Nutritional Megaloblastic Anemia Associated with Sickle Cell States

By Ulfar Jonsson, O. Stuart Roath and Charlotte I. F. Kirkpatrick

Bone marrow changes suggestive or diagnostic of megaloblastic erythropoiesis have been recognized on a number of occasions in patients with hemolytic anemia. In many of these patients evaluation of a possible response to agents effective in megaloblastic anemias has not been possible because of concurrent transfusions or for other reasons. A few case reports have appeared in recent years where such a therapeutic trial has been made and a specific response has been obtained with a similar time sequence as would be expected in patients with megaloblastic anemia without coincident hemolytic anemia. A reversal to normoblastic erythropoiesis has usually been observed to occur in these cases following response to specific therapy.

The present report deals with three cases of nutritional megaloblastic anemia which have been observed in patients with sickle cell disease or sickle cell-hemoglobin C disease. Other cases of megaloblastic anemia occurring in the course of hemolytic anemias are reviewed and possible etiologic relationships discussed.

Methods

Standard methods were used for routine counts of red blood cells and white blood cells. Hemoglobin was determined by the cyanmethemoglobin method and hematocrit determination by Wintroub's method, or by the micro method of Strumia et al. Blood indexes were calculated by the method of Wintrobe. Reticulocyte counts were done by the new methylene blue method. Platelet counts were done by the method of Brecker and Cronkite (normal range, 150 to 350,000 cu. mm.). Hemoglobin electrophoresis was done by the horizontal plate method of Smith and Conley. Fetal hemoglobin was determined by the method of Singer et al. The radioactive vitamin B12 urinary excretion was determined by the method of Schilling. Other studies were done by standard methods.

Case Histories

Case 1.—G.B., a 36 year old negro housewife, was admitted to Jackson Memorial Hospital on December 4, 1955 with a history of swelling of her hands, face and feet starting two weeks prior to admission, accompanied by shortness of breath. She got steadily worse and four days prior to admission she developed a high fever. A naturopath gave her penicillin injections and the fever subsided, but her shortness of breath got worse and her husband noted that she was pale. The patient was eight months pregnant and had had six previous pregnancies which had been uncomplicated, but she had received transfusions at the time of delivery of two of her previous children. She had had no prenatal care during the present pregnancy. On physical examination she appeared...
### Table 1.—Summary of Initial Laboratory Studies in Patients Reported

<table>
<thead>
<tr>
<th>Patient</th>
<th>Hgb. Gm.</th>
<th>RBC Mil.</th>
<th>H'rit. vol.</th>
<th>MCV CM</th>
<th>MCH 88</th>
<th>MCHC %</th>
<th>Retics. %</th>
<th>Normob. Per 100 WBC</th>
<th>WBC thous. cu.mm.</th>
<th>Plat. thous. cu.mm.</th>
<th>Bilirubin</th>
<th>Coombs Test</th>
<th>Ova</th>
<th>Stools</th>
<th>Hgb. electrophor.</th>
<th>Fetal Hgb.</th>
</tr>
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<td>Case 1</td>
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<tr>
<td>G.B.</td>
<td>2.0</td>
<td>5</td>
<td>1.2</td>
<td>3</td>
<td>15.7</td>
<td>90</td>
<td>0.53</td>
<td>1.4</td>
<td>neg.</td>
<td>neg.</td>
<td>neg.</td>
<td>neg.</td>
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<td>neg.</td>
<td>SC 7.1%</td>
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<tr>
<td>G.B.</td>
<td>7.0</td>
<td>2.39</td>
<td>21</td>
<td>88</td>
<td>29</td>
<td>33</td>
<td>0.8</td>
<td>8</td>
<td>10.5</td>
<td>80</td>
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<td>Case 2</td>
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<tr>
<td>B.W.</td>
<td>4.8</td>
<td>1.85</td>
<td>16</td>
<td>88</td>
<td>26.2</td>
<td>30</td>
<td>ND</td>
<td>46</td>
<td>10</td>
<td>566</td>
<td>1.06</td>
<td>2.25</td>
<td></td>
<td>neg.</td>
<td>neg.</td>
<td>SS 2.8%</td>
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<tr>
<td>Case 3</td>
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<tr>
<td>R.J.</td>
<td>3.7</td>
<td>1.25</td>
<td>14</td>
<td>112</td>
<td>30</td>
<td>26</td>
<td>4.0</td>
<td>40</td>
<td>15</td>
<td>300</td>
<td>0.19</td>
<td>1.32</td>
<td></td>
<td>neg.</td>
<td>neg.</td>
<td>SS 13.4%</td>
</tr>
</tbody>
</table>
acute ill, very pale and had severe air hunger. Temperature was normal but pulse was 140/min., respiration 44/min., and blood pressure was 80/0 mm. Hg. There was no evidence of bleeding. The edges of the tongue showed atrophy of the papillae. Neck veins were distended and moist rales were heard over the posterior aspect of the left lung. The second pulmonic sound was accentuated and a grade I systolic apical murmur was heard. Neither liver nor spleen were felt. The uterus was palpable 33 cm. above the symphysis and two fetuses were palpable.

