TPMT in the treatment of inflammatory bowel disease with azathioprine

We read with interest the recent article by Lennard on the role of thiopurine methyltransferase (TPMT) enzyme in predicting azathioprine related toxicity in patients with inflammatory bowel disease (IBD) (Gut 2002;51:143–6). He concludes that measurement of TPMT activity has no specific role in identifying the risk of significant bone marrow toxicity in long term users of azathioprine. This conclusion is in agreement with other published work and emphasises the importance of ongoing haematological monitoring in IBD patients receiving this drug.1 The importance of haematological monitoring in the early detection and prevention of azathioprine related toxicity is well recognised.2 However, the duration of early monitoring is a matter of controversy. The current British National Formulary guidelines recommend that patients undergo blood tests on at least a weekly basis for the initial four weeks of therapy.3 The key issue in determining the value of these different approaches to monitoring is the time of onset of potentially life threatening bone marrow suppression following initiation of azathioprine treatment. These data are not available for patients with IBD. In a retrospective study, we analysed the time of onset of all drug related toxicity in IBD patients post initiation of azathioprine therapy. A total of 110 consecutive IBD patients with a history of azathioprine use were identified (table 1). Patients were identified from the hospital inpatient enquiry system, IBD clinic, and pharmacy records. Mean azathioprine dose was 2 mg/kg/day (range 1–3). Mean age of the patients on azathioprine was 38.11 years (18–76). Seventeen of 110 patients (15%) suffered from azathioprine related early toxicity (table 1). Mean azathioprine dose in those showing drug toxicity was 100 mg/day (50–150). Most (77%) drug related toxic events manifested within the first 12 weeks of therapy (fig 1). However, the mean time of onset of drug related toxicity depended on the side effect observed. For example, most drug related nausea was observed within two weeks of commencing treatment while all cases of deranged liver function tests were detected within eight weeks of treatment onset. Significantly, this was not true for bone marrow suppression. The mean duration of treatment in the two patients who experienced this side effect was 11 weeks (range 10–12). Both cases occurred outside the “stringent” eight week monitoring period recommended by the drug’s manufacturer. Hence identification of bone marrow suppression would have been delayed using the current British and manufacturer’s guidelines. Three further episodes of neutropenia were identified during long term (>3 months) treatment in three patients who continued on maintenance azathioprine (mean duration 101 weeks/patient, range 2 weeks to 5 years). In our practice, we feel that significant toxicity during the early (<3 months) period of therapy could have been missed by strictly following existing guidelines.

Early detection of abnormalities in asymptomatic patients helped in dose adjustment with resolution of side effects. In addition, early detection of azathioprine related bone marrow suppression is likely to save lives. We recommend that gastroenterologists employ an extended (three month) period of intensive haematological monitoring after initiation of azathioprine therapy in IBD. Although neutropenia is occasionally observed beyond this point, intensive monitoring for the duration of treatment, which may continue for years, is clearly not practical from a patient or service perspective. However, this serves to emphasise the importance of continuous patient education concerning “alarm symptoms” throughout the duration of azathioprine therapy.

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References


Author’s reply

Measurement of thiopurine methyltransferase (TPMT) status, prior to the start of azathioprine therapy, has a role in identifying the TPMT deficient patient at risk of severe myelosuppression and TPMT heterozygous individuals who are prone to early myelosuppression.1 2 The risk of azathioprine toxicity is well recognised but, as the authors state, the duration of early monitoring is a matter of controversy. The matter for debate is the time of onset of potentially life threatening myelosuppression.

Table 1 Patient characteristics and side effects encountered during the initial period of therapy (three months) with azathioprine in patients with inflammatory bowel disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Male</th>
<th>Female</th>
<th>Nausea/vomiting</th>
<th>Abnormal LFTs</th>
<th>Neutropenia</th>
<th>Thrombocytopenia</th>
<th>Infections</th>
<th>Pancreatitis</th>
<th>Miscellaneous associated symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcerative colitis</td>
<td>17</td>
<td>48</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>25</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
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<td>5</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

LFT, liver function test.
Quasim et al state that this information is not available for patients with inflammatory bowel disease (IBD). However, data can be derived from observations in other patient groups which may serve as useful guidelines for this time interval.

