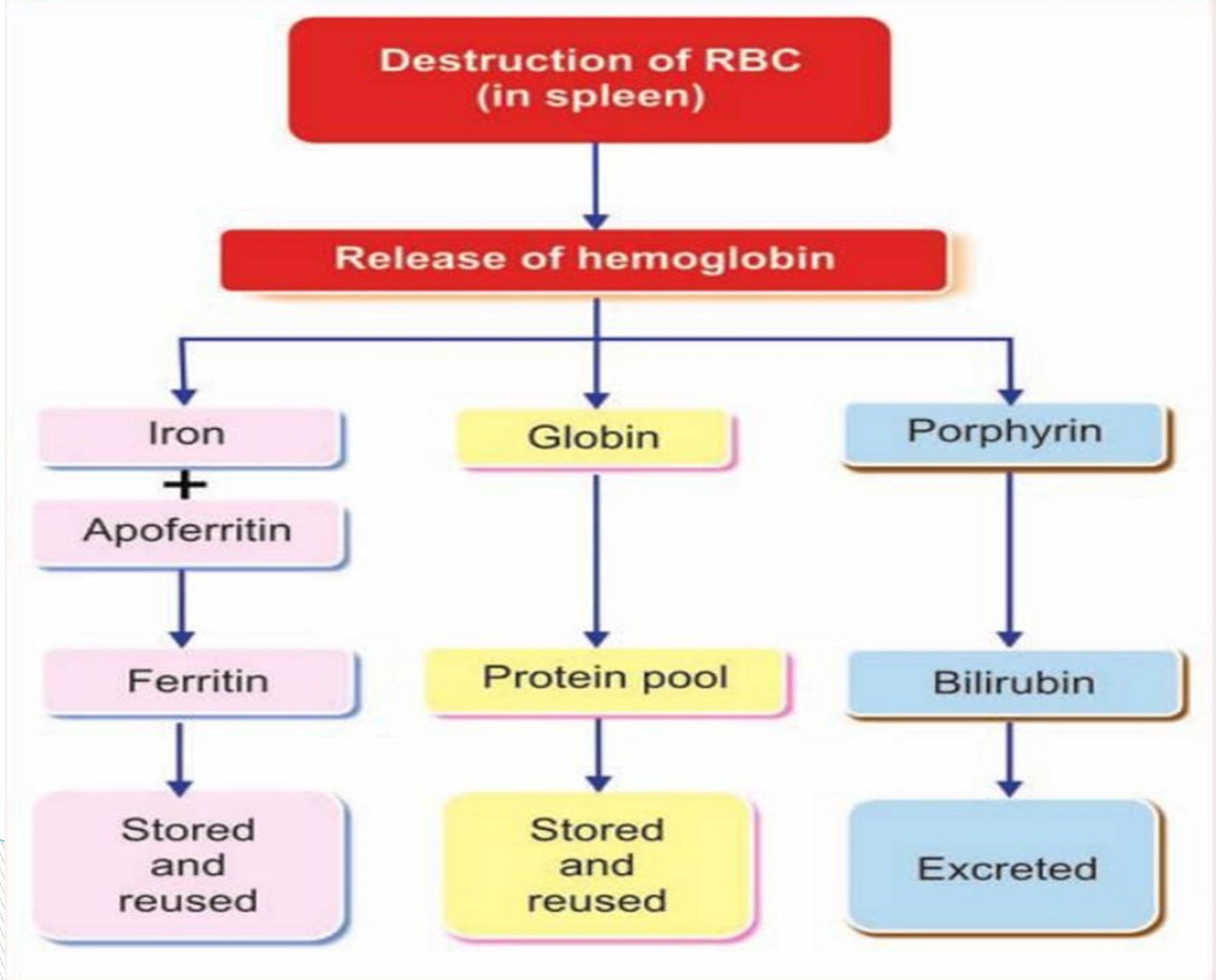
Hematology

Assist pro dr.Dina Saadoon

Destruction of RBCs

In a normal adult the red cells of about half a litre (almost one pint) of blood are produced by the bone marrow every week. A number of nutrient substances are required for this process. Some nutrients are the building blocks of which the red cells are composed For example, amino acids are needed in abundance for the construction of the proteins of the red cell, in particular of hemoglobin. Iron also is a necessary component of hemoglobin. Important among these are several vitamins such as riboflavin, vitamin B12, and folic acid, necessary for the maturation of the developing red cell; and vitamin B6 (pyridoxine), required for the synthesis of hemoglobin. The male sex hormone, testosterone, stimulates red cell production; for this reason, red cell counts of men are higher than those of women. Red cells have an average life span of 120 days. Because red cells cannot synthesize protein, reparative processes are not possible. As red cells age, wear and tear leads to loss of some of their protein, and the activity of some of their essential enzymes decreases. Phagocytic cells form a part of the lining of blood vessels, particularly in the spleen, liver, and bone marrow.

