Crohn's Disease in Transvaal Blacks

A REPORT OF THREE CASES WITH A REVIEW

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SUMMARY

Crohn's disease is rarely seen in Transvaal Blacks. Three cases are presented. The pathology and radiological features are discussed. The difficulty of diagnosing the extent of the disease in the acute stage both clinically and radiologically is emphasised. The acute case should be recognised at operation and nothing further done. The case presenting with intestinal obstruction should have conservative excision of the organically narrowed segment. Azathioprine may be of some use in the treatment of the acute episode. Its probable chief mode of action is by its antiphlogistic effect.

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Regional ileitis is an uncommon condition which is being recognised more often. In 1958 a leading article stated that after a quarter of a century, although we knew the disease better, we understood it less.[1] Today the truth of this is still valid, although the surgical approach to treatment is becoming more clear. In the past, most intestinal lesions that were not clearly either neoplastic or of an acute inflammatory nature, were likely to be regarded as tuberculotic. However, a study of these reports published between 1885 and 1930 lacks evidence to support this

diagnosis. It is possible that some of these cases were, in fact, suffering from regional ileitis. Since then, and especially since the disease was first described by Crohn *et al.* in 1932,[2] many case reports have been published.

The disease occurs most commonly in people living in north-west Europe and in the north-eastern part of North America.[3,4] It is common in Britain and in Scandinavia.[5-7] It appears to be uncommon in Australasia,[5] Japan and India.[3] Jews in the USA are said to be more likely to develop the disease.[8] However in Israel, where there are many who have migrated from other countries, it is very rarely encountered.[3]

The disease is particularly uncommon in Southern Africa[9]—it is seen in Whites, but hardly ever in Blacks. A possible case in a Ruanda native was described in 1946.[10] During a 10-year period up to 1968 4 cases were treated at this hospital,[11] all of whom suffered from the chronic form of the disease. It is uncommon in the Negro population of North America.[12,13]

Regional ileitis arises most frequently in young adults, but no age is exempt, as it is also seen in childhood and old age,[14,15] and it appears to affect the ileum mostly in younger patients, and the colon in the older age group. A genetic influence has been proposed and the disease has been encountered simultaneously in identical twins.[16]

Because of the comparative rarity of this illness in South African Blacks, the following 3 cases are reported.

Case 1

A Black man aged 30 years was admitted on 3 March 1973, complaining of intermittent attacks of colicky abdominal pain centred around the umbilicus. He had had intermittent attacks of pain for 9 months. On examination, his abdomen was distended and slightly tender to palpation. Radiological examination showed dilated loops of small bowel with fluid levels in the erect position. He was treated conservatively with decompression via a nasogastric tube, and his condition resolved rapidly. However, he then demanded to be discharged.

He returned to hospital on 22 March 1973, in severe pain, suffering from frequent severe attacks of central colicky abdominal pain, and vomiting dark brown fluid. He had, apparently, also passed small amounts of blood-stained faeces. His abdomen was markedly distended and rebound tenderness was present. He had a tachycardia and a temperature of 39,5°C. Straight X-ray examination of the abdomen showed marked distension of the small bowel with many fluid levels in the erect position. These films also demonstrated a thickening of the bowel wall (Fig. 1).

