

NUTRITIONAL AND METABOLIC FACTORS IN THE AETIOLOGY AND TREATMENT OF REGIONAL ILEITIS

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by

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IT IS WITH much trepidation and with the diffidence befitting a physician before the Royal College of Surgeons that I venture to present my observations and reflections on some of the problems of regional ileitis. I gain courage, however, by recalling that the condition I am to discuss is often more usefully called Crohn's disease (Crohn, Ginzburg and Openheimer (1932)) after that eminent New York physician, Burrill Crohn, and that in this country the first account of a patient so afflicted was communicated to the Royal College of Physicians by Dr. Saunders in 1806 (Combe and Saunders, 1813).

Sir William Osler has often been quoted as saying, "It is of use from time to time to take stock, so to speak, of our knowledge of a particular disease to see where exactly we stand in regard to it, to inquire to what conclusions the accumulated facts seem to point and to ascertain in what direction we may look for fruitful investigation in the future." This comment is particularly applicable to the disorder regional ileitis which over the past 20 years has received a great deal of attention but about which the literature has been and still is too concerned with the recording of surgical heroics and freakish modes of presentation. This is understandable in a disorder of which the causation is still unknown. The disease is not rare and during the past four years in the Birmingham United Hospital, the diagnosis has been made 75 times. It remains true, however, that there are few series of patients of sufficient magnitude, followed for adequate periods of time from which data as to the life history of the disorder can be drawn.

I propose, therefore, to discuss first the life history and features of the disorder in the light of the 90 patients that I have studied over the past 12 years, with the help and collaboration of my medical, surgical and radiological colleagues. Many were investigated prior to surgical intervention but others were first seen after a recurrence of the disorder. In Fig. 1 is portrayed the duration of the disease in the 90 patients from the time that the diagnosis was first made. It will also be seen that 14 of the patients have died.

Sex Incidence

In this series, women are more than men, totalling 47 females to 43 males. In larger series such as those collected from published literature by Ravdin and Johnston (1939) the pathological series of Warren and Sommers (1948), the personal series of Crohn (1949) and the recent large

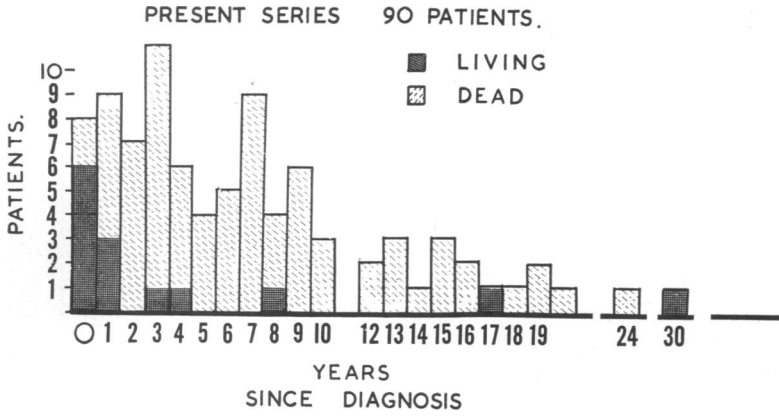


Fig. 1. Duration of the disorder from the time the diagnosis was first made.

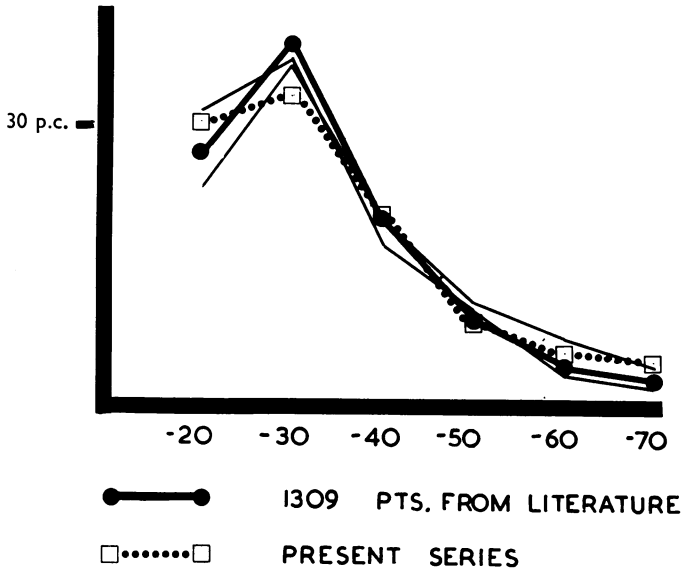


Fig. 2. Age of onset of symptoms.

series from the Mayo Clinic (Van Patter *et al.* (1954)), men have consistently predominated, forming 56 per cent. of these 1,309 patients. There is at present no evident reason for this.

Age of Onset

The age at which symptoms first make their appearance is before the age of 30 in two-thirds of the patients, as it was in my patients (Fig. 2).

Well authenticated instances of the disorder occurring in infancy are on record (Crohn, 1949): the youngest patient in this series was seven years old when his symptoms began, whilst the oldest was 64.

Area of Intestinal Involvement

There is general agreement that the area most frequently involved is the terminal ileum but that any area may be involved from the stomach to the colon. In this series, there is one patient with involvement of the stomach, 10 with predominant involvement of the jejunum and upper ileum and one with major involvement of the transverse colon. Though involvement of the oesophagus has been reported, doubts must be entertained as to whether such lesions are really manifestations of Crohn's disease.