Reports of azathioprine induced severe myelosuppression in the TPMT deficient patient indicate that bone marrow toxicity is recorded after 3–10 weeks (median 4) of azathioprine therapy.\(^2\) In these reports the drug dosage varied from 1 to 2.9 mg/kg (median 1.7). One patient taking azathioprine at a dosage of 1 mg/kg developed myelosuppression (white blood cell count (WBC) 1.6×10^9/L, platelets 25×10^9/L) at 10 weeks while another did so at 1 mg/kg developed myelosuppression (WBC 3.8×10^9/L, platelets 79×10^9/L) at 8 weeks. Because severe bone marrow toxicity can be precipitated by the addition of other medications to the TPMT deficient patient with an intermediate TPMT activity (0.9–2.9×10^9/L) within one month of starting azathioprine (2–3 mg/kg) as second line therapy, Black and colleagues\(^3\) advise that at a minimum, close adherence to the ABPI guidelines is required. The additional observation that patients with an intermediate TPMT activity may experience leucopenia (leucocyte counts 0.9–2.1×10^9/L) and thrombocytopenia (platelet counts 9–49×10^9/L) within 1–3 months of treatment indicates, particularly for the patient on low dosages of azathioprine at a dosage of 1 mg/kg, that the combination therapy of azathioprine and continuation of, at a minimum, weekly during the first eight weeks of therapy. Complete blood counts should be monitored weekly during the first eight weeks of therapy.

The data presented in the reports above illustrate the multifactorial nature of myelosuppression in this patient group and supports the need for continued vigilance with respect to blood count monitoring. The drug manufacturer’s guidelines, as stated in the Association of the British Pharmaceutical Industry (ABPI) medicines compendium, advise that a minimum, complete blood count monitoring should be undertaken weekly during the first eight weeks of therapy. The guidelines then continue, “this frequency may be reduced during later therapy to monthly intervals, or at least at intervals no longer than three months”.

The data presented in the reports above indicate, particularly for the patient on low dose azathioprine in whom TPMT status is unknown, close adherence to the ABPI guidelines and continuation of, at a minimum, weekly full blood counts during the first three months of treatment. Because severe bone marrow toxicity can be precipitated by the addition of aminosalicylate derivatives\(^1\) to the azathioprine regimen, the drug manufacturer’s more stringent blood count monitoring scheme should be considered following such adjustments in the combination therapy of refractory IBD.

Appendicectomy and ulcerative colitis

Cosnes et al demonstrated that previous appendicectomy is not only associated with a lower incidence of ulcerative colitis, but also with a less severe course of the disease. Although we can fully agree with this result, we disagree with the recommendation that patients genetically at high risk of developing ulcerative colitis may be considered as candidates for appendicectomy on the prejudice of preventing the development of ulcerative colitis and also decreasing its severity.\(^4\) All previous studies, as well as the present study, have demonstrated an association only between previous appendicectomy and ulcerative colitis. It has not been shown that performing appendicectomy in healthy persons at increased risk of developing ulcerative colitis is beneficial. The association may as well have been caused by an unknown confounding factor, both leading to an increased risk of appendicectomy and a decreased risk of developing (severe) ulcerative colitis. To illustrate this point is the following theoretical example: an epidemiological study on cardiovascular morbidity finds that the risk of cardiovascular events is inversely related to the risk of developing upper gastrointestinal haemorrhage. This could be due to the factor “treatment with aspirin” that could well explain the increased bleeding risk and the lower incidence of cardiovascular events. The confounding factor is the use of aspirin. It would be wrong to conclude that in patients without a history of bleeding, attempts should not be undertaken to induce upper gastrointestinal bleeding in order to prevent cardiovascular morbidity.

Another argument against performing this surgical procedure in healthy persons is the finding that appendicectomy in the absence of an inflamed appendix was not associated with a decreased risk of ulcerative colitis, suggesting that appendicitis rather than appendicectomy protects against ulcerative colitis.\(^1\) Cosnes et al state that these results may not be correct as they included all patients with previous appendicectomy and still found a less severe course. We believe they are incorrectly assuming this, as another possible explanation is that the effect of appendicectomy is actually higher than the effect of appendicec-tomy reported in the present study, which could have been due to the inclusion of patients without appendicitis. In conclusion, we believe that at present healthy persons at risk of developing ulcerative colitis should not be considered candidates for appendicectomy outside clinical trials as evidence showing that appendicectomy will protect these persons is lacking.

