Nutritional Anemias
Protein-calorie malnutrition

• In developed countries, protein-calorie malnutrition is seen most frequently in hospital patients with chronic illness, or in individuals who suffer from major trauma, severe infection, or the effects of major surgery. Such highly catabolic patients frequently require intravenous administration of nutrients.
In developing countries, an inadequate intake of protein and/or energy may be observed. Affected individuals show a variety of symptoms, including a depressed immune system with a reduced ability to resist infection. Death from secondary infection is common. Two extreme forms of malnutrition are kwashiorkor and marasmus.
Kwashiorkor occurs when protein deprivation is relatively greater than the reduction in total calories. Unlike marasmus, significant protein deprivation is associated with severe loss of visceral protein. Kwashiorkor is frequently seen in children after weaning at about one year of age, when their diet consists predominantly of carbohydrates. Typical symptoms include stunted growth, edema, skin lesions, depigmented hair, anorexia, enlarged fatty liver, and decreased plasma albumin concentration. A child with kwashiorkor frequently shows a deceptively plump belly as a result of edema.
Figure 27.20
Child with kwashiorkor.
Marasmus occurs when calorie deprivation is relatively greater than the reduction in protein. Marasmus usually occurs in children younger than one year of age when the mother's breast milk is supplemented with thin watery gruels of native cereals, which are usually deficient in protein and calories. Typical symptoms include arrested growth, extreme muscle wasting (emaciation), weakness, and anemia. Victims of marasmus do not show the edema or changes in plasma proteins observed in kwashiorkor.
Figure 28.1
Classification of the vitamins.
Figure 28.2
Classification of nutritional anemias by cell size. MCV = Mean corpuscular volume. The normal MCV level for people older than age 18 is between 80 and 100 μm³.
FOLIC ACID

- Folic acid (or folate), which plays a key role in one-carbon metabolism, is essential for the biosynthesis of several compounds. Folic acid deficiency is probably the most common vitamin deficiency in the United States, particularly among pregnant women and alcoholics.
A. Function of folic acid

- Tetrahydrofolate receives one-carbon fragments from donors such as serine, glycine, and histidine and transfers them to intermediates in the synthesis of amino acids, purines, and thymine—a pyrimidine found in DNA.
Folate and anemia

• Inadequate serum levels of folate can be caused by increased demand (for example, pregnancy and lactation), poor absorption caused by pathology of the small intestine alcoholism, or treatment with drugs that are dihydrofolate reductase inhibitors for example, methotrexate.
• A folate-free diet can cause a deficiency within a few weeks. A primary result of folic acid deficiency is **megaloblastic anemia**, caused by diminished synthesis of purines and thymidine, which leads to an inability of cells to make DNA and, therefore, they cannot divide. [Note: It is important to evaluate the cause of the megaloblastic anemia prior to instituting therapy, because vitamin **B12** deficiency indirectly causes symptoms of this disorder.]
Folate and neural tube defects in the fetus

Spina bifida and anencephaly, the most common neural tube defects, affect approximately 4000 pregnancies in the United States annually. Folic acid supplementation before conception and during the first trimester has been shown to virtually eliminate the defects. Therefore, all women of childbearing age should consume 0.4 mg./day of folic acid to reduce the risk of having a pregnancy affected by neural tube defects. Adequate folate nutrition must occur at the time of conception because critical folate-dependent development occurs in the first weeks of fetal life at a time when many women are not yet aware of their pregnancy.
The U.S. Food and Drug Administration has authorized the addition of folic acid to enriched grain products, resulting in a dietary supplementation of about 0.1 mg/day. It is estimated that this supplementation will allow approximately fifty percent of all reproductive-aged women to receive 0.4 mg of folate from all sources. However, folic acid intake should not exceed approximately 1 mg/day to avoid complicating the diagnosis of vitamin B₁₂ deficiency.
Figure 28.4
Bone marrow histology in normal and folate-deficient individuals.
B12 Vitamin is required in humans for two essential enzymatic reactions: the synthesis of methionine and the isomerization of methylmalonyl CoA that is produced during the degradation of some amino acids, and fatty acids with odd numbers of carbon atoms. When the vitamin is deficient, abnormal fatty acids accumulate and become incorporated into cell membranes, including those of the nervous system. This may account for some of the neurologic manifestations of vitamin B12 deficiency.
Figure 28.5
Reactions requiring cofactor forms of vitamin B₁₂.
Cobalamin contains a corrin ring system that differs from the porphyrins in that two of the pyrrole rings are linked directly rather than through a methene bridge. Cobalt is held in the center of the corrin ring by four coordination bonds from the nitrogens of the pyrrole groups. The remaining coordination bonds of the cobalt are with the nitrogen of 5,6-dimethylbenzimidazole and with cyanide in commercial preparations of the vitamin in the form of cyanocobalamin. The coenzyme forms of cobalamin are 5'-deoxyadenosyl-cobalamin in which cyanide is replaced with 5'-deoxyadenosine (forming an unusual carbon-cobalt bond), and methylcobalamin in which cyanide is replaced by a methyl group.
Structure of Vit. B₁₂ (cyanocobalamin) & Its coenzyme form methylcobalamin
Distribution of cobalamin

