THE VALUE OF VITAMIN B_{12} IN PERNICIOUS ANEMIA

Preliminary Report

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SINCE the original work on vitamin B_{12} was reported in 1948, numerous articles have appeared confirming the effectiveness and potency of vitamin B_{12} in producing remissions in pernicious anemia. The original work[1] was done in the laboratories of the Merck Company, who generously supplied the material used in our cases. It was shown by Shorb[2] and West[3] that a factor, the LLD, could be found in liver extracts in direct proportion to the unit potency of the extracts used in pernicious anemia. As hypothesized by Rickes et al, 1 unit of vitamin B_{12} is equivalent to 1 USP unit of liver extract, and may produce equivalent hematopoietic response. This material has been isolated from whole liver and is believed to contain cobalt, phosphorus, and nitrogen. It is commercially obtained from the growth of Streptomyces griseus. It has been shown, too, that satisfactory responses may be expected to occur neurologically. Vitamin B_{12} is ineffective when given orally, yet when mixed with gastric juice passed through a Berkefeld filter, its effectiveness in preventing a megaloblastic arrest is complete.[4]

The present communication deals with the first 5 cases whom we now have under observation and treatment for pernicious anemia with vitamin B_{12}.

Case Reports

Case 1. A woman, aged 55, was seen initially on February 19, 1949, with a chief complaint of "something eating my blood." She first consulted her physician in 1940 because of paleness and weakness and was found to be anemic. Treatment by pills and injections of iron was ineffective. In 1944 a cholelithiasis was demonstrated, and prior to surgical removal of the gallbladder, the patient was given liver and iron injections. Inasmuch as diarrhea, nausea, and vomiting occurred following each liver injection, it was discontinued. Following the removal of the gallbladder, the patient felt improved for a year and a half, but again consulted a physician in December 1948 because of weakness and paleness. She was given four transfusions and referred to the Cleveland Clinic for study. On physical examination the significant findings consisted of a pale but not atrophic tongue. A definite generalized vitiligo was noted. She had no evidence of neurologic involvement of the spinal cord. Her laboratory data revealed a fractional test meal with an absence of any free hydrochloric acid and a total acidity of only eight units at the end of sixty minutes. Urinalysis, blood sugar, blood serology, bromsulfalein, and basal metabolic rate determinations were all negative. Her initial blood count and subsequent blood counts are shown in table 1. Sternal marrow aspiration revealed a magaloblastic bone marrow.

A test dose of liver extract during treatment with vitamin B_{12} produced the previously noted complaints of diarrhea, nausea, and vomiting. Four days after the institution of vitamin B_{12} therapy, the patient began to notice subjective improvement, which has persisted, and she now has the feeling of complete well being. She receives 10 micrograms of vitamin B_{12} every other week, two months following the institution of therapy.

Case 2. A woman, 62 years of age entered the Clinic because of a lack of appetite and inability to sleep. In addition, in the past year she had noted numbness and coldness of the

