

CASE REPORT

Role of interferon α in promoting T helper cell type 1 responses in the small intestine in coeliac disease

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Abstract

Coeliac disease (CD) is caused by a CD4 T helper cell type 1 (Th1) response in the small intestinal mucosa to dietary gluten. As the major Th1 inducing cytokine, interleukin 12, is undetectable in CD gut mucosa, the mechanism by which Th1 effector cells are generated remains unknown. Interferon (IFN) α , a cytokine capable of promoting IFN- γ synthesis, has been implicated in the development of Th1 mediated immune diseases. Here we report a case of CD-like enteropathy in a patient receiving IFN- α for chronic myeloid leukaemia. Morphological assessment of duodenal biopsies taken from the patient showed total villous atrophy, crypt cell hyperplasia, and a high number of CD3⁺ intraepithelial lymphocytes. Both antigliadin antibodies and antiendomysial antibodies were positive. RNA analysis revealed pronounced expression of IFN- γ . Withdrawal of gluten from the diet resulted in a patchy improvement in intestinal morphology, normalisation of laboratory parameters, and resolution of clinical symptoms. By western blot analysis, IFN- α protein was seen in the duodenal mucosa from untreated CD patients but not in controls. This was associated with marked expression of IFN- γ protein in CD mucosa. Collectively, these results suggest a role for IFN- α in promoting Th1 responses to gluten.

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Keywords: coeliac disease; interferon; small intestine; T helper cell response

Coeliac disease (CD) affects the proximal small intestine and is caused by a local immune response to dietary gluten in genetically susceptible individuals. The characteristic features of CD inflammation are villus atrophy, crypt cell hyperplasia, and increased number of intraepithelial lymphocytes (IEL). Mucosal surface area is lost as the villi become shorter, causing malabsorption and diarrhoea.¹

A growing body of evidence indicates that CD4⁺ T cell mediated hypersensitivity plays a major role in tissue injury in CD. Lamina propria CD4⁺ T cells are phenotypically activated

and produce large amounts of proinflammatory cytokines when exposed to gluten.²⁻⁴ Previous experimental studies have also shown that direct activation of lamina propria T cells in explant cultures of human fetal gut produces villous atrophy and crypt cell hyperplasia.²⁻⁵⁻⁶ These pathological changes are associated with increased expression of T helper cell type 1 (Th1) cytokines, such as interferon (IFN) γ and tumour necrosis factor α .²⁻⁵⁻⁶ However, there is also increasing evidence that mucosal remodelling, which is seen in CD, is due to cytokine induced perturbations in the production of matrix degrading enzymes and epithelial growth factors by lamina propria fibroblasts.²⁻⁵⁻⁷

Differentiation of T cells towards the Th1 or Th2 subtype is influenced by many factors, including the nature and concentration of the antigen, type of antigen presenting cell (APC), and polarising signals present in the microenvironment.⁸ Paradoxically, the major Th1 inducing factor, interleukin (IL) 12, is virtually undetectable in the gut mucosa of patients with CD, despite the clear polarisation of T cell responses to gluten along the Th1 pathway.³ The mechanism by which Th1 effector cells are generated in CD mucosa therefore remains unknown.

IFN- α is a cytokine produced by virally infected cells. One of its main immunomodulatory activities is its ability to induce and maintain Th1 cells.⁹ There is a strong correlation between IFN- α expression and development of autoimmune diseases in humans and experimental animals.⁹⁻¹¹

In this study we first describe a case of CD, responsive to gluten elimination, in a patient receiving IFN- α treatment for chronic myeloid leukaemia. We also show elevated IFN- α in mucosal biopsies of patients with untreated CD, suggesting a role for IFN- α in promoting Th1 responses to gluten.

Abbreviations used in this paper: CD, coeliac disease; EMA, antiendomysial antibodies; AGA, antigliadin antibodies; Th1, T helper cell type 1; IFN, interferon; IL, interleukin; IEL, intraepithelial lymphocyte; APC, antigen presenting cell.

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Methods

PATIENTS AND CONTROLS

Three biopsy specimens from the distal duodenum of eight patients with untreated CD (aged 5–13 years) were obtained during upper gastrointestinal endoscopy. One specimen was used for routine histological examination whereas the remaining two were immediately frozen in liquid nitrogen and stored until tested. The delay between the beginning of abdominal symptoms and collection of biopsies was 3–12 months. No patient had a recent history of clinically evident intestinal infection. The histopathological diagnosis was based on typical mucosal lesions with crypt cell hyperplasia, villous atrophy, and increased number of IELs. All CD patients were positive for antiendomysial (EMA) and antigliadin (AGA) antibodies. In no patient was gluten challenge performed to confirm the CD diagnosis. A gluten free diet resulted in resolution of symptoms and disappearance of both EMA and AGA after 4–12 months. Control patients (n=5; aged 4–16) were under investigation for gastrointestinal symptoms but had normal histology and were EMA and AGA negative. Biopsy specimens were snap frozen in liquid nitrogen and stored at -70°C until used.

IMMUNOHISTOCHEMISTRY

Frozen sections (6 μm) were stained with anti-CD3 antibody using the indirect peroxidase method.^{5,6}

RNA EXTRACTION, cDNA PREPARATION, AND CYTOKINE RNA DETERMINATION

RNA was extracted from biopsy specimens using 1 ml of a monophasic solution of phenol and guanidine isothiocyanate (TRIZOL, Life Technologies, Paisley, UK) and chloroform, followed by isopropanol (Sigma Chemical, Co, St Louis, Missouri, USA) precipitation. Complementary DNA (cDNA) was synthesised from 1 μg of total RNA, as previously described.¹² Transcripts for IFN- γ were determined by Southern blotting.¹²

WESTERN BLOT ANALYSIS

Total protein was extracted from mucosal samples of CD patients and controls as previously reported.¹² For detection of IFN- α , 300 μg of total protein was separated using 15% sodium dodecyl sulphate-polyacrylamide gel electrophoresis. IFN- α was detected after incubation with a rabbit antihuman IFN- α polyclonal antibody (1:100 final dilution; Immunokontakt, Frankfurt, Germany) and subsequent incubation with a goat antirabbit IgG monoclonal antibody conjugated with peroxidase. After detection of IFN- α by enhanced chemiluminescence, blots were stripped by incubation for 30 minutes at 50°C in stripping medium (2% sodium dodecyl sulphate, 0.05 M Tris (pH 6.8), 0.1 mM β -mercaptoethanol), and subsequently incubated with a goat antihuman IFN- γ polyclonal antibody (Santa Cruz Biotechnology Inc., Santa Cruz, California, USA). IFN- γ protein was identified as above.

Case report

A 61 year old woman presented in May 1999. She had a history of chronic myeloid leukaemia (Philadelphia chromosome positive) diagnosed in June 1998. At the time of diagnosis she was found to have leucocytosis, anaemia, and thrombocytosis. Following initial treatment with hydroxyurea, she was entered into a controlled trial and randomised to treatment with high dose IFN- α 10 MU/day (Wellferon) subcutaneously, in September 1998. Before the start of treatment, she was clinically well with no abdominal or bowel symptoms. She weighed 91 kg (body mass index 33.8 kg/m^2) and had been overweight all of her adult life. She had no past history of note and there was no family history of autoimmune disease. Urea and electrolytes, liver biochemistry, B12 and red cell folate, and C reactive protein were within the normal range. The patient was reviewed regularly in the haematology clinic but felt unwell from the onset of IFN- α therapy, complaining of fatigue, anorexia, and loose bowel movements. During that time no other drug was administered. In December 1998, three months after starting treatment, a 7 kg weight loss was documented and symptoms persisted. In January 1999, the dose of IFN- α was reduced to 7 MU daily. During early 1999 she continued to experience worsening diarrhoea which did not respond to anti-diarrhoeal therapy. The dose of IFN- α was gradually reduced to 3 MU daily. In May 1999 she collapsed and was admitted to hospital. On admission, she complained of paraesthesiae in her hands and feet. Weight loss of 23 kg was documented and carpopedal spasm was witnessed by the admitting doctor. She had bilateral ankle oedema and stool examination revealed steatorrhoea. At the time of admission she was found to have macrocytic anaemia, haemoglobin 10.3 g/dl, mean corpuscular volume 103.3 fl, white cell count $5.2 \times 10^9/\text{l}$, and platelets $376 \times 10^9/\text{l}$. She was hypokalaemic, hypocalcaemic, hypomagnesaemic, hypoalbuminaemic, and folate deficient. Morphological assessment of duodenal biopsy specimens showed total villous atrophy and crypt cell hyperplasia (fig 1).

