Megaloblastic anemia during pregnancy and the puerperium

JACK A. PRITCHARD, M.D.
Dallas, Texas
With the technical assistance of
RUBLE A. MASON
MARJORIE R. WRIGHT

MEGALOBLASTIC anemia during pregnancy or the puerperium apparently is rarely identified in the United States since very few published reports concerned with this form of anemia have emanated from this country. Even so, during the past 8 years we have detected 20 cases of anemia during pregnancy or the puerperium in which there were frank megaloblastic changes in the bone marrow. Observations made on these cases are the basis of this report.

Material and methods

Three cases of megaloblastic anemia during pregnancy or the puerperium were detected at University Hospitals of Cleveland between 1953 and 1956 and 17 were detected at Parkland Memorial Hospital since 1956. At the latter institution a hematologic research laboratory operated by the Department of Obstetrics and Gynecology was established at that time and since then practically all new obstetric patients have been screened by this laboratory. This has contributed to the detection of a wide array of hematologic problems, including these cases of megaloblastic anemia.

Standard hematologic procedures have been utilized unless otherwise specified.[1] Serum iron levels were determined by the method of Peters and associates.[2] Total red blood cell volume, hemoglobin mass, and apparent blood volume were measured with the subject's own red blood cells labeled with chromium.[3] Approximately 20 μc of $Na_2Cr^{15}O_4$ bound to the red blood cells was injected per study except when the red blood cell survival time was measured and then 60 to 100 μc of radiochromium was used. Approximately 30 to 50 ml. of the subject's blood was obtained prior to any therapy, incubated with $Na_2Cr^{51}O_4$ for about 30 minutes, and returned to the subject. Radioactivity was measured until it was 10 per cent or less than that of blood drawn the day after reinjection.

In most instances a standardized special diet containing foods low in folic acid activity was fed to these patients; otherwise a general hospital diet was offered.

Observations

Megaloblastic anemia was detected ante partum 11 times in 9 women and post partum in 9 more. Recorded in Table I are the lowest hemoglobin concentrations and

From The Department of Obstetrics and Gynecology, The University of Texas Southwestern Medical School and Parkland Memorial Hospital.

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hematocrit values observed in each case. In the 11 cases diagnosed ante partum the mean hemoglobin concentration was 4.8 Gm. per 100 ml. and ranged from 2.9 to 7.9 per 100 ml.; the hematocrit value averaged 15.0 and varied from 9.5 to 24.0. In the 9 cases diagnosed post partum the hemoglobin concentration averaged 6.4 Gm. per 100 ml. and ranged from 2.9 to 8.0 per 100 ml.; the hematocrit value varied from 8.5 to 26.0.

Only 2 of these patients were pregnant for the first time. In the others it was not unusual during previous pregnancies for the diagnosis of "anemia" to have been recorded. Nine of the 18 women were white (4 of these were of Latin American origin), 8 were Negro, and one was an American Indian.

Even though this disease has been found by some to be more frequent in patients with twins or with toxemia of pregnancy, in none of these 20 cases were there twins and in only 3 instances (twice in one patient) was hypertension detected. It is probable that both of these multiparous women had chronic vascular disease.

Poverty was a common but not a universal finding. These patients had a very poor dietary intake from the standpoint of the quality of foods eaten. The initial dietary history often was misleading, since the patients usually were apathetic and gave a very poor history when first interviewed. Reinterrogation after response to therapy then revealed just how poor their diets actually had been.

Typically in these cases for several months the diet had been low in animal protein and nearly devoid of green or other colored vegetables. This was especially true for uncooked colored vegetables. Wheat and corn flour products, beans that had been cooked for prolonged periods, boiled potatoes, soft drinks, fruit juice concentrates, and occasionally some animal protein in the form of chicken, pork, luncheon meats, or processed cheese were the foodstuffs usually consumed. Persistent vomiting throughout pregnancy occurred frequently. Anorexia was the rule. Failure to establish and/or maintain a normal pregnancy weight gain was commonplace.

Seventeen out of 20, or 85 per cent, of the pregnancies resulted in living infants who were discharged from the hospital without any apparent residual effects produced by the maternal disease. One of the 3 perinatal deaths followed a difficult breech delivery with entrapment of the head in an abnormally small pelvis. The mother had sickle cell anemia as well as megaloblastic anemia (Patient I. G.). In spite of transfusion with 15 units of blood late in pregnancy this patient's hemoglobin concentration dropped to as low as 3.5 Gm. per 100 ml. There was one instance of gross prematurity with death early in the neonatal period (Patient P. C.). Prior to delivery the maternal hemoglobin level was as low as 5.9 Gm. per 100 ml.; lobar pneumonia further complicated the pregnancy at this time.

Table I. Lowest hemoglobin and hematocrit levels detected prior to hematologic response

Patient	*Hemoglobin (Gm./100 ml.)*	*Hematocrit (%)*
Antepartum cases		
1. D. Ca.	4.1	12.0
2. C. G.	6.9	22.0
3. I. G.*	3.5	11.0
4. G. M.	4.4	13.0
5. B. M.	4.8	14.0
6. R. S. (1)	6.1	18.0
7. R. S. (2)	7.9	24.0
8. C. T. (1)	3.6	10.5
9. C. T. (2)	2.9	9.5
10. C. W. T.	4.6	15.0
11. G. Ma.	4.5	14.0
Average	4.8	15.0
Range	2.9-7.9	9.5-24.0
Postpartum cases		
1. M. C.	7.3	22.0
2. A. H.	7.9	24.0
3. B. Hi.	8.0	23.0
4. B. Ho.	6.5	23.5
5. L. K.	6.7	20.0
6. D. Cr.	5.9	16.0
7. P. C.	2.9	8.5
8. B. B.	4.7	17.0
9. P. A.	7.8	26.0
Average	6.4	20.0
Range	2.9-8.0	8.5-26.0

*Also had sickle cell anemia.

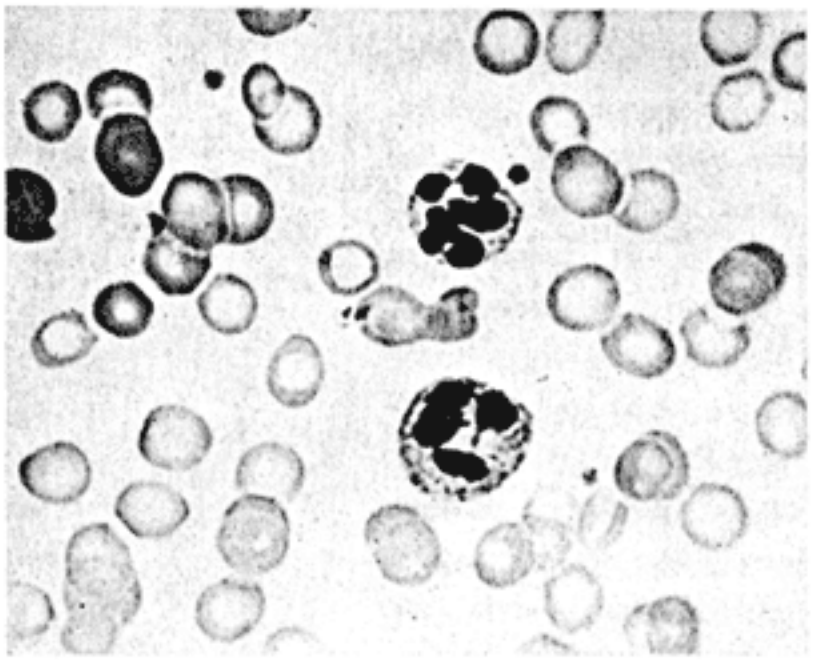

Fig. 1. Peripheral blood smear from a case (Patient B. Ho.) of megaloblastic anemia further complicated by severe iron deficiency. The possibility of megaloblastic anemia was suggested by the presence of hypersegmented neutrophils.

In the third instance of perinatal death the fetus died in utero at about the thirtieth week of gestation (Patient C. T.). The mother was first seen during this pregnancy 3 days before death of the fetus. Her hemoglobin level was 2.9 Gm. per 100 ml. and she had hypertension. The year before she had come to the hospital for the first time near term with severe anemia and thrombocytopenia, gross amnionitis following prolonged rupture of the membranes, and hypertension. The hemoglobin concentration then was 3.6 Gm. per 100 ml., the hematocrit value 10.5, and the platelet count 40,000 per cubic millimeter. Even so, the infant born a few hours later survived.

Hematologic examinations carried out on the liveborn infants consisted at the minimum of a hemoglobin determination and an examination of a blood smear. Anemia was not present in the newborn infants even in the instances where the mothers were severely anemic and had received no specific therapy prior to delivery. Cytologic examination of the infants' bone marrow in 2 such cases showed no megaloblastic changes.

To establish the diagnosis of megaloblastic anemia of pregnancy or the puerperium usually demands that bone marrow aspiration be performed. When compared with normal nucleated red blood cells in the bone marrow, megaloblasts are larger and contain much more finely dispersed chromatin in the nuclei. These changes in the chromatin tend to persist as maturation occurs and the cells continue to be larger than normal nucleated red blood cells at comparable stages of development. Another feature of megaloblastic erythropoiesis is asynchronism between the degree of nuclear maturation and the content of hemoglobin.[4, 5] Macrocytic, somewhat oval erythrocytes abundantly filled with hemoglobin but still containing particulate chromatin in the nuclei are commonplace in the marrow and may be present in the peripheral blood. Their detection in the peripheral blood is facilitated by preparing smears of the buffy coat so as to increase appreciably the number of nucleated cells examined.[6]

Characteristic changes are also seen in the white blood cell precursors. Quite large metamyelocytes, or so-called giant metamyelocytes, are usually present in the marrow of patients with megaloblastic anemia of pregnancy. This has been referred to as megaloblastic leukopoiesis.

