Helicobacter pylori

Helicobacter pylori infection and long term proton pump inhibitor therapy

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Should *Helicobacter pylori* infection be eradicated in patients requiring long term proton pump inhibitor therapy for gastro-oesophageal reflux disease?

Should *Helicobacter pylori* infection be eradicated in patients requiring maintenance proton pump inhibitor therapy for gastro-oesophageal reflux disease? This question has stimulated heated debate and contention over the past few years. The issue first came to prominence in 1996 when Kuipers *et al* published their study purporting to demonstrate that omeprazole accelerated the development of corpus atrophic gastritis in *H pylori* infected subjects.[1] This rung alarm bells due to the fact that atrophic gastritis is a well recognised risk factor for gastric cancer in *H pylori* infected subjects. There was therefore concern that proton pump inhibitor therapy was modifying the inflammatory response to *H pylori* infection in such a way as to increase the risk of gastric cancer. For this reason, some experts have recommended that *H pylori* infection should be eradicated prior to long term proton pump inhibitor therapy.[2]

The original paper by Kuipers *et al* was widely criticised due to weaknesses in its design,[3] and its claim that proton pump inhibitor therapy accelerated atrophy in *H pylori* infected subjects was not supported by the FDA Gastrointestinal Drugs Advisory Committee.[4] In 1999, Lundell *et al* published a study claiming that proton pump inhibitor therapy did not accelerate the development of corpus atrophy in *H pylori* infected subjects.[5] However, their conclusion was challenged because there was evidence of accelerated development of moderate and severe atrophy in the *H pylori* infected group on proton pump inhibitor therapy and the size of this effect was similar to that reported by Kuipers and colleagues.[6–8] The paper by Kuipers and colleagues[9] in the current issue of *Gut* confuses the issue further as they did not observe any progression of atrophy in their *H pylori* infected subjects **[see page 12]**. Indeed, there was not even a trend in favour of progression of atrophy that might have become significant in a larger study. Several other recent studies have also found no evidence of acceleration of corpus atrophy in *H pylori* infected subjects on proton pump inhibitor therapy.[10–13] Consequently, there is little evidence in support of the original concern that proton pump inhibitor therapy accelerates corpus atrophy in *H pylori* infected subjects.

One consistent finding however of all of these studies is that proton pump inhibitor therapy does change the pattern of *H pylori* induced gastritis, causing it to move from the antrum into the more proximal corpus mucosa of the stomach. In this way, it induces what is referred to as a corpus or body predominant gastritis. This may have significance with respect to the subsequent risk of *H pylori* associated gastric cancer. Uemura *et al* recently examined the association between the pattern of *H pylori* induced gastritis and the subsequent development of gastric cancer in patients not receiving proton pump inhibitor therapy.[14] Their study indicated that the strongest risk factor for cancer was the presence of corpus predominant gastritis and that this was a greater risk factor than either atrophy or intestinal metaplasia.[14] Irrespective of whether proton pump inhibitor therapy accelerates atrophy, there is cause for concern that it does induce the pattern of gastritis most associated with increased risk of gastric cancer. However, the association of two factors does not confirm a cause and effect relationship. It is not known whether corpus gastritis by itself increases the risk of cancer or whether it is just an epiphenomenon induced by some underlying factor which represents the link with cancer. Consequently, we do not know whether inducing a corpus predominant gastritis by proton pump inhibitor therapy will, in itself, increase the subsequent risk of gastric cancer.

The paper by Kuipers and colleagues[9] in this issue of *Gut* is useful in that it demonstrates that it is readily feasible to eradicate *H pylori* infection in patients on long term proton pump inhibitor therapy and by so doing achieve resolution of the corpus predominant gastritis.[9] The paper also claims that treating *H pylori* infection results in some resolution of corpus atrophy. However, there are concerns about assessing the severity of atrophy following eradication of *H pylori* infection.[15] Resolution of inflammation makes quantification of atrophy difficult and, of course, also makes it impossible for the observer to be blinded to the patient's *H pylori* status. However, as discussed above, resolution of the inflammation might be more important than any possible resolution of atrophy with respect to the risk of gastric cancer.

The question regarding the appropriateness of eradicating *H pylori* infection in patients with reflux disease must also address the effect this may have on the reflux disease itself and its response to treatment. There are now reliable data indicating that *H pylori* infected subjects have a lower prevalence of reflux disease[16] and some data indicating that patients with the more virulent CagA positive strain of *H pylori* infection have a lower incidence of reflux oesophagitis and its complications than those with CagA negative strains.[17 18] These observations have stimulated interest in the possibility that *H pylori* infection may afford some protection from reflux disease and that the increasing prevalence of this disease and its complications in the Western world may be partly explained by the fall in prevalence of *H pylori* infection. Again, however, we must recognise that associations do not confirm causality as they may be due to confounding factors. However, the observation that CagA positive strains are associated with less reflux oesophagitis than CagA negative strains does raise the real possibility of a protecting effect as this comparison within *H pylori* infected subjects removes confounding factors related to susceptibility to the infection.

If *H pylori* infection does provide protection against reflux disease then eradicating the infection should induce or aggravate the condition. The data on this question are also conflicting. Labenz *et al* reported that eradicating *H pylori* increased the incidence of oesophagitis in ulcer patients.[19] However, Moayyedi *et al* did not find any increase in reflux symptoms following eradication of *H pylori* in patients with symptomatic heartburn.[20] Swhwizer *et al* reported improvement in reflux symptoms following *H pylori* treatment[21] but their study was criticised for its small size and inadequate matching of randomised groups.[22] Two studies have observed development of reflux disease

following eradication of *H pylori* in patients with spontaneous corpus predominant gastritis and associated hypochlorhydria and attributed it to the recovery of acid secretion produced by treating such subjects.[23 24] It does seem likely that recovery of acid secretion following eradication of *H pylori* in patients with *H pylori* induced hypochlorhydria will increase their propensity to reflux disease.

