

Vitamin B₁₂ Absorption Following Vagotomy and Gastric Surgery*

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MACROCYTIC ANEMIA has been a known sequela of total gastrectomy.^{10, 16, 18, 22} This has been related to an absence of the intrinsic factor, which is formed in the stomach, and the consequent interference with the ileal absorption of vitamin B₁₂.^{9, 10, 22} More recently, subnormal levels of vitamin B₁₂ absorption have been noted following partial gastrectomy and the potential development of anemia has been appreciated.^{6, 16, 19} Recognition of this complication of gastric resection has been delayed because a period of three to five years elapses before the body reserves of vitamin B₁₂ are exhausted and anemia becomes evident.²³ The effect of vagotomy on vitamin B₁₂ absorption has not been studied and the clinical development of macrocytic anemia has not been reported following this procedure.⁷

It is well recognized that absorption of vitamin B₁₂ occurs in the distal ileum, both in humans and experimental animals.^{1, 20} Binding of the vitamin B₁₂ by the intrinsic factor, which is secreted by the gastric mucosa, is necessary for absorption.^{3, 5, 12, 14, 15, 25, 26} This binding action is enhanced by an acid medium and the optimum pH is 3.5.^{3-5, 13} Calcium has also been implicated in B₁₂ absorption³ and the administration of sorbitol has been shown to have an inhibitory effect.^{21, 22} The increasing clinical concern for anemia following gastric operations stimulated this experimental study.

Methods

In all studies, a modification of the Schilling test²⁴ was used to determine the ab-

sorption of orally administered radioactive cobalt-labeled vitamin B₁₂. At the time of this test, the dogs were partially anesthetized with pentobarbital sodium. A nasogastric tube was passed into the stomach and one microcurie of Rubratope 60 (Squibb), a radioactive cobalt-labeled vitamin B₁₂ with 0.96 microcurie of activity per cc., was diluted in 100 cc. of normal saline and administered to dogs which had been fasted. Two hours later, 1,000 micrograms of nonradioactive vitamin B₁₂ were injected intramuscularly in order to flush the radioactive vitamin B₁₂ through the kidneys, and the animals were placed in metabolic cages for urine collection. Special attention was directed toward the prevention of fecal contamination of the urine. After the urine was collected for a period of 24 hours, the animals were anesthetized and catheterized to empty the bladder. The voided and catheterized specimens were mixed, an aliquot of 10 cc. was counted by means of a scintillator and the radioactivity was expressed in per cent of the administered dose. Four major groups of animals were studied.

A. Control. Four healthy adult mongrel dogs with weights varying from 12 to 35 lb. were used. The amount of radioactivity recovered in the urine was determined. In an additional four dogs, a Witzel type duodenostomy was made in the second portion of the duodenum and a Foley catheter was introduced in such a fashion that the balloon was positioned at the ligament of Treitz. A week subsequent to this procedure, the prescribed amount of Rubratope 60 was administered via the catheter after the balloon had been inflated to prevent

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regurgitation into the proximal portions of the duodenum and the stomach. Measurement of urinary radioactivity was carried out after 24 hours of collection.

B. Total Gastrectomy. A transabdominal total gastrectomy was performed in four animals and an end-to-side anastomosis between the esophagus and duodenum was carried out. In an additional four dogs, previously prepared with sulphathalidine and colace for seven days, a segment of the transverse colon was interposed between the esophagus and duodenum following total gastrectomy. Those eight animals were studied in six weeks to determine the extent of vitamin B₁₂ absorption. Their weights were determined prior to operation and at the end of the experiment.

C. Subtotal Gastrectomy. In four animals, a 75 per cent subtotal gastrectomy was performed and intestinal continuity was re-established by means of a two-layer gastroduodenostomy. In another four dogs, a similar 75 per cent gastrectomy was effected and a gastrojejunostomy of the antecolic Polya type was performed. Both groups of animals were subjected to a Schilling test six to eight weeks following operation and changes of weight during that period were also determined.

D. Vagotomy and Pyloroplasty. In the fourth group, vagotomy was performed transabdominally by isolating the lower end of the esophagus and transecting the main trunks of the right and left vagi. Heineke-Mikulicz type pyloroplasty was also carried out. The Schilling test was performed in six weeks and the weights were determined at this period. Three months subsequent to operation a gastric analysis and insulin provocative test were performed. The Schilling test was repeated at that time. In three animals, which were followed for a prolonged period of time, additional studies were made. First, 20 cc. of a 10 per cent solution of hydrochloric acid were administered via the nasogastric tube prior to the instillation of radioactive vitamin B₁₂. In the second series of experiments, 250 mg. of intrinsic factor were

TABLE 1. *Effect of Vagotomy and Pyloroplasty on B₁₂ Urinary Excretion*

	6 Weeks Postop.	3 Months Postop.	HCl Added*	Intrinsic Factor Added**
1	8%	—	—	—
2	5%	—	—	—
3	6%	—	—	—
4	6%	—	—	—
5	7%	10%	9%	10%
6	7%	6%	6%	12%
7	9%	4%	7%	16%
Average	7%	7%	7%	13%

* 30 cc. 10% solution.

