



- PLASMA is the clear, yellowish fluid portion of blood, lymph, or intramuscular fluid in which cells are suspended. It differs from serum in that it contains fibrin and other soluble clotting elements and
- (SERUM) is the clear yellowish fluid obtained upon separating whole blood into its solid and liquid components after it has been allowed to clot. Also called *blood serum*.

THE BLOOD HAS MANY FUNCTIONS

• The functions of blood—except for specific cellular ones such as oxygen transport and cell-mediated immunologic defense—are carried out by plasma and its constituents.

Plasma consists of:

- water, electrolytes, metabolites, nutrients, proteins, and hormones.
- The water and electrolyte composition of plasma is practically the same as that of all extracellular fluids.
- Laboratory determinations of levels of Na+, K+, Ca2+, Cl-, HCO3-, PaCO2, and of blood pH are important in the management of many patients.

Major functions of blood.

- Respiration—transport of oxygen from the lungs to the tissues and of CO2 from the tissues to the lungs.
- Nutrition—transport of absorbed food materials.
- Excretion—transport of metabolic waste to the kidneys, lungs, skin, and intestines for removal.
- Maintenance of the normal acid-base balance in the body.



- Regulation of water balance through the effects of blood on the exchange of water between the circulating fluid and the tissue fluid.
- Regulation of body temperature by the distribution of body heat.
- Defense against infection by the white blood cells and circulating antibodies.

- Transport of hormones and regulation of metabolism.
- Transport of **metabolites**.
- Coagulation.



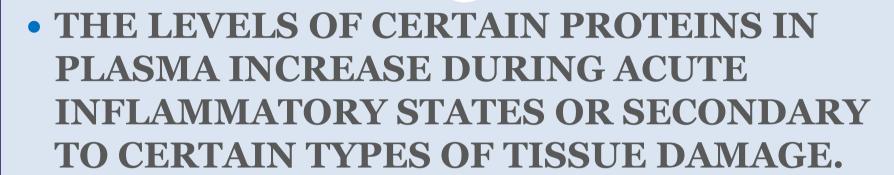
- The concentration of total protein in human plasma is approximately **7.0**–**7.5g**/**dL** and comprises the major part of the solids of the plasma.
- The proteins of the plasma are actually a complex mixture that includes not only simple proteins but also conjugated proteins such as **glycoproteins** and various types of lipoproteins.

- Albumin- 69,000.
- Hemoglobin- 64,500
- β1-Globulin-90,000
- γ-Globulin-156,000
- α1-Lipoprotein-200,000
- β1-Lipoprotein-1,300,000
- Fibrinogen- 340,000

Half lives of plasma proteins

- The half-lives obtained for albumin and haptoglobin in normal healthy adults are approximately 20 and 5 days, respectively.
- In certain diseases, the half-life of a protein may be markedly altered. For instance, in some gastrointestinal diseases such as regional ileitis (Crohn disease), considerable amounts of plasma proteins, including albumin, may be lost into the bowel through the inflamed intestinal mucosa.

Acute Phase Proteins



• These proteins are called "acute phase proteins" (or reactants).



- include C-reactive protein (CRP, so-named because it reacts with the C polysaccharide of pneumococci).
- α1-antitrypsin
- haptoglobin
- α1-acid glycoprotein
- and fibrinogen.

Functions of Plasma Proteins.

