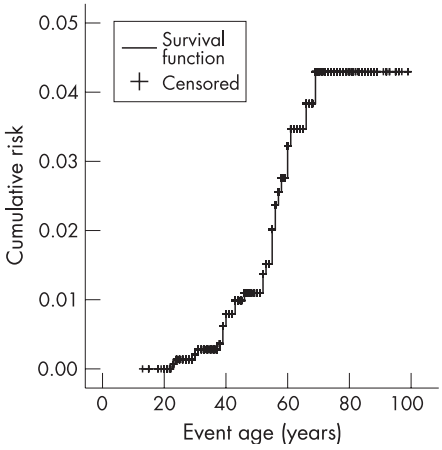
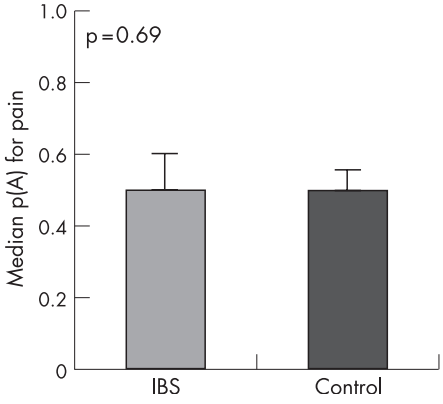
Digest

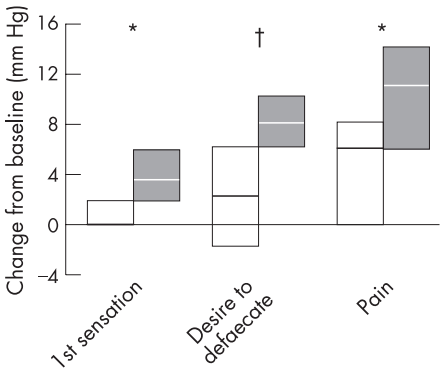
Robin Spiller and Emad El-Omar, *Editor and Deputy Editor*



Lifetime risk of developing small bowel cancer in MMR mutation carriers.



Sensory discrimination (p(A)) in IBS and controls.



Change in balloon pressure from baseline pressure to cause first sensation, desire to defaecate and pain for patients with IBS treated with pregabalin (grey area) or placebo (clear area).

LIFETIME RISK OF SMALL BOWEL CANCER IN FAMILIES WITH LYNCH SYNDROME

Lynch syndrome (hereditary non-polyposis colorectal cancer; HNPCC) is caused by a germ-line mutation in one of the DNA mismatch repair (MMR) genes. Mutations of the MLH1 and MSH2 genes account for 70–90% of cases. Such patients develop colorectal cancer at an early age and have an excess of extra colonic malignancies, including small bowel cancer with a relative risk >100. Knowing whether to screen such families for this rare condition depends on an accurate knowledge of the absolute risk. In this study, 1496 family members with a MMR mutation from 189 families on the Dutch HNPCC registry were examined. The cumulative risk of developing small bowel cancer in MMR mutation carriers is shown in the figure, with a lifetime risk of 4.2%. The specific MMR mutation did not alter the risk nor did gender. The authors conclude that the annual incidence is too small to justify invasive screening techniques such as double balloon enteroscopy but that the newer technique of videocapsule endoscopy might be more acceptable and requires further evaluation.

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LOWER PAIN THRESHOLDS IN IBS IN SPITE OF NORMAL SENSORY DISCRIMINATION

Abdominal pain and discomfort in patients with irritable bowel syndrome (IBS) has often been attributed to visceral hypersensitivity, as shown by a reduced threshold for pain during rectal distension. A study by Dorn *et al* used sensory discrimination testing to examine whether this reflects true hypersensitivity or a tendency to use lower criteria to report stimuli as painful. The authors confirmed reduced pain thresholds by the conventional ascending methods of limits (AML) protocol, in which the rectal balloon was progressively distended until a pain threshold was reached. They then exposed patients to rectal distension at a pressure of 30, 32 and 34 mm Hg in an unpredictable order and they rated these on a scale of 0–5. The ratings were used to calculate a discrimination index (p(A)), which did not differ between IBS and controls (see fig). The individual's report criteria, an overall measure of individuals' tendency to rate stimuli as either intense or weak, was also calculated. A higher criteria means a stoic tendency. They found the AML pain threshold correlated strongly with the report criteria ($r = 0.67$), suggesting that the lowered AML reflects an increased tendency to report pain rather than increased sensitivity, leading the authors to conclude that novel treatments for IBS pain should target centrally mediated mechanisms.

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ADRENERGIC $\alpha_2\delta$ AGONIST REDUCES VISCERAL HYPERSENSITIVITY IN IBS

Decreased threshold for pain induced by rectal distension is a characteristic feature of IBS and an appropriate target for novel treatments. So far, however, there is little evidence that normalising the threshold for pain correlates with improvement in symptoms. This randomised, placebo-controlled trial evaluated the effect of pregabalin, a second generation $\alpha_2\delta$ ligand, on both symptoms and the threshold for pain on rectal distension in patients with IBS previously shown to have visceral hypersensitivity. Pregabalin is already used in the treatment of neuropathic pain and epilepsy and is thought to be superior to the widely used related compound, gabapentin. The trial was completed by 26 patients. There was a significant increase in the threshold of pain, which rose by 5.4 mm Hg. This was associated with a tendency for daily pain scores to decrease; however, owing to small numbers, this did not reach significance. Pregabalin has been shown to exhibit anxiolytic properties and mild sedation, although the protocol was designed to minimise this effect. Certainly these results should encourage a large clinical trial of this agent in IBS.

