NUTRITIONAL ANEMIA IN PROTEIN ENERGY MALNUTRITION

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Protein energy malnutrition (PEM) is a problem of staggering magnitude. It has been estimated that the prevalence of malnutrition in children is about 33% in Asia(1). Poulten *et al.* in Bihar state, observed that the prevalence of PEM in children between the ages of 1 year and 5 years was 80% while the prevalence of anemia in them was 40%(2). Iron deficiency anemia is an important cause of nutritional anemia, while folate, vitamin B_{12} and protein deficiencies also play a significant role in its etiology. The pathogenesis of anemia in PEM is multifactorial. The extreme deficiency of nutrients is the primary cause but the role of repeated infections especially of the gastro-intestinal system further aggravates the prevalence and severity of anemia.

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Definition of Anemia

Nutritional anemia is a state wherein normal levels of hemoglobin cannot be maintained by erythropoiesis due to deficiencies of one or more nutrients. Normal hemoglobin level varies with age, sex and geographic altitude, being highest at birth, falling until 3 months of age and then gradually increasing to reach adult levels (*Table I*). Children with hemoglobin levels below normal for their age are considered anemic.

Classification of Nutritional Anemias

Anemia has been classified depending upon (*i*) the pathophysiology of the anemia, (*ii*) the red cell indices obtained by electronic cell counting, and (*iii*) the morphological classification.

(*i*) *Pathophysiologic Classification:* This is based upon the causative mechanism of the anemia whether it is due to increased red cell destruction, or due to decreased red cell production. The reticulocyte index (RI) is useful for this purpose. The reticulocyte index is obtained by adjusting the reticulocyte count to the maturation time RI = Reticulocyte count × Patient's hematocrit/normal hematrocrit × 1/maturation time(3) (*Table II*). A reticulocyte index 2.0 suggests adequate marrow function. Most nutritional anemias - iron, folate and B_{12} deficiency are associated with hypofunction of the marrow and low reticulocyte count, which is indicative of decreased proliferation and differentiation of erythropoietic cells in the marrow. The anemias of protein as well as copper deficiency are also secondary to decreased red cell production. The only nutritional anemia characterized by increased destruction of red cells occurs due to the deficiency of

TABLE I–*Definition of Anemia*

Age	Hb level below (g/dl)
Birth (cord)	13.5
1-3 days (capillary)	14.5
-1 week	13.5
-1 month	10.0
-2 months	9.0
3-6 months	9.5
6 months - 2 years	10.5
2 - 12 years	11.5
Adults	
Males	13.5
Females	12.0

TABLE II–*Calculation of the Reticulocyte Index*

Hematocrit %	Maturation time
45	1.0
35	1.5
25	2.0
15	2.5

$$RI = \text{reticulocyte count} \times \frac{\text{Pt. Hct}}{\text{N. Hct}} \times \frac{1}{MT}$$

vitamin E. This classification is impractical clinically; however, it serves as good basis for better understanding of the pathogenesis.

(*ii*) *Classification Based on Electronic Cell Indices:* Development of automated cell counters has made this classification possible and has reduced the errors associated with manual methods. It incorporates the Mean Corpuscular Volume (MCV) and the Red Cell Distribution Width (RDW) for the classification of anemias.

The RDW is a measure of anisocytosis expressed as a coefficient of variation of the red cell volume distribution:

$$RDW = \frac{\text{Standard deviation of the red cell vol.}}{MCV} \times 100$$

The normal values for RDW range from 11.5% to 14.5% in adults and older children and 15.5% to 16.0% in infants(4).

This method provides a mathematical model to the morphological classification of the anemias. The anemias have been classified in six different categories. A high RDW associated with a low mean corpuscular volume (MCV) is seen in iron deficiency, a high RDW associated with a normal MCV is observed in anemia of chronic inflammation and in states of mixed or multiple deficiencies. B_{12} and folate deficiencies are associated with a high RDW and high MCV(4).

(*iii*) *Morphological Classification:* Examination of the peripheral blood film is the most important and informative procedure in the evaluation of a patient with anemia. On the basis of red cell morphology the anemias have been classified as under:

1. *Hypochromic microcytic anemia* is often present when hemoglobin synthesis is impaired. Iron deficiency is the commonest cause while other causes in malnutrition include chronic infections and rarely copper deficiency.

