MEGALOBLASTIC ANEMIA OF INFANCY. RESPONSE TO VITAMIN B_{12}

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IN A comprehensive study, Zuelzer and Ogden[1] characterized the megaloblastic anemia of infancy in which the bone marrow presents the essential diagnostic findings of Ehrlich's megaloblastosis and giant metamyelocytosis. In the first few months of life, spontaneously, or after some nutritional digestive disorder, severe anemia supervenes. Morphologically, the anemia is sometimes hyperchromic and macrocytic, but normochromic patterns are common. White cells are not invariably abnormal, but considerable thrombocytopenia and leukopenia may occur. Crude liver extract[1] and folic acid[1–3] are curative; occasionally, spontaneous improvement is seen.[1]

This paper describes the response of 5 cases of megaloblastic anemia in infants to vitamin B_{12}.* Preliminary studies by one of us (G. C.) have indicated the extraordinary potency of this substance in the conversion to normal of bone marrow found in adult megaloblastic anemias.

MATERIAL, CRITERIA AND METHODS

Five infants under 6 months of age with megaloblastic anemia were observed at Los Angeles Childrens Hospital between July 30 and October 9, 1948. All were treated with vitamin B_{12}; neither folic acid nor liver extract was used. The final diagnosis of megaloblastic anemia in all cases was based on the finding of megaloblasts in material obtained from bone marrow by aspiration biopsy (see figs. 1, *A* through 1, *E*.)

Criteria: A specific response to therapy was considered to have taken place if a distinct reticulocytosis ensued between forty-eight hours and ten days after administration of vitamin B_{12}. The reticulocytosis in turn had to be followed by a steady rise in hemoglobin and/or red blood cell count.[13] The occurrence of a reticulocytosis of 5 per cent or more during preliminary observation period or prior to forty-eight hours after administration of vitamin B_{12} was considered evidence of a spontaneous remission.† One such case was observed and eliminated from this study.

A complete response was considered to have taken place when blood values were restored to within normal limits. "Normal" values for this age range were selected from the 6 months age group listed by Blackfan and Diamond.[14]

Methods. Tibial aspirations were performed in all instances; preparations for microscopic study were made by the technics described by Schleicher[9-11] and Tucker,[12] except in Case 5 where only enough material could be obtained by aspiration to make direct smears.

All smears were stained with Wright's stain and decolorized by the method described by Schleicher.[12] Differential counts were done on 1,000 cells (see table 4). The classification of cells in regard to various levels of maturation were made as follows: *Pronormoblasts* were considered to be any cell less differentiated than the basophilic normoblasts. *Late normoblasts* included all normoblasts from the basophilic stage through the orthochromatic stage. The same criteria were used in classification of the megaloblastic series of cells. The myeloblasts, leukoblasts, and promyelocytes were all included under *early granulo-*

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† Zuelzer and Ogden's Case 25 had a spontaneous remission; a 7.1 per cent reticulocyte count was present on their first observation.

cytes. The term *late granulocytes* referred to the remainder of the cells in the granulocytic series including the myelocytes. All levels of maturation of lymphocytes were included under *lymphocytes*, and *plasma cells* were likewise listed. *Monocytes*, *histiocytes* and *macrophages* were grouped together.

Platelet counts were done by Fonio's method, which in our hands gave a normal range of approximately 150,000 to 300,000. Reticulocyte counts were done by the "dry" method. Hemoglobins were done by an oxyhemoglobin method and determined with a photoelectric colorimeter.