These cells, called macrophages, are constituents of the reticuloendothelial system and are found in the lymph nodes, in the intestinal tract, and as free-wandering and fixed cells. Protein, including that of the hemoglobin, is broken down, and the component amino acids are transported through the plasma to be used in the synthesis of new proteins. The iron removed from hemoglobin passes back into the plasma and is transported to the bone marrow, where it may be used in the synthesis of hemoglobin in newly forming red cells. Iron not necessary for this purpose is stored within the reticuloendothelial cells but is available for release and reuse whenever iIn contrast, the porphyrin ring structure of hemoglobin, to which iron was attached, undergoes a chemical change that enables its excretion from the body. This reaction converts porphyrin, a red pigment, into bilirubin, a yellow pigment. Bilirubin released from reticuloendothelial cells after the destruction of erythrocytes is conveyed through the plasma to the liver, where it undergoes further changes that prepare it for secretion into the bile. The amount of bilirubin produced and secreted into the bile is determined by the amount of hemoglobin destroyed.


Destruction of RBC
(in spleen)
Release of hemoglobin
Iron
+
Apoferritin
Globin
Porphyrin
Ferritin
Protein pool
Bilirubin
Stored
and
reused
Stored
and
reused
Excreted

Pathological polycythemia is the abnormal increase in the RBC count. Red cell count increases above 7 million/ cu mm of the blood. Polycythemia is of two types, the primary polycythemia and secondary polycythemia.

Anemia Abnormal decrease in RBC count is called anemia.

VARIATIONS IN SIZE OF RED BLOOD CELLS Under physiological conditions, the size of RBCs in venous blood is slightly larger than those in arterial blood. In pathological conditions, the variations in size of RBCs are: 1. Microcytes (smaller cells) 2. Macrocytes (larger cells) 3. Anisocytes (cells with different sizes).

VARIATIONS IN SHAPE OF RED BLOOD CELLS

Shape of RBCs is altered in many conditions including different types of anemia.

1. Crenation: Shrinkage as in hypertonic conditions.
2. Spherocytosis: Globular form as in hypotonic conditions.
3. Elliptocytosis: Elliptical shape as in certain types of anemia.
4. Sickle cell: Crescentic shape as in sickle cell anemia.
5. Poikilocytosis: Unusual shapes due to deformed cell membrane. The shape will be of flask, hammer or any other unusual shape.

Anemia is the blood disorder, characterized by the reduction in:

1. Red blood cell (RBC) count
2. Hemoglobin content
3. Packed cell volume (PVC).

Generally, reduction in RBC count, hemoglobin content and PCV occurs because of:

1. Decreased production of RBC
2. Increased destruction of RBC
3. Excess loss of blood from the body

CLASSIFICATION OF ANEMIA

Anemia is classified by two methods:

1. Morphological classification
2. Etiological classification

MORPHOLOGICAL CLASSIFICATION

Morphological classification depends upon the size and color of RBC. Size of RBC is determined by mean corpuscular volume (MCV). Color is determined by mean corpuscular hemoglobin concentration (MCHC).

1. Normocytic Normochromic Anemia

Size (MCV) and color (MCHC) of RBCs are normal. But the number of RBC is less.

2. Macrocytic Normochromic Anemia

RBCs are larger in size with normal color. RBC count is less.

3. Macrocytic Hypochromic Anemia

RBCs are larger in size. MCHC is less, so the cells are pale (less colored).

4. Microcytic Hypochromic Anemia

RBCs are smaller in size with less color.

ETIOLOGICAL CLASSIFICATION

On the basis of etiology (study of cause or origin), anemia is divided into five types

1. Hemorrhagic anemia
2. Hemolytic anemia
3. Nutrition deficiency anemia
4. Aplastic anemia
5. Anemia of chronic diseases.

Platelets or thrombocyte

Platelets, also called thrombocytes are a component of blood whose function (along with the coagulation factors) is to react to bleeding from blood vessel injury by clumping, thereby initiating a blood clot.Platelets have no cell nucleus; they are fragments of cytoplasm that are derived from the megakaryocytes of the bone marrow or lung,which then enter the circulation. Platelets are found only in mammals, whereas in other vertebrates (e.g. birds, amphibians), thrombocytes circulate as intact mononuclear cells. ShapeCirculating inactivated platelets are biconvex discoid (lens-shaped) structures2–3 μm in greatest diameter.Activated platelets have cell membrane projections covering their surface.normal value15,000-400,000cell/mm3.

Disorders

Low platelet concentration is called thrombocytopenia, and is due to either decreased production or increased destruction. Elevated platelet concentration is called thrombocytosis, and is either congenital, reactive (to cytokines), or due to unregulated production: one of the myeloproliferative neoplasms or certain other myeloid neoplasms. A disorder of platelet function is called a thrombocytopathy or a platelet function disorder.

Normal platelets can respond to an abnormality on the vessel wall rather than to hemorrhage, resulting in inappropriate platelet adhesion/activation and thrombosis: the formation of a clot within an intact vessel. This type of thrombosis arises by mechanisms different from those of a normal clot: namely, extending the fibrin of venous thrombosis; extending an unstable or ruptured arterial plaque, causing arterial thrombosis; and microcirculatory thrombosis. An arterial thrombus may partially obstruct blood flow, causing downstream ischemia, or may completely obstruct it, causing downstream tissue death.

