1968

Pure red cell anemia

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PURE RED CELL ANEMIA

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A THESIS

Presented to the Faculty of

The College of Medicine in the University of Nebraska

In Partial Fulfillment of Requirements

For the Degree of Doctor of Medicine

Under the Supervision of Peyton T. Pratt, M.D.

Omaha, Nebraska

February 1, 1968

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I. INTRODUCTION

Pure red cell anemia is a disease about which signs and symptoms are fluidly described, etiologies are hesitantly postulated, and therapies are abundantly attempted. Yet this disease, first described in 1922, remains an enigma with many etiologies applicable and with numerous treatment plans successful, but with consistency obviously lacking.

Dr. Joseph Kaznelson[1] in 1922 first described this disease entity in a brief treatise on the formation of platelets. At that time two theories were being disputed: Wright's theory that megakaryocytes were the stem cell present in the bone marrow and Schilling's theory that platelets were the end product of the extruded nuclei of the normoblasts. Kaznelson contended that contrary to Schilling's theory there were cases in which no erythroblasts were found during which time thrombocytes continued to circulate in the blood, so that these blood platelets could not possibly stem from the erythroblasts. He had acquired this opinion from a case of his own not previously reported that dealt with a case of pure aplastic anemia, in which only the erythroblast mechanism was affected, while the leukopoiesis appeared perfectly normal. This first reported case was of a 58-year-old man with the appropriate symptoms of a high-grade anemia who died in three weeks. The laboratory determinations on admission were: RBC, 552,000/mm^3;

Hgb (Sahli), 13 gm%; WBC, 4,980/mm^3 with a normal differential; and platelets, 207,000/mm^3. In the erythrocytic series absolutely no regenerative appearance was detected in that no polychromatic cells, no erythrocytes with stainable nuclei, and no normoblasts had been found. At autopsy only a small amount of red marrow with much fat present was found in the cylindrical bones, and only pale red marrow was found in the flat bones. The red part of the marrow of several different bones showed profuse cell content of leukocytes and megakaryocytes only, with very few red blood corpuscles. The anemia was then adequately explained by this isolated depletion of erythroblastic tissue. His argument was that there had been a normal number of platelets in the complete absence of erythroblasts which would be incompatible with the assumption that the erythroblasts are the mother cells of blood platelets.

From this first case of an aplastic anemia involving only the red cell series arose a "new" type of anemia about which authors in succeeding years have proposed many theories regarding types, etiologies, and treatments. Kaznelson's case was in a 58-year-old man; the second case, presented by Barr[2] in January 1927 to the meeting of the Society of the Art in Vienna, was in a 3-year-old girl; the third report was published in 1931 by Lupu and Nicolai[3] who stated that in their case the formed elements were present in normal numbers, except the red cell and its precursors. The first two cases of Kaznelson[1] and Barr[2] illustrate the two major divisions existing in this disease--childhood and acquired. The agreement

of the several authors regarding the signs and symptoms of this disease (as will be discussed in Section III) is the only constant finding in the literature in the presence of the conflict over nomenclature, the varying speculations as to etiologies, and the disappointment in therapies.

To sort out the cases which demonstrated pure red cell anemia, signs and symptoms, laboratory findings, and especially bone marrow examinations were relied upon heavily. This thesis then is an attempt to clarify the disease entity of pure red cell anemia in the areas of its differing types, its multiple etiologic possibilities, and its varying responses to therapies, as well as an attempt to place all of this information under a single name.

II. NOMENCLATURE OF THE DISEASE

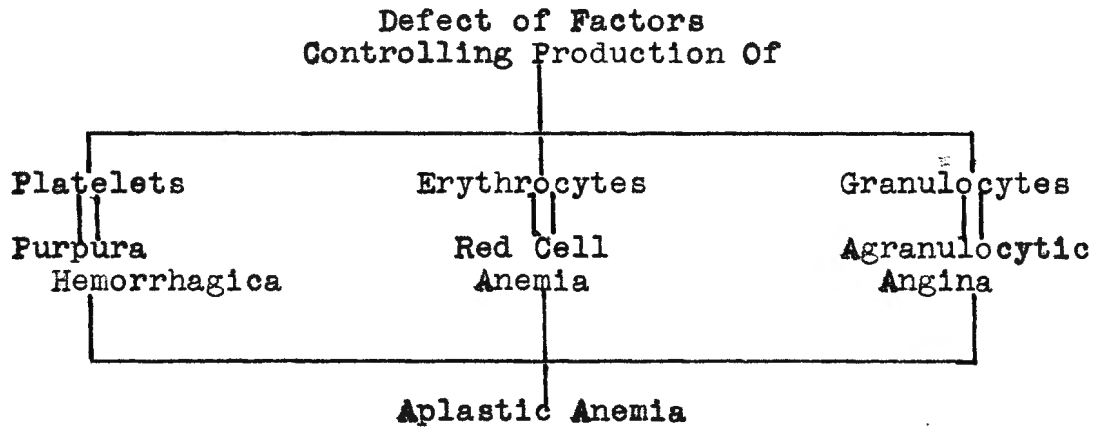
Kaznelson[1] in reporting the first case of this disease entity had offered no name; probably due to this lack in the first reported case and due to the limited communication among and isolated publication by separate authors, this disease entity has been described under a variety of names. In 1932 Lescher and Hubble[4] first proposed the term pure red cell anemia for this disease. These authors had been attempting to correlate blood diseases on the basis of cells depressed and had written the following:

> The fact that clear-cut individual types of deficient production of each of the blood elements occur, makes it likely that each element has its appropriate regulators, but the fact that intermediate cases occur, makes it equally certain that these regulating factors are not rigidly selective for any one cell.

They had listed the following:

Disease	Findings	Complications
aplastic anemia	all elements of bone marrow depressed	
agranulocytic angina	defective formation of granulocytes	infection
idiopathic purpura hemorrhagica	platelets depressed	hemorrhage
pure red-cell anemia	red cell series depressed	anemia

From the above initial observation, they proceeded through their discussion to arrive at this diagram in summary:



In 1937 Vogel, Erf, and Rosenthal[5] noted that the disease involving solely red cell production had been designated as chronic congenital aregenerative anemia. MacFarlane and Currie[6] in 1943 cited four cases in which they denoted that idiopathic aplastic anemia is generally applied where there is a progressive diminution in the formation of these erythrocytes, granulocytes, and thrombocytes, which develop in the bone marrow. They, however, argued that the term aplastic anemia should be reserved for failure of production of erythrocytes only and stated that one of their cases was the rare "true" aplastic anemia. Seven years later (1950) in his discussion of the disease, Cathie[7] stated that refractory anemia of infancy was clearly too non-specific, and the American workers had favored congenital hypoplastic anemia. However, from the results of bone marrow cultures Cathie had discovered that the developmental hold-up lay between the late normoblast and reticulocyte stages, and therefore he suggested that the condition be called erythrogenesis imperfecta. In 1953 in reporting a case of this disease, Kåss and Sundal[8] noted of the idiopathic forms that the anemia hypoplastica congenita belonged to the pathology

of infancy. Twelve years earlier in 1941 the American Kohlbry[9] had published an article dealing with pure red cell lack of production in the bone marrow and had called it congenital hypoplastic anemia--merely a reversed order of words. Tsai and Levin[10] called the name pure red cell anemia, first used by Lescher and Hubble[4] (1932), illustrious but ambiguous and noted that Donnelly[11] (1953) and Fountain and Dales[12] (1955) had used the term pure (or primary) red cell aplasia. Tsai and Levin then introduced another name, chronic erythrocytic hypoplasia. In 1959 Smith[13] noted that in restrictive terminology, pure red-cell anemia must be regarded as an aregenerative anemia with the depression confined exclusively to red cell production.