There are also concerns that eradicating *H pylori* infection will make it more difficult to adequately control reflux disease with proton pump inhibitor therapy. It has been clearly shown that proton pump inhibitor therapy is much more potent in *H pylori* positive subjects than in *H pylori* negative subjects.[25–27] Omeprazole 20 mg increases 24 hour median intragastric pH to 5.5 in *H pylori* infected subjects but this falls to 3.0 following *H pylori* eradication.[26] One would expect this impaired pH control to reduce the ability of proton pump therapy to control reflux disease. Holtmann *et al* have indeed demonstrated this in their study of 971 patients receiving proton pump inhibitor therapy for endoscopic oesophagitis.[27] They found that both the rate of healing of the endoscopic oesophagitis and the rate of control of symptoms was significantly higher in *H pylori* infected subjects. A study of 483 patients with uninvestigated heartburn also found that control of symptoms with omeprazole 20 mg was achieved in 86% of *H pylori* positive compared with only 65% of *H pylori* negative patients ($p<0.02$).[28] *H pylori* infection also protects against rebound acid hypersecretion following discontinuation of proton pump inhibitor therapy and this protection is lost following eradication of the infection.[29 30]

In their paper in this issue of *Gut*, Kuipers *et al* claim that treating *H pylori* infection did not make the reflux disease more difficult to control.[9] However, this conclusion is not supported by their own results. Thirty two per cent of those eradicated of *H pylori* had reflux symptoms on omeprazole compared with only 24% of those not eradicated. When their data are analysed looking at changes in symptoms over the two year follow up period, there is a −14% (−28% to 0%) difference in favour of the group not eradicated of *H pylori* ($p<0.05$). Contrary to the authors' conclusion, I believe the current study by Kuipers *et al* provides further evidence that eradicating *H pylori* infection does make it more difficult to achieve long term control of reflux disease with proton pump inhibitor therapy.

In summary, therefore, reviewing the available evidence does not provide a clear answer to our question of whether we should eradicate *H pylori* infection in patients requiring long term proton pump inhibitor therapy for reflux disease. There is some evidence in favour of eradicating the infection; namely the observation that proton pump inhibitor therapy induces a corpus predominant gastritis which is associated in other circumstances with an increased risk of gastric cancer and that eradicating the infection resolves that gastritis. However, we do not know whether this gastritis is actually increasing the risk of cancer to a level any higher than in any other *H pylori* infected subject. Against treating *H pylori* infection is the fact that there is some evidence that *H pylori* infection may afford some protection from reflux disease and its complications, in addition to some reasonably good evidence that eradicating *H pylori* infection makes the control of reflux disease by proton pump inhibitor therapy slightly more difficult. The evidence based answer to our question is that we do not know whether *H pylori* should be eradicated in reflux patients requiring long term proton pump inhibitor therapy.

Interestingly, Kuipers *et al* conclude that *H pylori* infection should be eradicated in patients requiring long term proton pump inhibitor therapy for reflux disease.[9] This is surprising and rather inconsistent with the findings they report. They observed no evidence of progression of corpus atrophy which had been their previous reason for recommending eradication of the infection. In addition, their study provides further evidence that eradicating *H pylori* impairs symptomatic control of reflux disease. The findings of their current study would therefore equally well support the opposite conclusion, namely that *H pylori* infection should not be eradicated in reflux patients requiring proton pump inhibitor therapy.

Gut 2004;**53**:5–7

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Helminths

Helminths and harmony

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Mounting evidence suggests that helminths help regulate mucosal inflammation

The frequency of Crohn's disease (CD) has increased substantially over the last 50 years. It is most prevalent in highly industrialised temperate regions. CD and ulcerative colitis (UC) are rare in less developed countries. This suggests that critical environmental factors affect the worldwide distribution of inflammatory bowel disease (IBD). The ''IBD hygiene hypothesis'' states that raising children in extremely hygienic environments negatively affects immune development which predisposes them to immunological diseases such as IBD.[1] It is also postulated that the modern day lack of exposure to helminths due to our hygienic practices is an important environmental factor contributing to IBD. Until modern times, nearly all children and most adults harboured intestinal helminths. Helminths and the immune system of *Homo sapiens* co-evolved in close proximity over many 1000s of years. Helminths regulate their host's immune system and prevent excessive inflammatory responses, which could underlie the mechanism of protection. Moreels and colleague[2] now lend further support for this hypothesis by reporting in this issue of *Gut* that infection with the helminth *Schistosoma mansoni* protects rats from trinitrobenzene sulphonic acid (TNBS) induced colitis **[see page 99]**.

Approximately two million people in the USA and Europe have CD or UC, which usually begins during the second to third decade of life. IBD probably results from an inappropriately vigorous immune response to contents of the intestinal lumen. Evidence supporting this contention includes the effectiveness of immune suppressants at controlling the disease and experimental data derived from mice prone to IBD because of defects in immune regulation.[3] In most of these murine models, the inflammation is driven by T helper 1 (Th1) circuitry and by substances in the intestinal lumen.

THE CASE FOR GENETICS IN IBD

UC and CD are disorders of complex derivation caused by the interplay of poorly defined environmental exposures and, at least in some instances, the inheritance of susceptibility genes. Often cited as evidence for genetic predisposition for IBD is the higher than expected occurrence of IBD in family members of patients with this condition and the high prevalence of the disease in Jewish populations of Western countries.[4] Yet IBD is much less prevalent in the Jewish population of Israel[5] with similar ethnic origin.[6] Twin studies provide evidence of genetic predisposition for at least CD.[7] A genetic defect in CARD15/NOD2, an intracellular protein that senses the bacterial product muramyl dipeptide,[8 9] leaves some people more susceptible to CD. Various other genetic alterations are proposed as IBD risk factors. Yet genetic predispositions do not explain the rapidly increasing incidence of disease.

THE CASE FOR ENVIRONMENT IN IBD

There certainly are important environmental factors that affect the regional frequency of these diseases worldwide. Smoking is a risk factor for CD.[10 11] Appendectomy for appendicitis under the age of 20 years decreases the incidence of UC.[12–14] The risk for IBD varies according to geography and occupation. There is a North-South gradient of IBD in the USA and Europe, with IBD being more common in people raised in the North.[15 16] US military veterans are at low risk for this disease if they were raised in the rural South,[17] were prisoners of war, or served in combat in tropical regions.[18] People with blue collar jobs exposing them to dirt and physical exercise are less prone to IBD.[19] IBD is more common in urban versus rural areas.[20] CD and UC are rare in South America,[21] Central America, Africa,[22 23] and Asia[24] with the White population of South Africa being the exception.[25] Migration studies show that children of people from regions of low CD or UC frequency acquire a greater risk for IBD if they move to areas of high disease prevalence.[26–28]

THE HABITAT OF HELMINTHS

Helminths are parasitic animals (worms) which, depending on species, live in locations such as the intestinal lumen, blood stream, or muscles of the host. These organisms colonise more than one third of the world population. Helminth colonisation is most common in children living in warm climates and subject to poor sanitation. The infective forms of these organisms are spread through contact with contaminated soil, food, or water. Before the 1940s, many children and adults in the USA carried helminths. Worm carriage was particularly common in rural areas of the South and in indigent populations of major cities.[1] In the USA and Europe, helminthic colonisation has steadily declined. They are found in recent immigrants from less developed countries[29] and in economically disadvantaged populations living in underserved regions of the USA such as some Indian reservations.[30] These groups are at low risk for IBD. There is an inverse relationship between the frequency of worm colonisation and the prevalence of CD. There is more CD in urban versus rural populations, in northern versus southern regions of the USA and Europe, and developed versus less developed countries. The opposite is true for worm carriage.