Hemoglobin (Hb)

The red, oxygen-carrying pigment in the red blood cells of vertebrates is hemoglobin

1-Is the iron containing coloring matter of red blood cell (RBC).

2-It is a chromo protein forming 95% of dry weight of RBC and 30% to 34% of wet weight.

3-Function of hemoglobin is to carry the respiratory gases, oxygen and carbon dioxide.

4-It also acts as a buffer. Molecular weight of hemoglobin is 68,000. The polypeptides are referred to collectively as the globin portion of the hemoglobin molecule. There are two pairs of polypeptides in each hemoglobin molecule.

Types of normal hemoglobin :

1. adult hemoglobin – HbA
2. fetal hemoglobin – HbF

A derivatives closely associated with hemoglobin A that represent glycated hemoglobin. One of these, hemoglobin A1c (HbA1c), has a glucose attached to the terminal valine in each β chain and is of special interest because it increases in the blood of patients with poorly controlled diabetes mellitus.

STRUCTURE OF HEMOGLOBIN

Hemoglobin is a conjugated protein. It consists of a protein combined with an iron containing pigment. The protein part is globin and the iron containing pigment is hem . Hem also forms a part of the structure of myoglobin (oxygen binding pigment in muscles) and neuroglobin (oxygen binding pigment in brain.

IRON

It is present in ferrous (Fe^{2+}) form. It is in unstable or loose form. In some abnormal conditions, the iron is converted into ferric (Fe^{3+}) state, which is a stable form.

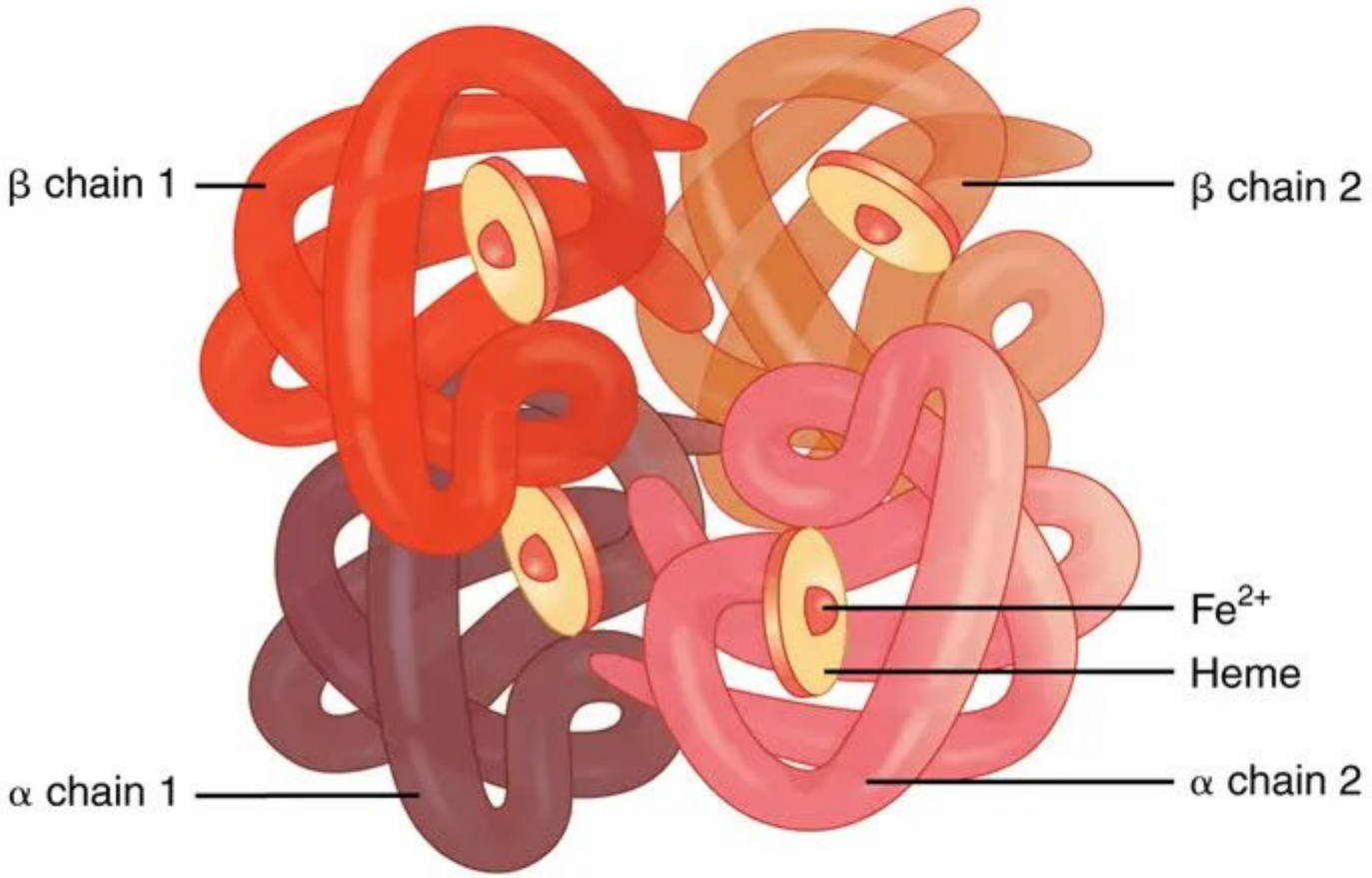
PORPHYRIN

The pigment part of heme is called porphyrin. It is formed by four pyrrole rings (tetrapyrrole) called, I, II, III and IV.

