

# PostScript

## LETTERS

### Pitfalls in diagnosing acute pancreatitis

We thank Jolobe for his letter (*Gut* 2005;54:1207-8) which mentions the difficulty of establishing the diagnosis of acute pancreatitis in patients with diabetic ketoacidosis.

We did not address diagnostic tests and medical intensive care treatment of acute pancreatitis in our article,<sup>1</sup> but reviewed the interventional and surgical treatment strategies in acute pancreatitis. There is no doubt that treatment of acute pancreatitis, including organ failure in its early phase, is solely supportive.<sup>2</sup> Due to improvements in intensive care medicine, mortality of severe disease has decreased dramatically over the past decades. However, to treat patient adequately, the correct diagnosis has to be made. Therefore, the first step in the diagnostic process of acute pancreatitis is to think of this disease. According to the latest classification from Atlanta,<sup>3</sup> acute pancreatitis is an acute inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ systems. From a clinical point of view, acute upper abdominal pain and elevated pancreatic enzyme levels are needed to diagnose acute pancreatitis. As pointed out by Jolobe in his letter, acute pancreatitis is still underdiagnosed under certain clinical conditions, including diabetic ketoacidosis, but also in other clinical situations, such as shock of unknown origin, patients under intensive care treatment, as well as rare causes of the disease. As acute pancreatitis can be associated with diabetic ketoacidosis and the association between these two is a two way cause-and-effect relationship, early imaging of the pancreas is recommended in these patients to establish the correct diagnosis.

Our article focused on the surgical and interventional treatment of severe acute pancreatitis.<sup>1</sup>

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International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992. *Arch Surg* 1993;128:586-90.

### Severe recurrent Crohn's disease of the ileocolonic anastomosis disappearing completely with antibacterial therapy

Intestinal bacteria play an important role in the pathogenesis of Crohn's disease, which occurs at sites with the highest concentrations of bacteria. Adherent invasive *Escherichia coli* associate with the ileal mucosa in Crohn's disease,<sup>1</sup> and *E coli*, *Bacteroides*, and fusiform bacteria are associated with early disease recurrence after surgical resection.<sup>2</sup> The incidence of clinical recurrence is approximately 50% at three years, with the risk higher in smokers than non-smokers. Endoscopic recurrence occurs in 73-90% of patients one year after surgery,<sup>3</sup> and clinical disease correlates reasonably well with the endoscopic score.<sup>4</sup> Current postoperative prophylaxis therapies are unsatisfactory. Mesalazine 3 g daily, 6-mercaptopurine 50 mg daily, and azathioprine 2 mg/kg daily are only slightly more effective than placebo.<sup>5</sup> Antimicrobial agents have demonstrated efficacy in postoperative prophylaxis reducing the recurrence at the ileocolonic anastomosis. Metronidazole reduced severe endoscopic recurrence at three months and reduced clinical relapse at one year, but was poorly tolerated with significant nausea and vomiting.<sup>6</sup> Ornidazole 1 g daily for one year post-operatively reduced severe endoscopic and clinical recurrence at one year but not at two or three years.<sup>7</sup> We report a case of severe recurrent ileocolonic disease successfully treated with combination ciprofloxacin and metronidazole.

A 23 year old man with a three month history of abdominal pain and diarrhoea was diagnosed with Crohn's disease in October 1996 after a small bowel series revealed narrowing and ulceration of the distal 10 cm of the terminal ileum. His symptoms were steroid responsive for two years. Colonoscopy in June 1998 for recurrent abdominal pain showed severe ulceration and stenosis of the ileocaecal valve and with his symptoms unresponsive to corticosteroids he underwent surgical resection of a segment of severe fistulising terminal ileal Crohn's disease. The remaining small bowel appeared normal. Histopathology confirmed severe active cicatrising Crohn's disease, with stenosis and gross wall thickening with a cobblestone appearance. He made an uncomplicated recovery and remained well without medication. Follow up colonoscopy in April 1999 demonstrated minor recurrent Crohn's disease affecting one third of the ileocolonic anastomosis. He commenced metronidazole 400 mg daily, and on colonoscopy in March 2000 had severe inflammation and narrowing of the entire circumference of the ileocolonic anastomosis preventing ileal intubation. Ciprofloxacin 750 mg/day was added to the metronidazole. Colonoscopy in August 2001 showed superficial ulceration of less than one third of the anastomosis, minimal narrowing,

and a normal neoterminal ileum and colon. He continued metronidazole 400 mg daily and ciprofloxacin 750 mg alternate daily until January 2003 when colonoscopy demonstrated a normal anastomosis, neoterminal ileum, and colon. The patient remained on ciprofloxacin 750 mg twice weekly and metronidazole was ceased. Colonoscopy 12 months later showed very minor ulceration affecting 5 mm of the anastomosis, no significant narrowing, and a normal neoterminal ileum.

