Evidence for Folic Acid Deficiency in the Genesis of Anemic Sickle Cell Crisis

By Lawrence E. Pierce and Charles E. Rath

ACUTELY DEPRESSED erythropoiesis in a decompensated hemolytic disorder such as sickle cell anemia results in a rapid fall in hematocrit which can be fatal if not promptly treated. Such intermittent inhibition of marrow activity has been previously reported in association with superimposed acute infection and nutritional deficiency. More recently, the observation of megaloblastic maturation arrest coincident with so-called hemolytic crisis has aroused interest in the increased cellular demand for nucleic acid synthesis attending increased red cell turnover rates. Both folic acid and vitamin B₁₂ play essential roles in purine and pyrimidine nucleoprotein metabolism and the vast majority of megaloblastic anemias are relieved by one or the other agent. Previous reports of maturation arrest occurring in hereditary spherocytosis and sickle cell anemia have not shown definite pretreatment evidences of folic acid deficiency. Elevated urinary formiminoglutamic acid has been observed in recurrent crises of thalassemia major. In none of these instances, however, has there been hematologic responsiveness to physiologic doses of vitamin B₁₂, folic acid, or folinic acid.

The present report concerns detailed observations in two patients with sickle cell anemia exhibiting biochemical evidence for folic acid deficiency. In one of these, there was a striking beneficial response to physiologic doses of oral folic acid both during an acute aregenerative crisis and again six and one-half months after cessation of folic acid during a period of gradual fall in hematocrit. Five additional sickle cell patients tested had similar laboratory evidence of folic acid deficiency.

Methods

Standard (Wintrobe) technics were employed in determining packed red cell volume and peripheral red cell counts. The cyanmethemoglobin method was used for hemoglobin determinations. Reticulocytes were stained with new methylene blue-N and counted in dried preparations. Quantitative formiminoglutamic acid (FIGlu) assays were performed after the enzymatic spectrophotometric technic of Tabor and Wyngarden. Starch hemoglobin electrophoresis was performed with a miniature plate modification of existing methods and alkali denaturation in addition to starch elution was utilized in measuring fetal hemoglobin. Serum iron levels were determined after the method of Ramsey and iron binding capacity by the technic of Rath and Finch. Serum B₁₂ assay employed L. Leishmanii as the test organism.

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Case No. 1

First admission: O. J., a 21-year-old Negro male handyman, was admitted to Georgetown University Hospital for the 13th time on January 18, 1960 because of fatigue and weakness. Sickle cell anemia had been established at age five incidental to a fracture of the left arm. He was seen at Georgetown Hospital for the first time when 13 years of age. Prior to this admission, he had received a total of 113 blood transfusions, 83 of them at Georgetown University Hospital. Since 1954, elevation of serum iron and full saturation of transferrin correlated with evidence in the liver biopsy of hemosiderosis and mild portal fibrosis. Four months prior to the present admission, he was observed to have a hematocrit of 14 per cent with 80 nucleated red blood cells per 100 leukocytes on the peripheral blood smear. Two units of packed red cells were given at that time. Pretransfusion serum bilirubin total was 2.1 mg. per cent with 0.8 mg. comprising the one-minute direct fraction.

The patient had three siblings. Two sisters were normal and one brother had sickle trait. The mother had AS hemoglobin. The putative father was not available for study. A paternal uncle was said to have died of complications of sickle cell anemia.

On examination, the patient was slim, appeared chronically ill, but looked younger than his stated age. The oral temperature was 100.6 F., the pulse regular at 102, and the blood pressure 120/70. There was pallor and slight scleral icterus. There was 0.5 x 0.5 cm. discrete adenopathy of the submandibular, anterior cervical, and inguinal areas. There was no soreness of the tongue nor atrophy of glossal papillae. There was no soreness of the tongue nor atrophy of glossal papillae. There was moderate cardiomegaly and an unchanging grade 3 ejection type systolic murmur heard maximally in the third left interspace parasternally. The liver extended 12 cm. below the right costal margin and obliquely into the left upper quadrant. The spleen was not felt.

