STUDIES ON THE ABSORPTION OF VITAMIN B₁₂
II. OBSERVATIONS IN THE JAPANESE GASTRECTOMIZED SUBJECTS

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A large body of researches have led to general acceptance of the fact that Castle's intrinsic factor plays an essential part in the physiologic mechanism of the intestinal absorption of vitamin B₁₂ (B₁₂) (1). Intrinsic factor is said to be a substance secreted into the gastric juice mainly by the cells located in the body and fundus of the stomach in man (2–4). In other words, the stomach is the very source where intrinsic factor is produced and secreted. This fact has attracted the author's attention to the effect on B₁₂ absorption in the gastrectomized subjects deprived of the source. Regarding the problem, a number of investigations have been reported in Europe and America, demonstrating that the gastrectomized subjects fail to absorb the physiologic amount of radioactive B₁₂ (5–15). In Japan, however, no absorption tests with radioactive B₁₂ has been carried out in gastrectomized subjects, despite the increase in the frequency with which the stomach is resected for the diseases of various etiologies. Meanwhile, the author observed in the previous study with Co⁶⁰·B₁₂ that there was no substantial difference in B₁₂ absorption between the Japanese and the European or the American subjects, so long as it concerns with normal controls and pernicious anemia patients (16). So the author was led to the necessity to investigate whether or not there could be any failure in B₁₂ absorption of the Japanese gastrectomized subjects.

MATERIALS AND METHODS

Absorption of Co⁶⁰·B₁₂¹ (oral dose, 0.2 or 0.5 μg) of high specific activity (0.98 or 1.12 μc/μg) was measured by means of either fecal or urinary excretion test or hepatic uptake method, the details of which have been described in the foregoing paper (16). The range of values in normal controls were found to be 14.4 to

¹ The author is indebted to Dr. Nathaniel Ritter, Merck Institute for Medical Research, Rahway, New Jersey, for generous supply of Co⁶⁰·B₁₂.
² Bifacton was kindly supplied through the courtesy of Dr. Kenneth Thompson, Organon Inc., U.S.A.
³ The capsule was purchased from the Abbott Laboratories, U.S.A.
⁴ D-Sorbitol is a commercial product available in Japan.
41.2% by fecal excretion test, 5.1 to 27.6% by urinary excretion test, and 5.21 to 13.26% by hepatic uptake method, respectively.

As intrinsic factor concentrate, hog intrinsic factor preparation was used in the study; 72 mg of “Bifacton” or 30 mg of intrinsic factor preparation in a capsule was given together with Co-B₁₂ to the subjects tested, when the test was repeated by adding hog intrinsic factor (IF) concentrate. In the meantime, in view of the reports (17-20) that D-sorbitol enhances B₁₂ absorption as intrinsic factor does, the enhancing effect of the agent was likewise studied by adding 5.0 g of D-sorbitol. This agent and hog intrinsic factor concentrates were kept in a screw-capped bottle until used, the former at room temperature and the latter at −20°C.

RESULTS

1. Fecal Excretion

The study was made on 11 subjects. As shown in Table I and Fig. 1, the fecal radioactivities of 7 subjects with partial gastrectomy were within the normal range, from 10.9 to 34.0% of the oral dose, with one exception of the Case No. 14, S.K. This case excreted 50.5% of the radioactivity in the oral dose, showing a slight failure in B₁₂ absorption. On the other hand, two subjects with total gastrectomy (Case No. 10, G.K. and Case No. 11, H.T.) and one subject with subtotal gastrectomy (Case No. 13, K.M.) excreted 65.7, 100 and 65.4%, respectively, thus indicating defective B₁₂ absorption. But the fecal radioactivities were significantly