Ciprofloxacin, a fluoroquinolone, is effective against intestinal aerobic Gram negative bacteria such as *E coli*, *Shigella*, *Salmonella*, and clostridial species. It is well tolerated even with prolonged use<sup>8</sup> but can cause hepatotoxicity and tendon fragility. In Crohn's disease trials, ciprofloxacin was superior to placebo in decreasing the Crohn's disease activity index in one study<sup>9</sup> but ciprofloxacin and metronidazole in combination with budesonide showed no benefit over placebo and budesonide. However, subgroup analysis by disease site revealed a clear improvement in the antibiotic treated group with Crohn's colitis.<sup>10</sup>

To our knowledge, this is the first report of antibacterial therapy producing complete endoscopic resolution of severe postoperative recurrence at the ileocolonic anastomosis. This patient has remained well, and has not developed any untoward side effects. We believe a controlled trial should be performed to test whether low dose ciprofloxacin alone or in combination can prevent recurrence of Crohn's disease at the ileocolonic anastomosis.

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## A new entity of hereditary colorectal cancer

Mueller-Koch *et al* describe clinical and molecular evidence for a "new entity" of hereditary colorectal cancer (CRC).<sup>1</sup> Clustering of CRC within families has been known for some time<sup>2</sup> and it is not surprising that some such families will meet the Amsterdam criteria (AC) even though they do not carry a germline mutation in a DNA mismatch repair gene. It has been demonstrated previously that AC positive families without evidence of a DNA mismatch repair defect do not show either the clinical or pathological features of the hereditary non-polyposis colorectal cancer/Lynch syndrome.<sup>3</sup> With respect to CRC, differences extend to multiplicity, anatomical site, histopathology, and DNA ploidy status.<sup>3</sup> With respect to colorectal adenomas, these are more frequent but less advanced in AC positive families in which there is no evidence of a DNA mismatch repair defect.<sup>4</sup> More recently it has been shown that the differences extend to the risks of developing both CRC and extracolonic cancer.<sup>5</sup> The fundamental issue is whether it is reasonable to continue to use the limited set of clinical features that comprise the AC as a diagnostic label when there is clear evidence that families that meet the AC are clinically heterogeneous.<sup>6</sup>

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## Antiapoptosis action of aged garlic extract (AGE) protects epithelial cells from methotrexate induced injury

Methotrexate (MTX) is widely used not only as a chemotherapeutic agent for the treatment of many cancers but also as an anti-inflammatory and immunosuppressive agent. MTX treatment is often accompanied by side effects such as nausea, vomiting, diarrhoea, stomatitis, gastrointestinal ulceration, and mucositis. The therapeutic use of MTX has been limited by its toxicity for proliferating cells, especially the rapidly dividing cells of intestinal crypts. MTX inhibited intestinal epithelial proliferation and induced apoptosis in the small intestinal crypts.<sup>1,2</sup> However, there is little effective treatment to reduce the MTX induced gastrointestinal toxicity.

Garlic (*Allium sativum*) has various biological properties such as antimicrobial and antithrombotic activities, immune system enhancement, and antitumour potential.<sup>3</sup> Aged garlic extract (AGE) and its constituents have been shown to prevent oxidative injury in endothelial cells<sup>4</sup> and suppress cancer cell growth.<sup>5</sup> We have previously shown that AGE protects the small intestine of rats from MTX induced injury.<sup>6,7</sup> Therefore, AGE seems to act on tumour cells and normal intestinal cells in different ways.

IEC-6 is an immortalised epithelial cell line derived from neonatal rat ileum which has been extensively used as an in vitro intestinal model.<sup>8</sup> Exposure of IEC-6 cells to MTX significantly decreased cell viability, depending on exposure time and MTX concentration, which was prevented by AGE. IEC-6 cells exposed to 1  $\mu$ M MTX for 72 h showed nucleus condensation by Hoechst staining. Addition of AGE (0.5%) to the medium containing 1  $\mu$ M MTX inhibited MTX induced nucleus condensation. DNA of IEC-6 cells treated with MTX and/or AGE was isolated and analysed by agarose gel electrophoresis (fig 1). MTX caused DNA fragmentation while AGE inhibited MTX induced fragmentation of DNA. Caspase-3 activity in

IEC-6 cells exposed to MTX was significantly upregulated. AGE (0.5%) significantly reduced activation of caspase-3 induced by MTX. Caspase-3, a key enzyme for execution of apoptosis in many instances, also plays a central role for MTX induced apoptosis in IEC-6 cells. MTX induced the release of cytochrome *c* from mitochondria into the cytosol, indicating a prominent downstream manifestation of the evolution of apoptotic cell death. Interestingly, AGE prevented the release of cytochrome *c*. These results indicate that MTX induced the death of IEC-6 cells through apoptosis, consistent with the previous observation that MTX induced apoptosis in the small intestine.<sup>2</sup>

