

## Co<sup>58</sup>B<sub>12</sub> absorption (hepatic surface count) after gastrectomy, ileal resection, and in coeliac disorders

D. J. FONE, W. T. COOKE, M. J. MEYNELL, AND E. L. HARRIS

*From the General Hospital, Birmingham*

**SYNOPSIS** This paper demonstrates that the hepatic surface counting technique is a reliable and satisfactory method of estimating the absorption of radioactive vitamin B<sub>12</sub>. It does not require the collection of faeces or urine and is therefore particularly useful in studying out-patients.

When Co<sup>58</sup>B<sub>12</sub> is absorbed from the intestinal tract, radioactivity accumulates in the liver, reaching its maximum in seven to 10 days and thereafter slowly declines. Glass, Boyd, Gellin, and Stephanson (1954) demonstrated that the degree of absorption of vitamin B<sub>12</sub> could be measured by scintillation counting over the surface of the liver and that hepatic surface radioactivity was a true measure of the content of radioactive B<sub>12</sub> in the liver. Baker and Mollin (1956) demonstrated good correlation between the hepatic uptake measured by direct counting over the liver and the amount of radioactive B<sub>12</sub> absorbed as estimated by the faecal excretion technique.

The method has certain practical advantages compared with the more widely used faecal (Heinle, Welch, Scharf, Meacham, and Prusoff, 1952) and urinary excretion methods (Schilling, 1953). It does not require the collection of faeces or urine and should therefore be of particular value for the investigation of out-patients, and secondly it does not require the administration of a large saturating dose of non-radioactive vitamin B<sub>12</sub> which may obscure the haematological picture and response. Despite these advantages it does not appear to have been adopted generally in Britain. The purpose of this paper is to check the validity of the technique and to assess its use in three common groups of intestinal disorders in which abnormalities of B<sub>12</sub> absorption may occur, namely, post-gastrectomy states, intestinal resection, and the coeliac group of disorders.

### METHODS

Co<sup>58</sup>-labelled vitamin B<sub>12</sub> (supplied by the Radiochemical Centre, Amersham, England) was administered orally in a dose of 0.25 to 0.50 µg. of vitamin B<sub>12</sub> containing 0.33-0.50 µc. Co<sup>58</sup>, dissolved in 20 ml. distilled water

after patients had fasted for at least 12 hours (overnight); no food or drink was allowed for the following two hours.

The technique of estimating the accumulated hepatic radioactivity was essentially similar to that described by Glass and his co-workers. The hepatic radioactivity was counted with an EKCO cylindrically collimated scintillation counter having a 1½ in. thallium-activated sodium iodide crystal. Initially, counting was performed in two or more planes over the liver surface, but it was found that the variation in counts obtained in different planes was small, and that entirely satisfactory results were obtained by counting in one only. The majority of tests were, therefore, performed with the collimator placed in contact with the skin in the anterior axillary line in the centre of the area of liver dullness. Counting was carried out for five minutes, the results obtained then being corrected for background radiation and expressed as counts per minute per 1 µc. of Co<sup>58</sup>.

The liver was counted in this manner before administration of the dose, and then again between the sixth and tenth days afterwards. Initially, two counts were made on different days in this period to ensure that the plateau had been reached; it soon became evident that a single count was quite satisfactory, and subsequently this was performed, usually on the seventh day.

When the absorption of Co<sup>58</sup>B<sub>12</sub> was found to be impaired, a second dose was given with 10 mg. of intrinsic factor concentrate (Lederle) active in pernicious anaemia in 5 to 10 mg. quantities. The hepatic surface count was then repeated seven days later. The difference between the two readings (after background corrections) was taken to represent the hepatic radioactivity resulting from increased absorption of vitamin B<sub>12</sub> as a result of the addition of intrinsic factor. On each occasion the radioactivity over the lower abdomen (just below the umbilicus) was also measured. If the counts in this region exceeded 50% of the liver count, the estimation was repeated after an interval of at least three days. This was, however, only occasionally necessary.

Serum levels of vitamin B<sub>12</sub> were estimated by the method of Meynell, Cooke, Cox, and Gaddie (1957), which gives a normal range of 105 to 672 μμg. per ml. with a mean normal concentration of 281 μμg. per ml.