GLOBIN

Globin contains four polypeptide chains. Among the four polypeptide chains, two are chains and two are α-chains

Hemoglobin Structure



Structural Difference

In adult hemoglobin, the globin contains two α-chains and two β-chains. In fetal hemoglobin, there are two α chains and two γ-chains instead of β-chains.

Functional Difference

Functionally, fetal hemoglobin has more affinity for oxygen than that of adult hemoglobin.

Synthesis Of Heme

Heme is synthesized from succinylCoA and the glycine.

The sequence of events in synthesis of hemoglobin:

1. First step in heme synthesis takes place in the mitochondrion. Two molecules of succinylCoA combine with two molecules of glycine and condense to form δ-aminolevulinic acid (ALA) by ALA synthase.
2. ALA is transported to the cytoplasm. Two molecules of ALA combine to form porphobilinogen in the presence of ALA dehydratase.

3. Porphobilinogen is converted into uroporphobilinogen I by uroporphobilinogen I synthase.
4. Uroporphobilinogen I is converted into uropor phobilinogen III by porphobilinogen III cosynthase.
5. From uroporphobilinogen III, a ring structure called coproporphyrinogen III is formed by uroporphobilinogen decarboxylase.
6. Coproporphyrinogen III is transported back to the mitochondrion, where it is oxidized to form protoporphyrinogen IX by coproporphyrinogen oxidase
7. Protoporphyrinogen IX is converted into protoporphyrin IX by protoporphyrinogen oxidase.
8. Protoporphyrin IX combines with iron to form heme in the presence of ferrochelatase.

FORMATION OF GLOBIN

Polypeptide chains of globin are produced in the ribosomes. There are four types of polypeptide chains namely, alpha, beta, gamma and delta chains. Each of these chains differs from others by the amino acid sequence. Each globin molecule is formed by the combination of 2 pairs of chains and each chain is made of 141 to 146 amino acids. Adult hemoglobin contains two alpha chains and two beta chains. Fetal hemoglobin contains two alpha chains and two gamma chains.

