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REVISED
6:52 am, Aug 23, 2006

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Components of the Cardiovascular System

Heart – pumps blood

Blood vessels:

arteries – carry blood to organs and tissues

veins – return blood to the heart

capillaries – allow for transport to and from tissues

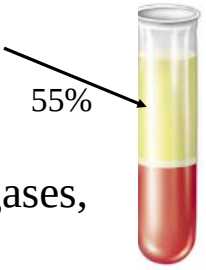
Blood - ? The fluid medium for transport.

Unlike the heart and the blood vessels, which are organs, blood is a complex tissue. It is one of the connective tissues based on its derivation, from mesenchyme cells, and its structure, which contains the intercellular matrix known as the plasma.

Composition of Blood

See Marieb, Figure 17.1

- Plasma - the blood's liquid portion
  - water 91+%
  - solutes - nutrients, wastes, blood gases, electrolytes, regulatory molecules
  - proteins - albumin, fibrinogens, globulins

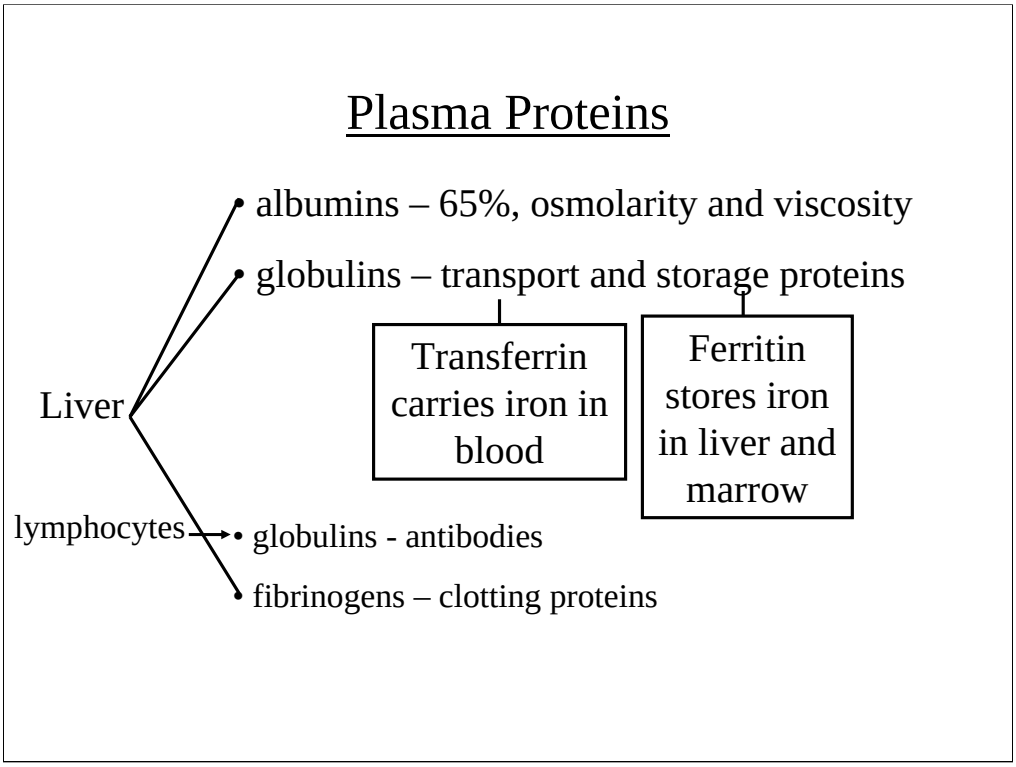


Plasma is the intercellular matrix of the blood.

Plasma Proteins

- albumins – 65%, osmolarity and viscosity
- globulins – transport and storage proteins
  - Transferrin carries iron in blood
  - Ferritin stores iron in liver and marrow
- globulins - antibodies
- fibrinogens – clotting proteins

Plasma proteins may have specialized functions, but they also contribute, along with other solutes, to the osmolarity and viscosity of the blood.



Most of the proteins found in blood plasma are manufactured in the liver.

❖ Formed Elements - cells and their derivatives - about 45% of the total blood volume (% of formed elements = the hematocrit)

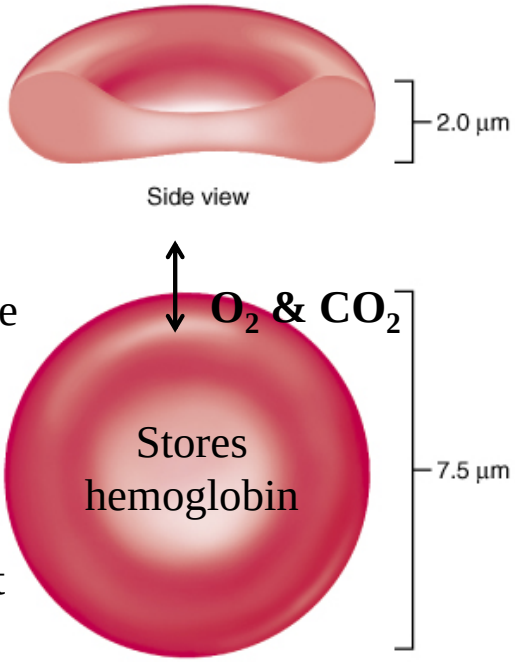
- erythrocytes - red blood cells $5 \times 10^6/mm^3$
- leukocytes - white blood cells $5\text{-}10 \times 10^3/mm^3$
- thrombocytes - platelets $150\text{-}200 \times 10^3/mm^3$

Hematocrit = % of formed elements

a.k.a. PCV , VPRC

The formed elements: these are blood cells and cell derivatives. All the formed elements are originally derived from a **pleuripotential** (multiple potential) stem cell known as a **hemocytoblast**. These cells are derived from mesenchyme cells which give rise to other types of connective tissue as well. Pleuripotential stem cells are also known as colony forming units (**CFU**) because their presence in marrow and other locations permits the formation of all types of blood cells.

Erythrocytes



Biconcave disk –

Optimizes both volume and surface area.

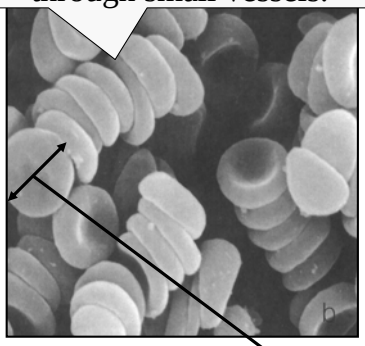
Volume important for storage.

Surface area important for transport.

They have no nuclei or other organelles and only rudimentary enzyme systems. But they do produce certain substances of importance, for example **carbonic anhydrase**. RBCs carry hemoglobin which carries oxygen and carbon dioxide.

Erythrocytes

Rouleaux formation – rbc's stack allowing transport through small vessels.