Duration of Symptoms Prior to Diagnosis

The duration of symptoms prior to diagnosis in this series of patients is shown in Fig. 3 expressed in percentages to allow comparison with the findings given by Crohn (1949). The findings for 600 patients from the Mayo Clinic (Van Patter *et al.* (1954)) are essentially similar to those of Crohn. The high percentage of recognition in the first year of symptoms in my group may only reflect the increased awareness of the disorder, perhaps the increased use of intestinal radiology or more likely a less searching history. The most important feature emerging is that many

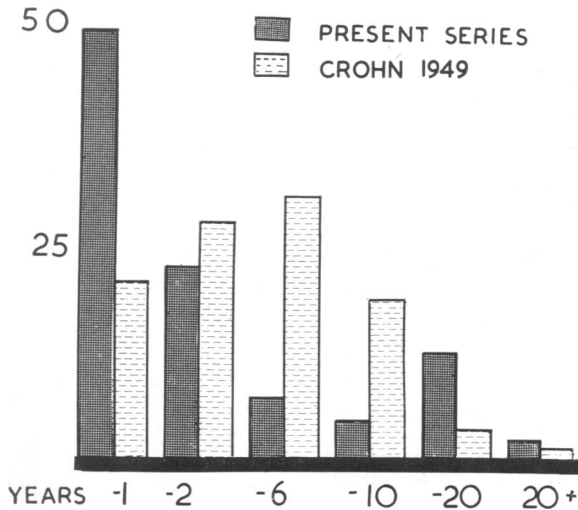


Fig. 3. Duration of symptoms prior to diagnosis, expressed as percentage of total patients studied.

patients may continue for many years with a chronic intestinal disorder without coming under more searching investigation often necessary for the uncovering of this disorder.

Course of Regional Ileitis

In attempting to make a quantitative assessment of the course of regional ileitis the inadequacy of the available data is immediately exposed.

The possibility of acute regional ileitis resolving completely is well recognised by many surgeons who refrain from resection in acute ileitis. Homb (1946) claimed that all of the 28 cases followed up, out of a total of 33, for one and a half to seven years were free from trouble, but his criteria are difficult to understand since one of the patients had undergone intestinal resection. Crohn (1949) has claimed that 25 per cent. (four cases) of his patients with acute regional ileitis have resolved completely, some of them having been followed 10 to 14 years. He quotes several other workers by whom 59 cases have been reported with 33 patients having complete healing of the lesion but he too underlines the inadequacy of the follow-up and more important the duration of the follow-up in the majority of the reports. In my series, there is only one patient followed for three years now who has given any sign of resolution. He (E.T., aged 35 years) developed subacute intestinal obstruction and was found to have six to 10 inches of his jejunum acutely involved. No excision was performed, his symptoms subsided following laparotomy and to date he has had no further trouble and radiologically he appears to be normal.

There is evidence that even cases of chronic regional ileitis may resolve completely as is well exemplified by the reports of Borgen (1954) and others, though such resolution has not been seen in this series with one doubtful exception. It must be stated too that the claims in some reports must be regarded as of doubtful validity.

The second possibility that the disease may remain stationary has great importance when considering treatment, though the number of reports of such lesions are few. Cutler (1939) has reported one such case in whom an extensive stenosing lesion remained stationary for 10 years. Kiefer and his colleagues (1950) found that five out of 24 localised lesions remained stationary for five to 11 years and six out of nine extensive lesions for periods of three to nine years. In this series there are seven patients in whom no operation has been carried out. One has died, and two are under therapy with corticoids. The remaining four patients have been followed in relatively good health for two, eight, 10 and 12 years respectively (Fig. 4, see also Cooke (1951) Fig. 194).

The third possibility, progression and recurrence, is the commonest result. Many of the earlier reports and not a few of the more recent reports on the incidence of recurrence following operation have been bedevilled by inadequate periods of follow-up or differing criteria of recurrence. For example, Garlock, Crohn, Klein and Yarnis (1951) reported an overall recurrence rate of 22·8 per cent. in a series of 126 patients which Bockus (1951) in the subsequent discussion challenged

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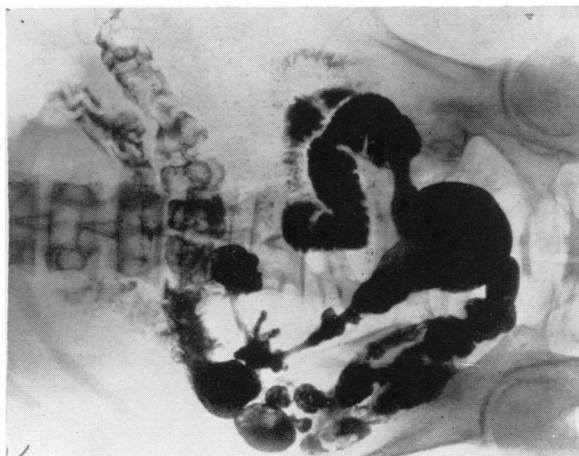


Fig. 4. X-ray showing extent of the involvement of the ileum; relatively unchanged after 12 years (c.f. Cooke, 1951, Fig. 194).

and interpreted the figures as being nearer 50 per cent. Garlock also noted that "a not insignificant group of their patients died years later of intestinal obstruction due to mechanical causes and that they did not believe that this late obstruction was any more frequent in this group than in other patients who had undergone an abdominal operation." However, the Boston and Philadelphia schools take a somewhat more pessimistic view with a recurrence rate around 50 per cent. for varying periods of follow-up as opposed to Crohn's claim to an 80 per cent. cure rate with surgery (1949). The most impressive series from which it is possible to derive quantitative data comes from the Mayo Clinic (1954). It will be seen that the recurrence rate at two, five, 10 and 15 years from operation in a group of 270 patients was 37, 50, 68 and 80 per cent. respectively. The recurrence rate for this series calculated on the same basis for two, five and 10 years was 45, 68 and 78 per cent. respectively. The trend is the same and the values are, I think, comparable. Any increase in the recurrence rate in this series may well be due to the fact that 60 of the 90 patients have been X-rayed within the last eight months and a small group has been having routine re-X-rays every 12 to 18 months (Fig. 5), and such asymptomatic recurrences as this have been included.

Another slant on the recurrence rate is given by the number of operations performed on the 83 patients so treated. One hundred and fifty-three operations have been performed, 42 patients having had only one operation, 22 two operations, 12 three operations, four four, one five and one eight operations on their intestines. Such a high recurrence rate can be criticised on the ground that more difficult cases are likely

to accrue at a teaching hospital and includes patients whose first operation may have been done at another hospital. Similar criticisms may perhaps be levelled at the figures from the Mayo Clinic.