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Reference


Authors’ reply

Many French surgeons in 1900 did recommend removing preventively all appendixes of young people (see Marcel Proust, “A l’ombre des jeunes filles en fleur”). That was not our purpose. Indeed, the sentence pointed out by ter Borg and van Buuren in our paper did not give a recommendation but only made a suggestion to consider for appendicectomy patients genetically at high risk of developing ulcerative colitis. Ter Borg and van Buuren speculate that appendicectomy and a benign course of ulcerative colitis may be linked through a confounding factor but they do not document their hypothesis. In fact, there is a large body of evidence supporting a causal relationship between appendicectomy and no (or benign) ulcerative colitis, and the strongest demonstration of this relationship is the protective effect of early appendicectomy in the T cell receptor α (TCR-α) knockout mouse model.\(^7\) Note also that the Swedish study\(^8\) which found that only appendicectomy for inflammatory conditions protects against ulcerative colitis did not take into account cases of mild ulcerative colitis, a subgroup in which appendicectomised patients may be over represented.

Finally, we do not believe that the effect of appendicectomy on the course of ulcerative colitis is so high that it would remain after excluding all patients without appendicitis, thus probably two thirds of our patients.\(^1\) A key point however, like in the TCR-α knockout mouse model, is the date of appendicectomy. Appendicectomy protects against severe ulcerative colitis only when performed at a young age, and therefore disease onset.\(^1\) This latter observation argues against any therapeutic effect of appendicectomy after onset of ulcerative colitis. The problem is different when considering patients at risk for the disease.

We do believe that in a few years it will be possible to screen out young patients with a
predisposing genotype for ulcerative colitis, and a clinical trial assessing the benefits of prophylactic appendicectomy will be warranted.

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References

Screening and surveillance for asymptomatic colorectal cancer in IBD
We would like to voice our concerns about some of the recommendations in the guidelines recently published by the British Society of Gastroenterology and Association of Coloproctology for screening and surveillance for asymptomatic colorectal cancer in patients with inflammatory bowel disease (Gut 2002;51 (suppl V):v12–21).

(1) In the present medicolegal environment, failure to comply with guidelines which carry the imprimatur of respected national bodies will require vigorous defence should mishap occur. We do not believe the evidence is strong enough to justify the recommendation that every patient with extensive colitis of duration greater than 8–10 years should undergo regular colonoscopy. Firstly, it must be determined at each hospital whether it is feasible to offer such a service within the constraint of local resources available. Secondly, if regular colonoscopy can be offered, then each patient should decide whether or not to accept regular colonoscopy after full discussion of its possible advantages and limitations.

(2) The success of colonoscopic surveillance programmes is disputed. Although some centres (including our own) have been protagonists for this approach, others have argued that it is not only labour intensive but also ineffective. Before imposing global national guidelines we should have firm evidence of a scheme’s efficacy or, failing this, we should have multicentre consensus. The guidelines, as published, appear to be the sincerely held opinions of a single consultant team based on their own research and assessment of the literature, followed by approval of a committee, but no indication is given of widespread consultation.

(3) The recommendations for patients with extensive colitis of Surveillance every third year during the second decade of disease, every second year during the third decade, and annual colonoscopy thereafter are complex. The evidence for an increasing risk of cancer in the second, third, and succeeding decades of disease duration is controversial, and is not borne out by the unstratified figures for patients with melphalan colitis based on 26 reported studies in the meta-analysis reported by the authors of the guidelines, although an increase was observed in stratified data. The strategy suggested therefore is not based on firm data, and in particular published data after the third decade are few due to the small numbers involved.