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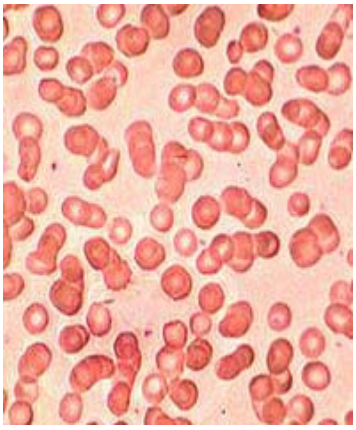
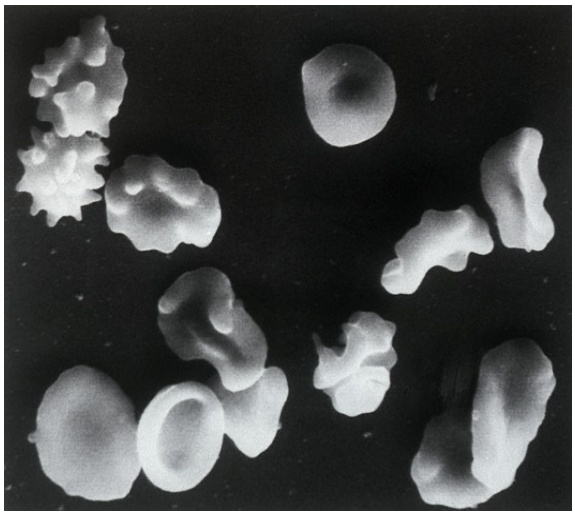


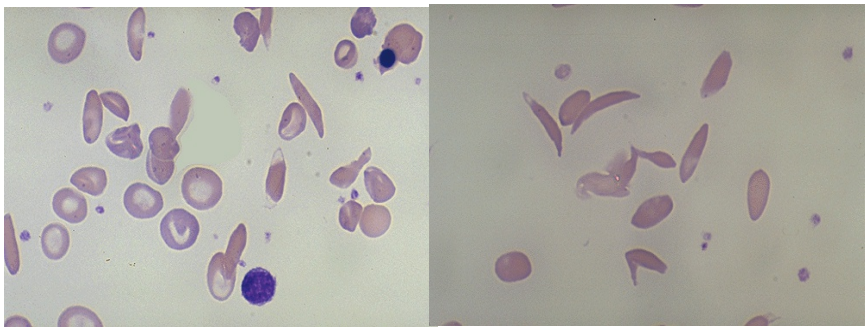
❖**Erythrocytes** - red blood cells, 5 to 6 million/mm^3 are **biconcave disks** which function in transporting oxygen and carbon dioxide to and from tissues. Their shape facilitates both volume and surface area. Their structure is that of a flexible membrane sack.

Sickle Cells



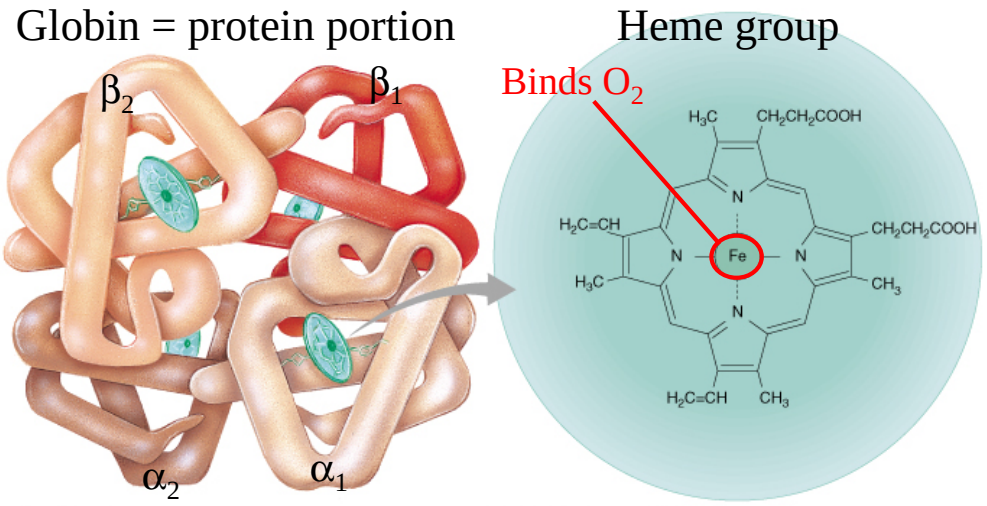
A single point mutation in the gene that codes for globin produces hemoglobin with a single amino acid difference on the beta chains. This results in aggregation of the HbS hemoglobin causing a loss of plasticity of the cell and the formation of comma shaped cells at low oxygen tension.

Sickle Cell Anemia Crisis



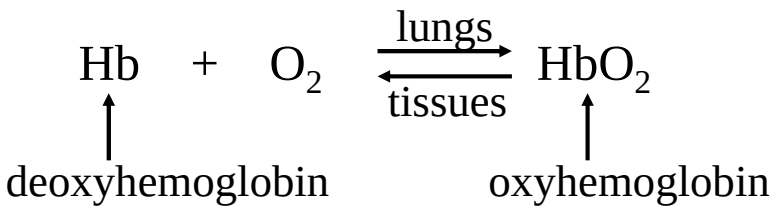
Substitution at position 6 of the hydrophobic valine for hydrophilic glutamic acid causes an abnormal hemoglobin (HbS) which crystallizes when oxygen tension is low, and the RBC's change shape to long, thin sickle forms that “sludge” in capillaries, further decreasing blood flow and oxygen tension. Sickled cells are prone to stick together, plugging smaller vessels and leading to decreased blood flow with ischemia.

Hemoglobin



Hemoglobin consists of four polypeptide chains, 2 alpha and 2 beta, each of which contains a **heme group**. Each heme group is composed of a **porphyrin ring** with an iron atom at its center. The iron atoms each bind to an oxygen molecule. They can also bind to carbon monoxide.

Reaction at each heme group:



Hemoglobin saturation = % of iron atoms carrying an oxygen molecule.

98% saturation in oxygenated blood at sea level.

Oxygen transport: 98% as oxyhemoglobin 2% dissolved as a gas in plasma

The binding of iron to oxygen is a reversible reaction which is determined by the concentration of oxygen, the pH, and other factors we will discuss in more detail later.

Iron will also bind to **carbon monoxide** (CO) in competition with oxygen. The strength of the bond with CO (called **carboxyhemoglobin**) is about 10 times that of the bond with oxygen. CO comes from polluted air resulting from incomplete combustion such as autos, woodstoves, etc. Removal of CO requires breathing clean air, or high concentration oxygen, or being placed in a hyperbaric (high pressure) chamber of pure oxygen.