The admission hematocrit was 10.5 per cent and reticulocyte count 4 per cent. The peripheral smear showed approximately 40 per cent sickled cells and 294 nucleated red blood cells per 100 leukocytes. Many of these nucleated erythrocytes were abnormal (fig. 1). Hypersegmented neutrophils and polychromatophilic macrocytes with Howell-Jolly inclusions were also found. The MCV was 114 cu. μ; MCH 41 μg.; and MCHC 37 per

Fig. 1.—Case 1. Photomicrograph (X 970) of admission peripheral blood smear showing changes consistent with a megaloblastic type of erythropoiesis.
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Fig. 2.—Case 1. Photomicrograph (X 970) of pretreatment posterior iliac marrow aspirate smear demonstrating megaloblastic erythropoiesis.

cent. The platelet count was 597,000/mm.$^3$ and corrected white blood count 7,000 mm.$^3$ with 57 per cent neutrophils, 36 per cent small lymphocytes, 4 per cent monocytes and 3 per cent eosinophils. Preparations of bone marrow aspirated from the posterior iliac crest were all hypocellular but demonstrated megaloblastic changes (fig. 2).

Control 24-hour urine collection for FIGlu assay (fig. 3) showed a marked increase of 5.8 $\mu$M/hr. (normal mean 0.5 $\mu$M/hr.) with a rise to 8.8 $\mu$M/hr. within the 24 hours after 3 Gm. oral histidine (normal mean 0.85 $\mu$M/hr.).

Paper and starch hemoglobin electrophoresis again showed an SS pattern. The fetal hemoglobin was 4.3 per cent. The serum B$_{12}$ level was 610 $\mu$g./ml. (normal 300-800 $\mu$g./ml.). Free acid was absent in the gastric juice after histamine stimulation. 8.8 per cent Co$^{57}$ labeled cyanocobalamin was excreted during the first 24 hours of a Schilling test and an additional 1.3 per cent excreted the following day. Intestinal absorption of d-xylose and serum carotene concentrations were both normal. The Sudan black stain of the feces was negative.

The Cr$^{51}$ erythrocyte half-life was eight days and concurrent body surface organ scanning for radioactivity showed the liver to be the dominant site of erythrocyte capture. The Coombs' test was negative. X-ray of the chest demonstrated cardiomegaly and the upper intestinal x-ray was within normal limits.

The serum bilirubin total was 2.8 mg. with a 0.4 mg. direct-reacting fraction. The total protein varied from 7.0 to 8.4 Gm. with albumin ranging 3.0-3.6 Gm. and globulin 4.0-4.8 Gm. The alkaline phosphatase was 3.6 Bessey-Lowery units and the thymol turbidity was 11.9 Maclagen units. The serum cholesterol was 144 and 139 mg. per cent.

Urinalysis revealed hyposthenuria and albuminuria with slightly acid pH. The blood urea nitrogen was 8 mg. The PSP excretion was 15 per cent in 15 minutes and 35 per cent in 30 minutes.

The patient received one unit of packed red cells on admission which raised the hematocrit to 14 per cent (fig. 3). Oral folic acid was begun in a "physiologic" dosage schedule of 1 mg. each day on the third hospital day. Four days later the reticulocyte count peaked at 52 per cent at which time the hematocrit had reached the usual level of
Fig. 3.—Case 1. Urinary FIGlu, reticulocyte, and hematocrit response to oral folic acid administration following acute hypoplastic crisis with megaloblastosis. Pre- and post-treatment comparisons for hematocrit and reticulocyte percentages are at either end of the graph. The symbol H plotted on the FIGlu excretion double line signifies a 3 Gm. oral histidine load. Indirect bilirubin is represented by the clear area of the total bilirubin bar.

