CROHN'S DISEASE

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No part of the human body presents problems of greater pathological and clinical interest than does the right iliac fossa, or more precisely the ileo-caecal angle. It is a matter of commonplace observation that where in a muscular tube there is an abrupt change in structure and function there we may expect to find disorder or disease. By way of illustration I need only mention the hypopharynx, the cardia, the ileo-colic and anal sphincters. In the case of the ileo-colic sphincter we have a complete change from the digestive and absorptive functions and rapid movements of the small intestine to the larger calibre, much slower progress and wholly different functions of the colon.

In 1932, Crohn, Ginzburg and Oppenheimer gave their well-known description of a syndrome in which the main symptoms were diarrhoea, lower abdominal pain and loss of weight, and the chief physical features, a mass in the right iliac fossa, evidence of fistula formation, emaciation and anaemia, the scar of a previous appendicectomy in half the cases and signs of intestinal obstruction. They were, however, not the first to recognize this condition. Dalziel of Glasgow, in 1913, described nine cases of a condition he called chronic interstitial enteritis, and in 1920 Moschowitz and Wilensky pointed out the non-tuberculous characters of many cases of so-called hyperplastic tuberculosis of the caecum. Crohn and his colleagues called their condition regional or terminal ileitis, but many terms, mostly pathological and descriptive of various phases of the disease, have been used since and are indicative of our uncertain knowledge. It is proposed here to speak of regional enteritis or Crohn's disease.

In the 16 years which have elapsed since their communication a considerable literature has grown up and well over a thousand cases have been recorded, mostly from America. Little of importance has been added to Crohn's original description. The morbid histology, gross pathology, symptomatology and appropriate treatment are now generally recognized; only the aetiology remains obscure. My object in this lecture is to

give a description more particularly of the clinical aspects of the disease as we see it today, stressing the common features rather than the rare, points of agreement rather than of disputation. It is based partly on a personal experience of some 20 cases and also a review of recent literature, for in so protean a disease the experience of one observer is unlikely to cover more than a fraction of its many manifestations.

The prevalence of the disease today suggests that it is on the increase, for even allowing for an increased awareness and accuracy in diagnosis it is difficult to believe that the number of cases now recorded had been masquerading under an erroneous diagnosis prior to Crohn's paper. Thus Kiefer and Ross (1945) described a series of 107 cases, and in May, 1948, Warren and Sommers gave the results of an analysis of 120 cases.

It is now recognized that the disease may involve any part of the alimentary tract, that the colon may be involved by extension of the process or by isolated regional involvement, that the disease may involve the jejunum by extension or by the so-called skip areas. Yet I would emphasize that in the large majority of cases the disease is primarily, and even entirely, a terminal ileitis. This was so in 93 per cent. of the cases reported by Warren and Sommers (1948). It is perhaps as unusual for regional ileitis to pass the ileo-colic sphincter as it is for ulcerative colitis to do so in the reverse direction. Bockus, in a small series of cases, found that the colon was involved in about half. In our experience such entero-colitis is exceptional. I know of only two cases in which it was diagnosed with certainty.

No age is immune but the great majority of cases occur before the age of 40 and the sexes are equally distributed. Race and climate do not appear to play any part, and though instances of familial susceptibility are increasing, their numbers cannot be regarded as significant.

Pathology

On opening the abdomen the affected bowel is seen to be thickened, rigid and hose-like, and may be entirely encircled by mesenteric fat. The mesentery itself is thickened, boggy and oedematous and contains a variable number of enlarged lymph

glands. On opening the resected bowel three features will be noticed: (1) Oedematous thickening of the bowel wall. (2) Marked narrowing of the lumen. (3) Lymphoid hyperplasia and varying degrees of mucosal ulceration.

I do not think that any subsequent description of the histological picture has improved on that of Hadfield in 1939. He regarded the earliest and possibly the specific histological lesion as a lymphoid hyperplasia with the formation of giant celled systems entirely similar to those seen in tuberculosis and sarcoidosis. In the bowel the earliest lesion is a lymphoedema due to lymphatic blockage from proliferating endothelial cells. A similar picture was obtained by Reichert and Mathes (1936) by injecting sclerosing solutions into the intestinal lymphatics in dogs. The intravenous injection of colon bacilli enhanced these changes. Secondary to the lymphoedema is a variable degree of ulceration of the mucous membrane, such variation being as striking a feature as the constancy in the sub-mucous thickening. Perforation into the peritoneum and fistula formation is invariably a late phenomenon and always localized, which would hardly be the case if ulceration was an initial factor in the process.