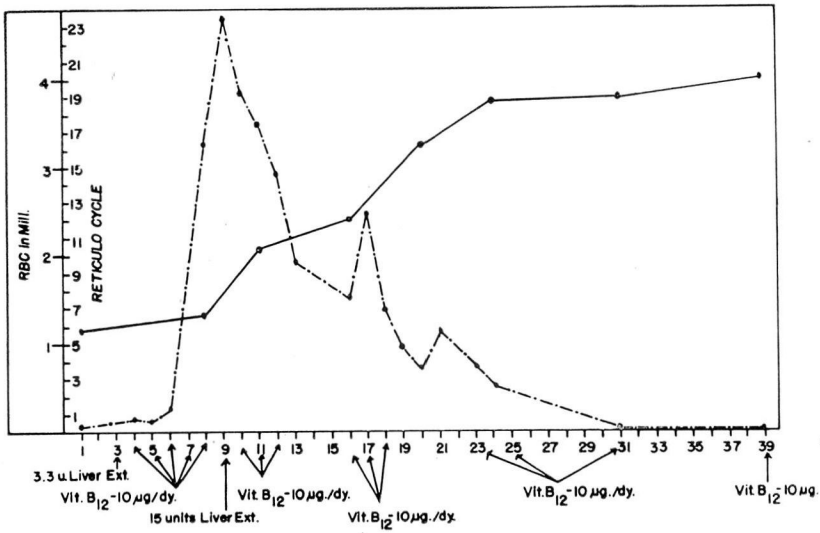

TABLE 1

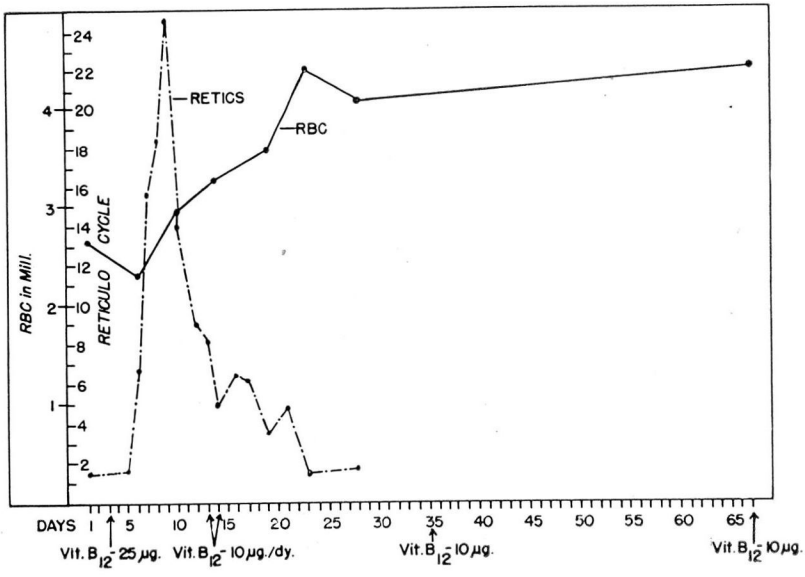

TABLE 2

lower extremities, associated with tingling and perspiration. Vague abdominal distress, nausea, bloating, and distention had been present for the past five years. A weight loss of nine pounds had occurred in the preceding seven months. For eight years she had received liver injections of unknown concentration, and developed swelling, redness, and tenderness at the site of the injection. For this reason no treatment had been received for eight months. On physical examination it was noted that her blood pressure was 170 systolic and 70 diastolic. The skin was sallow, and the tongue smooth and glossy. No spleen was felt, and the vibratory sense was intact. The urinalysis, blood urea, blood sugar, and cholesterol values were within normal limits. The serology was negative. The Ewald test meal revealed an absence of any free hydrochloric acid with a total acidity of only eight units. The bone marrow was megaloblastic.

Twelve days after the initial injection, all evidences of numbness and tingling had completely subsided. Her strength had returned to normal, and she was symptom free (table 2). Four months following initiation of treatment she was being adequately controlled with 10 micrograms every month.

Case 3. A woman, aged 52, presented herself because of rectal soreness of six years' duration, a "funny mouth" of fourteen months' duration, and a soreness of the mouth and

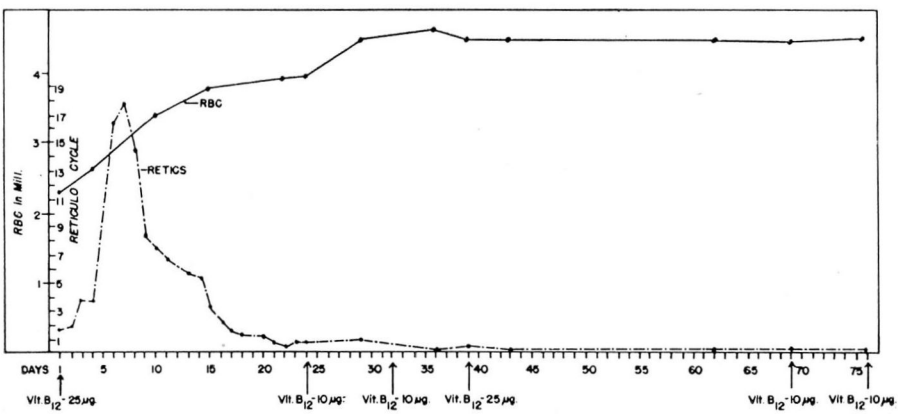

TABLE 3

tongue of sixteen months' duration. A diagnosis of pernicious anemia was made a number of years before and she stated that she had received liver extract of an unknown potency at irregular intervals since then, although a gastric analysis had never been done. A definite pallor was present, and the tongue was obviously atrophic. No spleen was palpable. Peripheral reflexes were normal. The vibratory sense was intact. The urinalysis, blood sugar, blood serology, and metabolism tests were normal. The Ewald test meal revealed no free hydrochloric acid with only eight units of total gastric acidity. An initial bone marrow was definitely megaloblastic, but it had become normoblastic five days following the initial injection of vitamin B_{12} (table 3).