Protocols

Case 1. A 3 month old white male, R. B., # 19607, was admitted on July 30, 1948, to Childrens Hospital. The patient was the product of a full-term normal pregnancy in a 23 year old, healthy white mother. Birth weight was 6 lb. 1 oz.; admission weight, 9 lb. 8 oz. The neonatal period was complicated by obscure episodes of cyanosis and episodes of questionable yellow coloring of the skin. Since birth the infant had been fed a proprietary modified powdered cow's milk. At 2½ months of age, the administration of a polyvitamin dispersion and ferrous sulfate was started because at that time pallor

Table 1.—*Summary of Hematologic Findings in Case 1*

Date	RBC Million/cu. mm.	Hb. Grams %	Retics %	Platelets/cu. mm.	WBC Total/cu.mm.	Differential				Therapy and Remarks
						Granulocytes %	Lymphocytes %	Monocytes %	Normo-/100 WBC	
7/30	1.43	4.6	1		9,400	47	52	1	0	M.C.V. = 94 Cu. Micra
										M.C.H. = 34 M.M. Gms.
8/2	1.32	4.2	3	58,000						Vitamins B_{12} 25 gamma I.M.
8/3		3.8	3.5							Weight 9 lbs. 8 oz.
8/4	1.34	4.0		100,000						
8/5		4.2	14.0							
8/6	1.61	5.1	36.6	82,000						
8/7		5.6	47.0							
8/9	2.2	6.4	28.0	66,000		33	59	8	13	
8/10		7.3	18.4							
8/13	2.92	7.3	16.6	130,000	9,400	27	58	15	14	
8/17	2.88	8.0	9.7	170,000						Weight 10 lbs. 12 oz.
9/7	3.9	10.6			21,000	41	51	8	0	
9/21	4.02	10.9			8,500	29	66	5		
10/19		12.6								Weight 15 lbs. 5 oz.

and a palpable spleen were noted. During the ensuing two weeks there was no clinical improvement, and the patient was hospitalized.

Physical examination revealed a well developed, and slightly undernourished, pale male infant who did not appear acutely ill. Rectal temperature was 100 F. The spleen tip was palpable 2–3 cm. below the left costal margin; the liver edge was felt 2 cm. below the right costal margin. Other physical findings were within normal limits. No lymphadenopathy nor petechiae were noted. Laboratory data revealed a negative reaction to the Kahn test; x-ray films of the long bones were negative. (Table 1 summarizes the hematologic data in this case, prior to, during and subsequent to therapy. Figure 1, *A* illustrates the cytology of the bone marrow obtained prior to starting specific therapy.)

During hospitalization the infant was given a multivitamin preparation ("Zymadrops") 10 drops per day and a standard evaporated milk formula; in addition one 25 gamma intramuscular dose of vitamin B_{12} was administered on August 2 (the third day of hospitalization). He remained afebrile throughout; and on discharge, his eighteenth hospital day, he had gained 4 oz.

Follow-up: On October 19, 1948, three months following discharge, the infant had gained 5 lbs. 9 oz. and his length had increased $5\frac{1}{2}$ cm. The spleen was palpable at the costal margin.

Case 2. A 3 month old white male, J. C., #20231, was admitted to Children's Hospital on August 13, 1948. The patient was the product of an 8 month pregnancy in a 21 year old white female primigravida. The pregnancy was complicated by excessive weight gain, albuminuria and edema. It was terminated by

