Review Article

Crohn's disease: ancient and modern

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In 1932, Crohn, Ginzburg and Oppenheimer published their classical paper on regional ileitis in the Journal of the American Medical Association (JAMA). Since then, it has been a popular pastime to document the many case descriptions of Crohn's disease which were published beforehand. Most of these were brief reports of small numbers. The most thorough studies were those of Moschowitz and Wilensky in 1923 which Crohn cited, and of Lesniowski in 1903 and Dalziel in 1913 which he did not. Lesniowski's description is limited but his contribution is remembered in Poland where the disease is known as Lesniowski-Crohn disease.

Dalziel recognized the similarity between regional enteritis in humans and Johne's disease in cattle, a condition caused by Mycobacterium paratuberculosis. This likeness passed Crohn by, although he and his co-workers went to great lengths to exclude known enteric pathogens in the patients they reported. Dalziel's description of his cases is much less thorough than Crohn's but he did describe colonic lesions which he believed to be part of the same disease. In this respect, he was much closer to the modern concept of Crohn's disease than Crohn himself. It was not until the descriptions both of Brooke, and of Morson and Lockhart-Mummery in 1959 and 1960 that Crohn's colitis became generally accepted. It has often been said that the 1932 paper gave rise to the eponym of Crohn's disease through two quirks of fate. The first was the policy of JAMA to list authors alphabetically rather than by the importance of their contribution; the second was the reluctance of the senior surgeon, Dr Berg, to put his name to a paper that he had not written. Another twist to the story is the assertion by Ginzburg that he and Oppenheimer wrote the majority of the paper. Ginzburg maintained that Crohn borrowed their description of 12 cases and that they never saw it again until it was published with two extra cases added. In the mean time, the programme for the forthcoming 1932 American Medical Association meeting was published containing the same title with Crohn's name at the top as sole author! Their names reappeared after an informal investigation. Crohn (Figure 1) was a popular man with many people, not least with Berg, and, in his defence, he was not alive to answer Ginzburg's allegations. The paper still stands as a thorough description of an important disease whose existence was not recognized widely before Crohn made his efforts to publicize it.

There has been as much disagreement about the possible cause of Crohn's disease as there has about its name. At present, no consensus exists regarding the aetiology. Theories have invoked host defects, environmental agent(s) or a combination of the two. Following the 1932 description, evidence for an aetiological role was first sought for inherited factors, foreign materials, lymphatic obstruction and a number of infectious agents. An abnormality of the immune response was also suspected, although the nature of intestinal immunity was poorly understood. At present, studies of intestinal immunity dominate Crohn's disease research but no immunological defects specific to Crohn's disease have yet been found. Neither has research into diet or intestinal permeability shed any light on the aetiology of Crohn's disease. The first areas to be investigated still represent major subjects of current research. What has been achieved since then?

1. Inheritance

The occurrence of inflammatory bowel disease in family members was first reported by Lewisohn in 1938. The familial incidence of Crohn's disease reported over the next 30 years varied from 2% to 11%, and a higher incidence was also observed in Ashkenazy Jews. These findings suggested a genetic contribution, but it was assumed to be of low penetrance. Reports of increased familial risk continue to be published. An increased inci-
3. Lymphatic obstruction

Submucosal oedema and lymph node enlargement were thought to be early features in Crohn’s disease. On the basis that lymphatic obstruction causes the pathological changes, injections of sclerosant were given to dogs in an attempt to create an animal model of Crohn’s disease. They produced little more than lymphoedema of the bowel wall. Bockus and Lee suggested that bacterial lymphangitis occurred rather than just lymphatic obstruction and that this led to a vasculitis. However, when Bell interrupted the mesenteric blood supply in animals, he failed to reproduce the pathological features of Crohn’s disease. This line of study was mostly abandoned until it was shown that mesenteric vascular injury occurs in macroscopically normal tissue in patients with Crohn’s disease, and that the great majority of granulomas are associated with blood vessels. Hudson et al. re-addressed the question of vascular occlusion and showed that, while ligation of the extramural blood vessels has little effect on the integrity of the bowel wall, vascular occlusion at the level of the submucosa produces transmural inflammation and ‘skip’ lesions. Many of the histological features of Crohn’s disease may be explained by intestinal vascular occlusion at the level of the submucosa and it is possible, therefore, that Crohn’s disease is an organ-specific vasculitis rather than a primary disease of the intestine.