Qualitative as well as quantitative changes affecting the erythrocytes, the leukocytes,

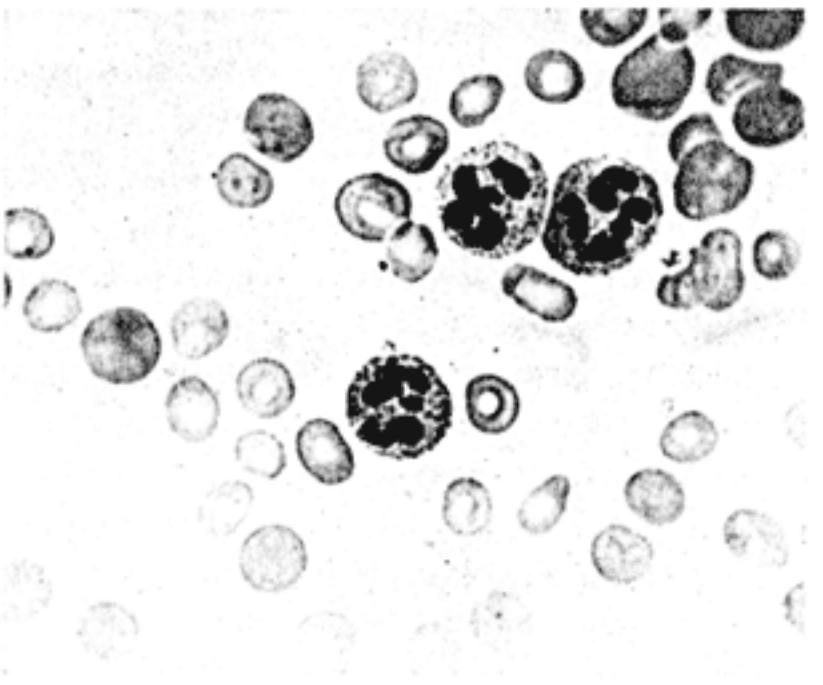

Fig. 2. Peripheral blood smear from a case (Patient M. C.) of iron deficiency and megaloblastic anemia previously treated with parenteral iron. Many hypochromic microcytic red blood cells and a smaller number of macrocytic erythrocytes well filled with hemoglobin are evident. Also hypersegmented neutrophils are seen.

and the platelets may be prominent in the peripheral blood. Varying degrees of macrocytosis, leukopenia, hypersegmentation of the nucleus of the neutrophils, and thrombocytopenia often with rather large platelets are found in the more severe cases of megaloblastic anemia. The nucleus of the neutrophil may consist of 8 or more lobes. When all of these changes are present in the cells of the peripheral blood, megaloblastic anemia is almost certain to be the correct diagnosis but some cases of aplastic anemia may show identical changes.

The typical macrocytic erythrocyte well filled with hemoglobin is uncommon in the peripheral blood when there is iron deficiency associated with megaloblastic anemia. Instead, most of the cells are normocytic or microcytic. In Fig. 1 erythrocytes are demonstrated from a case (Patient B. Ho.) of megaloblastic anemia of pregnancy further complicated by severe iron deficiency. The serum iron was 22 μg per 100 ml. Staining of sections of the bone marrow with Prussian blue failed to demonstrate any stored iron. A smear of the peripheral blood suggested the possibility of megaloblastic anemia only by hypersegmentation of some of the nuclei of neutrophils. The hemoglobin concentration was 6.5 Gm. per 100 ml., the mean corpuscular volume 65 μ, and the mean corpuscular hemoglobin content 17 $\mu\mu$g. Neither leukopenia nor thrombocytopenia was present. The bone marrow, however, showed classic megaloblastic changes.

If iron is given to such a patient during pregnancy without correction of the deficiency causing the megaloblastic anemia, the erythrocytes subsequently delivered to the peripheral blood are macrocytic and hyperchromic. The resulting mixture of hypochromic microcytic cells and more recently formed macrocytic cells well filled with hemoglobin is demonstrated in Fig. 2. About 2 months before, 600 mg. of iron as saccharated iron oxide had been given intravenously to this patient (M. C.). When this smear was obtained the hemoglobin value was 7.9 Gm. per 100 ml., the mean corpuscular volume 82 c. μ, and the mean corpuscular hemoglobin content 25 $\mu\mu$g. Although 2 distinct populations of red blood cells were evident in the smear, one macrocytic and one microcytic, measurement of the mean corpuscular volume did not aid in the identification of either of these populations.

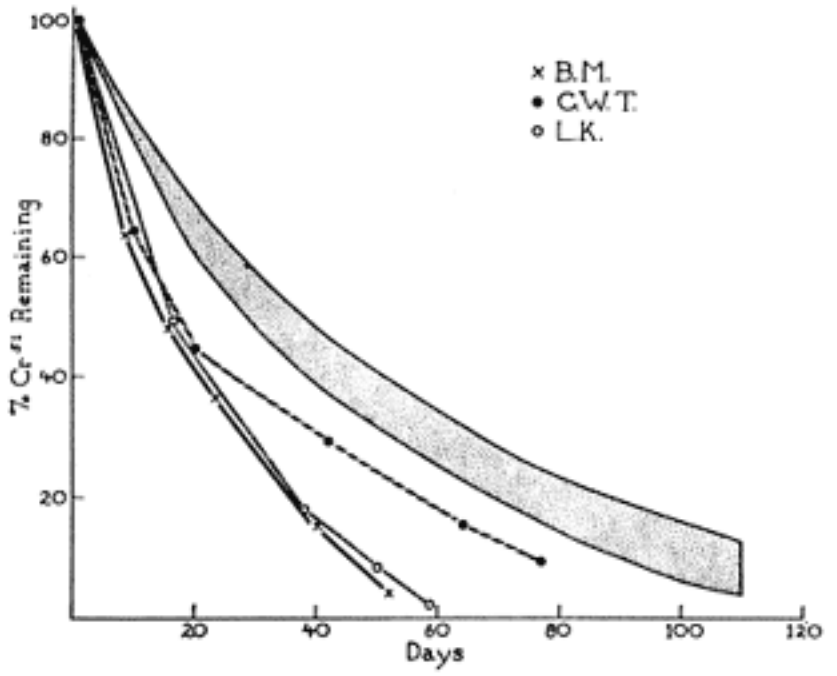

Fig. 3. Shown is the shortened survival of radiochromium-labeled red blood cells from 3 patients with megaloblastic anemia. The rate of disappearance is compatible with increased destruction. However, marked impairment of production resulting in a red blood cell population made up only of older cells at the time they were labeled could also produce these findings.

Failure to demonstrate an elevated erythrocyte mean corpuscular volume does not exclude the possibility of megaloblastic anemia of pregnancy. The mean corpuscular volume was greater than normal in only 6 of the 20 cases. In 7 it fell within the normal range of 80 to 95 c. μ, while in 7 the mean corpuscular volume was actually below normal, ranging from 65 to 80 c. μ.

Measurements of the serum iron concentration were not always helpful for determining the etiology of the anemia. In the case of megaloblastic anemia accompanied by severe iron deficiency the serum iron concentration was usually low or normal, whereas in the absence of gross iron deficiency it was high prior to therapy. In the instances where it was initially high it rapidly fell with the onset of a reticulocyte response as shown in Figs. 7, 8, and 9.

Hyperbilirubinemia with serum levels

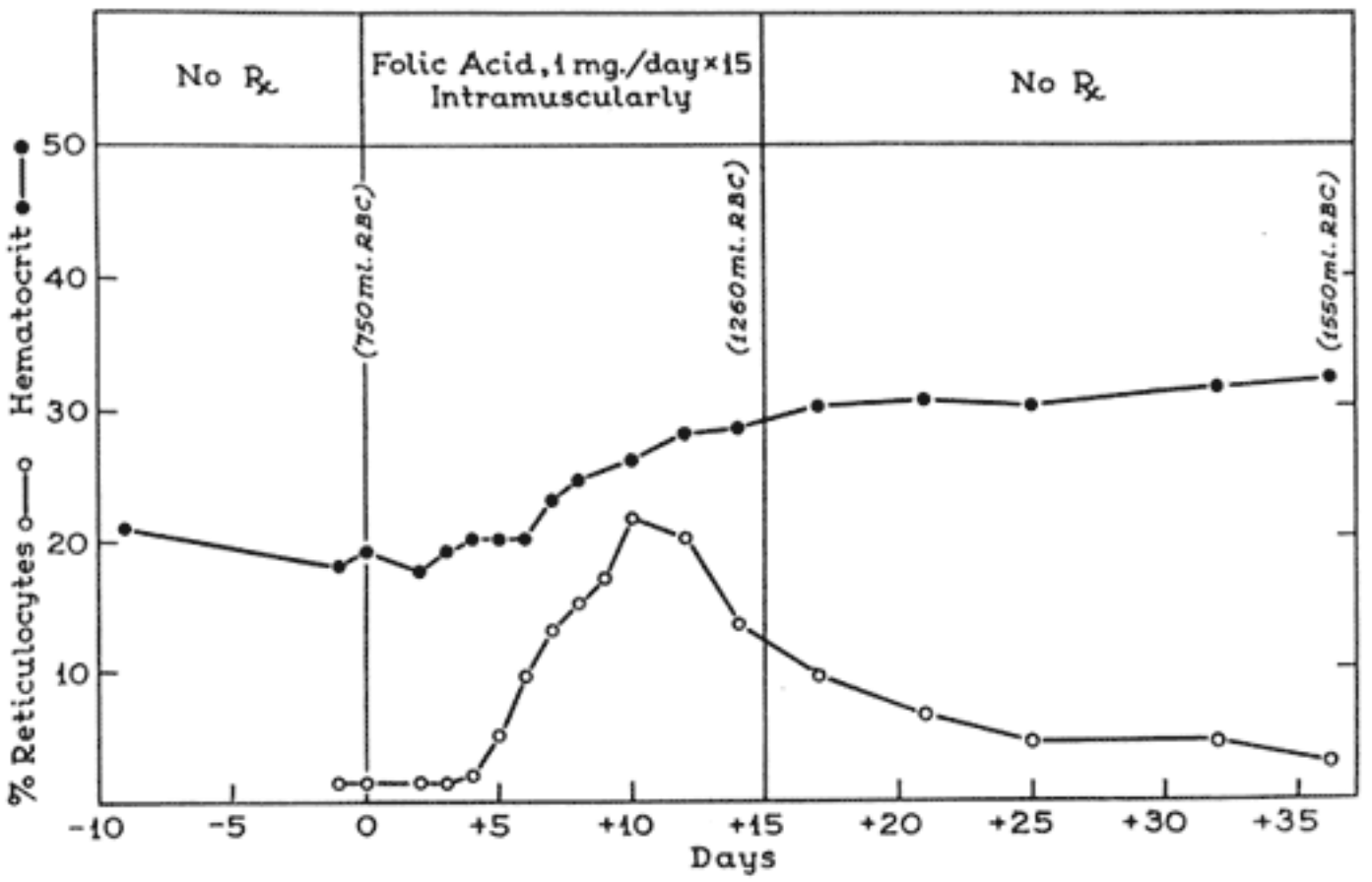

Fig. 4. R. S. (first pregnancy) responded promptly to 1.0 mg. of folic acid per day intramuscularly. Although a total of only 15.0 mg. of folic acid was given, the total volume of circulating red blood cells continued to increase to reach at least 1,550 ml.

from 1.0 to as high as 3.0 mg. per 100 ml. was a common finding. The bilirubin was predominantly unconjugated or "indirectly reacting." Also urinary urobilinogen excretion was sometimes elevated. Levels up to 5 Ehrlich units per 2 hours were demonstrated.