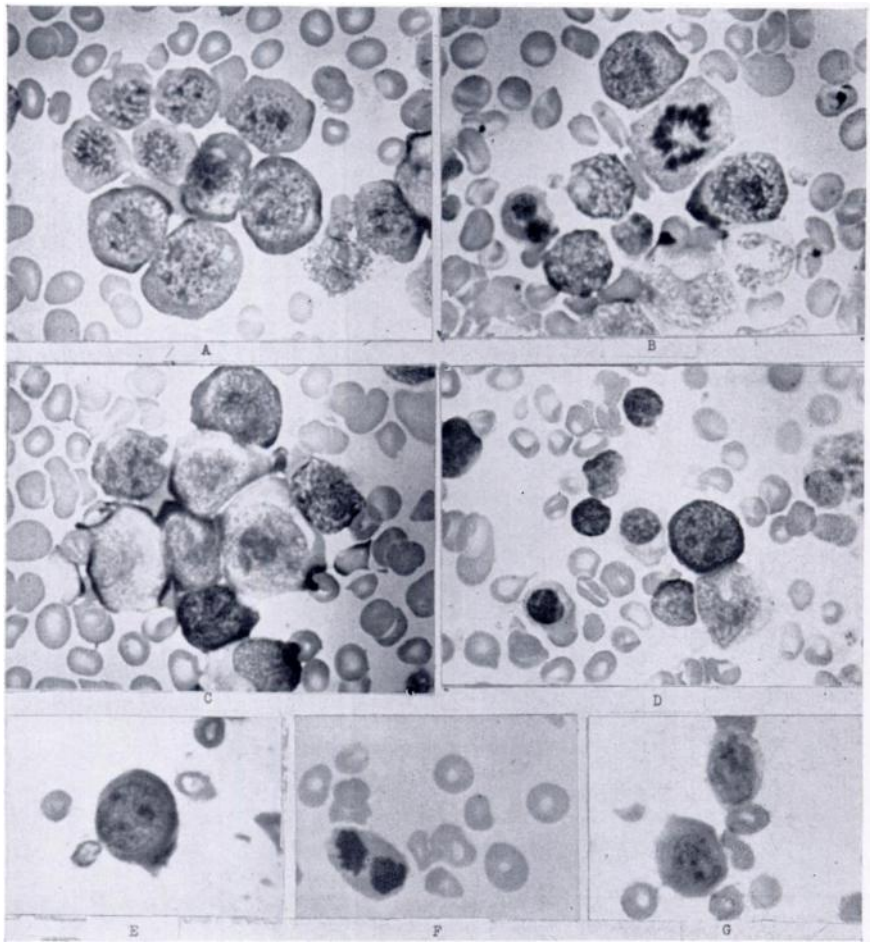

FIG. 1.—*A* through *E*: Megaloblast and abnormal granulocytes from bone marrow of Cases 1 through 5, respectively. *F* and *G*: Peripheral blood, Case 5, showing red blood cell changes and an orthochromatic megaloblast.

cesarean section, resulting in the delivery of a 4 lb. 1 oz. infant. The neonatal period was normal. After one month the infant was discharged from the premature nursery; his discharge weight was 5 lb. 8 oz. Feedings consisted exclusively of a proprietary modified powdered cow's milk formula until $1\frac{1}{2}$ months of age, when fruits, cereals, vegetables, and vitamins C and D were started. On a routine check-up a few days prior to entry, he was found to be anemic and was referred to Childrens Hospital.

Physical examination revealed a pale, well developed, small male infant who did not appear acutely ill but who had a peculiar wandering movement of the eyes. Rectal temperature was 101.8 F. The liver

was palpable 3 cm. below the right costal margin, and the spleen was palpable 2 cm. below the left costal margin. Other physical findings were within normal limits. No lymphadenopathy nor petechiae were noted. Laboratory studies included a negative reaction to the Kahn test and a negative reaction to 0.1 mg. tuberculin; the urine was not abnormal. X-ray films of the long bones were reported as follows: "Atrophy, coarse texture, and clubbing—consistent with severe anemia."* (Table 2 summarizes the hematologic data in this case. Figure 1,*B* illustrates the cytology of the bone marrow obtained prior to starting specific therapy.)

During nineteen days of hospitalization the infant was given a multivitamin preparation ("Vipenta"), 10 drops per day, and a standard evaporated milk formula. In addition, one 25 gamma intramuscular dose of vitamin B_{12} was given twenty-four hours after admission. The slight fever subsided to normal in twenty-four hours and remained within normal limits throughout his period of hospitalization. He gained 8 oz.; discharge weight was 8 lb. 9 oz.

