PostScript

LETTERS

Novel presentation of coeliac disease after following the Atkins' low carbohydrate diet

Low carbohydrate diets are currently being promoted as an effective treatment for weight reduction.[1] The most popular, the Atkins' diet, is a worldwide bestseller with over 10 million book copies sold (the earliest being *Dr Atkins' New Diet Revolution*[2]). Two randomised clinical trials in obese patients have shown effective weight loss at six months on the Atkins' diet compared with a low fat calorie reduced diet although the difference was not significant or sustained at 12 months.[3 4] The Atkins' diet recommends unlimited protein and fat intake, with carbohydrate intake initially restricted to 20 g/day (5–10% of daily calorie intake), mainly as salad greens and other non-starchy vegetables. In the longer term maintenance phase, the diet remains low in cereal grains (wheat, rye, and barley), which are toxic in coeliac disease.

We report three patients seen in the last year who sought medical advice because of symptoms noticed after stopping the Atkins' diet, which subsequently proved to be due to coeliac disease.

Case No 1

A 46 year old woman, with coexisting treated primary hypoadrenalism and autoimmune hypothyroidism, followed the Atkins' dietary regimen strictly as published. She described ''feeling amazing'' and ''wide awake'' on the regimen. After six months she lost 12 kg and decided to reintroduce bread. She soon noticed bloating, tiredness, and upper abdominal pain. Her physician suspected coeliac disease and initiated testing for antiendomysial antibody (positive), with subsequent diagnostic duodenal biopsy (crypt hyperplastic partial villous atrophy). All symptoms resolved on a gluten free diet.

Case No 2

A 45 year old woman, with coexisting treated autoimmune hypothyroidism, followed the Atkins' diet strictly as published for three months, losing 7 kg. On this regimen she described feeling ''really well'' and ''fantastic''. On reintroducing bread she noticed symptoms of tiredness, abdominal gurgling noises, and pain, and increased flatulence. Her father was diagnosed with coeliac disease around this time. These symptoms led her to suspect coeliac disease. Subsequent tests showed positive antiendomysial antibody and small intestinal crypt hyperplastic partial villous atrophy. Her symptoms resolved on a gluten free diet.

Case No 3

A 43 year old woman who commenced a low carbohydrate diet (cutting out bread, pasta, potatoes, and rice but including fruit and vegetables) noticed increased wellbeing on this regimen. She reintroduced some bread at one month and noticed abdominal bloating and pain, with increased tiredness. These symptoms led her to suspect coeliac disease. Her physician found iron deficiency anaemia and subsequent tests showed positive antiendomysial antibody and small intestinal crypt hyperplastic partial villous atrophy. Her symptoms resolved on a gluten free diet except for occasional abdominal bloating.

Recent large studies (using highly sensitive and specific serological screening tests) have suggested coeliac disease is much more prevalent (~1%) in the UK population than previously recognised.[5 6] In addition to those symptoms presenting clinically, untreated coeliac disease has silent features, including anaemia, osteoporosis, and modest increases in overall risks of malignancy and mortality.[7] In a recent prospective study of seven year old children, those with positive coeliac serology were significantly shorter and lighter.[5] Awareness of coeliac disease has recently been increasing, and all major UK supermarket chains now stock a varied range of gluten free products.

Symptoms induced by wheat ingestion in coeliacs are often more marked after a period following a gluten free diet than occur prior to diagnosis and treatment. Consistent with this observation, interferon γ peripheral blood T cell responses to the immunodominant A-gliadin epitope (QLQPFPQPELPYPQPQS) after short term oral gluten challenge are not observed in untreated coeliac cases but are detectable in significant numbers after two weeks of a gluten free diet.[8 9] The immunological basis of the heightened sensitivity after gluten withdrawal is unknown but intestinal immune responses to antigen are likely to be downregulated in conditions of ongoing chronic inflammation compared with those occurring in normal (treated) mucosa.

Although some individuals will have simple wheat intolerance, we conclude that the occurrence of gastrointestinal symptoms after a period following an Atkins-type low carbohydrate diet should prompt investigation for coeliac disease.

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Cap polyposis: an inflammatory disorder or a spectrum of mucosal prolapse syndrome?

We read with great interest the letter by Maunoury and colleagues (*Gut* 2005;**54**:313–14). They reported on a case of cap polyposis unresponsive to infliximab, in contrast with the successful report by Bookman and colleagues.[1] Maunoury *et al* stated that the success with infliximab reported by Bookman *et al* might have been due to spontaneous regression of cap polyposis. Maunoury *et al* speculated that a role for tumour necrosis factor α (TNF-α) in the pathogenesis of this rare disorder was unacceptable and other mechanism, such as abnormal colonic motility, may be important.

The pathogenesis of cap polyposis has been controversial. In particular, there have been discussions about whether cap polyposis is a specific form of inflammatory disorder or part of a spectrum of ''mucosal prolapse syndrome'' which is caused by abnormal colonic motility with subsequent local ischaemia and repeated mucosal trauma. We recently experienced a case of cap polyposis, highly suggestive of a role of inflammation in the progression of this disease.[2]

A 76 year old Japanese woman was diagnosed as having cap polyposis, with typical colonoscopic findings of multiple sessile polyps covered with caps of fibrinopurulent exudates throughout the total colon. Histological findings were also compatible with the disease. She had no history of straining during defecation, and an anorectal motility study was normal. Concomitantly, she had a 5 cm villous adenoma in the sigmoid colon, and underwent laparoscopic sigmoid colectomy for resection of the adenoma. Follow up colonoscopy three months after surgery revealed almost complete spontaneous remission of the cap polyposis throughout the residual colon, except along the anastomotic line where there was confined progression of multiple polyps (fig 1).

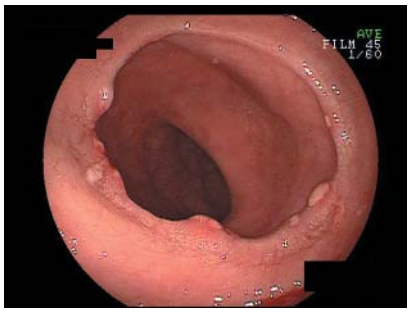

Figure 1 Endoscopic view of progression of cap polyposis confined along the anastomotic line three months after surgery. Note remission on the adjacent mucosa.

Although the polyps were located in a line on the anastomosis, the adjacent mucosa was normal. She showed no clinical symptoms at that point and so no additional treatment was performed.

