

# PostScript

## LETTERS

### Acute toxic gastric mucosal damage induced by Lugol's iodine spray during chromoendoscopy

Lugol's solution, named after the French Physician JGA Lugol (1786-1851), has a high affinity for glycogen in non-keratinised squamous epithelium.<sup>1</sup> Since the 1960s when Lugol's iodine was first used to investigate oesophageal diseases,<sup>2</sup> advances in the field of diagnostic endoscopy have resulted in its increasing use to detect early mucosal abnormalities and to target biopsies from unstained areas.<sup>3,4</sup> We have been performing chromoendoscopy using Lugol's solution for the last 10 years, carrying out 10-15 procedures every year. Here we report the first case of an acute toxic reaction affecting the gastric mucosa.

At gastroscopy of a 67 year old woman with reflux symptoms, a small nodule was noted at the gastro-oesophageal junction together with reflux oesophagitis (LA grade B). Biopsies from the nodule raised the possibility of dysplasia within the squamous epithelium. One month later a repeat examination was performed to reassess the squamous epithelium and target biopsies using Lugol's chromoendoscopy; 10 ml of 5% Lugol's iodine was sprayed using an Olympus PL spraying catheter. Multiple biopsies were targeted to the unstained areas together with random biopsies from the distal oesophagus. At the end of the examination, the stomach was again entered to remove any stagnant iodine. The gastric

mucosa underlying the pool of iodine was intensely oedematous and haemorrhagic (fig 1A, 1B) The patient did not complain of any symptoms either during or after the procedure. Gastric biopsies confirmed acute oedema of the lamina propria with loss of the superficial epithelium consistent with an acute toxic gastric mucosal injury induced by Lugol's iodine solution (fig 1C) The oesophageal biopsies showed no dysplasia.

During a follow up examination performed three months later to reassess the lower oesophagus, the gastric mucosa appeared endoscopically and histologically unremarkable.

Chromoendoscopy using Lugol's solution is not without hazards. Local irritation of the oesophageal mucosa may cause retrosternal pain.<sup>5</sup> General allergic reactions include laryngospasm, bronchospasm, and even cardiac arrest.<sup>6</sup> The concentration of the solution used in studies ranges from 0.5% to 5%, and higher concentrations (3-5%) may be associated with a higher risk of complications.<sup>6</sup> A Japanese study reported that washing the mucosa with sodium thiosulphate may neutralise the iodine solution and reduce retrosternal discomfort.<sup>7</sup> Only two cases of gastric mucosal erosions have been reported after the application of iodine.<sup>8</sup>

In this case, the histological features of localised oedema and loss of superficial gastric epithelium in the absence of significant inflammatory cell infiltrate supported an acute toxic injury to the gastric mucosa. The toxic reaction was confined to the columnar epithelium in the greater curve of the stomach that was in direct contact with the pooled 5% Lugol's iodine while the squamous oesophageal mucosa remained unremarkable both endoscopically and histologically. Gastric columnar epithelium may be more

susceptible to the toxic effect of Lugol's iodine and mucosal injury may go unrecognised unless the stomach is re-examined after application of the dye. To reduce the risks, we now use 10-20 ml of 1.5% Lugol's solution and routinely aspirate the gastric pool before assessing the oesophageal mucosa.

Previous studies have shown that Lugol's staining is useful in screening for early oesophageal cancer in high risk populations such as patients with previous or current non-oesophageal malignancy and those with a high alcohol intake.<sup>9,10</sup> However, none of these studies commented on the adverse reactions to Lugol's staining during endoscopy. We suggest that the adverse reactions and safety profile of iodine staining need to be addressed, in particular before recommending its routine use for screening purposes. Also, where it has to be used, a lower concentration of 1.5% may be less toxic to the gastric mucosa and is thus recommended.

