Pediatrics Hematological Disorders

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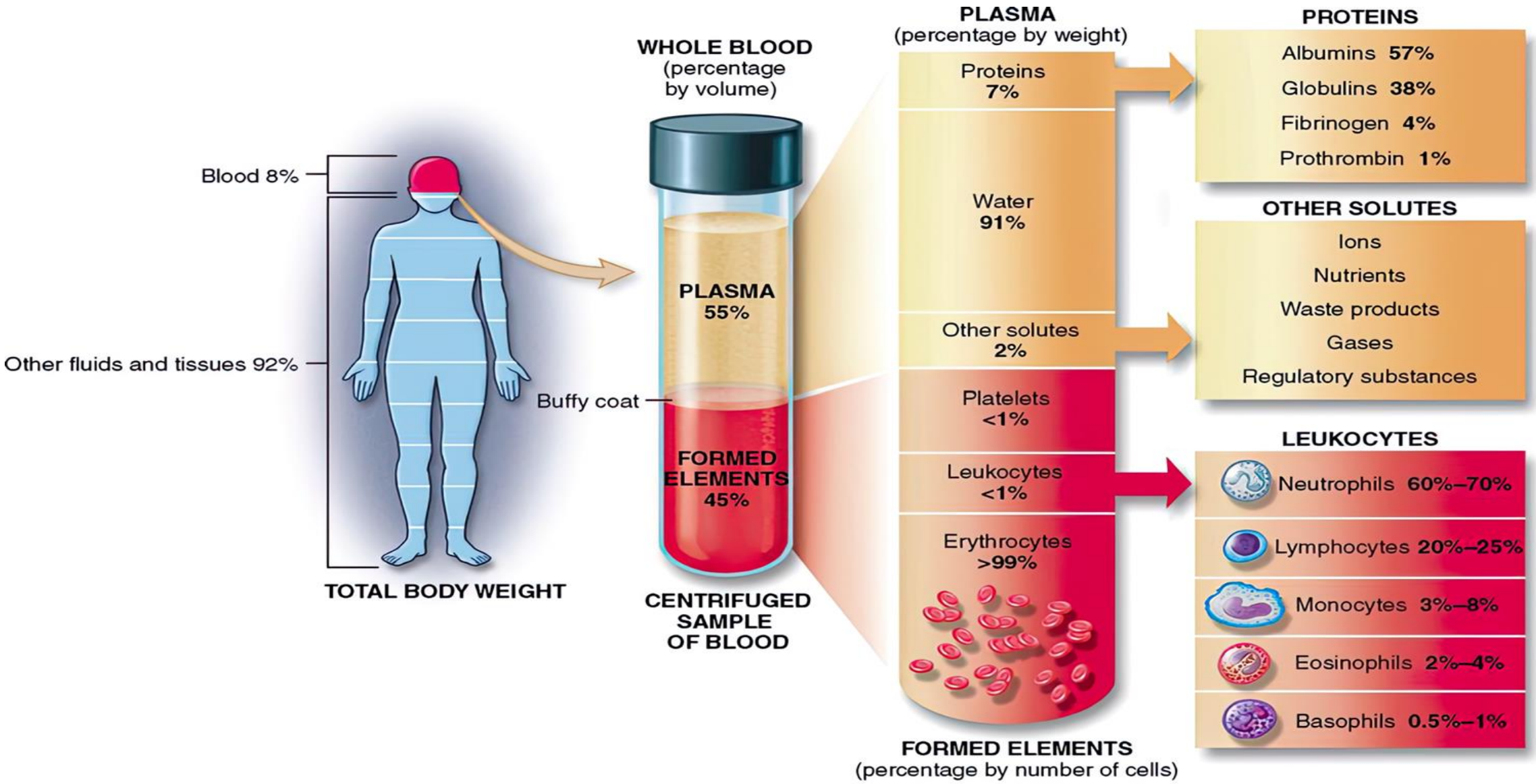
Objectives(Lectures one)

1. To understand the definition of anemia and recognize its different types according to their etiology
2. To be able to approaches to patient with iron deficiency anemia (investigations and treatment)
3. To differentiate iron deficiency anemia from other microcytic anemia
4. To be able to advice the mother about prevention of iron deficiency anemia


Blood 8%
Other fluids and tissues 92%
TOTAL BODY WEIGHT
WHOLE BLOOD
(percentage by volume)
PLASMA
55%
Buffy coat
FORMED ELEMENTS
45%
CENTRIFUGED SAMPLE OF BLOOD
PLASMA
(percentage by weight)
Proteins
7%
Water
91%
Other solutes
2%
Platelets
<1%
Leukocytes
<1%
Erythrocytes
>99%
FORMED ELEMENTS
(percentage by number of cells)
PROTEINS
Albumins 57%
Globulins 38%
Fibrinogen 4%
Prothrombin 1%
OTHER SOLUTES
Ions
Nutrients
Waste products
Gases
Regulatory substances
LEUKOCYTES
Neutrophils 60%–70%
Lymphocytes 20%–25%
Monocytes 3%–8%
Eosinophils 2%–4%
Basophils 0.5%–1%

Anemia

defined as a reduction in hemoglobin concentration, hematocrit (packed cell volume) or number of red blood cells per cubic millimeter (for age and sex)

