Hemoglobin

The major function of red blood cells is to transport hemoglobin, which in turn carries oxygen from the lungs to the tissues. Hemoglobin, the protein that makes red blood cells red, binds easily and reversibly with oxygen, and most oxygen carried in blood is bound to hemoglobin. Normal values for hemoglobin are 13–18 grams per 100 milliliters of blood (g/100 ml) in adult males, and 12–16 g/100 ml in adult females.

Formation of Hemoglobin

Synthesis of hemoglobin begins in the **proerythroblasts** and continues even into the **reticulocyte** stage of the red blood cells. Therefore, when reticulocytes leave the bone marrow and pass into the blood stream, they continue to form minute quantities of hemoglobin for another day or so until they become mature erythrocytes.

Figure 1 shows the basic chemical steps in the formation of hemoglobin. First, succinyl-CoA, formed in the Krebs metabolic cycle, binds with glycine to form a pyrrole molecule. In turn, four pyrroles combine to form protoporphyrin IX, which then combines with iron to form the heme molecule. Finally, each heme molecule combines with a long polypeptide chain, a *globin* synthesized by ribosomes, forming a subunit of hemoglobin called a *hemoglobin chain* (Figure 2). Each chain has a molecular weight of about 16,000; four of these in turn bind together loosely to form the whole hemoglobin molecule.

There are several slight variations in the different subunit hemoglobin chains, depending on the amino acid composition of the polypeptide portion. The different types of chains are designated alpha chains, beta chains, gamma chains, and delta chains.
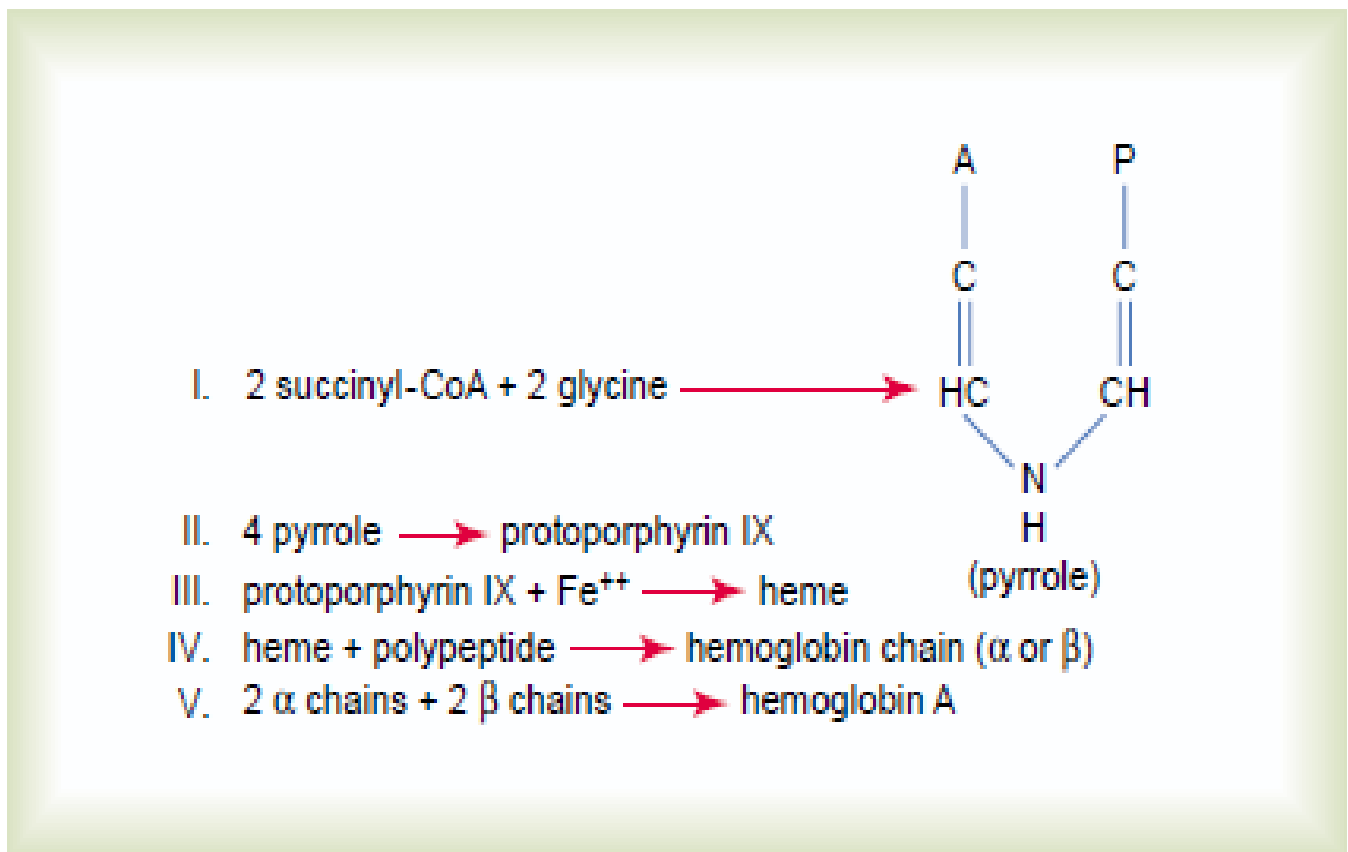

