PostScript

LETTERS

If you have a burning desire to respond to a paper published in *Gut*, why not make use of our "rapid response" option?

Log onto our website (www.gutjnl.com), find the paper that interests you, and send your response via email by clicking on the "eLetters" option in the box at the top right hand corner.

Providing it isn't libellous or obscene, it will be posted within seven days. You can retrieve it by clicking on "read eLetters" on our homepage.

The editors will decide as before whether to also publish it in a future paper issue.

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*0201 and HLA-DRB1*1301-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 TNF*2 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 TNFA*2 with PSC. This overrepresentation of TNFA*2 was seen only in subjects with HLA-A1-B8-DRB1*0301, indicating that the observed association of PSC with TNFA*2 might in fact be secondary to linkage disequilibrium within this haplotype.

Bernal and colleagues[5] 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 TNFA*2 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.[6–8] This population is of highly admixed origin with different percentages of Caucasoid, African, and Amerindian ancestries. The diagnosis of PSC was based on the findings of typical clinical, laboratory, cholangiographic, and histological features.[9] 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 (23 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).

No increase in the frequency of HLA-B, DRB3, DRB4, or DRB5 alleles was observed in PSC patients compared with healthy controls. Likewise, the distribution of TNFA alleles was similar in patients and controls. The frequency of HLA-DRB1*1301 (52% *v* 20% of controls; p=0.00009, RR=4.3) and HLA-DQB1*06 (59% *v* 41% of controls; p=0.04, RR=2.1) was significantly increased in PSC patients (table 1). However, one third of HLA-DRB1*13 positive patients carried other HLA-DQB1 alleles (data not shown). This overrepresentation of HLA-DRB1*13 was seen in both paediatric (44% *v* 20% of controls; p=0.02, RR=3.1) and adult patients (58% *v* 20% of controls; p=0.00009, RR=5.4). However, this association was seen only in patients with IBD (61% of patients with IBD *v* 20% of controls (p=0.00001, RR=6.1) and 36% of patients without IBD *v* 20% of controls (NS)).

Table 1 Frequencies of HLA-DRB, DQB1 alleles and tumour necrosis factor alpha promoter gene (TNFA) genotypes in patients with primary sclerosing cholangitis (PSC) and healthy controls

	PSC patients (n=63)	Healthy controls (n=83)	p Value
DRB1*03	12 (19)	23 (28)	
DRB1*13	33 (52)	17 (20)	0.00009
DRB3	53 (84)	62 (75)	
DQB1*02 *	20 (36)	41 (49)	
DQB1*06 *	33 (59)	34 (41)	0.04
TNFA*1/TNFA*1	41 (65)	63 (76)	
TNFA*1/TNFA*2	21 (33)	19 (23)	
TNFA*2/TNFA*2	1 (2)	1 (1)	
TNFA*2 allele carriage	22 (27)	20 (35)	

*Only 56 patients with PSC were typed for HLA-DQB1.
Numbers in parentheses are percentages.

In summary, our data indicate that predisposition to PSC in Brazil is primarily linked to HLA-DRB1*13 and suggest that the association with TNFA*2 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.[10]

Interestingly, AIH type 1 was also associated with HLA-DRB1*13 but not with the TNFA*2 allele in Brazil.[11 12] Of note, shared HLA antigens have also been associated with AIH type 1 and PSC in other populations.[13] These findings suggest that the same HLA-DRB1 alleles confer susceptibility to distinct autoimmune diseases of the liver such as AIH type 1 and PSC and point to the presence of similar immune mechanisms leading to different clinical outcomes.

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, Salvador-BA, Brasil; plbbr@uol.com.br