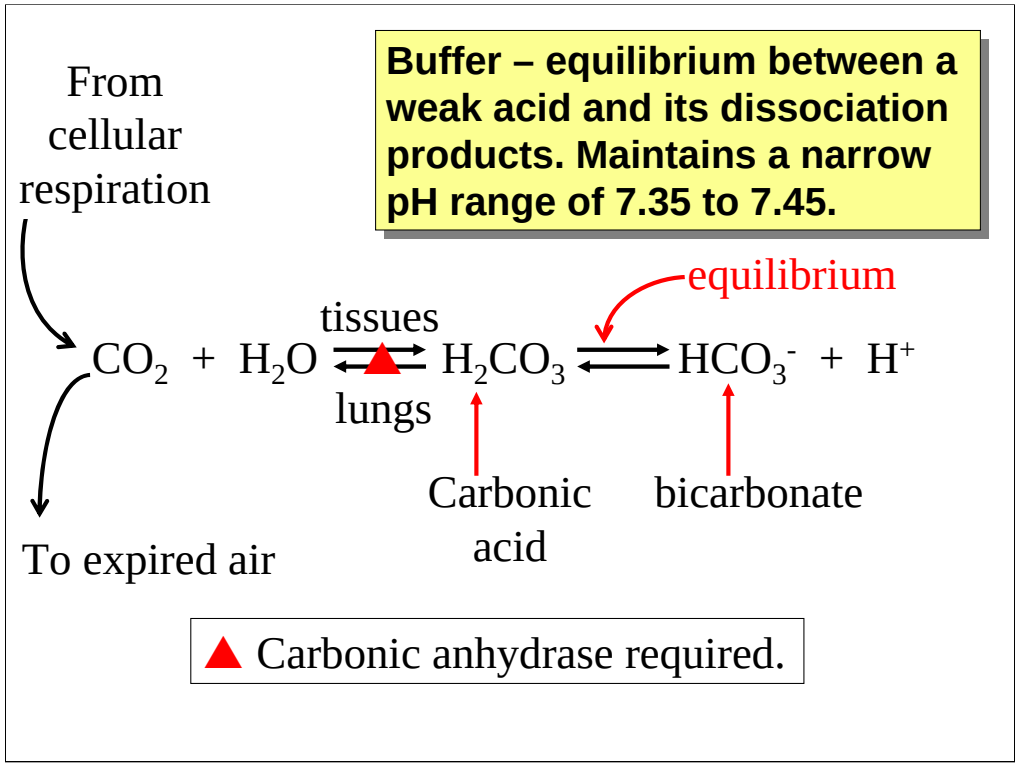
Carbon Dioxide Transport

7% dissolved as a gas in the plasma.

23% attached to amino acids on globin –
called carbaminohemoglobin.

70% reacts with water.

Carbon dioxide is transported in three ways as shown above. The majority is the third way. The result of its reaction with water is to produce and equilibrium of carbonic acid with its dissociation products. (See next slide)



The reaction of carbon dioxide with water requires **carbonic anhydrase**, an enzyme in the red blood cell. Carbonic acid is a weak acid and partially dissociates into hydrogen and bicarbonate ions. The reaction goes from left to right in the systemic tissues where carbon dioxide is produced, and right to left in the lungs where it is eliminated through respiration. Because the concentration of hydrogen ions (H^+) fluctuates the pH decreases slightly in the tissues and increases slightly in the lungs. The pH range of blood is 7.35 to 7.45 and is maintained by the buffering action of the dissociation products of H_2CO_3 as well as by the blood's protein buffers.

Assignment: Write the equations illustrating oxygen and carbon dioxide transport in such a way that you show

1) What happens in the lungs.

2) What happens in the systemic tissues.

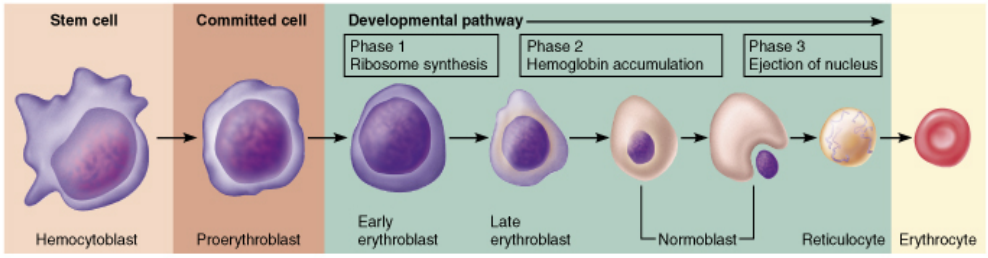
We will go over this next class. Do not send me the equations via email or in any other form.

This is a study assignment. Study assignments are not graded. They are study assignments, meaning they are given to help you study and understand the subject, and will not be graded. We will go over the assignment, usually in the next class period.

Erythropoiesis

Figure 17.5

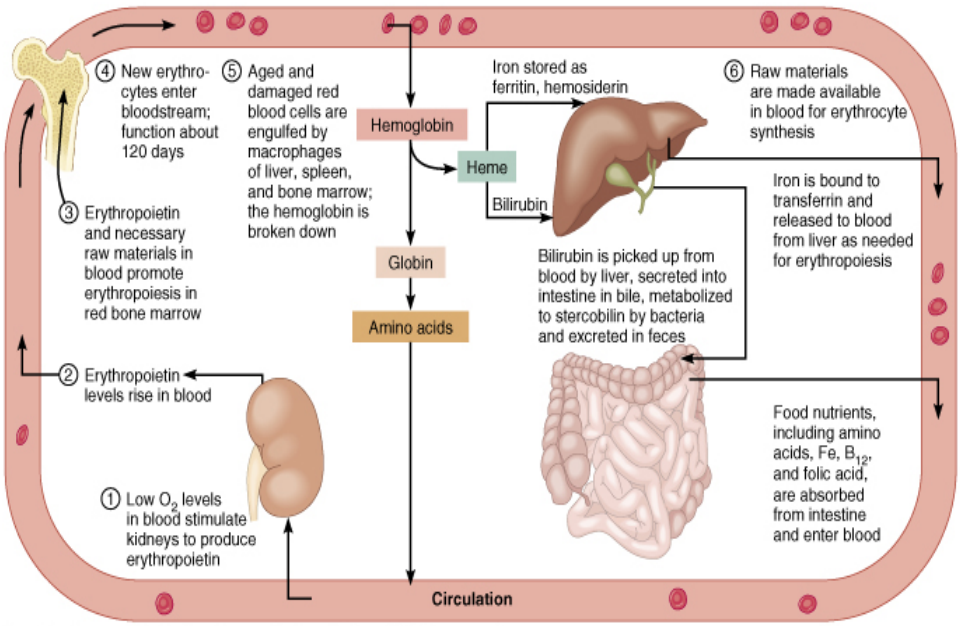
In the myeloid tissue in bone marrow.



