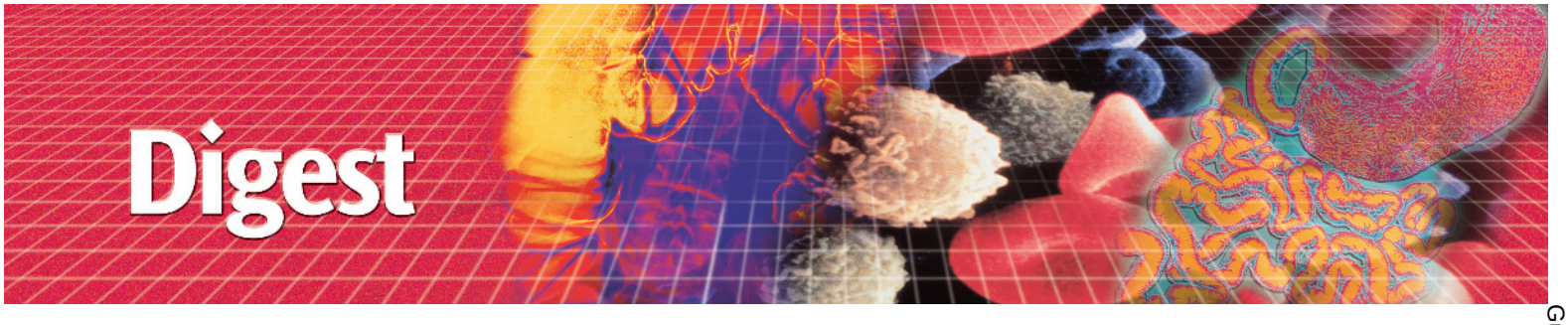
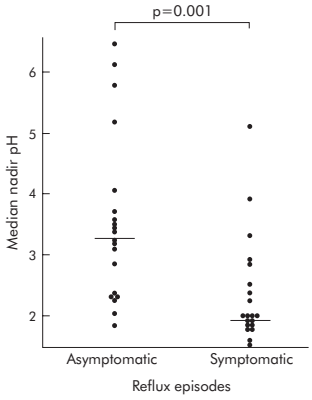


Robin Spiller and Alastair Watson, *Editor and Deputy Editor*



WHAT DETERMINES SYMPTOMS IN GASTRO-OESOPHAGEAL REFLUX?

Previous studies have demonstrated that symptoms are associated with lower pH, longer duration, and more proximal extent of reflux. The study combines the newly introduced impedance recording, which can detect non-acidic reflux, with traditional pH monitoring to assess which features best predict symptoms. The authors confirmed previous findings, that the main determinant of symptoms was refluxate pH, as shown in the figure. Interestingly 14.8% of the symptomatic episodes were only weakly acidic (ph 4-7). Pure gas reflux accounted for around a quarter of all reflux events, but only 3% were associated with symptoms, possibly due to aerosolised acid. Reflux events resulting in regurgitation of fluid were more often associated with gas reflux when compared with those preceding heartburn alone.

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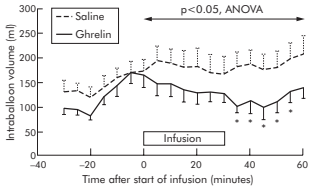

GHRELIN STIMULATES GASTRIC MOTILITY BY A MOTILIN INDEPENDENT PATHWAY

Ghrelin, a motilin related peptide found in gastric endocrine cells, is a growth hormone releasing peptide that also acts as a starvation signalling molecule in the periphery. In animals it stimulates food intake and accelerates gastric emptying. Blood levels rise during an overnight fast and fall to their lowest level after breakfast. The current study showed that a supra-physiological infusion caused a striking stimulation of motility in both the stomach and small bowel. As the figure shows, the volume of the barostat balloon fell during ghrelin infusion, indicating increased gastric tone. Ghrelin also simulated the premature appearance of a migrating motor complex. These changes occurred without a change in plasma motilin. These proven pro-kinetic effects suggest that Ghrelin analogues may be effective in gastroparesis, as recently reported in diabetic gastroparesis in the December 2005 issue of *Gut*.

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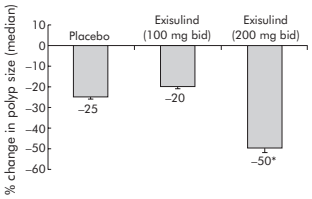

Percentage reduction in polyp size after 12 months treatment with placebo, Exisulind 100mg and 200mg bd.

EXISULIND CAUSES REGRESSION OF COLONIC ADENOMAS

Chemoprevention of colorectal cancer is an attractive strategy because frequently colorectal cancer does not present until it is advanced and incurable. It is now well established that prolonged treatment with aspirin can reduce the incidence of colorectal cancer by as much as 50%. However, aspirin is associated with significant gastric toxicity. Specific Cox-2 inhibitors avoid gastric toxicity to some extent, but have recently been associated with increased cardiovascular mortality. Exisulind, a sulphone metabolite of the NSAID sulindac, potentially avoids both toxicities because it has no inhibitory activity against either Cox-1 or Cox-2. This randomised controlled trial demonstrates that exisulind 200 mg taken twice a day for 12 months significantly reduces polyp size (See figure). The authors argue that reduction in polyp size is a valid surrogate for the prevention of progression to colorectal cancer. However, exisulind is associated with abdominal pain and mild rises in liver function tests. This study should stimulate the search for similar, less toxic compounds for the chemoprevention of colorectal cancer.