The faecal excretion of the administered Co<sup>58</sup>B<sub>12</sub> was estimated by counting the radioactivity appearing in the faeces daily until none was present on each of two consecutive days. The total faecal radioactivity was expressed as a percentage of the dose (after background corrections) obtained in the same counter.

**RESULTS**

**CORRELATION OF HEPATIC SURFACE COUNT WITH FAECAL EXCRETION OF Co<sup>58</sup>B<sub>12</sub>**

On 15 occasions the percentage absorption of the administered dose of Co<sup>58</sup>B<sub>12</sub> was estimated by the faecal excretion method at the same time as the hepatic radioactivity was measured (Fig. 1). The results indicate good correlation between these two methods.

**CONTROL GROUPS**

**NORMAL SUBJECTS (FIG. 2)** This group of 28 subjects consisted of 20 hospital patients with no gastro-

intestinal or haematological disorder, five with iron-deficiency anaemia, and three with ulcerative colitis but with no evidence of small intestinal involvement. All had normal serum levels of vitamin B<sub>12</sub>, and no clinical evidence of B<sub>12</sub> deficiency; hepatic radioactivity ranged from 1,600 to 4,633 counts per minute per microcurie with a mean of 2,914, S.D. 828; statistical range (mean ± 2 S.D.) 1,258-4,570. The test was repeated with the addition of intrinsic factor in six subjects. In each case the result was similar to that obtained by the ingestion of Co<sup>58</sup>B<sub>12</sub> alone.

**PERNICIOUS ANAEMIA (FIG. 2)** Nineteen patients with Addisonian anaemia were studied. In 12 the diagnosis had previously been established on adequate grounds and confirmed by continued normal haematological values with liver or vitamin B<sub>12</sub> therapy over periods of up to 10 years. In the remaining seven the test was performed as part of the initial diagnostic investigation. None of these patients had steatorrhoea. Following ingestion of Co<sup>58</sup>B<sub>12</sub> alone, hepatic surface counts varied from 0 to 720 per minute per microcurie (mean 237, S.D. 231). When intrinsic factor was added to the ingested Co<sup>58</sup>B<sub>12</sub>, the hepatic surface counts were increased in each