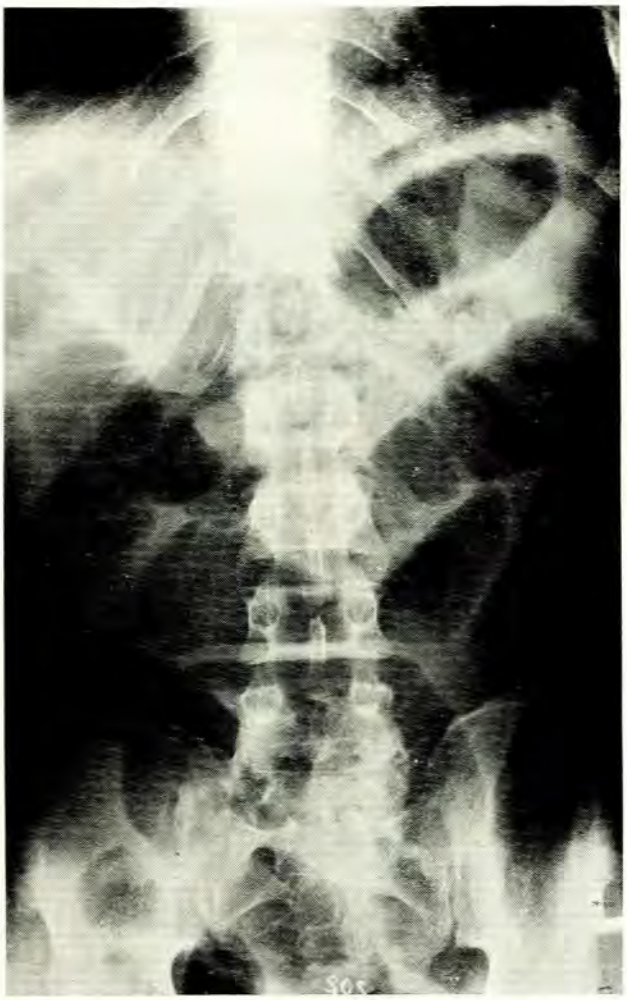

Fig. 1. Straight supine X-ray film of the abdomen in case 1, showing the dilated small bowel with a thickened wall.

At operation an area of markedly stenosed and thickened bowel, 61 cm in length in the mid-jejunum, was found. The serosa was inflamed and injected. Mesenteric hypertrophy appeared to extend onto the bowel wall. The mesentery itself was markedly thickened and large fleshy lymph nodes were present throughout. An adhesion was present between adjacent loops of the stenosed ileum.

A diagnosis of Crohn's disease was made. On further exploration it was estimated that 75% of the small bowel was involved in the disease, i.e. 122 cm from the duodenojejunal flexure to the ileocaecal valve. The criteria for this were marked thickening of the bowel wall and involvement of the adjacent mesentery. The diagnosis was, therefore, diffuse jejuno-ileitis or Crohn's disease. A biopsy of an enlarged lymph node in the mesentery showed reactive hyperplasia only. Because of the diffuse involvement, minimal surgery was undertaken, and the adhesion was simply removed by blunt dissection and the abdomen closed.

Thereafter the patient was treated with azathioprine 50 mg every 8 hours intravenously, nasogastric decompression, and intravenous therapy with Reverin (tetracycline). By the 4th postoperative day his condition had improved to such an extent that the nasogastric tube could be removed. Radiological examination showed marked improvement. On 30 March 1973, a small bowel Raybar meal examination was made and this showed the typical appearance of Crohn's disease affecting the small bowel, with multiple 'skip' lesions, thickening of

the bowel wall, thickened and blunted mucosal folds, and a cobblestone reticulated appearance of the mucosa. The caecum did not fill with the contrast medium. At this stage the appearances were consistent with a clinical diagnosis of diffuse jejuno-ileitis (Fig. 2).

