JEJUNAL DIVERTICULOSIS, MEGALOBlastic ANAEMIA AND PARTIAL GASTRIC ATROPHY

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DIVERTICULOSIS of the jejunum was first described by Sir Astley Cooper (1803-07). The condition is uncommon: Edwards (1939) estimated its incidence as 0.3% in 2,820 autopsies while Ritvo and Votta (1946) gave an incidence of 0.5% in small bowel radiographic studies. The association of diverticulosis with pernicious anaemia was recorded by Taylor (1930) whose patient also had a gastroenterostomy. In 1933 Harvey and Murphy reported a patient with extensive jejunal diverticulosis, diarrhoea and pernicious anaemia without achlorhydria. Badenoch and Bedford (1954), Badenoch, Bedford and Evans (1955) and Dick (1955) reported further cases and the possible relationship between diverticulosis and megaloblastic anaemia was considered. Crawford and Freeman (1961) reviewed the literature in which they found twenty-three cases of jejunal diverticulosis and megaloblastic anaemia, added a case of their own but omitted the case of Harvey and Murphy (1933). Of these, eleven had achlorhydria, or nearly complete achlorhydria, and in two cases no comment had been made of gastric acidity. Schiffer, Faloon, Chodos and Lozner (1962) reported a case with jejunal biopsy findings. Cooke, Cox, Fone, Meynell and Caddie (1963) again reviewed the literature, and in an excellent study reported on the clinical and metabolic effects in thirty-three cases of jejunal diverticulosis. Ten of these had megaloblastic anaemia whilst four others merely had low serum vitamin B₁₂ levels. Of these fourteen cases, three resembled pernicious anaemia in their response to intrinsic factor administration, but one case required both intrinsic factor and tetracycline to restore Vitamin B₁₂ absorption to normal.

We present a similar case showing massive jejunal diverticulosis, reduced gastric acidity and a partial deficiency of intrinsic factor.

Case Report

A man, aged 61, was admitted to Edgware General Hospital in March 1957 with a history of five attacks of momentary loss of consciousness in the previous four years, recent onset of lethargy and tiredness, pins and needles in the hands and feet and loose bowel motions two or three times a day for ten to fifteen years. The motions were difficult to flush from the toilet. He had a productive cough and sputum for many years with attacks of winter bronchitis.

On examination he was found to be sallow and anaemic. His tongue was smooth but not sore. There was no evidence of abnormal pigmentation but some early finger clubbing was present. There were signs of chronic bronchitis and emphysema. His blood pressure was 100/60 mm. Hg. The abdomen was distended and small gut peristalsis was visible. The liver and spleen were not enlarged. No abnormality was found in the cranial nerves. There was some impairment of sensation to pin prick in both hands and feet. The tendon reflexes could just be elicited and the plantar reflexes were flexor.

Investigations. Hb. 6.5 g./100 ml.; RBC 1.6 m./cu. mm.; WBC 3,500/cu. mm. The blood film showed macrocytosis and gross poikilocytosis of the red cells; scanty nucleated red cells were present; the neutrophil nuclei were hypersegmented. A histamine test meal showed no free acid in the stomach. The bone marrow was hypercellular with megaloblastic erythropoiesis and giant metamyelocytes, typical of a well-established pernicious anaemia. Blood urea and serum electrolytes within normal limits except for the serum calcium which was 8.2 mg./100 ml. Total serum proteins 4.5 g./100 ml., with a slight increase in gamma globulin. A six-day faecal fat analysis showed an average of 6.5 g. of fat excreted in twenty-four hours; vitamin A absorption was normal.

A barium meal showed no abnormality in the stomach, but arising from the third part of the duodenum and from the upper jejunum were about a dozen large diverticula.

A diagnosis of jejunal diverticulosis associated with megaloblastic anaemia and steatorrhoea was made, and he was treated with injections of vitamin B₁₂. The initial dose was 1,000 µg., followed by 200 µg. daily for 7 days. At the end of this time a second marrow biopsy showed normoblastic erythropoiesis. He was discharged on a diet containing 50 g. of fat a day, a monthly injection of 400 µg. of vitamin B₁₂ and oral iron.

The loose stools continued to be troublesome and he was given a five month course of tetracycline, starting with 250 mg. q.i.d., later reduced to 250 mg. twice weekly, with considerable symptomatic improvement. In November 1959 it was noted that

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FIG. 1.—A plain erect film showing multiple gas-fluid levels in the diverticula.

the reflexes in the lower limbs were absent. In May 1960 folic acid 5 mg. t.i.d. was added to his treatment, but in January 1962 he continued to complain of numbness in his feet. He was referred to the Experimental Haematology Unit, St. Mary's Hospital for further studies where the presence of a mild peripheral neuropathy was confirmed.