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Oral dose</th>
<th>Daily excretion after administration</th>
<th>Total excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>G.K.</td>
<td>51 m</td>
<td>Total g.</td>
<td>(5) 0.2 μg B₁₂</td>
<td>13.3 37.6 8.7 2.4 2.4 0.8 0.5 0 0</td>
<td>65.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+ 30 mg IF 28.1 3.1 0.4 0 0 0</td>
<td>31.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+ 5 g Sb 0 — 23.5 40.1 5.2 2.8 0 0</td>
<td>71.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>H.T.</td>
<td>43 f</td>
<td></td>
<td>(1.0) 0.2 μg B₁₂</td>
<td>54.1 30.0 12.4 2.5 1.1 0 0 0</td>
<td>100.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+ 30 mg IF -- 21.1 13.6 8.6 0.2</td>
<td>43.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+ 5 g Sb 2.0 44.7 11.3 5.6 0.3 0 0</td>
<td>87.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>T.K.</td>
<td>19 m</td>
<td>Subtotal g. (4.8) 0.5 μg B₁₂</td>
<td>5.6 45.8 14.2 4.4 1.4 0 0 0</td>
<td>71.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+ 72 mg IF 0 44.0 20.7 0 0 0</td>
<td>64.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+ 18 g TC 27.4 7.6 3.8 1.0 0 0</td>
<td>39.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>K.M.</td>
<td>64 m</td>
<td>Subtotal g. (7.0) 0.2 μg B₁₂</td>
<td>31.4 15.7 11.6 5.4 1.3 0 0 0</td>
<td>65.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+ 30 mg IF 6.7 10.8 7.1 2.2 0 0</td>
<td>26.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+ 5 g Sb 4.1 18.2 10.7 3.5 0.6 0 0</td>
<td>36.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>S.K.</td>
<td>71 m</td>
<td></td>
<td>(1.7) 0.2 μg B₁₂</td>
<td>— 22.5 24.8 3.0 0.2 0 0</td>
<td>50.5</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>S.M.</td>
<td>70 m</td>
<td></td>
<td>(1.9)</td>
<td>0.8 12.1 13.1 — 0.0 0</td>
<td>27.1</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>I.K.</td>
<td>61 f</td>
<td></td>
<td>(2.0)</td>
<td>0.6 6.8 3.5 0 0</td>
<td>10.9</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>M.M.</td>
<td>24 m</td>
<td>G. with colectomy</td>
<td>(2.0)</td>
<td>1.7 10.8 1.9 0.1 0 0</td>
<td>14.5</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>M.S.</td>
<td>28 f</td>
<td>G. with colectomy</td>
<td>0.5</td>
<td>12.6 1.1 0.3 0 0</td>
<td>23.8</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>S.A.</td>
<td>65 m</td>
<td>Partial g.</td>
<td>(2.2) 0.2 μg B₁₂</td>
<td>0 2.4 11.6 3.4 1.2 0 0</td>
<td>18.6</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>H.N.</td>
<td>52 f</td>
<td></td>
<td>(4.8) 0.2 μg B₁₂</td>
<td>2.3 15.4 14.1 2.2 0 0</td>
<td>34.0</td>
<td></td>
</tr>
</tbody>
</table>

The parenthesized figures indicate years after gastrectomy.

g., gastrectomy; IF, intrinsic factor; TC, tetracycline; Sb, D-sorbitol.
decreased to the normal level when 30 mg of hog intrinsic factor was given with the oral dose of Co$_6^{60}$-B$_{12}$. Of interest was the result of another subject with subtotal gastrectomy (Case No. 12, Ta. K.). As illustrated in Fig. 2, 71% of the oral radioactivity was recovered from the feces with the single dose of Co$_6^{60}$-B$_{12}$, and besides, the addition of 72 mg of hog intrinsic factor could not significantly reduce the value of fecal radioactivity, showing 64.7% However, when the test was repeated with a single dose of 0.5 μg of Co$_6^{60}$-B$_{12}$ after the administration of 18 g of tetracycline (1 g per day, for 18 days), the fecal radioactivity was strikingly decreased to 39.8% of the oral dose. This fact implies that the defective B$_{12}$ absorption in this subject was due to the abnormal overgrowth of the intestinal bacterial flora which presumably resulted from extensive resection of the stomach rather than to the lack of intrinsic factor secretion.

