New steroids for IBD: progress report

S B Hanauer

Corticosteroids remain the benchmark therapy for moderate to severe ulcerative colitis and Crohn's disease but are problematic due to unacceptable side effects and lack of maintenance benefits. Developments in corticosteroid chemistry have led to a series of anti-inflammatory glucocorticoids with enhanced topical (mucosal) potency and less systemic activity such as prednisolone-metalsulphobenzoate, beclomethasone dipropionate, tixocortol pivalate, fluticasone, and budesonide. To date, budesonide has been the primary alternative compound to hydrocortisone and prednisolone marketed in many parts of the globe and, most recently, has been introduced in an ileal release formulation in the USA.1–3

For many years, topical (rectal) steroids have had a primary role in the treatment of distal ulcerative colitis4–7 and have been incorporated as an adjunctive treatment to parenteral steroids for treatment of severe colitis.8,9 The relative potency of rectally applied steroids is increased compared with a similar systemic exposure, providing evidence that the mucosal and systemic effects of glucocorticoids can be divorced.10 In comparative controlled trials, the "non-systemic" rapidly metabolised formulations (tixocortol, beclomethasone dipropionate, and budesonide) had equal therapeutic properties to systemically active glucocorticoids.11,12 However, as first-line therapies for distal ulcerative colitis, the potent non-systemic glucocorticoids have been less effective than rectal formulations of mesalamine.13

The non-systemic glucocorticoids have yet to make an impact as oral therapies for ulcerative colitis as delivery of sufficient doses to the colon, and the distal colon in particular, is complicated by altered colonic motility in ulcerative colitis (delayed transit in the right colon and rapid transit in the left colon) allowing metabolism of the steroid molecule by normal colonic microbiota.14

Similar to conventional glucocorticoids, budesonide is well absorbed from the proximal and distal intestine, relying on rapid hepatic metabolism to reduce systemic impact, including inhibition of the hypothalamic-pituitary-adrenal axis. To achieve distal mucosal activity, budesonide has been formulated in oral controlled release formulations that minimise proximal absorption and allow high drug concentrations in the ileum and cecum. Theoretically, with such targeted delivery, the combination of increased topical potency and low systemic availability should provide benefits (improved efficacy with less systemic side effects) compared with conventional glucocorticoids.4 However, due to the increased potency at the steroid receptor (100 times that of hydrocortisone), suppression of the hypothalamic-pituitary-adrenal axis can occur with treatment.15 Budesonide in a controlled ileal release formulation, administered as 9 mg/day, has been shown to be efficacious for active ileal and ileocolic Crohn's disease.10,16

In addition to the reduction in intestinal symptoms and signs assessed by the Crohn's disease activity index, budesonide successfully improved quality of life as assessed by the inflammatory bowel disease questionnaire and extraintestinal arthritic manifestations associated with active Crohn's disease.17 The controlled ileal release formulation of budesonide has also been used to "switch" patients from prednisone with a 4–10 week transition and follow up for an additional three months of sustained clinical benefits and reduced steroid associated toxicity18 but, like other corticosteroids, at doses of 3–6 mg/day budesonide was ineffective for the maintenance of remission at one year19–21 or for the prevention of postoperative recurrence.22,23 Overall, compared with conventional steroids, the better side effect profile of budesonide is balanced by somewhat lower efficacy than conventional steroids in treating active disease.11,12

In summary, the concept of separating the mucosal effects of glucocorticoids from the systemic effects has been demonstrated in both ulcerative colitis and Crohn's disease. In ulcerative colitis, while rectal administration of budesonide and tixocortol are safe and effective, neither has been as effective as rectal mesalamine for distal disease and the complexities of pancolonic mucosal “coating” of steroids remains impractical. In Crohn's disease, controlled release formulations of budesonide have found a niche for the acute treatment of mild-moderate ileal and right colonic disease with intermediate efficacy superior to mesalamine, but are somewhat less effective than prednisone. There remains considerable potential for developments in steroid pharmacology and enteric delivery to improve both mucosal potency and rapid metabolism that would further improve the therapeutic potential for these agents to induce remission while minimising systemic impacts. The role for glucocorticoid therapy for maintaining remissions in either ulcerative colitis or Crohn's disease remains to be established.

Conflict of interest: S B Hanauer has worked as a consultant for Astra-Zeneca, Centocor, Proctor and Gamble, Salix, and Solvay. He has also carried out clinical research and given lectures on behalf of Astra-Zeneca, Centocor, and Proctor and Gamble.

Key points

- Non-systemic steroids for IBD have increased potency and first pass metabolism
- Rectal (enema) formulations are effective for active distal ulcerative colitis, but not as efficacious as rectal mesalamine
- Controlled (delayed) release budesonide is effective for active ileal and right colonic Crohn's disease with a low side effect profile
- Similar to other corticosteroids, no maintenance benefits have been identified for non-systemic steroids used on a long term (one year) basis

REFERENCES


Susceptibility to primary sclerosing cholangitis in Brazil is associated with HLA-DRB1*13 but not with tumour necrosis factor α −308 promoter polymorphism

Susceptibility to primary sclerosing cholangitis (PSC) is linked to HLA-A1-B8-DRB1*0301-DQB1*0603 haplotypes in different populations of Northern European origin and also to HLA-DRB1*1501-DQB1*0602 in the UK.1,4 Mitchell et al. have reported an association between tumour necrosis factor alpha promoter gene (TNFA) polymorphism at position −308 and PSC (Gut 2001;49:288–94). In this respect, increased distribution of the TNFα2 allele, in strong linkage disequilibrium with the HLA-A1-B8-DRB1*0301 haplotype, was observed in PSC patients from Norway but not from the UK. However, analysis of the combined data confirmed a significant association of TNFα2 with PSC. This overrepresentation of TNFα2 was seen only in subjects with HLA-A1-B8-DRB1*0301, indicating that the observed association of PSC with TNFα2 might in fact be secondary to linkage disequilibrium within this haplotype.

