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Investigation of il-8 release by mucosally-adherent E. Coli and Bacteroides species relevant to pathogenesis of inflammatory bowel disease

There is increasing consensus that the inflammatory bowel diseases ulcerative colitis and Crohn's disease both represent an altered response to the normal colonic flora. Although some research has implicated specific pathogens such as atypical *Mycobacteria*, these organisms are generally very hard to find, moreover the therapeutic response to agents such as the new biological infliximab, which is known to cause reactivation of tuberculosis, makes this seem even more unlikely. All the recently described genetic models of inflammatory bowel disease (mainly mice that have had a gene related to inflammation 'knocked out' at the embryo stage) have been shown to be dependent on the presence of the normal non-pathogenic bacterial flora. Litter-mates that are bred in germ-free conditions do not develop the colitis.

There is increasing interest in the likely importance of the bacteria that may lie under the layer of mucus that coats the intestine. Previous studies by a group in France have shown the increased presence of mucosa-associated *E. coli* in the small bowel of patients with Crohn's disease. These bacteria are 'harmless' in terms of their routine laboratory testing but probably have the potential to cause inflammation if they are closely adjacent to the cells (epithelial cells) lining the bowel. In recent studies funded by NACC, we have shown that similar *E. coli* can also be found close to the mucosal lining of the colon in Crohn's disease and that these bacteria are able to stimulate the release of the pro-inflammatory molecule interleukin 8 (IL-8), from colonic cells grown in the laboratory. This work has also shown that the association of these bacteria with cell surface structures to which they bind can be blocked by a soluble plant fibre from plantain (a member of the banana family). This line of research looks to have real promise in allowing scientifically targeted development of 'prebiotics' i.e. therapies that do not by themselves have a direct effect but which aim to correct the normal colonic flora.

The current proposal aims to expand these studies; firstly by clarifying the mechanism by which the *E. coli*-epithelial cell interaction results in inflammation; secondly by exploring the possibility that other bacteria, particularly a class of bacteria called *Bacteroides*, might also be involved, particularly perhaps in pouchitis (inflammation of the surgically formed neo-rectum or pouch in patients who have undergone colectomy) where there is a therapeutic response to the antibiotic metronidazole which attacks this type of bacterium; and thirdly by conducting further studies to define prebiotic agents, such as soluble dietary fibres and other complex sugars (oligosaccharides) that might be useful as therapeutic agents in inflammatory bowel disease.