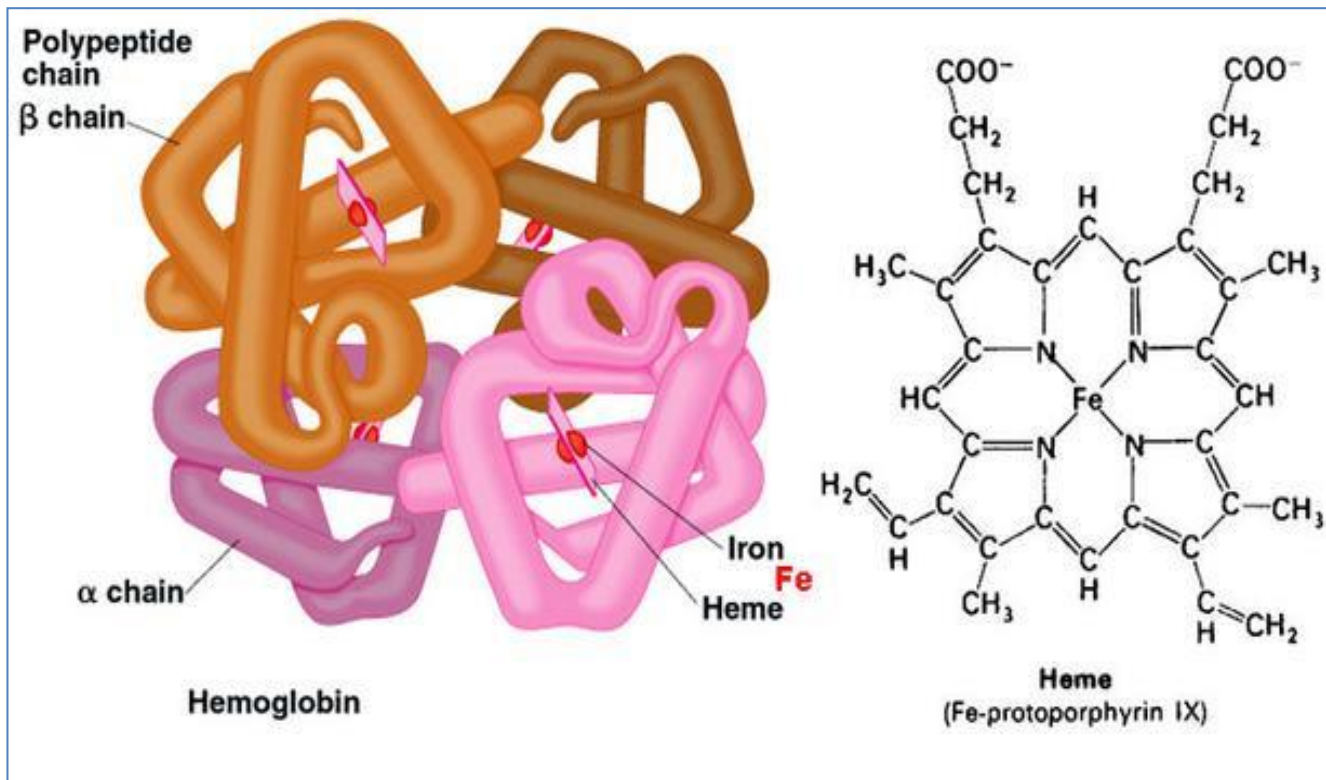**Figure (1) : Formation of Hemoglobin**

Figure (2) : Structure of Hemoglobin

Types of Hemoglobin

1. **Hemoglobin A:** is a combination of two *alpha chains* and two of *beta chains*, it is the most common form of hemoglobin (95-98%) in the adult human being.
2. **Hemoglobin A2:** is a combination of two *alpha chains* and two of *delta chains*, it represents 2-3% of hemoglobin in the adult human being.
3. **Hemoglobin F (fetus Hb):** is a combination of two *alpha chains* and two of *gamma chains*, also it found in newborns blood of about 1% of their hemoglobin.

Because each hemoglobin chain has a heme prosthetic group containing an atom of iron, and because there are four hemoglobin chains in each hemoglobin molecule, one finds four iron atoms in each hemoglobin molecule; each of these can bind loosely with one molecule of oxygen, making a total of four molecules of oxygen (or eight oxygen atoms) that can be transported by each hemoglobin molecule.

The types of hemoglobin chains in the hemoglobin molecule determine the binding affinity of the hemoglobin for oxygen. Abnormalities of the chains can alter the physical characteristics of the hemoglobin molecule as well.

For instance, in sickle cell anemia, the amino acid valine is substituted for glutamic acid at one point in each of the two beta chains. When this type of hemoglobin is exposed to low oxygen, it forms elongated crystals inside the red blood cells that are sometimes 15 micrometers in length. These make it almost impossible for the cells to pass through many small capillaries, and the spiked ends of the crystals are likely to rupture the cell membranes, leading to sickle cell anemia.