References

1 **Spurkland A**, Saarinen S, Boberg KM, *et al.* HLA class II haplotypes in primary sclerosing cholangitis patients from five European populations. *Tissue Antigens* 1998;**53**:459–69.
2 **Farrant JM**, Doherty DG, Donaldson PT, *et al.* Amino acid substitutions at position 38 of the DR beta polypeptide confer susceptibility to and protection from primary sclerosing cholangitis. *Hepatology* 1992;**16**:390–2.
3 **Mehal WZ**, Lo YM, Wordsworth BP, *et al.* HLA DR4 is a marker for rapid disease progression in primary sclerosing cholangitis. *Gastroenterology* 1994;**106**:160–7.
4 **Olerup O**, Olsson R, Hulcrantz R, *et al.* HLA-DR and HLA-DQ are not markers for rapid disease progression in primary sclerosing cholangitis. *Gastroenterology* 1995;**108**:937–40.
5 **Bernal W**, Moloney M, Underhill J, *et al.* Association of tumor necrosis factor polymorphism with primary sclerosing cholangitis. *J Hepatol* 1999;**30**:237–41.
6 **Bunce M**, Fanning GC, Welch KI. Comprehensive, serologically equivalent DNA typing for HLA-B by PCR using ssequence-specific primers (PCR-SSP). *Tissue Antigens* 1995;**45**:81–90.
7 **Olerup O**, Zetterquist H. HLA-DR typing by PCR amplification with sequence-specific primers (PCR-SSP) in 2 hours: An alternative to serological DR typing in clinical practice including donor-recipient matching in cadaveric transplantations. *Tissue Antigens* 1992;**39**:225–35.

8 **Wilson AG**, di Giovine FS, Blakemore AIF, *et al.* Single base polymorphism in the human tumor necrosis factor alpha (TNFα) gene detectable by NcoI restriction of PCR product. *Hum Mol Genet* 1992;**1**:353.
9 **Chapman R**, Arborgh B, Rhodes J, *et al.* Primary sclerosing cholangitis: a review of its clinical features, cholangiography and hepatic histology. *Gut* 1980;**21**:870–7.
10 **Donaldson PT**, Norris S, Underhill JA, *et al.* HLA associations in primary sclerosing cholangitis are present only in those patients with concurrent inflammatory bowel disease. *Hepatology* 1998;**28**:392A.
11 **Bittencourt PL**, Goldberg AC, Cançado ELR, *et al.* Genetic heterogeneity in susceptibility to autoimmune hepatitis types 1 and 2. *Am J Gastroenterol* 1999;**94**:1906–13.
12 **Bittencourt PL**, Palácios AS, Cançado ELR, *et al.* Analysis of tumor necrosis factor α polymorphisms in autoimmune hepatitis types 1 and 2. *J Hepatol* 2001;**35**:24–8.
13 **Czaja AJ**, Santrach PJ, Breanndan Moore S. Shared genetic risk factors in autoimmune liver disease. *Dig Dis Sci* 2001;**46**:140–7.

Slow transit constipation: more than one disease?

Emmanuel and Kamm 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.[1] Beyond that, Emmanuel and Kamm 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, presumably of the enteric nervous system.

Disturbances of oesophageal motility, gastric emptying, small bowel transit, and gall bladder motility have been described.[2] Dysmotility of the small intestine has been thoroughly investigated by manometry in STC patients[3 4] 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[5] using long term small bowel manometry in 30 clinical STC patients, disturbed aboral migration of phase III was present in 47%, and bursts/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 been reported to result in excellent long term outcome in 90% of patients with dysmotility limited to the colon whereas patients with generalised intestinal dysmotility experience a sustained relief in only 13%.[6] It is hard to understand how these manifestations of neuropathy, especially in the myenteric plexus of the small intestine, can be successfully treated by biofeedback therapy.

An alternative explanation is that STC is an inhomogeneous group of different aetiologies. In transit studies, slow transit can be the result of a right sided or global delay (the "classical" finding in idiopathic STC), a left sided delay, or a rectal marker accumulation.[7] In physiological evaluation, an overlap of slow transit and outlet obstruction can be seen in some patients.[8] At least in healthy volunteers, voluntary suppression of defecation resulted in a marked prolongation of colonic transit.[9]

Of the 22 slow transit patients studied by Emmanuel and Kamm, seven had marker 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,[5] 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, Englschalkinger Str 77, 81925 Munich, Germany