Immunostaining showed a high number of CD3⁺ IEL (55 IEL/100 enterocytes) (fig 1). There was no increase in epithelial $\gamma\delta$ T cells (<1/100 epithelial cells). Colonoscopy was normal. Tissue typing revealed that the patient had the HLA DQ2 haplotype. AGA and EMA were positive. Analysis of duodenal mucosal RNA showed enhanced transcripts for IFN- γ similar to that detected in patients with proven CD (fig 2, top). Cessation of IFN- α therapy resulted in substantial clinical improvement, although loose stools continued and there was no weight gain. A strict gluten free diet was commenced and all abdominal symptoms resolved. Her weight increased to 75 kg in December 1999 with normal laboratory parameters, including AGA and EMA. Repeat duodenal biopsies showed patchy improvement with appearance of short villi and a decrease in CD3⁺ IEL (20.7/100 enterocytes).

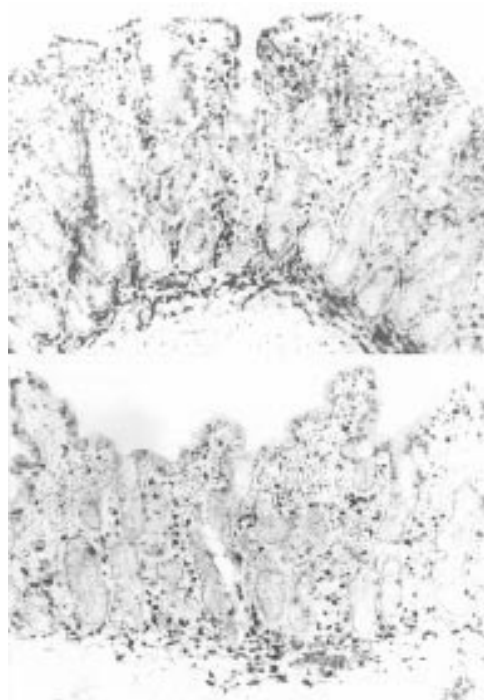


Figure 1 Frozen sections of duodenal biopsies taken from the patient receiving interferon α therapy before (top) and after (bottom) commencing a gluten free diet. Before the gluten free diet, the mucosa is flat, there is a dense infiltrate of intraepithelial lymphocytes (IEL), and there are a large number of non-specific inflammatory cells, as shown by the strongly positive endogenous peroxidase cells in the lamina propria. After four months of a gluten free diet, there are short villi, fewer IELs, and non-specific inflammatory cells are also markedly reduced. Immunoperoxidase with anti-CD3; original magnification $\times 120$.

IFN- α IS EXPRESSED IN CD MUCOSAL TISSUE

To investigate if IFN- α is expressed in CD tissue, western blot analysis was performed using total protein extracted from duodenal mucosal samples of CD patients and controls. In all CD patients, anti-IFN- α antibody detected a protein with a molecular size of 19 kDa, comigrating with recombinant human IFN- α on sodium dodecyl sulphate-polyacrylamide gel electrophoresis (fig 2, bottom). IFN- α was only seen at very low levels in the mucosa of one control subject. In the gut mucosa of patients with CD, IFN- γ was consistently associated with IFN- α expression (fig 2, bottom). No transcripts for IL-12/P40 were detected in mucosal samples of either CD patients or controls (not shown).

Discussion

In this study, we first reported a case of CD-like enteropathy, responsive to gluten elimination, in a patient receiving IFN- α treatment for leukaemia. As the patient was also positive for AGA and EMA, we believe it is fair to conclude that the patient had CD. Secondly, we have shown for the first time the presence of IFN- α in mucosal samples from untreated CD patients but not in controls. Collectively, these data are consistent with previous reports demonstrating that IFN- α can activate autoreactive cells and promote the development of T cell responses to autoantigens,⁹⁻¹¹ but this is the first time that IFN- α has been implicated in the development of a Th1 response to non-self

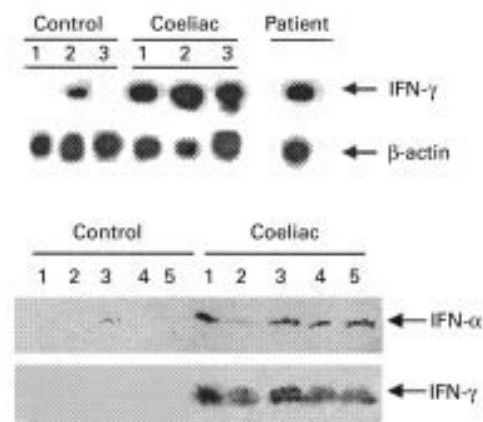


Figure 2 (Top) Southern blot analysis of transcripts for interferon (IFN) γ and β -actin in duodenal mucosal tissue homogenates from three normal controls, three untreated patients with coeliac disease (CD), and the patient with chronic myeloid leukaemia receiving IFN- α treatment before commencing a gluten free diet. A total of 3 or 1.5 μ l of cDNA was amplified using specific primers for IFN- γ (23 cycles) or β -actin (19 cycles), respectively. RT-PCR products were separated on agarose gel, blotted, and hybridised with specific probes for IFN- γ or β -actin. (Bottom) Western blot analysis of IFN- α and IFN- γ protein expression in mucosal samples taken from the distal duodenum of five normal controls and five patients with untreated CD. IFN- α protein was detected in mucosal samples of all CD patients and in one (lane 3) normal control. After stripping, the blot was incubated with an anti-IFN- γ antibody. A protein of approximately 19 kDa was detected only in mucosal samples of CD patients. One of two representative experiments is shown.

antigens. Indeed, we found no association between CD and IFN- α therapy in the literature. In a recently published letter, the occurrence of two cases of CD during treatment with IFN- α was indicated but there were no details on the patients.¹³

We cannot exclude the possibility that the patient had latent or silent CD before IFN- α treatment. We were unable to locate stored sera obtained prior to IFN- α therapy for measurement of EMA which would have helped to answer this question. None the less, the fact that the patient developed overt significant CD after IFN- α treatment indicates that the treatment either precipitated the lesion de novo or exacerbated a mild clinically silent lesion.

Although orally administered IFN- α has been reported to be beneficial in ameliorating immune diseases, there is a large body of evidence indicating the tendency of IFN- α to induce autoimmunity.^{9-11 14 15} The main reason for this is thought to be via induction of increased levels of costimulatory molecules such as B7.2 and ICAM-1 on APC.^{9 16} In normal circumstances where low levels of self antigen are presented on the MHC molecules of APC, a low affinity T cell receptor interaction with peptide/MHC coupled with low expression of costimulatory molecules on APC is insufficient to trigger T cell activation. However, overexpression of costimulatory molecules leads to enhanced costimulation and T cell activation against self peptides.⁸ The reason this patient received IFN- α was because of its ability to induce apoptosis of myeloid leukaemia cells, hence its therapeutic efficacy.⁹ However, IFN- α has opposite effects on

normal T cells in that it can prevent apoptosis induced by IL-2 deprivation of Th1 and Th2 clones in vitro.¹⁷ Similarly, when T blasts are cultured with IFN- α , the cells leave the cell cycle and enter a resting state but do not die.¹⁸ Thus in the context of this patient, the effects of IFN- α are likely to be related to its ability to prevent T cell apoptosis and to increase costimulatory molecules on APC.

