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.1-3 Mitchell et al have reported an association between tumour necrosis factor alpha promoter gene (TNFA) polymorphism at position −308 and PSC (Gut 2001;49:288-94). In this respect, increased distribution of the TNFα2 allele, in strong linkage disequilibrium with the HLA-A1/8/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 TNFA2 with PSC. This overrepresentation of TNFA2 was seen only in subjects with HLA-A1-B8-DRB1*0301, indicating that the observed association of PSC with TNFα2 might in fact be secondary to linkage disequilibrium within this haplotype.

Bernal and colleagues 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.12 This population of highly admixed origin with different percentages of Caucasoid, African, and Amerindian ancestry. 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 (25 males, mean age 34 (±11) years). Forty one patients had inflammatory bowel disease (IBD). None of the subjects, including all children, had any evidence of laboratory or histological features of overlapping syndromes of PSC and autoimmune hepatitis (AIH).

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=2.1) 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 TNFA2 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, TNFA*1 was also associated with HLA-DRB1*13 but not with the TNFA2 allele in Brazil.13 Of note, shared HLA antigens have also been associated with AIH type 1 and PSC in other populations.14 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.

| *Only 56 patients with PSC were typed for HLA-DQB1. Numbers in parentheses are percentages. |
|---|---|---|
| HLA-DRB1*03 | PSC patients (n=63) | Healthy controls (n=83) | p Value |
| DRB1*03 | 12 (19) | 23 (28) | 0.00009 |
| DRB1*13 | 33 (52) | 17 (20) | 0.0001 |
| DRB3 | 53 (84) | 62 (75) | |
| DQB1*02 * | 20 (32) | 41 (49) | |
| DQB1*06 * | 33 (59) | 34 (41) | 0.04 |
| TNFA1*/TNFA2 | 41 (65) | 63 (76) | |
| TNFA1*/TNFA2 | 21 (33) | 19 (23) | |
| TNFA2*/TNFA*2 | 1 (2) | 1 (1) | |
| TNFA2 allele carriage | 22 (37) | 20 (24) | |

References


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

Table 1

<table>
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<th>HLA-DRB1, DQB1 alleles and tumour necrosis factor alpha promoter genotype (TNFA) genotypes in patients with primary sclerosing cholangitis (PSC) and healthy controls</th>
<th>PSC patients</th>
<th>Healthy controls</th>
<th>p Value</th>
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<tr>
<td>TNFA2 allele carriage</td>
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</table>

*Only 56 patients with PSC were typed for HLA-DQB1. Numbers in parentheses are percentages.
Slow transit constipation: more than one disease?

Emmanuel and Kamm reported on the reaction of behaviour treatment, biofeedback, in constipated patients (Gut 2001;49:214–19). Biofeedback is an established therapy for outlet obstruction due to paradoxical anal sphincter contraction. Beyond that, Emmanuel and 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 enteric nervous system. Disturbances of oesophageal motility, gastric emptying, small bowel transit, and gall bladder motility have been described. Dysmotility of the small intestine has been thoroughly investigated by manometry in STC patients. Disturbled motility—for example, abnormal configuration or disturbed aboral migration of phase III of the migrating motor complex, bursts, and sustained uncoordinated activity—occur in up to 60% of these patients. In our recent study using long term small bowel manometry in 30 clinical STC patients, disturbed aboral migration of phase III was present in 79% of patients/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 effect in only 13% [1]. 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 explanatory mechanism 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 colonic marker accentuated delay. 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 obstructions, 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 to a second 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 influence of biofeedback therapy in patients with STC with and without small bowel pathomanometry.

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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 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. Behavioural treatment, which includes biofeedback, is a holistic treatment which we believe has both central and peripheral effects. Our study on the effects of biofeedback 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.

The existence of a panenteric disturbance of function, including the motor abnormalities described by Pehl et al, should not be interpreted as evidence of a neuropathy throughout the gut. We would disagree that these manometric findings are markers of neuropathy in patients with idiopathic constipation; they may be associated but causality has not been established.

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

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

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

We believe that too much emphasis should not be placed on different patterns of colonic delay, or the presence of disturbed pelvic floor function. We have shown that patients with different patterns of colonic delay, with or without 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 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.

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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 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 the 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, surveillance for hepatocellular carcinoma in liver cirrhosis 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 options.

