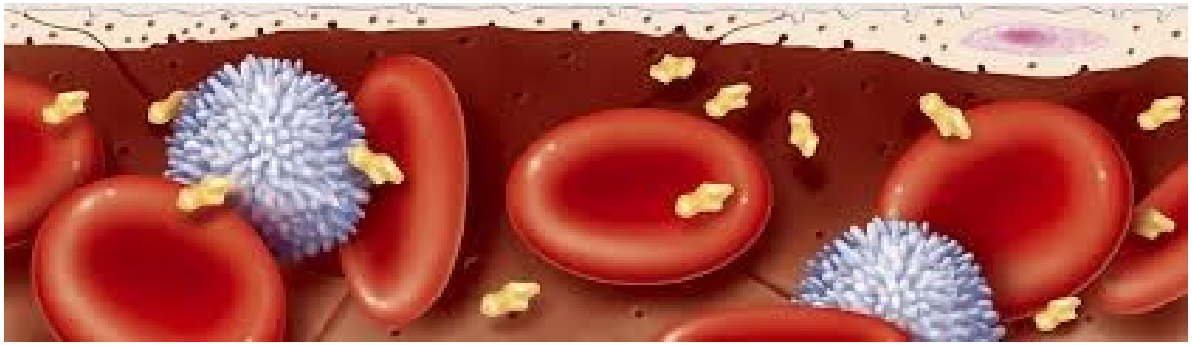
BLOOD



Course Name: Anatomy and Physiology 1

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Introduction

- The **cardiovascular system** (*cardio-* heart; *vascular* blood or blood vessels) consists of three interrelated components:

Blood, the heart, and blood vessels.

- The branch of science concerned with the study of blood, blood-forming tissues, and the disorders associated with them is **hematology** (he¯m-a-TOL-o¯-je¯; *hema-* or *hemato-* blood; *-logy* study of).

Functions and Properties of Blood

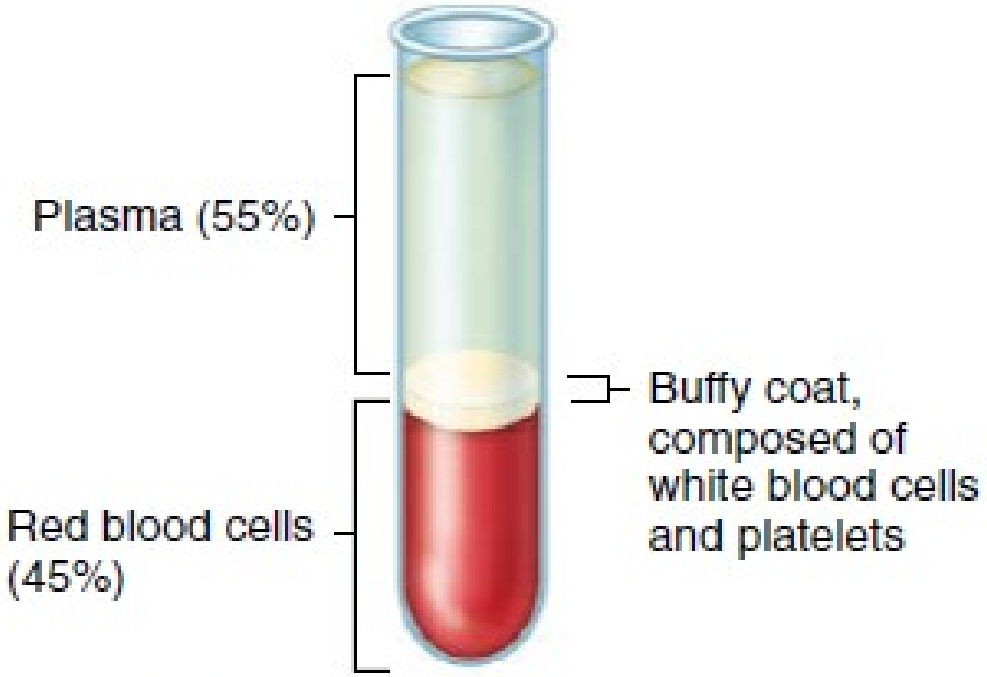
- **Blood** is a liquid connective tissue that consists of cells surrounded by a liquid extracellular matrix. The extracellular matrix is called blood plasma, and it suspends various cells and cell fragments.

- **Interstitial fluid** is the fluid that bathes body cells and is constantly renewed by the blood.

- *Blood transports oxygen from the lungs and nutrients from the gastrointestinal tract, which diffuse from the blood into the interstitial fluid and then into body cells. Carbon dioxide and other wastes move in the reverse direction, from body cells to interstitial fluid to blood. Blood then transports the wastes to various organs—the lungs, kidneys, and skin—for elimination from the body.*

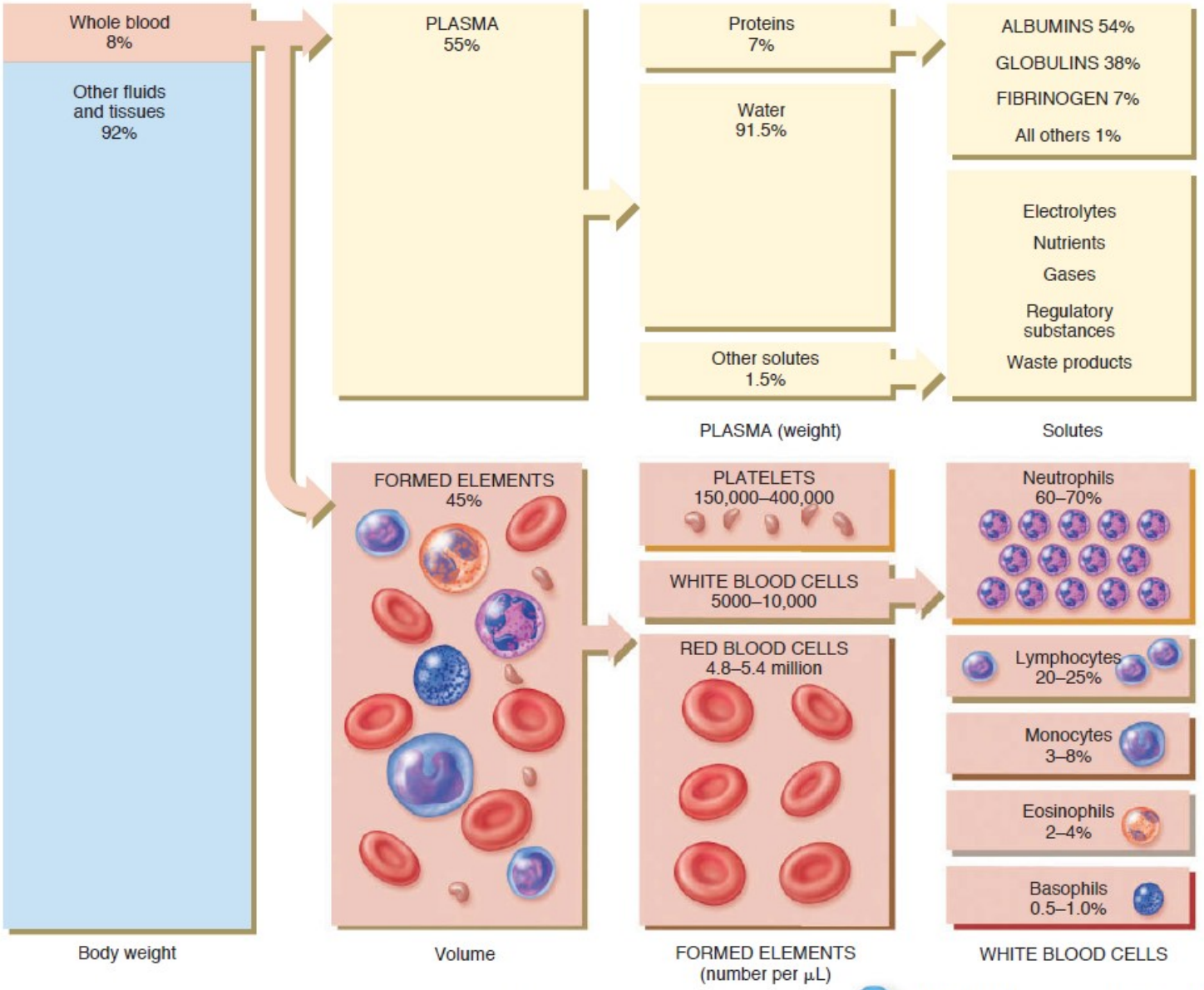
Components of blood in a normal adult,

Blood is a connective tissue that consists of blood plasma (liquid) plus formed elements (red blood cells, white blood cells, and platelets).



(a) Appearance of centrifuged blood

Components of blood in a normal adult - continued



(b) Components of blood

What is the approximate volume of blood in your body?

Functions of Blood

1. ***Transportation.*** Oxygen, carbon dioxide, nutrients, hormones, heat, and waste products.
2. ***Regulation.*** Circulating blood helps maintain homeostasis of all body fluids. Blood helps regulate pH through the use of buffers (chemicals that convert strong acids or bases into weak ones). It also helps adjust body temperature through the heat-absorbing and coolant properties of the water in blood plasma and its variable rate of flow through the skin, where excess heat can be lost from the blood to the environment. In addition, blood osmotic pressure influences the water content of cells, mainly through interactions of dissolved ions and proteins.
3. ***Protection.*** Blood can clot (become gel-like), which protects against its excessive loss from the cardiovascular system after an injury. In addition, its white blood cells protect against disease by carrying on phagocytosis. Several types of blood proteins, including antibodies, interferons, and complement, help protect against disease in a variety of ways.

Physical Characteristics of Blood

- Blood amount 8% of total body weight, ~ 5 liters → The gender difference in volume is due to differences in body size.
- Blood is denser and more viscous (thicker) than water and feels slightly sticky.

→ Viscosity – means thickness or resistance to flow; Viscosity is increased by presence of cells and proteins.

- The temperature of blood is 38C (100.4F), about 1C higher than oral or rectal body temperature,
- Slightly alkaline pH ranging from 7.35 to 7.45.
- The color of blood varies with its oxygen content.

→ Arterial blood: is blood leaving heart (It is bright red except of that going to lungs).

→ Venous blood: is blood returning to the heart (looks dark except for venous blood returning from lungs).

