

INFECTION AS CAUSE OF FOLIC ACID DEFICIENCY AND MEGALOBLASTIC ANEMIA

Experimental Induction of Megaloblastic Anemia by Turpentine Abscess

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A SURVEY of histories of infants with megaloblastic anemia reveals that infection and ascorbic acid deficiency are common features of possible etiologic significance.¹ A megaloblastic type of anemia usually implies a deficiency of vitamin B₁₂ or folic (pteroylglutamic) acid compounds; so some relation of infection and ascorbic acid deficiency to the metabolism of these compounds might be anticipated.

We have explored the relation of ascorbic acid deficiency to the development of folic acid deficiency, experimentally² and in megaloblastic anemia in infancy.³ All the evidence indicates that the requirement for folic acid is increased by a deficiency of ascorbic acid, especially when so severe as to lead to scurvy.⁴ This mechanism may be of importance in many infants with megaloblastic anemia, but in most infants megaloblastic anemia developed after a series of infections, even though the intake of ascorbic acid was unquestionably adequate.

It is to the latter group that the observations to be described in this report may apply. Considering the tendency for ascorbic acid to be depleted in the tissues during infections, one might suppose that infection, by producing a deficiency of ascorbic acid, could cause a disturbance of folic acid metabolism comparable to the

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1. Zuelzer, W. W., and Ogden, F. N.: Megaloblastic Anemia in Infancy, *Am. J. Dis. Child.* **71**:211, 1946.

2. May, C. D.; Sundberg, R. D.; Schaar, F.; Lowe, C. U., and Salmon, R. J.: Experimental Nutritional Megaloblastic Anemia: I. Nutritional Data and Manifestations of Animals, *A. M. A. Am. J. Dis. Child.* **82**:282, 1951.

3. May, C. D.; Nelson, E. N.; Lowe, C. U., and Salmon, R. J.: Pathogenesis of Megaloblastic Anemia in Infancy, *Am. J. Dis. Child.* **80**:191, 1950.

4. May, Sundberg, Schaar, Lowe, and Salmon.² May, Nelson, Lowe, and Salmon.³

situation in scurvy. While this may be true in some instances, we will show it is not a plausible explanation in all cases.⁵

SPONTANEOUS OCCURRENCE OF MEGALOBLASTOSIS WITH INFECTION IN MONKEYS

We had an opportunity in a colony of monkeys to follow the pattern of blood formation in the marrow during occasional isolated respiratory infections which appeared spontaneously among the animals. The monkeys under consideration were being fed cows' milk diets supplemented with an abundance of ascorbic acid (at least 50 mg. daily), orally and intramuscularly. In several monkeys in which acute infections developed the marrow was found to progress from a normal to a megaloblastic pattern. Other monkeys similarly infected revealed only a characteristic leucocyte response in the marrows with no trace of the megaloblastic type of reaction.

Analysis of the livers of these two groups of monkeys succumbing to infection revealed that those with megaloblastic marrows had much lower than normal levels of folic acid compounds in their livers. Those monkeys in which the marrow did not become megaloblastic had more nearly normal levels of folic acid compounds in the livers. A summary of the essential data from these monkeys⁷ is provided in Table 1.

TABLE 1.—Average Vitamin B₁₂ and Folic Acid Compounds in Livers of Monkeys Dyed of Respiratory Infection (Milk Diets, Abundant Ascorbic Acid)

	% Wet Wt		
	Vit. B ₁₂ *	Folic Acid †	Folinic Acid ‡
Marrow normoblastic (died 7th to 12th day of experiments).....	0.5	0.02	0.002
Marrow megaloblastic (died 44th to 166th day of experiments).....	0.5	0.05	0.008
Average values in normal monkeys fed same diets for long periods ⁸	1.00	1.00	0.020

* Vitamin B₁₂ determined by microbiassay using *Laetobacillus leichmannii*.
 † Total folic acid as measured by microbiassay with *Streptococcus faecalis* after liberation of free folic acid from conjugates by hog kidney conjugase.
 ‡ Free folinic acid (citrovorum factor) determined by microbiassay with *Leucomostoc citrovorum*.

