]

It seems to me remarkable that the authors of this and a number of studies cited above are reluctant to draw the obvious conclusion: the clinical penetrance of hereditary haemochromatosis is extremely low, so low that it has not been possible to detect it in very large population studies. For the past 20 years we have taught and have been taught that haemochromatosis is the most common disease of Northern Europeans. Until relatively recently I held this view.[7] However, the interpretation of the data should not be moulded by preconceived ideas, and the controlled study of 41 000 individuals which we concluded recently[1] make the facts abundantly clear: the *HFE* mutation is common, the biochemical phenotype is common, but haemochromatosis is, in fact, a rare clinical disease.

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Patterns of expression of MMR proteins in serrated adenomas and other polyps of the colorectum

We read with a great interest the study by Sawyer *et al* (*Gut* 2002;**51**:200–6). This well performed study of numerous genetic and immunohistochemical features of serrated adenomas (SAs) of the colorectum furnishes very important findings that may help to clarify the confusing field of colorectal tumorigenesis. Using both molecular and immunohistochemical techniques, Sawyer *et al* found in a series of 39 SAs a relatively low frequency of most abnormalities described in classical adenomas and adenocarcinomas of the colorectum. Comparative genomic hybridisation, performed in four cases, was always normal. These differences from classical adenomas may be due either to a distinct mechanism of tumorigenesis or to the presence of a large number of SAs showing only mild (64%) or moderate (28%) dysplasia. An interesting result obtained by Sawyer *et al* is the absence of high level microsatellite instability (MSI-H) in SAs, and the rarity of low level microsatellite instability (MSI-L) (two of 39 cases). Again, there is a debate in the literature concerning the frequency of MSI in SAs.[1–3] Sawyer *et al* also studied the expression of two mismatch repair proteins (MMR), hMLH1 and hMSH2, and they found no loss of cellular expression of these two proteins in SAs. This result confirms the MSI analysis, as many studies have now demonstrated that only MSI-H tumours lose expression of MMR proteins while microsatellite stable and MSI-L tumours have normal expression.[4]

In their study, Sawyer *et al* did not describe precisely the pattern of expression of hMLH1 and hMSH2 proteins. We recently performed an immunohistochemical study of MMR proteins in a series of 30 colorectal SAs (19 low grade and 11 high grade), 10 hyperplastic polyps (HP), and 20 classical adenomas (10 high grade and 10 low grade) of the colorectum. Two SAs came from patients with hereditary non-polyposis colorectal cancer (HNPCC) syndrome, one from a patient with familial adenomatous polyposis, and one from a patient with a juvenile polyposis. All classical adenomas were sporadic. Immunohistochemistry was performed on formalin fixed deparaffinised sections with the following antibodies: anti-hMLH1 (Pharmingen, clone G168-728, 1:70), anti-hMSH2 (Calbiochem, clone FE11, 1:100), and anti-hMSH6 (Transduction laboratories, clone 44, 1/100).

Loss of expression of hMLH1 protein was only observed in one high grade SA, developed in a patient with HNPCC syndrome due to a mutation of the hMLH1 gene. In the second SA (of low grade) occurring in a patient with HNPCC syndrome due to mutation of the hMSH2 gene, there was no loss of expression in the SA, while the synchronous colon adenocarcinoma in the same patient showed loss of hMSH2 and hMSH6. All other SAs expressed the three MMR proteins. This expression was also present in all HP and classical adenomas. These results confirm that MSI is highly uncommon in all types of adenomas of the colon, both in SAs and in classical adenomas.[5] Interestingly, we observed two distinct patterns of expression in the three types of polyps studied. One pattern was similar to that observed in the normal mucosa of the colon, with a moderate nuclear expression limited to the lower part of the crypts, and with a negative upper part of the crypts and surface epithelium. The other "dysplastic" pattern was characterised by strong nuclear expression of the surface epithelium and upper part of the lesion, with the lower part showing moderate positivity. This pattern was identical for the three antibodies. The normal pattern was always preserved in HP and low grade SAs, with a negative surface epithelium. In contrast, all classical adenomas, either low grade or high grade, showed strong surface staining. Among 11 high grade SAs, seven showed a "dysplastic" pattern with strong surface staining, and four showed a normal pattern.

