Highlights from this issue

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The 2007 UK audit of acute upper GI Bleeding

In this issue of *Gut*, Hearnshaw *et al*, report more information from their landmark 2007 UK audit of acute upper gastrointestinal bleeding (AUGIB). The previous large UK study was in 1993 and the interim period (1993–2007) has witnessed substantive attempts to reduce the risk of AUGIB from peptic ulcer disease (*Helicobacter pylori* eradication, co-prescription of proton pump inhibitors), and also a rise in excess alcohol consumption in the UK. With this background, the current study reports eagerly awaited data on patient characteristics, diagnoses and clinical outcomes. The current audit was a multi-centre survey set in all UK hospitals admitting patients with AUGIB. Participants were adults (>16 years) presenting in or to UK hospitals with AUGIB between 1 May and 30 June 2007. Data on 6750 patients (median age 68 years) was collected from 208 participating hospitals. The major findings show that bleeding from varices appears to have become more common, accounting for 11% of cases and 20% of new admissions aged <60 years. Surgical intervention is now uncommon, occurring in <2% of all cases of AUGIB. Overall mortality remains significant at 10%, 7% in new admissions and 26% for inpatients. The results offer a valuable resource that will inform management strategies and health economic issues relevant to AUGIB (***see page 1327***).

Nod2 and intestinal microbial communities

The Nod2 gene is an intracellular sensor for the bacterial cell wall component muramyl dipeptide, and loss of function variants in the human Nod2 gene have been associated with an increased susceptibility for Crohn's disease, a condition characterised by a severely altered intestinal microbial community structure. In this fascinating study in *Gut*, Rehman *et al* investigated the influence of Nod2 on the development and composition of the intestinal microbiota using a Nod2-deficient mouse model. They found that these mice display an increased load of commensal microbiota and altered microbial composition, which is evident at an early weaning stage. Looking at humans carrying NOD2 variants (SNP13), they show that these individuals have significantly increased loads of Bacteroidetes and Firmicutes compared to wild type individuals (see figure 1). The results point to an essential role of Nod2 for the temporal development and composition of the host microbiota, both in mice and in humans, which may contribute to the complex role of NOD2 for the pathogenesis of Crohn's disease (***see page 1354***).

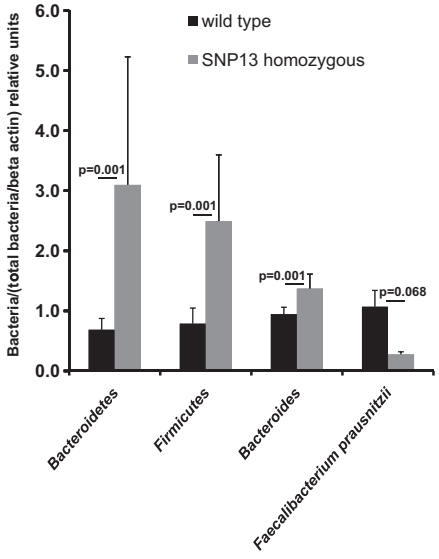

Figure 1 Relative abundance of ileal mucosa-attached microbiota with respect to SNP13 in humans.

NSAIDs and risk of lower GI tract bleeding: no clear way to reduce the risk

Every gastroenterologist knows all too well that the use of non-steroidal anti-inflammatory drugs (NSAIDs) is an important cause of ulcers and GI bleeding in the upper gastrointestinal tract. Selective COX-2 inhibitors can reduce this risk of NSAID related complications in the stomach and duodenum. In addition to inducing ulcers in the upper GI tract, it is also appreciated that NSAIDs can cause ulcerations and bleeding in the lower GI tract. However, the risk of these complications with non-selective and COX-2 inhibitors has not been carefully assessed. Lai and colleagues show in this issue of *Gut* that non-selective NSAIDs are associated with an increased risk for lower GI tract complications, and that the increased risk is seen with parenteral NSAIDs as well as oral NSAIDs. They also found that the risk for lower GI tract adverse events is similar between non-selective NSAIDs and COX-2 inhibitors. So, the risk of NSAID related toxicity in the lower GI tract needs to be considered in anyone receiving the medication regardless of the route or type of NSAID (***see page 1372***).