In vivo, in rats given MTX, AGE protected the small intestine from MTX induced injury.<sup>6,7</sup> In vivo IEC-6 cells originating from crypt cells of the rat small intestine, MTX induced loss of viable IEC-6 cells was almost completely prevented by the presence of more than 0.1% AGE. Chromatin condensation, DNA fragmentation, caspase-3 activation, and cytochrome *c* release, which were caused by MTX, were preserved to control levels by the presence of AGE. These results suggest that AGE inhibits MTX induced apoptosis in IEC-6 cells. The protective effect of AGE may be associated with depression of oxidative stress as AGE has the effect of antioxidation.<sup>9</sup> On the other hand, oxidative stress was shown to be involved in MTX induced toxicity of the small intestine.<sup>10</sup>

These cell culture studies indicate that AGE protects IEC-6 cells from MTX induced injury. The protective effect of AGE found in IEC-6 cells may possibly occur through the antiapoptosis action of AGE, newly found in this study, and can explain the reason why AGE administered to rats protects the small intestine from the injury induced by MTX administration.<sup>6,7</sup> AGE may be useful for cancer chemotherapy with MTX because it reduces MTX induced intestinal injury.

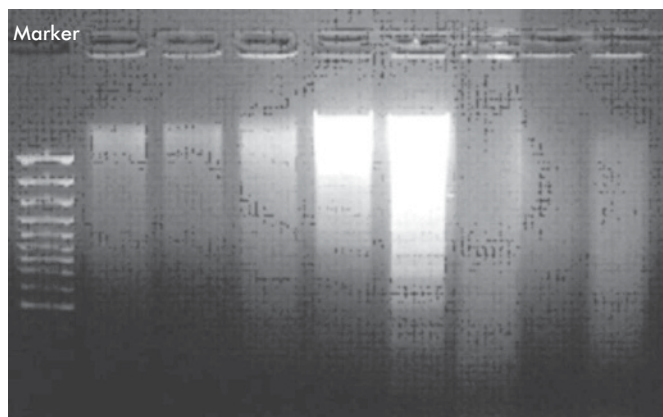
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MTX ( $\mu$ M)	0	0.01	0.1	1	10	0	1	1
AGE (%)	0	0	0	0	0	0.5	0.5	1



**Figure 1** Effect of aged garlic extract (AGE) on DNA fragmentation in methotrexate (MTX) treated IEC-6 cells. IEC-6 cells were treated with various concentrations of MTX and AGE for 72 h. DNA was extracted and subjected to agarose gel electrophoresis. Experiments were repeated three times with similar results.

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**Tuberculous colitis**

With great interest we read the tutorial by Forbes (*Gut* 2005;**54**:1156). We would like to stress that the count of CD4 lymphocytes (and possibly immunoglobulins) might be quite helpful in the differential diagnosis of chronic inflammatory bowel disease and tuberculosis, as evidenced by the following case report.

A 35 year old Iranian patient presented to our clinic with chronic diarrhoea, intermittent abdominal pain, and a 10 kg weight loss over the last four months. The right lower abdomen was slightly tender at physical examination. Routine laboratory tests revealed hypochromic microcytic anaemia, an elevated erythrocyte sedimentation rate (88 mm in the first hour), and a low serum albumin of 25 g/l (normal range 35–50). Multiple ulcers with signs of scarring were detected by colonoscopy in the distal ascending colon (fig 1A).

Histological examination of biopsy specimens disclosed granulomatous disease of the ascending colon (fig 1B) but normal mucosa in the more distal colon and rectum. Despite a normal peripheral leucocyte count, peripheral CD4 lymphocytes had decreased to 17/μl (normal range 400–1800).

Human immunodeficiency virus infection was excluded. However, the tuberculin test was positive, and Ziehl-Neelsen staining demonstrated acid fast bacilli in colonic biopsies (fig 1C). The left lung showed some pleural scarring on chest x ray. Ultrasound revealed slight pericardial effusion as well as some ascites. Antituberculous chemotherapy was initiated, and non-resistant *Mycobacterium tuberculosis* was finally cultured from colonic biopsies. Now, five years later, the patient is well, and peripheral CD4 lymphocyte count has normalised.

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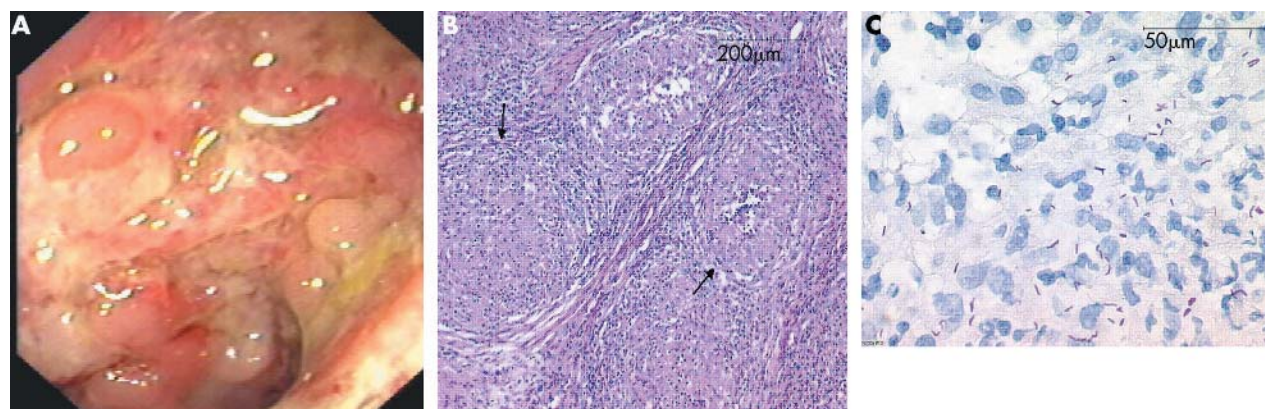
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**Endocinch treatment for GORD: where it stands**