Measurements of red blood cell life span were initiated prior to therapy in 3 instances. Whereas in normal pregnancy erythrocyte life span is more than 100 days, in these patients with megaloblastic anemia of pregnancy it ranged from about 50 to 80 days (Fig. 3).

Studies of hepatic function were carried out in several of these cases. In some but not all there was abnormal retention of intravenously injected Bromsulphalein prior to treatment. After therapy with folic acid the excretion of Bromsulphalein soon became normal. The cephalin-cholesterol flocculation test frequently was abnormal but serum glutamic oxaloacetic transaminase activity was not elevated. Serum protein concentrations were often somewhat lower than normal; the reduction involved both albumin and total globulin. These preliminary studies of hepatic function in cases of megaloblastic anemia of pregnancy will be extended.

In one patient who developed megaloblastic anemia during two successive pregnancies we were able to study the response to therapy prior to delivery during the former pregnancy and with the latter pregnancy also to observe in serial fashion the development of many of the hematologic changes leading to the development of classic megaloblastic anemia.

R. S., a 25-year-old American Indian, during her second pregnancy came to Parkland Memorial Hospital to obtain prenatal care when she was about 7 to 8 weeks from term. She complained only of feeling somewhat tired. In her first pregnancy when she was cared for at an Indian reservation hospital she had received blood transfusions for anemia prior to delivery.

Studies of the peripheral blood revealed the following: hemoglobin concentration 6.1 Gm. per 100 ml., hematocrit value 18.0, mean corpuscular volume 109 c. μ, reticulocyte count 1.4 per cent, white blood cell count 3,500 per cubic millimeter, platelet count 24,000 per cubic millimeter, serum iron 178 μg per 100 ml. Numerous macrocytic erythrocytes with many bizarre shapes, hypersegmented neutrophilic leukocytes, and a scarcity of platelets were noted

in the peripheral blood. The total red blood cell volume was only 750 ml. and the apparent blood volume was 3,840 ml. The gastric juice contained free hydrochloric acid. The bone marrow was megaloblastic.

There was no evidence of spontaneous remission during 8 days prior to any specific therapy. The platelet count ranged from 16,000 to 26,000 per cubic millimeter and there were episodes of gingival bleeding during this time. A diet poor in folic acid was continued and 1.0 mg. of folic acid as sodium folate was given intramuscularly each day for 15 days. The seventh day after the start of folic acid therapy the reticulocyte count was 13.0 per cent, hemoglobin concentration 7.2 Gm. per 100 ml., white blood cell count (including nucleated red blood cells) 27,500 per cubic millimeter and platelet count 44,000 per cubic millimeter (Fig. 4). By the thirteenth day the hemoglobin level was 8.6 Gm. per 100 ml., the hematocrit value 28.5 per cent, and the platelet count 146,000 per cubic millimeter. The total red blood cell volume now was 1,260 ml. and the apparent blood volume had risen by an amount equivalent to the added red blood cells.

Even though therapy with folic acid was discontinued after 15 days and the patient returned home, hematologic improvement continued. Thirty-eight days after the start of folic acid therapy the white blood cell and platelet counts remained normal, the hematocrit value was 32.5, and the circulating red blood cell and apparent blood volumes had risen to 1,550 ml. and 4,780 ml., respectively.

Fifty days after the start of therapy delivery of a normal infant weighing 3,610 grams was accomplished. When the patient was admitted in labor the hematocrit value was 34.0.

On the second postpartum day 550 ml. of blood was removed. The phlebotomy, combined with blood loss at delivery, estimated to have been at least 600 ml., lowered the hematocrit value to 23.0 and the total red blood cell volume to 850 ml. To insure adequate iron for erythropoiesis 750 mg. of iron as iron dextran was given intramuscularly and a regular hospital diet was offered but no more folic acid was administered. There were a prompt reticulocystosis and a progressive rise in the hematocrit value (Fig. 5). One week later when she was discharged from the hospital it was 30.0 and three weeks later it was 37.0. In spite of lack of therapy with folic acid, the total red blood cell volume now was 1,430 ml., while the apparent blood volume was 3,840 ml. Two months after delivery the hematocrit value was 42.0.

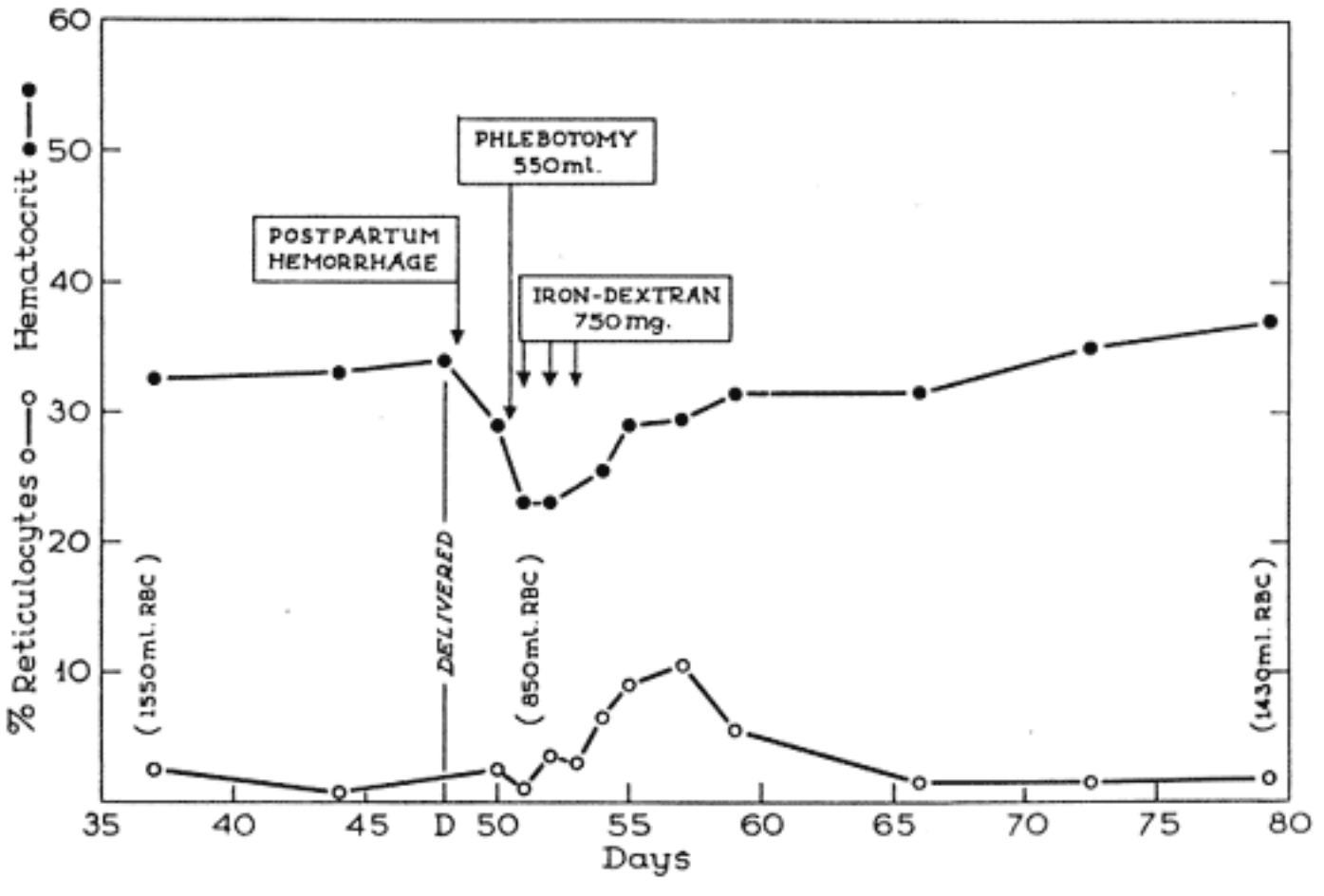

Fig. 5. Somewhat excessive blood loss at delivery by R. S. (first pregnancy) plus phlebotomy lowered the total red blod cell volume after delivery to 850 ml. Even though folic acid therapy had been discontinued 5 weeks before after a total dose of only 15.0 mg., there was a prompt reticulocyte response and rise in hematocrit value while she received only iron and a general diet. The red blood cell volume rose to at least 1,430 ml.

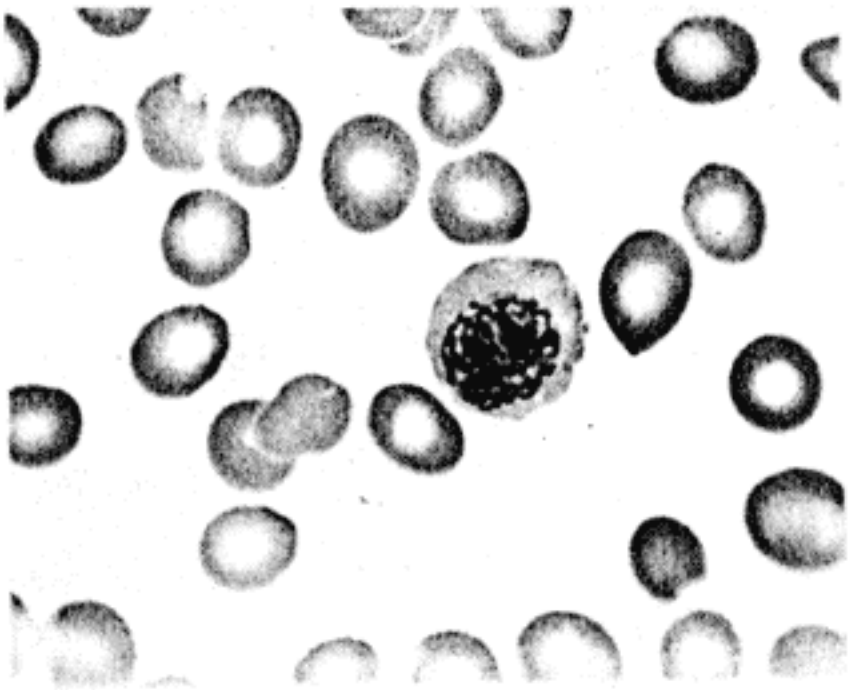

Fig. 6. Smear of peripheral blood from R. S. (second pregnancy) showing a large nucleated red blood cell which contains hemoglobin yet the chromatin is still dispersed throughout the nucleus. These features strongly suggest megaloblastic erythropoiesis.