20 per cent. After six days treatment with folic acid, the bone marrow was re-examined and showed complete reversion to normoblastic hyperplasia (Fig. 4). Folic acid therapy was stopped on February 22, 1960. The hematocrit remained stable at 20 per cent and the reticulocyte count persisted at a level significantly higher (35 per cent) than previous eight year averages (25 per cent) for the period from discharge on March 5 through June of 1960. A 24-hour control urine specimen of June 6 contained 2.1 μM FIGlu/hr.

Second admission: The patient had done well for the preceding six and one-half months while on no treatment. On September 11, 1960, he was re-admitted to the hospital complaining of fatigue and tiredness. The physical examination was not remarkably changed from that previously described.

The hematocrit on admission was 17 per cent and reticulocyte count was 19 per cent. There were 20 nucleated red cells per 100 leukocytes in the peripheral blood but no megaloblastic changes. The corrected WBC was 14,600 with 51 per cent neutrophils, 42 per cent small lymphocytes, 2 per cent monocytes, and 5 per cent eosinophils. The platelet count was 128,000/mm^3. The aspiration bone marrow preparations were hypercellular and showed normoblastic red cell hyperplasia.

The control 24-hour urinary FIGlu level was 3.1 μM/hr. The following day, after 3 Gm. oral histidine, the FIGlu level rose to 8.5 μM/hr. (fig. 5). The serum B_{12} level was 147 μg/ml. (normal 100–300 μg/g.). The serum iron was 220 μg. per cent and completely saturated. Bilirubin levels were of the same magnitude as on the previous admission.

The patient was observed for seven hospital days during which time there was no change
Case No. 2

A 36 year old Negro barber (E. A.) was admitted to Georgetown Hospital for the first time on November 4, 1960 because of a four-day history of fever and pleuritic-type chest pain.

He was unaware of any hematologic abnormality until age 23 when sickle cell disease was diagnosed after hospitalization for effusion into the right knee joint. His only other previous hospitalization was for pneumonia in 1954. He had received a total of five transfusions prior to this admission.

Both parents had died of hypertensive complications in the sixth decade. There were four brothers, one having sickle cell trait.

A control 24-hour urine for FIGlu was previously found to be normal (0.2 µM/hr.) during an asymptomatic steady state on September 24 (1960) when the hematocrit was 24 per cent.

On examination the patient was tall and thin and in moderate respiratory distress. The oral temperature was 100.8 F, and blood pressure 110/70. The fundi were normal and the sclerae icteric. Oral hygiene was poor and the teeth grossly carious. The tongue appeared normal. Examination of the lungs revealed bilateral inspiratory rales at both posterior bases and a pleural rub in the right midaxillary line. There was a normal sinus tachycardia of 116 and no cardiomegaly. Neither liver nor spleen was palpable. There was a granulating ulceration 2 cm. in diameter behind the left medial malleolus.
The hematocrit was 17 per cent and reticulocyte count 9 per cent. Thirty per cent sickling was noted in the peripheral blood smear and there were 14 nucleated red cells per 100 leukocytes. The MCV was 105 cu. µ; MCH 32 µg.; and MCHC 30 per cent. Platelets were increased to 548,000/mm³. The corrected WBC was 15,500/mm³ with 57 per cent neutrophils, 14 per cent bands, 1 metamyelocyte, 22 small lymphocytes and 6 monocytes.

The corrected WBC reached 31,000/mm³ on the seventh day and nucleated red cells increased to 228 per 100 leukocytes. The indirect Coombs was 4+. The serum contained anti-C, anti-M, anti-Kidd (Jk²) and anti-Duffy iso-antibodies. Bone marrow aspirates were hypercellular and consistent with severe hemolytic anemia. Paper, starch, and agar hemoglobin electrophoresis confirmed the diagnosis of SS hemoglobin disease. The fetal hemoglobin was 18.9 per cent. The serum iron was 85 µg. and unsaturated IBC 137 µg. per cent. Bilirubin was 3.0 mg. with the direct fraction constituting 0.8 mg. Chest x-ray showed bronchopneumonia of the right upper and middle and left lower lobes. This was identified as pneumococcal in etiology.