Bernal and colleagues5 have previously reported an increased frequency of TNFA*2 in another cohort of British patients with PSC. This association was dependent on the presence of HLA-B8 and DRB3*0101 but not of HLA-DRB1*0301. Based on these results, the authors proposed that the associations with TNFα2 and HLA-B8 were stronger than those observed with HLA-DRB1 and DRB3.

We have investigated the frequencies of HLA-B, DRB1, DQB1, and TNFA alleles in 63 Brazilian patients with PSC and 83 healthy controls from the metropolitan area of São Paulo, Brazil, using polymerase chain reaction based techniques, as previously described.6 This population is of highly admixed origin with different percentages of Caucasian, African, and Amerindian ancestries. The diagnosis of PSC was based on the findings of typical clinical, laboratory, cholangiographic, and histological features.7 None of the patients had evidence of concurrent hepatitis B or C or hepatic schistosomiasis. Twenty seven patients (18 males; mean age 15 (±7) years) were less than 16 years at disease onset and were considered children, and 36 subjects were adults (25 males, mean age 34 (±11) years). Forty one patients had inflammatory bowel disease (IBD). None of the subjects, including all children, had any evidence of laboratory or histological features of overlapping syndromes of PSC and autoimmune hepatitis (AIH).

In summary, our data indicate that predisposition to PSC in Brazil is primarily linked to HLA-DRB1*13 and suggest that the association with TNFα2 previously observed in Norwegian and British patients with PSC could be due to linkage with HLA-DRB1*0301. The association of HLA-DRB1*13 with PSC was observed in both children and adults with the disease but was restricted to patients with concurrent IBD, as previously described by Donaldson and colleagues.

**Table 1**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>PSC patients</th>
<th>Healthy controls</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRB1*03</td>
<td>12 (19)</td>
<td>23 (28)</td>
<td>0.00009</td>
</tr>
<tr>
<td>DRB1*13</td>
<td>33 (52)</td>
<td>17 (20)</td>
<td></td>
</tr>
<tr>
<td>DRB3</td>
<td>53 (84)</td>
<td>62 (75)</td>
<td></td>
</tr>
<tr>
<td>DQB1<em>02</em></td>
<td>20 (36)</td>
<td>41 (49)</td>
<td></td>
</tr>
<tr>
<td>DQB1<em>06</em></td>
<td>33 (59)</td>
<td>34 (41)</td>
<td>0.04</td>
</tr>
<tr>
<td>TNFA1/*TNFA1</td>
<td>41 (65)</td>
<td>63 (76)</td>
<td></td>
</tr>
<tr>
<td>TNFA1/*TNFA2</td>
<td>21 (33)</td>
<td>19 (23)</td>
<td></td>
</tr>
<tr>
<td>TNFA2/*TNFA2</td>
<td>1 (2)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>TNFA2 allele carriage</td>
<td>22 (37)</td>
<td>20 (25)</td>
<td></td>
</tr>
</tbody>
</table>

*Only 56 patients with PSC were typed for HLA-DQB1.

Numbers in parentheses are percentages.

P L Bittencourt
Portuguese Hospital of Salvador, Bahia and Department of Gastroenterology, University of São Paulo School of Medicine, São Paulo, Brazil

S A Palacios, E L R Cançado, F J Carrilho
Department of Gastroenterology, University of São Paulo School of Medicine, São Paulo, Brazil

G Porta
Children’s Institute-Liver Unit, University of São Paulo School of Medicine, São Paulo, Brazil

J Kalil, A C Goldberg
Laboratory of Immunology-Heart Institute, University of São Paulo School of Medicine, São Paulo, Brazil

Correspondence to: P L Bittencourt, Rua Tamoios 314, apto 302A, Rio Vermelho, Salvador84, Brazil, plb@uol.com.br

References

www.gutjnl.com
Of the 22 slow transit patients studied by Emmanuel and Kamman, seven had marked retention predominantly in the rectosigmoid, 13 had a paradoxical sphincter contraction as a marker of outlet obstruction, and seven could not expel a balloon during simulated defecation. In contrast, in our study of small bowel manometry in slow transit patients, all patients demonstrated a right sided or global delay and had no signs of outlet obstruction. Thus the response of behavioural treatment, biofeedback, in constipated patients with slow transit might be influenced by the existence of more than one disease as a possible aetiology of STC. We are looking forward to seeing data on the response of biofeedback therapy in patients with STC with and without pathological small bowel manometry.

C Pehl, T Schmidt, W Schepp,
Department of Gastroenterology, Hepatology, and Gastrointestinal Oncology, Bogenhausen Academic Teaching Hospital, Engelschalker Str 77, 81925 Munich, Germany

Correspondence to: C Pehl,
Christian.pehl@extern.lrz-muenchen.de

Slow transit constipation: more than one disease?

Emmanuel and Kamman reported on the response of behavioural treatment, biofeedback, in constipated patients (Gut 2001;49:214–19). Biofeedback is an established therapy for outlet obstruction due to paradoxical anal sphincter contraction. Beyond that, Emmanuel and Kamman demonstrated that slow transit constipation (STC) can also be improved by biofeedback with normalisation of the slow transit in most symptomatic responders. These results contrast with the common belief of STC as a manifestation of a panenteric disease, predominantly of the nervous system.

Disturbances of oesophageal motility, gastric emptying, small bowel transit, and gall bladder motility have been described. Dysmotility of the small intestine has been thoroughly investigated by manometry in STC patients. Disturbed motility—for example, abnormal configuration or disturbed aboral migration of phase III of the migrating motor complex, bursts, and sustained uncoordinated activity—occur in up to 60% of these patients. In our recent study using long term small bowel manometry in 30 clinical STC patients, disturbed aboral migration of phase III was present in 44%, that is, not sustained uncoordinated activity occurred in 33% of patients, respectively.