Iron Metabolism

Because iron is important for the formation not only of hemoglobin but also of other essential elements in the body (e.g., *myoglobin, cytochromes, cytochrome oxidase, peroxidase, catalase*), it is important to understand the means by which iron is utilized in the body.

The total quantity of iron in the body averages 3 to 5 grams in adults, which two-thirds are present in the O2-carrying molecule, **haemoglobin**; about 65 percent of which is in the form of hemoglobin. About 4 per cent is in the form of **myoglobin**, 1 percent is in the form of the various **heme compounds** that promote intracellular oxidation, 0.1 percent is combined with the protein **transferrin** in the blood plasma, and 15 to 30 percent is stored for later use, mainly in the reticuloendothelial system and liver parenchymal cells, principally in the form of **ferritin**.

Transport and Storage of Iron

Transport, storage, and metabolism of iron in the body are diagrammed in Figure 3 and can be explained as follows:

When iron is absorbed from the small intestine, it immediately combines in the blood plasma with a beta globulin, *apotransferrin,* to form *transferrin,* which is then transported in the plasma. The iron is loosely bound in the transferrin and, consequently, can be released to any tissue cell at any point in the body.

Excess iron in the blood is deposited *especially* in the liver hepatocytes and less in the reticuloendothelial cells of the bone marrow.