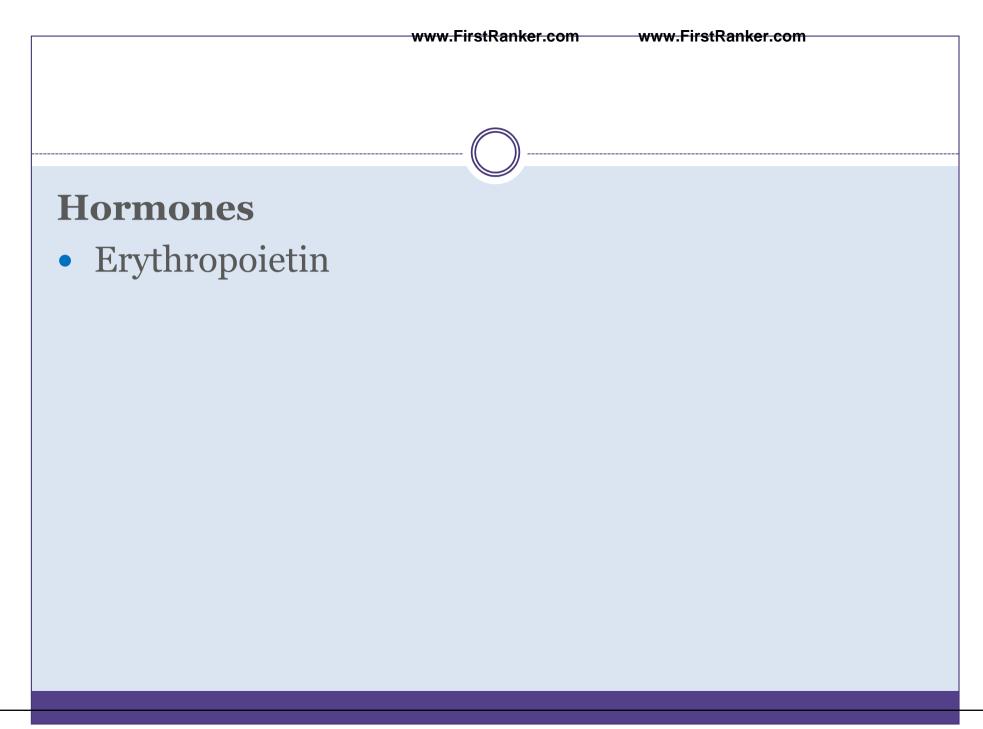


Antiproteases

- Antichymotrypsin
- α1-Antitrypsin (α1-antiproteinase)
- α2-Macroglobulin
- Antithrombin

Enzymes

- Function in blood, eg, coagulation factors,
- cholinesterase
- Leakage from cells or tissues, eg, aminotransferases



Immune defense

- Immunoglobulins,
- Complement proteins,
- β2-microglobulin



- proteins (eg,inflammatory C-reactive protein,
- α1-acid glycoresponses
- protein [orosomucoid])

Transport or binding proteins

• Albumin (various ligands including bilirubin, free fatty acids, ions [Ca2+], metals [eg, Cu2+, Zn2+], metheme, steroids, other hormones, and a variety of drugs.



- Ceruloplasmin (contains Cu2+;)
- Corticosteroid-binding globulin (transcortin) (binds cortisol)
- Haptoglobin (binds extracorpuscular hemoglobin)
- Lipoproteins (chylomicrons, VLDL, LDL, HDL)
- Hemopexin (binds heme)



- Retinol-binding protein (binds retinol)
- Sex hormone-binding globulin (binds testosterone, estradiol)
- Thyroid-binding globulin (binds T4, T3)
- Transferrin (transport iron)
- Transthyretin (formerly prealbumin; binds T4 and forms a complex with retinol-binding protein)

Albumin

• Albumin Is the Major Protein in Human Plasma.



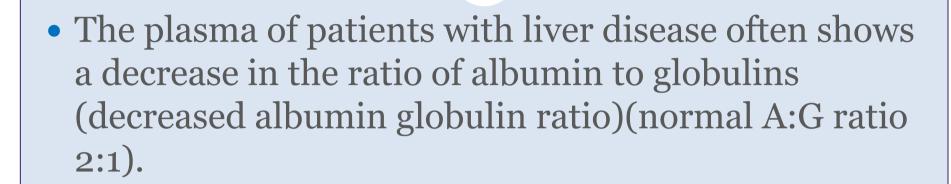
- Albumin (69 kDa) is the major protein of human plasma (3.4–4.7 g/dL) and makes up approximately 60% of the total plasma protein.
- About 40% of albumin is present in the plasma, and the other 60% is present in the extracellular space.



- The liver produces about **12 g** of albumin per day, representing about 25% of total hepatic protein synthesis and half its secreted protein.
- Albumin is initially synthesized as a **preproprotein.** Its **signal peptide is removed as it passes into the** cisternae of the rough endoplasmic reticulum.



