Vitamin B-12 deficiency after gastric surgery for obesity

Barbara M Rhode, Paul Arseneau, Bernard A Cooper, Max Katz, Brian M Gilfix, and Lloyd D MacLean

ABSTRACT Low serum vitamin B-12 concentrations after gastric bypass (GB) surgery for obesity were observed in 11 of 28 patients without detectable impairment of crystalline vitamin B-12 absorption. This was observed in 2 of 19 patients with vertical banded gastroplasty (VBG). In contrast, protein-bound vitamin B-12 absorption was markedly impaired, as demonstrated in eight of these patients after GB (n = 7) and VBG (n = 1). Correction of this impaired absorption occurred when protein-bound vitamin B-12 was incubated with an enzyme mixture before consumption. Simultaneous ingestion of the enzyme mixture with protein-bound vitamin B-12 did not improve absorption of the vitamin. In a separate experiment, 10 patients with a normal result from the Schilling test failed to correct low serum vitamin B-12 concentrations with a quantity of oral crystalline vitamin B-12 equal to the recommended dietary allowance of 2 μg, taken twice daily for 3 mo. Serum total homocysteine values declined during this interval. An oral daily dose of 350 μg crystalline vitamin B-12 raised the average serum vitamin B-12 concentration to an amount greater than the lower reference limit. A dose > 350 μg/d was required to raise all patients’ vitamin B-12 concentrations above this concentration rather than just above the population mean. We conclude that because concentrations of oral crystalline vitamin B-12 were required to normalize serum vitamin B-12 concentrations, that a mechanism other than formation of a vitamin B-12 intrinsic factor complex is responsible for crystalline vitamin B-12 absorption after GB for obesity. Am J Clin Nutr 1996;63:103-9.

KEY WORDS Vitamin B-12, absorption, Schilling test, intrinsic factor, severe obesity, gastric bypass, gastroplasty, dietary requirements

INTRODUCTION Dietary deficiency of vitamin B-12 is rare because of its widespread distribution in animal foods and its extensive storage in the liver. Nutritional vitamin B-12 deficiency has been found only in strict vegetarians who avoid meat, eggs, and milk. Because such dietary deficiency is unusual, it follows that deficiency of vitamin B-12 is usually the result of defective absorption.

The normal sequence of events leading to absorption of protein-bound vitamin B-12 begins with the release of vitamin B-12 from protein sources by the digestive action of hydrochloric acid and pepsin in the stomach. The freed vitamin B-12 attaches to R-binder proteins from the saliva and gastric juice, and in turn is released from these by pancreatic enzymes in the upper small intestine. The vitamin B-12 molecule is then rapidly transferred to intrinsic factor to form a complex that is resistant to tryptic proteolysis. The vitamin B-12 intrinsic factor complex usually remains intact until it adheres to specific receptors in the distal ileum in anticipation of absorption (1).

Vitamin B-12 deficiency after total or near total gastrectomy develops from 3 to 6 y after the procedure, and results from a lack of intrinsic factor. Megaloblastic anemia is inevitable if patients are not given prophylactic therapy (2). Low serum vitamin B-12 concentrations after lesser gastric resections have been attributed to poor absorption of protein-bound vitamin B-12, with absorption of crystalline vitamin B-12 remaining normal (3).

Such abnormally low serum vitamin B-12 concentrations have also been detected in > 25% of severely obese patients as early as 1 y after gastric-limiting surgery for weight control (4-9). Recent studies demonstrated malabsorption of protein-bound vitamin B-12 in patients after both gastric bypass and vertical banded gastroplasty (10-12). Normal absorption of crystalline vitamin B-12 as measured by the Schilling test is preserved, although the magnitude of absorption may be altered after surgery (11, 12). These authors speculate that the surgical reduction of the size of the stomach leads to achlorhydria, and thereby malabsorption of vitamin B-12 bound to protein (11). Others have suggested that the vitamin B-12 deficiency seen in these patients is due to inadequate secretion of intrinsic factor (13).