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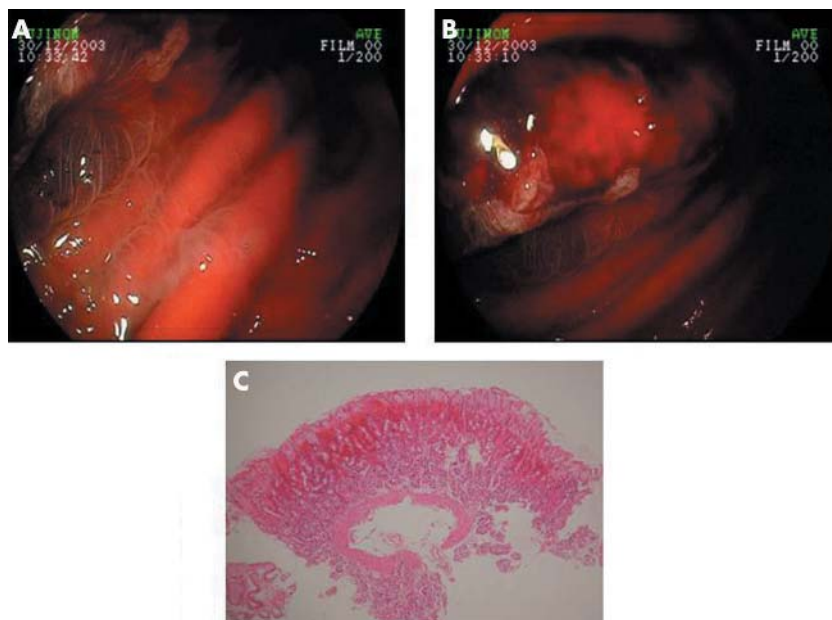
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**Figure 1** (A, B) Oedematous and haemorrhagic mucosa with loss of superficial gastric mucosal layer in the greater curve. (C) Mucosal oedema, loss of superficial gastric epithelium, and sparse inflammatory infiltrate in the lamina propria.

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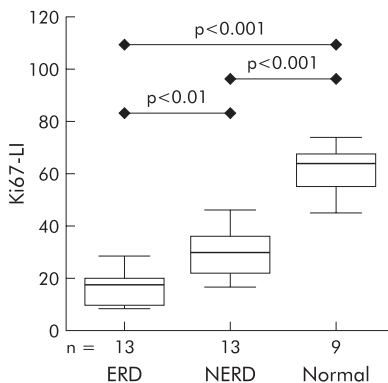
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### Erosions or not in GORD? The potential role of oesophageal cell proliferation

Gastro-oesophageal reflux is an almost universal daily occurrence, but only a small percentage of the population develops gastro-oesophageal reflux disease (GORD) and, among them, a small number develop erosive oesophagitis (ERD) or one of its complications.<sup>1,2</sup> It is well accepted that the pathophysiology of GORD is related to failure of antireflux mechanisms but several phenomena are not fully explained on the basis of this sequence.<sup>3</sup> There is no apparent relation between damage and the amount and quality of refluxate.<sup>4</sup> It is not known why the same amount of refluxate determines GORD in one patient and not in another.<sup>2</sup> It is also unclear whether there is a relation between these unexplained questions and the possible influence of proliferative responses of epithelial proliferating cells to damage. Hence we evaluated cell proliferation of the oesophageal epithelium using Ki67 immunostaining in normal subjects and in patients with GORD, with or without erosions.

Patients gave written informed consent to participate in the study which was approved by the ethics committee. The design was blinded for epithelial cell kinetic evaluation. Thirty five subjects were enrolled: nine were healthy voluntary controls with normal pH testing and normal endoscopic, histological, and ultrastructural patterns. Twenty six patients were affected by GORD, defined as frequent heartburn for at least a year, and abnormal 24 hour pH, histological, and ultrastructural parameters. Of these 26 patients, 13 had a normal appearing oesophageal mucosa at endoscopy (NERD) while 13 had ERD (table.1).

All subjects underwent gastroscopy; six biopsies were obtained within the lower 5 cm of the oesophagus from areas of macroscopically intact oesophageal mucosa. The presence of oesophagitis was graded according to the Los Angeles classification.<sup>5</sup>



**Figure 1** Box plots of Ki67-labelling index (LI), LI median (bold line in the box), and interquartile range (upper and lower lines of the box) in human oesophageal mucosa of healthy controls and of patients with erosive oesophagitis (ERD) and a normal appearing oesophageal mucosa (NERD). Whiskers indicate lowest and highest values.

pH parameters were not statistically different between NERD and ERD. At transmission electron microscopy (TEM), all patients with GORD, with or without erosions, showed ultrastructural signs of damage, defined by the presence of dilation of intercellular spaces (>0.74 µm).<sup>6</sup> No significant differences were observed between the two groups. For assessment of the proliferative activity of epithelial cells, we used the immunohistochemical approach based on the Ki67 marker of cell proliferation which provides an accurate estimate of the cell growth fraction.<sup>7</sup> Ki67-labelling index (LI) ranged from 8.9% to 74.4% among all patients (mean (SD) 33.5 (19.7)%; median 27.8%). Mean Ki67-LI values for the three groups of patients (normal, NERD, and ERD) were 62.2%, 29.8%, and 17.2%, respectively, and the difference among the groups was significant (p<0.01) (fig 1).