The question as to whether the infection depleted the tissues of ascorbic acid and thus provoked a deficiency of folic acid cannot be answered from this group of monkeys because the tissues were not analyzed for ascorbic acid. These were incidental observations rather than planned experiments.

It must be reemphasized at this point that infection was not the cause for depletion of folic acid and megaloblastosis in our previously reported experiments with scorbutic monkeys.² Careful clinical observation and microscopic examination of the tissues for evidence of infection excluded this explanation reasonably well.

5. Several forms of vitamin B₁₂ and folic acid have already been described. For clinical purposes all forms will be grouped under the terms "vitamin B₁₂" and "folic acid compounds" unless specific designation of particular derivatives, such as folinic acid, will add clarity. The final biological actions of all the compounds grouped under vitamin B₁₂ or folic acid are essentially those of the parent substances.

6. May, C. D.; Hamilton, A., and Stewart, C. T.: Experimental Megaloblastic Anemia and Scurvy in the Monkey: IV. Vitamin B₁₂ and Folic Acid Compounds in the Liver, Diet, Urine and Feces and Effects of Therapy, *Blood* 7:978, 1952.

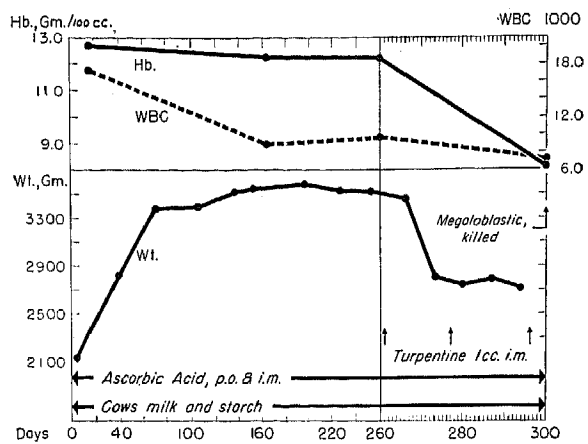


Fig. 1 (Monkey 73).—Megaloblastic anemia-turpentine abscess. Milk diet included abundance of ascorbic acid. For 260 days the animal thrived on this diet, and blood and marrow remained normal. Then the series of injections of turpentine was begun. After three injections within 39 days the marrow became megaloblastic. The animal was killed for tissue analyses (Table 4). Cells from the bone marrow are shown in Figure 2.