The patient was next seen 8½ months later when she was admitted to Parkland Memorial Hospital because of asthma and bronchitis complicating pregnancy. She was about 27 weeks pregnant. Numerous macrocytic erythrocytes including an occasional large nucleated red blood cell and neutrophils with nuclear hypersegmentation were seen in the peripheral blood. Anemia, leukopenia, and thrombocytopenia were absent. The hematocrit value was 37.0. The serum iron concentration was elevated to 205 μg per 100 ml. The bone marrow at this time contained giant metamyelocytes plus nucleated red blood cells strongly suggestive of megaloblasts.

During the next 8 weeks she was followed closely as an outpatient. She resumed her previous dietary habits, consuming chiefly salt pork, boiled pinto beans, biscuits, and coffee.

The results of some of the hematologic studies performed are summarized in Table II. During the next 8 weeks after the initial studies the hematocrit value progressively decreased to 27.0, the macrocytosis persisted, moderate leukopenia and quite marked thrombocytopenia with a platelet count of 50,000 per cubic millimeter developed, and the serum iron level became even more elevated. In a smear of the peripheral blood an occasional nucleated red blood cell with megaloblastic features was seen (Fig. 6). These were common in smears prepared from the buffy coat.

After admittance a diet of foods low in folic acid activity was supplied. During the next 10 days there was no evidence of any hematologic response. In the 9 weeks after its initial measurement the total red blood cell volume had dropped from 1,700 ml. to 965 ml. and the apparent blood volume had decreased by an almost identical amount.

Next 0.4 mg. of folic acid was given orally once a day for 10 days while the special diet was continued. There was a slight rise in the reticulocyte count to a maximum of 3.9 per cent at the end of the 10 days. The serum iron fell somewhat but still was abnormally high, suggesting minimal effective erythropoiesis. When the dose of folic acid was increased to 1.0 mg. by mouth once a day, there was a prompt rise in reticulocytes to 11.1 per cent on the third day and to 18.4 per cent 2 days later. The serum iron now was 39 μg per 100 ml. and the platelet count was 116,000 per cubic millimeter. These data are also plotted in Fig. 7.

The infant weighed 3,000 grams at birth and appeared perfectly normal. The day after delivery his hemoglobin concentration was 20.2 Gm. per 100 ml.

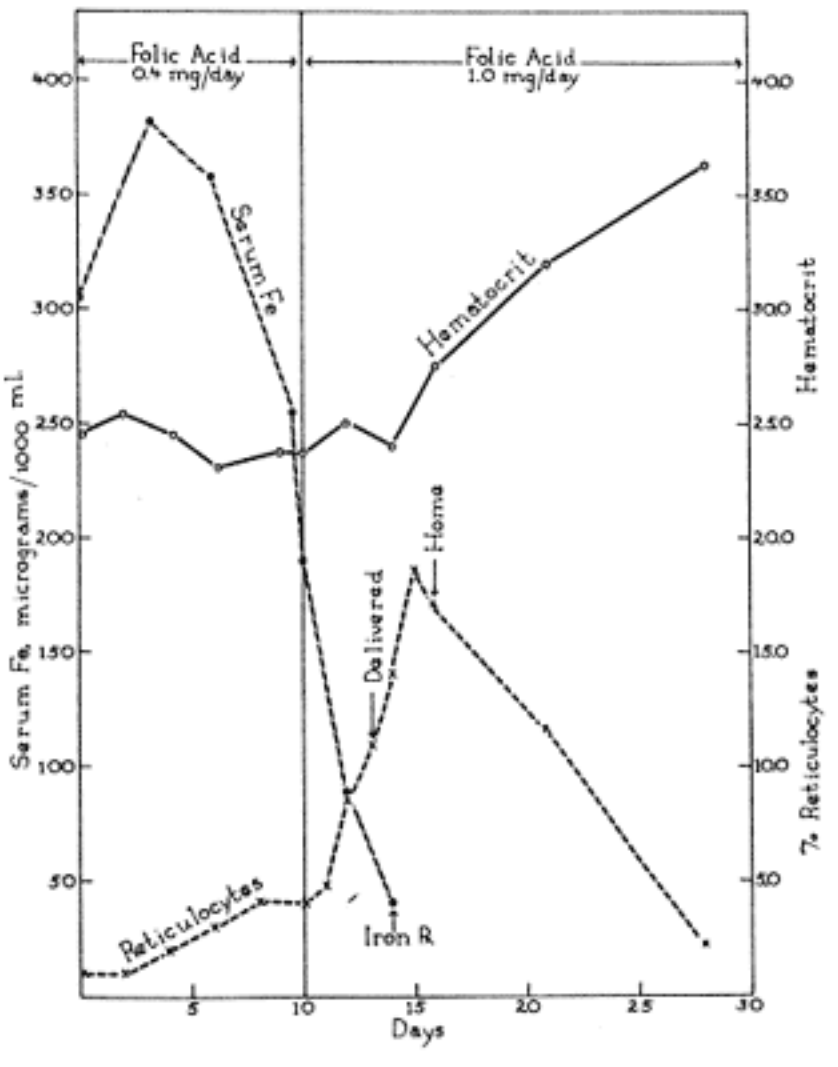

Fig. 7. R. S. (second pregnancy) developed only a slight increase in reticulocytes while receiving 0.4 mg. of folic acid orally and a folic acid–poor diet for 10 days. When the folic acid dosage was increased to 1.0 mg. per day orally the reticulocyte count promptly rose.

Table II. Summary of hematologic studies during the development of megaloblastic anemia of pregnancy

Gestation (weeks/days)		*Hemato-crit (%)*	*MCV (c. μ)*	*Reticu-locytes (%)*	*WBC (c.mm.)*	*Platelets (c.mm.)*	*Serum Fe (μg./100 ml.)*	*RBC vol. (ml.)*	*Blood vol. (ml.)*	*Bilirubin direct/ total (mg./100 ml.)*
27	--	37.0	107	0.9	9,300	156,000	205	1,700	4,610	---/0.9
30	--	33.5	105	2.8	12,300	---	---	---	---	---
32	--	32.5	118	0.3	8,400	"Ade-quate"	---	---	---	0.2/1.3
34	--	29.0	110	0.3	7,350	---	---	---	---	---
35	0*	27.0	104	0.4	6,500	50,000	208	1,290	4,780	0.4/1.1
--	10†	25.0	109	1.0	6,650	36,000	303	965	3,850	---
--	17	23.0	104	2.8	6,800	44,000	358	---	---	---
--	20‡	23.0	---	3.9	8,450	---	191	---	---	0.6/2.6
--	23§	25.0	---	11.1	9,600	95,000	93	---	---	---
Postpartum‡										
--	2	25.0	---	18.4	16,200	116,000	39	---	---	---
--	8	32.0	121	11.3	11,100	348,000	---	---	---	---
--	16	36.5	---	2.2	---	---	---	---	---	0.5/1.7
8	--	44.0	86	---	9,250	280,000	43	1,660	3,870	---/0.2

*Hospitalized.
†Began 0.4 mg. folic acid orally daily.
‡Folic acid increased to 1.0 mg. orally daily.
§Delivery.

Table III. Summary of therapeutic agents administered antepartum in cases of megaloblastic anemia of pregnancy

Patient	*Therapy*
R. S. (first pregnancy)	Folic acid–poor diet for 8 days, no response; same diet plus 1.0 mg. folic acid intramuscularly, good response (Fig. 4)
R. S. (second pregnancy)	Folic acid–poor diet for 10 days, no response; same diet plus 0.4 mg. folic acid orally for 10 days, poor response; same diet plus 1.0 mg. folic acid per day orally, good response (Fig. 7)
D. Ca.	Folic acid–poor diet plus 1.0 mg. folic acid orally per day, good response (Fig. 8)
C. T. (second pregnancy)	Folic acid–poor diet plus 0.4 mg. folic acid orally per day, good response (Fig. 9). Fetus was dead in utero
C. G.	Folic acid–poor diet plus 5.0 mg. folic acid intramuscularly per day, good response
C. W. T.	General diet plus parenteral iron for 10 days, no response; same diet plus 500 mg. ascorbic acid per day intramuscularly for 10 days, no response; folic acid 15.0 mg. intramuscularly per day, good response (Fig. 10)
I. G.	General diet plus 225 mg. ascorbic acid per day orally, bone marrow megaloblastic at end of 24 days; folinic acid 3.0 mg. per day intramuscularly, good response
G. M.	Folic acid–poor diet plus parenteral iron for 10 days, no response; same diet plus 1.0 μg vitamin B_{12} and 50 mg. ascorbic acid intramuscularly for 7 days, no response (bone marrow still megaloblastic); same diet plus 3.0 mg. folinic acid per day intramuscularly, good response (Fig. 11)
B. M.	General diet plus 5.0 μg vitamin B_{12} and 500 mg. ascorbic acid per day intramuscularly for 14 days, poor response; same diet plus folic acid 15.0 mg. per day intramuscularly, good response (Fig. 12)