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

References

1 **Enck P**. Biofeedback training in disordered defecation. A critical review. *Dig Dis Sci* 1993;**38**:1953–60.
2 **Altomare DF**, Portincasa P, Rinaldi M, *et al.* Slow-transit constipation: solitary symptom of a systemic gastrointestinal disease. *Dis Colon Rectum* 1999;**42**:231–40.
3 **Bassotti G**, Stanghellini V, Chiarioni G, *et al.* Upper gastrointestinal motor activity in patients wih slow-transit constipation. *Dig Dis Sci* 1996;**10**:1999–2005.
4 **Glia A**, Lindberg G. Antroduodenal manometry findings in patients with slow-transit constipation. *Scand J Gastroenterol* 1998;**33**:55–62.
5 **Schmidt T**, Soellner J, Pehl C, *et al.* Long-term small bowel manometry in the clinical evaluation of chronic constipation. *Neurogastroenterol Mot* 1999;**11**:A288.
6 **Redmond JM**, Smith GW, Barofsky I, *et al.* Physiological tests to predict long-term outcome of total abdominal colectomy for intractable constipation. *Am J Gastroenterol* 1995;**90**:748–53.
7 **Chaussade S**, Khyari A, Roche H, *et al.* Determination of total and segmental colonic transit time in constipated patients. Results in 91 patients with a new simplified method. *Dig Dis Sci* 1989;**34**:1168–72.
8 **Pemberton JH**, Rath DM, Ilstrup DM. Evaluation and surgical treatment of severe chronic constipation. *Ann Surg* 1991;**214**:403–13
9 **Klauser AG**, Voderholzer WA, Heinrich CA, *et al.* Behavioural modification of colonic function. Can constipation be learned? *Dig Dis Sci* 1990;**35**:1271–5.

Authors' reply

We thank Dr Pehl 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 and small bowel transit.[1] Behavioural treatment, which includes biofeedback, is a holistic treatment which we believe has both central and peripheral effects. Our study on the effects of behavioural treatment (*Gut* 2001;**49**:214–19) demonstrated enhanced activity of the autonomic nerves innervating the gut. Such a change in extrinsic nerve function might be expected to alter upper gut function as well as colonic function. In support of this, we have previously demonstrated that such treatment not only normalises colonic transit but also diminishes the sensation of bloating and abdominal pain.[2]

The existence of a panenteric disturbance of function, including the motor abnormalities described by Pehl *et al*, should not be interpreted as evidence of enteric neuropathology 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,[3] 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, with or without pelvic floor contraction, respond equally to behavioural treatment.[2] 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.

M A Kamm, A V Emmanuel

St Mark's Hospital, Watford Road, Harrow HA1 3UJ, UK

Correspondence to: Professor M Kamm; Kamm@ic.ac.uk

References

1 **van der Sijp**, Kamm MA, Nightingale JMD, *et al.* Disturbed gastric and small bowel transit in severe idiopathic constipation. *Dig Dis Sci* 1993;**38**:837–44.
2 **Chiotakakou-Faliakou E**, Kamm MA, Roy AJ, *et al.* Biofeedback provides long term benefit for patients with intractable slow and normal transit constipation. *Gut* 1998;**42**:517–21.
3 **Kamm MA**, Hawley PR, Lennard-Jones JE. Outcome of colectomy for severe idiopathic constipation. *Gut* 1988;**29**:969–73.

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 in 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 of 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.[1]

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 closely 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.[2] 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 *v* 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 most deaths were liver related (72%) rather than tumour related. Both of these points suggested that the better outcome observed in the group under surveillance was due to the better basal conditions of the patients and not to the procedures themselves. Lastly, 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*'s 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.[3–5] 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 who developed HCC and those who did not, thus emphasising the importance of residual liver function in relation to survival.[6] Therefore, what probably lies beneath 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 changed 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, V le Benedetto XV, No 6, 16132 Genoa, Italy; rtesta@unige.it

References

1 **The Cancer of the Liver Italian Program (CLIP) Investigators**. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients. *Hepatology* 1998;**28**:751–5.
2 **Giannini E**, Arzani L, Borro P, *et al*. Does surveillance for hepatocellular carcinoma in HCV cirrhotic patients improve treatment outcome mainly due to better clinical status at diagnosis? *Hepatogastroenterology* 2000;**47**:1395–8.
3 **Matsui O**, Kadoya M, Yoshikawa J, *et al*. Subsegmental transcatheter arterial embolization for small hepatocellular carcinomas: local therapeutic effect and 5-year survival rate. *Cancer Chemother Pharmacol* 1994;**33**(suppl):84–8.
4 **Livraghi T**, Bolondi L, Buscarini L, *et al*. No treatment, resection and ethanol injection in hepatocellular carcinoma: a retrospective analysis of survival in 391 patients with cirrhosis. *J Hepatol* 1995;**22**:522–6.
5 **Rust C**, Gores GJ. Locoregional management of hepatocellular carcinoma. Surgical and ablation therapies. *Clin Liver Dis* 2001;**5**:161–73.
6 **Cottone M**, Turri M, Caltagirone M, *et al*. Screening for hepatocellular carcinoma in patients with Child's A cirrhosis: an 8-year prospective study by ultrasound and alphafetoprotein. *J Hepatol* 1994;**21**:1029–34.