- Several hormones, regulated by negative feedback, ensure that blood volume and osmotic pressure remain relatively constant. Especially important are the hormones **aldosterone, antidiuretic hormone, and atrial natriuretic peptide**, which regulate how much water is excreted in the urine.

Components of Blood

Whole blood has two components:

(1) Blood plasma, a watery liquid extracellular matrix that contains dissolved substances → 55%

(2) Formed elements, which are cells and cell fragments.

→99% red color— red blood cells (RBCs),

→less than 1% of the formed elements are pale, colorless white blood cells (WBCs) and platelets.

→ *If a sample of blood is centrifuged (spun) in a small glass tube, the cells (which are more dense) sink to the bottom of the tube while the plasma (which is less dense) forms a layer on top* **buffy coat** *(Figure 19.1a).*

1- Blood Plasma

Straw-colored liquid consisting of:

(1) **Water** (91%)

(2) **Plasma proteins** (7-8%) and

(3) **Ions** mainly Na^+ and other materials like nutrients, wastes, salts (< 1%).

In addition, plasma contains other organic molecules such as:

Metabolites, hormones, waste products, antibodies, and other proteins.

Salts and proteins buffer the blood:

a. They effectively keep the blood pH near 7.4

b. They maintain the **blood osmotic pressure** which **pulls** tissue fluid **into** capillaries.

1- Blood Plasma (continued)

PLASMA PROTEINS

→7-8g/dL of plasma

→ There are THREE main types that are produced by liver:

1. **Albumins:** the smallest in size (MW= 70 kd); they function in:
A-Transports bilirubin, a breakdown product of hemoglobin.
B- Maintains the blood osmotic pressure so water enters capillaries.

2. **Globulins:** 3 subtypes:
- ✓α- and β-globulins; they are lipoproteins that transport cholesterol lipids and fat-soluble molecules.
- ✓γ-globulins: are antibodies produced by lymphocytes. They function in immunity.

3. **Fibrinogens** 4% of plasma proteins. They are important clotting factors that are converted to fibrin threads.

Serum: is plasma that lacks fibrinogen.

2- Formed Elements

- The **formed elements** of the blood include three principal components: ***red blood cells, white blood cells, and platelets***

1- Red blood cells (RBCs) or *erythrocytes* transport oxygen from the lungs to body cells and deliver carbon dioxide from body cells to the lungs.

2- White blood cells (WBCs) or *leukocytes* protect the body from invading pathogens and other foreign substances. There are several types of WBCs: *neutrophils*, *basophils*, *eosinophils*, *monocytes*, and *lymphocytes*. Lymphocytes are further subdivided into *B lymphocytes (B cells)*, *T lymphocytes (T cells)*, and *natural killer (NK) cells*. Each type of WBC contributes in its own way to the body's defense mechanisms.

3- Platelets, or *thrombocytes* the final type of formed element, are fragments of cells that do not have a nucleus. Among other actions, they release chemicals that promote blood clotting when blood vessels are damaged.

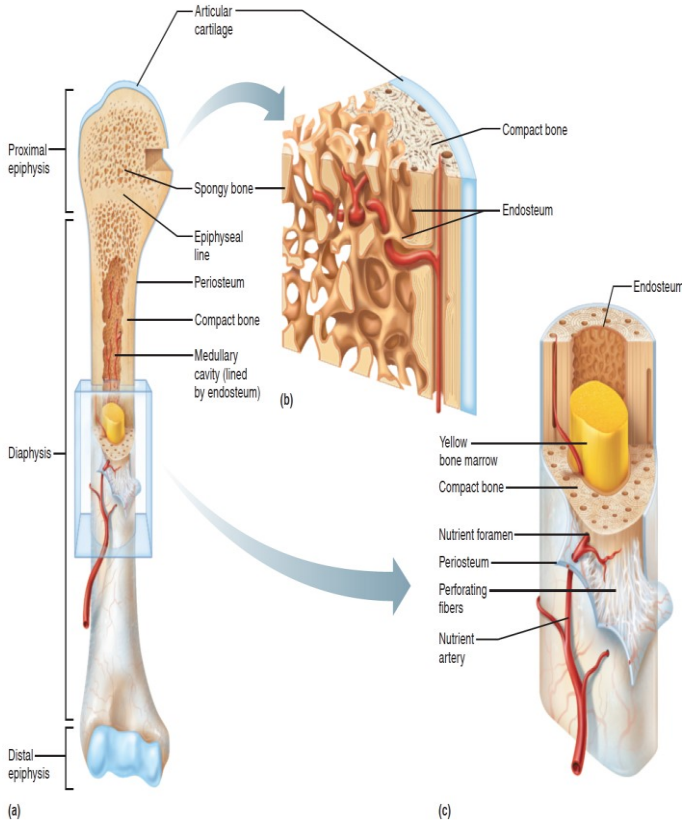
2- Formed Elements (continued)

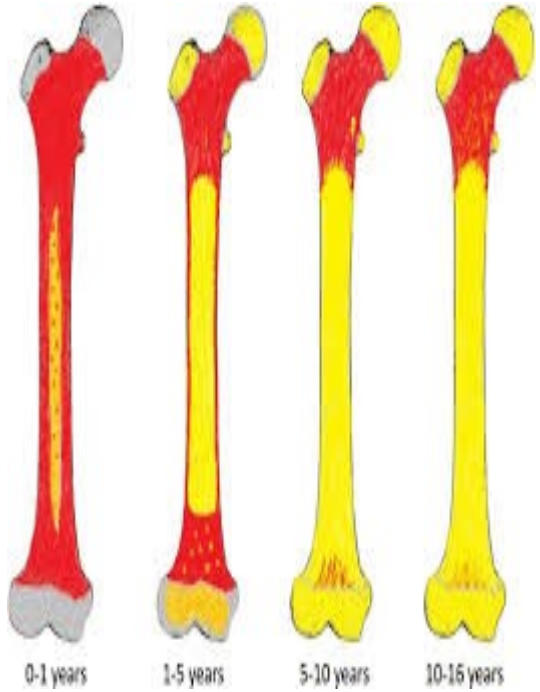
- **HEMATOCRIT : The percentage of total blood volume occupied by RBCs (RBC/BLOOD)**; a hematocrit of 40 indicates that 40% of the volume of blood is composed of RBCs. The normal range of hematocrit for adult females is 38–46% (average 42); for adult males, it is 40–54% (average 47).
- The hormone testosterone, present in much higher concentration in males than in females, stimulates synthesis of erythropoietin (EPO), the hormone that in turn stimulates production of RBCs. Thus, testosterone contributes to higher hematocrits in males. Lower values in women during their reproductive years also may be due to excessive loss of blood during menstruation.
- A significant **drop in hematocrit indicates *anemia***, a lower-than-normal number of RBCs.
- In **polycythemia** (pol-e¯-sı¯-THE¯-me¯-a) the percentage of RBCs is abnormally high, and the hematocrit may be 65% or higher. This raises the viscosity of blood, which increases the resistance to flow and makes the blood more difficult for the heart to pump. Increased viscosity also contributes to high blood pressure and increased risk of stroke. Causes of polycythemia include abnormal increases in RBC production, tissue hypoxia, dehydration, and blood doping or the use of EPO by athletes.

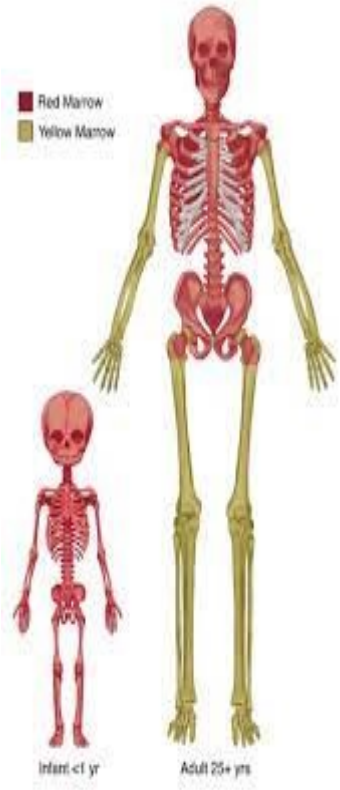
Formation of Blood Cells

- The process by which the formed elements of blood develop is called **hemopoiesis** (he¯m-o¯-poy-E¯ -sis; *-poiesis* making) or *hematopoiesis*.
- Before birth, hemopoiesis first occurs in the yolk sac of an embryo and later in the liver, spleen, thymus, and lymph nodes of a fetus.
- Red bone marrow becomes the primary site of hemopoiesis in the last 3 months before birth, and continues as the source of blood cells after birth and throughout life.
- **Red bone marrow** is a highly vascularized connective tissue located in the microscopic spaces between trabeculae of spongy bone tissue. It is present chiefly in bones of the axial skeleton, pectoral and pelvic girdles, and the proximal epiphyses (the end part of a long bone) of the humerus (upper arm) and femur (thigh).
- About 0.05–0.1% of red bone marrow cells are called **pluripotent stem cells** (ploo-RI-po¯- tent; *pluri-* several) or *hemocytoblasts* and are derived from mesenchyme (tissue from which almost all connective tissues develop). These cells have the capacity to develop into many different types of cells (Figure 19.3).