Etiologic Classification of Anemia in Children

I. Impaired red cell formation

A. Deficiency:e.g **Iron deficiency**, Folate deficiency, Vitamin B12 deficiency

B. Bone marrow failure

II. Hemolytic anemia

A. Corpuscular

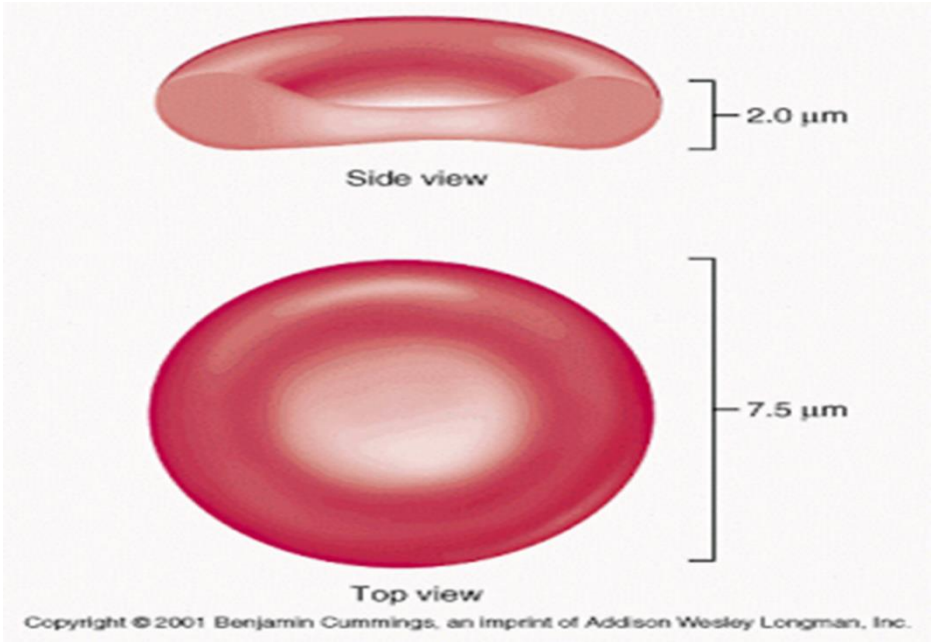
1. Membrane defects (**spherocytosis**,elliptocytosis)
2. Enzymatic defects (**G6PD**)
3. Hemoglobin defects
    a. Heme
    b. Globin (1) Qualitative (e.g., **sickle cell**)
    (2) Quantitative (e.g., **thalassemia**)

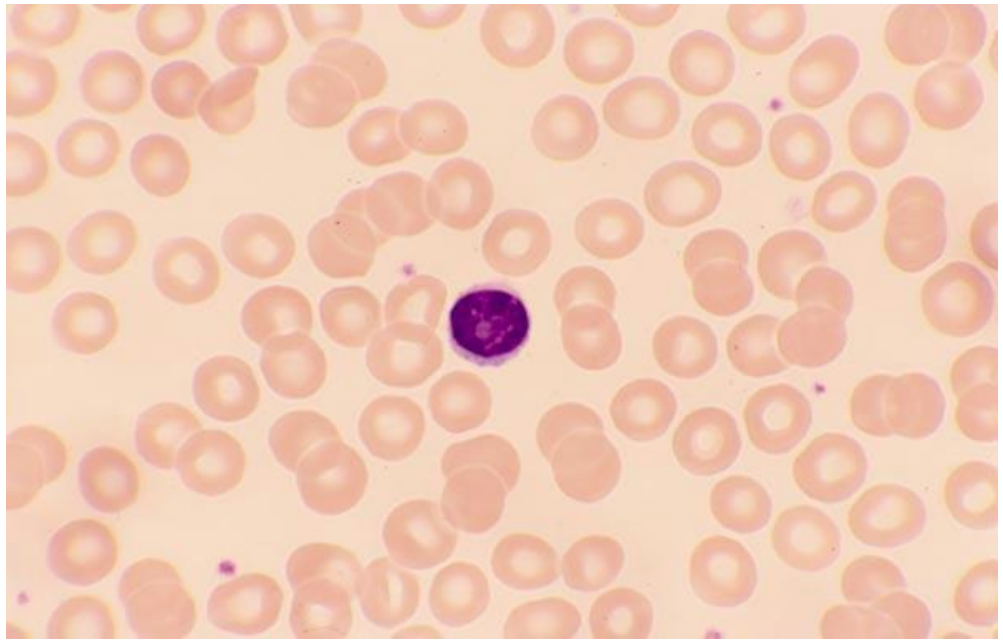
B. Extracorpuscular

1. Immune:
    a. Isoimmune
    b. Autoimmune
2. Nonimmune (idiopathic, secondary)

III. Blood loss

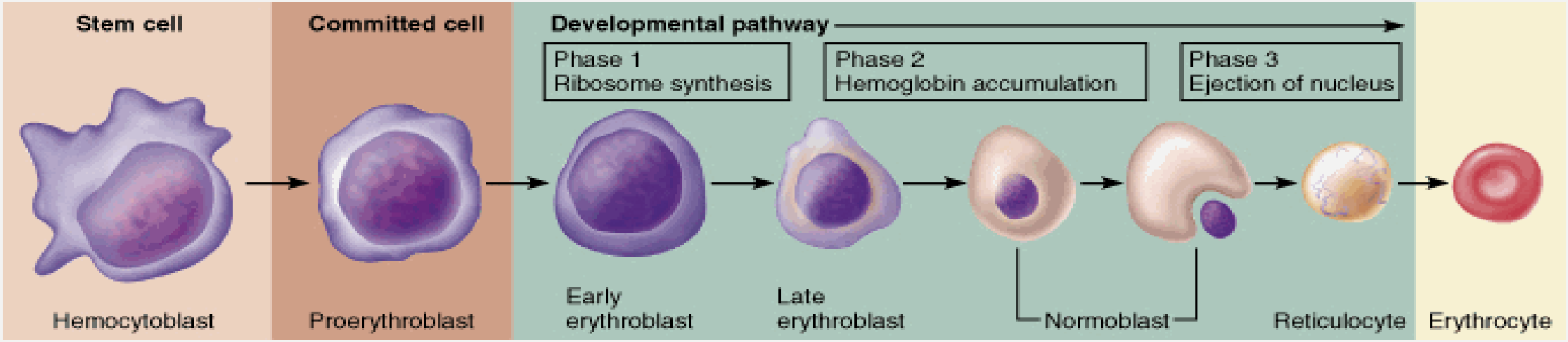
The blood smear(blood film) is very helpful in the diagnosis of anemia.
It establishes whether the anemia is
hypochromic, microcytic,
normocytic,
macrocytic
or shows specific morphologic abnormalities suggestive of red cell membrane disorders (e.g., spherocytes, stomatocytosis or elliptocytosis) or hemoglobinopathies (e.g. sickle cell disease).