Decided subjective improvement was noted within twenty-four hours following the first injection of vitamin B_{12}, and a definite feeling of well being five days following the institution of treatment. Two months later, the tongue was still red with the edges somewhat atrophic. However, upon 10 micrograms of vitamin B_{12} at weekly intervals, the tongue returned entirely to normal in four months, and adequate control is being maintained on this schedule.

Case 4. A man, aged 63, was initially seen at the Cleveland Clinic for a general check-up with relationship to beryllium poisoning. He was completely symptom-free with the exception of some manifestations of cardiac neurosis. His physical examination was entirely normal

at this time. The laboratory data revealed a normal urinalysis, blood sugar, and Wassermann and Kahn reactions. The blood count revealed 75 per cent hemoglobin with 4,230,000 red blood cells. One year later this patient returned because of extreme fatigue, anorexia, and loss in weight of twenty pounds in the past four months. Some diffuse generalized muscular aching had occurred recently. The physical examination was satisfactory with the exception of a clean but not atrophic tongue. There was no splenomegaly. The reflexes were all physiologic, but there was a decreased vibratory sense of the right leg, extending from the ankle to the mid right lower leg. At this time the Ewald test meal revealed the absence of any free hydrochloric acid with a total acidity of only eight units. The bone marrow was megaloblastic. Urinalysis and chest x-ray was normal. Electrocardiogram showed a first degree atrio-ventricular block. Vitamin B_{12} therapy was started, as noted in table 4, and one week following institution of treatment, the vibratory sense began to improve, as well as his appetite. Twelve days following treatment, the vibratory sense was completely intact, shortness of breath upon exertion had subsided, and the patient was gaining rapidly. He is being maintained on 10 micrograms at intervals of two weeks, adequate control having continued since ten weeks after institution of treatment.