Considerable evidence suggests that doses of vitamin B-12 contained in standard multivitamin formulas (1-15 μg) are insufficient for maintaining normal serum vitamin B-12 concentrations in these patients (6, 14). Provenzale et al (14) found that the recommended dietary allowance (RDA) of 2 μg in vitamin tablets taken orally was insufficient for maintenance of vitamin B-12 status in 30% of the patients after gastric bypass. Doses of oral vitamin B-12 > 100 μg have been used in an

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2 Organon Canada Ltd and CE Jamieson & Co Ltd supplied the Cotazym and cyanocobalamin tablets.
3 Reprints not available. Address correspondence to BM Rhode, Royal Victoria Hospital, 687 Pine Avenue West, Room H6.34, Montreal, Quebec, Canada H3A 1A1.
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effort to raise serum vitamin B-12 concentrations into the reference range (15, 16).

In light of the difficulty of maintaining serum concentrations of vitamin B-12 by oral ingestion, we set out to find a better vehicle by which vitamin B-12 could be given orally to patients after gastric-limiting surgery for obesity. To this end, we identified patients with low serum vitamin B-12 concentrations and normal findings after Schilling tests, and evaluated their ability to absorb oral vitamin B-12, either protein-bound or crystalline. We also monitored the response of serum concentrations of vitamin B-12 to different doses of the oral vitamin in a separate group of patients with low initial vitamin B-12 concentrations.

SUBJECTS AND METHODS

Surgical procedures

Two gastric-limiting procedures, vertical banded gastroplasty and Roux-en-Y gastric bypass (Figure 1, a and b), have been used for the treatment of severe obesity since 1982 at this clinic. Patients with a preoperative body mass index (BMI; in kg/m²) > 40 and with complications of obesity were selected for these operations, which were described in detail elsewhere (17).

Experiment 1

Schilling tests and serum vitamin B-12 determinations were performed on 47 patients (19 after gastroplasty; 28 after gastric bypass) who appeared sequentially in our clinic over 4 mo. The gastroplasty patients were 43 ± 9 y of age (x ± SD), had a BMI of 32 ± 7, had lost 32.6 ± 13.0% of their preoperative weight, and had been followed for 31.3 ± 26.6 mo after surgery. The gastric bypass patients were 36 ± 8 y of age, had a BMI of 30 ± 5, had lost 37.6 ± 8.9% of preoperative weight, and had been followed for 23.3 ± 14.0 mo after surgery. All had a normal finding from a Schilling test. Of the 47 patients, 13 (1 man, 12 women) with serum vitamin B-12 concentrations below the lower reference limit for our institution at the time of the study (< 200 pmol/L) were recruited. All had vitamin B-12 concentrations < 100 pmol/L, which is the vitamin B-12 value most frequently associated with metabolic evidence of vitamin B-12 deficiency (18). Of the 13 patients, 11 had had gastric bypass and 2 had had vertical banded gastroplasty.

Experiment 2

Of the 13 patients identified in experiment 1, 8 women with a low serum vitamin B-12 concentration volunteered to participate in the second part of the evaluation of vitamin B-12 status using protein-bound vitamin B-12 absorption tests ~2 y after the start of experiment 1. Three female hospital employees volunteered to serve as control subjects. Measurements of the following biochemical and hematologic indexes were made in all subjects: electrolytes, urea, creatinine, glucose, calcium, total protein, albumin, bilirubin, cholesterol, serum folate, vitamin B-12, ferritin, homocysteine, and gastrin; liver-function tests and a complete blood cell count were also performed. A Schilling test was repeated in these eight patients before protein-bound vitamin B-12 absorption tests were performed. The integrity of the gastric pouch was verified by gastroscopy in all patients.

