

Treatment of Pernicious Anemia with Citrovorum Factor.* (18395)

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Sauberlich and Bauman(1) first described a factor (CF) present in liver which is necessary for the growth of *Leuconostoc citrovorum* 8081. The relationship of folic acid and ascorbic acid to this factor has been recently reported by Sauberlich(2), and Nichol and Welch(3,4).

The present study was undertaken to investigate the effect of parenterally administered CF to 5 patients with pernicious anemia in relapse. Each case showed hyperchromic macrocytic anemia, histamine-fast achlorhydria, and megaloblastic bone marrow. Roentgen examinations of the gastrointestinal tract, urinalyses and blood chemistry determinations disclosed no abnormalities. The concentrate contained 20 million CF units per ml.[†] Four of the patients received 1 ml of the concentrate intramuscularly, daily, and the fifth was given one-half of this dose. Hemoglobin and red blood cell determinations were made three times a week, leukocyte counts once a week, and reticulocyte estimations daily.

Procedure. A. R., white female, age 62, was admitted to the hospital with a history of Paget's disease of 30 years' duration. The patient had no symptoms referable to the anemia. Physical examination revealed the typical findings of Paget's disease and an atrophic smooth tongue. Neurologic status

was normal insofar as it could be determined. The initial blood examination showed hemoglobin 4.5 g per 100 ml and red blood cells 1.44 million per cmm. She received 1 ml of CF intramuscularly, daily. Her appetite was increased on the fourth day. She became more cheerful and talkative than she had been in many years. Her strength gradually improved and there was an increased sense of well being. The reticulocyte response was submaximal (15.3%). The hemoglobin and red blood cells rose slowly, and remained stationary at a level of 8.5 g and 2.50 million per cmm, respectively, after 42 days of treatment (Fig. 1). Accordingly, the dose of medication was doubled and a secondary rise in hemoglobin and erythrocytes ensued. During the first phase of treatment with 1 ml of CF daily the leukocytes remained below 5,000 per cmm. After the dose of CF was increased to 2 ml per day the white blood cells rose to a level between 5,000 and 6,000 per cmm. After 2 months of treatment the hematologic values did not reach normal values. The neurologic status was unchanged. Clinically the patient was improved.

E. Mc., white female, age 63, was a known case of pernicious anemia since 1936 who had intermittent and frequently incomplete treatment because of her failure to attend the clinic regularly. She received no therapy for 4 months prior to the present admission. Her chief complaints were weakness and a burning sensation in both legs. Physical examination revealed an enlarged liver 4 cm below the right costal border, loss of position and vibratory senses in both lower extremities, weakness and flexion deformities of both legs, and weakness of ankle jerks bilaterally. The initial hemoglobin and red blood cell values were 9.0 g per 100 ml and 2.60 million per cmm, respectively. She was given 1 ml of CF intramuscularly, daily. Improvement in appetite and sense of well being was not ob-

* Supplied by Dr. J. M. Rueggsegger, Lederle Laboratories Division, American Cyanamid Co., Pearl River, N. Y.

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[†] One CF unit is equivalent to 0.00015 μ g of the anhydrous free acid of CF(5).

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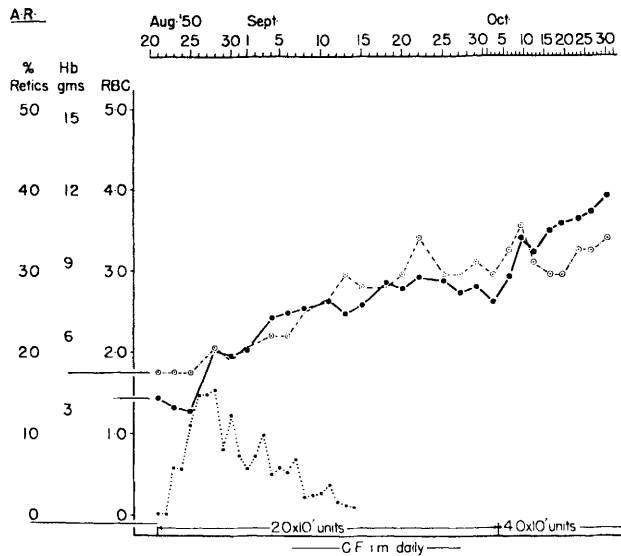


FIG. 1.