We read with great interest the article by Schiefke and colleagues (*Gut* 2005;**54**:752–8) on the long term failure of endoscopic gastroplication (Endocinch). The authors reported more than 80% of patients had lost at least one suture and only 17% had all sutures in situ after 18 months (clip device). Loss of plications has been reported both with knot<sup>1</sup> as well as clip devices (*Gut* 2005;**54**:752–8) used for anchoring sutures but seems to be more with the later. Further

studies are needed to confirm above. However, a previous study did not find a significant difference between the mean tensile failure force (tissue tear out and suture disruption) for the knot compared with the clip device anchoring technique.<sup>2</sup> The depth of a suture seems to be an important factor in the durability of a suture. With the present size of a suction chamber in a sewing capsule after an appropriate suction an average depth of a suture would be 2.86 ± 0.91 mm.<sup>3</sup> This enable placement of most of the sutures in the submucosal layer of the stomach and some sutures may enter the muscular wall. Hence increasing the size of the suction chamber may increase the depth of suture, which may improve the durability of sutures.

The procedure has been followed up for 1–4 years in other published series. At one year of follow up, the marked improvement in gastro-oesophageal reflux disease (GORD) symptoms, quality of life, and reduced requirements for proton pump inhibitors (PPIs) using the Endocinch technique is associated with some continuing oesophageal acid reflux.<sup>1,4</sup> Those patients who did not revert to PPIs at 12 months had a significantly lower degree of acid reflux at three months than those who went back on PPIs. The reason why some patients went back on PPIs is unclear but it may relate to the higher DeMeester score in this group pre-procedure.<sup>1</sup> Two years post-procedure follow up (n = 33) from the US multicentre study revealed a sustained significant improvement in symptom score and regurgitation. Twenty five per cent were completely off antisecretory medication and 26% were requiring less than or equal to half of their initial PPI/H<sub>2</sub> blockers.<sup>5</sup> In the paediatric group at 33 months post-procedure, 82% maintained their symptomatic improvement and remained off all antireflux medications.<sup>6</sup> Most patients with good improvement maintain their improvement at 2–4 years.<sup>7</sup> A non-randomised comparison study between Endocinch and the gold standard laparoscopic Nissen fundoplication (LNF) revealed significant reduction in symptom and regurgitation score, requirement for antisecretory medications, and improved quality of life in both groups. However, physiological control of acid reflux was significantly better in the LNF group at the expense of a higher incidence of post-procedure dysphagia and difficulty in vomiting and belching.<sup>8</sup>



**Figure 1** (A) Colonoscopy showing multiple ulcers with signs of scarring in the distal ascending colon. (B) Histological examination of biopsy specimens of the ascending colon showed granulomatous disease. (C) Ziehl-Neelsen staining demonstrated acid fast bacilli in colonic biopsies.

Better outcome shown by Thomson and colleagues<sup>6</sup> in respect of symptom improvement and oesophageal pH control was probably due to better sedation which may have provided a relaxed and safe environment for taking deeper stitches. Also, they took three as compared with two plications in all other Endocinch studies. Hence further studies are necessary to determine what modifications to this technique are required in order to produce the maximum clinical benefit and to prevent complications associated with GORD. At this stage in its development it is important that medical practitioners using Endocinch should enter their results into formal trials to assess and improve its efficacy and durability. Nevertheless, the Endocinch technique has added a new and exciting era which has the potential to improve the quality of life of patients with GORD.

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## PMS2 mutations in childhood cancer

We refer to the recent paper by Durno *et al* "Family history and molecular features of children, adolescents, and young adults with colorectal carcinoma" (*Gut* 2005;**54**:1146–50).

Among other patients with early onset colorectal cancer (CRC), the authors discuss a girl with CRC onset at the age of 12 years, and a subsequent second primary tumour

(glioblastoma). This patient appears to be the sister of a male Turcot syndrome patient described in 1995.<sup>1</sup> However, although referred to in that original report, she was not explicitly stated to carry the same *PMS2* mutation (R134X) as her brother, and so whether her mutation was assumed or verified by Durno *et al* is unclear.