As regards the enhancing effect of D-sorbitol on B$_{12}$ absorption, it was demonstrated that the administration of the agent did result in a reduction of fecal radioactivity in a subject with subtotal gastrectomy, but did not in a subject with total gastrectomy (Fig. 1—3, and Table 1).
FIG. 3  Intestinal Absorption of Orally Administered Co₆₀-B₁₂ in a Case of Total Gastrectomy
Fecal excretion and hepatic uptake by G.K., 51-year-old male, total gastrectomy (Case No. 10)

\[
\begin{align*}
\text{Fecal excretion} & \quad \text{Hepatic uptake} \\
\text{Co₆₀-B₁₂ alone} & \quad \text{Co₆₀-B₁₂ + 5 g n-sorbitol} & \quad \text{Co₆₀-B₁₂ + 30 mg hog IF} & \quad \text{Co₆₀-B₁₂ alone} & \quad \text{Co₆₀-B₁₂ + 5 g n-sorbitol} & \quad \text{Co₆₀-B₁₂ + 30 mg hog IF}
\end{align*}
\]

TABLE II  Organ Uptakes of Co₆₀-B₁₂ in Gastrectomy when Hepatic Uptake Reached Maximal

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Name</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Oral Dose</th>
<th>Liver</th>
<th>SI (^a)</th>
<th>Colon</th>
<th>Heart</th>
<th>Spleen</th>
<th>St. (^b)</th>
<th>Sac (^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>G.K.</td>
<td>51 m</td>
<td>Total g</td>
<td></td>
<td>0.2 µg</td>
<td>1.69</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+5 g Sb</td>
<td>0.86</td>
<td>0</td>
<td>0.17</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>13</td>
<td>K.M.</td>
<td>64 m</td>
<td>Subtotal g</td>
<td></td>
<td>0.2 µg B₁₂</td>
<td>2.40</td>
<td>2.11</td>
<td>3.04</td>
<td>2.54</td>
<td>2.41</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+5 g Sb</td>
<td>6.41</td>
<td>3.01</td>
<td>3.86</td>
<td>2.42</td>
<td>2.44</td>
<td>0.18</td>
<td>—</td>
</tr>
<tr>
<td>14</td>
<td>S.K.</td>
<td>71 m</td>
<td>Partial g</td>
<td></td>
<td>0.2 µg B₁₂</td>
<td>2.33</td>
<td>1.86</td>
<td>1.53</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>12</td>
<td>Ta.K.</td>
<td>19 m</td>
<td>Subtotal g</td>
<td></td>
<td>0.5 µg B₁₂</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+18 mg TC</td>
<td>6.82</td>
<td>1.63</td>
<td>1.27</td>
<td>2.00</td>
<td>2.33</td>
<td>2.35</td>
<td>2.06</td>
</tr>
<tr>
<td>16</td>
<td>I.K.</td>
<td>61 f</td>
<td>Partial g</td>
<td></td>
<td>0.2 µg B₁₂</td>
<td>4.99</td>
<td>2.80</td>
<td>3.01</td>
<td>2.30</td>
<td>2.64</td>
<td>—</td>
<td>0.26</td>
</tr>
<tr>
<td>15</td>
<td>S.M.</td>
<td>70 m</td>
<td></td>
<td></td>
<td></td>
<td>5.51</td>
<td>2.26</td>
<td>3.19</td>
<td>2.20</td>
<td>2.30</td>
<td>—</td>
<td>0.35</td>
</tr>
<tr>
<td>19</td>
<td>S.A.</td>
<td>65 m</td>
<td></td>
<td></td>
<td></td>
<td>6.01</td>
<td>3.08</td>
<td>4.00</td>
<td>1.99</td>
<td>2.12</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>17</td>
<td>M.M.</td>
<td>24 m</td>
<td></td>
<td></td>
<td></td>
<td>12.21</td>
<td>3.07</td>
<td>3.91</td>
<td>3.17</td>
<td>3.20</td>
<td>—</td>
<td>0.26</td>
</tr>
<tr>
<td>20</td>
<td>H.N.</td>
<td>52 f</td>
<td></td>
<td></td>
<td></td>
<td>6.61</td>
<td>2.66</td>
<td>1.74</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>18</td>
<td>M.S.</td>
<td>22 f</td>
<td></td>
<td></td>
<td>0.5 µg B₁₂</td>
<td>7.44</td>
<td>2.23</td>
<td>4.87</td>
<td>1.92</td>
<td>2.57</td>
<td>1.49</td>
<td>2.60</td>
</tr>
</tbody>
</table>

\(^{a}\) Small intestine; \(^{b}\) Sternum; \(^{c}\) Sacrum.