Hematologic data on patient A.R. with pernicious anemia treated with 20 and 40 million units of CF intramuscularly daily. The reticulocyte response was submaximal and the hematologic values were suboptimal.

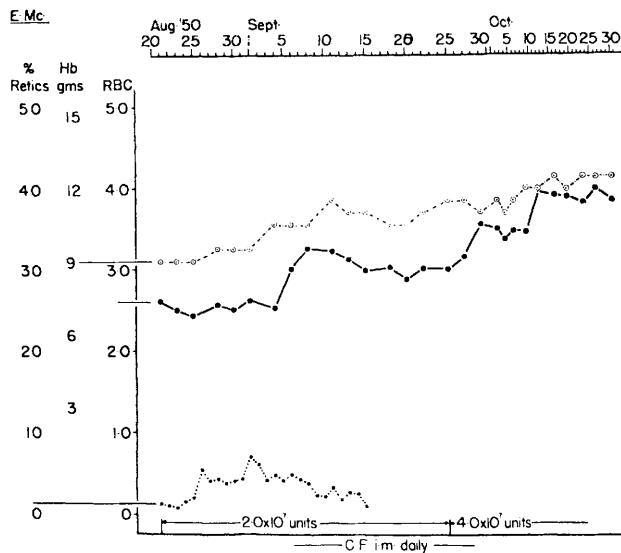


FIG. 2.

Hematologic data on patient E.Me. with pernicious anemia treated with 20 and 40 million units of CF intramuscularly daily. The reticulocyte response was submaximal and the hematologic values were suboptimal.

served until the tenth day of treatment and was very slow thereafter. A prolonged submaximal reticulocytosis (up to 7%) was noted (Fig. 2). The hemoglobin and erythrocyte values rose slowly to a stationary maximal

level of 11.5 g per 100 ml and 3.05 million per cmm, respectively, after 35 days of treatment. The neurologic status improved in that the patient no longer complained of burning of her legs. The dose of CF was increased

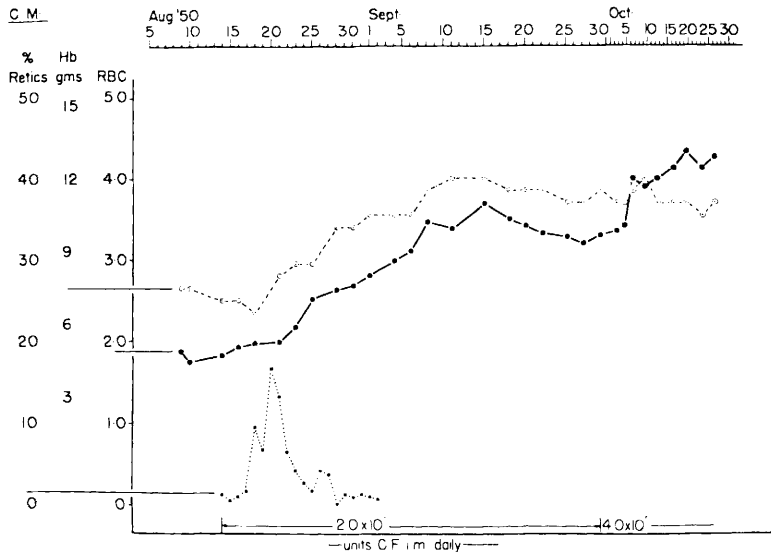


FIG. 3.

Hematologic data on patient C.M. with pernicious anemia treated with 20 and 40 million units of CF intramuscularly daily. The reticulocyte response was submaximal and the hematologic values were suboptimal.

to 2 ml, intramuscularly, daily. A rise in the amount of hemoglobin and the number of red blood cells followed; at the end of 66 days of treatment they were 12.5 g per 100 ml and 4.00 million per cmm, respectively.