Four weeks after the repeat Schilling test, a protein-bound vitamin B-12 absorption test using chicken serum was carried out in the eight patients (see below). One month after the latter test these patients were alternatively assigned to undergo one of two vitamin B-12 absorption tests. In the first test, patients ingested pancrelipase preparation (Cotazym; Organon Canada Ltd, Scarborough, Ontario) paste, which was washed down with the chicken serum mixture. The paste was made with the contents of three pancrelipase preparation capsules mixed with dry coffee granules (see below). In the second test, patients consumed a mixture of chicken serum and pancrelipase preparation preincubated together before ingestion. The three control subjects underwent the protein-bound vitamin B-12 absorption tests in this order: chicken serum alone, chicken serum followed by pancrelipase preparation paste, and chicken serum preincubated with pancrelipase preparation. These absorption tests were separated by 1-mo intervals.

The guidelines of the Royal Victoria Hospital Surgical Ethics Committee were followed.

Vitamin B-12 absorption studies

Schilling test

Absorption of crystalline vitamin B-12 was measured with a stage 1 Schilling test (19) and two sequential 24-h urine collections, each preceded by an intramuscular injection of 1000 µg unlabeled cyanocobalamin (Sabex Inc, Boucherville, Quebec), in patients after they had fasted overnight (20). A 1.0-µg oral dose of [57Co]cyanocobalamin (37 GBq/g vitamin B-12) was given as the free vitamin (Merck Frosst Canada Inc, Kirkland, Quebec). Radioactivity in urine was measured in a γ scintillation counter for 5 min or 10,000 counts, whichever came first. Results were expressed as the percentage of the radioactive dose administered (reference range: 10–30%). The total vitamin B-12 binding capacity and antibody blocking of the intrinsic factor were measured in serum by the albumin-charcoal method of Gottlieb et al (21).

Protein-bound vitamin B-12 absorption tests

Chicken serum [57Co]vitamin B-12

Blood from the jugular vein of one electrocuted chicken was collected into a 750-mL glass jar at a poultry plant. Serum was

FIGURE 1. Reprinted from reference 17. A: Vertical banded gastroplasty with division between the vertical staple lines. A Malone bougie no. 28 is in place and the polypropylene mesh band is 45–47 mm in external circumference. B: Gastric bypass made with a 10- to 15-mL gastric pouch placed in the dependent position, which encourages prompt emptying. The Roux limb was 40 cm long and was placed in the retrocolic, retrogastric position.
pipetted in 2-mL aliquots into glass vials and promptly frozen at -20 °C. On the day of the test, the oral dose was prepared by mixing 1.0 μg [§-CO]cyanocobalamin (37 GBq/g vitamin B-12) and 2 mL chicken serum. The mixture was incubated at room temperature for 30 min and diluted with tap water to a final volume of 100 mL. The chicken serum had a vitamin B-12 binding capacity of 0.75 mg/L. The fasting subjects were first given the chicken serum mixture to drink and the remainder of the procedure was the same as that for the Schilling test.

**Chicken serum pancrelipase preparation paste**

The contents of three pancrelipase preparation capsules were mixed with 7.5 mL (1.5 tsp) dry instant coffee and diluted with sufficient tap water to form a paste. The paste was ingested and washed down with the chicken serum solution described above.

**Chicken serum pancrelipase preparation incubation**

Two milliliters of chicken serum was incubated with 1.0 μg [§-CO]cyanocobalamin (37 GBq/g vitamin B-12) in a 100-mL volumetric flask for 30 min at room temperature. Three pancrelipase preparation capsules were opened and added to the volumetric flask. Warm tap water was added and the solution diluted to a final volume of 100 mL. This mixture was incubated in a water bath (37 °C) for 45 min, with frequent agitation. The incubated mixture was then ingested by the fasting subjects.