This study was carried out on biopsies taken only in normal appearing mucosa at endoscopy. In this way we studied the behaviour of the mucosa exposed to chronic

acid insult but far from erosions, and in particular from reparative changes secondary to lack of superficial mucosa where basal cell hyperplasia and elongation of papillae have been reported.<sup>8</sup> We found that in all patients, oesophageal epithelium exposed to chronic acid exposure in normal appearing mucosa had a proliferation rate inferior to that of normal subjects: GORD patients had cell kinetics that were reduced to 50% and 25% in NERD and ERD patients, respectively. In order to explain the reduced proliferation rate observed in GORD patients, two different pathogenetic mechanisms can be suggested. Cell proliferation changes could be a consequence of either chronic cell damage or an intrinsic reduced ability of cells to proliferate, the one mechanism not excluding the other. Regarding the first hypothesis, little is known of the behaviour of the oesophageal mucosa stressed by chronic acid and pepsin insult. The second pathogenetic hypothesis concerns the existence of an individual predisposition to stronger or weaker cell proliferative efficacy of epithelial mucosa to chronic insults. This concept supports the idea that in genetically susceptible individuals, chronic acid and pepsin exposure may trigger or accelerate the development of ERD while in others more efficient cell proliferative activity can repair the damage due to acid and pepsin insults. We believe that the second hypothesis is worth considering in future studies, also because cell replication of basal layers has been hypothesised to be one of the causes implicated in the resistance of the mucosa and in structural epithelial defence. To date, this concept has not been taken into account.

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**Table 1** Demographic, endoscopic, pH monitoring, histological, and ultrastructural data of the studied population (normal healthy controls, and gastro-oesophageal reflux disease patients with erosive oesophagitis (ERD) and those with a normal appearing oesophageal mucosa (NERD))

	Normal	NERD	ERD
No of subjects	9	13	13
Sex (M/F)	4/5	4/9	7/6
Age (y) (mean (SD) [range])	38.67 (17.36) [26–63]	41.62 (11.77) [22–59]	42.54 (13.33) [25–65]
% Time oesophageal pH <4	5.42 (1.1)	9.1 (2.3)	10.4 (1.9)
Endoscopy			
Normal	9	13	0
A	0	0	0
B	0	0	7
C	0	0	5
D	0	0	1
Histology			
Normal	9	13	8
Mild	0	0	5
Moderate	0	0	0
Severe	0	0	0
TEM value (mean (SD))	0.54 (0.08)	2.24 (0.53)	2.39 (0.44)

TEM, transmission electron microscopy.

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### Role of IL-10 promoter haplotypes in *Helicobacter pylori* associated gastric inflammation

We read with great interest the article by Rad *et al* (*Gut* 2004;**53**:1082–9) on the influence of cytokine gene polymorphisms on mucosal cytokine expression, gastric inflammation, and host specific colonisation in *Helicobacter pylori* infection. The authors reported an association of the contrainflammatory interleukin 10 (IL-10) promoter haplotype (GCC) with higher mucosal mRNA levels and colonisation with more virulent cagA+, vacAs1+, and babA2+ strains in 207 patients with *H pylori* induced chronic gastritis. Rad *et al* identified pathogenicity genes of *H pylori* isolates by polymerase chain reaction based techniques from gastric biopsies.

However, the human stomach is colonised by more than one strain of *H pylori*, which obscures the investigation of germline mutations and host specific colonisation.<sup>1</sup> Moreover, within an apparently homogeneous population, remarkable genetic differences exist among single colony isolates. The capacity of *H pylori* to lose and possibly acquire exogenous DNA is consistent with a model of continuous microevolution within its cognate host.<sup>2</sup> Thus identification of bacterial virulence factors is directly dependent on localisation of the biopsy. This means that if cagA+, vacAs1+, and babA2 were not detected in biopsy specimens, cocolonisation with strains harbouring these genes at another location cannot be excluded. Interestingly, the degree of inflammation and frequency of gastric atrophy and intestinal metaplasia was not different in patients carrying pro- or contrainflammatory haplotypes. The significance of genetic association studies is highly dependent on a well defined phenotype. In contrast with the degree of granulocytic and lymphocytic infiltration in chronic gastritis, which may again vary

regionally, the development of gastric ulcer is an unambiguous hallmark for the severity of *H pylori* induced mucosal damage.

We recruited 614 consecutive Caucasian patients from Northern Germany who underwent gastroscopy with confirmed *H pylori* infection by rapid urease test or histology. Endoscopic findings and results of histopathological examination of biopsies, classified according to the Sydney classification, were recorded. In total, 316 patients presented with chronic gastritis and served as controls and 124 patients suffered from gastric ulcer. DNA was extracted by standard techniques from 5 ml of EDTA blood. All patients were genotyped for IL-10 –1082, –819, and –592 by TaqMan technology. Samples were recoded and genotypes assigned without knowledge of clinical status. Single marker and haplotype analysis was conducted to assess associations with development of gastric ulcer.