The urine specific gravity ranged from 1.008 to 1.010. PSP excretion was 20 per cent in 15 minutes, BUN normal, and IVP revealed a dichotomous right renal pelvis with a superior calyceal cyst.

He received one unit of packed red cells on admission which raised the hematocrit to 20 per cent. FIGlu excretion on the second hospital day was 1.4 µM/hr. and the following day rose to 4.6 µM after histidine stimulation (fig. 6). Spontaneous reticulocytosis occurred and stabilized for 8 days at 20 per cent. One mg. oral folic acid daily was begun on November 18. The reticulocyte count rose to 30 per cent with an accompanying rise in hematocrit above the previous steady state (24 per cent) to 29 per cent. The FIGlu excretion then fell toward the normal range and folic acid was discontinued with discharge from the hospital on December 20, 1960. On January 5, 1961, the packed cell volume was 26 per cent and reticulocyte count 9.5 per cent.

**DISCUSSION**

The two patients reported here focus attention on the possible role of folic acid deficiency in the development of anemic sickle cell crisis. The abnormally
increased formiminoglutamicaciduria demonstrated in both patients during periods of exacerbation of anemia is consistent with the increased urinary FIGlu found in folic acid deficient subjects. That increased urinary FIGlu explicitly signifies folic acid deficiency has been challenged and is as yet not completely settled. Luhby et al. have stated that increased FIGlu excretion following histidine loading distinguishes anemia due to folic acid deficiency from that due to deficiency of vitamin B₁₂. Baker, Herbert and associates, on the other hand, suggested the FIGlu technic to be of limited usefulness and reliability after documenting increased urinary FIGlu in a patient regarded to have uncomplicated pernicious anemia. We have occasionally but not regularly detected elevations of FIGlu after histidine stimulation in patients considered to have classical pernicious anemia in relapse. This FIGlu increase, when it occurs with histidine augmentation, has ranged from 1.0 μM/hr. to 4.0 μM/hr. in the most severe cases with a mean value of 2.0 μM/hr. Therapeutic response to folic acid can only rarely be assessed since the control levels pre- and post-histidine stimulation are frequently normal or barely elevated. In contrast, patients with folic acid deficiency (and the two patients with sickle cell anemia herein reported) have elevated FIGlu values before histidine stimulation which fall slowly toward the prestimulation levels over a period of one to two days. Consequently, we regard the FIGlu assay as a valuable procedure and as satisfactory as any other single diagnostic test in the diagnosis of folic acid deficiency. Its usefulness is not negated by the cited exception. We have not
yet encountered a patient who responded to folic acid after a treatment failure was predicted by normal FIGlu levels.

The first patient (O. J.) had particularly severe hypoplasia with maturation arrest. The usual causes of megaloblastosis were excluded. He was a teetotaller and both midday and evening meals consisted of cooked meat and vegetables. He ascribed to no dietary fads, and gastrointestinal malabsorption as a possible influence was eliminated by absorption tests during hospitalization. The peripheral blood and bone marrow changes were evidently not due to $B_{12}$ deficiency since both serum $B_{12}$ levels and $CO^{58}$ $B_{12}$ absorption proved to be normal. Gastrointestinal roentgen survey served to rule against any anatomic deformity that might induce megaloblastosis. His presenting severe anemia, leukopenia and relative reticulocytopenia with unchanging bilirubin fractions suggested marrow failure to explain his clinical situation. Histamine-fast achlorhydria was of interest but appeared to play no active role in his anemia. The hematocrit rapidly returned to its usual “normal” level in four days simultaneous with the reticulocyte peak. The reticulocyte peak in subjects with hemolytic anemia responding to folic acid has been observed in the third to sixth treatment day$^{9,10}$ and is conditioned by prior transfusion and the degree of anemia. Subsequent folic acid treatment of O. J. was not continuous. During his second admission, he was more anemic than usual but his marrow was normoblastic rather than megaloblastic. He nonetheless responded to folic acid administration again after a seven-day control period.