**Experiment 3**

The response of serum vitamin B-12 and serum total homocysteine concentrations to oral ingestion of crystalline vitamin B-12 was assessed in an independent group of patients who had had a gastric bypass. Ten patients (one man, nine women) with low serum vitamin B-12 concentrations at a clinic visit were recruited because of their ability to comply with the experimental protocol. They were asked to refrain from donating or having blood drawn at other centers during this time. The first part of this experiment consisted of the patients ingesting 4 μg oral crystalline vitamin B-12/d for 3 mo. It was administered as two drops on a sugar cube twice a day, in the morning and evening. This preparation was made by diluting parenteral vitamin B-12 (1 g cyanocobalamin/L; Sabex Inc) in sterile water (1:50) to yield a concentration of 1 μg/drop. The solution was dispensed with plastic droppers from 20-mL brown glass bottles. The stability of the cyanocobalamin solution was monitored bimonthly over the 3-mo period by the laboratory using a radiodilution assay.

Before the start of the experiment, patients were shown how to add the crystalline vitamin B-12 drops to the sugar cube. They were instructed to consume the crystalline vitamin B-12 after fasting. No ascorbic acid–containing foods were allowed within 2 h of the ingestion of these drops. Special attention was paid to chewing the sugar cube and mixing it with saliva in the mouth for several minutes before swallowing. This was followed by ingesting ≥ 240 mL tap water each time.

In the second part of the experiment, 10 patients ingested 350 μg crystalline vitamin B-12/d for 3 mo in the form of vitamin B-12 tablets (CE Jamieson & Company Limited, Windsor, Ontario). Instructions for taking the crystalline vitamin B-12 were the same as described previously.

**Laboratory techniques and other items**

Biochemical indexes were analyzed on a Technicon SMAC II analyzer (Miles Inc, Diagnostic Division, Tarrytown, NY) using reagents supplied by the manufacturer. Blood counts were done with a Technicon H1 (Miles Inc, Diagnostic Division). Serum vitamin B-12 and folate concentrations were assayed by using the Quantaphase radioassay technique (Bio-Rad Laboratories Ltd, Mississauga, Ontario). Serum ferritin was determined with the Fer-Iron MT kit (Ramco Laboratories Inc, Houston). Serum total homocysteine was measured by the method of Chadeauf et al (22). To evaluate the functional status of the gastric mucosa, serum gastrin was measured with a commercially available radioimmunoassay kit (Becton Dickinson and Co, Orangeburg, NY). Each capsule of the pancrelipase preparation contained 8000 USP units of lipase activity, 30,000 USP units of amylase activity, and 30,000 USP units of protease activity.

**Statistical analysis**

Statistical procedures performed included Spearman’s rank correlation, paired and unpaired Student’s t tests and chi-square and nonparametric analyses. Data are reported as means ± SDs. INSTAT for Macintosh (version 2.03; Graph Pad Software, San Diego) was used for the statistical analyses.

**RESULTS**

**Experiment 1: absorption of crystalline vitamin B-12**

Schilling test results of 47 patients with serum vitamin B-12 concentrations < or ≥ 100 pmol/L. 26.5 ± 20.4 μg after vertical banded gastroplasty or gastric bypass are illustrated in Figure 2. These two groups had significantly different serum vitamin B-12 concentrations (244 ± 155 compared with 166 ± 161 pmol/L; P = 0.0143) and ages (43.1 ± 9.4 compared with 36.3 ± 8.1; P = 0.0176), respectively. Schilling test results were not significantly different between groups (28.8 ± 5.9% compared with 24.9 ± 8.7%; P = 0.0593); all patients had values within or above the reference range (10–30%). All patients who excreted radioactive vitamin B-12 concentrations greater than the reference range had normal serum vitamin B-12 concentrations, whereas 41% of all patients whose excretion values were within the reference range had low values (P = 0.020). There was no detectable relation between percentage urinary excretion, current BMI, percentage weight

