

Folic Acid Therapy in Macrocytic Anemias of Infancy.

WOLF W. ZUELZER, AND F. N. OGDEN. (Introduced by Icie G. Macy.)

From the Anemia Clinic of the Children's Hospital of Michigan, Detroit, and the Department of Pediatrics, Wayne University College of Medicine.

The clinical and hematological picture of macrocytic anemias of infancy has not been sharply defined. Favorable responses to liver extracts have been reported sporadically. In studying infants with macrocytic anemia characterized by a megaloblastic type of erythropoiesis we treated a number of cases with folic acid in the form of a concentrate prepared from liver, "L. Casei factor," or with synthetic folic acid.* This report presents the results obtained with the 4 patients for whom the data have been calculated. A full report on the entire group, presenting the morphologic criteria used in determining this type of anemia, with a review of the literature, is now in preparation.

The patients were white infants, ranging from 2 to 12 months in age, one male and 3 females. All came from average homes and had been well cared for. They had received good diets, supplemented by cod liver oil and orange juice in adequate amounts. One patient (Case 3), born prematurely, had weighed 4 pounds at birth. The others had been full-term babies.

The clinical picture was not characteristic. All patients had a short history of vomiting, anorexia and pallor, as a rule preceded by signs of an upper respiratory infection and fever, which usually persisted. Three patients had had mild diarrhea; 2 had been treated with sulfadiazine.

The pertinent findings of the physical examination on admission to the hospital were marked pallor, usually slight cardiac enlargement and a soft systolic murmur. The spleen was moderately enlarged and firm.

After admission, daily complete blood counts were made. Hemoglobin was determined as oxyhemoglobin with the Evelyn photoelectric colorimeter. Reticulocyte counts were ob-

tained by the "dry" method. Bone marrow was aspirated from the lower end of the femur on admission and at intervals during the period of observation. The liquid marrow was heparinized, centrifuged and the volumetric pattern determined. Smears of the buffy coat were stained with modifications of the Romanowsky stain and differential counts of at least 500 nucleated cells were made.

All patients had severe macrocytic anemia, accompanied by moderate to marked diminution of the blood platelets. Case 2 showed mild leukopenia and neutropenia. A few nucleated red cells were invariably present in blood smears and often suggested a megaloblastic origin. The bone marrow was characterized by a megaloblastic type of erythropoiesis and changes in the granulocytes closely resembling, but not identical with, the marrow lesion in Addisonian pernicious anemia. Volumetric readings indicated moderate hypoplasia rather than hyperplasia.

In 3 cases blood transfusions were deemed necessary. These were followed by temporary increases in hemoglobin and red blood cells. Before treatment was started the hemoglobin level had begun to fall. Treatment with folic acid was not begun until preliminary observation had established the absence of a spontaneous reticulocytosis.

The response to folic acid was characterized by a rise in the reticulocyte count on the third or fourth day, which reached a maximum on the sixth or seventh day and was followed by steady rises in the hemoglobin values and red blood cell counts. The curves were virtually identical with those obtained in pernicious anemia following adequate treatment with purified liver extract. (Fig. 1). The hemoglobin tended to reach normal levels in approximately 3 weeks. The platelets became plentiful within one week. Character-

* Both preparations were made available through the courtesy of the Lederle Laboratories.

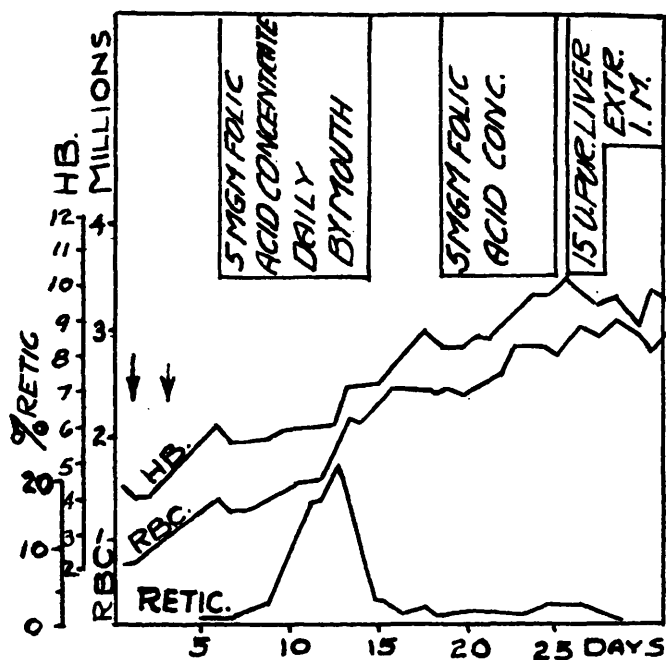


Fig. 1.

Case I illustrating the typical response to folic acid concentrate given orally.

istic changes in the bone marrow took place as early as the fourth day. Megaloblastic erythropoiesis yielded to a normoblastic pattern and the cellularity of the femoral marrow increased markedly.

With improvement in the blood picture, the clinical symptoms disappeared, the appetite improved and healthy color returned gradually. The spleen usually remained palpable for some time. A second course of folic acid or injections of purified liver extract produced no appreciable additional response.

We consider therapy with folic acid specific in this type of anemia because: (1) it produces an adequate reticulocyte response, followed by a marked, lasting improvement in the red blood counts and hemoglobin values; (2) equally important, the megaloblastic pattern of the bone marrow is transformed into a normoblastic one. Analogous changes oc-

cur in Addisonian pernicious anemia after specific therapy with liver extract^{1,2} and, recently, have been shown in nutritional macrocytic anemias of adults.^{3,4}

The genesis of this disturbance which is specifically influenced by folic acid remains obscure.

Conclusion. Certain macrocytic anemias of infancy, characterized by megaloblastic erythropoiesis respond specifically to folic acid.

¹ Jones, O. P., in Downey, H., *Handbook of Hematology*, Vol. 3, p. 2045, Paul H. Hoeber, Inc., New York, 1938.

² Naegeli, O., *Wien Klin. Wochensh.*, 1935, **48**, 225.

³ Spies, T. D., Vilter, C. S., Koch, N. B., and Caldwell, M. H., *Southern Med. J.*, 1945, **38**, 707.

⁴ Moore, C. V., Vilter, R., Minnich, V., and Spies, T. D., *J. Lab. Clin. Med.*, 1944, **29**, 1226.