Further Investigations: Hb. 15.8 g./100 ml., PCV 47% MCHC 34%, WBC 7,000/cu. mm., platelets 170,000/cu. mm. and reticulocytes 2.2%. The bone marrow showed normoblastic erythropoiesis and ample iron stores. Serum iron 149 μ g./100 ml., proteins 6.2 g./100 ml. (albumin 4.2 g., globulin 2.0 g.), electrolytes normal, calcium 9.1 mg./100 ml.

The following tests of intestinal absorption were undertaken: faecal fat excretion estimations showed excessive fat in the stools on an intake of 70 g. a day, the stools containing an average of 11 g. a day over one three day period, and 8.6 g. per day on a further three day estimation. When the fat intake was reduced to 20 g. per day the daily faecal fat output fell to 4.3 g. Glucose tolerance test: fasting blood sugar 75 mg., at forty five minutes 125 mg., at ninety minutes 160 mg., and at one hundred and twenty minutes 110 mg./100 ml. The D-xylose excretion test showed poor absorption; after 25 g. of D-xylose were given orally, 2.5 g. were recovered from the urine in five hours on one estimation, and 3.0 g. after a repeat examination. Folic acid absorption was normal; a 2.4 mg. oral dose produced blood levels of 82 μ g./ml. at one hour and 52 μ g./ml. at two hours. The absence of folic acid deficiency was confirmed by urinary FIGLU estimation, when a 15 g. dose of histidine produced 8 mg. of urinary FIGLU on one occasion and 15 mg. on another.

FIG. 2.—Barium meal showing a single diverticulum on the concavity of the third part of the duodenum and a group of diverticula partially filled with barium in the proximal part of the jejunum.

Absorption studies were also carried out using ^{55}Co -labelled vitamin B₁₂ (Schilling, 1953) before and after a seven day course of tetracycline. Attempts to secure adequate intrinsic factor were made by giving this, or by injection of carbachol to stimulate endogenous intrinsic factor production at the same time as giving the ^{55}Co -vitamin B₁₂ (Mollin, Booth and Baker 1957). The results (Table 1) showed that absorption increased after tetracycline and particularly so after additional intrinsic factor was given, the pattern being similar to that seen in Addisonian pernicious anaemia.

TABLE 1
PERCENTAGE OF ORAL DOSE OF ^{55}Co -VITAMIN B₁₂ RECOVERED IN URINE

Intrinsic Factor Source	Before Tetracycline	After Tetracycline
Endogenous from Carbachol stimulus	0.02%	5.0%
Exogenous: Oral intrinsic factor	0.02%	9.0%

An estimation of intrinsic factor production was performed by utilising a patient known to have pernicious anaemia on whom a Schilling test was performed, first giving ^{55}Co -vitamin B₁₂ alone, then supplemented with a preparation of hog intrinsic factor and finally with 50 ml. of gastric juice collected from our patient over a period of three days.

These results (Table 2) indicate the presence of intrinsic factor in the gastric juice, but this was not as effective in potentiating the absorption of Vitamin B₁₂ in the patient with known pernicious anaemia as was hog intrinsic factor concentrate.

FIG. 3.—Erect follow-through film, the multiple diverticula being partially filled with barium and showing layering of the contents.

TABLE 2
PERCENTAGE OF ORAL DOSE OF $^{58}\text{Co-B}_{12}$
RECOVERED IN URINE

^{58}Co -Vitamin B_{12} alone	2.0%
Added hog intrinsic factor	21.0%
Added gastric juice	12.0%

An augmented histamine test meal produced small volumes of gastric juice with no free acid on one occasion and some on another (pH 6.0). A gastric biopsy showed chronic gastritis with partial mucosal atrophy but with some chief cells and oxyntic cells present. Jejunal mucosal biopsy showed normal mucosa.

Plain radiographs of the abdomen showed a slight increase in the quantity of intestinal gas, particularly in the small intestine. In the erect position numerous short fluid levels were seen due to gas trapped in the diverticula (Fig. 1). A barium meal showed the oesophagus, stomach and duodenal cap to be normal. A solitary diverticulum was shown to arise from the concavity of the third part of the duodenum, while at the duodeno-jejunal junction a group of diverticula were seen (Fig. 2). Numerous diverticula were also seen throughout the jejunum, becoming more sparse in the ileum and entirely absent in the terminal ileum. The barium became finely flocculated in the small bowel, but erect pictures taken during the follow-through examination, clearly showed the formation of levels in the diverticula (Fig. 3). A large quantity of barium was still present in the diverticula at 6 hours, but had been entirely cleared from them at 24 hours. The initial rate of transit of barium through the small bowel was rather rapid, but some barium was still present in the large bowel at 48 hours.

The results showed that the patient had jejunal

diverticulosis with steatorrhoea and poor absorption of D-xylose. The megaloblastic anaemia resulted from inadequate absorption of vitamin B_{12} , for folic acid was shown to be neither malabsorbed nor deficient. Two factors were shown to affect vitamin B_{12} absorption in this patient: firstly malabsorption associated with the diverticulosis and corrected with tetracycline, and secondly a partial gastric atrophy with impaired production of endogenous intrinsic factor.