It is well established that these manometric findings are markers of a neuropathy of the myenteric plexus and occur in an identical way in patients with chronic intestinal pseudo-obstruction of neuropathic origin. Furthermore, treatment by colectomy has demonstrated that approximately half of all patients with slow transit constipation have a neuropathy. Work from our own unit has previously demonstrated that such treatment not only normalises colonic transit but also diminishes the sensation of bloating and abdominal pain.

The existence of a panenteric disturbance of function, including the motor abnormalities described by Pehl et al., should not be interpreted as evidence for a neuropathy throughout the gut. Such disturbed function could also result from altered central autonomic control of a neurologically normal gut. We would disagree that these manometric findings are markers of neuropathy in patients with idiopathic constipation; they may be associated but causality has not been established.

Ultimately, the value of behavioural treatment can be judged best by careful prospective evaluation of patient symptoms and physiological function. Such assessment has demonstrated the benefit of such treatment, suggesting that disturbances of upper gut function and motility are often secondary and reversible.

We would also disagree that the long term results of colectomy are excellent. In our own experience of the long term results of colectomy, only 50% of patients had a good outcome, one third experienced diarrhoea, and 10% experienced recurrent constipation. Two thirds of patients continued to experience some pain.

We agree that not all patients with constipation are the same. Some have slow transit while in others transit is normal. There are probably some patients with underlying irreversible gut changes but our pathological techniques are not good enough to distinguish these patients from those who will respond to simple treatment. Therefore, for practical reasons, we suggest using simple treatments first and investigating patients who have failed treatment later.

We believe that too much emphasis should not be placed on different patterns of colonic delay, or the presence of disturbed pelvic floor function. We have shown that patients with different patterns of colonic delay, or with pelvic floor contracture, respond equally to behavioural treatment. Too much emphasis has been placed on these physiological observations.

Small bowel manometry is invasive while behavioural treatment is non-invasive. We feel that manometry should therefore be reserved for patients in whom invasive treatment, such as surgery, is being contemplated after other treatments have failed. Even then we feel it does not have a proven role in predicting the outcome of surgery.

References

Authors’ reply

We thank Dr Schiep and colleagues for their interest in our paper (Gut 2001;49:214–19). Our findings do not contrast with the belief that slow transit constipation is a condition associated with a panenteric disorder of function. Work from our own unit has previously demonstrated that approximately half of all patients with slow transit constipation have delayed gastric emptying, small bowel and rectal marker accumulation. In physiological evaluation, an overlap of slow transit and outlet obstruction can be seen in some patients. At least in healthy volunteers, voluntary suppression of defecation resulted in a marked prolongation of colonic transit.
Surveillance for hepatocellular carcinoma in liver cirrhosis: have programmes improved because patients have?

In their commentary (Gut 2001;48:149–50), Bruix and Llovet discuss the paper by Bolondi et al (Gut 2001;48:251–9) and emphasise the fact that survival of patients with hepatocellular carcinoma (HCC) is mainly related to tumour stage and degree of liver function impairment at diagnosis. This is most likely true because if the peculiar features of HCC, which almost inevitably arises in the “minefield” of a cirrhotic liver whose residual function is one of the main factors influencing therapeutic options and prognosis.

Nevertheless, a trend towards increased survival after diagnosis of HCC has recently been observed, although the surveillance programme has not changed over the years (liver ultrasonography and α-fetoprotein determination every six months). As Bruix and Llovet affirm, this increase in survival may be due to advances in diagnosis even in the absence of effective treatment, to the availability of multiple treatment, or both.

However, it must be emphasised that HCC stage (parameter of the tumour) and residual liver function (parameter of the affected patient) are independently related and influence each other, and that both can influence the choice of treatment and prognosis. Therefore, what should improved survival over the years be attributed to since surveillance programmes are only able to detect a minority of “early” HCCs?

Bolondi et al analysed the outcome and cost-effectiveness of HCC surveillance programmes. They compared the outcome of a cohort of mixed aetiology cirrhotic patients screened by means of biannual liver ultrasonography and serum α-fetoprotein measurement to the outcome of patients whose HCC had been discovered incidentally. They found that there were no significant differences in eligibility for treatment between patients who had been under surveillance and those who had not (although a higher number of patients in the former group had been transplanted). However, survival at three years was significantly better in the group that had been kept under surveillance. Lastly, both liver function and tumour stage were selected in multivariate analysis as predictors of survival.

We recently performed a similar study in a cohort of hepatitis C virus positive cirrhotic patients. We compared clinical parameters, eligibility for treatment, and survival of patients whose HCC had been discovered during a surveillance programme (biannual liver ultrasonography and α-fetoprotein measurement) with patients whose HCC had been incidentally diagnosed. Although age, serum α-fetoprotein levels, and unifocality of the tumour were no different between the two subgroups of patients, we found that more patients in the group under surveillance were eligible for treatment (32/33 vs 18/27; p=0.003, Fisher’s exact test). Moreover, we found that clinical status at diagnosis was better in the group under surveillance compared with patients with an incidental diagnosis of HCC. Lastly, we observed that longer survival was obtained in treated patients, regardless of diagnosis modality or treatment modality. On the basis of these findings, we attempted to determine whether the longer survival observed in the group under surveillance might be due to better basal conditions, or perhaps they were more likely to benefit from treatment due to their improved clinical status. We thus compared patients treated with the same procedures and analysed the results on the basis of modality of diagnosis. We observed that there was no difference in survival between the groups, and that overall mortality was liver related (72%) rather than tumour related. These findings suggest that the better outcome observed in the group under surveillance was due to the better basal conditions of the patients and to the screening programmes. A multivariate analysis showed that liver function, tumour stage, treatment, and HCC surveillance were independent predictors of better survival. Thus what emerges from our study as well as from that of Bolondi et al is that survival of HCC patients is mainly linked to preserved liver function. This probably allows patients to undergo treatment even when this is not classically considered “curative” as even therapeutic options considered “non-curative” have reportedly obtained increasingly positive results in terms of survival.

