The Anemia of Malnutrition

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Malnutrition is one of the most significant problems afflicting humanity today. Children, in the midst of growth and development, helpless and ill-equipped to withstand adverse factors, fall easy prey to the ravages of malnutrition. Rapid population growth; inadequate food production coupled with inequitable distribution; poverty; regional conflicts; and social, political, and educational factors all play a significant role in the etiology of malnutrition. Protein-energy malnutrition (PEM) of varying degree is the most prevalent form, affecting primarily the young child (1). In Asia, Africa, and parts of Latin America, the disease is essentially primary, but secondary malnutrition due to chronic diseases such as cystic fibrosis and acquired immunodeficiency syndrome (AIDS) is becoming more common among the affluent nations (2–4).

PEM may be regarded as a generalized disorder affecting the structure and function of the entire body. Changes in the hematologic system are an invariable accompaniment of the syndrome, and anemia has always been a constant feature. Current knowledge of the anemia in PEM is based on extensive clinical observations along with human and animal experimental work. The results of many studies are conflicting and confusing, but it is useful to remember that the subjects studied vary widely with respect to geographic location; age; race; dietary habits; associated vitamin and mineral deficiencies; prevalence of bacterial, viral, and parasitic infections; and degree of blood loss. The methodology employed and the technical problems in some studies could also be limiting factors in comparing results. Viewed as a whole, some of the changes in the erythron may be visualized as an adaptation to a state of reduced metabolic requirements, whereas other findings are often secondary to pathologic accompaniments (iron deficiency, sickle cell disease, etc.) (5). However, many important questions about the problem still remain unanswered, and new ones continually emerge.

MORPHOLOGY OF ANEMIA IN PEM

Practically every type of anemia has been described in PEM (1,6–8). In the majority of uncomplicated cases, a normocytic, normochromic, or mildly hypochromic
anemia is common, along with some degree of anisocytosis and poikilocytosis (6,8). Associated vitamin and mineral deficiencies, as well as infections, may modify this picture (9,10). In parts of the world (i.e., Asia) where hookworm infestation or other forms of chronic blood loss are common, a hypochromic microcytic picture is seen. Macrocytosis and a dimorphic picture have also been described in several instances (8,11,12).

The bone marrow in most patients is characterized by erythroid hypoplasia and shows an increased myeloid/erythroid ratio, with predominantly normocytic maturation. Occasional giant pronormoblasts may be seen. In the absence of iron deficiency, some iron can always be demonstrated in the marrow by special stains. In severe cases, the functioning marrow gets progressively replaced by fatty tissue. Megaloblastosis is occasionally noted, and giant and atypical megaloblasts have also been seen (8).

PATHOPHYSIOLOGY OF ANEMIA IN PEM

The various factors influencing the anemia of PEM include (a) metabolic changes in the red cell, (b) protein deficiency and adaptation anemia, (c) iron deficiency, (d) deficiency of vitamins (folic acid, B₁₂, E, pyridoxine, riboflavin) or trace elements (copper, selenium, zinc), (e) erythropoietin deficiency, (f) infection, and (g) chronic diseases.

Metabolic Changes in the Red Cell

Glucose is the main energy source of the red cell and is metabolized along two pathways: (a) the direct Embden Meyerhof glycolytic pathway, which supplies energy necessary for maintaining ionic equilibrium, energy for reduction (NADH) and 2,3,-diphosphoglycerate (2,3 DPG); and (b) the hexose-monophosphate shunt, which reduces nicotinamide adenine dinucleotide phosphate (NADP) to NADPH, essential for reducing glutathione-containing disulfides in the cell. The enzymes in both pathways are very sensitive to hypoxia and acidosis, commonly associated problems in PEM. Various abnormalities of red blood cell (RBC) metabolism have been described in PEM. These include elevated levels of glucose, phosphate, adenosine triphosphate (ATP), Na⁺, hexokinases, and ATPases (13). MacDougall et al. (14), in their study of red cell metabolism, found a moderately increased red cell enzymatic activity in cases of PEM. This has been described as a compensatory mechanism to prevent excessive intracellular accumulation of Na⁺ following altered membrane permeability. None of these metabolic abnormalities is, however, clinically significant, but they are associated with a mild reduction in RBC survival.