Most of the laboratory studies are recorded in table 1. Serum NPN was 32 mg. per cent. Urine contained 20 mg. per cent of protein but no bile, hemoglobin or hemosiderin. Urine urobilinogen test on undiluted urine was slightly positive. Gastric analysis showed free hydrochloric acid to be present. Stool examinations failed to show ova, parasites or increased fats. Chest x-rays showed generalized cardiac enlargement and an infiltrative lesion in the right lower lung base. Abdominal x-ray confirmed the presence of twin pregnancy.

HOSPITAL COURSE. The patient received 2000 ml. of whole blood in the first 24 hours after admission, because of the seriousness of her condition and because the resident staff believed that she had an acute hemolytic anemia. Her blood values after transfusions are noted in table 1. At this time it was noted that macrocytes and multinucleated polymorphonuclear cells were present in the blood smears, and bone marrow smears were found to show intermediary megaloblasts and giant metamyelocytes and myelocytes. Following this a diagnosis of megaloblastic anemia of pregnancy was made and folic acid, 20 mg. a day, was administered by mouth. She responded well with a reticulocyte response up to 9.3 per cent on the eighth day after treatment with folic acid was started, with concurrent rise in blood values (fig. 1). She was discharged from the hospital thirteen days after admission and continued treatment with folic acid, 20 mg. a day. She was admitted again in active labor on January 6, 1956 and had a normal twin delivery. Bone marrow done at this time was normoblastic. The patient was not seen again until September, 1957 when she was admitted to the hospital for study of intermenstrual bleeding and was found to have carcinoma in situ of the uterine cervix. At
this time she was also noted to have an enlarged spleen. Blood counts were found to be as follows: hemoglobin 12.5 Gm. per cent; red blood cell count 3.8 million cu. mm.; hematocrit 35 vols. per cent; reticulocyte count 2.5 per cent; white blood cell count 6,150 cu. mm.; and platelet count 217,000 cu. mm. A sickle cell test was positive and target cells were noted in peripheral blood smears. Bone marrow again showed normoblastic hyperplasia. Hemoglobin electrophoresis showed a mixture of sickle cell and C hemoglobin consistent with sickle cell-hemoglobin C disease. Fetal hemoglobin was 7.1 per cent.

Case 2.—B.W., an 18 year old negro girl, was admitted to Jackson Memorial Hospital on March 11, 1956 complaining of anorexia and weakness for three weeks and of swollen ankles for several days. She was eight months pregnant. She had been healthy prior to this time except for leg ulcers in 1954 for which she had been treated over a period of several months.