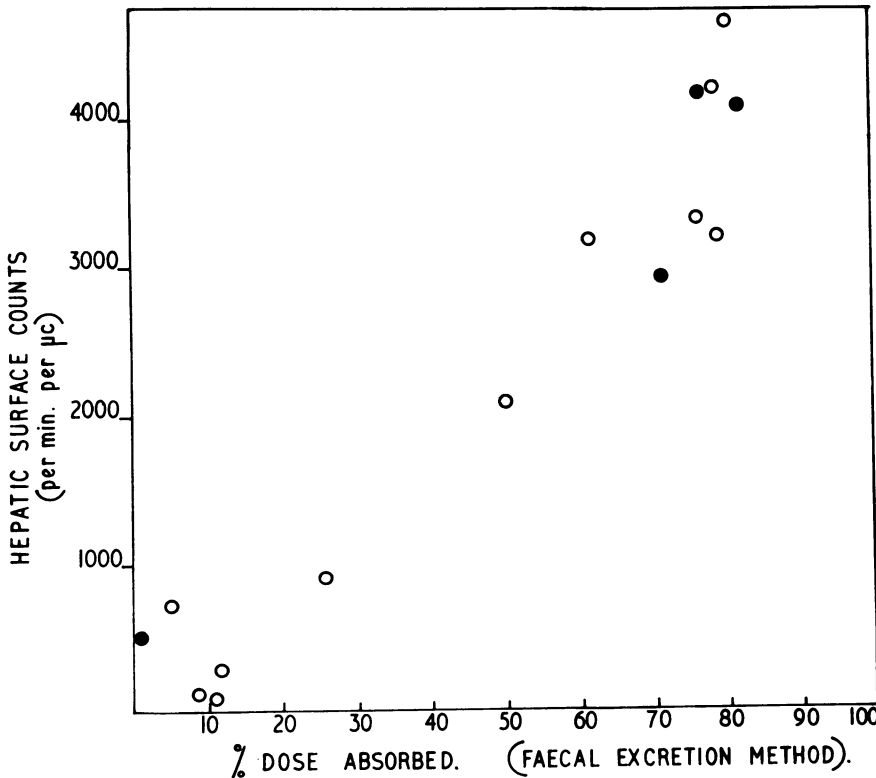


FIG. 1. *Hepatic surface radioactivity compared with the percentage of Co<sup>58</sup>B<sub>12</sub> absorbed as determined by the faecal excretion technique. Open circles represent a test performed with Co<sup>58</sup> vitamin B<sub>12</sub> alone. Closed circles represent a test performed with Co<sup>58</sup> vitamin B<sub>12</sub> plus intrinsic factor.*

case to the same range as obtained in the normal subjects (range 1,574 to 4,268).

**TOTAL GASTRECTOMY** Two patients were studied four and 10 years after total gastrectomy. Both had received regular B<sub>12</sub> therapy since the time of operation. In both the hepatic surface counts following ingestion of Co<sup>58</sup>B<sub>12</sub> alone were very low (0 and 66), but on the addition of intrinsic factor increased to the normal range (2,365 and 2,172).

#### INTESTINAL DISORDERS

**PARTIAL GASTRECTOMY** Twenty-four patients were studied following partial gastrectomy, the interval since operation being three months to 12 years (Fig. 2). In 18 the results were within the normal range. None of these patients had any clinical manifestation of B<sub>12</sub> deficiency, and in the majority serum vitamin B<sub>12</sub> levels have been persistently normal; occasional moderately low levels of serum vitamin B<sub>12</sub> have been

encountered in three of these subjects in whom absorption was found to be normal.

In four cases the hepatic surface counts were in the same range as seen in pernicious anaemia (261, 282, 292, 723), and in each increased to the normal range upon the addition of intrinsic factor to the ingested Co<sup>58</sup>B<sub>12</sub> (2,799, 3,000, 1,907, 2,919). These four patients had had a Polya type gastrectomy seven, nine, 10, and 12 years previously, in two instances for gastric carcinoma and in two for chronic peptic ulcer. They have all developed clinical evidence of deficiency of vitamin B<sub>12</sub>. Three developed megaloblastic anaemia (seven, nine, and 12 years after operation), associated with very low serum B<sub>12</sub> levels and responded adequately to B<sub>12</sub> therapy. The fourth developed subacute combined degeneration of the spinal cord 10 years after operation, associated with a very low serum B<sub>12</sub> level. He, also, responded excellently to B<sub>12</sub> therapy.

In two patients the hepatic surface counts were below normal (1,028 and 1,034 counts per minute