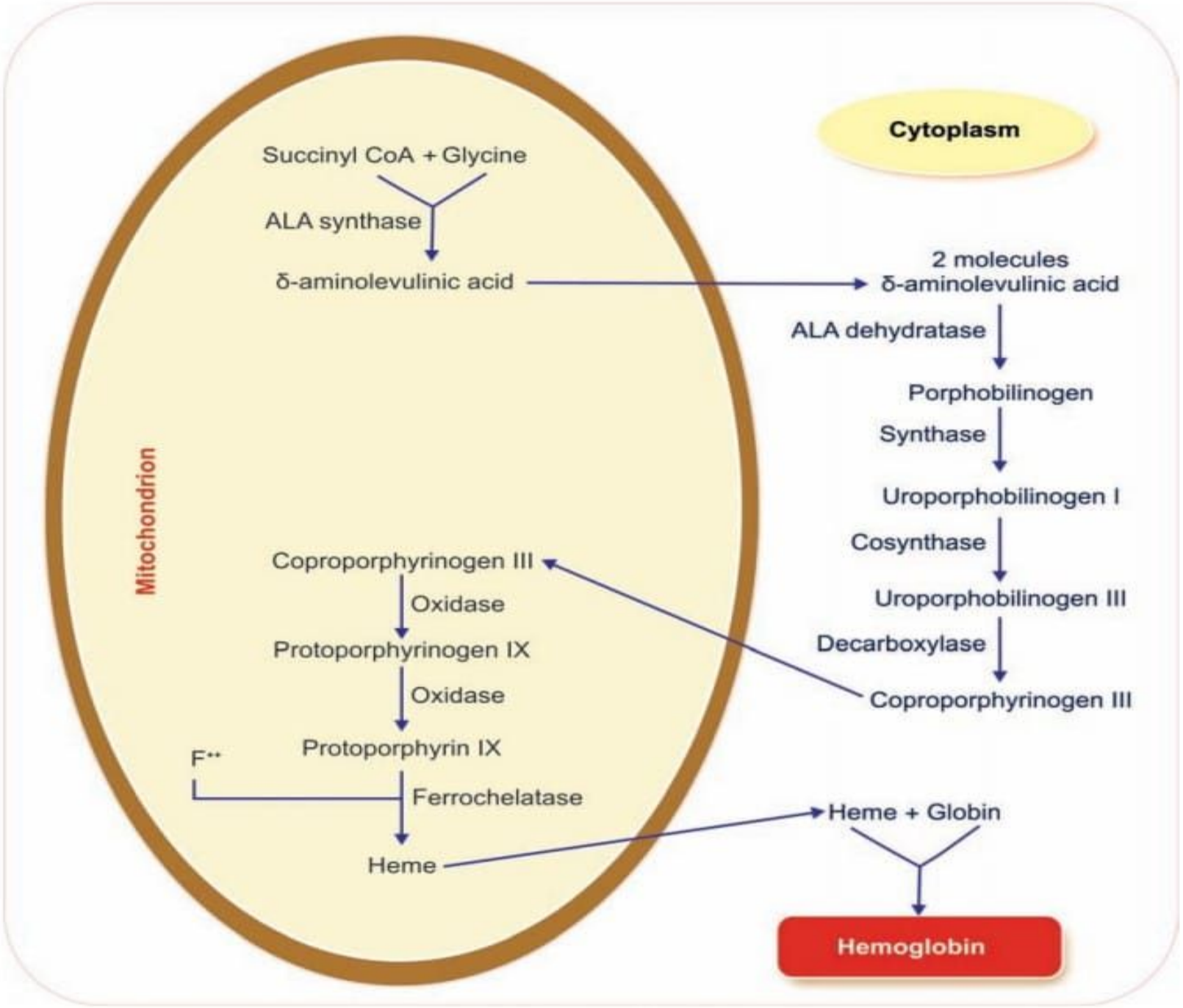


FIGURE 11.1: Synthesis of hemoglobin

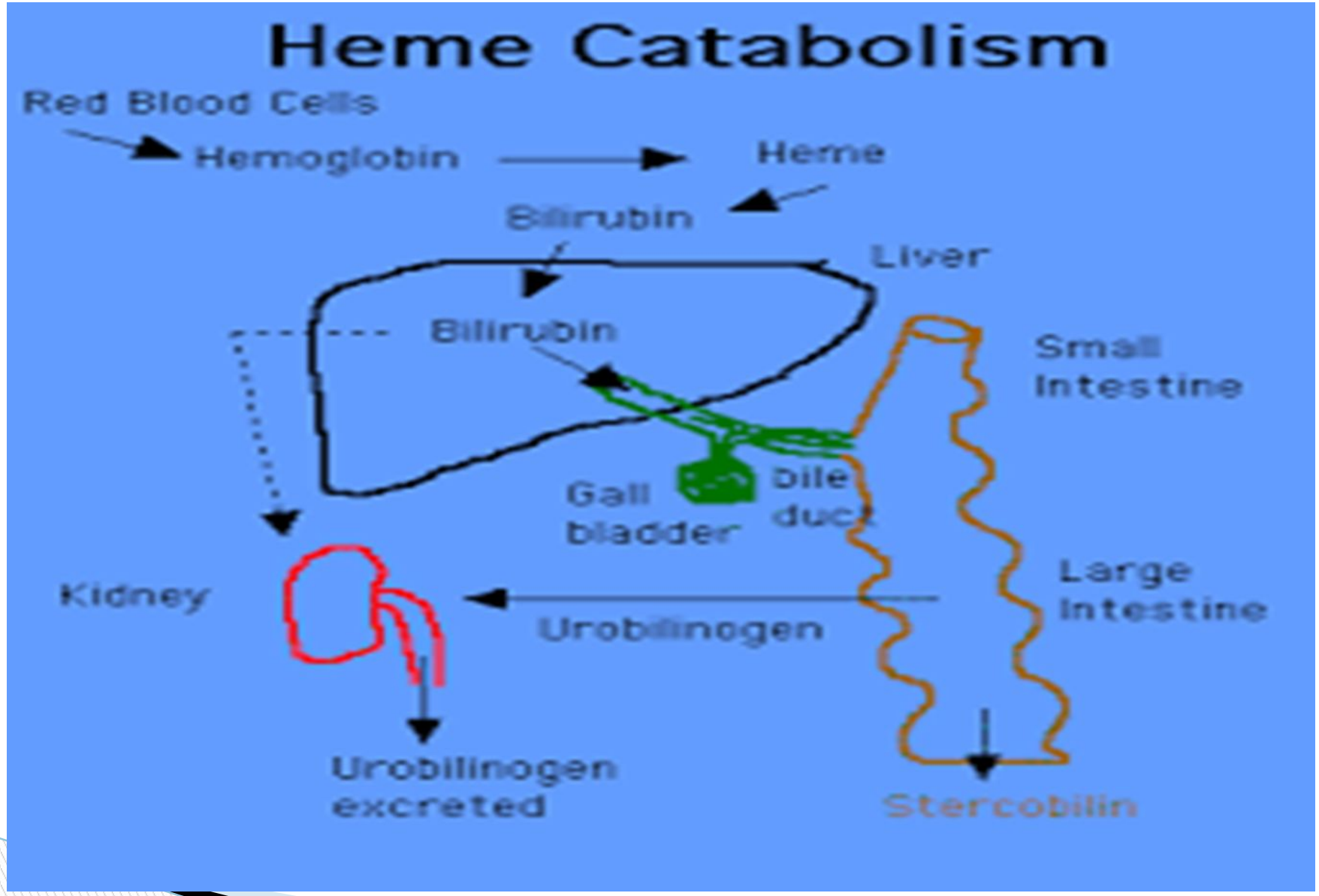
Destruction Of Hemoglobin

After the lifespan of 120 days, the RBC is destroyed in the reticuloendothelial system, particularly in spleen and the hemoglobin is released into plasma. Soon, the hemoglobin is degraded in the reticuloendothelial cells and split into globin and heme. Globin is utilized for the resynthesis of hemoglobin.