Red bone marrow







Formation of Blood Cells (continued)

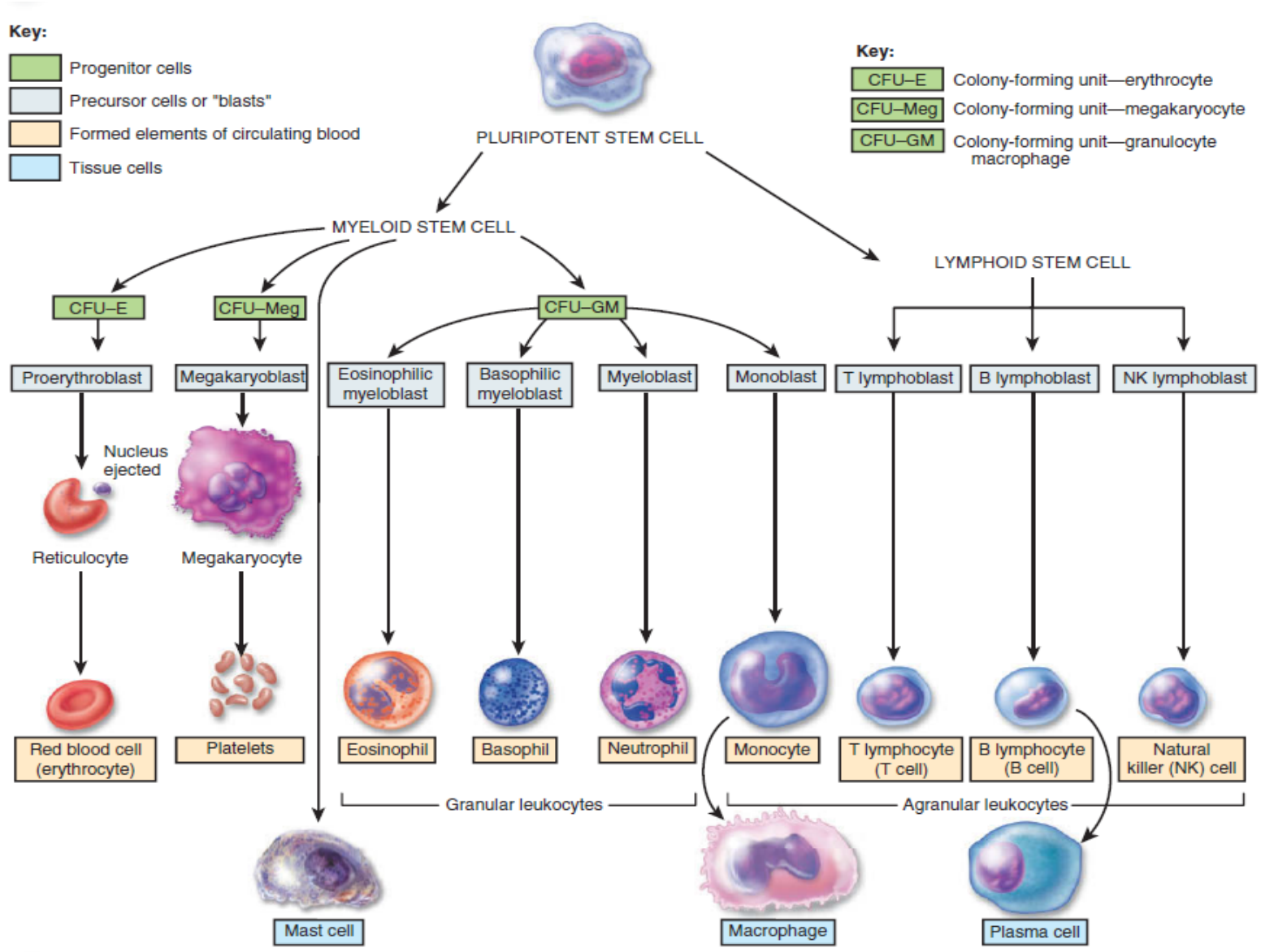
- In newborns, all bone marrow is red and thus active in blood cell production.
- As an individual ages, the rate of blood cell formation decreases; red bone marrow in the medullary (marrow) cavity of long bones becomes inactive and is replaced by yellow bone marrow, which consists largely of fat cells.
- Under certain conditions, such as severe bleeding, yellow bone marrow can revert to red bone marrow; this occurs as blood-forming stem cells from red bone marrow move into yellow bone marrow, which is then repopulated by pluripotent stem cells.

Hemopoietic growth factors

- Several hormones called **hemopoietic growth factors** (he¯-mo¯- poy-ET-ik) regulate the differentiation and proliferation of particular progenitor cells.
- **Erythropoietin (EPO)** (e-rith-ro¯-POYe ¯-tin) increases the number of red blood cell precursors. EPO is produced primarily by cells in the kidneys that lie between the kidney tubules (peritubular interstitial cells). With renal failure, EPO release slows and RBC production is inadequate. This leads to a decreased hematocrit, which leads to a decreased ability to deliver oxygen to body tissues.
- **Thrombopoietin (TPO)** (throm- bo¯-POY-e¯-tin) is a hormone produced by the liver that stimulates the formation of platelets from megakaryocytes. Several different cytokines regulate development of different blood cell types.
- **Cytokines** (SI¯-to¯-kı¯ns) are small glycoproteins that are typically produced by cells such as red bone marrow cells, leukocytes, macrophages, fibroblasts, and endothelial cells. They generally act as local hormones (autocrines or paracrines). Cytokines stimulate proliferation of progenitor cells in red bone marrow and regulate the activities of cells involved in nonspecific defenses (such as phagocytes) and immune responses (such as B cells and T cells). Two important families of cytokines that stimulate white blood cell formation are **colony-stimulating factors (CSFs)** and **interleukins** (in-ter-LOO-kins).

Figure 19.3 Origin, development, and structure of blood cells. A few of the generations of some cell lines have been omitted.

→ Blood cell production, called hemopoiesis, occurs mainly in red bone marrow after birth.



From which connective tissue cells do pluripotent stem cells develop?

Red Blood Cells (Erythrocytes)

- **Red blood cells (RBCs)** or *erythrocytes* (e-RITH-ro¯-sı¯ts; *erythro-* red; *-cyte* cell) contain the oxygen-carrying protein **hemoglobin**, which is a pigment that gives whole blood its red color.
- A healthy adult male has about 5.4 million red blood cells per microliter (μL) of blood,* and a healthy adult female has about 4.8 million.
- To maintain normal numbers of RBCs, new mature cells must enter the circulation at the astonishing rate of at least 2 million per second, a pace that balances the equally high rate of RBC destruction.

RBC Anatomy

- RBCs are biconcave discs with a diameter of 7–8 μm

- **Mature red blood cells have a simple structure**:

➢ Their plasma membrane is both strong and flexible, which allows them to deform without rupturing as they squeeze through narrow blood capillaries.

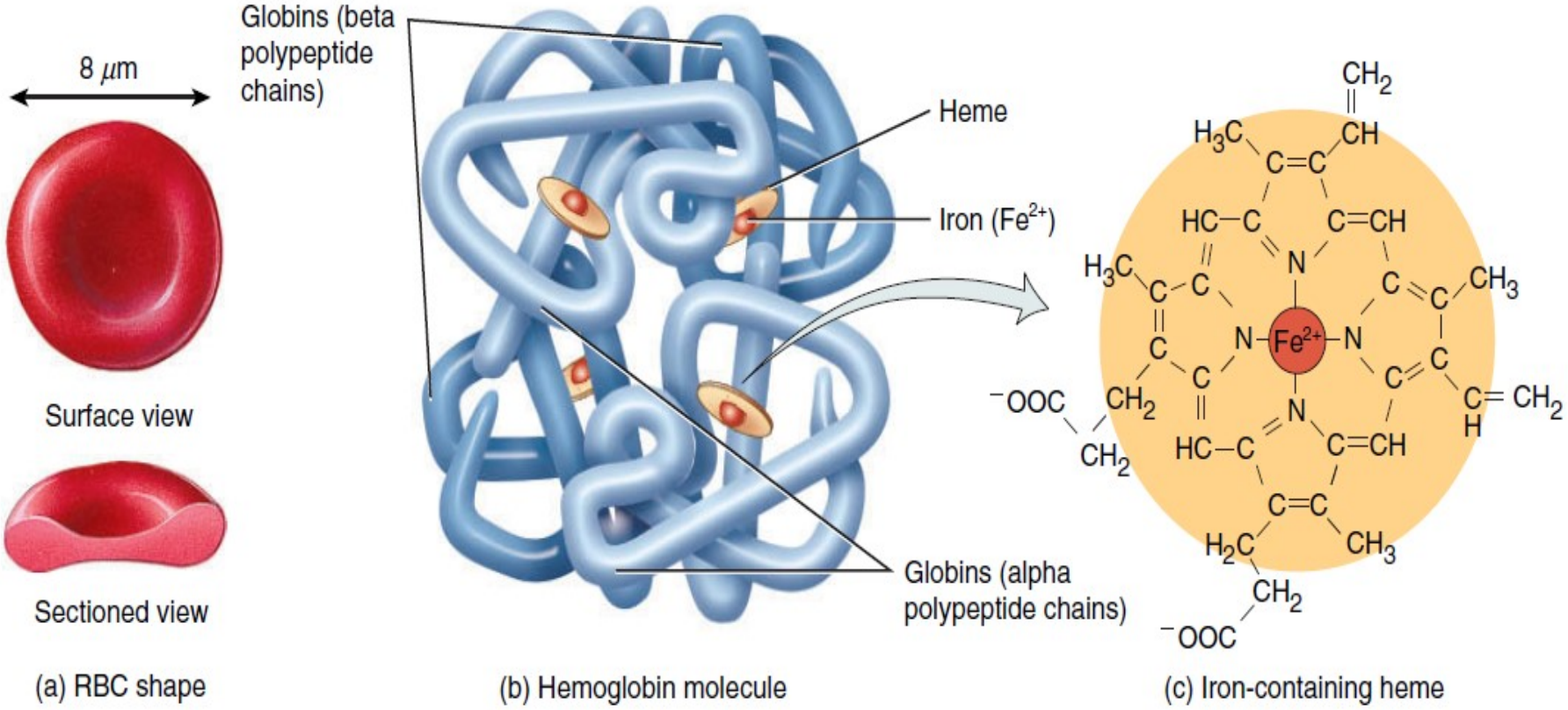
➢ Certain glycolipids in the plasma membrane of RBCs are antigens that account for the various blood groups such as the ABO and Rh groups.

➢ RBCs lack a nucleus and other organelles and can neither reproduce nor carry on extensive metabolic activities.

➢ The cytosol of RBCs contains hemoglobin molecules; these important molecules are synthesized before loss of the nucleus during RBC production and constitute about 33% of the cell's weight.

Figure 19.4 The shapes of a red blood cell (RBC) and a hemoglobin molecule. In (b), note that each of the four polypeptide chains of a hemoglobin molecule (blue) has one heme group (gold), which contains an iron ion (Fe^{2+}), shown in red.

→ *The iron portion of a heme group binds oxygen for transport by hemoglobin*



RBC Physiology

- **Red blood cells are highly specialized for their oxygen transport function.**

- Because mature RBCs have no nucleus, all of their internal space is available for oxygen transport.

- Because RBCs lack mitochondria and generate ATP anaerobically (without oxygen), they do not use up any of the oxygen they transport.

- Even the shape of an RBC facilitates its function. A biconcave disc has a much greater surface area for the diffusion of gas molecules into and out of the RBC than would, say, a sphere or a cube.