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 pertaining 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, leaves 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^2 or an adjusted r^2 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)". Obviously not 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; kfilio@po-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 cell regeneration 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 performed, including Ki67, Rb1, Bcl2, p53, and cytokeratins, without statistical analysis.

H K Seitz
Salem Medical Centre, Heidelberg, Germany

C Conradt
Department of Biostatistics, University of Heidelberg, Heidelberg, Germany

Correspondence to: H K Seitz, Department of Medicine, Salem Medical Centre, Zeppelinstrasse 11-13, D-69121 Heidelberg, Germany; helmut_karl.seitz@urz.uni- heidelberg.de

Motilin 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 this 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 t50% recorded in healthy subjects (130±50 (SD?) minutes) is remarkably outside the normal range reported using the gold standard scintigraphy (mean 110±4 (SEM) minutes, 10th percentile 70 minutes, 90th percentile 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.[1–4] It is claimed that the method 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 the absence of 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 motilin agonist, previously demonstrated in the study of Verhagen and colleagues.[5] However, other prokinetics, indeed other motilin agonists, may prove effective in the treatment of dyspepsia in diabetics with impaired gastric emptying.[6 7]

Fourthly, the observation that over time some of the symptoms continued to be aggravated in the active arm 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 motilin 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 pharmacodynamic 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, accommodation, and postprandial symptoms. These methods permit proper dose-response studies prior to exposing patients to potentially harmful agents or inappropriately 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* intrinsic nitrergic 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.[8] 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 effective therapies. 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 whether the medication or a derivative with improved pharmacokinetics should be given a "second chance".

M Camilleri
Gastroenterology Research Unit, Mayo Clinic, Rochester, Minnesota, USA; camilleri.michael@mayo.edu

References

1 **Maes BD**, Mys G, Geypens BJ, *et al.* Gastric emptying flow curves separated from carbon-labeled octanoic acid breath test results. *Am J Physiol* 1998;**275**:G169–75.
2 **Lee J-S**, Camilleri M, Zinsmeister AR, *et al.* Toward office-based measurement of gastric emptying in symptomatic diabetics using [13C]octanoic acid breath test. *Am J Gastroenterol* 2000;**95**:2751–61.
3 **Lee J-S**, Camilleri M, Zinsmeister AR, *et al.* A valid, accurate, office-based, nonradioactive test for gastric emptying of solids. *Gut* 2000;**46**:768–73.
4 **Viramontes BE**, Kim D-Y, Camilleri M, *et al.* Validation of a stable isotope gastric emptying test for normal, accelerated or delayed gastric emptying. *Neurogastroenterol Motil* 2001;**13**:567–74.
5 **Verhagen MA**, Samsom M, Maes B, *et al.* Effects of a new motilide, ABT-229, on gastric emptying and postprandial antroduodenal motility in healthy volunteers. *Aliment Pharmacol Ther* 1997;**11**:1077–86.
6 **Jian R**, Ducrot F, Ruskone A, *et al.* Symptomatic, radionuclide and therapeutic assessment of chronic idiopathic dyspepsia. A double-blind placebo-controlled evaluation of cisapride. *Dig Dis Sci* 1989;**34**:657–64.
7 **Janssens J**, Peeters TL, Vantrappen G, *et al.* Improvement of gastric emptying in diabetic gastroparesis by erythromycin. Preliminary studies. *N Engl J Med* 1990;**322**:1028–31.
8 **Camilleri M**, Balm RK, Zinsmeister AR. Determinants of response to a prokinetic agent in neuropathic chronic intestinal motility disorder. *Gastroenterology* 1994;**106**:916–23.