The reticulocyte count are helpful in the differential diagnosis of anemia. An elevated reticulocyte count suggests blood loss or hemolysis; while normal or depressed count suggests impaired red cell formation. The reticulocyte count must be adjusted for the level of anemia to obtain the reticulocyte index,* (a more accurate reflection of erythropoiesis).

*Reticulocyte index=reticulocyte countXpatient's hematocrit/normal hematocrit. Example: reticulocyte count6%, hematocrit 15%, reticulocyte index=6X15/45=2%.



bone marrow examination

In more refractory cases of anemia, may be indicated
to
-estimate iron stores
-diagnose the presence of a normoblastic, megaloblastic, or sideroblastic morphology.

Iron-Deficiency Anemia

is the most common hematologic disease of infancy. It is estimated that **40-50%** of children under 5 years of age in developing countries are iron-deficient .

Peak prevalence occurs during late infancy and early childhood when the following may occur:

- Rapid growth
- Low levels of dietary iron
- Complicating effect of cow’s milk-induced enteropathy due to whole cow’s milk ingestion

A second peak is seen during adolescence due to rapid growth and suboptimal iron intake. This is amplified in females due to menstrual blood loss.

The body of a newborn infant contains about **0.5 g** of iron, adult content **5 g**.
So **0.8-1 mg** of iron must be absorbed each day during the first 15 yr of life to reach the adult level.

In addition to this growth requirement, a small amount is necessary to balance normal losses of iron by shedding of cells. Absorption of dietary iron is assumed to be about **10%**; So a diet containing **8–10 mg** of iron daily is necessary for optimal nutrition. Iron is absorbed in the proximal small intestine.

Causes of iron-deficiency anemia

Deficient intake

1. Breastfeeding without supplemental iron

A newborn infant is fed predominantly on milk.
Breast milk and cow's milk contain (0.5–1.5 mg/L).
Breast-fed infants absorb 49% of the iron, in contrast to about 10% absorbed from cow's milk.
Formulas with 7–12 mg Fe/L for full-term infants and premature infant formulas with 15 mg/L for infants <1,800 g at birth are effective.

2. Excessive cow milk intake
3. Low iron diet (vegan, vegetarian diet without appropriate supplementation)

Inadequate/impaired absorption

1. Antacid therapy or high gastric pH
2. Gastrointestinal disorder (inflammatory bowel disease, celiac disease)
3. Intestinal failure (malabsorption) /resection
4. Infection (prolonged diarrhea; Helicobacter pylori infection-associated gastritis)

Increased demand

1. Low birth weight, prematurity, twins

stores usually are sufficient for blood formation in the first **6–9 months** of life in term infants and by **3–4 months** in a premature infant

2. Growth (infancy, adolescence, and pregnancy)

Growth is particularly rapid during infancy and during puberty. Each kilogram gain in weight requires an increase of(35–45 mg) body iron.

3. Cyanotic congenital heart disease

Blood loss

Blood loss must be considered as a possible cause in every case of iron-deficiency anemia, particularly in older children. Hemorrhage may be either occult or apparent.

1. **Perinatal** (Placental, Umbilicus)

Delayed clamping of the umbilical cord (~2 min) in developing countries may reduce the incidence of iron deficiency.

2. **Gastrointestinal tract**

a. Hypersensitivity to whole cow's milk due to heat-labile protein, resulting in blood loss and exudative enteropathy (leaky gut syndrome)
b. Anatomic gut lesions, including substantial intestinal resection
c. Gastritis
d. Intestinal parasites [e.g., hookworm (Necator americanus or Ancylostoma duodenale) and whipworm (Trichuris trichiura)]

3. **Menstrual**
4. **Other**

a. Recurrent epistaxis
b. Idiopathic pulmonary hemosiderosis
c. Renal disease: infectious cystitis, microangiopathic hemolytic anemia, nephritic syndrome (urinary loss of transferrin), Berger disease,Goodpasture syndrome, and chronic intravascular hemolysis (hemoglobinuria)

CLINICAL MANIFESTATIONS

*__Pallor(palmar pallor)__ is the most important sign of iron deficiency.