2. *Normocytic normochromic anemia* occurs in protein and vitamin E deficiency. The anemia of chronic infections often has a normochromic and normocytic picture.

3. *Macrocytic anemia* occurs due to the deficiency of either folate or vitamin B_{12}

in the diet. The anemia results from a reduced number of cell divisions in erythroid tissue.

4. *Mixed/dimorphic 'masked' anemia* occurs when the peripheral blood smear shows multiple cell populations such as microcytes together with macrocytosis suggesting an incomplete supplementation of more than one of the nutrients. This is also a commonly encountered situation in malnutrition.

In India parasitic infestations by protozoa and helminths are very common in the setting of severe PEM(5) and contribute to the significant iron deficiency in the protein depleted state. This may lead to making of iron deficiency as severe deficient erythropoiesis because of overwhelming protein deficiency cannot further deplete the iron stores to manifest as iron deficiency anemia. Consequently, treatment of the PEM by increasing the intake of proteins and calories without adequate supplementation of iron leads to the development of a microcytic hypochromic anemia which was previously of the normocytic normochromic type. This point needs to be borne in mind while planning therapy of a child with PEM, as an incomplete or unbalanced diet causes greater harm especially during phases of rapid growth.

Sharma *et al.*(6) in a study on anemia in malnourished children demonstrated that the microcytic hypochromic picture of the peripheral blood was the commonest (68%) in these children while a dimorphic picture was seen in 25% and 7% had a normocytic normochromic anemia. The bone marrow examination, however, showed a megaloblastic picture in 24% and 73% had a normoblastic marrow.

Iron Deficiency Anemia

This constitutes the single largest cause of anemia in children, the peak incidence being in preschool children. Severe iron deficiency may be an addition result in (*i*) retardation of physical growth, (*ii*) delay in language and cognitive development, (*iii*) clumsiness and poor performance in school, (*iv*) attention deficit disorder, and (*v*) repeated infections(7).

Major clinical features of iron deficiency include fatigue, headache, dyspnea, apathy, behavioral problems together with symptoms secondary to abnormalities of the epithelial surfaces such as koilonychia, glossitis, papillary atrophy, dysphagia, diarrhea and malabsorption, Koilonychia is characteristic of iron deficiency anemia. Congestive heart failure is produced in severe anemia even in the absence of heart disease. Examination of the lips, nails, tongue and conjunctiva enables us to assess the presence and degree of anemia.

Cause of Iron Deficiency

Iron deficiency anemia may occur secondary to: (*i*) Depleted iron stores at birth; (*ii*) Decreased iron intake; (*iii*) Increased loss of iron from the body; (*iv*) Reduced iron absorption; and (*v*) Increased demands.

(*i*) *Iron stores:* The iron released from sensescent red cells during the first 8-12 weeks of life (a period of quiescent erythropoesis) is stored in the body and helps to maintain erythropoiesis upto 4-6 months age in the normal term infant and upto three months in the low birth weight or preterm infant. Subsequently, iron should be made available in the diet to prevent anemia. At birth the total iron content in a term infant is about 75 mg per kg, 25% of which is in the liver. The iron stores in the reference adult male (weight 70 kg) are about 50 mg per kg, and in the female 35 mg per kg. It is important to note that the iron containing oxida-

tive enzymes and the myoglobin in the skeletal muscles increase rapidly during early development and thus any lack of iron during this phase has a significant deleterious effect on the body.

(*ii*) *Decreased intake:* Milk is a poor source of iron (human milk 0.29-0.45 mg of iron per 100 g and cow's milk 0.01-0.38 mg/100 g) the bioavailability of iron in breast milk is much higher and to some degree compensates for the low concentration. Delayed introduction of iron rich food supplements plays an important role in the pathogenesis of IDA. Iron in the food occurs mainly in the non-heme form. The heme form occurs only in non-vegetarian diets which few can afford. There is a marked difference in the absorption of the two forms. The heme iron is much more readily absorbed, as the heme moiety is assimilated intact and the iron is released by a heme splitting enzyme in the mucosal cell; the absorption of the heme is also less affected by other dietary components such as phytates, tannates, calcium, fiber and phosphates all of which reduce the absorption of non heme iron considerably(4).