Two cases of recurrent cap polyposis after colorectal resection have been reported previously,[3 4] of which one was very similar to the present case in that the recurrent polyps were located only along the anastomotic line.[4] The process of wound healing on the anastomosis is known to involve a complex network of numerous inflammatory cells and their secretory products, including TNF-α, which accelerates the wound healing process by inducing angiogenesis, fibroblast proliferation, and production of several growth factors.[5–7] Therefore, progression of cap polyposis confined along the anastomotic line observed both in the present case and in the report mentioned previously[4] may provide evidence that local inflammation plays, at least in part, a role in the progression of cap polyposis. With acceptance on this point, suppression of inflammation could be a clue to treat cap polyposis, as in the case of metronidazole whose anti-inflammatory action plays a central role in the healing of cap polyposis.[8]

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Conflict of interest: None declared.

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Chronic intestinal pseudo-obstruction due to lymphocytic leiomyositis: is there a place for immunomodulatory therapy?

There is a rare cause of chronic intestinal pseudo-obstruction (CIPO) characterised by a lymphocytic infiltrate in the muscle of the intestine, which is called idiopathic lymphocytic leiomyositis. Few cases have been reported and prognosis is very poor. We present a case with a comparatively benign evolution, showing good response to immunosuppressive therapy.

The patient was a healthy 16 year old female who presented with a crisis of postprandial bloating followed by diarrhoea and vomiting. During the following months she lost 10 kg in weight and any attempt at oral feeding resulted in severe abdominal distension and vomiting. Therefore, total parenteral nutrition was finally prescribed. Plain abdominal film and small bowel follow through indicated huge dilatation of the small intestine with air fluid levels. Gastroscopy and colonoscopy were normal, as were mucosal biopsies.

Human immunodeficiency virus, hepatitis A, B, and C virus, cytomegalovirus, *Salmonella*, *Leptospira*, *Coxiella*, *Borrelia burgdorferii, Treponema pallidum,* faecal cultures and parasites, tuberculin skin test, and cultures for *Mycobacterium tuberculosis* were all negative, as were autoimmune markers.

Intestinal manometry showed severe hypomotility in the duodenum and jejunum. Laparotomy was performed, showing a very dilated small intestine and colon, plenty of liquid, with thinned walls. Full thickness intestinal biopsies were taken.

Histologically, the intestinal mucosa and submucosa were normal. Both muscle layers presented with a heavy diffuse lymphocytic infiltrate (fig 1), composed of small CD3 and CD8 lymphocytes (no CD20). Muscular fibres were atrophic with some fibrosis. The submucosal and myenteric plexuses were normal and the muscularis mucosae was not affected. Immunohistochemical stain for smooth muscle actin was negative or faintly positive in the muscularis propria, with preservation of a thin ribbon at the innermost portion of the circular layer. A final diagnosis of lymphocytic intestinal leiomyositis was made.

The patient started prednisone 1 mg/kg/day and azathioprine 1 mg/kg/day. She was hospitalised for eight months during the first year due to multiple complications. Complete response was not obtained until one year later when the azathioprine dose reached 2 mg/kg/day, and budesonide 9 mg/day was added. Prednisone was then discontinued and abdominal films became normal.

Two years after diagnosis she has not needed hospitalisation or parenteral nutrition in the last 15 months, and has followed a normal oral diet.

Review of the world literature on CIPO associated with lymphoid infiltrates in the gut revealed only 12 cases, as shown in table 1. A critical review could restrict the number to three, plus the present case, as true lymphocytic enteric leiomyositis.

McDonald's[1] and Arista-Nasr's[2] cases showed predominantly mucosal infiltrate with secondary extension into deeper layers.

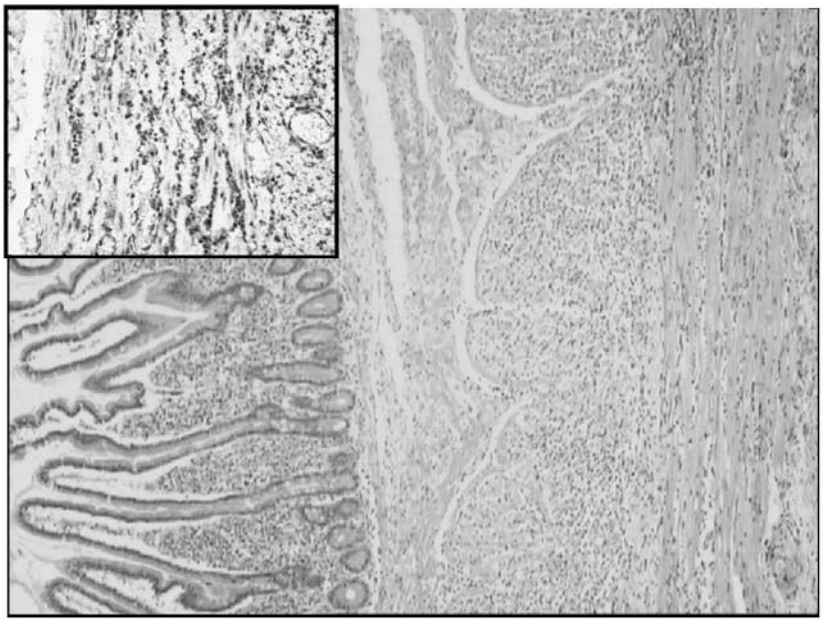

Figure 1 Full thickness biopsy of the small intestine with haematoxylin-eosin. The section shows a normal mucosal layer of jejunum without atrophy or excessive amounts of round cells. The muscularis mucosae is also normal. In contrast, the muscularis propria shows a heavy lymphocytic infiltrate (haematoxylin-eosin). Insert: immunohistochemical stain for CD8 lymphocytes in the muscularis propria.

Table 1 Clinical and histological features of our present case and cases in the literature

	Sex/age (y)	Histological features	Treatment	Evolution	True lymphocytic intestinal leiomyositis
Present case	F 16	T lymphocytic infiltrate in muscularis propria	Steroids and later budesonide. Azathioprine	Mild symptoms, oral nutrition 2 y later	Yes
Nezelof[5]	M 6 mo	Mononuclear infiltrate in muscularis propria	Steroids	Death 4 y later	Yes
Ruuska[6]	M 2	Predominant T lymphocytic infiltrate	Steroids, azathioprine, ciclosporin	Total PN	Yes
Mann[7]	M 47	Chronic inflammatory infiltrate + fibrosis of longitudinal muscle	NR	Death 2 y later	Probably yes
Rigby[3]	F 27	Predominant fibrosis of the circular layer	Immunosuppression	Oral diet plus gastrostomy feeds. Alive at 21 months	Probably no
Giniès[4]	F 6 mo	Very polymorphic infiltrate: lymphocytes, plasmocytes, histiocytes, and eosinophils	Steroids	Oral nutrition. Normal weight and height	No (probably B lymphocytes)
McDonald[1] cases 1/2/3/4	F 51/F 21/ F 29/F 18	Mucosa predominantly affected	Cyclophosphamide and steroids/steroids/ antibiotics/cisapride	Mild symptoms at 9 y/PN one year later/NR/NR	Probably no (B lymphocytes)
Arista-Nasr[2] cases 1/2/3	F 23/F 29/ F 23	Mucosa predominantly affected	Cyclophosphamide/ tetracycline, tinidazol, PE/ tetracycline, steroids, chemotherapy.	Death from inanition/ death from inanition/alive, severe inanition	Probably no (B lymphocytes)

M, male; F, female; NR, not reported; PN, parenteral nutrition; PE, pancreatic enzymes.

