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) 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 after 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 time, 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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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>Characteristic</th>
<th>Ulcerative colitis</th>
<th>Crohn’s disease</th>
<th>Indeterminate</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>17</td>
<td>25</td>
<td>3</td>
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</tr>
<tr>
<td>Female</td>
<td>15</td>
<td>48</td>
<td>2</td>
<td>65</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Abnormal LFTs</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Infections</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>- Hepatitis rash</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>- Pancreatitis</td>
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<td>0</td>
<td>1</td>
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<tr>
<td>Miscellaneous associated symptoms</td>
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<td>- Tiredness</td>
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<tr>
<td>- Headache</td>
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<tr>
<td>- Allergic skin rash</td>
<td>0</td>
<td></td>
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</tbody>
</table>

LFT, liver function test.

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.
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. 11 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 1.6x10^9/L, platelets 25x10^9/L) at 10 weeks’ while another did so at 1 mg/kg developed myelosuppression (WBC 8.5x10^9/L, platelets 7.5x10^9/L) at 12 weeks. Similar observations have been made by Schwab and colleagues 12 who reported myelosuppression (leucocytes with one variant and one wild-type allele, Black and colleagues 13 who reported myelosuppression in a TPMT deficient patient with an intermediate TPMT activity (heterozygotes with one variant and one wild-type allele), Black and colleagues 13 reported leucopenia (leucocyte counts 0.9–2.9x10^9/L) within one month of starting azathioprine (2–3 mg/kg) as second line therapy for rheumatic disease. The guidelines then continue, “this frequency of complete blood counts should be monitored weekly full blood counts during the first three months”. Longer than three months”.

The data presented in the reports above 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 higher 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 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 appendectomy in the absence of an inflamed appendix was not associated with a decreased risk of ulcerative colitis, suggesting that appendix does not protect against ulcerative colitis. 14 Cosnes et al state that these results may not be correct as they included all patients with previous appendectomy and still found a less severe course. We believe they are incorrectly assuming this, as another possible explanation is that the effect of appendicitis is actually higher than the effect of appendectomy reported in the present study, which could have been due to 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 appendectomy outside clinical trials as evidence showing that appendectomy will protect these persons is lacking.

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Reference

Authors’ reply
Many French surgeons in 1900 did recommend removing preventing all appendices 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 appendectomy patients genetically at high risk of developing ulcerative colitis.

Ter Borg and van Buuren speculate that appendectomy 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 appendicec- tomy and no (or benign) ulcerative colitis, and the strongest demonstration of this relationship is the protective effect of early appendectomy in the T cell receptor α (TCR-α) knockout mouse model. 15 Note also that the Swedish study which found that only appendectomy 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. 16 A key point however, like in the TCR-α knockout mouse model, is the date of appendectomy. Appendectomy protects against severe ulcerative colitis only when performed at a young age, and therefore disease onset. 16 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 severe course of ulcerative colitis, suggesting that appendicitis rather than appendicectomy protects against ulcerative colitis. 14 Cosnes et al state that these results may not be correct as they included all patients with previous appendectomy and still found a less severe course. We believe they are incorrectly assuming this, as another possible explanation is that the effect of appendicitis is actually higher than the effect of appendicectomy reported in the present study, which could have been due to inclusion of patients without appendicitis.
predisposing genotype for ulcerative colitis, and a clinical trial assessing the benefits of prophylactic appendectomy 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):v10–12). (1) In the present mediocrelent 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 a colonoscopy 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 non-colon 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. 2 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 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 patients with left sided colitis and (by implication) those with Crohn’s disease.

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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 the point that before and since 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 controlled trials. Not even those eventual found to have cancer. They also decided to exclude patients whom in whom cancer was found at an initial colonoscopy undertaken at least 12 years after the onset of symptoms. We feel that finding dysplasia is the very aim of surveillance and therefore it is found on the first colonoscopy in a surveillance programme it should not be deemed a failure of surveillance.

As Forbes et al point essentially there was no randomised controlled trial was performed to conﬁrm the guidelines. The national audit of the surveillance programme it should not be deemed as debatable value. Therefore, they limited their audit to those eventually found to have cancer. They also decided to exclude patients whom in whom cancer was found at an initial colonoscopy undertaken at least 12 years after the onset of symptoms. We feel that finding dysplasia is the very aim of surveillance and therefore it is found on the first colonoscopy in a surveillance programme it should not be deemed a failure of surveillance.