Obesity and colorectal cancer: another reason to eat right and exercise

Obesity has been associated with an increased risk of colon adenoma and colorectal cancer. Epidemiologic studies as well as studies in mouse models of colon cancer suggest a link between obesity and colorectal cancer. Obesity may increase the risk of colorectal cancer by causing adipose tissue dysfunction and by altering serum levels of adipokines, including leptin. However, it is still not clear which adipokines are playing a causal role in

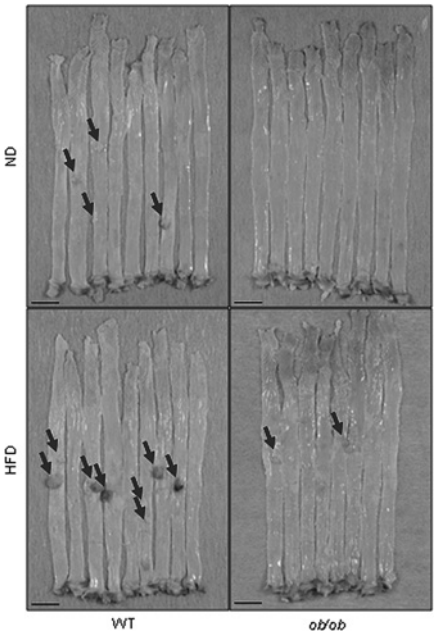

Figure 2 Leptin regulates azoxymethane induced colon tumour growth. Gross findings of colon tumours are shown. Arrows indicate large tumours. Scale bars1/41 cm. ND, normal diet; HFD, high fat diet.

Table 1 Risk of individual lower GI events associated with current use of selective and non-selective of NSAIDs

	Diverticulosis/diverticulitis of small intestine with haemorrhage (N=66)		Diverticulosis/ diverticulitis of colon with haemorrhage (N=309)		Haemorrhage of rectum and anus (N=256)		Perforation of intestine (N=477)		Angiodysplasia/Dieulafoy lesion (hemorrhagic) of intestine with haemorrhage (N=189)	
	Adjusted OR*	95% CI	Adjusted OR*	95% CI	Adjusted OR*	95% CI	Adjusted OR*	95% CI	Adjusted OR*	95% CI
Celecoxib	–	–	2.52	0.64 to 9.84	–	–	4.89	0.56 to 42.92	1.29	0.28 to 5.96
Non-selective NSAIDs overall (oral)	0.99	0.39 to 2.51	2.01	1.27 to 3.17	2.82	1.72 to 4.64	2.38	1.52 to 3.72	3.21	1.60 to 6.46
Non-selective NSAIDs overall (parenteral)	–	–	2.96	0.81 to 10.86	0.99	0.33 to 2.98	19.82	6.17 to 63.68	6.45	1.30 to 32.02

*Conditional logistic regression adjusted for important potential time-varying confounding variables including proton-pump inhibitors, histamine-2 receptor blockers, systemic corticosteroids, and low-dose aspirin.

colorectal cancer formation. In this issue of *Gut*, Endo *et al* use elegant mouse models of colorectal cancer to show that leptin is likely one of the mechanisms through which obesity is inducing colorectal cancer. They demonstrate that leptin acts as a growth factor for colorectal cancer at stages subsequent to tumour initiation in colon carcinogenesis (figure 2). They also show it may be an important factor that affects the behaviour of colon cancers that arise in obese people (***see page 1363***).