There were no associations between any of the single nucleotide polymorphisms tested and *H pylori* related pathological findings (data not shown). The proinflammatory low secreting haplotype ATA did not confer a risk factor for the development of an ulcer and the contrainflammatory haplotype GCC did not protect patients from gastric ulcer (table 1). Our results are in agreement with the study of Hida *et al* who reported higher IL-10 mRNA expression in cagA+ *H pylori* gastritis, with no relation to endoscopic diagnosis.<sup>3</sup> Therefore, we conclude that genetic variations in the IL-10 promoter may influence mucosal cytokine expression but pro- and contrainflammatory haplotypes do not influence the clinical course of gastric inflammation, at least in Northern Germany. Furthermore, we suggest that association studies of germline polymorphisms with the outcome of chronic *H pylori* infection should focus on clearly defined phenotypes such as ulcer disease, gastric carcinoma, or primary gastric B cell lymphoma.

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### Gastric ulceration due to chronic mesenteric ischaemia treated by stenting of the inferior mesenteric artery

We report a case of gastric ulceration due to visceral ischaemia treated successfully by stenting of the inferior mesenteric artery (IMA) alone. Gastric ulceration has very rarely been described as a result of chronic mesenteric ischaemia.[1–3] Four of the five cases described in these reports were treated surgically and one by angioplasty to the superior mesenteric artery (SMA). All were reported to have successful resolution of gastric ulcers. To our knowledge, there is no other case of successful stenting of the IMA alone, with resolution of gastric ischaemia described in the medical literature.

Our patient was a 50 year old woman presenting with abdominal pain, loss of appetite, vomiting, and weight loss. Pain was maximal in the epigastrium and precipitated by meals. Apart from being a smoker there was no other significant medical history. She was empirically started on omeprazole. Oesophagogastroduodenoscopy (OGD) revealed multiple serpiginous ulcers affecting the body of the stomach with extension to the cardia (fig 1D). Histology from the ulcers demonstrated ulceration with regenerative hyperplasia with no evidence of *Helicobacter pylori* infection. An abdominal computed tomography scan showed non-specific thickening of the pylorus and first part of the duodenum but was otherwise normal. A small bowel follow through revealed no abnormality.

Fasting gut hormone levels, including gastrin level, after stopping omeprazole were normal and a vasculitis screen (including serum ANCA) was negative.

Her abdominal pain was controlled by morphine 120 mg/day. A repeat OGD 10 weeks after treatment with omeprazole 40 mg once daily showed continuing ulceration with no improvement since the previous examination. Further histology showed similar findings as before.

Abdominal angiography demonstrated complete occlusion of the SMA origin (fig 1B), and tight ostial stenoses of the IMA (fig 1A) and coeliac axis. The SMA branches filled sluggishly and were reconstituted almost exclusively via the left colic branch of the IMA.

Attempts to bypass the coeliac axis stenosis and proximal SMA occlusion were

**Table 1** Haplotype analysis of the interleukin 10 (IL-10) promoter in 440 patients with chronic gastritis and gastric ulcer disease

IL-10 promoter			Chronic gastritis (n = 316)	Gastric ulcer (n = 124)	OR	p Value ( $\chi^2$ )
–1082	–819	–592				
G	C	C	48.0%	48.3%	1.01	0.939
A	T	A	23.6%	24.2%	1.03	0.862
A	C	C	28.2%	27.5%	0.97	0.842

OR, odds ratio.



**Figure 1** (A) Inferior mesenteric artery (IMA) stenosis, (B) superior mesenteric artery occlusion, (C) stented IMA, and (D) gastric ulcer.

unsuccessful. The IMA was catheterised; initial pressure measurements demonstrated a mean IMA pressure of 20 mm Hg (mean pressure gradient between the IMA and the aorta of 70 mm Hg) which persisted after angioplasty with a 5 mm balloon. A 5 mm diameter, 16 mm long balloon mounted stent was therefore placed across the ostial stenosis (fig 1C) resulting in marked improvement of the angiographic appearance and almost complete obliteration of the mean pressure gradient. The patient was commenced on aspirin and warfarin and an international normalised ratio of 2 was maintained. She was weaned off the opiate analgesia and was discharged on omeprazole, aspirin, warfarin, and amitriptyline.

Her symptoms resolved completely and amitriptyline and warfarin were discontinued three months later. A repeat OGD showed complete healing of the ulcers. She was continued on aspirin 150 mg and omeprazole 10 mg daily and advised to stop smoking, but unfortunately was not successful in doing so. She has been followed up for 18 months and has had no recurrence of her symptoms.

