The history of Crohn’s disease

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I can only regret that the aetiology of the condition remains in obscurity but I trust that ere long further consideration will clear up the difficulty.

Dalzeil, T. K. (1913) British Medical Journal, ii, 1668.

The purpose of this article is to review the history of regional enteritis (Crohn’s disease), to trace the development of the condition and to discuss whether it is a new disease or merely one that is being diagnosed more frequently.

It is well known that Crohn’s disease is named after the first of the three co-authors whose names were arranged alphabetically at the head of their clinical and pathological study of regional ileitis which appeared in 1932 [1]. It is equally well known to gastroenterologists and medical historians that this important paper was not the first description of this condition. However, this is where unanimity ends. Over the years there have been many publications suggesting that various individual reports of a Crohn’s-like condition had been the first actual case report.

In a historical retrospective the diagnosis of the genuine condition may be difficult to prove. A terminal ileal involvement may be seen with tuberculosis, Yersinia enterocolitis and lymphoma. It is likely that without modern diagnostic tools these conditions would be indistinguishable. In addition, the common presentation of bloody diarrhoea, weight loss and vague ill health may be produced by a number of gastrointestinal disorders, particularly the infectious enteritides. These conditions would have been widespread in previous generations and merely add to the diagnostic confusion. Nevertheless, even with these provisos, it is possible to find reports of Crohn’s-like conditions extending back many centuries.

Early history

Soranus of Ephesus was the first to describe a Crohn’s-like proctitis (Hawkins). Hippocrates and Aerateus the Cappadocian both described rectal diseases with rectal bleeding and weight loss. Although these may have been dysentery, Crohn’s disease could explain these findings [2].

Louis XIII’s personal physician described a non-specific enteritis [3]. In 1769 Morgagni performed a post-mortem on a 34 year old man who had died of intestinal perforation and peritonitis. His illness had started 14 years previously with diarrhoea and abdominal pain: the terminal ileum and colon were inflamed, ulcerated and strictured, with large mesenteric lymph nodes. Although this illness was attributed to intestinal tuberculosis, Crohn’s disease remains a strong diagnostic candidate [4].

Two centuries ago probable cases were recorded in the medical literature; they appeared under various synonyms, from chronic cicatrising enteritis to non-specific granuloma of the intestine.

A case of stricture and thickening of the ileum was demonstrated at the Royal College of Physicians in 1813 by Combe and Saunders: the ileum was ‘contracted for the space of three feet to the size of a turkey quill’ [5]. In 1828 Abercrombie [6] described a 13 year old girl with inflammatory thickening of the terminal ileum and proximal colon with skip lesions. The clinical history and gross pathological findings are quite compatible with a presumptive diagnosis of juvenile Crohn’s ileitis.

Fielding [7] has commented that Crohn’s disease would appear to have potential medico-legal implications in the result of a celebrated murder trial in 1859. A certain Dr Smethurst was found by jury trial to have murdered his wife by administration of an unknown poison. However, the Home Secretary, taking the advice of Sir Benjamin Brodie, surgeon to St George’s Hospital, granted Dr Smethurst a free pardon since there was not ‘absolute and complete evidence of his guilt’ [8]. Subsequently the post-mortem findings suggested that his wife had Crohn’s disease. In the small intestine ‘nothing remarkable was observed until the lower end of the ileum was reached, when at about three feet from its termination in the caecum, the mucous membrane commenced to exhibit an inflammatory response’. In the caecum ‘inflammation of the most acute and violent character was observed . . . the bare muscular coat was seen beneath. The muscular coat itself in the caecum was likewise infiltrated with this exudation . . . and there is no doubt that through this part of the intestine some transudation had occurred which had set up the peritonitis. No actual perforation was discoverable’ [9]. Recent work has suggested that this case may represent the first recorded instance of the recently described non-steroid anti-inflammatory drug-induced terminal ileitis [10].

In 1859 Samuel Wilks [11] suggested that idiopathic colitis should be considered in a different category from
specific epidemic dysentery. Wilks and Moxon [12] described 'severe acute ileitis in the shape of a thickening of the whole of the coat including the valvulae conniventes which stood out stiffly, while the whole wall was thick with inflammatory lymph, the microscope showing a generalised charging of the whole tissue with pyoid corpuscles. This condition was found in a circumscribed patch from 6 inches to 2 or 3 feet'.

In 1882 Moore [13] described microscopic and macroscopic features of Crohn's disease in a patient with intestinal obstruction in whom a colostomy had been performed. There were no acid-fast bacilli and no evidence of malignancy but there were chronic inflammatory cell infiltrates. The patient died because the colostomy had been fashioned distal to the obstruction.