Diamond, Allen, and Magill[14] reported in 1961 on thirty children studied at Children's Hospital Medical Center in Boston. In this report they made reference to the several titles given to this disease in the fifty cases reported in the literature by 1954. The titles included: (1) aregenerative anemia, (2) erythrophthisis, (3) idiopathic hypoplastic anemia, (4) stationary hypoplastic anemia, (5) chronic erythroblastopenia, (6) erythrodisgenetic anemia, (7) chronic erythrocytic hypoplasia, (8) primary red cell aplasia, and (9) erythrogenesis imperfecta. They themselves used the term congenital (erythroid) hypoplastic anemia.

Pure red cell anemia would seem to be a term which adequately can be applied to this disease. According to Whitby and Britton[15], pure red cell anemia represents a true aplasia

of erythroblastic tissue only with production of no red cell precursors and in which the leukoblastic and megakaryocytic divisions are unaffected. The word "anemia" implies the signs and symptoms of the disease; the phrase "red cell" denotes the hematologic picture presented; and "pure" indicates that this is the only series affected and rules out many of the complications such as infection and hemorrhage that occur when other series are involved. This title also avoids the limitations and controversy imposed by including either "hypoplastic" or "aplastic." Since the disease may appear as a crisis or may run a chronic course, and since the etiologies are so obscure, this title does not mislead in any direction. Tsai and Levin[10] may have felt the term to be ambiguous; however, to this author the ambiguity is not misleading, and the illustrative description of the disease which it offers makes the title "pure red cell anemia" a clear-cut and excellent choice to apply to this disease entity.

III. THE DISEASE IN CHILDREN AND IN ADULTS

An aplasia of the erythroblastic tissue only was referred to as a medical curiosity.by Robson and Sweeney[16]. They went on to note that the aplasia may be complete with no formation of normal red-cell precursors or partial which should then be termed hypoplastic. This disease can occur in infants, children, and adults, and may be acute or chronic, presumably depending upon the degree of aplasia of the red-cell elements in the bone marrow. Congenital hypoplastic anemia is a form of chronic marrow hypoplasia manifesting itself soon after birth and involving only the erythropoietic series. Such cases are therefore related to the adult type of pure red cell anemia, at least from the hematological aspect.

Descriptions of cases are fairly well split between the children (reported in pediatric journals usually) and the adults (reported in the other medical journals). The signs and symptoms of the disease in these two different groups of victims are very similar. In both groups the onset is insidious; the symptoms are those of dyspnea, pallor, weakness, fatigue, or failure to thrive; and the laboratory findings are similar to those of this 22-year-old woman reported by MacFarlane and Currie[6]: hemoglobin of $< 20\%$; red cell count of $950{,}000/mm^3$ with no reticulocytes or nucleated red cells; white cell count of $8{,}000/mm^3$ with a normal differential count; and thrombocytes

of 280,000/mm^3. Bone marrow examination showed aplasia of the erythrocytic series with few macro-normoblasts. This patient subsequently died of a fatal pyrexia resultant from her second transfusion. The authors noted that this case exhibited features which can be explained by assuming failure of the nucleated red cells to reproduce their own kind and to mature normally. They also noted that the treatment and progress are summed up in the ability of the patient to continue transfusions about once a fortnight. The prognosis cannot be determined; everyone involved must only hope for spontaneous cure[17].

The largest variance of opinion is found in etiologies proposed which would classify the types. Many authors feel that the disease in children is congenital, although a few cases related to antibody formation have been reported. The disease in adults, however, is usually related by the author to allergic or toxic etiology, presence of a thymoma, vitamin or mineral deficiency, hormone effects, and similar proposals. Although a basis for dividing the disease may be according to congenital or acquired etiology, cases have been found in children with acquired causes like those usually attributed to adults and a few cases thought to be congenital have lived to adulthood before being discovered. An example of this latter exception is the case reported by Koszewski and Hubbard[18] of a 26-year-old white man with hereditary ectodermal dysplasia, poorly developed and poorly nourished, presenting with hemoglobin of 6 gm%, red cell count of 2.2 mill/mm^3, hematocrit of 20%, reticulocyte count of 0.5%, white cell count of 3,500/mm^3, and platelets of 180,000/mm^3.

This patient's leukocyte count was capable of response as white cell counts of 10,500/mm^3 and 12,000/mm^3 were recorded in the ensuing year. The normal platelet count and ability of granulocytic response would tend to cast doubt on the presence of a pancytopenic aplastic anemia, but the authors felt this to be a variant of Ehrlich-Fanconi's syndrome. Yet in spite of this assumption that the etiologies do cross age divisions, the relationship between congenital hypoplastic anemia of infancy and pure red cell anemia in the adult may well be no more than a superficial hematologic resemblance[15].

Cases of aplastic anemia limited to the erythrocytes with normal leukocytic and thrombocytic factors are extremely rare, as noted in 1938[19]. Nevertheless, by 1963 115 cases had found their way into the literature since 1922 (sixty in children, fifty-five in adults) in support of etiologies, treatments, or observations of the disease. The disease was divided by Whitby and Britton[15] into two types: congenital hypoplastic anemia of infants and chronic refractory anemia in adults. Wintrobe[20] also contrasted congenital hypoplastic anemia (in infants) with acquired erythrocytic hypoplasia (in adults). Both authors separate the disease in infants from Fanconi's syndrome which is a pancytopenia associated with multiple congenital defects and also separate the acquired disease in adults from aplastic anemia as first described by Ehrlich in 1888. However, Leavell and Thorup[21] list these pure red cell anemias of infancy and adulthood as variants of the more common aplastic anemias of Fanconi's and Ehrlich's descriptions.

To this author the disease entity of pure red cell anemia is distinct from aplastic anemia because of the basic difference in blood cell series affected. And on this basis rests this endeavor to describe pure red cell anemia as a separate entity. Within this disease entity then exist the two types--the congenital anemia of children and the acquired anemia of adults--with noted exceptions that must be taken into consideration.

In 1936 Josephs[22] published a very comprehensive review of "Anemia of Infancy and Early Childhood" in which he cited two cases of children with refractory aplastic anemia confined to a failure of erythropoiesis. Of these he stated:

> There are a number of cases of chronic "hypoplastic" anemia of obscure origin occurring usually in older children, which begin gradually and progress slowly, with exacerbations and remissions, usually to a fatal termination in the course of months or years.

He felt that transfusions might bring about a remission and occasionally repeated transfusions have caused an apparent cure; however, the chronicity of the condition requires that recovery be viewed with skepticism.

In 1938 Diamond and Blackfan[23] described a slowly progressive anemia beginning early in infancy as seen in their patient, a ten-week-old infant, who presented with pallor. The patient's hemoglobin was 1.5 gm%, reticulocytes were $<0.5\%$, white cell count was 5,000/mm^3, and platelets were 110,000/mm^3. At the time of their report this patient had been hospitalized 55 times and had received 113 transfusions for this chronic progressive anemia involving mostly the erythro-elements. They noted that in this case and in four other patients whom they had studied

both physical and mental growth had continued unabated, and the patients were indeed surprising in not being more susceptible to infection. Pearson and Cone[24] reported that the bone marrow is characterized by marked decrease of erythrocyte progenitors, and this is reflected by low or absent reticulocyte response despite the severity of the anemia. There may be a relatively normal number of early erythroid precursors with a distinct failure of maturation beyond the stage of the basophilic normoblast. On the basis of their information, then, Pearson and Cone felt that the onset of this condition early in infancy separates congenital hypoplastic anemia as a syndrome from other types of acquired pure erythrocytic anemia.