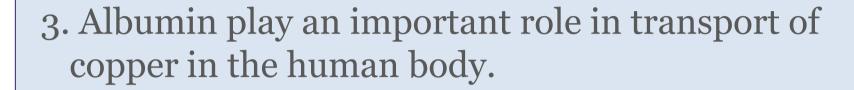
- Its signal peptide is removed as it passes into the cisternae of the rough endoplasmic reticulum, and a hexapeptide at the resulting amino terminal is subsequently cleaved off farther along the secretory pathway.
- The synthesis of albumin is depressed in a variety of diseases, particularly those of the liver.



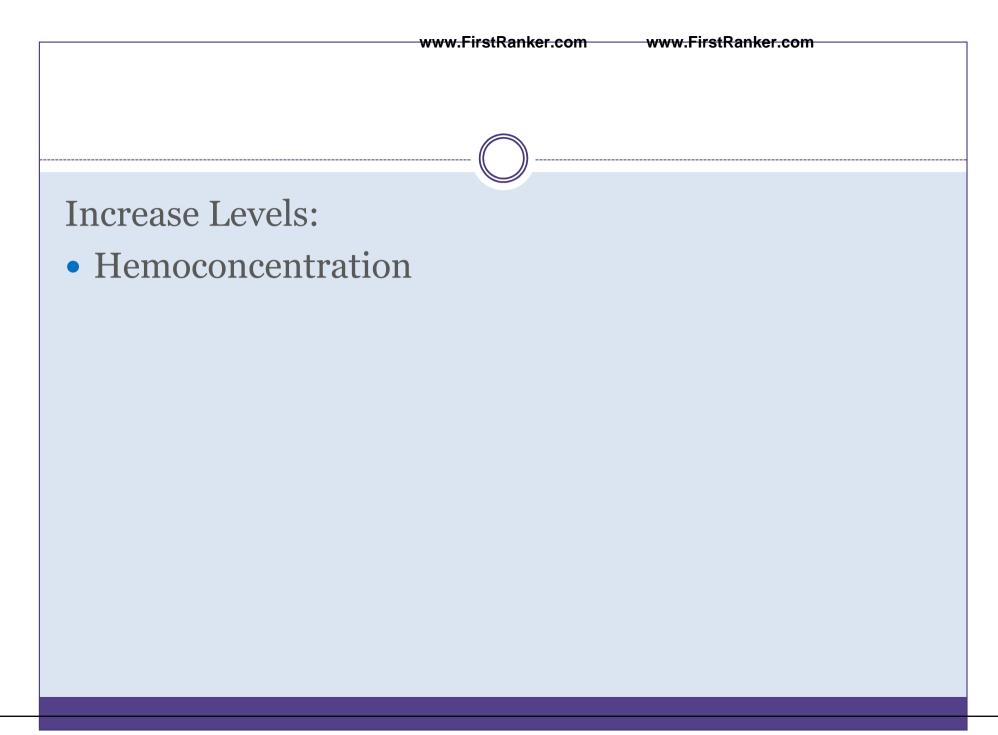
• The synthesis of albumin decreases relatively early in conditions of protein malnutrition, such as kwashiorkor.



• free fatty acids (FFA), calcium, certain steroid hormones, bilirubin, and some of the plasma tryptophan.



