Problems in Clinical Nutrition

Vitamin B_{12} Absorption Studies in a Vegetarian with Megaloblastic Anemia

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The primary purpose of this section is to present clinical cases in which nutrition is an integral part of the disease and its treatment. Contributions for this section are welcome.

MEGALOBLASTIC anemia is a common disorder in India and other tropical countries. How frequently malabsorption is a contributing factor to the development of vitamin B_{12} or folic acid deficiency in megaloblastic anemia is difficult to estimate from published reports. Tasker and Lond,[1] reporting on an extensive clinical experience with this disorder in Malaya, state that clinical steatorrhea is not found. Baker[2] found convincing clinical and laboratory evidence of intestinal malabsorption in the patients he studied in South India. He stated that the administration of antibiotics to his Indian patients with megaloblastic anemia and tropical intestinal malabsorption syndrome rarely improved vitamin B_{12} absorption. Das Gupta et al.[3] reported hematologic responses, usually suboptimal, in their patients with megaloblastic anemia after the injection of vitamin B_{12}. Because some of these patients failed to give a hematologic response to the oral administration of similar amounts of vitamin B_{12}, these authors believed that vitamin B_{12} absorption was subnormal in at least some of them. Patel and Bhende[4] noted that in Bombay most of their patients with megaloblastic anemia responded to doses of purified liver extract comparable to those used in the treatment of pernicious anemia. They suggested that the deficiency in the majority of such patients is similar to that in pernicious anemia.

We have observed a young graduate student from India, a vegetarian, who suffered from megaloblastic anemia. At the height of his anemia, and for five months thereafter, he was unable to absorb vitamin B_{12}. When retested a year later, during which he had learned to eat and enjoy meat, the amount of vitamin B_{12} absorbed was normal. Because our series of one is not likely to be enlarged, we are reporting the data on this patient.

CASE REPORT

A twenty-seven year old Hindu student from the United Province of India was admitted to our hospital on June 1, 1955, because of diffuse epigastric distress, weight loss and macrocytic anemia. The epigastric distress was first noted in India in 1952, at which time he was given a few injections of liver, and abatement of symptoms followed. He did not continue treatment and had intermittent episodes of abdominal distress which were associated occasionally with emesis of undigested food. The patient was a vegetarian and had adhered to his dietary customs even after coming to the United States in September 1954. He was seen in the Student Outpatient Clinic on three occasions between March 8 and June 1, 1955. Each time he complained of epigastric distress and slightly increased frequency of bowel movements (two to three times daily) which were not watery, bulky or greasy. Recently he

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TABLE I
Hematologic Response to Vitamin B_{12} Therapy

Date	Vitamin B_{12} Therapy	Reticulocytes (%)	Hemoglobin (gm./100 ml.)	Packed Cell Volume (%)	Red Blood Cells (million/cu. mm.)	Weight (lb.)
6/7/55*	None	0.7	8.3	26	2.0	121
6/8/55	None	...	8.3	27	...	...
6/9/55	1 μg. orally	1.9	...	...	...	...
6/10/55	1 μg. orally	2.0	...	...	...	...
6/11/55	1 μg. orally	1.9	...	...	...	...
6/12/55	1 μg. orally	1.4	...	...	...	...
6/13/55	1 μg. orally	1.3	...	...	...	...
6/14/55	1 μg. orally	2.4	...	...	...	...
6/15/55	1 μg. orally	...	...	...	...	...
6/16/55	1 μg. orally	3.0	...	...	...	...
6/17/55	1 μg. orally	2.5	...	...	...	...
6/18/55	1 μg. orally	...	...	...	...	...
6/19/55	1 μg. orally	...	...	...	...	...
6/20/55	1 μg. orally	2.2	...	...	...	...
6/21/55	1 μg. orally	2.0	8.2	28	...	...
6/22/55	1,000 μg. intramuscularly	2.2	...	...	...	...
6/27/55	None	11.7	...	...	...	...
6/30/55	1,000 μg. intramuscularly	9.0	...	...	...	...
7/11/55†	50 μg. intramuscularly	...	11	39	3.04	...
7/14/55	1,000 μg. intramuscularly	...	...	...	...	...
7/20/55	50 μg. intramuscularly	...	11.7	40	3.31	...
8/2/55	None	...	12.6	41	3.84	140
8/9/55‡	50 μg. intramuscularly	...	...	...	...	...
11/21/55§	None	...	14.3	42	4.82	...
8/56‖	Irregular injections	...	...	...	...	...
9/56	Irregular injections	...	14.1	46	5.1	...
10/56¶	Irregular injections	...	...	...	...	...
1/57	None	...	14.9	49	5.6	160
2/62	None	...	...	...	...	180

* Marrow megaloblastic.
† Diet changed to include meat.
‡ Absorption studies of oral iron and glucose.
§ Vitamin A absorption test.
‖ Fat balance test.
¶ Folic acid absorption-excretion study.

also had noted numbness of the hands and a burning sensation of the tongue and in the abdomen.