Derangements in erythrocyte lipid metabolism with resultant alterations in red cell membrane and survival have been documented by many workers (15). Coward (16) reported that the cholesterol and phosphatidylcholine concentration per unit area of the RBC membrane is increased in PEM, with a relative decrease in the den-
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Anemia of malnutrition is a disease state that occurs due to the deficiency of proteins, thus predisposing to abnormal forms with increased osmotic fragility. These membrane changes are similar to those found in hepatitis and obstructive jaundice. Studies of the red cell membrane in Kivu children showed an increased ratio of surface area to volume and increased target cells due to excessive cholesterol and phosphatidylcholine in the cell (17). Lanskowsky et al. (18) have demonstrated an improved RBC survival following a protein-rich diet devoid of any vitamins and minerals. Abnormalities of the red cell membrane lipids with resultant changes in shape, size, and deformability may thus be a contributory factor in hemolysis. These changes are more common in kwashiorkor than in marasmus, as seen by an increased susceptibility of the red cells to detergent lysis in the former (19).

Protein Deficiency

Deprivation of protein has been shown to cause anemia in various experimental models such as rats, pigs, and monkeys (20,21). A similar anemia has been seen in prisoners of war (22) and in malnourished children (7,8). Such an anemia is usually of mild to moderate severity, with an average hemoglobin decrease of about 20%, and is normocytic and normochromic in morphology. The reticulocyte count is normal, while the marrow may show reduced erythroid elements. The plasma iron levels are low, with a reduced iron-binding capacity but a normal or increased transferrin saturation. The turnover of radiolabeled iron is low. These findings suggest a reduced production of RBCs. The exact mechanism of this anemia is still unclear, but several views have been proposed. Lack of an adequate supply of essential amino acids may not be the only factor.

Viteri et al. (8) believe that severely malnourished children have a decrease in lean body mass and reduced metabolic demands. The reduction in hemoglobin and the total RBC mass may be an adaptation to decreased active tissue mass, a picture that may, however, be changed with stress-producing situations such as infection or fever. Other adaptive mechanisms subsequently come into play to promote better oxygenation of tissues. The moderate degree of chronic anemia leads to an increase in intracellular 2,3 DPG and a shift of the O$_2$ dissociation curve leading to better tissue O$_2$ delivery and probably to reduced erythropoietin secretion. However, studies in Kivu have shown that 2,3 DPG and P$_{50}$ levels (a measure of the affinity of hemoglobin for O$_2$) in erythrocytes are normal in PEM on admission and increase with refeeding (23). This finding could not be explained adequately, but it does indicate that the anemia in PEM is not merely one of adaptation, but that other factors are also involved. The question of whether the anemia is due to lack of erythropoietin per se or is as a result of a nonresponsive marrow is debatable. Other mechanisms through which protein deficiency could lead to anemia are: (a) maturation block in the erythroblast leading to a poor reticulocytic response, (b) mild decrease in the number of erythropoietin-sensitive precursor cells in chronic PEM, or (c) increased hemolysis due to faulty cell membrane and/or lack of protective factors in the serum of such patients (8).
Iron Deficiency

Iron has been described as "the energy backbone of vertebrate physiology" (24) and is essential for erythroid proliferation and hemoglobin synthesis. The incidence of associated iron deficiency anemia in PEM is extremely variable and depends on a number of factors such as dietary habits, parasitic infections, and chronic blood loss. It is more common in those children who were preterm and in marasms in the first year of life. A higher incidence of iron deficiency anemia has been seen in parts of Asia (especially India) (25) and Egypt but is relatively less common in Africa and Latin America (8,26).

The anemia in such patients is usually moderate to severe. The red cell morphology is hypochromic and microcytic. The serum iron levels are low (<40 μg/dl), with a reduced total iron-binding capacity. The transferrin saturation may be normal or low (<16%), but the erythrocyte free protoporphyrin is elevated (>70 μg/dl). The serum ferritin level is usually less than 10 ng/ml, but false elevations due to infection or inflammation may be misleading. In cases of PEM in which the anemia is normocytic and normochromic, dietary repletion without iron supplementation will usually precipitate a latent iron and folate deficiency.

