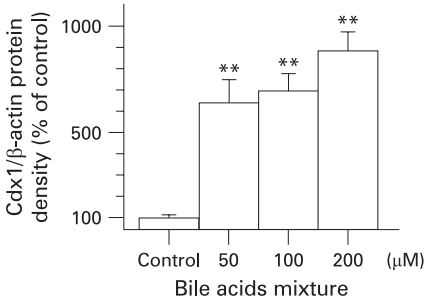
Digest

Robin Spiller and Magnus Simren, *editor and deputy editor*

Increased caudal-related homeobox gene Cdx1 expression precedes development of intestinal metaplasia

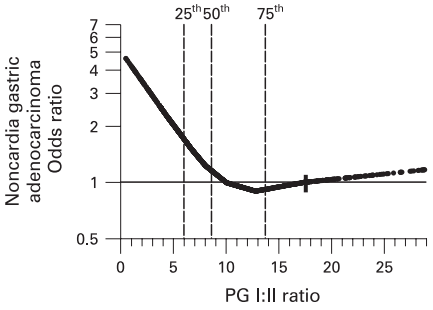
Although it has been recognised for many years that reflux of bile into the oesophagus is associated with the development of Barrett's oesophagus, the precise mechanism has been unclear. Cdx1 and Cdx2 genes code for intestinal specific transcription factors that govern the differentiation of intestinal epithelial cells during development. When expressed in the stomach, Cdx1 induces gastric epithelial cells to differentiate to intestinal type cells. This study used a rat model of Barrett's oesophagus, in which the oesophagus was re-implanted into the upper jejunum. This exposes the oesophagus to bile reflux and intestinal metaplasia develops over a period of 6 months. At 2 months, there was increased expression of Cdx1 and at 6 months, 30% had developed columnar lined epithelium, which stained for both Cdx1 and Cdx2 proteins. In vitro bile acids induced expression of Cdx1 in both adenocarcinoma and the normal oesophageal cell line in a dose–response fashion (see fig). Transfection of a normal oesophageal cell line Het-1A with Cdx1 increased Cdx2 promoter activity and the authors suggest that Cdx1 may mediate the expression of Cdx2, which in turn leads to the development of Barrett's metaplasia. ***See page 620***



Bile acids increase expression of Cdx1 protein.

Serum pepsinogens: risk factors for gastric but not oesophageal cancers

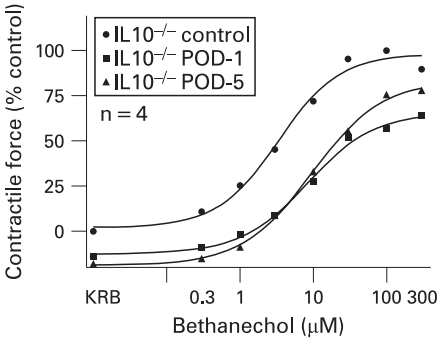
Atrophy of the gastric fundic mucosa is considered to be a risk factor for gastric cancer. It has also been suggested that chronic atrophic gastritis might be a risk factor for oesophageal squamous cell carcinoma. Low serum pepsinogen (PG) I and low PGI/PGII ratio are markers for fundic atrophy. In this large Chinese case–cohort study with over 15 years follow-up, the association between PGI/II ratio and risks of gastric and oesophageal cancers were determined. A low PGI/II ratio was found to increase the risk of both non-cardia and cardia gastric adenocarcinomas, whereas the authors failed to find evidence for an association with oesophageal squamous cell carcinoma. By using quartile and continuous models, no single valid cut-off point for a clearly increased risk for cancer development could be found (see fig), implicating that measurement of serum PG is not very useful in cancer screening programmes. This large-scale study has confirmed the association between gastric fundic atrophy as measured by PGI/II ratio and the subsequent risk of developing gastric adenocarcinomas. Strategies for preventing this form of cancer are needed. ***See page 636***



Nonlinear continuous model of the association between serum pepsinogen (PG) I/II ratio and the risk of non-cardia gastric adenocarcinoma.

Will treatment with interleukin 10 be useful to prevent postoperative ileus?

Postoperative ileus (POI) is still a significant problem with large unmet needs. The knowledge about mechanisms behind the development of POI has increased over the past years thanks to excellent research performed in different animal models. From these studies, it is clear that intestinal manipulation leads to the development of a proinflammatory milieu with potent inhibitory effects on the neuromuscular apparatus (see fig), resulting in POI. In this study, Stoffels and colleagues investigated the putative role of interleukin (IL) 10 in the development of POI. In IL10 knockout mice, a clear accentuation of the inflammatory response was seen, motility never recovered and the majority of these animals died. In wild-type animals, functional recovery occurred in all animals within 7 days and there was no mortality. Treatment with recombinant murine IL10 clearly reduced the inflammatory response following intestinal manipulation and prevented the POI. This study suggests that treatment with IL10 might be an option to prevent the development of POI. Studies in humans are warranted! ***See page 648***



Betanechol-stimulated mechanical activity recorded in vitro from small intestinal muscle strips of interleukin (IL) 10 knockout mice (IL10 -/-) without (control) and with intestinal manipulation (POD-1, POD-5; postoperative day 1 and 5).