IMMUNE REGULATION AND IBD

Inflammation can generate various regulatory agents such as interleukin (IL)-10, transforming growth factor β (TGF-β), IL-4, IL-13, and prostaglandin E_2 (PGE_2) that help modulate immune responses and limit tissue injury at

mucosal surfaces. IL-10 is a mediator with strong immunomodulatory actions. For instance, IL-10 inhibits macrophage and dendritic cell function and suppresses the production of important proinflammatory cytokines such as tumour necrosis factor α, IL-12, IL-1, nitric oxide, and various chemokines. Mice with a disruption of the IL-10 gene develop severe colitis showing the importance of IL-10 for mucosal immune homeostasis.[31] TGF-β mediates highly pleiotropic immunoregulatory functions, and transgenic mice with a T cell selective blockade in TGF-β signalling develop colitis.[32] PGE_2 is another well known factor that influences T helper 1 cell/T helper 2 cell (Th1/Th2) activation. It preferentially downregulates IL-12 receptor expression, inhibits the differentiation of Th1 cells, blocks IL-12 production from antigen presenting cells, and more. Mice deficient in the PGE receptor EP4 are more subject to dextran sodium sulphate induced colitis[33] suggesting that PGE_2 is important for mucosal protection.

Regulatory T cells can induce peripheral tolerance and limit mucosal reactivity.[34] In various animal models, several regulatory T cell phenotypes have been reported. Some express CD4 while others CD8. In some systems, they are distinguished through differential expression of surface molecules, such as CD25, CD45RB, and CTLA-4. This pattern of cell surface protein expression suggests that they may be in a primed effector or memory state. These regulatory cells may mediate some of their affects through production of IL-10 and TGF-β. Described is an anergic regulatory T cell (Tr1) that produces high levels of IL-10 and TFG-β. Another cell called Th3 suppresses induction of experimental autoimmune encephalomyelitis primarily through production of TGF-β. Still others are not dependent on soluble IL-10 or TGF-β but instead express on their surface latency associated peptide, which is the amino terminal domain of the TGF-β precursor peptide.[35] These cells can induce suppression via cell-cell contact.

Rag mice reconstituted with CD4+, $CD45^{high}$ T cells can develop severe colitis, which can be prevented by cotransfer of CD4+, $CD45^{low}$ T cells.[36] TGF-β and IL-10 are required for protection, suggesting a role for these cytokines in the regulatory process. These studies suggest that regulatory T cells are also important in preventing IBD.

THERE IS AN IMMUNOLOGICAL BASIS FOR HELMINTHIC PROTECTION

Populations experiencing deworming also undergo other socioeconomic alternations that could affect risk for disease. These include changes in diet, housing, and sanitation among others. Yet there is an immunological basis to suspect deworming as a risk factor. People bearing helminths display dampened immune responses to unrelated concurrent antigenic exposures.[1 37 38] These changes in immune responsiveness can persist long after elimination of these helminthic exposures.[37 39] Mice colonised with helminths have blunted Th1 responses.[40–43] Helminths promote Th2 responses associated with production of IL-4 and IL-13.[44 45] IL-4 helps impede Th1 cell differentiation. Thus induction of IL-4 could underlie the alternations seen in host immunity. However, the mechanism of protection is not simply ''Th2 suppresses Th1'' as helminths also appear to protect the host from aberrant Th2 diseases such as asthma and food allergy.[46 47] Interactions between these parasites and their hosts are complex and multifaceted as would be expected for such a successful co-evolutionary process that leads to ''peaceful'' coexistence. Helminths not only trigger Th2 responses, which help to limit worm number in the host, they also promote production of powerful immunomodulatory molecules such as IL-10[48] and TGF-β, and ''regulatory'' T cells.[49]

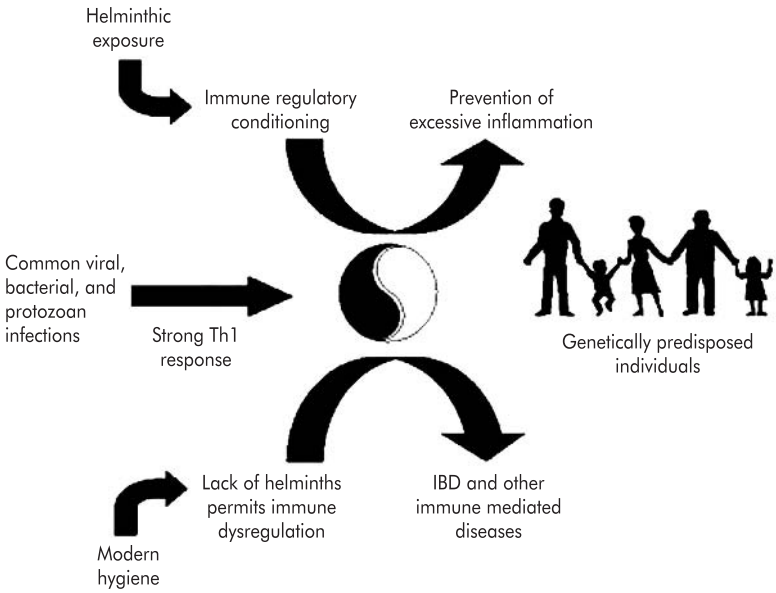

Figure 1 The inflammatory bowel disease (IBD) hygiene hypothesis.