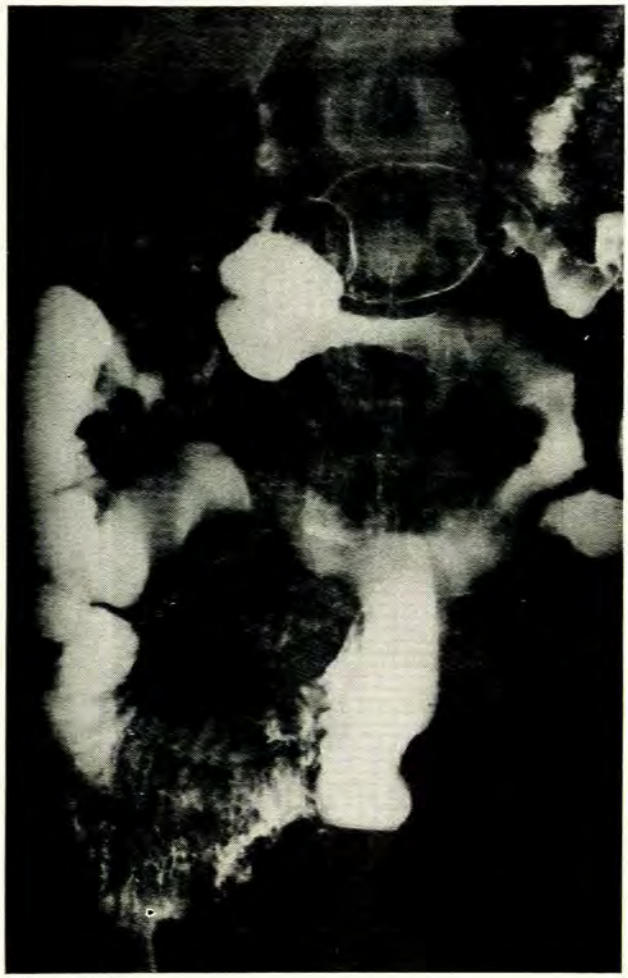

Fig. 2. Barium contrast study of case 1, showing the typical radiological appearances. Multiple 'skip' lesions, stenosed areas, a cobblestone appearance, and ulceration and spiculation of the mucosa. The appearance is that of diffuse involvement.

Although he recovered from the acute episode, the patient remained symptomatic. He still complained of recurrent colicky abdominal pain and irregular bowel actions. He then developed 2 further episodes of subacute obstruction, which were treated conservatively with moderate success.

Because of his moderate response to conservative treatment it was decided to reoperate on 18 April 1973. At operation, the condition appeared to have improved markedly. The area of involvement appeared to be localised to the 61 cm of jejunum previously examined. The rest of the small bowel appeared free of the disease. The involved area did not appear as inflamed as before. The mesenteric lymph nodes were estimated to be at least half their previous size. The involved bowel was excised through normal bowel, with a 5,1-cm margin on each side, and a conventional end-to-end anastomosis was performed.

The patient made an uneventful recovery. He tolerated a normal diet 14 days later, and he was discharged fit. All treatment was stopped on discharge and he remains well. Just before discharge a small-bowel barium meal examination appeared completely normal.

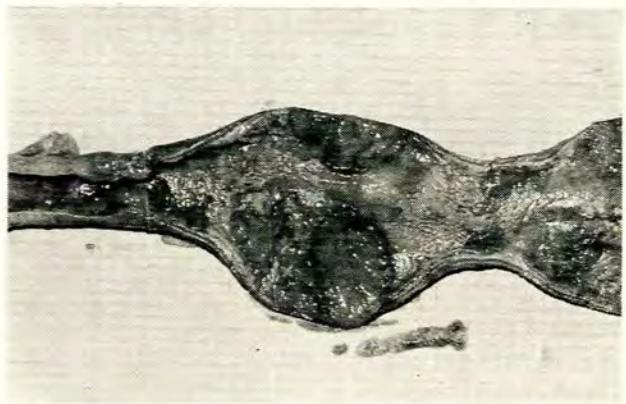

Fig. 3. Case 1. Small bowel showing narrow portions with thickened walls and dilated areas.

The excised specimen (Fig. 3) consisted of 45 cm of small bowel which showed several dilated and constricted areas. The mucosa was abnormal with shallow ulcers, fissuring, and a cobblestone appearance. In the narrowed areas the wall of the bowel was markedly thickened. Microscopical examination showed the typical features of Crohn's disease with transmural inflammation and mucosal ulcerations and fissures. In some areas the inflammatory reaction was acute and in others it was more chronic in nature. The submucosa and serosa were thickened. Vascular obliterative change was present in some submucosal vessels, while other areas showed dilated lymphatics (Fig. 4).

The mesenteric lymph nodes showed intense reactive changes with chronic lymphadenitis and occasional ill-defined granulomas.

Case 2

A Black man aged 63 years was admitted on 2 April 1973, with a history of central colicky abdominal pain, and occasional diarrhoea. His was a long history of abdominal pain, dating back several years before a prostatectomy 2 years previously. Since then, however, it had become worse and more frequent. On examination, he had a distended abdomen with visible peristalsis. He was tender to palpation, but no masses could be felt. Radiological examination showed marked small-bowel distension with thickening of the bowel wall. A diagnosis of carcinoma of the caecum was entertained and a barium enema X-ray

