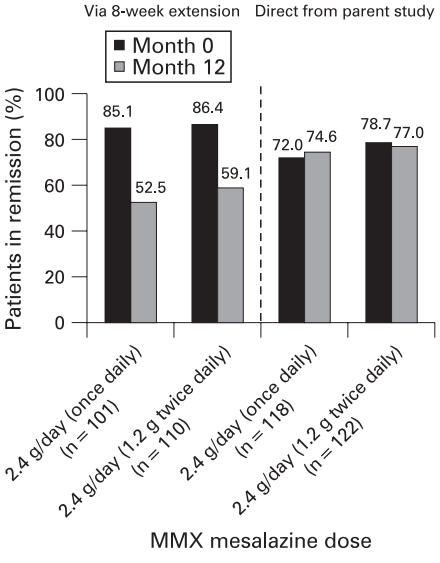
Robin Spiller, Magnus Simren, *editor, deputy editor*

Once daily slow release mesalazine is equivalent to twice daily for the maintenance of remission in ulcerative colitis

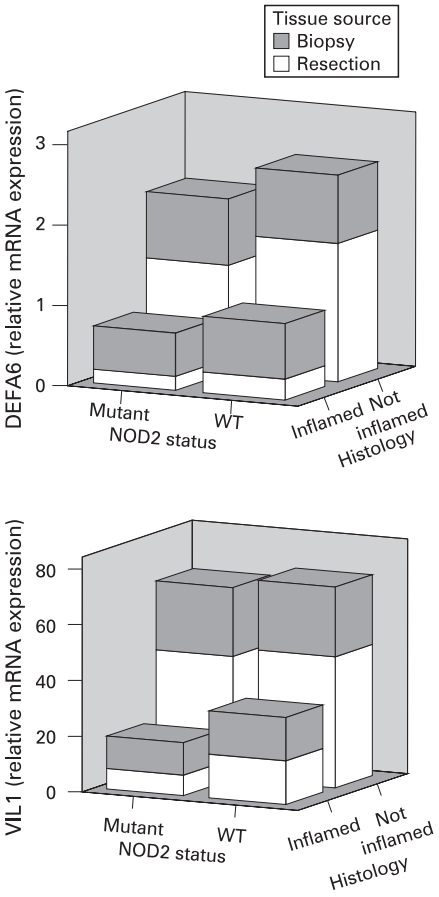
Once daily dosing undoubtedly improves compliance, so this study, comparing once daily with twice daily dosing of mesalazine, is encouraging. Patients with mild to moderate acute ulcerative colitis achieving remission in a previous 8-week study of either 2.4 g once daily, 1.2 g twice daily or 4.8 g once daily were entered into the present open-labelled 12-month maintenance trial comparing 1.2 g twice daily with 2.4 g daily. Those failing to respond to the initial 8-week's treatment were offered a further 8 weeks of 2.4 g twice daily and, if they then achieved remission, were also entered into the maintenance trial. Of 459 patients randomised, 213 required the additional 8 weeks at 4.8 g daily to achieve remission. Adverse events were equally distributed between the two groups. Only one serious adverse event was considered to be related to the study treatment. Remission rates at 12 months were similar for the two doses (see fig), although lower in those who had required a further 8 week's treatment at high dose to achieve remission. This encouraging result suggests that once daily treatment will soon become standard. ***See p 893***



Remission rates at month 0 and 12 divided according to entry route (either direct from parent study or after an extra 8 weeks at 4.8 g daily) to the study comparing 2.4 g given once daily with 1.2 g twice daily.