In 1905 Wilmanns [14] reported a case of inflammation of the ileocaecal valve which had resulted in intestinal obstruction. Resection of the involved segment resulted in resolution of the symptoms.

Two contributions from the Leeds surgical school are of great interest. In 1907 Moynihan [15] discussed the differential diagnosis of colonic malignancies and attributed some of the complete cures seen after resection to chronic inflammatory masses. The following year, Robson [16] stated that over a period of 12 years he had seen 5 cases of inflammatory tumours of the large bowel which simulated malignancy.

In 1909 Braun [17], a German surgeon, reviewed chronic inflammatory disease of the large intestine. He distinguished the idiopathic chronic inflammatory changes from those of tuberculosis, syphilis and actinomycosis. He also mentioned that much diagnostic confusion had arisen due to hitherto inadequate microscopic examination of resected specimens. He considered the idiopathic chronic inflammation in small and large intestine to be distinct diseases.

Several isolated case reports followed. Schmidt (1911) described a chronic inflammatory mass in the colon which had been pre-operatively diagnosed as malignancy. Von Bergmann reported 12 cases of appendiceal masses, some of which were probably Crohn's disease. Goto (1912), in separate publications, reported strictures of both small and large intestine which showed simple chronic inflammatory changes on histology; these had pre-operatively been diagnosed as malignancy [18].

Sir Kennedy Dalzell [19], surgeon to the Western Infirmary, Edinburgh, described 9 patients with chronic interstitial enteritis. He saw his first patient in 1913, a doctor who had originally been diagnosed to be suffering from enteritis. Dalzell also had patients with involvement separately of the jejunum, middle and lower ileum and transverse and sigmoid colon. In his two fatal cases both large and small intestines were extensively affected.

Dalzell's description is still an accurate exposition of the features of the syndrome: 'The affected bowel gives the consistence and smoothness of an eel in a state of rigor mortis, and the glands though enlarged are evidently not caseous'. Both Dalzell and Crohn were careful to exclude intestinal tuberculosis as a cause of these features. Many of Dalzell's patients had subacute intestinal obstruction.

When considering prognosis and treatment, Dalzell states 'As far as I am aware the prognosis is bad except in cases where the disease is localized, and even then seems rather hopeless unless operation be had recourse to'. He advocated radical resection for the condition.

In 1914 Lawen [20] described an entity which he named fibroplastic appendicitis. He suggested that chronic inflammation started in the appendix and then spread to the caecum, the ileum and the ascending colon. He specified that it was distinct from hyperplastic intestinal tuberculosis and classified this condition into three groups:

1. Inflammatory tumours of the caecum and adjacent ascending colon separate from the appendix.
2. Inflammatory tumours which originate in the appendix and spread into the anterior or posterior abdominal wall, or into the surrounding intestine or omentum.
3. Inflammatory tumours which originate in the appendix and remain localised in the appendix itself, the caecum, ascending colon and terminal ileum.

In the following decade several reports of Crohn's-like conditions appeared. Inflammatory tumours of the intestine simulating malignancy were reported in both the USA and Europe. The common feature of all these was their good response to resection. Frohlich (1922) was the first to recognise the association of this condition and a right iliac fossa mass, and mentioned carcinoma of the caecum, appendix mass and ileocaecal tuberculosis in the differential diagnosis of this physical sign [21].

Moschowitz and Wilensky [22] (1923), from Mount Sinai Hospital, New York, predated Crohn's paper from the same institution by almost a decade with a comprehensive survey of non-specific intestinal granulomas. They emphasised the unknown aetiology, the presence of giant cells and their resemblance to hyperplastic ileocaecal tuberculosis. They reviewed the literature on ileocaecal tuberculosis and were the first to suggest that, because of the paucity of positive bacteriology in many of these cases, several of the reported cases were in reality simple inflammatory processes. In the same year further reports were made of fibroplastic appendicitis and concurred with Lawen's classification as discussed previously [20].

During the 1920s many isolated reports of similar observations appeared in the literature. In 1925 Horsley described a case of typical regional ileitis. In the same year Metge described a similar process in the mid small gut, and analogous conditions were cited by Cabot in 1926. Markiewitz reported a similar case involving the caecum. In 1927, Razzaboni speculated on the possibility that a virus might be the aetiologic agent of these growths. In 1928 most reports were of inflammatory tumours of the stomach and ileocaecal region, and in 1931 Fischer published a case of regional ileitis [23].