TABLE 2.—*Summary of Hematologic Findings in Case 2*

Date	RBC Million/cu. mm.	Hb. Grams %	Retics %	Platelets/cu. mm.	WBC Total/cu.mm.	Differential				Therapy and Remarks
						Granulocytes %	Lymphocytes %	Monocytes %	Normo-/100 WBC	
8/13	1.8	5.7			4,300	38	59	3		M.C.V. = 88 Cu. Micra M.C.H. = 36 M.M. Gms.
8/14	1.8	5.8	0.3							Vitamin B_{12} 25 gamma I.M.
8/16	1.78	5.6	0.6							Weight 8 lbs. 1 oz.
8/17		5.1	3.9							
8/18		5.7	10.1							
8/20	2.04	6.4	16.2							
8/21		8.5	12.4							
8/23		7.1	11.2							
8/24	2.44	7.5	11.3							
8/26	2.63	7.7	10.3							
8/28	3.20	9.5	8.2							
8/30	3.09	8.7	7.1							Weight 8 lbs. 9 oz.

Follow-up: This was not carried out because the family had moved, making further observation impossible.

Case 3. A 3 month old, white female, D. B., #21505, was admitted to Childrens Hospital on September 18, 1948. The patient was the product of an 8½ month pregnancy in a 23 year old primipara, whose pregnancy was terminated two weeks early because of pre-eclamptic signs. The patient's birth weight was 5 lb. 12 oz.; admission weight, 11 lb. 6 oz. At one month of age the child began "spitting up." Several changes in formula were made up to 1½ months of age; but in the subsequent one and one-half months the child was fed goat's milk exclusively. One month prior to admission to the hospital, the child was started on a multivitamin preparation ("Vipenta"), 10 drops per day. Two weeks prior to entry, she again started to "spit up." Five days preceding hospitalization she was seen by the family physician, who noted pallor and prescribed an iron preparation, but because of the marked pallor the patient was hospitalized.

Physical examination revealed an irritable, pale, white, blue-eyed female infant, not acutely ill; her rectal temperature was 98.6 F. The liver edge was palpable 2 cm. below the right costal margin; other-

* In the authors' experiences, "clubbing" is not uncommonly seen in blood dyscrasias of infancy associated with a hyperplastic bone marrow. Zuelzer and Ogden report widening of the medullary spaces in the long bones of 2 of their cases.[1]

wise, physical examination was negative. No splenomegaly, lymphadenopathy nor petechiae were noted. Laboratory data revealed a negative urine and a negative reaction to the Kahn test.

During the ten days of hospitalization she was fed a standard evaporated milk formula; no vitamin supplements were given. Within twelve hours from the time of admission, 10 gammas of vitamin B_{12} were given intramuscularly. On the third hospital day, a 50 cc. blood transfusion was given. The child remained essentially afebrile and was discharged on the tenth hospital day. (Table 3 summarizes the hematologic findings in this case. Figure 1,*C* illustrates the cytology of the bone marrow obtained prior to starting specific therapy.)

TABLE 3.—*Summary of Hematologic Findings in Case 3*

Date	RBC Million/cu. mm.	Hb. Grams %	Retics %	Platelets, cu.mm.	WBC Total/cu.mm.	Differential				Therapy and Remarks
						Granulocytes %	Lymphocytes %	Monocytes %	Normo-/100 WBC	
9/28	1.39	4.4	0.1	44,000	7,600	32	68			Weight 11 lbs. 7 oz. Vitamin B_{12} 10 gamma I
9/29		4.2	0.6							
9/30	1.41	4.1	0.3	50,000						Transfusion 50 cc. whole blood
10/1		5.8	1.0			38	56	6	4	
10/2		6.7	4.2							
10/4	2.54	8.2	16.7	50,000	8,000	10	83	7	4	Weight 11 lbs. 10 oz.
10/5		7.5	16.8							
10/6		8.0	14.6		5,800	17	77	6	2	
10/7		8.3	12.6	140,000						
10/8		8.6	12.0		4,800	23	64	13		Weight 12 lbs.
10/22	3.0	10.8	3.6	260,000	8,600	20	78	2		Weight 13 lbs. 8 oz.
1/4/49	3.98	13.1		"Normal"	9,300	26	65	9		

Follow-up: Observation through the twenty-fourth day since administration of the vitamin B_{12} revealed that the patient had gained 1½ lbs. She no longer was irritable, and her general condition was much improved. At last observation, January 4, 1949, her condition remained satisfactory.

