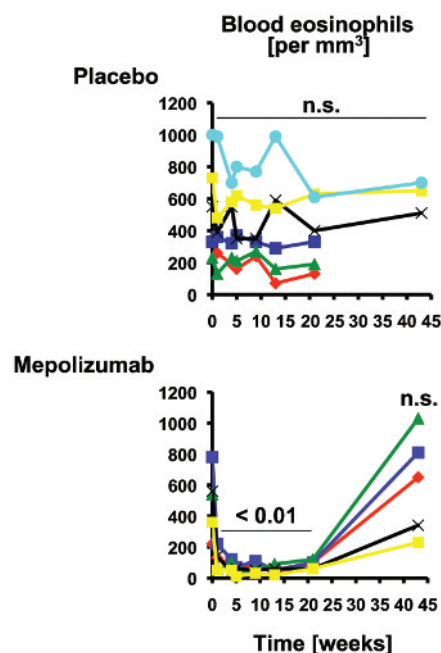


New treatment for eosinophilic oesophagitis? The first steps

Eosinophilic oesophagitis is an emerging disorder characterised by eosinophilic infiltration in the oesophageal mucosa often associated with dysphagia. Although treatment with corticosteroids often helps, some patients are resistant or suffer significant side effects. Such patients (n = 11) were the subject of this trial of mepolizumab, a monoclonal interleukin-5 (IL-5) antibody, which was given by intravenous infusion at 0 and 7 days, repeated after 8 weeks if needed. Patients were assessed by endoscopic biopsy and symptom questionnaire and all other treatments were discontinued. As expected since IL-5 is a major driver of eosinophilia, there was a marked fall in peripheral eosinophil counts (see fig) and a smaller though significant fall in oesophageal mucosal eosinophil count. Disappointingly there was no significant difference in improvement in dysphagia. However, markers of tissue remodelling, tenascin and TGF β 1 were reduced, suggesting that if given for a longer period the associated fibrosis might be reduced.

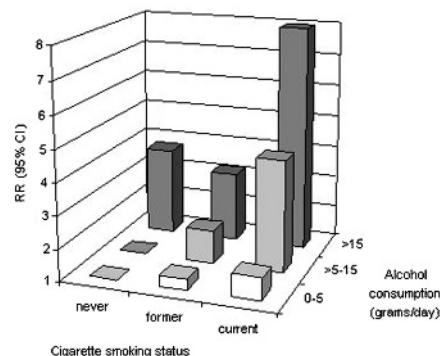


Mepolizumab caused a striking fall in blood eosinophils and a smaller but significant fall in oesophageal mucosa eosinophils (not shown) compared with placebo.

The authors speculate that a more prolonged or perhaps combination treatment with corticosteroids would improve symptoms and since the treatment was well tolerated this is certainly possible. *See page 21.*

Alcohol and smoking synergistically increase the risk of oesophageal squamous cell carcinoma

While the incidences of oesophageal squamous cell carcinoma (OSCC) and gastric noncardia carcinoma (GNCA) are declining or stable in Europe and the USA, the incidence of oesophageal adenocarcinoma (OAC) and gastric cardia adenocarcinoma (GCA) are increasing. The current study used the prospective Netherlands Cohort Study on diet and cancer, which includes 120 852 individuals followed up for on average 16.3 years. After adjusting for a range of dietary and social factors consuming ≥ 30 g alcohol daily increased the risk of OSCC with an adjusted relative risk of 4.6 (95%CI 2.2–9.5). However, alcohol did not alter the risk of the other cancers. The effect of alcohol was greater for women than men. After adjusting for total alcohol intake, beer was associated with increased risk while wine appeared protective. As expected, smoking increased the incidence of all cancers, particularly OSCC and GNCA. Combining smoking and alcohol increased the risk multiplicatively for OSCC (see fig) but not the other

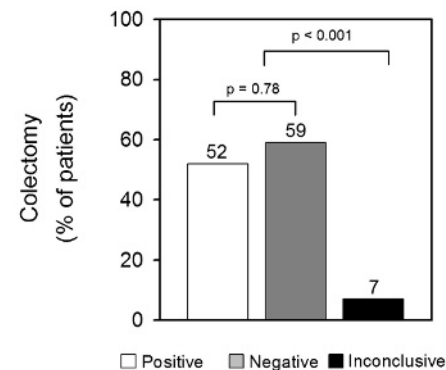


Increasing risk of oesophageal squamous cell carcinoma (OSCC) with increasing levels of smoking and alcohol. This multiplicative effect was not seen with the other three cancer types.