In an era of multimodal therapeutic approaches to HCCs, these findings further support the results of screening programmes performed almost a decade ago on patients with compensated cirrhosis and whose sole options were liver surgery or percutaneous ethanol injections. No differences were reported regarding survival of patients treated and those who did not, thus emphasising the importance of residual liver function in relation to survival. Therefore, what probably lies behind these findings is that improved medical therapy of the complications of liver cirrhosis, increased efficacy of HCC treatment, and better management of treatment induced sequelae have led to better care of the patients. This has likely affected both the type of patients who enter HCC surveillance studies and their therapeutic outcomes.

E Giannini, R Testa
Gastroenterology Unit and Postgraduate School of Gastroenterology and Digestive Endoscopy, Department of Internal Medicine, University of Genoa, Italy
Correspondence to: Professor R Testa, Gastroenterology Unit, Department of Internal Medicine, University of Genoa. Via Benedetto XV, No 6, 16132 Genoa, Italy; rttesta@unig.e.it

References

Rectal proliferation and alcohol abuse

The study by Simanowski et al described some important features of rectal proliferation and alcohol abuse (Gut 2001;49:418–22). However, there are some methodological issues worthy of attention to the study which need clarification.

Firstly, when performing multiple linear regression, it is essential to perform and report sample size and power estimate calculations. This omission, especially with a sample size of only 39 patients, would leave the reader wondering if this sample is sufficient in size and power to adequately support the conclusions drawn from their regression analysis. Furthermore, by not reporting a r or an adjusted r value, the accuracy of the model is also not addressed. Possible correlations between independent variables should be investigated and discussed when reporting multiple regression results to further support the validity of the analysis.

Secondly, clarification of their patient populations is also required. They originally reported a cohort of 27 heavy drinkers (23 males, four females) and 12 control patients (five males and seven females) in the early paragraphs of the materials and methods section. Later, the authors discuss “rectal biopsies of 17 alcohol abusers (10 males, seven females) and 14 age matched controls (six males, eight females)” Only 17 heavy drinkers and 14 age matched controls were compared from the original cohort based on the different number of female patients and not referred to in any of the figures, the origin of this second group is unclear.

In summary, clarification regarding the above mentioned omissions would greatly solidify the conclusions of their research.

K Filion
Department of Physiology, McGill University, Montreal, Quebec, Canada; kfilion@lapo.box.mcgill.ca

Author’s reply

We appreciate the interest of Dr Filion which gives us the opportunity for additional clarification.

As the effect of alcohol on colonic cell proliferation was found to be significant (p<0.05), no type 2 error with respect to the effect of alcohol has to be considered. In this context it should be noted that in case of statistically significant findings, only type 1 errors may occur. The effect of alcohol on colonic cell proliferation was the primary question which was investigated in the study. As stated in the methods section of the paper, a multiple regression analysis was performed to assess possible confounders due to sex and smoking. Thus the p values reported for sex and smoking should only be interpreted in a descriptive manner.

On the basis of numerous epidemiological studies it is generally accepted that the independent variables alcohol, smoking, and sex do correlate. This is in fact the reason for performing an adjusted analysis on the impact of alcohol on cell regeneration.

In 27 heavy drinkers and 12 controls, statistics on proliferative cell nuclear antigen (PCNA) expression were performed. In a second group of 17 alcoholics and 14 age matched controls, various staining procedures were attempted performed, including Ki67, Rb, p53, and cytokeratins, without statistical analysis.

H K Seitz
Salem Medical Centre, Heidelberg, Germany
Mobilin agonists and dyspepsia: throwing out the baby with the bath water

I read with great interest the paper by Talley and colleagues (Gut 2001;49:395–401) and the accompanying editorial by Tack and Peeters (Gut 2001;49:317–8). There are many important issues that are raised in the paper and editorial. I believe the paper provides an opportunity to identify areas where study design might be enhanced in future studies.

Firstly, the fact that gastric emptying was not measured at the end of the study leaves wide open the question of whether the prokinetic approach should be abandoned in the treatment of dyspeptic symptoms in diabetics. Thus it would be inappropriate to conclude from the present study that prokinetics are not indicated. This point is also emphasised in the editorial by Tack and Peeters.

Secondly, the authors conclude that baseline gastric emptying does not influence the response to ABT-229. This conclusion is based on weak foundations as the method used to measure gastric emptying appears to provide data that are scarcely believable. Thus the 19 patients recorded in healthy subjects (130±45 (SD7) minutes) is remarkably outside the normal range reported using the gold standard scintigraphy (mean 110±4 (SEM) minutes, 100±40 minutes at 70th percentile to 150 minutes in our laboratory). The methods section does not unequivocally state what mathematical analysis was used with the stable isotope breath test at the central laboratory used in the study. Improved mathematical analyses of gastric emptying using breath tests in the more recent literature provide a higher level of accuracy relative to scintigraphy. It is claimed, that the method used was validated in 19 diabetics in whom a significant correlation (r=0.73) was observed between scintigraphy and breath test data. Correlation does not equate to accuracy and, in a Bland-Altman or similar analysis, the gastric emptying data are suspect and cannot be used to classify patients to assess the relationship between symptoms and emptying, or to address the role of baseline gastric emptying as a covariate in the response to treatment. It is also unclear if the study was sufficiently powered to appraise an effect of delayed gastric emptying on response to therapy, given the fact that only 29% of the study cohort were classified as having delayed gastric emptying. A type II error cannot be excluded.