Case 4. A 6 month old white female, N. B., #21530, was admitted to Children's Hospital on October 9, 1948. The patient was the product of a full-term uncomplicated pregnancy in a 20 year old primipara. Birth weight was 7 lb. 6 oz. She had been fed a proprietary modified powdered cow's milk formula, and cod liver oil was the only supplement taken with any regularity. Orange juice was taken sporadically; solid foods were offered at 5 months of age but were almost entirely refused by the patient.

Physical examination revealed a small, pale, brown-eyed, white, irritable, chronically ill appearing female infant in no distress; rectal temperature was 99.4 F. There was suggestive beading of the ribs; a loud systolic localized apical murmur was heard. No hepatosplenomegaly, lymphadenopathy nor petechiae were noted.

Laboratory work revealed a negative urine and negative reaction to the Kahn test. An x-ray film of the chest was interpreted as showing bronchopneumonia in both lung fields. The report of the x-ray examination of the long bones read as follows: "Ground glass in consistency but no other changes suggestive of scurvy."

She was fed a standard evaporated milk formula. On the third hospital day, 25 gammas of vitamin B_{12}

were given intramuscularly. On the fourth hospital day, because of the suggestive roentgen evidence of pneumonia and scurvy, sulfadiazine, penicillin, ascorbic acid and a multivitamin preparation ("Vi-penta"), 10 drops per day, were started. In addition two 50 cc. blood transfusions were given at that time. The child's rectal temperature rose to 103 F. on the third day and subsided to normal by the fifth day; there it remained until discharge on the eleventh hospital day. (Table 4 summarizes the hematologic findings in this case. Figure 1,*D* illustrates the bone marrow cytology prior to starting specific therapy.

Follow-up: Observation through the fifteenth day after administration of vitamin B^{12} showed the infant had gained 1 lb. and was generally much improved; she was less irritable and more alert.

TABLE 4.—*Summary of Hematologic Findings in Case 4*

Date	RBC Million/cu. mm.	Hb. Grams %	Retics %	Platelets/ cu.mm.	WBC Total/ cu.mm.	Differential				Therapy and Remarks
						Granulocytes %	Lymphocytes %	Monocytes %	Normo-/100 WBC	
10/9		5.5								Weight 12 lbs. 8 oz.
10/11	1.44	4.1	2.0		3,600	49	44	7	6	Vitamin B_{12} 25 gamma I. M.
10/12										Transfusion 50 cc. blood × 2
10/13	2.55	7.1	1.1	33,000	5,100	39	53	8	1	
10/14		7.0	1.3							
10/15	2.63	7.1	4.6	31,000	4,100	34	53	13	8	
10/16		8.0	8.2							
10/18		7.2	15.6	"Normal"	4,100	30	54	16		Weight 12 lbs. 8 oz.
10/22	3.95	12.5	7.0	380,00	12,700	15	84	1		Weight 13 lbs.