Heme is degraded into iron and porphyrin. Iron is stored in the body as ferritin and hemosiderin, which are reutilized for the synthesis of new hemoglobin. Porphyrin is converted into a green pigment called biliverdin. Biliverdin is converted into a yellow pigment called bilirubin.

„ Importance Of Iron

Iron is an essential mineral and an important component of proteins, involved in oxygen transport. So, human body needs iron for oxygen transport. Iron is important for the formation of hemoglobin and myoglobin. Iron is also necessary for the formation of other substances like cytochrome, cytochrome oxidase, peroxidase and catalase

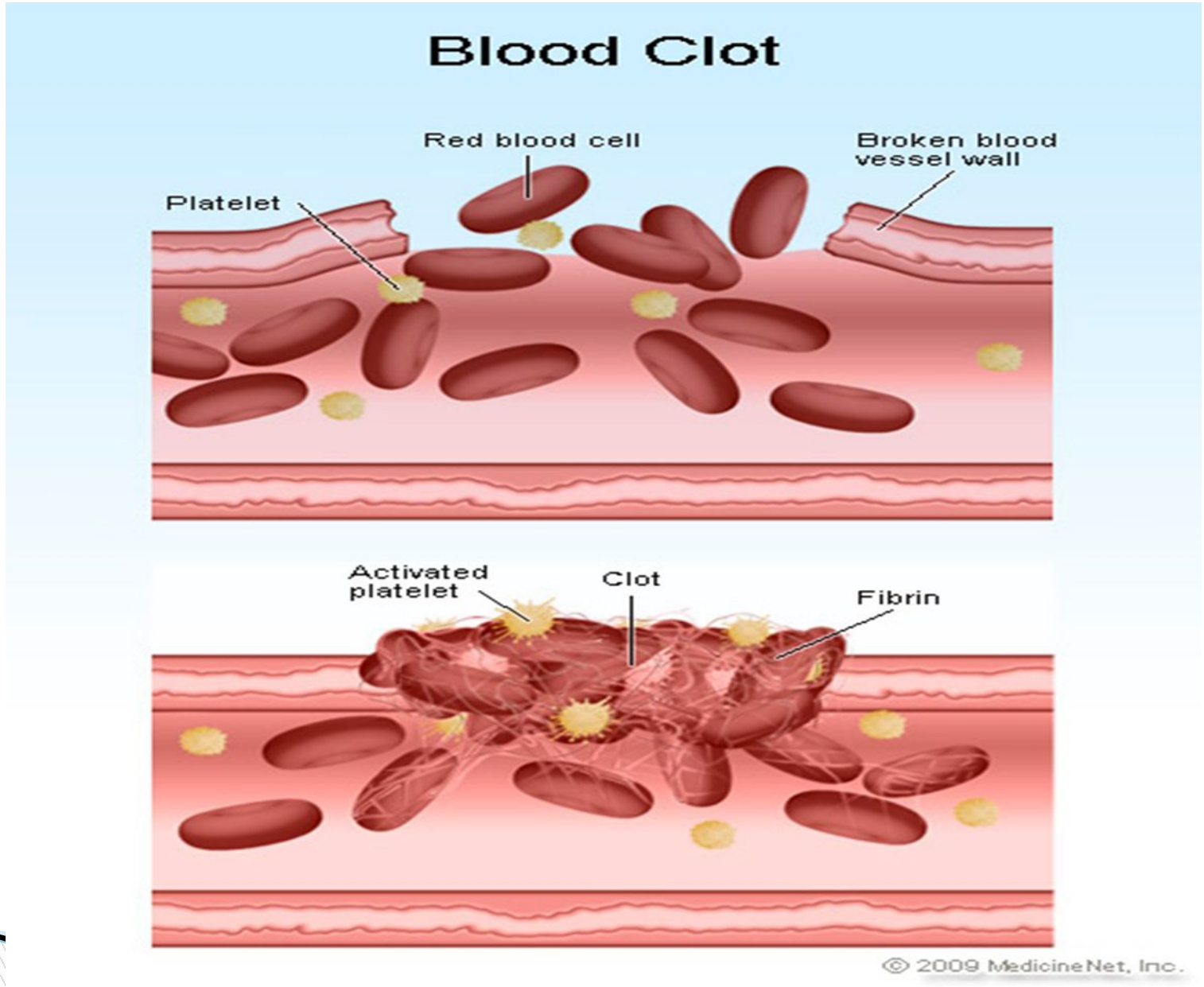

Heme Catabolism
Red Blood Cells
Hemoglobin
Heme
Bilirubin
Liver
Bilirubin
Small Intestine
Gall bladder
bile duct
Kidney
Large Intestine
Urobilinogen
Urobilinogen excreted
Stercobilin

HEMOSTASIS

Hemostasis is the process of forming clots in the walls of damaged blood vessels and preventing blood loss while maintaining blood in a fluid state within the vascular system. A collection of complex interrelated systemic mechanisms operates to maintain a balance between coagulation and anticoagulant.