RBC Physiology (continued-1)

- **Each RBC contains about 280 million hemoglobin molecules.**

- A hemoglobin molecule consists of a protein called **globin**, composed of four polypeptide chains (two alpha and two beta chains); a ringlike nonprotein pigment called a **heme** (Figure 19.4b) is bound to each of the four chains.

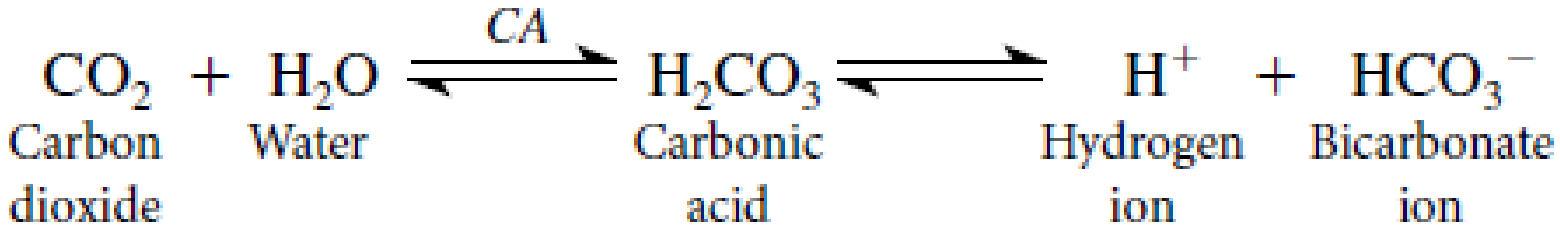
- At the center of each heme ring is an iron ion (Fe^{2+}) that can combine reversibly with one oxygen molecule (Figure 19.4c), allowing each hemoglobin molecule to bind four oxygen molecules. → the hemoglobin – oxygen bond is **loose.**
- Each oxygen molecule picked up from the lungs is bound to an iron ion. As blood flows through tissue capillaries, the iron–oxygen reaction reverses. Hemoglobin releases oxygen, which diffuses first into the interstitial fluid and then into cells.

RBC Physiology (continued-2)

- Hemoglobin also transports about 23% of the total carbon dioxide, a waste product of metabolism. (The remaining carbon dioxide is dissolved in plasma or carried as bicarbonate ions.)
- Blood flowing through tissue capillaries picks up carbon dioxide, some of which combines with amino acids in the globin part of hemoglobin.
- As blood flows through the lungs, the carbon dioxide is released from hemoglobin and then exhaled.
- In addition to its key role in transporting oxygen and carbon dioxide, hemoglobin also plays a role in the regulation of blood flow and blood pressure. The gaseous hormone **nitric oxide (NO)**, produced by the endothelial cells that line blood vessels, binds to hemoglobin.
- Under some circumstances, hemoglobin releases NO. The released NO causes *vasodilation*, an increase in blood vessel diameter that occurs when the smooth muscle in the vessel wall relaxes. Vasodilation improves blood flow and enhances oxygen delivery to cells near the site of NO release.

RBC Physiology (continued-3)

- Red blood cells also contain the enzyme carbonic anhydrase (CA), which catalyzes the conversion of carbon dioxide and water to carbonic acid, which in turn dissociates into H^+ and $HCO3^-$.
- The entire reaction is reversible and is summarized as follows:



- This reaction is significant for two reasons:

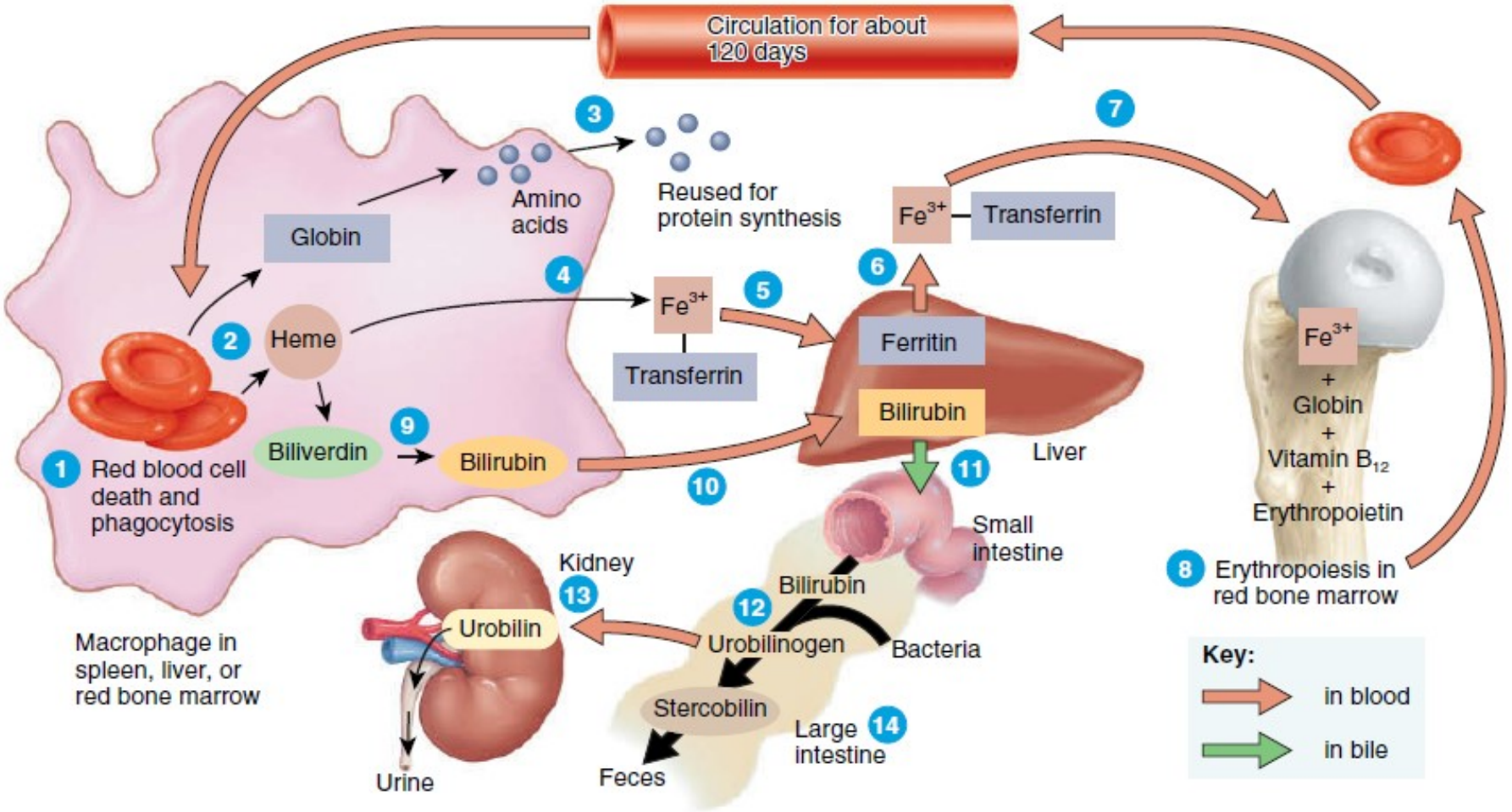
(1) It allows about 70% of CO2 to be transported in blood plasma from tissue cells to the lungs in the form of HCO_3^-.

(2) It also serves as an important buffer in extracellular fluid

Figure 19.5 Formation and destruction of red blood cells, and the recycling of hemoglobin components. RBCs circulate for about 120 days after leaving red bone marrow before they are phagocytized by macrophages.

→ The rate of RBC formation by red bone marrow equals the rate of RBC destruction by macrophages.

→ Transferrin= Iron <u>transfer</u> in bloodstream, Ferritin or hemosiderin = Iron <u>storage</u> in liver, muscle or spleen



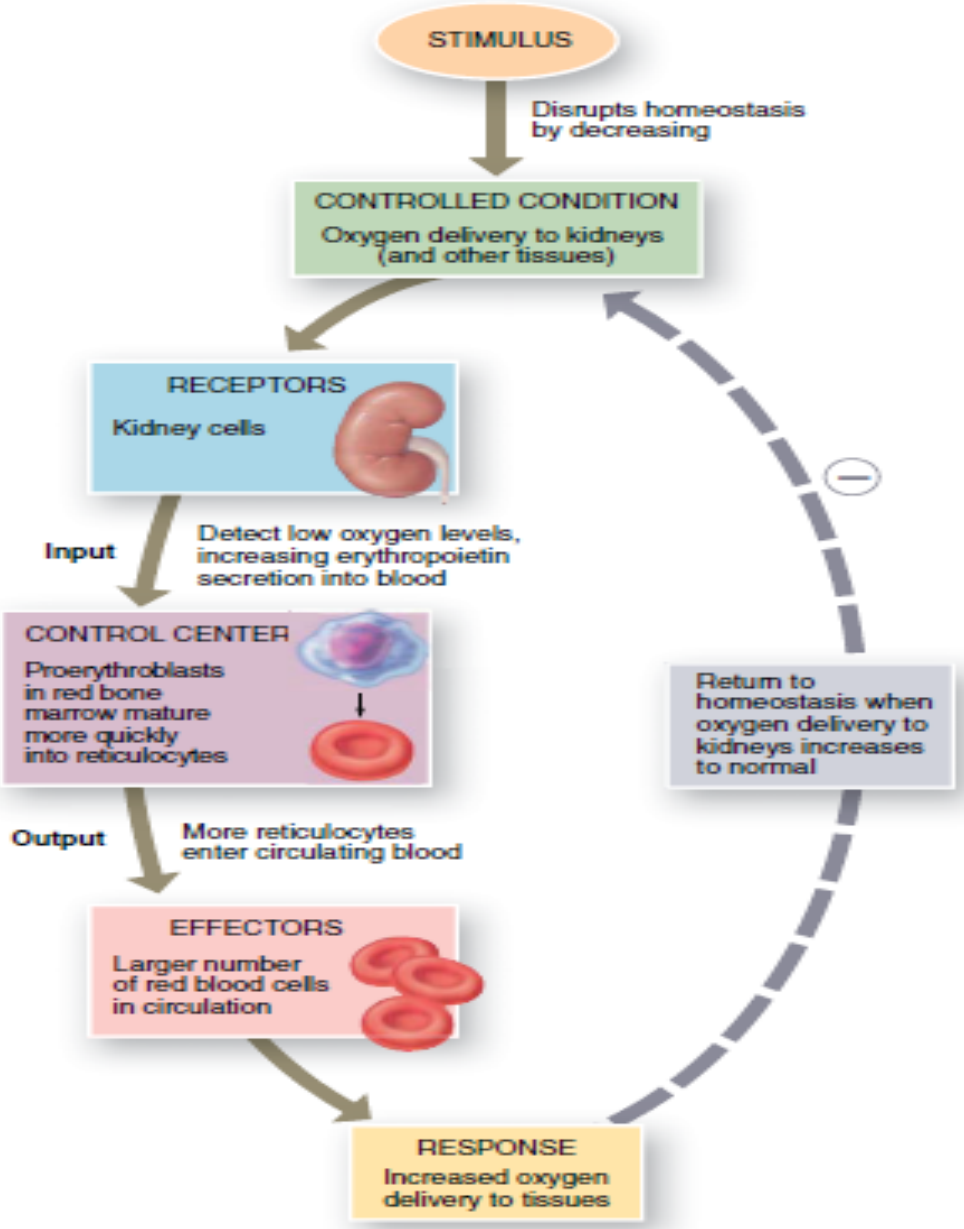
Fenton reaction ???

