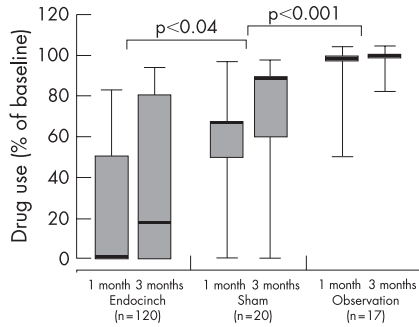
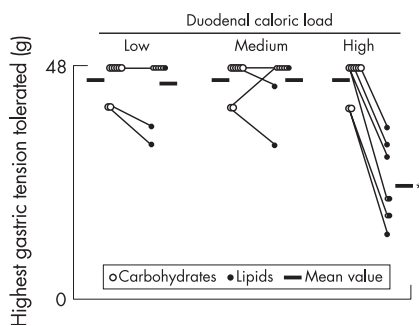


Robin Spiller and Alastair Watson, Editor and Deputy Editor



Use of antisecretory agents expressed as percent of baseline dose.



Gastric wall tension thresholds for discomfort during low, medium and high loads of intraduodenal carbohydrate or lipids, showing the greater sensitising effect of lipids compared with carbohydrate.

## ENDOSCOPIC GASTROPLICATION REDUCES PPI USE IN PATIENTS WITH REFLUX

Improving the barrier to gastro-oesophageal reflux using endoscopic suturing is undoubtedly attractive, but placebo effects are likely to be large. This study, the first randomised sham-controlled trial of this treatment, is therefore welcomed. Patients who were reliant on proton pump inhibitors (PPIs) were randomised to three groups; active treatment, sham treatment or observation only. Sixty patients were enrolled and partial or complete 3-month data were available for 57 of them. After 3 months, 65% of patients in the active group had reduced use of PPIs compared with 25% in the sham group and none in the observation-only group. The benefit persisted, although with diminishing magnitude at 6 and 12 months. Symptoms and quality of life were also improved. Surprisingly, both active and sham groups showed a similar fall in acid exposure, raising the question of exactly how endoscopic gastroplication works. The authors found a large percentage of loose sutures during re-treatment, which was needed in 29% within the year of follow up. They caution against the widespread adoption of such a technique until it has been further improved.

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## GREATER POTENCY OF FAT COMPARED WITH CARBOHYDRATE ON GASTRIC ACCOMMODATION AND SENSITIVITY TO DISTENSION

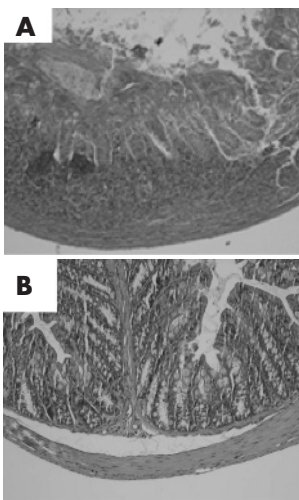
Patients with dyspepsia often complain of early satiety and bloating, symptoms that may reflect either impaired postprandial gastric accommodation or enhanced sensitivity to distension. As patients often report fat intolerance, this study evaluated the effects of fat and carbohydrate on gastric accommodation and sensitivity induced by infusing nutrients intraduodenally. A computerised tensostat was used to expose the gastric wall to a known tension, which was increased in 4 g steps every 3 min, up to a maximum of 48 g. There were no differences between carbohydrate and lipid infusion when the caloric load was low or medium (0.2 or 0.5 kcal/min) but at the highest caloric load tested (1 kcal/min) there was a much reduced tolerance for gastric distension (see fig) during lipid infusion, which also caused greater gastric relaxation. In spite of the much lower gastric tension level during lipid infusion, the perception scores were higher, and in particular lipids were much more likely to induce nausea. This sensitisation may be regarded as a protective mechanism to avoid overloading the gut with fat by counteracting the greater gastric accommodation induced by fat.

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## SIGNALLING THROUGH THE GLUCOCORTICOID-INDUCED TNF RECEPTOR REDUCES EXPERIMENTAL COLITIS IN MICE

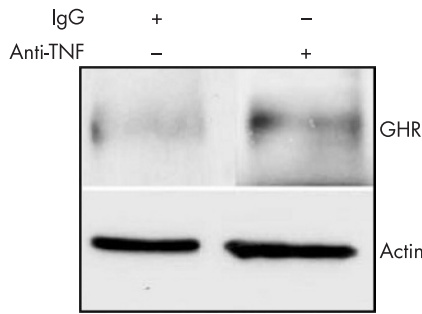
The glucocorticoid-induced tumour necrosis factor receptor (GITR) is a member of the tumour necrosis factor (TNF) receptor superfamily. The authors investigated its role in an experimental model of Crohn's disease, in which colitis is induced by the intrarectal instillation of 2,4,6-trinitrobenzene sulphonic acid (TNBS). GITR is expressed by both T cells and cells of the innate immune system, such as macrophages and polymorphonuclear leucocytes. Mice in which GITR has been genetically knocked out have low levels of interleukin 12 (IL12) release and, as a consequence, have blunted Th1 cytokine responses to TNBS. Macrophages from GITR <sup>-/-</sup> also have attenuated responses to TNBS, with reduced secretion of IL6 and TNF $\alpha$ . The most striking observation is that TNBS colitis is prevented by administration of an antibody that blocks GITR signalling, suggesting anti-GITR treatment should be explored in human Crohn's disease.