Physical examination revealed a thin (121 pounds, 6 feet tall) man who appeared moderately and chronically ill, depressed and fearful. Blood pressure was 98/56 mm. Hg. The tongue was coated but smooth on the edges. There was diffuse abdominal tenderness, but the liver and spleen were not enlarged. The results of neurologic examination, including vibratory and position senses were normal.

Laboratory data included a normal urinalysis. The red blood cell data are shown in Table I. The leukocyte count was 5,000 per cu. mm., with a normal differential except for an occasional neutrophil with 6 lobes. A peripheral blood smear showed macrocytic red cells and a rare normoblast. The bone marrow was megaloblastic. Gastric juice was adundant and acid to Toepfer's reagent on several occasions following histamine stimulation. Fasting blood glucose, nonprotein nitrogen, creatinine and serum alkaline phosphatase, serum albumin, globulin, cephalin cholesterol flocculation and bromsulfalein clearance determinations were normal. Serum agglutination reactions for typhoid, paratyphoid, brucella and tularemia were negative. Grossly, the stools were normal in appearance and negative for blood, ova and cysts of parasites and trophozoites of amoeba. Roentgenograms of the chest, gallbladder and gastrointestinal tract, including the small bowel, were normal. The patient was discharged on June 8 1955, to be followed as an outpatient.

TABLE II
Radioactive Vitamin B_{12} Absorption Studies

Test No.	Date	Urine Radioactivity* (% of oral dose)	Red Blood Cells (million/cu. mm.)	Clinical Response
1	6/22/55	0	2.0	First injection of vitamin B_{12}†
2	6/30/55	0	...	...
3	7/14/55	0.9‡	3.04	Much improved
4	11/22/55	1.0	4.82	Asymptomatic
5	9/17/56	9.0	5.1	Asymptomatic
6	10/2/56	10.0	...	Asymptomatic

* Vitamin B_{12} absorption as estimated by the urinary radioactivity technic.[5]
† On June 22, 1955, parenteral administration of vitamin B_{12} was started and continued throughout the period of dates shown. A reticulocyte response of 12 per cent occurred on June 27, 1955. There was no reticulocyte response to daily oral doses of 1 μg. vitamin B_{12} from June 8, 1955 to June 21, 1955.
‡ A potent source of intrinsic factor was given along with the usual 1 μg. oral test dose of vitamin $B_{12}Co^{60}$.

VITAMIN B_{12} ABSORPTION AND RESPONSE TO TREATMENT

The hematologic response to the oral and parenteral administration of vitamin B_{12} (cyanocobalamin) is presented in Table I. For each of thirteen days the patient was given 1 μg. of vitamin B_{12} orally. No hematapoietic response occurred after thirteen days and then vitamin $B_{12}Co^{60}$ absorption was tested by the urine radioactivity technic, as previously described.[5] Failure of vitamin B_{12} absorption was shown by the absence of urine radioactivity after the oral administration of 1 μg. $B_{12}Co^{60}$ (Table II, test 1). The 1,000 μg. nonradioactive vitamin B_{12} injected as a part of this test was the first treatment, and a reticulocyte response of 12 per cent occurred on the fifth day (Table I). About thirty days after the first injection of vitamin B_{12}, the patient was encouraged to eat meat. The patient had been in complete remission for eighteen months when he left this city to return to India. Five years later, in response to our inquiry, we received word from him that he continues to feel well. He weighs 180 pounds, compared to 120 when the megaloblastic anemia was discovered.

Early in the period of observation the patient's gastric juice proved to be a potent source of intrinsic factor when assayed by the urine radioactivity technic in two patients with pernicious anemia. Vitamin $B_{12}Co^{60}$ absorption studies in the patient were carried out at intervals while he was under observation and treatment with vitamin B_{12}. The results of these tests are correlated with hematologic and clinical improvement in Table II. The initial studies showed a defect of vitamin B_{12} absorption which reverted to normal only after there was a hematologic and clinical remission of the anemia. It should be noted that on one occasion the patient was tested for vitamin B_{12} absorption with the addition of a known potent source of hog intrinsic factor; this did not enhance absorption (Table II, test 3).