2. Hepatic Uptake

The measurement of hepatic uptake of the oral Co₆₀-B₁₂ was performed in 10 gastrectomized subjects with the results given in Figs. 2—3, and Tables II—III. The hepatic uptake was in trace or none in a subject with total gastrectomy (Case No. 10, G.K.) and two subjects with subtotal gastrectomy (Case No. 12, Ta.K. and Case No. 13, K.M.), showing 1.69, 0 and 2.40 %, respectively. The impaired
hepatic uptake in total gastrectomy (Case No. 10, G. K.) and subtotal gastrectomy (Case No. 13, K. M.) was restored to the normal level by the addition of 30 mg hog intrinsic factor (Fig. 3 and Table III). However, the abolished hepatic uptake in another case of subtotal gastrectomy (Case No. 12, Ta. K.) could not be amended by 72 mg of hog intrinsic factor, but instead, it was completely corrected to the normal level after tetracycline administration (Fig. 2 and Table III). Thus, it was again confirmed that the excessive bacterial population in the intestine was responsible for the impaired hepatic uptake in this case. In partial gastrectomy, however, the hepatic uptake was within the normal range. d-Sorbitol did not enhance the defective hepatic uptake in total gastrectomy (Case No. 10, G. K.), though it raised the uptake to some extent in subtotal gastrectomy (Case No. 13, K. M.) (Table III).

3. Urinary Excretion

Urinary excretion test was carried out in 9 gastrectomy subjects. As illustrated in Table IV, urinary excretions of the oral dose ranged from 0 to 21.7%. In total gastrectomy (Case No. 10, G. K.), the urinary radioactivity was 0.9% of the oral radioactivity, indicating a strikingly defective B₁₂ absorption. Equivocal decrease in urinary excretion of orally administered Co⁶⁰-B₁₂ was observed in a subject with partial gastrectomy (Case No. 14, S. K.), but the urinary excretions were within the normal range in all the remaining subjects with partial gastrectomy. In a subject with subtotal gastrectomy (Case No. 12, Ta. K.), tetracycline administration resulted in a rise in urinary radioactivity to the normal, whereas no radioactivity was detected in the urine when 0.5 μg of Co⁶⁰-B₁₂ was given with or without hog intrinsic factor (Fig. 4 and Table IV).
DISCUSSION

In 1953, Castle reported that intrinsic factor was responsible for effecting the transfer of the physiologic amount of B12 across the intestinal mucosa and into the blood stream (1). At present, this is generally accepted through subsequent large body of researches. The investigations by many workers over the past years indicate (5—10) that the subjects totally gastrectomized fail to absorb the normal amounts of Co60-B12 unless the dose is given together with a potent source of intrinsic factor. This failure in B12 absorption is attributed to the lack of intrinsic factor secretion resulted from the removal of the stomach. There are many observations (11—14) to show that the similar failure can occur in partial gastrectomy as well and is followed by mild B12 deficiency. This failure is likewise accounted for by the diminished secretion of intrinsic factor from the partially resected stomach. In the meantime, it was reported (7, 15) that most of the subjects partially gastrectomized do not necessarily fail to absorb the normal amounts of B12, and the failure, if any, is rather slight.

Regarding B12 absorption in subtotal gastrectomy, Brodine et al. (21) and Maclean (15) demonstrated that defective B12 absorption could be observed as well in some cases. Lowenstein (14) reported that only three subjects who had undergone subtotal gastrectomy over 6 years ago failed to absorb the normal amounts of B12. Glass et al. (7) also revealed the lowered hepatic uptake of Co60-B12 in subtotal gastrectomy. Some experimental studies (22—24) demonstrate that the gastrectomized rat is unable to absorb B12 either.