In the cell cytoplasm, iron combines mainly with a protein, *apoferritin,* to form *ferritin.* Apoferritin has a molecular weight of about 460,000, and varying quantities of iron can combine in clusters of iron radicals with this large molecule; therefore, ferritin may contain only a small amount of iron or a large amount. This iron stored as ferritin is called *storage iron.*

Smaller quantities of the iron in the storage pool are in an extremely insoluble form called *hemosiderin.* This is especially true when the total quantity of iron in the body is more than the apoferritin storage pool can accommodate. Hemosiderin collects in cells in the form of large clusters that can be observed microscopically as large particles. In contrast, ferritin particles are so small and dispersed that they usually can be seen in the cell cytoplasm only with the electron microscope.

When the quantity of iron in the plasma falls low, some of the iron in the ferritin storage pool is removed easily and transported in the form of transferrin in the plasma to the areas of the body where it is needed. A unique characteristic of the transferrin molecule is that it binds strongly with receptors in the cell membranes of erythroblasts in the bone marrow. Then, along with its bound iron, it is ingested into the erythroblasts by endocytosis. There the transferrin delivers the iron directly to the mitochondria, where heme is synthesized.

In people who do not have adequate quantities of transferrin in their blood, failure to transport iron to the erythroblasts in this manner can cause severe *hypochromic anemia*—that is, red cells that contain much less hemoglobin than normal.

When red blood cells have lived their life span and are destroyed, the hemoglobin released from the cells is ingested by monocyte-macrophage cells. There, iron is liberated and is stored mainly in the ferritin pool to be used as needed for the formation of new hemoglobin.
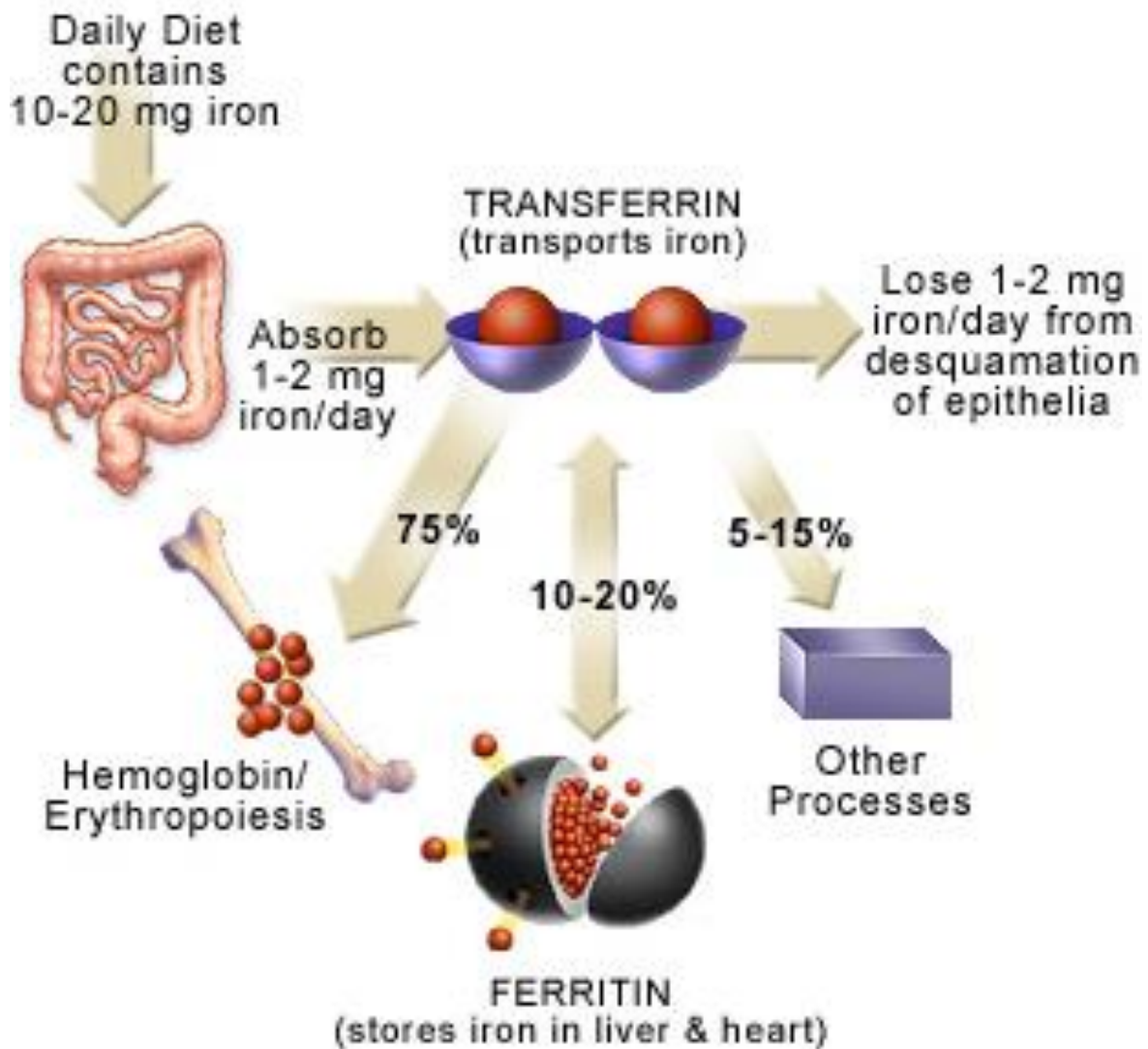