HELMINTHS PROTECT

There is now substantial human epidemiological data and several animal studies supporting the hypothesis that helminths protect the host from immunological disease. For instance, people colonised with helminths have high serum levels of IL-10, which may protect them from atopy.[50] Helminths protect mice[51 52] and rats from TNBS induced colitis, experimental autoimmune encephalomyelitis,[53 54] and other diseases of immunity[47 55] most likely in part through induction of IL-4. They also reverse ongoing colitis in IL-10KO animals via induction of regulatory T cells (manuscript submitted). Thus natural exposure to helminths may guard people from developing IBD and other immunological diseases through induction of IL-4, IL-10, TGF-β, regulatory T cells, or perhaps by other means. In a preliminary and uncontrolled trial, we have demonstrated that oral administration of *Trichuris suis* ova to patients with active ulcerative colitis or Crohn's disease is safe and possibly effective.[56] Controlled clinical trials in both disorders are also being conducted and are nearing completion using a similar approach.

SUMMARY

Environmental factors affect the worldwide distribution of IBD. Supported by a growing volume of both epidemiological and experimental data, it appears plausible that exposure to helminths is a factor that protects people from IBD (fig 1). As reported by Moreels and colleagues[2] in this issue of *Gut*, helminths protect mice from experimental colitis. Many factors help initiate and maintain immunological diseases. Targeting one or just a few cytokines in most cases may not prove sufficient to permanently suppress disease activity. Helminths have broad immunoregulatory properties that evolved as part of the successful host-parasite interaction.

Studying helminths and how they alter the host's immune response could lead to new and highly effective therapeutic strategies for human IBD. Such studies may also provide new insight into the pathogenesis of CD, UC, and other emerging immunological diseases.

ACKNOWLEDGEMENTS

The study was supported by grants from the National Institutes of Health (DK38327, DK58755, DK02428, DK25295), and the Crohn's and Colitis Foundation of America, Inc.

Gut 2004;**53**:7–9

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Inflammatory bowel disease

Do steroids ameliorate bile acid malabsorption in Crohn's disease?

R S Kwon, M C Carey

Steroids may partially restore impaired bile salt absorption in Crohn's disease patients, highlighting a new modus operandi for steroids as their beneficial effects have traditionally been attributed to immunomodulatory effects alone

Steroids are among the mainstays of medical therapy for Crohn's disease but may lead to unfavourable long term complications. Recently, budesonide has been shown to be effective in inducing remission in mild to moderate disease while undergoing less systemic absorption compared with other corticosteroids.[1] It is hypothesised that steroids exert their salutary effect through an immunomodulatory action on the small bowel mucosa.[2] In this issue of *Gut*, Jung and colleagues[3] shed light on the possibility of another potentially beneficial effect of steroid therapy—namely, the partial restoration of impaired bile salt absorption in Crohn's patients with distal ileal involvement **[see page 78]**.

The integrity of the enterohepatic circulation of bile salts is dependent on active uptake from the ileum, which is mediated by SLC10A2, known previously as the apical sodium dependent bile acid transporter (ASBT).[4] Given the malady's proclivity for the distal ileum, one of the classic hallmarks of intestinal Crohn's disease is bile salt malabsorption.[5–7] Bile salt malabsorption occurs when intestinal transport is appreciably disrupted, and the degree to which this occurs depends on the length of ileal involvement and/or resection.[8] Therefore, the activity and functioning of the remaining ASBT, as well as colonic compensation by passive absorption of bacterially modified (secondary) bile acids are essential for keeping the enterohepatic circulation of bile salts partially intact.[9 10] Mild bile salt malabsorption may result in cholerrhoeic enteropathy that is easily controlled with low dose bile salt sequestrants. However, more extensive ileal involvement is accompanied by severe bile salt malabsorption, fat malabsorption, and steatorrhoea, as well as frequent diarrhoea made worse by sequestrants.

Previously, ASBT expression was shown to be upregulated by glucocorticoids in a rat model.[11] Jung and colleagues[3] have built upon this framework by showing that this response also takes place in humans. Employing ileal biopsies obtained at colonoscopy, the authors determined that a 21 day course of budesonide induced a 34% increase in ileal ASBT expression in 10 apparently normal volunteers. Within the promoter region of ASBT, the authors identified two inverted repeat (IR3) motifs that were shown to function as glucocorticoid response elements (GRE). They cotransfected the glucocorticoid receptor (GR) with a luciferase promoter construct of the ASBT gene into an in vitro cell line. When the cells were treated with dexamethasone, a known GR ligand, and budesonide (both at concentrations of 0.1–1 μmol/l), ASBT promoter activity increased 15–20-fold. Utilising electrophoretic mobility assays, the authors demonstrated that the IR3 sequences formed DNA-protein complexes with GR that could be inhibited with anti-GR antibodies.

A most interesting finding was that when compared with normal control tissue, ASBT expression was reduced significantly in ileal biopsies taken from 16 Crohn's disease patients obtained from a Zurich inflammatory bowel disease (IBD) tissue bank. This seems to us rather surprising given that there were no inflammatory histological changes in the biopsies, except one with ''mild'' inflammation. Unfortunately, the Jung[3] study did not include detailed clinical information on the patients, such as demographics (for example, age), duration, extent or symptomatology of their disease, how the biopsies were obtained, their Crohn's disease activity index scores, use of any medications, or whether these patients exhibited any evidence of clinically significant or subclinical bile salt malabsorption. This dearth of clinical information makes it difficult to interpret the true significance of the reduction in ASBT expression in ex vivo banked tissue samples. If a similar reduction could be found in the ileum of patients with newly diagnosed disease and therefore with no prior therapy, then this would support the possibility that functional ileocyte abnormalities occur prior to microscopic inflammatory changes classically associated with Crohn's disease. Clearly the authors' findings will need to be validated in further in vitro and clinical studies but their observations raise the intriguing question that bile salt malabsorption may be a precursor to histologically evident Crohn's disease. This would be a novel concept especially if the reduction in ASBT expression serves as a marker for the extent and even activity of the disease, particularly when the inflammation primarily affects other sites in the gastrointestinal tract, such as the colon. Nevertheless, the possibility must be borne in mind that if the index patients in this study[3] had resolving ileitis aided by the use of medications, then the biopsies could represent histological ileocyte recovery in the face of delayed return of physiological ASBT expression.