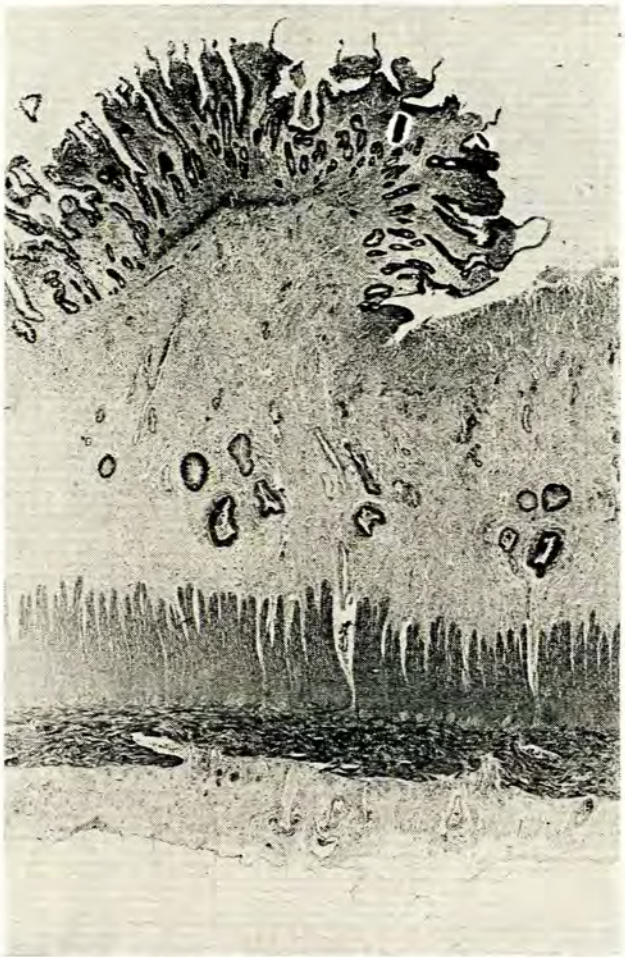

Fig. 4. Case 1. Low-power view of small-bowel section showing mucosal ulceration and fissuring, submucosal fibrosis with obliterative vascular changes and serosal thickening (elastic Masson × 16).

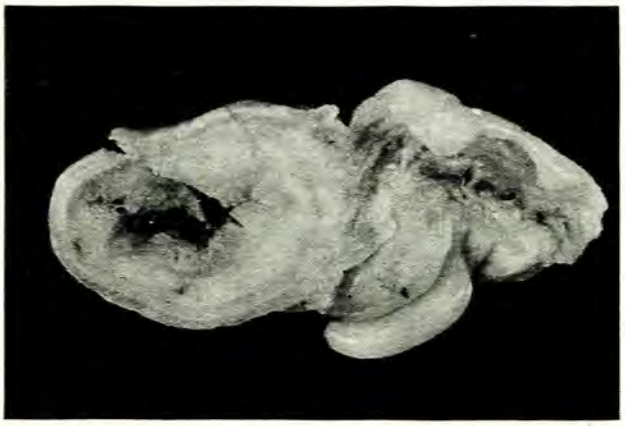

Fig. 5. Case 2. Cross-section showing marked thickening of bowel wall and narrowing of the lumen. Several fissures extending into the submucosa can be seen.

Fig. 6. Case 2. There is marked fissuring with swelling of intervening mucosa producing a 'cobblestone' appearance.

examination was performed. This was normal, although the caecum did not fill. Sigmoidoscopy was normal. At laparotomy, 20,3 cm of the distal ileum was found to be involved by a stenosing lesion. The bowel was markedly thickened and inflamed, and several 'skip' areas were present. The mesentery was not markedly thickened and the lymph nodes appeared normal. The involved area was resected through normal bowel on each side and a routine end-to-end anastomosis performed. The pathological specimen showed the typical features of Crohn's disease without much histological evidence of acute inflammation (Figs 5 and 6). The patient made an uneventful recovery and remains asymptomatic.

Case 3

A Black man, 23 years old, presented with an acute illness which was consistent with Crohn's disease. He complained of the acute onset of vague abdominal pain which became localised to the right iliac fossa, and was associated with vomiting and 1 loose stool. A diagnosis of appendicitis was made. However, at operation, 5 cm of the distal ileum, 10 cm from the ileocaecal valve, was stenosed by a pale thickening of all the bowel wall. The lumen of the bowel appeared markedly compressed, and could not be invaginated. There was no associated lymphadenopathy. The lesion was resected through normal bowel, and the appendix removed.

On pathological examination the appendix was unremarkable, but the small bowel showed marked mucosal oedema which had spread throughout the wall in one area only. This was accompanied by a mild small round-cell infiltrate, and mucosal erosions and ulcerations were present in some areas (Fig. 7). No fibrosis was present. There were many acute inflammatory cells and some areas of lymphatic vessel dilatation.