The majority of recurrences take place within the first two years after operation but periods of up to 20 years may occur. The longest in this series was 10 years. Some idea of the prognosis in this respect may be gained from a rearrangement of the data from the Mayo Clinic (Van Patter *et al.* (1954)) from which it appears that 13 per cent. of those free of recurrence, 10 years after operation, develop trouble during the next five years. Kiefer (1950) has considered that the older the patient or lesion, the less likely was a recurrence. It is doubtful, however, whether there is adequate data to verify this though it does appear to be likely.

Some consideration must also be paid to the type of operation for it is obviously possible that the high rate of recurrence was due to faulty



Fig. 5. X-ray showing recurrence at site of ileo-colic anastomosis. Asymptomatic.

surgery. Indeed, the literature contains many articles extolling the virtues of total excision, partial excision and other types of palliative operation in preventing recurrences. The analysis carried out by the Mayo workers shows quite clearly that there is no essential difference. In this series, numbers are insufficient to give such a clear cut answer though in analysing the types of operation carried out, all seem to be equally liable to be followed by recurrence.

Mortality

In this group, 14 patients have died. One died of a carcinoma of the pancreas in a mental hospital 30 years after the onset of his disorder, 10 years after his last complication. One died of the steady progress of her disorder over 17 years also in a mental hospital, six died of post-operative complications, one of pulmonary tuberculosis, two of severe malnutrition and three of the steady progress of the disorder within three years of the onset. Of the surviving patients, only nine can be said to be physically incapacitated at this moment, including two under treatment for tuberculosis and three who have only recently been operated upon. It is, however, difficult to make an accurate assessment of the disabilities for the majority suffer with colics and attacks of diarrhoea which do not prevent them earning their living or running a household. Some idea of the extent of the disability may be gained from perusal of the description given by one of this group in the series "Disabilities" published in the *Lancet* a few years ago (1952). The relatively low rate of invalidism is indeed surprising, for 76 patients have existed for 531 patient years, an average of seven years since the diagnosis of the disease or their first operation.

Familial Incidence

The disease occurred in a brother and sister and also in two brothers in this series as well as one instance occurring in the son of a man with idiopathic steatorrhoea. Crohn (1949) has, of course, stressed the familial aspect which to me appears significant though Felsen (1955) would explain such findings as being due to a past exposure to the same infective organism rather than to any familial predilection.

The various functional disabilities may now be separately considered.

ABSORPTIVE FUNCTION OF THE GUT

Steatorrhoea

A ready way of checking the absorptive power of the gut is to measure the amount of fat in the faeces. The healthy intestine is able to absorb large amounts of fat up to 150 gms. daily without more than four to five grammes appearing in the stools. On average fat intakes of 80 to 100 gms. daily, relatively long lengths of bowel are not missed if the bowel prior to resection had been otherwise normal and there are a number of reports of lengths of intestine up to 50 per cent. of the total length being resected

for volvulus or mesenteric embolus without serious impairment of absorption taking place (Althausen *et al.* (1949), Prioleau (1944) and Weckesser *et al.* (1951)).

In this group, steatorrhoea was present in 45 of the 57 patients in whom this aspect was investigated. Twenty-one of these patients were studied prior to operation. Nine had no steatorrhoea and in one of these, at least five foot of small intestine was resected without impairing the ability of the patient to absorb fat. In the patients not operated upon with involvement of the jejunum and upper ileum, steatorrhoea was invariable. In the table below is shown the recurrence rate seen in those with and without steatorrhoea prior to operation together with the mean duration that the patients have been followed. The two groups give significantly different results. It suggests to me that the steatorrhoea is an indication of an extensive functional derangement of the intestine and that this may not be evident macroscopically at the time of operation. In patients who have undergone operation, the finding of steatorrhoea does not necessarily indicate extensive recurrence for a blind loop, a by-passed but not excluded segment of gut and certain types of internal fistulation will all give rise to steatorrhoea and their correction may result in some cases in the restoration of normal fat excretion.

FAECAL FAT EXCRETION PRIOR TO OPERATION

	No.	Mean Duration Follow Up (years)	Recurrences	Dead
Normal	9	4.2	1	0
Abnormal	12	3.6	7	4

Water

The occurrence of steatorrhoea is not synonymous with diarrhoea nor is the occurrence of diarrhoea necessarily accompanied by steatorrhoea. In those patients troubled by diarrhoea alone, purely mechanical factors should be suspected such as bands causing intermittent obstruction or involvement by fistulation or adhesions affecting the sigmoid colon.

Electrolyte Depletion

Any condition which is associated with steatorrhoea or diarrhoea will tend to lose excess electrolytes in the stools and of particular importance is the chronic loss of potassium which over long periods of time may lead to great depletion of the body stores of this electrolyte. Should anorexia and high fevers be present also, then these are additional factors for depletion. The actual body store can be estimated by radioactive K. The degree to which stores of body potassium can be depleted have been reported elsewhere (Blainey, Cooke, Quinton and Scott (1954)).

In three recent patients, in whom low serum values were not present and who had not lost much weight, the total exchangeable potassium was 1,500

to 1,700 m.eq. as opposed to mean values of 2,300 to 2,500 m.eq. In severe malnutrition, these values may fall as low as 500 m.eq. or a sixth of normal values. There is no convenient way determining this potassium loss quickly but the presence of low serum potassium (less than 3.4 m.eq. per litre) indicates clearly the presence of depletion. Low serum values have been noted in 16 of the 90 patients despite the fact that in the earlier part of the series these estimations were not carried out. In the face of potassium depletion, the body finds it difficult to maintain nitrogenous equilibrium and normal muscle mass. Potassium deficiency is, therefore, a factor which must be considered in explaining the weight loss shown by so many of these patients. This can sometimes be demonstrated quite dramatically as in a patient who over a period of 18 months lost weight and regained it in two months and in whom the only change in the therapy was the addition of intensive potassium administration. At the same time it must be pointed out that unless an adequate intake of protein is provided as well, it is unlikely that muscle mass will be quickly restored just as increased protein intake alone will not be as effective as with the addition of potassium therapy.