However, it must be emphasised that HCC stage (parameter of the tumour) and residual liver function (parameter of the affected patient) are strongly related and influence each other, and that both can influence the choice of treatment and prognosis. Therefore, what should improve survival over the years is attributed to survival 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 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)”.

Fisher’s exact test. Moreover, we found that clinical status at diagnosis was better in the group under surveillance. This has likely changed both the type of patients who enter HCC surveillance studies and their therapeutic outcomes.

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, can leave the reader wondering if this sample is sufficient in size and power to adequately support the conclusions drawn from their regression analysis. Furthermore, by not reporting a 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)”.

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

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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 error 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 a cohort of 17 alcoholics and 14 age matched controls, various staining procedures were performed, including Ki67, Rb1, p21, p53, and cytokeratins, without statistical analysis.
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 130±50 recorded in healthy subjects (130±50 (SD7) minutes) is remarkably outside the normal range reported using the gold standard scintigraphy (mean 110±45 (SEM) minutes, 100±50 (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. It is claimed that the method used was validated in 19 diabetics in whom a significant correlation (r=0.73) was observed between scintigraphy and breath test data. Correlation does not equate to accuracy and, in a Bland-Altman or similar analysis, the gastric emptying data are suspect and cannot be used to classify patients to assess the relationship between symptoms and emptying or to address the role of baseline gastric emptying as a covariate in the response to treatment. It is also unclear if the study was sufficiently powered to appraise an effect of delayed gastric emptying on response to therapy, given the fact that only 29% of the study cohort were classified as having delayed gastric emptying. A type II error cannot be excluded.

Thirdly, the theoretical point is made by Talley 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 prove effective in the treatment of dyspepsia in diabetics with impaired gastric emptying.1

Fourthly, the observation that over time some of the symptoms continued to be aggravated and the aim 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 pharmacodynamics studies have an important role to play in the drug development process. This is especially relevant in the context of “gastroparis” or dyspepsia as there are no invasive approaches to study gastric emptying and postprandial symptoms, accommodation or tachyphylaxis. 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 observed by Talley et al., assessment of autonomic neuropathy requires a more formal assessment than the “opinion of the attending endocrinologist”. In fact, disturbances of the autonomic nervous system, evaluated with detailed tests, have been shown to significantly influence the symptom response to a prokinetic. Approaches that carefully characterise the drug before exposure of patients and selecting subgroups of patients after thorough understanding of the effects of the drug may save potentially effective medications from being abandoned. These patients may benefit from 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”.

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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.1 Our data (both in the text 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.2 Cisapride releases the fundus and improves 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 C13-octanoic acid breath testing, we believe that the data are 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 is an absence of reliable standardised reference methods for gastric emptying that can be applied in multicentre trials. However, we agree that it is optimal in prokinetic trials to test gastric emptying at baseline and on drug, and this should be the “gold standard”.

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

We stand by the study design used although further improvements are feasible. Phase 1 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
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.

They found that a number of interventions might reduce dyspepsia costs. 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 the intervention or to natural variation. Of particular interest is the proportion of admissions for Helicobacter pylori related peptic ulcer bleeds in west compared with east Gloucestershire.

The high prevalence of non-definitively treated H pylori associated peptic ulcer disease in primary care has been demonstrated in a number of studies and remains a difficult management issue. In Australia, in 1999 only 1.3% of all antilucer prescriptions were for H pylori eradication therapy.

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.

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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;49:409–13). 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 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 indicated 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 inpatient series demonstrated that 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 concerned that the intervention might have adverse effects on other health outcomes related to dyspepsia.

The authors also highlight the value of the aspartate aminotransferase:total bilirubin ratio in the assessment of such patients. In contrast with this, our inpatient series demonstrated that 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 concerned that 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 related peptic ulcer bleeds in west compared with east Gloucestershire.

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

References


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 poor ability of the step-down approach to relieve dyspepsia unless agents in this class with different physiological effects are developed.
a significant inpatient death rate (32% in Whitehead’s series and 19% in our own).

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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 correspondents 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 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 shared the 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, for in 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 and in most patients with intrinsic hepatocyte dysfunction did.

(5) Our observations on aspartate aminotransferase (AST):bilirubin ratios were of 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.