The glands in the area of supply are enlarged and succulent. Microscopically they show giant-celled systems and a tendency to regress as in the lymphoid tissue of the bowel wall, but in chronic lesions this appearance is overshadowed by lymphadenitis, consequent upon a low grade infection from the intestinal lumen, which renders a histological diagnosis often difficult and sometimes impossible as all traces of the earlier, more specific lesion may have disappeared. Hadfield stresses the importance of examining and removing all enlarged glands at operation, as they may contain primary lesions and determine recurrence later. Most authorities, including Bockus (1944), have accepted his interpretation of the histological findings and regard the disease as primarily a lymphadenopathy.

As to the aetiology there is much difference of opinion. The early lesion resembles that of tuberculosis but with certain striking and probably fundamental differences. (1) The lesion is capable of regression. (2) Caseation never occurs. (3) The tubercle bacillus has never been demonstrated in the lesion either by direct staining or by inoculation. (4) Pulmonary tuberculosis is never demonstrated by X-ray examination as it almost invariably is in true hyperplastic tuberculosis.

A relation to sarcoidosis has not been established, though the early histology is identical, the only differences depending on peculiarities of location. The lesions of regional ileitis are never disseminated and sarcoidosis does not involve the

bowel. In spite of these facts there are those, and again notably Bockus (1944), who believe that the primary infection may yet prove to be the tubercle bacillus. On the other hand, Crohn and I think most authorities would take the view that if in any case tubercle bacilli were identified then the disease was certainly not regional enteritis. Other agents have been cited as of aetiological significance, dysentery bacilli and the products of fat digestion; while Schepers (1945) regards the primary disorder as a neuropathy, a visceral herpes zoster involving the cells of Auerbach's and Meisner's intra-mural plexuses and perhaps, too, more central sympathetic ganglia. The experimental evidence supporting these views is far from convincing and it may well be that the initial agent is of more than one kind and that the disease will ultimately be shown to be one of multiple aetiology.

Symptomatology

We now pass to a consideration of the clinical manifestations, and as one might expect from the variations in gross pathology these are manifold. Regional enteritis may present itself as a clinical problem in the following ways: (1) Chronic diarrhoea. (2) Abdominal pain. (3) An acute emergency simulating appendicitis. (4) Subacute intestinal obstruction. (5) Unexplained fever, P.U.O. (6) Nutritional deficiency states. (7) Inflammatory masses with fistulae in the right iliac fossa or pelvis.

The commonest type of onset is undoubtedly one with abdominal pain and diarrhoea. The pain is situated in the mid-abdomen or right iliac fossa; it is gnawing or gripping in character and often has an onset two to three hours after meals when the intestinal contents are approaching the lower ileum. Green vegetables and fruit are particularly liable to bring on the pain which may occur in periods of about three weeks' duration over a number of years. Diarrhoea is often associated with the pain; it may be profuse and watery but characteristically consists of four to five semi-fluid stools daily, often associated with the taking of food. Gross blood and mucus are rare unless the colon is involved; pus cells are few in number and often absent; occult blood may or may not be present. Evidences of faulty digestion and absorption, such as fatty acid crystals, starch granules and creatorrhoea are found only in cases where the intestinal involvement is very extensive.

A low grade, intermittent fever may be present though the course may occasionally be afebrile throughout. The scar of a previous appendicectomy has been reported in about half the cases, and this with tenderness and resistance in the right iliac fossa complete a picture strongly

suggestive of regional enteritis. Some would go so far as to say that even in the absence of positive X-ray findings such a story would justify a confident diagnosis and laparotomy. On these clinical findings at some stage in the course of the disease, late rather than early, may supervene evidence of sub-acute obstruction with vomiting, loss of weight, a palpable tender mass, or, failing that, the temporary distension and peristalsis of coils of small intestine striving to overcome an obstruction. In some cases obstructive symptoms are the first evidence of the disorder. It should be noted that an inflammatory mass, though commonly in the right iliac fossa, may occasionally be felt centrally or even on the left side, especially when the diseased ileum has become adherent to the pelvic colon. A diagnosis of diverticulitis might then suggest itself.

So far we have been considering features of the sub-acute or chronic phase of regional enteritis. Many cases have now been described with an acute onset, central abdominal pain and local tenderness, strongly suggestive of appendicitis. In the past the appendix has usually been removed, but with greater experience, recognition of the characteristic appearance of the terminal ileum and the tendency of many cases to undergo spontaneous regression, the abdomen should be closed without further interference, and the case kept under observation. Though there can be little doubt as to the continuity of the pathological progress, the clinical transition of an acute ileitis, if such a thing exists, to the chronic form has rarely been observed.