The patient made an uneventful recovery. Three months later a barium enema examination revealed no abnormality, and the patient remains in good health.

No patient showed the presence of *Yersinia enterocolitica* antibodies on serial studies.

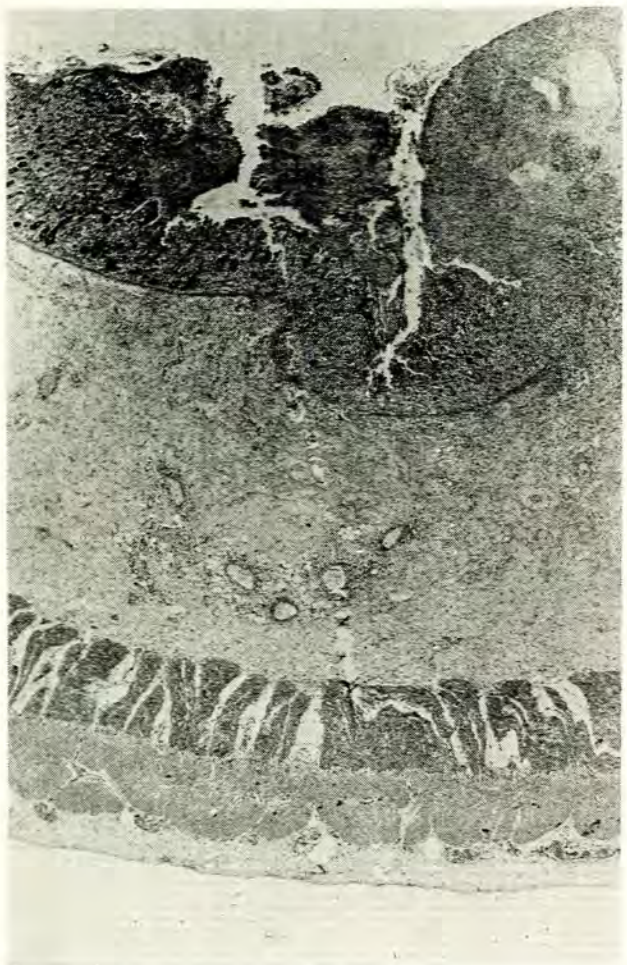

Fig. 7. Case 3: Section of bowel showing transmural oedema with inflammatory reaction and mucosal fissures (H. and E. × 18).

DISCUSSION

Pathology

There appear to be 3 main macroscopic types of Crohn's disease. These are stricture formation, mucosal ulceration, and a typical 'cobblestone' mucous membrane, with fissure formation. The bowel wall is usually considerably thickened and the inflammation obviously transmural. Histologically, the presence of submucosal oedema lymphangiectasia, neuromatous hyperplasia, and typical sarcoid-like granulomata, is diagnostic.[17] The differentiation from tuberculosis may be difficult, and Tandon and Prakashi,[18] describing 212 cases of small-bowel disease encountered in New Delhi, could not, in fact, classify 43 of them; 159 cases were tuberculotic and 10 were suffering from Crohn's disease. The microscopic picture appears to be more helpful in the differentiation, whereas the macroscopic appearances may be very similar. Evidence of caseation is almost always present in tuberculosis. The oedema of the submucosa is never as severe as that in Crohn's disease. Fissuring may occur, but it is never as deep. It is in the long-established cases where much fibrosis has occurred, that confusion might arise. In the acute stage there are typical tuberculous mucosal ulcers. However, in healed tuberculosis the mucosa is hardly ever ulcerated, and is usually smooth. The extent of the fibrosis is usually more extensive in tuberculosis. The granulomas encountered in tuberculosis are usually much larger and tend to be confluent.

