

Excretion of Cobalt⁶⁰-Labeled Vitamin B₁₂ after Total Gastrectomy.* (20315)

MARIAN E. SWENDSEID, JAMES A. HALSTED, AND RAYMOND L. LIBBY.

*From the Veterans Administration Center, and the Departments of Medicine and Radiology,
University of California Medical Center, Los Angeles.*

The development of a macrocytic anemia in persons without gastric tissue has been attributed to removal of a source of Castle's intrinsic factor(1,2). There is now evidence, from studies in patients with pernicious anemia, that the role of intrinsic factor is to potentiate the hemopoietic activity of orally administered vit. B₁₂(3,4). More specifically, Heinle and coworkers found that Co⁶⁰-labeled vit. B₁₂ was not absorbed when administered orally to patients with pernicious anemia unless a source of intrinsic factor was given simultaneously(5). It therefore seemed pertinent to study the absorption of vit. B₁₂ in a series of totally gastrectomized subjects and to observe the possible effect of simultaneous administration of intrinsic factor as present in gastric juice.

Clinical material and methods. Four patients who had been subjected to a total gastrectomy for carcinoma of the stomach were studied. In each instance from 0.5 to 1 cm of the distal esophagus and from 2.5 to 5 cm of proximal duodenum were removed along with the entire stomach. The spleen was removed in all cases, and from one-third to one-half of the pancreas (tail and body) in cases 1, 2, and 4. A jejunal transplant to act as a "substitute stomach" or holding reservoir was inserted between esophagus and duodenum in these 3 cases. No metastases were found at operation except one positive regional node in Case 1, and there was no clinical evidence of metastatic carcinoma in any of the cases at the time of this study. Other relevant data in each case include the following: Case 1. M.E., a male, aged 57, had a total gastrectomy 3 months ago. There was no anemia either before operation or at the time of study. He has had no injections of vit. B₁₂ or liver extract. Sternal biopsy

showed a normoblastic marrow. Weight before operation was 121 lb and at present is 106 lb. He feels entirely well and eats a full diet without digestive complaints, but has large, greasy stools 2-3 times daily. Case 2. F.P., a male, aged 60, had a total gastrectomy 10 months ago. He had no anemia before operation but a mild anemia was detected 3 months before this study. (R.B.C. was 3.4 mil. per cmm; Hgb, 12.6 g per 100 ml). The bone marrow was normoblastic. Vit. B₁₂ injections resulted in improved appetite and strength and a 5 lb gain in weight. He weighed 135 lb before operation and weighs 120 lb at present. He has an excellent appetite without digestive complaints, but the stools (1-2 daily) are large and greasy. Case 3. G.S., a male, aged 43, had a total gastrectomy 6 years ago. There has been no anemia at any time and sternal marrow is normal. He received liver extract for 2 months after operation, but none since and no vit. B₁₂. His weight before operation averaged 150 lb, but since then he has never weighed more than 120 lb. He has excellent appetite without digestive difficulties except for diarrhea for a day or 2 about once a week. Case 4. W.V., male aged 32, had a total gastrectomy 9 months ago. There has been no anemia at any time, and he has had no injections of vit. B₁₂ or liver extract. He feels entirely well and is without digestive complaints. He has 1-2 formed stools daily, which are fatty, and he has maintained his normal weight of 145 lb. 0.5 γ doses of the Co⁶⁰-labeled vit. B₁₂[†] containing 0.046 μ c of radioactivity, were administered orally to the subjects in 2 or more successive tests, either alone or with added neutralized gastric juice from normal or duodenal ulcer patients. All stools were collected daily for a period of 4

* This study was supported in part by a grant from Parke, Davis and Co., Detroit, Mich.

† We are indebted to Dr. Charles Rosenblum of Merck and Co. for generous supplies of this material.

TABLE I. Fecal Excretion of Co⁶⁰ Following Oral Administration of Radioactive Vit. B₁₂ to Persons with a Total Gastrectomy; 4 Cases.

Dose	% Co ⁶⁰ excreted—	
	Test 1	Test 2
.5 µg B ₁₂	103	96
.5 µg B ₁₂ + 50 ml gastric juice	12	17
.5 µg B ₁₂	96	94
.5 µg B ₁₂ + 100 ml gastric juice	6	—
.5 µg B ₁₂	86	89
.5 µg B ₁₂ + 50 ml gastric juice	64*	18
.5 µg B ₁₂	98	—

* Patient became ill with diarrhea on day following test dose.

days after administration of the test substances. Each day's stools were kept separate, dried on the steam bath and ashed in a muffle furnace. The ash was transferred to an ointment tin, made up to a constant weight of 25 g, and measured for gamma radioactivity in a scintillation counter(6). The amounts found in each day's stool were cumulated to determine the total excretion of Co⁶⁰.

Results. The test method developed by Heinle and his associates(5) for measurement of vit. B₁₂ absorption was found to be eminently satisfactory as used under the conditions described above. Confirmation of their results in pernicious anemia has been obtained by us. In 3 such patients, all of whom were in hematologic remission, from 89 to 100% of the administered radioactivity was recovered in the stool samples. Control individuals excreted approximately 25% with variations in some subjects depending on whether the vitamin was given at meal time or between meals.