A variation of this anemia in both children and adults is the temporary aregenerative crisis as described by Moeschlin and Rohr[25] in a 23-year-old woman with complete reticulocytopenia. Eisemann and Dameshek[26] ascribe this severe anemia to marked exaggeration of the usual hemolytic mechanism and arrested maturation of red cells in the marrow induced by a humoral hypersplenic inhibitory effect. They noted that complete reticulocytopenia in association with complete lack of erythropoiesis in the marrow is thus unique in acquired autoimmune anemia. Supporting this occurrence of hematologic aregenerative crises is Gasser's[27] description of ten cases aged 1½ to 12½ years seen during 1948 who were hospitalized with very different illnesses. During their main illness, the erythroblasts suddenly disappeared from the bone marrow without affecting leukopoiesis or thrombocyte production. The peripheral blood showed complete disappearance

of reticulocytes. However, four to eight days after the crisis, reticulocytes appeared in the bone marrow, and erythroblasts appeared about two weeks later. Different etiologic mechanisms such as toxin, drug, and infection were postulated, and several patients indeed had allergic diseases plus a family history of allergy. Thus, these crises appeared both in the 58-year-old adult cited by Eisemann and Dameshek[26] and in the ten children cited by Gasser[27] and would appear to be acquired disease.

Pure red-cell anemia occurs as an acquired erythrocytic hypoplasia in adults without a proven common etiology. Infection, allergy, red-cell autoantibodies in hemolytic anemia, and chemical exposure have been incriminated, according to Smith[13]. The following case reported by Kark[28] in 1937 illustrates the acquired disease in adults: a 21-year-old woman who had been receiving transfusions presented in January 1936 with hemoglobin of 68%, red cell count of 3.4 mill/mm^3, white cell count of 9,500/mm^3, and plentiful platelets. Sternal puncture at that time revealed an almost complete absence of erythroblasts and was described as a gross aplasia of the red forming marrow but not of the white. Kark then went on to postulate:

> It would seem that the failure of erythropoiesis is due to some missing factor necessary for the production of the most primitive red cells rather than an atrophy of this tissue through some selective agent within the body.

The preceding discussion of types of pure red cell anemia has included accounts of the disease and the proposal that the disease in children is <u>usually</u> congenital and in adults is <u>usually</u> acquired. However, no real evidence is available yet to definitely distinguish the disease in children from adults except by age.

IV. SIGNS AND SYMPTOMS OF THE DISEASE

The disease has an insidious onset with progressive pallor, anemia, irritability, listlessness, and anorexia, which are usually apparent at the age of two to three months or later in the first year. Except for pallor, there is little to be observed on physical examination. Liver, spleen, and lymph nodes are not enlarged; there is no jaundice, and no bleeding is manifest. There is noted a striking absence of nucleated precursors of the red cells from the bone marrow, which frequently contains varying numbers of primitive cells, which possibly represent progenitors of the erythrocytic series. This description of pure red cell anemia in children is by Smith[13]. Blackfan and Diamond[29] had noted five cases of chronic hypoplastic anemia arising in infancy and presumably congenital in origin. Of these they noted that each had a severe normocytic, normochromic anemia which developed in the first three months of life without hepatosplenomegaly. No familial incidence was recognized, and the disease interfered very little with growth and development. The marrow showed aplasia of the red cell elements only with the only effective treatment that of blood transfusions at intervals of six to eight weeks. Of these 5 cases two recovered spontaneously after receiving a number of transfusions, one died of pneumococcal septicemia (and at autopsy showed only signs of hemosiderosis), and two needed regular transfusions at publication.

In a report on twenty-five patients seen at Children's Hospital Medical Center in Boston, Diamond, Allen, and Magill[14] noted the following in the children:

a) normocytic, normochromic anemia developing in early childhood

b) deficiency of red cell precursors in the bone marrow

c) absence of significant lowering of leukocytes or platelets.

The following data were recorded:

Hgb of 1.7-9.4 gm%	Red Cell Survival of 110-130 days
WBC of 4,400-18,600/mm^3	Bone Marrow Erythroids of 0-13% (mean of 4.3%)
Platelets of >100,000/mm^3	
Reticulocytes of <1%	

In their study of 28 families, two families had two affected children in this group of thirty Caucasians--17 girls, 13 boys--and three families had another child dead of anemia. Of these the significant feature had been pallor first noted from birth to age four years. The median age of the first transfusion was three months. It was further noted that either the continuing hemosiderin deposition or subclinical serum hepatitis produced severe liver damage, which ultimately resulted in severe growth retardation, failure of sexual maturation, osteoporosis leading to vertebral collapse, portal hypertension, and secondary hypersplenism, and finally death from liver failure ten to twenty years after the onset.

The distinctive hematologic features of acquired pure red cell anemia have been succinctly stated by Seaman and Koler[30] as follows:

1. A chronic, profound, normocytic, normochromic or macrocytic, normochromic anemia with decreased or absent reticulocytes.
2. A cellular marrow exhibiting normally active leukocytic and thrombocytic series, but marked hypoplasia to virtual absence of nucleated cells of the erythrocytic series.
3. Normal differential and usually normal total leukocyte counts, although leukopenia and leukocytosis may occur.
4. Normal thrombocyte count and absence of hemorrhagic phenomena.
5. No extra-medullary hematopoiesis.
6. In the absence of spontaneous recovery following early diagnosis and prompt discontinuance of a marrow depressant, all but one of the previously reported patients have not responded to any therapy and have required repeated blood transfusions.

Except for no proven common etiology, all are sufficiently similar to constitute a clinical entity, according to Seaman and Koler[30]. Thus, the disease, pure red cell anemia, presents with the same signs--as listed above--and symptoms--dyspnea, listlessness, fatigue, failure to thrive--in both children and adults. But because of the absence of a common etiology, they are regarded as separate and distinct entities within a disease bearing only the same hematologic findings.

V. ETIOLOGIES OF THE DISEASE

A. IN CHILDREN

> The most vulnerable period for damage to erythropoiesis is from the sixth to the twelfth week of fetal life, at which time the liver, spleen, and bone marrow are simultaneously involved in the proliferation of erythroblasts. Presumably, a noxious agent acting at this critical period selectively injures the red blood cell precursor.

Smith[13] had thus noted a period of time when indeed erythropoiesis could be damaged and lead to a congenital defect. Smith[31] had previously (1953) postulated that pure red-cell anemia and related hypoplastic anemias represent examples of congenital hematopoietic anomalies comparable to other somatic malformations originating from disturbances in embryonic and fetal life. Diamond and Blackfan[23] in 1938 proposed two theories: (1) congenital insufficiency of red marrow tissue and inability on the part of the hemopoietic system to respond, and (2) an inborn error in the metabolism of some blood-building substance which may have produced a deficiency state. Cathie[7] in 1950 had noted:

> Two points are in favour of there being a maturation factor deficiency. First, these children are born normal, as far as we know. This suggests that a factor might have been acquired from the maternal serum during gestation and that its supply fails following parturition. Secondly, in none of our cases has there been a complete lack of reticulocytes. At no time have there been enough to indicate participation in blood regeneration. But the fact that some, at least, of the normoblasts achieve the reticulocyte state may indicate

> that a factor is present in sufficient amount to permit slight maturation, but insufficient to produce a physiological replacement of obsolete blood corpuscles.

In 1961 Diamond, Allen, and Magill[14] stated that the arrest of maturation apparently involved steps necessary for differentiation from stem cells. They then postulated that the elevated erythropoietin levels in their patient suggested that the defect in this disease is at the end-organ (bone marrow?) level rather than being due to failure of a control mechanism. In contrast to this end organ failure, Gurney et al.[32] had previously reported that their studies of the hormonal regulation of erythropoiesis led to considering the possibility of a deficiency of an essential plasma factor. To test this theory they obtained "anemic" plasma from donors who had been bled to 25% of their packed cell volumes and then gave this "anemic" plasma in daily infusions of 300 ml to two patients. In the first patient, who responded with a transient rise in hemoglobin as well as a reticulocytosis, the marrow showed increased numbers of proerythroblasts and all stages of normoblasts. In the second patient, no rise in hemoglobin accompanied the reticulocytosis, and marrow changes were less striking although early normoblasts were increased. They therefore concluded that in this disease some factor present in "anemic" plasma is capable of stimulating erythropoiesis. This suggests congenital hypoplastic anemia is the result of a congenitally-determined deficiency of some essential plasma factor.