Beyond the part potassium plays in weight loss, a common complaint in most patients is general lassitude and muscle weakness. A more important manifestation is the effect on the intestine in producing distension and atony. This may well be one of the factors leading to obstruction in those cases with relatively short areas of stenosis, the progressive atony and lack of tone causing the gut proximal to the lesion to become more and more distended until the intestinal contents are no longer able to be propelled through the affected loop, even though the normal and electrolytically replete intestine may have been doing this effectively. This physiological ileus or atony is now well recognised in patients with steatorrhoea (Glazer and Adlersberg (1953)) who have no actual mechanical narrowing in their intestine and must be more seriously considered in the patients with regional ileitis. In this series there have been six post-operative deaths and in retrospect since they all occurred over eight years ago, it seems certain that they all were electrolytically depleted and that this factor was mainly responsible for their deaths. One can only add that recognition and treatment of this depletion has enabled extensive resections to be undertaken with virtually no post-operative morbidity and no ileus. The third manifestation that should be considered is uncommon but important and that is the production of mental symptoms. The patient who has already been depicted with the severe weight loss was confused and had not been allowed out by herself for 12 months. She was forgetful and indeed had had complete amnesia of the first few days of her last hospital admission. These symptoms all cleared up and for the past five years she has been regularly travelling 20 miles on her own to attend the follow-up clinic and running her own home. A second patient, E.H., was not so easy to control and was admitted mildly confused on a number of occasions

readily responding to more intensive therapy. She was, however, admitted to another general hospital where she was regarded as completely psychotic and transferred to a mental hospital. There her diarrhoea suddenly stopped and within 14 days she was completely back to her normal mental state. A third patient, D.P., was admitted on two occasions to a mental hospital following a relapse of her diarrhoea. It is not possible to say that this was the result of K depletion but her subsequent course is strongly suggestive that this was the case.

Protein Depletion

In a number of chronic intestinal disorders, it has been noted that there may be an increased loss of nitrogen in the faeces (Peters and Van Slyke (1946)). This is certainly common in chronic regional ileitis where the daily faecal loss may average as much as 4 gms. per day. The cause for this increased loss varies. Where there is an increased excretion of fat, then there is invariably an increased faecal nitrogen, the reason for which remains obscure. Faecal nitrogen is also high where there is excessive intestinal ulceration or intestinal fistulae and in such cases the stool fat will not necessarily be greatly increased.

It is possible that this tendency for increased nitrogen excretion in the stools may be one of the factors in producing low serum proteins which in this group at any rate appear to be generally lower than for example, a comparable series of patients with idiopathic steatorrhoea and a group of post-gastrectomy cases. In checking the serum proteins it was somewhat surprising to find that no fewer than 19 had serum albumin levels of less than 3.5 gms. per 100 ml. and in 16 of these it was less than 3.0 gms. It must be admitted that 8 of these 19 patients died, though they did not represent the most severe depletions. Low serum values did not persist with treatment and except in the fatal cases were rapidly restored to normal values. The other factor is the excess utilisation of body protein when fat absorption is grossly disturbed. With low serum protein values and a chronic intestinal disorder, it might be expected that evidence of liver disease might be found. It was, therefore, somewhat unexpected to find no evidence of this as assessed by routine flocculation tests and the presence of hepatomegaly and splenomegaly. This contrasted very markedly with the series of patients with non-specific entero-colitis in whom there was a high incidence of such disorders (Cooke and Brooke (1955)).

Anaemia

The majority of patients had no anaemia as has been pointed out by Crohn (1949). This correlated well with the relative rarity of positive occult blood tests in the stools. Only a small number had a simple iron deficiency anaemia. Eighteen patients or 20 per cent. of the series had a macrocytic anaemia at some time though often it was not of severe degree. Nevertheless, in nine it was sufficiently severe to need prolonged or

permanent therapy with folic acid or vitamin B.12. Most authorities consider that macrocytic anaemia is rare in this disorder but the presence of macrocytosis will readily be detected by the more frequent examination of the peripheral blood films and determination of the mean cell volume, as has been also pointed out by the Mayo workers (Van Patter *et al.* (1954)). In none of the patients in whom a test meal was performed was there absence of free hydrochloric acid.

Other Nutritional Deficiencies

As evidence of a systemic disturbance of unknown causation, finger clubbing was present in 48 patients of this group, a considerably higher proportion than has been noted previously. Glossitis was noted in 34 patients, at times being very severe and not necessarily being associated with an exacerbation of diarrhoea. Two patients who died with severe malnutrition developed skin lesions highly suggestive of pellagra together with marked mental confusion. Three others had "pellagroid" skin rashes, i.e., pavement epithelium, dark brown pigmentation affecting the face, neck, extensor surfaces of the arms similar to the rashes seen in many chronic nutritional disorders. There was no case of evident beriberi, peripheral neuritis or cord involvement, though such cases may occur. There was no particular body build to be noted in this group but the onset of the disorder before puberty did appear to exert a profound depressent effect upon general growth (Alvarez (1945), Van Patter *et al.* (1954)). For example, a 17 year old boy with at least a seven year history and involvement of only seven inches of terminal ileum but with fistulation to the sigmoid, prior to operation weighed only 86 lbs. and had no pubic hair. He had no steatorrhoea and it is therefore of interest to note that now, two and a half years later, he has been six months in the Army, successfully passed through a battle course and weighs 155 lbs.