Our case showed a particularly affected muscle with a respected mucosa. In Rigby's case,[3] the muscular layer seemed to show fibrosis rather than inflammation. Our case showed a homogeneous lymphocytic T infiltrate which is different from the polymorphic infiltrate of Giniès' case.[4]

We believe that only the cases presented by Nezelof,[5] Ruuska,[6] and perhaps Mann's[7] fourth case, are truly similar to ours. The lymphocytic infiltrate was similar and there were degenerative changes of the smooth muscle. Clinically, these three cases shared a very poor prognosis: two patients died and one was on parenteral nutrition, despite immunosuppressive therapy. This treatment was employed in at least two of the patients. Our case had a better outcome, with azathioprine and budesonide allowing discontinuation of prednisone.

In CIPO, if full thickness biopsies[8] are typical of lymphocytic leiomyositis, based on what little information is available, it is reasonable to start high dose steroids and another form of immunosuppression. Based on our case, we would recommend budesonide 9 mg/day and azathioprine 2 mg/kg/day while tapering off conventional steroids, if clinical response continues.

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UK guidelines for management of acute pancreatitis: is it time to change?

The incidence of acute pancreatitis is increasing in the UK,[1] with a current hospital admission rate of 9.8 per year per 100 000 population.[1] However, there has only been a marginal decrease in the overall one year case fatality rate, from 12.7% in 1975–86 to 11.8% in 1987–98.[1] Gall stones and alcohol are the main aetiological factors for acute pancreatitis.[2] Nearly 25% of episodes of acute pancreatitis are severe[3] and approximately 45% of these are due to gall stones.[2]

The UK guidelines for the management of acute pancreatitis were formulated and released by the British Society of Gastroenterology (BSG) in 1998.[4] MEDLINE, EMBASE, and the Cochrane databases were searched to find recent evidence in the management of acute pancreatitis. The search terms included pancreatitis (MeSH), sphincterotomy-endoscopic (MeSH), cholangiopancreatography - magnetic - resonance (MeSH), acute NEAR pancreatitis (text), MRCP (text), ERCP AND sphincterotomy (text).

A management plan, modified from the BSG guidelines in light of the new evidence available since its release in 1998, is proposed in fig 1. Firstly, acute pancreatitis is stratified according to severity. Glasgow-Imrie scoring together with C reactive protein are recommended by the BSG for stratification of severity of acute pancreatitis.[4] However, with the availability of one stop tests, such as urinary trypsinogen activation peptide,[5] and with the likelihood of mild acute pancreatitis transforming into severe acute pancreatitis being rare,[6] severity stratification of pancreatitis can now be performed on admission.

The next step is to determine aetiology. Imaging to find aetiology should be performed within 24 hours, in contrast with the BSG recommendations of a CT scan between three and 10 days. The rationale behind imaging within 24 hours is to facilitate early endoscopic retrograde cholangiopancreatography (ERCP) and sphincterotomy, as there is strong evidence that ERCP and sphincterotomy performed less than 72 hours decreases the complication rate in acute severe gall stone pancreatitis.[7] This imaging, within 24 hours during the acute resuscitation phase, is made possible because of the shorter time to perform spiral computed tomography (CT) of the abdomen,[8] which has a high sensitivity and specificity in diagnosing choledocholithiasis.[9] If the aetiology is still unknown after the CT scan, a magnetic resonance cholangio(pancreato)-gram (MRCP) may be performed, as this has a higher sensitivity than the CT scan in the diagnosis of choledocholithiasis.[10]

A simple calculation based on the incidence of pancreatitis (9.8 per year per 100 000 population),[1] the incidence of severe pancreatitis (approximately 25%),[3] and the incidence of gall stones as the aetiological factor in acute severe pancreatitis (45%)[2] reveals that severe acute gall stone pancreatitis has an incidence of approximately 1.1

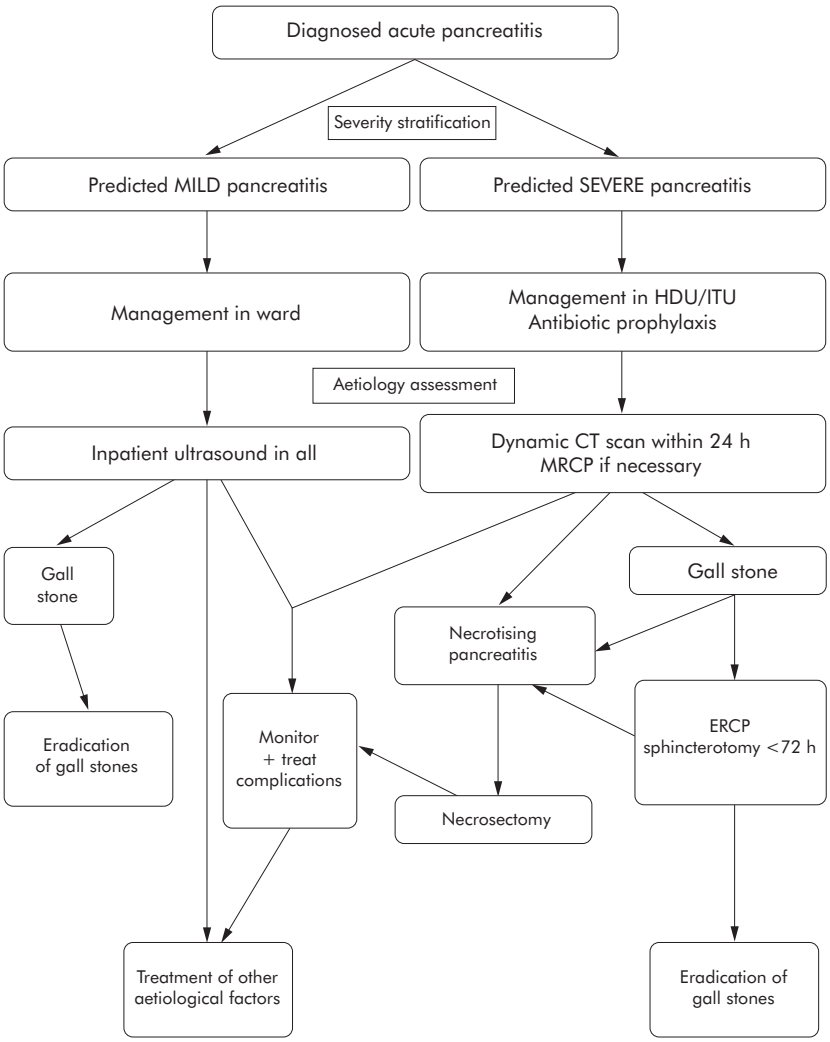

Figure 1 Algorithm for the management of acute pancreatitis. MRCP, magnetic resonance cholangiopancreatography; ERCP, endoscopic retrograde cholangiopancreatography; CT, computed tomography; HDU, high dependency unit; ITU, intensive therapy unit.

per year per 100 000 population. In a NHS trust with a catchment population of 500 000, it is only five additional emergency ERCP with sphincterotomies annually. This appears to be a feasible option. However, if ERCP with sphincterotomy cannot be performed within 72 hours in a hospital, patients should be transferred early (after stabilising the vital signs) to a hospital where such facilities are available.