Reduced defensin expression in ileal Crohn's disease is secondary to inflammation and independent of NOD2 status

The recent discovery of the link between Crohn's disease (CD) and a mutation in the NOD2 gene was followed by a report of reduced defensin production in patients with ileal CD with this mutation, an idea further explored in a study by Simms and colleagues. Biopsies from both inflamed and non-inflamed ileal mucosa were obtained from 65 patients with CD and 11 healthy controls. mRNA was assessed for the inflammatory cytokines interleukin (IL) 6 and IL8 together with Paneth cell products including defensin 5 and 6, as well as villin 1, an epithelial cell marker. Inflamed tissue had significantly less defensin mRNA but also a proportionate reduction in villin 1. Furthermore, this reduction in defensins and villin was seen equally in those with wild type and mutant NOD2 genes (see fig). IL6 and IL8 were shown to be markedly reduced in the NOD2 mutants, confirming the associated impairment of the innate immune system. Although this refuted the idea that lack of defensins is a primary defect in CD the authors did show that once inflammation had damaged the epithelium the loss of defensins will render the crypts vulnerable to further bacterial invasion and tissue damage. ***See p 903***

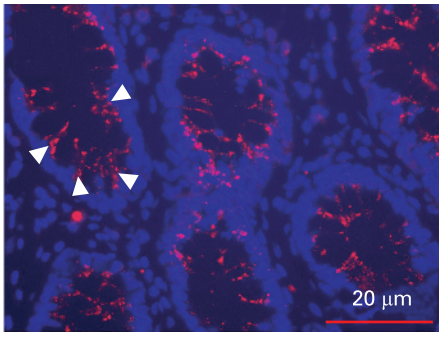


Three-dimensional plots showing the effect of inflammation (defined according to histology) and NOD2 mutation status on mRNA levels for defensin A6 (DEFA6) and villin 1 (VIL-1).

Loss of sympathetic nerves in patients with Crohn's disease

Substance P (SP) has pro-inflammatory actions, whereas sympathetic neurotransmitters are anti-inflammatory. In this study, Straub and co-authors investigated the nerve fibre densities of SP and sympathetic nerve fibres in colonic specimens from patients with CD, controls and patients with diverticulitis. Moreover, as a potential causative factor behind loss of sympathetic nerve fibres, the levels of the nerve repellent factor semaphorin 3C (SEMA3C) were evaluated. The role of sympathetic nervous function was also tested in dextran sodium sulphate (DSS) and *IL10*$^{-/-}$ colitis in mice. Patients with CD demonstrated loss of sympathetic nerve fibres and sprouting of SP^{+} nerve fibres into the inflamed areas of the gut. The levels of SEMA3C were markedly increased in the crypts of the mucosa of patients with CD (see fig) and the number of SEMA3C-positive crypts was negatively related to the density of mucosal sympathetic nerve fibres. Interestingly enough, they also demonstrated a pro-inflammatory effect of sympathectomy in the chronic colitis models in mice (DSS colitis and *IL10*$^{-/-}$ colitis). This study implicates an important role of the sympathetic nervous system in CD and

may potentially also open new treatment avenues in patients with inflammatory bowel disease. ***See p 911***



Large vesicles within epithelial cells positive for semaphorin 3C (red staining, arrow heads) in a patient with Crohn's disease.

Chromosomal instability in colorectal cancer— an important prognostic marker

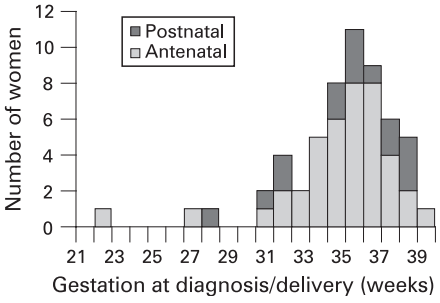
Two major types of genomic instability are recognised as alternative mechanisms of colorectal carcinogenesis, chromosomal instability (CIN), inferred from finding aneuploidy and/or polyploidy and microsatellite instability (MIS). MIS seems to be a favourable prognostic marker but the importance of CIN for the prognosis in patients with colorectal cancer is less well established. In this meta-analysis Walther and co-authors assessed the prognostic significance of CIN for survival. Sixty-three studies reporting the outcome of 10 126 patients were included in the analysis and the hazard ratio for death was the main outcome measure. CIN was found to increase the risk of death (HR 1.45; 95% CI 1.35 to 1.55; p<0.001) and this was also true when assessing stage II-III colorectal cancers only. The effect was also similar for progression-free survival (see table). Importantly, there was no evidence of significant inter-study heterogeneity. Based on these data, the authors suggest that CIN should be included as a prognostic marker together with MIS status in future colorectal cancer trials. ***See p 941***

