

# ORAL TREATMENT OF PERNICIOUS ANEMIA WITH SUBMINIMAL DOSES OF FOLIC ACID AND VITAMIN B<sub>12</sub>\*

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Early investigations with folic acid in the treatment of pernicious anemia indicated that the simultaneous administration of 5 to 10 mg. of folic acid orally and one-half unit of liver extract intramuscularly, daily, resulted in a better than anticipated reticulocytosis and a remission of the clinical and hematologic picture to normal.<sup>6</sup> Subsequent studies disclosed that patients with pernicious anemia receiving adequate doses of liver extract or vitamin B<sub>12</sub> and a folic acid antagonist showed either a poor or no symptomatic or hematologic response.<sup>1, 7</sup> Animal experiments have indicated an interrelationship of folic acid and vitamin B<sub>12</sub> in the induced anemia in swine.<sup>3</sup> Clinical experience has demonstrated that the minimal effective oral dose of vitamin B<sub>12</sub> in pernicious anemia is 75 to 150  $\gamma$  a day.<sup>8, 9</sup> Ingestion of 2.3 to 3.6 mg. a day of folic acid failed to induce a hematologic response in patients with pernicious anemia.<sup>2</sup>

The following data were obtained after the daily administration of 1.67 mg. of folic acid and 25  $\gamma$  of vitamin B<sub>12</sub> (Rubramin)<sup>†</sup> to 3 patients with typical addisonian pernicious anemia in relapse. All three persons showed macrocytic hyperchromic anemia, histamine-fast achlorhydria, and megaloblastic bone marrow. X-ray examinations of the gastrointestinal tract, urinalysis and blood chemical determinations were all normal. One of the patients showed moderately advanced "combined system" disease and severe glossitis.

*Case 1.* E. W., a woman, 88 years old, was admitted to the hospital because of pallor, weakness, nausea, vomiting, severe burning of the tongue and difficulty in walking. Positive physical findings included a smooth, red tongue, hyperactive deep tendon reflexes, bilateral Babinski's sign and loss of position and vibratory senses in both lower extremities. She was given a transfusion of 500 ml. of blood and treated with daily oral doses of 1.67 mg. of folic acid and 25  $\gamma$  of vitamin B<sub>12</sub> (Rubramin). Four days after the onset of treatment there was a return in appetite and improvement in general well-being. She was completely free of tongue symptoms after one week. The clinical improvement continued during the period of observation. Three weeks after the beginning of treatment a partial return of vibratory sense in the lower extremities was observed. The hematologic data are shown in Figure 1. The reticulocyte peak (33 per cent) occurred on the eighth day of treatment. The rise in hemoglobin and erythrocytes was steady during the first three weeks of therapy. A plateau during the fourth week was observed. The rise in leukocytes above 5000 per cu. mm. did not take place until the twelfth day of treatment.

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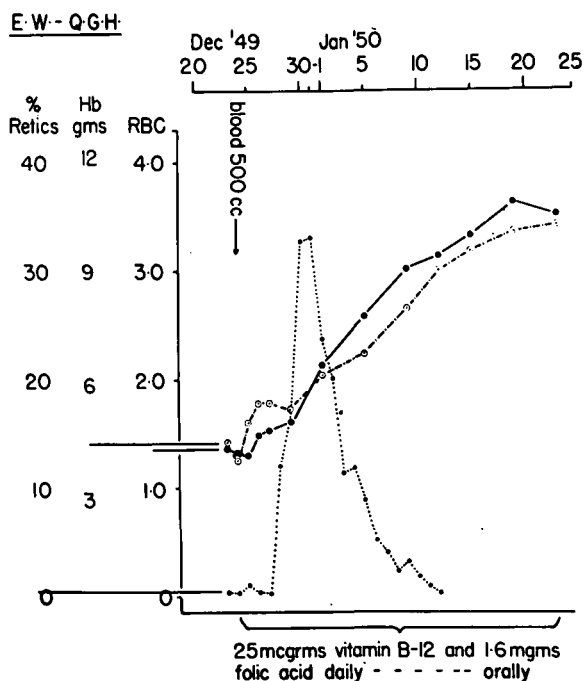


FIG. 1. E. W. Patient with pernicious anemia treated with daily oral doses of 25 $\gamma$  of vitamin B<sub>12</sub> (Rubramin) and 1.67 mg. of folic acid. The reticulocyte response was maximal and the rise in hemoglobin and erythrocytes was rapid. Glossitis disappeared in one week and neurologic improvement was apparent in three weeks.