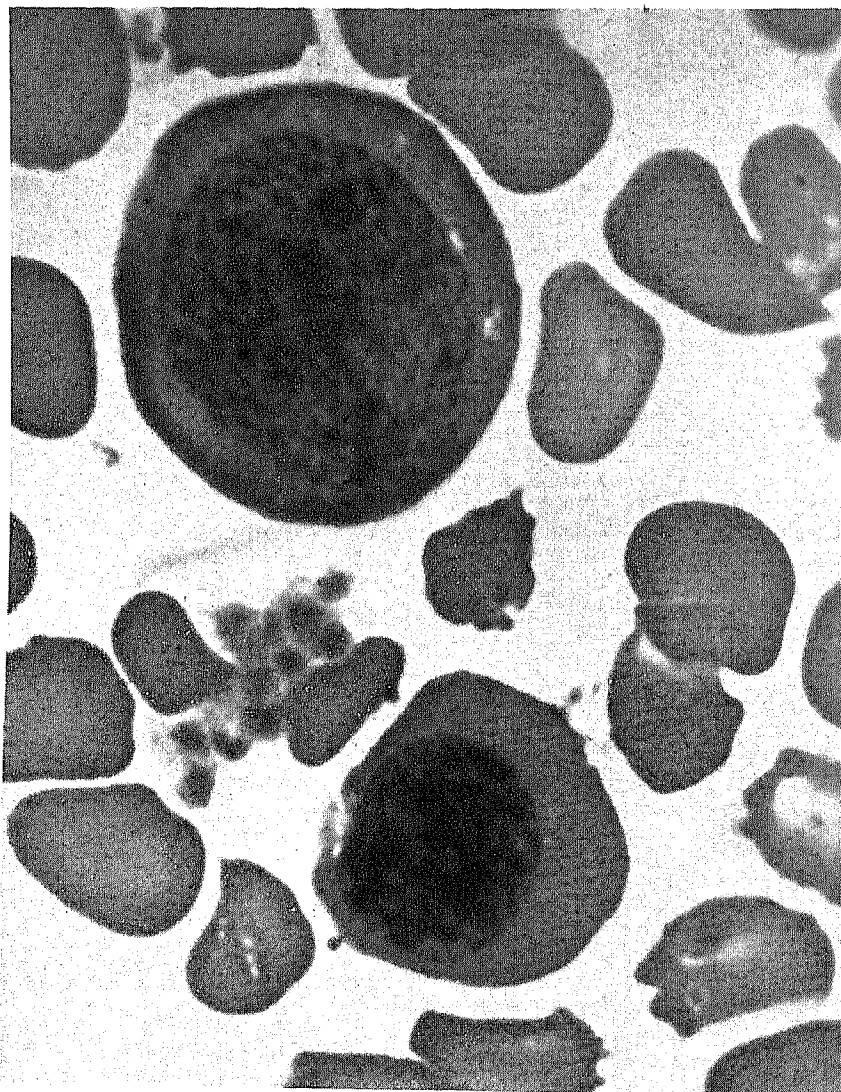


Fig. 2.—Megaloblasts from bone marrow of Monkey 73 (Fig. 1) on 39th day after turpentine injections were begun. Larger nucleated cell is a basophilic megaloblast and smaller one is an orthochromatic megaloblast.

Further evidence differentiating the scorbutic megaloblastic animals from those acquiring megaloblastosis following infection will be presented in the following experiments, contrived to study these relationships.

EXPERIMENTAL INDUCTION OF MEGALOBLASTOSIS BY TURPENTINE ABSCESS

It so happened that while we were interested in producing megaloblastic anemia in ascorbic-acid-deficient monkeys some other unrelated studies in our laboratory required the creation of sterile abscesses in monkeys. Because of our preoccupation with anemia we examined the bone marrow in the animals in which abscesses were being produced. The marrow samples were taken somewhat unsystematically at various intervals after the intramuscular injections of turpentine. The course of such an animal (Monkey 73) which received turpentine injections intramuscularly is depicted in Figure 1. This animal had been fed a diet of cows' milk to which starch had been added. Optimal tissue saturation with ascorbic acid was assured by providing 50 mg. orally each day and 100 mg. intramuscularly once a week. This monkey had been maintained in good health on this regimen for 260 days; no anemia or leucopenia developed, and the marrow remained normal. One cubic centimeter of turpentine was injected into the muscles of the legs on the 261st, 277th, and 296th days. The appetite, activity, and weight declined during the series of turpentine injections, but diarrhea did not develop. Marrow samples examined from time to time revealed only the leucocyte activity expected with suppurative processes until 4 days after the third injection of turpentine (39 days after the first injection), when a definite megaloblastic pattern of hemopoiesis was encountered (Fig. 2). The leucocyte series also had the changes characteristically found in megaloblastosis.

On the basis of this chance discovery of megaloblastosis following turpentine injections we set about to repeat the observation, to determine the tissue concentrations of ascorbic acid, vitamin B₁₂, and folic acid compounds, and to follow the effect of therapy on the marrow. Another animal, which had been thriving on a diet of cows' milk and starch for 150 days (Monkey 72), and four animals (Monkeys 105, 118, 135, 138) recently received from an animal dealer and placed on a diet of cows' milk⁷ were selected for study. The hemoglobin and bone marrow

7. Experimental Diet 4F

Dried Cows' Milk, 12 gm.
Water to make 100 cc.
5% CuSO₄, 1 drop per 100 cc.
Daily Supplement, orally
Ascorbic Acid, 50 mg.
Vitamin A, 4000 I. U.
Vitamin D, 400 I. U.
15 mg. *d*-alpha toco-
pherol acetate } water-miscible
Elixir ferrous gluconate, 4 cc.