Pleuripotential stem cell (hemocytoblast) derived from mesenchyme

Myeloid (blood producing) tissue is found in the red bone marrow located in the spongy bone. As a person ages much of this marrow becomes fatty and ceases production. But it retains stem cells and can be called on to regenerate and produce blood cells later in an emergency. RBCs enter the blood at a rate of about 2 million cells per second. The stimulus for erythropoiesis is the hormone **erythropoietin**, secreted mostly by the kidney. This hormone triggers more of the **pleuripotential stem cells** (**hemocytoblasts**) to follow the pathway to red blood cells and to divide more rapidly.

Red Cell Cycle (Figure 17.7)



RBCs enter the blood at a rate of about 2 million cells per second. The stimulus for erythropoiesis is the hormone **erythropoietin**, secreted mostly by the kidney. RBCs require Vitamin B12, folic acid, and iron. The lifespan of RBC averages 120 days. Aged and damaged red cells are disposed of in the spleen and liver by macrophages. The globin is digested and the amino acids released into the blood for protein manufacture; the heme is toxic and cannot be reused, so it is made into bilirubin and removed from the blood by the liver to be excreted in the bile. The red bile pigment bilirubin oxidizes into the green pigment biliverdin and together they give bile and feces their characteristic color. Iron is picked up by a globulin protein (apotransferrin) to be transported as **transferrin** and then stored, mostly in the liver, as **hemosiderin** or **ferritin**. Ferritin is short term iron storage in constant equilibrium with plasma iron carried by transferrin. Hemosiderin is long term iron storage, forming dense granules visible in liver and other cells which are difficult for the body to mobilize.

Anemias:

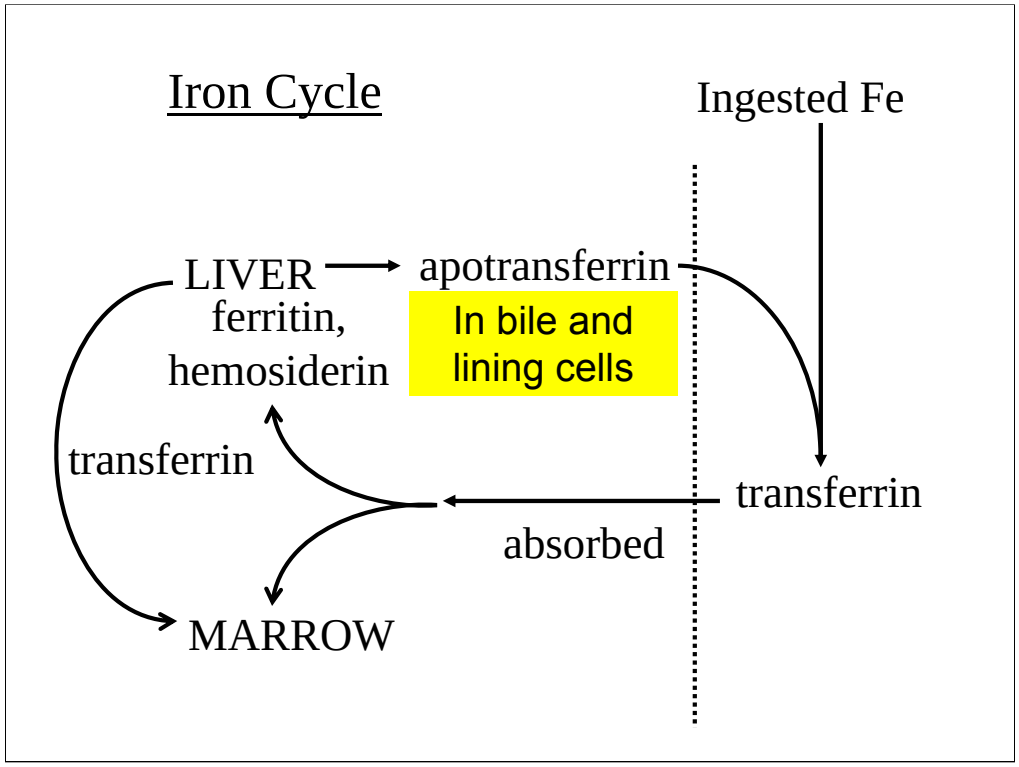
Deficiency anemias:

iron, B_{12}, folic acid

Hemorrhagic anemia – anemia due to loss of blood due to hemorrhage.

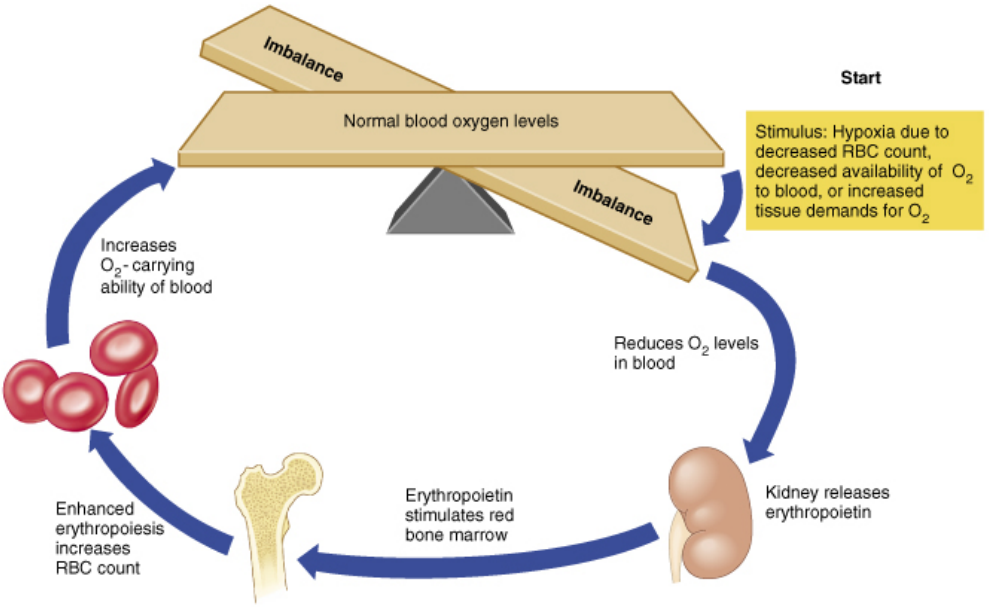
Apastic anemia – bone marrow ceases function due to toxic chemicals, radiation or drugs.

Pernicious anemia – often due to lack of **intrinsic factor** from stomach lining cells, which is required for B_{12} absorption. May result from stomach lining damage from ulcers, alcohol abuse, etc.



Some iron is lost from the blood due to hemorrhage, menstruation, etc. and must be replaced from the diet. On average men need to replace about 1 mg of iron per day, women need 2 mg. **Apotransferrin** (**transferrin** without the iron) is present in GI lining cells and is also released in the bile. It picks up iron from the GI tract and stimulates receptors on the lining cells which absorb it by **pinocytosis**. Once through the mucosal cell iron is carried in blood as transferrin to the liver and marrow. Iron leaves the transferrin molecule to bind to **ferritin** in these tissues. Most excess iron will not be absorbed due to saturation of ferritin, reduction of apotransferrin, and an inhibitory process in the lining tissue.