These results suggest that SAs may be a heterogeneous group of tumours that includes lesions close to HP, especially when only low grade dysplasia is present, but also high grade lesions with a similar pattern as high grade classical adenomas, and probably a similar risk of malignant transformation. It is interesting to note that the same relation between SAs, HP, and adenomas has been noted regarding the apoptotic pattern.[6] Increased expression of MMR proteins has also been noted in precancerous skin lesions.[7] Therefore, it may be hypothesised that intense surface expression of MMR proteins is a marker of neoplastic proliferation. This possibility has to be tested prospectively in various precancerous lesions, and also in regenerative non-neoplastic changes.

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Balloon occluded retrograde transvenous obliteration: a feasible alternative to transjugular intrahepatic portosystemic stent shunt

We read with interest the article by Tripathi *et al* (*Gut* 2002;**51**:270–4) on the therapeutic effect of transjugular intrahepatic portosystemic stent shunt (TIPSS) on gastric variceal bleeding. They concluded that TIPSS could only improve mortality in patients with bleeding at a portal pressure gradient (PPG) >12 mm Hg. When treating gastric varices, we should pay attention to the fact that the behaviour of these varices varies according to their location. Isolated fundal varices (FV) are confined to the fundus only (or the cardia and fundus), and are not associated with oesophageal varices. Chikamori and colleagues[1] reported that the portoazygos venous system

contributes to the formation of oesophageal and cardiac varices whereas the portophrenic venous system contributes to the formation of FV. They also showed that the main (85%) drainage route in patients with FV was via a gastrorenal shunt.

According to Watanabe *et al*, in a series of patients who developed FV, superior mesenteric venous flow was diverted away from the liver and directed into the veins feeding the varices. Therefore, the portal venous pressure of patients with large FV is quite low but collateral flow into the FV is abundant. Additionally, such patients are likely to develop hepatic encephalopathy.[2] We believe that some of the FV patients in group 1 treated by Tripathi *et al* had this pattern of portal haemodynamics. Gastric variceal bleeding is massive, and is frequently more severe than bleeding from oesophageal varices. As the course of patients with FV is adversely modified by variceal bleeding, identification of large high risk FV and their prophylactic obliteration has been proposed.[3] However, high risk FV have not been fully defined. Kim *et al* determined the one year probability of bleeding in relation to all possible combinations of two endoscopic variables (variceal size and the presence of red spots) for patients in Child's class A, B, and C.[4] According to their criteria, FV with a one year probability of bleeding ⩾16% can be considered as high risk and are comparable with high risk oesophageal varices.[5] How should we treat FV in patients with a low PPG?

Balloon occluded retrograde transvenous obliteration (B-RTO) is a new interventional radiology technique that was recently developed in Japan.[6] B-RTO is similar to but less invasive than TIPSS and it achieves excellent prevention of recurrent bleeding with few major complications (fever, haemoglobinuria, and worsening of oesophageal varices), even in patients with poor liver function.[7] Additionally, this procedure can improve hepatic encephalopathy.[8] The main limitation of B-RTO in an emergency setting seems to be the requirement for temporary control of bleeding. We recommend elective B-RTO for the management of bleeding FV associated with a gastrorenal shunt at any PPG value. A prospective randomised trial of TIPSS versus B-RTO should be performed to determine the management of bleeding FV with a PPG ⩽12 mm Hg.

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Endoscopic surveillance in Barrett's oesophagus

I read with interest the debate on endoscopic surveillance in Barrett's oesophagus (*Gut* 2002;**51**:313–14 , 314–15). My reading of the literature supports the view of Dr Playford—there is insufficient evidence to justify surveillance endoscopy in this condition.

I am always interested in the uses and misuses of statistical data to support a personal view, and to that end I have some questions that should be honestly answered by those advocating screening: firstly, where is the evidence, prospectively collected, that shows that Barrett's oesophagus is a consequence of acid reflux disease? The quoted references do not support this allegation. Secondly, I believe that it is deliberately obfuscatory to liken Barrett's oesophagus to a colonic polyp in terms of malignant potential—abundant evidence supports the role of screening in the latter common condition. Lastly, this issue of absolute risk should indeed be addressed. Colon cancer is common—at least 20 times more common than the oft quoted epidemic of oesophageal adenocarcinoma—which may not be associated with Barrett's oesophagus.