In the gut there is a delicate balance between the need to recognise antigens of pathogenic micro-organisms and the need to prevent unwanted immune responses to foods or the normal flora. The site at which this occurs is in the organised lymphoid tissue of Peyer's patches.¹⁹ We have recently demonstrated that T cells in human Peyer's patches are sensitised to dietary proteins but that this is predominantly a Th1-type pathway due to the high local expression of IL-12.²⁰ This response was demonstrated to β -lactoglobulin of cow's milk but there is no a priori reason that the same response should not occur to wheat proteins. Following sensitisation in Peyer's patches, CD4 cells leave via the lymphatics, enter the blood, and migrate back to the lamina propria.¹⁹ These cells are actively secreting IFN- γ . They do not cause disease however because they rapidly undergo apoptosis. They all express Fas, a proportion express FasL, and they express low levels of the Bcl2 survival gene.²¹ In addition, T cells in the lamina propria are actively downregulated. There is low level expression of B7.1 and 2 on lamina propria APC and there is high local concentrations of the immunosuppressive cytokine IL-10 and the non-specific immunosuppressive prostaglandin E₂.^{19, 22} It is noteworthy that in an animal model, inhibition of prostaglandin E₂ can result in T cell mediated responses to food proteins and crypt hyperplasia.²²

Although there is no direct evidence, data produced in other systems suggest that a possible reason why this patient developed CD is because IFN- α prevented apoptosis of lamina propria T cells and increased local expression of accessory molecules in the lamina propria. Gluten reactive CD4⁺ T cells arriving from Peyer's patches could therefore recognise low amounts of dietary gluten presented on lamina propria APC and be triggered because of the high expression of costimulatory molecules. Another potential contributor to the development of excess Th1 responses to gluten in the lamina propria could be due to the fact that IFN- α , after binding to its receptors on T cells, activates transcription factors (for example, STAT1 and STAT4) which then bind to the IFN- γ promoter.⁹ Consistent with this we showed that activation of T cells in the lamina propria of fetal gut explants with IFN- α resulted in marked expression of Th1 cytokines (manuscript in preparation). Finally, it has been demonstrated recently that signalling cross talk occurs between IFN- α/β and IFN- γ , and that IFN- γ mediated cellular events are dependent on IFN- α/β signalling.²³ When inflammation is initiated, local fibroblasts and macrophages produce sufficient IFN- α to maintain Th1 responses,⁹ which is why the

patient's gastrointestinal symptoms did not improve on cessation of IFN- α therapy. This may also be the explanation for the elevated concentrations of IFN- α in untreated CD mucosa.

We do not yet know what induces IFN- α and how IFN- α production is regulated in CD. IFN- α is produced by APC, mostly in response to viruses.⁹ Although IFN- α synthesis is normally a transient phenomenon, abnormal IFN- α expression has been documented in humans in the absence of clinically evident infections.^{9, 18} It is therefore conceivable that low grade viral infections in the gut may elevate local concentrations of IFN- α and in a genetically susceptible individual (for example, HLA-DQ2 positive) may be an important determinant in generating the persistent Th1 gluten reactive cells in the lamina propria which cause the disease.

Taken together, our data are consistent with studies showing the ability of IFN- α to promote the development or exacerbate Th1 mediated diseases.^{24, 25} On the other hand, IFN- α has proved to have beneficial rather than detrimental effects in patients with Crohn's disease, an intestinal inflammatory disorder characterised by an IL-12 dependent Th1 response.^{24, 26} The reason why IFN- α differently modulates immune responses in the gut is unclear. However, it is known that the inflammation ongoing in the intestine of patients with Crohn's disease, but not CD, is associated with an abnormal response to antigens of the intestinal flora.²⁷ Interestingly, type I IFN has been reported to inhibit the synthesis of inflammatory molecules, including IL-12, by bacteria stimulated APCs,²⁸ and thus this mechanism may be responsible for the beneficial effect of type I IFN in Crohn's disease.

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LETTERS TO THE EDITOR

Percutaneous drainage of echinococcal cysts

EDITOR.—We read with interest the critical reply of Dr Morris (*Gut* 2000;47:156-7) to the letter on the use of PAIR (puncture, aspiration, injection, reaspiration) in the treatment of echinococcal cysts. He questioned the safety and efficacy of PAIR and wondered whether there was any other place for PAIR than in situations where surgery was not available. We comment on the risk of sclerosing cholangitis.

We agree with Dr Morris that injection of scolicalid agents into hydatid cysts is a potential risk for sclerosing cholangitis. However, this complication can be avoided when scolicalids are used for the correct indications. Scolicalids are not advocated at surgery because they have been associated with sclerosing cholangitis. The scolicalid probably enters pericystic liver tissue through breaks in the laminated membrane which cannot be identified by the surgeon's eyes.^{1,2} Therefore, in PAIR, as a standard procedure, cystography is performed before scolicalids are used.³ Scolicalids can be safely instilled into the cyst if the laminated layer is intact and a cystobiliary fistula has been excluded. In our experience, cystography is only appropriate in Gharbi type 1 or type 2 cysts but not in type 3 cysts (so-called mother-with-daughter cysts). In type 3 cysts, the many daughter cysts prevent the injected contrast from reaching and demasking a possible fistula (fig 1; left). Therefore, we do not advocate the use of scolicalids in type 3 cysts.

Can patients with type 3 cysts be treated safely with percutaneous drainage? Faced with serious complications such as bile duct obstruction, cholangitis, rupture of cyst content into the biliary tree, sepsis due to cyst infection, and obstruction of portal and

hepatic veins, we modified the PAIR procedure in these patients. After puncture and aspiration, the cyst content is evacuated via a 8-18 F catheter by frequent injection and reaspiration of small amounts of isotonic saline (20-40 ml) using a 60 ml syringe. The daughter cysts readily rupture when aspirated into the catheter. Puncture of each single daughter cyst is not necessary. We avoid injection of alcohol into the mother cyst because of the high occurrence of a cystobiliary fistula. Six of the 10 patients with type 3 cysts that we treated in this way had a cystobiliary fistula. In three the fistula was present before percutaneous aspiration was initiated. In the other three patients the fistula became apparent only after the procedure was completed (fig 1; right). In patients with type 3 cysts, scolicalids may therefore only be used, if at all, after percutaneous evacuation of all daughter cysts and subsequent exclusion of a cystobiliary fistula by cystography. Following the procedure we treat our patients with albendazole 800 mg at breakfast and dinner, for six months. During a follow up period of at least two years, ultrasound and serology are checked at regular intervals.

We do not share Dr Morris' opinion that the best indications for PAIR are only those where surgery is not available. Compared with surgery, PAIR of type 1 cysts is a simple procedure, less invasive, equally effective, and can be carried out in poorly equipped hospitals.^{4,5} Patients with type 3 cysts should be treated by experienced doctors in well equipped hospitals. Currently, most clinicians consider that surgery is the treatment of choice in these latter patients. However, the experience with percutaneous drainage as initial treatment of these complicated cases is growing. In the near future we will learn more about its pros and cons. An open mind for the clinical experience of the WHO working group and of others will be helpful in making up our minds.

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Cystography pre-PAIR



Cystography 6 weeks post-PAIR



Figure 1 Echinococcus cyst Gharbi type 3 in the liver dome of a patient. Left: The many daughter cysts which became apparent after injection of contrast into the mother cyst prevented reliable visualisation of a possible cystobiliary fistula. Right: Six weeks following percutaneous evacuation of the daughter cysts, a cystobiliary fistula was demonstrated by cystography.