4. Infective agents

In the first few years after Crohn’s description, no bacterial agents were consistently identified in Crohn’s disease. In contrast, numerous pathogens were proposed as causative agents in ulcerative colitis. In 1976, Parent and Mitchell isolated cell wall-deficient bacteria from cultured intestinal homogenates taken from patients with Crohn’s disease. These were later shown to be Pseudomonas spp. Interest in this line of research dwindled as attempts to confirm these findings met with varying degrees of success. It was also suggested that intestinal conditions in Crohn’s disease favoured the development of cell wall-deficient bacteria, and that their presence may be a secondary event unrelated to the aetiology. However, such bacteria may still have importance in the pathogenesis of Crohn’s disease, in that secondary invasion of damaged intestinal tissues may exacerbate the inflammatory process. This is supported by the observation in 1981 of non-specific bacterial overgrowth in Crohn’s disease and the demonstration of clinical benefit following treatment with metronidazole.

A revival of interest in mycobacteria as aetiological agents in Crohn’s disease followed the
publication by Chiodini et al. in 1984 of their isolation of mycobacteria, subsequently shown to be *M. paratuberculosis*, from the intestine of two patients with Crohn's disease. This organism, the causative agent of Johne's disease, proved very difficult to culture and slow progress was made in this field until more sensitive molecular biological techniques became available. In 1989, McFadden and his co-workers identified a DNA sequence specific to *M. paratuberculosis* (IS-900), which was then used to design primers for the polymerase chain reaction. Using this technique, *M. paratuberculosis* DNA was demonstrated in the intestine in two-thirds of patients with Crohn's disease. However, another group found no *M. paratuberculosis* DNA in any of their samples by this method. The presence of *M. paratuberculosis* DNA in patients with ulcerative colitis and controls further diminishes the significance of the original findings. At present, the role of mycobacteria in Crohn's disease remains undefined. Evidence from serological studies is conflicting while trials of antimycobacterial chemotherapy have shown no benefit.

At the same time as Parent and Mitchell were investigating cell wall-deficient bacteria, other groups were using similar methods to look for viruses. Inoculation of intestinal tissues filtrates from patients with Crohn's disease on to cell cultures frequently produced a cytopathic effect. Analysis of the physicochemical characteristics of the agents involved suggested the presence of small RNA viruses such as picornaviruses or reovirus-like agents. These findings were supported by electron microscopic studies. However, subsequent examination of specimens from one of the laboratories concerned showed mycoplasma contamination in some samples. It was later shown that a cytopathic effect could be produced by innoculating normal bowel homogenates on to cell cultures. Although these observations cast doubt on the presence of viral agents in some of the specimens examined, they do not account for many of the ultrastructural and physicochemical findings.

At the outset of their work on intestinal vascular injury, Wakefield and his co-workers hypothesized that Crohn's disease is a cell-mediated response to a persistent viral infection of mesenteric microvascular endothelium. Of the viruses known to infect vascular endothelium, measles is of particular interest for two reasons. Firstly, it localizes to the intestine during the acute infection and secondly, it causes subacute sclerosing panencephalitis. This is a rare organ-specific disease which occurs up to several years after clinical measles infection, indicating viral persistence. Evidence was sought for measles virus infection in Crohn's disease by the technique of *in situ* hybridization. Intestinal tissue sections from patients with Crohn's disease were probed using a biotinylated riboprobe specific for negative-stranded (genomic) measles virus RNA. Measles virus RNA was identified in all 10 cases of Crohn's disease examined and, specifically, within vascular endothelial cells associated with foci of inflammation in nine of 10 cases with Crohn's disease. Vascular staining was seen in four of 10 cases of ulcerative colitis although this bore no relation to inflammation. Similarly, vascular staining was seen in three of 10 non-inflammatory controls. Positive staining of the sections from patients with Crohn's disease was also obtained by immunohistochemistry using a monoclonal antibody specific for measles nucleoprotein. Further evidence of this association was obtained by an ultrastructural study of the submucosal vascular endothelium and granulomas in Crohn's disease. Cytoplasmic inclusions resembling *Paramyxoviridae* nucleocapsids were identified within endothelial cells in association with granulomas. Similar particles were observed by Knibbs et al.

These findings require confirmation, both by other techniques and from other centres. On present evidence, it appears that measles virus is associated with Crohn's disease and that its distribution within the bowel correlates with areas of granulomatous vasculitis. This lends support to the hypothesis that Crohn's disease results from a vasculitic process initiated by measles virus.

Dalziel wrote in 1913 that 'the aetiology of the disease remains in obscurity'. No doubt he would have been disappointed to know that his statement still holds true. However, with recent advances in our understanding of Crohn's disease, we now have grounds for optimism. Perhaps 'ere long further consideration will clear up the difficulty' and the eponym will be consigned to the history books.

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**References**