- Vitamins B12 synthesized only by microorganisms; it is not present in plants. Animals obtain the vitamin preformed from their natural flora or by eating foods derived from other animals. Cobalamins present in appreciable amounts in liver, whole milk, eggs, oysters, fresh shrimp, pork, and chicken.
Absorption of Vit. B12
Clinical indications for vitamin B₁₂

• In contrast to other water-soluble vitamins, significant amounts 4 to 5 mg. of vitamin B₁₂ are stored in the body. As a result, it may take several years for the clinical symptoms of B₁₂ deficiency to develop in individuals who have had a partial or total gastrectomy (who, therefore, become intrinsic factor-deficient) and can no longer absorb the vitamin.
Pernicious anemia

Vitamin B12 deficiency is rarely a result of an absence of the vitamin in the diet. It is much more common to find deficiencies in patients who fail to absorb the vitamin from the intestine, resulting in pernicious anemia. The disease is most commonly a result of an autoimmune destruction of the gastric parietal cells that are responsible for the synthesis of a glycoprotein called intrinsic factor.
Patients with cobalamin deficiency are usually anemic, but later in the development of the disease they show neuropsychiatric symptoms. However, central nervous system (CNS) symptoms may occur in the absence of anemia. The CNS effects are irreversible and occur by mechanisms that appear to be different from those described for megaloblastic anemia. The disease is treated by giving high-dose B12 orally, or intramuscular injection of cyanocobalamin. Therapy must be continued throughout the lives of patients with pernicious anemia.
• [Note: Folic acid administration alone reverses the hematologic abnormality and, thus, masks the B12 deficiency, which can then proceed to severe neurologic dysfunction and pathology; therefore megaloblastic anemia should not be treated with folic acid alone, but rather with a combination of folate and vitamin B12]
Iron Metabolism

- Iron deficiency is the most common cause of anaemia throughout the world.
- Control of iron balance being at the level of iron absorption
- **Sources:**
  - The **best sources** of food iron include liver, meat, egg yolk, green leafy vegetables, dates, whole grains and cereals.
Iron in diet and body

• The normal daily diet contains about 10 to 20 mg of iron, mostly in the form of heme.
• About 20% of heme iron and only 1% to 2% of non-heme iron) is absorbable.
• The total body iron content is normally about 2 gm in women and as high as 6 gm in men divided into functional and storage pools.
• About 80% of the functional iron is found in hemoglobin; myoglobin and iron-containing enzymes such as catalase and the cytochromes contain the rest.

• The storage pool (hemosiderin and ferritin) contains about 15% to 20% of total body iron.

• Healthy young females have smaller stores of iron than do males.
Factors affecting iron absorption

• Factors increasing the iron absorption:
  • Iron is mainly absorbed in the ferrous form.
  • Ascorbic acid & cysteine favors the reduction of ferric form of iron to ferrous form.
  • HCL also favors the reduction of ferric form of iron to ferrous form.
  • In iron deficiency state, the iron absorption is increased to 2-10 times that of normal.
Factors decreasing iron absorption

• Phytates and phosphates in the food decreases iron absorption.

• **Achlorohydria:**
  • The deficiency of HCL results in impaired conversion of ferric form of iron to ferrous form of iron.
  • Iron absorption is deceases in the presence of gastrointestinal diseases.
Iron Distribution in Healthy Young Adults (mg)

<table>
<thead>
<tr>
<th>Pool</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>3450</td>
<td>2450</td>
</tr>
<tr>
<td><strong>Functional</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>2100</td>
<td>1750</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>300</td>
<td>250</td>
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<tr>
<td>Enzymes</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td><strong>Storage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin, hemosiderin</td>
<td>1000</td>
<td>400</td>
</tr>
</tbody>
</table>
Transport of iron between storage and functional pools

• Iron in the body is recycled extensively between the functional and storage pools.
• It is transported in plasma by an iron-binding glycoprotein called transferrin, which is synthesized in the liver.
• Transferrin is about one third saturated with iron, yielding serum iron levels that average $120 \, \mu\text{g/dL}$ in men and $100 \, \mu\text{g/dL}$ in women.
• The major function of plasma transferrin is to deliver iron to cells, including erythroid precursors, which require iron to synthesize Hb. Erythroid precursors possess high-affinity receptors for transferrin, which mediate iron import through receptor-mediated endocytosis.
Iron homeostasis
Removal of iron

• Free iron is highly toxic and it is important that iron be removed.

• This is achieved by binding iron in the storage pool tightly to either ferritin or hemosiderin.

• Ferritin is a protein-iron complex that is found at highest levels in the liver, spleen, bone marrow, and skeletal ms.

• In liver, most ferritin is stored within the parenchymal cells;

• In spleen and bone marrow, it is found mainly in macrophages.