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Body mass and gastro-oesophageal reflux symptoms

EDITOR.—In a recent article, Lagergren *et al* (*Gut* 2000;47:26-9) reported no relation between body mass and gastro-oesophageal reflux in a Swedish population and concluded that reflux symptoms occur independently of body mass index. As the authors point out, the evidence on this subject is conflicting. A large recent US cross sectional study¹ reported a strong positive association between body mass index and the prevalence of reflux symptoms (table 1). One possible explanation for the difference between the two studies is the younger age distribution of the US cohort. The prevalence of overweight has increased dramatically throughout Europe and North America in recent decades.² As a consequence, the younger US cohort is likely to have accumulated more person years of overweight by any given age and the risk of reflux symptoms may be related to both the magnitude and years of overweight exposure. The authors also concluded, in the light of their findings, that weight reduction may not be justifiable as an antireflux therapy. Even if overweight is a poor predictor of reflux symptoms, this does not necessarily imply that weight reduction will not be of benefit in providing symptom relief. A significant beneficial effect of weight loss on symptoms of gastro-oesophageal reflux in overweight patients has recently been reported in a small study involving 34 patients.³ In addition, the degree of weight loss was directly correlated with improvement in symptom score. Elsewhere, strong and independent associations have been reported between both overweight and reflux symptoms and oesophageal adenocarcinoma.^{4,5} The evidence suggests that an overweight individual with reflux symptoms is at significantly increased risk of oesophageal adenocarcinoma. Further studies clarifying the role of weight loss in the management of reflux symptoms are clearly warranted.

Table 1 Prevalence of reflux symptoms by body mass index (BMI)

Category	Lagergren <i>et al</i>	Locke <i>et al</i>
Setting	Sweden	USA
Sample size	820	1524
Sex	M/F	M/F
Mean age (y)	66	50
Measurement of BMI	Maximum	Current
BMI <25/<24	16%	15%
BMI 25-29/24-27	16%	17%
BMI 27-30	No data	20%
BMI >30	17%	30%

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Reply

EDITOR.—Like Maric and Cheng, we are also fascinated by the conflicting results in the literature on body weight and its possible association with gastro-oesophageal reflux. The critical question is whether the variation in results is explained by biologically meaningful differences (that is, if there is relevant effect modification) or if the discrepancies should be attributed to various biases, technical flaws, or simply to chance. Although it deserves to be pointed out that our data (*Gut* 2000;47:26-9) primarily pertain to an elderly Swedish population (mean age 66 years), we believe that effect modification by age is a less likely explanation for the discrepancy between our results and those of Locke and colleagues.¹ Unpublished analyses stratified by age in our material showed the same absence of association both in relatively young (age <60 years) and old subjects. The combination of effects of age and nationality (as a proxy for early onset of overweight in the USA), as proposed by Maric and Cheng, seems in our view to be an even more improbable explanation. If the occurrence of reflux symptoms is dependent primarily on accumulated "exposure" to overweight, one would expect to find a stronger relation in our study, which involved older people, presumably with longer exposure time. One would then also expect that the prevalence of reflux symptoms would increase with age. But Locke and colleagues¹ found, if anything, a tendency towards falling rates with age. An increasing prevalence with age was found in only a minority² of numerous similar epidemiological studies. Moreover, if Maric and Cheng's hypothesis on the importance of accumulated time with overweight is correct, our study, which assessed body mass index at different points in time in the past should have had a greater chance of ascertaining any true association compared with the study of Locke *et al* which dealt with only current body mass index.

Non-differential misclassification of both exposure (body mass index) and outcome (reflux symptoms) due to imperfect recollection in our study may have attenuated our estimates.³ But prevalence rates for reflux symptoms well in agreement with the previous literature, and the strong association that we observed between these measures and the

risk of oesophageal adenocarcinoma⁴ somewhat allays this concern. A further possibility that may explain the conflicting results is if the relation between body mass index and reflux propensity is non-linear with a definite trend only in the very high end of the body mass index distribution, and hence the range of body mass index values in the negative studies was insufficient to detect it. The proportion (15%) of obese subjects (body mass index >30) in our sample was considerably lower than that in the Mayo study (23%), and few subjects (n=17) had ever had a body mass index greater than 35. The data of Locke *et al* were not however consistent with such a threshold effect, and although statistical precision was poor, we did not see any important tendency towards a positive relation, even in the very highest end of our body mass index distribution (unpublished data).

Thus the variation in results remains unexplained. Given that there is no clear geographical pattern among positive and negative studies, it appears that genetic differences between populations is an unlikely explanation. While uncontrolled non-randomised intervention studies, like the one cited by Maric and Cheng, contribute relatively little to our understanding of the importance of body weight (patients who manage to lose weight may differ from those who fail to do so in several important aspects), more in depth clinical and epidemiological studies are needed to resolve the apparent enigma.

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Faecal calprotectin levels and colorectal neoplasia

EDITOR.—We read with interest the paper by Kronborg and colleagues (*Gut* 2000;46:795-800)—a large multicentre study measuring faecal calprotectin levels in high risk populations for colorectal neoplasia.

The authors did not discuss their results in comparison with those of Roseth and colleagues¹ or Kristinsson and colleagues² who

did the ground breaking work in this area and where calprotectin levels were shown to be far higher in patients with colonic polyps and cancer compared with normal controls (table 1).

Median values for the control subjects were higher and median values for the colorectal cancer (CRC) and polyp groups were much lower compared with the Norwegian group (who had much greater numbers in the CRC group), combining to markedly reduce the sensitivity of this test.

Furthermore, in the discussion, the authors claim that their results showing no fall in calprotectin levels in patients after polypectomy are similar to those of Kristinsson and colleagues² before and after resection for colon cancer. This is a gross misrepresentation of their findings which clearly show that 24/26 patients who underwent colonic resection had a significant fall in faecal calprotectin levels. The other two patients had bypass operations.

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Reply

EDITOR.—The values in our 488 controls (median 7 mg/l, range 5-7) did not differ from those in the 125 controls in the paper by Kristinsson¹ (median 5.2 mg/l and not 2.5 as quoted by Brydon *et al*).

The lower median values in our 23 cancer patients compared with those in the two other studies^{1,2} is probably due to the less advanced cancers found in our study (six Duke's A, five Duke's B), which mostly included patients in the surveillance programmes. Unfortunately, nothing is told about the size and multitude of the polyps in the study by Roseth and colleagues² but in our study the majority of patients had small adenomas and no more than 1-2, which may explain the slightly lower median values.

Brydon *et al* seem to have misunderstood our discussion of calprotectin levels after polypectomy. We mentioned that the levels after colonic resection for cancer in the study by Kristinsson and colleagues¹ (median 10.3 mg/l, range 1-200) were similar or even higher than those after polypectomy in our

Table 1 Median and range calprotectin levels (mg/l) in the studies of Roseth *et al*, Kristinsson *et al*, and Kronborg *et al*

Study	No of patients	Range	Median	Sensitivity (%)
Roseth (1993) ¹				
Controls	49	0-12	2.5	
Polyps	40	1.5-160	16	80
CRC	53	4-1000	40	95
Kristinsson (1998) ²				
Controls		0-12	2.5	
CRC	119	2-950	52	93
Kronborg (2000)				
Controls	488	5-7	7	
Polyps	300	5-10	9	43
CRC	23	12-31	18	73

CRC, colorectal cancer.

study (median 7.07 mg/l, range 5.26–8.67), lending support to the possibility of a general intestinal mucosal defect.

The calprotectin test still has a sensitivity for colorectal neoplasia which is higher than that of ordinary guaiac tests, but the rather low specificity limits its usefulness to high risk groups.

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Sporadic HEV hepatitis in Italy

EDITOR.—We read with great interest the paper of McCrudden *et al* concerning acute hepatitis E (HEV) in the UK (*Gut* 2000;46:732–3). We agree wholeheartedly with the authors that this form of hepatitis is on the increase in industrialised countries. In Italy, the reported prevalence of anti-HEV IgG positivity ranges from 0.74% to 1.94%,¹ although a recent study found a prevalence of 2.6% in one small town in central Italy.² A value of 1.5% has been reported for the general adult population of the Republic of San Marino.³

We have recently observed two cases of acute hepatitis E with no evidence of any known risk factors.

Case 1. In September 1997, a 45 year old Italian woman (not pregnant) was admitted with a one week history of fever (38°C), dark urine, and upper abdominal pain. The past medical history was unremarkable, and the patient denied recent travel abroad. There was no history of the use of drugs, alcohol, or herbal products that would justify a suspicion of toxic hepatitis.

