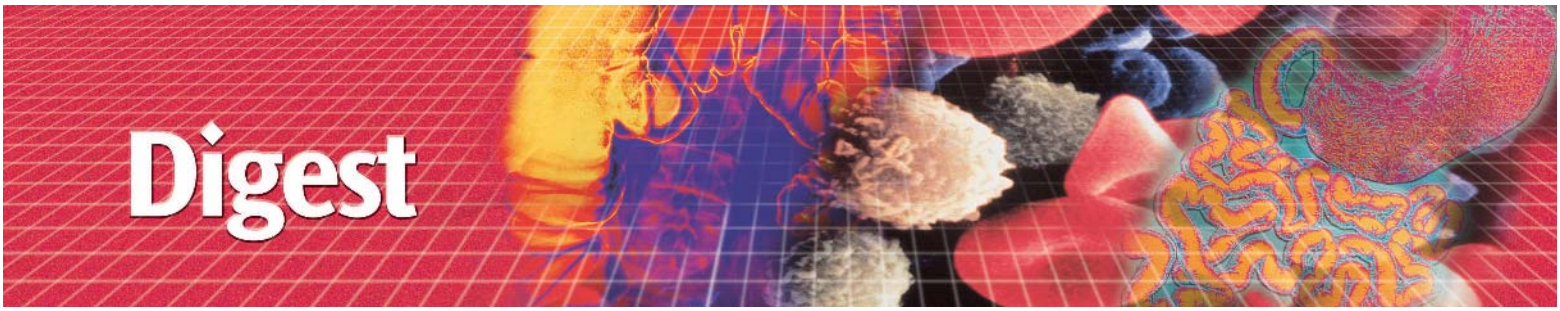

Robin Spiller, *Editor*

SIGNIFICANCE OF CYTOKINE GENE POLYMORPHISMS IN HOST RESPONSE TO *HELICOBACTER PYLORI*

Helicobacter pylori infection is associated with an acute inflammatory response which involves an up-regulation of interferon (IFNγ), tumour necrosis factor (TNF) and interleukin1-β. The counter regulatory cytokine IL-10 is also increased and the balance of these pro- and anti-inflammatory cytokines influences disease outcome. Functional polymorphisms in the IL-10, IL-1β, TNFα, IFNγ and IL-10 have all been reported. The current study aims to assess the overall impact of these polymorphisms on the response to *H pylori*, which for most patients produces few symptoms and only modest inflammation. Over 200 patients were characterised as regards their genetic polymorphisms and response to *H pylori* infection. The mucosal production of IL-1β in response to *H pylori* infection was shown to be highest in those with the combination of the IL-1β 511T and the interleukin receptor antagonist IL-RN*2+ polymorphisms. Likewise the high producing IL-10 polymorphism – 1082 GG resulted in a nearly three fold increase in IL-10 production compared with other IL-10 polymorphisms. Interestingly, prevalence of *cag A+* strains were commoner among the patients with the high IL-10 secreting haplotypes suggesting some mutual selection between host and pathogen. This has important implications for genetic influences on a wide range of inflammatory GI diseases.
See page 1082

ASCA IDENTIFIES CROHN'S PATIENTS AT HIGH RISK FOR EARLY SURGERY

The wide range of therapies for Crohn's disease with differing potencies and toxicities means that it would be extremely valuable to be able to identify at the start of the illness, patients whose disease was destined to follow an aggressive course. The current issue **[see page 1117]** contains a case-controlled cohort study of 35 patients requiring early surgery compared with 30 cases not requiring surgery but matched as regards known risk factors (sex, age, disease location and smoking). The detection of Anti-*saccharomyces cerevisiae* antibodies (ASCA) was associated with a substantially increased risk of surgery with an Odds Ratio of 8.2, 95% confidence interval (2.0 - 75.9). The relationship was strongest with ileocecal resection or intra-abdominal abscess drainage, for which the Odds Ratio was 13 (2-552), but not with colonic or peri-anal surgery. This study opens the way to a more aggressive approach to patients with ASCA positivity at the time of diagnosis.
See page 1117

IMPLICATIONS OF ELEVATED 1,25-DIHYDROXYVITAMIN D IN CROHN'S DISEASE

Although steroid use is an important contributing factor in osteoporosis this may predate any treatment. Bone calcium is mobilised by parathormone, which increases the level of renal 1α- hydroxylase, an enzyme which converts 25-hydroxyvitamin D to 1,25-OH vitamin D. This in turn stimulates osteoclastic activity. The authors examined the levels of this vitamin D metabolite in 138 Crohn's disease (CD) patients and 29 patients with ulcerative colitis **[see page 1129]**. Bone mineral density was significantly decreased in patients with CD compared with ulcerative colitis (UC). Furthermore, an inappropriately increased level of 1,25-dihydroxyvitamin D was found in 42% of the CD patients, but just 7% of those with UC. Immunohistochemical staining was used to demonstrate increased expression of 1α-hydroxylase in epithelial cells, macrophages and multi-nucleated giant cells, findings which were supported by increased mucosal 1α-hydroxylase mRNA. The author suggests measuring serum 1,25 dihydroxyvitamin D may be useful for indicating those at increased risk from osteoporosis and in need of preventative treatment.
See page 1129

DECREASED PROSTAGLANDIN RECEPTOR 3 IN COLON CANCER

Numerous studies have suggested that colon carcinogenesis can be inhibited by inhibition of prostaglandin production via cyclo-oxygenase enzyme systems. However, the full effect of inhibiting mucosal prostaglandins on cell kinetics in the colonic mucosa is as yet unknown. Prostaglandins act via a range of receptors which signal, both via increased intracellular calcium (EP1), increased cyclic AMP (EP2 & 4) and decreased cyclic AMP (EP3). The current study **[see page 1151]** shows that animals lacking the EP3 receptor are more prone to develop colon cancer and furthermore that EP3 agonists inhibit colon cancer cell lines. Finally, they show that both rodent and human colorectal cancers show decreased expression of EP3. Taken together, these studies suggest that decreased EP3 in human cancer might be important in the causation of disease, rather than a mere epi-phenomenon. Excitingly, they demonstrate that demethylation of DNA by 5aza-dC in certain cell lines can restore EP3 receptor expression. The implication is that more selective manipulation of the prostaglandin system using specific agonists rather than simple COX inhibitors may increase the benefits obtained by this approach.
See page 1151

ADENOVIRAL TREATMENT VIA THE BILE DUCT?

Current adenoviral vectors for gene therapy have limited efficacy owing to destruction of adenoviral vector transduced cells by circulating antibodies. The present study examined whether administration direct into the bilary tract would overcome this problem. The authors show **[see page 1167]** a striking expression of a reported gene *lac Z* was achieved using an adenoviral vector infused into the rat bile duct. As expected, expression of the reporter gene declined in the 2 weeks following the first administration and neutralising antibodies developed. However, re-infusion was able to re-establish expression of the gene, an effect which was not altered by immunosuppression. A similar result was seen with a third administration. The authors suggest that reported adenoviral vector administration at ERCP would be feasible and effective in gene therapy for the range of diseases. They suggest that vector given by this route can avoid the systemic immune response and hence retain its efficacy.
See page 1167