Extensive work has been done relating plasma proteins to iron transport and hemoglobin synthesis. Plasma proteins involved in iron metabolism (e.g., transferrin) have been shown to take precedence over other tissue and organ proteins in protein- and iron-depleted animals (27). Hallgren (28) in 1953, working on rats, showed that due to decreased erythropoietic activity in protein-depleted rats, iron becomes a rate-limiting factor only when severely reduced. Beard et al. (29), on the other hand, stressed that iron deficiency (rather than protein deficiency) accounted for most of the anemia seen in protein- and iron-depleted animals.

Apart from blood loss, protein deficiency per se can predispose to iron deficiency. Cook et al. (30), in a collaborative study of nutritional anemia in Latin American children, observed a close relationship between plasma protein levels and iron deficiency. This was related to the presence of heme iron in meat diets, which has an excellent bioavailability unaffected by other dietary factors. Chronic protein deficiency in such a population would thus predispose to an iron-deficient state. In countries of Asia (e.g., India), on the other hand, most of the dietary iron is non-heme, with poor bioavailability (<5%), and iron deficiency may exist in such populations in the absence of protein deficiency.

Severe iron deficiency itself may have an indirect effect on protein synthesis by limiting the amount of ribonucleic acid (RNA) available. Rosch et al. (31), in their studies on immune tissues of pups, showed that iron deficiency significantly altered protein synthesis as measured by the incorporation of radiolabeled tyrosine into protein.

Lack of iron is the most important rate-limiting factor during refeeding. With dietary repletion, there is a fall in body stores of iron (concomitant with an increase in hemoglobin), along with an increase in its intestinal absorption. Supplementation
with iron in the nutritional management of PEM is, therefore, of utmost importance in ensuring efficient erythropoiesis.

**Vitamin and Trace Element Deficiencies**

Associated and interrelated deficiencies of several water soluble and fat soluble vitamins and trace elements are common in PEM. These deficiencies often manifest during periods of protein repletion.

**Folic Acid**

Megaloblastic changes with low folate values have been described in some parts of the world (Kenya, Jamaica, Egypt) but not others (Thailand, India, Kivu) (26). The correlation between serum folate levels and the degree of megaloblastic change has been poor in most studies. Folate deficiency, as shown by an increased urinary excretion of formiminoglutamic acid (FIGLU) following a histidine load, invariably gets unmasked during refeeding (32). The diagnosis can be made by the presence of hypersegmented neutrophils and macrocytes in the peripheral smear, serum folate level less than 3 ng/ml, and RBC folate level less than 140 ng/ml. The bone marrow in these cases shows megaloblastic change, with asynchronous nuclear-cytoplasmic maturation. It is, therefore, safer to supplement the diet of all patients with folate (0.5–1.0 mg/day) during repletion.

**Vitamin B<sub>12</sub>**

The serum levels of vitamin B<sub>12</sub> have been reported as normal or high in all studies that have evaluated the role of this vitamin in PEM (8). Very high levels seen in malnourished children have been attributed to fatty changes in the liver (33) and to an increase in the circulating carrier proteins. At this time, vitamin B<sub>12</sub> has no definite role in the anemia of PEM though there are isolated reports of its value in treating anemia in malnourished individuals (8).

**Vitamin E**

The normal levels of vitamin E depend on the amount of dietary tocopherols ingested. Asians and Africans have lower serum values than their European counterparts (34). Levels may be low in cases of PEM as the serum lipoprotein levels (carriers for vitamin E) are decreased. Vitamin E plays a role in preventing oxidant hemolysis, and its role in anemia of the preterm is well documented (35). A megaloblastic change responsive to vitamin E administration has been reported by some authors (36) but refuted by others (37). Although reports from Egypt and Jordan have
indicated a good response of the anemia in malnourished children to vitamin E and coenzyme Q₁₀ administration (38), in a study in Thailand, Kulapongs (39) demonstrated that the anemia of PEM with low vitamin E levels responded primarily to protein and iron replacement and not to vitamin E.

The role of other vitamins is unclear. There are a few isolated reports of the usefulness of pyridoxine (anemia associated with severe hemosiderosis), riboflavin, and prednisolone (red cell aplasia) in the treatment of anemia in PEM (8).