More importantly, the authors have overlooked the fact that both of these siblings have since been shown to be compound heterozygotes for the *PMS2* mutations R134X and 2184delTC.<sup>2</sup> The fact that these patients have germline mutations on *both* alleles offers an explanation for the earlier observation of a high degree of microsatellite instability (MSI) in their constitutional DNA, not just in tumour DNA.<sup>3</sup>

We have previously pointed out that in the childhood cancer families so far described, *PMS2* mutations behave recessively, the parents of the homozygous or compound heterozygous patients being, by and large, tumour free.<sup>2</sup>

While other recent publications do suggest that heterozygous *PMS2* mutations can predispose to CRC,<sup>4–7</sup> these mutations appear, for unknown reasons, to be less penetrant than "classical" hereditary non-polyposis colorectal cancer alleles of, for example, *MLH1* or *MSH2*. Certainly, on the present evidence, a heterozygous *PMS2* mutation is unlikely to account for a childhood cancer presentation.

Indeed, given that one of the other cases described by Durno *et al* was also homozygous for an *MLH1* mutation, we would like to emphasize again that a childhood (as opposed to early adult) presentation of CRC or other MSI positive tumour should signal the possibility of a biallelic mismatch repair defect. Demonstration of MSI in constitutional DNA would in such circumstances point directly to the likelihood of biallelic mutation of one of the mismatch repair genes, with important implications for genetic management.

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## Epithelial cells in bone marrow: do they matter?

We read with great interest the letter of Steinert and colleagues (*Gut* 2005;**54**:1045–6). They described disseminated epithelial cells in the bone marrow of patients with colorectal adenomas. As adenomas are non-cancerous, it is questionable whether these epithelial-like cells really represent disseminated cancer cells. If so, the benign nature of intraepithelial neoplasia is basically challenged.

The search for micrometastatic disease in the bone marrow of cancer patients is an intriguing field in which many different diagnostic molecular modalities are being explored. However, the clinical impact of bone marrow micrometastatic disease is not clear. Patients with breast cancer frequently develop clinically manifest bone marrow metastases and in these patients detection of this type of micrometastatic disease has been shown to have prognostic impact.<sup>1,2</sup> Gastrointestinal cancers, however, rarely develop overt bone marrow metastases and also the clinical impact of the detection of bone marrow micrometastases in these patients is less clear.

We studied the impact of bone marrow micrometastases in patients with oesophageal adenocarcinoma and encountered a concern which might be relevant for the interpretation of the conflicting findings, as described by Steinert *et al*. We obtained bone marrow samples of 20 patients who underwent a potentially curative oesophagectomy for oesophageal adenocarcinoma. Cytospins of these samples were stained with Ber-EP4 (Dako, Hamburg, Germany) and A45-B/B3 (Micromet, Munich, Germany) using the alkaline phosphatase-antialkaline phosphatase technique. In this series we found positive staining for these epithelial markers in four (20%) and five (25%) of the patients for Ber-EP4 and A45-B/B3, respectively. As a negative control group we obtained a bone marrow sample in 20 patients who underwent cardiac surgery and had no known cancerous disease. In this control group, to our surprise, we found positive stainings in three (15%) and four (20%) patients for Ber-EP4 and A45-B/B3, respectively. Positive staining in the bone marrow of patients with no known cancerous disease indicates that such results should be interpreted with caution and that these cells do not necessarily represent micrometastatic disease.

Many groups have studied micrometastatic disease for which many different detection methods have been used. Studies that have examined negative control patients have also reported positive bone marrow staining for Ber-EP4 cells in up to 10% of patients.<sup>3,4</sup> One study focused on the methodology of the alkaline phosphatase-antialkaline phosphatase staining and reported positive staining in up to 42% of patients without cancer. Based on these results it was suggested that plasma cells can directly react to alkaline phosphatase.<sup>5</sup> Morphology of the cells is another important factor in the evaluation of possible micrometastases. In fig 1 of the letter Steinert

*et al*, the cells do not have the morphological aspect of a tumour cell and also in other papers on micrometastases, morphology of the cells is not taken into account. In our data set, we could not detect cells in the bone marrow cytopins which had the morphological aspect of a tumour cell.

With current techniques, epithelial-like cells can be detected in the bone marrow of many patients not known to have cancer. Probably these cells have no clinical relevance in patients with adenomas. In future studies, more attention should be paid to the morphological criteria of the cells.

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## Symptomatic eosinophilic gastritis cured with *Helicobacter pylori* eradication

Eosinophilic gastroenteritis is a disorder of unknown aetiology, characterised by eosinophilic infiltration of the gastric and intestinal mucosa and peripheral eosinophilia. To date, only two cases have reported the coexistence of *Helicobacter pylori* gastritis and eosinophilic gastroenteritis. In none of these cases was a causal association between these two entities documented.<sup>1,2</sup> We present a case of eosinophilic gastritis cured with *H pylori* eradication therapy.