4. A variety of drugs, including sulfonamides, penicillin G, dicumarol, and aspirin, are bound to albumin.

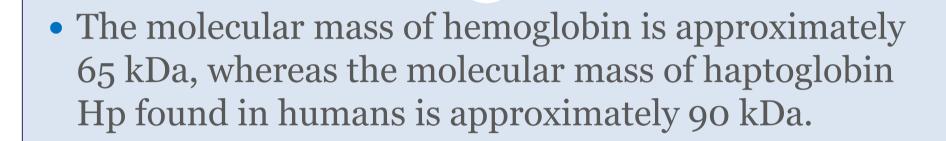




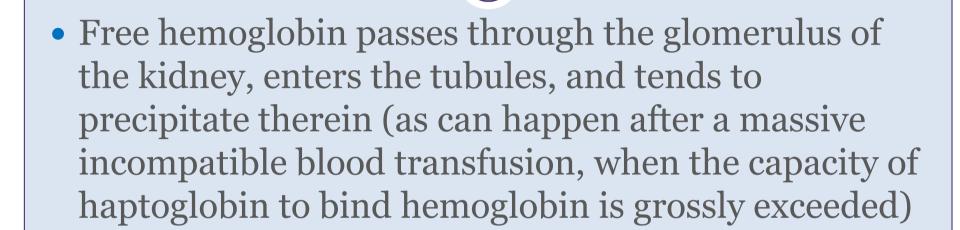
- Inflammation, infection, trauma, surgery, malignancy.
- Liver disease
- Nephrotic syndrome
- Malnutrition
- Pregnancy
- Premature infants
- Genetic analbuminemia

Haptoglobin

 Haptoglobin Binds Extracorpuscular Hemoglobin, Preventing Free Hemoglobin From Entering the Kidney.



• Thus, the Hb-Hp complex has a molecular mass of approximately 155 kDa.



• However, the Hb-Hp complex is too large to pass through the glomerulus.

Fibrinogen

- Fibrinogen is converted to fibrin by thrombin.
- Fibrin monomers polymerizes to form fibrin clot.

Transferrin



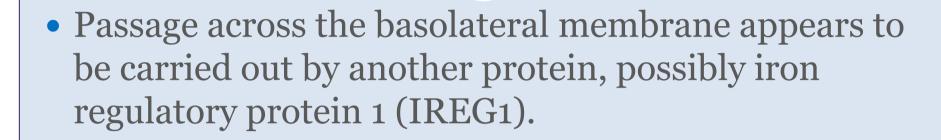
• Transferrin (Tf) is a plasma protein that plays a central role in transporting iron around the body to sites where it is needed.



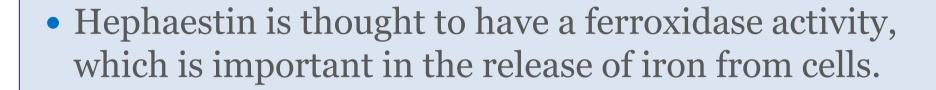
- Enterocytes in the proximal duodenum are responsible for absorption of iron. Incoming iron in the Fe₃₊ state is reduced to Fe₂₊ by a **ferri** reductase present on the surface of enterocytes.
- Vitamin C in food also favors reduction of ferric iron to ferrous iron.



- This protein is not specific for iron, as it can transport a wide variety of divalent cations.
- Once inside an enterocyte, iron can either be stored as ferritin or transferred across the basolateral membrane into the plasma, where it is carried by transferrin.



• This protein may interact with the copper-containing protein hephaestin, a protein similar to ceruloplasmin .



• Thus, Fe2+ is converted back to Fe3+, the form in which it is transported in the plasma by transferrin

Overall regulation of iron absorption

1. Dietary regulation

• The level of the enterocyte, where further absorption of iron is blocked if a sufficient amount has been taken up (so-called dietary regulation exerted by "mucosal block").



Erythropoeitic Regulation

- It also appears to be responsive to the overall requirement of erythropoiesis for iron (erythropoietic regulation).
- Absorption is excessive in hereditary hemochromatosis

Transferrin Shuttles Iron to Sites Where It Is Needed.

• There are receptors (TfRs) on the surfaces of many cells for transferrin. It binds to these receptors and is internalized by receptor-mediated endocytosis.

Ferritin



Ferritin Stores Iron in Cells

- Ferritin contains approximately 23% iron
- Ferritin is composed of 24 subunits of 18.5 kDa, which surround in a micellar form some 3000–4500 ferric atoms.



• In patients with excess iron, the amount of ferritin in plasma is markedly elevated.

• The amount of ferritin in plasma serves as an index of body iron stores.