C. M., white female, age 60, was admitted to the hospital because of Parkinson's disease, cerebral arteriosclerosis, and a history of left hemiplegia 6 years previously. Physical examination disclosed generalized rigidity and tremors. Numerous purpuric areas were seen. Neurologic examination showed a positive Babinski sign on the left side, diminution of position sense in toes, and vibratory sense reduced in both legs. The initial blood examination showed hemoglobin 7.5 g per 100 ml and erythrocytes 1.86 million per cmm, respectively. The patient was given 1 ml of CF, intramuscularly, daily. Within 3 days she felt stronger. No new purpuric spots appeared. Two days later her appetite was increased. After this the patient showed rapid clinical improvement and gained weight. Six weeks later the Babinski sign was negative bilaterally. The patient was able to detect vibration in both legs and position sense was now intact in both feet. The reticulocyte response was submaximal (16.6%). The hemo-

globin and erythrocyte values rose to a stationary level of 11.5 g and 3.30 million per cmm, respectively, after 56 days (Fig. 3). The dose of CF was increased to 2 ml daily. A rise of red blood cells to 4.20 million per cmm followed but the hemoglobin was unchanged after a total course of treatment of 84 days. The neurologic status showed no further improvement.

O. J., white male, age 70, was admitted to the hospital completely disoriented and with no available history. On examination he was pale and weak. Neurologic examination was unreliable. The initial hemoglobin and erythrocyte values were 5.0 g per 100 ml and 1.75 million per cmm, respectively. He was given 500 ml of blood and then treated with 1 ml of CF, intramuscularly, daily. Clinical improvement was observed on the third day as evidenced by an increase in appetite, strength, and sense of well being. He was out of bed on the sixth day. A maximal reticulocyte count was observed (26.7%). The hemoglobin level and red blood cell count rose to 12.5 g per 100 ml and 4.60 million per cmm, respectively, after 47 days of treatment (Fig. 4). The patient died suddenly at home of a coronary thrombosis.

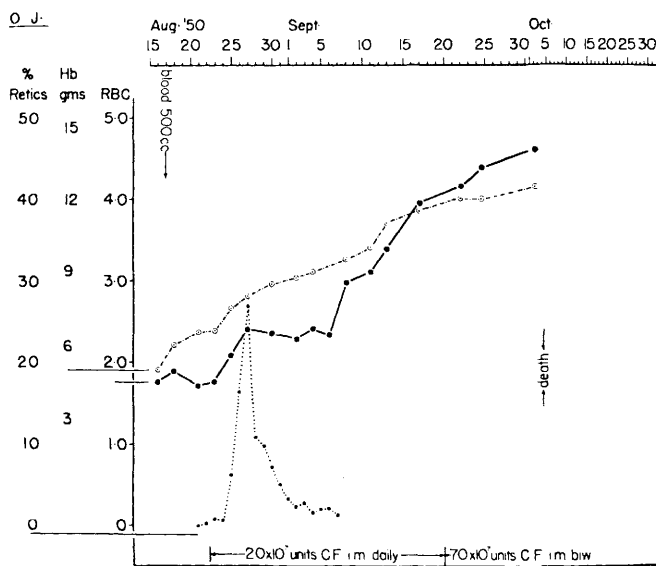


FIG. 4.

Hematologic data on patient O.J. with pernicious anemia treated with 20 million units of CF intramuscularly daily. The reticulocyte response was maximal and the hematologic values reached near normal levels after 47 days of treatment.

B. H., white female, age 63, was admitted to the hospital because of anorexia, weakness, loss of 50 lb, and numbness and tingling of fingers and toes. Physical examination revealed mild Parkinsonism, smooth tongue, and absence of position and vibratory senses in toes. The initial hemoglobin and erythrocyte values were 4.0 g per 100 ml and 1.01 million per cmm, respectively. The patient was transfused with 500 ml of blood and treated with 0.5 ml of CF, intramuscularly, daily. Subjective improvement was reported on the eighth day, at which time a submaximal reticulocyte peak (13.7%) was noted (Fig. 5). The following day she suddenly became dehydrated. She was transfused with 500 ml of blood and the dose of CF was increased to 1 ml per day. A secondary reticulocytosis (13.0%) followed. At this time the urine contained large numbers of clumps of leukocytes. She was treated with penicillin, streptomycin, fluids, and large doses of vitamin B₁₂. A third reticulocytosis (14%) occurred 2 days later. She became comatose and died 3 days later.