A 44 year old woman presented with a two month history of vomiting, nausea, and crampy abdominal pain. Her past medical history included idiopathic thrombocytopenic purpura, splenectomy at the age of 11 years, hyperlipidaemia, hypertension, diabetes mellitus type II, and depression. Her medication included valsartan, atenolol, nifedipine, glimepiride, metformin hydrochloride, indapamide, and venlafaxine hydrochloride. No food allergy or intolerance was reported.

She lived on a Greek island and did not smoke or drink alcohol. Physical examination revealed only mild diffuse epigastric and

abdominal tenderness, and no signs of systemic vasculitis or connective tissue disease were present. Laboratory evaluation revealed a white blood cells count of 14 900 cells/mm<sup>3</sup> (normal 4000–10 000) with an eosinophilic count of 2680 cells/mm<sup>3</sup> (normal 0–800), and a normal platelet count (187 000/mm<sup>3</sup>) and haemoglobin level (12.8 g/dl). Serum glucose was 158 mg/dl (normal 70–105), alanine aminotransferase 38 mU/ml (normal 10–28),  $\gamma$ -glutamyl transferase 44 mU/ml (normal 9–30), erythrocyte sedimentation rate 29 mm, and C reactive protein 9.19 mg/l (normal 0.00–6.00). Stool studies for ova and parasites and stool cultures were negative. Thyroid function tests, serum IgE, abdominal ultrasound, and computed tomography scan were normal. No findings of extra-abdominal malignancy were evident. Colonoscopy with terminal ileoscopy was normal, as was histology of the ileum and colon. Gastroscopy showed small erosions at the corpus, the antral mucosa, and the duodenal bulb. Biopsies were taken from the gastric corpus, antrum, and from the second part of the duodenum. Gastric biopsies showed *H pylori* infection and dense eosinophilic infiltration (29 eosinophils per high power field) of the gastric mucosa, but biopsies from the 2nd–3rd parts of the duodenum were normal.

She was discharged with a diagnosis of eosinophilic gastritis and *H pylori* erosive gastritis, and was treated with esomeprazole (40 mg/day), amoxicillin (1 g/day), and clarithromycin (1 g/d) for seven days. No treatment was given for eosinophilia. There were no known reports implicating her medications in the aetiology of her symptoms and so it was decided that she should remain on her regular medical treatment. Two months after completion of the eradication therapy repeat gastroscopy was normal. Gastric biopsies showed no *H pylori* infection and only trivial (five eosinophils per high power field) eosinophilic infiltration. She was symptom free, with a white blood count of 3280 cells/mm<sup>3</sup> and a normal eosinophilic count of 780 cells/mm<sup>3</sup>. No significant change in platelet count was noted.

Ours is the third reported case of the coexistence of *H pylori* infection and eosinophilic gastroenteritis. In contrast with the previous cases, blood and tissue eosinophilia resolved completely after successful eradication of *H pylori* infection.

Although no confirmed association between *H pylori* gastritis and eosinophilic gastroenteritis can be documented in the literature, our case shows that *H pylori* may play a pathogenic role in the development of blood eosinophilia and eosinophilic gastroenteritis and that *H pylori* eradication may be of value in treating certain cases of this rare syndrome.

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## Uneventful pregnancy and neonatal outcome with tacrolimus in refractory ulcerative colitis

Tacrolimus is currently approved only in patients receiving allogeneic liver or kidney transplants.<sup>1</sup> We and others have demonstrated its successful use in refractory colitis.<sup>2,3</sup> Here we report the first patient who was successfully maintained in remission during pregnancy and delivered a healthy baby.

Our patient was diagnosed with ulcerative colitis at the age of 25 years. Her first baby was delivered by Caesarean section prematurely at 29 weeks' gestation. Frequent flare ups of her pancolitis required repeated steroid rescue and she was soon started on azathioprine. Unfortunately, she was unable to tolerate purine analogues due to heterozygous thiopurine methyltransferase deficiency causing severe pancytopenia and life threatening sepsis.

Discussing the remaining therapeutic options, the patient refused proctocolectomy and ileoanal pouch anastomosis and chose a trial on oral tacrolimus. She was started on 0.1 mg/kg body weight oral tacrolimus, divided into two daily doses. The dose was adjusted aiming for serum trough levels of 4–6 ng/ml. Her condition improved quickly within the following weeks and complete remission was achieved. The patient was discouraged from conceiving while on tacrolimus. When weaning off tacrolimus resulted in repeated disease flare ups, she underwent granulocyte aphaeresis (Adacolumn) at age 27 years but was unable to attain prolonged remission without tacrolimus.

At the age of 31 years she became intentionally pregnant with her second child. Sonographic malformation screening during the second trimester did not detect any fetal abnormalities. She spontaneously delivered a healthy baby girl (Apgar score 9/10/10; birth weight 3500 g; height 51 cm) at 40 weeks' gestation. She was continued on tacrolimus throughout the pregnancy and following delivery, aiming for serum trough levels of 4–6 ng/ml, and maintained a stable remission. To date she is 33 years old and still in remission. Because of the unknown immediate and long term side effects of tacrolimus in the newborn, we recommended refraining from breastfeeding. There is no evidence of any functional impairment or developmental delay in her now two year old daughter.