** 200 mg.

mixed with the radioactive vitamin B₁₂ and administered by the nasogastric tube.

Results

A. Control. In the first group of control animals, the average urinary excretion of radioactive vitamin B₁₂ was 35 per cent, ranging between 15 per cent and 56 per cent (Table 1, Fig. 1-3). In the four animals, in which the radioactive vitamin B₁₂ had been administered into the fourth portion of the duodenum via a duodenostomy, essentially similar findings were noted, with an average urinary excretion of 24 per cent.

B. Total Gastrectomy. In the four animals subjected to total gastrectomy with esophago-duodenostomy, the average urinary excretion of radioactive vitamin B₁₂ was 0.5 per cent.

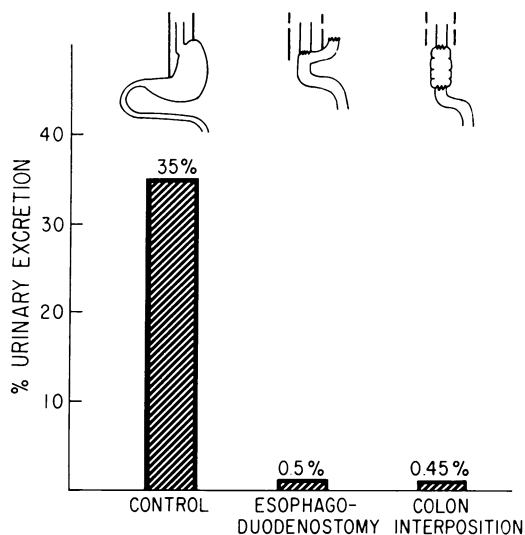


FIG. 1. The effect of total gastrectomy on Vitamin B₁₂ absorption.

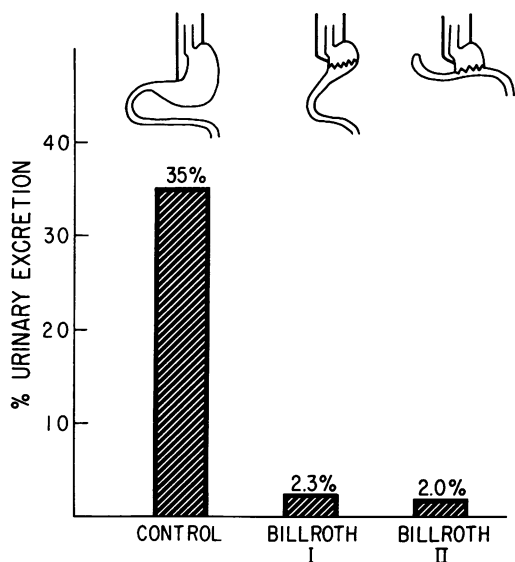


FIG. 2. The effect of subtotal (75%) gastrectomy on Vitamin B₁₂ absorption.

phagoduodenal anastomosis, a negligible urinary excretion of vitamin B₁₂ was measured, thus indicating absence of absorption (Table 1, Fig. 1). During the six-week period between operation and performance of the Schilling test, these animals experienced an average weight loss of 35 per cent of their original body weight. In four animals with total gastrectomy and interposition of a segment of transverse colon, similar findings were noted (Table 1, Fig. 1). These animals lost an average of 40 per cent of their original body weight.

C. Subtotal Gastrectomy. No statistically significant difference could be demonstrated for either the degree of weight loss or the urinary excretion of vitamin B₁₂ between the two types of anastomosis. With both gastroduodenostomy and gastrojejunostomy, a weight loss of about eight to ten per cent of original weight was noted over the six week period. At that time, urinary excretion of radioactive vitamin B₁₂ averaged 2 per cent for the two groups of animals, ranging between 1.6 to 3.1 per cent (Table 1, Fig. 2).

D. Vagotomy and Pyloroplasty. Four animals were studied six weeks following the surgical procedure. There was no weight loss during this period. The urinary excre-

tion of radioactive vitamin B₁₂ averaged 7 per cent (Table 2, Fig. 3). This represented a definite decrease but was significantly less than that associated with subtotal gastrectomy. Three of these animals were evaluated at the end of three months, at which time similar findings of absence of weight loss and an average urinary excretion of vitamin B₁₂ of 7 per cent were noted. The completeness of vagotomy was evaluated in all of these animals by means of an insulin provocative test which revealed no free acid.