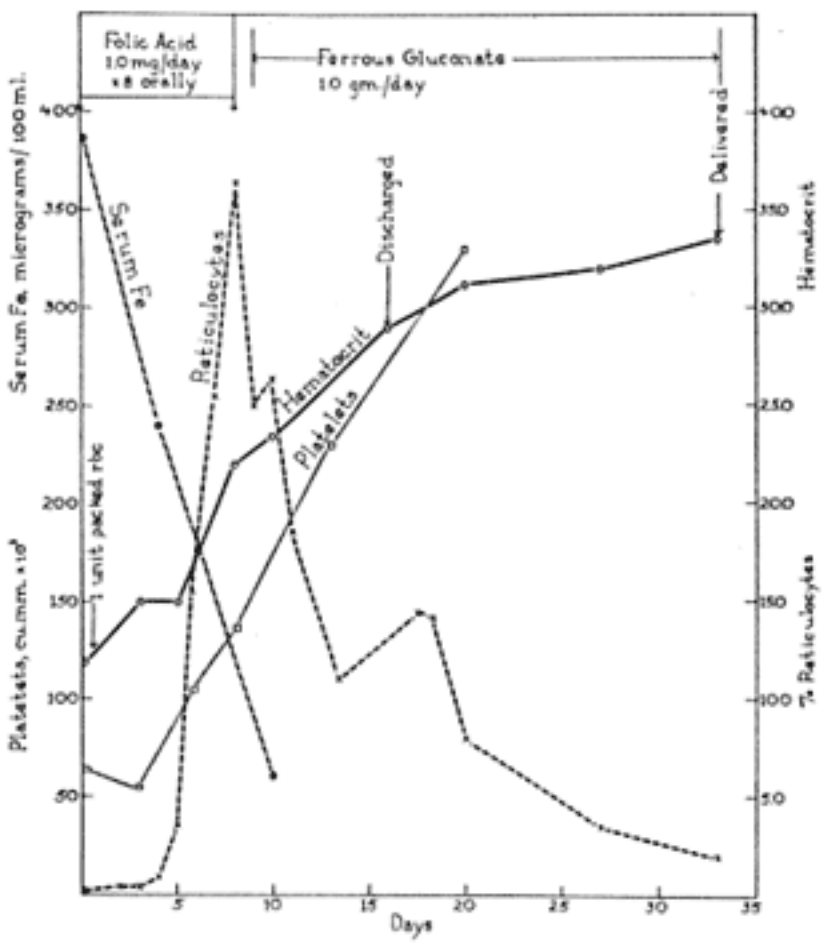

Fig. 8. D. Ca. prior to delivery received folic acid, 1.0 mg. per day for 8 days orally, plus a folic acid–poor diet. There was a marked reticulocyte response accompanied by an increase in hematocrit value and platelet count. Note the fall in serum iron concentration with the onset of the reticulocytosis.

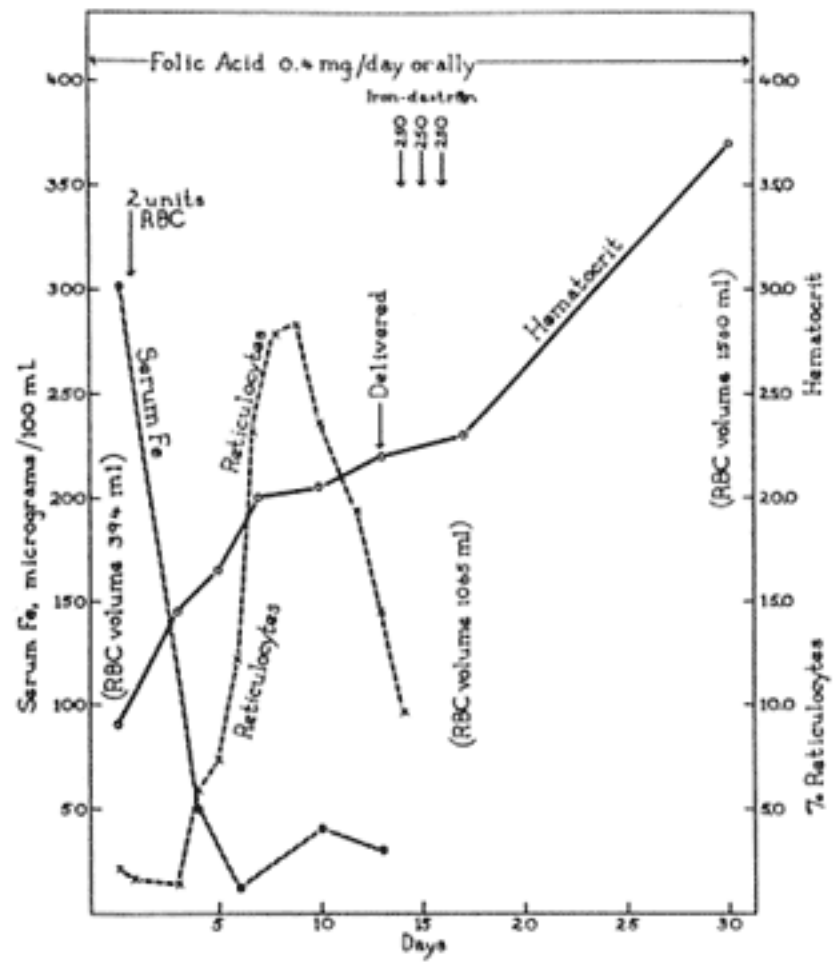

Fig. 9. C. T. (second pregnancy) prior to delivery responded well to only 0.4 mg. of folic acid per day by mouth while receiving a folic acid–poor diet. The fetal heartbeat was audible the first day of therapy but not after that. Changes typical of longstanding fetal death were apparent at the time of delivery.

The mother continued to receive 1.0 mg. of folic acid per day by mouth and iron supplementation was begun. Two and 8 weeks after delivery the hematocrit values were 36.5 and 44.0. There was no residual evidence of megaloblastic anemia when the patient was last studied.

Some idea of the amount of folic acid necessary to produce a hematologic remission in a pregnant woman with megaloblastic anemia of pregnancy can be derived from these studies. The special diet alone resulted in no evidence of hematologic response in this case. Folic acid orally for 10 days in a daily dose of 0.4 mg. produced only a minimal reticulocytosis. Folic acid in a daily dose of 1.0 mg. given parenterally during one pregnancy and orally during the next produced a prompt reticulocytosis followed by correction of the anemia, leukopenia, and thrombocytopenia.

In one other case (Patient D. Ca.) treated during the antepartum period and receiving an identical folic acid–poor diet, 1.0 mg. of folic acid orally per day for a total of only 8 days also produced a prompt hematologic response (Fig. 8). In a third patient (C. T.) who was undelivered and received an identical diet, 0.4 mg. of folic acid per day orally produced a prompt hematologic response (Fig. 9). She differed from the other 2 in that the fetus was dead in utero during the period of therapy.

Other agents administered to undelivered women, including ascorbic acid, ascorbic acid plus 1.0 to 5.0 μg per day of vitamin B_{12} given parenterally for 7 to 14 days, and antibiotics for similar periods of time failed to produce significant hematologic improvement (Figs. 10, 11, and 12). Marked hematopoiesis promptly occurred in all of these patients when folic or folinic acid was administered. The responses to the several forms of therapy tried are summarized in Table III.

After delivery hematologic improvement *sometimes but not always* occurred spontaneously. Three patients (M. C., B. H., M. H.) in whom the diagnosis was established within 38 hours of delivery by the presence of anemia plus classic megaloblas-

tic changes in the bone marrow developed reticulocytosis followed by a progressive rise in hemoglobin and hematocrit value while receiving no specific therapy and a folic acid–poor diet.

In 2 patients (R. S., and D. Ca.) with megaloblastic anemia who were treated with total doses of folic acid of only 15.0 and 8.0 mg., the last dose being given 34 and 25 days before delivery, phlebotomy was performed early in the puerperium to render them anemic once more. While receiving only iron and a general hospital diet but no more folic acid there was a prompt correction of the anemia. The response after phlebotomy in the case of R. S. is demonstrated in Fig. 5.

In other cases, however, in the absence of specific therapy no response was evident during the puerperium. In one instance (Patient A. H.) hematologic improvement did not develop during the first 9 days after delivery while a folic acid–poor diet was offered. There was a prompt reticulocytosis and rise in the hematocrit value when 0.4 mg. of folic acid per day was given orally along with the special diet. In the

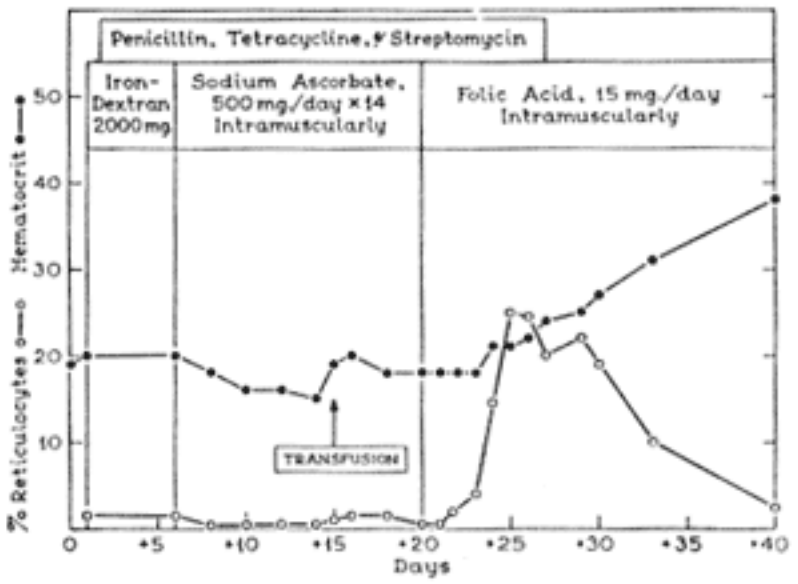

Fig. 10. C. W. T. failed to show hematologic improvement while receiving a general diet, iron, ascorbic acid, and antibiotics. Folic acid therapy was followed by prompt improvement.

case of L. K. severe anemia and pneumonitis were present early in the puerperium. From the third through the thirteenth postpartum day she received penicillin, tetracycline, and streptomycin along with parenteral iron and a blood transfusion. There was no evidence of hematologic improvement until therapy was started with folinic acid, 3.0 mg. intramuscularly at first every day and then 3 times a week (Fig. 13). Six months after