![FIGURE 2. Percentage §-Co]vitamin B-12 excreted per 48 h as a function of serum vitamin B-12 concentration. Vertical banded gastroplasty (): n = 2 < 100 pmol/L and n = 17 ≥ 100 pmol/L. Gastric bypass (): n = 11 < 100 pmol/L and n = 17 ≥ 100 pmol/L.](https://academic.oup.com/ajcn/article-abstract/63/1/103/4650665)
loss, follow-up time, and type of surgery (r < 0.40). Schilling test results correlated with serum vitamin B-12 concentrations (r = 0.49; P = 0.0009) and age, with older patients excreting the most radioactive vitamin B-12 concentrations (r = 0.45, P = 0.0013). Of 13 patients with low serum vitamin B-12 status, 5 were taking multivitamins containing ≥ 2 μg crystalline vitamin B-12.

Experiment 2: effect of various ingested agents on urinary excretion of radioactive vitamin B-12

Clinical data on the eight patients with a low serum vitamin B-12 concentration and three control subjects who underwent the standard Schilling and protein-bound vitamin B-12 absorption tests are shown in Table 1. Only one patient was obese at the time of study (BMI > 35). Protein-bound absorption studies were done 30.4 ± 11.8 mo (range: 8–49 mo) after surgery. Seven patients had had a gastric bypass (Figure 1b) and one had had a gastroplasty (Figure 1a). The control subjects were free of gastrointestinal complaints and had had no abdominal operations. Two patients were not taking any vitamin supplements during the study. Four were taking a standard multivitamin and ferrous sulfate supplement of 300 mg twice daily. Two took only the multivitamin. Six of eight patients were taking a brand of multivitamins containing 5 μg vitamin B-12/tablet.

All patients had one or more abnormalities of serum folate, ferritin, or vitamin B-12 concentrations. Anemia was seen in five patients and in one control subject. Serum ferritin concentrations were depressed in these anemic patients and in the one control subject, indicating depleted iron stores. Low serum folate values were seen in two patients. Two other patients had just completed a 3-mo supplementation period with folic acid, 5 mg three times daily. Although serum vitamin B-12 concentrations rose during the 2-y period before the protein-bound absorption tests in all but one patient, they remained below the reference range (67 ± 15 compared with 100 ± 27 pmol/L; P = 0.008). One patient had been receiving parenteral vitamin B-12 for 1 y but the patient stopped supplementation when the study began. Dietary intake of vitamin B-12–containing foods had not changed substantially over this 2-y period. Intrinsic factor antibodies were not detected in any study subject. Serum homocysteine concentrations and serum gastrin values were all within the reference range.

Table 2 shows the results of protein-bound vitamin B-12 absorption in patients and control subjects. Absorption of crystalline vitamin B-12 from the Schilling test was significantly higher than that of the protein-bound vitamin from chicken serum in the eight patients (P < 0.0001). Patients had a significantly lower mean vitamin B-12 absorption rate from chicken serum when compared with control subjects (P < 0.001). Values for absorption of vitamin B-12 from chicken serum for the control subjects were similar to those reported previously (10, 23, 24). When enzyme paste was ingested with the chicken serum, the patients again had a significantly lower absorption rate when compared with control subjects (P = 0.028). In contrast, there was no statistical difference in absorption of vitamin B-12 between patients and control subjects when the chicken serum was incubated in vitro with the enzyme mixture before ingestion (P = 0.106).

[57Co]Vitamin B-12 excretion was not significantly different between patients who ingested chicken serum with and without enzyme paste (P = 0.54). The change in control subjects was significantly higher than the change induced in patients (3.87 ± 3.51% compared with −0.09 ± 0.25%; P = 0.034). With preevacuation of chicken serum and pancrelipase preparation before ingestion, absorption as indicated by an increased [57Co]vitamin B-12 excretion increased for both patients and control subjects (1.55 ± 1.32% compared with 3.13 ± 2.92%; P = 0.48).

Experiment 3: response to orally administered crystalline vitamin B-12

Ten patients (one man, nine women) aged 40 ± 10 y with a low serum vitamin B-12 concentration and a BMI of 27 ± 4 were studied 19.4 ± 6.5 mo after gastric bypass. Only one patient was obese. One woman was being treated for microcytic anemia with 300 mg ferrous sulfate three times daily. All patients were taking standard multivitamins.

