Absorption of Cobalt\(^{60}\)-Labeled Vitamin B\(_{12}\) After Subtotal Gastrectomy

By Fritz Loewenstein

MEGALOBLASTIC ANEMIA is common in patients who survive total gastrectomy by several years.\(^1\) Absorption of radioactive vitamin B\(_{12}\) is impaired after total gastrectomy and can be corrected with intrinsic factor.\(^5\) Subtotal gastrectomy, on the other hand, seldom leads to megaloblastic or macrocytic anemia; there are only occasional reports of such an occurrence.\(^7\) This is presumably because not enough of the stomach is resected to remove the entire source of intrinsic factor. Badenoch et al.,\(^9\) however, were able to study five patients who developed megaloblastic anemia after subtotal gastrectomy, and they demonstrated impaired vitamin B\(_{12}\) absorption in all five. The present studies concern the absorption of vitamin B\(_{12}\) in a large number of patients who had had subtotal gastrectomy. The effects of gastric resections varying in site and extent have been compared.

MATERIALS AND METHODS

Absorption of cobalt\(^{60}\) labeled vitamin B\(_{12}\) was measured by means of a modification\(^7\) of the Schilling urinary excretion test,\(^7\) the results being expressed as the per cent radioactivity of the oral dose (0.5 \(\mu\)g Co\(^{60}\) B\(_{12}\)) excreted in the urine in 48 hours. With this procedure, the range of values was found to be 21 to 48 per cent in 16 control subjects and 1 to 7 per cent in 9 patients with pernicious anemia. Successive tests in the same patients were done at intervals of no less than two weeks.

Human gastric juice was used as a source of intrinsic factor. After aspiration, it was tested with Topfer’s reagent and was used only if acid. It was then filtered through wide-mesh gauze, neutralized with sodium hydroxide, and stored at \(-20\) C. It was given in 75 to 100 ml. amounts, together with the test dose of Co\(^{60}\) B\(_{12}\).

All of the subjects of this study, except patient 16, table 2, were males. An effort was made to find and test as many patients as possible who had anemia or gastrointestinal symptoms. The description of the gastrectomy was usually derived from the surgeon’s dictated notes. In the few cases (patients 9, 16, 17, and 25, table 2) in which such a record was not available, the x-ray appearance of the barium-filled stomach remnant was used to assess the extent of resection. In almost all cases, the report of the pathologist specified that a small portion of the duodenum was attached to the resected segment of stomach, thus insuring that the entire distal portion of the stomach had been removed.

RESULTS

Five patients who underwent a conventional (distal) subtotal gastrectomy because of peptic ulcer were studied before and after operation (table 1). The absorption of vitamin B\(_{12}\) was normal in all five and did not change significantly as a result of the removal of most of the stomach. In one patient,
who had had a two-thirds gastrectomy five years previously, a transabdominal vagotomy produced no change in ability to absorb vitamin B₁₂.

Tables 2 and 3 give data in 24 patients who were studied at variable periods of time after a distal subtotal gastrectomy. All of these patients had benign gastric or duodenal ulcers, except patient 27, who at operation was found to have a gastric carcinoma near the pylorus. When anemia was present, it was almost always hypochromic, microcytic, and associated with a low serum iron concentration. All 22 patients who had had a conventional subtotal gastrectomy absorbed vitamin B₁₂ normally, except for the three patients listed in table 3. In these, absorption was in or near the range of values obtained in pernicious anemia and was corrected to or near the normal range when gastric juice was given with the test dose. At the time of operation the gastric aspirate was acid and the gastric mucosa had a normal microscopic appearance in two of the patients listed in table 3 (No. 28 and No. 30). No information on these points is available in the case of patient 29. Two patients, (No. 26 and No. 27, table 2), had had very extensive subtotal resections which left behind only a few centimeters of the cardiac portion of the stomach. In these two, absorption of vitamin B₁₂ was subnormal, but not in the range found in pernicious anemia.

Three patients were studied who had had removal of only the superior portion of the stomach plus several centimeters of the lower esophagus (table 4). In each one, the result of the vitamin B₁₂ absorption test fell into the normal range.

**DISCUSSION**

In general, the results of this study indicate that impairment of vitamin B₁₂ absorption is unusual after subtotal gastrectomy, even in a group of patients selected for their anemia and gastrointestinal complaints. When gastrectomy was virtually total, impaired absorption was observed (patients 26 and 27, table 2).