Authors' reply

A number of the issues raised by Dr Camilleri are important and relevant although some of the points require clarification. We stand by our position that drugs which act solely as gastric prokinetics are unlikely to be beneficial in either diabetic gastropathy or functional dyspepsia. Our data (both in this study and eleswhere[1]) suggested that the motilin agonist tested actually worsened symptoms in both diabetics and non-diabetics with unexplained dyspepsia, regardless of baseline gastric emptying status. Other recent data suggest that motilin agonists impair fundic accommodation and this physiological disturbance may induce symptoms in a subset with dyspepsia.[2] Cisapride relaxes the fundus and this may explain its therapeutic benefits in dyspepsia.[3] Our observations have important implications for future drug development; we agree with Dr Camilleri that ideally the mechanisms of drug action need to be understood prior to planning clinical trials, although this is often completely impractical and could impair progress at times. It is also fair to point out that data on fundic accommodation have only become available relatively recently, and preceded the planning of the trials.

While we agree that there are limitations with C^{13}-octanoic acid breath testing, we believe that the data are reasonably robust. Indeed, we applied 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 motilin agonist tested.[1]

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.[4] Furthermore, there remains 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[1]). 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[1]). 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 motilin agonist class is likely to be disappointing in unexplained dyspepsia unless agents in this class with quite different physiological effects are developed.

N J Talley
Department of Medicine, University of Sydney, Nepean Hospital, PO Box 63, Penrith, NSW 2751, NSW, Australia

M Verlinden
Department of International Clinical Research and Development, Janssen Research Foundation, Beerse, Belgium

Correspondence to: Professor N J Tally; ntalley@med.usyd.edu.au/ ntalley@blackburn.med.su.oz.au

References

1 **Talley NJ**, Verlinden M, Snape W, *et al*. Failure of a motilin receptor agonist to relieve the symptoms of functional dyspepsia in patients with and without delayed gastric emptying: a randomised double-blind placebo-controlled trial. *Aliment Pharmacol Ther* 2000;**14**:1653–61.
2 **Piessevaux H**, Tack J, Wilmer A, *et al*. Perception of changes in wall tension of the proximal stomach in humans. *Gut* 2001;**49**:203–8.
3 **Tack J**, Broeckaert D, Coulie B, *et al*. The influence of cisapride on gastric tone and the perception of gastric distension. *Aliment Pharmacol Ther* 1998;**12**:761–6.
4 **Veldhuyzen van Zanten SJ**, Jones MJ, Talley NJ. Efficacy of cisapride and domperidone in functional (nonulcer) dyspepsia: a meta-analysis. *Am J Gastroenterol* 2001;**96**:689–96.

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.[1]

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.[2,3] In Australia, in 1999, only 1.3% of all antiulcerant prescriptions were for *H pylori* eradication therapy.[4]

Analysis of the volume of prescriptions for eradication therapies in each region during the study period would allow assessment of the impact of their strategy on the prevalence of *H pylori* associated peptic ulcer disease.

A Duggan
John Hunter Hospital, Locked Bag 1, Hunter Region Mail Centre, NSW 2310, Australia

J Westbrook
Centre for Health Informatics, University of NSW, Kensington, NSW 2052, Australia

Correspondence to: A Duggan; aduggan@hunter.health.nsw.gov.au

References

1 An evidence-based appraisal of reflux disease management. The Genval workshop report. *Gut* 1999;**44**:S1–16.
2 **Duggan A**, Bilku J, Ledger K, *et al*. Eradicating *H. pylori* in patients with a past history of documented peptic ulcer: Is the juice worth the squeeze? *J Qual Clin Pract* 2001;**21**:76–9.
3 **Ryder S**, O'Reilly S, Miller R, *et al*. Long term acid suppression treatment in general practice. *BMJ* 1994;**308**:827–30.
4 **Westbrook JI**, Duggan AE, McIntosh JH. Antiulcerant prescriptions in Australia—volume, trends and costs. *BMJ* 2001;**323**:1338–9.

Author's reply

Details of individual drug usage were not available for the entire study period and therefore it was not possible to analyse changes for particular drugs.

The purpose of providing the gastrointestinal bleed unit and other data was to give an indication of whether the intervention might have adverse effects on other health outcomes related to dyspepsia. We were particularly concerned that the intervention might increase demand for endoscopy or increase morbidity from peptic ulcer complications. We acknowledge that during the study period it is possible that there may have been a natural decline in referral for endoscopy and gastrointestinal bleeding. Thus without a control group for these outcomes it is possible that the stable levels demonstrated in the study represent a real increase. However, we believe that this is exceedingly unlikely given the continued strong demand for endoscopy elsewhere and the steady rise in emergency medical admissions in the UK. We do not have sufficiently accurate data to make comment on whether the intervention reduced *Helicobacter pylori* related peptic ulcer bleeds.