Erythropoietin (Figure 17.6)



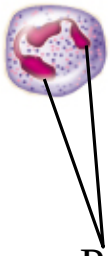
Erythropoietin Mechanism: (See Figure 17.6) Hypoxia (reduced oxygen in blood or tissues) stimulates an increase in erythropoietin secretion by the kidney. This triggers more of the **pleuripotential stem cells** (**hemocytoblasts**) to produce rbc (See Figure 17.5) and to do so at a faster rate. More rbc will carry more oxygen and thus raise blood oxygen levels, reducing erythropoietin secretion by negative feedback.

Leukocytes = White Blood Cells

- Originate from the same hemocytoblast stem cell as the red cells and platelets.
- Produced normally in a proportion of about 1/700 the number of red cells.
- Colorless, have nuclei and granules which can be made visible by staining.

The term for white blood cells can be spelled **leukocytes** or **leucocytes** (the anglicized version).

- Granulocytes - have observable granules when stained.

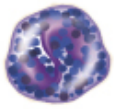


Neutrophils are 60-65% of leukocytes, the most common wbc, they perform active and passive phagocytes.

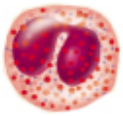
A.k.a. PMN leucocytes

Polymorphonuclear = many shaped nucleus

neutrophils - the most numerous wbc, making up about 65% of normal white count. These cells are the most important phagocytic cell in the circulation. Also called PMN (polymorphonuclear) neutrophils because of their nuclear shape. These cells spend 8 to 10 days in the circulation making their way to sites of infection etc. where they engulf bacteria, viruses, infected cells, debris and the like. They have two types of granules: the most numerous are **specific granules** which contain bactericidal agents such as lysozyme; the **azurophilic granules** are lysosomes containing peroxidase and other enzymes.



Basophils <1% of leukocytes - important in inflammatory reactions by secreting histamine and a heparin-like molecule. Functionally similar to mast cells.



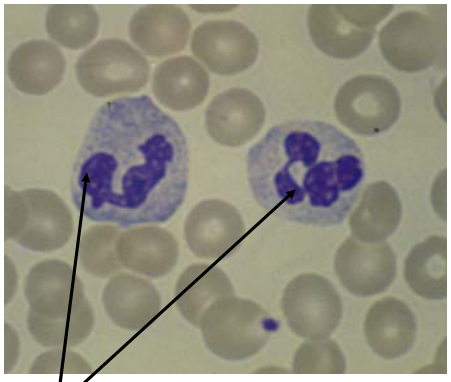
Eosinophils 2% - increase in number during allergic reactions, they secrete anti-inflammatory chemicals such as histaminase.

Attack antigen-antibody complexes and multicellular parasites.

basophils- rare except during infections where these cells mediate inflammation by secreting **histamine** and **heparan sulfate** (related to the anticoagulant *heparin*). **Histamine** makes blood vessels permeable and heparin inhibits blood clotting. Basophils are functionally related to **mast cells**.

eosinophils - also rare except during allergic reactions, these cells counteract the action of the basophils by secreting an **anti-histamine** (histaminase) and other enzymes which combat inflammation in allergies, they help to remove antigen-antibody complexes, and also are high during defense against multicellular parasites.

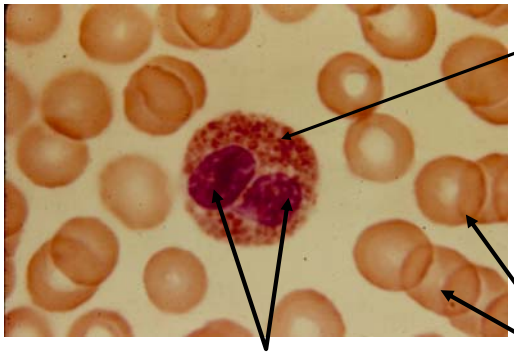
Neutrophils



Nucleus is composed of several lobes connected by thin nuclear strands.

Note that the nucleus in **neutrophils** is composed of lobes which are usually connected by thinner bands. The nucleus can therefore take many shapes (**polymorpho**nuclear) and this can sometimes be confusing in differentiating these cells from others. Neutrophils have granules which are very faintly stained compared with those in other granulocytes.

Eosinophils



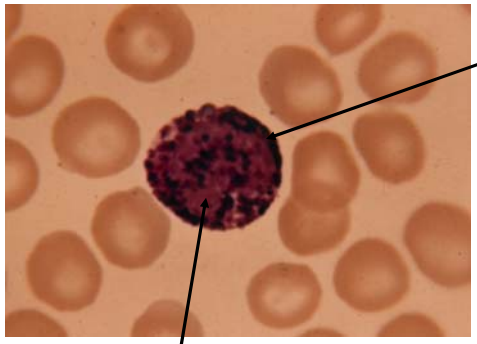
Acidophilic granules are lysosomes which contain peroxidase, histaminase, and other hyrolytic enzymes.

Typical bi-lobed nucleus.

erythrocytes

Red granules give **eosinophils** a definite reddish cast.

Basophils



Large, basic-staining granules contain histamine, SRS of anaphylaxis, heparan sulfate (related to the anti-coagulant heparin) and hydrolytic enzymes. Histamine and SRS cause dilation of small blood vessels, a large cause of inflammation. These dark blue granules give basophils a definite bluish appearance, nearly masking the nuclear lobes. They can sometimes be confused with lymphocytes.

❖Agranulocytes - Don't have observable granules when stained

Lymphocytes 25-30% of all leukocytes; B and T cells provide specific immunity, they are produced in adults in lymph tissue.

Monocytes ~9% of leukocytes, they transform into macrophages in connective tissue; produced in the bone marrow.

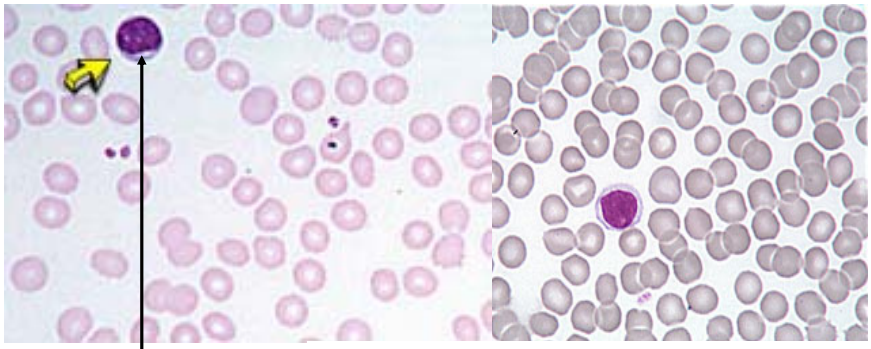
Agranulocytes - (a.k.a. mononuclear leucocytes) these cells have no observable granules.