Kåss and Sundal[8] had noted in 1953 that these anemias due to deficient functioning of the bone marrow are usually of

the secondary type and are provoked by a suppression of the normal bone marrow by inactive, pathological tissue or by an actinic, infectious, toxic, or allergic injury of the marrow. Less frequent is failure due to exhaustion of the bone marrow. They also postulated the presence of a splenogenic inhibitive mechanism. In line with this possibility of suppression by allergic injury is the reference by Osgood[33] that persons respond differently to drugs and may have an idiosyncrasy to a particular drug. This allergic manifestation might in turn suppress mitosis, since the initial occurrence in hypoplasia was noted to be prolongation of the intermitotic interval or complete cessation of cell division in the marrow. Gasser[27] also had noted in his report of ten cases with aregenerative crises in erythropoiesis that the patients frequently had allergic diseases themselves and/or had a positive family history for allergy.

Cathie[7] in his report in 1950 had noted in his five cases that the facies appeared similar with snub noses, thick upper lips, and wide-set eyes. He felt that if this facial resemblance meant anything, it might be due to an endocrine cause or might be genetically determined, although the normal fetal develment and the complete absence of any family history would tend to dispute the latter. Yet Diamond, Allen, and Magill[14] felt that because of the observed familial incidence in five of their cases and the early onset in most of the others, this was probably a genetically determined condition possibly affecting an unknown enzyme system essential to normal erythropoiesis.

However, Cathie[7] had raised the possibility of an endocrine cause. Chalmers[34] considered an endocrine cause of the anemia as a possibility and mentioned the polycythemia seen in some cases of Cushing's syndrome, which might be regarded as the extreme opposite. Pearson and Cone[24], in reporting a case of a seven-week-old infant with pure red cell anemia (Hgb, 2.2 gm%; reticulocytes, 0-1.2%) who had had a reticulocytosis in response to cortisone therapy, wondered whether cortisone exerted a direct stimulating effect on the marrow or whether it counteracted some inhibitor of erythrocyte maturation. Allen and Diamond[35] in their study of thirty children reported that 12 of 22 patients who were given therapeutic trials with corticosteroids showed a sustained remission within two weeks of the onset of therapy, as manifested by a significant reticulocytosis, normalization of erythropoiesis in the bone marrow, and a subsequent elevation of hemoglobin, hematocrit, and erythrocyte counts to normal levels. They noted that cortisone had been shown to induce the activity of the enzyme tryptophane oxidase in rat liver and went on to speculate:

> If an enzyme activity can be induced or increased in the body by exogenous cortisone, it seems reasonable that it may later become responsive to endogenous levels. Modifying or maturing factors, such as with the enzyme glucuronyl transferase in the neonate liver, may play an important role in the persistence of remission off treatment or in spontaneous remission.

In keeping with this consideration of effects of steroids is the report of Foy, Kondi, and Macdougall[36] of pure red-cell aplasia or hypoplasia developing in nine of twenty-three patients with marasmus and kwashiorkor. These patients had gross malnutrition

and diarrhea and developed the anemia during therapy. They postulated that this red-cell aplasia might be another manifestation of the "recovery syndrome" in malnutrition. Noting that serum riboflavin is low in kwashiorkor, the patients were given their first dose of riboflavin at a time when red-cell precursors in the bone marrow were <5%; one week later the red-cell precursors numbered 25-78%. They concluded from their observations:

> Whatever factors are involved in the high incidence of pure red-cell aplasia in marasmus and kwashiorkor, it seems that riboflavin is playing an important part in haemopoiesis and is one of the substances that take part in some enzyme system that potentiates the maturation of a primitive stem cell into erythroblasts acting either directly or through the steroid hormones.

To support the effect of riboflavin in these children, attention is drawn to the report that reticulocytopenias recently have been observed in experimental riboflavin deficiency in man[37].

Riboflavin is known to act in the metabolic pathway of the amino acid tryptophan. Altman and Miller[38] in 1953 reported a patient with this rare type of anemia who excreted a strongly bluish-fluorescent substance in the urine, identified as anthranilic acid by chromatographic methods, isolation from the patient's urine, and by spectroscopic techniques. This urinary excretion increased when the patient was given a loading dose of L-tryptophan and decreased when given riboflavin; none of his family members excreted the substance. They also noted the finding of eight additional patients with red cell anemia who excreted anthranilic acid and reported that in urine samples collected at random on the pediatric ward, no case was found with anthranilic acid. From this they observed that these tryptophan-loading tests

had given rise to increased excretion of intermediary metabolites of tryptophan in about half of their cases. Altman and Miller then suggested that anthranilic acid was most likely to accumulate in excessive amounts under conditions of riboflavin deficiency and concluded that the findings they reported were suggestive of an inborn error in tryptophan metabolism.

In accord with these experiments, Pearson and Cone[24] four years later recorded the case of a seven-week-old infant with marked erythroid depression with an abnormality of tryptophan metabolism, as evidenced by the finding of anthranilic acid in the urine. The anthranilic aciduria persisted during cortisone therapy despite a beneficial effect on production of reticulocytes and hemoglobin. Concentration of tryptophan in the blood and urinary excretion of 5-hydroxyindole acetic acid (end product of serotonin, also involved in tryptophan metabolism) were normal.

Marver[39] in 1961 commented that vitamins B, B_2, B_6, and niacin are important in the proper functioning of the tryptophan-kynurenine-niacin pathway. He reported that among his thirty-nine subjects were an 11-year-old girl and an 8-year-old boy with confirmed diagnoses of pure red cell anemia. After loading doses of L-tryptophan (2 gm) both exhibited increased excretion of anthranilic acid, of kynurenine, and its conjugates. Marver then speculated:

> Because tryptophan is oxidized principally by way of the kynurenine pathway, an elevation of these metabolites probably represents a metabolic block or deficiency in this route, although no diminished or absent intermediate has yet been demonstrated. An interruption of another pathway with an increased load

> on the kynurenine route or a diminished tubular reabsorption of these metabolites are two possibilities which cannot be excluded.

He went on to raise the questions of a primary abnormality of pyridoxine function, vitamin B6 dysfunction secondary to polyvalent cation imbalance, abnormal riboflavin metabolism. This question of a vitamin dysfunction rather than deficiency would certainly be reinforced by Pearson and Cone's[24] observation of the known refractoriness of congenital pure red cell anemia to therapy with B-vitamins, at least in the usual therapeutic dosage, and the fact that these children, except for the anemia, are healthy and show none of the stigmata of avitaminoses.

Another etiology proposed is illustrated by this case (and will be discussed more fully under the adult section): A three-month-old male infant was diagnosed as having pure red cell anemia. Through transfusions he was kept alive and underwent thymectomy at age ten months. His reticulocyte count then went from 0 to 7%, and by the thirteenth postoperative day, normoblasts were present in the bone marrow in appreciable numbers. However, the child then had a relapse and did not respond to further therapy. This report by Chalmers[40] raises the question of hormonal or lymphoid-cell influence on the bone marrow giving rise to pure red cell hypoplasia.

The suggestion in 1949 by Smith[41] that prolonged depression in erythrocyte production may result from an antibody directed solely against the red cells in fetal life or from the early neonatal period raises still another possible etiology. He had reported the case of a two-month-old white male infant

with hemoglobin of 29% and absence of nucleated erythrocytes in the bone marrow; the infant had been jaundiced in the first week of life. The baby's father had A+ blood type, and his mother had O+ blood and an anti-A titer of 1:128 at this time, two months postnatally. The infant was a non-secretor as determined from tests on saliva, and Smith felt this was strong support for the role of isoimmunization by factor A. He suggested as the etiology in an incompatible pregnancy the possibly injurious effect upon fetal erythropoiesis of the anti-A agglutinin elaborated by the mother. This particular patient at time of publication was seventeen months old and required regular blood transfusions.