It was not possible in this study to identify individual *H pylori* prescriptions. A more relevant outcome might have been the number of patients who, following eradication therapy (for whatever reason), no longer needed long term acid suppressing medication. Feedback from general practitioners suggests that there were many patients who responded in this way. Unfortunately, we have no hard data to support the anecdotal reports of the impact of *H pylori* eradication on drug costs.

R Valori
Gloucestershire Royal Hospital, Great Western Road GL1 3NN, UK; r.valori@step1.net

Causes of obvious jaundice in South West Wales

We read with interest the article describing the causes of obvious jaundice (serum bilirubin >120 μmol/l) in South West Wales (*Gut* 2001;**48**:409–13). The authors make the point that contrary to the perception of many doctors, viral hepatitis is an unusual cause of jaundice (two of 121 cases) while sepsis/shock is a relatively common cause (27 of 121 cases).

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 often occurs in a particular clinical setting such as an intensive care unit, postoperatively, or in patients with multiple medical problems. In this context we doubt the aetiology of the jaundice is "overlooked". Our own study clearly indicates that shock/sepsis is indeed an unusual reason for patients to present to medical care with jaundice.

The authors also noted that 16 of 61 patients with common bile duct (CBD) stones had a bilirubin level greater than 120 μmol/l, and comment that such high levels of bilirubin are more likely to be related to malignant obstruction. In contrast with this, our own series demonstrated that 10 of 29 patients with CBD stones had bilirubin values greater than 120 μmol/l. There was no difference in mean bilirubin values between patients with CBD stones and those with malignant disease (120 (±15) *v* 168 (±28) μmol/l), nor indeed with those with ALD (142 (±18)).

We also have a concern about the accuracy of diagnosis on a retrospective review of the causes of liver disease, particularly as gastroenterologists managed only one third of patients in the Welsh study. In our series we noted that few patients had a "complete" serological screen for liver disease. It is therefore possible that patients might have been inadequately investigated and so were placed in an inappropriate diagnostic group.

The authors also highlight the value of the aspartate aminotransferase:bilirubin ratio in the assessment of jaundice. A further analysis of our own data does not substantiate the use of this value in diagnosis. Mean values for ALD, gall stone related jaundice, and malignancy were 3.5, 3.8, and 2.7, respectively (NS).

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

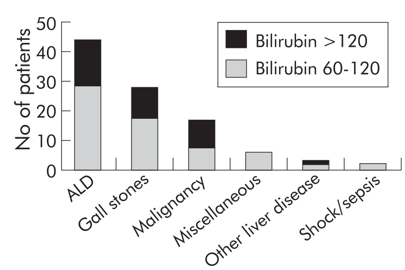

Figure 1 Causes of jaundice. ALD, alcoholic liver disease.

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 100 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 of differences in methodology and case ascertainment. In particular, our study was prospective, community and hospital based, and included all patients with bilirubin values greater than 120 μmol/l. Forrest and Forrest's observations are retrospective, relate specifically to patients presenting to hospital because of jaundice, and use a cut off bilirubin level of >60 μmol/l.

We will respond to their comments seriatim.

(1) The commonest cause of presentation with jaundice to Stobhill Hospital was alcoholic liver disease. In Swansea, if analysis is restricted to those 95 patient *presenting* to hospital with jaundice, then alcoholic cirrhosis ran a very close second to malignancy as the commonest cause.

(2) As Forrest and Forrest point out, sepsis/shock is not a common cause of jaundice *requiring admission* to hospital either in Glasgow or Swansea, but in our experience was the predominant cause of jaundice *developing while in hospital for other reasons*. As to whether it is overlooked, our results speak for themselves—in over one third of our sepsis/shock cases jaundice had been erroneously attributed to some other cause by the clinical team managing the case.

(3) Ten of 29 (34%) Glasgow cases and 16 of 61 (26%) Swansea cases with common bile duct (CBD) stones had bilirubin levels >120 μmol/l. Given the relatively small sample sizes we consider these to be similar rather than dissimilar proportions. The absolute values of bilirubin from the two centres cannot be compared without knowledge of the timing of samples. Clearly, samples taken on admission might show lower bilirubin levels than samples taken later on, particularly with malignant biliary obstruction awaiting mechanical relief. Our experience is that gall stone biliary obstruction was often transient and not profound whereas malignant obstruction led to ever increasing levels of bilirubin unless there was mechanical intervention.