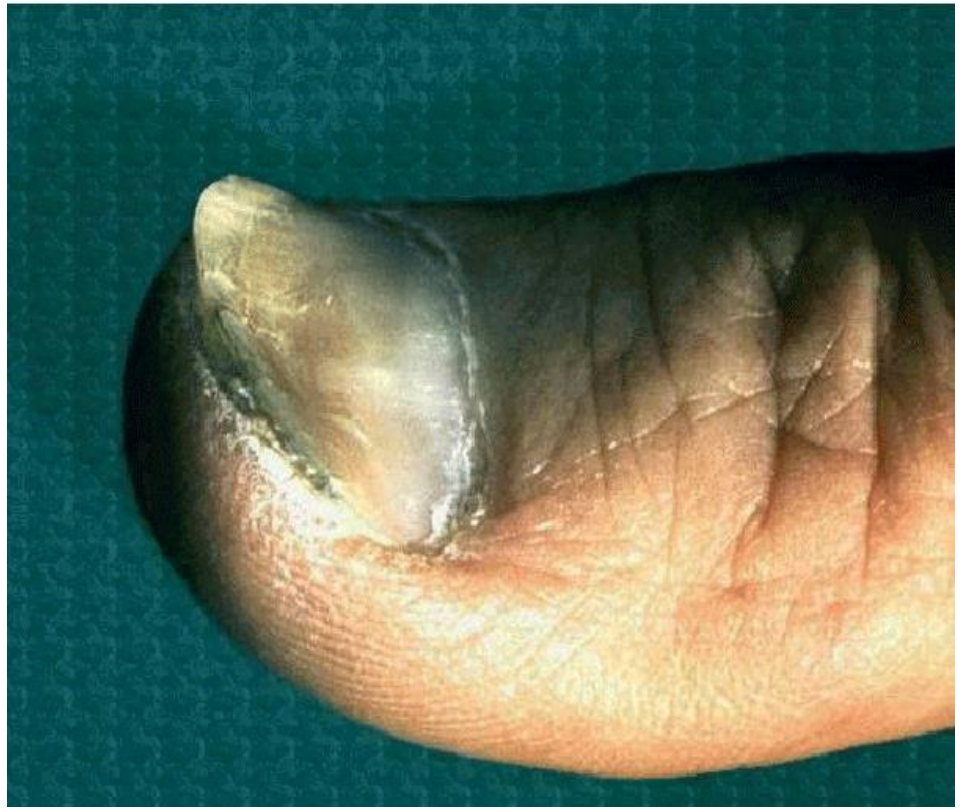
*__Pagophagia(pica),__ the desire to ingest unusual substances such as ice or dirt, may be present. In some children, ingestion of lead-containing substances may lead to concomitant __plumbism__ (chronic lead poisoning)

*When the hemoglobin level falls to <5 g/dL,
__Irritability, anorexia, Tachycardia, cardiac dilation , and systolic murmurs__ are often present.

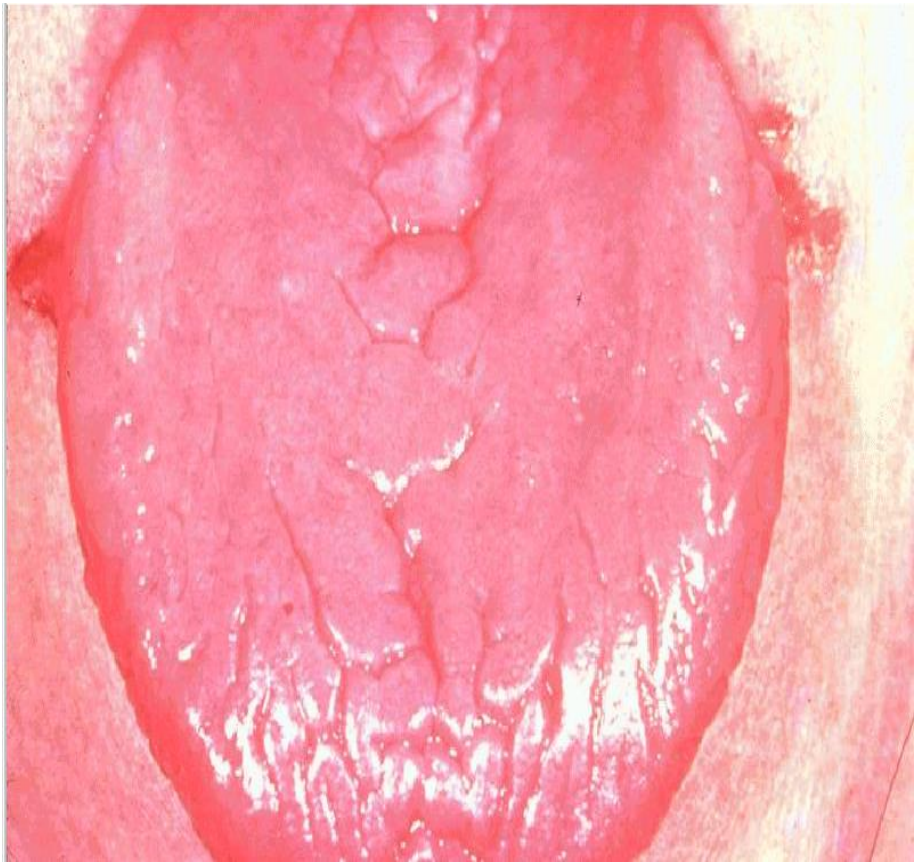
*Children with iron-deficiency anemia may be obese or may be underweight.

