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# CHRONIC CONGENITAL AREGENERATIVE ANEMIA (PURE RED-CELL ANEMIA) ASSOCIATED WITH ISO-IMMUNIZATION BY THE BLOOD GROUP FACTOR "A"

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MANY VIEWS have been advanced to explain the pathogenesis of aplastic and hypoplastic anemia. The causative factors include chemical and physical agents, infection, exhaustion of the bone marrow, and specific blood dyscrasias and malignant tumors with bone marrow replacement. When these factors have been eliminated a relatively rare group of idiopathic aplastic anemia remains whose etiology is unknown and for which a congenitally inferior bone marrow has been postulated. In the classification of constitutionally defective bone marrow may be included examples of the "Fanconi syndrome,"[1] a type of anemia which is frequently familial and occurs in conjunction with a number of congenital abnormalities, chiefly pigmentation of the skin and testicular hypoplasia. Estren, Suess and Dameshek[2] recently described as a case of Fanconi's syndrome an 11 year old American-born child in whom hypoplastic anemia was associated with pigmentation of the skin, deafness, skeletal deformities and congenital heart disease.

It is the purpose of the present paper to describe a case reported in part of a previous communication[3] in which the failure of the bone marrow was confined to erythropoiesis without simultaneous depression of the granulocytes or platelets or their precursors. In considering the pathogenesis of this group of blood disorders the terms aplastic, hypoplastic and chronic congenital aregenerative anemia require definition. Aplastic anemia is a chronic progressive disease, characterized by a simultaneous depression of the three principal cellular elements in the bone marrow and resulting in a peripheral blood picture of profound anemia, leukopenia, neutropenia and thrombocytopenia. During the course of the disease the bone marrow shows a progressive decrease in the total count so that the megakaryocytes eventually disappear, the myeloid elements and nucleated red cells are greatly reduced and the lymphocytes predominate in the smears. Cases with normal or hyperplastic bone marrows with the peripheral blood picture of aplastic anemia have been interpreted as a maturation arrest or bone marrow block.

Hypoplastic anemia differs from aplastic anemia in that the formation of red blood cells is impaired with lesser involvement of the granulocytes and platelets. Earlier reports such as those of Josephs[4] and of Diamond and Blackfan[5] emphasized

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the feature of chronic progressive anemia and correlated with it a failure of erythropoiesis without an equivalent depression of the white blood cells or platelets. Although hypoplastic anemia implies a less severe course and occasionally a more hopeful outcome than aplastic anemia, the term has, nevertheless, been applied in recent years to intermediate conditions in which the three blood elements of the bone marrow are involved in variable degree. Reports of cases of hypoplastic anemia now range from those limited to a failure of red cell production[6] to those in which leukocytes and platelets are simultaneously depressed but to a lesser degree than the red cells. In many of the earlier reports of congenital hypoplastic anemia, descriptions of the bone marrow[7] revealed a marked reduction in the number of nucleated red cells as well as an increase in the number of primitive cells or hematogones and of eosinophilic leukocytes. Estren and Dameshek[8] have recently described as hypoplastic anemia, familial cases with generalized quantitative hypoplasia of all the elements in the bone marrow with the nucleated red cells in normal or elevated percentages. In one of their cases of severe anemia with an increased number of reticulocytes and thrombocytopenia, splenectomy resulted in moderate clinical and hematologic improvement.

The elucidation of the factors responsible for the causation of the variety of blood disorders now included in the general category of the aplastic-hypoplastic type of anemia will be facilitated by segregating those cases which possess similar clinical and hematologic features. One group that lends itself for separate consideration concerns those instances in which the failure of hematopoiesis is restricted entirely to the erythrocytes without impairment of leukocytes or platelet production. This condition involving solely red cell production has been designated as chronic congenital aregenerative anemia by Vogel, Erf and Rosenthal,[9] but a more descriptive term is that of "pure red-cell anemia," employed by Lescher and Hubble[10] who contributed 3 cases of their own. This unusual feature, in which a single cell type is depressed, constitutes the cardinal feature of this hematologic entity, and is illustrated by the following case history.

## Report of Case

A. K., a white male infant, was born three weeks prematurely on December 28, 1946. The infant was firstborn. The delivery was normal, and the infant was well for four days. At this time jaundice appeared which deepened and did not finally disappear until the third to the fourth week. At 8 days the blood count was 78 per cent hemoglobin with 3.7 M. red blood cells and the next day the values were slightly lower. No study of the blood factors was undertaken and no transfusion was given. On March 1, 1947, at approximately 2 months of age, the baby developed an upper respiratory infection with a mucopurulent discharge. The child was admitted to a local hospital where a blood count revealed a hemoglobin of 29 per cent and a red count of 1.3 M. per cu. mm. One transfusion of 125 cc. of blood was given, and the child was discharged on March 4, 1947.