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + OH^{\cdot} + OH^{-}$$

Figure 19.6 Negative feedback regulation of erythropoiesis (red blood cell formation).

- Lower oxygen content of air at high altitudes, anemia, and circulatory problems may reduce oxygen delivery to body tissues.

- The main stimulus for erythropoiesis is hypoxia, a decrease in the oxygen-carrying capacity of the blood.



White Blood Cells

- **White blood cells (WBCs)** or *leukocytes* (LOO-ko¯-sı¯ts; *leuko-* white) have nuclei and a full complement of other organelles but they do not contain hemoglobin.
- WBCs are classified as either granular or agranular, depending on whether they contain conspicuous chemical-filled cytoplasmic granules (vesicles) that are made visible by staining when viewed through a light microscope.

- ***Granular leukocytes*** include **neutrophils, eosinophils, and basophils** → also called *polymorphonucleocytes* contain granules in their cytoplasm and a lobed nucleus. life span 100-300 days.

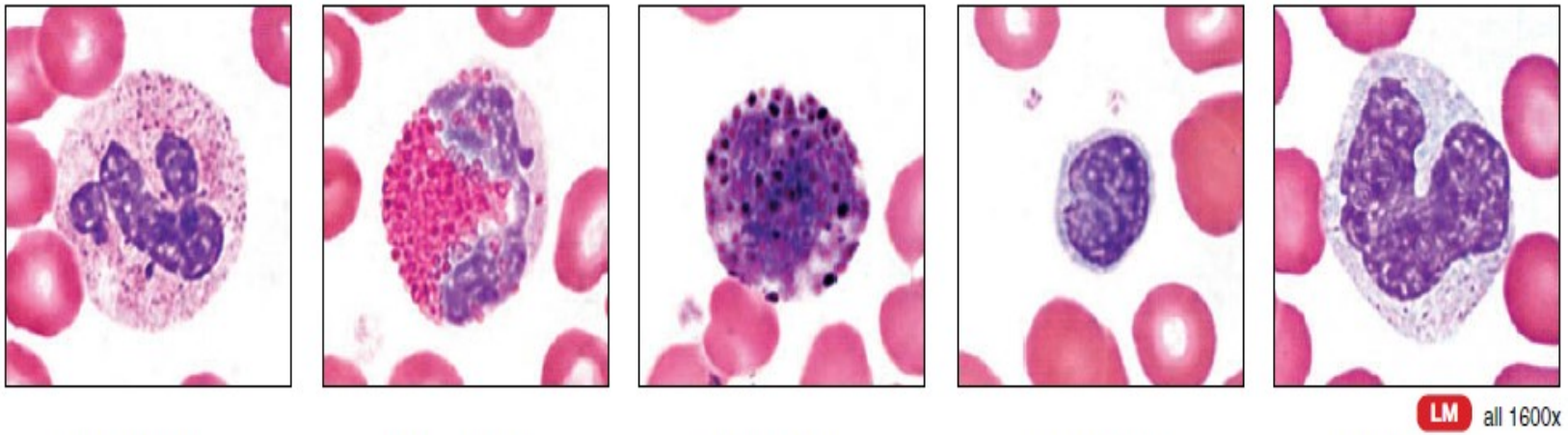
- ***Agranular leukocytes*** include **lymphocytes** and **monocytes**→ life span 12hr to 3 days.

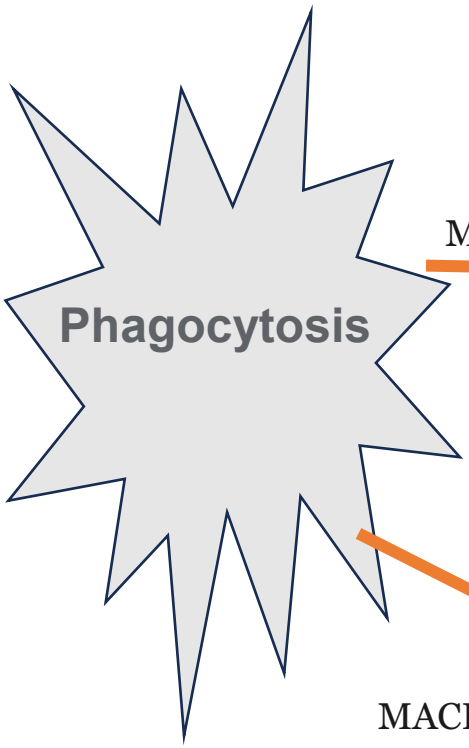
- As shown in Figure 19.3, **monocytes and granular leukocytes develop from myeloid stem cells.**

- In contrast, **lymphocytes** develop from **lymphoid stem cells**.

Figure 19.7 Types of white blood cells.

→ The shapes of their nuclei and the staining properties of their cytoplasmic granules distinguish white blood cells from one another.





MICROPHAGES

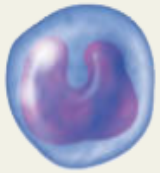
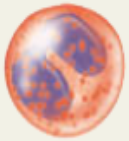
MACROPHAGES

*__High__ basophil levels (basophilia) may be a sign of low thyroid function, or **hypothyroidism**

* **Low** basophil levels (basopenia) is associated with **hyperthyroidism**

TABLE 19.2

Significance of High and Low White Blood Cell Counts

WBC TYPE	HIGH COUNT MAY INDICATE	LOW COUNT MAY INDICATE
Neutrophils 	Bacterial infection, burns, stress, inflammation.	Radiation exposure, drug toxicity, vitamin B_{12} deficiency, systemic lupus erythematosus (SLE).
Lymphocytes 	Viral infections, some leukemias, infectious mononucleosis.	Prolonged illness, HIV infection, immunosuppression, treatment with cortisol.
Monocytes 	Viral or fungal infections, tuberculosis, some leukemias, other chronic diseases.	Bone marrow suppression, treatment with cortisol.
Eosinophils 	Allergic reactions, parasitic infections, autoimmune diseases.	Drug toxicity, stress, acute allergic reactions.
Basophils 	Allergic reactions, leukemias, cancers, hypothyroidism.	Pregnancy, ovulation, stress, hypothyroidism.

Functions of White Blood Cells

- In a healthy body, some WBCs, especially lymphocytes, can live for several months or years, but most live only a few days.
- During a period of infection, phagocytic WBCs may live only a few hours.
- WBCs are far less numerous than red blood cells; at about 5000–10,000 cells per microliter of blood, they are outnumbered by RBCs by about 700:1.

- **Leukocytosis** (loo-ko¯-sı¯-TO¯ -sis), an increase in the number of WBCs above 10,000/μL, is a normal, protective response to stresses such as invading microbes, strenuous exercise, anesthesia, and surgery.
- An abnormally low level of white blood cells (below 5000/μL) is termed **leukopenia** (loo- ko¯-PE¯-ne¯-a). It is never beneficial and may be caused by radiation, shock, and certain chemotherapeutic agents.