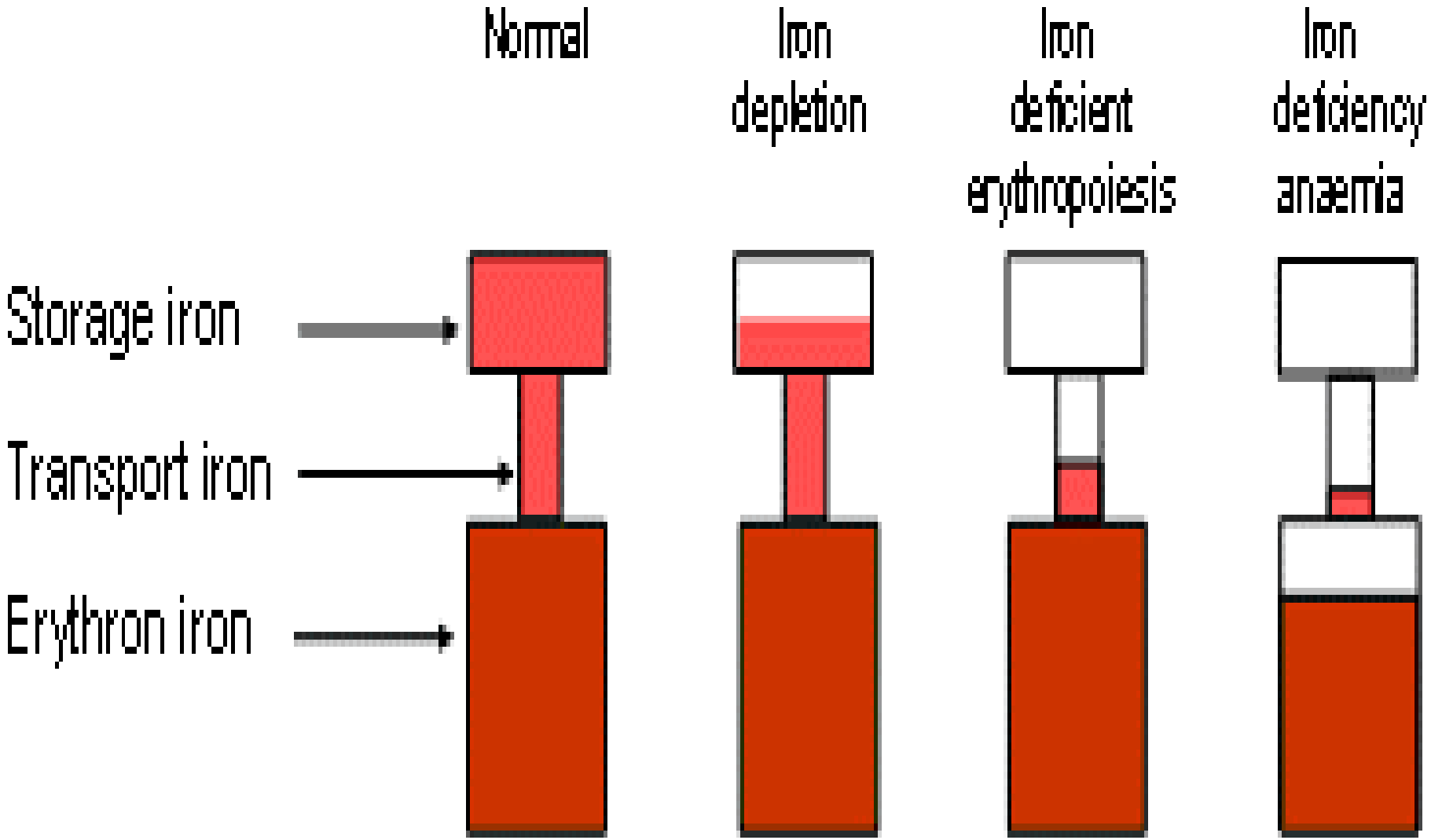
*Iron deficiency may have effects on neurologic and intellectual function. So it may affects __attention span, alertness, and learning__ in both infants and adolescents.

Koilonychia (Spooning of the nails)



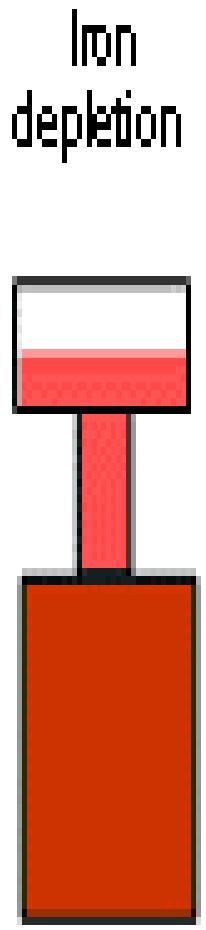
Glossitis




Normal
Iron depletion
Iron deficient erythropoiesis
Iron deficiency anaemia
Storage iron
Transport iron
Erythron iron

Stage I

. **Iron depletion:** This occurs when tissue stores are decreased without a change in hematocrit or serum iron levels. This stage may be detected by low serum ferritin measurements.
serum ferritin, an iron-storage protein, provides a relatively accurate estimate of body iron stores in the absence of inflammatory disease.



Stage II

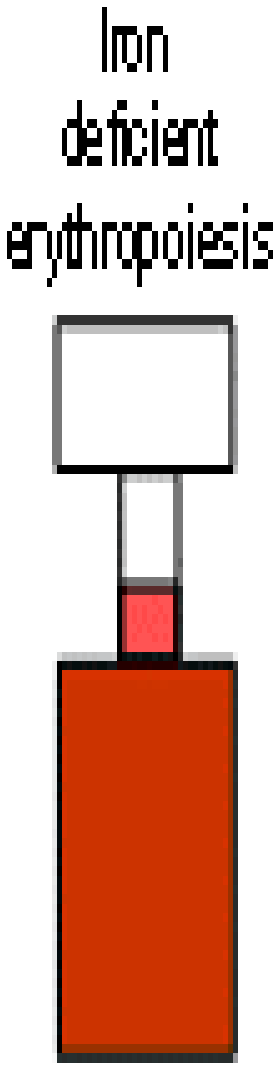
Iron-deficient erythropoiesis:

This occurs when iron stores are completely depleted.

serum iron level drops

total iron binding capacity(serum transferrin) increases,

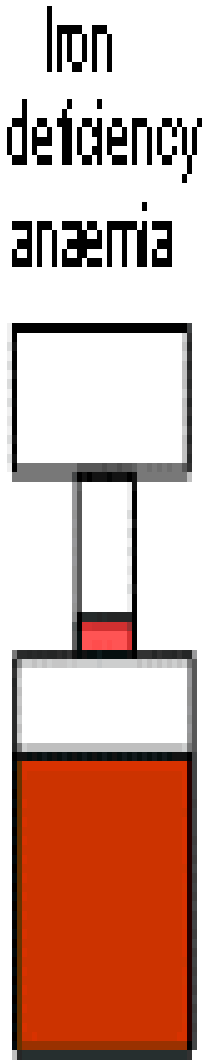
without a change in the hematocrit.