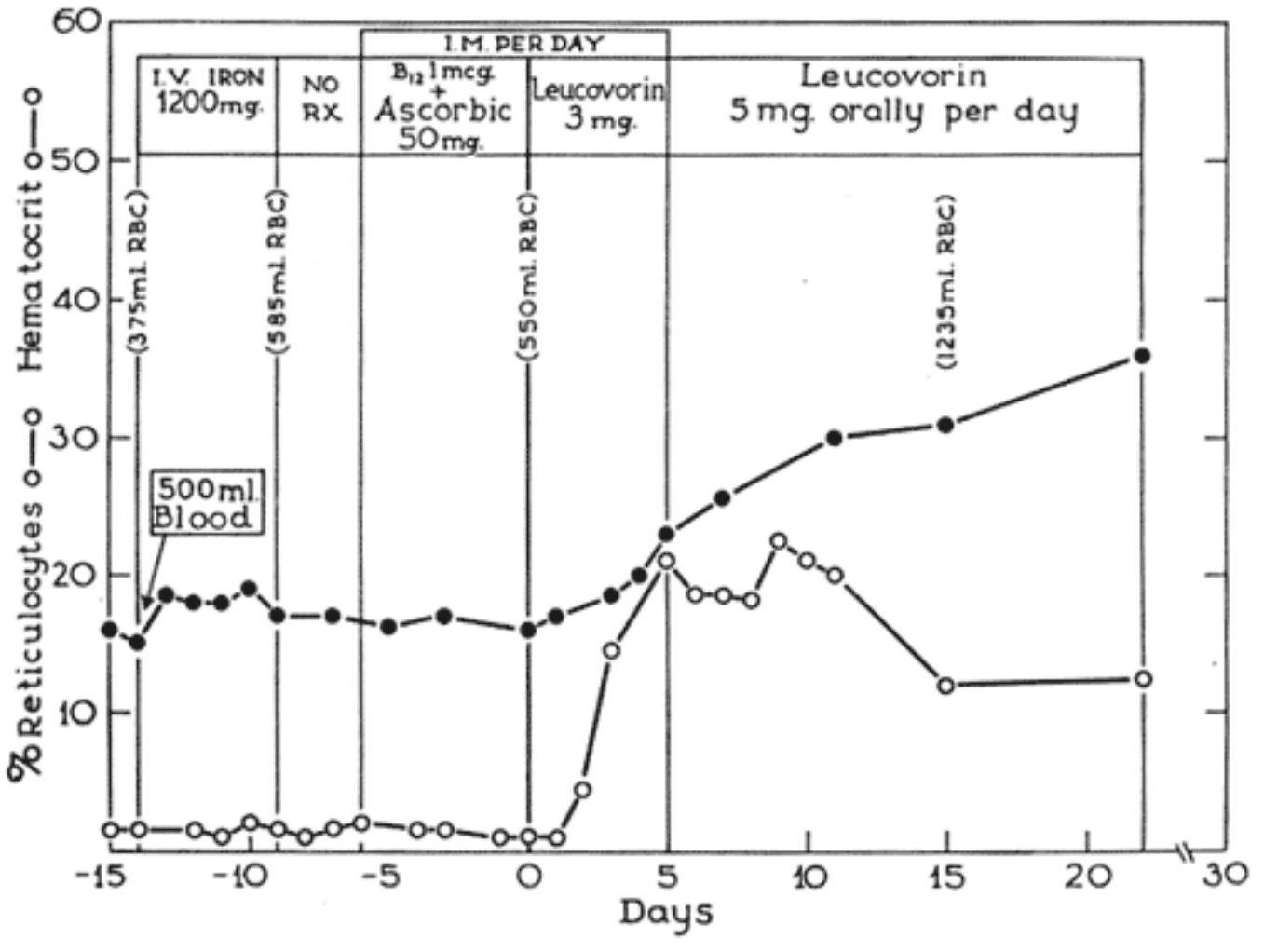

Fig. 11. G. M. failed to respond either to iron or to vitmain B_{12} and ascorbic acid therapy. While she was still on a folic acid–poor diet folinic acid proved effective.

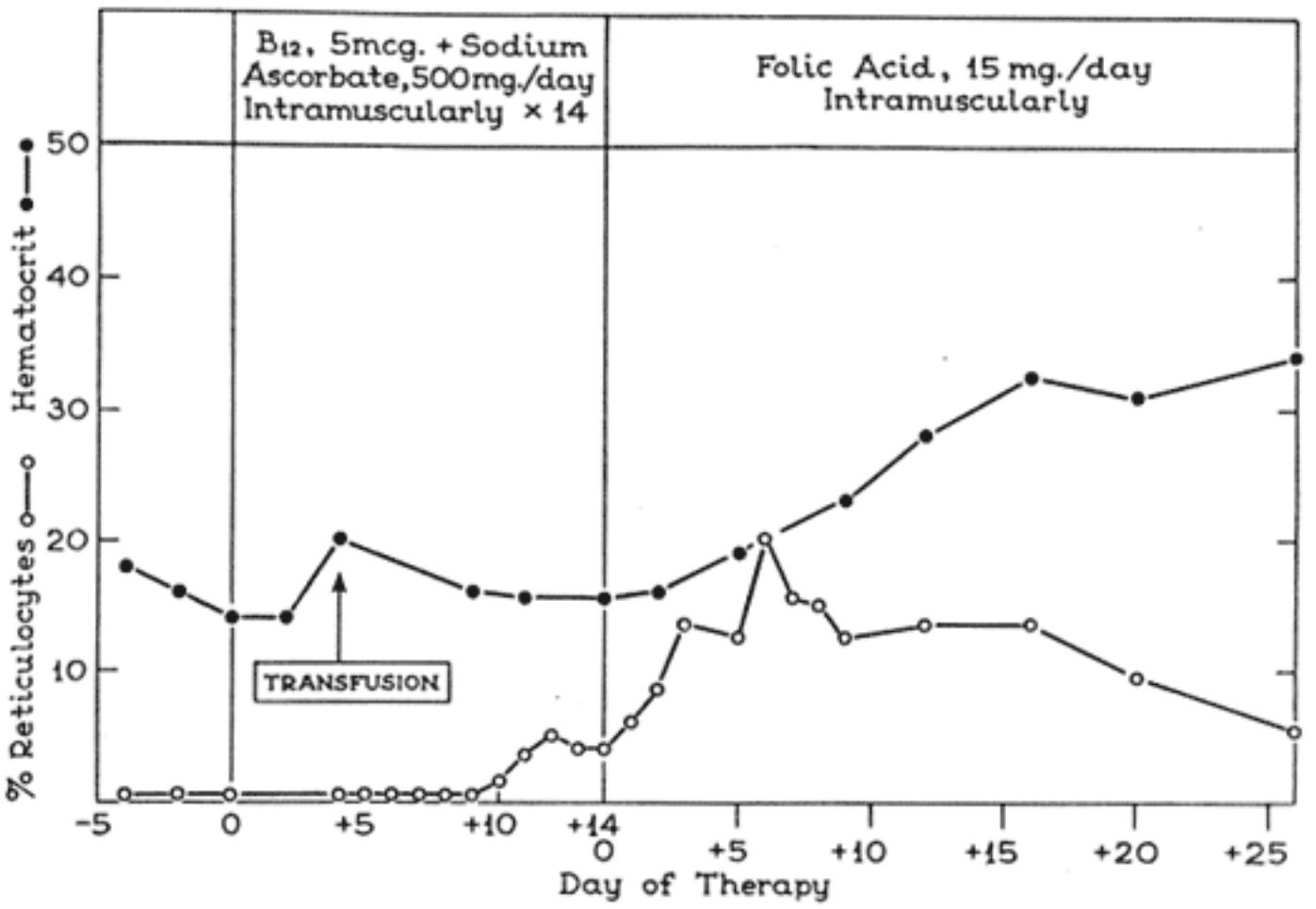

Fig. 12. B. M. developed only a slight rise in reticulocytes during the 14 days that she received a general diet plus 5 μg of vitamin B_{12} and 500 mg. of sodium ascorbate intramuscularly per day. Folic acid therapy proved effective.

delivery and 5 months after therapy was discontinued she remained nonanemic.

In 2 other cases in which anemia was present at the time of delivery severe megaloblastic anemia was detected 7 weeks post partum. In one it proved fatal. These 2 cases are summarized below.

P. C., a 25-year-old Negro gravida vii, was admitted to another hospital early in the third trimester because of pneumonitis and severe anemia. Oral iron had been prescribed previously by her physician. During her entire pregnancy she had vomited frequently and her main source of nourishment had been soup. The hemoglobin level was reported to be 5.9 Gm. per 100 ml. and the white blood cell count 4,500 per cubic millimeter.

She was treated with chloramphenicol for 2 days, chlortetracycline for 8 days, and a transfusion of 1 unit of blood. She soon went into labor and a grossly premature infant that did not survive was delivered.

Seven weeks later the patient was admitted to Parkland Memorial Hospital complaining of weakness and anorexia since delivery. Following delivery vomiting and frequent watery bowel movements had been an almost daily occurrence. Dyspnea had troubled her for 2 or 3 weeks. Her diet had continued to consist primarily of soup. Pepto-Bismol was taken for diarrhea.

The pulse rate was 160 per minute, respiratory rate 56 per minute, and blood pressure 110/40 mm. Hg. There was marked pallor of the mucous membranes and palms. Râles were

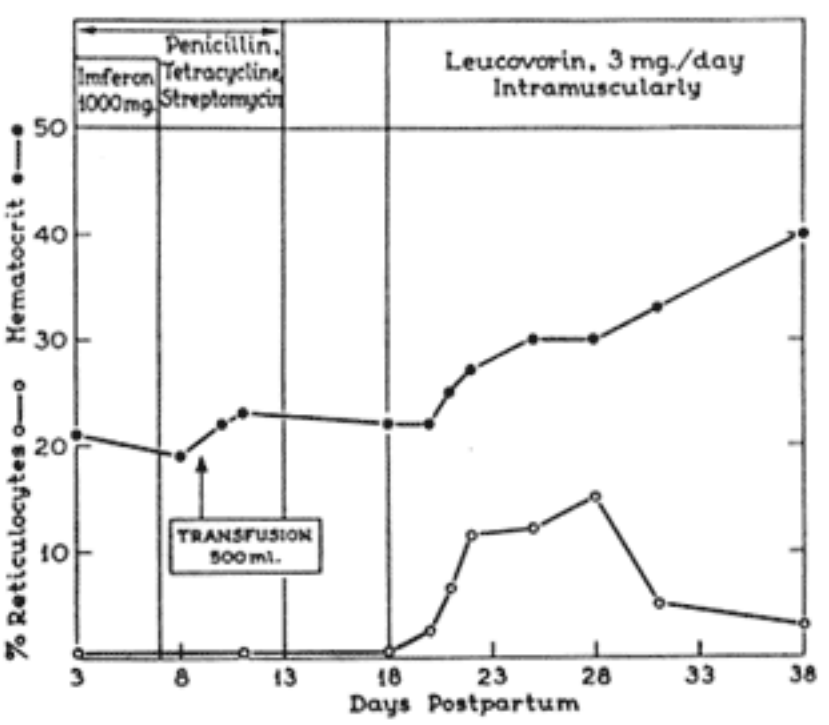

Fig. 13. There was no evidence of remission in this patient (L. K.) during a period of 18 days after delivery. She was treated with 3 mg. of folinic acid a day intramuscularly and responded promptly.

present in the bases of both lungs and the liver was palpated below the right costal margin.