Transaminase levels were elevated on admission and reached maximum levels approximately one week later (aspartate aminotransferase (AST) 1990 IU/l; alanine aminotransferase (ALT) 1626 IU/l). Eight days after admission total bilirubin was 280.44 µmol/l, direct bilirubin 210.33 µmol/l, alkaline phosphatase 469 IU/l, and lactate dehydrogenase 1011 IU/l. The patient was hepatitis A (HAV) IgG positive and negative for anti-HAV IgM, hepatitis C (HCV), hepatitis B (HBV), hepatitis G (HGV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV) markers. Serum antinuclear, anti-smooth muscle, and antimitochondrial antibodies were absent. The patient was positive for anti-HEV IgG and negative for anti-HEV IgM.

On abdominal sonography the liver appeared mildly enlarged with no intra- or extra-hepatic bile duct dilatation. One month later there was a significant increase in anti-HEV IgG, and serum transaminase levels began to drop. The patient was discharged, and six weeks later jaundice had disappeared and transaminases were within normal limits.

The patient has been followed for approximately three years, during which time she has remained asymptomatic with normal transaminases, bilirubin, alkaline phosphatase, and γ -glutamyl transpeptidase levels.

Anti-HEV IgG titres have decreased but are still positive.

Case 2. A 60 year old housewife presented in our outpatient clinic with a one week history of jaundice, pale stools, and dark urine preceded by malaise, anorexia, and fever. On liver ultrasonography no bile stones or obstruction were found. She had no identifiable risk factors for liver disease, and no history of foreign travel, contact with infected individuals, or toxic exposure. She refused hospitalisation and was followed as an outpatient.

Transaminase levels were elevated (AST 1000 IU/l, ALT 2000 IU/l). Total bilirubin was 328.32 µmol/l, direct bilirubin 241.11 µmol/l, and alkaline phosphatase 450 IU/l. Markers for HAV, HCV, HBV, HGV, CMV, and EBV were negative; she was positive for anti-HEV IgM and negative for anti-HEV IgG. Three weeks later jaundice subsided and transaminases returned to near normal. Six weeks later she was anti-HEV IgG positive, and her liver function tests were normal.

As in the McCrudden series, neither of our two patients presented risk factors for HEV. The increased prevalence of this infection among haemodialysis patients in developed countries⁴ and the association observed in Italy between HEV and hepatitis C clearly show that the orofaecal route is not the only means of transmission.⁵ In light of the acute sporadic HEV cases reported in non-endemic countries with high hygienic standards, it is important that clinicians consider the possibility of HEV infection in patients with clinical and biochemical features of acute non-toxic hepatitis without evidence of exposure to the major hepatitis viruses, even if there are no known risk factors for HEV.

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Re-epithelialisation of Barrett's oesophagus

EDITOR.—We were interested to read the case report by Van Laethem and colleagues of a carcinoma arising under a re-epithelialised segment of Barrett's oesophagus (*Gut* 2000;46:574–577). This raises issues in the debate over ablation of Barrett's epithelium. There has been interest in ablating the columnar epithelium to encourage squamous

regrowth which may reduce the risk of progression to adenocarcinoma. However, there have been numerous reports of buried glands under the regenerated mucosa.^{1–3}

While we accept that columnar glands may persist under the squamous epithelium and that this may represent a continuing carcinoma risk, this is difficult to quantify. Indeed, this is the first report of such a malignant change. It may be that as any buried glands are no longer exposed to potential carcinogens in the form of acid or bile reflux, the risk is reduced. Although the ultimate aim of treatment is to eliminate the risk of potential malignant change, any means of reducing such risk, for example by diminution of the volume of metaplastic tissue, would be worthwhile. This whole issue needs further evaluation by appropriately designed clinical trials.⁴

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Adenocarcinoma arising in columnar lined oesophagus following treatment with argon plasma coagulation

EDITOR.—Following the recent report by Van Laethem *et al* (*Gut* 2000;46:574–7) of adenocarcinoma developing in a patient whose columnar lined oesophagus had been treated by argon plasma coagulation, we wish to highlight a second case.

A 67 year old man presented with epigastric discomfort but no "alarm" symptoms of dysphagia or weight loss. Endoscopy revealed a 5 cm length of columnar lined oesophagus with no evidence of ulceration or stricture. Histology showed intestinal metaplasia with low grade dysplasia. He consented to enter a study of argon plasma coagulation treatment in Barrett's oesophagus.

One half of the affected oesophagus was treated with argon plasma coagulation (Erbe APC 300, Erbe Elektromedizin GmbH, Germany). He was commenced on omeprazole 40 mg. Repeat endoscopy at two months showed macroscopic regrowth of the squamous epithelium in the area treated by argon plasma coagulation. This was confirmed histologically and the previously noted dysplasia had disappeared. He did not attend for repeat endoscopy at four months but was admitted because of significant weight loss and dysphagia. Endoscopy showed a stricture at the gastro-oesophageal junction and biopsies confirmed poorly differentiated adenocarcinoma. CT scanning of the thorax and abdomen showed thickening of the oesophageal wall but no obvious metastases. However, at laparotomy, he was found to have an

unresectable tumour with extensive local spread and distant metastases to the liver.

This case illustrates two key points. Firstly, carcinoma developed in spite of argon plasma coagulation treatment. Only half of the affected mucosa was treated in this study to allow the remaining half to serve as an internal control and so it is impossible to state whether this oesophageal carcinoma arose in the argon plasma coagulation treated or untreated segment. The central issue is whether squamous re-epithelialisation abolishes the malignant potential of the gastro-oesophageal junction. Destruction of columnar epithelium by argon plasma coagulation followed by restitution of squamous epithelium may reverse dysplastic changes but could simply hide them.

Secondly, and perhaps more importantly, this carcinoma went undetected in spite of rigorous endoscopic follow up and a well defined biopsy protocol, raising further doubts over the effectiveness of conventional endoscopic surveillance of columnar lined oesophagus. The surveillance process is subject to several potential sampling errors. The dysplastic process may be patchy and changes may be missed at biopsy. The histological interpretation of dysplasia is subjective and observer dependent. Finally, carcinoma may arise from the submucosal layers of the oesophagus, with very little mucosal abnormality, and beyond the reach of conventional endoscopic biopsy forceps. Such carcinomas are likely to remain undetected until a very late stage.

No evidence of the phenomenon of "buried glands" was seen following argon plasma coagulation treatment in this case. Other authors have reported this appearance following thermal ablative treatment of columnar lined oesophagus.¹⁻⁴ These islands of persistent metaplastic tissue may retain the potential for malignant transformation. Their significance is as yet unclear but, in this case at least, they cannot be implicated in the progression to carcinoma.

All patients with columnar lined oesophagus who have participated in clinical studies of argon plasma coagulation will require close follow up over many years to ensure that potentially malignant tissue has truly been ablated and not merely covered by a "white-wash" of squamous epithelium.

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Reply

EDITOR,—Dr Shand and colleagues clearly underlined, as we did (*Gut* 2000;46:574-7), the major concerns about the eradication of Barrett's mucosa by thermocoagulation. Their case differs from ours in the followings ways: our patient did not show any dysplasia at baseline diagnosis, has completed full eradication of the Barrett's segment, and showed recurrence of neoplastic glands after a period of 18 months, clearly beneath the squamous; this last finding supports the fact that emergence of neoplastic glands was probably newly developed. The present case is interesting because it raises another concern with this type of management; as no buried glands were evidenced under the new squamous layer and the interval between endotherapy and occurrence of unresectable tumour was very short (approximately four months), this case clearly illustrates the need for a complete and optimal staging and mapping of the target areas before starting the destruction of Barrett's mucosa disclosing dysplasia.

As stated and discussed by the authors, the initial dysplastic process was probably patchy and changes may be missed or under staged at biopsy; in this situation, argon plasma coagulation treatment only hides the dysplastic areas.

Furthermore, submucosal origin of the carcinoma ideally should be excluded by performing endoscopic ultrasonography and profound biopsies with large forceps.

Reporting these cases clearly shows that:

- (a) Barrett's mucosa destruction remains experimental and surveillance has to be strictly maintained.
- (b) Selection of patients is paramount and should include accurate staging and mapping of the target areas before endotherapy.