In this study, a marked defect in B12 absorption was observed to occur almost uniformly in total or subtotal gastrectomy by either fecal or urinary excretion test or by hepatic uptake method unless hog intrinsic factor was added. On the contrary, any defect in B12 absorption was not in general observed in partial gastrectomy.
with only one exception of Case No. 14, S.K. These results indicate that extensive gastric resection such as total or subtotal gastrectomy results in the lack or diminution in the intrinsic factor secretion, eventually giving rise to the failure in $B_{12}$ absorption. It is of interest to note that the defective $B_{12}$ absorption in case No. 12, Ta.K. was corrected to normal after tetracycline administration. This fact indicates that the defective $B_{12}$ absorption was due to excessive bacterial population in the intestine which presumably resulted from gastrectomy rather than to the lack of intrinsic factor. Burkholder (25) isolated in 1952 vitamin $B_{12}$-binding strains of bacteria from the gastric and jejunal juice of patients suffering from pernicious anemia and showed that hog stomach concentrates could prevent the bacterial uptake of $B_{12}$ by binding the vitamin. Thus he suggested that intrinsic factor might have inhibited the uptake of $B_{12}$ by the intestinal flora. Similarly, Pribilla et al. (10), Witts (26), and Naish et al. (27) reported that abnormal overgrowth of intestinal bacterial flora might play an important role in the defective $B_{12}$ absorption or in the development of megaloblastic anemia. Moreover, a number of investigators (28–31) showed that treatment with antibiotics such as tetracycline or oxytetracycline restored the defect in $B_{12}$ absorption in many patients with anatomical lesions of the small intestine, indicating that the removal of abnormal intestinal bacterial flora by such antibiotics administration was quite effective for the correction of defective $B_{12}$ absorption.

Meanwhile, it is readily acceptable that the defect in $B_{12}$ absorption is followed by a decrease in blood $B_{12}$ level or by the development of megaloblastic anemia in a period of time after gastrectomy. Mollin et al. reported that in totally or partially gastrectomized subjects blood $B_{12}$ levels were lowered on the average as compared with those in the normals (31) and besides the lowering occurred prior to the development of megaloblastic anemia (32). Ikemoto (33) claimed in the study of blood $B_{12}$ level in gastrectomized subjects by microbiological assay using Ochromonas malhamensis that the decrease in blood $B_{12}$ levels were, in general, in good proportion with years after gastrectomy or with the extensiveness of gastric resection. Pitney et al. reported (34) that the decrease below normal blood $B_{12}$ level was observed as early as 11 months after total gastrectomy. The results in the present study are suggestive of the possibility that the more extensive the gastric resection, the more defective the $B_{12}$ absorption. This is illustrated in Fig. 4. However, as to the relation between the defective $B_{12}$ absorption and years after gastrectomy, no definite conclusion was drawn from the results obtained. It may go without saying that the failure in $B_{12}$ absorption in gastrectomy has nothing to do with years after gastrectomy, since the failure had possibly already begun to occur at the very time when the source of intrinsic factor was removed by
gastrectomy, and thereafter it may remain uncorrected for subsequent years, while manifestations of B₁₂ deficiency may become more and more apparent with the elapse of years after gastrectomy.

As regards the megaloblastic anemia following gastrectomy, many reports (35–38) indicate that it occurs in more than 3 years after the resection. As a matter of fact, approximately 500 to 1000 µg of B₁₂ is stored in normal human body, chiefly in the liver, as a body store. Therefore, it would take at least 500 to 1000 days before the exhaustion of the vitamin stored in the body, supposing that the daily requirement for B₁₂ does not exceed 1.0 µg. In this study, however, megaloblastic anemia was not observed in all the gastrectomized subjects but one (Case No. 12, Ta. K.). Case No. 12, Ta. K. had subtotal gastrectomy for gastric ulcer 4.8 years ago and received no antianemic drugs ever since the operation.

As was already described, abnormal bacterial population in the intestine was responsible for the defective absorption of Case No. 12, Ta. K., which possibly led to the development of megaloblastic anemia. At present, it is accepted that megaloblastic anemia does not necessarily result from gastrectomy. This may be accounted for as follows: (a) As a rule, total or subtotal gastrectomy is carried out for gastric cancer, which often recurs with its additional metastases to other organs, so that most subjects who had such an extensive gastrectomy are unable to live long enough to suffer from megaloblastic anemia. (b) Even after extensive gastrectomy, a small area of the cardia may be occasionally preserved, which serves as a source of intrinsic factor, making it possible to absorb B₁₂. (c) It is after a long period of time that the depletion of the body store of B₁₂ occurs following gastrectomy. (d) In addition, on behalf of recent advance in antianemic drugs, gastrectomized subjects are often given the drugs such as B₁₂, folic acid, etc., whereby the manifestations of megaloblastic anemia are prolonged or overshadowed. Halsted et al. (39) likewise made a similar explanation.