The interest in this case lies in the fact that only the IMA needed to be stented to achieve an appropriate vascular supply to the stomach, despite severe occlusions and reduced flow in the coeliac and mesenteric axes. This has not been described before, and demonstrates that minimally invasive radiological stenting of only one territory of the mesenteric axis, even the IMA alone, can provide enough blood flow to treat the complications of chronic mesenteric vascular disease. This case is a reminder that chronic mesenteric vascular disease should be considered as a cause of resistant gastric ulceration. This case also demonstrates that minimally invasive radiological stenting of only one territory of the mesenteric axis, even the IMA alone, can provide enough blood flow to treat the complications of chronic mesenteric vascular disease.

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### Diagnostic radiation exposure and cancer risk

Diagnostic and therapeutic radiological investigations are an essential part of the workup of patients with a number of clinical problems across a variety of medical specialties. Although new non-x ray technologies have started to replace traditional investigations these have not led to a reduction in radiation exposure. In contrast, based on global statistics and projections, radiation exposure of patients is increasing, in particular as a result of new indications and use in cross sectional imaging.<sup>1</sup> In addition, multiple investigations of patients with chronic disease can lead to substantial individual radiation exposure as surgical practice increasingly relies on the use of cross sectional imaging to aid diagnosis and treatment.<sup>2</sup> New imaging techniques, in particular computed tomography (CT) colonography, have become attractive alternatives to conventional colonoscopy.<sup>3</sup> However, the necessity for both prone and supine scanning means that radiation exposure is double that of a conventional abdominal scan which can lead to a theoretical increase in the risk of exposure related cancer and death.<sup>4</sup>

The awareness of hospital doctors about radiation exposure and associated cancer risk is poor.<sup>5</sup> From personal experience, many gastroenterologists involved in diagnostic and therapeutic procedures using ionising radiation do not routinely wear full protective clothing (0.35 mm lead equivalent aprons, thyroid shield, lead glasses) on a regular basis. This is also shown in a survey of endoscopic retrograde cholangiopancreatography (ERCP) practices by Campbell *et al* in which only 52% of respondents reported wearing a thyroid shield all of the time.<sup>6</sup> An audit of radiation exposure to personnel performing ERCP found that both patients and staff are exposed to significant radiation exposure. This was equivalent to an estimated additional lifetime fatal cancer risk of between 1 in 3500 and 1 in 7000.<sup>7</sup> These studies highlight the substantial underestimation by medical staff of patient and operator related radiation induced cancer risk.

The National Radiological Protection Board (NRPB) has recently revised the radiation dose for typical x ray examinations. For example, an abdominal/pelvic CT scan would typically lead to an effective dose of 10 mSv, which is an equivalent of 4.5 years of natural background radiation.<sup>8</sup> This radiation exposure was estimated to carry a 1:2000 risk of fatal cancer in the 16–69 year old patient

population (personal communication from NRPB). For older patients, this may be halved but for younger patients increased up to fivefold. Put another way, this is equal to 250–300 fatal cancers for every 1 million abdominal/pelvic CT scans.

These values are calculated using a probability coefficient, which was developed by the International Commission on Radiological Protection (ICRP), based on historical epidemiological cohorts and other research.<sup>9</sup> It is worth noting that the cancer risk attributed to radiation exposure has constantly risen over time as longer term follow up information from the Hiroshima and Nagasaki cohorts have become available. It is therefore possible that radiation attributed cancer risk will continue to rise in the future.

In the UK, diagnostic x rays related cumulative risk of cancer to age 75 years was recently estimated at 0.6%, which is equivalent to approximately 700 cases of cancer per year.<sup>10</sup> In the same report, this rate was estimated to be up to five times higher for countries with a higher use of diagnostic x rays. The British Society of Radiology has made specific recommendations to reduce radiation exposure.<sup>11</sup> Adherence to these guidelines may well be an explanation for the comparatively low frequency of diagnostic x ray in UK practice.<sup>12</sup> Clinicians should use these recommendations when considering radiological investigations. Protection of operators and nursing staff using recommended protective clothing should also be followed. Change in clinical practice may not be easy to achieve as, for example, endoscopic capacity to reduce the number of alternative radiological investigations, such as barium enemas, is limited. In contrast, barium enemas are often used to reduce the demand on endoscopic services. New technologies and methods may well reduce radiation exposure. Examples in gastroenterology include magnetic resonance cholangiopancreatography or endoscopic ultrasound instead of ERCP and magnetic resonance enteroclysis instead of small bowel enema. Technological advances, in particular low dose helical CT colonography, may reduce radiation exposure by 40–70%.<sup>13</sup> However, availability of these technologies is limited or only slowly increasing and it is therefore unlikely that their use will influence radiation exposure in the near future.