We need to remember that despite an increase in the reported incidence of oesophageal adenocarcinoma in recent decades, limited endoscopic resources may be better devoted to reducing the disease burden in a condition where reliable evidence supports surveillance.

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Author's reply

Dr Jeremy Ryan's contribution to the debate is most welcome. He will not be surprised that I find his and Professor Playford's arguments incorrect, but accept that they both pose insightful and valuable questions, which are correct.

Sufficient evidence

Firstly, without entering a philosophical dialectic, I must address his view of sufficient evidence. It is important to be mindful that "life is the art of drawing sufficient conclusions from insufficient premises" Samuel Butler. There are now further data to support the case for surveillance. A population based study of a cohort of patients with adenocarcinoma of the oesophagus and gastric cardia has concluded that surveillance detected Barrett's oesophagus related cancers were associated with low stage disease and improved survival with no patient dying directly of cancer.[1] A major problem of this study is that most patients were excluded because they did not have a diagnosis of Barrett's oesophagus made six months prior to the diagnosis of cancer.[2] The major challenge is finding Barrett's oesophagus as it is an adaptive phenotype. It is becoming clear that many patients with Barrett's oesophagus are asymptomatic, not complaining of reflux symptoms.[3]

Misuse of data supporting a personal view

Dr Ryan is absolutely correct that I do have a strong personal view, hopefully displayed in the debate. In the opening argument I alluded, perhaps obscurely, to the postmodern Nieztzschian philosophy of there being "no facts merely interpretations". This is an approach I personally reject and in doing so, results correctly but perhaps harshly to a charge of lack of equipoise and misuse of data. I hope Dr Ryan accepts this explanation in mitigation. I am happy to inform him that there is a small amount of prospective evidence that reflux disease leads to Barrett's oesophagus. McDougall and colleagues[4] conducted a careful natural history study of patients with reflux oesophagitis. To my mind the most striking feature was that 11% of patients with oesophagitis developed Barrett's mucosa after 3.5–4 years. These clinical data support substantial pathophysiological and experimental data.[5 6]

Barrett's oesophagus and the colonic polyp

Again, I find that Dr Ryan is correct in part; stating that the burden of colon cancer is much greater than that of gastro-oesophageal cancer. My purpose in the debate was to highlight consequential rather than absolute risk. Most patients will survive a diagnosis of symptomatic colon cancer; very few will survive a diagnosis of symptomatic oesophageal cancer. Most Barrett's patients are asymptomatic,[3] and very few patients with a diagnosis of gastro-oesophageal cancer have a prior diagnosis of Barrett's oesophagus.[1] Those patients fortunate enough to be detected must be surveyed, as the consequence for the patient of ignoring their Barrett's oesophagus is to inform them to return when they notice "alarm" symptoms of dysphagia. This latter strategy I strongly contend is wrong as the patient is unlikely to survive

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Mucosal tears on endoscopic insufflation

We read the paper by Cruz-Correa *et al* (*Gut* 2002;**51**:600) with great interest. They reported that similar haemorrhagic lacerations in the colon had not been described in any other gastrointestinal disease. We would like to present a patient with ulcerative colitis (UC) and diversion colitis showing an identical endoscopic finding.

A 32 year old Japanese man suffering from UC for 11 years was referred to our hospital in 1997 for treatment of intractable UC. His past medical history and family history were unremarkable. He had received more than 20 g of oral steroid at the time of referral. Furthermore, his condition was not relieved with medical treatment, and he underwent subtotal colectomy with ileostomy and mucous fistula formation in January 1998. At that time, it was planned to perform pouch operation a few months later. After the first operation, he was free from frequent bowel movements and the condition of the rectal remnant was under control with topical steroids. He was satisfied with the state of the ileostomy and did not want to undergo pouch operation in spite of our recommendation. Instead, he received surveillance colonoscopy to detect dysplasia of the rectal remnant annually after the operation. On surveillance colonoscopy in 2001, the rectal remnant was torn and the muscularis mucosa was exposed on endoscopic insufflation (fig 1), as in the reported case. Endoscopically, the remaining mucosa showed mild proctitis with a decreased vascular pattern, mucous exudate, and oedema, but no ulcers. The post endoscopic course was uneventful without any treatment, partly because the rectal remnant was diverted from the faecal stream.

