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 (1934), 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; scantly 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 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
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 Hematology 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 μg./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: fecal 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 fecal 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 μg./ml. at one hour and 52 μg./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.

Absorption studies were also carried out using 58Co-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 58Co-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 anemia.

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<td><strong>PERCENTAGE OF ORAL DOSE OF</strong> 58<strong>CO-VITAMIN B12</strong> <strong>RECOVERED IN URINE</strong></td>
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<tr>
<td>Intrinsic Factor</td>
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<td>Endogenous from Carbachol stimulus</td>
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<td>Exogenous: Oral intrinsic factor</td>
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An estimation of intrinsic factor production was performed by utilising a patient known to have pernicious anemia on whom a Schilling test was performed, first giving 58Co-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 anemia as was hog intrinsic factor concentrate.
diverticulosis with steatorrhoea and poor absorption of D-xylose. The megaloblastic anaemia resulted from inadequate absorption of vitamin B₁₂, for folic acid was shown to be neither malabsorbed nor deficient. Two factors were showed to affect vitamin B₁₂ 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 Wyssor, 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 labeling 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 Gæstø 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 excessively 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 ³⁵S-Co-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, paraesthesiae, 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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