The patient (O. J.) received a total of 113 blood transfusions, 83 of them at Georgetown University Hospital. The usual indications for transfusion were a matter of clinical judgement but usually these were given because of symptomatic dyspnea and increased fatigability with a fall in hematocrit into the range of 14 to 16 per cent. He had not received fewer than seven transfusions during any calendar year of the previous nine, with a high of 16 in 1958. Since the diagnosis of associated folic acid deficiency and subsequent intermittent folic therapy, however, he had maintained his usual comfort with hematocrit of 20–22 per cent for a period in excess of 15 months without transfusion (fig. 7).

The second patient (E. A.) had fewer problems secondary to his sickle cell disease, perhaps in part due to the persistence of a relatively large percentage of fetal hemoglobin. His FIGlu excretion had been known to be normal during steady-state, and it was only during an acute respiratory complication that it advanced to pathologic excretion. The apparent response to folic acid in the second phase of his recovery is of importance because of the development of difficulty in cross-matching blood for transfusion. The accumulation of iso-antibody following six transfusions made alternative therapy desirable.

We have not included any data on patients with megaloblastic anemia of pregnancy associated with hemolytic anemia because of the difficulty in dissecting the relative contribution made by each to the total picture. Two of the highest levels of FIGlu excretion we have observed were associated with the third trimester of pregnancy, 14.6 and 16.1 $\mu$M/hr.; one in a sickle cell
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Fig. 7.—Case 1. Blood transfusions received by patient O. J. during eight and one-half years observation at Georgetown Hospital.

patient* and the other in a patient with AA hemoglobin. In two of Johnnson's three cases, pregnancy was associated with S-C disease in one and S-S in the other. Oliner and Heller noted a sickle cell patient with acquired hemolytic anemia and nutritional inadequacy who developed megaloblastic erythropoiesis with "slightly elevated FIGlu." No values were included, however, and the patient was not improved by folinic acid. The occurrence of virtually simultaneous aplastic crises in three members of the same family has recently been reported by Hilkowitz, but none of the three were benefited by folic acid.

Marshall and Jandl have suggested the physiologic dose of folic acid necessary to induce hematologic remission in folic deficiency states as 0.4 mg. each day intramuscularly. It has become apparent, however, that some patients require supranormal or pharmacologic doses of folic acid to revert to normalcy, even in circumstances where no clear-cut deficiency state can be demonstrated except responsiveness to therapeutic trial. A thalassemia major patient with recurrent relapses responsive to the larger doses of folic acid has been reported from the same laboratory. Their patient had intense bone pain after treatment was begun, a feature searched for but lacking in our first patient. Because of such reports, a 31 year old negro female (V. K.) with repeated painful crises at monthly intervals without wide swings in hematologic parameters but with modest formiminoglutamicaciduria was treated with increased dosages of folic acid (fig. 8). Neither dosage schedule (1 mg. and 5 mg. each day orally) afforded improvement.

FIGlu levels in four additional sickle cell patients are shown in figure 9. This also details mean values in 15 normal subjects and 8 normals stimulated with 3 Gm. of oral histidine.