Three months of a daily dose of 4 μg crystalline vitamin B-12 did not increase mean serum vitamin B-12 concentrations to the reference range (> 200 pmol/L; P = 0.086) (Table 3). The 350-μg dose raised mean serum values into the reference range (P < 0.01), but still failed to correct the serum vitamin B-12 concentration in 5 of 10 patients. Serum homocystine

| TABLE 1 |
| Clinical data in subjects undergoing vitamin B-12 absorption tests

<table>
<thead>
<tr>
<th>Reference Range</th>
<th>Control subjects (n = 3)</th>
<th>Patients (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>37.3 ± 5.3</td>
<td>36.0 ± 6.7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>—</td>
<td>22 ± 4</td>
</tr>
<tr>
<td>Time postoperative (mo)</td>
<td>—</td>
<td>30.4 ± 11.8</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>120–160</td>
<td>131 ± 12</td>
</tr>
<tr>
<td>MCV (FL)</td>
<td>81–99</td>
<td>88.1 ± 3.4</td>
</tr>
<tr>
<td>Serum ferritin (μg/L)</td>
<td>20–200</td>
<td>17 ± 9</td>
</tr>
<tr>
<td>Serum folate (mmol/L)</td>
<td>9–45</td>
<td>19.1 ± 6.3</td>
</tr>
<tr>
<td>Serum vitamin B-12 (pmol/L)</td>
<td>200–740</td>
<td>370 ± 165</td>
</tr>
<tr>
<td>Serum homocysteine (μmol/L)</td>
<td>&lt; 24.0</td>
<td>9.1 ± 1.6</td>
</tr>
<tr>
<td>Serum gastrin (ng/L)</td>
<td>0–100</td>
<td>40.5 ± 11.2</td>
</tr>
</tbody>
</table>

¹± SD. MCV, mean corpuscular volume.
²Significantly different from control subjects (unpaired two-tailed t test): ²P = 0.04, ²P = 0.001, ²P = 0.0008.

| TABLE 2 |
| Percent urinary excretion of radioactive vitamin B-12 in control subjects and patients

<table>
<thead>
<tr>
<th>Absorption tests</th>
<th>Control subjects</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schilling</td>
<td>—</td>
<td>19.8 ± 6.0 [8]</td>
</tr>
<tr>
<td>Chicken serum</td>
<td>2.4 ± 0.7 [3]</td>
<td>0.4 ± 0.4 [8]² ⁴</td>
</tr>
<tr>
<td>Enzyme paste</td>
<td>6.3 ± 4.1 [3]</td>
<td>0.2 ± 0.2 [4]⁴</td>
</tr>
<tr>
<td>Incubation</td>
<td>5.5 ± 3.2 [3]</td>
<td>2.0 ± 1.5 [4]⁴</td>
</tr>
</tbody>
</table>

¹± SD; n in brackets. Vitamin B-12 absorption tests were separated by ≥ 1-mo intervals.
²Significantly different from control subjects (unpaired t test): ²P < 0.001, ²P = 0.028.
⁴Significantly different from control subjects, P = 0.0121 (Mann-Whitney test).
²Not significantly different from control subjects, P = 0.106 (unpaired t test).
TABLE 3
Response of vitamin B-12 and serum total homocysteine concentrations to oral ingestion of 4 and 350 µg crystalline vitamin B-12 for 3-mo periods

<table>
<thead>
<tr>
<th>Vitamin B-12 status</th>
<th>Before ingestion</th>
<th>4 µg</th>
<th>350 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum vitamin B-12</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| (pmol/L)            | 87 ± 25          | 124 ± 43 | 214 ± 88
| Serum homocysteine  | 18.2 ± 5.0       | 12.5 ± 2.0 | 13.4 ± 3.5|

1. x ± SD; n = 10.
2. Significant difference from 350-µg value (Tukey Kramer posttest):

DISCUSSION

Vitamin B-12 deficiency as measured by a low serum concentration has been described in 26–70% of patients within 2 y after gastric bypass for obesity (4–9). Of 193 patients followed for 1–2 y in our clinic, the serum vitamin B-12 concentration was below the lower limit of the reference range in 57 patients (30%).