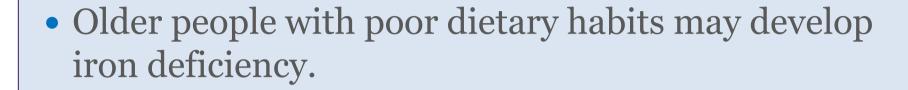


- In contrast, when iron levels are low, the TfR mRNA is stabilized and increased synthesis of receptors occurs, while ferritin mRNA is apparently stored in an inactive form.
- This is an important example of control of expression of proteins at the **translational level.**

- Liver disease- Cirrhosis
- Infection, inflammation, surgery
- Chronic renal infection
- Chronic viral infection

Iron Deficiency Anemia

- iron metabolism is **particularly important in** women due to:
- 1. Menstural loss
- 2. Increase fetal demand in pregnancy.

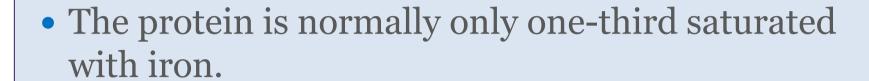


Iron deficiency anemia is due to:

- inadequate intake,
- Inadequate utilization
- excessive loss of iron

Total iron-binding capacity

- The concentration of transferrin in plasma is approximately 300 mg/dL.
- This amount of transferrin can bind 300 μg of iron per deciliter, this represents the **total iron-binding capacity of plasma.**



• In **iron deficiency anemia**, **the protein is even less** saturated with iron, whereas in conditions of storage of excess iron in the body (e.g, hemochromatosis) the saturation with iron is much greater than one-third.

Hereditary Hemochromatosis

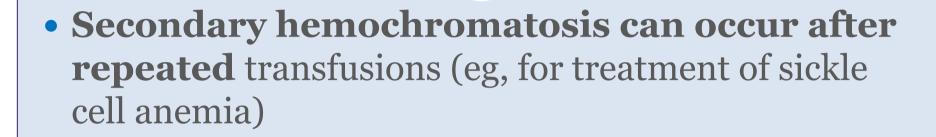
- Hereditary (primary) hemochromatosis is a very prevalent autosomal recessive disorder in certain parts of the world (e.g, Scotland, Ireland, and North America).
- It is characterized by excessive storage of iron in tissues, leading to tissue damage.
- Total body iron ranges between **2.5 g** and **3.5 g** in normal adults; in primary hemochromatosis it usually exceeds **15 g**.



protein product.

- Accumulation of iron in various tissues, but particularly liver, pancreatic islets, skin, and heart muscle.
- Iron directly or indirectly causes damage to the above tissues, resulting in hepatic cirrhosis, diabetes mellitus, skin pigmentation, and cardiac problems

Secondary hemochromatosis



• excessive oral intake of iron (eg, by African Bantu peoples who consume alcoholic beverages fermented in containers made of iron), or a number of other conditions.

Laboratory tests for assessing patients with disorders of iron metabolism

- Red blood cell count and estimation of hemoglobin
- Determinations of plasma iron, total iron-binding capacity (TIBC), and % transferrin saturation
- Determination of ferritin in plasma by radioimmunoassay
- Prussian blue stain of tissue sections
- Determination of amount of iron $(\mu g/g)$ in a tissue biopsy

Ceruloplasmin

• Ceruloplasmin Binds Copper, & Low Levels of This Plasma Protein Are Associated With Wilson Disease.

Copper Is a Cofactor for Certain Enzymes

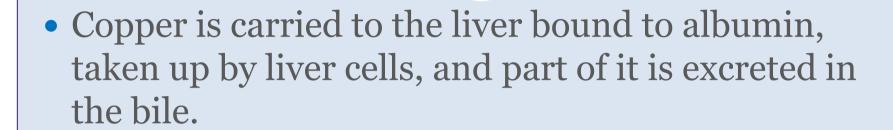
- Copper is an essential trace element. It is required in the diet because it is the metal cofactor for a variety of enzymes.
- Copper accepts and donates electrons and is involved in reactions involving dismutation, hydroxylation, and oxygenation.

- The body of the normal adult contains about 100 mg of copper, located mostly in bone, liver, kidney, and muscle.
- The daily intake of copper is about 2–4 mg, with about 50% being absorbed in the stomach and upper small intestine and the remainder excreted in the feces.