Diversion colitis occurs relatively frequently after stoma formation for a variety of disorders, including inflammatory bowel disease (IBD), malignancy, congenital disorders, and functional disorders.[1] As both the clinical and endoscopic presentations are quite similar to those of IBD, it is very difficult to differentiate IBD from diverting colitis. However, Frisbie *et al* reported that colonoscopy revealed mucosal erythema or friability in 94% of patients who had undergone diverting colostomy for neuropathic large bowel.[2] Furthermore, we have never experienced the mucosa being torn by endoscopic insufflation in patients with ulcerative colitis in routine surveillance colonoscopy. Taken together, these results suggest that the mucosal tear might be attributable to diversion colitis in addition to UC in our case.

As annual surveillance colonoscopy is mandatory for longstanding UC, it should be noted that the defunctioned colorectum must be surveyed with great care in such cases.

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Author's reply

Thank you for your interest in our article reporting colonic mucosal tears on endoscopic insufflation in three patients with collagenous colitis (*Gut* 2002;**51**:600). We read with great interest your case report of a patient with ulcerative colitis (UC) with diverting colitis who presented an identical mucosal tear during colonoscopic insufflation. To our knowledge this is the first time such a mucosal finding has been described in diverting colitis. We may be dealing with some underlying mucosal pathology that decreases the compliance of the colonic mucosa and results in mucosal tears. It would be interesting to know what were the histological findings of the colonic mucosa in your patient.

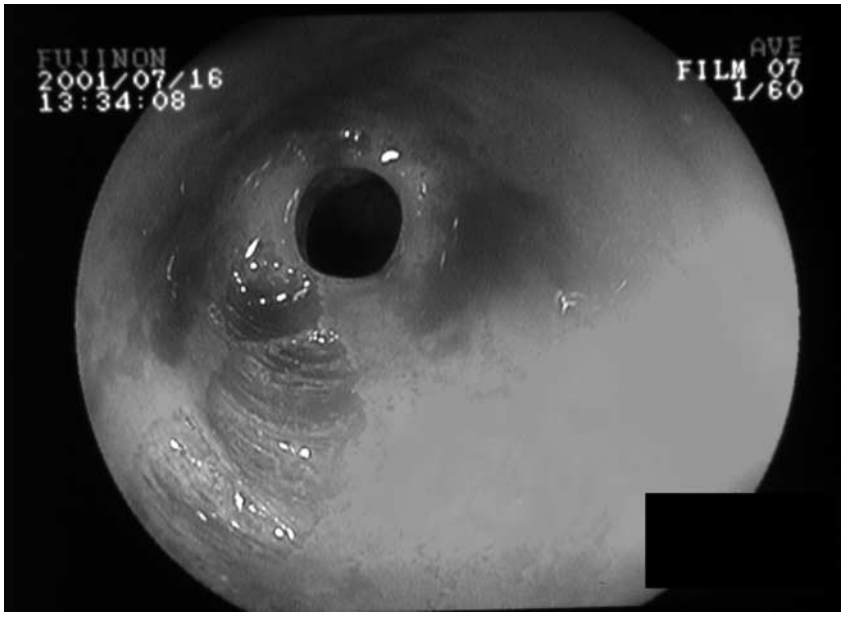

Figure 1 Endoscopic insufflation of the rectal remnant resulted in a mucosal tear in a patient with ulcerative colitis undergoing subtotal colectomy, ileostomy, and mucous fistula formation. The hole seen in the centre was a mucous fistula.

Your report might elicit further reports from other cases, which may contribute towards elucidating the pathophysiological process underlying these endoscopic findings.

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Finding mucosal tears in collagenous colitis during colonoscopic insufflation

Recently, I had the opportunity to review the interesting retrospective descriptive study of Cruz-Correa *et al* (*Gut* 2002;**51**:600). In brief, the authors described three patients who underwent colonoscopic examination for evaluation of chronic diarrhoea. During the colonoscopic examination, prominent mucosal tears in the ascending and transverse colon regions were noted. Biopsies of macroscopically normal appearing mucosa revealed changes supportive of underlying collagenous colitis. The authors attributed the mucosal tears, and their distribution, to the collagenous colitic process.