Thirdly, the theoretical point is made by Tack and Peeters regarding tachyphylaxis of this particular mobilin agonist, previously demonstrated in the study of Verhagen and colleagues. However, other prokinetics, in-distinguishably other mobilin agonists, may prove effective in the treatment of dyspepsia in diabetics with impaired gastric emptying.

Fourthly, the observation that over time some of the symptoms continued to be aggravated is one of the study suggests that the drug was still effective and worsened symptoms, rather than simply being ineffective in the patients evaluated.

Fifthly, the study illustrates the importance of thoroughly characterising the pharmacology of a novel agent before embarking on expensive potentially harmful therapeutic trials. Inhibition of accommodation by mobilin agonists may indeed be responsible for aggravation of bloating and other symptoms over time. Fortunately, these effects are likely to be reversible and no permanent harm was reported.

However, it is still worth emphasising the general point—clinical pharmacology and pharmacodynamics studies have an important role to play in the drug development process. This is especially relevant in the context of “gastroparesis” or dyspepsia as there are non-invasive approaches to study gastric emptying and accommodation and study of syndromes. These methods permit proper dose–response studies prior to exposing patients to potentially harmful agents or inadvertently selecting subgroups of patients for such large and expensive studies. Among patients with diabetes, neuropathy may alter both gastric emptying and gastric accommodation via different mechanisms (for example, extrinsic vagal v intrinsically mediated (autonomic) neuropathy). Thus selection of those with only impaired emptying (based on a reliable test) and normal accommodation might have provided a fairer opportunity to assess the efficacy of the drug.

Finally, as acknowledged by Talley et al., assessment of autonomic neuropathy requires a more formal assessment than the “opinion of the attending endocrinologist”. In fact, disturbances of the autonomic nervous system, evaluated with detailed tests, have been shown to significantly influence the symptom response to a prokinetic. Approaches that carefully characterise the drug before exposure of patients and selecting subgroups of patients after thorough understanding of the effects of the drug may save potentially effective medications from being abandoned. These patients need to be studied. As one of many physicians who struggle to help relieve these patients’ symptoms, we cannot afford to “...throw out the baby with the bath water”. I trust that this appeal may encourage pharmaceutical companies to reconsider the part of the pharmaceutical industry to cooperate with the part of the medical profession to promote research by applying a number of cut-offs for delayed gastric emptying versus normal but were unable to identify any influence of baseline gastric emptying on the response of the mobilin agonist tested.

Dr Camilleri has emphasised the fact that gastric emptying was not measured at the end of the study. There has been a reluctance on the part of the pharmaceutical industry to re-measure gastric emptying in clinical trials because of the recognised lack of correlation of changes in gastric emptying with symptom improvement. Furthermore, there is an absence of reliable standardised reference methods for gastric emptying that can be applied in multicentre trials. However, we agree that it is optimal in prokinetic trials to test gastric emptying at baseline and on drug, and this should be the “gold standard”.

The issue of tachyphylaxis is important. We conclude, based on the available evidence, that tachyphylaxis was unlikely but agree the issue needs to be carefully considered in all studies evaluating prokinetics. Indeed, in our studies, as Dr Camilleri points out, the drug was actually deleterious (this study and Talley and colleagues’). This strongly suggests that tachyphylaxis did not occur and did not explain the negative results with ABT-229.

We stand by the study design used although further improvements are feasible. Phase I data were available indicating that there were unlikely to be any significant serious effects of ABT-229 and therefore we dismiss the concern raised about potential harm; this was borne out in the phase II trials (present study and Talley and colleagues’). However, we agree that this may not apply to other novel pharmacological agents in development for diabetic gastropathy and functional dyspepsia. We conclude that the mobilin agonist class is likely to be disappointing in unexplained effects.
Reducing dyspepsia costs in the community

Valori and colleagues (Gut 2001;49:495–501) assessed the effectiveness of an educational programme to reduce dyspepsia costs in the community. Given one of the hypotheses was that quality of care would be improved because of “a more active stepdown approach for reflux symptoms and a switch from ranitidine to generic cimetidine” an analysis of changes in the type and volume of specific drugs would appear warranted to support the authors conclusions. It would also provide much needed data on the effectiveness of the “stepdown” approach recommended for the management of gastro-oesophageal reflux disease. The authors also report a subsequent fall in admissions to the gastrointestinal bleed unit in West Gloucestershire. Data are needed to assess whether this is due to their intervention or to natural variation. Of particular interest is the proportion of admissions for Helicobacter pylori related peptic ulcer bleeds in West compared with east Gloucestershire.

The high prevalence of non-definitively treated H pylori associated peptic ulcer disease in primary care has been demonstrated in a number of studies and remains a difficult management issue. In Australia, in 1999 only 1.3% of all antibiotic prescriptions were for H pylori eradication therapy. Analysis of the volume of prescriptions for eradication therapies in each region during west compared with east Gloucestershire. Of particular interest is the proportion of admissions for Helicobacter pylori related peptic ulcer bleeds in West compared with east Gloucestershire.

In conclusion, we believe that the perception of most clinicians that shock/sepsis is an unusual cause for patients to present with jaundice to medical care is an accurate one. Shock/sepsis related jaundice is much more likely to develop among inpatients with complex disease. We do agree that viral hepatitis is an unusual cause for jaundice, although investigation of viral disease is still an important aspect of the assessment of such patients. We also agree that jaundice is associated with alcoholism.

We have performed a retrospective assessment of 100 cases of jaundice identified on biochemical testing who had presented to the Accident and Emergency Department or had been admitted to the acute medical or surgical admission wards at Stobhill Hospital, Glasgow. Our survey therefore looked at acute admissions with jaundice while that of Whitehead et al also included established inpatients who developed jaundice (22 of 117 inpatient cases). We drew a lower cut off level of serum bilirubin (≥60 µmol/l) as above this level jaundice should be clinically detectable.

