Aetiology of Crohn’s disease

Crohn’s disease is an idiopathic inflammation of the gastrointestinal tract occurring anywhere from the mouth to anus, although it is predominantly ileoecal. It is characteristically patchy, transmural, contains non-caseating granulomas, and has a chronic clinical course with recurrent relapses. It is not specific for children and can develop in children as young as 6 years of age. Thereafter the incidence increases reaching a peak in late adolescence. It is difficult to determine the exact prevalence of Crohn’s disease in the UK but it may be around 50 per 100,000 of the population and 10 per 100,000 children. Thus Crohn’s disease is a significant paediatric problem. Moreover as active disease is associated with diarrhoea, malabsorption, and a general malaise, children with Crohn’s disease may be undernourished and a significant proportion are growth impaired. To determine the cause of Crohn’s disease is the most significant challenge in gastroenterology today and has been the subject of intense interest over the last 20 years.

Basically, there are three main theories for the cause of Crohn’s disease. Firstly, there are those who consider that Crohn’s disease is due to an infectious agent which they call ‘catch’ Crohn’s disease from an environmental agent; it is however worth pointing out that the epidemiology of Crohn’s disease shows no evidence of transmissibility. Secondly, there are those who consider that Crohn’s disease is due to an immunological hypersensitivity response to antigens (as yet unidentified) in the gut wall. These are most likely to be antigens and components of the normal flora. Thirdly, there are those who consider Crohn’s disease to be vasculitic of the submucosal vessels and that mucosal ulceration is a secondary event due to ischaemia. Evidence for these three points of view will be considered. There are also a number of other theories, such as food hypersensitivity or that Crohn’s is caused by baker’s yeast, but as the evidence for these is scant, they will not be considered here.

Crohn's disease, a few ulcerative colitis patients, but not from the control tissue. No quantitative bacteriology has been carried out, but presumably these mycobacteria are present in very low numbers and are environmental contaminants.

This, however, has not deterred some investigators from continuing to pursue the idea that infection with *M. paratuberculosis* is the cause of Crohn's disease, despite the fact that serologically there is no evidence for this infection, and that by immunohistochemistry, mycobacteria cannot be detected in the gut wall in Crohn's disease. Using a CDNA probe specific for *M. paratuberculosis*, no mycobacterial DNA can be detected in Crohn's bowel by Southern blotting. Using the more sensitive polymerase chain reaction (PCR) to detect *M. paratuberculosis* DNA, positive signals were reported from 65% of Crohn's patients, 4-3% of patients with ulcerative colitis, and 12-5% of controls. With this technique it is difficult to determine how many bacteria are present in the tissues, but it would be of the order of only several hundred per gram of tissue. From an immunological point of view it is difficult to see how so few organisms could elicit such a strong inflammatory response, especially if, in vivo, the *M. paratuberculosis* lacks a cell wall, as the cell wall is the major stimulus for the immune response in mycobacterial infections. These studies were carried out with full thickness resected material from patients with long standing disease and it would be of great interest to determine if the same results would be obtained from mucosal biopsy specimens of children with new disease.

Finally, it is clear that *M. paratuberculosis* is ubiquitous in the environment as it was found in a proportion of healthy individuals. Thus the presence of this organism in the gut is clearly not associated with disease.

**Crohn's disease is an immunological hypersensitivity disease**

This theory is not incompatible with a distinct infectious aetiological agent as the local immune reaction has to be driven by antigen(s), which might be that agent. There is no doubt, however, that the tissue damage and mucosal ulceration in Crohn's disease are due to immunological hypersensitivity. The earliest signs of Crohn's disease are focal accumulations of mononuclear cells (T cells and macrophages) in the lamina propria and aphtous ulceration of the intestinal lymphoid follicles. More diseased mucosa contain large numbers of phenotypically activated T cells and macrophages, and there are large numbers of IgG plasma cells, extensive local complement activation, and an abundance of non-specific effector cells such as mast cells, eosinophils, and neutrophils. Standard treatment is with immunosuppressives such as prednisolone and azathioprine, and more recently with cyclosporin. The crucial question however is the antigenic stimulus for this inflammatory response and which aspect of the immune response is responsible for the primary lesion. It has always seemed clear to the author that many of the features of Crohn's disease, such as granulomas, macrophage infiltrate, and fibrosis are also those seen in chronic cell mediated immune reactions. Thus it was little surprise that an ongoing cell mediated immune response has recently been identified functionally in the mucosa of Crohn's disease, but not ulcerative colitis, by both quantitative PCR and functional lymphokine analysis. The observation that activated T cells are not seen in the mucosa in ulcerative colitis shows that T cell activation in Crohn's disease is not a non-specific secondary effect due to increased antigen uptake across a damaged epithelium, but may be a primary event. However until the specificity of these T cells is identified, the stimulus for the local T cell hypersensitivity will remain unknown. Cell mediated immunity in the mucosa and lymphokine production (for example interferon gamma) can cause mucosal ulceration and increase epithelial permeability. Subsequent secondary ingress of lumenal contents may then elicit a vigorous phlogistic IgG response that perpetuates and increases tissue damage. The IgG response is markedly higher adjacent to ulcers than in the areas between the lesions.