(4) We share Forrest and Forrest's concern about the accuracy of diagnosis on retrospective case note review but respectfully point out that our study was prospective while theirs was retrospective. We accept that not every patient in the Swansea series had every investigation but we cannot consider it good practice to perform tests unless clinically indicated. Thus most patients with proven obstructive jaundice did not have serological tests whereas most patients with intrinsic hepatocyte dysfunction did.

(5) Our observations on aspartate aminotransferase (AST):bilirubin ratios were for interest alone. We did not propose that this should be used as a test but simply commented that the ratio had some diagnostic value. Our only comment on the Glasgow figures relates to their patients with alcoholic liver disease where the ratio was reported to be 3.5. Mean bilirubin level for this group was 142 μmol/l which translates to a mean AST value of approximately 500 IU/l. This is an exceptionally high figure for AST in alcoholic liver disease where AST is characteristically much lower, usually <200 IU/l.

(6) Causes of jaundice and causes of jaundice requiring hospital admission are not the same and clinicians should guard against using the experience of one clinical setting when assessing another.

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 6NL, UK

Correspondence to: Dr J G C Kingham; jkingham@swansea-tr.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 (*Gut* 2001;**49**: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 hardly ever 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[1] or in fact to any clinician caring for patients with Crohn's disease. More 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 invariable progression 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; david.sachar@mssm.edu

References

1 **Gasche C**, Scholmerich J, Brynskov J, *et al*. A simple classification of Crohn's disease: report of the Working Party for the World Congresses of Gastroenterology, Vienna 1998. *Inflamm Bowel Dis* 2000;**6**:8–15.

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 stricturing or as a penetrating disease (Crohn's disease behaviour) has been considered for some time as a potential suitable phenotype for genetic correlations. However, results to date 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 essentially due to shared 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 strictures and fistulas 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. As we have shown, even the most recent and reproducible classification[1] is not suitable as patients change categories over time. As emphasised by Sachar, it seems from our data that patients who are classified as B2 (stricturing) 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 1–30 years). It seems as if patients who develop penetrating lesions (B3) associated with stricturing 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 stricturing lesions (B2) developed after 10 years of evolution. Therefore, in our experience, patients who develop a pure stricturing 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-stricturing phenotype (B1). Therefore, the subgroup of patients with non-penetrating non-stricturing disease 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 within two years 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 stricturing 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 stratify patients according to these factors or to consider these factors in multivariate analyses.

E Louis, J Belaiche
Department of Gastroenterology, CHU of Liège, Belgium

Correspondence to: E Louis; edouard.louis@ulg.ac.be

References

1 **Gasche C**, Scholmerich J, Brynskov J, *et al.* A simple classification of Crohn's disease: report of the Working Party of the World Congresses of Gastroenterology, Vienna 1998. *Inflamm Bowel Dis* 2000;**6**:8–15.

BOOK REVIEWS

Pediatric Gastroenterology and Nutrition in Clinical Practice

Edited by C H Lifschitz. New York: Marcel Dekker, 2002, B/W, pp 869. ISBN 0 8247 0510 6

"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 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" more by accident than design, and all forms of the written word compete with each other.

Books have a historical advantage over what we still regard as more ephemeral sources of information—journals and the Internet. Books are portable and we like to think that the effort that goes into writing them is a measure of the quality and authority of their contents. But how confident can we be that this is the case?

Peer review has become the test of quality of original articles, and we take most notice of papers published in journals that are most rigorous in this respect. Books on the other hand rely for their credibility on the reputation of their authors. Things are not so clear when it comes to new multiauthor compilations, such as *Pediatric Gastroenterology and Nutrition in Clinical Practice*. Collecting together and publishing papers and reviews from international conferences must be commercially profitable for some publishers, and worthwhile for many authors, even though the price of such books is often extraordinary. This book is not the result of a meeting but brings together chapters from a variety of eminent paediatric gastroenterologists from around the world. Its editor intends it to present a "clear and useful summary of the most relevant new facts in molecular biology and genetics, as well as recently acquired information, in conjunction with a practical approach to pediatric gastroenterology and nutrition".

At first sight the book has no structure, containing 33 chapters with titles as diverse 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), alongside more familiar titles such as "Short bowel syndromes", "Celiac disease" and "Food allergy". It seems to fall somewhere between a textbook and a multiauthor collection; it not suitable for undergraduates and it is not the book to reach for when faced with a difficult clinical problem. Its layout and contents assume 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!"

