Stress, inflammation and the irritable bowel syndrome

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The irritable bowel syndrome (IBS) is a clinical descriptor for a number of chronic abdominal symptom complexes, but the term does not provide insight into the underlying pathophysiological and pathogenetic mechanisms. IBS is heterogeneous not only in terms of its clinical presentation but also in terms of its pathophysiology and pathogenesis. Indeed, there is little congruency between the clinical presentation, and the underlying pathophysiology and pathogenesis. A possible exception is a subgroup of IBS patients who develop chronic symptoms after an enteric infection. This occurs in about 30% of patients with salmonella gastroenteritis (1), and this subgroup comprises...
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one-third of the IBS patient population (2). Recent studies have provided insights into factors that predispose patients to the development of postinfectious IBS (PI-IBS). PI-IBS is more common in females than males, and is associated with a higher incidence of stressful life events in the six months preceding the infection (3). Patients with PI-IBS have been shown to have abnormal sensory-motor function in the anorectum (4). These observations prompt consideration of a model in which stress and possibly other psychological factors converge with infection to produce a state of intestinal dysfunction that persists long after recovery from the infection.

Another pertinent observation is the increased prevalence of gastrointestinal symptoms in patients in remission from inflammatory bowel disease (IBD), as demonstrated previously by Isgar et al (5). That study showed that patients with endoscopically proven ulcerative colitis in remission had a higher than expected prevalence of IBS-like symptoms. Moreover, these symptoms, which included constipation, could not be easily explained on the basis of ongoing inflammatory activity. Again, this finding suggests that inflammation per se leads to persistent dysfunction of the motility apparatus of the gut. This is supported by the demonstration of altered anorectal function in patients with histologically proven ulcerative colitis in remission (6).

These results are important in that the inflammatory process in ulcerative colitis is restricted to the mucosa and lamina propria, and does not usually penetrate the deeper neuromuscular tissues that are implicated in the abnormal anorectal function.

What, therefore, is the mechanism whereby mucosal inflammation causes dysfunction in the neuromuscular tissues? Are these changes restricted to the site of infection and inflammation? Can they persist after recovery from the infection? What is the role of stress? To address these questions, one needs to turn to basic research.

**Does Mucosal Inflammation Alter Function in the Deeper Neuromuscular Tissues?**

Castro et al (7) and Schanbacher et al (8) first showed that enteric infection is accompanied by changes in gut motility. Farmer et al (9) demonstrated that enteric infection was accompanied by changes in the contractility of intestinal muscle. Studies have subsequently been extended to show that enteric infection is accompanied not only by changes in smooth muscle contraction (10) but also by changes in muscle growth (11), and in neurotransmitter release and content in the myenteric plexus (12-14). These changes are a consequence of the inflammatory response rather than a direct effect of the infective organism and involve T lymphocytes (15) and cytokines including interleukin-1-beta (16,17). Subsequent work has been extended to the colon and has shown clearly that changes in smooth muscle and enteric nerves occur even with very mild and superficial inflammation (18). Taken together, these observations demonstrate that nonpenetrating mucosal inflammation causes changes in enteric nerve and muscle function, and alters motility. Mild inflammation is, therefore, a candidate process to account for gut dysfunction in a subset of IBS patients.

**Are These Changes Restricted to the Site of Inflammation?**

It is observed clinically that an infection of the proximal intestine (salmonella gastroenteritis) produces changes in neuromotor function in the anorectum (4). Studies in animal models have demonstrated that inflammation at one site produces changes in smooth muscle contraction and in neurotransmitter release at noninfamed sites (19,20).

**Can Changes in Neuromuscular Function Persist After Recovery From the Infection?**

Studies in animal models support the concept that acute transient inflammation of the gut may result in motor disturbances that persist after resolution of the mucosal inflammation. In a cat model of colitis induced by local installation of acetic acid, motor abnormalities occurred not only during the acute inflammation, but also after the inflammation had resolved (21). Studies in nematode-infected mice have shown that acute inflammation induces changes in enteric nerve and smooth muscle function that persist long after the inflammatory response has resolved (22,23).

**What Is the Role of Stress?**

Previous studies have shown not only that stress alters motility in vivo, but also that repeated stress causes sustained changes in smooth muscle contractility in vitro (24). Stress also influences the inflammatory response. Gue et al (25) showed that prior stress enhanced the inflammatory response of rats to subsequent exposure to trinitrobenzene sulphonic acid. This suggests that stress may play a role in priming the gut for inflammatory stimuli, which may have clinical bearing in the context of postinfectious IBS (3,4).

Studies in animal models have also shown that stress may reactivate previous colitis (26). In one study, animals were allowed to recover for six weeks after acute colitis was induced with trinitrobenzene sulphonic acid, with no chemical or histological evidence of residual inflammation. Animals that were then exposed to three days of mild restraint stress developed a reactivation of the inflammatory process, with an attendant deterioration of colonic physiology. Thus, stress may precipitate functional disturbances in a previously inflamed gut, such as in quiescent IBD (5).

**Links to Human Data**

At least two clinical scenarios in IBS are relevant to the present article. One is the relationship between IBS and IBD. Isgar et al (5) showed that IBS-like symptoms occur with a higher than expected prevalence in patients with ulcerative colitis. Patients in the study were in remission from their IBD, as reflected by normal biopsies from the rectosigmoid. Rao et al (6) studied sensory-motor changes in patients with
ulcerative colitis and found abnormalities in motility as well as an increase in sensory perception following rectal distension. These changes were evident not only in patients with active disease, but also in those with quiescent colitis. While it is theoretically possible that these changes are independent of the colitis, when these observations are taken in conjunction with results emerging from the animal studies cited above, it is more likely that the physiology of the colon is altered by the active colitis and that these changes persist after resolution of the mucosal inflammation, thereby providing a basis for IBS-like symptom generation.

This notion may be taken one step further in the context of PI-IBS. This term was first coined by Chaudhary and Truelove (2) in their 1962 review of a large IBS population in Oxford, United Kingdom. They found that as many as one-third of their patients developed IBS following what appeared to have been an episode of food poisoning or some other acute episode. McKendrick and Read (27) followed an outbreak of salmonella food poisoning in Sheffield, United Kingdom, and their prospective analysis indicated that almost one-third of individuals with food poisoning went on to develop an IBS-like syndrome in the subsequent three months. Studies of anorectal motility in these patients demonstrated perturbed sensory and motor function (1), and biopsies indicated an increased cellularity, but not overt inflammation, in the rectal mucosa (4). Interestingly these patients had no prior history of IBS but exhibited a psychological profile similar to that previously associated with IBS, with high scores for anxiety and depression (3). The authors also found that those who went on to develop IBS had a higher incidence of stressful life events in the six months before infection (3). These data may be interpreted in a number of ways, but it is clear that the Sheffield study has provided the first prospective data supporting a link between enteric infection and IBS (27). The concept that stress and behaviour may have been predisposing factors is tantalizing and is supported by scientific data from recent work on animals. Taken together, a number of clinical applied and basic scientific observations support a model of IBS which, at least a subset of patients, involves a triangular relationship among stress, inflammation and disturbed gut physiology.

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REFERENCES


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