In conclusion, a review of the UK guidelines is recommended following evidence that morbidity is less in early ERCP and sphincterotomy (<72 hours) in severe gall stone pancreatitis. Also, because of the accuracy of MRCP in the diagnosis of choledocholithiasis and the new one stop tests available for severity stratification of acute pancreatitis on admission, we recommend one stop tests for severity stratification of pancreatitis and imaging within 24 hours of admission in acute pancreatitis in order to find the aetiology so that ERCP and sphincterotomy can be performed within 72 hours.

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RANK ligand and osteoprotegerin: emerging roles in mucosal inflammation

We read with interest the study by Byrne and colleagues (*Gut* 2005;**54**:78–86) outlining the significant therapeutic opportunities provided by manipulation of the RANK/RANK ligand (RANKL)/osteoprotegerin (OPG) system using recombinant Fc-OPG. There are, however, a number of physiological effects of OPG that were not discussed and which demonstrate the depth of influence of the RANK/RANKL/OPG system on both inflammatory disease and possibly immune surveillance mechanisms. These additional actions may provide both novel therapeutic approaches in inflammatory disease and point to other clinical effects of the Fc-OPG construct.

Work published by our own group[1] studying the interleukin 2 deficient mouse model of inflammatory bowel and bone disease, using identical doses of Fc-OPG to Byrne *et al*, demonstrated the effects on gut inflammation, dendritic cell (DC) numbers, and macrophage (Mø) activation, as analysed by both colonic histology and flow cytometry. In the April issue of *Gut*, Moschen and colleagues (*Gut* 2005;**54**:479–487) showed that OPG can be demonstrated on both DC and Møs, also indicating that the molecule has the potential to influence these cells. These observations are in keeping with previous publications which have outlined the role of the RANK/RANKL/OPG system in DC survival, function, and the development of antigen specific memory T cell responses.[2] Hence modulation of inflammatory responses in the gut using Fc-OPG could theoretically provide both direct treatment for gut inflammation alongside the associated bone loss described by Bryne *et al*. OPG has also been shown to influence TRAIL mediated signalling[3] which may also impact on the DC microenvironment, preventing DC death, but more significantly has shown effects in prevention of TRAIL induced apoptosis in a number of tumour types.[3 4]

These findings highlight the fact that OPG can significantly influence survival of different cell types and the full extent of the actions of Fc-OPG in vivo are undoubtedly still yet to be shown.

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Synbiotic therapy for ulcerative colitis

We read with interest the article by Furrie and colleagues (*Gut* 2005;**54**:242–9). While we believe this approach represents a very interesting advance in our understanding of aspects of the mucosal response to synbiotic therapy in ulcerative colitis (UC), we would like to raise some questions about the design of the study, which relate in particular to the conclusion that the synbiotic cocktail produces some improvement in disease activity in UC.

Five patients were taking steroids, and six patients were taking immunosuppressants in each of the active treatment and placebo groups (see table 2). While the study design states that no treatment changes were made once the patients were started on test therapy, no information is given as to whether either the steroids or immunosuppressants were started, or had their dose changed, in the period immediately before the test therapy began. Given that the lag between recruitment and initiation of the test treatment was up to two months, we need reassurance that no treatment changes were made during this period that could have contributed to the later clinical and histological changes associated with the test therapies.

Two of the outcome measures seem to have been scores of sigmoidoscopic appearance and microscopic disease activity, which have not been previously validated formally. Can we be reassured that the conclusions drawn from these results would have been the same had the authors used an unmodified Baron sigmoidoscopic score,[1] and a more widely used histological activity index?[2] Indeed, we note that there were in fact no significant changes after the symbiotic therapy in either the simple colitis activity index, sigmoidoscopic score ($p = 0.06$, using a *t* test which assumes normal distribution), bowel habit index, or histological score.

During the lag period between enrolment in the trial and initiation of the test treatment, one patient in the placebo group went into spontaneous remission (SCAI 1, modified Baron score 0) and so no longer fulfilled the entry criteria for the study. However, this subject still appears to have been included in the evaluation of the response to placebo and hence may have skewed the results for this group.

The authors reported a significant reduction in expression of mRNA for human beta- defensins 2–4 and the inflammatory cytokines tumour necrosis factor α and interleukin 1α in mucosal biopsies. It is of course possible that these changes might be associated with subsequent clinical, sigmoidoscopic, and/or histological improvement, but we would question whether the data presented convincingly show initiation of the resolution of inflammation stated in the title. We agree with the authors that a much larger scale randomised controlled clinical trial of this synbiotic cocktail is needed, using conventional and well validated measures of response, before we can draw firm conclusions about its efficacy (or safety).

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Deranged smooth muscle α-actin expression as a biomarker of intestinal pseudo-obstruction

We read with interest the article by Knowles and colleagues (*Gut* 2004;**53**:1583–9) in which the authors concluded that immunostaining of the adult jejunum with smooth muscle α-actin (ASMA) may be a valuable biomarker of chronic idiopathic intestinal pseudo-obstruction (CIIP). We recently published a similar study in which 17 archival formalin fixed, paraffin wax embedded samples of small intestine and 12 samples of large intestine were immunostained with ASMA, desmin, and smooth muscle myosin heavy chain, using the same antibody for ASMA as Knowles and colleagues.[1] In two of the three cases investigated in our study, ileal samples were examined from patients with clinical evidence of intestinal pseudo-obstruction. We found that both of these CIIP cases and all 15 control ileal samples showed weak or absent ASMA expression within the inner circular layer of the muscularis propria, with an identical pattern to that identified within the case and control ileal samples examined by Knowles *et al*.

Knowles *et al* found that 24% of CIIP cases showed absent or partial inner circular muscle ASMA expression within the jejunum while this pattern was not identified in any control jejunal samples. However, in the ileum, absent or weak ASMA expression was universal in their controls and present in 69% of CIIP cases.