• Hepatocyte iron is derived from plasma transferrin, whereas storage iron in macrophages is derived from the breakdown of red cells.
Iron-donating tissues and iron stores

- Macrophages 500 mg
  - RE stores
  - Ineffective erythropoiesis
- Hepatocytes 250 mg
  - Liver stores
- Gut
  - Absorption ≈ 1 mg/day
  - Loss ≈ 1 mg/day
- Plasma (transferrin) 4 mg

Iron receptor tissues and functional iron compounds

- Red cell haemoglobin 2500 mg
- Bone marrow
  - Erythroblasts 150 mg
- Tissues
  - Iron-containing enzymes 150 mg
  - Myoglobin 300 mg
Storage of iron

• Intracellular ferritin is located in the cytosol and in lysosomes.
• Partially degraded protein shells of ferritin aggregate into hemosiderin granules.
• Iron in hemosiderin is chemically reactive and turns blue-black when exposed to potassium ferrocyanide, which is the basis for the Prussian blue stain.
• Normally only trace amounts of hemosiderin are found in macrophages in the bone marrow, spleen, and liver.
• In iron-overloaded cells, most iron is stored in hemosiderin.
Iron absorption

- Iron is absorbed in the proximal duodenum.

- As body iron stores rise, absorption falls, and vice versa.

- Luminal nonheme iron is mostly in the Fe\([3]+\) (ferric) state and must first be reduced to Fe\([2]+\) (ferrous) iron by ferrireductases, such as b cytochromes.

- Fe\([2]+\) iron is then transported across the apical membrane by divalent metal transporter 1 (DMT1).
Duodenal epithelial cell uptake of heme and nonheme iron.
• Hepcidin is now acknowledged to be the main iron regulatory hormone. It is a 25-amino acid peptide exclusively synthesized by the liver.

• **Function. Hephaestin** is involved in the metabolism and homeostasis of iron and possibly copper. It is a transmembrane copper-dependent ferroxidase responsible for transporting dietary iron from intestinal enterocytes into the circulatory system. The highest expression of **hephaestin** is found in small intestine
Fate of absorbed iron

• Iron that enters the duodenal cells can follow one of two pathways: transport to the blood or storage as mucosal iron.

• Fe\(^{2+}\) iron destined for the circulation, is transported from the cytoplasm across the basolateral enterocyte membrane by ferriportin.

• This process is coupled to the oxidation of Fe\(^{2+}\) iron to Fe\(^{3+}\) iron, which is carried out by the iron oxidases hephaestin and ceruloplasmin.

• Newly absorbed Fe\(^{3+}\) iron binds rapidly to the plasma protein transferrin, which delivers iron to red cell progenitors in the marrow.
DMT1 and ferriportin are widely distributed in the body and are involved in iron transport in other tissues as well.

DMT1 also mediates the uptake of “functional” iron (derived from endocytosed transferrin) across lysosomal membranes into the cytosol of red cell precursors in the bone marrow.

Ferriportin plays an important role in the release of storage iron from macrophages.
causes for dietary iron deficiency

• Infants, who are at high risk due to the very small amounts of iron in milk.
• Poverty, who can have suboptimal diets for socioeconomic reasons at any age.
• The elderly, who often have restricted diets with little meat because of limited income or poor dentition.
• Teenagers who eat too much “junk” food.
Other causes of iron deficiency

• Impaired absorption is found in sprue, other causes of fat malabsorption (steatorrhea), and chronic diarrhea.

• Gastrectomy impairs iron absorption by decreasing hydrochloric acid and transit time through the duodenum.

• Chronic blood loss is the most common cause of iron deficiency in the Western world.

• Iron deficiency in adult men and postmenopausal women must be attributed to gastrointestinal blood loss until proven otherwise.
Pathogenesis

• Whatever its basis, iron deficiency produces a hypochromic microcytic anemia.
• At the outset of negative iron balance, reserves in the form of ferritin and hemosiderin may be adequate to maintain normal hemoglobin and hematocrit levels as well as normal serum iron and transferrin saturation.
• Progressive depletion of these reserves first lowers serum iron and transferrin saturation levels without producing anemia.
• In this early stage there is increased erythroid activity in the bone marrow.
• Anemia appears only when iron stores are completely depleted and is accompanied by low serum iron, ferritin, and transferrin saturation levels.
Hypochromic microcytic anemia of iron deficiency (peripheral blood smear). Note the small red cells containing a narrow rim of peripheral hemoglobin. Scattered fully hemoglobinized cells, present due to recent blood transfusion, stand in contrast.
Both the hemoglobin and hematocrit are depressed, usually to a moderate degree, in association with hypochromia, microcytosis, and modest poikilocytosis.

The serum iron and ferritin are low, and the total plasma iron-binding capacity (reflecting elevated transferrin levels) is high.

Low serum iron with increased iron-binding capacity results in a reduction of transferrin saturation to below 15%.

In uncomplicated iron deficiency, oral iron supplementation produces an increase in reticulocytes in about 5 to 7 days.
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