STAGES OF HEMOSTASIS

1. Vasoconstriction
2. Platelet plug formation
3. Coagulation of blood.


Blood Clot
Red blood cell
Broken blood vessel wall
Platelet
Activated platelet
Clot
Fibrin
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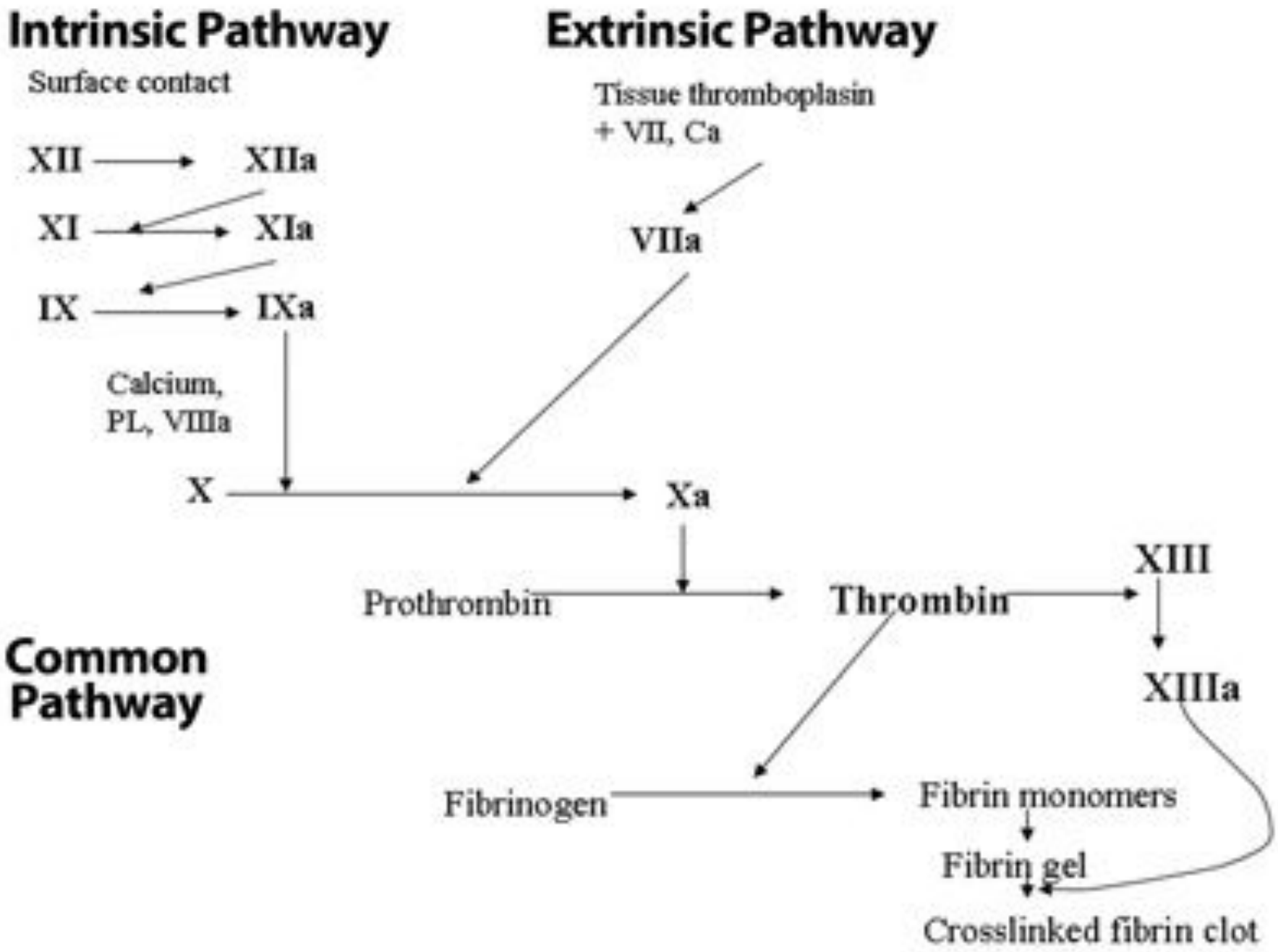
The Clotting Mechanism