This study supports the findings of Yale et al (10) and Smith et al (11), who showed malabsorption of protein-bound vitamin B-12 but normal absorption of crystalline vitamin B-12 as measured by the Schilling test. Behrns et al (12) found that crystalline vitamin B-12 absorption was decreased after gastric bypass surgery, albeit remaining within the reference range, suggesting that less intrinsic factor was available for binding of vitamin B-12 after surgery than before. Various authors have suggested various causes for these observations, including poor mixing of the vitamin with intrinsic factor beyond the jejunojejunal junction, insufficient secretion of intrinsic factor, or proteolytic destruction of intrinsic factor before it had a chance to bind with vitamin B-12. In our study, the simultaneous ingestion of protein-bound vitamin B-12 with an enzyme paste did not improve absorption of the vitamin. This suggests that the upper gastrointestinal tract after gastric bypass does not favor enzymatic activity to free protein-bound vitamin B-12, likely because of both rapid transit and achlorhydria.

This absorption defect was partially corrected when protein-bound vitamin B-12 was incubated with an enzyme mixture before ingestion. Sufficient vitamin B-12 was made available in the chicken serum to produce increased absorption in two of three control subjects and in all four patients. The change in absorption from chicken serum alone was greater in control subjects than in patients, indicating that the vitamin B-12 that had been released by the incubation process was not as easily utilized by patients as it was by control subjects.

These data suggest that vitamin B-12 may not be sufficiently available to meet the vitamin requirements of these patients. Consumption of enzymes with foods to effect release from proteins, or incubation of foods before ingestion, are not feasible alternatives for providing the vitamin. Therefore, supplementation is required, an issue that we addressed in the latter part of our study.

Despite that normal phase-1 Schilling tests indicated absorption of crystalline vitamin B-12 in these patients, treatment with multivitamin preparations containing the RDA did not prevent or ameliorate existing low vitamin B-12 concentrations. This confirms the findings of Provenzale et al (14). The use of twice the RDA for vitamin B-12 for 3 mo was also ineffective in correcting low serum vitamin B-12 concentrations. It is unclear why serum vitamin B-12 did not increase significantly or at all in patients taking 4 µg oral crystalline vitamin B-12/d, but serum homocysteine did decrease in these patients, suggesting that vitamin B-12 was being utilized. Correction of low concentrations of vitamin B-12 by oral administration of physiologic amounts (1–10 µg) of vitamin B-12 requires the mediation of intrinsic factor.

The use of 350 µg cyanocobalamin produced a serum vitamin B-12 concentration greater than the lower reference limit in one-half of our patients, but the other one-half still had low concentrations after 3 mo. Other studies from this clinic suggest that all patients can be treated successfully with oral vitamin B-12 if doses are increased to 600 µg/d (16), doses that far exceed the capacity of the vitamin B-12 intrinsic factor absorption mechanism (25).

Is this lowered serum concentration of vitamin B-12 clinically significant? Many studies support the idea that low serum concentrations and a normal result from a Schilling test are frequently encountered and can be accompanied by significant neuropsychiatric complications without the development of megaloblastic anemia, which was absent in our patients (26).