*Trace Elements: Copper, Selenium*

Lack of trace elements has also been incriminated in the metabolic disturbances, particularly copper and selenium (40–43). Copper is essential as a cofactor for many enzyme systems in the body including cytochrome oxidase, monoamine oxidase, etc. It is also necessary for the synthesis of superoxide dismutase. Copper deficiency in experimental animals reduces the absorption of iron, the release of iron from body stores, and the utilization of iron in hemoglobin synthesis through the ferro-oxidase activity of ceruloplasmin (40). However, administration of copper to malnourished children with anemia makes only a marginal difference after iron therapy (41). Selenium is essential for formation and catalytic activity of glutathione peroxidase (42). In the absence of superoxide dismutase and glutathione peroxidase, the red cell is vulnerable to membrane damage and oxidative hemolysis following exposure to superoxide radicals or hydrogen peroxide (28,43). Deficiency of zinc and cobalt does not appear to contribute significantly to the anemia of PEM.

*Erythropoietin*

The role of erythropoietin (EPF) in the anemia of PEM remains controversial (44). Significantly reduced erythropoietic activity has been noted in protein-deprived or starved rats (45). An impaired EPF secretory response to hypoxia was seen in rats and other animals fed a protein-free diet (46,47). Experimental work in humans fed protein-deficient diets has also shown that the EPF response to phlebotomy is suboptimal (48). In the light of these findings, it has been proposed that the anemia of PEM may be due to a reduced production of EPF as a consequence of protein deficiency or due to a deficiency of energy (probably mediated through decreased levels of and sensitivity to triiodothyronine) (49). In animals, the anemia of PEM can be prevented or alleviated by the exogenous administration of EPF (50) or by stimulating endogenous production through phlebotomy (46), androgens (46), or cobalt (51). These findings probably argue against any marrow abnormality in PEM. They may also indicate that in times of need, proteins required for red cell production may be preferentially supplied to the marrow at the expense of other organs and tissues (5).
In direct contrast, several other groups working with malnourished children in Asia and Africa have shown that EPF production remains unaffected or is elevated. Wickramasinghe et al. (52) estimated immunoreactive EPF in the sera of 23 Nigerian children with PEM and found the levels to be normal or elevated in all cases and appropriate to the degree of anemia. Similarly, MacDougall et al. measured EPF levels by hemagglutination inhibition assay in malnourished children in Johannesburg and showed that the levels were high on admission, remained elevated during the period of peak reticulocytosis (following refeeding), and did not return to normal for as long as 4 weeks (14). They proposed that the failure of raised serum EPF levels to elicit an adequate increase in erythropoiesis may be due either to a decreased responsiveness of the erythropoietin-sensitive cells or to ineffective erythropoiesis (compounded by iron or folate deficiencies).

A study in Thailand estimated 24-hr urinary EPF excretion in 25 malnourished children with and without anemia. All children showed increased levels of EPF excretion, with no significant difference between those who were anemic and those with normal hemoglobin. A decreased utilization of EPF by an inactive marrow or increased urinary losses may explain this finding (Suttajat M, Suskind R, Kulapongs R, Olson RE, personal communication).

Infection

Infection and malnutrition have a synergistic relationship, and sepsis is a frequent and sometimes fatal complication of PEM. Inflammatory states may affect the erythron in any of the following ways (53–55):

1. **Shortened cell survival**: extracorpusscular factors that promote increased phagocytic removal by stimulating the reticuloendothelial system (RE cells).
2. **Impaired response to erythropoietin**: in response to a hypoxic stimulus.
3. **Impaired iron availability**: due to inadequate release of iron by the RE cells and reduced absorption from the gut.

Infections and infestations of the gastrointestinal tract along with chronic diarrhea may contribute to the anemia by malabsorption and/or blood loss from the gut. In general, the anemia in PEM is unlikely to respond to treatment unless the associated infection is brought under control.