Hepatology

Kupffer cell activation in portal hypertension

Ample evidence suggests a role for infections in the increase in portal pressure and as a trigger for variceal haemorrhage in cirrhosis. Kupffer cells constitute the majority of the body's fixed macrophages. They come in close contact with gut-derived bacteria and thus are intimately involved in the innate immune response. Animal data show that activation of Kupffer cells results in a prompt and long-lasting increase in portal pressure. This interesting study from Denmark provides evidence for the role of Kupffer cell activation in *human* portal hypertension. The authors report that cirrhotic patients have a threefold increase in serum concentration of sCD163, a sensitive marker of macrophage activation (figure 3). sCD163 was related to portal pressure, but not affected by TIPS insertion. The authors interpret their findings as evidence for a constitutive role of Kupffer cell activation in patients with cirrhosis and portal hypertension (***see page 1389***).

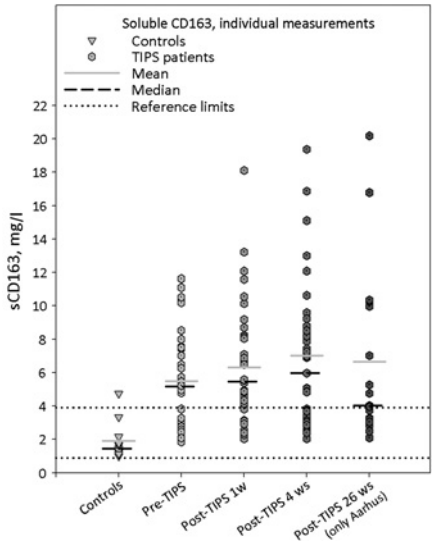

Figure 3 sCD163, a marker of macrophage activation is increased in patients with cirrhosis, but not affected by reduction of portal hypertension following TIPS.

The hepatic apelin system: a new player in human fibrosis

Inflammation, fibrogenesis and angiogenesis are closely related in chronic liver disease. Recently, a role for the pro-angiogenic protein apelin has been suggested in animal models of cirrhosis. This elegant study from Barcelona provides evidence for the importance of the apelin system in *human* cirrhosis. The apelin receptor was highly expressed in hepatic stellate cells and to a lesser degree in hepatocytes of patients with cirrhosis (figure 4). Further experiments involving cell lines show activation of the apelin system by hypoxia and by inflammatory mediators resulting in angiogenic and pro-fibrotic responses. Thus, targeting of the apelin system seems a logical next step with the aim to inhibit progression of chronic liver disease (***see page 1404***).

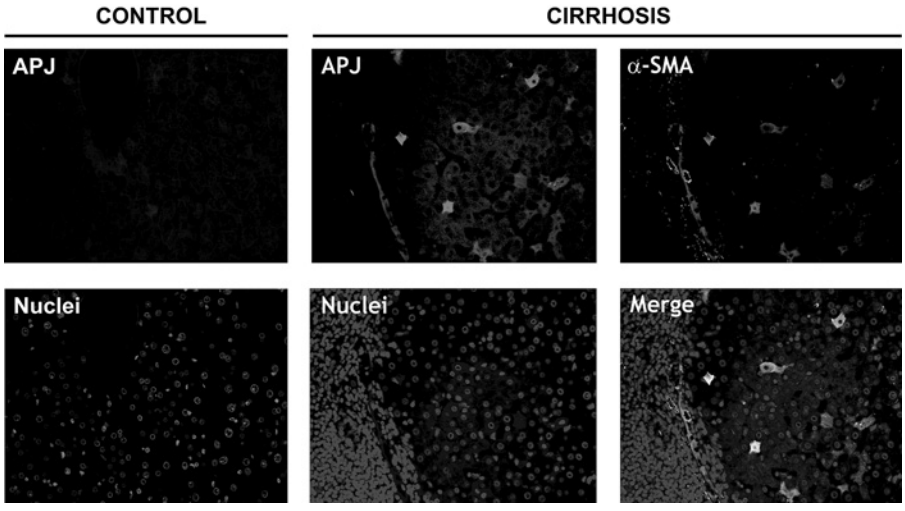

Figure 4 Overexpression of the Apelin receptor (APJ) in human cirrhotic liver.