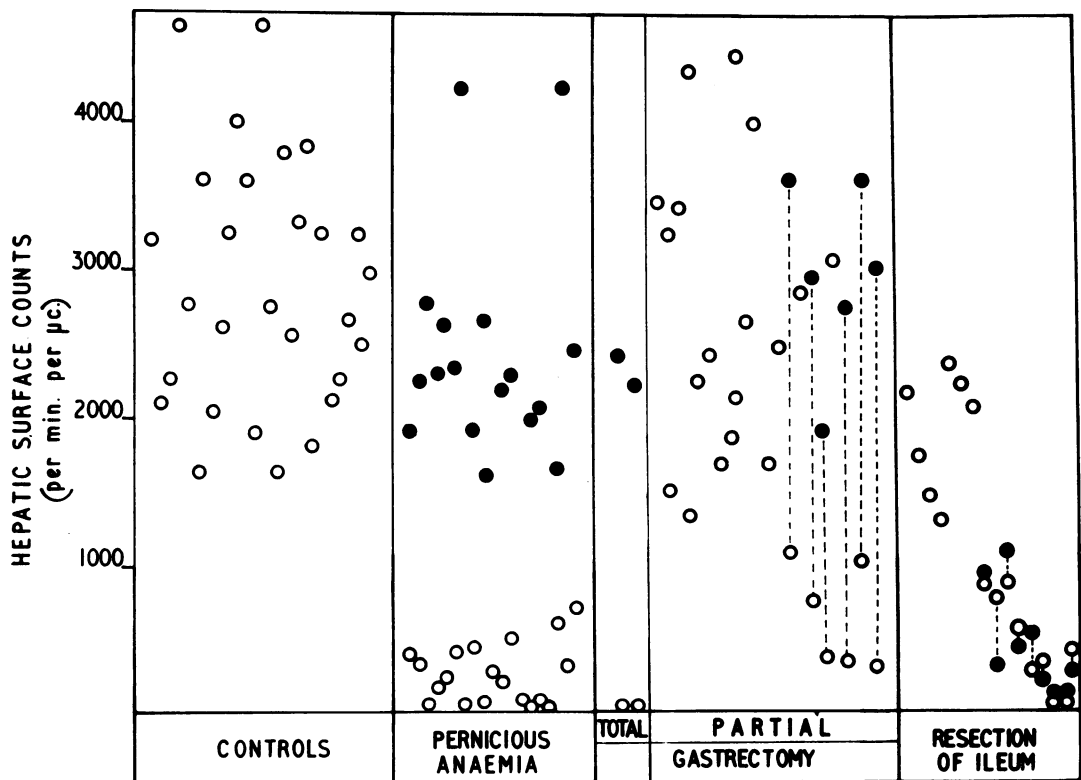


FIG. 2. Hepatic surface radioactivity in control subjects and in patients with pernicious anaemia, following gastrectomy and resection of the ileum.

Open circles represent a test performed with Co<sup>58</sup> vitamin B<sub>12</sub> alone.

Closed circles represent a test performed with Co<sup>58</sup> vitamin B<sub>12</sub> plus intrinsic factor.

per microcurie) but not as low as those seen in pernicious anaemia. In each the count rose considerably after the addition of intrinsic factor to the ingested dose (3,600 and 3,646 counts per minute per microcurie). In one, megaloblastic anaemia occurred five years after partial gastrectomy for gastric and duodenal ulcers; full response followed vitamin B<sub>12</sub> therapy, which was discontinued after three years. Two years later macrocytosis and glossitis recurred, which again responded to vitamin B<sub>12</sub> therapy. The other patient was seen eight years after operation with a severe iron-deficiency anaemia and an associated low serum B<sub>12</sub> level of 50 μg. per ml. Her marrow showed normoblastic erythropoiesis with no evidence of megaloblastic change.

**AFTER RESECTION OF THE ILEUM** Sixteen patients were studied after resection of a portion of the ileum (Fig. 2). In 14 this resection was performed for regional ileitis (right hemicolectomy in 11, resection of the distal ileum alone in two, and resection of a segment of the mid-ileum in one). In one patient a right hemicolectomy was performed for carcinoma of the caecum; in one 24 in. of distal ileum was resected for an argentaftin tumour.

In seven patients, in whom resection was performed from one to 14 years previously, the hepatic surface radioactivity was within the normal range. All seven have maintained normal serum vitamin B<sub>12</sub> levels and none has developed macrocytic anaemia.

In the other nine patients in whom resection was performed from one to 13 years previously, the hepatic radioactivity was below normal, varying from 60 to 876 counts per minute per microcurie after the ingestion of Co<sup>58</sup>B<sub>12</sub>. When intrinsic factor was added to the Co<sup>58</sup>B<sub>12</sub>, the counts were not significantly altered (72-1,156). In two cases a third dose was given following the administration of tetracycline for five days: in neither was there any significant improvement in the absorption. These nine patients have all had abnormally low serum vitamin B<sub>12</sub> levels since their operation (25 to 85 μg. per ml.). Six were receiving parenteral vitamin B<sub>12</sub> therapy; in three this was begun because of the development of macrocytic anaemia (the marrow was megaloblastic in the two patients in whom it was examined), and in three because of persistently low serum vitamin B<sub>12</sub> concentrations, though anaemia was not present. Three have not yet received vitamin B<sub>12</sub> therapy, though they also have persistently low serum B<sub>12</sub> levels but no anaemia.

The area of ileum resected in the patients who have retained normal vitamin B<sub>12</sub> absorption was the terminal ileum in six, the lengths being 6 in., 9 in., 12 in., 12 in., and 4 ft. (it was unknown in one case); the seventh patient had 16 in. of mid-ileum removed.