TABLE 5.—*Summary of Hematologic Findings in Case 5*

Date	RBC Million/cu. mm.	Hb. Grams %	Retics %	Platelets/ cu.mm.	WBC Total/ cu.mm.	Differential				Therapy and Remarks
						Granulocytes %	Lymphocytes %	Monocytes %	Normo-/100 EBC	
9/27	0.98	4.4			12,700				13	Vitamin B_{12} 25 gamma I. M.
9/28	1.09	3.9	2.4	2,000	9,700	15	84	1		
9/29		3.6	2.8							
9/30	0.91	2.8	5.3	5,500	13,400	23	67	10	14	Transfusion 40 cc. expired

Case 5. A 3 month old, white male infant, M. C., #21410, was admitted to Children's Hospital on September 27, 1948. The patient was the product of a 7 month pregnancy in a 31 year old primigravida mother who during her pregnancy was suffering from rheumatic heart disease with signs of congestive failure. The patient's birth weight was 3 lb. 2 oz.; admission weight, 7 lb. He had been fed a proprietary modified powdered cow's milk formula, dextrimaltose, and a cod liver oil preparation but no other vitamins or other foods. Two days prior to entry, he began to have projectile vomiting, became irritable, restless and developed a rectal temperature of 102 F. The family physician noted generalized pallor and also some petechiae over the abdomen; because of these findings he had the child hospitalized.

Physical examination revealed a small, pale, irritable, white, blue-eyed male infant. Rectal temperature was 100.2 F. No hepatosplenomegaly, lymphadenopathy nor petechiae were noted. (Table 5 summarizes the hematologic findings in this case. Figure 1,*F* and *G* are photographs of a peripheral blood smear made prior to therapy. Figure 1,*E* illustrates a megaloblast obtained from this patient's bone marrow prior to instituting therapy.)

Within twelve hours after entry to the hospital the child was given one 25 gamma intramuscular dose of vitamin B_{12}. During the following two days his clinical condition remained unchanged. On the third hospital day, however, he was noted to be distinctly listless. He was immediately given a small transfusion but failed to respond and expired two hours later. Terminally, he showed unequal pupils and had a slow pulse and short gasping respirations. Laboratory data obtained the day the patient expired showed the hemoglobin had dropped markedly. Postmortem examination, gross and microscopic, failed to reveal any pathology which could have been considered a cause of death.

(Table 6 summarizes the bone marrow findings in Cases 1, 2, 3, and 4. Bone marrow data from Case 5 is not included since material was not adequate for a significant differential count.)

TABLE 6.—*Tibial Marrow Cellular Distribution Per Cent in Megaloblastic Anemia of Infancy**

		Promegaloblast	Late megaloblast	Pronormoblast	Late normoblast	Early granulocytes	Late granulocytes	Lymphocytes	Plasma cells	Macrophages Histiocytes Monocytes
Case 1	7-31-48	20	22	0	10	8	28	12	0	0
	8-3-48			9	57	2	17	14	1	0
Case 2	8-13-48	16	23	0	4	3	9	45	0	0
Case 3	9-28-48	20	18	0	1	7	44	10	0	0
Case 4	10-11-48	34	45	0	3	2	11	3	0	2
	10-12-48	15	67	0	4	0	11	2	0	1
	10-13-48	6†	81†	0	4	0	7	1	0	1
Case 5‡	9-27-48									

* Adjusted to nearest 1 per cent, 1000 cells counted.

† Intermediate between megaloblast and normoblast.

‡ Material inadequate for significant differential.

DISCUSSION

All 5 cases described showed evidences of responding to Vitamin B_{12}.

The data presented from Cases 1 and 2, as judged by accepted criteria, indicate clearly that there was a specific response of the megaloblastic anemia. In Case 2, follow-up observations were not available over an adequate period of time nor in adequate detail to determine whether or not the response was complete. These specific reactions occurred to a single 25 gamma intramuscular injection of vitamin B_{12}. Neither the multivitamin preparation nor the evaporated milk formulas administered simultaneously with vitamin B_{12} have, in the authors' experience, exerted any influence on the megaloblastic marrow found in this type of anemia, nor in megaloblastic anemias in general.