The mesenteric lymph nodes are often markedly enlarged in both. It is not unusual to find caseating granulomas in these nodes in tuberculosis, where the bowel is not affected, whereas this is not the case in regional ileitis. The size and appearance of the nodes in regional ileitis are not dependent upon the presence of granulomas, and are not related to the prognosis. They are non-caseating granulomas resembling those seen in sarcoidosis. Cook[19] studied 34 cases and encountered granulomas in the nodes of 38% of cases, and in 63% of those who also had granulomas in the bowel wall. This is a higher proportion than usually reported.[20]

Apart from tuberculosis, no other disease of the small bowel is readily confused with Crohn's disease by the pathologist, although malignant lymphoma should be borne in mind. The situation is, however, different in the large bowel where there is difficulty in distinguishing between Crohn's disease and ulcerative colitis,[21] diverticulitis[22] and ischaemic colitis.[23]

The typical macroscopic picture as described above in cases 1 and 2 should alert one to the diagnosis. If, as in case 1, no direct biopsy material was obtained initially, the diagnosis is presumptive. The typical features exhibited by radiography[24] will assist. Any patient suspected of having this illness should have a rectal biopsy and sigmoidoscopy. An abnormal biopsy will be encountered in 73% of patients with colonic disease, and up to 25% of those with small-bowel disease.[25]

Acute Ileitis

Most patients whose Crohn's disease mimics acute appendicitis are admitted as emergencies. In most cases a long history associated with intermittent attacks of colicky abdominal pain and occasional diarrhoea should draw attention to the true diagnosis. At operation the terminal ileum is usually found to be swollen, red and oedematous with enlarged mesenteric lymph nodes. This is the typical so-called 'red sausage' appearance. Lesions of Crohn's disease are, histologically, not as vascular as this, so that this appearance is almost certainly due to some other disease. In a follow-up of 25 such patients, in most of whom no definitive surgery was done, Schofield[14] found only 2 in whom the typical disease developed later. An even lower incidence after acute ileitis was found by Davis[25] and Atwell *et al.*[26] Most of these cases are probably not Crohn's disease, and various other aetiologies have been suggested. In Scandinavia, *Yersinia enterocolitica* has been commonly encountered.[27] In Japan, acute ileitis has been caused by *Anisakis* larvae.[28] However, a few cases are probably acute Crohn's disease from the outset. The entire wall is infiltrated with acute inflammatory cells,

and there may be plasma cells and eosinophils with marked hyperaemia.[14,29] One of the patients described by Crohn[29] required a further operation after 9 days, and in this short period the typical epithelioid cell granulomas and giant cells had appeared.

Most writers advise against resection or by-pass in these cases.[14,25] It is, however, probably wise to remove the appendix if the caecum is normal, so as to avoid future diagnostic confusion. The reported incidence of fistula formation after appendicectomy, varies from 0%[26] to 30%.[30] There is general agreement that a biopsy of unhealthy ileum is hazardous, and that any form of operation through involved bowel will be accompanied by the hazard of anastomotic breakdown and fistula formation. Where excision was undertaken in the patients reported, the edges of the excised bowel were histologically free of disease, and they made an uneventful recovery. This conforms to the observations of many,[26,31] that resection or by-pass will be successful providing no breach is left through diseased bowel.

Radiological Features

The earliest suspicion of Crohn's disease in the small intestine arises from irritability of the terminal ileum seen on careful screening of the area. Another characteristic sign is deformity of the medial wall of the caecum, which is attributed to an oedematous ileocaecal valve or spasm secondary to adjacent ileitis, or both, or extrinsic pressure from enlarged mesenteric lymph nodes.

In case 1, radiographically, the disease at first appeared to be far more extensive than was eventually the case. This is explained by Marshak and Linder.[32] They found irritability and spasm occurring in essentially normal small bowel adjacent to diseased loops. In addition, when stenosis is severe, dilatation of the proximal intestine may be marked, and it may be difficult to be sure whether disease is present in the proximal dilated segments.

Due to retained secretions, secondary inflammatory changes, tension ulcers, and muscle hypertrophy, the appearances of the dilated loops may be confused with the alterations seen in Crohn's disease without stenosis. This is an important feature to consider when surgery is contemplated, as many patients have not been operated on because the surgeon and the radiologist believed that extensive involvement of the intestine was present.