Discussion

Diverticula of the jejunum and ileum occur as out-pouchings on the mesenteric side of the bowel at the sites of vascular penetration. Their aetiology is uncertain but since they are found in older age groups they might be acquired. The diverticula are usually 1-3 cm. in diameter, and cases with gross diverticulosis are particularly uncommon. Small intestinal diverticula are characteristically grouped in the proximal jejunum, becoming sparser distally and are rare in the ileum. Diverticula of the oesophagus and duodenum are frequently associated (Ritvo and Votta, 1946). The radiological diagnosis of diverticula should not be difficult although cases have been misinterpreted. On the plain erect film of the abdomen the multiple fluid levels may be confused with small bowel obstruction (Johnson and Wysor, 1961; Stromme, 1956). Diverticula usually produce short isolated levels, in distinction to small bowel obstruction, where the levels are long, or obviously paired at the end of dilated loops. On barium studies the diverticula may be confused with the "clumping" seen in steatorrhoea. Use of non-flocculent barium preparations should prevent this (Laws and Pitman, 1960). An erect film taken during the follow-through examination may show the layering of barium, fluid and gas as in the present case.

Until recent years, small intestinal diverticula were thought to be symptomless, although Benson, Dixon and Waugh (1943) listed various surgical complications that could arise. The metabolic consequences of diverticulosis have only more recently been appreciated (Badenoch and Bedford 1954, Badenoch and others 1955, Dick 1955) and it appears that anaemia and steatorrhoea can occur either separately or together. (Booth 1960, Crawford and Freeman 1961). Cooke and others (1963) point out how frequently patients with this condition present with significant gastrointestinal symptoms, as well as the metabolic consequences of this disorder. The development of malabsorption appears to follow stasis in the diverticula and bacterial proliferation. No radiological criteria for stasis have been suggested although in the present case barium was cleared from the diverticula in between 6 and 24 hours. That bacteria are implicated in malabsorption is suggested from the beneficial effects of tetracycline (Dick 1955) or surgical excision, when feasible, of affected bowel (Watkinson, Leather, Harson and Dossett 1959). Other antibacterial

agents such as sulphafurazole may merely alleviate the diarrhoea without affecting the absorption defect (Halstead, Lewin and Gæsten 1956) or in the case of neomycin actually initiate a malabsorption state with changes in the intestinal mucosa. (Jacobsen, Chodos and Faloon, 1960a; Jacobsen, Prior and Faloon, 1960b). Donaldson (1962) presents evidence that the malabsorption of Vitamin B₁₂ is due to uptake of the vitamin by the proliferating organisms in the diverticula, rather than to lack of intrinsic factor, bacterial elaboration of toxins, or impaired intestinal function. However, Cooke and others (1963) suggest that intrinsic factor is normally protected in the duodenum and jejunum by the higher pH and by combination with vitamin B₁₂ to form a stable complex, but bacterial proliferation renders the jejunum more acid and thereby alters this protective mechanism. Badenoch and others (1955) showed that increasingly large doses of intrinsic factor could improve vitamin B₁₂ absorption in this condition. A possible mechanism whereby intestinal bacteria give rise to steatorrhoea is suggested by Dawson and Isselbacher (1960). They showed that the normally secreted bile salts, glycocholate and taurocholate act to promote fat absorption, but when unconjugated, as cholate and desoxycholate, they may cause mucosal damage and the last may also inhibit palmitate esterification. Since desoxycholate is a bacterial degradation product of cholate it can be seen how intestinal bacteria may be instrumental in causing steatorrhoea. Further, they point out that commercially produced bile salts frequently contain substantial amounts of the deconjugated salts, which may account for the poor results obtained when they are used therapeutically.

It is interesting to note that 11 of the 24 cases considered from the literature by Crawford and Freeman (1961) showed impaired gastric acid production, while four of the cases of Cooke and others (1963) had presumptive evidence of inadequate intrinsic factor production. The present case has evidence of partial gastric atrophy as shown by biopsy and augmented histamine test meal. Further, it was shown that although the gastric juice from this patient promoted some absorption of ⁵⁸Co-vitamin B₁₂ in a patient known to have Addisonian pernicious anaemia, it was much less effective in this than hog intrinsic factor concentrate.

Summary

A male patient who presented with anaemia, paræsthesiæ, and diarrhoea was found to be suffering from megaloblastic anaemia and jejunal diverticulosis. Further investigation also revealed a partial intrinsic factor deficiency. The clinical and radiological features of jejunal diverticulosis are reviewed and the possible mechanisms whereby small intestinal infection may give rise to malabsorption are considered. The incidence of

achlorhydria and intrinsic factor deficiency in other cases is noted.

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