Section of Medicine

President Sir Max Rosenheim KBE PRCP

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Crohn's Disease [*Abridged*]

Dr B C Morson
(*St Mark's Hospital, London*)

Histopathology of Crohn's Disease

Crohn's disease was originally conceived by Crohn, Ginzburg & Oppenheimer in 1932 as an inflammatory condition of the terminal ileum. The histopathology was accurately described for the first time by Hadfield at St Bartholomew's Hospital (Blackburn *et al.* 1939). Over the past thirty years it has gradually become clear that Crohn's disease is not only a disease of the terminal ileum, but may involve any part of the gastrointestinal tract from the stomach to the anus inclusive. This modern concept of Crohn's disease has been accepted rather reluctantly, in particular by those who have the difficult task of distinguishing between ulcerative colitis and Crohn's disease of the colon. The situation has also been aggravated by a confused terminology. In this country and on the European continent we persist in using the eponym 'Crohn's disease' whatever part of the gastrointestinal tract is involved. On the other hand, in the United States the terms 'regional enteritis', 'granulomatous colitis', 'enterocolitis', 'regional colitis', 'granulomatous gastritis' and other expressions are used to describe the disease as it affects different parts of the gastrointestinal tract. This purely anatomical approach is a major cause of confusion.

Macroscopic Appearances

Careful macroscopic examination of well-prepared surgical specimens is of the utmost importance. In many cases the naked-eye appearances are so characteristic that microscopic examination serves only to confirm the diagnosis in more detail. There are three main types: (1) The development of strictures which may be short or long, single or multiple; the classic type is, of course, the single stricture of the terminal ileum, but stricturing can affect any part of the gastrointestinal tract, although the appearances are modified by differences in anatomy and physiology. (2) The type which is predominantly an ulcerative condition of the mucous membrane. This ulceration is discontinuous and serpiginous. In its earliest form it presents as a small 'aphthoid' ulcer (Brooke 1953). (3) The classic cobblestone appearance of the mucous membrane in Crohn's disease is present in not more than a quarter of all cases. It all depends on what is called cobblestone, but in its most obvious form it is absolutely diagnostic. The cobblestones are formed as the result of intercommunicating crevices or fissures surrounding islands of mucous membrane which are raised up by underlying inflammation and oedema. Fissuring is an important sign of Crohn's disease and must be looked for carefully both at the macroscopic and microscopic level of observation. Whether it presents primarily as an ulcerative, stricturing or cobblestone form or as a mixture of these appearances Crohn's disease is nearly always a discontinuous pathology of gut. Multiple lesions are common and may be widely separated but even in extensively diseased small intestine or colon there are always small patches of normal bowel.

Microscopic Diagnosis

The most valuable diagnostic feature of Crohn's disease is the presence of a sarcoid or tuberculoid reaction in the affected tissue of the bowel wall and in the regional lymph nodes. This sarcoid reaction is essentially the same as the tissue response in sarcoidosis, noncaseating tuberculosis and beryllium poisoning, for example. However, in the context of inflammatory diseases of the intestines Crohn's disease in Great Britain today is by far the commonest cause of a sarcoid reaction. It is present in only about 50–75% of all cases. It can be very florid in the sense that the lesions are present in very great numbers; alternatively there may be so few that they escape detection except by the examination of many sections.

Although the sarcoid reaction remains the most reliable diagnostic feature there are other signs of equal importance. Fissuring, already referred to, is pathognomonic of Crohn's disease (Fig 1). It can be found in at least 25% of all cases, but this