The persistence of FIGlu reactive material after treatment with folic acid was a point requiring special attention. It seemed probable that this represented some substance other than FIGlu but capable of reacting with the

*Sample kindly supplied by Dr. Paul McCurdy, Georgetown Medical Division, D. C. General Hospital, Washington, D. C.
Fig. 8.—Abnormally elevated FIGlu excretion values were recorded during symptomatic crisis without demonstrable depression in hematocrit or reticulocyte percentage. The occurrence of painful crisis is coincident with packed red blood cell transfusions arrows. Treatment with folic acid in both physiologic and increased dosage schedules did not significantly improve the packed red cell volume or level of reticulocytes. FIGlu excretion was lessened but not completely eliminated.

enzyme employed in assaying FIGlu and persisting after correction of folic deficiency. In investigating the three major possibilities, histidine itself was found to be nonreactive with the enzyme employed. Imidazolepropionic acid is extremely unstable at alkaline pH, is heat labile, and requires special anaerobic precautions for isolation. The third possibility considered was urocanic acid. Measured amounts of urocanic acid added to normal FIGlu negative urine, then subjected to alkalinization and autoclaving, showed 95 per cent stability. Sodium formiminoglutarate similarly treated was 95 per cent destroyed. Recovery of either artificially added compound was in excess of 93 per cent. In patient O. J., the heat alkali resistant fraction percentages with FIGlu reactivity after histidine were least in the acute episode (15 per cent of 8.8 μM), somewhat more in the subacute setting of the second admission (35 per cent of 5.0 μM), and greatest (50 to 60 per cent of 2.5 μM) during the relatively stable periods. This suggests a relatively unchanging handicap along a similar metabolic pathway upon which folic acid deficiency was additive. The assay liver enzyme was shown to possess urocanase activity by conversion of O. J.’s post heat-alkali urinary FIGlu positivity to 5–10 methenyl-tetrahydrofolic acid and by plotting the disappearance of aqueous solutions of purified urocanic acid in the ultra-violet spectrum under the
influence of the routinely used hog liver enzyme. Each of five separate enzyme preparations showed the same properties. Similar degrees of FIGlu positivity not influenced by folic acid have been found in some patients with chronic liver disease, particularly alcoholic cirrhosis. Consequently, an association may exist between this substance and chronic liver dysfunction, perhaps of diverse etiology, and including the liver disease of sickle cell anemia. Recent liver function testing in the three patients treated with folic acid are outlined in table 1.

There is as yet no adequate explanation for the development of folic dependence in the congenital hemolytic anemias. Increased requirement consequent to accelerated erythropoiesis is the most often advanced theory. Accurate hepatic storage data similar to that obtained for vitamin B₁₂ with cobalt labeling is not available for folic acid. The recent availability of tritiated folic acid, however, may shed light on its biologic half-life in the near future.

**Summary and Conclusions**

Two cases are presented of sickle cell anemia demonstrating evidence of folic acid deficiency during a period of anemic crisis.

One patient had acute hypoplastic crisis associated with megaloblastic
erythropoiesis not in conjunction with acute infection, dietary inadequacy, gastrointestinal malabsorption or chronic alcoholism. An increased excretion of urinary formiminoglutamic acid of 8.8 \( \mu \)M/hr. after histidine stimulation was observed in association with more severe anemia than had been noted previously during nine years observation. Prompt reticulocytosis and rise in hematocrit to previous levels occurred when 1 mg. oral daily folate acid was administered. Improvement was accompanied by a fall in FIGlu excretion to normalcy. Since the observation of folic acid responsiveness in this patient, it has not been necessary to transfuse him for a period in excess of 15 months whereas his previous average requirement approached one unit each month for the past seven and one-half years.

A second patient demonstrated increased formiminoglutamic aciduria coincident with anemic sickle cell crisis following bilateral bronchopneumonia with pulmonary thrombosis. There was a beneficial hematologic response to oral folic acid supplementation in physiologic doses. Previously determined control urinary FIGlu levels had been within normal limits.

Increased urinary FIGlu has been observed in five additional sickle cell patients not in anemic crisis. One of these (V. K.) was tested for sensitivity to higher dosage levels of folic acid (5 mg. each day) without improvement.