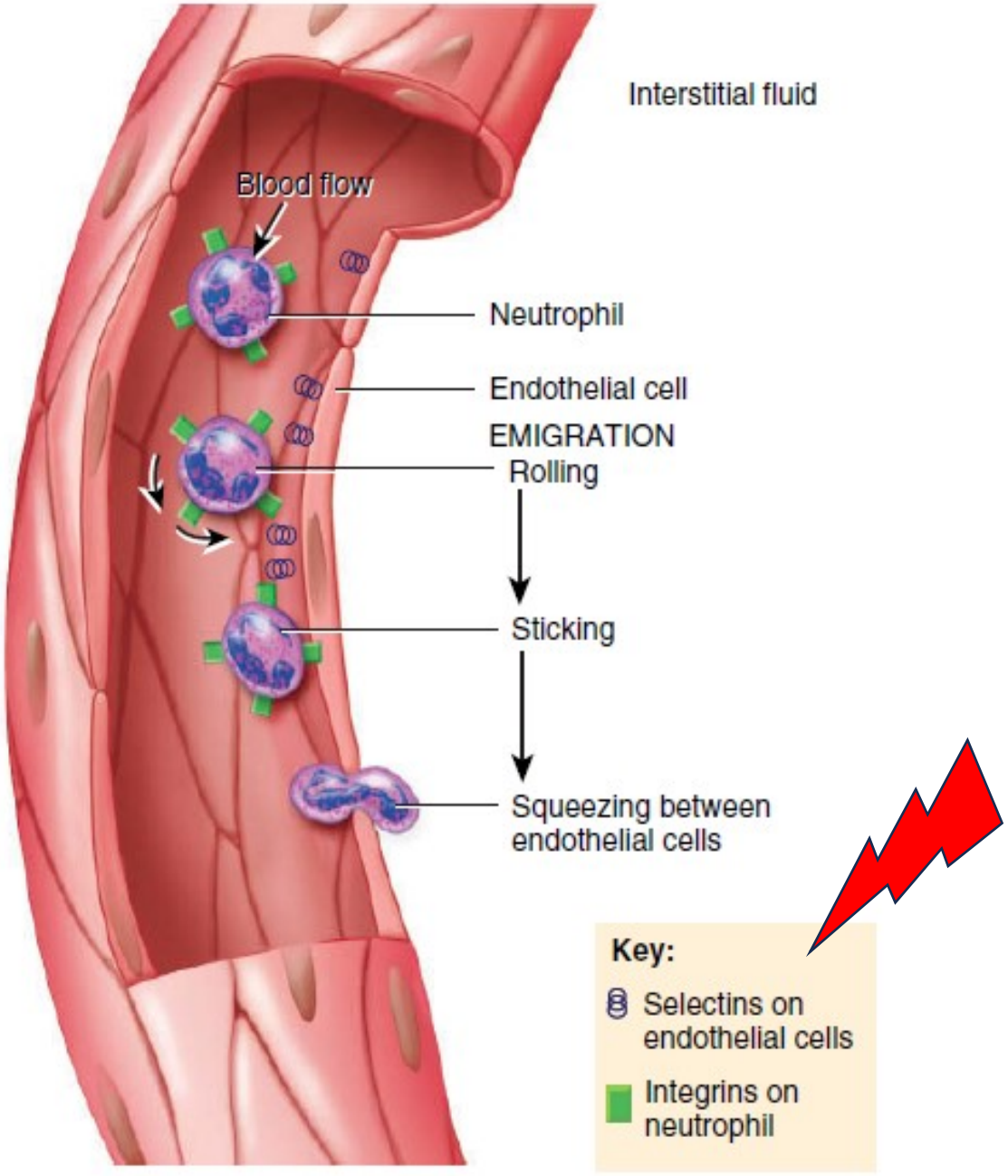
Emigration Of White Blood Cells

- Many WBCs leave the bloodstream and collect at sites of pathogen invasion or inflammation. Once granular leukocytes and monocytes leave the bloodstream to fight injury or infection, they never return to it.
- Lymphocytes, on the other hand, continually recirculate—from blood to interstitial spaces of tissues to lymphatic fluid and back to blood.
- Only 2% of the total lymphocyte population is circulating in the blood at any given time; the rest is in lymphatic fluid and organs such as the skin, lungs, lymph nodes, and spleen.
- WBCs leave the bloodstream by a process termed **emigration** (em-i-GRA¯ - shun; *e-* out; - *migra-* wander), also called *diapedesis* (dı¯-ape- DE¯-sis), in which they roll along the endothelium, stick to it, and then squeeze between endothelial cells (Figure 19.8).

Emigration Of White Blood Cells (continued)

- The precise signals that stimulate emigration through a particular blood vessel vary for the different types of WBCs.
- Molecules known as **adhesion molecules** help WBCs stick to the endothelium.
- For example, endothelial cells display adhesion molecules called *selectins* in response to nearby injury and inflammation.
- Selectins stick to carbohydrates on the surface of **neutrophils**, causing them to slow down and roll along the endothelial surface.
- On the neutrophil surface are other adhesion molecules called *integrins*, which tether neutrophils to the endothelium and assist their movement through the blood vessel wall and into the interstitial fluid of the injured tissue.

Figure 19.8
Emigration of white blood cells.
Adhesion molecules (selectins and integrins) assist the emigration of WBCs from the bloodstream into interstitial fluid.



Platelets

- Under the influence of the hormone thrombopoietin, myeloid stem cells develop into megakaryocyte colony-forming cells that in turn develop into precursor cells called *megakaryoblasts* (see Figure 19.3).
- Megakaryoblasts transform into megakaryocytes, huge cells that splinter into 2000 to 3000 fragments.
- Each fragment, enclosed by a piece of the plasma membrane, is a **platelet**.
- Platelets break off from the megakaryocytes in red bone marrow and then enter the blood circulation.
- Between 150,000 and 400,000 platelets are present in each microliter of blood. Each is irregularly disc-shaped, 2–4 μm in diameter, and has many vesicles but no nucleus.
- Their granules contain chemicals that, once released, promote blood clotting. Platelets help stop blood loss from damaged blood vessels by forming a platelet plug.
- Platelets have a short life span, normally just 5 to 9 days.
- Aged and dead platelets are removed by fixed macrophages in the spleen and liver.

TABLE 19.3: Summary of Formed Elements in Blood

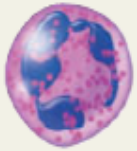
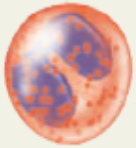
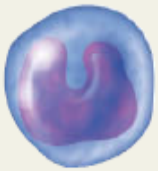
NAME AND APPEARANCE	NUMBER	CHARACTERISTICS*	FUNCTIONS
RED BLOOD CELLS (RBCS) OR ERYTHROCYTES 	4.8 million/μL in females; 5.4 million/μL in males.	7–8 μm diameter, biconcave discs, without nuclei; live for about 120 days.	Hemoglobin within RBCs transports most oxygen and part of carbon dioxide in blood.
WHITE BLOOD CELLS (WBCS) OR LEUKOCYTES	5000–10,000/μL.	Most live for a few hours to a few days.†	Combat pathogens and other foreign substances that enter body.
Granular leukocytes			
Neutrophils 	60–70% of all WBCs.	10–12 μm diameter; nucleus has 2–5 lobes connected by thin strands of chromatin; cytoplasm has very fine, pale lilac granules.	Phagocytosis. Destruction of bacteria with lysozyme, defensins, and strong oxidants, such as superoxide anion, hydrogen peroxide, and hypochlorite anion.
Eosinophils 	2–4% of all WBCs.	10–12 μm diameter; nucleus usually has 2 lobes connected by thick strand of chromatin; large, red-orange granules fill cytoplasm.	Combat effects of histamine in allergic reactions, phagocytize antigen–antibody complexes, and destroy certain parasitic worms.
Basophils 	0.5–1% of all WBCs.	8–10 μm diameter; nucleus has 2 lobes; large cytoplasmic granules appear deep blue-purple.	Liberate heparin, histamine, and serotonin in allergic reactions that intensify overall inflammatory response.

TABLE 19.3: Summary of Formed Elements in Blood (continued)

NAME AND APPEARANCE	NUMBER	CHARACTERISTICS*	FUNCTIONS
Agranular leukocytes			
Lymphocytes (T cells, B cells, and natural killer cells) 	20–25% of all WBCs.	Small lymphocytes are 6–9 μm in diameter; large lymphocytes are 10–14 μm in diameter; nucleus is round or slightly indented; cytoplasm forms rim around nucleus that looks sky blue; the larger the cell, the more cytoplasm is visible.	Mediate immune responses, including antigen–antibody reactions. B cells develop into plasma cells, which secrete antibodies. T cells attack invading viruses, cancer cells, and transplanted tissue cells. Natural killer cells attack wide variety of infectious microbes and certain spontaneously arising tumor cells.
Monocytes 	3–8% of all WBCs.	12–20 μm diameter; nucleus is kidney- or horseshoe-shaped; cytoplasm is blue-gray and appears foamy.	Phagocytosis (after transforming into fixed or wandering macrophages).
PLATELETS 	150,000–400,000/μL.	2–4 μm diameter cell fragments that live for 5–9 days; contain many vesicles but no nucleus.	Form platelet plug in hemostasis; release chemicals that promote vascular spasm and blood clotting.

*Colors are those seen when using Wright's stain.
†Some lymphocytes, called T and B memory cells, can live for many years once they are established.

Stem Cell Transplants from Bone Marrow and Cord Blood

- A **bone marrow transplant** is the replacement of cancerous or abnormal red bone marrow with healthy red bone marrow in order to establish normal blood cell counts.
- The red bone marrow from a donor is usually removed from the iliac crest of the hip bone under general anesthesia with a syringe and is then injected into the recipient's vein, much like a blood transfusion. The injected marrow migrates to the recipient's red bone marrow cavities, where the donor's stem cells multiply. If all goes well, the recipient's red bone marrow is replaced entirely by healthy, noncancerous cells.

- A more recent advance for obtaining stem cells involves a **cord-blood transplant**. Stem cells may be obtained from the umbilical cord shortly after birth. The stem cells are removed from the cord with a syringe and then frozen. Stem cells from the cord have several advantages over those obtained from red bone marrow.

Hemostasis

- **Hemostasis** (he¯-mo¯-STA¯ -sis), not to be confused with the very similar term *homeostasis*, is a sequence of responses that stops bleeding.
- When blood vessels are damaged or ruptured, the hemostatic response must be quick, localized to the region of damage, and carefully controlled in order to be effective. **Three mechanisms reduce blood loss:**

(1) Vascular spasm→ caused by damage to the smooth muscle, by substances released from activated platelets, and by reflexes initiated by pain receptors.

(2) Platelet plug formation→ (Plt. Adhesion + Plt. Aggregation)

(3) Blood clotting (coagulation)→ fibrin production

When successful, hemostasis prevents **hemorrhage** (HEM-o-rij; *-rhage* burst forth), the loss of a large amount of blood from the vessels. Hemostatic mechanisms can prevent hemorrhage from smaller blood vessels, but extensive hemorrhage from larger vessels usually requires medical intervention.

BLOOD CLOTTING

- **Functions of Platelets.** In intact vessel, endothelial lining produces **prostacyclin** (a type of prostaglandin PGI_2) and nitric oxide NO that 1-act as vasodilators 2-repels platelets from each other & from the endothelium.
- Vessel damage exposes sub-endothelial tissue to the blood. Platelets proteins bind to exposed negative collagen.

- **von Willebrand factor** (protein secreted by endothelial cells) binds collagen and Platelets thereby hindering blood flow from pulling Platelets away.

- Platelets contain secretory granules, when Platelets stick to collagen they degranulate as secretory granules release their contents: ADP, serotonin, and thromboxane A2 (a type of prostaglandin).
- Serotonin, and thromboxane A2 stimulate **vasoconstriction** to decrease blood flow to the injured vessel.
- ADP and thromboxane A2 recruit new platelets which result in plug formation.

