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 extrahepatic 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 countries[4] and the association observed in Italy between HEV and hepatitis C clearly show that the orofaecal route is not the only means of transmission.[2 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 "whitewash" 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 neoplasic 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* (*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