three cancer types. The increasing risk may be explained by synergism between the carcinogenic compounds in both cigarettes and alcohol. *See page 39.*

Trough serum infliximab levels predict clinical outcome to infliximab in steroid-refractory ulcerative colitis

The anti-TNF monoclonal antibody infliximab (IFX) is used for treatment of Crohn's disease and ulcerative colitis. Loss of response may occur, due to low serum concentrations of IFX and/or antibodies (ATI). The relation between trough serum IFX and clinical outcomes was evaluated in a cohort of 115 patients with acute steroid-refractory ulcerative colitis. Patients all received induction IFX at weeks 0–2 and 6 followed by q8 week maintenance. Remission rates at weeks 10 and 54 were 32% and 37%, respectively. Colectomy occurred in 40% of patients. Detectable trough IFX was present in 39% of patients and, among patients with undetectable IFX, 41% were ATI positive and 20% were ATI negative. The ATIs did not have a significant impact on outcome but detectable serum IFX was associated with higher rates of remission (69% vs 15%; $p < 0.001$) and endoscopic improvement (76% vs 28%, $p < 0.001$). An undetectable serum IFX predicted increased risk for colectomy (55% vs 7%, OR 9.3; 95% CI 2.9–29.9; $p < 0.001$). The authors conclude that an undetectable trough level, irrespective of antibody status, is



Colectomy risk according to the presence or absence of detectable trough serum IFX concentration.

associated with less favourable outcomes. Therefore, measuring trough levels of IFX is useful and may optimise treatment. **See page 49.**

Gut microbes define liver cancer risk in mice exposed to chemical and viral transgenic hepatocarcinogens

Hepatocellular carcinoma (HCC), the third leading cause of cancer mortality worldwide, frequently arises in a setting of chemical and infectious carcinogen exposures. The highest incidence of HCC is observed in regions endemic for the food-borne contaminant aflatoxin B1 (AFB1) and hepatitis B virus (HBV) infection. The authors investigated whether intestinal bacteria promote liver cancer in mice. They incubated *Helicobacter*-free C3H/HeN mice with AFB1 and/or *Helicobacter hepaticus* and looked at incidence, multiplicity and surface area of liver tumours. They also analysed molecular pathways involved in tumourigenesis. Their results show that intestinal colonization by *H hepaticus* was sufficient to promote aflatoxin- and HCV transgene-induced HCC. *H hepaticus* activated Nuclear factor- κ B-regulated networks associated with innate and Th1-type adaptive immunity both in the lower bowel and liver. Biomarkers indicative of tumour progression included hepatocyte turnover, Wnt/ β -catenin activation, and oxidative injury with decreased phagocytic clearance of damaged cells. They conclude that enteric microbiota define HCC risk in mice exposed to carcinogenic chemicals or hepatitis virus transgenes. These results have implications for human liver cancer risk assessment and prevention. **See page 88.**

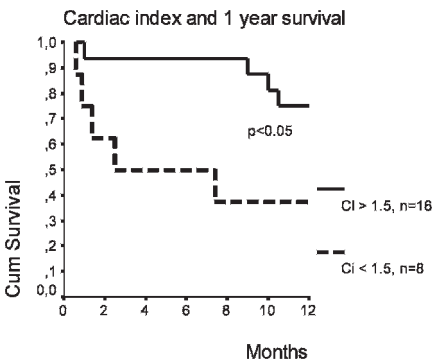
Low cardiac output predicts development of hepatorenal syndrome and survival in patients with cirrhosis and ascites