On physical examination she did not appear acutely ill. Her sclerae were slightly icteric. She was thin, with long, slender extremities and hands. Examination of lungs and heart was normal, but abdominal examination revealed a large uterus, the level of the fundus being compatible with eight months pregnancy. She had slight edema of both feet, with scars on both ankles. Laboratory findings on admission are indicated in table 1. It was noted on initial blood examination that there was rather striking macrocytosis of many of the red cells in the peripheral blood as well as marked hypersegmentation of polymorphonuclear leukocytes. Bone marrow examination revealed erythroid hyperplasia and the presence of megaloblastic blood formation (fig. 2A). Giant metamyelocytes were seen, and many of the neutrophils in the bone marrow showed giant forms and hypersegmentation. Serum NPN was 21 mg. per cent. Reticulocyte count done three days after admission was 21.1 per cent. Sickle cell preparations showed the presence of sickling and electrophoresis of hemoglobin showed a pattern consistent with sickle cell anemia. Fetal hemoglobin was 2.8 per cent. Three stools were examined for ova, parasites and blood and were found to be normal. Gastric analysis showed free hydrochloric acid to be present. The patient was given tetracycline immediately after admission because of an unexplained low-grade fever and suspected early bronchopneumonia. During the following week, there was a rise in hemoglobin from 4.8 Gm. per cent to 6.1 Gm. per cent and the hematocrit rose from 16 to 21 vols. per cent. She had a reticulocytosis consistently ranging about 20 per cent, and on the ninth day after admission she was started on folic acid. There was a further slight rise in hemoglobin from 6.1 Gm. per cent to 6.4 Gm. per cent, and of the hematocrit from 21 vols. per cent to 22 vols. per cent. Reticulocyte counts at the end of this time had fallen to about 15 per cent. Subsequent observations on this patient have indicated that her “normal”
Figu. 3.—Rise in hemoglobin and hematocrit with persistent reticulocytosis higher than usual for this patient. Response to tetracycline?

reticulocyte count is between 10 per cent and 15 per cent. The laboratory studies on this patient are graphically shown in figure 3.

It is believed that this patient had a "spontaneous" improvement or possibly responded to tetracycline rather than to folic acid. The patient improved, and bone marrow examination done after ten days of folic acid therapy revealed a normoblastic marrow (fig. 2B). Because of the advanced stage of her pregnancy, she was given 1500 ml. of blood at this time and was discharged from the hospital on April 4, following transfusions. She was admitted again four days later in labor. She had an uneventful delivery of a normal boy, and the child was not anemic at birth. The boy has a hemoglobin electrophoretic pattern of sickle cell trait.

FOLLOW-UP. The patient was followed, and during the subsequent months her blood counts fell to levels similar to those that she had been known to have prior to her pregnancy and delivery. A radioactive vitamin B₁₂ excretion test was done and showed a normal urinary excretion (18 per cent). X-ray study of the small intestine showed a normal pattern. The patient has been followed up to the present time and has been admitted on several occasions for painful sickle cell crises. She has not become pregnant again.

Case 3.—R.J., a 33 year old negro male restaurant worker was admitted to Jackson Memorial Hospital on March 11, 1958, complaining of weakness, nausea, vomiting and headaches of three weeks' duration. At the onset of his illness, he had had a cough productive of a small amount of white sputum with low-grade fever. These symptoms cleared in a few days, but he began to feel weak and short of breath. He gradually
Fic. 4.—Case 3. Appearance of bone marrow before (A) and after (B) therapy with folic acid. Notice hypersegmented giant polymorphonuclear leukocyte at left edge, and also diploid megaloblast. (× 699)

got worse and began to be nauseated and vomited a few times. No disturbance of bowel habits was noted. History of exposure to drugs or potential toxic agents could not be obtained. He had been completely well prior to this illness and had served in the United States Navy for eight years without any illnesses. On one occasion in 1955 he was rejected as a blood donor because of anemia. His twin brother had died at one year of age from unknown causes.

On physical examination he had a temperature of 99.8°F. and blood pressure of 140/50 mm. Hg. Sclerae were slightly icteric. Edges of the tongue were smooth, although the dorsum was normal. Examination of lungs was normal, but a grade I systolic murmur was heard over the precordium. The liver was palpable one finger-breadth below the right costal margin, but the spleen was not palpable. Physical examination was otherwise normal. Laboratory studies on admission are recorded in table 1. Bone marrow was megaloblastic (fig. 4A). Fasting blood sugar, blood urea nitrogen, BSP test, serum calcium, phosphorus and alkaline phosphatase were normal. Cephalin flocculation test was 3+ in 48 hours. VDRL test was negative. Paper electrophoresis of the patient’s hemoglobin showed a pattern consistent with sickle cell anemia, and fetal hemoglobin was 13.4 per cent. Gastric analysis showed free hydrochloric acid to be present. An x-ray study of the small intestine failed to show any abnormality. A diagnosis of nutritional megaloblastic anemia and sickle cell anemia was made.

