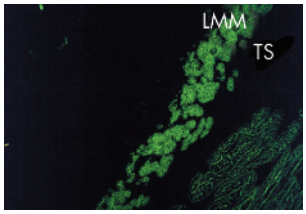
Digest

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



Tissue transglutaminase expression in the wall of the oesophagus.

CROSS LINKING OF GLIADIN BY TISSUE TRANSGLUTAMINASE IS A CRITICAL PART OF THE PATHOGENESIS OF COELIAC DISASE

It is know that short peptides from α-gliaden stimulate T cells in coeliac disease. The binding of these peptides to human leukocyte antigens (DQ2 and DQ8) is greatly enhanced when the peptides are deamidated by tissue transglutaminase. It has been hypothesised that the deamidation of a few specific gliadin peptides is responsible for the chronic inflammation of coeliac disease. However, this hypothesis has not been tested directly. Data are presented that tissue transglutaminase can deamidate a wide range of gliadin peptides. Furthermore, deamidation causes the binding and long term immobilisation of gliadin peptides to collagen, which contributes the chronicity of inflammation. This binding is also associated with increased titres of anticollagen antibodies, which may explain the high incidence of autoimmune disease in coeliac patients.

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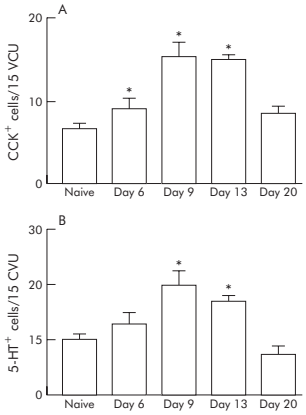

HOW JEJUNAL INFLAMMATION INDUCES ANOREXIA: ROLE OF CCK AND 5-HT

Many inflammatory illnesses are associated with anorexia but the mechanisms involved are uncertain. The authors had previously found increased cholecystokinin (CCK) levels in patients with giardiasis, an illness often associated with anorexia and nausea. They undertook a mechanistic study using *Trichinella spiralis* infected mice and found (see figure) that the number of CCK and 5-HT containing cells peaked at the height of inflammation on day nine. This effect on CCK containing cell numbers required the presence of functional CD4+ cells, which the authors showed using genetically modified animals to be dependent on the IL-4 receptor. The fall in food intake was partially antagonised by a CCK-antagonist, suggesting that the morphological changes have functional significance.

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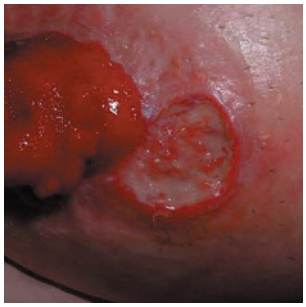

INFLIXIMAB IS AN EFFECTIVE TREATMENT FOR PYODERMA GANGRENOSA

Pyoderma gangrenosa is an uncommon, although rightly feared, complication of inflammatory bowel disease (IBD), which until now has never been subjected to a randomised controlled trial (RCT) of treatment. Thirty patients, of whom 19 had associated IBD (ratio of Crohn's colon to ulcerative colitis, 2:1), underwent RCT of infliximab 50 mg/kg or placebo given at week 0 and 2 weeks later. In the infliximab group, 46% improved compared with just 6% (1/17) in the placebo group. Neither site nor presence or absence of IBD nor its particular subtype predicted response. However, although 13 of 14 with a duration of pyoderma <12 weeks improved, only 7 of 15 in whom the pyoderma had been present >12 weeks did so. In this difficult and potentially dangerous condition many toxic drug regimes have been used with variable success. This study suggests that infliximab should be the first line of treatment in such patients.

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CORRECTION

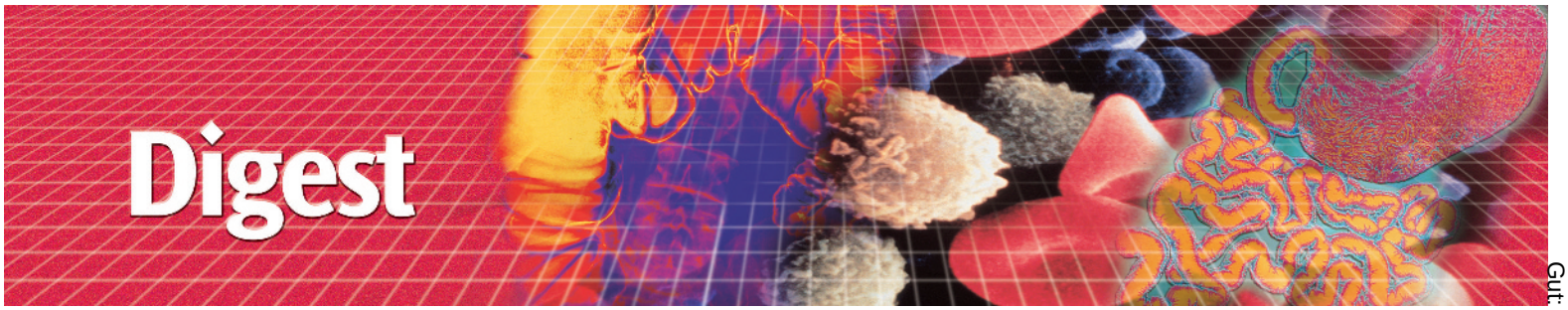
It has come to our attention that there is a dosage error in the print version of the ECCO Consensus on the Management of Crohn's Disease supplement to Gut (March 2006, Volume 55, Supplement I).