Surgery in Crohn's Disease

The by-pass operation was made popular by the Mount Sinai group in 1951[33] because of the poor initial results from resection. However, there has been a definite swing back to resection.[34] Statistically, it is very difficult to compare 2 dissimilar groups operated upon sequentially. The findings of Williams *et al.*[35] in 110 cases, appear to favour resection. They performed an ileotransverse by-pass on 21 cases, and primary excision in 89. A long-term follow-up with a mean of 13,8 years, showed the risk of recurrence to be twice as great with a bypass, as with excision. The following are the indications for elective resection: localised quiescent disease, failure of adequate medical therapy, inability to enjoy life, retardation of growth, subacute intestinal obstruction, persistent uraemia and hypoproteinaemia, a persistent mass, external fistulae and extra-abdominal complications.[31] Elective resection should definitely clear diseased bowel proximally and distally. Where more than 50% is diseased, the remaining portion should be suspect. This type of case is generally unsuitable for resection and should be treated medically. It must be emphasised that in a suitable case, resection is safe, but provides no guarantee of cure. At Mount Sinai the policy is to wait, if possible, until the disease is 'burnt out' before elective operation.[36] Kyle[3] believes that patients in whom remission occurs spontaneously or as a result of medical therapy, and who remain well for a while, will do better than if they were operated upon during the active and uncontrolled phase.

Subacute intestinal obstruction may commonly require treatment with nasogastric decompression. This will usually result in improvement. However, it is clear that unless the mechanical organic obstruction is eventually overcome by surgical means, this incapacitating complication will persist. Less than 10% of all chronic cases of Crohn's disease have their first operation because of obstruction,[37] but obstruction is a more common cause for second and subsequent surgical interventions.

Total, complete obstruction is most unusual. In most cases it should be treated by resection, providing that adequate margins of normal tissue can be assured. Where most of the ileum is involved, the situation becomes difficult, as in the case reported. If the evidence indicates that the stage of the disease is acute, it is probably wise to rely in the first instance upon medical treatment and close observation. With extensive resection survival on 50 cm of small bowel is possible, but hazardous. If the remaining bowel is diseased, then the extensive resection, or by-pass, is most certainly not warranted. The objective should be to attempt to induce a remission of the disease and then to operate upon the strictured area if this persists radiologically and clinically, in terms of chronic obstruction. This should probably improve the quality of survival and there is an impression that even with obstruction in the presence of diffuse disease, removal of the local obstructed segments may not, in fact, be followed by an increased incidence of fistula formation.

Azathioprine in Crohn's Disease

At present the exact place of azathioprine (Imuran; Burroughs Wellcome) is not clear. The first report described 6 cases with advanced disease, 4 of whom had fistulae.[38] All were markedly improved by the treatment and the fistulae healed. This 100% success rate has not been achieved since then.

Rhodes *et al.*[39] in a double-blind study of 14 patients, using a placebo and azathioprine, found little difference, and in 1971 advised caution in its use.[40] In 1972 Rhodes again reported a double-blind crossover trial in 16 patients.[41] In none did azathioprine cause a striking

improvement, and 2 showed a marked deterioration—1 because of an allergic response. Other reported complications, such as leucopenia and thrombocytopenia, are dose-related and have not been encountered at a dose of 2 mg/kg.[42] Azathioprine has been incriminated as an aetiological factor in intra-abdominal abscess formation.[43] Patients with extensive inoperable disease, with fistulae, with recurrent disease, and severe systemic manifestations, appear however, to be suitable for this form of treatment. Combined therapy with steroids would also appear to be beneficial, especially during a steroid-induced remission.[41]

It is still uncertain whether the effects of azathioprine are due to immunosuppression or to its antiphlogistic effect.[44] Azathioprine appears to have a specific affinity for the lymphocyte which is a prominent cell in Crohn's disease. It has been used with conflicting results in ulcerative colitis as well.[45]

There appears to be no clinical indication when withdrawal of the drug may safely be undertaken. The ESR is not a good guide, and Javett[42] recommends that treatment should be continued until clinical stability or restitution to normal health has been established. With the possible exception of colitis and acute small-bowel disease, the disease may be only suppressed and not cured. Maximal improvement may take a long time, even up to a year, before it occurs.

Indefinite treatment is probably inadvisable as lymphoma and carcinoma have been encountered in transplant patients receiving azathioprine.[46,47] An unequivocal cause-effect relationship has, however, not been established.

Crohn's disease includes a wide involvement of the gastro-intestinal tract. Its aetiology and pathogenesis are poorly understood. It is chronically progressive and has a long and clinically latent phase, before structural changes give rise to symptoms. Surgery is not at all successful from a curative point of view, and the recurrence rate is high. There is a prolonged morbidity and a possible development of malignancy.[48] The general mortality rate is more than twice that for a control group of the same age and sex.[49]

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