Both parents were healthy and there was no history of any hereditary blood disorder. There had been no preceding pregnancies.

The infant was admitted to the Children's Clinic of The New York Hospital on March 8, 1947 because of a progressive anemia.

*Physical Examination:* The infant was well developed and well nourished and in no distress. There was no jaundice, the heart and lungs were normal, the spleen and liver edge were palpable at the costal margin. There were no petechiae or other manifestations of bleeding into the skin.

*Laboratory Examinations:* The blood count on admission (table 1) revealed a hemoglobin of 9.5 grams per 100 cc., RBC 3.5 M. The white cells numbered 13,000 per cu. mm. with 25 per cent segmented

polymorphonuclear leukocytes, 68 per cent lymphocytes, 3 per cent monocytes and 4 per cent eosinophiles. On March 13 the hemoglobin was 8.9 grams per 100 cubic centimeters, the volume of packed red cells was

TABLE 1.—*Representative Blood Counts in Case A. K.*

| Date | Hemoglobin content | Red cells | Packed red cells, volume per cent | White cells per cu. mm. | Neutrophiles | Lymphocytes | Monocytes | Eosinophiles | Platelets | Reticulocytes |
|---|---|---|---|---|---|---|---|---|---|---|
| 1947 | | | | | | | | | | |
| | *Gm. per 100 cc.* | *millions per cu. mm.* | | | *per cent* | *per cent* | *per cent* | *per cent* | *cu. mm.* | *per cent* |
| March 8 | 9.5 | 3,500 | | 13,000 | 25 | 68 | 3 | 4 | | |
| March 13 | 8.9 | | 24 | | | | | | 290,000 | 0.2 |
| April 4 | 8.5 | 2,910 | 26 | | | | | | | |
| May 3 | 8.0 | 3,500 | | 8,500 | 32 | 64 | 16 | 0 | | |
| June 2 | 8.0 | 2,600 | | 16,800 | 26 | 68 | 6 | 0 | | |
| July 3 | 7.5 | 3,200 | | 9,500 | 48 | 47 | 2 | 0 | | |
| October 8 | 10.0 | 3,040 | 28 | 15,400 | 37 | 57 | 4 | 2 | 296,000 | 0 |
| November 17 | 8.5 | 2,300 | | 15,800 | 47 | 46 | 7 | 0 | | |
| 1948 | | | | | | | | | | |
| April 9 | 7.0 | 2,550 | 26 | 16,100 | 17 | 75 | 7 | 1 | Numerous | 0 |
| May 13 | 8.0 | 2,750 | 28 | 9,200 | 31 | 66 | 2 | 1 | Numerous | 0 |

TABLE 2.—*Hematologic Data in Case (A. K.) Showing Persistent Depression of Erythropoiesis in the Course of Chronic Congenital Aregenerative Anemia*

| Bone marrow aspiration | March 14, 1947 | May 3, 1947 | Nov. 18, 1947 |
|---|---|---|---|
| Total nucleated cell count per c.mm. | 132,500 | 143,000 | 154,000 |
| Megakaryocytes per c.mm. | 66 | 77 | 77 |
| Myeloblasts | 0 | 0.5 | 3.0 |
| Myelocytes | 12.5 | 11.0 | 19.5 |
| Metamyelocytes | 7.5 | 5.0 | 7.0 |
| Polymorphonuclears non-segmented | 30.5 | 27.0 | 31.0 |
| segmented | 9.0 | 12.0 | 6.5 |
| Lymphocytes | 39.5 | 44.0 | 30.0 |
| Nucleated red cells | 1.0 | 0.5 | 0 |
| Hematogones | 0 | 0 | 1.5 |
| Monocytes | 0 | 0 | 1.5 |

Blood groups: Father, A Rh positive; Mother, O Rh positive; Infant, A Rh positive

| | March 3, 1947 | April 7, 1947 |
|---|---|---|
| Maternal anti-A agglutinin titer | 1:128,000 | 1:640–1:1280 |

24 per cent, the platelets numbered 290,000 per cubic millimeter, the reticulocytes were 0.2 per cent, the bleeding time was 3 minutes 35 seconds and the clotting time 3 minutes.