(4) We have concerns about the benefits during routine colonoscopic examinations of taking two to four random biopsy specimens every 10 cm. This approach is time consuming for both the colonoscopist and the pathology department, and adds a considerable financial burden to the programme (which is not included in Eaden and Mayberry’s cost analysis). In theory, the risk of a false negative examination is reduced as more biopsies are taken but in practice the additional yield is very low indeed. During a recent study at St Mark’s Hospital, almost 3000 random surveillance biopsies from such patients yielded no dysplasia (unpublished data).

(5) Considering the disputed efficacy of current colonoscopic surveillance programmes for patients with extensive ulcerative colitis, it is inappropriate at present to extend this to default to patients with left sided colitis or (by implication) those with Crohn’s disease.

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Reference

Authors’ reply
We would like to thank Dr Forbes et al for their response to the guidelines published by the British Society of Gastroenterology (BSG) and the Association of Coloproctology of Great Britain and Ireland on screening and surveillance for asymptomatic colorectal cancer in patients with inflammatory bowel disease (Gut 2002;51 (suppl V):v10–12). They raise a number of points which will be answered in turn.

(1) There are medicolegal implications of failing to comply with recommendations from a respected body but a guideline is precisely that—a guideline. They are not etched in stone and may need to be amended at future dates to continue to reflect best practice. The case of Wilsher v Essex Area Health Authority demonstrates that guidelines are not based on evidence in order to practice to the highest standards. However, the courts (Early v Newham Health Authority) will consider local guidelines. This will be of particular importance for units that are unable to deliver standards that have been identified nationally, provided the local practice has been formulated into a local guideline.

There is a wealth of data supporting the increased cancer risk in patients with ulcerative colitis and evidence of the effectiveness of surveillance as practice in many centres is uncertain, such an approach is widespread. The purpose of guidelines is to identify good practice and to introduce a uniform approach throughout the country. The alternatives are to abandon surveillance or to offer haphazard and unstructured surveillance (and therefore ineffective) service. The anticipated cost of surveillance for both colitis and Crohn’s patients is estimated to be £9600 per annum. Hopefully, an agreed strategy will be able to meet this cost but we realise funds may not be available initially which is one of the reasons for suggesting the guidelines have been audited in five years. It is clearly stated in the guidelines that a discussion should take place between the doctor and patient informing them of their individual risk so that the patient can make an informed decision before embarking on a surveillance programme. Gone are the days of a paternalistic attitude, as patients should now accept some responsibility for their illness.

(2) Forbes et al raise the point that before guidelines are imposed there should be firm evidence of a scheme’s efficacy. There are no randomised studies comparing different surveillance protocols or for that matter even a scheme based on firm evidence. Forbes et al are well aware, it will never be possible to provide grade A recommendations on this issue and the best we can do is to assess surveillance programmes retrospectively. Data are accumulating that surveillance participants have reduced morbidity and mortality, as outlined in the guidelines, and one of the signatories to your letter has stated that surveillance improves survival.1 One notable review of surveillance programmes from the Leeds group did not show any benefit from surveillance but the group had very stringent criteria.2 They felt inclusion of dysplasia alone as a measure of success was of debatable value. Therefore, they limited their audit to those eventually found to have cancer. They also decided to exclude patients in whom cancer was found at an initial colonoscopy undertaken at least 12 years after the onset of symptoms. We feel that finding dysplasia in the very early aim of surveillance programme because it is found on the first colonoscopy in a surveillance programme it should not be deemed a failure of surveillance.

As you suggest, it was possible to be obtained before the guidelines were published. A national audit of the surveillance practices of gastroenterologists was conducted which revealed that although 94% of gastroenterologists performed surveillance, there was wide variation in practice.3 This alone suggests there would be little chance of a consensus opinion across the UK. Once the guidelines had been formulated, the Clinical Services and Standards Committee comprising approximately 40 individuals reviewed them. They then went through the usual guidelines process after being seen by the Clinical Services Committee and approved by the IBD section of the BSG. After this they were posted on the BSG website for six weeks to attract comments from other members of the society. The guidelines went back to the Clinical Services Committee after amendments were made on the basis of comments from the wide range of consultants.