The spread of the disease upwards, either by direct extension or isolated regional involvement may ultimately interfere with small intestine function and produce serious nutritional defects. Such a syndrome is decidedly uncommon but must be remembered, especially when extensive resection is contemplated. We have no absolute knowledge of the amount of small intestine necessary for normal nutrition. Measurable quantitative amounts may be offset by immeasurable qualitative effects in apparently normal intestine. In all cases of regional enteritis, especially those with diarrhoea and loss of weight it is desirable to have knowledge of the digestive and absorptive functions of the small intestine, particularly of fats, and also of blood changes. In exceptional cases the picture is clinically one of idiopathic steatorrhoea; the stools are fatty with excess of split fat, carbohydrate absorption is faulty, clinical avitaminosis may be present, and the blood shows the typical refractory hyperchromic anaemia of the sprue syndrome. This picture, as has been said, points to extensive disease and possibly irreversible

changes, and an assessment of ileo-jejunal function is therefore highly desirable in all cases.

Fistulae may occur; ileum to ileum, ileum to transverse colon, ileum to pelvic colon, ileum to abdominal wall and there has been in our series one example of an ileo-vesical fistula. These add to the patient's discomfort, the surgeon's embarrassment and the radiologist's difficulties in interpretation, and in the cases of a jejunotransverse fistula may grossly interfere with nutrition much as does a jejuno-colic fistula following gastro-jejunostomy.

Radiology

The radiology of regional enteritis should include examinations by barium meal and barium enema, and of these a barium meal is the more important. Films should be taken at frequent intervals up to eight hours after a barium meal, by which time the normal small intestine will have emptied itself into the colon. A delay at the ileo-colic sphincter or elsewhere may be evident. Distended coils and areas of constriction may be visible and a slow and inadequate filling of the terminal ileum giving an empty appearance to the right lower quadrant and finally Kantor's string sign will be diagnostic. The appearance of the terminal ileum may be confirmed by a barium enema. The sphincter is often incompetent and allows the ileum to fill, while the caecum may show a characteristic filling defect.

But if the X-ray appearances are not characteristic, what then? If the clinical manifestations are suggestive, the examination should be repeated at safe intervals, perhaps once in three months with close scrutiny of the films. Yunich and Crohn (1941) described a few cases where the radiological appearances were not diagnostic and in these they suggested the clinician must have the courage of his convictions and apply the appropriate treatment, even laparotomy if need be. In the presence of a clear-cut symptomatology there should be no need to wait for tumours to develop, obstructive phenomena to appear and fistulae to form. Valuable time may be lost and irreversible nutritional defects occur.

In the follow-up of cases radiology is essential. A barium meal should always be undertaken after operative treatment before the patient leaves hospital. This will show the relation of the parts from a radiological standpoint and subsequent examinations at regular intervals should, when compared with the post-operative films, reveal recurrence at an early stage. The failure to do either of these in one of my patients whose symptoms recurred three years after resection led to so complex a radiological picture as to baffle interpretation and preclude further surgery.

Differential Diagnosis

Carcinoma and carcinoid tumours of the caecum may give rise to initial difficulties but the age of the patient with the longer history and characteristic X-ray picture of enteritis should establish a diagnosis which laparotomy will confirm. Intestinal tuberculosis can be excluded with certainty by a negative X-ray chest film and the absence of tubercle bacilli from the faeces, but it must be remembered that the hyperplastic form is an ileitis and has a radiological appearance similar to that of Crohn's disease.

An amoebic granuloma or amoeboma is a rare but possible source of confusion especially after the recent war. The typical sigmoidoscopic appearances of amoebiasis and the recovery of amoebae from the stools should suffice to indicate the true nature of the condition.

In some cases ulcerative colitis may be simulated and difficulties in differential diagnosis are stressed by certain authors. In the writer's opinion the differences are far more striking than the resemblances. Regional enteritis seldom attacks the colon primarily, whereas ulcerative colitis always does, invasion of the ileum being exceptional. Ulcerative colitis starts as a rule in the rectum and recto-sigmoid, which is rarely involved in Crohn's disease and then only at a late stage. The stools in ulcerative colitis contain pus, mucus and blood; in enteritis this is unusual. Pain in enteritis is typically situated in the central abdomen and right iliac zone. In colitis severe pain is uncommon and more often left sided than right. Finally in ulcerative colitis the X-ray appearances of the small intestine are usually normal down to the ileo-colic sphincter. In Crohn's disease when the colon is involved as in entero-colitis the involvement is either isolated and regional or proceeds distally from the caecum and not in the reverse direction. To sum up, there is usually little similarity between the two diseases, involvement of the colon in Crohn's disease occurring late when the diagnosis is already evident.