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Outcome of lamivudine resistant hepatitis B virus infection in liver transplant recipients in Singapore

EDITOR,—We read with interest the article by Mutimer and colleagues (*Gut* 2000;46:107-113). The Birmingham group described the clinical course of four liver transplant patients who developed graft infection with lamivudine resistant virus. Lamivudine resistant hepatitis B developed after a mean duration of nine months (range 8-11) after the transplant. Liver function abnormalities occurred at a mean duration of six months (range 3-12) after the emergence of lamivudine resistant virus and three of the four patients died 5-20 months later. The authors concluded that the lamivudine resistant phenotype can cause severe graft damage.

In our liver transplant centre, 12 patients with chronic hepatitis B (four with hepatocellular carcinoma) underwent liver transplantation over a five year period. All were given lamivudine before and after transplant. Lamivudine resistant hepatitis B developed in six of the nine survivors at a mean duration of 60 weeks (range 1-127) after liver transplant. Apart from weaning off immunosuppression aggressively, no further antiviral treatment was added. All six had normal liver function at their last follow up (mean 28, range 0-123

weeks after emergence of lamivudine resistant virus).

Contrary to what the Birmingham group experienced, all of our patients with lamivudine resistant virus were well, with no evidence of graft dysfunction. Long term outcome of such patients remains unknown and it may be premature to conclude that the lamivudine resistant phenotype causes severe graft damage.

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Gastric cancer in patients with benign dyspepsia

EDITOR,—There is an ongoing debate regarding the value of endoscopy in younger patients presenting with dyspepsia. One important consideration is the likelihood of detecting an underlying cancer which might be cured by early treatment. The large retrospective study by Breslin and colleagues in the January issue of *Gut* (2000;46:93-97) indicates that underlying cancer will be diagnosed in about 1 in 1000 patients presenting with uncomplicated dyspepsia under 45 years of age. However, the calculated 95% confidence intervals for this are wide (1 in 2963 to 1 in 300).

An important question in considering the significance of this finding is whether the prevalence of cancer in these patients with benign dyspepsia is any different from that in the general population. In our own country, Scotland, the chance of a patient presenting with gastro-oesophageal cancer before the age of 50 is 1 in 909 (ISD Scotland Cancer Surveillance Group Data Request and Analysis Service) and half of those have presented with the cancer within the age band 45-49. Most of these patients will have had the tumour present in their stomach for a considerable time prior to clinical presentation, which would have been detected by screening endoscopy five years earlier. Even allowing for the fact that population based rates of gastro-oesophageal cancer are higher in Scotland than Alberta,¹ this suggests that the prevalence of underlying cancer in patients presenting with uncomplicated dyspepsia may not be different from that in the general population. Consequently, offering endoscopy to patients with simple uncomplicated dyspepsia to detect cancer may merely represent screening of the general population.

There has been a general assumption that a tumour growing in the stomach will produce dyspeptic symptoms. However, there is no evidence for this. Tumours developing in the colon or other parts of the gastrointestinal tract rarely, if ever, cause symptoms until they produce complications such as bleeding or obstruction.

A very small proportion of patients presenting with uncomplicated dyspepsia will have underlying cancers but this finding may be unrelated to their symptoms. Unless uncomplicated dyspepsia is confirmed to be a symptom of underlying malignancy, then one would be as well to recommend offering endoscopy to patients presenting with a

sprained ankle in order to pick up underlying gastro-oesophageal cancer.

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BOOK REVIEWS

Malignant Liver Tumours. Edited by P-M Clavien (Pp 363; illustrated; £112.00). USA: Blackwells, 1999. ISBN 0-632-04406-3.

Surgeons, hepatologists, and oncologists involved in the management of malignant tumours of the liver now have a variety of recent books available for reference. Some of these texts are primarily concerned with surgical management, with subsidiary chapters on diagnosis, pathology, and other modes of treatment. Others are written from the point of view of the physician or oncologist. This new book has been edited with a change of emphasis in that it attempts to examine and compare critically all of the current modalities of treatment as well as some of those which may be successful in the future. I was pleased with the emphasis on maintaining the quality of life in patients with incurable disease rather than trying everything to gain a little more survival time, a very important principle for physicians and surgeons dealing with this group of malignancies.

In the preface, Professor Clavien emphasises that the optimal management of this difficult and often complicated group of tumours depends on a multidisciplinary team approach and he has edited the text to integrate the investigatory, surgical, and oncological aspects of treatment. Firm editorial control allows each of the chapters to be read as a complete essay but I found that the book also read well as a sequential text with minimal duplication of material in each of the sections. The up to date nature of the book is well illustrated by an example from the section on gene therapy which gives details of a phase one study, from November 1998, of recombinant p53 adenovirus gene therapy.

The book is based on the experience at Duke University, North Carolina, and approximately one third of the 48 contributors are from that institution. However, European practice is well represented by the 12 contributors from six countries, including the UK, on this side of the Atlantic.

The structure of the chapters is sound and each has a small but useful list of additional reading material which is presented as an addendum with short critical comments on each reference. The main reference lists are comprehensive and up to date.

An introductory section includes chapters on pathology, epidemiology, imaging, and

tumour markers. I agree with the authors that the ideal sequence of the investigation of malignant liver tumours remains to be defined and that too many patients receive all possible modalities of imaging as well as a biopsy. They suggest that once the accuracy of the various scanning modalities is decided, it will be possible to reduce the high costs of current investigations. The section on tumour markers is a good critical review of both the value and limitations of the wide range of possible investigations.

The book includes four further main sections. The second section concerns systemic and local therapies such as hepatic artery ligation. This section is well illustrated, as is the remainder of the book, and is followed in the next section by a series of chapters on methods of tumour ablation which include standard liver resection techniques, transplantation, cryoablation, and ethanol injection. Although this is not a book primarily concerned with the details of surgical technique, the important surgical points are described clearly.

The fourth section is an exciting glimpse into the future of gene therapy, immunotherapy, and angiogenesis, and is completed with a clearly written essay on apoptosis (programmed cell death) and its significance in the possible development of new strategies in cancer therapy. The book concludes with a variety of special topics, such as the management of tumours in children, in the elderly, and in pregnancy.

This is a timely book in view of the rapid increase in the numbers of investigations and treatments now available for the management of liver tumours. It provides an excellent introduction to the subject for trainees but at the same time includes enough thoughtful discussion, up to date information, and practical advice to be of use to any general gastroenterologist or liver specialist.

E R HOWARD

Self Assessment Colour Review of Gastroenterology. Edited by A Forbes, NH Gilinsky (Pp 188; illustrated). UK: Manson Publishing, 1999. ISBN 1 874545 47 2.

Recertification or subspecialty exit examinations may trigger a proliferation of self assessment texts, although candidates for part 2 MRCP are currently this book's main market in the UK. On the whole it serves its purpose well and complements the similar sized *MCQs in Gastroenterology* (Bateson and Stephen, 1996; Petroc Press).

The book presents almost 200 illustrated case histories, with questions and well informed answers from 28 gastroenterologists, half from the UK and half from the USA. This is good transatlantic collaboration. Cases cover the range of luminal gastroenterology (including biliary and pancreatic disease), from the common and uncomplicated to the obscure. They are interesting and informative. Some questions are insufficiently concise for MRCP although it is only fair to say that the authors do not set out to follow the format of this examination. Other questions ask the reader to match statements and data, which are good tests of knowledge, especially that of basic gastrointestinal physiology. Indeed, I would have liked to see more physiological questions at the expense of some "picture recognition" cases. This is because the photographic reproduction of some of the 350 or so images is very variable.

Some endoscopic and radiographic images have not reproduced well or are too small to be interpretable. The variety of cases and illustrated answers are, however, stimulating.

Doctors taking MRCP may want to buy a copy although many topics are more appropriate for specialist trainees. Consultant gastroenterologists will find it an entertaining and instructive exercise to dip into the book but I suspect that this will be from the library shelf where it will be one of a series of self assessment titles.