Cases 3 and 4 received transfusions during the period between the time of administration of vitamin B_{12} and the onset of reticulocytosis; hence, it is possible that the reticulocytosis could have resulted in some manner from the transfused blood. Zuelzer and Ogden presented 2 cases given transfusions prior to the onset of specific treatment which, without specific therapy, were followed by lasting improvement of the blood "*though not by characteristic reticulocytosis.*"[1] In Cases 3 and 4, in contrast, a distinct reticulocytosis developed. It seems more likely that the administration of a blood transfusion subsequent to starting specific therapy might tend to delay the onset of reticulocytosis and to decrease its percentage. This latter effect would be due at least in part to the increase in total red cells per

cubic millimeter. There would be a corresponding numerical reduction in the percentage of reticulocytes with the total number per cubic millimeter remaining the same.[14] It is unlikely, therefore, that the transfusion of whole blood could be responsible for the otherwise characteristic remissions noted in the above 2 cases.

The possibility of spontaneous remissions should be considered. In the 14 cases of megaloblastic anemia of infancy observed by one of us (P. S.), but one remission prior to the administration of any therapy has been noted. This is the approximate incidence of spontaneous remission reported in Zuelzer and Ogden's series.[1] The chances, therefore, are rather remote that spontaneous remissions occurred in this series coincident with the onset of the anticipated specific reticulocytosis.

Case 4 also received antibiotics and large doses of ascorbic acid because of fever and roentgen evidence of pneumonia and scurvy. Zuelzer and Ogden have pointed out that ascorbic acid given in 11 of their cases failed to produce either a characteristic reticulocyte response or a change in the marrow pattern. Similar observations have been made by one of us (P. S.) in a case of megaloblastic anemia of infancy given, in addition to many other vitamins, large doses of ascorbic acid, penicillin and sulfa for twelve days preliminary to starting specific treatment. It seems quite reasonable, therefore, to attribute to the administered vitamin B_{12} the 16.8 per cent and 15.6 per cent reticulocyte count noted in these 2 cases seven days after starting specific therapy.

Case 5 does not satisfy established criteria for a specific response to medication. The megaloblasts noted in the peripheral blood in themselves establish the diagnosis. The 5.3% reticulocyte count is suggestive of a response since preliminary reticulocyte counts were approximately one-half this amount.

In view of the data presented in this paper, the red cobalt-containing crystalline pigment vitamin B_{12} joins folic acid as hematologically active in cases of infantile megaloblastosis. The great potency of this material has been shown (1) in pernicious anemia by West et al.[4] and subsequently by others,[5] (2) in subacute combined degeneration of the cord,[6] (3) in sprue,[7] and (4) possibly in nutritional macrocytic anemia. Smith[8] has shown that a similar red pigment derived from liver is active in the treatment of pernicious anemia and subacute combined degeneration.

Because of the above reports, the response of infantile megaloblastosis to vitamin B_{12} was anticipated. In the limited number of cases herein reported, the response has been quite similar to the response of pernicious anemia in adults treated with similar medication. In view of the completeness of adult response to 25 gamma of vitamin B_{12}, the 10 to 25 gamma dosage used in this study probably was more than necessary.

Subsequent to completing the above observations, preliminary reports by others, on the failure of megaloblastic anemias to respond to vitamin B_{12}, have come to our attention. Luhby[15] observed 3 cases of megaloblastic anemia of infancy that did not respond to very large total doses of vitamin B_{12}, but which responded subsequently to folic acid, folic acid and liver extract, and whole milk and vegetables respectively.

May et al.[16] have produced megaloblastic anemia in monkeys, but only if the

diets lacked vitamin C. They found that vitamin B_{12} alone did not affect the anemia, but that prompt remission occurred if vitamin C was given prior to or simultaneously with the vitamin B_{12}. Vitamins C and B_{12} were without effect if the animals were given aureomycin to depress fecal flora and no food other than glucose and saline was given during the trial of these substances. On the other hand, folic acid produced remission without the addition of vitamin B_{12} even while the animals remained vitamin C deficient.