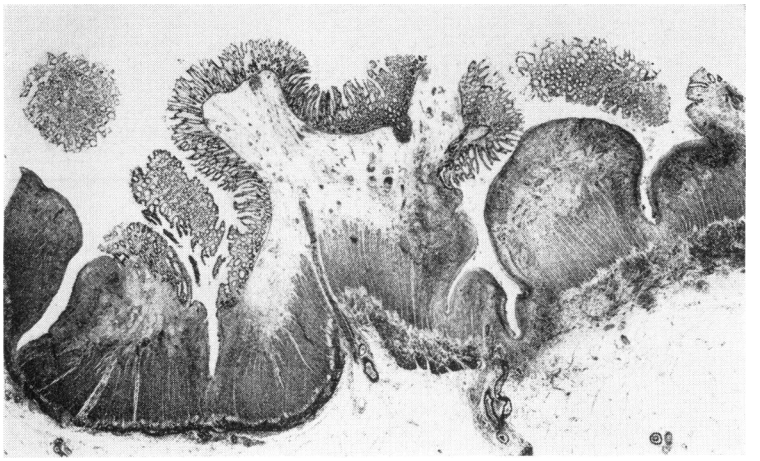

Fig 1 *Fissuring in Crohn's disease of the colon. Deep knife-like clefts, some of them branching, passing deep into the bowel wall. The mucosal ulceration is discontinuous. H. & E. × 6·5. (Photograph by Mr Norman Mackie)*

incidence is greatly raised by a careful search for likely areas of fissuring when the macroscopic examination is carried out. Fissures are particularly valuable in the diagnosis when the sarcoid reaction is absent.

Crohn's disease in surgically resected material is usually a transmural inflammation (Fig 2). Its features include widening of the submucosa by œdema and inflammatory infiltrate, scattered aggregations of lymphoid tissue and certain other features which support the diagnosis although not pathognomonic. These include thickening of the muscularis mucosæ, lymphangiectasia particularly of the submucosal lymphatics, neuromatous hyperplasia, focal arteritis and pyloric gland metaplasia of the mucosa. No satisfactory clinicopathological correlation has ever been established between the various microscopic features and the behaviour of the disease (Antonius *et al.* 1960).

Difficulties in the Diagnosis of Crohn's Disease

One of the principal difficulties in the diagnosis of Crohn's disease is the distinction from intestinal tuberculosis. The sarcoid reaction of Crohn's disease taken by itself can be indistinguishable from noncaseating tubercle. However, the sarcoid reaction is usually much less florid in Crohn's disease than tuberculosis. The foci of epithelioid cells and giant cells tend to be smaller and fewer in number. However, there are cases in which the distinction between Crohn's disease and tuberculosis cannot be made on histopathological evidence alone. In these the co-operation of clinician, radiologist and bacteriologist is essential for accurate diagnosis. We are fortunate in this country that the problem is not a common one because of the decline in the incidence of intestinal tubercle. But in certain countries, such as India, the distinction between Crohn's disease and intestinal tuberculosis is an important and growing problem. Apart from tuberculosis there are no other diseases which are readily confused by the pathologist with Crohn's disease of the small intestine, although it can be misdiagnosed as malignant lymphoma. The situation is very different in the large bowel where there is the difficult problem of the distinction between Crohn's disease and ulcerative colitis (Lockhart-Mummery & Morson 1964), diverticulitis (Schmidt *et al.* 1968) and ischæmic colitis (Marston *et al.* 1966) – difficult in particular, from the point of view of the clinician and radiologist.

Incidence of Disease in Different Parts of the Gastrointestinal Tract

The terminal ileum is still the part of the gastrointestinal tract most commonly affected by Crohn's disease. Disease of the jejunum is uncommon and involvement of the stomach is rare. Rarely, the appendix may be involved alone (Hollings 1964) but more commonly in association with terminal ileitis. At the present time no figures are available for the relative incidence of the disease in different parts of the gastrointestinal tract. Indeed it is doubtful whether diagnosis is sufficiently accurate at the present time for such figures to become available. In particular, this is true for the frequency of involvement of the colon, rectum and anus. There is no doubt that Crohn's disease of the colon is much commoner than previously thought and it is still being misdiagnosed as ulcerative colitis. Although colonic involvement is less common than classical disease

of the terminal ileum it can probably claim a close second place. The importance of Crohn's disease of the anal region has been emphasized in publications from St Mark's Hospital (Morson & Lockhart-Mummery 1959, Gray *et al.* 1965). It is frequently involved in association with disease of the small and large bowel. Indeed, examination of anal lesions and their recognition as a manifestation of Crohn's disease are an important signpost to clinically latent disease higher up the gastrointestinal tract.