S P L TRAVIS

Pancreatic Disease. Edited by PJ Lankisch, EP DiMugno (Pp 272; illustrated; £49.50). Germany: Springer-Verlag, 1999. ISBN 3-540-65357-0.

This is a meetings book ("songs from the show") containing 24 contributions in just over 260 pages on the state of the art in pancreatic disease, as of September 1998. It is a virtual textbook with eight chapters on acute pancreatitis, eight on chronic pancreatitis, three on cystic fibrosis, four on cancer, and one on epidemiology ("lessons from"). The chapter titles are intriguing, focusing on biological mechanisms and current management attitudes. Genetics features strongly, as well as an emphasis on clinical care and directions for research. The flavour is strongly European: for pancreatic inflammatory disease, both acute and chronic, 11 of the 16 contributions are from Germany (the meeting was, after all, in Munich) giving a welcome access to a literature which is not often cited in English language journals. Most of the chapters are approximately 10 pages long, fully referenced, and up to date. As is inevitable, there is a fair amount of overlap and repetition and the quality is certainly uneven, ranging from detailed molecular pathology suitable for research workers (for example, the chapters on cystic fibrosis, mechanisms of fibrosis in chronic pancreatitis, and growth factors in carcinoma) to what would be more suitable for a lecture to undergraduates (exocrine pancreatic secretion).

However, for those interested in pancreatic disease, this little book (it is a pocket size paperback) offers a useful work of reference. The introductory chapters on the genetics of cellular injury, intracellular events, and immune mechanisms in acute pancreatitis are particularly well done, although the subsequent contributions on varieties of clinical management contain nothing new. The section on chronic pancreatitis contains some overlap between chapters but the contribution on mechanisms of fibrosis and potential therapy using inhibitors is fascinating, if still a distant dream. The chapters on cystic fibrosis are detailed and very interesting with good reviews on the status of gene therapy today and problems with enzyme therapy. The chapter on what we now call idiopathic chronic pancreatitis is certainly worth a careful read. The section on pancreatic cancer is, like the disease, disappointing, representing the essentially bleak situation of specialists searching around for mechanisms and treatment modalities with little success.

In all, as meetings books go, this one should be worth a place in the departmental library if you can afford it. There are lots of good references, figures, and diagrams, and it covers the ground of pancreatic disease very thoroughly.

M SARNER

Clinician's Manual on Managing Dyspepsia. G Holtmann, NJ Talley (Pp 96; £7.75). London: Science Press, 2000. ISBN 1-85873-376-6.

Picture the scene. An international conference on gastroenterology, delegates flow in from the four corners of the earth, a nice hotel near the sea and golf courses, and one of those keypad voting systems. Dyspepsia? Easy! Dish out a PPI and lets get on to the really interesting stuff like fucosyltransferases and Ki-ras gene point mutations.

But wait! The audience has been asked what it would do with a 43 year old man with an 18 month history of vague upper abdominal pain, a stressful life, and a variable response to OTCH₂ blockers. The voting screen reveals an astonishing divergence of opinion about management. A *Helicobacter pylori* test followed by endoscopy if positive? Plenty of PPI and symptomatic review in a couple of months? Urgent or once in a lifetime endoscopy? The Austrian delegation are muttering about psychotherapy and a shady group of surgeons in the corner are all for an exploratory laparotomy.

This is why people keep writing books about dyspepsia and why this book by Gerald Holtmann and Nick Talley is particularly welcome. It succeeds in combing Germanic thoroughness and a degree of didacticism with clarity of thought and a healthy scepticism about what passes for the "literature". The book has clearly been sponsored by Byk Gulden who make pantoprazole because one of their staff has written the preface. However, the authors are scrupulous and objective about their references to individual drugs, and there is nowhere a hint of commercial bias.

The arrangement of the material is traditional but contains some little gems. The section on the definition and clinical presentation of abdominal syndromes includes very helpful information about subgroups of dyspepsia categories and ways of distinguishing between functional dyspepsia and irritable bowel syndrome. The epidemiology is, as you would expect, thorough, and the chapter on the pathophysiology of functional dyspepsia, supported by almost 100 references, is a mine of information with implications for research as well as clinical practice. There is a good section on psychosomatic factors, once again well referenced and reasonably up to date. The chapters on diagnosis and management also cover most of the recent publications but although the cisapride problem is acknowledged, the recent work on a *Helicobacter pylori* test and treat strategy from Bytzer's group did not quite get in. There is a terrifying looking algorithm on the management of dyspepsia which, on closer inspection, turns out to be perfectly sensible. Two randomised controlled trials of herbal medicines in the treatment of dyspepsia are referenced. The section on psychological treatment is short but contains an invaluable table describing the basis of the therapeutic relationship between patient and physician.

There is something here for everyone. The family physician will have to be selective but will find useful guidance on diagnostic and management approaches. Trainees in gastroenterology will find the book stimulating and might well start asking some new research questions about dyspepsia. Established gastroenterologists will need to read this book on the plane when they are next subjected to scrutiny on the Costa del Golf.

R JONES

Clinician's Manual on Management Issues in Gastro-esophageal Reflux Disease. Edited by JJ Misiewicz (Pp 66; illustrated; £11.95) UK: Science Press. ISBN 1-85873-353-7.

I started reading this book not entirely sure whose bookshelf it was designed to be placed on. It is written largely by mainland European gastroenterologists, with one American contribution, and most contributors will be unfamiliar to British readers. The first chapter gets off to an inauspicious start, being in a very stilted language style and giving a rather simplistic overview. The use of various reflux terms is not clear and there seems a surprising statement about the lack of utility of 24 hour pH studies in endoscopy negative reflux patients. In addition, no mention is made of the Dentsleeve catheter in the manometry section, which is an oversight in view of the fact they are discussing LOS relaxation. Thankfully the content and presentation improve dramatically after chapter 1, giving a very useful and informative book on the subject which can be appreciated at all levels of medical training. Specialist registrars will probably find it most helpful as consultants may wish for something a bit more "meaty".

There is a clear concise chapter on short term management, with useful supplementary information and good references, but I detect a slight commercial bias with the PPI recommendations, which is unfortunate as this is clearly a sponsored publication. Long term management is up to date, with even a discussion on the recent conflicting views on *Helicobacter pylori* and proton pump inhibitors, coming down, rightly in my view, on the side of non-eradication. There is a useful summary of the Genval workshop with two clear flowcharts and some specific recommendations on treatment strategies and dosages, which I found particularly helpful. Interestingly, in the "Special management problems" chapter, a different author gives a completely different viewpoint on the *Helicobacter pylori*/proton pump inhibitor debate, which adds a bit of spice. There is a sensible summary of non-cardiac chest pain and clear guidelines on drug treatment of reflux disease in pregnancy. Within the confines of a very short chapter, Barrett's is sensitively handled, as well as other complications of reflux disease, and in the final chapter the indications for surgery are discussed. There follows a description of surgical techniques, including laparoscopic fundoplication, and a detailed analysis of short and long term complications. Overall, this book packs a fair amount into its diminutive size and is sensibly priced. It deserves to be widely read.

A IRELAND

Recent Advances in Coloproctology. Edited by J Beynon, ND Carr (Pp182; illustrated; £80/\$149). Germany: Springer-Verlag, 1999. ISBN 1-85233-169-0.

This book addresses 10 topics in which there has been significant development over the past decade. The subjects discussed are diverse, ranging from the combined surgical treatment for advanced pelvic malignancy to incontinence surgery, and from imaging of the anal canal and rectum to the management of anal fissure.

All topics have dual authorship with the exception of the useful chapter on legal matters by PF Schofield. These authors are all UK based apart from MR Salum and SD Wexner (Cleveland Clinic, Florida).

Do you have comprehensive answers to the following questions? If yes, do not read this book!

Question 1. What surgical procedures are now possible for the elderly unfit patient in whom you have just discovered a small malignant rectal polyp?

The outstanding chapter by Cook and McC Mortensen (John Radcliffe Hospital) on transanal endoscopic microsurgery describes this recent advance eloquently. There is an unusually large number of good illustrations and tables in this chapter which cover all aspects of this minimally invasive technique.