This case is the first report of tacrolimus use during pregnancy for refractory ulcerative colitis. Most experience with tacrolimus in pregnancy exists with transplant patients. In a recent study, 37 female liver transplant recipients who delivered 49 babies were reported. Thirty six mothers (97%) survived the pregnancy. One patient who clotted an infra-aortic arterial graft during labour died. The mean gestational period was 36.4±3.2 weeks, excluding two premature

deliveries at 23 and 24 weeks' gestation. Twenty two babies (46.9%) were delivered by Caesarean section. One baby, who was born to a mother with Alagille syndrome, died from congenital birth defects. Preterm delivery and low birth weight were in the same range as seen in all solid organ transplant patients under any form of immunosuppression.<sup>4</sup> The results for 15 kidney transplant and simultaneous kidney-pancreas transplant mothers were similar.<sup>5</sup>

In an older survey of 100 pregnancies in 84 mothers from multiple centres, 71 pregnancies progressed to delivery (68 live births, two neonatal deaths, and one stillbirth), 24 were terminated (12 spontaneous and 12 induced), two pregnancies were ongoing, and three were lost to follow up. Preterm delivery occurred in 41% and low birth weight in 10% of patients. Four neonates presented with malformations without any consistent pattern.<sup>6</sup>

As tacrolimus is excreted into human milk, nursing is discouraged because of potential short term and long term toxicity due to immature metabolism of tacrolimus in the neonate. However, one uncomplicated case with breastfeeding under tacrolimus has been published.<sup>7</sup>

Based on the experience in the transplant population and this case, the use of tacrolimus in pregnancy may be justified under special circumstances in carefully selected non-transplant patients. Unlike in her first pregnancy, our patient was able to deliver a full term healthy baby girl vaginally after an uneventful pregnancy, maintaining sustained remission of her ulcerative colitis.

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Conflict of interest: declared (the declaration can be viewed on the Gut website at <http://www.gutjnl.com/supplemental>).

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**First case of paralytic intestinal ileus after double balloon enteroscopy**

Double balloon enteroscopy is a new method allowing the exploration of the whole intestine by the oral or anal route,<sup>1</sup> with the possibility of endoscopic intervention. We describe here the first case of enduring paralytic ileus following this technique.

**Case report**

A 47 old woman was referred to our unit for chronic and obscure undiagnosed gastrointestinal bleeding. Unremarkable conventional upper and lower endoscopies were performed twice. Small bowel follow through studies, abdominal computed tomography (CT), and pushed enteroscopy were also normal. A capsule enteroscopy was performed showing three angiodysplasias in the distal jejunum, all measuring 2-3 mm. To reach them, we performed a double balloon enteroscopy which showed two of the three lesions. Electrocoagulation with an argon plasma coagulator (50 W, 1.5 l/min) was performed on both lesions. Twelve uneventful hours followed the procedure, after which nausea and vomiting occurred. Abdominal examination showed abdominal meteorism with diffuse moderate pain and no focal tenderness. No fever or other clinical signs apart from those of intestinal occlusion were observed. An abdominal CT showed localised and moderate dilation of a few intestinal loops with normal proximal and distal ileum (fig 1). No complications such as pneumoperitoneum, abscess, intestinal haematoma, or intussusceptions were observed. Oral intake was stopped and intravenous fluids given. The clinical state remained stable but transit remained totally interrupted without passage of stool or flatus, and 2-3 litres of gastric aspirate was obtained per day. As the intestinal occlusion had not resolved by day 7, erythromycin 3 mg/kg/day was given intravenously in two doses, of 30 minutes each, with disappearance of signs of occlusion within 48 hours. Total recovery was observed after four days, allowing discharge with no further events over the following five months.

**Discussion**

Double balloon enteroscopy was first reported by Yamamoto *et al* in 2001 in a series of four patients, with insertion of the endoscope as far as 30-50 cm distal to the ligament of Treitz in three cases and to the ileocaecal valve in one, without any complications.<sup>2</sup> Since then, two larger series of 123<sup>1</sup> and 62 patients<sup>3</sup> have been reported, with two and no complications recorded, respectively. In the former,<sup>1</sup> a total of 178 procedures were performed. The first complication was multiple perforations in a patient with intestinal lymphoma thought to be due to chemotherapy whereas the second complication was of spontaneously resolving postoperative fever and abdominal pain in a patient with Crohn's disease. Elsewhere, a total of eight papers<sup>4-11</sup> reported 20 patients having DBE with only



**Figure 1** Abdominal computed tomography: dilated (white arrows) small bowel loops.

one recorded complication (post polypectomy sepsis).<sup>10</sup> Two large series of 62 and 125 patients, respectively, have been published in abstract form,<sup>12,13</sup> with no complications in the former and two in the latter. The two reported complications were intra-abdominal abscess and mild pancreatitis thought to be due to balloon inflation near the ampulla of Vater.