Pathogenesis

Little is known of the cause of Crohn's disease. However, histopathological studies do give some clues to the pathogenesis. Blackburn *et al.* (1939) expressed the opinion that Crohn's disease was a disease of lymphadenoid tissue and certainly there is some evidence to support this. It must be significant, in the first place, that Crohn's disease most often affects the terminal ileum, which is the part of the gastrointestinal tract containing the largest aggregations of mucosal lymphoid tissue. Moreover, the incidence of Crohn's disease roughly parallels the distribution of lymphoid tissue in the intestinal tract. The earliest lesion of Crohn's seems to be in the lymphoid follicles and Peyer's patches which undergo hyperplasia followed by chronic suppuration and ulceration. The sarcoid foci can often be found lying within lymphoid follicles. A further point, clearly expressed by Hadfield and his colleagues, is the focal lymphadenoid hyperplasia across the bowel wall which is such a characteristic feature of the histological picture (Fig 2). The fissuring in Crohn's disease also begins in the mucosa at the site of lymphoid aggregations. Other features in the histology which support the lymphadenoid theory of pathogenesis are the œdema and characteristic situation of lymphadenoid and sarcoid foci alongside blood vessels as if they were developing within or in close association with lymphatic channels. Lastly, the spread of sarcoid foci to the regional lymphatic glands is likely to be significant.

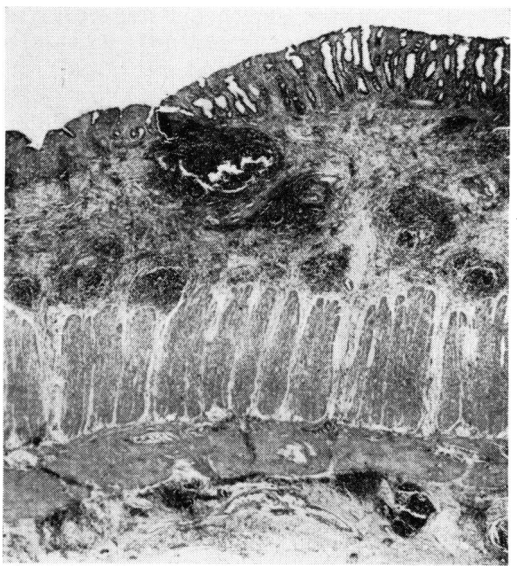

Fig 2 *Transmural inflammation in Crohn's disease of the colon. There is widening of the submucosa with focal lymphadenoid hyperplasia in both the submucosal and serosal layers. H. & E. ×15. (Photograph by Mr Norman Mackie)*

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Dr J E Lennard-Jones
(University College and St Mark's Hospitals, London)

Medical Aspects of Crohn's Disease

Scattered case reports of the condition which we call, for want of a better descriptive term, Crohn's disease, appeared for many years before Crohn, Ginzburg and Oppenheimer published their classic paper in 1932. Their particular contribution was to draw together 14 similar cases all with disease limited to the terminal ileum, to distinguish the condition clearly from ileocæcal tuberculosis and to delineate the main clinical features such as the liability to fistula formation. Since then our concept of the disease has widened steadily so that in 1933 ileojejunitis was described, then ileocolitis and, more recently, Crohn's disease affecting solely the colon or anus.

At the present time there is no specific diagnostic test for the disease and it is best regarded as a clinicopathological syndrome with several characteristic features, not all of which may be present in every case.

Ætiology

The ætiology of the disease is at present unknown. Immunological studies have so far been unre-