Furthermore, attentions have been recently attracted to the atrophic lesions in the mucosa of the partially resected stomach. A large number of reports (10, 11, 14, 15, 26) were made on the coexistence of gastric atrophy and defective B₁₂ absorption in gastrectomized subjects. Siurala et al. (40, 41) have demonstrated that chronic atrophic gastritis revealed by gastric suction biopsy, the end sequel of which is almost indistinguishable from the atrophic lesion of pernicious anemia, may lead to deficient secretion of intrinsic factor and possibly to pernicious anemia. Glass et al. (42) made a correlative study of gastric suction biopsy and hepatic uptake, and confirmed that the severity of gastric atrophic lesion was well correlated with lowered hepatic uptake, indicating that gastric atrophic lesion might be an underlying cause for the defective B₁₂ absorption. In the present study, however, no observation was made on the gastric mucosa of gastrectomized subjects, on which it will be dealt with in the following paper.

Since Chow et al. (17) and Greenberg et al. (18) reported that D-sorbitol enhanced intestinal B₁₂ absorption in the normal person and rat, a great interest in this agent was aroused. However, according to the results obtained in this study, D-sorbitol did not always exert the enhancing effect; i.e., it was observed by either fecal excretion or hepatic uptake method that D-sorbitol did enhance the B₁₂ absorption in
subtotal gastrectomy, but did not in total gastrectomy at all. Herbert (43) demonstrated in an in vitro experiment that the agent had no effect on either the intrinsic factor-dependent or the intrinsic factor-independent uptake of B$_{12}$ by rat liver slices. On the other hand, there is also a report (44) that D-sorbitol had no enhancing effect in patients suffering from pernicious anemia. Thus Herbert (46) emphasized to accept the possibility that the mode of action of D-sorbitol was solely to enhance the secretion of intrinsic factor. Judging from intrinsic factor secretion, there exists a clearcut difference between total and subtotal gastrectomy. In the latter the source of intrinsic factor is still, more or less, preserved, while in the former there remains very little, if any, source on which D-sorbitol may exert its effect to chance intrinsic factor secretion. So the present author feels it to be justified to conclude that D-sorbitol has no intrinsic factor activity itself, but exert its enhancing effect only when the capacity of the stomach to secrete intrinsic factor is still retained more or less, i.e., only in the coexistence of intrinsic factor source. However, another possibility that D-sorbitol enhances the absorption of B$_{12}$ across the intestinal wall in the presence of intrinsic factor should also be considered.

**SUMMARY**

The intestinal absorption of orally administered Co$^{60}$-B$_{12}$ was studied in Japanese subjects having undergone gastrectomy by means of either fecal or urinary excretion test or hepatic uptake method. At the same time, in conformity of the reports that D-sorbitol is able to enhance B$_{12}$ absorption in normal persons, the effect of the agent was investigated in gastrectomized subjects. Results obtained are as follows:

1. In extensive gastric resection such as total or subtotal gastrectomy, a strikingly defective B$_{12}$ absorption was observed in all the cases tested by either method. The defect in B$_{12}$ absorption was corrected by the addition of hog intrinsic factor, indicating that the lack of intrinsic factor is responsible for the defect. In partial gastrectomy, however, B$_{12}$ absorption was found to be normal in all the cases but one. Thus the author was led to a conclusion that the more extensive the gastric resection, the more defective the B$_{12}$ absorption in general.

2. As regards the enhancing effect of D-sorbitol, it was noted that the addition of the agent did correct the defective B$_{12}$ absorption in subtotal gastrectomy, but did not in total gastrectomy. So it was concluded (a) that D-sorbitol had no intrinsic factor activity itself and (b) that the agent could enhance B$_{12}$ absorption only when the resected stomach preserved the function of intrinsic factor secretion, no matter how little it may be.

3. Of interest was the B$_{12}$ absorption in a case of subtotal gastrectomy; neither hog intrinsic factor nor D-sorbitol was effective for the enhancement of the B$_{12}$ absorption, whereas tetracycline administration resulted in a marked improvement of the defective B$_{12}$ absorption. Thus the defective absorption was demonstrated to be due solely to abnormal bacterial population in the intestine rather than to the lack of intrinsic factor.

4. In addition, some brief comments were made on the relation between B$_{12}$ absorption and megaloblastic anemia following gastrectomy.
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REFERENCES