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Behaviour of Crohn’s disease according to the Vienna classification


We share Sachar’s concern for the stability categories. As to whether patients change categories over time. As emphasised by Sachar, it seems from our data that patients who are classified as B1 (non-penetrating) 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 strictureing 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 strictureing lesions (B2) developed after 10 years of evolution. Therefore, in our experience, patients who develop a pure strictureing disease over 10 years of evolution seem to represent a homogeneous phenotype that may be suitable for studies of genetic factors potentially involved in stricture development. However, this does not seem to be the case for penetrating disease (B3). In our patients, penetrating phenotypes continued to develop at a constant rate (approximately 25% of patients/five years), even after 20 years of evolution, mainly directly from the non-penetrating non-strictureting phenotype (B1). Therefore, the subgroup of patients with B1 phenotype who develop non-strictureting 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 without concurrent penetrating phenomena may be biologically and genetically very different from a patient who develops such lesions after 25 years. To some extent this point can also be applied to the strictureting phenotype (B2).

An alternative would be to take into account the speed of development of the B2 or B3 phenotype. Indeed, the inclination to develop such a phenotype is most probably multifactorial. We would be surprised if a 

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 characterisation. 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 environmental factors; (b) the genes involved have not yet been tested and it is true that only a small number of candidate genes have been tested in this setting; and (c) patients with Crohn’s disease have not been classified adequately into subphenotypes and, it is true that several classifications have been proposed and that the application of these various classifications does not result in homogeneous categories.

In relation to the first two hypotheses, progress in the understanding of the physiology and biology of stricturing and fistulising disease as well as 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 to whether 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 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 strictureing 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 strictureing lesions (B2) developed after 10 years of evolution. Therefore, in our experience, patients who develop a pure strictureing disease over 10 years of evolution seem to represent a homogeneous phenotype that may be suitable for studies of genetic factors potentially involved in stricture development. However, this does not seem to be the case for penetrating disease (B3). In our patients, penetrating phenotypes continued to develop at a constant rate (approximately 25% of patients/five years), even after 20 years of evolution, mainly directly from the non-penetrating non-strictureting phenotype (B1). Therefore, the subgroup of patients with B1 phenotype who develop non-strictureting 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 without concurrent penetrating phenomena may be biologically and genetically very different from a patient who develops such lesions after 25 years. To some extent this point can also be applied to the strictureting phenotype (B2).

An alternative would be to take into account the speed of development of the B2 or B3 phenotype. Indeed, the inclination to develop such a phenotype is most probably multifactorial. We would be surprised if a
when it comes to new multitutor 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 syndrome”, “Celiac disease” and “Food allergy”. It seems to fall somewhere between a textbook and a multiauthored collection; it is not suitable for undergraduates and it is not the book to reach for when faced with a difficult clinical problem. The layout and contents suggest an assumption of 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 cover to cover. However, I would not go as far as Sydney Smith, cleric and wit, who committed suicide by consuming a whole book in one sitting. “Your enemies at the Christmas party), along 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 polypl. 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 appearance, and some of the 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.

**Upper Gastrointestinal Surgery, 2nd Edn**


The Companion to Specialist Surgical Practice series aims to meet the need of higher surgical trainees and busy practising surgeons by keeping them up to date of recent developments in the field and secondly to provide a sound 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 main contributions of the first established figures in the field of upper gastrointestinal surgery and bring an authoritative viewpoint to each chapter. The format is pleasing with
The evidence in ways that allow each chapter analyses of “the most recently available received from their authors highly critical volume, the editors have demanded and a final chapter tackles the subject of some treatments are worse than the disease); cancer surveillance; two pertain to long term management, including medical, nutritional, and deal with diagnosis and assessment; the large, aetiological, and pathogenetic issues; two to 1999). Six chapters address epidemiological are pertinent and up to date (at least through ined critically with scores of references that tres 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 work, the editors have demanded and received from their authors highly critical analyses of “the most recently available evidence”. The authors analyse and interpret the evidence in ways that allow each chapter to reach reasonably well founded conclusions.

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

In the sections of 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 conclusions, and then offers specific recommendations. The issue being so contentious, 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.

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.”

M Winslet

Challenges in Inflammatory Bowel Disease


This latest entry into the inflammatory bowel disease textbook sweepstakes is intended neither as a comprehensive reference work nor as a guide to everyday management. This description 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). The current volume, rather, adopts a self 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). The current volume, rather, adopts a self-categorised approach to the field. 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—their world class trio of clinician researcher, pathologist, and surgeon—have recruited 38 renowned authors from top centres across 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.

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D Sachar

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:

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• 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.
Reducing dyspepsia costs in the community

A Duggan and J Westbrook

Gut 2002 51: 613
doi: 10.1136/gut.51.4.613

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