What remains is the judicious use of radiological investigations and close liaison with radiologists in order to keep the radiation exposure of patients and staff as low as possible.

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## Adalimumab use in pregnancy

Infliximab, a chimeric antibody to tumour necrosis factor alpha (TNF- $\alpha$ ), has demonstrated efficacy for the induction and maintenance of remission in patients with Crohn's disease.<sup>1,2</sup> Antibodies to the chimeric component of infliximab can lead to infusion reactions and possible loss of response.<sup>3</sup> A human recombinant monoclonal antibody to TNF- $\alpha$ , adalimumab, has recently demonstrated safety and efficacy for induction of remission in Crohn's disease.<sup>4</sup> It has also been effective in patients who have lost response to infliximab.<sup>5</sup> Currently, this drug is FDA approved for the treatment of rheumatoid arthritis but it is being administered off label to patients with Crohn's disease who are intolerant of infliximab. The safety profile during pregnancy is not well known for either drug. We report a patient who has had two successful pregnancies, one while on infliximab and the other while on adalimumab.

A 34 year old woman with longstanding ileocolonic and perianal Crohn's disease had severe disease activity at the time of conception. She had been on mesalamine, budesonide, and prednisone, and was unable to attain remission. She was intolerant of purine analogues. Infliximab had been successful in the past but she lost response over time. Adalimumab was started and she was on a maintenance regimen approximately one month prior to conception. During her pregnancy, she received a total of 38 doses of adalimumab at 40 mg subcutaneously every week. She continued on adalimumab following delivery and breast fed while on the drug. She had severely active disease at conception but had mild improvement by the first trimester and had moderately active disease throughout the third trimester. Post

partum, she had mild to inactive disease. She successfully tapered her prednisone from 15 mg daily to 2.5 mg every other day by one month post partum. The pregnancy was uncomplicated and surveillance sonograms revealed normal growth without visible congenital anomalies. Due to a history of perianal disease, an elective Caesarean section was performed without complications at 38.5 weeks. No neonatal abnormalities were noted, and APGAR scores were 8 and 9. The child is now six months with normal growth and development.

This case is the first report of maintenance adalimumab use during pregnancy. With infliximab, animal studies for treatment of rheumatoid arthritis have not revealed fetotoxicity or teratogenicity.<sup>6</sup> Katz *et al* reported on 96 human pregnancies exposed to infliximab with known outcomes.<sup>7</sup> Of 100 progeny, 69 were live births, 13 were miscarriages, and 18 were elective terminations. This is similar to what is expected in the general Crohn's population. We reported 10 women who had maintenance infliximab use during pregnancy<sup>8</sup>: all ended in live births with three premature infants and one with low birth weight.

While the health of the mother is our priority as gastroenterologists, the safety of inflammatory bowel disease medications during the childbearing years is always of concern. As biological agents are increasingly being used for maintenance therapy in Crohn's disease, more patients are healthy enough to consider conception. Careful data collection and prospective study is required to be able to guide the management of men and women with inflammatory bowel disease desiring conception to ensure the health of the parent and child.

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

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## Can gastro-oesophageal reflux be predicted while advancing the endoscope through the laryngeal area?

We read with great interest the article by Mullhaupt *et al* regarding examination of the laryngopharyngeal area during upper gastrointestinal endoscopy, after being trained for examination of these anatomical structures (*Gut* 2004;**53**:1232–4). Twenty six laryngeal pathologies were discovered in 1311 cases, the most important of which was demonstration of an early supraglottic cancer.

Upper gastrointestinal endoscopy has been performed in children for various indications. In paediatric gastroenterology practice, endoscopy is an important procedure beginning from the mouth. After inserting the endoscope through the oral cavity, the uvula, epiglottis, and cricoarytenoid cartilages with the vocal cords above are seen. While passing through the epiglottic area, the concomitant laryngitis, oedema, hyperaemia or ulceration of the arytenoids, and laryngeal granulomas can be visualised. Examination of the laryngopharyngeal area is not a routine part of the endoscopic procedure in children.

Although supraglottic cancer is extremely rare among children, a more common problem of the laryngeal area during childhood is gastro-oesophageal reflux (GOR), which affects almost 10% of children. Vomiting, recurrent upper or lower respiratory tract infections, and weight loss are frequent clinical findings with GOR. Extraoesophageal manifestations of GOR have been identified and recognised more during the past decade.<sup>1</sup> The phrase "extraoesophageal reflux" refers to the effects of refluxed gastric material far from the oesophagus. It has been shown that the contents of the gastric juice, including hydrochloric acid and pepsin, are damaging not only to the oesophagus but also to pharyngeal and laryngeal tissues. Resistance of the laryngeal mucosa to refluxed gastric contents and the presence of the adequate buffering effect of saliva are important factors predicting the severity of laryngeal injury. Gaynor and colleagues<sup>2</sup> reported the otolaryngological manifestations of gastro-oesophageal reflux, and stated that the presence of erythema, oedema of the arytenoids and posterior part of the vocal cords, or more chronic changes such as the presence of granulomas might suggest GOR in aetiology.