Chronic Diseases

Secondary malnutrition occurring during the course of diseases such as sickle cell anemia, hemophilia, human immunodeficiency virus infection, childhood cancer, and cystic fibrosis is becoming more apparent (2–4,55). Multiple mechanisms contribute to the anemia seen in such cases. Malnutrition, with its associated anemia, may significantly increase the morbidity of cystic fibrosis (4).
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CLINICAL RELEVANCE OF THE ANEMIA OF PEM

Most cases of PEM have some degree of anemia with a hemoglobin concentration between 8 and 10 g/dl. Lower values should make one suspect other associated diseases such as hookworm infestation, malaria, and sickle cell disease. The symptoms of anemia are usually few, in view of its long-standing nature. The risk of heart failure is highest in cases of kwashiorkor who have an expanded blood volume and poor cardiac function.

A complete hemogram with an examination of the peripheral smear would be the starting point for evaluation of the anemia. Further investigations would depend on the smear, the severity of the anemia, and other associated clinical features.

MANAGEMENT OF THE ANEMIA

In most cases, the anemia responds well to dietary repletion along with iron and folic acid supplementation. Oral iron may be prescribed in a dose of 3 to 6 mg/kg-day of elemental iron along with vitamin C. Parenteral iron may be given if indicated, provided the serum albumin level is greater than 2 g/dl and the child is free of infection or is being treated for suspected sepsis with broad-spectrum antibiotics.

Severe anemia (<4 g/dl), with signs of cardiac decompensation, should be treated with small packed cell transfusions (5 ml/kg). Great caution has to be exercised while transfusing patients having kwashiorkor, as a high mortality rate has been reported in those children who were transfused (26). Heart failure is best controlled with diuretics, since these children are very sensitive to the effects of digoxin.

The improvement in hemoglobin is gradual, even with the use of specific hematins. There may be a slight fall initially (probably due to plasma volume expansion), followed by a slow rise in hemoglobin (Hb), hematocrit, and red cell counts. Occasional cases of normoblastic erythroid aplasia after 4 to 6 weeks of treatment have been documented. Such patients often respond to a combination of riboflavin and prednisone. Therapy in all patients should be continued for at least 6 to 8 weeks after restoration of a normal hemoglobin, in order to replenish body stores, along with appropriate dietary modification and nutritional rehabilitation.

CONCLUSION

Anemia has been recognized in association with PEM almost since the earliest descriptions, but more needs to be learned about its pathophysiology. Protein and iron deficiency appear to have a major role in the anemia of this complex disease, with vitamins, minerals, and infection playing subsidiary and interactive roles.
REFERENCES

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**DISCUSSION**

**Dr. Haschke:** I agree that iron deficiency is uncommon in children with protein-energy malnutrition (PEM). Golden, in Jamaica, found that iron stores were not depleted in children
admitted with PEM. We confirmed this in 54 children with secondary malnutrition due to untreated celiac disease. All infants had ferritin values above 10 ng/ml. Iron stores became depleted, however, during nutritional therapy and the period of rapid catch-up growth.

There is also the great difficulty in diagnosing iron deficiency during a period of infection. During infection, iron is redistributed throughout the body by being rapidly eliminated from the bloodstream and shifted to the reticuloendothelial system (RES). Synthesis of new hemoglobin is reduced, which results in a decrease of hemoglobin by 1.0 to 1.5 g/dl within a few days. Ferritin in serum increases. Then, while the patient is recovering from infection, hemoglobin synthesis restarts, and serum ferritin decreases.

Dr. Pudjiadi: In Indonesia, the ratio of marasmus to kwashiorkor has changed. In 1955, patients tended to have kwashiorkor, with a normocytic, normochromic anemia. By 1981, most were marasmic or marasmic-kwashiorkor with a microcytic, hypochromic anemia (1-4).

Dr. Suskind: We found that the anemia of PEM was not responsive to vitamin E but was responsive to protein and calories, as well as iron. In the course of rehabilitation, iron became the limiting nutritional factor in hemoglobin synthesis. Although bone marrow iron stores were adequate initially, they decreased as the process of hemoglobin synthesis continued.