Clotting Factors: *Formation of Fibrin*

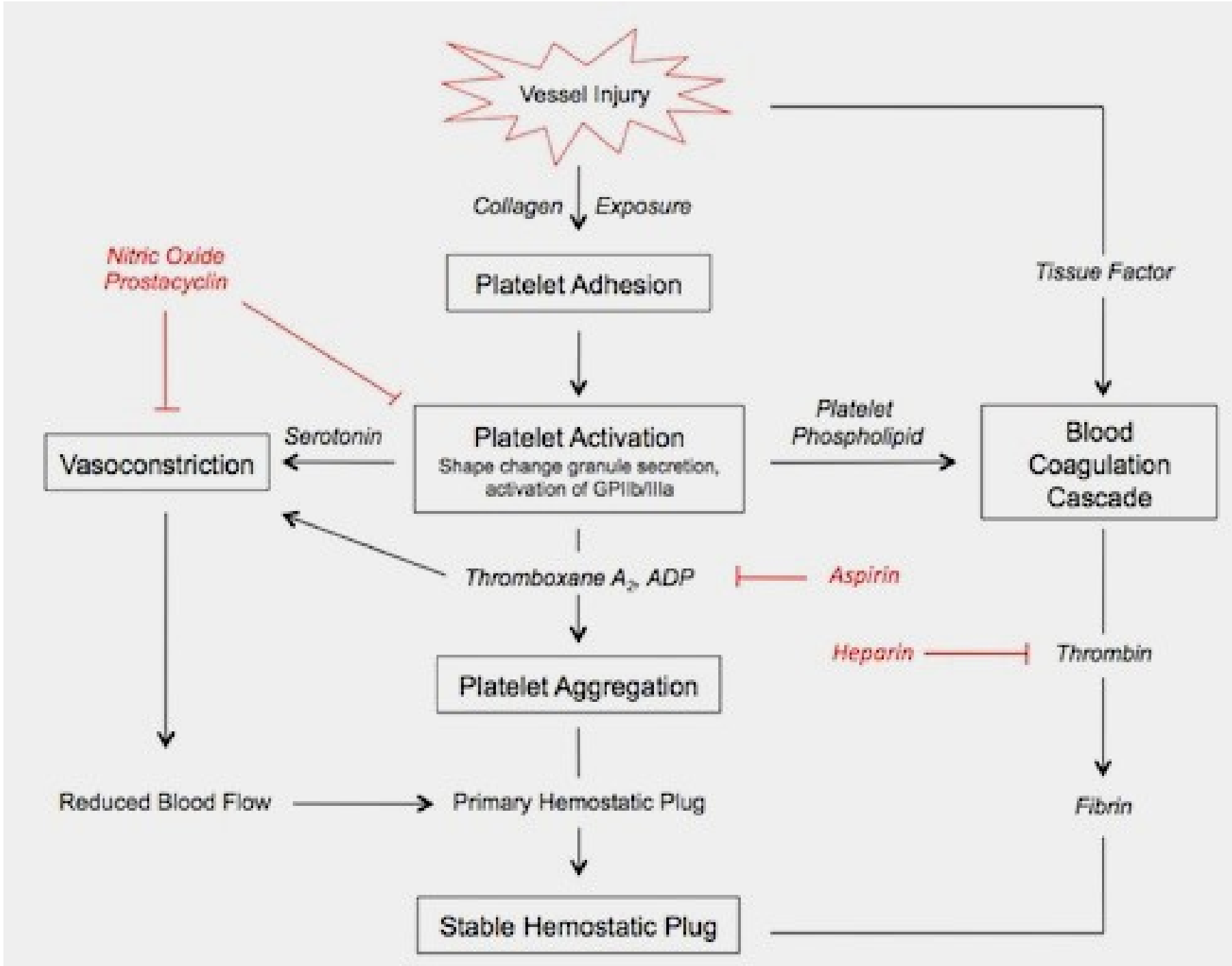
- **When a blood vessel is damaged,**

The conversion of fibrinogen into fibrin occurs via either of 2 pathways:

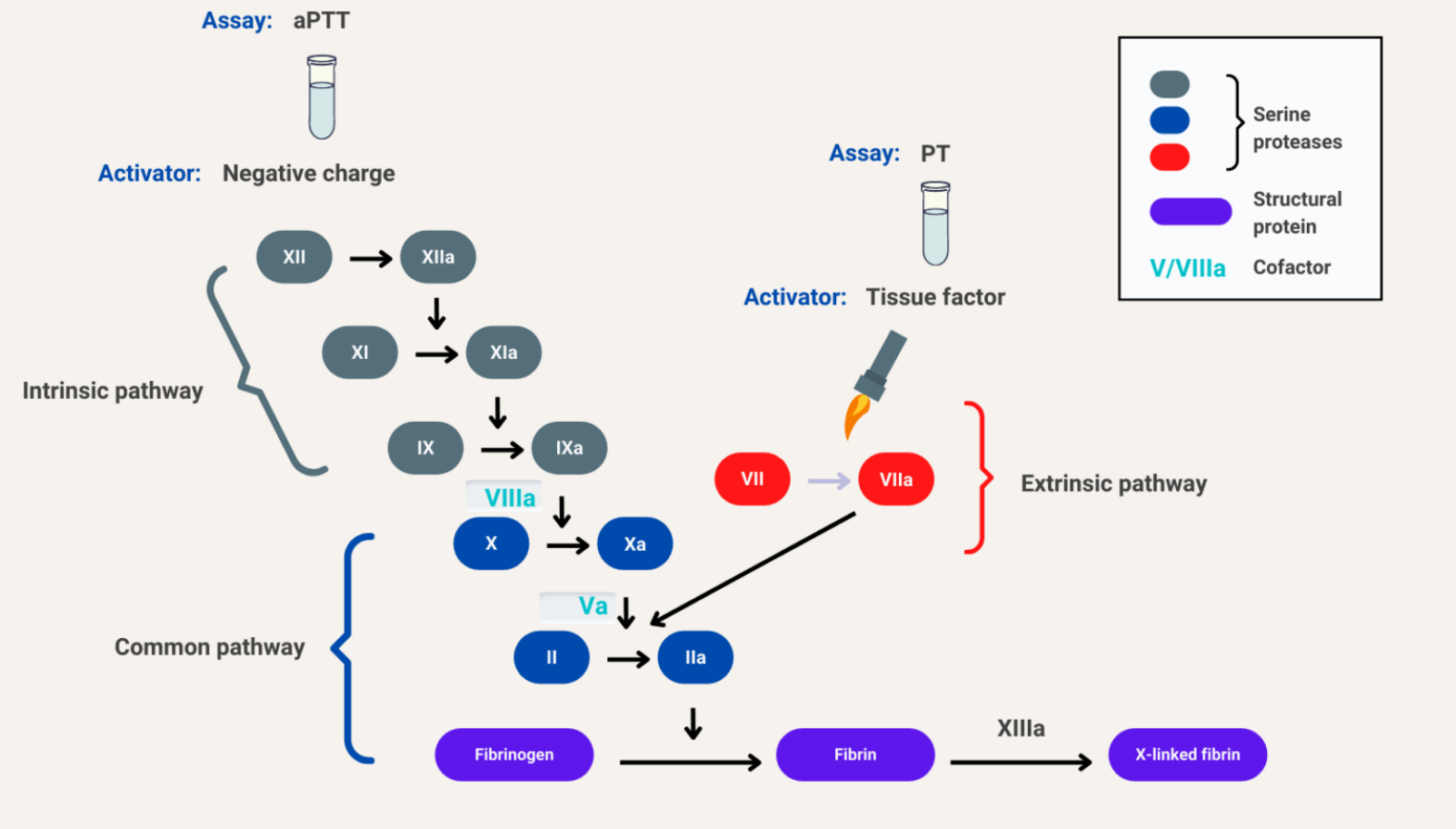
(1) **intrinsic pathway**, where blood left in a test tube will clot without the addition of any external chemicals.

(2**) extrinsic pathway** where damaged tissue release chemicals that initiates a "shortcut" to the formation of fibrin. Because chemicals are not part of blood the pathway is called **extrinsic**

intrinsic & extrinsic pathway finally merge to form a **Common Pathway** leading to the formation of a **fibrin clot !**

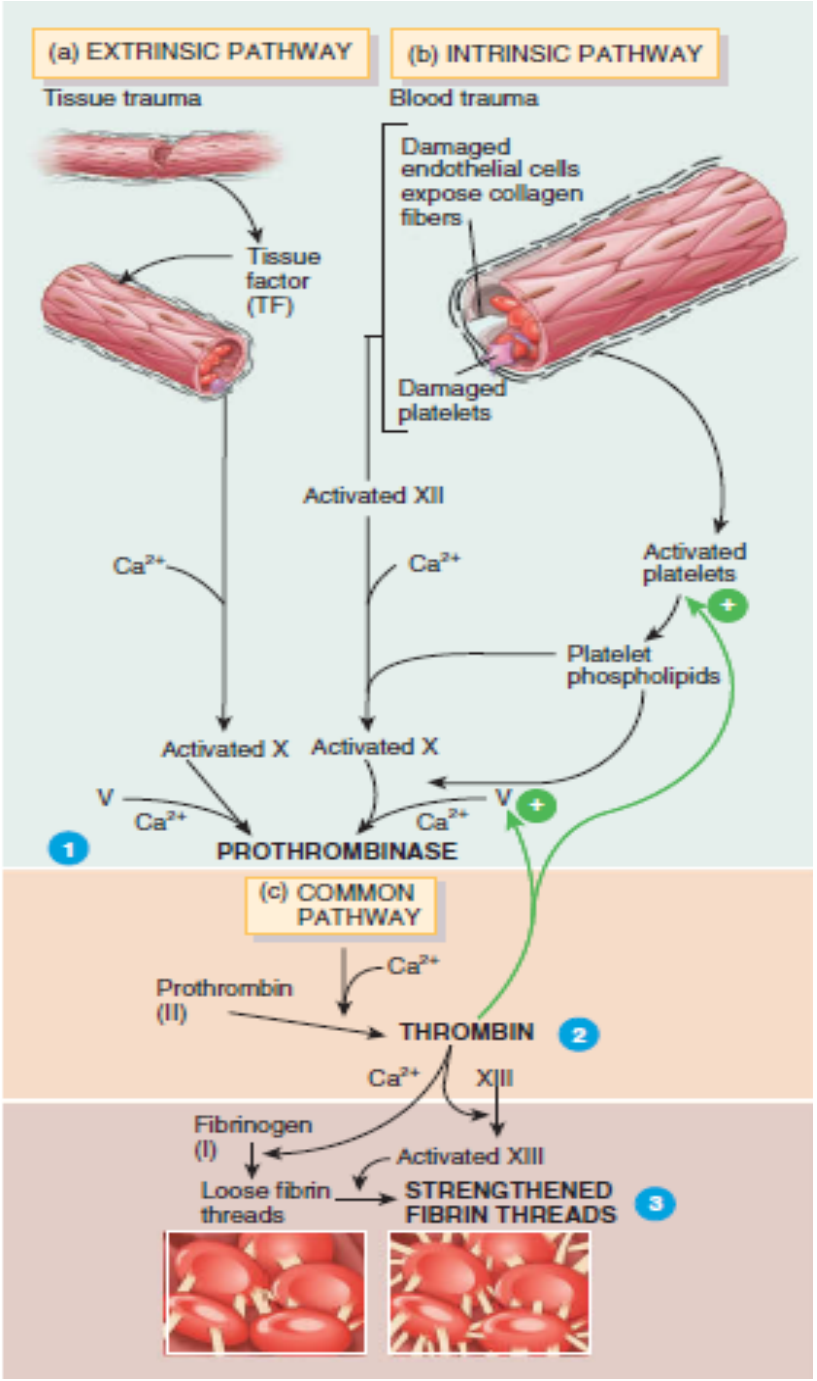

Vessel Injury
Collagen Exposure
Nitric Oxide
Prostacyclin
Platelet Adhesion
Tissue Factor
Vasoconstriction
Serotonin
Platelet Activation
Shape change granule secretion, activation of GPIIb/IIIa
Platelet Phospholipid
Blood Coagulation Cascade
Thromboxane A2, ADP
Aspirin
Heparin
Thrombin
Platelet Aggregation
Reduced Blood Flow
Primary Hemostatic Plug
Fibrin
Stable Hemostatic Plug