The following are the lymphoid cells:

Lymphocytes - about 25% of wbc, these cells come in B and T cell types (see Immune System Notes) and are responsible for the specific immune response. Lymphocytes acquire immunocompetence in the thymus and other areas and subsequently proliferate by cloning in the lymph nodes. They circulate between the lymph, circulation, lymph and back again for long periods of time.

monocytes - originate in marrow, spend up to 20 days in the circulation, then travel to the tissues where they become macrophages. Macrophages are the most important phagocyte outside the circulation. Monocytes are about 9% of normal wbc count.

Lymphocytes

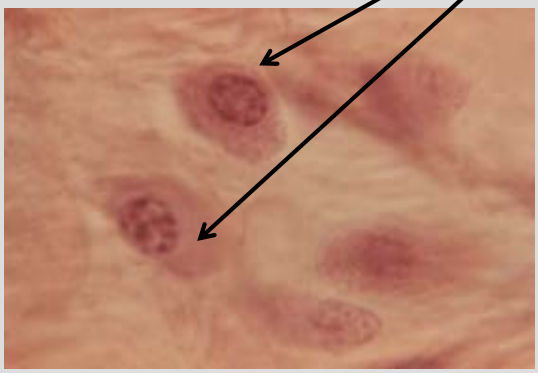


Small lymphocytes display little cytoplasm

Large lymphocytes function as T-cells and “Natural killer cells”

Lymphocytes come in small, medium, and large varying in diameter from 6 to 18m. They make up 25 to 30% of all leukocytes. Most are recirculating immunocompetent cells. **T-cell lymphocytes** are responsible for cell-mediated immunity, while **B-cell lymphocytes** secrete antibodies (humoral immunity).

Plasma Cells are B-Lymphocytes

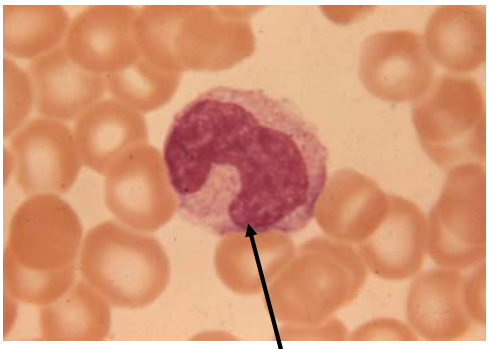


Plasma cells are specific B-cells which have been activated by antigen challenge to generic B-cells.

Plasma cells secrete antibodies as part of the specific immune response.

Once lymphocytes become activated by an antigen, they clone to produce **plasma cells** and **memory cells**. The plasma cells secrete **antibodies**, while the memory cells retain the ability to quickly clone again in a **secondary response** to subsequent activation by the same antigen. Plasma cells can often be seen in blood smears.

Monocytes



Monocytes exhibit a characteristic horseshoe-shaped nucleus.

Macrophage Video Clip

Monocytes,about 9% of all leukocytes, originate in bone marrow, spend up to 20 days in the circulation, then travel to the tissues where they become macrophages. Macrophages are the most important phagocyte outside the circulation, and are critical to wound healing by removing debris, bacteria and even spent neutrophils. Macrophages also act as mediators for the T-cell response.

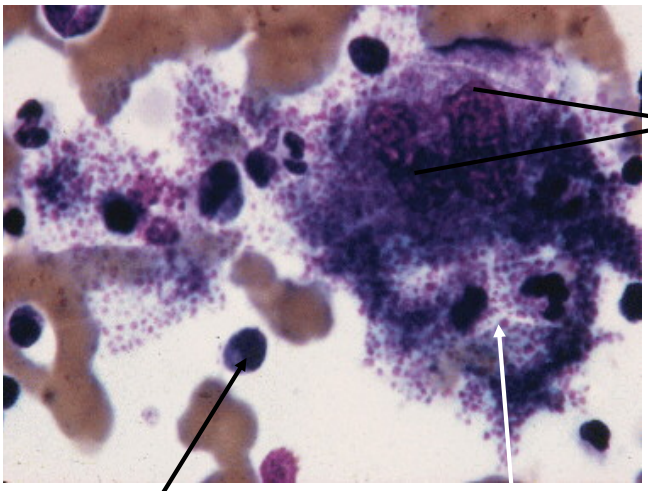
Processes Exhibited by Leukocytes

- Chemotaxis - the chemical attraction which stimulates movement of wbc, especially neutrophils and monocytes, to the site of infection.
- Amoeboid movement - wbc motility in which pseudopodia are extended and the rest of the cell pulled forward in a “crawling” action along and through the vascular wall.
- Diapedesis - name for the process in which wbc’s flatten and move through the vascular wall into the interstitial tissue.

All leukocytes exhibit these processes, but they are especially important in circulating phagocytic cells.

Platelets Derived From Megakaryocytes

Figure 17.12

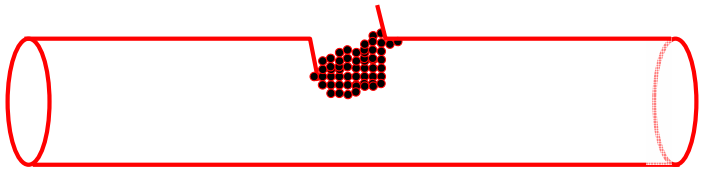


Thrombocytes are cellular derivatives from **megakaryocytes** which contain factors responsible for the intrinsic clotting mechanism. They represent fragmented cells (See Figure 17.12) which contain residual organelles including rough endoplasmic reticulum and Golgi apparati. They are only 2-microns in diameter, are seen in peripheral blood either singly or, often, in clusters, and have a lifespan of 10 days. Partitioning of the granular cytoplasm by invagination of the plasma membrane produces platelets. Inside the platelets, the granulomere, an intensely stained core, contains granules which release serotonin and protease enzymes.

Hemostasis – arrest of bleeding.

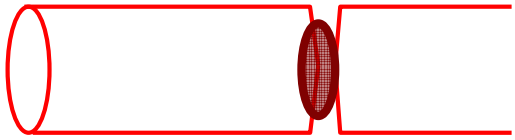
1) Platelet plug
2) Vascular spasm and vasoconstriction
3) Coagulation

Hemostasis is the arrest of bleeding to avoid blood loss from the vessel. It usually, but not always, involves formation of a blood clot.