The causes of jaundice we identified differed significantly from those of Whitehead et al (fig 1). The predominant cause in our series was alcoholic liver disease (ALD) which may reflect the catchment area of our hospital. Only two patients presenting with jaundice had a diagnosis of “shock/sepsis”. It should be noted that 20 of the 27 patients with “shock/sepsis” in the South West Wales series developed jaundice as inpatients. Rather than suggest “shock/sepsis” as a common reason for jaundice which is often overlooked, it might have been more accurate to note that jaundice due to shock/sepsis is an unusual cause for jaundice even in a particular clinical setting such as an intensive care unit, postoperatively, or in patients with multiple medical problems.

In conclusion, we believe that the perception of most clinicians that shock/sepsis is an unusual cause for patients to present with jaundice to medical care is an accurate one. Shock/sepsis related jaundice is much more likely to develop among inpatients with complex disease. We do agree that viral hepatitis is an unusual cause for jaundice, although investigation of viral disease is still an important aspect of the assessment of such patients. We also agree that jaundice is associated with alcoholic liver disease.
a significant inpatient death rate (32% in Whitehead's series and 19% in our own).

E H Forrest, J A H Forrest
Department of Gastroenterology, Victoria Infirmary,
Langside Rd, Glasgow G42 9TY, UK

Correspondence to: E H Forrest;
Ewan.Forrest@gvic.scot.nhs.uk

Authors' reply
We thank Drs E and J Forrest for the interest they have shown in our article on jaundice and we were pleased to learn of their retrospective assessment of 180 cases of jaundice presenting to acute services in a large Glasgow hospital. Although they emphasised the differences between their experience and ours, this is the nature of medical correspondence and we were more struck by the similarities which we found gratifying. The series cannot be compared too closely because similarities which we found gratifying. The differences between their experience and ours is not a common cause of jaundice.

J G C Kingham, M W Whitehead
Department of Gastroenterology, Singleton Hospital,
Sketty, Swansea SA2 8QA, UK

I Hainsworth
Department of Pathology, Morriston Hospital,
Swansea SA6 6N1, UK

Correspondence to: Dr J G C Kingham;
j.kingham@swansearead.wales.nhs.uk

Behaviour of Crohn's disease according to the Vienna classification
I hasten to congratulate Louis et al on their meticulous and insightful study on the stability of Crohn's disease phenotypes according to the Vienna classification (J Gastroenterol Hepatol 2001; 16:777–82). It was particularly gratifying to learn from them (in a separate communication) of the remarkably high degree of interobserver agreement in classifying patients by this system.

The principal message that the authors draw from their study is that the initial “behavioural” classification of B1 (non-stricturing non-penetrating) at the onset of Crohn's disease remains stable over the lifetimes of the patient but almost invariably progresses in time to either B2 (stricturing) or B3 (penetrating) disease. Naturally, this finding hardly comes as a surprise either to the authors of the Vienna classification or to any clinician caring for patients with Crohn's disease. Moreover, it is important and revealing, in my opinion, is the observation by Louis et al that “the proportion of initially B2 patients changing from B2 to B3 was [only] 15.4% (only 2/13 patients)”. Therefore, once “inflammatory” (B1) disease has made its almost invariably progressive to either B2 or B3, why should we not be able to incorporate this relatively stable “choice” of pathway into a phenotyping system suitable for genotypic correlations?

D B Sachar
Division of Gastroenterology, Mount Sinai School of Medicine, New York, New York, USA;

Correspondence to: D B Sachar; dsachar@msm.edu

References

Authors' reply
We thank Professor Sachar for his kind comments on our work. As it has become obvious that Crohn's disease is a multifactorial polygenic heterogeneous entity, apart from molecular genetic studies a major task is now to identify stable phenotypes of Crohn's disease that may correspond to particular genetic backgrounds. The propensity of Crohn's disease to develop as a penetrating disease (Crohn's disease behaviour) has been considered for some time as a potential suitable phenotype for genetic correlations. However, results so far have been inconclusive. Several explanations are plausible: (a) there is no major genetic influence on Crohn's disease behaviour and the significant concordance within multiply affected families is essential due to environmental factors; (b) the genes involved have not yet been tested and it is true that only a small number of candidate genes have been tested in this setting; and (c) patients with Crohn's disease have not been classified adequately into subphenotypes, and it is true that several classifications have been proposed and that the application of these various classifications does not result in homogeneous categories.

In relation to the first two hypotheses, progress in the understanding of the physiology and biology of stricturing and fistulising disease as well as of the influence of environmental factors, including smoking and medical treatment of the disease, is needed. Regarding the third point, the classification used necessarily must result in stable categories of patients. We have shown, even the most recent and reproducible classification is not suitable as patients change categories over time. As emphasised by Sachar, it seems from our data that patients who are classified as a stricturing phenotype tend to remain B2 over time. This is mainly true for patients who are already B2 at diagnosis as 88% remained B2 over a median follow-up of seven years (range 10 years). It seems as if patients who develop penetrating lesions (B3) associated with strictureing lesions tend to develop these simultaneously and thus are directly classified as B3 while patients who develop clinically significant stricturing disease without concurrent penetrating lesions do not tend to develop such lesions afterwards. Furthermore, in our population, only a few pure strictureing lesions (B2) develop after 10 years of evolution. Therefore, in our experience, patients who develop a pure strictureing disease over 10 years of evolution seem to represent a homogeneous phenotype that may be suitable for studies of genetic factors potentially involved in stricture development. However, this does not seem to be the case for penetrating disease (B3). In our patients, penetrating phenotypes continued to develop at a constant rate (approximately 25% of patients/five years), even after 20 years of evolution, mainly directly from the non-penetrating non-stricture phenotype (B1). Furthermore, the subgroup of patients with non-penetrating non-stricture phenotype can never be considered as homogeneous as even after 25 years some may evolve to the penetrating phenotype (B3). Furthermore, a patient who develops penetrating lesions with evolution, the rate of evolution may be biologically and genetically very different from a patient who develops such lesions after 25 years. To some extent this point can also be applied to the strictureting phenotype (B2).