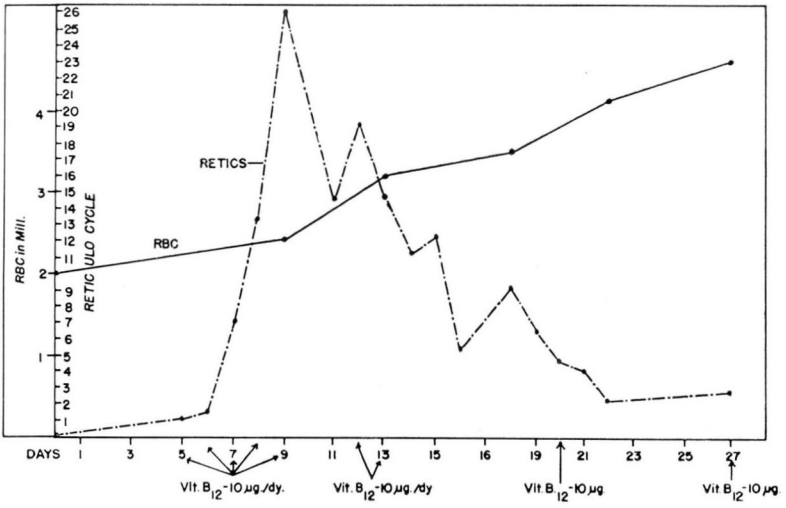

TABLE 4

Case 5. A 73-year-old woman was initially seen in the Department of Endocrinology because of a rapid heart and palpitation. Her physical examination revealed a pulse of 100, but no exophthalmus, lid lag, or tremor. The goiter was nodular and of an estimated weight of 80 Gm. Her tongue was smooth and atrophic. The reflexes of the knees and ankles were absent, and the vibratory sense was impaired in both knees and ankles. The chest x-ray, urinalysis, and blood sugar examinations were normal. The bone marrow was megaloblastic. The Ewald test meal revealed no free hydrochloric acid with a total acidity of only 3 units. The basal metabolic rate was plus 22, and a true hyperthyroidism was indicated when the basal metabolic rate remained high even following adequate control of the pernicious anemia with vitamin B_{12}. Ten mc. of I^{131} were accordingly given following the return of the blood picture to normal. Her glossitis had subsided by February 21, 1949, but slight impairment of the vibratory sense persisted until March 21, 1949 (table 5). The dosage of this patient is altered by the increased basal metabolic rate with adequate control of her hyperthyroidism, she is being maintained on 10 micrograms of vitamin B_{12} every other week over an observation period of three months.

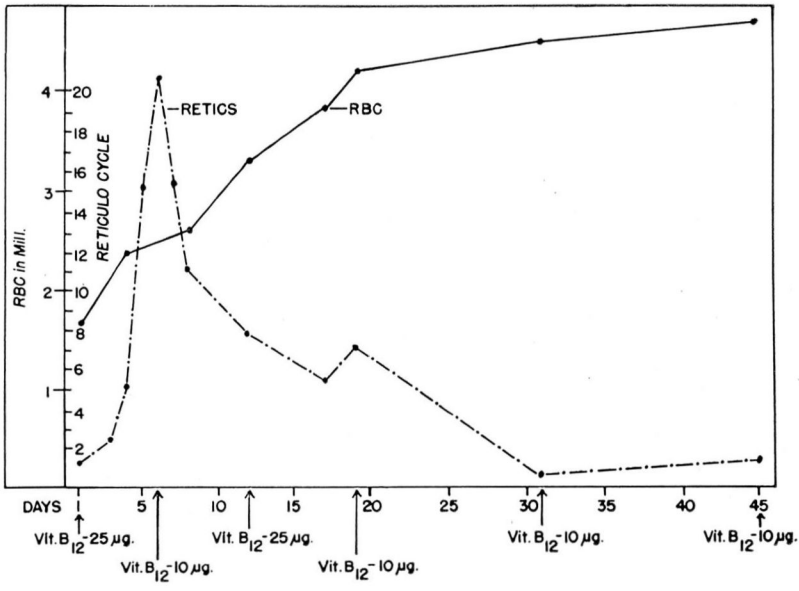

TABLE 5

Conclusion

The inconstancy of any dosage schedule which we have followed merely confirms the fact that there has been no accepted schedule for optimal response and maintained remission. If the observation is correct that a microgram of vitamin B_{12} is equivalent to a unit of liver extract 15 micrograms at monthly intervals should be sufficient for continued remission. Certainly bone marrow changes may be demonstrated within a very few hours following institution of vitamin B_{12} therapy. The height of the reticulocyte response is equivalent to that which one might expect under liver therapy. Interestingly enough, the patients all seem to develop a feeling of well being shortly after beginning treatment with vitamin B_{12}. Strength and vigor returned upon one occasion within twelve hours. The red blood count and hemoglobin return quickly to normal, but there apparently is a lag in the volume index in falling to normal limits. Leukopenia slowly resumes normal levels. An effort is now being made to maintain patients on 10 micrograms at two-week and four-week intervals. It is suspected that in due course of time, an ampule containing 15 micrograms will permit adequate control at monthly intervals. Vitamin B_{12} has also been effective in the treatment of nutritional macrocytic anemia, as well as non-tropical[5] and tropical sprue,[6] but has been ineffective in the treatment of the macrocytic anemia of pregnancy as reported by Day, Hall, and Pease.[7] Although vitamin B_{12} is the only substance yet isolated which apparently produces hematologic and neurologic remissions in patients with

pernicious anemia, similar to those which we have come to expect with liver extract, it must still be recognized that until vitamin B_{12} has been proven by the test of time, parenteral liver extract in proper doses is still the treatment of choice for pernicious anemia.

Addenda. Since the preparation of this paper 3 additional patients with pernicious anemia have been placed on vitamin B_{12} therapy. The one patient had severe pyramidal tract involvement which responded well to intensive vitamin B_{12} treatment. The second patient has failed hematologically to return entirely to normal, and the diagnosis of coexistent chronic liver disease is being entertained; and the third patient with coexistent carcinoma of the prostate is responding satisfactorily.

References

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