Weekly Supplement, orally
Vitamin B₁₂, 15 γ.
Thiamine hydrochloride, 5 mg.
Riboflavin, 2 mg.
Nicotinamide, 75 mg.
Sodium pantothenate, 2.5 mg.
Pyridoxine hydrochloride, 5 mg.

Monkeys 72 and 73 were given 100 mg. of ascorbic acid intramuscularly weekly as well as 50 mg. orally throughout the experiments.

Details concerning the usual manifestations of monkeys fed this type of diet have already been published.²

were found to be normal in each animal, and then 1 cc. of turpentine was injected intramuscularly. The turpentine gave rise within a day to marked cellulitis, the animals became mildly ill and ate less for a few days, but they quickly resumed normal behavior except for favoring the affected leg. Fluctuation soon developed in the injected area, and usually in about a week a purulent material burrowed to the surface and drained freely before the wound healed. The purulent material was cultured and found to be sterile. During this sequence of events, after the first injection of turpentine, the marrow revealed activity in the leucocyte series with only minor changes in the erythrocyte series. After two or more injections a characteristic megaloblastic metamorphosis was observed in the erythrocyte series. The time and number of injections required to produce a megaloblastosis was variable. The composite data from the experimental animals may be seen in Table 2. The megaloblastosis finally achieved in all six monkeys given turpentine

TABLE 2.—Summary of Data on Monkeys in Which Megaloblastosis Was Induced by Turpentine Abscesses (Milk Diets, Abundant Ascorbic Acid)

Monkey	Turpentine Injected, (Day of Experiment)	Megalo-blastic (Day of Experiment)	Hemo-globin,* Gm./100 Cc.	Leuco-cytes* per Cu. Min.	Treatment †	Effect on Marrow
72	1, 37, 105	73	10.8	5,870	15 γ B ₁₂ intramuscularly, 2 days	No effect; died
73	1, 16, 35	39	8.1	7,150	None	Killed 39th day for tissue analyses
105	1, 17, 25	32	9.0	6,900	Folic acid heptaglutamate ‡ orally, 12 days	No effect; killed on 44th day for tissue analyses
118	1, 17, 25, 30	40	9.3	4,800	None	Killed on 41st day for tissue analyses
135	1, 17, 33, 50, 59, 90	65	30 γ B ₁₂ intramuscularly, 3 days 15 mg. folic acid intramuscularly, 2 days	No effect in 7 days Normoblastic 11 days later
138	1, 17, 33, 50, 59	65	Abscess allowed to heal	Normoblastic by 74th day

* Average normal values \bar{x} : hemoglobin 12.7 gm. per 100 cc.; leucocytes 15,400.

† Ascorbic acid continued and abscesses maintained through trials of therapy, except in 138 abscess was allowed to heal.

‡ A concentrate of folic acid heptaglutamate derived from yeast was assayed in our laboratory to contain 0.79% heptaglutamate. The daily oral dose of 37 mg. provided the equivalent of 100 γ folic acid activity as determined by treatment with conjugase and assay with *Str. faecalis*. The concentrate was supplied by Dr. Richard D. Greene, of E. R. Squibb & Sons.

injections was typical in every respect, including characteristic alterations in the leucocytes, and was quite like the marrow seen in megaloblastosis in infants and in scorbutic monkeys. Our criteria for designating a marrow as megaloblastic have been fully discussed and illustrated in other publications from this laboratory.^{2,8} An illustration typical of the megaloblasts which appeared in the marrows after a series of turpentine injections is provided in Figure 2. When megaloblastosis was established the animals failed rapidly, became very anorexic and apathetic, and lost weight precipitously, and the fur appeared lusterless and disheveled. Two animals acquired mild diarrhea, but the stools remained normal in the others. It is interesting to note that although large areas of necrosis were present at the sites of the turpentine injections a leucopenia rather than leucocytosis was found in the peripheral

8. Sundberg, R. D.; Schaar, F., and May, C. D.: Experimental Nutritional Megaloblastic Anemia: II. Hematology, *Blood* 7:1143, 1952.

blood. This is characteristic in folic acid deficiency. At the time of megaloblastosis the hemoglobin was 8 to 10 gm., compared with the average value of 12.7 gm. found in control monkeys. The animals were killed for tissue studies or treated as soon as megaloblastosis was discovered.

