

BILE AND ACID IN THE GULLET

While we all experience gastro-oesophageal reflux, exposure of the oesophagus to gastric contents is normally rapidly terminated by peristalsis, a process known as volume clearance. Gastric acid is also neutralised by bicarbonate, both locally secreted and from swallowed saliva, so called “chemical clearance”. However it is well recognised that bile is a very important component of refluxate, and that in patient studies, episodes of reflux containing bile appear to clear less rapidly than those containing only acid. The study from Leuven compared volume and chemical clearance rates using a combination of scintigraphy, pH and bile detecting probes. They found that peristaltic clearance of citric acid solutions or duodenal contents instilled into the lower oesophagus in normal subjects was no different. Somewhat unexpectedly bilirubin in the duodenal contents, as detected by the Bilitec^R monitor, was cleared faster than acid. The authors speculate that this may be because lipophilic bile contents penetrate oesophageal mucus less well than protons and hence are cleared more easily. They conclude therefore that the reason why episodes of bile reflux are longer in patients is not because the material is intrinsically more difficult to clear, but more likely because bile reflux episodes are associated with greater volumes of refluxate.

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INFLAMMATORY MEDIATORS IN CHOLERA?

Medical students have been taught for many years that cholera is an example of a toxin-induced secretory diarrhoea without an inflammatory component. The current substantial study from the International Centre for Diarrhoeal Diseases Research in Dhaka, Bangladesh shows that this is an oversimplification and that cholera has both secretory and inflammatory components. Marked neutrophil infiltration was found 2 days after admission in rectal as well as duodenal biopsies, which also showed strikingly

increased immuno-staining for many components of the innate immune response. These included myeloperoxidase, lactoferrin, defensins as well as cytokines such as tumour necrosis factor (TNF). Mast cells and their products appeared particularly prominent at day 7 and 30, when eosinophils were also much increased. Eotaxin, which is a chemoattractant for eosinophils, was increased early in the disease, possibly driving the subsequent eosinophilic infiltration. The authors comment that a vaccine should aim to enhance as many as possible of these protective responses.

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LEARNING ABOUT CROHN'S DISEASE FROM THE RESULTS OF INFlixIMAB TREATMENT

The classic paradigm of advances in science driving advances in therapy has been somewhat turned on its head by the exciting developments in the treatment of Crohn's disease with infliximab. The success of treatment with this chimeric anti-TNF antibody has led to major advance in our understanding of the pivotal role of TNF in disease pathogenesis. A major effect of infliximab appears to be to correct the defective apoptosis in T lymphocytes, which otherwise leads to continued mucosal inflammation. Di Sabatino et al take our understanding further in this issue of Gut by showing that, after 3 infusions of infliximab at 0.2 and 5 weeks, apoptosis in the lamina propria T lymphocytes was markedly increased to reach the normal range. Further in vitro studies using lamina propria T lymphocytes isolated from biopsies showed that infliximab acts via a caspase-dependent pathway. Plainly as we dissect out the mechanisms of action of infliximab we will learn a lot more about, not only Crohn's disease, but also other diseases characterised by defective T lymphocyte apoptosis.

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SURPRISES IN THE CAUSES OF COLORECTAL CANCER

Familial adenomatous polyposis (FAP) and inflammatory bowel disease (IBD) are long established causes of colorectal cancer. More recently Hereditary Nonpolyposis Colorectal Cancer (HNPCC) has been characterised. Remarkable advances have been made in our understanding of the molecular pathogenesis of these syndromes but much less are known about the proportion of cancers that are caused by these conditions. On page 115, de Leon and colleagues report a population-based study of the causes of colorectal cancer in 2462 Italian patients and come up with some surprising results. FAP and IBD were extremely rare causes of colorectal cancer, being found in only 0.1% of patients. The commonest genetic cause was HNPCC with patients fulfilling the Amsterdam diagnostic criteria accounting for 2.4% of cases. However half the patients fulfilling these clinical criteria had no detectable microsatellite instability or germline mutations. Ninety six percent of patients have no known cause. Although diet and lifestyle are of importance in the aetiology the precise causative agents remain unknown. Thus there is much to learn about the causes of colorectal cancer."

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LACK OF BENEFIT FROM ADDING AMANTIDINE TO INTERFERON AND RIBAVIRIN

Treating hepatitis C infection and its sequelae of cirrhosis and hepatocellular carcinoma is now a major contributor to hepatological health care costs. The prospect of improved success in achieving a sustained virological response by adding an inexpensive well known agent such as amantidine to interferon and ribavirin treatment regimens has obvious appeal. As so many times in the past, the initial smaller studies were highly optimistic but the current issue of Gut dashes these hopes with a study, quadruple the size of earlier studies, which convincingly shows that adding amantidine to interferon and ribavirin has no additional benefit.

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