(*iii*) *Increased losses:* The iron losses from the body are small, amounting to about 0.9 mg per day in adult males and 1.5 mg in adult females. Iron losses in the feces are insignificant but in the presence of parasitic infestations, diarrhea or dysentry the losses may increase manifold. However, iron losses through the urine and skin are practically negligible. Acute or chronic blood loss is one of the important causes of anemia in children. Prevalence of hookworm infestation is high in children from the poorer sections of society who are also prone to PEM. Each hookworm of *Ancylostome* species causes a blood loss of 0.2 - 0.3 ml/day, while each *Necator* hookworm causes a loss of 0.04 - 0.1 ml/day(8,9). This leads to an exacerbation of the IDA in these children. Normally fecal loss of iron is minimal but in association with gastroenteritis, episodes of which are very common in chkldren with PEM(5), iron loss is enhanced as a result of increased loss of epithelial cells which are rich in iron. Cow milk feeding also leads to chronic blood loss from the gut and is an important cause of IDA during infancy in the west. This is possibly related to intestinal intolerance to large amounts of unprocessed cow milk(10,11).

(*iv*) *Reduced absorption:* The intestinal mucosa plays an important role in regulation of iron absorption. Absorption of iron is in inverse relation to the amount present in the diet. Ascorbic acid, citrate, alcohol, sugars, amino acids such as histidine and cystine enhance iron absorption. Iron is rather poorly absorbed from wheat and rice (5% or so) as they are rich in phytates. Iron absorption from nonvegetarian sources (fish and meat) is around 30% or so(4).

(*v*) *Increased demands:* Rapid growth states such as infancy, catch up of growth in low birth weight and preterm babies are periods of increased demands of iron and are thus more prone to IDA. In PEM this phase may be observed during treatment with a diet adequate in calories and proteins, but not providing sufficient iron. The above diet therapy often leads to the 'unmasking' of IDA.

Laboratory Diagnosis of IDA

(*i*) *Marrow Stainable Iron:* This is a measure of iron stores and is the earliest to be depleted in iron deficient states even before the changes in iron levels of serum or red cell. This is an invasive procedure and is seldom performed except for research purposes.

(*ii*) *Serum Ferritin:* This is an indirect measure of iron stores and is currently

recommended as the method of choice for estimation of iron stores. Levels less than 15 μg/L suggest decreased stores. Infections, liver disease or inflammatory processes lead to falsely elevated levels which do not correlate with the iron stores. However, its cost is prohibitive.

(*iii*) *Serium Iron, Total Iron Binding Capacity (TIBC) and Transferrin Saturation:* These parameters get affected only after decrease in the ferritin levels and before fall in the hemoglobin or peripheral smear changes. Serum iron is very variable but fasting levels less than 75 μg/dl suggest iron deficiency while levels less than 30 μg/dl are indicative of severe deficient state(4). TIBC levels are subject to more analytical errors than iron levels. The normal levels are 250 to 400 μg/dl. Transferrin saturation = Serum iron/TIBC × 100 - if less than 15% imply iron deficiency.

(*iv*) *Erythrocyte Protoporphyrin* : Recently available simple flourometric assays have rekindled interest in this procedure for screening of iron deficiency. The levels are only modestly raised in iron deficiency (>70 to 80 μg/dl of RBC) and are low in the other common hypochromic microcytic anemia due to beta thalassemia minor.

(*v*) *Screening Tests:* Hemoglobin levels and assay of the hematocrit are commonly used tests. Skin puncture techniques commonly used, provide inconsistent results and need to be performed carefully after warming of the extremity. Hematocrit values less than 32% in children <5 years suggest IDA.

If an individual does not respond to adequate iron therapy supplementation, one must rule out other causes of hypochromic microcytic anemia such as thalassemia minor, chronic infection, sideroblastic anemia and anemia of lead poisoning.

Management of IDA

Important points to keep in mind regarding the treatment are

(*i*) Oral therapy is the best form of treatment.

(*ii*) Dose of iron for the treatment is 6 mg/kg body weight in two or three divided doses on an empty stomach.