The time required to produce scurvy in monkeys by milk diets devoid of ascorbic acid is fairly uniform, averaging 78 days. Megaloblastosis rarely develops until overt signs of scurvy appear, usually after about two weeks of conspicuous evidence of scurvy. Megaloblastosis associated with spontaneous infections naturally occurred at most variable times. Megaloblastosis induced by turpentine injections follows a somewhat more regular pattern than that associated with spontaneous infections and develops more quickly than when induced by scurvy. These points are demonstrated by typical data in Table 3. One significance of this information is to indicate

TABLE 3.—Megaloblastic Anemia in Monkeys

Day of Occurrence in Experiments Under Different Circumstances				
Ascorbic Acid Deficient		Ascorbic Acid Adequate		
Scurvy	Megalo- blastic	Infection	Turpentine Abscesses	
70	90	43	32	
70	90	44	39	
72	92	99	40	
83	93	111	65	
84	102	160	65	
88	119	..	73	
Average	78	92	52	

TABLE 4.—Vitamins in Livers of Monkeys on Milk Diet (γ/gm., wet, average values)

	Total Animals	Ascorbic Acid	B ₁₂	Total Folic Acid	Free Folic Acid
Controls, ^o adequate ascorbic acid.....	5	129	1.0	1.10	0.026
Turpentine abscess, adequate ascorbic acid Megaloblastic	3	151	0.8	0.30	0.014
Scurbutic Megaloblastic	7	8	0.6	0.14	0.006
Normoblastic, supplementary folic acid.....	1	4	0.6	1.43
Infection, adequate ascorbic acid Megaloblastic	5	103	0.5	0.16	0.008
Normoblastic	6	...	0.5	0.62	0.042

that it is quite unlikely that spontaneous infection, which would be acquired irregularly, could be a primary factor in the regularity of appearance of megaloblastosis in the course of scurvy.

Data concerning the liver content of vitamin B₁₂, the folic acid compounds, and ascorbic acid found in monkeys in which megaloblastosis developed in the different circumstances mentioned above are presented in Table 4. Several features should be noted which distinguish these groups. The turpentine-injected group had considerably lower than normal folic acid level in the liver even though the

ascorbic level was maintained at the level of the controls by supplementation of the diet. In the group suffering spontaneous infections those in which megaloblastic marrows developed had much lower levels of folic acid in the liver than similarly infected animals in which the marrow remained normoblastic. An animal rendered scorbutic but given supplementary folic acid did not acquire megaloblastosis, and the liver content of folic acid was maintained at a normal level in the presence of severe scurvy. The concentration of vitamin B₁₂ was less affected in all the groups.

EFFECTS OF TREATMENTS

The turpentine abscesses were maintained active during trials of therapy, by repeated injections if necessary. The responses in the marrows to various treatments (Table 2) correspond to the findings in the liver analyses (Table 4). Neither vitamin B₁₂ nor ascorbic acid was able to prevent or to eliminate the megaloblastosis in the marrow resulting from turpentine injections. The same had been found to be true of the megaloblastosis arising in monkeys in the course of spontaneously acquired infection. Folic acid was promptly effective in eliminating the megaloblastic pattern from the marrow of both the turpentine-injected and the spontaneously infected monkeys. Either ascorbic acid or folic acid will eliminate the megaloblastosis complicating scurvy, but vitamin B₁₂ alone is without effect. When the turpentine abscess was allowed to heal, the megaloblastic reaction in the marrow disappeared simultaneously and was replaced by a normal normoblastic pattern without any therapy. The animal improved correspondingly. Oral administration of a heptaglutamate of folic acid, in a larger amount than would be obtained from the diet or intestinal flora, was unable to furnish an animal with sufficient folic acid to cure megaloblastosis while the turpentine abscess persisted, even though the ascorbic acid intake was abundant. We have found folic heptaglutamate to be poorly absorbed by monkeys; only 4% of an oral dose appears to be absorbed.