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Histological signs of TNBS colitis (A) are completely prevented by an antibody that blocks GITR signalling (B).

# Digest

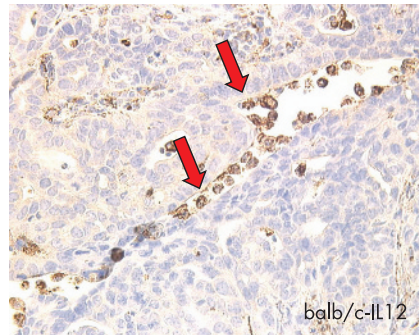


Western blot demonstrating that neutralisation of TNF $\alpha$  increases growth hormone receptor in experimental colitis.

## BLOCKADE OF TNF $\alpha$ INDUCES A GROWTH HORMONE PATHWAY THAT CONTRIBUTES TO RESOLUTION OF COLITIS

Patients with Crohn's disease, especially children, are resistant to growth hormone, with consequent growth failure. Administration of growth hormone has been shown to reduce mucosal inflammation in Crohn's disease. It is known that blockade of TNF $\alpha$ , for example with infliximab, restores growth hormone function. The authors demonstrate that neutralisation of TNF $\alpha$  increases growth hormone receptor, with activation of the growth hormone dependent transcription factor Stat5. This stimulates production and nuclear localisation of the growth hormone target gene peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ), which decreases inflammation by reducing NF- $\kappa$ B activation. Anti-TNF treatment is already known to stop inflammatory reactions in the intestine by inducing apoptosis of T cells. This newly identified pathway must be added to the therapeutic actions of anti-TNF treatment.

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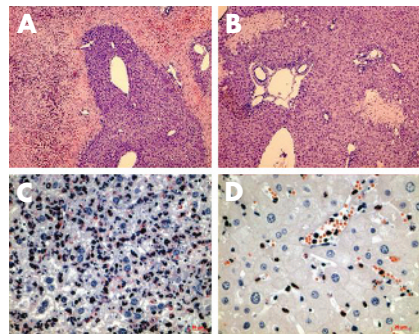


Invasion of peritoneal cancer deposits by macrophages stimulated by IL12.

## TREATMENT OF PANCREATIC PERITONEAL CARCINOMATOSIS WITH FIBROBLASTS GENETICALLY ENGINEERED TO SECRETE IL12

Peritoneal carcinomatosis from pancreatic cancer is untreatable and carries an appalling prognosis. IL12 is a potent pro-inflammatory cytokine that stimulates production of interferon  $\gamma$ , TNF $\alpha$  and IL2 promoting expansion of natural killer T cell and CD4 and CD8 T cell populations (Th1 response). Clinical trials of IL12 for the treatment of a variety of human cancers show promise. However, systemic administration of IL12 is severely limited by its toxicity and degradation. To circumvent these problems, the authors transfected fibroblasts *ex vivo* to secrete IL12. *Ex vivo* gene therapy avoids many of the difficulties of *in vivo* gene transfer. The transfected fibroblasts were injected into the peritoneal cavity of mice, in which peritoneal carcinomatosis had been generated by injection of human pancreatic cancer cells. The authors show that the IL12 secreting fibroblasts reduce tumour mass and increase the lifespan of these mice. This is due to an increase in macrophages, natural killer cells and reactive oxygen species within the peritoneal tumours.

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Haematoxylin and eosin stains showing reduced hepatic injury in the common bile duct ligated mice (B), associated with reduced neutrophil infiltration (D) compared with controls (A and C).

## PROTECTIVE EFFECT OF CHOLESTASIS ON LIVER REPERFUSION INJURY

Ischaemia followed by reperfusion, as seen for example in liver transplantation, causes the release of reactive oxygen species and generates an inflammatory cascade, typically peaking 24 h after reperfusion. Although clinicians believe that cholestasis has a uniformly negative effect on clinical outcomes, in this somewhat surprising study cholestasis was shown to ameliorate ischaemia-reperfusion injury. Groups of mice were subjected to common bile duct ligation, selective bile duct ligation or sham laparotomy. Common bile duct ligation protected against reperfusion injury, as shown in the figure. There was a striking reduction in liver injury, myeloperoxidase activity and serum enzymes at 4 and 24 h post reperfusion. Selective bile duct ligation, which was not associated with hyperbilirubinaemia, produced similar effects, leaving the authors to conclude that bilirubin was not responsible, but some unknown systemic circulating factor. Whether this factor can be identified and used therapeutically to facilitate liver transplant remains to be determined.

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