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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 a very important improvement on the prevailing routine practice of some gastroenterologists.

The whole point of stratified data was to see if the cancer incidence still increased by decade of disease! The unstratified cumulative probability of disease is more complicated than 1–2 years, and 12.7% (95% CI 6.0–19.3%) at 30 years. The principles, evidence available at present. Surveillance colonoscopy. Yes it is time consuming and it actually requires a lot of time to calculate and it actually reduces the number of colonoscopies being performed initially, so this must be regarded as a very important improvement on the prevailing routine practice of some gastroenterologists.

We accept that the cost of biopsies was not included in the cost analysis. There are other screening services.

Acknowledgements

This work was supported in part by U01 GM63340.

References


Doctor or technician

In 1984, Sir Christopher Booth (President British Society of Gastroenterology (BSG) 1979) gave a lecture in Berlin on the effect of technology on clinical practice. He lauded the rapidly expanding benefits of diagnostic and interventional gastrointestinal endoscopy but was led to ask “Will the gastroenterologist simply become a technician who carries out a series of procedures without being able to interpret the results?”

Most gastroenterologists remain general physicians but in talking with specialist gastroenterologists, it is not too difficult to calculate and it actually reduces the number of colonoscopies being performed initially, so this must be regarded as a very important improvement on the prevailing routine practice of some gastroenterologists.

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registrar. I have been surprised by their over-whelming interest in honing endoscopic skills. If this leads to a simplistic approach to the prevention 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 pre-ceding 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-duodeno-scopony (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 discharged to the gold standard, 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 sigmoid colon through one of which instruments in a deformed duodenal cap. At colonoscopy no abnormality was shown apart from a little fresh bleeding, the cause of which was not apparent. The patient was discharged to the gold standard, 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.

Which 5-ASA?
I read Dr Travis’ therapy update (Gut 2002;51:548–9) with interest; the topic is timely in a new area about to be challenged by new generic mesalazine brands. I note the choice of time dependent mesalazine (Penta- tasa) but, if mesalazine is to be relied upon exclusively, some patients do not respond to Penta- tasa may not be the best choice. The recent study by Kruijs 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 both 2 g/day and 4 g/day.2 This latter study highlights the lack of efficacy of mesalazine released by a time dependent delivery system in active UC. In contrast, three studies comparing balsalazide with mesalazine (pH dependent release),3–5 containing a total of 762 patients, suggest that balsalazide to be superior in active UC, with rapid resolution of symptoms (median 10 days in one study1) and superior sigmoidoscopic scores (in all three studies). Plasma concentrations of 5-aminosalicylic acid (5-ASA) were 4.5-fold lower in patients treated with balsalazide than mesalazine (p=0.018).6 Patients with most to benefit are new patients with distal disease. The use of 5-ASA in the initial treat- ment of UC does not require mega doses, as Dr Travis suggests, indeed mega doses of mesala-zine delivered by Asacol or Pentasa are ineffective, but it does require a reliable delivery system, such as the azo bond, and an inert carrier, as with balsalazide. The clinical impli-cation of this efficacy in mild to moderate active UC is that the threshold for the use of steroids can be raised. Of interest in the North American trials of balsalazide versus mesal-azine, 60 patients failing mesalazine therapy were treated after the trial with balsalazide open label, with 60% response (data on file, Shire Pharmaceuticals Ltd).

Advocates of newly released mesalazine (SASP) and those wishing to use the least expensive treat- ment crite trials of SASP versus newer agents7 and conclude that SASP is the most cost effective; these trials are in patients with known UC and specifically exclude patients who are SASP intolerant. In two recently published studies8,9 patients who were diagnosed or previously untreated UC were randomised to SASP or balsalazide; 34% were intolerant of SASP at the modest dose of 3 g daily as compared with 5% who required 6.75 g daily. The number needed to treat to avoid SASP intolerance at this rate is only 3, and in new patients it seems particularly important to use well tolerated effective treatment first line and avoid the loss of confidence that drug intolerance produces.

It seems a sad reflection on the pharmaceu-tical industry sponsored research that the most recent trial on UC treatment with 5-ASA quoted in the therapy update was from 1998. Large clinical trials of one 5-ASA brand against another are expensive and the advent of generic mesalazine preparations is unlikely to improve this situation. My interpretation of recent evidence is that the mesalazine release mechanism is important for the efficacy, reliability of delivery, and safety of the oral preparations and that balsalazide is now cost standard for other agents to be judged against.