Cardiac dysfunction may precede development of hepatorenal syndrome. In this study, the authors investigated the relation between cardiac and renal function in 24 patients with cirrhosis and ascites, followed for 12 months, and studied the impact of cardiac systolic function on survival. Cardiac function was investigated by gated myocardial perfusion imaging for assessment of cardiac index (CI) and cardiac volumes. The renal function was assessed by determination of glomerular filtration rate (GFR) and renal blood flow (RBF). They found that in patients with a CI below 1.5 L/min/m², GFR was lower (39 \pm 24 vs 63 \pm 23 mL/min, p = 0.03), RBF was lower (352 \pm 232 vs 561 \pm 229 mL/min, p = 0.06), and serum creatinine was higher (130 \pm 46 vs 78 \pm 29 μ mol/L, p < 0.01). The number of patients who developed hepatorenal syndrome type 1 within 3 months was higher in the group with low CI than in the high

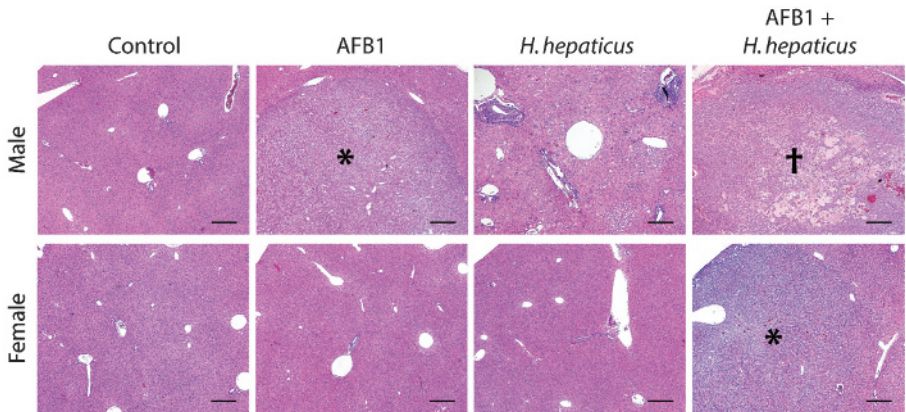
CI group (43% vs 5%, p = 0.04). Patients with the lowest CI (n = 8) had significantly poorer survival at 3, 9 and 12 months compared with those with a higher CI (n = 16, p < 0.05). In contrast, the MELD score failed to predict mortality in these patients. They conclude that the development of renal failure and poor outcome in patients with advanced cirrhosis and ascites seems related to a cardiac systolic dysfunction. **See page 105.**

Flexible sigmoidoscopy for colorectal cancer (CRC) screening: poor uptake but superior yield

The efficacy of CRC screening programmes are much dependent on a high participant uptake, which explains why faecal occult blood screening has such appeal despite its low sensitivity and specificity. Flexible sigmoidoscopy has much higher sensitivity but it is unclear whether this is really an advantage since its uptake is likely to be poor. This important study tested this randomizing 15 011 individuals from SW Netherlands to one of three screening methods: 1) faecal occult blood testing using guaiac-based test (gFOBT) 2) immunochemical FOBT (FIT), and 3) flexible sigmoidoscopy (FS). Uptake was significantly lower for FS at 32.4% versus 49.5% for gFOBT and 61.5% for FIT. However despite this the diagnostic yield of advanced neoplasia per 100 invited subjects was significantly higher with FS at 2.4 (95%CI 2.0–2.8) compared with FIT at 1.5 (1.2–1.9) or gFOBT with just 0.6 (0.4–0.8). Improving uptake needs to address why females were less likely to take part in FS screening while younger males were less likely to take part in FOB screening. **See page 62.**



Survival curve with respect to cardiac index.



Liver histopathology of mice in 4 treatment groups: *adenoma, †HCC.

Odds ratio compared to guaiac based faecal occult blood test (gFOBT) for probability of detecting colorectal neoplasia using immunochemical FOB (FIT) or flexible sigmoidoscopy (FS)

	Advanced neoplasia OR, (CI)	Colorectal cancer OR, (CI)
gFOBT	1	1
FIT	2.0 (1.3 to 3.2)	1.8 (0.7 to 4.7)
FS	7.0 (4.6 to 10.7)	2.2 (0.8 to 6.3)

Advanced neoplasia: adenoma \geq 10 mm, villous component (\geq 25% villous) or high-grade dysplasia; colorectal cancer. CI, confidence interval; FIT, immunochemical faecal occult blood test; FS, flexible sigmoidoscopy; gFOBT, guaiac-based faecal occult blood test.