Nevertheless, there were three patients who absorbed relatively low amounts although they did have unusually extensive gastrectomies (table 3). Since the defect in absorption was corrected by normal gastric juice, it can be
attributed to a lack of intrinsic factor and not to stagnation in intestinal blind loops, which occasionally develop after subtotal gastrectomy. In the presence of such blind loops, absorption of vitamin B₁₂ may be impaired but not corrected when intrinsic factor is given. These patients, therefore, resemble those described by Badenoch et al. who studied five patients with megaloblastic anemia developing from two to twelve years after subtotal gastrectomy. Three showed low serum concentrations of vitamin B₁₂ and a good hematologic response to vitamin B₁₂. All had abnormally low cobalt-labelled B₁₂ absorption, which was corrected to normal when intrinsic factor was given with the test dose. In four of the five patients, gastric biopsy showed atrophy of the mucosa, which had not been present at the time of gastrectomy. The authors were unable to explain the failure to secrete intrinsic factor. They observed, however, that the patients who were shown to have gastric atrophy were originally operated upon because of gastric ulcer, which may in itself have led to gastritis, atrophy, and loss of secretory function.

There were no obvious differences between the 19 patients who absorbed vitamin B₁₂ normally and the three who did not. Two of these three patients had duodenal ulcers and one a gastric (pyloric) ulcer. Two of them had iron deficiency anemia when studied, but this was a common finding in those patients who absorbed vitamin B₁₂ normally. On the other hand, the only patient who had iron depletion severe enough to produce koilonychia (patient 28, table 3) was among the three with low absorption, and a recent study suggests that long continued tissue sideropenia may lead to gastric atrophy and intrinsic factor deficiency. In this particular patient vitamin B₁₂ absorption was still demonstrated to be low five months after the first absorption test—at a time when 1.6 Gm. of intravenous iron had been given, the hemoglobin had returned to 15.6 Gm., and the fingernails had begun to assume their normal shape.

It may be significant that all three patients with low vitamin B₁₂ absorption after a conventional gastrectomy were tested more than six years post-operatively, whereas most of the patients who had normal absorption had had their gastrectomies within six years (on an average three years) since gastrectomy. This finding suggests that the causes of intrinsic factor deficiency after subtotal gastrectomy require years to have their effect. Macrocytic anemia was not observed in the patients whose absorption was low, perhaps because the absorptive defect had not existed long enough to produce a deficiency state.