Two aspects are of interest in this case. Firstly, this is, to our knowledge, the first case of small bowel ileus following double balloon enteroscopy. This is of interest because the ileus appeared without the diagnosis of perforation, abscess, gastrointestinal haemorrhage, or haematoma following the procedure, indicating isolated motility impairment. Indeed, plasma argon coagulation is not known to induce an ileus lasting seven days without other complications.<sup>14</sup> Therefore, it could be that the ileus was caused by the double balloon technique itself due to the pronounced stretching of the small bowel and possibly the mesentery.<sup>1</sup> Secondly, it should be emphasised that conservative medical management should be tried first, and that treatment may include prokinetic agents such as erythromycin which improve motility impairment disorders.<sup>15</sup>

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## BOOK REVIEW

### Atlas of Clinical Gastroenterology, 3rd Edn

A Forbes, J J Misiewicz, C C Compton, et al. Oxford: Elsevier Mosby, 2005, pp 358. ISBN 07234283X

"A picture is worth a thousand words", Napoleon Bonaparte. In this atlas, every picture tells a story. It is not surprising, considering the pace at which gastroenterology has moved ahead, that the third edition of this visual extravaganza is radically different from the second edition published in 1994. The chapters are generally arranged in anatomical sequence, and each chapter provides a brief anatomical introduction. Contrast barium radiology, ultrasonography, and endoscopy dominate the atlas, and there is a rich selection of histopathology of gastrointestinal diseases. There are also some nice operative photographs. However, magnetic resonance imaging scans are fewer in number and there is only a token representation of endoscopic ultrasonography. Magnetic resonance cholangiopancreatography of the biliary and pancreatic ducts is also somewhat neglected. Computed tomography (CT) scans are well represented in the hepatic and pancreatobiliary sections. Wireless capsule endoscopy is now represented, although the pictures are not the best that may be obtained,

nor extensive. Sonde enteroscopy is depicted but not the more recent double balloon enteroscopy. Virtual CT colonoscopy also makes a debut. Some of the advances in endoscopic imaging, such as zoom endoscopic pictures and confocal endoscopy, are missing.

Most common and many rare diseases are represented in a wide selection of photographs. Going through the index, some omissions are notable, such as Behcet's disease, amyloidosis, and immunoproliferative small intestinal disease, common in some parts of the world.

Despite some of these limitations, the atlas is extremely well balanced and a true page-turner. It is a great aid to teaching by including a free accompanying CD which is easy to navigate. The CD also makes the atlas very portable, a drawback of large heavy volumes. The CD is also enhanced by inclusion of videos. The text is concise and appropriate to a visual atlas enhancing, rather than distracting, the visual appeal. It is well worth having a copy simply as a treasure chest of the specialty and for those commencing their specialist career, a superbly efficient way of increasing their clinical acumen. Some sections are truly outstanding, such as hepatic histopathology and the section on infective colitis. Paediatric gastroenterology is also represented with some outstanding contributions.

The quality of the volume is outstanding, the pictures crisp, and the colours vibrant. Hiding the figure legends is a good way of testing clinical diagnostic skills. Gastroenterology specialist nurses and endoscopy nurses also enjoy this type of learning experience and it is well worth ensuring that the volume is easily available to them.

"If I could tell the story in words, I wouldn't need to lug around a camera", Lewis Hine. I do hope this atlas stimulates every gastroenterologist to photographically record interesting findings, as gastroenterology is a very visual specialisation. Buy one and keep it, and it will keep its value for years, like a 1998 Mouton Rothschild.

S Ghosh

## EDITOR'S QUIZ: GI SNAPSHOT .....

### Answer

*From question on page 1817*

Rectoscopy showed a rectal stricture (white arrow), 3 cm cephalic to the dentate line, a rectal ulcer (blue arrow) (fig 1), and a rectovaginal fistula (yellow arrow) (fig 2), through which the vagina was visualised (black arrow) (fig 3). She was treated surgically. A diagnosis of rectovaginal fistula (RVF) secondary to ergotamine suppositories was retained as no other aetiology was found.

In the past 20 years there have been several cases of "anorectal ergotism" which were reported as proctitis, rectal ulcers, perianal ulceration, rectal stenosis, and rarely RVF.<sup>1–2</sup> Because ergotamine acts on the arterial and venous tree of the capillaries, local rather than systemic damage is more likely to be seen with suppository use.<sup>3</sup> Ischaemia induced by vasoconstriction leads to local inflammation ("anorectal ergotism") which may lead to RVF that can easily occur because the vagina and rectum are separated by a thin septum. Normally, anorectal ergotism resolves after discontinuation of the drug. Only rectal stricture and RVF have to be treated endoscopically or surgically.

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