The nine patients with impaired vitamin B<sub>12</sub> absorption all had terminal ileum resected, the lengths in seven being 12 in., 18 in., 2 ft., 2 ft., 3 ft., 6 ft., and 'a few feet'. In one 11 in. of terminal ileum was resected as well as a further 9 in. about 2 ft. proximally. The ninth had a right hemicolectomy for carcinoma of the caecum.

None of the 14 patients with Crohn's disease has had clinical evidence of recurrence, and in none is there evidence of stricture or formation of a blind loop. Only two have biochemical evidence of active disease with increased serum seromucoid concentration (Cooke, Fowler, Cox, Gaddie, and Meynell, 1958). In one of these absorption is normal, in the other it is impaired. Liver function tests were normal in all.

**ADULT COELIAC DISEASE AND IDIOPATHIC STEATORRHOEA** Fifty patients were studied in whom a diagnosis of adult coeliac disease (Cooke, 1958) or 'idiopathic steatorrhoea' (Cooke, Peeney, and Hawkins, 1953) had been made. The results of the hepatic radioactivity are shown in Fig. 3, in which these patients are classified according to criteria recently described (Fone, Cooke, Meynell, Brewer, Harris, and Cox, 1960) with special reference to the histological appearances of the upper small intestine obtained by peroral biopsy.

In 22 patients with adult coeliac disease and a 'flat' jejunal mucosa, the hepatic radioactivity was within the normal range in 18; in four it was below normal (in three as low as that seen in pernicious anaemia), but was not significantly improved by the addition of intrinsic factor.

On the 28 patients with jejunal biopsies showing 'abnormal villi' (partial atrophy), eight resembled those of adult coeliac disease in many respects but differed particularly in the histology of the jejunal mucosa. Hepatic radioactivity was normal in five; in three it was below normal, but improved to the normal range when intrinsic factor was added. These three each had histamine-fast achlorhydria, and in the two in whom gastric biopsy was performed the mucosa showed severe inflammation and glandular atrophy.

In seven patients the major feature was a severe megaloblastic anaemia associated with low serum levels of vitamin B<sub>12</sub> which responded adequately to parenteral B<sub>12</sub> therapy. In five hepatic radioactivity was much below normal, but was improved to the normal range by the addition of intrinsic factor. All five had histamine-fast achlorhydria, and severe gastric atrophy was present in all four in whom biopsy was performed. One patient had normal hepatic radioactivity; his gastric mucosa was normal. The seventh patient had impaired absorption which