Acute appendicitis has already been considered and the diagnosis often necessitates a laparotomy, but generally speaking the enteritis is associated with diarrhoea and appendicitis with constipation, and a leucocytosis is more in favour of appendicular disease.

Treatment

There is no doubt that in the established case of regional ileitis the treatment is surgical. Although regression may occur and a spontaneous recovery is occasionally recorded it is not possible to say in which cases this will happen or how it may be influenced therapeutically. Theoretically, it should be possible to watch the progress of the disease by

repeated X-ray studies, but there are obviously many practical difficulties. The slow extension of the disease to a point where fistulae become established and nutritional deficiency a factor renders surgery unnecessarily hazardous.

It is not my purpose here to consider surgical treatment in any detail but sufficient experience has now been obtained to justify certain conclusions. There are three possible approaches: (1) to short-circuit the diseased area by such a procedure as ileo-transverse colostomy, without excluding it. (2) To short-circuit the lesion and exclude it from continuity with the bowel. (3) Complete resection and short-circuit.

It has now been established beyond doubt that short-circuiting without exclusion is almost invariably followed by extension of the disease, and is unjustifiable except as a temporary measure in patients gravely ill. As to short-circuiting with or without exclusion the argument still continues and perhaps the data are not yet sufficient to supply a firm answer. I prefer to leave the last word to Bockus (1944), who regards the short-circuiting with exclusion as a satisfactory procedure, more especially in those too ill to withstand a long operation or in those cases where sepsis or fistulae are present, but in clean cases and if a master surgeon be present he prefers resection and, of course, a careful radiological follow-up in either case for a period of at least five years.

Surgery is therefore the treatment of choice and nowadays the hazards of operations on the bowel have been greatly lessened by the use of the insoluble sulphonamides and penicillin. There remain, however, a few cases in which medical management may be required if only as a temporary measure. Patients may decline operation or they may be unfit for it. It may also be justifiable in a mild case with a very localized lesion which can be kept under close scrutiny. The treatment resembles that for ulcerative colitis—a high calorie, low fat (50-60 gm.), low roughage diet with vitamin supplements especially when there is evidence of nutritional defects. Pancreatinum B.P. 4-5 gm., after meals is useful and is experimentally effective. Secondary anaemia requires iron, but occasionally the typical hyperchromic anaemia of the sprue syndrome occurs. This is notoriously refractory to refined liver preparations but may respond slowly to crude preparations such as Plexan and perhaps yeast.

Water and mineral salt balance are most important. Many patients with severe diarrhoea suffer not only from dehydration but from salt depletion and this must be made good. One patient of the writer with recurrence of the disease

after wide excision three years previously, complained chiefly of severe diarrhoea and loss of weight. Her admission to hospital and in the meantime and abundance of common salt were advised. The result was dramatic. The diarrhoea ceased, she put on many pounds in weight and it was a year before she was willing to come into hospital for investigation, which showed extensive multiple recurrences of the disease rendering surgery impracticable. In most cases the disease process continues though at a variable rate, and I know of a man who declined operation for established Crohn's disease in 1943. He still remains in reasonable health and maintains his weight but it is obvious from periodical X-ray studies that obstructive phenomena will occur sooner or later.

Summary

Regional enteritis, Crohn's disease, enterocolitis, cicatrising stenosing enteritis, pseudo-tuberculosis or whatever title one likes to give, is a non-specific granulomatous disease, similar histologically to tuberculosis and sarcoidosis, but differing from each in certain fundamental respects. Its aetiology is unknown and may well be multiple. It gives a clear-cut clinical picture which

is usually sufficient for a diagnosis and well marked X-ray appearances which are rarely absent. Regression is possible but extension is the rule, with fibrosis, obstruction and fistula formation. The treatment is usually surgical, either by a short-circuit operation with exclusion or a short-circuit operation with resection. It is difficult at present to assess the value of these two operations but where practicable resection is probably the treatment of choice. Whatever method is used recurrence is possible and a radiological follow-up essential. Medical treatment may be effective in a few cases where the disease is localized and can be kept under observation.

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