Discussion. From the foregoing data it

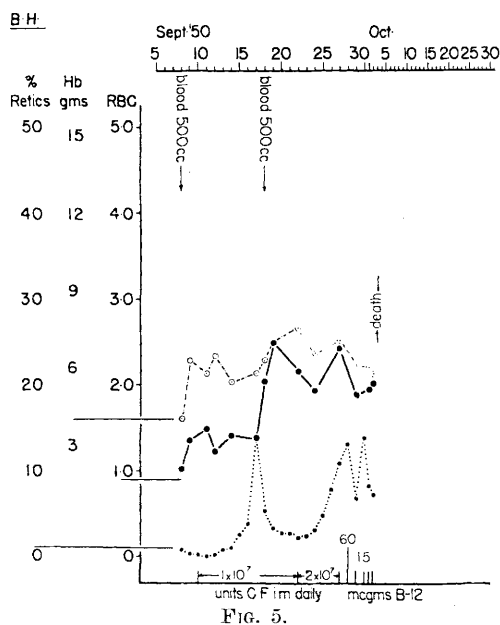


FIG. 5.

Hematologic data on patient B.H. with pernicious anemia treated with 10 million units of CF intramuscularly daily. The reticulocyte response was poor. The daily administration of 20 million units of CF produced a second reticulocyte response. The further administration of large doses of vitamin B₁₂ was followed by a third reticulocyte peak.

is evident that the daily administration of 10 or 20 million units of citrovorum factor intramuscularly was insufficient to produce a satisfactory reticulocytosis in 4 of 5 patients with pernicious anemia in relapse. Three of these persons reached stationary blood levels below 12.0 g of hemoglobin per 100 ml and 4.0 million erythrocytes per cmm, respectively, after 35, 42, and 66 days, respectively. A fourth patient appeared to have attained near normal values when he died suddenly of a vascular accident. The fifth patient clearly showed a poor response to daily administration of 10 million units of citrovorum factor. In view of the intercurrent infection the efficacy of the 2 ml dose cannot be evaluated in this subject. Because of complicating associated disease clinical and subjective reactions were difficult to estimate. Improvement in appetite, strength, and well being appeared to follow in all instances but not so dramatically as with adequate amounts of liver extract, vitamin B₁₂, or folic acid. This is probably due to the inadequacy of 20 million units per day as an optimal dose. Significant increases in erythrocytes were observed in 3

patients when the citrovorum factor was increased to 40 million units a day. Further evidence of the inadequacy of the initial dose was shown in patient A. R. in whom leukopenia persisted until the medication was increased to 2 ml a day. Neurologic examinations were difficult to evaluate because of associated complicating diseases. In one case, however, a distinct improvement followed treatment with 20 million units a day.

Summary. The daily administration of 10 or 20 million units of citrovorum factor to 5 patients with pernicious anemia in relapse usually is followed by a submaximal reticulocyte response, suboptimal levels of hemoglobin and red blood cells, and moderate to good clinical remissions. In one case a theoretically maximal reticulocyte response followed the daily administration of 20 million units of citrovorum factor. Neurologic signs improved in one patient. Although the daily administration of 40 million units produced a further rise in erythrocytes in 3 cases, normal blood values were not attained.

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Effect of Photodynamic Action on the Viscosity of Desoxyribonucleic Acid.* (18396)

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Recent observations(1) have indicated the possibility that photodynamic action (the combined effect of radiations and sensitizing agents) is mutagenic as well as lethal to certain bacteria. Since genes are thought to contain desoxyribonucleic acid (DNA), it is conceivable that mutations occur when the native structure of the DNA is altered. Some strength to this contention is given by the reports that several mutagenic agents, such

as ultraviolet radiations(2), X-rays(3,4), mustard gas and the nitrogen mustards(5,6), and peroxides(7) apparently are able to

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