Norrby had shown that even 3 mg/kg body weight of elemental iron as ferrous sulphate may be sufficient(12). Ferrous sulphate is the cheapest and best form for therapy, however since a large number of iron preparations are available in the market it is important that the physician be aware of the amount and concentration of elemental iron in commonly used preparations. Elemental iron content of common pharmaceutical preparations has been tabulated in our earlier communication(13).

(*iii*) Therapy must continue for at least 6-8 weeks or 3 weeks after correction of the hemoglobin levels so that stores are adequately replenished.

(*iv*) Assessment of response to the treatment is made by the reticulocyte count which rises after 2-4 days of therapy in children.

(*v*) Parenteral iron therapy is indicated only when oral iron is either not tolerated or compliance is poor, or in presence of malabsorptive states. The requirement for iron is calculated by the formula:

Iron required in mg = weight in kg × hemoglobin deficit × 1.5 × 3.4 × 80/100. Iron (as iron dextran) should be given by deep intramuscular injection (Z route). Total dose infusion is recommended by some hematologists but should be given after careful sensitivity test.

Prevention of Iron Deficienty

(*a*) *Nutritional Counselling:* The current recommendations of the American Academy of Pediatrics are a daily intake of 1 μg/kg/day upto a maximum of 15 mg for full term infants to start at 4 months age up to 3 years of age. Then 10 mg/day from 4-10 years age(4). Milk is a poor source of iron and solids such as green vegetables, pulses and peas should be introduced by 4 months age. Hookworm infestation should be prevented by proper footwear and sanitation, and treated if present by antihelminthic therapy. In view of very high prevalence of parasitic infestation, periodic deinfestation at about 6 monthly intervals is being recommended.

(*b*) *Fortification:* Supplementation of biologically active and acceptable form of iron to food is an appropriate method of preventing iron deficiency. In the West, iron fortified cereals and flour have been tried to prevent iron deficiency(14,15). India has an agriculture based economy, so the fortification of wheat is not feasible. Salt which is produced only in a few centres, but is consumed by all was considered to be the most suitable vehicle for fortification with iron(15). About 5 grams of salt is consumed daily on an average thus providing 5 mg of elemental iron to prevent iron deficiency. Success of the programme will depend on the free availability of the salt and its acceptability to the community(16). The National Institute of Nutrition in Hydreabad has developed a successful method for fortification of common table salt. The formula for iron fortified salt is: Ferrous sulphate 3.2 g, Sodium acid sulphate 5.0 g and Orthophosphoric acid 3.2 g all in one kg of common salt to give an iron content of 1 mg/g of salt in the preparation(17). In pilot studies the salt has been found to reduce the prevalence of anemia significantly. The Government of India has initiated necessary measures to implement the fortified salt programme at the national level in a phased manner.

Nutritional Megaloblastic Anemias

Megaloblastic anemias are caused by the deficiency of vitamin B_{12} and folate in the diet. It occurs more often due to vitamin B_{12} deficiency in the infant and folate deficiency in the older child(18). The incidence of megaloblastic anemia is about 2% in preschool children(19). Almost a quarter of patients with severe PEM show megaloblastoid changes in the bone marrow and in equivalent number show dimorphic anemia on the peripheral smear(6). Its etiology can be classified on the lines of IDA, *i.e.,* poor stores, decreased intake, exaggerated losses, decreased absorption and excessive demands.

Poor stores: The high level of folate binder in fetal blood facilities folate extraction by the fetus from the mother, thus even newborns of mothers with folate deficiency have normal folate levels(20). Premature infants have smaller hepatic stores, and about 30% of premature infants and about 70% of infants with birth weights <1700 g show biochemical deficiency of folate at 1-2 months age(21).

The neonate possesses about 50 μg of cobalamins at birth, if there is maternal cobalamln deficiency during pregnancy then the infant is born with about 20% or less of the normal stores and receives very little B_{12} from breast milk. In such situations megaloblastic anemia may develop in the first few months of life and present with failure to thrive and involuntary movements(4).

Decreased intake: Goat's milk is a poor source of folic acid and when used for feeding of infants results in megaloblastic

anemia(22). The folate in the diet occurs in the form of polyglutamates, boiling of milk and cooking of food destroys almost 50 to 90% of the folate(4). The deficiency of vitamin B_{12} more often occurs in breast fed infants of mothers with low serum levels(22).

