

## VALUE OF SECOND LOOK ENDOSCOPY IN PEPTIC ULCER HAEMORRHAGE

After successful endoscopic control of a bleeding peptic ulcer there is often a temptation to rest on one's laurels. Such patients, however, still have a 5–30% chance of rebleeding with a significant risk of mortality. Whether to merely watch and hope or to actively re-examine the bleeding site is often a difficult decision in patients who often have significant comorbidity. The large, single centre, prospective, randomised study of repeat endoscopy 16–24 hours after initial homeostasis reported in this issue goes some way to address this issue. The authors showed a significant reduction in rebleeding rates and reduction in the number requiring surgery strongly supporting the adoption of this vigorous intervention policy. Interestingly, there was no increase in complication rates for the second treatment, which the authors explain is due to the clear endoscopic view obtained in a scheduled second endoscopy, which allows better targeting of treatment than when bleeding is ongoing.

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## PLATELETS ARE THE SOURCE OF INCREASED CD40 LIGAND IN IBD

CD40 ligand (CD40L) is a membrane glycoprotein related to tumor necrosis factor. Expression of CD40L and its receptor CD40 is known to be increased in B cells, macrophages, and T cells in a range of inflammatory conditions including inflammatory bowel disease (IBD). They are also expressed in platelets and CD40L is released as a circulating, biologically active, soluble form. This soluble form activates a range of non-immune cells including fibroblasts and endothelial cells resulting in the production of pro-inflammatory cytokines and upregulation of cell adhesion molecules. As the paper by Danese *et al* makes clear, the major source of this circulating CD40L is platelets rather than peripheral blood lymphocytes. IBD patients show increased circulating expression of CD40L especially when the disease is active, the increase being proportional to the extent of disease.

The activation of platelets probably occurs as they circulate through the inflamed microvasculature of the gut. This upregulation of the CD40/CD40L system may well be important in the thrombosis that can accompany active IBD. Ways of modulating this system might be of therapeutic benefit.

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## HOW SHORT CHAIN FATTY ACIDS STIMULATE EPITHELIAL MUCUS SECRETION: ROLE OF PROSTAGLANDIN E<sub>1</sub> PRODUCTION BY MYOFIBROBLASTS

Mucus is an important but neglected component of the epithelial barrier whose breakdown is likely to be important in IBD pathogenesis, which depends critically on the interaction between luminal bacteria and the mucosal immune system. Certain intestinal bacteria (probiotics) can improve mucosal barrier integrity and as the paper by Willemsen *et al* shows, this may be mediated by the short chain fatty acids (SCFAs) they produce. Co-culturing epithelial cells and myofibroblasts enhanced epithelial mucin (MUC-2) expression, which was further increased by prostaglandin E<sub>1</sub> (PGE<sub>1</sub>). SCFAs enhanced myofibroblast PGE<sub>1</sub> but not PGE<sub>2</sub> production and hence increased the PGE<sub>1</sub>:PGE<sub>2</sub> ratio. Finally, enhancement of MUC-2 expression by supernatants from myofibroblast culture exposed to SCFAs was blocked by simultaneous exposure to indomethacin, suggesting that SCFAs work by stimulating myofibroblast PGE<sub>1</sub> production. This shows a potential mechanism whereby probiotics could enhance mucosal barrier integrity and possibly play a role in therapy for IBD.

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## HCV AND PRISONERS

Hepatitis C virus (HCV) is a major public health concern that is concentrated in high risk groups which are themselves concentrated within the prison population. A close association between illicit drug injection, criminality, and HCV infection makes prisoners a particularly high risk group. Indeed, with the prevalence estimated at between 0.02% and 0.8% of the UK population, the results of this survey by Skipper, showing that at a minimum 2.6% of all prisoners had active infection with HCV, makes this point eloquently. Only 8.5% opted to be tested but 30% of these had detectable HCV with 42% having evidence of previous infection. Regrettably, most were ineligible for treatment, due either to psychiatric illness or persisting high risk behaviour—for example, injecting drugs or failure to undergo liver biopsy. Somewhat alarmingly, 33% of those testing positive admitted to having injected drugs while in the prison, suggesting the risk of intravenous drug misusers being infected in prison is high. Many problems were identified which will need to be corrected before this high risk group can be adequately treated.

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## ALTERED VASCULAR RESPONSE TO ENDOTHELIN-1 IN CIRRHOSIS

Patients with advanced cirrhosis exhibit a hyperdynamic circulation with high cardiac output and low vascular resistance in spite of marked sympathetic activation which would normally antagonise these effects. These changes contribute to fluid retention, ascites, and renal failure characteristic of end stage liver disease. Endothelin is a vasoactive peptide that binds to two receptors, ET<sub>A</sub> and ET<sub>B</sub>, on vascular smooth muscle leading to vasoconstriction. Binding to ET<sub>B</sub> receptors on vascular endothelial cells, however, produces the opposite effect through release of various vasodilatory factors including nitric oxide and vasodilatory prostanoids. As Vaughan and colleagues show, cirrhotics show a paradoxical response to intra-arterial infusion of ET-1 with a rise in forearm blood flow compared with a dramatic fall in controls. This abnormality is completely corrected by transplantation. They suggest that this is because patients with advanced liver disease have a pre-existing intense activation of vasoconstrictor systems and under these circumstances the vasodilatory effect of endothelin outweighs the vasoconstrictor response. Whether therapeutic intervention manipulating the endothelium pathways will be of value in correcting vascular abnormalities in cirrhosis remains to be determined.

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