It is possible that absent or weak inner circular muscle ASMA expression within the jejunum may represent a biomarker of CIIP. However, the universal incidence of this phenomenon within the ileum in both studies and its presence at this site in a greater proportion of controls than cases, according to Knowles *et al*, indicates that ASMA expression should be interpreted with caution in these patients. In particular, although Knowles *et al* suggest that this phenomenon may be a biomarker of CIIP when identified within the jejunum, a definitive study of the geographical variation in ASMA expression within the muscularis propria of the small intestine is now indicated to determine the precise significance of this finding. The observation that manometric studies have shown pressure tracing patterns more suggestive of a neural defect than a primary muscular abnormality in most CIIP patients casts further doubt on the biological significance of apparent alterations in ASMA expression.

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Inflammatory biomarkers predict relapse in IBD

After reading the paper presented by Costa *et al* (*Gut* 2005;**54**:364–8) and the additional commentary by Pardi and Sandborn (*Gut* 2005;**54**:321–2), we would like to underscore the potential importance of biomarkers to assess intestinal inflammation and we would like to add a clarification on the faecal calprotectin assay.

We agree with Pardi and Sandborn that other serological markers have not demonstrated clinical utility as predictors or monitoring tools of inflammatory bowel disease (IBD) activity.[1] Studies are emerging to support the sensitivity and clinical utility of more selective and specific non-invasive markers of intestinal inflammation, such as faecal calprotectin.[2 3] As we deepen our understanding of the molecular basis of IBD, we may find that the degree of inflammation and its role in recurrence differs between Crohn's disease and ulcerative colitis. This is an important question raised in both articles.

When comparing the Costa study with the earlier paper by Tibble and colleagues,[4] one must ensure that the patient populations for each of the two disease states are equivalent. Disease activity was assessed by the Crohn's disease activity index (CDAI), a test that is highly subjective and correlates poorly with inflammatory activity assessed by In^{111} labelled white cells and endoscopic indices, both objective markers of disease activity. It is also clear from a recent analysis by Sands and colleagues[5] that there is wide variation in how researchers apply the parameters of the

CDAI. Saverymuttu[6] compared the excretion of In^{111} labelled leucocytes and found that the CDAI underestimated the degree of inflammation in 89% of patients with a CDAI <150 (that is, in clinical remission). This suggests that the CDAI does not necessarily reflect the inflammatory component of IBD.

In the Costa study (an unusually high) 71% of Crohn's patients had small intestinal disease alone, with only 31% having ileocolitis or colitis. These values are compared with 47% and 53%, respectively, in the Tibble study. Thus we see different cohorts of Crohn's patients being evaluated in the two, apparently similar, studies. Given the significant variability in CDAI, lack of correlation of CDAI with inflammation, and unmatched patient cohorts, it is not surprising that there is a difference in the results of the Costa study in comparison with Tibble's previous trial.

Both studies (Tibble and Costa) demonstrate the clinical utility of faecal calprotectin in predicting remission in ulcerative colitis. Neither study makes clear the ability of biomarkers to predict remission in small bowel Crohn's. CDAI as a marker of remission adds further confusion. The level of inflammatory biomarkers may vary anatomically, based on neutrophilic flux, chemotaxis, surface area, and disease process. Saverymuttu[6] found higher levels of In^{111} labelled leucocytes among large bowel Crohn's compared with Crohn's in the small bowel. Assessment of calprotectin as a predictor of relapse in small intestinal Crohn's is an issue for future investigation, utilising objective evaluation of intestinal inflammation.

Finally, in addition to potential selection bias in the specificity and predictive value of calprotectin in small bowel Crohn's disease, there is also an important misunderstanding regarding assay performance that should be clarified. The studies published by Tibble and colleagues[2 4] and most studies reported before 2003, evaluated faecal calprotectin using an earlier stool extraction process.[7] The anti-calprotectin antibodies used in the earlier assay come from the same source. Eurospital has since developed an ELISA kit using the new extraction procedure and known calprotectin standards. The updated extraction process gives a five times higher yield during extraction of faecal calprotectin[8] but does not change the performance of the kit in any other way. Thus the results in the Costa study should be effectively compared with a calprotectin cut off point of 250 mg/l, correcting Pardi and Sandborn's puzzlement regarding the decline in NPV differences as the calprotectin cut off point ''appeared'' to decrease. Effective translation of values from the older calprotectin literature will help to clarify any confusion about the meaning of a given value. The new extraction process effectively removes nearly 100% of the calprotectin protein from the cytosol of neutrophils, thus maximising its sensitivity and reproducibility as a marker of intestinal inflammation.[9]

We encourage a broader use of these biomarkers as a clinical end point in future studies of the natural history and treatment of IBD.[10] The role of inflammatory biomarkers in mucosal healing will be an important parameter to evaluate effective treatment for IBD.[11] We thank the authors for their commitment to, and input in, this important effort.

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Colitis evolving into ulcerative colitis

We observed the development of ulcerative colitis (UC) in a 37 year old young woman with clinical and histological features of lymphocytic colitis (LC) after a period of six years. Seven years ago, the patient was admitted to our gastroenterology unit complaining of watery diarrhoea (≥6 stools/day). She had never smoked and she was not taking any drugs affecting gastrointestinal secretion or motility. Laboratory tests, including autoimmune antibody and upper endoscopy, were normal. Parasitological and bacteriological faecal stools were negative. Biopsies of the jejunum did not show a pattern of coeliac disease. Colonoscopy with terminal ileoscopy was macroscopically normal. Ten biopsy specimens were taken from the rectum, revealing the histological pattern of LC (intraepithelial lymphocytes 41/100 epithelial cells, inflammation in the lamina propria, and surface epithelial changes consisting of degeneration). 5-ASA therapy (2.4 g/day) was administrated for 24 weeks. Within the first two weeks of treatment the patient experienced clinical remission (≤2 stools/day). At end of therapy the patient underwent colonoscopy and 10 biopsy specimens were taken from the rectum. At histology we observed complete regression of the inflammatory cells (intraepithelial lymphocytes ≤10/100 epithelial cells) and restoration of the surface epithelium. In this way we obtained complete control of symptoms. Colonoscopy with biopsies of the rectum was repeated every year, confirming remission of the disease.

After six years the patient experienced abdominal pain and bloating with progressive worsening of diarrhoea. The stools became watery, sometimes bloody, and frequency was up to 8–10 times/day. She denied intake of non-steroidal anti-inflammatory drugs, ASA, or estro-progestinic therapy. Parasitological and bacteriological faecal stools were negative. Colonoscopy was performed and revealed a micro granularity of the rectal mucosa with oedema and hyperaemia, and several erosions of the left colon were noted. No other lesions were found on the remaining colon or terminal ileum. Biopsies were taken and histology showed a moderately active ulcerative colitis. Laboratory tests were consistent with an elevated white blood cell count and increased inflammatory parameters. The patient was treated with oral prednisolone and 5-ASA (4.8 g/day). Complete regression of symptoms was obtained after two weeks of treatment. The patient continues to be in remission 18 weeks after the initial diagnosis of UC. She is still receiving 2.4 g/day 5-ASA, and oral prednisolone has been discontinued, with maintenance of resolution of symptoms.