OTHER ABSORPTION STUDIES

The patient had good evidence for malabsorption of nutrients other than vitamin B_{12}. Blood levels of glucose, iron and vitamin A following generous oral doses of each are shown in Table III. Only the iron values show a normal rise. The glucose and vitamin A absorption studies were repeated approximately one year later, when vitamin B_{12} absorption had become normal; the results again indicated failure to absorb these compounds normally.

Fecal fat content was determined over a four day period in August 1956 while the patient was on a diet containing 110 gm. fat per day. The fecal fat was 5 gm. per day.

A folic acid absorption-excretion test was carried out in October 1956 according to the

TABLE III
Absorption Tests

Time Sample (hr.)	Serum Iron* (μg./100 ml.) 8/55	Blood Glucose† (mg./100 ml.) 8/55	Blood Glucose† (mg./100 ml.) 9/56	Serum Vitamin A‡ (μg./100 ml.) 11/55	Serum Vitamin A‡ (μg./100 ml.) 9/56
Fasting	119	102	112	42	40
1/2	...	129	115	...	...
1	217	129	82	42	...
2	264	102	109	48	48
3	286	...	109	42	...
4	...	...	...	45	53

* Oral dose 250 mg. iron as ferrous gluconate.
† Oral dose 50 gm.
‡ Oral dose 15 ml. oleum percomorphum (60,000 units vitamin A per gm.).

method of Girdwood.[6] The result was normal (index value = 125 per cent).

COMMENTS

Our observations demonstrate that the megaloblastic anemia in the patient was cured by the injection of generous amounts of vitamin B_{12}, but they do not prove that he was deficient in the vitamin. We think it likely because of his gross inability to absorb vitamin B_{12} and his vegetarian diet.

The clinical and hematologic features of the patient described are classic for megaloblastic anemia as seen in vegetarian Asiatic Indians. Vitamin B_{12} deficiency is common in these patients.[2,7] Tasker and Lond[1] have stated that they did not see clinical sprue in a Malayan population of Indians and Chinese laborers and artisans with megaloblastic anemia. They report normal vitamin A absorption and normal intestinal roentgenographic patterns in typical examples of megaloblastic anemia. There was no evidence of steatorrhea in our patient, and the roentgenographic patterns of the small intestine were normal. Several of the absorption tests, however, showed gross defects; of interest is the normal fat balance study at a time when vitamin A was poorly absorbed. The tests for fat and folic acid absorption were made more than a year after the megaloblastic anemia was corrected.

Does habitual ingestion of a diet grossly deficient in a nutrient lead to an inability to absorb that nutrient? Considering the rapid DNA synthesis in intestinal epithelium one would anticipate difficulty in synthesizing mucosal cells in the face of severe vitamin B_{12} or folic acid deficiency. Theoretically, functional failure of the vitamin B_{12} absorbing mechanism in the ileum might be caused by vitamin B_{12} deficiency. Injections of vitamin B_{12} might lead then to improved absorption of intestinal vitamin B_{12}. Data to support this hypothesis are not available from studies on patients with severe vitamin B_{12} deficiency due to pernicious anemia.

The vitamin B_{12} absorption studies reported here demonstrate unequivocal improvement of intestinal absorption of this vitamin after the parenteral administration of vitamin B_{12}. After therapy with a gluten-free diet for one year, Mollin *et al.*[8] noted improvement in vitamin B_{12} absorption in two patients with the malabsorption syndrome. Baker[2] also has noted occasional improvement in vitamin B_{12} absorption in Indians who had been treated for tropical megaloblastic anemia. In our patient the ability of the gastric juice to promote vitamin B_{12} absorption in subjects with pernicious anemia excludes intrinsic factor deficiency as a cause for failure of orally administered vitamin B_{12} to produce a reticulocyte response. Thus, it appears that this patient had an intestinal absorptive defect which was conditioned by malnourishment and unrelated to intrinsic factor activity; this defect reverted to normal with parenterally administered vitamin B_{12} and an adequate diet. Obviously, one cannot exclude a concomitant folic acid deficiency corrected by an improved diet. Of interest are the absorptive defects for glucose and vitamin A remaining after vitamin B_{12} absorption reverted to normal.

SUMMARY

Results of absorption studies are reported in an Asiatic Indian (a vegetarian) with megaloblastic anemia which was responsive to treatment with parenterally administered vitamin B_{12}. Vitamin B_{12} absorption was shown to be defective by failure to obtain a reticulocyte response from the oral administration of the vitamin and by the urine radioactivity technic. In this patient the gastric juice contained abundant intrinsic factor at a time when he could not absorb vitamin B_{12}. Upon treatment, the vitamin B_{12} absorption defect disappeared. Defective absorption of glucose and vitamin A persisted.

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