In view of these more recent data, it appears possible that vitamin B_{12} may not be the treatment of choice for this type of anemia; and it is suggestive that the responses of the cases reported in this paper were the result of the interaction of vitamin B_{12}, vitamin C and possibly folic acid.

The histories of 3 of the patients (Cases 1, 2, 3) reported in this paper closely parallel the experimental conditions which May has found necessary to produce a megaloblastic type of anemia in monkeys: that is for several weeks early in their lives, these infants were on vitamin C deficient diets. It would seem from the above histories, and from May's communication that vitamin C* deficiency may play a role in the development of this type of anemia.

Conclusions

1. The response to vitamin B_{12} of 5 cases of megaloblastic anemia of infancy has been studied.

2. Three cases of megaloblastic anemia of infancy showed a specific and complete response to a single intramuscular dose of 25 gammas or less of vitamin B_{12} (Cases 1, 3, and 4).

3. Two additional cases showed equivocal responses to similar treatment (Cases 2 and 5).

4. Vitamin B_{12} is effective therapeutically in some cases of megaloblastic anemia of infancy. Its effectiveness is possibly enhanced by adjunct therapy with ascorbic acid.

REFERENCES

[1] Zuelzer, W. W., and Ogden, F. W.: Megaloblastic anemia in infancy. Am. J. Dis. Child. *71:* 211, 1946.

[2] Paterson, J. C.: Pernicous anemia in children: Response to folic acid. Proc. Soc. Exper. Biol. & Med. *61:* 176, 1946.

[3] Sieberthal, B. J.: Megaloblastic anemia in infancy. Am. J. Dis. Child. *73:* 578, 1947; J. Pediat. *32:* 188, 1948.

[4] West, R.: Activity of B_{12} in addisonian pernicious anemia. Science *197:* 398, 1948.

[5] Spies, T. D., Stone, R. E., and Aramburu, T.: Observation on the anti-anemic properties of B_{12}. South. M. J. *41:* 522, 1948.

[6] Berk, L., Denny-Brown, D., Finland, M., and Castle, W. B.: Effectiveness of vitamin B_{12} in combined system diseases. New England J. Med. *239:* 328, 1948.

[7] Spies, T. D., and Suarez, R. M.: Response of tropical sprue to vitamin B_{12}. Blood *3:* 1213, 1948.

* It should be noted that approximately eighteen months ago, the manufacturers of certain modified powdered milk products enriched their product with vitamin C, and, quite significantly, that in the thirteen months subsequent to observing the last case reported in this paper we have not observed any further cases of megaloblastic anemia of infancy.

[8] SMITH, LESTER: Purification of anti PA factor from liver. Nature *161:* 638, 1948.

[9] SCHLEICHER, E. M.: The volumetric pattern of aspirated normal human sternal marrow of males 18 to 40 years. Am. J. Clin. Path. *14:* 370, 1944.

[10] ——: Isolation of particles from aspirated sternal marrow for biopsy. Am. J. Clin. Path. *17:* 909, 1947.

[11] ——: Staining aspirated human bone marrow with domestic Wright stain. Stain Technol. *17:* 161, 1942.

[12] TUCKER, B.: Method for histologic preparations from gross marrow units. Minnesota M. Technologist *8:* No. 3, 1945.

[13] WINTROBE, M. M.: Clinical Hematology. Philadelphia, Lea & Febiger, 1946. P. 80.

[14] BLACKFAN, K. D., AND DIAMOND, L. K.: Atlas of the blood in children. New York, The Commonwealth Fund, 1944. P. 8.

[15] LUHBY, A. L.: Vitamin B_{12} in megaloblastic anemia of infancy; Contribution to the etiology of this anemia and the interrelationship of folic acid, vitamin B_{12}, liver extract, and the products of the interaction of lean beef with normal gastric juice. Read at the Conference on Blood at the Harvard Medical School, Boston, January 7, 1949.

[16] MAY, C. D.: Personal communication. J. Lab. & Clin. Med. *34:* 1724, 1949.