Interestingly, in Thailand, it was found that bone marrow that had been aspirated and incubated with radioactive leucine had a very high incorporation rate when the child was most malnourished. It appeared as if the marrow were ready to take up all available essential amino acids and incorporate them into hemoglobin. With nutritional recovery, this very active hemoglobin synthesis decreased to normal levels. We also found that these children, on admission, had significantly elevated urinary erythropoietin excretion. With recovery, this decreased to control levels. There was a situation, therefore, in which the end organ, that is, the erythron, was not able to produce hemoglobin because essential amino acids were not available even though erythropoietin was continuously produced to stimulate a nonfunctioning system.

We also found, especially in the marasmic-kwashiorkor and kwashiorkor children, circulating red cells with a significantly shortened halflife. Increase and normalization of red cell survival began during recovery and adequate nutrient intake.

Examination of the red cell membrane on admission demonstrated the fact that these children also had a significantly increased red cell membrane cholesterol and phospholipid as compared with control red cells. With recovery, red cell cholesterol decreased, osmotic fragility improved, and red cell survival increased.

Our conclusions were that there was a defect in hemoglobin synthesis that was related to the deficit in available essential amino acids. The system was turned on by erythropoietin, but ineffectively, because of substrate deficiency. The resulting product did not have a normal red cell survival because of the changes in the red cell membrane. Red blood cell (RBC) membrane changes may be a reflection of changes in other cell membranes.

Dr. Warrier: Is it possible to correlate the enzyme changes in the red cell to enzyme changes in other tissues?

Dr. Ballabriga: Because changes in erythrocyte lipid stroma in the premature infant are in relation to dietary fat composition, the fatty acid composition of phosphoglycerides can be modified by changing the fatty acid composition of the diet. We studied the effect of varying amounts of C18:n6 on fatty acid composition in breast milk and three formulas with different quantities of vegetable fat. When the formula was low in C18:2n6, an increase was found of the main fatty acid of the n9 series, oleic acid, leading to a decrease in the stearate/oleate ratio in the red cell.
Dr. Suskind: One hypothesis suggests that decrease in cholesterol acyltransferase may be a factor in the elevated RBC cholesterol. This is an area that deserves far more attention, since the etiology of anemia of malnutrition is probably the same as the anemia of chronic disease. Studying a population of malnourished children may produce a better understanding of the process that causes the chronically ill patient to become anemic.

Dr. Ballabriga: This question will depend on the fatty acid composition of the membrane, and the possibility of peroxidation will depend on the existence of a corresponding mechanism to prevent it. A diet can be deficient in protein and energy but rich in essential fatty acids, depending on the vegetables and cereals consumed. With high intake of fatty acids of the n6 family, the phenomenon of peroxidation can be developed, especially if the quantity of vitamin E has not been increased or if other deficiencies, for instance, in selenium and ceruloplasmin, which act as antioxidants, are present. An interesting study would be the determination of malonic dialdehyde to detect the start of peroxidation or to look at expired air for detection of ethane or pentane.

Dr. Husaini: Most of our patients with severe PEM suffer from severe anemia. We did not, however, find a significant difference in the prevalence of severe anemia when mildly and moderately malnourished children were compared with normal, well-nourished controls. What suggestions would you have concerning improvement of hematologic status?

Dr. Worrier: When malnourished children are given protein alone, the deficiencies of iron and folic acid become obvious. Without iron supplementation, plasma iron and transferrin saturation decrease, as in iron deficiency.

The reduction in hemoglobin in both primary and secondary PEM is usually about 20 to 30%. Iron should be started simultaneously with protein to avoid iron deficiency. Several studies looking at children admitted with and without infection have shown that infection did not affect hemoglobin levels.

Dr. Suskind: Children with cystic fibrosis have a decreased red cell survival, which increased with vitamin E supplementation. We now give vitamin E to all children with cystic fibrosis. The hemolytic anemia of infancy, which usually disappears after vitamin E supplementation, is another indication that vitamin E may act as an antioxidant in protecting red cell membranes.

Regarding the nutritional implications of human immunodeficiency virus (HIV) positivity in children with hemophilia, one can observe height and weight deficits long before the onset of clinical autoimmune deficiency syndrome (AIDS).

Dr. Worrier: One often finds normal serum albumin but decreased levels of prealbumin in HIV-positive patients. We are beginning a 5-year study to look at immune status in relationship to the nutritional status of AIDS patients.

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