In the literature, four cases of collagenous colitis (CC) evolving into UC have been reported[1–4] and two cases that developed into Crohn's disease.[4 5] This is the first case of LC evolving into UC. These phenomena suggest that both CC and LC could be part of a spectrum of inflammatory bowel diseases. The triggering factor in this transformation is still unknown. UC should be considered in patients with LC if they develop acute changes in their clinical course, with bloody diarrhoea and systematic features of UC.

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Is there an ideal prognostic model for hepatocellular carcinoma?

We read with interest the paper by Grieco *et al* (*Gut* 2005;**54**:411–8). It is an elegant study that retrospectively compared the prognostic power among the Okuda, Cancer of the Liver Italian Program (CLIP), and Barcelona Clinic Liver Cancer (BCLC) staging systems for patients with hepatocellular carcinoma (HCC). The authors concluded that BCLC and CLIP were good models for non-surgical HCC, and BCLC had better predictive value compared with the others for patients with early stage HCC. As the CLIP system has been prospectively validated and proposed as the primary staging system for HCC,[1] it would be interesting to examine how these commonly used HCC staging systems were derived and explore the potential limitations of the authors' conclusions.

The main reason why the authors have reached this conclusion is probably related to the distinct characteristics of the study population, as the majority (249/268; 93%) had undergone active treatment (percutaneous ablation or arterial chemoembolisation), suggesting most had early or intermediate stage disease. These characteristics made the BCLC system, which contains treatment derived parameters,[2] a prevailing model for prognostic prediction. A recent study comparing the various staging systems consistently showed that BCLC was best compared with CLIP, Okuda, and other systems in a surgically oriented referral centre.[3] It should be noted that the CLIP and Okuda systems were originally derived from a large unselected patient population and the majority had been treated conservatively.[4 5] Therefore, although the prognostic predictors selected for the currently used staging systems are not mutually exclusive, the derived predictive models from these predictors may have an otherwise variable differentiation power. Certain important risk factors, such as tumour size <3 or 5 cm, used in BCLC, can only be significant in the patient population that predominantly undergo active locoregional therapies.[6 7] In these instances, the predictive power of a given staging model, constructed from selected risk factors, could be drastically impaired if the majority of patients do not have early stage HCC. Such an effect may explain why the BCLC system is better than the CLIP and Okuda systems in the current study because clinical outcome was intimately associated with patient demographics and subsequent treatment strategy. Consistent with this notion is that a Canadian study group demonstrated that CLIP was a good predictive model for their HCC patients in whom more than half (52%) had only been treated conservatively due to a relatively advanced tumour or cirrhotic stage.[8] Therefore, it is not surprising that BCLC is better that its competitors in an appropriate study environment.

In summary, the BCLC system contains treatment derived parameters and may work well in areas where HCC is diagnosed at a relatively early stage, whereas the CLIP or Okuda system would only prevail in patients with intermediate or late stage disease, under which conditions any aggressive forms of therapy are less likely to succeed. As the clinical presentation of HCC is tremendously heterogeneous, it is necessary to consider all known predictive factors, from early to advanced stages, in building an ideal staging system to fit all patient populations.

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Response to steroid therapy of sclerosing cholangitis after duodenopancreatectomy due to autoimmune pancreatitis

Autoimmune pancreatitis is a chronic inflammation of the pancreas due to aetiopathogenic mechanisms of autoimmunity. There are no established definitive diagnostic criteria although histological, analytical, and radiological characteristics enable us to identify this entity in the differential diagnosis with chronic alcoholic pancreatitis and cancer of the pancreas.[1–3] Nevertheless, this is not always possible, and the patient undergoes surgery with suspected cancer of the pancreas. Lymphoplasmacytic infiltration and the autoimmune response do not only affect the pancreas but can occasionally involve the retropancreatic and extrapancreatic biliary system. The relationship between the appearance of sclerosing cholangitis in patients with pancreatic pseudotumour due to autoimmune pancreatitis has even been considered the result of a systemic fibroinflammatory response.[1 4] We present the exceptional case of a patient who, after a cephalic duodenopancreatectomy due to pancreatic pseudotumour, in lymphoplasmacytic pancreatitis, presented with a clinical-radiological picture of post-surgical sclerosing cholangitis, which resolved after therapy with steroids. In common with Kamisawa and colleagues,[4] we consider autoimmune pancreatitis a lesion more as part of a condition with multifocal fibrosclerosis and we believe that this sclerosing cholangitis is an additional manifestation of an autoimmune systemic condition, possibly stimulated by surgery.

A 78 year old male patient was admitted to our service for obstructive jaundice of a few days' history, not accompanied by constitutional syndrome. The patient had undergone surgery 75 days previously, with a preoperative radiological diagnosis of suspected cancer of the head of the pancreas. A radical pylorus preserving cephalic duodenopancreatectomy was performed. The patient was discharged 12 days after operation. The histopathology report of the resected sample revealed the presence of intense fibrosis and inflammatory, lymphoplasmacytic infiltration of the biliary wall with no evidence of malignancy. Similarly, the pancreatic gland presented with intense inflammatory, lymphoplasmacytic, glandular atrophy, and no signs of malignancy. Biochemical work up on admission revealed: BbT 16.2 mg/dl; BbD 12.2 mg/dl; GGT 1264 IU/l; ALP 831 IU/l; CEA 2.81 ng/ml; CA 19.9 >500 IU/ml; anti-IgM (HAV) (−); HBsAg (−); HBcAc (−); anti-HCV (−); IgG 1520 mg/dl; IgA 445 mg/dl; IgG4 28 mg/dl; and IgM: 206 mg/dl. Abdominal echography showed dilation of the intrahepatic biliary tract. Magnetic cholangioresonance revealed moderate dilation of the complete intrahepatic tract with no visualisation of the principal biliary tract or hilar plate, and no anastomotic complications. Transparietohepatic cholangiography demonstrated dilation of the right intraheptic biliary tract and diffuse stenosis affecting the common hepatic duct, hepatic hilum, and segmented biliary branches. External-internal percutaneous drainage of the biliary tract was performed using radiology.