Stage III

Iron-deficiency anemia: As the deficiency progresses, the red blood cells (RBCs) become smaller than normal (**microcytosis**), and their hemoglobin content decreases (**hypochromia**), **increased red cell distribution width (RDW)** and **free erythrocyte protoporphyrins (FEP) accumulate(increase)**.

*The **red cell distribution width** (**RDW**) is a mathematical description of the variation in RBC sizes; a high RDW indicates greater variation in RBC size.*



Laboratory parameters consistent with iron-deficiency anemia

1. **Hemoglobin**: below the acceptable level for age; final stage of iron deficiency.
2. **Red cell indices:** ***Lower than normal MCV***(Decrease in MCV generally parallels decreases in hemoglobin)

widened RDW:In general, though not absolute, the RDW is high (more than 14.5%) in iron deficiency and normal in thalassemia (less than 13%).

3. **Reticulocyte count:** relative number of reticulocytes often increased, but when corrected for anemia the reticulocyte count is usually normal. In severe IDA associated with bleeding, a reticulocyte count of 3-4% may occur.
4. **Reticulocyte hemoglobin content/equivalent (Ret-He, CHr):** low, occurs prior to a drop in hemoglobin; one of the first parameters to correct with initiation of iron therapy.

The mean reticulocyte hemoglobin content (CHr) and reticulocyte hemoglobin equivalent (Ret-He) are **two equivalent parameters that capture the amount of hemoglobin available to the reticulocytes within the previous**

3-4 days. Both parameters directly correlate with the functional availability of iron in the bone marrow.

5. **Platelet count:** varies from thrombocytopenia to thrombocytosis; thrombocytopenia more common in severe IDA.
6. **Blood smear:** red cells are hypochromic and microcytic with anisocytosis and poikilocytosis; thrombocytosis may also be noted.

7. Serum ferritin: The level of serum ferritin reflects the level of body iron stores; it is specific and sensitive. Normal ferritin levels, however, can exist in iron deficiency when bacterial or parasitic infection, malignancy or chronic inflammatory conditions co-exist because ferritin is an acute-phase reactant and its synthesis increases in acute or chronic infection or inflammation.

8. Serum iron and iron saturation percentage(total iron binding capacity): It has the following limitations:

- Wide normal variations (age, sex, laboratory methodology)
- Time consuming
- Subject to error from iron ingestion
- Diurnal variation
- Falls in mild or transient infection.

The **transferrin saturation percentage** with iron is calculated by dividing the serum iron concentration by the total iron binding capacity (TIBC) and multiplying by 100. Normally, about 1/3 of transferrin (33%) has iron bound to it:

TS = Serum Iron Concentration / TIBC x 100

A transferrin saturation value of 30 percent means that 30% of iron-binding sites of transferrin are being occupied by iron.

Interpretation of saturation values

Transferrin saturation, measured as a percentage, helps evaluate iron deficiency anemia or on the contrary, iron overload (in hemosiderosis, iron poisoning or hemochromatosis):

<20% in males, <15% in females – indicates iron deficiency;

>50% – indicates iron overload or hemochromatosis.

9. Bone marrow: not indicated to diagnose iron deficiency. If performed, shows hypercellularity of red cell precursors; distortion of normoblast nuclei may occur.

10. FEP: incorporation of iron into protoporphyrin represents the ultimate stage in the biosynthetic pathway of heme; failure of iron supply will result in an accumulation of free protoporphyrin not incorporated into heme synthesis and the release of erythrocytes into the circulation with high FEP levels. This process occurs prior to the development of microcytic anemia:

