RESPONSE OF TROPICAL SPRUE TO VITAMIN B\(_{12}\)

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Throughout the world the macrocytic anemias are of great interest to physicians. Sprue, perhaps the most common syndrome in this group, has a geographic distribution restricted to India, Ceylon, the Malay States, the Philippine Islands and, to a lesser extent, the Southern United States and the countries bordering or near the Caribbean sea. After Minot and Murphy\(^1\) demonstrated that liver was effective in promoting blood regeneration in persons with Addisonian pernicious anemia, it was found that tropical sprue could be treated with liver and liver extracts with some success. In recent years two pure chemical compounds, pteroylglutamic acid (folic acid) and 5-methyl uracil (thymine), have been shown to be effective in the treatment of sprue.\(^2\) Still a third chemical substance, vitamin B\(_{12}\), has recently been isolated which is infinitely more potent per unit of weight than liver extract, folic acid, or thymine; but it has not been synthesized, and at the present time it is available only in small amounts for experimental use. This compound, shown by Shorb\(^4\) to be a growth factor for Lactobacillus lactis Dorner and to bear an almost linear relationship to the potency of concentrated liver extract, was isolated from liver by Rickes, Brink, Koniuszy, and Folkers.\(^5\) West\(^6\) has demonstrated its positive hemopoietic action in three cases of pernicious anemia. Spies, Stone, and Aramburu\(^7\) have reported both a hematologic and a clinical response in two cases of pernicious anemia, two cases of nutritional macrocytic anemia, and one case of nontropical sprue. Spies, Garcia Lopez, Milanes, Lopez Toca, and Culver\(^8\) have reported a hematologic and clinical response following its administration to two cases of tropical sprue. The present communication is concerned with the response of five cases of tropical sprue in Puerto Rico to vitamin B\(_{12}\).

These patients were selected for study using the following criteria: (1) The patient must have macrocytic anemia as determined by Wintrobe indices. (2) The bone marrow must show the typical megaloblastic type of maturation arrest seen in macrocytic deficiency anemias. (3) The erythrocyte counts must be below 3.5 million. (4) The patient must be untreated, or must not have been treated recently enough to interfere in any way with the evaluation of the vitamin B\(_{12}\). (5) He must have persistently low reticulocyte counts during the preliminary period of...
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Fig. 1: Hematologic Response of Patient (E. R.) with Tropical Sprue to Vitamin B₁₂
Fig. 1. Hematometric Response of Patient (D. R.) with Trypanosoma to Vitamin B₁₂.
Fig. 3. Hematologic response of patient (A. S.) with tropical sprue to vitamin B₁₂.
Fig. 4. Hematological response of patient (M. C.) with topical salve to vitamin B12.
(6) He must have alimentary tract symptoms consistent with diagnosis of tropical sprue.

Hematocrit studies were made using pipets certified by the United States Bureau of Standards. The hemoglobin content was determined by means of the Photovolt photoelectric hemoglobinometer, calibrated so that 14.5 grams was equivalent to 100 per cent. The reticulocytes were counted in dry preparations of brilliant cresyl blue counterstained with Wright's stain. Platelets were enumerated in the counting chamber used for red blood cells by means of a fresh solution of sodium citrate.

Sternal bone marrow was obtained by aspiration prior to treatment and again near the peak of reticulocytosis.

Gastric analyses were performed in each case.

On admission the patients were given the "preliminary" sprue diet previously described and were maintained on this diet throughout the period of study. After the baseline studies were completed, the five patients selected were treated and the results are shown in figures 1, 2, 3, 4, and 5, which illustrate the hematologic response in each case.

**Observations**

Reticulocytosis occurred in each case and usually began around the fourth day, being followed by erythrocytosis and hemoglobin production. Coincidental with the reticulocytosis, clinical improvement occurred in cases 1, 2, 3, and 5. This improvement was characterized in each patient by a gain of strength and a great increase in appetite and feeling of well-being. As can be seen by a glance at the figures, the red blood cells and the amount of hemoglobin increased after the peak of the reticulocytosis, but in no instance did these patients respond maximally.

In case 4, receiving 4 micrograms of vitamin B₁₂, it is questionable whether the response which occurred was due to the very small amount of vitamin B₁₂ administered. This case responded in a characteristic way to large amounts of pteroyl-diglutamic acid (fig. 4).

Case 3, who responded both clinically and hematologically to a single dose of 20 micrograms of vitamin B₁₂, ate 400 grams of liver fifteen days later. A spectacular improvement occurred (fig. 3); this figure also shows the subsequent response to the administration of pteroyltriglutamic acid.

It is of considerable interest that after a second injection of vitamin B₁₂ in case 5, she again responded well. A similar response was noted following additional injections of vitamin B₁₂ in cases 1 and 2. Not only was there an additional increase in blood values, but additional clinical improvement occurred and the alimentary tract function tended to return toward normal as the bowel movements decreased in number and the stools became darker and better formed.

**Summary and Conclusions**

These findings show that the administration of vitamin B₁₂ to patients with tropical sprue was followed by general clinical and hematologic improvement provided the dosage was adequate. A single dose of 4 micrograms administered in case 4
produced little or no change. The larger dosage of 10–25 micrograms administered in the other cases was accompanied by striking increase in strength and vigor and a decrease in the diarrhea; however, in no instance was a maximal dose given and these patients quickly tended to relapse clinically and hematologically. They could be relieved promptly again either by another injection of vitamin B₁₂ or by a compound of folic acid. (The conjugated compounds of folic acid used in these cases were used for experimental purposes, and they produced the same hematologic response as that of folic acid per se.) Case 3, who had an excellent hematologic response after eating one serving of 400 grams of liver, is regarded as especially significant in that it suggests that, as powerful as vitamin B₁₂ is as a therapeutic agent, it is more effective when given with liver. It is especially noteworthy that cases 1 and 2, who had three injections of vitamin B₁₂, have had steady clinical and hematologic improvement. The reader should have in mind that a single injection of approximately 100 micrograms of vitamin B₁₂ probably would be needed to produce a full hematologic response in persons so ill. This tentative appraisal would suggest that this therapeutic compound, per unit of weight, is more effective in treating human disease than any compound that yet has been used.

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REFERENCES

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