Mental Changes

Little comment has been made upon the incidence of mental disorder in association with regional ileitis. In this series, apart from the two patients that had mild mental confusion associated with pellagra, two patients have died in a mental hospital, one after several admissions and the other already mentioned in connection with K depletion. A third has been a certified inmate for the past four years. A fourth already mentioned has had two admissions for lengthy periods, whilst a fifth has needed electro-convulsive therapy whilst under A.C.T.H. treatment. There was no autopsy on either of the two fatal cases but in one there had been radiological evidence of a by-passed and partially excluded loop as was also the case in two of the other deranged patients. The mental complication of A.C.T.H. therapy may perhaps be dismissed from further consideration as evidence on aetiology in such complications is insufficient even to begin to explain such psychotic episodes (Quarton, Clark, Cobb and Bauer (1955)). In the literature, it is a little difficult to

sort out whether the mental disorder preceded the intestinal upset or not. Stewart (1949) held that psychiatric factors were present in 20 out of the 27 patients examined. Crohn (1949) admits that 10 of his 222 patients needed psychiatric treatment. One of Blackburn's (Blackburn, Hadfield and Hunt (1939)) 22 patients was suffering from a true psychosis whilst four others were referred for psychiatric opinion. Eleven of the 86 patients reviewed by Rappaport and his colleagues (Rappaport, Burgoyne and Smetana (1952)) needed psychiatric consultation for mental symptoms. The Mayo report (Van Patter *et al.* (1954)) makes no specific mention of the incidence though from the text it is apparent that some of the series were in mental institutions. It is to be hoped that more study will be devoted to this possible association between regional ileitis and mental disorder.

OTHER ASSOCIATED DISEASES

Tuberculosis

Three patients have had pulmonary tuberculosis. In two of them, the pulmonary disease developed some time after the appearance of regional ileitis whilst in the third two conditions were diagnosed at approximately the same time. This incidence of 3.3 per cent. was approximately the same as the 5 per cent. found in 100 patients with idiopathic steatorrhoea (Cooke, Peeney and Hawkins (1953)) and 3 per cent. in patients following gastrectomy (Thorne and Brookes (1955)).

Peptic Ulceration

An unexpected finding was the high incidence of peptic ulceration. Ten patients had radiological evidence of duodenal ulceration and one of a gastric ulcer. In the two patients who underwent gastrectomy, there was no evidence of Crohn's disease in either the stomach ulcer or the duodenal ulcer. Besides these 11, one patient further underwent gastrectomy for stomach symptoms in whom the histological findings were those of Crohn's disease. According to Van Patter *et al.* (1954) the incidence of peptic ulceration in their series of 600 cases was 4 per cent., an incidence which might be regarded as being within normal limits. It is of interest that Halsted *et al.* (1954) found five duodenal ulcers in 40 consecutive patients with ulcerative colitis.

Disease v. Surgery in the Production of these Syndromes

It can be quite briefly stated that all these defects can be brought about by the disease itself, and, therefore, no further time be devoted to it. Resection of long lengths of intestine has already been mentioned and I will only emphasize that when long lengths need to be excised it is probable, though not certain, that much of the remainder of the intestine is involved and severe nutritional difficulties are likely to ensue. As an exception, this patient has had six or eight feet of her intestine removed, and the relative short amount remaining can be gathered from Fig. 6. Nevertheless, her steatorrhoea is minimal and her health satisfactory except for five or

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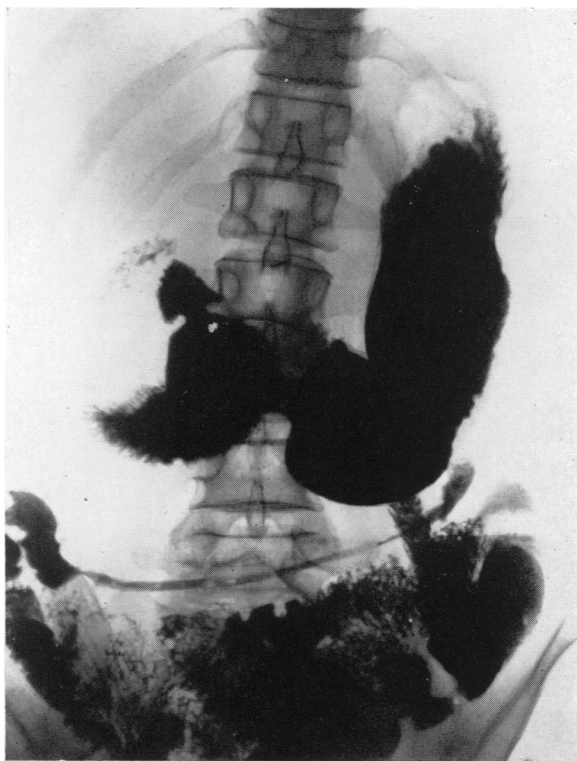


Fig. 6. X-ray taken within 15 minutes of ingestion of barium, showing the rapid transit and barium already in the colon.

six loose stools daily. The remaining small intestine must be functionally good. By-passing with partial exclusion of the involved gut has been extensively used and indeed is sometimes the only surgically feasible course. Often this by-passed loop will give no trouble but its presence is a potential source of danger, as many workers have emphasized (Barker and Hummel (1939), Cameron, Watson and Witts (1949)). In producing anaemia, for example, a woman now aged 60 presented nine years ago with a severe macrocytic anaemia and intermittent diarrhoea. Seven years previously she had undergone a by-passing operation for terminal ileitis. Since that date she has had no further trouble from abdominal pain or obstructive symptoms though the last nine years she has had continuous treatment for her anaemia and steatorrhoea. G.P., a woman aged 51, underwent ileotransverse colostomy with partial exclusion at the age of 44. Since this time, she has had no further intestinal upsets and has maintained her weight and blood count. For the past four years, however, she has been a certified patient in a mental hospital. D.P. is another patient