Increased losses: Increased folate losses are rare and are encountered in patients with extensive skin disease such as dermatitis herpetiformis(23) and in chronic infective states or malignancies(24). Increased losses of vitamin B_{12} are observed in situations of small bowel bacterial overgrowth as in the blind loop syndrome or fish tapeworm infestation.

Decreased absorption: In chronic diarrheal states such as tropical sprue and gluten enteropathy folate malabsorption may occur. Long term phenytoin therapy for a seizure disorder may cause decreased folate absorption by inhibition of folate conjugate activity in the intestine(25).

Congenital pernicious anemia caused by intrinsic factor deficiency is an established cause of B_{12} malabsorption. Children with this autosomal recessive disorder usually present in the second year of life with anemia, failure to thrive, weakness and mild hepatosplenomegaly(4). Juvenile pernicious anemia is usually of autoimmune origin and commonly associated with antibodies to the intrinsic factor. It may also occur with endocrinopathies such as Addisons disease or myxedema. A specific defect of absorption at the ileal level is also known, usually associated with proteinuria (Imerslund's syndrome) but this is rare and ileal resection is a commoner case of cobalamin malabsorption(4).

Increased demands: The growing infant needs almost 10 times as much folate (on a weight basis) per day as an adult (0.02-0.05 mg/day). Most types of hemolytic anemias - especially those with ineffective erythropoiesis such as Thalassemia major, sickle cell disease and warm type autoimmune hemolytic anemia have increased requirement for folate. These children should receive routine supplementation with folate to prevent deficiency and aplastic crises.

Rapid growth states such as recovery from malnutrition and catch up growth of low birth weight infants are important and preventable causes of B_{12} secondary to increased demands.

The recommended daily dietary allowance of Folacin are 30 μg/day during early infancy and rising to 400 μg/day in adults. The cobalamin requirements range from 0.5-3.0 μg/day for the corresponding periods(26).

Pathophysiology of Megaloblastic Anemia

(*a*) *Folate deficiency:* Pteroyl glutamic acid or Folic acid is reduced to its active form of tetrahydrofolate which is responsible for the transfer of one carbon moieties, *e.g.,* reactions which are important for the synthesis of purine and pyrimidines. Serum and red blood cell folate levels are important indicator of early folate deficiency(27) (*Table III*).

(*b*) *Cobalamin Deficiency:* Vitamin B_{12} is essential in the catabolism of cholesterol, methionine and the pyrimidines; and in the synthesis of methionine from homocysteine. Transcobalamin II per cent saturation and cobalamin levels are the early indicators of vitamin B_{12} deficiency(27) (*Table IV*).

Interrelation of Vitamin B_{12} and Folate Deficiency(28)*:* The lack of cobalamin results in the following defects in folate metabolism:

TABLE III–*Stages of Folate Deficiency*

Parameter	Normal	Negative folate balance	Folate depletion	Folate deficient erythro-poiesis	Folate deficiency anemia
Plasma folate	n	1	1	11	11
Serum folate (ng/ml)	>5	<3	<3	<3	<3
RBC folate (ng/ml)	>200	>200	>160	<120	<100
Liver folate (μg/g)	>3	>3	<1.6	<1.2	<1
Lobe average	<3.5	<3.5	<3.5	>3.5	>3.5
RBC	n	n	n	n	Macro
MCV	n	n	n	n	1
Hb	>12	>12	>12	>12	<12

TABLE IV–*Stages of Vitamin B_{12} Deficiency*

Parameter	Normal	Negative balance	B_{12} depletion	B_{12} deficient erythro-poiesis	B_{12} deficient anemia
Holo TCII	>30	<20	<20	<12	<12
TCII Sat %	>5	<5	<2	<1	<1
dU Suppr	n	n	n	abnormal	abnornal
Hyperseq	no	no	no	yes	yes
TBBC sat %	>15	>15	>15	<15	<10
RBC folate (ng/ml)	>160	>160	>160	<140	<140
MCV	n	n	n	n	1
RBC	n	n	n	n	Macro
Hb	n	n	n	n	1

Holo TCII (pg/ml): Holotranscobalamin II.
dU Suppt : Deoxyuridine suppression test.
TBBC % Sat: Total B_{12} binding capacity of plasma.
MCV : Mean corpuscular volume..