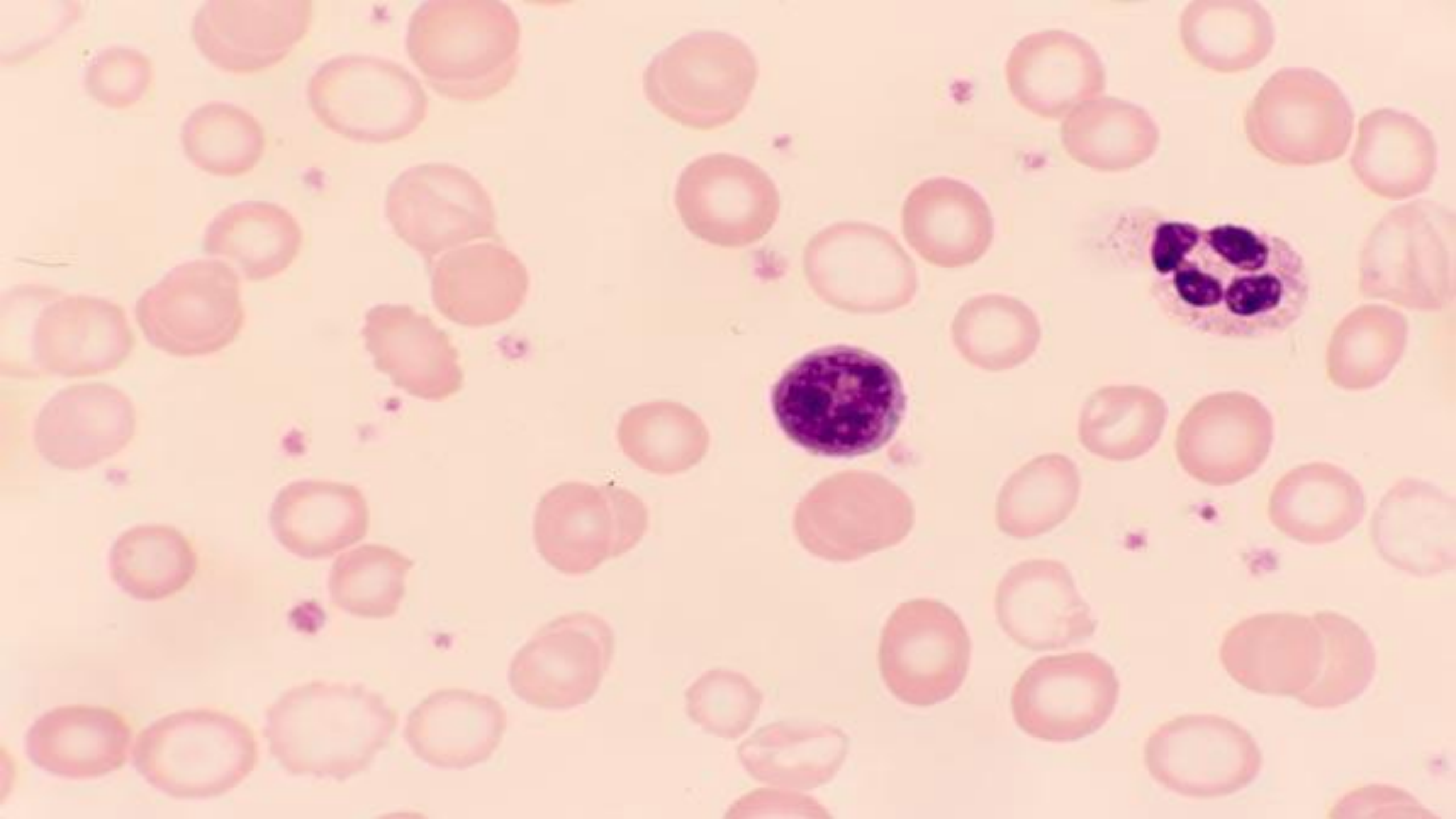
a. Elevated in both iron deficiency and lead poisoning but much higher in lead poisoning; normal in thalassemia trait.

b. Elevated FEP level, an indication for iron therapy even when anemia and microcytosis have not yet developed.

11. Red blood cell (RBC) zinc protoporphyrin/heme ratio: increased when there is disruption of normal heme production. Nonspecific—raised in iron deficiency, lead poisoning; markedly raised in protoporphyria, congenital erythropoietic porphyria. **When there is not enough iron available, as in iron deficiency, or when the insertion of iron is inhibited, as in lead poisoning**, then protoporphyrin combines with zinc instead of iron to form zinc protoporphyrin. ZPP serves no useful purpose in red blood cells since it cannot bind to oxygen

12.Soluble transferrin receptor (STfR) levels: sensitive measure of iron deficiency; correlates with hemoglobin and other laboratory parameters of iron status. STfR is increased in instances of hyperplasia of erythroid precursors such as IDA and thalassemia. It is unaffected by infection and inflammation, unlike serum ferritin. It is, therefore, of great value in distinguishing iron deficiency from the anemia of chronic disease and in identifying iron deficiency in the presence of chronic inflammation or infection. With erythroid hypoplasia or aplasia, for example, aplastic anemia, red cell aplasia, or chronic renal failure, the STfR concentration is decreased.

14.Occult blood in the stool: In about ⅓ of cases, can be detected. Negative guaiac tests for occult bleeding may occur if bleeding is intermittent; for this reason, occult bleeding should be tested for at least five occasions when gastrointestinal bleeding is suspected.



Differential Diagnosis

1. Hemoglobinopathies : thalassemia (α and β)

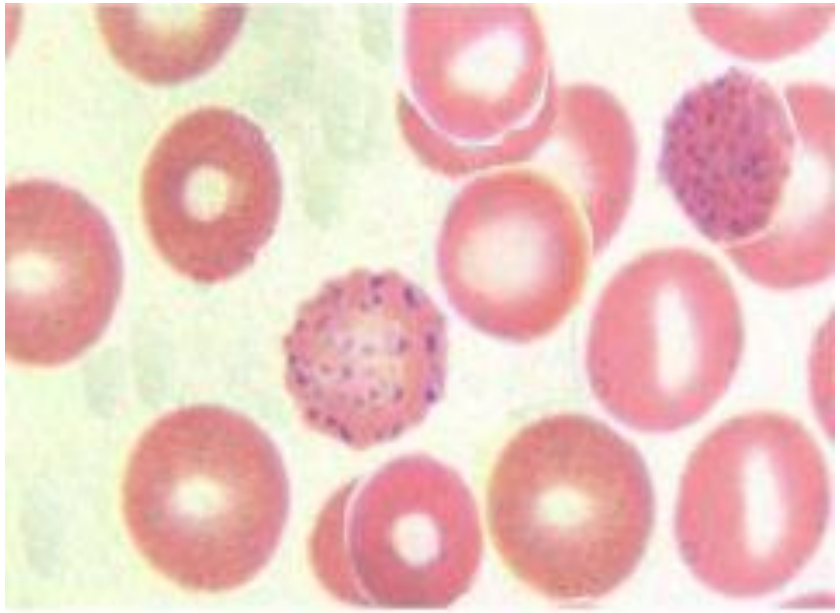
β-thalassemia trait,

- The red cell distribution width is normal in patients with thalassemia but high in those with iron deficiency.
- β-Thalassemia trait characterized by elevated levels of hemoglobin A_2 and/or increased fetal hemoglobin concentration.
- Normal (serum iron, total iron-binding capacity (transferrin), and ferritin) .