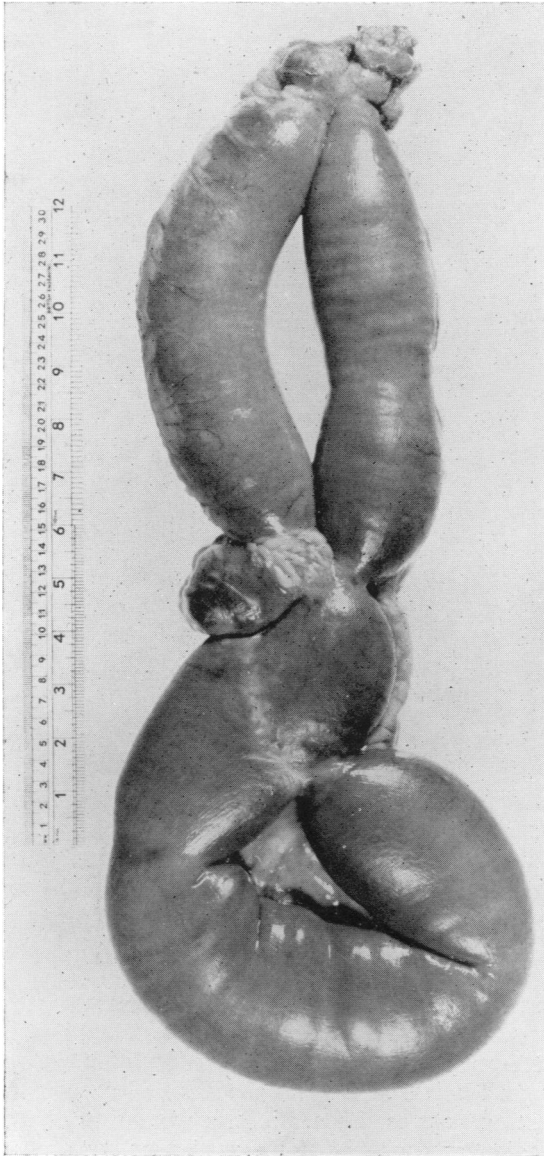


Fig. 7. Showing the excised intestine which had been partially excluded with resultant distension and elongation.

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already referred to who has had two admissions to a mental hospital whose intestine is depicted in Fig. 7. This was satisfactorily excised. There is now good evidence to ascribe responsibility for anaemia and other nutritional defects to such partially by-passed loops. Our own experience in two patients with a macrocytic anaemia and steatorrhoea following such an operation for obstruction after appendectomy has shown that removal of the by-passed loop has led to complete restoration of the blood count and disappearance of the steatorrhoea. Relationship of such loops to mental disorder, however, has not received attention, but our own as yet unpublished observations on neuropathological changes in chronic intestinal disorders lead me to believe that there may well be a connection between the loops and the psychotic episodes. In addition to these major manifestations, patients with such loops or blind loops (Fig. 8) following on a side to side anastomosis are liable to sudden explosive attacks of diarrhoea, attacks of weakness and palpitation analogous to those seen in the dumping syndrome and probably brought about by a similar mechanism, the rapid filling with fluid and distension usually in some relationship to meals. If these possibilities exist, and they have been known since the experiments of Cannon and Murphy in 1906, then the finding of such arrangements of the intestines

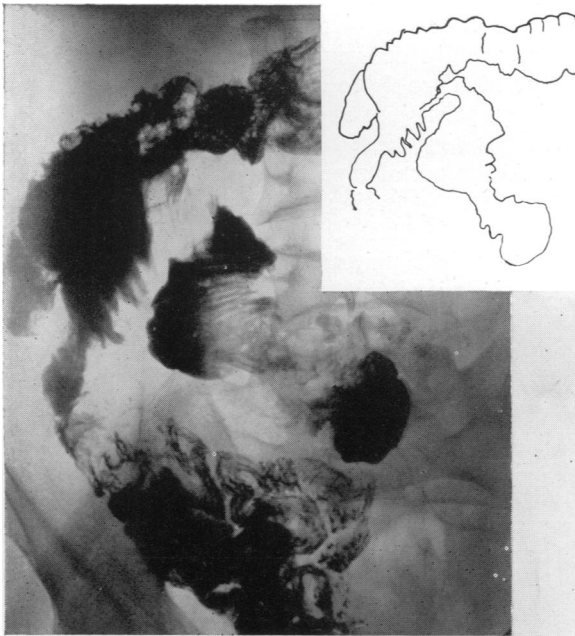


Fig. 8. The late result of a side to side anastomosis of ileum to colon, showing secondary distension and elongation of distal portion of ileum.

should warrant serious consideration for further surgery. Furthermore, since these manifestations usually arise many years later, any patient who has had ileotransverse colostomy with partial exclusion or lateral anastomoses must be kept under regular medical supervision.

Treatment

From consideration of the various factors and clinical observations we have considered certain points emerge. Thus the course of the disorder in any given patient must be regarded as relatively unpredictable, and the period during which extension or recrudescence of the disorder may take place is at least 15 years in span. I would, therefore, lay down the first principle in the treatment of the disorder, namely, that once the disorder has been diagnosed, the patient must be kept under regular medical supervision. The second point is that it is clear that some patients may continue to lead a useful life even though they have long areas of intestine involved as I have already illustrated.

Kiefer (1950) has put forth some good evidence in support of his plea to regard this condition as primarily for medical treatment. It also appears to be probable that the longer the condition has existed the more likely it is to be predominantly sclerosing rather than reactive and infiltrating. It seems to me, therefore, that the basic background for treatment lies in an adequate period of rest, preferably with a sanatorium type of régime with supportive measures directed towards counteracting anaemia, protein deficiency or electrolyte depletion. This can best be done by a high protein low fat diet with due regard to any question of milk sensitivity, potassium supplements, Vitamin B₁₂ injections and folic acid. The question must be answered: Has corticoid therapy any part to play? A number of reports have appeared on this point; some need not be considered appearing as they did in the early days of corticoid therapy when doses of insufficient size or for insufficient length of time were administered. The majority of reports, however, have recorded varying results (Sauer *et al.* (1952), Gray *et al.* (1952), Kirsner *et al.* (1952) and Stanley *et al.* (1951)) though Machella (1951) has claimed good results in 14 out of 15 patients treated with cortisone. Since one of the most constant effects of cortisone and A.C.T.H. upon the intestinal tract is an increase in water reabsorption it is rare for a patient with a debilitating diarrhoea not to gain some temporary benefit from its administration. In this series, seven patients have received this treatment. One gained temporary and symptomatic improvement before coming to surgery in a somewhat improved nutritional state with a recurrence of her obstructive symptoms. The second had a short period of therapy following laparotomy but the result must be considered doubtful, although she is now in excellent health three years after her operation even although her radiological pictures have not changed. The third patient had some transient benefit before having further surgery and one patient has had considerable improvement over the past 12 months on a maintenance dose of cortisone.