Bonham-Carter, Cathie, and Gasser[42] five years later reported the case of a five-year-old girl with red cell anemia who had positive direct and indirect Coombs tests, no reticulocytes, and only 1.5% erythroblasts. Cortisone therapy helped for a year; then because of exacerbation her spleen was removed, and she was given more cortisone. Her blood picture improved dramatically, and the Coombs tests both became negative announcing the disappearance of the autoantibodies. The authors felt that their case showed the dependence of the loss of erythrocyte beginnings on the existence of serologic comprehensible erythrocyte antibodies. And they further felt that so-called bone marrow exhaustion failed to dispute their etiology.

Gasser[43] cited the case of a seven-week-old girl with hemoglobin of 30% and no reticulocytes in the peripheral blood who had had an exchange transfusion with Rh-hegative blood one

week before. She had a negative direct Coombs test but a positive indirect Coombs test secondary to a very high titer of incomplete Rh-antibodies in the serum. In this patient the author proposed a disappearance of reticulocytes in the peripheral blood due to activity of incomplete Rh-antibodies. He also recorded the case of a 4½-year-old boy with hemoglobin of 17%, no reticulocytes, and only 1% erythroblasts found in the bone marrow. After splenectomy and cortisone therapy of nineteen days, the bone marrow had 68% erythroblasts and the peripheral smear showed 75% reticulocytes. From these cases Gasser postulated that antibodies work not only on erythrocytes and reticulocytes, but also on the erythroblasts in the marrow.

Thus we have advanced causative factors which include chemical and physical agents, infection, exhaustion of the bone marrow, and specific blood dyscrasias and malignant tumors with bone marrow replacement, but Smith[41] went on to postulate a congenitally inferior bone marrow for a group of idiopathic aplastic anemias, whose etiology is unknown. The following cases illustrate the disease and the etiological quandary: Donnelly[11] in 1953 reported the case of an eleven-week-old male infant with hemoglobin of 16%, white cell count of 5,850/mm^3, and bone marrow examination with red-cell precursors almost entirely absent and with no gross abnormality of white cells. In response to this report Kidd and Aldridge[44] wrote of a thirteen-week-old male infant with hemoglobin of 17%, white cell count of 4,000/mm^3, and bone marrow examination with red-cell precursors virtually absent. Both children at the time of

publications had been kept alive by transfusions every three to five weeks and were doing satisfactorily when hemoglobin was kept above 40%.

Among the etiologies for the disease in children, evidence has been presented for (1) deficiency of plasma factor, (2) end-organ failure, (3) enzyme involvement in the tryptophan-kynurenine-niacin metabolic pathway perhaps related to riboflavin deficiency or increased demand, (4) isoimmunization secondary to incompatible pregnancy, (5) suppression by pathological tissue or toxic or allergic manifestations, and (6) presence of a thymoma. Further postulations reviewed include (1) the presence of a noxious agent in fetal life, (2) congenital insufficiency of red marrow, (3) bone marrow exhaustion, (4) inborn error in metabolism of a blood-building substance, (5) endocrine abnormality, and (6) a maturation factor deficiency. Perhaps the etiology is an inborn error somewhere still undiscovered or a combination of several of the above causes or still another factor as yet unknown. Thus far evidence points to several etiologies applicable in varying numbers of cases.

V. ETIOLOGIES OF THE DISEASE

B. IN ADULTS

In 1957 Tsai and Levin[10] published a report on pure red cell anemia in adults including a case of their own and a comprehensive review of the twenty-six cases (ages 20 to 67) then in the literature. In this they noted that the clinical manifestations of chronic erythrocytic hypoplasia in adults differ little from those in children, but the etiologic factors involved seem to be even more variable in adults. Under the question of etiology they noted that it had been suggested that the disease may begin as an initial total depression of the marrow from which there is recovery of the other series, but irreversible damage of the erythrocytic series. They noted the apparent toxic effect of sulfathiazole in three cases and benzol in one and noted that allergy associated with infection and toxin has been suggested to be the cause; however, there has been no laboratory proof of an immune body reaction. They wondered if the coexistence of benign thymoma and pure red cell anemia might <u>not</u> be a chance occurrence, as it was present in seven of the twenty-six. Tsai and Levin further speculated on a congenital etiology and the effect of administration of riboflavin on the excretion of anthranilic acid.

In the above section on etiologies in children the findings of Marver[39] have been quoted in regard to possible difficulties in the tryptophan metabolic pathway. Marver had gone on to note that in one of the three adults with acquired hypoplastic anemia whom he had studied, he had found an abnormality resembling that of the children with erythrogenesis imperfecta and had wondered if this was a similar defect in tryptophan metabolism. Foy and Kondi[45] in 1953 reported the case of a 46-year-old African man who on admission had hemoglobin of 2.3 gm%, no reticulocytes, white cell count of 5,650/mm^3, and marrow puncture with a total absence of all red-cell precursors. Treatment with riboflavin 4 mg every day led to the appearance of reticulocytes six days after beginning therapy; the reticulocyte count reached 27% six days later, the same day that a bone marrow examination showed increased red-cell precursor activity. They noted that the feeding of various animals on synthetic diets lacking certain specific factors had shown that such substances as riboflavin, nicotinic acid, pyridoxine, and folic acid are essential for normal hemopoiesis. In these dogs, pigs, and monkeys riboflavin appeared to control the diameter of new red cells. Attention must here also be called to the abstract published in 1960 by Montague, Mengel, and Doherty[37] in which was noted that reticulocytopenias have been observed in experimental riboflavin deficiency in man. Foy and Kondi went on to note:

> Riboflavin may have acted as part of an enzyme system concerned with red-cell production. It appears from this case that riboflavin acted on the primitive reticulum cells, stimulating the development of red-cell precursors which, once formed, matured normally without the addition of other hemopoietic substances.

Kaznelson, Reimann, and Weiner[46] in 1929 reported two cases which they called achlorhydric anemia in which iron extract led to improvement. They reported that in spite of the striking parallels of this disease entity with that of pernicious anemia, it behaved as an entirely different sickness. Sternal puncture had found an excessive disappearance of the erythroblasts. Dameshek[47] in 1931 reported an erythronormoblastic anemia subject to spontaneous remissions and relapses and associated with such symptoms as sore tongue and usually achlorhydria. Their case too showed a prompt and dramatic response to large doses of iron. The etiology proposed by the former authors was that achlorhydria and perhaps the alimentary canal or a chronic intoxication of the bowel led to this disease. These anemias had responded to iron therapy, so iron deficiency must be a consideration. Both had noted an excessive disappearance of the erythroblasts in the presence of an abundant bone marrow and supposed a disturbance in maturation which the iron in some way improved.

Osgood[33] noted that the decrease in reticulocytes and in nucleated erythrocytes (life span of 36 to 48 hours each) occurs soon after the prolongation of the intermitotic interval or complete cessation of cell division in the marrow in pure red cell anemia. He postulated drug idiosyncrasy as an etiology here; however, he felt that some risk of drug-induced hypoplasia is unavoidable. Seaman and Koler[30] substantiated a toxic effect in their reports of (1) a 62-year-old man treated for pneumonia four times with sulfonamide and four years later presented with

hemoglobin of 4.8 gm% and reticulocytes of 1.8%, and of (2) a 40-year-old woman who had used drycleaning fluid two months before, developed blisters on her hands, and then presented with hemoglobin of 2.6 gm% and no reticulocytes. Both cases had iliac bone marrow examinations which showed a complete absence of nucleated cells of the erythroid series. Seaman and Koler postulated that perhaps only the erythrocytic series had been irreversibly damaged or a second possibility might be the specific injury of erythropoietic tissue without damage to the leukocytic and thrombocytic series.