An alternative would be to take into account the speed of development of the B2 or B3 phenotype. Indeed, the inclination to develop such a phenotype is most probably multifactorial. We would be surprised if a
unique gene were responsible for stricture development for example. Therefore, if a gene is involved it may be rather by facilitating or by speeding up the development of these phenotypes, together with other genes and environmental factors. In this hypothesis we may have more chance to disclose predisposing genes when comparing patients who have rapidly developed stricturing or penetrating phenotypes (within five years for example) with other patients. We believe that when performing genotype-phenotype correlations for Crohn's disease behaviour, several classification options have to be tested according to these various hypotheses of gene implication. Furthermore, we should aim towards disclosing environmental factors and stratifying patients according to these factors or to consider these factors in multivariate analyses.

**References**


---

**Pediatric Gastroenterology and Nutrition in Clinical Practice**


"Of the making of many books there is no end and much study is a weariness of the flesh."

We spend too much time reading—or rather we are expected to take in vast volumes of information from text. Not just the written word in books but from journals and more directly from the screen. Few of us have time to sit down to read systematically, and most of us scan contents pages, chapter titles, and abstracts. We take in "new knowledge about protein" as “New knowledge about protein” and "Microorganisms administered for the benefit of the host" (sounds like a good way to poison your enemies at the Christmas party), along-side more familiar titles such as "Short bowel syndrome", "Celiac disease" and "Food allergy". It seems to fall somewhere between a textbook and a multiauthor collection; it is not suitable for undergraduates and it is not the book to reach for when faced with a difficult clinical problem. It is not an easy read. Each chapter begins with an overview and contents, and then assumes a basic understanding of the subject, and a familiarity with areas that are topical. It is most likely to be of value to specialists in paediatric gastroenterology and nutrition who wish to keep up to date.

At 854 pages, assuming a reading speed of a page per minute, this book represents 14.2 hours of CPD. In a perfect world I should read it before I pass judgement. Even though I am keen to clock up maximum CPD points, I admit that I have not read this book from cover to cover. However, I would not go as far as Sydney Smith, cleric and wit, who confessed that "he never read a book before reviewing it; it prejudices a man so!"

**Gastrointestinal Polyps**


I suspect that to the vast majority of gastrointestinal histopathologists, and probably to general histopathologists and endoscopists too, the idea of a book devoted solely to gastrointestinal polyps is appealing. After all, most endoscopists see such lesions every day and most pathologists will see at least one a week. Often a verdict of “hyperplastic” or “inflammatory” polyp is the best that can be offered but this diagnosis is not very satisfying for pathologists and clinicians alike. Consequently, it was with eager anticipation and in the hope of transforming my approach to gastrointestinal polyps that I started to read this book.

As luck would have it, the slides for the EQA in gastrointestinal pathology had landed on my desk the previous day. They included at least two difficult polyoid lesions for which a diagnosis was currently eluding me. I thought that this book would be a useful reference and turned to it for help. I was pleasantly surprised when the answer to my conundrum was available within minutes. A little while later I was approached by one of my SHOs with a question on the genetics of juvenile polyposis. After a short consultation of the book, I was able to give the answer confidently; no need for Internet searches this time.

This book is the first to my knowledge that deals solely with gastrointestinal polyps. It covers all regions of the gastrointestinal tract and is abundantly illustrated with endoscopic photographs and colour photomicrographs. For each type of polyp, descriptions of epidemiology, endoscopic appearance, endoscopic aspects of pathological features are given, followed by a discussion of biological behaviour and associated conditions. For some types of polyp, details of management strategies are also provided.

All of the authors are well known gastrointestinal pathologists with a wealth of experience in this field, so it is not surprising that they have managed to put together such a comprehensive text. I could not think of any entities they had omitted, and there were several that I had never heard of. Overall, the presentation of this book is of a high quality; the text is succinct but readable, and apart from a few exceptions, the illustrations are excellent.

This is primarily a diagnostic book and if it does have a defect it is in the descriptions of molecular biology and therapeutic approaches which inevitably lack detail that some purists would desire. This aside, the book will undoubtedly appeal to histopathologists and endoscopists alike, not only for the diagnostic details it provides, but also for the associated clinicopathological information. I have found it an ideal companion and am sure that others will think the same.

**Upper Gastrointestinal Surgery, 2nd Edn**


The Companion to Specialist Surgical Practice series aims to meet the need of higher surgical trainees and busy practising surgeons by keeping them up to date of recent developments in the field and consolidating our understanding on key topics. The first series of seven texts met with high critical acclaim and in the second edition of the series this has been expanded to eight volumes. The second edition of Gastrointestinal Surgery comprehensively covers the field of hollow organ upper gastrointestinal surgery. There are some minor omissions such as impedance assessment and management of gastric polyps. This however is only a minor criticism of what is otherwise an excellent text. The book occupies an important niche in the field of surgery as each volume is produced in a short period of time in order to ensure that it is up to date, in contrast with some of the larger texts in the field which by virtue of the time it takes to produce a new edition are already somewhat out of date at the time of publication.

The new edition benefits from an emphasis on evidence based practice with up to date key references, some of which include a short commentary. Unfortunately, there is a degree of non-uniformity among chapters, which would benefit from correction in the next edition.

The main contributors are all established figures in the field of upper gastrointestinal surgery and bring an authoritative viewpoint to each chapter. The format is pleasing with...
copious diagrams and tables. The use of a scalpel icon to highlight text and references associated with reasonable evidence based practice is a particularly good idea.