This provocative study also sheds further light on the clinical relevance of bile salt malabsorption during the course of Crohn's disease and its complications. The first dysfunctional ASBT mutation was actually identified in the ileum of a Crohn's disease patient.[12] Diminution in ASBT expression found by Jung and colleagues[3] suggests the importance of including early therapy against bile salt malabsorption (for example, bile acid sequestrants) in conjunction with traditional immunomodulatory therapy for Crohn's disease. The findings from the current study would suggest that budesonide itself would be particularly beneficial in early Crohn's disease as it may be capable of targeting both therapeutic goals. Therapy against bile salt malabsorption may not only be beneficial in terms of controlling diarrhoea but also in preventing pigment gall stone formation, for which Crohn's disease patients are at appreciably higher risk.[13] In a systematic study, Brink and colleagues[14] demonstrated elevations in total bilirubin levels in gall bladder bile (hyperbilirubinbilia) obtained from Crohn's disease patients with extensive ileitis (>50 cm) or ileal resections, work that was confirmed by another group.[15] The likely mechanism for this pigment lithogenicity is passive enterohepatic cycling of bilirubin from the large intestine caused by solubilisation of unconjugated bilirubin (UCB) by increased colonic bile salt concentrations, as well as prevention of urobilinoid formation.[13] UCB resorbed from the

colon is taken up and reconjugated in the liver and secreted in excess into bile where the elevated levels provide supraphysiological substrate concentrations for deconjugation by biliary β-glucuronidase. The resulting higher biliary concentrations of UCB may precipitate as calcium salts in gall bladder bile and therefore increase the risk of ''black'' pigment gall stone formation.

The work by Jung and colleagues[3] also contributes to the recent explosion of studies investigating the regulation of the enterohepatic circulation and of bile salt metabolism. In particular, information on the extraordinary complexity of control of ASBT expression continues to grow at an amazing pace. Two recent studies, including one from the same Zurich group, have demonstrated the central role of hepatocyte nuclear factors HNF-4α and HNF-1α in the transcriptional regulation of ASBT.[16 17] Now, with the addition of the GREs in the ASBT gene identified in the current study,[3] our understanding of the complexity of ASBT regulation increases further. The authors' findings, in conjunction with the observation that expression of fatty acid binding protein (FABP6), formerly known as ileal bile acid binding protein (IBABP), is also regulated by glucocorticoids,[18] highlight a new modus operandi for steroids as their salutary results have traditionally been attributed to their immunomodulatory effects alone. Perhaps this knowledge will yield a role for earlier and more frequent use of corticosteroids in this disease and, in particular, budesonide which reduces the risk of untoward systemic complications associated with chronic steroid therapy. Certainly, the authors' findings of lower ASBT levels in Crohn's disease brings to mind the benefits of early and routine use of newer bile acid sequestrants that are now in existence (for example, colesevelam), which are more potent and better tolerated than traditional ones. However, before such changes in the management of Crohn's disease occurs, the functional and clinical relevance of decreased ASBT expression in histologically normal ileal biopsies from IBD patients will need to be clarified. In addition, to answer our rhetorical title, it remains to be shown whether the regulatory effect of budesonide or other corticosteroids on ASBT expression can be observed in acutely inflamed ileal tissue and whether this will translate into any clinical benefit for Crohn's patients.

Gut 2004;**53**:10–11

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PostScript

LETTERS

ITPA genotyping test does not improve detection of Crohn's disease patients at risk of azathioprine/6-mercaptopurine induced myelosuppression

The thiopurine drugs azathioprine (AZA) and 6-mercaptopurine (6-MP) are effective for the treatment of inflammatory bowel disease (IBD) and their prescription is increasing. Haematotoxicity, which can lead to potentially life threatening bone marrow suppression, represents the most serious side effect of thiopurine therapy. It has been attributed to the accumulation of active cytotoxic metabolites of AZA/6-MP, collectively called 6-thioguanine nucleotides, resulting from a deficiency in thiopurine catabolism specifically catalysed by the thiopurine *S*-methyltransferase (TPMT) enzyme. Genotyping tests are now available to identify deficient and intermediate methylators who are, respectively, homozygous and heterozygous for non-functional alleles of the TPMT gene. As pointed out by Lennard in the leading article (*Gut* 2002;**51**:143–6), it is clear that myelosuppression may be caused by other factors in addition to variable TPMT.

Since the identification of the molecular basis of inosine triphosphate pyrophosphatase (ITPAse) deficiency,[1] a clinically benign condition characterised by abnormal accumulation of inosine triphosphate in erythrocytes, the possibility of a correlation between thiopurine toxicity and ITPAse deficiency has been raised. Complete ITPase deficiency was found to be associated with a homozygous missense 94C>A mutation that encodes a $Pro^{32}Thr$ exchange, whereas an intronic IVS2+21A>C polymorphism was shown to have a less severe effect, homozygotes retaining 60% ITPAse activity. It was then postulated that in ITPAse deficient patients treated with thiopurine drugs, a 6-thio-ITP metabolite could accumulate resulting in toxicity.[1] A recent study in 62 patients with inflammatory bowel disease reported a significant association between the *ITPA* 94C>A polymorphism and AZA related adverse effects, specifically flu-like symptoms, rash, and pancreatitis.[2] No correlation was observed with occurrence of neutropenia but only 11 patients were studied. We previously reported *TPMT* genotype analysis in 41 Crohn's disease (CD) patients who had experienced leucopenia during AZA/6-MP therapy.[3] Even though this study confirmed the efficiency of *TPMT* genotyping in identifying patients at risk of developing myelosuppression, it also highlighted its limitations, as only 27% of patients carried mutant alleles of the TPMT gene that were associated with enzyme deficiency. This prompted us to investigate the occurrence of *ITPA* mutations in this series of patients in order to evaluate whether genotyping of the ITPAse gene could improve the detection rate of patients at risk of thiopurine myelotoxicity.

Our population comprising 41 patients with CD has been described in detail previously.[3] Briefly, all patients had either leucopenia (white blood cell count $<3000/mm^3$; n = 24) or thrombocytopenia (platelets $<100\ 000/mm^3$; n = 30), or both (n = 14), leading either to discontinuation of treatment or reduction of dose by 50% or more during AZA (n = 33) or 6-MP (n = 8) treatment. Patients were genotyped for the *ITPA* 94C>A and IVS2+21A>C mutations according to a previously described procedure based on endonuclease digestion of polymerase chain reaction products.[1] Distribution of the 41 patients according to their *ITPA* genotype is presented in table 1 and compared with that of a previously published control population of 100 healthy Caucasians.[1] Allele frequencies in the CD population were 0.085 for the 94C>A mutation and 0.12 for the IVS2+21A>C mutation, similar to frequencies observed in the control population (0.06 and 0.13, respectively). There was no significant difference in the genotypes distribution between the two populations, which confirmed the lack of association between ITPAse deficiency and myelosuppression during thiopurine therapy. Due to the retrospective nature of the study, no correlation with other side effects could be investigated.