In our paediatric gastroenterology outpatient clinic, 375 upper gastrointestinal endoscopies were performed in children aged

three months to 17 years, between 2003 and September 2004. The laryngopharyngeal area was investigated in 207 children during the endoscopic procedure and of these, 40 children had oedema of the vocal cords or arytenoids. Sixteen of these cases were due to caustic material ingestion; the remaining 24 had upper gastrointestinal endoscopy for other indications. Among the 24 cases with laryngopharyngeal pathology, 11 had hyperaemia and mucosal nodularity in the proximal, and 14 in the distal, part of the oesophagus. When the proximal and distal oesophageal biopsies were compared in this group, 37% had proximal and 66% had distal histological oesophagitis. Therefore, the presence of laryngeal oedema made us suspect GOR, and it is now routine for us to take oesophageal biopsies from the upper and lower parts of the oesophagus.

In the study of Mullhaupt *et al.*, the importance of macroscopically noticeable laryngeal lesions during endoscopy among adult patients was emphasised and the most important was reported to be discovery of an early supraglottic carcinoma. Upper gastrointestinal endoscopy is also an important procedure for the diagnosis of GOR and its supraoesophageal manifestations, if it is performed by an endoscopist who has been trained in the normal anatomy and pathology of the laryngeal area. Thus we agree with inspection of the laryngopharyngeal area, not only for evaluation of malignancies (although seen extremely rare among children) but also for extraoesophageal manifestations of GOR.

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## Is stool DNA multitarget testing an unreliable strategy for colorectal cancer screening?

The availability of a simple non-invasive test capable of detecting colorectal cancer specific products with reasonable sensitivity and specificity might avoid the invasiveness, unpleasant bowel preparation, and risk of bleeding and perforation related to colonoscopy. Molecular marker combinations in faecal DNA testing have been shown to produce high rates of both colorectal cancer and advanced adenoma detection in selected patient populations,<sup>1</sup> and observations from large representative groups are emerging.

Imperiale and colleagues<sup>2</sup> have recently reported the results of the first large study of faecal DNA testing in asymptomatic

subjects. A total of 4404 average risk adults, who were at least 50 years old, underwent faecal occult blood testing, faecal DNA testing, and colonoscopy, which was considered the reference standard. Comparing test results in a random subgroup of 2507 persons, the authors found that the faecal DNA test was much more sensitive than faecal occult blood testing in detecting colorectal cancer and adenomas with high grade dysplasia. However, the sensitivity for both the faecal DNA panel and faecal occult blood testing was low. In particular, the faecal DNA test detected only 52% of colorectal cancers and 15% of adenomas, rates that were far lower than those previously reported in the literature for multitarget testing.<sup>3–5</sup> Furthermore, in the same study,<sup>2</sup> the sensitivity of faecal occult blood testing (13%) was unexpectedly low.

Interestingly, in the results section, Imperiale and colleagues<sup>2</sup> reported that “among 1423 subjects with negative findings on colonoscopy, 79 had a positive faecal DNA panel and 68 had a positive Hemocult II test, for specificities of 94.4% and 95.2%, respectively”. The question immediately arises as to whether these patients subsequently developed “advanced neoplasia” or minor polyps and consequently whether the results from the DNA stool test or faecal occult blood test were falsely or truly positive. In fact, colonoscopy could have produced false negative results for several reasons, including misinterpretation of what was visualised or failure to perform adequate biopsy of the lesions seen.<sup>6</sup> In this case, it could be intriguing to compare the ability of faecal DNA panel versus that of the Hemocult II test in predicting the early occurrence of “advanced neoplasia” when colonoscopy misses the disease.

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## CD40 antisense based strategy for inflammatory bowel disease: shutting down multiple cellular communication systems

We read with great interest the paper by Gao *et al.*, where the authors elegantly proved the efficacy of a CD40 antisense oligonucleotide for the treatment of trinitrobenzene sulphonic acid (TNBS) induced colitis in rats (*Gut* 2005;**54**:70–7). Their results are in keeping with previous reports in which immunoblockade of CD40 ligand (L) was also able to ameliorate experimental colitis. The authors conclude that interruption of interactions between CD40 bearing monocytes and endothelial cells and CD40L positive T cells is crucial for the beneficial effect exerted by CD40 antisense oligonucleotide in TNBS induced experimental colitis.