This is a welcome addition to what has become established, in a very short space of time, as an essential read. It will continue to appeal to surgical trainees and consultants alike, but will also be of interest to medical, radiological, and pathology colleagues who wish to have a broader understanding of their own area of expertise. I unreservedly recommend it.

M Winslet

Challenges in Inflammatory Bowel Disease


This latest entry into the inflammatory bowel disease textbook sweepstakes is intended neither as a comprehensive reference work nor as a guide to everyday management. This demurral is just as well. After all, the former category of texts is already well represented by such heavyweights as Kirsner (WB Saunders), Allain et al (Churchill Livingstone), or Tingmour and Shanhahan (Williams and Wilkins); the latter arena is quite thoroughly covered in works by Gitschin (Igaku-Shoin) and even more notably by Bayless and Hannauer (BC Decker).

The current volume, rather, adopts a self-described "new approach." It focuses on specific questions ranging from basic science to clinical management, and it seeks to adduce best evidence in addressing controversies in these fields. In taking this particular tack, the editors and publishers have succeeded admirably in at least three respects.

Firstly, they have assembled an all-star cast of contributors. The editors, Derek Jewell, Bryan Warren, and Neil Mortensen—themselves a world class troika of clinician researcher, pathologist, and surgeon—have recruited 38 renowned authors from top centers around the world to join their various specialties together.

Secondly, they have constructed this monograph ingeniously. Each chapter title is phrased as a question, which is then examined critically with scores of references that are pertinent and up to date (at least through to 1999). Six chapters address epidemiological, aetiological, and pathogenetic issues; two deal with diagnosis and assessment; the largest section comprises eight chapters on management, including medical, nutritional, and surgical aspects; four chapters are devoted to cancer surveillance; two pertain to long term complications (in a section subtitled "disease versus therapy" mischievously implying that some treatments are worse than disease); and a final chapter tackles the subject of prognosis.

As a third defining feature of this ambitious volume, the editors have demanded and received from their authors highly critical analyses of "the most recently available evidence". The authors analyse and interpret the evidence in ways that allow each chapter to reach reasonably well founded conclusions.

The six chapters on epidemiology and genetics are particularly thorough. If the chapter on inflammatory bowel disease genes is a bit technically dense, it still provides a helpful historical perspective on the accumulation of knowledge over the past decade, and it offers some thoughtful methodological considerations for future research. The chapter on microorganisms covers the topic from putative specific through animal models to therapeutic implications. The chapter on genetics versus environment explores the potential mechanisms of functional interaction between genes and environment.

In the sections on diagnosis and assessment, two pathologists take wonderful advantage of the book's format by posing and discussing 18 "controversies in histopathologic diagnosis", while a second chapter on "new diagnostic tools" deals with advanced imaging techniques but neatly avoids the thorny thicket of serodiagnostics. The eight chapters on management cover the range from specific medical and nutritional therapies to a particular disease presentation (refractory distal colitis) and current surgical controversies. It is especially noteworthy that after a thoughtful review of the conflicting data on the role of mesalazine in Crohn's disease, Hillary Steinhart pointedly reminds us not to forget the often overlooked consideration of patient preferences.

The section on cancer surveillance opens with Karel Geboes's nicely illustrated chapter on dysplasia in ulcerative colitis. (Indeed, the only really good illustrations in this book are the photomicrographs; even the pretty looking cover displays only a very poorly reproduced radiograph.) The cancer section then continues with two lively chapters that debate the utility of endoscopic surveillance. The arguments on each side are thoughtful and provocative, even when occasionally slipping into polemic. The chapter on low-grade dysplasia in flat mucosa: "...unequivocal low-grade dysplasia is thus a reasonable indication for surgery"; but then, one sentence later, "repeat endoscopy within 6 months of a first diagnosis of low-grade dysplasia appears advisable"... The final one chapter section on prognosis by Kelly Burak and Lloyd Sutherland effectively comes to grips with the biases that perhaps he should be forgiven for "hedging" slightly on the problem of low grade dysplasia in flat mucosa: "...unequivocal low-grade dysplasia is thus a reasonable indication for surgery"; but then, one sentence later, "repeat endoscopy within 6 months of a first diagnosis of low-grade dysplasia appears advisable..." The final one chapter section on prognosis by Kelly Burak and Lloyd Sutherland effectively comes to grips with the biases that perhaps he should be forgiven for "hedging" slightly on the problem of low grade dysplasia in flat mucosa: "...unequivocal low-grade dysplasia is thus a reasonable indication for surgery"; but then, one sentence later, "repeat endoscopy within 6 months of a first diagnosis of low-grade dysplasia appears advisable..."

In summary, the audience for this book is best described in the publishers' own words (with my italics added): "an ideal text for those who already know the tried and tested information, but who now want to know about the areas of controversy in this fast-moving field."

D Sachar

NOTICES

Sir Francis Avery Jones BSG Research Award 2003

Applications are invited by the Education Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 2003 Award. Applications (TWENTY COPIES) should include:

• A manuscript (2 A4 pages ONLY) describing the work conducted
• A bibliography of relevant personal publications
• An outline of the proposed content of the lecture, including title
• A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

Entrants must be 40 years or less on 31 December 2002 but need not be a member of the Society. The recipient will be required to deliver a 30 minute lecture at the Annual meeting of the Society in Birmingham in March 2003. Applications (TWENTY COPIES) should be made to the Honorary Secretary, British Society of Gastroenterology, 3 St Andrews Place, London NW1 4LB by 1 December 2002.

Corrections

Due to an error in the production process, the Therapy Update in the August issue of the journal (Gut 2002;51:182–3) was missing references 14 to 24. The references are printed below, and Gastroapologises for the omission.