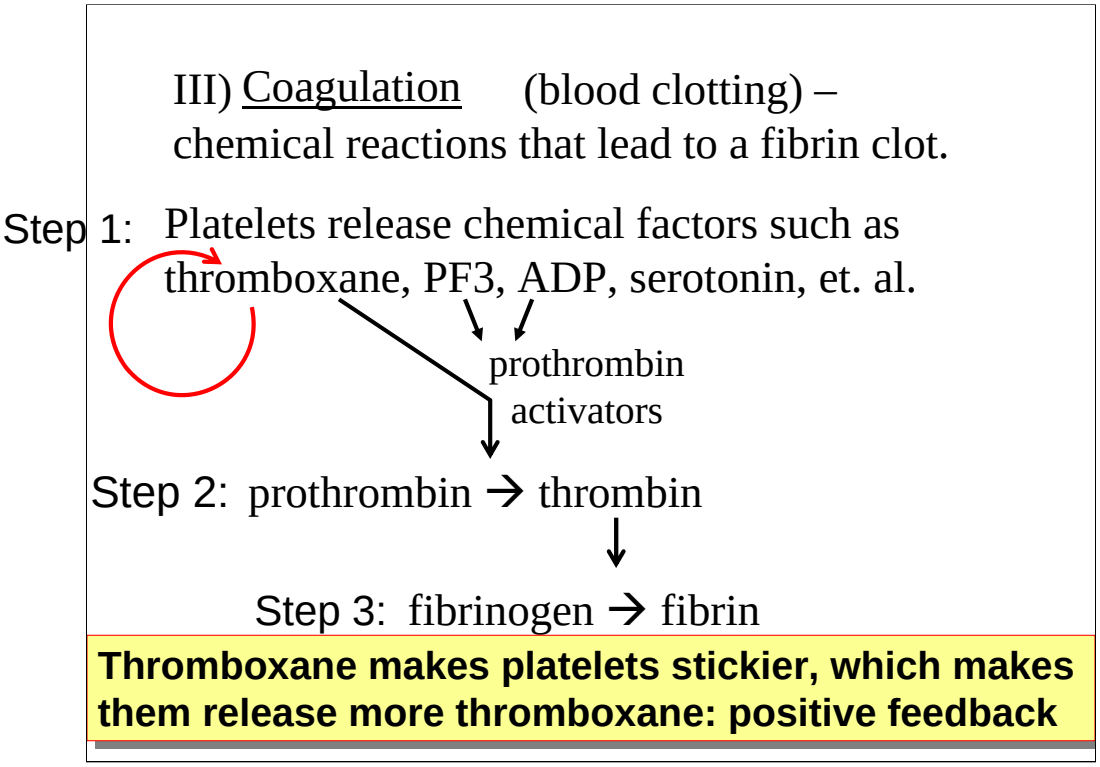
I) <u>Platelet plug</u> - platelets stick to themselves and to collagen present in broken endothelium.

With small blood vessels such as capillaries the platelets themselves may enable hemostasis as they stick to one another and to the vascular wall.

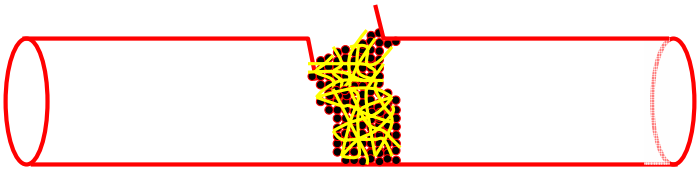


II)Vascular Spasm - In larger vessels smooth muscle spontaneously constricts when damaged. This can reduce blood loss even from injuries to major vessels.

Smooth muscle responds to damage by constricting. This reduces blood flow from damaged vessel and explains how people can survive even severe and traumatic injuries without lethal blood loss.



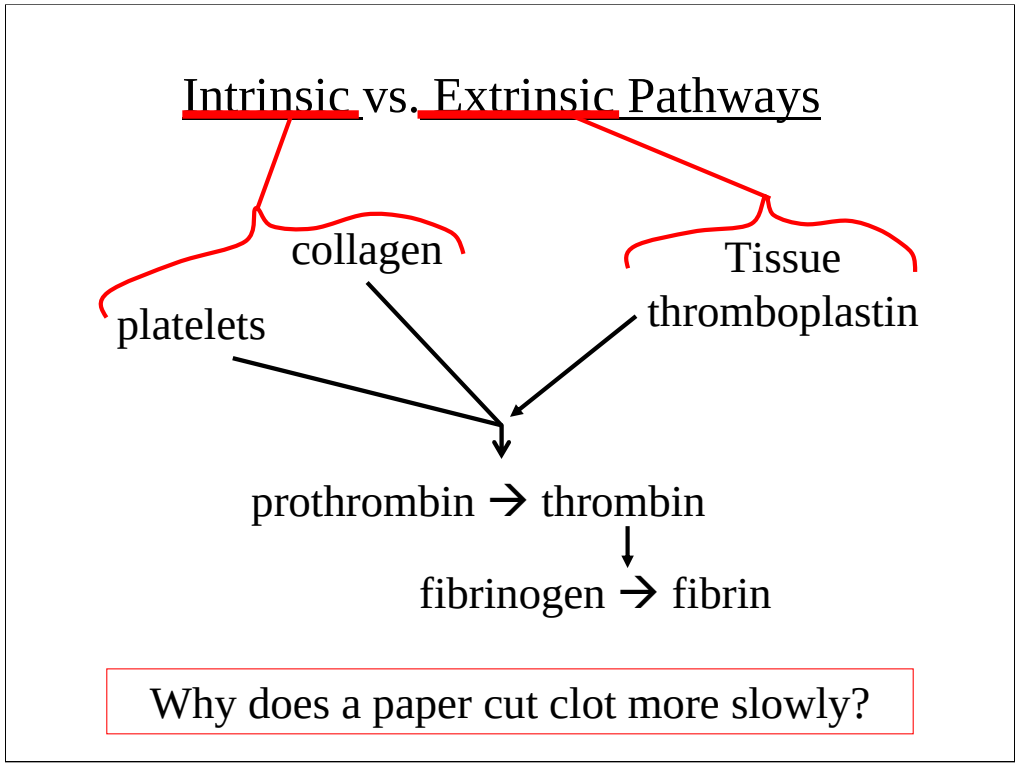
Coagulation is the actual formation of a blood clot. It results from a chemical "cascade" which begins with the **prothrombin** activators released by platelets. Sometimes referred to as "platelet thromboplastin", these chemicals cause the macromolecule prothrombin to break down into smaller units including **thrombin**. Thrombin acts on **fibrinogen**, a soluble polymer present in the plasma, and breaks it into monomers which re-polimerize into insoluble **fibrin**. The fibrin forms threads which knit the platelets and other cells into the clot.