After two days there was no obvious sign of improvement and the biochemical work up was as follows: BbT 19.6 mg/dl; BbD 16.5 mg/dl; GGT 673 IU/l; ALP 648 IU/l; GOT 104 IU/l; and GPT 111 IU/l. Exploratory laparotomy was performed with no pathological findings which justified cholestasis. Intraoperative echography showed only enlargement of the biliary wall with no intraluminal obstructive findings. Immediately after surgery, because of suspicion of a basic inflammatory condition, treatment was begun with methylprednisolone 1 mg/kg/24 h intravenously. Once intake was tolerated, this treatment was maintained for a month orally before being reduced to 10 mg orally/24 h during the second month. The analytical follow up was excellent, with BbT reduced to 1.8 mg/dl, and the remaining biological parameters were normal. Similarly, the episode of bicipital tenosynovitis of the left shoulder evolved satisfactorily. The patient maintained treatment with methylprednisolone, 10 mg orally for a further two months, with clinical-radiological and analytical resolution of the cholestatic process (fig 1).

What is exceptional about this patient is the triggering of a severe autoimmune inflammatory response in the biliary system based on the presence of lymphoplasmacytic infiltration, coexistence with other

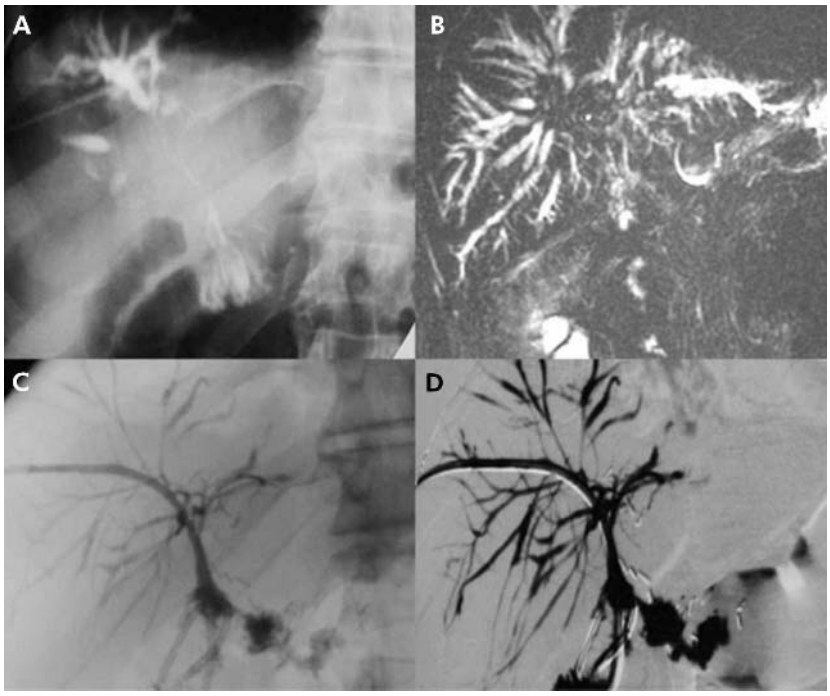

Figure 1 (A) Transparietohepatic cholangiograph showing the existence of diffuse stenosis of the principal biliary tract and hepatic hilum. (B) Magnetic cholangioresonance which shows absence of uptake in the principal hepatic ducts, hepatic hilum, and principal biliary tract. (C, D) Transparietohepatic cholangiograph after steroid therapy with radiological improvement of the principal biliary tract, hepatic hilum, and principal hepatic ducts.

autoimmune processes (episode of tenosynovitis in the shoulder of our patient), and good response to steroids that would reveal an autoimmune aetiopathogenesis. Our group would include the possibility of exclusive biliary tract involvement, as was the case with our patient, after the stress of surgery. Taniguchi and colleagues[5] reported relapse of autoimmune pancreatitis after cephalic duodenopancreatectomy although they do not refer to alterations in the biliary tract. Toosi and colleagues[6] reported the appearance in two of their patients of post-surgical sclerosing cholangitis although only after biopsy of the pancreatic head. The appearance of sclerosing cholangitis after duodenopancreatectomy has not been reported previously. The short period of biliary involvement and the progression maintained in the biliary involvement led us to suspect an inflammatory process similar to that of autoimmune pancreatitis.

Neither therapy nor its duration have been well defined, and this can be seen in the different regimens used both for autoimmune pancreatitis and autoimmune pancreatocholangitis. Erkelens and colleagues[7] used prednisone 0.5–1 mg/kg/day, followed by maintenance doses for six months. Some patients also received, albeit exceptionally, azathioprine at 50 mg/day, and this was used temporarily until resolution of the biliary endoprosthesis process. The results were satisfactory, although no therapeutic protocol has been defined. This disparity in criteria is manifested in other studies, such as that of Toosi and colleagues[6] who used ursodeoxycholic acid at 750 mg/24 h with almost complete return to a normal clinical and analytical picture. Other authors, such as Kojima and colleagues,[8] maintained treatment according to the clinical-radiological changes, using a loading dose of 40 mg/24 h, with maintenance doses of 5 mg/24 h. Taniguchi and colleagues[5] used prednisolone at 30 mg/24 h for one month, followed by 5 mg/24 h for nine months with satisfactory evolution. Kamisawa and colleagues,[9] on the other hand, used a loading dose of prednisolone of 30–40 mg/24 h and maintenance doses of 5 mg/24 h until clinical check-up. Based on the hypothesis of an excessive fibrosclerotic inflammatory response in our patient, we started therapy with prednisolone 1 mg/kg for four weeks, with progressive reduction to 10 mg/24 h over the following four weeks. The maintenance dose was continued for a further two months, with analytical, radiological, and clinical resolution of the process.

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Calprotectin and IBD

Costa and colleagues (*Gut* 2005;**54**:364–8) recently reported a study describing the ability of faecal calprotectin to predict relapse in the following year in patients with inflammatory bowel disease (IBD). They concluded that a calprotectin level >150 μg/g was predictive of relapse in Crohn's disease (CD) *and* in ulcerative colitis (UC), but was *more effective* in predicting relapse in UC. Unfortunately, we believe that the authors failed to demonstrate these two points.

If faecal calprotectin >150 μg/g was clearly predictive of relapse in UC patients, this was not the case in CD ($p = 0.07$ and $p = 0.31$ for the likelihood ratio test in univariate and multivariate analyses, respectively). This may be due to the method used to determine the cut off value for calprotectin. Firstly, the receiver operating curve (ROC) method did not provide any cut off value for CD as the curve was not different from the diagonal and the confidence interval of the area under the curve included 0.5 (0.40–0.77). Secondly, the ROC curve method was not appropriate as it does not take into account the time to relapse, in contrast with the proportional hazards model used to test the predictive value of calprotectin. Classical methods related to time to relapse should have been preferred.[1 2]

The assertion, both in the title and in the text, that calprotectin was a stronger predictive marker of relapse in UC than in CD was not statistically tested by the authors. This assertion probably came from the high value for the hazard ratio in UC, compared with that in CD, but theses values are misleading because of the exponential transformation of the coefficient in the proportional hazard model. When roughly calculating these coefficients and their standard error, the figures are much less convincing. In the univariate analysis the results are 1.39 (0.76) for CD and 2.55 (0.75) for UC, and the comparison between these two estimates gives a p value of 0.28 ($p = 0.15$ with estimates from the multivariate analysis). These disappointing results may be the consequence of a lack of power due to the relatively small number of patients.