Laboratory studies performed on blood collected prior to transfusion were as follows: hemoglobin 2.9 Gm. per 100 ml., hematocrit value 8.5, red blood cell count 980,000 per cubic millimeter, white blood cell count 6,700 per cubic millimeter, reticulocyte count 1.0 per cent, total plasma protein 4.9 Gm. per 100 ml., hemoglobin A detected only by filter paper electrophoresis, serum glutamic oxaloacetic transaminase activity 32 units (at 25° C.). The smear of the peripheral blood was of poor quality but did contain hypersegmented polymorphonuclear leukocytes. The venous pressure was 19 cm. of water and the arm-to-tongue circulation time was 13 seconds.

A diagnosis of severe anemia, possibly megaloblastic in type, complicated by cardiac failure was made. It was noted that 3 years before when the patient was seen for an abortion the hematocrit value was 40.0.

Attempts were made to digitalize the patient rapidly and then transfusion with the packed red blood cells from 2 units of blood was begun. Four hours later when about three fourths of the packed cells had been given she developed severe pulmonary edema. Positive pressure breathing and tourniquets to the extremities were used but the patient soon died.

The significant findings at autopsy were as follows: megaloblastic hyperplasia of the bone marrow with extramedullary hematopoiesis in the liver and spleen; acute pulmonary congestion and edema, massive pleural effusion; acute congestion and fatty metamorphosis of the liver; no abnormalities of the mucosa of the stomach or small intestine.

This patient had severe megaloblastic anemia resulting in cardiac failure and pulmonary edema which proved fatal when blood transfusion therapy was instituted. Phlebotomy simultaneously with the administration of the packed erythrocytes along with continuous positive pressure breathing prior to and during transfusion might have proved lifesaving. The autopsy findings were not compatible with true pernicious anemia. Moreover, true pernicious anemia would have been most unlikely in a 25-year-old Negro woman who was known not to be anemic 3 years before.

D. Cr., a 19-year-old Negro woman, was admitted 7 weeks following delivery with severe anemia accompanied by anorexia, fever, diarrhea, and weight loss. Laboratory studies showed the following: hematocrit value 16.0, mean corpuscular volume 113 $c\mu$, reticulocytes 0.8 per cent, leukocytes 4,600 per cubic millimeter, and platelets 38,000 per cubic millimeter. The hemoglobin level 3 days post partum was recorded as 8.8 Gm. per 100 ml. She had been given a prescription for iron and sent home.

Initially 1 unit of blood was given and 5 μg of vitamin B_{12} plus 500 mg. of sodium ascorbate was injected intramuscularly each day. Six days later the reticulocyte level started to rise. By the tenth day of therapy the reticulocyte count had reached 18.4 per cent. The hematocrit value promptly rose to normal.

She was restudied one year later. The hematocrit value was found to be 41.0 and she was asymptomatic.

Comment

Probably the first detectable hematologic changes in the peripheral blood in cases of megaloblastic anemia of pregnancy even prior to the development of anemia are the appearance of polymorphonuclear leukocytes with nuclear hypersegmentation and macrocytic red blood cells. Erythrocyte macrocytosis may not be apparent because iron deficiency commonly accompanies megaloblastic anemia of pregnancy.

Anemia develops next and at a rate in some instances which suggests that there is an increased rate of destruction of at least some erythrocytes as well as decreased delivery of red blood cells from the bone marrow to the peripheral blood. By the time the anemia has become severe it is commonly accompanied by leukopenia and thrombocytopenia. Now, if not before, a careful search of a smear of the peripheral blood will usually reveal nucleated red blood cells whose nuclear maturation lags well behind that of the cytoplasm. Detection of these megaloblastic cells in the peripheral blood can be facilitated by examining a smear of the buffy coat as emphasized by Goodall.[6] The sequence of events in the development of megaloblastic anemia of pregnancy is the same as described in megalo-

blastic anemia from other causes including true pernicious anemia.[5]

Deficiencies of either folic acid or vitamin B_{12} will result in megaloblastic anemia. Folinic acid, the metabolically active form of folic acid, is protected from oxidation by ascorbic acid. A lack of each of these vitamins has been suggested as the cause of megaloblastic anemia of pregnancy.[7, 9] It is quite possible that varying degrees of deficiency of all 3 vitamins may occur, but judging from the response to therapy with each of these agents in these cases, as well as those studied by others, a major deficiency of folic acid must be present.[10] In the undelivered patient folic acid in doses as low as 1.0 mg. per day by mouth will cause a prompt hematologic response. On the other hand, therapy with ascorbic acid plus vitamin B_{12} in doses which will produce a response in true pernicious anemia or vitamin B_{12} alone in large doses often does not produce a response.[7, 10, 11] Doses of ascorbic acid ranging from 50 to 500 mg. per day given to 4 undelivered patients in this study did not result in augmented erythropoiesis. There is no evidence from either these studies or those of Holly[7] that ascorbic acid alone will influence hematopoiesis favorably in megaloblastic anemia of pregnancy.

Once delivery of the fetus has been accomplished significant hematologic improvement may develop in the absence of specific therapy. Therefore, it is apparent that it is hazardous to try to evaluate the effect of various agents in the treatment of megaloblastic anemia during the puerperium. The response which appears to have been produced by some vitamin or antibiotic might just as well have occurred in their absence. On the other hand, spontaneous remission does not always follow delivery. In 2 of these cases it is likely that megaloblastic anemia was present prior to delivery and that during the next 7 weeks after delivery it actually became worse.

There has been much speculation as to why megaloblastic anemia sometimes develops during pregnancy. A number of possible explanations can be offered. In this group of patients a common finding was a very poor diet, especially in regard to foods that are considered good sources of folic acid. Anorexia, nausea, and sometimes vomiting persisted throughout pregnancy until the time of diagnosis and treatment or until delivery in the cases detected post partum. Consequently decreased folic acid intake may be implicated. On the other hand, it is quite difficult to produce evidence of folic acid deficiency in nonpregnant individuals, although occasionally it may be found in nonpregnant individuals with chronic alcoholism and cirrhosis, some psychological aberration which leads to a very rigidly restricted diet, or a malabsorption state such as sprue.[5, 12, 13]

An increased demand for folic acid during pregnancy seems almost certain. The fact that none of the infants in this series was anemic, even in the absence of any maternal therapy, is further evidence that folic acid is concentrated on the fetal side of the placenta. Fetal demands for folic acid are undoubtedly of significance. Obviously the data are quite meager but it is of interest that one patient with a living fetus responded poorly to 0.4 mg. per day of folic acid plus a folic acid–poor diet, while another patient with a fetus dead in utero responded quite promptly to identical therapy.

The possibility of decreased absorption of folic acid by apparently normal pregnant women has been considered and data to support this have been presented. Serum folic acid activities after an oral dose of folic acid were found by Chanarin and coworkers[14] to be definitely lower in pregnant than in nonpregnant subjects. There are several possibilities to account for these observations other than just decreased absorption. Delayed absorption during pregnancy without a decrease in the total amount absorbed could contribute to these findings. Another possibility must take into account the expanded plasma volume during pregnancy. During the third trimester this averages at least 50 per cent with a single fetus and 70 per cent or more with twins.[15] Consequently absorption of identical amounts of folic

acid by pregnant and nonpregnant individuals could be expected to produce a smaller augmentation of the serum folic acid concentration during pregnancy. Furthermore, active transfer of absorbed folic acid across the placenta to the fetus or fetuses would further lower the plasma concentration after an oral test dose of folic acid.

On the other hand it is likely that the malabsorption syndrome of tropical sprue is the end result of a dietary deficiency of folic acid and that the malabsorptive state resulting from the folic acid deficiency ultimately leads to impaired absorption of folic acid.[5] Perhaps a similar mechanism helped to perpetuate such a deficiency in the 2 cases in which the diagnosis of megaloblastic anemia was made several weeks after delivery.

When a standard dose of folic acid was given by injection Chanarin and associates[16] found that the serum levels fell more rapidly in pregnant than in nonpregnant subjects and that the rate of fall increased as pregnancy advanced. In the presence of twins it fell even more rapidly. Their conclusion that the increased rate of disappearance from the plasma is due mainly to the fetal requirements for folic acid seems warranted. Whether more rapid disappearance of folic acid from the blood stream can be interpreted to indicate actual folic acid deficiency is open to question.

The first but not the final reaction to all of these observations is to conclude that all women should received routinely supplemental folic acid during pregnancy and the puerperium. Such a program was instituted by Lowenstein and associates[10] in Montreal and thereafter the disease was not detected in any patient who had been cared for in the clinic. It is also quite unlikely that megaloblastic anemia would have developed in any of these 20 cases if folic acid in a daily dose as low as 1.0 mg. had been ingested during the latter half of pregnancy. However, in 13 instances megaloblastic anemia was already present by the time the patient was first seen. Therefore with a program of routine supplementation it would have been possible to prevent the disease in only 7 of the 20. During the same interval close to 40,000 women were delivered without having received any folic acid supplementation. It is recognized that very probably many less severe cases of megaloblastic anemia were not detected during this time. In such undiagnosed cases most likely in the absence of specific therapy there was spontaneous remission after delivery.

One argument presented against the widespread administration of vitamin supplements containing folic acid even in relatively small amounts is that such "prophylaxis" can mask the anemia of true pernicious anemia while serious neurological damage develops.[17, 18] The likelihood of undiagnosed true pernicious anemia, however, is remote in the reproductive age group. An even stronger argument against routine supplementation with folic acid it would seem is that it is improbable that a pregnant woman could consume a diet adequate in all ways for pregnancy except for a deficiency in folic acid. Consequently folic acid supplementation would not assure an adequate dietary intake. Is it not more logical to try to detect and correct poor dietary habits rather than simply ignore this aspect of prenatal care and automatically dispense folic acid to be taken routinely by all pregnant women?

These studies will be continued to try to obtain more information concerning the folic acid requirements of pregnancy, the frequency of megaloblastic anemia of pregnancy in the absence or routine prenatal folic acid supplementation, and, finally, the safest way to prevent the development of megaloblastic anemia of pregnancy.