*Blood Group Factors:* The mother's group was O, Rh positive and that of the infant and father A, Rh

TABLE 3.—*Representative Blood Counts in Case K. H.*

| Date | Hemoglobin content | Red cells | Packed red cells, volume per cent | White cells per cu. mm. | Neutrophiles | Lymphocytes | Monocytes | Eosinophiles | Basophiles | Additional data |
|---|---|---|---|---|---|---|---|---|---|---|
| 1947 | | | | | | | | | | |
| | *Gm. per 100 cc.* | *Millions per Cu. mm.* | | | *per cent* | *per cent* | *per cent* | *per cent* | *per cent* | |
| October 16 | 11.5 | 2,580 | | 7,400 | 62 | 34 | 2 | 2 | | 65 nucleated red cells per 100 white blood cells |
| October 17 | 10.4 | 2,700 | | 12,300 | 72 | 21 | 2 | 2 | 3 | 17 nucleated red cells per 100 white blood cells |
| October 29 | 9.7 | 3,000 | | 7,400 | 25 | 74 | 1 | | | 1 nucleated red cell per 100 white blood cells |
| November 4 | 11.0 | 3,400 | | | | | | | | 0.2% reticulocytes |
| November 5 | | | | 18,950 | 28 | 63 | 2 | 5 | 1 | 1 myelocyte |
| November 8 | 9.2 | 2,900 | | | | | | | | 0.2% reticulocytes |
| November 14 | 11.5 | 3,600 | | | | | | | | |
| November 16 | | | | 11,050 | 29 | 63 | 3 | 2 | | |
| December 1 | 8.9 | | | | | | | | | |
| December 2 | 7.5 | | | | | | | | | |
| December 4 | | | | 10,800 | 25 | 68 | 5 | 2 | | |
| December 9 | 12.6 | 3,600 | | | | | | | | |
| December 23 | 15.9 | | 39 | | | | | | | |
| 1948 | | | | | | | | | | |
| February 3 | 12.0 | | 40 | | | | | | | |
| May 4 | 13.5 | | 44 | | | | | | | |

TABLE 4.—*Hematologic Data in Case (K. H.) Showing Temporary Depression of Erythropoiesis in the Course of Erythroblastosis Fetalis.*

| Bone marrow aspiration | Nov. 5, 1947 | Nov. 16, 1947 | Dec. 4, 1947 |
|---|---|---|---|
| Total nucleated cell count per c.mm. | 145,000 | 25,450 | 146,000 |
| Megakaryocytes per c.mm. | 11 | 11 | 22 |
| Myeloblasts | 2.5 | 2.0 | 0 |
| Myelocytes | 16.0 | 12.5 | 18.5 |
| Metamyelocytes | 6.5 | 4.5 | 2.0 |
| Polymorphonuclears non-segmented | 23.0 | 6.5 | 19.5 |
| segmented | 9.5 | 13.5 | 3.0 |
| Lymphocytes | 16.0 | 37.0 | 20.5 |
| Nucleated red cells | 7.0 | 0 | 30.0 |
| Hematogones | 19.5 | 24.0 | 6.5 |

Blood groups: Father, O Rh positive; Mother O Rh negative; Infant, O Rh positive

| Anti-Rh antibody titer (blocking) | Oct. 17, 1947 | Oct. 27, 1947 | Nov. 4, 1947 | Dec. 3, 1947 |
|---|---|---|---|---|
| Mother | 1:512 | | | |
| Infant | 1: 64 | 1:128 | 1:64 | 1:16 |

Treatment—9 transfusions—total 555 cc. blood from Oct. 16, 1947 to Dec. 9, 1947.

positive. The clinical course and hematologic features in the infant appeared to be similar to those of mild erythroblastosis fetalis, perhaps caused in this instance by isoimmunization of an Rh positive type O mother by an "A" offspring. Tests of the infant's saliva showed him to belong to the nonsecretor type.* The mother's anti-A serum titer on March 3, 1947 was 1:128,000† and on April 7 it had dropped to a level of 1:640 to 1:1280.* At no time was anti-A agglutinin detected in the infant's serum and his red cells gave a negative Coombs test. In cases of this sort, it is necessary to exclude the possibility that other rare factors may be responsible for the isoimmunization. However, antibodies in the mother's serum for the five Rh-Hr antigens in bloods of type $Rh_1Rh_2$ could not be demonstrated.* Consequently, the fact that the infant was of the nonsecretor type constitutes strong support for the role of isoimmunization by the factor A.