In the past few years we have been investigating the role of the CD40/CD40L pathway in the pathogenesis of inflammatory bowel disease (IBD).<sup>1</sup> We and others have recently shown that, apart from endothelial cells and monocytes, human intestinal fibroblasts (HIF) also express CD40 on their surface.<sup>2,3</sup> HIF significantly upregulate CD40 expression, both at the mucosal and submucosal levels, in patients with active IBD. Moreover, we and others have shown that coculture of CD40 expressing HIF with CD40L T cells induces fibroblast activation, leading to chemokine and cytokine production, cell adhesion molecule upregulation, and activation of the intracellular signalling machinery, by triggering MAP kinases and nuclear factor  $\kappa$ B activation. All of these events are biologically relevant for the inflammatory process as fibroblast derived chemokines mediate T cell recruitment.<sup>2,3</sup> Another intriguing observation is the demonstration that CD40L T cells modulate collagen synthesis by HIF, thus suggesting the potential involvement of the CD40/CD40L pathway in stricture formation in Crohn's disease (CD).<sup>4</sup> Therefore, blockade of HIF CD40 is another potential mechanism for the therapeutic efficacy of CD40 antisense.

We have also shown that platelets express high levels of biologically active surface CD40 in a constitutive manner.<sup>5</sup> This molecule provides a novel pathway for platelet activation, as shown by the observation of RANTES release after platelet stimulation.<sup>5</sup> These events are particularly relevant at sites of intense immune activation where local inflamed endothelial cells retain RANTES on their surface and mediate T cell adhesion, thus locally amplifying the inflammatory response.<sup>5</sup> Moreover, Vowinkel and colleagues recently showed that the CD40/CD40L system also plays a critical role in mediating platelet adhesion to and activation of intestinal microvasculature or leucocytes.<sup>6</sup>

Gao *et al.* (*Gut* 2005;**54**:70–7) suggest that CD40L positive T cells could stimulate CD40 endothelium, and that CD40 antisense could prevent such cell interactions. Recently, we

have described that apart from T cells, activated platelet also express CD40L.<sup>7</sup> Platelets display enhanced levels of membrane bound CD40L in CD and ulcerative colitis patients, and secrete higher amounts of soluble CD40L, compared with healthy controls.<sup>8</sup> These phenomena have biological relevance in terms of intestinal microvascular activation as IBD activated platelets trigger chemokine production, VCAM-1, ICAM-1, and CD40L upregulation, and T cell adhesion to the gut endothelium.<sup>7-9</sup> Therefore, abrogation of endothelial or platelet CD40 expression would not only block T cell-endothelial interactions but also interrupt platelet-endothelial and platelet-leucocyte cell cross-talk in the gut microvasculature.

Taken together, these observations suggest that the CD40 antisense oligonucleotide used by Gao *et al* exerts its beneficial effect not only by disrupting the interaction between CD40 bearing monocytes and endothelial cells and CD40L positive T cells, but also by acting on a much wider array of cell types able to express either CD40 or CD40L. We conclude that the use of CD40 antisense oligonucleotides appears to be a very promising therapeutic approach to turn off intestinal inflammation, by disconnecting a crucial and almost ubiquitous communication system used by multiple cell types during inflammation.

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Conflict of interest: None declared.

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## NOTICES

### Masterclass in Crohn's disease

A masterclass in Crohn's disease will be held in Oxford on Wednesday 31 August 2005.

This masterclass has been designed for consultants and registrars, including those who do not specialise in gastroenterology. Topics will include aetiology, differential diagnosis, and management. The course fee is £110 and board and accommodation is available at Wadham College at extra cost.

Six bursaries will be available for applicants training in gastroenterology or in research posts in British hospitals.

For further details and application forms contact: Professor Derek P Jewell, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE, UK; tel +44 1865 224829; fax: +44 1865 790792; email: [derek.jewell@ndm.ox.ac.uk](mailto:derek.jewell@ndm.ox.ac.uk); website: <http://www.medicine.ox.ac.uk/gastro>.

### Asian Pacific Digestive Week 2005

This will be held on 25–28 September 2005 in COEX, Seoul, Korea. It is hosted by APDW 2005 Organizing Committee in conjunction with Asian Pacific Association of Gastroenterology (APAGE), Asian Pacific Society of Digestive Endoscopy (APSDE), Asian Pacific Association for the Study of the Liver (APASL), and International Society for Digestive Surgery (ISDS). The theme is "Rediscovery of Asia for gastrointestinal diseases". The abstract submission deadline is 15 June 2005 and early bird registration deadline is 30 June 2005.

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