Question 2. What's the latest on troublesome haemorrhoids?

The chapter by EA Carapeti and RKS Phillips (St Mark's Hospital) on the treatment of haemorrhoids is very thorough, ending by focussing on the perioperative care package that has made day case surgery possible. The goal posts really have moved since the days of lengthy inpatient care for all.

Question 3. So doctor, what is the chance that this pouch surgery will work?

Are you up to date on the extensive knowledge that has been gained over the past 15 years on complications and long term outcome of pelvic pouch surgery? In the UK, none has performed more first time pouches nor has anyone as great an experience in revisional pouch surgery as John Nicholls, who addresses this topic.

Question 4. Is laparoscopic colorectal surgery here to stay? What are the indications for it and is there any evidence that it is better than open surgery?

Interestingly, the editors decided to look further afield for the answers in this controversial area.

Coloproctology is the most popular subspecialty among general surgical trainees. One reason for this is that it is a specialty on the move. There are recent advances in many other areas left for future editions of this book: management of acute colitis, colonic stenting, training, the input of colorectal nurse specialists, to name a few. I hope these future editions will also have input from gastroenterology, nursing, oncology, and radiology. After all, the editors acknowledge in the preface that coloproctology has now been transformed from a purely surgical to a multidisciplinary specialty.

The reputation of the colorectal unit at Singleton Hospital (where the editors are based) will certainly be further enhanced by this well collated and useful book.

A LEATHER

CORRECTIONS

Errors occurred in the UEGW abstracts supplement *Gut* 2000;47(suppl III). For abstracts A136 and A160, the complete author list for both abstracts is M M Diculescu, E M Ionescu, M Ciocirlan, M Prunescu, R Iacob, S Iacob, C Apetrechioaie, A Oproiu. For abstract A271, the complete author list is H J Tan and D G Nasmyth.

The authors of a case report published in March (*Gut* 2001;48:425-9) would like to add C McKenzie as the second last author. Her affiliation is the University of Southampton. The authors would also like to acknowledge that the work was supported by the Biotechnology and Biological Sciences Research Council (BBSRC).

NOTES

GASTRO 2001

The Annual Scientific Meeting of the Malaysian Society of Gastroenterology and Hepatology (MSGH) will be held on 5-8 April 2001 in Sabah, Borneo. Further information: GASTRO 2001, 19, Jalan Folly Barat, 50480 Kuala Lumpur, Malaysia. Tel: +603 2530100/2530200; fax: +603 2530900; email: acadmed@po.jaring.my; website: gastro2001.homestead.com/files/index.htm

Redefining Priorities in Gastroenterology

This congress will be held on 11-14 April 2001 in Monte Carlo, Italy. It will be chaired by Professor Massimo Crespi (Rome, Italy) and Professor Eammon Quigley (Cork, Ireland). Further information: Maddalena Massaro, Project Leader, AISC-AIM Group, Via A Ristori 38, 00187 Rome, Italy. Tel: +39 06 809681; fax: +39 06 80968229; email: gastro2001@aisc.it.

3rd European Federation of Autonomic Societies (EFAS)

The third European Federation of Autonomic Societies (EFAS) meeting in conjunction with the annual meeting of the sections "Autonomic nervous system" of the German Neurological Society, "Diabetes and Nervous System" of the German Neurological Society, and "Autonomic Nervous System" at the University of Erlangen-Nuremberg, Germany, will be held in Erlangen, Germany on 26-28 April 2001. Further information: Professor Dr M J Hinz, Department of Neurology, University of Erlangen-Nuremberg, Schwabachanlage 6, D-91054 Erlangen, Germany. Tel: +49 0131 8534444; fax: +49 9131 8534328; website: www.neurologie.med.uni-erlangen.de/oeffentliche_Veranstaltungen.htm

Falk Workshop

The workshop entitled Update in Inflammatory Bowel Diseases will be held in Ljubljana, Slovenia, on 5 May 2001. Further information: Prof Dr S Markovič, University Medical Center Ljubljana, Division of Internal Medicine, Japljeva 2, 1525 Ljubljana, Slovenia. Tel: +386 (1) 231 6925; fax: +386 (1) 433 4190; email: sasa.markovic@kclj.si

11th International Workshop of Digestive Endoscopy, Ultrasonography, and Radiology

This workshop will be held on 17-18 May 2001 in Marseille, France. Further information: Nathalie Fontant, Atelier Phenix, 41 rue Docteur Morucci, 13006 Marseille, France. Tel: +33 (0)4 91 37 50 83; fax: +33 (0)4 91 57 15 28; email: nfontant@aphenix.com

EPGS Endosonography Live in Amsterdam

This European Postgraduate Gastro-Surgical School congress will take place on 31 May and 1 June 2001 in Amsterdam, the Netherlands. Further information: Mrs Helma Stockmann/Mrs Joy Goedkoop, European Postgraduate Gastro-Surgical School, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. Tel: +31 20 566 3926; fax: +31 20 566 6569; email: W.J.Stockmann@amc.uva.nl; website: www.epgs.nl.

33rd European Pancreatic Club

The meeting will take place on 13-16 June 2001 in Toulouse, France. A training course will be organised on 13 June on "Genomics and post genomics: developments in biomedical sciences". Further information: Dr Nicole Vaysse, Inserm U531, CHU Rangueil, 31403 Toulouse, France. Tel: +33 (0)5 61 32 24 02; fax: +33 (0)5 61 32 24 03; email: nicole.vaysse@rangueil.inserm.fr; website: www.e-p-c.org.

Gastroenterology and Endotherapy: XIXth European Workshop

This course, to introduce the experienced gastroenterologist to the growing field of therapeutic endoscopy, will be held on 18-20 June 2001 in Brussels, Belgium. Further information: Mrs Nancy Beauprez, Gastroenterology Department, Erasme Hospital, Route de Lennik 808, B-1070 Brussels. Tel:

+32 02 555 49 00; fax: +32 02 555 49 01; email: beauprez@ulb.ac.be

Falk Symposium

The symposium Inflammatory Bowel Disease: A Clinical Case Approach to Pathophysiology, Diagnosis, and Treatment will be held in Bologna, Italy on 22-23 June 2001. Further information: Prof Dr M Campieri/ Dr P Gionchetti, Policlinico S. Orsola - Malpighi, Dipartimento di Medicina Interna e Gastroenterologia, Via Massarenti 9, I-40138 Bologna, Italy. Tel: +39 (051) 6364 116 or 6364 122; fax: +39 (051) 392538; email: campieri@med.unibo.it or paolo@med.unibo.it

Summer Abdominal Imaging Conference

A five day course designed for the practising radiologist with a primary interest in abdominal imaging, emphasising the most recent advances in helical CT, MRI, US, and gastrointestinal imaging. It will be held on 23-27 July 2001 in Banff Springs, Canadian Rockies. Twenty-five category 1 credit hours. Further information: Janice Ford Benner, University of Pennsylvania Medical Center (Radiology), 3400 Spruce Street, 1 Silverstein Building, Philadelphia, PA 19104, USA. Tel: +1 215 662 6904; fax: +1 215 349 5925.

Torino-Toronto First Jointed Workshop on Therapeutic Endoscopy

This workshop will be held on 13-15 September 2001 in Turin, Italy. Further information: Anna Botto, MAF Servizi, Congress Division, Via GB Vico, 7, 10128 Turin, Italy. Tel: +39 011 505 900; fax: +39 011 505 976; email: abotto@mafservizi.it

ICGH-2: The Second Iranian Congress of Gastroenterology and Hepatology

The main Iranian meeting of gastroenterologists and researchers in this field will be held on 27 October to 1 November 2001 in Tehran, Iran. Further information: Dr Shahin Merat, Digestive Diseases Research Center, Shariati Hospital, N. Kargar Street, Tehran 14114, Iran. Tel: +98 911 717 3966; fax: +98 21 225 3635; email: merat@ams.ac.ir; website: www.ams.ac.ir/icgh. **Deadline for submission of abstracts is 31 May 2001.**