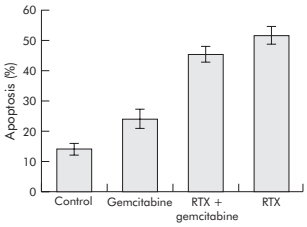
The error occurs on page i22 in section 5.4.7. The first line of this section should read:

Methotrexate 25 mg/**week** (oral, subcutaneous or intramuscular injection, unlicensed therapy for IBD) may be used in a similar fashion to thiopurines.

The online version of this article is correct.

The authors apologise for this error.





VALLINOIDS FOR TREATMENT AND CONTROL OF PAIN IN PANCREATIC CANCER

Ductal cancer of the pancreas has a dismal prognosis and is often accompanied by severe pain that is difficult to control adequately. The field is therefore ripe for the introduction of new and more effective therapies. Here it is shown that resiniferatoxin, a member of the vanilloid family, is a potent inducer of apoptosis in a number of cell lines derived from pancreatic cancers. It has synergistic killing activity with gemcitabine, the standard chemotherapeutic agent for pancreatic cancer at present (see figure). However, its toxic effects are not limited to cancer cells. The authors show that the vallinoid 1 receptor is upregulated in nerve fibres within the pancreas of patients with cancer, although not in controls with chronic pancreatitis. This suggests that resiniferatoxin may have analgesic properties as well as anticancer activity. This exciting hypothesis needs to be tested urgently in clinical trials.

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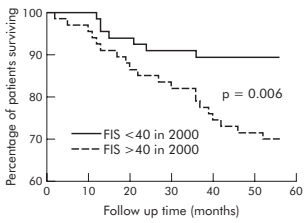

Survival of patients with high fatigue scores (>40) is less than those with low fatigue scores (<40).

FATIGUE IN PRIMARY BILIARY CIRRHOSIS CORRELATES WITH MORTALITY

Fatigue is a common and debilitating symptom of primary biliary cirrhosis (PBC). Its cause is not understood, although some data suggest it may relate to abnormalities in the central nervous system rather than directly to liver dysfunction. In 2000, the authors studied a cohort of PBC patients, documenting the symptom of fatigue in this population. It is not know whether fatigue improves or declines with disease progression. Using the same cohort, the authors compared original fatigue levels to those in 2004. They found that the levels do not appreciably change with time. Furthermore, they found that fatigue is an independent risk factor for death with the majority of patients with fatigue dying from cardiac causes. This study highlights the need for further understanding of the pathogenesis of fatigue in PBC and its treatment.

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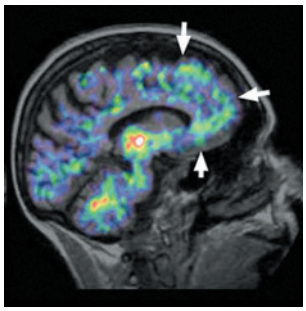

FUNCTIONAL MAGNETIC RESONANCE IMAGING SHOWS ABNORMALITIES IN HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy can be a disabling feature of chronic liver disease but its mechanisms are poorly defined. Postmortem studies have suggested a significant increase in peripheral benzodiazepine binding sites (PBBS). Such sites are not found in normal brain but microglia can rapidly express these in response to immune activation. PBBS can be imaged using PET by their binding to a C^{11} labelled ligand, PK11195. The present study examined five patients with biopsy proven cirrhosis and hepatic encephalopathy and showed binding of this ligand not seen in healthy controls (see figure). Striking abnormalities were especially seen in the pallidum, the right putamen, and the right dorsal lateral pre-frontal region, confirming other studies suggesting that the frontal-limbic-basal ganglia circuits are abnormal in hepatic encephalopathy. The ligand used binds exclusively to non-neuronal structures and supports the hypothesis that the hepatic encephalopathy is associated with glial activation. These insights offer new targets for therapy in this difficult condition.

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