Important factors in the development of megaloblastic anemia so readily following infection or turpentine abscess in monkeys are (1) the low content of folic acid compounds in the diet, (2) poor absorption of the conjugated form of folic acid that occurs in food and the intestinal contents, and (3) the immaturity of the animals and increased requirements for growth.

COMMENT

Infants are probably unable to synthesize folic acid or vitamin B₁₂ but depend upon such sources as food and the production of these vitamins by the intestinal bacterial flora to meet their requirements. The steps followed in the absorption and utilization of vitamin B₁₂ and folic acid compounds are not yet known in detail but may be roughly outlined as in Table 5. It is apparent in this scheme that numerous opportunities are afforded for pathological disturbances to interfere with absorption and utilization of these vitamins. It may be noted in Table 6 that, except for the dietary intake of vitamin B₁₂ and folic acid, all the other factors which may lead to a deficiency of these substances pertain to abnormal or diseased persons. The milk feedings commonly employed in early infancy all contain about the same, but rather small, amounts of vitamin B₁₂ and folic acid compounds (Table 7). Normal infants receiving such diets, when the diets are complete and balanced in other vitamins, thrive on the amounts of vitamin B₁₂ and folic acid ingested or produced by the

intestinal bacteria. It is in the sick and abnormal infants, in whom ingestion, intestinal synthesis, absorption, or utilization may be disturbed or for whom requirements may be increased, that one might expect to find evidences of deficiency of folic acid or vitamin B₁₂.

TABLE 5.—Steps in Absorption and Utilization of Vitamin B₁₂ and Folic Acid Compounds

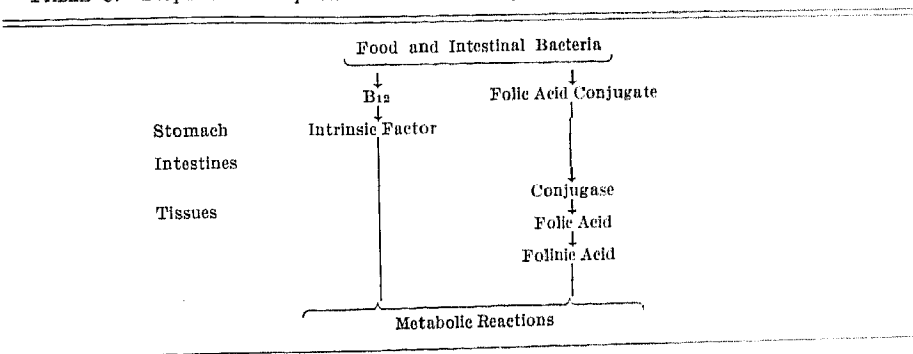


TABLE 6.—Possible Factors Leading to Deficiency or Increased Requirements of Vitamin B₁₂ or Folic Acid

Deficiency of vitamin B₁₂ or folic acid in infancy could result from the following:

- Deficient diet
- Inadequate synthesis by intestinal bacteria
- Lack of intrinsic factor in stomach
- Defective intermediary metabolism
- Inadequate stores from mother

Increased requirements could result from the following:

- Infection
- Loss of sparing effects
- Rapid growth
- Prematurity
- Dietary imbalance
- Vitamin inhibitors or antagonists

TABLE 7.—Average Content of Common Milk Feedings*

	Vitamin B ₁₂ , γ/L.	Folic Acid, γ/L.
Human milk.....	2	3
Fresh cows' milk formula †.....	2	3
Dried cows' milk formula †.....	2	3
S-M-A® †.....	2	3
"Similac" †.....	2	3
Evaporated cows' milk formula †.....	2	3
Evaporated goats' milk formula †.....	2	2

* Data were obtained in our laboratory by microbioassay procedures yielding total vitamin B₁₂ and folic acid compound activities.⁹

† Customary 2/3 milk, 1/3 water dilutions.