(*i*) Reduced formation of tetra hydrofolate (THF).

(*ii*) Reduced cell concentration of S-adenosyl methionine (SAM) leading to a greater accumulation of methyl-THF.

(*iii*) Diminished formation of fromyl-THF which is substrate for folate storage. SAM deficiency has been attributed for the neurological lesions of cobalamin deficiency(4).

It is important to mention that treatment with folate alone may partially improve the hematologic picture of megaloblastic anemia in a B_{12} deficient state but does not correct the neurological damage caused by B_{12} deficiency. Thus, it is important to know that all megaloblastic anemias should be treated with adequate doses of both folacin and cobalamin.

Clinical features of megaloblastic anemias are similar irrespective of this etiology and underlying factors. These children look sicker than their degree of anemia warrants. Mental apathy, depression, fatiguability and anorexia are early symptoms. A red sore tongue, papillary atrophy, recurrent glossitis and diarrhea may occur. Hyperpigmentation especially over the knuckles is also reported(29). Purpura may be present secondary to thrombocytopenia, more often seen in cobalamin deficiency. Folate deficiency also leads to depression of cell mediated immunity(30).

Vitamin B_{12} deficiency is an important cause of neuropathy, manifesting as paraesthesias. Subacute degeneration of the dorsolateral columns of the spinal cord, secondary to a demyelinating process is a known complication.

Diagnosis of Megaloblastic Anemia

The peripheral blood smear is the best indicator of megaloblastic anemia with the typical picture of macro-ovalocytosis and hypersegmentation of neutrophils. Nearly, 94% of B_{12} and/or folate deficient patients have hypersegmentation (*i.e.,* presence of at least one neutrophil with six or more lobes)(31). The lobe average obtained after a lobe count of 100 neutrophils on the smear is also used. A lobe average of 3.4 or greater is suggestive of megaloblastic anemia(32). The red cells show macro-ovalocytes with a raised MCV usually between 110-140 fl. There may be evidence of thrombocytopenia and granulocytopenia in severely deficient states.

Bone Marrow: Changes in the marrow are similar regardless of whether there is a deficiency of folate or cobalamin. The marrow is usually hypercellular with a reversal of the myeloid to erythroid ratio with an increased proportion of early cells (pronormoblasts and myeloblasts). The metamyelocytes are abnormally large with a horseshoe nucleus. Megakaryocytes may show an increase in nuclear lobes. The severity of the megaloblastic changes is related to the degree of deficiency(32).

Serum Folate Levels: Normal range for serum folate varies widely from 5 to 200 ng/ml. Elevated levels (20 ng/ml) are found in about 30% of patients with B_{12} deficiency. Low serum folate level is a sensitive and reliable indicator of folate deficiency. However, it is very sensitive to folate intake and therefore, folate deficiency cannot be made out in a recently treated patient. In such situations red cell folate is helpful.

Red Cell Folate: The normal range is 160-640 ng/ml and is low in patients with megaloblastic anemia due to folate deficiency. The level is also subnormal in 60% of patients with megaloblastic anemia caused by B_{12} deficiency and thus it does not help to differentiate between these two states(33).

Normal levels of red cell folate in the presence of folate deficiency may occur when there is reticulocytosis due to any cause such as hemolysis or hemorrhage, or in patients given blood transfusion 2-3 weeks before assay.

Deoxyuridine (dU) Suppression Test: Incorporation of labelled Thymidine into normal marrow cells is decreased to less than 10% after preincubation with dU. A smaller decrease in labelled thymidine incorporation is seen in cells from patients with megaloblastic anemia caused by folate or B_{12} deficiency.

FIGLU Excretion Test: Formiminoglutanic acid (FIGLU) requires tetrahydrofolate (THF) for conversion to glutamic acid. When THF is deficient then FIGLU is excreted in the urine, serving as an indicator of folate deficiency. Normal persons excrete 2 mg of FIGLU per hour but in folate deficiency the value may be 3.5 mg/h or greater. Nearly, 50% and 60% of B_{12} deficient patients, patients with liver disease, tuberculosis and some autoimmune diseases also show a positive test. FIGLU test may be negative despite severe deficiency of folate in kwas-hiorkor because a lack of enzyme Urocanase which blocks FIGLU production(34). This FIGLU test is not a very reliable test.