The loose aggregation of platelets in the temporary plug is bound together and converted into the definitive clot by fibrin. Fibrin formation involves a cascade of enzymatic reactions and a series of numbered clotting factors . The fundamental reaction is conversion of the soluble plasma protein fibrinogen to insoluble fibrin . The process involves the release of two pairs of polypeptides from each fibrinogen molecule. The remaining portion, fibrin monomer, then polymerizes with other monomer molecules to form fibrin. The fibrin is initially a loose mesh of interlacing strands. It is converted by the formation of covalent cross-linkages to a dense, tight aggregate (stabilization). This latter reaction is catalyzed by activated factor XIII and requires Ca2+. The conversion of fibrinogen to fibrin is catalyzed by thrombin. Thrombin is a serine protease that is formed from its circulating precursor, prothrombin, by the action of activated factor X. It has additional actions, including activation of platelets, endothelial cells, and leukocytes via so-called proteinase activated receptors, which are G protein-coupled. Factor X can be activated by either of two systems, known as intrinsic and extrinsic .

The initial reaction in the intrinsic system is conversion of inactive factor XII to active factor XII (XIIa). This activation, which is catalyzed by high-molecular-weight kininogen and kallikrein, can be brought about in vitro by exposing the blood to glass, or in vivo by collagen fibers underlying the endothelium. Active factor XII then activates factor XI, and active factor XI activates factor IX. Activated factor IX forms a complex withactive factor VIII, which is activated when it is separated from von Willebrand factor. The complex of IXa and VIIIa activate factor X. Phospholipids from aggregated platelets (PL) and Ca2+ are necessary for full activation of factor X. The extrinsic system is triggered by the release of tissue thromboplastin, a protein–phospholipid mixture that activates factor VII. Tissue thromboplastin and factor VII activate factors IX and X. In the presence of PL, Ca2+, and factor V, activated factor X catalyzes the conversion of prothrombin to thrombin. The extrinsic pathway is inhibited by a tissue factor pathway inhibitor that forms a quaternary structure with tissue thromboplastin (TPL), factor VIIa, and factor Xa.


Intrinsic Pathway
Surface contact
XII
XIIa
XI
XIa
IX
IXa
Calcium,
PL, VIIIa
X
Extrinsic Pathway
Tissue thromboplasin
+ VII, Ca
VIIa
Xa
Prothrombin
Thrombin
XIII
XIIIa
Common Pathway
Fibrinogen
Fibrin monomers
Fibrin gel
Crosslinked fibrin clot

Anticlotting Mechanism In The Body

Under physiological conditions, intravascular clotting does not occur. It is because of the presence of some physicochemical factors in the body.

1. Physical Factors
2- chemical factors

Anticoagulants

Substances which prevent or postpone coagulation of blood are called anticoagulants.

Anticoagulants are of three types:

1. Anticoagulants used to prevent blood clotting inside the body.
2. Anticoagulants used to prevent clotting of blood that is collected from the body.
3. Anticoagulants used to prevent blood clotting both inside and outside the body.

1. HEPARIN

2. COUMARIN DERIVATIVES

Coumarin derivatives prevent blood clotting by inhibiting the action of vitamin K. Vitamin K is essential for the formation of various clotting factors, namely II, VII, IX and X.

„ 3. EDTA

Ethylenediaminetetraacetic acid (EDTA) is a strong anticoagulant. It is available in two forms:

i. Disodium salt (Na2 EDTA).

ii. Tripotassium salt (K3 EDTA).

4. OXALATE COMPOUNDS

5. CITRATES

Sodium, ammonium and potassium citrates are used as Anticoagulants.

LYMPH

Lymph is tissue fluid that enters the lymphatic vessels. It drains into the venous blood via the thoracic and right lymphatic ducts. It contains clotting factors and clots on standing in vitro. In most locations, it also contains proteins that traverse capillary walls and return to the blood via the lymph. Its protein content is generally lower than that of plasma, which contains about 7 g/dL. Water-insoluble fats are absorbed from the intestine into the lymphatics, and the lymph in the thoracic duct after a meal is milky because of its high fat content . Lymphocytes enter the circulation principally through the lymphatic, and there are appreciable numbers of lymphocytes in thoracic duct lymph.

Hemophilia

Is a rare disorder in which the blood doesn't clot in the typical way because it doesn't have enough blood-clotting proteins (clotting factors). If you have hemophilia, you might bleed for a longer time after an injury than you would if your blood clotted properly. Hemophilia is almost always a genetic disorder.

Treatment includes regular replacement of the specific clotting factor that is reduced. Newer therapies that don't contain clotting factors also are being used.

Thalassemia

Are inherited blood disorders characterized by decreased hemoglobin production. Symptoms depend on the type and can vary from none to severe.

Thalassemia are genetic disorders inherited from a person's parents. There are two main types, alpha thalassemia and beta thalassemia.The severity of alpha and beta thalassemia depends on how many of the four genes for alpha globin or two genes for beta globin are missing. Diagnosis is typically by blood tests including a complete blood count, special hemoglobin tests, and genetic tests

Treatment depends on the type and severity. Treatment for those with more severe disease often includes regular blood transfusions, iron chelation, and folic acid.