In Seaman and Koler's[30] case of the 40-year-old woman reported above, nucleated cells of the erythrocytic series were seen in the peripheral blood on the 64th day of therapy with cobaltous chloride 100 mg orally every day. Voyce[48] in 1963 recorded the case of a 47-year-old man with marrow erythroid hypoplasia. Five years after the discovery of this man's disease, cobaltous chloride therapy was instituted for the third time; reticulocyte response reached 12% on the 22nd day of therapy, and bone marrow examination on the 14th day showed active normoblastic erythropoiesis. Voyce then speculated that the function of cobalt in the body is obscure, although in its ionic form it may accelerate enzyme reactions and incorporated in the cyanocobalamine molecule, it had an important part to play in erythropoiesis.

Eisemann and Dameshek[26] reported the case of a 58-year-old woman in whom existed simultaneously red-cell aplasia of the bone marrow and an autoimmune hemolytic mechanism. One year

after discovery of her disease, and after the failure of improvement with ACTH and cortisone therapy, splenectomy was performed. On the eighteenth postoperative day, the first reticulocytes appeared in the blood simultaneously with the appearance of a large number of erythroblasts in the bone marrow; she went on to make an uneventful recovery. Perhaps this might have been a hypersplenic mechanism secondary to repeated transfusions; however, the authors speculated:

> The recovery of complete bone marrow erythropoiesis that followed splenectomy...strongly suggests the presence in the spleen of a factor that acted on the red-cell precursors, resulting in a complete inhibition of their maturation. It is also possible that the specific aregenerative state of the nucleated red cells in the marrow was the result of a direct action of the incomplete erythrocyte antibodies on the red-cell precursors, with complete inhibition of erythropoiesis.

The relationship of benign thymoma and suppression of erythrogenesis is not a chance one. So commented Bayrd and Bernatz[49] in 1957 when they published the report of two cases in which these two uncommon entities were combined. Soutter and Emerson[50] in 1960 published the case of a 57-year-old man in whom thymectomy was performed electively in an unsuccessful attempt for remission of his pure red cell aplasia; they too felt that this association of the two diseases implied more than coincidence. In reporting the case of a 44-year-old woman with a substernal tumor known for three years prior to the development of severe anemia and the case of a 45-year-old woman with severe anemia and a mediastinal tumor, Ross and associates[51] noted that no improvement in the hematologic picture resulted from removal of the tumor. They suggested the following

considerations regarding the coexistence of benign thymoma and pure red cell anemia:

1) that they occurred simultaneously by chance alone,
2) that the thymomas caused the anemias,
3) that the anemias caused the thymomas, or
4) that some etiologic factor was common to both.

The first possibility was considered unlikely because this chance coexistence should be rare, and there were already seven known cases at that time; the third possibility was dismissed also because no neoplastic change was known to follow chronic tissue anoxia and besides, one of their cases had the thymoma first. The second and fourth considerations led them to believe that the evidence supporting etiologic relationship of the thymoma to the anemia is suggestive, but not definite.

The following two cases will serve to illustrate the features of these combined diseases. Freeman[52] in 1960 reported the case of a 74-year-old man with pallor who had hemoglobin of 6.1 gm%, white cell count of 6,000/mm^3, and reticulocytes of <1%; bone marrow examination showed a marked diminution or absence solely of red-cell precursors with <4% erythroid elements present. Roentgenograms showed an anterior mediastinal mass which when removed proved to be a spindle-celled thymoma. The patient showed no postoperative improvement and died on the eighteenth day. Barnes and O'Gorman[53] in 1962 reported the case of a 42-year-old woman with a lobulated mass in the anterior mediastinum on X-ray noted three months before her admission with hemoglobin of 28%, reticulocytes of 0.6%, white cell count of 6,500/mm^3; sternal marrow had shown no undisputed red cell

precursors. The patient died of bronchopneumonia five months later and at autopsy the mediastinal mass proved to be a lymphoepithelioma, poorly differentiated. It should also be noted that in the case of the 58-year-old man reported by Bayrd and Bernatz[49], the mass in the mediastinum had been known to be present for six years prior to his presentation with dyspnea secondary to a hymoglobin concentration of 4.3 gm%.

Chalmers[34] noted that thymomas and selective erythroblastic aplasia were most uncommon and suggested the existence of a correlation between thymic tumors, erythroblastic activity in the marrow, and the possible action of the spleen, pituitary, and adrenals. In reporting two patients with these two findings in 1954, Chalmers[54] had commented on the possibility of endocrine dysfunction or lymphoid proliferation in the thymus, marrow, and possibly other sites which may have impeded erythropoiesis. Jacobs et al.[55] in 1959 reviewed the then reported 26 cases of benign thymic tumor in association with selective erythroid aplasia of the bone marrow. Oneeof their own reported cases had had a mediastinal mass known for eighteen years prior to his admission in 1957 for pure red cell anemia; at autopsy the mass proved to be a thymoma which was benign, or at worst locally malignant. These authors noted that of the 46 cases of erythroid aplasia in the literature, the twenty-six with benign thymomas illustrated an incidence of thymoma in the patients with pure red cell anemia of 52%. They stated that in none of the patients was there evidence that the hematological abnormality could be attributed to bone marrow invasion by tumor cells;

however, no histologic criteria could be found that would consistently characterize thymoma with anerythroid anemia nor indicate an unique secretory activity. Havard and Scott[56] the next year added three more patients to the above numbers and went on to postulate:

> It is unlikely that the thymic tumour is the direct cause of the disorder which accompanies it, but the possibility exists that both are the result of some common agency. The association of thymic tumour or hyperplasia with myasthenia gravis, with erythroblastic aplasia, with Cushing's syndrome, and with acquired agammaglobulinemia is sufficiently well documented to suggest an aetiological relationship. The frequent occurrence of auto-antibodies in diseases associated with abnormal proliferation of lymphoid tissue raises the possibility that antibodies directed against the red-cell precursors may be derived from the thymic tumour.

Thus, many of the same hypotheses applied to the so-called "congenital" pure red cell anemia of children have been considered in the "acquired" pure red cell anemia of adults. Evidence for the possibility of a relationship with benign thymoma has been extensive, but no etiology has been proved. Again the possibility of an enzyme defect in tryptophan metabolism related perhaps to riboflavin is suggested. Drug idiosyncrasy and autoimmune antibodies have been the causes in cases presented here. Achlorhydria as in pernicious anemia but in a different disease has been proposed. Perhaps cobalt has a function which is unknown, but which might lead to anemia when deficient. Again the question of bone marrow exhaustion, endocrine etiology, and enzyme defect must be considered.

Evidence has been presented that suggests many etiologies but with few cases directly attributable to one similar cause, and there are still several cases without etiology applicable. Thus the question of etiology of this disease is unresolved.

VI. TREATMENT OF THE DISEASE

A. IN CHILDREN

In most cases the course of congenital pure red cell anemia is one of chronic and progressive anemia with a fatal outcome. According to Smith[13] in 1959:

> Death results from cardiac failure, from hepatitis during the course of transfusions and from overwhelming infection and sepsis. In these terminal events, the factor of hemosiderosis from excessive iron deposition resulting from transfusions and hemochromatosis may conceivably play an important complicating role. An important factor...is the possibility of spontaneous recovery.

Diamond[57] had earlier noted that spontaneous remissions occurred in three of twelve patients he had seen. This possibility of remission is no doubt the ceaseless push behind all of the forms of therapies tried and the continuing use of transfusions in an effort to keep the patient alive long enough to undergo a spontaneous cure.

Smith[31] had earlier noted that the possible suppressive effect of long-continued transfusions on erythropoiesis may obscure the capacity for inherent blood formation and interfere with the appraisal of a specific blood picture. Of major importance is to determine the actual need for transfusions in relation to the clinical signs and symptoms manifested by the patient, with promise of their relief by giving blood. However, Cathie[7] had observed in 1950 that the replenishment

of the peripheral red cells with donor cells as fresh as possible had been the only method of keeping these children alive. Diamond, Allen, and Magill[14] emphasized that abandoning transfusions could not be justified on any basis.