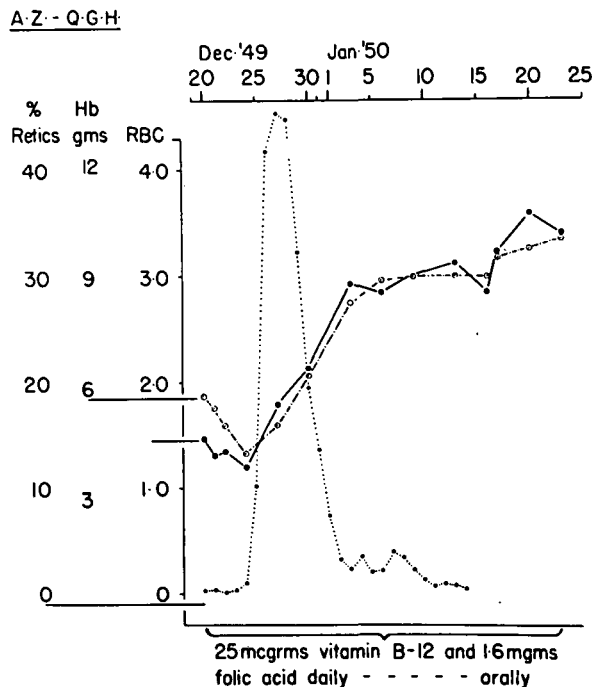


FIG. 2. A. Z. Patient with pernicious anemia treated with daily oral doses of 25 $\gamma$  of vitamin B<sub>12</sub> (Rubramin) and 1.67 mg. of folic acid. The reticulocyte response was greater than anticipated and the rise in hemoglobin and erythrocytes was rapid. Clinical improvement occurred early and progressed satisfactorily.

*Case 2.* A. Z., a woman 48 years of age, was admitted to the hospital because of weakness, anorexia, lethargy, pallor and diarrhea. The positive physical findings were lemon-yellow color of the skin, evidence of weight loss, retinal hemorrhages and smooth tongue. Neurologic examination was negative. She received daily oral doses of 1.67 mg. of folic acid and 25  $\gamma$  of vitamin B<sub>12</sub> (Rubramin). Two days after the onset of therapy there was marked subjective improvement with increase in appetite. Diarrhea diminished the following day and stopped by the end of the first week. The subsequent course was uneventful and with progressive improvement. Hematologic data are shown in Figure 2. The reticulocyte peak (45 per cent) occurred on the seventh day. The levels of hemoglobin and erythrocytes increased during the first month with a brief plateau during the third week. The leukocytes did not rise above 5000 per cu. mm. until the end of the fourth week of treatment.

*Case 3.* A. H., a 49-year-old man, had pernicious anemia in relapse and was treated with daily oral doses of 1.67 mg. of folic acid and 25  $\gamma$  of vitamin B<sub>12</sub>. Starting with an initial level of hemoglobin 7.0 Gm. and 1,450,000 erythrocytes, there was a sustained reticulocytosis of 12.2 per cent to 15.3 per cent in seven days. At the end of one month of treatment the hemoglobin rose to 13.0 Gm. and the erythrocyte count to 3,440,000 per cu. mm. Clinical remission was noted within 72 hours of the beginning of treatment.

#### DISCUSSION

There is widespread speculation as to the role and interrelationship of folic acid and vitamin B<sub>12</sub> in erythropoiesis. The essentiality of pteroylglutamic acid is suggested by the studies in patients with pernicious anemia treated with a folic acid antagonist and either liver extract or vitamin B<sub>12</sub>.<sup>1, 7</sup> Corroboration of this thesis has been demonstrated in the induced anemia in swine.<sup>3</sup> In the latter experiments the need for vitamin B<sub>12</sub> for satisfactory hematologic remission was noted. It is probable that the small amounts of vitamin B<sub>12</sub> in one-half unit of liver extract was responsible for the mutually potentiating effect when administered with 5 to 10 mg. of folic acid.<sup>6</sup> Luhby and Doan<sup>5</sup> made similar observations in megaloblastic anemia of infancy, using minimal doses of folic acid and adequate amounts of vitamin B<sub>12</sub> intramuscularly. The mutual dependability of these vitamins is shown in the present study by the hematologic and clinical remission following the simultaneous administration of subminimal doses of each.

These data are reminiscent of the experiments of Jacobson<sup>4</sup> who demonstrated that in pernicious anemia quantities of folic acid inadequate for hematologic response evoked a satisfactory reticulocytosis when first incubated with a "cream enzyme". The relationship of this "enzyme" to vitamin B<sub>12</sub> has not been established.

In the present studies folic acid acts like "intrinsic factor" since it promotes utilization of orally administered vitamin B<sub>12</sub> (extrinsic factor?) in subminimal doses. The relationship of folic acid to "intrinsic factor" is at present under investigation.

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#### ADDENDUM

Since the completion of this manuscript three additional patients with pernicious anemia in relapse received oral therapy consisting of folic acid and vitamin B<sub>12</sub> (Rubramin). The clinical and hematologic response in one case to doses identical to those above was completely satisfactory. Two other persons each received 0.67 mg. of folic acid and 10  $\gamma$  of vitamin B<sub>12</sub> (Rubramin), daily, by mouth. The reticulocytosis was optimal, and the rise in hemoglobin and erythrocytes rapid. Signs of clinical remission occurred within three days after treatment was begun.