**Crohn, Ginzburg and Oppenheimer**

The modern history of granulomatous disease of the intestinal tract begins with the classic paper by Crohn, Ginzburg and Oppenheimer on their 14 cases of terminal ileitis [1,24].

Much controversy surrounds the development of the
work; several other investigators were involved, notably Dr Berg the surgeon [25]. Although, in a sense, the eponym Crohn's disease may be considered fortuitous, there is no doubt that the careful clinico-pathological studies carried out at Mount Sinai Hospital laid the basis for the modern understanding of the disease. The article described a disease ‘affecting mainly young adults, characterized by a subacute or chronic necrotizing and cicatrizing inflammation’. The clinical findings were faithfully described and the complications of steriosis, fistulae and perforation described. Some of the X-ray findings were discussed and differential diagnoses described. Medical treatment was described as ‘purely palliative and supportive’. The patients were treated by surgery and, reflecting perhaps the novelty of the disease, a good prognosis was given—‘the course is relatively benign, all the patients who survive operation being alive and well’.

The detailed radiology and microscopic histology were described later by Kantor [26] and Hadfield [27] respectively.

Modern history

The next phase in the history and development of the condition was the acceptance of granulomatous colitis as an entity distinct from ulcerative colitis.

Colp (1934) described a medical student who had non-specific granulomatous disease involving the caecum and terminal ileum [28].

Rappaport et al. (1951) reviewed 100 cases of histologically confirmed regional enteritis. In 55 of these they found similar, though much less severe, disease in the colon. This involvement in the colon was usually discernible only on microscopical examination and consisted of oedema, fibrosis, hyperplasia of submucosal lymph follicles and, in 17 cases, characteristic granulomas. Primary small intestinal regional enteritis appeared to be a disease distinct from the segmental non-specific granulomatous disease limited to the colon. Supporting this assertion was the presence of circumscribed, eccentric, tumour-like involvement and absence of sarcoid-like granulomas in the colonic disease. The frequent absence of these granulomas even in regional enteritis suggested a heterogeneous aetiology for this group of diseases [29].

Wells [30] of Liverpool was probably the first (1952) to report that certain cases previously considered to be idiopathic ulcerative colitis had characteristics which pathologically more closely resembled regional enteritis of the small intestine, with which they were often associated anatomically. He was the first to suggest that segmental colitis was a colonic form of Crohn's disease without any associated ileitis; interestingly, in his paper he insisted that it was not a variant of ulcerative colitis, since Crohn himself ‘did not sanction this extension of the entity to which we give his name’.

In 1954 Warren and Sommers [31] pointed out that regional enteritis was restricted to the small intestine in about 85% of cases but that in less than 10% there were skip areas of involvement in the large intestine.

Bryan Brooke [32] in 1959 made two fundamental statements that altered the definition of regional enteritis. He thought that regional enteritis was not limited to the small intestine and that not all idiopathic colitis was ulcerative. This was supported by information obtained from the Birmingham Crohn’s disease register: in 121 cases in which he was able to determine the primary site of granulomatous disease, in 62 the initial lesion was confined to the terminal ileum or higher in the small intestine. In the remaining 59 the initial involvement with Crohn's disease affected the colon (7 alone and 52 ileocolonic). Furthermore, he thought that ulcerative colitis and Crohn's disease of the colon should be differentiated from each other because they varied in their response to medical therapy and in prognosis after surgery. Most important, he recognised that Crohn's disease recurs after total colectomy and ileostomy, whilst this operation may be regarded as curative for ulcerative colitis [33].

Work from St Mark's Hospital followed which delineated the pathology and clinical features of Crohn’s disease of the colon. Papers by Morson and Lockhart-Mummery were landmarks in the acceptance of Crohn’s disease of the colon as a clinical entity [34,35].

Since then, much more work has been carried out on all aspects of this condition, particularly on its aetiology and on novel means of treatment [36–39].

Is Crohn's disease, therefore, a deserved eponym for a condition that has existed possibly for several centuries, the modern development of which has been stimulated by many workers? As is so often characteristic of seminal advances in medicine, the paper by Crohn and colleagues...
provided the insight and the clinical guidelines for recognition of this entity. Thus, although the cause and pathogenesis of Crohn's disease remain elusive, surgery and gastroenterology are indeed indebted to Crohn, Ginzburg and Oppenheimer and to their associates for stimulating worldwide interest in an emerging and serious disease. However, 'All this is now ancient history' (B. B. Crohn, December 1982).

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