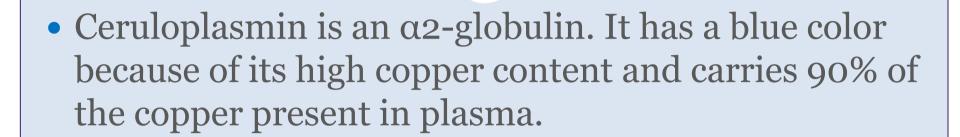


Enzymes with Cu as cofactor:

- 1. Superoxide dismutase
- 2. Cytochrome oxidase
- 3. Tyrosinase
- 4. Amine oxidase



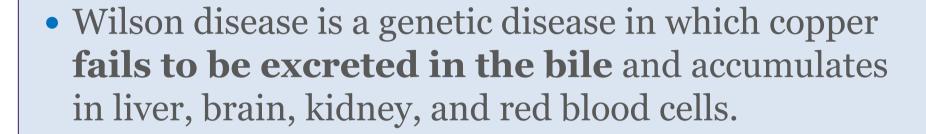
 Copper also leaves the liver attached to ceruloplasmin, which is synthesized in that organ.



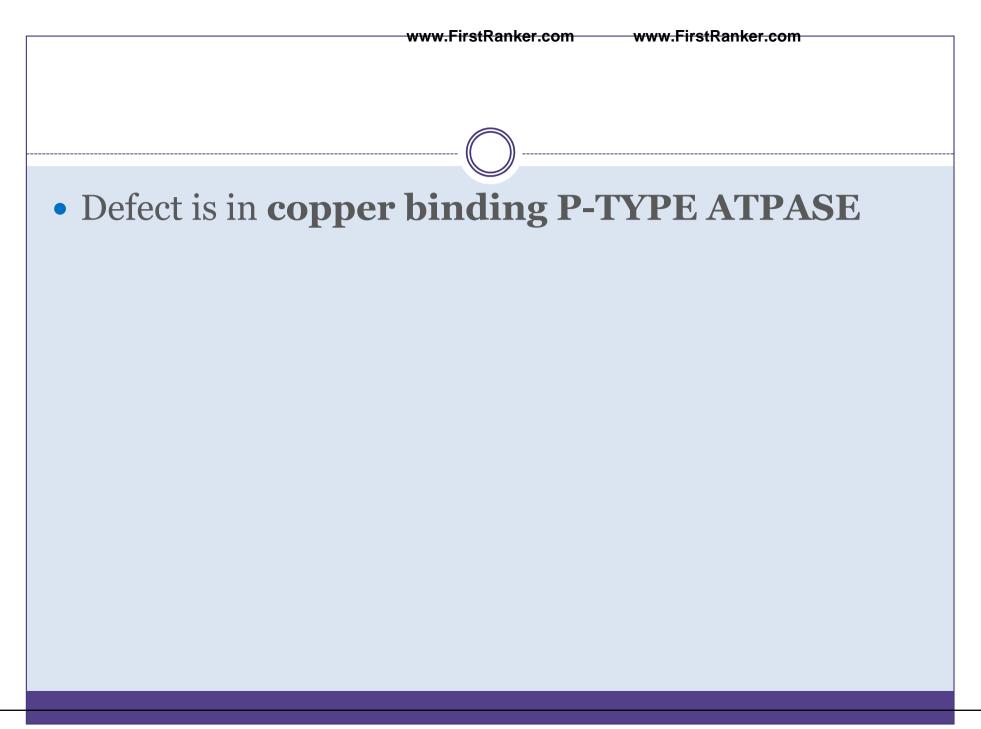
• Each molecule of ceruloplasmin binds six atoms of copper.

• Albumin carries the other 10% of the plasma copper.

Wilson disease



• The increase of copper in liver cells appears to inhibit the coupling of copper to apoceruloplasmin and leads to low levels of ceruloplasmin in plasma.



Menkes Disease



- 3. Menkes Disease Is Due to Mutations in the Gene Encoding a Copper- Binding P-Type ATPase
- Menkes disease ("kinky" or "steely" hair disease) is a disorder of copper metabolism.
- It is X-linked, affects only male infants, involves the nervous system, connective tissue, and vasculature, and is usually fatal in infancy.



2. Secondly the incorporation of copper into apoceruloplasmin.

Learning resource

• Harpers Biochemistry