Finally, the guidelines were endorsed by the Executive Committee of the BSG for a further review and signing off. Thus the guidelines were eventually accepted and published. They are not simply the opinions of two consultant gastroenterologists.
We appreciate that increasing the colonoscopy frequency with increasing duration of disease is more complicated than 1–2 yearly surveillance. However, we are sure that it is not too difficult to calculate and it actually reduces the number of colonoscopies being performed initially, so this must be regarded as an important improvement in the present routine practice of some gastroenterologists.

The meta-analysis does show an increasing cancer risk in the second and third decades of disease. In 1984, 8.6% (95% CI 4.0%–13.3%) at 20 years, and 12.7% (95% CI 6.0%–19.3%) at 30 years. The whole point of stratified data was to see if the cancer incidence did increase by decade of disease. It is only stratified data that can be used in this way. Such data will give the most accurate estimate as it is only these data that included studies which reported cancer incidence stratified by decade and duration of patient follow up (19 studies). The decade specific incidence rates correspond to a cumulative risk of 1.6% (95% confidence interval (CI) 1.2%–2.2%) by 10 years, 8.3% (95% CI 4.8%–11.7%) by 20 years, and 18.4% (95% CI 13.5%–21.5%) by 30 years.

The 26 studies Forbes et al refer to also included stratified incidence rates which reported cancer incidence where only duration of patient follow up was reported—that is, the incidence rates were not broken down for each decade. Even with these the unstratified data were examined the cancer incidence still increased by decade of disease! The unstratified cumulative probabilities give a risk of 4.4% (95% CI 2.0%–6.8%) at 10 years, 8.6% (95% CI 4.0%–13.3%) at 20 years, and 12.7% (95% CI 6.0%–19.3%) at 30 years.

Therefore, the strategy suggested is based on firm data. Of course the numbers of patients by the third decade are few but this is the nature of the beast. The use of a meta-analysis of cancer risk in ulcerative colitis overcomes the inadequacies of any reliance on smaller studies from single specialist centres.

We accept that the cost of biopsies was not included in the cost analysis. There are numerous articles debating the number of biopsies which should be taken during a surveillance colonoscopy. ‘Yes it is time consuming’ but we all know that to stand any chance of detecting dysplasia to be low.

For example only 10 biopsies were being taken from the unpublished St Mark’s data how many biopsies were taken per colonoscopy. If them from a surveillance programme.

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registrars I have been surprised by their overwhelming interest in honing endoscopic skills. If this leads to a simplistic approach to the management of possible gastrointestinal pathology, it has its dangers. Analysis of two cases in the past month reminded me of this.

Case No 1

An elderly man was admitted to hospital with severe anaemia. The houseman obtained a history of aspirin ingestion and, over the preceding few weeks, recurrent melena. He described feeling a hard liver edge. A blood count showed haemoglobin (HB) 4.3, mean corpuscular volume (MCV) 55.7, white blood cell count (WCC) 6.6, and platelets 63. The patient was transfused and without further investigation the physician/gastroenterologist arranged for oesophageo-gastro-duodenoscopy (OGD) and colonoscopy.

At OGD the stomach was described as showing a moderate erythematous/exudative gastritis. At colonoscopy no abnormality was seen apart from a little fresh bleeding, the cause of which was not apparent. The patient was allowed to go home only to be admitted 36 hours later with faecal peritonitis. The colon had been perforated at the rectosigmoid junction. The patient recovered well from reparative surgery but died six weeks later of multiorgan failure. At necropsy he was found to have cirrhosis of the liver. In retrospect, photographs of the gastric mucosa were consistent with portal gastropathy.

Case No 2

An elderly man taking diclofenac for osteo-arthritis of the hip began drinking heavily after the death of his wife. One Saturday he felt faint, vomited black fluid, and passed melena. After the weekend he was admitted to hospital. His blood count showed HB 9.7, MCV 105, WCC 10.3, and platelets 240. As in case No 1, he was listed for OGD and colonoscopy. At OGD he was found to have a marked antral gastritis and multiple duodenal erosions in a deformed duodenal cap. At colonoscopy, multiple diverticulae were found in the antral gastritis and multiple duodenal erosions. At OGD he was found to have a marked antral gastritis and multiple duodenal erosions in a deformed duodenal cap. At colonoscopy, multiple diverticulae were found in the antral gastritis and multiple duodenal erosions in a deformed duodenal cap. The colon had been perforated at the rectosigmoid junction. The patient recovered well from reparative surgery but died six weeks later of multiorgan failure. At necropsy he was found to have cirrhosis of the liver. In retrospect, photographs of the gastric mucosa were consistent with portal gastropathy.