The most striking results, however, have been seen in three children, two of whom are now back at school taking a daily administered dose of Acthar gel. These two had both undergone resection and ileotransverse anastomoses.

X-ray Therapy

If corticoids suppress the exudative phases X-ray therapy would appear to facilitate the fibrotic phase. Bargaen (1950 and 1954) has treated 50 patients with such therapy and has claimed some success as did Kiefer (1950) rather cautiously in seven patients so treated. However, Bargaen (Van Patter *et al.* (1954)) commented that many of the patients came subsequently to operation for obstructive symptoms. In this series, two patients have developed radiological and pathological evidence of regional ileitis following deep X-ray therapy for carcinoma of the uterus and for carcinoma of the bladder. With the increasing knowledge of the destructive powers of radiation therapy on the intestinal mucosa, I doubt whether radiation therapy has any place in the treatment of regional ileitis.

Surgery

The place and indications for surgery are becoming clearer, severe obstructive symptoms, intestinal fistulae, distended loops and failure to thrive after a long period of medical treatment. Since the majority of patients come to surgery, the ideal time to operate is when the condition has localised and fibrosed in as small an area as possible, clearly an optimistic ideal but one which should be aimed at since the general tendency is towards fibrosis and localisation, if the tissues are given the chance. It would seem wrong to me, therefore, that extensive surgery should be attempted to eradicate the disorder for there is no evidence that such extensive excisions are any more successful in avoiding recurrences but rather that as little as possible should be excised to allow such bowel as can to resolve completely and resume its role in maintaining the nutrition of the body.

Mesenteric Lymphadenitis

Non-specific mesenteric lymphadenitis has its greatest incidence in childhood and the relationship between this and ileitis has often been propounded though denied by many. It is, however, significant that the age incidence of mesenteric lymphadenitis is only slightly earlier than that in regional ileitis. Since the glands may undergo necrosis and actual pus formation it might be expected that some would undergo calcification. Warren and Sommers (1954), however, in their series of 120 pathological examinations encountered only three calcified glands. Rappaport *et al.* (1952) had similar results but I find this difficult to accept, for reviewing the radiological findings in this group the incidence of calcification in presumed mesenteric glands was slightly less than 50 per cent. though not as great as in a control group of unspecified X-rays taken for intravenous pyelograms. From other studies we have undertaken on calcified glands,

we believe that calcification of the mesenteric glands is only rarely tuberculous. It may well be that the reaction of the mesenteric glands in these young patients is in many instances the manifestation of the same process that gives rise to regional ileitis. Kiefer (1950) has commented that the association of regional ileitis and ulcerative colitis is more than that which can be regarded as coincidental. Felsen also holds the view that the two conditions have essentially the same aetiological basis. Warren and Sommers (1954), however, consider that the two conditions have an entirely different aetiology and pathology, a view with which I agree. The colon is liable to react to a number of stimuli by producing blood and mucous and eventually atrophy and secondary ulceration. One of the most potent stimuli to this reaction is the faeces containing abnormal products of excretion or malabsorption in the small intestine. My colleague, Mr. Brooke, and I (1955) have put forward the suggestion that many of the right-sided colitis patients, other than those with regional ileitis, are examples of nonspecific enterocolitis, the colonic lesion being secondary to the steatorrhoea or creatorrhoea of the damaged small intestine. Though the jejunal mucosa may show numerous small ulcers (Cooke and Brooke (1955)), the external appearances of the bowel, however, show little evidence of abnormality and may easily be missed. The radiological appearances have been published elsewhere (Cooke and Brooke (1955)). As yet none of the 20 patients has developed a stenosing lesion which would liken the condition to regional ileitis.

Intestinal lipodystrophy or Whipple's disease has provided further interest and difficulties in diagnosis and pathological interpretation. Macroscopically the small intestine in the early stages may provide many similarities. Fig. 9 illustrates the radiographs of a girl with diffuse jejuno-ileitis and that of a 41-year-old man with intestinal lipodystrophy. At operation both had minimal oedematous thickening of the jejunum and ileum and moderate enlargement of the mesenteric glands. The histological changes in the glands were those of giant cell system in the first patient and changes characteristic of Whipples in the second. Two years later this girl had developed extensive stenosing lesions of chronic regional ileitis. In intestinal lipodystrophy a somewhat comparable radiological pattern to the later stages of regional ileitis occurs as can be seen in this patient in whom a confident diagnosis of regional ileitis was made by myself and my radiological colleague (Fig. 10). Subsequent post-mortem examination revealed intestinal ulceration but no stenosis, the radiological appearances being produced by the shortened fat-laden mesentery and the histological findings were those of intestinal lipodystrophy. A study of these and eight other patients with Whipple's disease lends support to the suggestion that the disorder may be the end result of some type of jejuno-ileitis and bear a relationship to regional ileitis as was suggested by Avery Jones and Paulley (1949).

According to Boels and Tverdy (1950), the histological study of intestines of patients with idiopathic steatorrhoea usually shows some

HUNTERIAN LECTURE

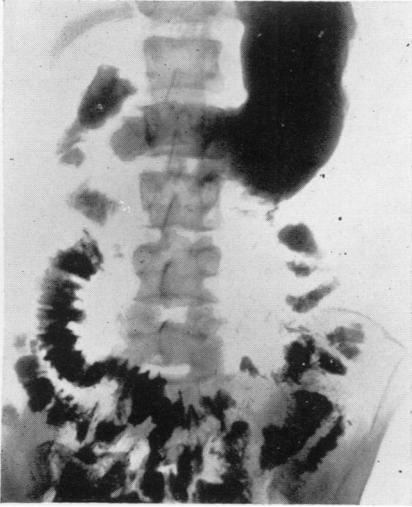


Fig. 9a. Diffuse involvement of jejunum and ileum in early stages of regional ileitis.