Although it is still contentious, the stimulus for the inflammation is likely to be from the faecal stream. After resection of diseased bowel, there is no disease in the neoterminal ileum if the segment is bypassed. After reconnection to the faecal stream, aphthous ulceration and inflammation develop.

**INTESTINAL PERMEABILITY**

The predisposing factors to develop Crohn's disease are still not known and the genetic link is not strong. There was some excitement with the demonstration that relatives of Crohn's patients appeared to have increased intestinal permeability, thereby providing a mechanism whereby immunological sensitisation to the flora could occur. Unfortunately, this observation has not been repeated.

**ELEMENTAL DIET**

Proponents of an immunological origin for Crohn's disease have some difficulty explaining the proved efficacy of elemental or polymeric liquid diets in inducing remission of Crohn's disease, especially as there is little evidence for sensitivity to foods in Crohn's disease. Many patients with active Crohn's disease are undernourished but it is puzzling that improved nutrition can be as effective as immunosuppressive treatment in healing the intestine. Improved nutrition may allow the development of a previously suppressed immunological feedback loop, so that the host's own endogenous immunomodulators can suppress the active inflammation. Alternatively, elemental diet may quantitatively or qualitatively alter the gut flora, removing or reducing the stimulus for inflammation from the faecal stream. It should also be remembered that the faecal flora in Crohn's disease is different from normal, with higher numbers of anaerobic cocci.

**Crohn's disease is a vasculitis caused by multifocal gastrointestinal infarction**

It has been recognised for many years that there are vascular changes in the submucosa in active Crohn's disease, although it was assumed that these were secondary to the transmural inflammation originating in the mucosa. Extremely detailed studies on vasculature in Crohn's disease by Wakefield and colleagues however suggested that vascular injury and focal arteritis were early events, even occurring in the submucosa underlying normal mucosa. Arterial occlusion follows the arteritis and there is multiple gastrointestinal infarction, so that the mucosal changes are due to ischaemia. In further studies it was shown that many of the granulomas in Crohn's disease were associated with vessels, further implicating the intestinal microvasculature in the pathogenesis.

The key to this notion is the definition of the earliest lesion. Traditionally it has been considered that discrete punctate aphthous ulceration of the mucosa overlying lymphoid follicles, visible endoscopically, is the earliest sign of Crohn's disease. However any underlying vascular changes would not be seen endoscopically. In resected specimens, although vascular abnormalities may be visible below normal mucosa, the mucosa may have been previously diseased, but healed. In addition, even the association of granulomas with blood vessels does not prove that the granulomas arose in the vessel.
as tumour necrosis factor-α, produced by cells in the granuloma, is angiogenic. Finally, granulomatous vasculitis does not spontaneously develop, but is more likely a consequence of delayed hypersensitivity reactions. Again, there must be a stimulus to initiate the inflammation.

Conclusions

Research on Crohn’s disease has progressed on two fronts. If a specific aetiological agent could be identified, then avoidance or prophylactic steps could be taken. If however there is no single aetiologic agent, but the disease is a host intestinal hypersensitivity response to different stimuli in different individuals, then focus should take place on ways of specifically subverting the immune response. This latter point is urgently needed as although steroids, the mainstay of treatment, are effective at inducing clinical remission, endoscopic examination of the mucosa in patients in remission frequently continues to show mucosal damage. Thus even in remission there is ongoing subclinical, low grade mucosal inflammation which undoubtedly contributes to the mucosal ulceration, scarring, fibrosis, and strictures that are characteristic of the disease.

It would be foolish to predict that no discrete aetiologic agent will be found. However, it is now clear that terminal ileitis indistinguishable from Crohn’s disease can be seen in children with neutrophil deficiency syndromes, such as glycogen storage disease or chronic granulomatous disease. This tells us that antigens and bacteria from the gut are continually entering the mucosa, a process called translocation, but that these are degraded and destroyed by neutrophils. If this system is defective, there is antigen persistence and a terminal ileitis develops, presumably due to local immune reactions. Although there is little evidence for a primary neutrophil defect in Crohn’s disease, persistent lumenal antigen penetration into the mucosa and sensitisation would explain the immunological features of the disease, without invoking a specific aetiologic agent.

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