Serum homocysteine concentrations can be used as a measure of the tissue concentrations or functional abundance of vitamin B-12. This may differ from the abundance indicated by the serum concentrations of the vitamin because homocysteine catabolism is a function of the activity of both vitamin B-12–dependent methionine synthase and pyridoxal phosphate–dependent cystathione β-synthase. Consequently, during vitamin B-12 depletion homocysteine accumulation may occur only at a later stage in the process (27). One can only speculate that patients in this study, despite having low serum vitamin B-12 concentrations, were not fully depleted of tissue vitamin B-12 concentrations as evidenced by serum homocysteine concentrations below the upper reference limit (Table 3). That they did respond to vitamin B-12 with a reduction in homocysteine concentrations suggests that they were not fully replete.

This study does not explain why our patients had a normal result from a Schilling test, indicating normal absorption of crystalline vitamin B-12, but at the same time, a low serum concentration despite the administration of two times the RDA or even 350 µg vitamin B-12/d for 3 mo.

There are examples in the literature of discrepancies between results of the Schilling test and serum vitamin B-12 concentrations. Pancreatic insufficiency does interfere with the normal process of absorption of vitamin B-12 as reflected by abnormal Schilling test results in nearly all patients with cystic fibrosis. Despite the frequency of abnormal Schilling test results, vitamin B-12 deficiency is very rare in cases of exocrine pancreatic dysfunction (28). Partial or subtotal gastrectomy can lead to
vitamin B-12 deficiency over time and this is frequently associated with normal absorption of crystalline vitamin B-12 (29, 30). Likewise, atrophic gastritis successively decreases production of gastric acid, pepsin, and intrinsic factor. These patients absorb crystalline vitamin B-12 but develop a serum vitamin B-12 deficiency in 14–22% of cases (31). All patients in this study had normal serum gastrin concentrations, indicating a normal intrinsic factor production (32).

Schilling (33) stated that testing a patient’s ability to absorb the vitamin will not establish the diagnosis of deficiency per se. There can be a substantial decrease in the binding of intrinsic factor to vitamin B-12 after gastric bypass concomitant with a normal Schilling test result because it takes only 10% of normal intrinsic factor secretion for the absorption of 0.5–1.5 μg vitamin B-12—the amount used for the crystalline vitamin B-12 absorption test (34).

Vitamin B-12 deficiency is less likely after vertical banded gastroplasty because there is no diminution of acid production and the food passes via the usual route. In this study, only 2 of 19 patients with gastroplasty had low serum vitamin B-12 concentrations (Figure 2). These patients had normal Schilling test results. Further experience in this clinic indicated a low serum vitamin B-12 concentration in 5 of 63 gastroplasty patients (8%) followed-up for 67.6 ± 12.4 mo. Why these patients had a deficiency of vitamin B-12 cannot be explained by the arguments used above to explain the deficiency in patients after gastric bypass. One gastroplasty patient in this series showed impaired absorption of protein-bound vitamin B-12. Yale et al (10) also found decreased protein-bound vitamin B-12 absorption after gastroplasty, but this defect was less severe than after gastric bypass. It was corrected by boiling the chicken serum before ingestion, which was not so after gastric bypass. Many patients do not consume foods rich in vitamin B-12, especially meat, after vertical banded gastroplasty. We also know that vegetarians are at high risk for vitamin B-12 deficiency over long periods of time.

Patients frequently and rapidly develop a serum vitamin B-12 deficiency after gastric bypass. This is due to a failure to absorb protein-bound vitamin B-12. Despite a normal result from the Schilling test, not all the deficient patients corrected their serum concentrations with doses of oral crystalline vitamin B-12 that were equal to the RDA (2 μg ingested twice daily or 350 μg/d, each taken for 3 mo). A dose > 350 μg/d was necessary to increase serum vitamin B-12 concentrations to values greater than the lower reference limit in every patient.

The therapeutic dose of vitamin B-12 required far exceeds that explainable by the vitamin B-12 intrinsic factor mechanism. Oral treatment of vitamin B-12 deficiency after gastric bypass is effective, but at doses much larger than stipulated by the current nutritional guidelines. A vitamin B-12 deficiency after gastroplasty is much less common. The mechanism is not as yet clear but dietary insufficiency is a distinct possibility.

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REFERENCES