

Title of Project

How much does psychological stress exacerbate ulcerative colitis? Roles of mucosa-associated bacteria, mast cells and catecholamines.

Lay Summary

Psychological stress has been cited for many years by patients and doctors as worsening disease activity in inflammatory bowel disease (IBD). Although prospective studies of the relationship between psychological stress and disease activity in IBD are difficult to do well, recent reports have suggested that unpleasant life events, chronic stress and acute daily stress can increase the frequency of subsequent relapse in patients with IBD. The mechanism by which this occurs is unknown. A favoured theory is that nerve connections between the brain and gut stimulate inflammatory cells in the gut wall, particularly the so-called mast cell, to release chemicals which worsen inflammation; this may, in turn, lead to increased entry of potentially harmful bacteria into the wall of the gut from its interior. Stress may theoretically also worsen IBD by delaying healing of the damaged gut lining.

Our own recent work has shown that a 50 minute session of acute mental stress (doing an IQ test while music of different types is played into each ear) causes inflammatory changes in the wall of the large intestine in patients with inactive ulcerative colitis (UC). These changes included increases in the production of inflammatory chemicals such as tumour necrosis factor (TNF α), and, according to our preliminary results, activation of mast cells in the gut wall, and increased entry of bacteria into the gut wall.

The aims of this project are to explore further the mechanisms by which stress leads to inflammation. We shall undertake further studies of the sort described above in patients with UC (*in vivo* studies), as well as experiments in the test tube to clarify how stress hormones affect the working of various types of cell found in the lining of the colon, and how they affect healing of damaged layers of cells grown from the inner lining of the colon (*in vitro* work).

In vivo studies: Using the protocol above, we aim to confirm that stress leads to an increased entry of bacteria into the gut wall, activation of mast cells, and release of inflammatory chemicals in patients with inactive UC. We will also measure the effect of mental stress on the leakiness of the gut wall. Thereafter we shall study the effects on these factors of pre-treatment with drugs which block pathways which we believe may mediate the harmful effects of stress: these include ketotifen (which reduces the activation of mast cells), and propranolol (which blocks the actions of the stress hormone adrenaline). We shall also study the effect of taking by mouth a probiotic (so-called 'friendly bacteria' – *lactobacillus GG*) which may reduce the entry of harmful bacteria into the gut wall.

In vitro experiments: We plan to perform experiments to study the effects of stress hormones which are released as part of the stress response on the function of various cell types in the large intestine. In particular, we wish to see whether such hormones cause

release by these cells of inflammatory chemicals such as interleukin-8 (IL8), and expression on their surface of special receptors such as toll-like receptor-4 (TLR4) which might increase entry into the gut wall of potentially harmful bacteria. In addition, we shall see whether these hormones slow down the healing of scratches made in layers of cells grown from the inner lining of the colon.

It is hoped that these studies will shed light on how mental stress contributes to relapse in inflammatory bowel disease, and in particular ulcerative colitis. They may also lead to new therapies to maintain remission by preventing stress-induced inflammation in the gut wall.