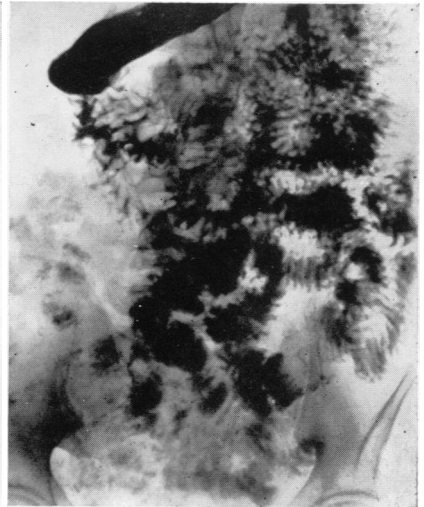


Fig. 9b. A diffuse involvement of jejunum and ileum in intestinal lipodystrophy.



Fig. 10. X-ray of patient with intestinal lipodystrophy simulating regional ileitis.

abnormality and our own observation supports this. If to this fact is added the important observation that some of these patients may be cured by removal of gluten from the diet (Van de Kamer and Weijers (1953)), then it is not difficult to visualise that other substances might produce somewhat different reactions in the intestinal wall and mesenteric glands to produce what is now known as intestinal lipodystrophy, non-specific enterocolitis or regional ileitis. Since many of the patients with regional ileitis have histories of diarrhoea for 10 to 20 years and diagnosis can only be made radiologically or by inspection, the possibility that some may have been initially idiopathic steatorrhoea cannot be excluded.

CONCLUSIONS

To what conclusion does all this lead? The nutritional and metabolic factors in the treatment of the disorder as we know it are clear but in the aetiology are still completely speculative. The features that appear to me to be worthy of emphasis are the age incidence, the self-limiting nature of the disease given the proviso that supportive therapy can be maintained sufficiently long to allow this to take place; the frequency of a generalised intestinal involvement as shown by the occurrence of steatorrhoea; the occurrence of familial cases and the similarities with certain other types of disorders as shown by the difficulty there may be in deciding the clinicopathological diagnosis.

Infection in terms of a definite organism must, I think, be ruled out. Tuberculosis no longer is a contender, though some will develop phthisis as a complication of malnutrition. Lymphatic blockage is unlikely to play a primary part though it may produce secondary effects. The pathological changes which I have not dealt with are those of an exudative reaction which in disease in general is commonest at the ages at which the onset of regional ileitis is most frequent. There is much in Barger's contention (Van Patter *et al.* (1954)) that the agent for producing this reaction is to be found in the faecal stream. The work of Chess and his colleagues (1950) would appear to me to provide a clue as to how these reactions might come about, the piezoelectric theory in which they showed that an absorbed agent—in their experiments this was fine sand or glass—would, following a conditioning factor, in their experiments—this was an induced bacteraemia—give rise to changes simulating regional ileitis. Using this idea, it would appear to me that Barger's faecal agent might be the products of either protein or fat digests or some dietary product analogous to gluten, but the resultant reaction would depend upon whether the intestinal cell was normal, in which case normal reactions would continue, or abnormal, when the characteristic reactions would take place. The disturbance of normal cellular function might well depend upon a number of factors, such as recent infection, constitutional deficiency or ischaemia following trauma or local infection. Should this be so, then no single factor will be responsible so that the clinicopatho-

logical picture of regional ileitis must be the end result of a number of differing factors.

Finally, what lines should future research take? In the field more careful factual data on the life history of the disorder is required, and in the laboratory a closer investigation of the enzymatic changes occurring in the intestinal wall using the modern techniques of histochemistry and enzymology which in the clinic can be made easier by more frequent intestinal biopsy in patients and experimentally by an extension of the feeding experiments initiated but not further pursued by Chess and his colleagues.

My lecture must finish by concluding that few if any questions have as yet been solved and express my hope that co-ordinated research may resolve the unanswered problems in the future.

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RESTORATION AND REBUILDING OF THE COLLEGE

THE FRONT ELEVATION of the Nuffield College is now assuming an interesting aspect with its mixture of stone and brick. The stonework extends a little above the height of the ground floor, above which the wall consists of bricks relieved by a certain amount of stone, including the surrounds of the windows, and these latter are in position on the first floor. Deliveries of stone to the site have not kept pace with requirements, with the consequence that the present height of the front wall only reaches the second floor, whereas at the back where only bricks are concerned, it is two floors higher. There is a corresponding effect on internal partitions, which are being erected at the back of the building as high as the mezzanine and third floors, whereas at the front they only exist in the basement. The concrete floor slabs and those of the roof are virtually completed.

The third phase of building began on Monday, 29th August, when the contractors, Messrs. Higgs & Hill, took possession of the site and began their preparations. The amount of the tender, £325,993, reflects a disturbing increase in building costs since a provisional figure was assessed a few years ago, and leaves the Council with an additional sum of £150,000 to raise for this part of the building, with a further sum yet to be found for the final phase. At any rate the competition was keen between the six firms who tendered, the difference between the highest and lowest being £25,791 and between the two lowest only £2,122. Messrs. Higgs & Hill have carried out many building operations for the College in the past, including the erection of Rooms I and II of the Museum, the Erasmus Wilson end of the Library and the fourth and fifth floors in the 1890s, the reconstruction of the upper floors to form the Bernhard Baron Laboratories in 1937-38, and a variety of lesser works at various dates.

DONATIONS

General Funds :—

- | | | | | | |
|------|------|-----|----|----|---|
| £200 | 0s. | 0d. | .. | .. | Mr. Antenor Patino of Paris (<i>from funds put at the disposal of Messrs. Gordon, Dadds & Co. for distribution amongst British Charities</i>) |
| £52 | 10s. | 0d. | .. | .. | Mr. A. B. May |