In order to determine the possible mechanism of interference with vitamin B₁₂ absorption following vagotomy, the three latter animals were studied. The oral administration of hydrochloric acid did not result in an increased vitamin B₁₂ absorption. Supplementary ingestion of intrinsic factor approximately doubled excretion of vitamin B₁₂, which, however, remained below the control level (Table 2, Fig. 3).

In order to determine if the diminished absorption of radioactive vitamin B₁₂ was a function of delayed transit time, carmine red was administered orally and the animals were explored in three hours. At that time the dye was apparent in the region of the ileocecal valve.

Discussion

Although a variety of technics for the determination of vitamin B₁₂ absorption had

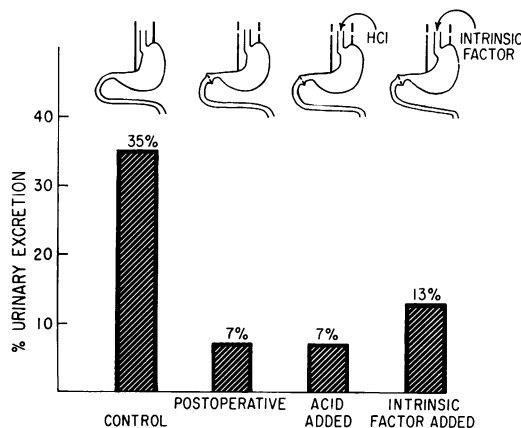


FIG. 3. The effect of vagotomy and pyloroplasty on Vitamin B₁₂ absorption.

TABLE 2. Effect of Gastrectomy on B₁₂ Urinary Excretion*

	Subtotal (75%) Gastrectomy	Total Gastrectomy
	A. Billroth I	A. Esophagoduodenostomy
	1. 3%	1. 0.5%
	2. 2%	2. 0.3%
	3. 2%	3. 0.4%
	4. 2%	4. 0.8%
Control	2.3% average	0.5% average
1. 24%		
2. 56%		
3. 15%		
4. 45%		
	B. Billroth II	B. Colon Interposition
	1. 2%	1. 0.5%
	2. 3%	2. 0.5%
	3. 2%	3. 0.4%
	4. 1%	4. 0.4%
35% average	2% average	0.45% average

* Modified Schilling Test.

been proposed, a combination of accuracy and simplicity led to the selection of the Schilling test.⁹ The absence of absorption of vitamin B₁₂ following gastrectomy was anticipated and confirmed clinical findings. Gastrectomy results in removal of the intrinsic factor which is necessary to bind vitamin B₁₂ and permit absorption in the ileum. The interposition of a reservoir to prolong emptying time into the duodenum in no way altered the situation. Following 75 per cent resection of the stomach, sufficient intrinsic factor is removed to effect a marked decrease in vitamin B₁₂ absorption. The critical element is the extent of gastrectomy rather than the type of re-establishment of intestinal continuity, as evidenced by similar depressions of vitamin B₁₂ absorption following gastroduodenostomy and gastrojejunostomy. These studies suggest that patients subjected to subtotal gastrectomy should also be followed closely for macrocytic anemia.

A depression of vitamin B₁₂ absorption following vagectomy and pyloroplasty was not anticipated. Similar results at the six week and three month periods indicate that the effect of vagectomy is permanent. The fact that oral ingestion of hydrochloric acid caused no significant increase in the absorption of vitamin B₁₂, while the addition of intrinsic factor resulted in a 100 per

cent increase, suggests that vagectomy has a direct effect on the production of intrinsic factor. Also, substantiating this theory is the demonstration of normal transit time in these animals. The results of these studies indicate that patients following vagectomy should also be evaluated on a long-term basis with reference to the development of macrocytic anemia.

Summary

1. A modification of the Schilling test was used to determine the absorption of orally administered radioactive cobalt-labeled vitamin B₁₂ in dogs following a variety of surgical procedures related to the stomach.

2. In control dogs, an average of 35 per cent of the radioactive vitamin B₁₂ was recovered in the urine during a 24-hour collection period.

3. In dogs subjected to total gastrectomy, less than 1 per cent of the radioactive vitamin B₁₂ was recovered in the urine. The interposition of a colon reservoir did not alter these results.

4. Following subtotal gastrectomy, only 2 per cent of the vitamin B₁₂ was excreted in the urine. Similar results were noted for animals with gastroduodenostomy and gastrojejunostomy.

5. Vagectomy and pyloroplasty effected a sustained reduction in vitamin B₁₂ ab-

sorption. The urinary excretion was 7 per cent. This was not augmented by the oral administration of hydrochloric acid but was increased when intrinsic factor was mixed with the radioactive vitamin B₁₂ prior to oral administration.

6. These studies indicate the advisability of an extended hematologic evaluation of patients subjected to total gastrectomy, subtotal gastrectomy and even vagectomy in consideration of the possible development of macrocytic anemia.

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