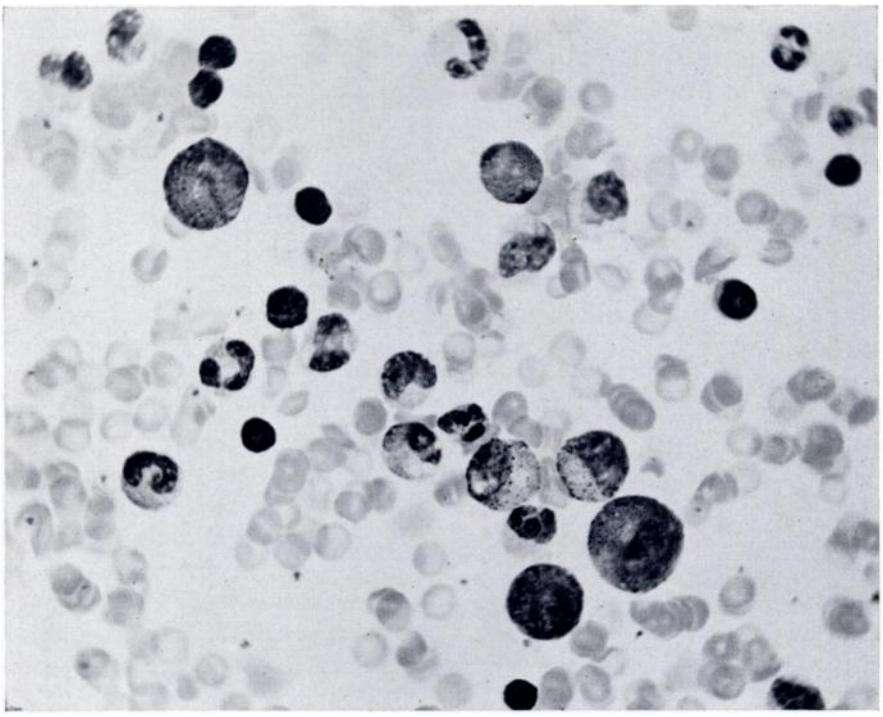

FIG. 1.—(Patient A. K.) Smear (×850) from sternal aspiration of November 18, 1947 (see table 1), showing polymorphonuclear leukocytes, myelocytes, metamyelocytes, lymphocytes and hematogones. Note absence of nucleated red blood cells.

*Course in Hospital:* Between March 8, 1947 and November 17, 1947, there were nine hospital admissions, in each instance for treatment of progressive anemia. Eighteen transfusions were given, at first employing O blood to which the Witebsky A and B substances were added, and later with compatible Type A Rh positive whole blood. From December 26, 1947 until the present, blood has been given at intervals of approximately 3 weeks in the Outpatient Transfusion Clinic at The New York Hospital. Growth and nutrition have been normal in every respect and susceptibility to infection has not been increased. There has been no enlargement of the liver, spleen or lymph nodes.

Tables 1 and 2 summarize the more significant blood, serologic and bone marrow studies. Early in the

* These tests were carried out by Dr. Philip Levine.

† Titration by Dr. Harry Wallerstein.

course the peripheral blood revealed evidences of macrocytosis and anisocytosis; later the red blood cells were normochromic and normocytic. The hematologic data confirmed the failure of erythropoiesis without involvement of the granulocytes and platelets or their bone marrow precursors.

## Discussion

From the age of 2 months, when thorough hematologic studies were initiated, until the present age of 17 months, examination of the peripheral blood and bone marrow have consistently shown that the defect in hematopoiesis was confined to a failure of red cell formation. This anemia, in which granulocyte and platelet formation are unaltered, may be rightfully termed "pure red cell anemia."

The only causative factor for the anemia that can be postulated in this case is the possibly injurious effect upon fetal erythropoiesis of the anti-A agglutinin elaborated by the mother in an incompatible pregnancy. The evidence for erythroblastosis fetalis in this infant is based on the history of jaundice and anemia noted in the first week of life. The relationship of erythroblastosis fetalis to sensitization by A and B agglutinogens in Rh positive mothers has been demonstrated by many observers[11–18] and its occurrence in this type of immunization in the firstborn has been pointed out by Wiener.[17]

While the blood disorder at the onset of this patient's illness can probably be safely classified as erythroblastosis fetalis, the relationship of the anti-A agglutinin to depression of the erythropoietic centers and continuance of the anemia require further elucidation. In 2 cases observed by Wiener,[19] sensitization by the A-B agglutinogens was associated with an aregenerative anemia. Recent studies[20] which relate structural defects at birth to disturbances in the fetus may possibly be extended to include fetal anomalies of blood formation originating during critical periods of hematopoietic function. It is conceivable that erythropoiesis in the fetus may be impaired by prolonged reaction with an antibody in high titer against its own red cells in the course of an incompatible pregnancy. Levine[21, 22] pointed out that the A and B blood agglutinable factors can be demonstrated in the fetus between the second and third month and suggested the possibility of early isoimmunization in the first months of fetal development. It is possible, therefore, that prolonged exposure of the red blood cells and their precursors during a vulnerable period of fetal life by the anti-A agglutinin may be responsible not only for the anemia at birth but for its persistence in the neonatal period.