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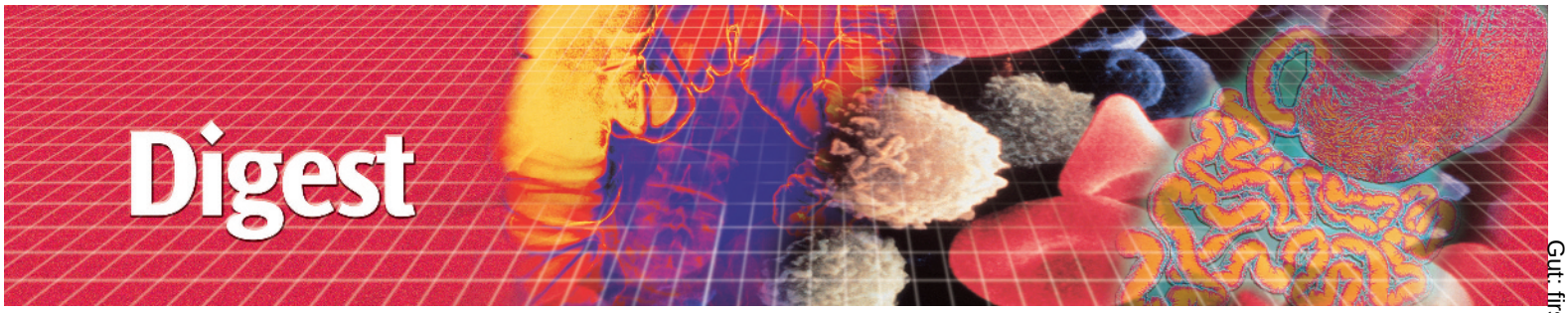

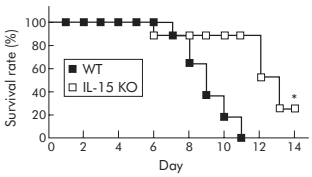

Survival of IL-15 KO mice (open squares) from DSS-induced acute colitis compared to wildtype controls (closed squares).

IL-15 AND COLITIS INDUCED BY DEXTRAN SODIUM SULPHATE

IL-15 is a cytokine known to play an important role in innate and adaptive phases of the immune response through stimulation of dendritic cells, macrophages, natural killer cells, and mucosal T cells. Increased production of IL-15 has been observed in ulcerative colitis. The role of IL-15 in the pathogenesis of IBD was assessed by the study of the severity of colitis induced by dextran sodium sulphate (DSS) in IL-15 knockout mice. The main result is shown in the accompanying figure, in which IL-15 knockout mice survive DSS induced acute colitis longer than wildtype controls. Accumulation of TNF-α, IL-12, IFN-γ and $CD8^+$ T cells is reduced in IL-15 deficient mice. The authors conclude that IL-15 plays a key role in the pathogenesis of colitis and is a potential target molecule for the prevention and treatment of IBD.

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Table 8 Death or liver transplantation in 43 patients with primary biliary cirrhosis-systemic sclerosis (PBC-SSc) and 82 patients with PBC alone matched by serum bilirubin at referral to Royal Free Hospital

	PBC-SSc (n = 43)	PBC (n = 82)
Death	9 (21%)	9 (11%)
Liver related deaths	2 (5%)	6 (7%)
SSc related deaths	6 (14%)	–
Non-liver and non SSc related deaths	–	2 (2%)
Cause of death unknown	1 (2%)	1 (1%)
Liver transplantation	7 (16%)	21 (26%)
Liver transplantation for liver failure	6 (14%)	20 (24%)
Liver transplantation for symptoms	1 (2%)	1 (1%)

Values are number (%).

CLINICAL FEATURES AND PROGNOSIS OF PRIMARY BILIARY CIRRHOSIS ASSOCIATED WITH SYSTEMIC SCLEROSIS

In about 8% of cases primary biliary cirrhosis (PBC) is associated with systemic sclerosis (SSC). The skin, gastrointestinal tract, and kidneys are the prime sites of involvement in systemic sclerosis; the liver is only rarely involved. Primary biliary cirrhosis is characterised by the antimitochondrial antibody, whereas systemic sclerosis is characterised by the anticentromere antibody. In this study the clinical features and prognosis of patients with both PBC and SSC were compared with patients with PBC alone. Patients with both conditions had a lower rate of liver transplantation and lower rates of liver deaths compared with patients with PBC alone (See table). These differences were not accounted for by earlier SSC related deaths. The reason for the better prognosis of patients with both conditions is not known.

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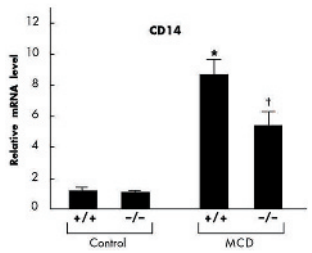

HOW TNF-α ACTION'S ON KUPFFER CELLS MEDIATE LIVER FIBROSIS IN NASH

TNF-α is known to play a major role in alcohol induced liver injury and TNF-α mRNA is known to be increased in individuals with non-alcoholic steatohepatitis (NASH) who develop liver fibrosis. The current study used double knockout mice lacking both TNF receptors (1 and 2) to explore the role of TNF-α signalling in steatohepatitis induced by feeding on a diet deficient in methionine and choline (MCD). Mice deficient in both TNF receptor 1 and 2 (TNFRDKO) accumulated less fat and less fibrosis. They also showed reduced activation of Kupffer cells on the MCD diet as illustrated in the figure, which shows the mRNA level for CD-14, a part of the heteromeric lipopolysaccharide receptor, strongly expressed on macrophages. Part of the effect of TNF-α appears to be via an anti-apoptotic action mediated through tissue inhibitors of metalloproteinase 1 (TIMP-1). TNFRDKO animals showed marked reduction in TIMP-1. The authors conclude that blockade of the TNF-α receptor signalling pathways is a promising therapeutic target for the treatment of hepatic fibrosis in NASH.

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