In view of the general belief that intrinsic factor is secreted by the gastric fundus, it is of considerable interest that the three patients who had had the upper (proximal) portion of the stomach removed were able to absorb vitamin B₁₂ normally. In these patients, intrinsic factor could not have originated at a site other than the stomach, since previous studies have indicated that the stomach is the only source of intrinsic factor. Normal duodenal secretions, uncontaminated by gastric juice, produced no reticulocytosis when given to patients with pernicious anemia, and in another study jejunal juice obtained after total gastrectomy also failed to produce a reticulocyte
**Table 2.—Clinical and Laboratory Data in Patients with Distal Gastrectomies**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Present Age</th>
<th>Interval Since Gastrectomy</th>
<th>Reason for Gastrectomy</th>
<th>Type of Operation</th>
<th>Estimated Extent of Gastrectomy</th>
<th>Present Symptoms</th>
<th>Hemoglobin (Gm./100 ml.)</th>
<th>MCV, MCH, MCHC</th>
<th>48-Hr. Urinary Radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>T.McG.</td>
<td>61</td>
<td>6 yrs.</td>
<td>Gastric Ulcer</td>
<td>Polya with posterior gastroduodenostomy</td>
<td>2/3</td>
<td>Numbness of hands</td>
<td>15.4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>D.M.</td>
<td>51</td>
<td>3 yrs.</td>
<td>Pyloric Ulcer</td>
<td>Polya with anterior gastrojejunostomy</td>
<td>4/5</td>
<td>Postprandial weakness and sweating</td>
<td>14.7</td>
<td>—</td>
<td>92</td>
</tr>
<tr>
<td>J.C.</td>
<td>24</td>
<td>6 mos.</td>
<td>Bleeding Duodenal Ulcer</td>
<td>Billroth I</td>
<td>1/3</td>
<td>None</td>
<td>15.6</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>M.S.</td>
<td>57</td>
<td>4 mos.</td>
<td>Bleeding Pyloric Ulcer</td>
<td>Hofmeister with anterior gastrojejunostomy</td>
<td>3/4</td>
<td>None</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>W.E.</td>
<td>27</td>
<td>3 ½ yrs.</td>
<td>Duodenal Ulcer</td>
<td>Hofmeister with anterior gastrojejunostomy</td>
<td>3/4</td>
<td>None</td>
<td>18.7</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>A.S.</td>
<td>61</td>
<td>5 mos.</td>
<td>Perforated Duodenal Ulcer</td>
<td>Hofmeister with anterior gastrojejunostomy</td>
<td>2/3</td>
<td>None</td>
<td>18.7</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>E.H.</td>
<td>63</td>
<td>16 mos.</td>
<td>Duodenal Ulcer</td>
<td>Hofmeister with anterior gastrojejunostomy</td>
<td>3/4</td>
<td>Numbness of legs; generalized weakness</td>
<td>7.6</td>
<td>72, 20, 28</td>
<td>17, 37</td>
</tr>
<tr>
<td>W.A.</td>
<td>62</td>
<td>2 ½ yrs.</td>
<td>Bleeding Duodenal Ulcer</td>
<td>Hofmeister with anterior gastrojejunostomy</td>
<td>2/3</td>
<td>Epigastric pain</td>
<td>13.2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>W.B.</td>
<td>27</td>
<td>15 mos.</td>
<td>Bleeding Duodenal Ulcer</td>
<td>Hofmeister with anterior gastrojejunostomy</td>
<td>2/3</td>
<td>Numbness of legs; generalized weakness</td>
<td>16.6</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>M.C.</td>
<td>45</td>
<td>4 mos.</td>
<td>Duodenal Ulcer</td>
<td>Gastrojejunostomy</td>
<td>2/3</td>
<td>Serum hepatitis with vomiting and jaundice</td>
<td>10.4</td>
<td>—</td>
<td>29</td>
</tr>
<tr>
<td>J.R.</td>
<td>39</td>
<td>3 ½ yrs.</td>
<td>Duodenal Ulcer</td>
<td>Gastrojejunostomy</td>
<td>2/3</td>
<td>Epigastric pain; vomiting</td>
<td>18.7</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>A.T.</td>
<td>40</td>
<td>4 yrs.</td>
<td>Bleeding Duodenal Ulcer</td>
<td>Hofmeister with anterior gastrojejunostomy</td>
<td>2/3</td>
<td>Mild diarrhea</td>
<td>18.4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>E.A.</td>
<td>41</td>
<td>16 mos.</td>
<td>Duodenal Ulcer</td>
<td>Gastrojejunostomy</td>
<td>2/3</td>
<td>Weight loss</td>
<td>12.9</td>
<td>30</td>
<td>—</td>
</tr>
</tbody>
</table>
### Table 2, continued

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Age</th>
<th>Condition</th>
<th>Procedure</th>
<th>Symptoms</th>
<th>GC</th>
<th>controlId</th>
</tr>
</thead>
<tbody>
<tr>
<td>(20)</td>
<td>A.V.</td>
<td>62</td>
<td>5 yrs. Bleeding Gastric Ulcer</td>
<td>Hofmeister with gastro-duod...</td>
<td>Angina pectoris &amp; anemia 8.9</td>
<td>78, 21, 28</td>
<td>29</td>
</tr>
<tr>
<td>(21)</td>
<td>F.K.</td>
<td>35</td>
<td>14 mos. Gastric Ulcer</td>
<td>Hofmeister with gastro-jejuno...</td>
<td>Weight loss 8.7</td>
<td>— —</td>
<td>48</td>
</tr>
<tr>
<td>(22)</td>
<td>G.H.</td>
<td>74</td>
<td>4 yrs. Bleeding Gastric Ulcer</td>
<td>Hofmeister with anterior gastro-jej...</td>
<td>None 10.4</td>
<td>90, 27, 29</td>
<td>51 37</td>
</tr>
<tr>
<td>(23)</td>
<td>C.H.</td>
<td>58</td>
<td>11 yrs. Bleeding Duodenal Ulcer</td>
<td>Hofmeister with posterior gastro-jejuno...</td>
<td>Dyspnea and anemia 9.1</td>
<td>67, 18, 27</td>
<td>— 27</td>
</tr>
<tr>
<td>(24)</td>
<td>G.C.</td>
<td>49</td>
<td>2 yrs. Bleeding Duodenal Ulcer</td>
<td>Hofmeister with anterior gastro-jejuno...</td>
<td>Weight loss; postprandial nausea &amp; sweating 10.0</td>
<td>— —</td>
<td>— —</td>
</tr>
<tr>
<td>(25)</td>
<td>J.D.</td>
<td>42</td>
<td>8 yrs. Perforated Duodenal Ulcer</td>
<td>Gastrojejunostomy 1/2</td>
<td>Recurrent acute pancreatitis 11.1</td>
<td>78, 24, 31</td>
<td>31 24</td>
</tr>
<tr>
<td>(26)</td>
<td>A.M.</td>
<td>60</td>
<td>1 mo. Gastric Ulcer</td>
<td>Gastro-duodenojejunostomy</td>
<td>Almost Total Postprandial epigastric discomfort 11.2</td>
<td>— —</td>
<td>10</td>
</tr>
<tr>
<td>(27)</td>
<td>T.W.</td>
<td>61</td>
<td>2 mos. Gastric Carcinoma Near the Pylorus</td>
<td>Gastro-duodenojejunostomy</td>
<td>Almost Total Diarrhea 11.6</td>
<td>— —</td>
<td>15</td>
</tr>
</tbody>
</table>
### Table 3.—Clinical and Laboratory Data in Patients with Distal Subtotal Gastrectomies and Subnormal Vitamin B₁₂ Absorption