In the group of hemolytic anemias which includes erythroblastosis fetalis, examination almost uniformly reveals hyperplasia of the bone marrow. Potter[23] has pointed out, however, that in some instances the bone marrow in erythroblastosis is either normal or hypoplastic, and that the latter state may account for the progression of the anemia. Diamond[24] states that bone marrow hypoplasia constitutes almost a uniform complication of any severe hemolytic anemia in the newborn. After the second or third week of life the infant, even after receiving multiple transfusions, often develops a relatively aplastic stage. It should be pointed out that Shapiro and Bassen[25] have shown that in full-term infants a marked drop occurs normally in the erythroid elements of the bone marrow at the end of the first week of life. It would be expected, however, that except for unusual circum-

stances, the increased hemolysis characteristic of erythroblastosis should result in a hyperplasia of nucleated red cells even at one week of age. In a series of fatal cases of erythroblastosis occurring at The New York Hospital, the bone marrow was recorded as showing hyperplasia in each instance.

To test further the hypothesis that erythropoiesis may become depressed in the course of erythroblastosis fetalis, bone marrow aspiration was carried out in several instances of this disease during the period of protracted anemia. Individual examinations have shown a decreased percentage of nucleated red cells in several cases, regardless of whether treatment consisted of subtotal blood replacement or multiple transfusion. In one case in which successive bone marrow aspirations were obtained (K. H., table 3), the mother was Rh negative and the infant Rh positive. This patient was also firstborn and this circumstance could be explained by a series of transfusions received by the mother before the birth of the child. Tables 3 and 4 demonstrate the temporary depression of erythropoiesis during the progress of the anemia in which nine transfusions of blood were required to maintain normal blood levels before recovery set in.

It appears, therefore, that the temporary failure of erythropoiesis occurring in erythroblastosis may conceivably be related to the exhausting effects of persistent hemolysis in this disease, or from the suppression of the erythropoietic centers in the bone marrow or in other fetal organs of blood formation by anti-A, anti-B, or anti-Rh agglutinins in susceptible individuals. It is possible that in the case of chronic congenital aregenerative anemia described in this paper the depression of erythropoiesis may have persisted from fetal life or from the period immediately following the newborn period as illustrated in the case of K. H. It should be pointed out that the high anti-A agglutinin titer detected in the maternal serum nine weeks after the birth of the infant may be an exaggeration of the actual agglutinin titer that was operative during fetal life. Boorman, Dodd, and Mollison[26] have shown the peak immune anti-A isoagglutinin titer produced in the maternal serum in response to stimulation by a group A or AB foetus, was not attained in the majority of cases until ten to twenty days after delivery.

The hypothesis that a prolonged depression in red blood cell production may result from an antibody specifically directed against the red cells in fetal life or during the early neonatal period and of a sufficient intensity to produce a chronic anemia extending into later infancy and childhood requires more extensive support. It should be emphasized that the concept offered to explain the mechanism of the anemia in this case is not expected to provide a uniform explanation for the pathogenesis of all cases of this entity. Although the circumstances noted in this patient may be unique, they afford a basis for further investigation of the causation of this unusual blood dyscrasia.

## Summary

Chronic congenital aregenerative anemia describes a "pure red-cell" anemia in which the failure of hematopoiesis is restricted entirely to the erythrocytes without simultaneous impairment of leukocyte or platelet production. The separation of this entity from the category of the increasing number of cases designated as

hypoplastic anemia will facilitate a more direct examination of the factors involved in its pathogenesis.

In the case described in this paper illustrating this condition, the onset of the anemia dated to the newborn period with the clinical and hematologic features of a mild type of erythroblastosis fetalis. The mother's blood group was O, Rh positive and that of the infant and father A, Rh positive. The anti-A serum titer in the mother reached a maximum of 1:128,000. The infant was shown to be a nonsecretor. The patient, now 17 months of age, requires repeated transfusions to maintain normal blood levels. The bone marrow reveals a persistent depression of erythropoiesis but the platelet and granulocyte levels are entirely unaffected.

It is postulated that prolonged depression in red blood cell production may result from an antibody directed solely against the red cells in fetal life or from the early neonatal period. This concept finds substantiation in other cases of erythroblastosis in which temporary failure of erythropoiesis as confirmed by bone marrow studies is reflected in a state of protracted anemia.

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