‡ Normal dilutions.

The most definitive sign of deficiency of folic acid or vitamin B₁₂ is the appearance of a megaloblastic type of hemopoiesis in the bone marrow. Failure in growth,

fatty changes in the liver, and other phenomena also may be attributed to deficiency of these vitamins but are much less specific, or even equivocal, signs. Apparently both vitamin B₁₂ and folic acid are required for normal hemopoiesis. In order to determine which is the predominant deficiency in a patient with megaloblastic anemia, vitamin B₁₂ must be tested first because all clinical types of megaloblastic anemia will respond to large doses of folic acid regardless of the pathogenesis.

APPLICATION TO MEGALOBlastic ANEMIA OF INFANCY

The majority of infants recognized to have acquired megaloblastic anemia may be included in three broad groups: those responding to vitamin B₁₂; those failing to respond to vitamin B₁₂ but effectively treated with folic acid, and those acquiring a deficiency of folic acid in association with a lack of ascorbic acid, in which case the megaloblastosis may be eliminated by either folic acid or ascorbic acid. Charts of infants illustrating each of these groups are presented in Figures 3, 4, and 5.

The infant whose chart is presented in Figure 3 illustrates the development of megaloblastosis as a complication of scurvy and its disappearance on treatment with

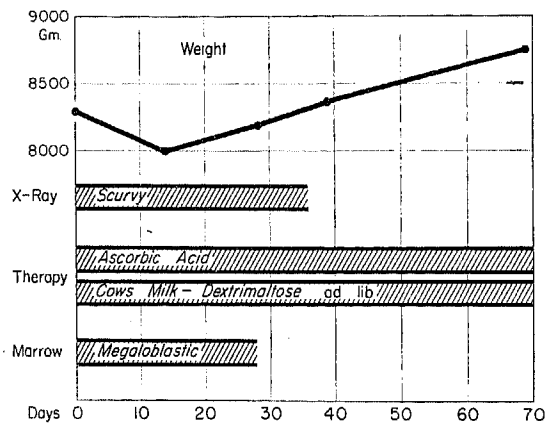


Fig. 3.—Scurvy with megaloblastic marrow. An 8-month-old infant admitted because of signs of scurvy and found to have megaloblastic anemia. Treated without changing diet by large doses of ascorbic acid alone. Marrow gradually reverted to normoblastic pattern during period of 28 days. Uneventful lasting recovery.

ascorbic acid alone. Ordinarily it would be preferable to treat such an infant with both folic acid and ascorbic acid.

The infant whose chart is presented in Figure 4 illustrates the situation in which a deficiency of folic acid predominates; as can be seen, ascorbic acid did not prevent the megaloblastosis and vitamin B₁₂ could not cure it. Folic acid was promptly effective. The infant carried the burden of a chronic infection, pyuria, from birth. Other factors, such as antibiotic therapy, may have contributed to the deficiency of folic acid. To be noted is the marked leucopenia characteristic of folic acid deficiency.

In the infant whose chart is presented in Figure 5 the megaloblastosis was eliminated by vitamin B₁₂ alone, indicating that this was the predominant deficiency; ascorbic acid intake was known to be adequate. Infection was not a conspicuous feature in the clinical history or findings. This patient serves to indicate that infants