| Patient | Present Age | Interval Since Gastrectomy | Reason for Gastrectomy | Type of Operation | Estimated Extent of Gastrectomy | Present Symptoms | Hb (Gm./100 ml.) | MCV - MCH | Serum Iron (mg./100 ml.) | Without Gastric Juice | With Gastric Juice | 6-Hr. Urinary Radioactivity (%)
<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>J.M.</td>
<td>30</td>
<td>6 yrs.</td>
<td>Duodenal Uleer</td>
<td>Hofmeister with anterior gastrojejunostomy</td>
<td>3/4</td>
<td>Epigastric Pain</td>
<td>8.4</td>
<td>20</td>
<td>20,13</td>
<td>8</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>J.B.</td>
<td>36</td>
<td>7 yrs.</td>
<td>Perforated Duodenal Uleer</td>
<td>Gastrojejunostomy</td>
<td>3/4</td>
<td>Weight Loss</td>
<td>9.7</td>
<td>20</td>
<td>39,16</td>
<td>6</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>J.V.</td>
<td>58</td>
<td>7 yrs.</td>
<td>Pyloric Uleer</td>
<td>Polyectomy with gastrojejunostomy, vagotomy</td>
<td>2/3</td>
<td>Epigastric Pain, Vomiting</td>
<td>12.7</td>
<td>10</td>
<td>10</td>
<td>8</td>
<td>88</td>
<td></td>
</tr>
</tbody>
</table>

*Five months after initial test and after anemia had been corrected with 1.8 Gm. of saturated ferrous oxide given intravenously.*

### Table 4.—Clinical and Laboratory Data in Patients with Proximal Subtotal Gastrectomies

| Patient | Present Age | Interval Since Gastrectomy | Reason for Gastrectomy | Type of Operation | Estimated Extent of Gastrectomy | Present Symptoms | Hb (Gm./100 ml.) | MCV - MCH | Serum Iron (mg./100 ml.) | Without Gastric Juice | With Gastric Juice | 6-Hr. Urinary Radioactivity (%)
<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>J.P.</td>
<td>35</td>
<td>4½ yrs.</td>
<td>Gastric Carcinoma</td>
<td>Esophagogastrostomy</td>
<td>2/3</td>
<td>Occasional Heartburn</td>
<td>12.0</td>
<td>—</td>
<td>—</td>
<td>21</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>R.S.</td>
<td>69</td>
<td>4 yrs.</td>
<td>Carcinoma of Cardia</td>
<td>Esophagogastrostomy</td>
<td>1/3</td>
<td>None</td>
<td>12.0</td>
<td>—</td>
<td>—</td>
<td>56</td>
<td>—</td>
<td>22</td>
</tr>
<tr>
<td>D.L.</td>
<td>63</td>
<td>6½ yrs.</td>
<td>Achalasia</td>
<td>Esophagogastrostomy</td>
<td>3/4</td>
<td>Dysphagia</td>
<td>12.0</td>
<td>56</td>
<td>22</td>
<td>88</td>
<td>42</td>
<td></td>
</tr>
</tbody>
</table>
ABSORPTION OF COBALT$^{60}$-LABELLED VITAMIN B$_{12}$

response.$^{17}$ With radioactive vitamin B$_{12}$, a loss of intrinsic factor has been demonstrated in patients who have undergone gastrectomy.$^{5,6}$