Summary hazard ratios (HR) for death in colorectal cancer based on the presence of chromosomal instability (CIN)

Analysis	HR (95% CI)	Significance
Overall survival	1.45 (1.35 to 1.55)	<0.001
Progression-free survival (all patients)	1.71 (1.51 to 1.94)	<0.001
Anatomical location		
Colon (all patients)	1.67 (1.32 to 2.11)	<0.001
Rectum (all patients)	1.63 (1.33 to 1.99)	<0.001
Stage		
Stage II	1.68 (1.25 to 2.25)	0.001
Stage III	1.38 (1.14 to 1.67)	0.001
Stage II – III (combined, all patients)	1.45 (1.27 to 1.65)	<0.001
Adjuvant therapy		
Treatment (CIN vs diploid)	1.85 (1.21 to 2.82)	0.004

Risk factors for acute fatty liver in pregnancy (AFLP)

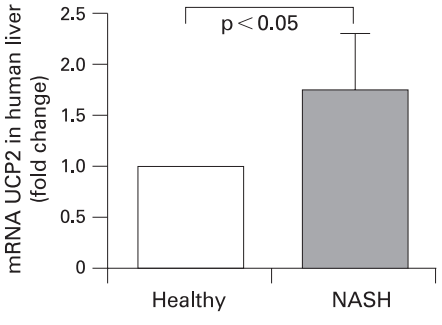
AFLP is a rare but extremely dangerous condition. A study by Knight and colleagues used the United Kingdom Obstetric Surveillance System for rare disorders of pregnancy in which all UK obstetricians are sent a monthly card asking them to report cases of AFLP. Fifty-five cases were confirmed using the Cardiff criteria in 1 329 640 pregnancies, giving an incidence of 5 cases per 100 000 maternities (95% CI 3.8 to 6.5). Sixty-one per cent of mothers were primiparus (national average 42%), 18% had twins (national average 1%) and 20% had a body mass index <20. As the figure shows, most were diagnosed in the last trimester, 74% antenatally; 15 women were diagnosed postnatally, all within 4 days of delivery. As currently recommended, 98% were delivered within 4 days of diagnosis, three-quarters by caesarean section. Sixty per cent were admitted to an intensive care unit for a median of 3 days, eight developed renal failure and four required ventilation. Perinatal mortality was 7 out of 67 and one patient who required a liver transplantation died. The authors conclude that twin pregnancies have a higher risk for developing AFLP but the mechanism remains unknown. ***See p 951***



Gestation at diagnosis (antenatal cases) or delivery (postnatal cases).

Upregulation of uncoupling protein-2 in the liver is an important factor leading to non-alcoholic steatohepatitis (NASH) and cirrhosis

NASH is prevalent in Western countries and it is considered to be an important cause of cryptogenic cirrhosis. However, the pathogenesis of NASH is not completely understood but mitochondria, the main cellular site for fatty acid oxidation, ATP synthesis and reactive oxygen species (ROS) production, are thought to play a key role in the development to steatohepatitis. In this study by Serviddio and co-authors the role of the uncoupling protein 2 (UCP2)—a mitochondrial inner membrane protein—in controlling mitochondrial proton leak and ROS production in rats and humans with NASH was evaluated, as well as the effect of acute liver damage in rats with NASH. NASH mitochondria demonstrated an increased rate of proton leak due to upregulation of UCP2 and this correlated with increased ROS production and decreased hepatic ATP content. In line with this, the livers from patients with NASH exhibited UCP2 upregulation (see fig) and mitochondrial oxidative stress. Moreover, in the acute liver damage model applied to rats with NASH, depleted ATP stores and increased ROS production were seen. The present findings suggest that UCP2-dependent mitochondria uncoupling is involved in the progression to NASH and liver cirrhosis. ***See p 957***



Expression of mRNA uncoupling protein 2 (UCP2) in human liver from patients with non-alcoholic steatohepatitis (NASH) compared with healthy controls by real-time PCR.