References

1 Booth CC. What has technology done to gastroenterology? Gut 1985;26:1088–94.

Which 5-ASA?

I read Dr Travis’ therapy update (Gut 2002;51:548–9) with interest; the topic is timely in a situation about to be challenged by new generic mesalazine brands. I note the choice of time dependent mesalazine (Pentasa) but, if mesalazine is to be relied upon exclusively, some doubt is expressed. Pentasa may not be the best choice. The recent study by Kruis and colleagues1 in the maintenance of remission in ulcerative colitis (UC) found that with Pentasa 1.5 g/day, the six month remission rate was 56.8% compared with 77.5% with balsalazide 3 g twice daily (p=0.045).

The assertion that the advantages of the azo bond delivery to the distal colon can be matched by simply increasing the dose of pH dependent (Asacol) or time dependent release (Pentasa) has not been borne out by laboratory or clinical studies. Tissue level studies have indicated that double dose mesalazine is delivered to the kidney, not the colon. A large clinical trial of Pentasa in mild to moderate active UC found remission rates of 29% for mesalazine release mechanism is important for the efficacy, reliability of delivery, and safety of the oral preparations and that balsalazide is now the gold standard for other agents to be judged against.

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Conflict of interest: The author has accepted hospitality from the manufacturers of all of the current 5-ASA preparations, and sat on an advisory panel for Shire.

References

1 Kruis W, Schreiber S, Theuer D, et al. Low does balsalazide [1.5 g twice daily] and mesalazine [0.3 g three times daily] maintained remission of ulcerative colitis but high dose balsalazide [3 g twice daily] was superior in preventing relapses. Gut 2001;49:733–9.
TIPS for gastric varices
We recently read with interest the study by Tripathi and colleagues investigating the outcome of TIPS in patients with gastric (GV) compared to oesophageal varices (OV). This study confirmed the previous finding of lower mean portosystemic pressure gradient (PPG) in patients with GV bleeding relative to those with a history of OV bleeding. Indeed in this study 35% (14/40) of GV patients compared to only 8% (20/232) of OV patients had a PPG <12 mm Hg. The group of patients who bled at PPG <12 mm Hg (group 1) is particularly intriguing. As mentioned by the authors, low PPG in GV patients has been shown to predict the presence and size of a spontaneous gastrorenal shunt (GRS) which is present in up to 85% of GV patients but present in only about 20% of OV patients.² Previously, Sanyal et al. found that 50% (6/12) of patients who underwent TIPS for prevention of GV rebleeding failed to decompress the varices as documented by endoscopy. 4/6 of these patients had a large GRS and a PPG <12 mm Hg. Thus based on probability, the group 1 patients in the current study (both GV and OV) are likely to have had a spontaneous GRS already decompressing the portal system. It would be valuable to know if the authors have any data on the presence of GRS in their patient population, perhaps documented by portogram taken at the time of TIPS. Also, did they document decompression of varices post-TIPS as an indicator of the clinical efficacy of the procedure? For example, it would be interesting to know if patients in group 1 failed to decompress varices post-TIPS more often than patients in group 2. Alternatively, we have experience of a number of patients with large GV who had a baseline PPG of <12 mm Hg and a large GRS. Following TIPS in these patients, there was a minimal or no reduction in PPG and filling of the GRS was not shown to be reduced on post-TIPS portogram.

Finally the authors noted in group 2 (baseline PPG >12 mm Hg) that lower post-TIPS PPG was associated with a lower risk of bleeding. This was based on probability, the group 1, there was no difference in post-TIPS PPG between patients who did and did not re-bleed, suggesting that PPG may not be a critical determinant of variceal bleeding in patients who have a low PPG to start with. The role of PPG in dictating the natural history of GV is not known. Conceptually, insertion of an artificial portosystemic shunt into a patient who already has a large spontaneous shunt effectively offloading the portal pressure would not seem to confer much benefit. Do these GV (and possibly OV) patients with low PPG pre-TIPS and with a possible GRS really benefit from TIPS?