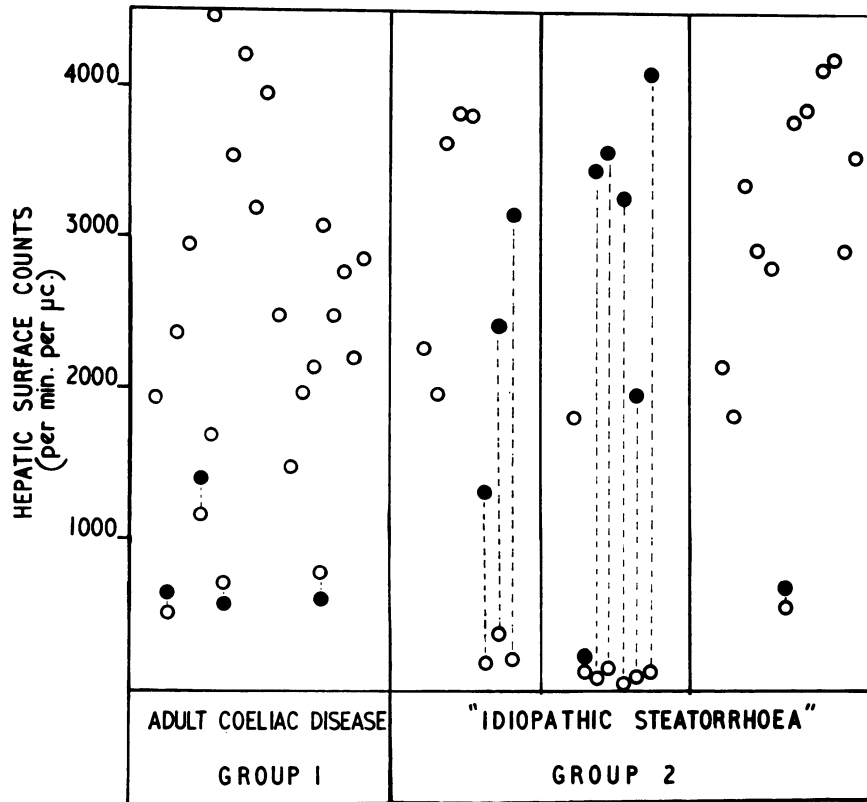


FIG. 3. Hepatic surface radioactivity in patients with 'idiopathic steatorrhea'. Open circles represent a test performed with Co<sup>58</sup> vitamin B<sub>12</sub> alone. Closed circles represent a test performed with Co<sup>58</sup> vitamin B<sub>12</sub> plus intrinsic factor.

was not improved by the addition of intrinsic factor.

In 12 patients the major clinical feature was a severe megaloblastic anaemia associated with normal serum vitamin B<sub>12</sub> levels, free gastric HCl; it responded adequately to folic acid therapy. In 11 the hepatic radioactivity was normal. The gastric mucosa was normal in the three examined. In one patient hepatic radioactivity was low and not improved by intrinsic factor; he also had a normal gastric mucosa.

#### DISCUSSION

An intrinsic factor defect was clearly demonstrated in all our patients with pernicious anaemia, whilst the complete lack of intrinsic factor secretion expected to follow total gastrectomy was confirmed in our two patients. As was shown by Baker and Mollin (1956), there is good correlation with the faecal excretion method of Heinle *et al.* (1952), hence the hepatic radioactivity after an oral dose of radioactive vitamin B<sub>12</sub> appears to be closely related to the amount absorbed. Our results in the control groups confirm previous observations that the hepatic surface counting technique is a reliable method of

estimating the degree of absorption of radioactive vitamin B<sub>12</sub>.

A varying degree of impairment of intrinsic factor secretion is a recognized, but uncommon, sequel of partial gastrectomy (Badenoch, Evans, Richards, and Witts, 1955; MacLean, 1957; Loewenstein, 1958) and was seen in six of our 24 patients. Each of these six had developed evidence of B<sub>12</sub> deficiency. As these cases did not form an unselected series, the results do not reflect the true incidence of B<sub>12</sub> deficiency as a result of partial gastrectomy which has been estimated as 0.6% (MacLean, 1957).

Since partial gastrectomy does not remove much of the intrinsic factor secreting area of the mucosa—fundus and body—as does total gastrectomy, some other factor must be involved. Badenoch *et al.* (1955), on the basis of gastric biopsy studies in five patients, suggested that persistence of gastritis with mucosal atrophy in the gastric remnant is the explanation of the intrinsic factor defect. A similar conclusion was reached by MacLean (1957) in a study of the mucosa of resected stomachs; he suggested that the development of megaloblastic anaemia following partial gastrectomy might be predicted by such study.

The observation of moderately low serum B<sub>12</sub>



levels despite normal B<sub>12</sub> absorption in three patients following partial gastrectomy is of interest. As reported by Cox *et al.* (1959), the serum levels in such patients do return to normal with the administration of iron. A possible explanation might be that although the B<sub>12</sub> is absorbed when given under the 'ideal' conditions of the test, it may not be absorbed as well when presented in food. This phenomenon has been demonstrated with the absorption of iron (Baird and Wilson, 1959), and may apply to B<sub>12</sub> as well. Glass *et al.* (1960) have found low serum B<sub>12</sub> levels in some cases of gastritis with histamine-fast acidity in which absorption of radioactive B<sub>12</sub> was normal. They conclude that the explanation for these inter-relationships must await more complete knowledge of the natural history of gastric atrophy and B<sub>12</sub> deficiency.