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www.gutjnl.com
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 portal systemic pressure gradient (PSSG) 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% (2/23) 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 associated with 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.

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. Additionally, 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 GV 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 and this would be hoped. However in 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. 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 (HVP)) is <12 mm Hg, then perhaps other therapeutic options such as B-ROTO (balloon occluded retrograde transvenous obliteration) should be considered.

Hopefully more prospective data, examining the role of PPG, TIPS, and B-ROTO in the management and outcome of GV will help clarify these issues.

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References


Authors’ reply

We agree that the presence of gastrorenal shunts (GRS) is likely to explain the low portal pressure gradient (PPG) post-transjugular intrahepatic portosystemic stent shunt (TIPS). Portography at the time of index TIPS insertion was primarily performed to identify varices and not specifically to look for the presence of GRS, although the splenic vein was visualised if not always in its entirety. Given these limitations, we have looked at the portograms of over 400 patients who have had TIPS for any cause, and identified shunts in 18.3%.

A wider portographic review and a prospective magnetic resonance angiography study will be required to answer the questions raised. For the study period, we used a transjugular intrahepatic portosystemic stent shunt (TIPSS). Portography at the time of index TIPS insertion was primarily performed to identify varices and not specifically to look for the presence of GRS, although the splenic vein was visualised if not always in its entirety. Given these limitations, we have looked at the portograms of over 400 patients who have had TIPS for any cause, and identified shunts in 18.3%.

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available evidence about different management approaches. The book also has a feel of having been constructed from an upstream viewpoint. Apart from a hepatologist, the other five contributors are all surgeons—perhaps because of the incurability of the liver diseases which they are keen to seek out the veritable pharmacological antidote. 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, four, bour, 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 invoke each other’s “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 omissions 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. Aah! Catherine my lifelong companion has just brought me a wee dram (Talisker single malt whiskey with 10% v/v local water). Life just does not get much better than this. My euphoria is however marred by the knowledge that the COX-2 selective drugs are not available to the citizens of Cuba as a result of the USA’s embargo.

**Therapeutic Roles of Selective COX-2 Inhibitors**


The review editor sent me a book to review for *Gut* with holidays looming. He left a week between what seemed an unusually long July weekend, and is currently observing whales off the east coast of the USA where I hope he will encounter the albino whale, I., on the other hand, am in a more peaceful location surrounded by the truly magnificent lochs, standing stones, stone circles, chambered cairns, duns, and crannogs on the Outer Hebridean island of North Uist.

The book *Therapeutic Roles of Selective COX-2 Inhibitors* is the latest in a series of similar books edited by Vane and Bolting, and I have found it in many ways as interesting and extraordinary as my surroundings. It exceeded all expectations, bringing together some of the people that have driven the COX-2 story through from birth of a concept to a marketable drug.

Vane and Bolting set the pace with an authoritative introduction, elegantly outlining the history, biochemistry, and physiology of COXs from their clinical perspective. In this book they gracefully allow etodolac and nimesulide into the privileged COX-2 selective drawer or, as they call it, the “COX-1 sparing drug” club. Then follow high quality chapters on the discovery and studies on rofecoxib and celecoxib along with discussions on the various test systems to assess selectivity. The excitement from an upstream viewpoint is infectious. Derek Willingham’s chapter on COX-2 in inflammation in experimental models kept me awake for the whole night. This is a true master at work!

**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 unwinding 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, the jewel in a 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 succinct and up-to-date 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 up 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 believe that they are being poisoned by their medication and in the case of anticoagulants, which are keen to seek out the veritable pharmacological antidote that can be found in the average health food store or in Chinatown, an authoritative compendium on alternative medicines, vita-mins, and natural hepatotoxins. With the increasing incidence of certain liver tumours, I found sections on the adverse effects of hormones (covering everything from adrenocortical, focal nodular hyperplasia, and frank malformations to vascular abnormalities in the liver) and on environmental toxins very interesting and informative.

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While it is true 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!
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/Bt, Germany. Tel: +49 761 15 140; fax: +49 761 15 14 399; 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, 35–45 Lincoln’s Inn Fields, London WC2A 1PE. Tel: +44 (0)20 7973 0307; fax: +44 (0)20 7430 9235; email: acgbi@acgbi.org.uk; website: www.acgbi.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 Cadière, 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

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