Interaction between mismatch repair polymorphisms and lifestyle factors increases the risk of colon cancer

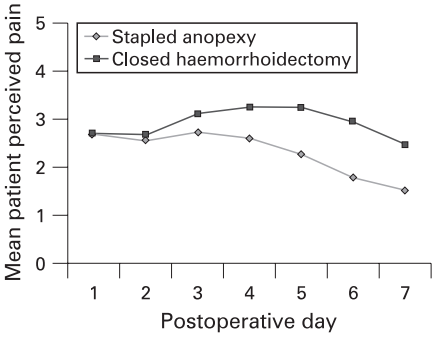
Colon cancer is a major health problem in the Western world. Studies assessing risk factors and the interaction between these are, therefore, of great value. Different risk factors have been identified and deficiency of DNA mismatch repair (MMR) has been causally linked to its aetiology. In this case–control study, the authors evaluated the role of common polymorphisms in MMR and the potential interaction with microsatellite instability (MSI) status and lifestyle factors, for example smoking, Western diet, alcohol intake and obesity. A total of 1609 subjects with colon cancer and 1972 controls were investigated. The authors were able to demonstrate that two polymorphisms in MMR genes (*MSH6 Gly39Glu* (see fig) and *MLH1 -93G>A*) were associated with risk of overall colon and MSI-positve colon cancers. Moreover, interactions with smoking and Western diet were also demonstrated. This study further strengthens the interaction between genetic and environmental factors in the development of colon cancer. Hopefully, these kinds of investigations will lead to preventive measures in order to reduce the incidence of colon cancer. ***See page 661***

Participants heterozygous (*Gly/Glu*) or homozygous (*Glu/Glu*) for the *MSH6* variant were at 17% increased risk for colon cancer

	Overall		
Genotype	**Cases No**	**Controls No**	**OR (95% CI)**
MSH6 Gly39Glu (116G>A)			
Gly/Gly	1037	1340	1 (referent)
Gly/Glu	514	557	1.19 (1.03 to 1.38)
Glu/Glu	48	62	0.99 (0.67 to 1.46)
Gly/Glu or Glu/Glu	562	619	1.17 (1.02 to 1.35)

Patients prefer stapled anopexy to haemorrhoidectomy

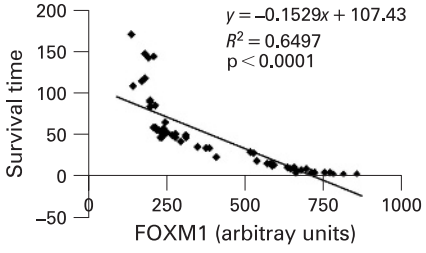
Haemorrhoids are a frequent source of discomfort for patients and this worsens—albeit temporarily—after surgical treatment. The optimum surgical treatment is contentious. This study is notable for its large size and careful delineation of the patients' perspective. A total of 182 patients were randomised to stapled anopexy (SA) (3–4 cm above the dentate line) or a traditional closed haemorrhoidectomy (CH). Postoperative pain and symptoms were monitored at 6, 12, 24 and 48 weeks. The operations were similar in terms of patient satisfaction with symptom control but there was a strikingly faster decline of pain after the SA (see fig). By the end of the first week, 63% of patients were off all analgesia, compared with just 37% undergoing CH. Of those having SA, 65% were willing to undergo the same operation again if required, compared with 45% after CH. Pain and physical function were more impaired by CH than SA but faecal urgency was greater after SA, being experienced by 59% compared with 41% after CH. Hospital stay and time to back to work were similar, as was reoperation and admission for complications, which were both acceptably low. ***See page 668***



Patients who underwent stapled anopexy showed a faster decline of pain compared with those undergoing conventional haemorrhoidectomy.

Transcription factor FOXM1 and its relationship to hepatocellular carcinogenesis in rats and man

Treatment for hepatocellular carcinoma (HCC) is poor, despite it being one of the commonest tumours worldwide. Rats that are genetically susceptible to develop HCC show overexpression of a number of genes important in cell cycling. Forkhead box M1B (FOXM1) is a transcription factor that promotes proliferation and is over-expressed in several human tumours. FOXM1 depletion reduces proliferation and increases resistance to hepatocarcinogenesis. This study examines the development of HCC following dosing with diethylnitrosamine followed by a hyperprotein diet and partial heptectomy. FOXM1 expression increased progressively from early neoplastic nodules to hepatocellular carcinoma and was greater in the F34 rats, which are genetically susceptible to develop HCC, compared with the resistant Brown Norway rats. FOXM1 expression was increased in patients with HCC with a poor prognosis and correlated inversely with the length of survival (see fig). In vitro cell line work showed that FOXM1 increased HCC proliferation and its inactivation by small interfering RNA (siRNA) markedly reduced proliferation. This work suggests that FOXM1 could represent a therapeutic target for this dismal condition. ***See page 679***



FOXM1 expression inversely correlated with survival time shown in months after partial liver resection of patients with hepatocellular carcinoma.