A list of therapies used in the study[14] at Children's Hospital Medical Center in Boston without effect follows:

Bone Marrow Powder p.o.	Folic Acid
Citrovorum Factor	Pentnucleotide
Cobalt	Testosterone
Copperin	Ventriculin
Crude Liver Extract	Vitamin B Complex
Ferrous Sulfate	Vitamin B_{12}

Eighteen of their thirty cases failed to respond at all and required transfusions every three to eight weeks. The results observed in the thirty children were:

10 received steroids without benefit
12 received steroids and obtained remission
6 had spontaneous remissions: 2 have died, 4 are living
2 died without remission, either spontaneous or induced.

Of the group, eight had subsequent splenectomies; of these the following results were demonstrated:

2 developed spontaneous remissions: 1 died nine years later of unrelated renal disease
2 died three months and four years later of septicemia and chicken pox, respectively
4 continued needing regular transfusions: 2 developed spontaneous remissions much later.

Nine of the eighteen (excluding those who obtained remissions with steroid therapy) are still living with four in remission. Complications arising in this group included hypersplenism, hemosiderosis and cirrhosis in 11 of 11 receiving transfusions over five years, growth and bone age retardation up to four years, marked osteoporosis seen after three to four years,

failure of secondary sex characteristics even after age fourteen years due to immature gonads in the presence of hemosiderosis. Severe infections occurred only in the splenectomized group.

Riboflavin was used by Foy, Kondi, and Macdougall[36] in nine children with marasmus and kwashiorkor who developed pure red cell anemic crises. These children responded to the riboflavin with a significant rise in bone marrow red-cell precursors. In a report from Gurney et al.[32] the infusion of "anemic" plasma, donated by persons bled to 25% of their hematocrits, into patients with pure red cell anemia brought about increased erythropoiesis as evidenced by the reticulocyte increase. And Osgood[33] in reporting erythroid hypoplasia resulting from drug idiosyncrasy stated:

> Recovery depends on prompt recognition of the hypoplasia, immediate discontinuance of the causal agent, precautions to prevent its ever being given again to the same person, and use of the known effective measures in controlling infection, bleeding, and anemia until spontaneous cell division begins again in the marrow.

Shahidi and Diamond[58] in 1961 commented that the administration of testosterone and corticosteroids to these patients often resulted in more rapid marrow regeneration and consequently in a higher and earlier reticulocyte peak. Käss and Sundal[8] reported the case of a three-month-old girl who had been treated with liver preparations and transfusions for over three years and then was given steroids. She responded to treatment with two courses of ACTH with a marked rise in the reticulocyte count and a spontaneous remission of the blood values, which would indicate that the ACTH medication either

directly or indirectly is acting on the inhibition at the normoblast-reticulocyte stage.

Burgert, Kennedy, and Pease[59] in 1954 made reference to a personal communication in which was noted by Diamond that five patients had been successfully treated with daily cortisone adminitration of varying amounts. Loeb, Moore, and Dubach[60] had reported two brothers who, at age 17 years, had successively developed severe anemia with selective erythroid hypoplasia; both responded to ACTH and cortisone with complete cure following splenectomy. In the same year (1953) Fisher and Allen[61] had recorded a case in which ACTH and cortisone produced and maintained hematologic remission. According to Arrowsmith, Burris, and Segaloff[62], it had been reported frequently that reticulocytosis follows cortisone administration. Pearson and Cone[24] noted that in normal persons evidence of increased proliferation of erythrocytes follows administration of corticosteroids or increased adrenal activity.

Allen and Diamond[35] reported in 1961 of thirty patients whom they had seen and treated at Children's Hospital Medical Center in Boston and of whom twenty-two had been given therapeutic trials with corticosteroids. Ten of these showed no response, but twelve of the 22 developed a steroid-induced remission. Of the twelve, three are now well without medication; seven are on intermittent steroid therapy, and two have died--one of pneumonia possibly attributable to the therapy and one of a preexisting degenerative central nervous system disease. However, the chief complication of long-term steroid

therapy had been growth retardation; also the patients developed early signs of a Cushingoid appearance during the "priming" stage, but this completely disappeared on maintenance doses. The doses used in the patients who responded varied from 5 mg to 50 mg of prednisone (or its equivalent) per day for the "priming" doses; subsequently, a sustained reticulocytosis was evident in four to eleven days with an average of eight days. The adequate maintenance dose was found to be 5.0 mg to 7.5 mg of prednisone per day orally to maintain the hemoglobin above 9 to 10 gm%. These authors emphasized:

> Corticosteroids have been shown to have an important role in the management of patients with this disease, and continue as the treatment of choice. We see no justification for watchful waiting once the diagnosis is established, since spontaneous remissions are not missed...and...there seems to be a significantly greater chance for a steroid-induced remission early in the course.

It is apparent that in treating children with pure red cell anemia the first and continuing line of treatment is transfusions. ACTH and/or cortisone should be tried in an attempt to produce improvement; hope should not be abandoned for these unresponsive patients, since steroid remissions after as many as ten years of transfusion therapy have been reported. The use of hematinics such as vitamins, iron, riboflavin, and cobalt may be used with occasional response; testosterone might be considered. Splenectomy may become indicated when transfusions are required at increasingly frequent intervals to maintain a physiologically sufficient, although reduced, hemoglobin level due to an extracorpuscular hemolytic component

which has presumably developed in the spleen. It would seem that spontaneous remission is the cure to be hoped for, but steroids have produced significant response and ought to be used early in treatment. Transfusions should never be abandoned short of remission, be it spontaneous or induced.

VI. TREATMENT OF THE DISEASE

B. IN ADULTS

Many approaches have been made in the treatment of this disease, and most have been discouraging to the physician and the patient. Seaman and Koler[30] presented the following list of unsuccessful therapies which they attempted:

Antihelminthics	Hydrochloric Acid
Arsenic	Pentnucleotide
Ascorbic Acid	Quinine
Bone Marrow Transfusions	Stomach Extracts
Copper Sulfate	Thyroid
Folic Acid	Ultraviolet Light
High Protein Diet	Vitamin B
	Vitamin B_{12}

Tsai and Levin[10] in 1957 published a comprehensive review of chronic erythrocytic hypoplasia in adults in which they noted that the disease in adults is much less likely to be fatal than the classic type of aplastic anemia. Of the twenty-six cases they reviewed including their own case of a 64-year-old man, they tabulated these results:

10 died:	5 of transfusion reactions
	4 of bronchopneumonia or sepsis
	1 of unknown cause
5 improved:	4 due to repeated transfusions
	1 due to ACTH after thymectomy and splenectomy
11 recovered:	2 had spontaneous remissions
	2 due to removal of benign thymoma
	2 due to splenectomy
	2 due to corticosteroids after splenectomy
	2 due to cobalt
	1 due to riboflavin.

However, it should be noted that the same measures and agents had been used in other patients of this series without such good results as follows:

--thymectomy was without value in 4
--splenectomy was without value in 5
--corticosteroid therapy after splenectomy was without value in 2
--cobalt was without value in 5
--riboflavin was without value in 1.

The problem that exists with each form of treatment, then, is not that it does not produce improvement, but that it does not work consistently. This suggests the possibility of several etiologies or of differing individual responses, perhaps according to heredity.

Loeb[63] in 1951 had presented a case that appeared to be acquired pure red cell anemia who had developed reticulocytosis and active marrow erythropoiesis with ACTH therapy. In a report including both congenital and acquired types of this anemia, Shahidi and Diamond[58] had noted that the administration of testosterone and corticosteroids often resulted in more rapid marrow regeneration. In light of the good results of Allen and Diamond[35] in treating children with corticosteroids, more attempts will surely be made in adults. Good results have occurred occasionally with ACTH and/or cortisone therapy following thymectomy and/or splenectomy, when these were indicated.