I have wondered about another possibility. Although the examinations were performed by experienced endoscopists, could these lesions have been induced by barotrauma? Along these lines, were the lacerations seen as the colonoscope was actually in the ascending colon and insufflation was performed, or were they found "unexpectedly" as the proximal colon was intubated, as has been reported in barotrauma induced colon lacerations.[1] Barotrauma induced colon injury can obviously occur when even an experienced endoscopist has performed the colonoscopic examination. Furthermore, the authors suggest that the distribution of the lacerations correlated with the distribution where one usually documents the "thickest" collagen tables—in the proximal colon. Could the distribution of these lacerations been related not to the thickness of the subepithelial collagen table but to the diameter of the colon where the lacerations were noted, being found where the colon is usually of greatest diameter? The diameter of the colon is usually greatest in the caecal and ascending colon regions. According to Laplace's law, the tension on the wall of a cylindrical vessel is proportional to its radius. It is therefore most likely that barotrauma induced lacerations would be found in the proximal colon, regardless of where the "thickest" subepithelial collagen deposition might be found.

In summary, I would be interested in the authors' opinions regarding the hypothesis that the findings they described might be related to barotrauma, as opposed to the underlying collagenous colitic process. The authors are correct that similar lesions have not been reported in other gastrointestinal diseases but have been described in patients undergoing colonoscopy and, at the least, they are certainly not specific for the presence of underlying collagenous colitis.

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Reference

1 **Felig DM**, Brand MH, Vender RJ. Unexpected right colon mucosal bleeding on colonoscopy. *Gastrointest Endosc* 1996;**44**:471–3.

Author's reply

Thank you for your interest in our article reporting colonic mucosal tears on endoscopic insufflation in three patients with collagenous colitis (*Gut* 2002;**51**:600). Your hypothesis of barotrauma induced colonic mucosal lacerations is interesting. However, we believe it unlikely that the observed mucosal tears were induced by barotrauma. We based our conclusion on the following observations. Firstly, the mucosal lacerations were seen after the colonic segment was intubated as the segment was insufflated, different from previous barotrauma induced colonic lacerations.[1] Secondly, all three colonoscopies were performed by highly experienced endoscopists who had performed over 10 000 colonoscopies, which makes it unlikely that excessive air was used. Thirdly, all three patients had documented collagenous colitis on biopsy, different from the barotrauma induced colonic lacerations described previously.[1] Fourthly, all three colonoscopies were performed without difficulty to the caecum, which makes it improbable that manipulation of the colon could have been implicated in the pathogenesis of these findings. Finally, we have not seen this type of mucosal tears in any other group of patients. The endoscopic images and description published by Felig *et al* were significantly different from our cases. Felig *et al* described the endoscopic findings as "haemorrhagic colitis".[1]

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Acupuncture for gastrointestinal disorders

Sung, in his article on acupuncture and gastrointestinal disorders (*Gut* 2002;**51**:617–19), states that despite the lack of scientific basis, acupuncture is widely used.

I disagree. There are published papers[1 2] showing that:

(1) Yang and Yin are characterised as phased flows of bioelectromagnetic energy emanating from various organ specific generators.

(2) This flow called qi has four different biochemical components ranging from small ions, free radicals (thus creating bioelectromagnetic field and current, while causing cascading billiard effects as well), to various neurotransmitters, macromolecules like opiods, and further.

(3) Meridians are four anatomically distinct channels of the above bioactive agents, eg, afferent/efferent nerves, arteries/veins, muscles and interstitial spaces.

These physicomathematical and physiological analyses make understanding of the "Mysterious East" a bit easier to the inquisitive "rational" Western mind.

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Unsuccessful rescue therapy with adefovir dipivoxil for lamivudine resistant HBV in a patient with liver failure

Adefovir dipivoxil is a new nucleoside analogue which is active against lamivudine resistant hepatitis B virus (HBV). A 48 week course of adefovir in human immunodeficiency virus type 1 infected patients with lamivudine resistant HBV induces a rapid and major decrease in serum HBV DNA levels with improvement in liver inflammation.[1] Although reassuring, this efficacy of adefovir may be influenced by the timing of its initiation after the emergence of lamivudine resistant HBV. We report here the case of a cirrhotic patient treated with lamivudine for four years who died of liver failure due to the emergence of lamivudine resistant HBV, despite the introduction of adefovir.