MR angiography can accurately assess for presence of a spontaneous GRS.³ There is a compelling argument that this should be an essential part of the assessment algorithm of patients with GV if a large spontaneous shunt is present, and PPG (as measured by hepatic vein wedge pressure gradient (HVPG)) is <12 mm Hg, then perhaps other therapeutic options such as B-RTO (balloon occluded retrograde transvenous obliteration) should be considered. Hopefully more prospective data, examining the role of PPG, TIPS, and B-RTO in the management and outcome of GV will help clarify these issues.
available evidence about different management approaches. The book also has a feel of having been composed upstream versus an ‘upstream viewpoint’. Apart from a hepatologist, the other five contributors are all surgeons—perhaps it might have been useful to have had the perspectives of a general physician and a general practitioner, even if only to raise the pragmatic questions that arise at the early stage of management of hepatobiliary problems. An example is the potential prophylactic management of patients with varices. As it stands, variceal management in this publication commences essentially after the bleed with only a few lines on prophylactic management, and even those largely dismissive of possible measures apart from the global use of beta blockers. So what should a primary care practitioner dealing with a patient who might have varices actually do, and at what stage of abnormal liver tests or clinical findings is referral likely to be rewarding?

Increasingly, on a worldwide basis, a primary care clinician or a general practitioner with generic interests provides initial health-care. Many of them will rely on such publications as a ready source of information. Ease of access to the information is important—this is assisted in this ABC by the use of summary points and clear illustrations. The aim of the publication is given as the desire to provide an overview and to enable the clinician to keep abreast of advances in the common and the rarer conditions. It succeeds in this.

Drug-Induced Liver Disease


On the face of it, this hardback does not sound like a very good bedtime read and splashing out £195 might seem a little extravagant for what might appear to be some dry tome that would readily gather dust on a shelf. It was therefore with some trepidation that I received this ostensibly unwieldy 773-page bound and green covered book, and turning the pages quickly, the casual reader might still be deceived into casting it into the nether regions of a desk drawer or the dimmer corners of an office. However, I am pleased to say that these were all poorly grounded misapprehensions, because this is an expertly written and very readable book. It is not only edited by the whole galaxy of experts, covering the mechanisms of drug-induced liver injury in an easily readable format (who cannot stand up and say that paracetamol/acetaminophen poisoning is a mystery to most mere mortals, despite the fact we all know the antidote?). The book also contains a comprehensive set of chapters on the hepatotoxicity of specific drugs for quick and easy reference, which is set firmly in clinical context, and for the generalist, a very useful clinical section on diagnosis and management of drug-induced liver disease.

Another reason not to look at such a book might be that many of those emanating from the USA have an American perspective only, but this is a real exception as at least one third of the chapters are written by authors from countries as far apart as Switzerland and India and the book as a whole develops a truly international theme. It is well referenced in a very authoritative and up to date way, and sheds light on a whole host of topics that are bothersome to most gastroenterologists, such as the usage of methotrexate in psoriasis and rheumatoid arthritis (with helpful guidelines on when to offer baseline and follow liver biopsy and to whom), antituberculous agents (and when to worry!), and in this day and age, sections on psychotropic agents, drugs of abuse, and importantly, when many patients might not be seen to be at risk (such as the knowledge that can be found in the average health food shop or in Chinatown, an authoritative compendium on alternative medicines, vitamins, and natural hepatotoxins. With the increasing incidence of certain liver tumours, I found sections on the adverse effects of hormones (covering everything from adrenals, focal nodular hyperplasia, and frank malignancies to vascular abnormalities in the liver) and on environmental toxins very interesting and informative.

I therefore have to say that at the price, most people would not want to rush out and buy a copy immediately, I would wholeheartedly recommend that every hospital library invests in a copy for use by gastroenterology trainees, trainees from other disciplines, and even the odd consultant gastroenterologist! The book would be very useful for hospital pharmacists, nurse practitioners, and also for medical students who need to reference the subject in more depth. However, on considered reflection, I think that most gastroenterology units should think carefully about buying a copy—with increasing drug usage by patients, illicit or otherwise, it is an exploding problem. The book provides an aide memoire for those that need it and it won’t gather dust for long!