In conclusion, application of *ITPA* genotyping tests does not seem to improve the identification of patients at risk of myelosuppression with AZA/6-MP therapy. Although we believe that conventional *TPMT* genotyping tests should still be applied before the initiation of thiopurine treatment, further work is needed on the role of other candidate genes that may be involved in thiopurine haematotoxicity.

Acknowledgements

We thank N Ferrari and A Vincent for their assistance in performing the study and the members of the GETAID for recruiting patients in the study.

Table 1 Distribution of *ITPA* genotypes in 41 Crohn's disease (CD) patients and 100 healthy Caucasians

ITPA genotype	CD patients (n = 41)	Control population† (n = 100)
Wt/Wt	26 (0.63)*	64 (0.64)
Wt/94C>A	6 (0.15)	10 (0.10)
Wt/IVS2+21A>C	7 (0.17)	24 (0.24)
94C>A/94C>A	0 (0.00)	0 (0.00)
IVS2+21A>C/IVS2+21A>C	1 (0.02)	0 (0.00)
94C>A/IVS2+21A>C	1 (0.02)	2 (0.02)

*Values in parentheses represent genotype frequencies.
†The control population comprised 100 healthy Caucasians who were genotyped in a previous study.[1]

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doi: 10.1136/gut.2004.055947

Competing Interests: None declared.

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Small bowel malignancy at diagnosis of coeliac disease

We were very interested in the paper by Rampertab *et al* (*Gut* 2003;**52**:121–14) and the correspondence by Hawdle *et al* (*Gut* 2004;**53**:470). Their data are quite similar to ours, from the Italian Registry of Complications of Coeliac Disease.

We collected information on 1968 patients over 18 years of age (mean age at diagnosis: 36.7 years; female/male ratio 3:1), diagnosed with coeliac diseases between January 1982 and December 2002 at 20 Italian clinical centres specialised in gastrointestinal disease. The diagnosis was made according to revised ESPGHAN criteria.[1] We found five (0.25%) patients with a small bowel malignancy at the time of diagnosis of coeliac disease. Age range was 49–69 years (mean 59 years) with a predominance of females (4:1). Survival rate was very poor as three patients died within 36 months of diagnosis.

These results indicate that there is an increased risk of developing small bowel malignancy in patients with coeliac disease. This correlation was confirmed by the female/male ratio. In fact, while small bowel neoplasms are usually more frequent in males, in our population four of five cases were female. Moreover, mean age at diagnosis of these cases was higher than that of patients overall, emphasising that the risk of a neoplasm increases with longstanding coeliac disease.

In conclusion, early diagnosis of coeliac disease should be made to prevent small bowel neoplasms from developing, and screening for this cancer should be carried out at diagnosis of coeliac disease, especially in patients diagnosed during adulthood.

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Competing Interests: None declared.

Reference

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Hypergastrinaemia in patients infected with *Helicobacter pylori* treated with proton pump inhibitors

We read with interest the commentary by McColl on *Helicobacter pylori* infection and long term proton pump inhibitor (PPI) therapy (*Gut* 2004;**53**:5–7).

It is remarkable that he did not mention gastrin although hypergastrinaemia is a result of reduced gastric acidity[1] as well as *Helicobacter pylori* infection,[2] and that patients with *H pylori* infection treated with PPI have additive hypergastrinaemia.[3] Hypergastrinaemia predisposes to gastric carcinoids in animals[4 5] and humans[6 7] as well as to malignant ECL cell derived tumours (gastric carcinomas) in animals[8] and humans.[9 10]

Interestingly, the carcinogenic effect of *H pylori* infection may be completely explained by its hypergastrinaemic effect,[11] a work where McColl was one of the authors. Furthermore, the increased gastric cancer frequency in moderate hypergastrinaemic INS-GAS mice concomitantly infected by *H pylori* infection[12] may also be caused by increased hypergastrinaemia in infected mice.[13]

To conclude, it is odd that gastrin was not taken into consideration when discussing the risk of gastric cancer following treatment with PPI in patients infected with *H pylori*. Animal as well as human studies linking gastrin to gastric cancer give support for a strategy where *H pylori* is eradicated in patients on long term PPI treatment.

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Competing Interests: None declared.

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Terminal ileal biopsies should not be used to document extent of colonoscopic examination

We commend the British Society of Gastroenterology and the authors for the excellent publication of guidelines for the management of inflammatory bowel disease in adults (*Gut* 2004;**53**(suppl V):vi–16). However, we feel that their recommendation for routine terminal ileal biopsying is inappropriate. Although it is important to biopsy the terminal ileum if there is macroscopic evidence of an abnormality, their statement that ''a terminal ileal biopsy performed at colonoscopy documents the extent of examination'' is not recommended practice, due to the potential risk of variant Creutzfeld-Jacob disease transmission from prion proteins which are prevalent in the lymphoid tissue of Peyer's patches in the ileum. Although the use of disposable forceps may reduce the risk of transmission, there could still be contamination of the intubation channel of the colonoscope and prion protein is resistant to the standard endoscopic cleaning process.[1] If the extent of examination needs to be documented, then a photograph of the ileocaecal valve or ileal mucosa is preferable.

It is worth emphasising that prion protein may be present in any part of the gastrointestinal tract[2] and random biopsy of gastrointestinal mucosa for reasons other than confirming an endoscopic abnormality or excluding microscopic colitis is not acceptable. Similarly, for surveillance colonoscopy where multiple biopsy is recommended, the risk benefit ratio of this policy must be supported by the clinical indications.

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Competing Interests: None declared.