Data on 4 persons with a total gastrectomy receiving radioactive vit. B₁₂ are recorded in Table I. In all cases, from 86 to 100% of the administered radioactivity was excreted in the stool samples, indicating a condition of negligible absorption of vit. B₁₂. This non-absorption occurred whether the vitamin was given with meals as in Cases 2 and 3, or between meals in the inter-digestive phase, as in Cases 1 and 4. When gastric juice was administered with vit. B₁₂, the excretion of radioactive Co⁶⁰ dropped to levels similar to those obtained in control individuals, except in one instance where the patient was ill.

Discussion. The above experiments indi-

cate that patients who have had a total gastrectomy do not absorb orally administered vit. B₁₂ and therefore cannot depend on dietary sources to supply their metabolic requirement for this vitamin. Each of the patients studied apparently had steatorrhea and in 3 cases there was inability to regain normal weight despite adequate caloric intake. These facts suggest a general defect in intestinal absorption. However, such an explanation for the non-absorption of vit. B₁₂ does not appear to be tenable since absorption of the vitamin did occur when gastric juice was given simultaneously. This observation, when considered in conjunction with the experiments of Heinle *et al.*(5) in pernicious anemia patients, indicates that patients with a total gastrectomy do not absorb vit. B₁₂ because of a lack of intrinsic factor. It adds evidence to the original observations of Castle(7) that the gastric mucosa is the principal source of intrinsic factor, although other interpretations are possible.

Reports in the literature show that a macrocytic anemia can develop in patients after a total gastrectomy but that this is not the invariable result, even after long periods of time (8-10). Since it has been the consistent finding of the present study that vit. B₁₂ is not absorbed in such patients it would appear, as Ungley(2) has suggested, that other factors besides deprivation of dietary vit. B₁₂ may operate in the production of the anemia when it does occur.

Summary. Co⁶⁰-labeled vit. B₁₂ was administered orally in 0.5 γ doses to 4 patients who had had a total gastrectomy. Each patient excreted in the stools essentially all of the administered radioactivity. When gastric juice was given with the vitamin there was a decrease in Co⁶⁰ excretion to levels similar to those found in control subjects.

We gratefully acknowledge the assistance of Mrs. Elizabeth Hvolboll, Miss Panchita B. Thomas, and Mr. Frank Cramer.

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Received May 11, 1953. P.S.E.B.M., 1953, v83.

Urinary and Fecal Coproporphyrin Excretion in Rats: I. Results in Normals and Castrates.* (20316)

F. W. HOFFBAUER, C. J. WATSON, AND SAMUEL SCHWARTZ.

From the Department of Medicine, University of Minnesota School of Medicine, Minneapolis.

An increase in the excretion of urinary coproporphyrin has been referred to frequently as a sensitive index of liver functional impairment(1). In view of the extensive employment of the white rat in laboratory studies of liver damage, an investigation of this animal's excretion of coproporphyrin was conducted. As a preliminary step, it was necessary to determine the pattern of excretion in the normal well-fed animal. In the course of these investigations, normal male animals were observed to excrete more coproporphyrin in the urine than did females. Accordingly, the effects of castration and the influence of androgenic and estrogenic substances were studied. Since coproporphyrin is excreted both in the urine (UCP) and the feces (FCP), simultaneous measurements of each were made in all experiments.

Methods. In all the experiments, white rats of a uniform strain (Sprague-Dawley) were employed. The animals were fed a stock diet (Purina Fox-chow) *ad libitum* and had free access to water. The animals under study were housed in individual metal cages. In all experiments, 48 hour collections of urine and feces were made for the coproporphyrin

analyses. During the collection periods, the rats were housed in individual cages suspended over large glass funnels (25 cm diameter). The associated all-glass unit used for separation of urine and feces was essentially similar to that described originally by Gross and Connel(2). The successful separation of these two forms of excreta was deemed of utmost importance in a study that involved the separate determination of a pigment common to both. The collections were interrupted for 60 minutes at the end of the first 24 hours to permit feeding of the animal and to store the first day's urine and fecal specimens. The sides of the funnels were rinsed with 10 ml of water at the end of each 24-hour period. The washings, the urine and the feces were immediately refrigerated. No preservatives were employed. The test tubes that received the voided urine were painted black to prevent exposure of the contents to light. The urine and the washings were stored in brown bottles while in the refrigerator. The urine and the washings for the 48-hour period were pooled for analysis. Although average values are given in most of the data reported, individual analyses of the 48-hour urine and fecal collections of each rat were made. Plastic cages with glass rod bottoms were used in the early experiments in order to avoid contact of the urine with metal. This was done to reduce the tendency to form metal coproporphyrin complexes. However,

*Supported in part under contracts from the Office of the Surgeon General, U. S. Army, under the sponsorship of the Commission on Liver Disease, Armed Forces Epidemiological Board, and the Atomic Energy Commission; and by a grant from the U.S.P.H.S..