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. 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-α2 allele, in strong linkage disequilibrium with the HLA-A1/8-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 have previously reported an increased frequency of TNF-α2 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 TNF-α2 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 65 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. 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. 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*0601 (59% v 41% of controls; p=0.04, RR=2.1) was significantly increased in PSC patients compared with healthy controls (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=5.1) 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)).

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.

Interestingly, IBD type 1 was also associated with HLA-DRB1*13 but not with the TNF-α2 allele in Brazil. Of note, shared HLA antigens have also been associated with AIH type 1 and PSC in other populations. 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.

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

<table>
<thead>
<tr>
<th></th>
<th>PSC patients (n=63)</th>
<th>Healthy controls (n=83)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRB1*03</td>
<td>12 (19)</td>
<td>23 (28)</td>
<td></td>
</tr>
<tr>
<td>DRB1*13</td>
<td>33 (52)</td>
<td>17 (20)</td>
<td>0.00009</td>
</tr>
<tr>
<td>DRB3</td>
<td>53 (84)</td>
<td>62 (75)</td>
<td></td>
</tr>
<tr>
<td>DQB1*02 *</td>
<td>20 (31)</td>
<td>41 (49)</td>
<td></td>
</tr>
<tr>
<td>DQB1*06 *</td>
<td>33 (52)</td>
<td>34 (41)</td>
<td>0.04</td>
</tr>
<tr>
<td>TNFA1/TNFα1</td>
<td>41 (65)</td>
<td>63 (76)</td>
<td></td>
</tr>
<tr>
<td>TNFA1/TNFα2</td>
<td>21 (33)</td>
<td>19 (23)</td>
<td></td>
</tr>
<tr>
<td>TNFA2/TNFα2</td>
<td>1 (2)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>TNFA2 allele carriage</td>
<td>22 (27)</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.

References

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, apt 302A, Rio Vermelho, Salvador-BA, Brazil, plbittencourt@iol.com.br

For reprints and permission queries, please visit SAGE’s Rights and Permissions website at http://www.sagepub.com/journalsPermissions.nav

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.

www.gutjnl.com
In physiological evaluation, an overlap of slow back, in constipated patients (Emmanuel and Kamm reported on the Slow transit constipation: more voluntary suppression of defecation resulted in up to 60% of these patients. In our recent study motility of the small intestine has been 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, pres- entation of enteric nervous system. Disturbances of oesophageal motility, gas- tric emptying, small bowel transit, and gall bladder motility have been described. Dist- motility 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—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 71% 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 biofeedback 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 success rate of only 13%. It is hard to understand how these manifestations of neu- ropathy, 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. 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.

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, all patients demonstrated a right sided or global delay and had no signs of outlet obstruction. Thus the response of behavioural treat- ment, biofeedback, in constipated patients with slow transit might be influenced by the existence of more than one disease as a possi- ble 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 Gastroenterological Oncology, Bogenhausen Academic Teaching Hospital, Engelschalkinger Str 77, 81925 Munich, Germany

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

References

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 is a condition associated with a panenteric disorder of func- tion. 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. Behavioural treatment, which includes biofeedback, is a holistic treatment which we believe has both central and peripheral effects. Our attention on the effects of biofeedback treatment (Gut 2001;49:214–19) demonstrated enhanced activity of the auto- nomic 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.

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 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 treat- ment can be judged best by careful prospec- tive 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 consti- pation are the same. Some have slow transit while in others transit is normal. There are probably some patients with underlying irre- versible gut changes but our pathological techniques are not good enough to distin- guish 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 contractures, 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 treat- ment, such as surgery, is being contemplated after other treatments have failed. Even then we feel it does not have a proven role in predict- ing the outcome of surgery.

M A Kamm, A V Emmanuel
St Mark’s Hospital, Warrington Road, Harrow HA1 3UJ, UK

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

References
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 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 tendency towards increased survival after diagnosis of HCC has recently been observed, although the surveillance programme has not changed over the years (liver survival after diagnosis of HCC has recently improved). The question is whether patients have? A study 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 HCC and those who did not, thus emphasising the importance of residual liver function in relation to survival. Therefore, what probably lies beneath these findings is that improved medical therapy of the complications of liver cirrhosis, increased efficacy of HCC treatment, better management of treatment induced 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.

We recently performed a similar study in a cohort of hepatitis C virus positive cirrhotic patients. We compared clinical parameters, eligibility for treatment (32/33 v 18/27; p=0.003), number of patients in the former group who 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. This has led to the development of 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 XIV, No 6, 16132 Genoa, Italy. rtesta@unige.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 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, may cause 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 r² or an adjusted r² 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)” performing an adjusted analysis on 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, kfilio@pop.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 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, p53, and cytoketin, without statistical analysis.

H K Seitz
Salem Medical Centre, Heidelberg, Germany
Miotilin 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 ± 57 MD7 minutes) is remarkably outside the normal range reported using the gold standard scintigraphy (mean 110 ± 45 SEM minutes, 100th percentile 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. The study 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 therapy. 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. However, other prokinetics, including other motilin agonists, may be more 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 out of the 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 “gastroroposis” or dyspepsia as there are non-invasive approaches to study gastric emptying and accommodate gastrointestinal 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 or intrinsic nitrergic neuropathy). The 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 stressed 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 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 long-term 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

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 ‘published’ and elsewhere) 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. Cisapride relaxes the fundus 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 13C-octanoic acid breath testing, we believe that the data are not flawed. 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.

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. However, this is not 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 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 Verlinde
Department of International Clinical Research and Development, Janssen Research Foundation, Beerse, Belgium
Correspondence to: Professor N J Talley; ntalley@med.usyd.edu.au
ntalley@blackburn.med.usyd.edu.au

References

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.

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 the number of studies and remains a difficult issue. 2


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 enterologists managed only one third of patients with “shock/sepsis” as a common reason for admission and other data was to reflect the catchment area of our hospital. We noted that 20 of the 27 patients with “shock/sepsis” in the South 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 was due to shock/sepsis on occasion 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 of 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 aetiology 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 appropriate aminotransferase (ALT) levels 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 3.3, 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.
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 should be 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—only 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 with admission—most patients with intrinsic hepatico-pancreatic dysfunction did.

(5) Our observations on separate 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 range 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

J Hainsworth
Department of Pathology, Morriston Hospital, Swansea SA6 6NJ, UK

Correspondence to: Dr J G C Kingham; jkingham@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 insightul study on the stability of Crohn's disease phenotypes according to the Vienna classification 

I 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 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 invariably 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;
sachar@mountsinai.org

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 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 fibrotic 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 stricturing (Crohn's disease) 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 1–25 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 stricture disease without concurrent penetrating lesions do not tend to develop such lesions afterwards. Furthermore, in our population, only a few pure stricture lesions (B2) developed after 10 years of evolution. Therefore, in our experience, patients who develop a pure stricture 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 after 10 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 stricture phenomenon (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
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 de-mural 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 Tan 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 Hanauer (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—they themselves a world class troika of clinician researcher, pathologist, and surgeon—have recruited 38 renowned authors from top centers in the field. Secondly, they have constructed this monograph ingeniously. Each chapter title is 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

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.