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IgG food antibodies should be studied in similarly treated groups

The recent paper by Atkinson and colleagues (*Gut* 2004;**53**:1459–1464) regarding IgG food antibodies and irritable bowel syndrome (IBS) fails to compare like with like. Regardless of the IgG results, the treatment group excluded significantly different foods to the control group, particularly those foods which appear to exacerbate symptoms of IBS. Of particular concern is the ''yeast exclusion'' diet. A low yeast diet is not a recognised diet in standard textbooks of dietetics and nutrition. However, alternative practitioners offering such a ''yeast exclusion diet'' sometimes recommend exclusion of a wide range of foods, such as: bakery products, alcoholic beverages, many other beverages including commercial fruit juices, cereals, condiments, dairy produce, fungi, meat products (hamburgers, sausages, and cooked meats made with bread or breadcrumbs), yeast extracts (Bisto, Marmite, Oxo, Bovril, Vegemite, gravy browning, and all similar extracts), all B vitamin preparations, and sometimes, most worryingly, ''sugar foods'' (sugar, sucrose, fructose, maltose, lactose, glycogen, glucose milk, sweets, chocolate, sweet biscuits, cakes, candies, cookies, puddings, desserts, canned food, packaged food, hamburgers, honey, mannitol, sorbitol, galactose, monosaccharides, polysaccharides, date sugar, turbinado sugar, molasses, maple syrup, most bottled juices, all soft drinks, tonic water, milkshakes, raisins, dried apricots, dates, prunes, dried figs, and other dried fruit).

Therefore, regardless of IgG antibody status, the dietary restrictions in one group are not controlled for by the other group, and hence the conclusion may not be valid.

It would also be helpful to know if any of the patients with IgG antibodies to a particular antigen also had IgE antibodies to the same antigen.

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Competing Interests: None declared.

IgG antibodies to foods in IBS

We read with interest the article by Atkinson *et al* (*Gut* 2004;**53**:1459–64). The authors describe an important advance in our understanding of the putative role of inflammation in irritable bowel syndrome (IBS). However, we wonder whether their conclusion that assay of IgG antibodies may have a role in identifying candidate foods for elimination to treat patients with IBS may be a step too far. The four foods to which the patients most commonly formed antibodies and hence the four foods most commonly eliminated from the ''true diet'' were yeast (86.7%), milk (84.3%), whole egg (58.3%), and wheat (49.3%). The ''sham diet'' involved eliminating foods to which the patients had not formed antibodies and, therefore, in the sham group the exclusion rates for yeast, milk, whole egg, and wheat were very low (0%, 1.3%, 26.7%, and 8% respectively). It is therefore difficult to assess whether a diet excluding these foods would have led to symptomatic improvement in all patients, regardless of their antibody status.

Furthermore, the foods to which the study group commonly formed antibodies were similar to those already identified as leading to symptomatic benefit in patients with IBS when excluded from their diet. In a review cited by Atkinson and colleagues,[1] it was noted that in eight trials of exclusion diets in IBS, seven identified dairy products and five identified wheat as worsening symptoms. It is not clear whether the difference in improvement in symptoms seen in the current study between true and sham groups can be explained simply by the omission of these foods. This could in practice eliminate the need for antibody testing.

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Competing Interests: None declared.

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Influence of dietary factors on the clinical course of inflammatory bowel disease

Jowett *et al* reported in their elegant study on the role of diet in maintaining remission in patients with ulcerative colitis (*Gut* 2004;**53**:1479–84). Surely the effect of diet has an essential, but often forgotten, role in altering the course of disease in all types of inflammatory bowel diseases. This role does not necessarily act by maintaining patients in remission clinically, but perhaps more importantly by minimising the activities of the disease and rendering it quiescent.

We have recently reported a case of active stricturing Crohn's disease in an adult female patient with high stoma output.[1] She was treated solely with casein base formula (Modulen IBD-Nestle, Vevey, Switzerland) for three weeks. Her stoma output was reduced from 2800 ml to 400 ml per day by day 10. Serum albumin and serum protein significantly increased also. She subjectively felt better and pain free and stopped her opiate and non- opiate formula. The casein based formula is a nutritionally complete formulation containing a natural anti-inflammatory growth factor, transforming growth factor $\alpha 2$. The mechanism for inducing remission in our patient was possibly inhibition of expression of MHC class II protein in downregulating the inflammatory response.[2]

Previous studies have shown that there is a decrease in plasma antioxidant defences in all types of inflammatory bowel disease.[3] This is mirrored by an increase in free radical peripheral leucocyte DNA damage. It is therefore possible that the casein based formula acts as an antioxidant to minimise the oxidative stress that occurs in patients with active Crohn's disease. Another possible mechanism is that this formula may have a role as a prebiotic by stimulating the activity of bacteria which are already present in the gut.

Remission induced in our case study highlights the part played by a casein based formula in the management of adult Crohn's disease. The encouraging result demonstrates the need to treat similar cases with dietary measures first. This opportunity should not be missed as it may well obviate the need for surgical intervention or administration of potent pharmacotherapeutic agents which carries the risk of several comorbidities.

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Competing Interests: None declared.

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Identification of ferroportin disease in the Indian subcontinent

Haemochromatosis is a common inherited disorder of iron metabolism, characterised by excessive iron absorption and deposition in tissues. The majority of cases are associated with mutations in the *HFE* gene and inherited in an autosomal recessive manner.[1] Autosomal dominant forms of haemochromatosis have been reported, mainly associated with mutations in the *ferroportin 1* gene.[2] This syndrome, termed type 4 haemochromatosis or more recently ferroportin disease,[3] is usually characterised by an early increase in serum ferritin with normal transferrin saturation. Iron accumulation is most prominent in Kupffer cells and other macrophages, in addition to hepatocytes. Some patients do not tolerate venesection therapy well and can develop anaemia. Hereditary iron overload disorders appear to be uncommon in Asia. Secondary iron overload due to beta thalassaemia is relatively common in the Indian subcontinent. However, primary iron overload disorders and *HFE* mutations appear to be rare and cases have not been well characterised in this region.[4 5] We identified a patient from the Indian subcontinent with features typical of ferroportin disease.

A 36 year old female of Sri Lankan origin presented for a routine medical examination in December 2003. She was found to have an elevated serum ferritin of 3145 µg/l. Her serum iron (17.1 µmol/l) and transferrin saturation (29%) were normal. Liver functions tests, blood glucose, and thyroid studies were all normal. Physical examination was normal and she had no significant past medical history or risk factors for iron overload.