HOSPITAL COURSE. The patient was given folic acid, 20 mg. a day, by mouth. A reticulocyte response occurred following this with a peak of 40 per cent on the eighth day after treatment was started with concurrent rise in hemoglobin (fig. 5). He improved markedly symptomatically. All his symptoms disappeared, his appetite improved and he gained 6 lbs. in weight in the next two weeks. A radioactive vitamin B₁₂ excretion (Schilling) test was normal with urinary excretion of 8 per cent of the dose given in 24 hours.

DISCUSSION

The three patients reported here entered the hospital because of weakness, shortness of breath, anorexia and in two cases, with swelling of feet and hands. None of the patients had pains in the abdomen or extremities immediately prior to, or at time of admission. Two of the patients were noted to have loss of papillae on the edges of the tongue, although none of them had subjective sensations of glossitis. The bone marrow in all the patients was hypercellular rather than aplastic at the time of admission.
The three patients had strikingly similar blood findings at the time they were first seen. All were more severely anemic than they were prior to, or subsequent to, the episode leading to admission to the hospital. All showed evidence of macrocytosis in the peripheral blood, although only a moderate number of the circulating red cells were macrocytic. Howell-Jolly bodies were very noticeable in the red blood cells before treatment, but disappeared completely after treatment. This phenomenon has been reported by other authors following successful treatment with folic acid. Sickled red cells were noted in the two patients with sickle cell anemia, and hypersegmentation of polymorphonuclear leukocytes was noted in all of the patients in the peripheral blood and marrow (fig. 6). Subsequently, when reticulocytosis developed, there was a marked temporary increase in nucleated red blood cells in the peripheral blood.

It should be pointed out that patients with sickle cell states usually have fairly predictable levels of hemoglobin, red blood cell count and hematocrit, and each patient seems to maintain fairly stable blood levels in the absence of complications or "aplastic" crises. The three patients reported here were found to have stable blood levels at other times than during the episodes described.

Review of the literature regarding the occurrence of megaloblastic blood formation in the course of hemolytic anemias is a somewhat difficult task. If morphologic features alone are used, it can always be debated whether the author is using the same criteria for megaloblastosis as are generally accepted. We have therefore tried to collect only those cases in which reticulocyte response with concurrent rise in blood values has occurred following specific therapy with liver extract, vitamin B_{12} or folic acid. Thirteen such patients were found in addition to the three patients reported here. A summary of the findings in these 16 cases is tabulated in table 2. It can be seen that megaloblastic anemia has been observed in association with most types of hemolytic anemias. A diagnosis of pernicious anemia was made in four of the 16 cases. By the evidence given by the authors reporting these cases,
this diagnosis is irrefutable in one case (case 1 of Rubio and Burgin). The other three cases may well have been instances of pernicious anemia, but absolute proof of the diagnosis is not available. The case reported by Waugh was probably an example of pernicious anemia, but the response to liver extract was quite slow and suboptimal. Pernicious anemia seems somewhat unlikely in the patient reported by Crosby and Sacks as the patient was only 26 years old and although he had histamine fast achlorhydria at the time he was in relapse, he did not have gastric atrophy by gastroscopic examination, and he showed reversion to megaloblastic blood formation within three months after adequate treatment with purified liver extract. This is quite unusual in patients with pernicious anemia. The second case of Rubio and Burgin had adequate criteria for the diagnosis of pernicious anemia, but the megaloblastosis developed while the patient was receiving 10 micrograms of vitamin B₁₂ weekly. The patient subsequently responded to larger doses of vitamin B₁₂.

Pernicious anemia seems quite unlikely in the other 12 cases listed in table 2. This diagnosis is ruled out in these cases by the demonstration of free hydrochloric acid on gastric analysis, by occurrence during pregnancy,
or its occurrence in spite of administration of vitamin B₁₂ or purified liver extract. In some cases it is ruled out by a second reticulocyte response to the administration of folic acid after a partial response to vitamin B₁₂.

