Recent advances in inflammatory bowel disease

Recent developments in our knowledge of inflammatory bowel disease (IBD) have been dramatically exciting, but the speed and diversity of progress may seem bewildering. A forthcoming conference on IBD, in association with the *British Journal of Hospital Medicine* (see p. 351 or www.mahealthcareevents.co.uk/ for full details), provides an opportunity to reflect on the significance of new findings in the pathophysiology of these disorders and ways of improving disease management.

IBD has long been suspected to be an autoimmune disorder, but an exciting concept is that the intestinal mucosa may not itself be the direct target of this process, but an 'innocent bystander' damaged by its proximity to a reaction between the immune system and the intestinal bacterial flora. The human intestinal bacterial flora is complex, and has yet to be fully characterized. It is still possible that an unsuspected pathogen – a '*Helicobacter colitidis*' responsible for IBD – could lurk within its depths. However, to date such candidates as have been proposed have lacked credibility, and may be the effects of secondary colonization of damaged bowel, or non-specific inflammation, rather than true pathogens.

Nevertheless, the flora in IBD is abnormal in many ways. It is unstable, with overgrowth of facultative anaerobes, and an excess of organisms present in the biofilm immediately overlying the intestinal mucosa. Evidence of immune attack includes the findings that in IBD the great majority of gut bacteria are coated with immunoglobulin, compared to less than 20% in health. Furthermore, mononuclear cells from the lamina propria of the intestinal mucosa at sites of active Crohn's disease have been shown to react not only to foreign organisms but to host bacteria as well.

Such responses in individuals with a predisposition to IBD are likely to be related to genetic factors. The first gene established as increasing susceptibility to Crohn's disease, CARD15, is known to be important in the intracellular recognition of bacterial products. Will further recently discovered genes also predisposing to Crohn's disease have similar functions?

The role of immunosuppression

For years immunosuppression, whether by corticosteroids or azathioprine and its relatives, has formed the cornerstone of the medical management of IBD. The importance in IBD of activity of CD4+ lymphocytes with a type 1 helper T cell phenotype (Th1) has recently been supported by the demonstration of improvement in Crohn's disease by deliberate infection of affected patients with pig whip worms, which provoke a Th2 response and reduced Th1 activity. Suggestions, therefore, that the immune system may be underactive in IBD have provoked surprise. Is reduced immune reactivity in other organs, such as the skin, merely a consequence of overpowering activity in the gut? Can there be a case for immune stimulation?

Whatever the final position on the activity of the immune system, the use of immunosuppression in IBD is becoming increasingly sophisticated. Monoclonal antibodies to pro-inflammatory cytokines such as tumour necrosis factor-α have proved dramatically successful in both Crohn's disease and, more recently, ulcerative colitis. A series of further similar biological agents are now under trial. These, however, bring new problems in their train. All are very expensive, and may have dangerous side effects. How should they be combined with established treatment protocols? Which patients should we choose? May they influence the need for surgery?

The importance of the gut microflora in IBD presents a quite separate treatment option – manipulation of bacterial activity. Antibiotics have long been known to be beneficial in IBD, and attempts to change the flora with probiotic bacteria, or prebiotic chemicals such as fructose oligosaccharide, proceed apace. Is the benefit of elemental diet related to bacterial activity – and if so, why is it helpful in Crohn's disease, but not in ulcerative colitis? Does bacterial manipulation offer a treatment modality effective without the use of immunosuppressives at all?

Questions are many, but answers are rapidly forthcoming. The uncertainty, caution and pessimism formerly associated with IBD have been replaced by an optimistic confidence. This conference will reinvigorate not only gastroenterologists and their trainees, but also surgeons and general physicians who share an interest in the management of these complex, but now eminently treatable, conditions. BJHM

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KEY POINTS

- An autoimmune attack on the normal host intestinal microflora in genetically susceptible individuals appears the most convincing model for the pathogenesis of inflammatory bowel disease.
- Successful treatment may involve blunting of the immune attack, such as by immunosuppressive drugs, or by diverting a Th1 response into the Th2 pathway.
- The importance of the gut microflora opens up the possibility of new therapeutic options – reduction of bacterial metabolic activity by antibiotics, probiotic bacteria or diet.
- The discovery of further genes which predispose to the development of inflammatory bowel disease may allow more detailed understanding of the mechanisms of the interaction between the immune system and the bacteria of the intestine in these diseases.