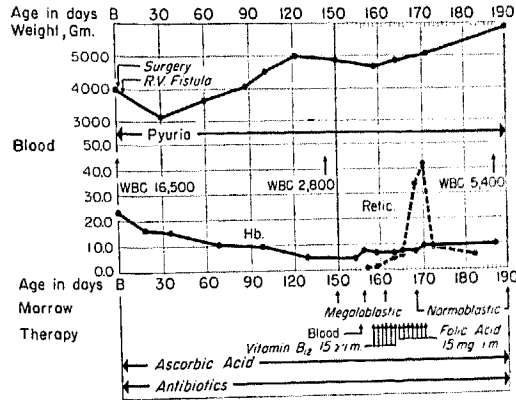


Fig. 4.—Megaloblastic anemia—response to folic acid following failure of ascorbic acid and vitamin B₁₂. A newborn infant with imperforate anus. Surgery second day. Complicating rectovesicle fistula and pyelonephritis. Colostomy required on fourth day. Hemoglobin fell steadily in spite of four transfusions of blood prior to 150th day, when a megaloblastic pattern was found in the marrow. The blood urea nitrogen stabilized at 15 mg. per 100 cc. Various antibiotics were employed, orally and parenterally, throughout course. Ascorbic acid provided in 50 to 100 mg. doses orally from birth. Roentgenograms revealed no evidence of ascorbic acid deficiency. Vitamin B₁₂ administered intramuscularly had no effect on blood or marrow in 10 days. Marrow promptly became normoblastic after folic acid therapy and there was marked reticulocytosis. Subsequent course was one of striking improvement in clinical symptoms and marrow remained normal with continued oral folic acid therapy. Therapy with iron before and after above therapy was without additional effect.

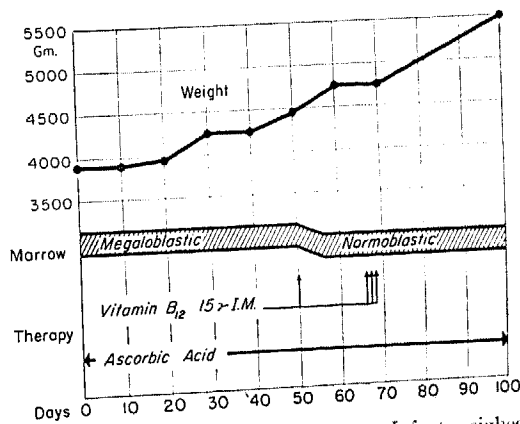


Fig. 5.—Megaloblastic anemia—response to vitamin B₁₂. Infant weighed 2,700 gm. at birth. He had a cleft palate and was kept in a hospital 22 days after birth because of difficulty in feeding. Reared on standard cow's milk formula, but always difficult to feed. Received adequate supplements of ascorbic acid and vitamins A and D. No diarrhea or infections had been noted. When first seen at 10 weeks of age was found to be undernourished and to have a hemoglobin value of 8 gm. per 100 cc. and a megaloblastic pattern in the marrow. Intensive therapy with ascorbic acid alone had no effect. Vitamin B₁₂ caused prompt return of the marrow to normal and marked clinical improvement which persisted for many months without further vitamin B₁₂ therapy.

may acquire a deficiency of vitamin B₁₂, but further clarification of the pathogenesis is required. The prematurity, cleft palate, and consequent nutritional difficulties in this infant may have been important. The role of intrinsic factor in the absorption of vitamin B₁₂ in infancy needs to be studied.

The practical consequences are these: Normal infants on the usual feeding regimens including adequate ascorbic acid do not require supplementary vitamin B₁₂ or folic acid compounds. Sick infants require special consideration, since infection, ascorbic acid deficiency, and many other pathological circumstances may lead to increased requirements for vitamin B₁₂ and folic acid. In cases of severe or prolonged infections it would probably be wise to include additional amounts of vitamin B₁₂ and folic acid in the treatment during the infection and immediate convalescent period.

SUMMARY

The spontaneous occurrence of megaloblastic anemia in association with infection in infants and in monkeys is described.

Megaloblastic anemia was induced experimentally in monkeys by producing abscesses with intramuscular injections of turpentine.

Analyses of the liver for ascorbic acid, vitamin B₁₂, and folic acid compounds in natural and experimental infections are presented.

The low content of folic acid compounds in the liver in both natural and experimental infections and the elimination of megaloblastosis from the marrow by folic acid, but not by vitamin B₁₂ or ascorbic acid, leads to the conclusion that infection can cause a deficiency of folic acid compounds.

The application of these observations to the various types of megaloblastic anemia seen in infants and to treatment is discussed.