It should be added that the cases listed in table 2 are by no means the only ones reported to have megaloblastic anemia superimposed on hemolytic anemia, but they have been collected because they were confirmed by therapeutic response. For example, Dacie²⁵ and Schlagetter⁴ each mention a case of megaloblastic anemia of pregnancy in patients with congenital spherocytic anemia, and Zuelzer and Rutsky²⁶ include a one year old boy with sickle cell anemia and complicating megaloblastic anemia of infancy in their series of cases of this disease. These and other cases are not included here, as responses to treatment either were not mentioned or were obscured by transfusions.

The cases reported here, and other similar ones, raise primarily two questions: The first one is whether the megaloblastic anemia in these cases is due to a deficiency of folic acid or vitamin B₁₂ or both. The second question is whether there is an etiologic relationship between the two conditions or whether the association is coincidental. The cases with definite pernicious anemia we can probably dismiss as coincidental, as these cases seem to be extremely rare. The other cases can all be classified as being types of megaloblastic anemia other than pernicious anemia. Most of them had free hydrochloric acid in the gastric juice, and half of them were believed to have megaloblastic anemia of pregnancy. Patients with this type of megaloblastic anemia in temperate climates have been found to have normal vitamin B₁₂ serum levels and normal vitamin B₁₂ absorption in almost all instances, and this anemia is believed now by most authors to be typically a folic acid deficiency.²⁷,²⁸ However, from the evidence at hand we cannot be certain whether these cases have folic acid deficiency or vitamin B₁₂ deficiency, although circumstantial evidence indicates that most of them are due to a deficiency of folic acid.