Impaired absorption which was not corrected by the addition of intrinsic factor was demonstrated in nine of the 16 cases following resection of ileum. In all 16 cases the degree of absorption of vitamin B<sub>12</sub> was in excellent agreement with other features of vitamin B<sub>12</sub> metabolism. All seven patients in whom normal absorption was demonstrated had maintained normal serum B<sub>12</sub> levels and normal blood pictures since operation: the nine with impaired absorption had all developed low serum vitamin B<sub>12</sub> levels with macrocytic anaemia in three. It is generally believed that in man vitamin B<sub>12</sub> is absorbed in the distal small intestine. Booth and Mollin (1959) found that absorption of vitamin B<sub>12</sub>, with and without intrinsic factor, was invariably subnormal in the patients who had had more than 6 to 8 ft. of ileum resected or short circuited; the terminal ileum was involved in each of their cases. In general, the length of resected ileum was greater in our patients with impaired absorption than in those in whom absorption remained normal. It is of particular interest, however, that absorption was impaired in two patients in whom only 12 in. and 18 in. of terminal ileum was resected. All but two of our group had had the resection performed for Crohn's disease; there was no significant difference between those with normal and those with abnormal absorption as regards severity of the lesion before operation or incidence of recurrence after operation. The diminution in absorption appears more closely related to the extent of involvement by the disease process than from intestinal stasis or blind loops. These cases provide further evidence that the distal ileum is the most important site for absorption of vitamin B<sub>12</sub> in man. They also emphasize the need for constant observation for the occurrence of vitamin B<sub>12</sub> deficiency or alternatively the routine prophylactic administration of vitamin B<sub>12</sub> after resection of even short lengths of ileum.

A similar type of absorptive defect was found in only six of 50 patients with adult coeliac disease and 'idiopathic steatorrhoea'. Contrary to the findings of Oxenhorn, Estren, Wasserman, and Adlersberg (1958) and Glass (1959), absorption of radioactive B<sub>12</sub> was found to be normal in the majority of our cases of adult coeliac disease, and these observations correlate well with the maintenance of normal serum B<sub>12</sub> levels in the majority and the absence in this group of any instance of megaloblastic anaemia due to vitamin B<sub>12</sub> deficiency.

A total of 11 patients with 'idiopathic steatorrhoea', *i.e.*, with abnormal jejunal villi or 'partial atrophy', had a megaloblastic anaemia due to vitamin B<sub>12</sub> deficiency; in all but one the deficiency was due to impaired secretion of intrinsic factor. The combination of intrinsic factor defect and steatorrhoea has been previously described by Mollin, Booth, and Baker (1957), Järvinen and Latvalahti (1958), Williams, Coghill, and Edwards (1958), and Doig and Girdwood (1960). We consider these patients to be a group distinct from adult coeliac disease. They also differ from patients with pernicious anaemia, whom they resemble clinically in that dysfunction of the small intestine can be demonstrated (Fone, Cooke, Meynell, and Cox, 1961).

One patient, a man of 39 years, was seen with megaloblastic anaemia, low serum vitamin B<sub>12</sub>, and normal gastric mucosa in whom B<sub>12</sub> absorption was found on two occasions to be normal. Haematological response to B<sub>12</sub> therapy was complete. There was no history of anticonvulsant therapy. We have no adequate explanation for this finding at present, and he is the only patient in this series in whom the hepatic radioactivity could be considered inconsistent with other features of vitamin B<sub>12</sub> metabolism.

#### SUMMARY AND CONCLUSIONS

The hepatic surface counting technique is a reliable and satisfactory method of estimating the absorption of radioactive vitamin B<sub>12</sub>. It does not require collection of faeces or urine, or the administration of a flushing dose of non-radioactive vitamin B<sub>12</sub>. It is therefore particularly useful for the study of out-patients, and its convenience and accuracy justify more general use.

Results in patients following partial gastrectomy were comparable to those reported by others. Nine of 16 patients who had undergone ileal resection mainly for regional ileitis had impaired absorption of Co<sup>58</sup>B<sub>12</sub>, not improved with the addition of intrinsic factor. There was some general relationship between the degree of impairment and the amount of intestine resected. In contradistinction to other reports, only

six out of 50 patients with adult coeliac disease and 'idiopathic steatorrhoea' showed this type of impaired absorption of  $\text{Co}^{58}\text{B}_{12}$  but 10 with abnormal villi (partial atrophy) demonstrated an intrinsic factor deficit as the cause for their failure to absorb  $\text{Co}^{58}\text{B}_{12}$ .

We are indebted to the Endowment Research Fund of the United Birmingham Hospitals for a grant for equipment and for the financial support of a research associate (D.J.F.).

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