L T Weaver

Gastrointestinal Polyps

Edited by N Haboubi, K Geboes, N Shepherd, *et al.* Greenwich: Medical Media, 2002, £65.00, colour, pp170. ISBN 1-90015-121-9

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 pathologist and clinician 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 polypoid lesions for which a diagnosis was currently eluding me. I thought that this book would be an ideal 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 prevalence, endoscopic appearances, and pathological features are given, followed by 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 the 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.

P Domizio

Upper Gastrointestinal Surgery, 2nd Edn

Edited by S M Griffin, S A Raimes. Philadelphia: WB Saunders, 2001, B/W, pp 474. ISBN 0 7020 2587 9

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

Edited by D P Jewell, B F Warren, N J Mortensen. Oxford: Blackwell Science, 2001, £59.50, B/W, pp 294. ISBN 0 632 05169 8

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), Allan *et al* (Churchill Livingstone), or Targan and Shanahan (Williams and Wilkins); the latter arena is quite thoroughly covered in works by Gitnick (Igaku-Shoin) and even more notably by Bayless and Hanuaer (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 centres in six countries besides their own.

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 the 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 section 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) to 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 how dysplasia is recognised. (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. In any event, it ultimately requires the soothing voice of John Lennard-Jones to provide "a balanced view" that reviews options, presents the arguments pro and con, reaches both pragmatic and general conclusions, and then offers specific recommendations. The issue being so contentious, 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 obscure our search for the "natural history" of the inflammatory bowel diseases.

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.

CORRECTION

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 *Gut* apologises for the omission.

14 **Campieri M**, Ferguson A, Doe W, *et al.* Oral budesonide is as effective as oral prednisolone in active Crohn's disease. The Global Budesonide Study Group. *Gut* 1997;**41**:209–14.
15 **Thomsen OO**, Cortot A, Jewell D, *et al.* A comparison of budesonide and mesalamine for active Crohn's disease. International Budesonide-Mesalamine Study Group. *N Engl J Med* 1998;**339**:370–4.
16 **Irvine EJ**, Greenberg GR, Feagan BG, *et al.* Quality of life rapidly improves with budesonide therapy for active Crohn's disease. Canadian Inflammatory Bowel Disease Study Group. *Inflamm Bowel Dis* 2000;**6**:181–7.
17 **Florin TH**, Graffner H, Nilsson LG, *et al.* Treatment of joint pain in Crohn's patients with budesonide controlled ileal release. *Clin Exp Pharmacol Physiol* 2000;**27**:295–8.
18 **Cortot A**, Colombel JF, Rutgeerts P, *et al.* Switch from systemic steroids to budesonide in steroid dependent patients with inactive Crohn's disease. *Gut* 2001;**48**:186–90.
19 **Lofberg R**, Rutgeerts P, Malchow H, *et al.* Budesonide prolongs time to relapse in ileal and ileocaecal Crohn's disease. A placebo controlled one year study. *Gut* 1996;**39**:82–6.
20 **Greenberg GR**, Feagan BG, Martin F, *et al.* Oral budesonide as maintenance treatment for Crohn's disease: a placebo-controlled, dose-ranging study. Canadian Inflammatory Bowel Disease Study Group. *Gastroenterology* 1996;**110**:45–51.
21 **Gross V**, Andus T, Ecker KW, *et al.* Low dose oral pH modified release budesonide for maintenance of steroid induced remission in Crohn's disease. The Budesonide Study Group. *Gut* 1998;**42**:493–6.
22 **Ewe K**, Bottger T, Buhr HJ, *et al.* Low-dose budesonide treatment for prevention of postoperative recurrence of Crohn's disease: a multicentre randomized placebo-controlled trial. German Budesonide Study Group. *Eur J Gastroenterol Hepatol* 1999;**11**:277–82.
23 **Hellers G**, Cortot A, Jewell D, *et al.* Oral budesonide for prevention of postsurgical recurrence in Crohn's disease. The IOIBD Budesonide Study Group. *Gastroenterology* 1999;**116**:294–300.
24 **Papi C**, Luchetti R, Gili L, *et al.* Budesonide in the treatment of Crohn's disease: a meta-analysis. *Aliment Pharmacol Ther* 2000;**14**:1419–28.