The second question, i.e., whether the occurrence of megaloblastic anemia with hemolytic anemias is coincidental or not, requires further elucidation. On review of the literature, we have little evidence to support the idea that folic acid or other hematopoietic factors are required in increased amounts at times of increased erythropoiesis or increased growth. There is some indirect evidence to indicate that folic acid or vitamin B₁₂ is required in excessive amounts at certain periods of particularly active growth. In temperate climates we see nutritional megaloblastic anemia arise mainly under certain specific conditions, i.e., with extremely deficient diets such as are found almost only in alcoholics or food faddists, in sprue and other malabsorption syndromes where absorption of folic acid and vitamin B₁₂ may be impaired²⁷,²⁹,³⁰ and in infancy and in pregnancy. In the last two circumstances it seems likely that with rapid growth there is an additional strain on folic acid reserves superimposed on a deficient diet. Zuelzer and Rutsky²⁶ believe that megaloblastic anemia of infancy is due to a combination of circumstances, i.e., a diet deficient in folic acid and ascorbic acid and increased need dur-
<table>
<thead>
<tr>
<th>Author &amp; Ref.</th>
<th>Year</th>
<th>Hemolytic Anemia Type</th>
<th>Therapy and Response</th>
<th>Type of Megaloblastic Anemia Diagnosed</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Haenel, [3]</td>
<td>1950</td>
<td>Congenital spherocytic anemia</td>
<td>Liver extract (purified?). Double reticulocyte response.</td>
<td>Type not specified</td>
<td>Patient age 27. Gastric HCl present. No evidence of combined system disease.</td>
</tr>
<tr>
<td>4. Grunland, S. [4]</td>
<td>1950</td>
<td>Type not specified</td>
<td>Initial response to liver extract. Subsequent failure to respond. Response to folic acid?</td>
<td>Type not specified</td>
<td>Patient age 69. Gastric HCl present.</td>
</tr>
<tr>
<td>5. Davidson, L. S. P. [5]</td>
<td>1952</td>
<td>Congenital spherocytic anemia</td>
<td>Response to folic acid.</td>
<td>Megaloblastic anemia of pregnancy</td>
<td>Patient had had weekly injections of liver extract for twelve years prior to this episode.</td>
</tr>
<tr>
<td>6. Goldberg, M. A. &amp; Schwartz, S. D. [6]</td>
<td>1954</td>
<td>Mediterranean anemia trait</td>
<td>Responded to both $B_{12}$ and folic acid in succession. See Comments</td>
<td>Megaloblastic anemia of pregnancy</td>
<td>Developed megaloblastic anemia of pregnancy 3 times. Responded to vitamin $B_{12}$ initially. Subsequently developed same condition in spite of vitamin $B_{12}$ injections and responded to folic acid twice. Free HCl present in gastric juice. Patient also had hemochromatosis. Free HCl present in gastric juice.</td>
</tr>
<tr>
<td>7. Heffernan, C. K. &amp; Jaswon, N. [7]</td>
<td>1955</td>
<td>Paroxysmal nocturnal hemoglobinuria</td>
<td>Responded to folic acid after failing to respond to vitamin $B_{12}$</td>
<td>Nutritional megaloblastic anemia</td>
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<tr>
<td></td>
<td>Author(s)</td>
<td>Year</td>
<td>Diagnosis</td>
<td>Response to vitamin B₁₂</td>
<td>Vitamin B₁₂ deficiency but not pernicious anemia</td>
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<td>8</td>
<td>Baike, A. G. &amp; Firrie, R.</td>
<td>1956</td>
<td>Acquired hemolytic anemia</td>
<td>Responded to vitamin B₁₂</td>
<td>Vitamin B₁₂ deficiency but not pernicious anemia</td>
</tr>
<tr>
<td>9</td>
<td>Gross, R. &amp; Ludwig, H.</td>
<td>1957</td>
<td>Congenital spherocytic anemia</td>
<td>Double reticulocyte response with vitamin B₁₂ followed by folic acid</td>
<td>Megaloblastic anemia of pregnancy</td>
</tr>
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<td>10</td>
<td>Drury, M. I. &amp; Geoghegan, F.</td>
<td>1957</td>
<td>Congenital spherocytic anemia</td>
<td>Response to folic acid on two occasions</td>
<td>Megaloblastic anemia of pregnancy</td>
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<td>12</td>
<td>Rubio, F. &amp; Burgin, L.</td>
<td>1957</td>
<td>Congenital spherocytic anemia</td>
<td>See Comments</td>
<td>Pernicious anemia</td>
</tr>
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<td>13</td>
<td>Jandl, J. H. &amp; Greenberg, M. S.</td>
<td>1958</td>
<td>Mediterranea anemia</td>
<td>Folic acid</td>
<td>Megaloblastic bone marrow not specified</td>
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</table>
ing the most active period of growth of the child. Wills\textsuperscript{31} believes that megaloblastic anemia of pregnancy in the tropics is due to a combination of deficient diet and increased requirement during pregnancy. In addition to this, it was her belief that malaria and hookworm disease predisposed patients to nutritional megaloblastic anemia. Other authors\textsuperscript{27} have confirmed this belief, although no accurate evidence is available which verifies these clinical impressions. In general, we can say that there has been a fairly widely held clinical impression that the need for folic acid or vitamin B\textsubscript{12} or both was increased during periods of active growth and possibly in the presence of active erythropoiesis. These clinical observations have not been confirmed up to the present time either by measurements of folic acid activity in serum or urine of such patients, or experimentally in animals. The cases of hemolytic anemia associated with megaloblastic anemia discussed here may be another clinical indication that hematopoietic substances such as folic acid and vitamin B\textsubscript{12} are utilized more rapidly than normal when erythropoiesis is accelerated. Indirect evidence has been obtained in our laboratory indicating that this may be true at least of folic acid. We have found that patients with hemolytic anemias are exceptionally sensitive to the administration of a folic acid antagonist, pyrimethamine.\textsuperscript{32} Further work is under way to investigate this and will be reported at a later date.

**Summary**

Three patients with megaloblastic anemia complicating sickle cell anemia or sickle cell-hemoglobin C disease are reported. Previously reported cases of megaloblastic anemia in patients with pre-existing hemolytic anemia are reviewed. It is concluded that the megaloblastic blood formation in such patients may be due to excessive need for folic acid or vitamin B\textsubscript{12}.

**Summary in Interlingua**

Es reportate le casos de tres patientes con anemia megaloblastic como complication de anemia a cellulas falciforme o de morbo a cellulas falciforme e hemoglobina C. Es presentate un revista del previemente reportate casos de anemia megaloblastic in patientes con pre-existente anemia hemolytic. Es concluide que le formation de sanguine megaloblastic in tal patientes es possiblemente le effetto de excessive requerimientos de acido folic o de vitamina B\textsubscript{12}.

**References**

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