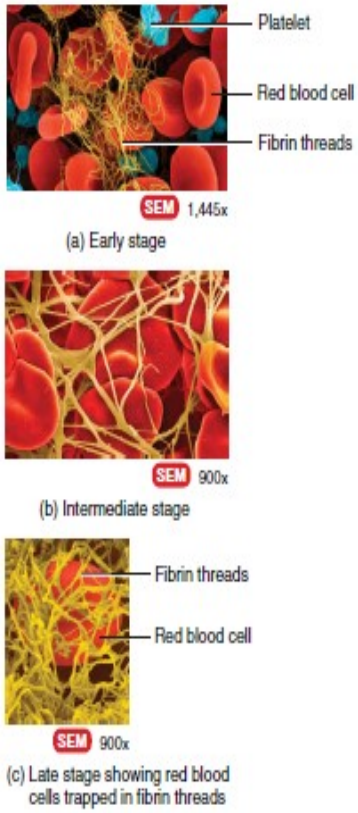
The blood-clotting cascade



The blood-clotting cascade
Green arrows represent positive feedback cycles.

In blood clotting, coagulation factors are activated in sequence, resulting in a cascade of reactions that includes positive feedback cycles.





At least 12 clotting factors in the blood participate in blood clotting. Factors are designated by a roman numeral

TABLE 19.4

Clotting (Coagulation) Factors

NUMBER*	NAME(S)	SOURCE	PATHWAY(S) OF ACTIVATION
I	Fibrinogen.	Liver.	Common.
II	Prothrombin.	Liver.	Common.
III	Tissue factor (thromboplastin).	Damaged tissues and activated platelets.	Extrinsic.
IV	Calcium ions (Ca^{2+}).	Diet, bones, and platelets.	All.
V	Proaccelerin, labile factor, or accelerator globulin (AcG).	Liver and platelets.	Extrinsic and intrinsic.
VII	Serum prothrombin conversion accelerator (SPCA), stable factor, or proconvertin.	Liver.	Extrinsic.
VIII	Antihemophilic factor (AHF), antihemophilic factor A, or antihemophilic globulin (AHG).	Liver.	Intrinsic.
IX	Christmas factor, plasma thromboplastin component (PTC), or antihemophilic factor B.	Liver.	Intrinsic.
X	Stuart factor, Prower factor, or thrombokinase.	Liver.	Extrinsic and intrinsic.
XI	Plasma thromboplastin antecedent (PTA) or antihemophilic factor C.	Liver.	Intrinsic.
XII	Hageman factor, glass factor, contact factor, or antihemophilic factor D.	Liver.	Intrinsic.
XIII	Fibrin-stabilizing factor (FSF).	Liver and platelets.	Common.

*There is no factor VI. Prothrombinase (prothrombin activator) is a combination of activated factors V and X.

Role of Vitamin K in Clotting

- ✓ Normal clotting depends on adequate levels of vitamin K in the body.
- ✓ Although vitamin K is not involved in actual clot formation, it is required for the synthesis of four clotting factors.
- ✓ Normally produced by bacteria that inhabit the large intestine, vitamin K is a fat-soluble vitamin that can be absorbed through the lining of the intestine and into the blood if absorption of lipids is normal.

Clot Dissolution

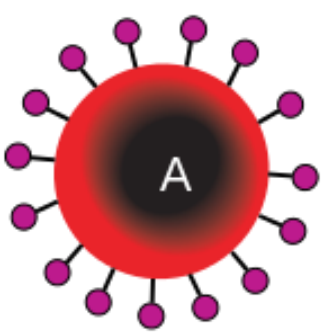
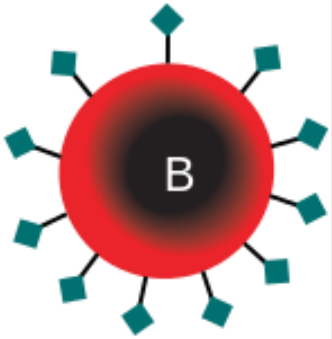
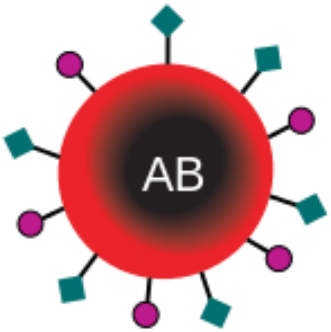
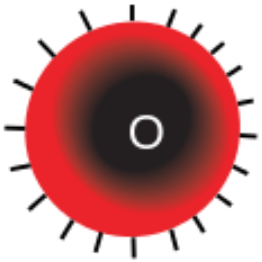
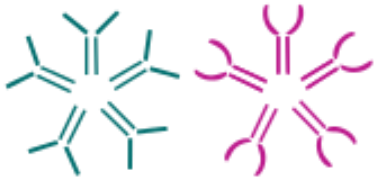
- When blood vessel is repaired, activated factor XII (Hageman factor) promotes kallikrein (plasma protein) formation

⇨catalyzes the conversion of inactive plasminogen into active plasmin (enzyme digests fibrin)

⇨clot dissolution.

Blood Groups and Blood Types

- The surfaces of erythrocytes contain a genetically determined assortment of **antigens** composed of glycoproteins and glycolipids.
- These antigens, called **agglutinogens** (a-gloo-TIN-o^{-}-jens), occur in characteristic combinations.
- Based on the presence or absence of various antigens, blood is categorized into different **blood groups**.
- Within a given blood group, there may be two or more different **blood types**.
- There are at least 24 blood groups and more than 100 antigens that can be detected on the surface of red blood cells.
- The two major blood groups—ABO and Rh.
- Other blood groups include the Lewis, Kell, Kidd, and Duffy systems.
- The incidence of ABO and Rh blood types varies among different population groups

	Group A	Group B	Group AB	Group O
Red blood cell type				
Antibodies in Plasma	 Anti-B	 Anti-A	None	 Anti-A and Anti-B
Antigens in Red Blood Cell	 A antigen	 B antigen	 A and B antigens	None

Summary of ABO Blood Group Interactions

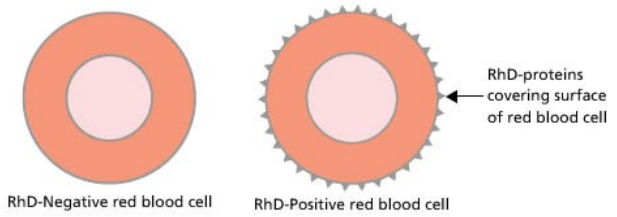
	BLOOD TYPE			
CHARACTERISTIC	A	B	AB	O
Agglutinogen (antigen) on RBCs	A	B	Both A and B	Neither A nor B
Agglutinin (antibody) in plasma	anti-B	anti-A	Neither anti-A nor anti-B	Both anti-A and anti-B
Compatible donor blood types (no hemolysis)	A, O	B, O	A, B, AB, O	O
Incompatible donor blood types (hemolysis)	B, AB	A, AB	—	A, B, AB

Rhesus Blood Group

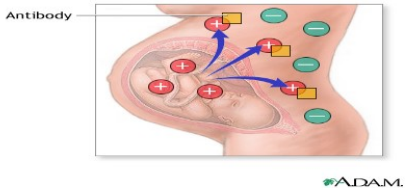
- Rh factor is an important **antigen** in human blood types. The Rh antigen is termed D and is indicated as RhoD : 85% of population Rh+; 15% are Rh-.

- Rh positive (Rh+) has the Rh factor on red blood cells; Rh negative (Rh-) lacks the Rh antigen on RBCs
- Rh-negative individuals do not have antibodies to Rh factor but make them if exposed to Rh+ blood.

- Rh positive is a genetically dominant trait; an Rh negative mother and an Rh positive father pose a Rh conflict.



Hemolytic Disease of the Newborn



- ✓ Rh factor is particularly important if Rh negative mother is pregnant with Rh positive child
- ✓ **Erythroblastosis fetalis:** Hemolytic disease of the newborn is possible if the mother is Rh negative and the father is Rh positive.
- ✓ Normally **during pregnancy** the maternal blood and the fetal blood are kept separate across the placenta.
- ✓ At **time of birth** variable degrees of exposure may occur. The child's Rh positive RBCs can leak across the placenta into the mother's circulatory system when the placenta breaks down.
- ✓ The mother immune system may produce antibodies against Rh antigen
- ✓ Anti-Rh antibodies pass across the placenta and destroy the RBCs of the Rh positive child. Baby is born with hemolytic disease of newborn called **Erythroblastosis fetalis**
- ✓ The Rh problem has been solved by giving Rh- women an Rh immunoglobulin (antibody) injection (called Rho-Gam) either midway through the first pregnancy or no later than 72 hours after giving birth to an Rh+ child.
- ✓ The injection includes anti-Rh antibodies that attack and destroy any fetal RBCs that have entered the mother circulation before her immune system can respond to produce antibodies.
- ✓ The injection is not effective if the mother has already produced antibodies; timing is important.