Serum B_{12} levels: Normal values range from 200-800 pg/ml, but deficiency states are usually associated with levels less than 100 pg/ml. Nearly, 30% of patients with folate deficiency also have borderline or low levels of serum B_{12}. The presence of antibiotics in the serum affects the accurate measurement of serum folate as well as B_{12} as they are both microbiologic assays.

Methyl Malonic Acid Excretion: Defects in the conversion of methyl malonyl coenzyme A to succinyl CoA due to B_{12} deficiency cause methyl malonic acidemia and its excretion. Urinary excretion of methyl malonic acid does not get corrected by treatment with folic acid but returns to normal slowly after initiating therapy with cobalamin. Other tests such as measurement of holotranscobalamin II, *i.e.,* transcobalamin II with B_{12} attached or assay of total B_{12} binding capacity are still only used as research tools and is available in few laboratories.

Management of Megaloblastic Anemia

Treatment of folate deficiency essentially requires only 100 to 200 μg/day. However, it is administered in doses of 5 mg/day for 14 to 21 days for adequate response and to replenish stores. Vitamin B_{12} is available in meat, fish, liver, eggs and milk, but most vegetables are poor sources. Infants require only 0.3 μg/day for a hematologic response but therapeutic doses are 100 to 250 μg I/M on alternate days for 15 to 21 days, or oral doses of 100 μg/day or so. Higher doses by the intramuscular route are recommended in pernicious anemia.

Forms of megaloblastic anemia unresponsive to adequate B_{12} and folate therapy include those caused by antimetabolite drugs, inborn errors of metabolism such as hereditary orotic aciduria and lastly conditions such as erythroleukemia(28).

Anemia of Protein Deficiency

This is usually a mild anemia but is rendered severe by the common association of other deficiencies of iron, B_{12} and folate. The clinical picture may include any of the forms of malnutrition such as maramus, kwashiorkor and marasmic kwashiorkor.

Seventy per cent of severely malnourished African children were anemic at admission(35). Evidence of iron deficiency was uncommon on admission. However, serum ferritin levels declined significantly on refeeding and nineteen per cent of patients had red cell folate levels < 100 ng/dl.

Several authors have demonstrated high serum vitamin B_{12} and transcobalamin levels in children with protein energy malnutrition(36,37).

High levels of B_{12} and transcobalamin are not really high in malnourished children as these levels significantly decrease on correction of malnutrition. Vitamin B_{12} and transcobalamin levels are falsely higher in patients associated with underlying infection which are quite common in these children(38).

The anemia of protein deficiency is of the normocytic normochromic type and is corrected by adequate diet therapy starting with a relatively low protein intake (1 g/kg/day) initially then gradually increasing to 3-4 g/kg/day. Care must be taken to provide adequate supplementation of proteins with iron and vitamins as otherwise it may lead to the 'unmasking' of anemias due to latent deficiencies of either iron, B_{12} and/or folic acid. The period of recovery from severe protein energy malnutrition is prolonged and the hemoglobin levels may decrease initially (especially in kwashiorkor) during the first week even with adequate treatment. This is due to an increase in the blood volume as surplus extra vascular fluid is absorbed. After this the levels gradually increase to reach normal levels by 2-3 months. Hematinics in adequate doses are recommended for 6 months in these children or to be continued during the period of rapid growth.

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NOTES AND NEWS

SYMPOSIUM-CUM-WORKSHOP ON GROWTH AND DEVELOPMENT

The Growth and Development Chapter of Indian Academy of Pediatrics will organize a symposium-cum-workshop at each zone. These symposia are meant for every one who is entrusted with the care of newborn, infancy, childhood through adolescence and are of paramount importance for residents and postgraduate students. The first of this kind will be held at Ramakrishna Mission Seva Pratishthan, Calcutta on *December 24 and 25, 1993* in collaboration with IAP, West Bengal and VIMS.

Dr. M.C.K. Nair and Dr. Dilip Mukherjee will be conducting the symposium,.

Registration of Rs. 150/- by demand draft to be sent to Dr. Dilip Mukherjee, Convener, at 9/1, Ramanath Pal Road, Calcutta favoring "IAP Chapter on Growth & Development" by December 22, 1993.