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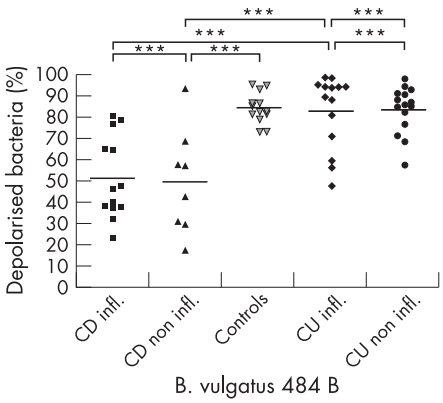

Reduced antimicrobial activity against *B vulgatus* 484 B of cationic extracts from biopsies of patients with Crohn's disease and ulcerative colitis compared with controls.

REDUCED MUCOSAL ANTIMICROBIAL ACTIVITY IN CROHN'S DISEASE OF THE COLON

The intestinal microbiota plays an important role in the pathogenesis of irritable bowel disease (IBD). Epithelial cells produce a variety of cationic antimicrobial peptides, including defensins and cathelicidins. Nuding *et al* looked at the antimicrobial activity in colonic mucosa of patients with IBD and healthy controls. They quantitated the bacterial killing of cationic peptide extracts from colonic biopsies taken from patients with active or inactive Crohn's disease, ulcerative colitis and controls. They specifically looked at bacterial killing of clinical isolates of *Bacteroides vulgatus*, *Enterococcus faecalis*, *Escherichia coli* and *Staphylococcus aureus*. Patients with Crohn's disease had a significantly reduced antimicrobial effect compared with patients with ulcerative colitis and healthy controls, which was most evident against *B vulgatus* (see fig). Killing of *E coli* and *E faecalis* was significantly lower in Crohn's disease compared with ulcerative colitis. The inflammation status or concurrent steroid treatment had little effect on these differences. The authors conclude that this compromised functional bacterial activity in patients with Crohn's disease, compared with patients with ulcerative colitis and controls, may represent an important and likely primary pathogenic mucosal defect of colonic Crohn's disease.

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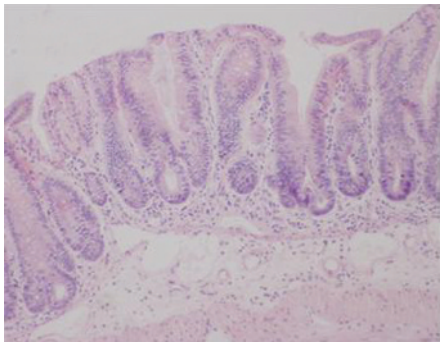

Histological damage induced by DSS colitis in wild-type compared with CD40L knockout and CD40 knockout mice.

CD40–CD40-LIGAND PATHWAY REGULATES INFLAMMATION ASSOCIATED ANGIOGENESIS

Angiogenesis is a key feature of many chronic inflammatory diseases, including rheumatoid arthritis and IBD. This is regulated by numerous factors, including vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF) and interleukin 8 (IL8), which promotes tubule formation in human intestinal microvascular endothelial cells (HIMECs). The study by Danese *et al* assessed the role of the CD40–CD40-ligand (CD40L) pathway in stimulating these angiogenic factors. VEGF, HGF and IL8 release from human intestinal fibroblasts were markedly and specifically stimulated, both by soluble CD40L (sCD40L) and by lamina propria T cells preactivated by adding CD40L. HIMEC migration was stimulated by sCD40L, which also promoted tube formation. The importance of this pathway in vivo was tested by studying the effect of CD40 and CD40L gene knockout on acute dextran sodium sulphate (DSS)-induced colitis. The knockout mice appeared to be protected from DSS-induced colitis. Similar reduction in inflammation and microvascular density was noted in chronic DSS-induced colitis, suggesting this pathway might be significant in IBD. Monoclonal antibodies to CD40L have already been used in haematological patients and the authors suggest that these findings would encourage exploration of their possible use in IBD.

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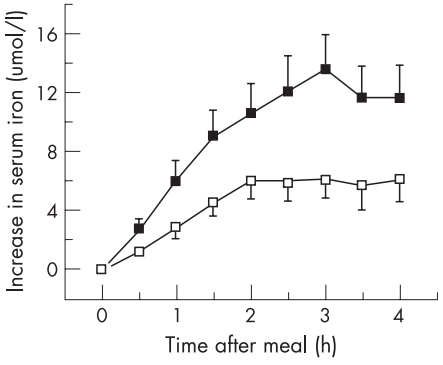

Serum iron after test meal before (■) and at the end of a 7-day course of a PPI (□).

PPIs REDUCE REQUIREMENTS FOR MAINTENANCE PHLEBOTOMY IN HEREDITARY HAEMOCHROMATOSIS

Currently, the only approach to counteracting the excessive absorption of iron in hereditary haemachromes involves repeated venesection to deplete iron stores. Reducing dietary iron absorption is an attractive alternative and gastric acid production has been known to be an important factor in the absorption of iron in normal subjects. The authors of this study reviewed the case records of seven individuals who had had maintenance phlebotomy over a period of about 10 years, in whom proton pump inhibitors (PPIs) had been initiated. The annual phlebotomy sessions required to control iron stores before PPIs (2.5 l (mean 0.25 l)) fell to 0.5 l (mean 0.25 l) after administration of a PPI. Suspecting that this was related to inhibition of iron absorption, the authors then studied the effect of PPIs on iron absorption in 14 patients with hereditary haemochromatosis who had normal iron stores following phlebotomy. Serum iron curves were measured following ingestion of a meal containing highly bioavailable iron on two occasions before and during the administration of a PPI. As the figure shows, there is a striking reduction in absorption of iron on PPIs. This simple but important study suggests that PPI treatment could produce worthwhile reduction in the need for phlebotomy in this patient group.

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