Observation

A 55 year old woman was diagnosed with decompensated cirrhosis due to HBV infection in December 1996. Serum HBV DNA level, as assessed by molecular hybridisation (Murex), was 1695 pg/ml and hepatitis B e antigen (HBeAg) was positive. Lamivudine 100 mg daily was started and resulted in rapid clinical and biological improvement and undetectable HBV DNA by polymerase chain reaction (PCR) (Monitor Roche, positive threshold 1000 copies/ml) in April 1997. HBV replication remained undetectable by PCR during follow up for almost four years. By 21 February 2001, PCR HBV became positive (48 000 copies/ml) while alanine aminotransferase (ALT) levels remained normal until four months later when they increased to five times the upper limit of normal (ULN). One month later, jaundice, ascites, and encephalopathy developed, prompting hospitalisation on 14 July. HBeAg remained positive. The patient never discontinued lamivudine or consumed alcohol. There was no evidence of sepsis, gastrointestinal haemorrhage, renal failure, or hepatocellular carcinoma. ALT was 20 ULN, bilirubin 337 µmol/l, and prothrombin time 19 seconds above normal. Viral load was high (>40 000 000 copies/ml) and HBV polymerase gene sequencing demonstrated substitution of Met to Val at position 550 in the YMDD motif (M550V). Adefovir 10 mg daily was added to lamivudine on 18 July. Ten days later, serum HBV DNA decreased to 4 062 000 copies/ml but encephalopathy and liver failure worsened. The patient died on 5 August.

Discussion

Data from pivotal clinical trials of lamivudine have shown frequent emergence of YMDD variants with long term therapy (67% after four years)[2 3] but without a major clinical impact on the course of HBV infection. Indeed, the increase in ALT level remains below pretreatment values while anti-HBe seroconversion and histological improvement can still be achieved.[4] However, most of these patients have mild liver damage. In cirrhotic patients, isolated reports of severe[5–9] or fatal[10] breakthrough related to YMDD variants have been reported. Adefovir is effective and now available for the treatment of lamivudine resistant HBV, but the timing of its initiation is still unknown. In this case, although adefovir induced a potent and rapid suppression of HBV replication, death from liver failure could not be avoided. HBV replication usually precedes the occurrence of symptomatic hepatitis by several months, which in cirrhotic patients can precipitate serious liver injury. Therefore, we suggest that adefovir should be promptly introduced in cirrhotic patients after significant viral relapse is documented (that is, increase of sensitive HBV DNA above 10 000 copies/ml), without waiting for changes in transaminases. This could avoid death from cirrhosis decompensation.

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BOOK REVIEWS

Diseases of the Liver and Biliary System

S Sherlock, J Dooley. London: Blackwell, 2002, £85.00, colour, pp 706. ISBN 0-6320-5582- 0

The book by Professor Dame Sheila Sherlock and James Dooley may be considered one of the great classics among texts dedicated to clinical training, and has undoubtedly had extraordinary success. Eleven editions have now been published in English, and it has been translated into many other tongues, including Spanish, French, German, Japanese, and Italian. This book must surely be counted in any list of the most widely read medical books in the last 50 years.

With this new edition, hepatologists, gastroenterologists, and general physicians may again learn from Sheila. This edition was finished only a few days before her peaceful death. As in the previous edition, another well known hepatologist at the Royal Free, James Dooley, has collaborated on this book.

As always, this book is excellent and, as in the past, will aid in the formation of young hepatologists and gastroenterologists. The present edition is a faithful representation of Sheila's personality. Her essence may be found on each page as may her capacity of synthesis and the clinical sense of our "master". Through the pages of the book, the Sheila that we knew can clearly be seen and felt, particularly for Europeans. This book should be read not only by hepatologists and gastroenterologists of a certain age but also by the younger generations of physicians.

The personality of Sheila Sherlock cannot be repeated. She was tenacious, brilliant, intelligent, as well as incisive and, on occasions, tough on insincere and irresponsible non- scientific attitudes. We all remember her questions and comments during the European Association for the Study of the Liver meetings. I can assure you that this book is of great use for physicians in training and that it truly reflects Dame Sheila's notable talent as a clinical teacher of hepatology. Therefore, if hepatologists and gastroenterologists wish to be up to date or learn modern clinical hepatology, they should read and study this book.