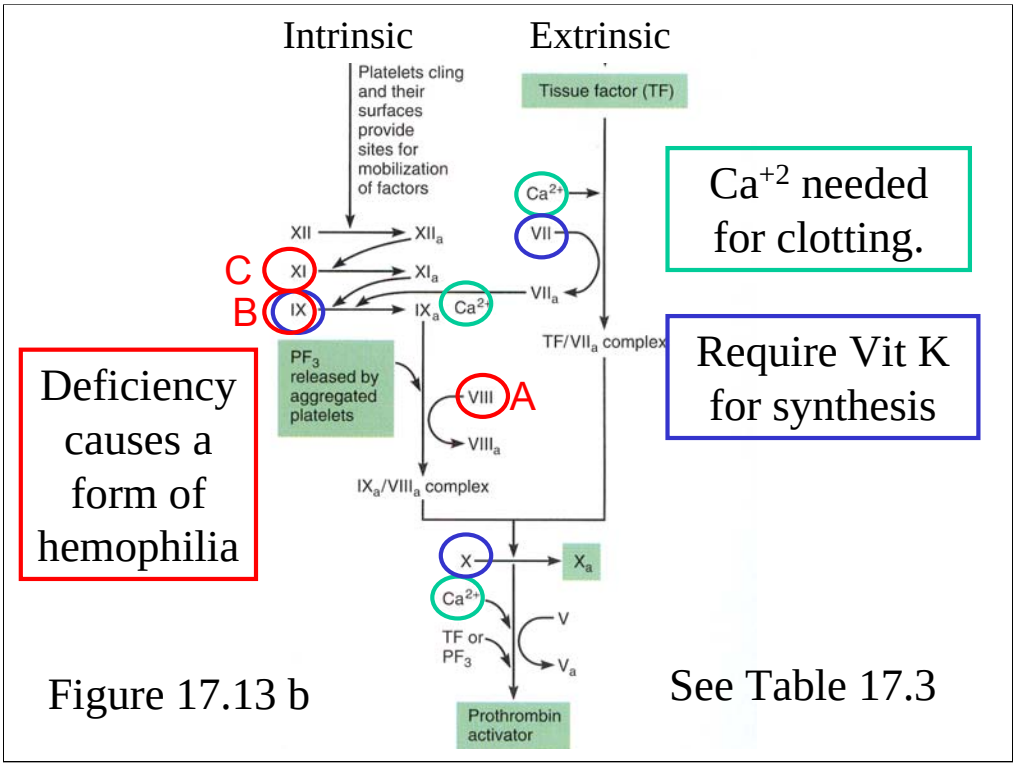
Blood Clotting Video

- Fibrin threads knit clot together
- Cross-linkages form more stable clot (>5-15 min.)
- Fibrin threads retract to pull clot together.
- Depending on location, fibrous tissue may be produced and epithelium reformed as vessel and tissue heals.
- Clot is dissolved and debris removed.

Stuck-together platelets and other cells form the substrate on which the fibrin threads are established. These threads begin by wrapping around the platelets and other cells. At first this makes a weak clot, easily dislodged. But after 5 or 6 minutes cross-linkages are established between adjacent fibrin threads, forming a more stable structure. After about 15 minutes coagulation is complete. From that point on the clot is slowly broken down by plasmin and other enzymes present in plasma. Phagocytic cells remove debris, and epithelium is regrown as the vascular wall heals.

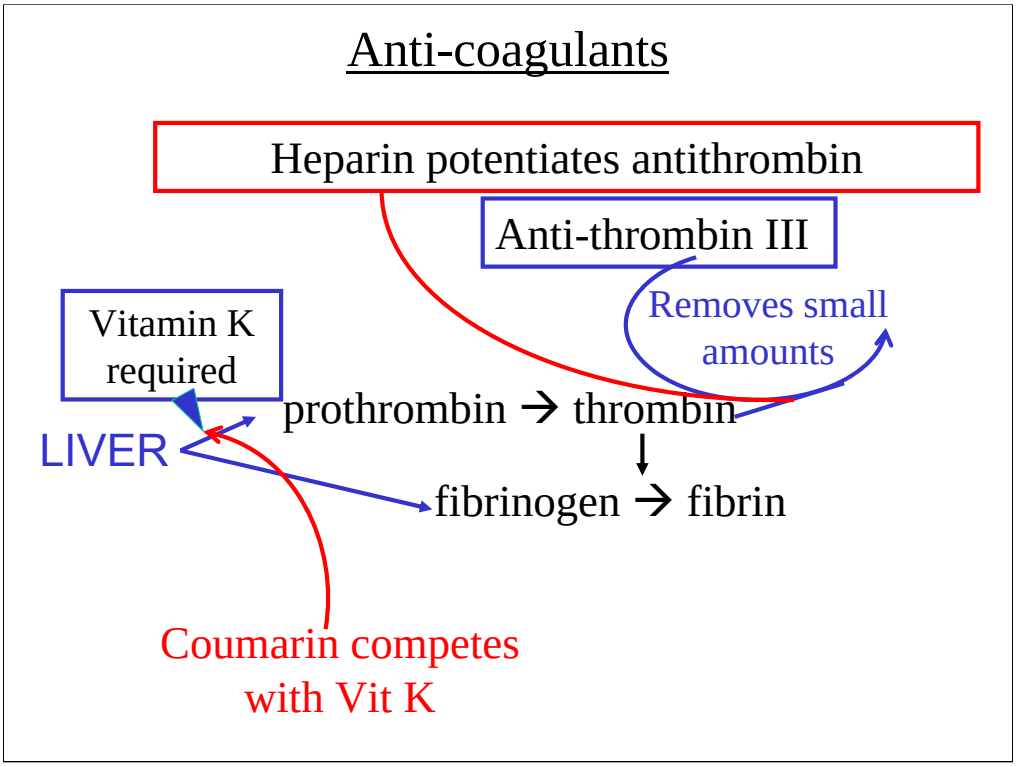


Components from damaged tissue enhance clotting. This usually works to make a clot form faster and stronger when some tissue damage is involved. This occurs with most external wounds, but extrinsic factors are not involved in internal hemorrhaging.



Since calcium ions are needed in all phases of clotting, removal of these ions will prevent coagulation. Citrate was formerly used to complex the calcium as insoluble calcium citrate, thus preventing clotting during storage.

Note that the three forms of hemophilia are caused by deficiency of factors in the intrinsic pathway. Individuals with these disorders will suffer internal hemorrhaging from bruises etc. but their blood will clot, although more slowly, from external wounds which involve tissue damage. Factors synthesized by genetically engineered bacteria are used to treat these conditions.



Coumarin is a plant product which competes with Vitamin K. Since this is a competitive inhibition the degree of anticoagulant effect can be regulated. Conversely, administering Vitamin K will increase the level of plasma clotting proteins somewhat.

Antithrombins are naturally present and remove the small amount of thrombin produced spontaneously. Heparin is also present in small amounts which normally have little effect. But when released from mast cells or basophils heparin significantly increases the effect of the antithrombins, thus inhibiting clotting. This effect is used clinically as a short-term anticoagulant. Giving Ca^{+2} will neutralize the heparin.

Other Factors

- Serotonin – released from platelets, causes vasoconstriction of blood vessels.
- Ice is used to cause vasoconstriction to reduce blood flow.
- Compression is used to reduce blood flow to area, thus enhancing clotting.

We know serotonin today as a brain neurotransmitter. But its first known effects were on blood vessels (sero-tonin = blood tension), causing them to constrict. Released from platelets the serotonin acts on the vascular smooth muscle and reduces the blood flow.