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@shlj.cea.fr

www.gutjnl.com

At last (Ballou et al) a detailed and intelligent account of the lessons that we should have learned from the study of COX-1 and -2 deficient animals. Indeed, both, cardioprotective response, if not silence, to “unexpected” data obtained from these animals, such as the lack of gastrointestinal damage in COX-1 knock-outs, simply allows prevailing simplistic theories on the role of the two enzymes to be maintained a bit longer. The following chapters on enzymes in nocioception, Alzheimer’s disease, kidney, apoptosis, labour, cardiovascular system, arthritis, and bone are a treat, and reflect the scope of the book. Whittle, Hawkey, and Rodriguez could have combined their three chapters on the gastrointestinal toxicity of NSAIDs as their knowledge is complementary. They invade each others “intellectual” territory which gives the impression of conflict and confusion where none exists. The chapter by DuBois on COX-2 in colorectal cancer is only disappointing because of its brevity; the man has so much more knowledge to share! However, this is partially compensated by an excellent review of the role of COX-2 in other cancers. The book ends with rather biased accounts on the virtues of each of the COX-2 selective agents.

This book is currently the best available reference source on a subject that is growing in importance and complexity. The only irritations are some unnecessary self-congratulatory comments and unashamed pleas for financial support that will raise the eyebrows of the purchaser of this book in Hay-on-Wye bookshops at the end of this century. I can thoroughly recommend it for all established prostaglandin and COX researchers, and PhD students. Clinical gastroenterologists will find something new of interest. Those with time, concentration, and a biochemical background will surely enjoy this book as much as I did. Aahh! Catherine my lifelong companion has just brought me a wee dram (Talisker single malt whisky with 10% v/v local water). Life just does not get much better than this. My thanks to the use of summary boxes, and and the dimmer corners of an office. Another reason not to look at such a book is the very authoritative and up to date way, and shed light on a whole host of topics that are bothersome to most gastroenterologists, such as the usage of methotrexate in psoriasis and rheumatoid arthritis (with helpful guidelines on when to offer baseline and follow liver biopsy and to whom), antituberculous agents (and when to worry!), and in this day and age, sections on psychotropic agents, drugs of abuse, and importantly, when many patients might not be seen to be at risk (such as the knowledge that can be found in the average health food shop or in Chinatown, an authoritative compendium on alternative medicines, vitamins, and natural hepatotoxins). With the increasing incidence of certain liver tumours, I found sections on the adverse effects of hormones (covering everything from adrenals, focal nodular hyperplasia, and frank malignancies to vascular abnormalities in the liver) and on environmental toxins very interesting and informative.

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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: 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

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, 33–43 Lincoln’s Inn Fields, London WC2A 3PE. Tel: +44 (0)20 7973 0307; fax: +44 (0)20 7430 9235; email: acgb@asgb.org.uk; website: www.acgb.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

Falk Symposium 135—Immunological Diseases of Liver and Gut
This symposium will be held on 12–13 September 2003 in Prague, Czech Republic. Further details - see Falk Symposia above

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

XII Falk Liver Week
The XII Falk Liver Week, in honour of Hans Popper's 100th birthday, will be held on 15–22 October 2003 in Freiburg, Germany. Further details - see Falk Symposia above.

European Course on Laparoscopic Endoscopy
This course will be held on 18–21 November 2003 in Brussels, Belgium. Further details: Secretary to Professor Cadire, Service de Chirurgie Digestive, Rue Haute 322, Brussels 1000, Belgium. Tel: +32 (0)2 648 07 60; fax: +32 (0)2 647 86 94; email: straeb.asmb@proximedia.be; website: www.straeb-asmb.com

Hong Kong-Shanghai International Liver Congress 2004
This conference will be held on 14–17 February 2004 in Hong Kong. The topic of the conference is “Liver Diseases in the Post-Genomic Era”. Further details: Ms Kristie Leung, Room 102–105 School of General Nursing, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong. Tel: +852 2818 4030; email: kristieleung@hepa2004.org; website: www.hepa2004.org