Low levels of FIGlu-like material persisted in some patients with sickle cell anemia after treatment with folic acid. Indirect evidence would indicate that this material is urocanic acid and may be related to the chronic liver dysfunction frequently present in sickle cell disease.

Evidence has been presented which indicates that folic acid may be a

### Table 1.—Summary of Steady State Liver Function Studies in Patients Reported

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<thead>
<tr>
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<tr>
<td><strong>Palp. Hepar below RCM</strong></td>
<td>O. J.</td>
<td>E. A.</td>
<td>V. K.</td>
</tr>
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<td>12 cm.</td>
<td>Not palpable</td>
<td>Not palpable</td>
</tr>
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<td>4%</td>
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<td>2.8/3.8</td>
<td>3.5/4.9</td>
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<td>2.4</td>
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<tr>
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<td>22</td>
<td>75</td>
</tr>
<tr>
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<td>9.8</td>
<td>10.2</td>
</tr>
<tr>
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<td>0.75/2.5</td>
<td>0.8/3.6</td>
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<tr>
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<td>4+</td>
<td>2+</td>
</tr>
<tr>
<td><strong>Cholesterol mgm%</strong></td>
<td>139</td>
<td>195</td>
<td>147</td>
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FOLIC ACID DEFICIENCY IN SICKLE CELL ANEMIA

limiting factor in the development of and recovery from anemic sickle cell crisis.

SUMMARIO IN INTERLINGUA

Es presentate duo casos de anemia a cellulas falciforme con evidentia de deficientia de acido folic durante un periodo de crise anemic.

Un patiente habeva acute crise hypoplastic associate con erythropoiese megaloblastic non in conjunction con infection acute, inadequatia dietari, malabsorption gastrointestinal, o alcoholismo chronic. Esseva observate un augmentate excretion de urinari acido formiminoglutamic de 8,8 \( \mu \)M per hora post stimulation per histidina in association con un plus sever anemia que habeva essite notate previemente durante novem annos de observation. Prompte reticulocytese e elevation del hematocrite a previe nivellos occurreva quando 1 mg per die de acido folic esseva administrate per via oral. Melioration esseva accompaniate per un reduction, usque al livello normal, in le excretion de acido formiminoglutamic (FIGlu). Depost le observation del responsivitate a acido folic in iste patiente ille ha requirite nulle transfusion durante un periodo de plus que 15 menses ben que previemente su requerimento medie esseva proxime a un unitate per mense durante le passate septe annos e medie.

Un secunde patiente monstrava augmentate excretion urinari de acido FIGlu coincidente con crise de anemia a cellulas falciforme post bilateral bronchopneumonia con thrombosis pulmonar. Un benefic responsa hematologic sequava supplementation de acido folic in doses physiologic per via oral. Previemente determinate nivellos de controlo de acido FIGlu urinari habeva essite intra le limits normal.

Augmentate nivellos de acido FIGlu urinari ha essite observate in cinque patientes additional de anemia a cellulas falciforme, qui non esseva in crise anemic. Un de istes (V. K.) esseva testate pro sensibilite a plus alte doses de acido folic (5 mg per die). Nulle melioration sequava.

Basse nivellos de material simile a acido FIGlu persisteva in certe patientes de anemia a cellulas falciforme post tractamento con acido folic. Evidentia indirecte pare indicar que iste material es acido urocanic e que illo es possibilemente connectite con le chronic dysfunction hepatic que es frequentemente presente in morbo a cellulas falciforme.

Es presentate evidentia que indica que acido folic es un factor limitante in le disveloppamento de—e le restablimento ab—crises de anemia a cellulas falciforme.

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The authors wish to express their sincere appreciation to Dr. Herbert Tabor for his guidance in setting up the enzymatic FIGlu assay. Dr. Donald Watkin, NIH, Bethesda, kindly performed the serum \( B_{12} \) assay on patient O. J. during his first admission. Mrs. Norita Chaney performed many of the microbiologic and enzymatic assays.

REFERENCES


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