Splenectomy was performed in the case of a 58-year-old woman reported by Eisemann and Dameshek[26] with encouraging findings. She had been found to have a complete absence of reticulocytes in the blood and of nucleated red cells in the

bone marrow. Eleven months after diagnosis, splenectomy was performed; eighteen days later the first reticulocytes appeared. By the 28th day after the operation, the reticulocyte count was 6.8% with hyperplasia of the bone marrow; she went on to an uneventful recovery. Thus, here is a case in which splenectomy alone brought about a cure.

Jahsman, Monto, and Rebuck[64] in 1962 noted that of the twenty-eight published cases of pure red cell anemia occurring with mediastinal tumor, complete surgical resection was preformed in sixteen. In all sixteen cases, the tumor was a benign thymoma. Improvement in the anemia occurred in nine of these sixteen resected cases. Three years prior to this, Jacobs et al.[55] had tabulated the results in the nine patients who had improved:

2 had shown immediate improvement but died in the postoperative period
1 needed fewer transfusions for maintenance
2 showed improvement with cure after ACTH therapy
4 had remissions due to thymectomy alone.

They then calculated a cure rate of 29% (4/14) after deleting from their figures the two postoperative deaths. Because of this late improvement in two cases that had shown no remission soon after thymectomy, Soutter and Emerson[50] had suggested that a repressive effect is exerted by the thymus or some other agency upon red cell formation, and, thus, the removal of this agent will not necessarily be followed immediately by bone marrow recovery. To illustrate this dramatic response the following case of Jacobs et al.[55] is cited: A 67-year-old woman entered with these data: Hb, 5.0 gm%; RBC, 1.32 mill/mm^3;

WBC, 10,600/mm^3; platelets, 231,000/mm^3; and no reticulocytes. X-rays showed a mediastinal mass, and three bone marrow aspirations demonstrated normal granulopoiesis and normal megakaryocytes with a complete absence of erythroid precursors. She was given transfusions and the mass was removed--a large benign thymoma. For ten days the hematocrit fell, and no reticulocytes were seen; then reticulocytes began to appear in the peripheral blood, and the hematocrit stabilized within the normal range. A bone marrow obtained three weeks postoperatively showed normal erythroid activity.

Foy and Kondi[45] reported the case of a 46-year-old African man with total absence of all red-cell precursors on marrow examination. He was given riboflavin 4 mg per day; reticulocytes appeared six days later with a peak of 30.5% resulting in the next ten days, and the red-cell precursor activity in the bone marrow actively increased. The remission was thought to be due to the action of riboflavin, since the response had been highly specific. In 1953 Seaman and Koler[30] reported the case of a 40-year-old woman who had developed an absence of nucleated erythrocytic cells two months after using drycleaning fluid. Over the course of five years, she received 158 transfusions; then cobaltous chloride 100 mg orally every day was begun. On the 64th day nucleated red cells were seen in the peripheral blood, and nine months later she was in good hematologic remission. Two years later in 1955 Fountain and Dales[12] reported the case of a 49-year-old woman with hemoglobin of 4.5 gm%, white cell count of 7,600/mm^3, platelets of 350,000/mm^3,

reticulocytes of 0.1%, and bone marrow revealing red-cell precursors as only 4% of the total. She was given oral cobaltous chloride 50 mg twice daily, and at time of publication she had been in good condition for seven months. Voyce[48] in 1963 had reported the case of a 47-year-old man with pure red cell anemia who had been given transfusions every six to eight weeks for fourteen months with no improvement. His first trial with oral cobaltous chloride 100 mg twice daily was followed by a period of six months during which he needed no transfusions. Three years later his third trial produced a reticulocytosis which reached 12% on the 22nd day and an active normoblastic erythropoiesis in his bone marrow by the fourteenth day. Following this he was maintained on cobaltous chloride 100 mg twice daily for one week of each month and needed no more transfusions. These reports of cases successfully treated with riboflavin and cobalt offer another possibility for treatment.

With the occasional exception of the use of splenectomy, thymectomy, and transfusions, and the administration of corticotropin and cortisone, treatment has been futile, as Bayrd and Bernatz[49] wrote in 1957. Admittedly, treatment of this disease has been less than successful, but nevertheless the responses that have occurred with thymectomy, splenectomy, isolated and adjunctive use of corticosteroids, riboflavin, and cobalt would lead the physician to attempt these therapies, whenever applicable, with some hope of recovery. And transfusions are the primary resource for keeping these patients alive in order to repeatedly attempt to induce remission.

VII. DISCUSSION

Pure red cell anemia is neither benign nor easily treated in spite of the fact that the striking feature of the patient with hypoplastic anemia is his fundamentally healthy status, as noted by Crosby et al.[65] in 1957. Without therapy the hemoglobin continues to drop toward 0 gm%, and the bone marrow continues to fail in producing mature erythrocytes. Yet the only truly effective treatment of the disease is a symptomatic one--giving transfusions when the patient begins feeling discomfort. With the maintenance of blood volume and values within a range at which the patient functions satisfactorily, usually hemoglobin of 8 to 10 gm%, the patient will show no signs of his disease nor experience any symptoms. Some growth retardation is noted in children, but most is attributed to complications from the transfusions. This therapy is not without its toll, however; transfusion reactions may be fatal, continuing use over five years results in hemosiderosis and hemochromatosis which cause cirrhosis and endocrine abnormalities such as failure of secondary sex characteristics, osteoporosis occurs after three to four years which may cause collapse of vertebrae, and the development of hypersplenism may require splenectomy.

The etiology of the disease is subject to many considerations and will no doubt prove to be multiple. Because of the frequent occurrence of benign thymoma with pure red cell anemia

as evidenced by Jahsman, Monto, and Rebuck's[64] report in 1962 that there were 28 published cases of these coexistent diseases with four of sixteen thymectomies resulting in cure, the thymus must be suspect until a common etiology is found. The effects of riboflavin and cobalt in treatment and the finding of anthranilic aciduria suggest an enzyme defect in metabolism perhaps in the tryptophan pathway. The occasional finding of autoantibodies in infants and in adults makes it mandatory to search for these. Drug idiosyncrasies, toxins, and allergies have produced crises. The results of Allen and Diamond[35] in their therapy with ACTH and cortisone lead one to question an endocrine defect.

Treatment should never be discontinued because of the continuing possibility of spontaneous remission. Transfusions of packed red cells are the primary therapy and should be used as indicated without question. Secondly, attempts at steroid-induced remission should be made early in the disease; cobalt and riboflavin ought to be tried; splenectomy should be performed when transfusions become so frequent as to indicate it; thymectomy may be done when an anterior mediastinal mass is demonstrated; just never give up short of remission, be it spontaneous or induced.

In 1961 Diamond, Allen, and Magill[14] stated that 60 cases in children had been reported; in 1963 Voyce[48] noted that 55 cases in adults had been published. Not every physician will see a case of this; however, pallor early in infancy or dyspnea and fatigue in adults and low hemoglobin, reticulocytes, and RBC values with normal WBC and platelet counts should alert one to make a bone marrow examination. The presence of an erythrocytic hypoplasia solely will make the diagnosis of pure red cell anemia.

VIII. SUMMARY

A review of the reported cases of pure red cell anemia has been undertaken, beginning with the first published case in 1922. The disease is divided into two types, that in children and that in adults, primarily on the basis of age, since signs and symptoms are similar in both groups. Pure red cell anemia is suggested as the name for this disease to avoid controversy and to unite the literature.

Etiologies have been proposed with emphasis on congenital causes in children and acquired factors in adults but with obvious amalgamation. Transfusions should be given whenever necessary, and early treatment using steroids, cobalt, riboflavin, and splenectomy and thymectomy where indicated should be attempted in hope of remission.

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