J Rodes

ABC of the Upper Gastrointestinal Tract

Edited by R P H Logan, A Harris, J J Misiewicz, *et al*. London: BMJ Books, 2002, colour, pp 54. ISBN 0-7279-1266-6

Our comprehension of upper gastrointestinal disease has been extended in the past three decades by the introduction of endoscopy, ultrasonography, computed tomography scanning, pH monitoring, and manometry. This burgeoning of investigational modalities coincided with the development of acid suppressing drugs that for the first time enabled the control of peptic ulcer and gastro-oesophageal reflux disease. However, by the 1990s, long term acid suppression for the majority of patients with peptic ulcer was rendered obsolete by the discovery that *Helicobacter pylori* eradication resulted in permanent cure. This strategy has been so successful that non-steroidal anti-inflammatory drugs are now the commonest cause of ulcer disease in the developed world.

Despite the decline in ulcer disease there has been no reduction in dyspeptic patients presenting to general practitioners, and the flow of referrals to endoscopy and gastroenterology clinics is undiminished. Patients with functional dyspepsia now greatly outnumber those with peptic ulcer and although the aetiopathogenesis is being unravelled, its management remains problematic. The Hippocratic maxim "I am more interested in the man who has the disease than the disease the man has" always needs to be borne in mind when managing such patients.

Non-gastroenterologists must have struggled to keep abreast of these advances and evolving concepts. I presume therefore a wide range of non-specialists, including general surgeons, family practitioners, house officers, and nurses, will welcome this compilation of articles, which first appeared in the *British Medical Journal* under its ABC services banner, as a means of regaining lost ground. The specialist readers of this journal will find the excellent coloured figures and photographs invaluable for illustrating lectures and seminars. If, like your reviewer, you failed to retain the original articles or have lost them in your "filing system", this is a second chance to obtain a valuable resource in a highly convenient format.

The authority of the texts is not questioned, written as they are by acknowledged experts, but the absence of references and in many cases even the omission of suggestions for further reading are deficiencies, which in the era of evidenced based practice, need to be addressed when planning subsequent series.

M Lancaster-Smith

Mechanisms and Consequences of Proton Transport

Edited by T Urushidani, J G Forte, G Sachs. Amsterdam: Kluwer, 2002, b/w, pp 372. ISBN 1-4020-7059-4

For someone who attended one of the early proton transport meetings and who lived through the era of the discovery of histamine H_2 receptor antagonists and proton pump inhibitors, this volume makes fascinating reading. The elegant application of modern biochemical and molecular biology techniques has increased our knowledge of the intimate working of the proton pump in a remarkable manner. The book, written by key players in the field, describes, to use a hackneyed phrase, the cutting edge research that is being undertaken. The contributions are not restricted to proton transport but address the K^+ and Cl^- channels in the parietal cell and the role of Ca^{2+} in the secretory process. In the latter context, it is interesting that our knowledge of the structure of the gastric H^+/K^+ ATPase has depended heavily on studies of the crystal structure of the calcium pump of the sarcoplasmic reticulum. New, to the reviewer at least, is the existence of parchorin, a chloride intracellular channel related protein which appears to play an important role in the regulated movement of body fluid via Cl^- transport in a range of tissues, including the gastric mucosa, salivary gland, and kidney. As an old acid inhibitory man, I viewed, at least initially, a role for *Helicobacter pylori* in the aetiology of peptic ulcer with some scepticism. However, I found the current chapters on this bacterium absorbing, particularly in the cunning ways it combats the low intragastric pH by, for example, downregulation of H^+/K^+ ATPase gene expression. Similarly, the fact that the H^+/K^+ ATPase is the dominant gastric autoantigen in *H pylori* infection has important implications for our understanding of autoimmune gastritis and possibly gastric cancer.

In their preface, the editors state that the field is still filled with a multitude of potential targets for drug development but it is not exactly clear what they have in mind. The chapter on inhibition of acid secretion using a myosin light chain kinase inhibitor applied locally is scientifically interesting but do we really need another antisecretory drug to add to the already highly effective armamentarium of H_2 antagonists and proton pump inhibitors? The same argument applies to potential inhibitors of the potassium channel. Are there pathological states associated with the non-gastric H^+/K^+ ATPase found in the kidney and colon? Probably not, as they play an important role in the normal maintenance of body K^+ homeostasis.