C282Y, H63D, and S65C *HFE* gene mutations were all negative and she had no family history of iron overload. Her mother and three siblings all had normal serum ferritin levels. Her father died of ischaemic heart disease aged 48 years.

A magnetic resonance imaging scan showed hepatic iron overload. Liver biopsy showed grade 3–4 iron deposition within hepatocytes and Kupffer cells; no fibrosis or cirrhosis was evident (fig 1). The hepatic iron concentration was 17 700 µg/g dry weight and hepatic iron index was 9.1.

Venesection therapy was initially poorly tolerated with the development of anaemia following the first two 500 ml venesections. Her haemoglobin is now stable on a programme of 300–500 ml venesections every three weeks.

The features of ferroportin disease in this patient led us to sequence the *ferroportin 1* gene, as previously described.[6] Analysis of the DNA sequence revealed a heterozygous three base pair deletion (TTG) in exon 5. This is the same deletion, V162del, described by us and others in haemochromatosis patients from Australia, the UK, Italy, and Greece.[6–9]

This is the first report to identify V162del or indeed any *ferroportin 1* mutation in an individual from the Indian subcontinent. Identification of V162del in an Asian patient confirms that this mutation is likely to be the most common mutation of *ferroportin 1* and the most common cause of non-*HFE* associated haemochromatosis. The wide geographical distribution of this mutation suggests that it is a recurrent mutation that has repeatedly arisen in distinct populations, probably by slippage mispairing.

Iron overload in this patient was typical of ferroportin disease. At the time of diagnosis she was asymptomatic and had no fibrosis on liver biopsy. Whether fibrosis or clinical complications will develop with age if iron stores are not depleted is unclear.

In conclusion, we have identified the V162del mutation of *ferroportin 1* in a fifth geographical location, emphasising that this mutation is the most common and widely distributed mutation which causes non-*HFE* haemochromatosis. We have identified V162del in a region where iron overload disorders have not been well characterised. Analysis of this and other *ferroportin 1* mutations may be useful in the study of iron overload disorders in this region and may be the basis of hitherto unexplained cases of iron overload.

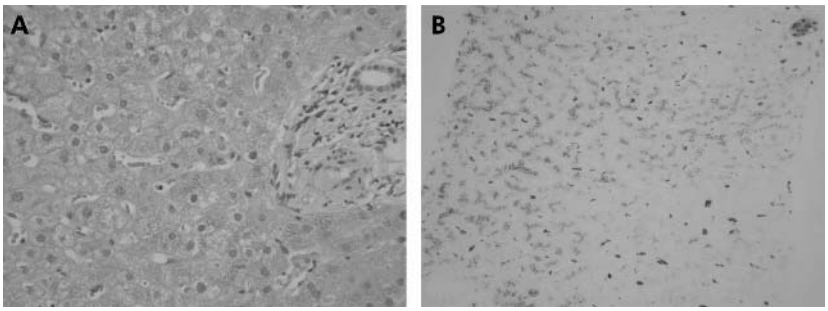

Figure 1 Liver biopsy sections from our patient stained with (A) haematoxylin and eosin and (B) Perls' Prussian blue (magnification 100×). Grade 3–4 iron is prominent in hepatocytes and Kupffer cells.

Acknowledgements

This work was supported in part by grants from the National Health and Medical Research Council of Australia (953219), the National Institutes of Health, USA (5R01DK057648-02), and the Haemochromatosis Society of Australia to VNS.

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doi: 10.1136/gut.2004.060988

Competing Interests: None declared.

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BOOK REVIEW

Morson and Dawson's Gastrointestinal Pathology, 4th edn

Edited by D W Day, J R Jass, A B Price, *et al*. Massachusetts: Blackwell Publishing, 2003, £175.00, pp 692. ISBN 0-632-04204-4

Why do people buy s book such as this, which involves a not inconsiderable financial outlay (even if you box clever and make it tax deductible)? I think for two main reasons—firstly, for use as a bench book, and secondly, for information on the pathological basis of gastrointestinal disease for interest, teaching, or indeed research purposes.

On the first criterion, this book succeeds, usually quite brilliantly. As a *vade mecum* on gastrointestinal pathology it should be on the shelf of every pathologist who engages in the reporting of such material. In my view, the book is more user friendly than the competition—Fenoglio-Preiser and Goldman to name but two—and is certainly more readable. I would therefore extol its virtues unreservedly in this respect.

On the second criterion, as a source book, I suppose the correct word is patchy. Some sections, for example that on colorectal tumours, is admirable in this respect, whereas other sections are more limited in scope and even cursory in their treatment of the pathobiology. There is also the problem of the unavoidable intrinsic delay in producing such a book, resulting in reference lists which are some years away from the publication date. I am aware however that my personal outlook is not that of most individuals who will purchase this volume so I am probably being over critical. It is, after all, quintessentially a bench book, and excellent at that.

However, I do have one real beef. In any multiauthor work there is bound to be variation, but here we are not told which one of the stellar caste were responsible for which section or chapter. Of course we can make informed guesses about the Barrett's or colorectal carcinoma sections, but who did the GIST bit? Because of some (minor) errors in the criteria for the diagnosis of malignancy, I have tried to berate a number of authors who have all denied responsibility, and blamed someone else—usually the author(s) absent at the time. Not good enough.

I have to concede however that the authors have succeeded in producing perhaps *the text* in gastrointestinal pathology, which is a credit to both themselves and the discipline in the UK. I congratulate them.

N A Wright

CORRECTIONS

doi: 10.1136/gut.2003.025494corr1

In the January 2005 issue of *Gut*, one of the author's names of the paper entitled Human peripheral and gastric lymphocyte responses to *Helicobacter pylori* NapA and AphC differ in infected and uninfected individuals (H J Windle, Y S Ang, V A Morales, R McManus, and D Kelleher. *Gut* 2005;**54**:25–32) was cited incorrectly. V A Morales should read V Athie-Morales. The journal apologises for this mistake.

doi: 10.1136/gut.2003.026807corr1

In the December issue of *Gut* fig 1 in the paper by AJG Bell *et al* (Human lymphocyte stimulation with pouchitis flora is greater than with flora from a healthy pouch but is suppressed by metronidazole. *Gut* 2004;**53**:1801–1805) is incorrect. The labels for fig 1C are inverted; the squares should have been labelled HetNon and the triangles HetPM. The legend is also incorrect because the label for flora grown on agar without metronidazole is HetNon, not HetP as stated.