Another important point is that the analysis was based on the assumption that the biomarker is able to predict relapse with the same strength whether the relapse occurs early after evaluation or later during follow up. If this is true it means that the calprotectin level is a characteristic of the

disease, including the whole 12 month follow up period. As discussed by the authors, calprotectin, as well as erythrocyte sedimentation rate (ESR) or C reactive protein (CRP), are probably markers of the degree of infra-clinical disease activity at the time of their measurement, and therefore can change with time in a given subject. To test this hypothesis, it should have been verified that their hazard ratios varied with time during follow up (the power of this analysis will however be limited).

Comparison of calprotectin with other classical predictive markers is also debatable. Indeed, cut off values for calprotectin were assessed using ROC curves, with some success for UC, and were three times higher than the upper limit of the normal range. In contrast, for ESR and CRP, the upper limits of the normal range were chosen as cut off values, following failure of the ROC curve method which was unfortunately not appropriate.

Finally, the authors stated that three variables were significant predictors of relapse—namely, calprotectin level, smoking habit, and UC activity index (UCAI) or CDAI—whereas only calprotectin and CDAI were found to be independently correlated to time to relapse in UC and CD, respectively.

In conclusion, if we agree with Pardi and colleagues[3] that identification of biomarkers predictive of relapse could have important implications for the management of IBD patients, we are less convinced by the data presented by Costa *et al* with regard to the methodological weaknesses of their study.

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Conflict of interest: None declared.

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3 **Pardi DS**, Sandborn WJ. Predicting relapse in patients with inflammatory bowel disease: what is the role of biomarkers? *Gut* 2005;**54**:321–2.

Author's reply

We thank Lemann and Mary for their comments on our article (*Gut* 2005;**54**:364–8). We appreciate their careful reading of the text, and their questioning of the validity of our study gives us a unique opportunity for further articulating our findings.

We agree that other methods could be used instead of the receiver operating curve (ROC) to assess a cut off value for calprotectin. As Lemann and Mary noted however, the chosen cut off value of 150 μg/g proved to be optimal in ulcerative colitis (UC) patients. In our opinion, no unique cut off value, however carefully chosen, could improve on the prediction of relapse in Crohn's disease (CD) patients. Perhaps assessment based on a continuous, rather than a binary, score might provide a somewhat better alternative. Evaluation of predictive models of time to relapse, if worthwhile, would require a larger sample size and it was beyond the scope of our study.

Also, we agree with Lemann and Mary that only calprotectin and CD activity index (CDAI) were found to be independently correlated with time to relapse in UC and CD, respectively. Nevertheless, the important role of smoking habit and UCAI should have been explicitly referred to as confounding. The proportionality of the hazard over time was evaluated to some extent as part of testing the interaction terms for all of the variables. As acknowledged in the letter, the power of this analysis was however limited.

We disagree with Lemann and Mary if they wish to downplay the remarkable difference between the diagnostic groups. Firstly, we strongly discourage comparing estimates for coefficients from the univarate analysis. The conspicuous confounding effect of smoking and CDAI in CD patients makes the crude estimate for the coefficient associated with calprotectin >150 μg/g useless for making any meaningful inference. Secondly, comparing estimates from the multivariate models yielded a p value of 0.10, not 0.15 as reported in the letter. Given the relatively small sample size and the inherent lack of power, appropriately pointed out, such a p value should not be overlooked. Thirdly, it makes no difference to the p value whether hazard ratios or regression coefficients are compared, and we believe that the former are easier to interpret than the latter. Fourthly, the lack of power can certainly explain the fact that the sizeable hazard ratio of 2.2 in CD patients was not statistically significant. But the p value should not divert attention from the estimated magnitude of the effect and its confidence interval.

In conclusion, although our findings should not be considered definitive, they are highly suggestive that a calprotectin level >150 μg/g is predictive of relapse in CD and in UC, but is more effective in predicting relapse in UC.

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BOOK REVIEWS

Surgical Pathology of the GI Tract, Liver, Biliary Tract and Pancreas

Edited by R D Odze, J R Goldblum, J M Crawford. Pennsylvania: Saunders, 2004, pp 1067. ISBN 0-7216-9318-0

I thought this was a great bench book for surgical pathology of the gastrointestinal tract. The book was well up to date with recent molecular advances across a wide variety of pathologies. The images were excellent, sharp, representative colour photomicrographs. There was excellent handling of opportunistic infections and of inflammatory diseases, often not well represented in surgical pathology books, which often resemble tumour catalogues. There was good coverage of some areas neglected by many histology textbooks, including biliary cytology. The approach to many of the more difficult topics was mature, balanced, honest, and informative. Most of all, the book was concise, with scarce wasted words. All in all, highly recommended.

J J Boyle

The Inflammatory Bowel Disease Yearbook 2004

Edited by C N Bernstein. London: Remedica Publishing Ltd, 2003, £25.00, pp 200. ISBN 1901346579

This is the second edition of an annual update on inflammatory bowel disease (IBD). Yearbooks are useful resources for quickly catching up with a field, ''Readers Digest'' style. Being concise as well as giving coverage of the advances of the entire field in a year are therefore requisites for success. This yearbook is certainly concise and can be finished cover to cover within a Glasgow to London train trip. Six essays constitute the entire book, covering pathogenesis, clinical, molecular, and serological subtyping of Crohn's disease, nutritional therapy, surgical management, cancer in IBD, and osteoporosis. The essays are written conventionally and do not necessarily cover advances within the past year or two. Indeed, in some chapters there is a predominance of references from the 1990s or even earlier. The chapter on surgical management is superb and the chapter on cancer in IBD comprehensive.

The field of IBD is now replete with review articles and most of the topics chosen in this yearbook are already well served by review articles published within the last year. In addition, there are now at least four major textbooks focused on IBD and several monographs. Omission of the major advances in biological therapies and other molecular targets of therapy is a significant one, and advances in this area are so rapid as to consider this to be a rolling topic each year.

A general gastroenterologist or even an internist might want to read this as a quick update on IBD but might fail to feel fully updated unless he acquires a volume each year. Many would focus on the excellent quality reviews now being regularly published in all leading gastroenterology journals. However, this volume is easy to read from cover to cover and would slip easily into one's briefcase for portable reading. In future, this volume may better serve its purpose by publishing very short updates on a wider range of topics, strictly focusing on original papers published within the past two years.

S Ghosh

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