As is inevitable with a book based on presentations at a conference, some of the chapters are short and drop the reader almost immediately into the detailed science without much background introduction. The first chapter is excellent, setting the scene for the research based chapters that follow, although a little more discussion on the proton pump inhibitors both of the covalent class and K^+ competitive-type would have been useful.

In these days of "all singing, all dancing" computer enhanced images, the cover of the book is disappointing and far from eye catching. The book is obviously required reading for those actively involved in the field of proton transport. Whether it will appeal to a broader audience is less clear.

M Parsons

NOTICES

38th EASL Annual Meeting

The European Association for the Study of the Liver will be holding its 38th annual meeting on 29 March–1 April 2003 in Istanbul, Turkey. Further information can be found on the website www.easl.ch/easl2003.

Falk Workshop—Inflammatory Bowel Disease: Turning New Advances into Practice

This will be held on 3 April 2003 in Berne, Switzerland. Further details: Falk Foundation e.V., Congress Division, PO Box 6529, Leinenweberstr. 5, 79041 Freiburg/Br, Germany. Tel: +49 761 15 140; fax: +49 761 15 14 359; email: symposia@falkfoundation.de; website: www.falkfoundation.de

International Symposium on Viral Hepatitis and Liver Disease

This conference will take place on 6–10 April 2003 in Sydney, Australia. Further information: ISVHLD 2003 Congress Managers, GPO Box 128, Sydney NSW 2001, Australia. Tel: +612 9262 2277; fax: +612 9262 3135; email: isvhld@tourhosts.com.au; website: www.tourhosts.com.au/isvhld

New In Vivo Imaging Modalities for Molecular Biology, Cell Biology and Physiology

This Jacques Monod conference will be held on 31 May–4 June 2003 in Roscoff, France. Further information: Bertrand Tavitian, INSERM M10103, Service Hospitalier Frédéric Joliot, CEA Direction des Sciences du Vivant, Direction de la Recherche Médicale, 4 place du Général Leclerc, 91401 Orsay Cedex, France. Tel: +33 169 867 779; fax: +33 169 867 739; email: tavitian@shfj.cea.fr

Prague Hepatology Meeting

To be held on 5–7 June 2003 in Prague, Czech Republic. Leading speakers from Europe and the USA will present new ideas and suggestions on pathophysiology, diagnostics, and therapy of liver diseases in ten programmes blocks. Further details: Ms Veronica Revicka. Tel: +420 241 445 759; fax: +420 241 445 806; email: veronika@congressprague.cz

Falk Symposia—New Findings on Pathogenesis and Progress in Management of IBD

Two symposia and a workshop will be held on 10–14 June 2003 in Berlin, Germany. Further details - see Falk Workshop details above.

Gastroenterology and Endotherapy: XXIst European Workshop

This will be held on 16–18 June 2003 in Brussels, Belgium. Further details: Nancy Beauprez, Administrative Secretariat of the Workshop, Gastroenterology Department, Erasme Hospital, Route de Lennik 808, B-1070 Brussels, Belgium. Tel: +32 (0)2 555 49 00; fax: +32 (0)2 555 49 01; email: beauprez@ulb.ac.be

The Association of Coloproctology of Great Britain & Ireland

This annual meeting will be held on 7–10 July 2003 in Edinburgh, UK. Further details: Conference Secretariat, The ACGBI at the Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PE. Tel: +44 (0)20 7973 0307; fax: +44 (0)20 7430 9235; email: acpgbi@asgbi.org.uk; website: www.acpgbi.org.uk

European Helicobacter Study Group (EHSG)

This meeting, on Helicobacter infections and gastroduodenal pathology, will be held on 3–6 September 2003 in Stockholm, Sweden. Further details: Professor Torkel Wadstrom, President- EHSG, Lund University, Department of Infectious Diseases & Medical Microbiology, Division of Bacteriology, Solvegatan 23, SE-223 62 Lund, Sweden. Tel: +46 46 173 241; fax: +46 46 152 564; email: Torkel.Wadstrom@mmb.lu.se; website: www.helicobacter.org

The European Society of Parenteral and Enteral Nutrition (ESPEN)

ESPEN will celebrate its silver anniversary at the time of the annual congress, which is to be held on 20–23 September 2003 in Cannes, France. Further details: www.espen.org