Figure (3): Iron transport and storage

Daily Loss of Iron

A man excretes about 0.6 milligram of iron each day, mainly into the feces. Additional quantities of iron are lost when bleeding occurs. For a woman, additional menstrual loss of blood brings longterm iron loss to an average of about 1.3 mg/day.

Absorption of Iron from the Intestinal Tract

Iron is absorbed from all parts of the small intestine, mostly by the following mechanism. The liver secretes moderate amounts of *apotransferrin* into the bile, which flows through the bile duct into the duodenum, where the apotransferrin binds with free iron and also with certain iron compounds, such as hemoglobin and myoglobin from meat, two of the most important sources of iron in the diet. This combination is called *transferrin.* It, in turn, is attracted to and binds with receptors in the membranes of the intestinal epithelial cells. Then, by pinocytosis, the transferrin molecule, carrying its iron store, is absorbed into the epithelial cells and later released into the blood capillaries beneath these cells in the form of *plasma transferrin.*

Iron absorption from the intestines is extremely slow, at a maximum rate of only a few milligrams per day. This means that even when tremendous quantities of iron are present in the food, only small proportions can be absorbed.

Iron Balance

When the body has become saturated with iron so that essentially all apoferritin in the iron storage areas is already combined with iron, the rate of additional iron absorption from the intestinal tract becomes greatly decreased. Conversely, when the iron stores have become depleted, the rate of absorption can accelerate probably five or more times normal. Thus, total body iron is regulated mainly by altering the rate of absorption.

Feedback Mechanisms for Regulating Iron Absorption

Two mechanisms that play at least some rules in Regulating Iron Absorption are the following:

1. When essentially all the apoferritin in the body has become saturated with iron, it becomes difficult for transferring to release iron to the tissue. As a consequence, the transferring, which is normally only one-third saturated with iron, now becomes almost fully bound with iron, so that the transferring accepts almost no new iron from the mucosal cells. Then, as a final stage of this process, the excess iron in the mucosal cells themselves depresses active absorption of iron from the intestinal lumen.

2. When the body already has excess stores of iron, the liver decreases its rate of formation of apotransferrin, thus reducing the concentration of this iron-transporting molecule in the plasma and also in the bile. Therefore, less iron is then absorbed by the intestinal apotransferrin mechanism, and less iron can also be transported away from the intestinal epithelial cells in the plasma by plasma transferrin.