Summary

Studies in 20 cases of megaloblastic anemia during pregnancy or the puerperium are presented.

The hematologic changes in order of appearance were, first, the development of hypersegmented polymorphonuclear leukocytes accompanied by macrocytic erythrocytes unless there was also iron deficiency.

Next, progressively more severe anemia developed. Finally, pancytopenia was prominent. At this time there usually was evidence of hepatic dysfunction and relative hypovolemia. Effective therapy reversed these changes with those which appeared last disappearing first.

The diet consumed by these patients was very poor in regard to the quality of the foods eaten. Typically, for several months at least, it had been deficient in animal protein and in green and other vegetables, especially uncooked green vegetables.

Iron deficiency was common and in such cases erythrocyte macrocytosis was usually absent. Therefore measurement of the mean red corpuscular volume was often misleading when used to rule out the possibility of megaloblastic anemia. Examination of the buffy coat did prove of value.

After delivery hematologic improvement sometimes but not always occurred spontaneously. However, megaloblastic anemia was detected up to 7 weeks after delivery.

A deficiency of folic acid, vitamin B_{12}, and ascorbic acid each has been suggested as the cause of megaloblastic anemia during pregnancy or the puerperium. While there may be varying degrees of deficiency of all 3 vitamins, most likely the major deficiency is that of folic acid.

The observations made in these cases do not necessarily warrant the conclusion that folic acid should be administered routinely to all pregnant women.

Much of the folic and folinic acid used was supplied by Lederle Laboratories Division, American Cyanamid Company, New York, New York.

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Discussion

Dr. George B. Maughan,* Montreal, Quebec. At the Royal Victoria Hospital in Montreal, the Haematologic Service to our obstetric unit has been very interested, over the past 13 years, in the anemias of pregnancy generally and in the megaloblastic anemias particularly. In 1955 our Haematologic Service reported observations on a group of 19 cases of megaloblastic anemia in pregnancy collected over the 1949 to 1952 period, as referred to by Dr. Pritchard. In this series a coexisting iron deficiency was observed in most cases before treatment or during the specific response to treatment of the megaloblastic anemia; 4 of the 19 patients responded to vitamin B_{12} therapy alone. All patients treated primarily by folic or folinic acid or secondarily by folic acid, following failure of vitamin B_{12} therapy, responded satisfactorily. It is noteworthy that, just as Dr. Pritchard has reported, the best and most consistent response

*By invitation.

to therapy was obtained with folic acid and/or folinic acid.

Nutritional deficiency study. Over the past 2 years our Obstetric Haematologic Service has studied a series of 60 pregnant patients and a control group of nonpregnant patients for evidence of nutritional deficiency in iron, vitamin B_{12}, and folic acid. In the pregnant group, in the absence of iron therapy during pregnancy it was found that the serum iron level was somewhat decreased and stainable iron was usually absent from the bone marrow at term. This was not replenished completely, even 6 months post partum. In a group receiving either oral or intramuscular iron, the serum iron was higher at term than in the nontreated group and stainable marrow iron was present at term, and 6 months post partum. All differences between the treated and control groups had disappeared in the peripheral blood 6 months post partum, and only the difference in the iron content of the marrow persisted.

On this same group of pregnant women, without adjuvant vitamin B_{12} the serum B_{12} levels fell in varying degrees so that a "normal" level for pregnancy was almost impossible to determine, but 100 $\mu\mu$g per cent has been tentatively set as the lower limit of "normal."

The serum folic acid level fell likewise during pregnancy, but not below 3.0 mμg per cent in any of the 60 patients. Thus it would appear that, even making allowance for the normal hydremia of pregnancy, there is a relative deficiency of iron, vitamin B_{12}, and folic acid. There is very good evidence that at least part of this is due to the great demands of the fetus as indicated by Dr. Pritchard.

Megaloblastic anemia. Most recently a series of 26 cases of megaloblastic anemia of pregnancy have been studied on our Haematologic Service by complete hematologic study (blood volume determinations, serum vitamin B_{12} concentrations, serum folic acid activity, serum iron and unsaturated iron–binding capacity determinations, and bone marrow aspirations).

By Dr. Pritchard's criteria all of these cases would be considered mild. In only 2 cases were there significant numbers of macrocytes in the circulating blood and in only 9 cases were hypersegmented neutrophils found. The most significant marrow change was macrogranulocytosis, present in all 26 patients, and intermediate megaloblastic erythropoiesis, present in only 7.

In at least 23 of the 26 patients marked iron deficiency was observed with no stainable iron in the bone marrow of 21 patients. Iron therapy improved the status of the anemia in the peripheral blood without any change, except in the iron content in the bone marrow.

In 16 patients the serum vitamin B_{12} concentration was less than 100 $\mu\mu$g per cent, and in 5 of these it was less than 50. In 5 patients the serum folic acid activity varied between 3.0 and 4.0 mμg per cent, and in 13 patients it was less than 3.0.

In 10 cases values for both serum folic acid activity and serum vitamin B_{12} were abnormally decreased. In 5 patients a normal serum folic acid activity was associated with an abnormally low vitamin B_{12} level, and in another 8 cases the reverse was true. In none of the 26 patients were both of the determinations at or above normal levels. Thus in 23 of our 26 cases of megaloblastic anemia in pregnancy there was an iron deficiency and in all 26 cases there was a serum vitamin B_{12} deficiency, or a serum folic acid deficiency, or both.

From these findings we have concluded:

1. That all pregnant patients should receive supplemental iron.
2. That in some cases of mild or moderate anemia with macrogranulocytic and/or megaloblastic changes in the bone marrow the anemia will improve when iron is administered, but without altering the megaloblastic or macrogranulocytic changes in the bone marrow.
3. That there was good correlation of low values of serum vitamin B_{12} and/or folic acid activity with the presence of macrogranulocytic changes in the bone marrow.
4. That routine administration of supplements of folic acid and of vitamin B_{12} is indicated in pregnancy when inadequate dietary intake is suspected. In this connection it is interesting to note that at least one of the pharmaceutical houses has an antenatal mineral-vitamin supplement on the market containing adequate amounts of iron, folic acid, and vitamin B_{12} (plus other vitamins and minerals) at a daily cost of less than 6 cents.

Still further, the work of Peers and his coworkers has indicated that the incidence of congenitally anomalous offspring from experimentally damaged animals can be greatly decreased when these animals are protected by the administration of pyridoxine and folic acid. For the past several years in our clinic we have been attempting to demonstrate a correlation

between pyridoxine, folic acid, and vitamin B_{12} deficiencies and the production of congenitally anomalous infants in a group of women with a statistically increased chance of such tragedy. We are not yet prepared to draw conclusions but in the interim it would appear that 6 cents per day, or approximately $15.00 for the full course of pregnancy, is a small price to pay for the prevention of megaloblastic anemia and, possibly, the avoidance of giving birth to a congenitally anomalous child.

Dr. Curtis J. Lund, Rochester, New York. I have noted comparatively little megaloblastic anemia in our patients at Rochester. The majority of these people have had rather good prenatal care. However, when such anemia has appeared, it has come almost as a bolt out of the blue. The rather sudden onset of a severe degree of anemia has impressed us as being one of the points which one should consider as symptomatic of megaloblastic anemia. I wonder if Dr. Pritchard had a chance to observe his patients before the onset of the disease?

I would also like to ask Dr. Pritchard whether he has seen in this group or in others any evidence of neurological complications, a combined system disease. Finally, I would like to point out an isolated clinical feature which we have observed infrequently but rather significantly, the appearance of unexplained fever as a symptom.

Dr. Roy G. Holly, Omaha, Nebraska. Two pregnant patients with megaloblastic anemia whom I have studied and treated offer points at variance with the material presented by Dr. Pritchard. The fact that each of these women responded to a combination of ascorbic acid and vitamin B_{12} provides a possible clue to the etiology of this interesting anemia.

The 2 patients were found to have all of the diagnostic features of megaloblastic anemia. The bone marrow changes were typical of those illustrated so beautifully by Dr. Pritchard. In addition the erythrocyte protoporphyrin values were normal and the serum iron values were elevated. The first patient was placed on ascorbic acid, 500 mg. per day for 5 days, and no hematologic response was noted. When vitamin B_{12} was added a complete remission occurred.

The treatment procedure was reversed in the second patient. Vitamin B_{12} alone failed to alter the hematologic picture but when ascorbic acid was added a complete remission was produced. It seems important to realize that the basic deficiency is not of ascorbic acid, folic acid, or vitamin B_{12} alone, but is a disturbance in nucleic acid metabolism.

Megaloblastic anemia in pregnancy differs in one important respect from true Addisonian pernicious anemia. The latter represents a combined ribonucleic and desoxyribonucleic acid deficiency. True pernicious anemia is created by a vitamin B_{12} deficiency and responds completely to its administration. In this case we have a disturbance in the biosynthetic pathway between the pyrimidine bases and uracil. In pregnancy anemia we are probably dealing with a number of factors necessary in the synthesis of desoxyribonucleic acid. The pathway is altered between uracil and desoxyribonucleic acid. Ribonucleic metabolism is not altered. Multiple factors are involved in desoxyribonucelic synthesis, consequently multiple and varied deficiencies can produce megaloblastic anemia in pregnancy.

I would like to stress an important feature of megaloblastic anemia in pregnancy, namely, the frequent coexistence of iron deficiency. Iron therapy is nearly always necessary in treating megaloblastic anemia.

Dr. Pritchard (Closing). We have not observed any neurological involvement. Fever of unknown etiology was rather common. It probably is from undetected foci of infection rather than of metabolic origin.

The rate of development of anemia in these patients was mentioned in the text but could not be considered because of lack of time. The very rapid fall in hemoglobin concentration or hematocrit value which has been described by Lowenstein, for instance, was not noted during this study. However, anemia did develop more rapidly than does uncomplicated iron deficiency.

I am not prepared to discuss whether all women should receive vitamin supplements including folic acid throughout pregnancy. While it is true that some vitamin deficiencies in some animals while pregnant will result in congenital anomalies, the reverse is also true. Some vitamins in excess seem to cause anomalies.

In regard to the deficiency or deficiencies in megaloblastic anemia of pregnancy, undoubtedly there may be many. The only agent to date, however, which has uniformly produced prompt hematologic remission is folic acid or a related compound.