α-Thalassemia trait is a diagnosis of exclusion except during the newborn period, when infants with α-thalassemia trait have 3–10% hemoglobin Barts (γ_4) .

2. Lead poisoning: Disorders of heme synthesis caused by a chemical e.g Lead : and iron-deficiency anemia both are associated with elevations of FEP.

- Coarse basophilic stippling of the RBCs often is prominent.
- Elevated blood lead, and urinary coproporphyrin levels are seen.



representing aggregated ribosomes and caused by ineffective heme formation

3. Chronic infections or other inflammatory states:

The anemia of chronic disease (ACD) and infection usually is normocytic, although occasionally it may be slightly microcytic . In contrast to iron-deficiency anemia, in these inflammatory conditions

- **Serum iron level and iron-binding capacity (transferrin) are reduced**
- **Serum ferritin levels are normal or elevated** (ferritin is an acute phase reactant).
- **Serum transferrin receptor levels(STfR)** is increased in instances of hyperplasia of erythroid precursors such as iron-deficiency anemia and thalassemia. It is unaffected by infection and inflammation.It is therefore of great value in distinguishing iron deficiency from the anemia of chronic disease and in identifying iron deficiency in the presence of chronic inflammation or infection. It can be measured by a sensitive enzyme-linked immunosorbent assay (ELISA) technique

4. Sideroblastic anemias

5. Copper deficiency

Dietary counseling

Infants and young children

1. Promote breastfeeding for at least 6 months, if possible.
2. An alternate to breastfeeding is iron-fortified infant formula until 1 year of age. Avoid cow's milk until after the first year of age because of the poor bioavailability of iron in cow's milk and because the protein in cow's milk can cause occult GI bleeding.
3. Provide supplemental iron (2 mg/kg/day) to premature infants by 2 weeks of age.
4. Provide supplemental iron (1 mg/kg) to breastfed infants by 4-6 months of age.
5. Introduction of table foods with iron is imperative in young children.

School-age children/adolescents

Iron-rich foods should be provided to children in all age-groups to support growth and meet the recommended daily allowance as described previously. Facilitators of iron absorption such as vitamin C rich foods (citrus, tomatoes, and potatoes), meat, fish, and poultry should be included in the diet.
Inhibitors of iron absorption such as tea, phosphate, and phytates common in vegetarian diets should be minimized in children with a diagnosis of IDA.

Oral iron medication

The goal of therapy is both correction of the hemoglobin level and replenishment of body iron stores.

1. **Product:** ferrous iron (e.g., ferrous sulfate, ferrous gluconate, ferrous ascorbate, ferrous lactate, ferrous succinate, ferrous fumarate, or ferrous glycine sulfate) is effective.

Ferric irons are often better tasting but absorbed less efficiently.

2. Dose:

a. infants and young children: **3 mg/kg** elemental iron, administered once daily.

b. older children: **65 to 130mg** elemental iron given once daily

c. children with significant GI side effects or resolution of anemia: iron once every other day may be better tolerated with good effect.

3. Duration: a minimum of 3 months of iron therapy is needed in order to replete the iron stores. Assessment of a serum ferritin level prior to iron discontinuation can assist with determining whether further iron therapy is indicated.

4. Response: the more severe the anemia (i.e., lower the hemoglobin to start), the higher the reticulocyte response, and more rapid the rise in hemoglobin:
a. Peak reticulocyte count on days 5-10 following initiation of iron therapy.
b. Then hemoglobin rises on average by 0.25 - 0.4 g/dL/day or hematocrit rises 1% /day during first 7-10 days.
c. Thereafter, hemoglobin rises slower: 0.1 - 0.15 g/dL/day.

5. Failure to respond to oral iron: the following reasons should be considered:
a. Poor adherence: failure or irregular administration of oral iron
b. Inadequate iron dose, ineffective iron preparation, or insufficient duration
c. Persistent or unrecognized blood loss
d. Incorrect diagnosis: thalassemia, sideroblastic anemia
e. Coexistent disease that interferes with absorption or utilization of iron (e.g., chronic inflammation,inflammatory bowel disease)

6. Side effects: constipation, diarrhea, abdominal cramps, nausea, and metallic taste.
Note: Although stools may be dark, oral iron does not produce false-positive results on tests for occult blood.

Intravenous iron therapy

Indications

1. Nonadherence, poor tolerance of oral iron (i.e., failure of oral iron therapy).
2. Severe bowel disease (e.g., inflammatory bowel disease) where the use of oral iron might aggravate the underlying disease of the bowel or iron absorption is compromised, after gastrectomy or duodenal bypass surgery, atrophic gastritis, and celiac disease.
3. Chronic hemorrhage (e.g., congenital coagulation disorders, hereditary telangiectasia, menorrhagia, and chronic hemoglobinuria from prosthetic heart valves). Losing blood at a rate too rapid for oral intake to compensate for the loss.
4. Severe iron deficiency requiring rapid replacement of iron stores.
5. Concomitant iron deficiency and inflammation, resulting in poor iron absorption.
6. Patients anemic after receiving erythropoietin therapy (e.g., renal dialysis and in patients receiving chemotherapy) to ensure an ample and steady supply of iron.
7. Iron deficiency in heart failure.

Intramuscular iron

This is no longer recommended in settings where intravenous iron therapy is available due to the side effects of intramuscular iron, which include pain and iron staining at the injection site, along with variable absorption.

Blood transfusion

A packed red cell transfusion should be given in

-severe anemia requiring correction more rapidly than is possible with oral iron or parenteral iron.

-for debilitated children with infection, especially when signs of cardiac dysfunction are present, and the hemoglobin level is 4 g/dL or less.

Any Questions...
Just Ask!