Previous methods of localizing the gastric site of intrinsic factor formation have involved the feeding of mucosal preparations from various parts of the stomach to patients with untreated pernicious anemia. The first intrinsic factor assays were done with hog stomach preparations. Activity was uniformly present in the gastric mucosa adjacent to the pylorus and in duodenal mucosa, but the middle and upper third of the stomach were only partially effective.$^{18}$ Experiments with human stomach preparations gave different results. The upper two-thirds of the human stomach have appeared to be the most active hematopoietically, but pyloric preparations and, in one instance even a duodenal preparation, have shown some effect.$^{19,21}$ Experiments such as these are, of course, cumbersome, the number of assays necessarily small, and the results sometimes contradictory. However, the general conclusions are supported by the fact that at autopsies of patients with pernicious anemia, the most severe mucosal atrophy has been found in the upper portion of the stomach, whereas the pyloric portion has shown either no abnormalities$^{22}$ or only partial changes.$^{23,24}$ It should be remembered, on the other hand, that cases of pernicious anemia without gastric atrophy have been observed,$^{27}$ and, therefore, that atrophy of the upper and middle portions of the stomach may not be the cause of intrinsic factor deficiency.

In all three of our patients with proximal gastrectomies, the distal portion of the stomach produced sufficient intrinsic factor to allow normal vitamin B$_{12}$ absorption, even when only one-quarter of the stomach remained (patient 33, table 3). MacLean demonstrated impaired radioactive B$_{12}$ absorption in three patients who had a proximal subtotal resection with esophagoantrostomy.$^{28}$ Details about the size of the gastric remnant were not given, and it may be that only a few centimeters of gastric mucosa were left behind. If so, one might expect intrinsic factor deficiency just as in patients 26 and 27 (table 2) who had resections sparing only a few centimeters of cardiac mucosa. From the data presented above, it is impossible to be certain that the pyloric antrum is as active in intrinsic factor secretion as the upper portion of the stomach. In at least one instance, however, the retention of as little as 3 cm. of pyloric antrum after a very extensive proximal gastrectomy has protected a patient against megaloblastic anemia for over 10 years after operation.$^{29}$ In contrast, patients inevitably develop megaloblastic anemia within six to seven years after total gastrectomy.$^{24}$

Since both the distal fourth and proximal fourth of the stomach can produce enough intrinsic factor to maintain normal B$_{12}$ absorption, it appears that the secretion of intrinsic factor takes place in a wide area of the stomach.

**Summary**

Vitamin B$_{12}$ absorption has been studied in patients with subtotal gastrectomy by means of the Co$^{60}$ B$_{12}$ urinary excretion test. Five patients tested before and after a conventional subtotal gastrectomy showed no significant change in absorption.

Of 22 patients who were tested at various intervals after a conventional (distal) subtotal gastrectomy, 19 had normal vitamin B$_{12}$ absorption and
three had low absorption that was corrected to normal by giving gastric juice with the test dose. Three patients who had had a proximal gastrectomy showed normal vitamin B\textsubscript{12} absorption, indicating that intrinsic factor was being produced by the remaining distal portion of the stomach.

**SUMMARIO IN INTERLINGUA**

I.e absorption de vitamina B\textsubscript{12} esseva studiate in patientes con gastrectomia subtotal per medio del test del excretion urinari de B\textsubscript{12} marcate con Co\textsuperscript{60}. Cinque patientes qui esseva testate ante e post un conventional gastrectomia subtotal monstrava nulle significative alteration del absorption.

Ex 22 patientes qui esseva testate a varie intervallos post un conventional gastrectomia subtotal (distal), 19 habeva un absorption normal de vitamina B\textsubscript{12}; tres habeva basse grados de absorption que esseva normalisate per le administration de succo gastric con le dosage experimental. Tres patientes qui habeva habite un gastrectomia proximal monstrava un normal absorption de vitamina B\textsubscript{12}. Isto indicava que factor intrinsec esseva producite per le remanente portion distal del stomacho.

**REFERENCES**

relationship of achylia gastrica to pernicious anemia. III. The nature of the reaction between normal human gastric juice and beef muscle leading to clinical improvement and increased blood formation similar to the effect of liver feeding. Am. J. Med. Sc. 180:305, 1930.


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