Hematology lecture

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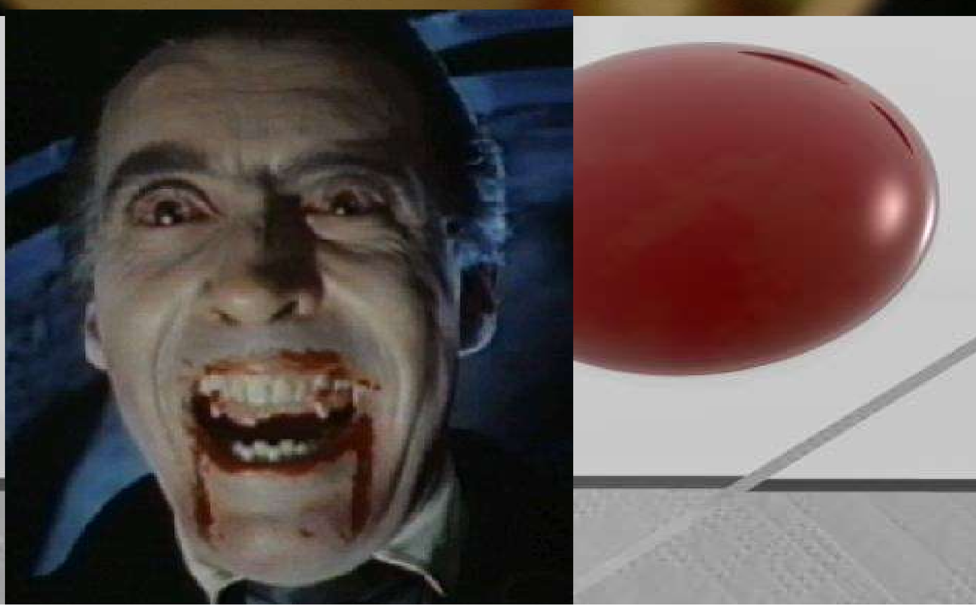


Table 18.1 Physical Characteristics of Blood

Characteristics	Normal Values
Color	Scarlet (oxygen-rich) to dark red (oxygen-poor)
Volume	4–5 L (females) 5–6 L (males)
Viscosity (relative to water)	4.5–5.5× (whole blood)
Plasma concentration	0.09%
Temperature	38°C (100.4°F)
pH	7.35–7.45

- **PFC stands for perflourocarbons.**

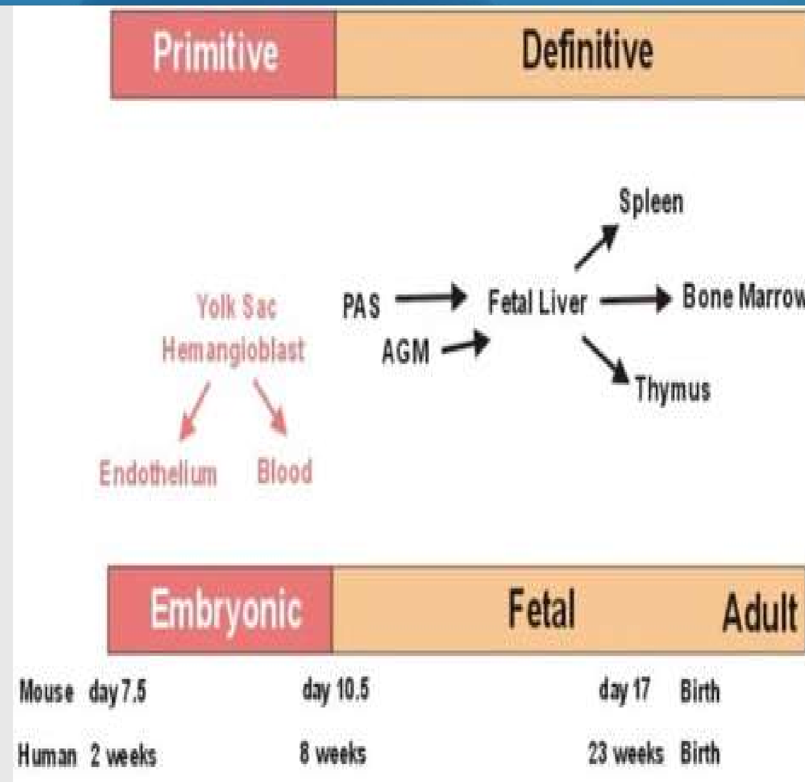
  Perflourocarbons are a type of synthetic blood that helps carry dissolved gases in the blood.
  They are mixed with an emulsifier to create a liquid suspension that can be mixed with blood.
  PFCs can carry about 20 percent more gas than blood plasma.

  PFCs may be especially helpful in these areas:

  -Restoring the delivery of oxygen in the body
  -Treating traumatic brain injury
  -Treating anemia
  -Increasing the effectiveness of chemotherapy
  -Preventing the need for surgical blood transfusion

HEMOPOIESIS

- **Hemo**: Referring to blood cells
- **Poiesis**: "The development or production of"
- The word Hemopoiesis refers to the production & development of all the blood cells:
  - Erythrocytes: Erythropoiesis
  - Leucocytes: Leucopoiesis
  - Thrombocytes: Thrombopoiesis.
- Begins in the 2th week of life, embryo.
  - in the fetal liver & spleen
  - continues in the bone marrow till young adulthood & beyond!



SITES OF HEMOPOIESIS

- **Active Hemopoietic marrow is found, in children throughout the:**
  - **Axial skeleton:**
    - **Cranium**
    - **Ribs.**
    - **Sternum**
    - **Vertebrae**
    - **Pelvis**
  - **Appendicular skeleton:**
    - **Bones of the Upper & Lower limbs**
- **In Adults active hemopoietic marrow is found only in:**
  - **The axial skeleton**
  - **The proximal ends of the appendicular skeleton.**

- Before birth, blood cell formation takes place in
  - **The fetal yolk sac,**
  - **Liver,**
  - **Spleen**
- By the **seventh month, red bone marrow is the primary hematopoietic area**
- Blood cells develop from ***mesenchymal cells called blood islands***
- **The fetus forms HbF**, which has **a higher affinity for oxygen** than adult hemoglobin

- Felal erythrocytes arc produced in different locations throughoul the life of the fetus.
  - **Yolk sac (3-8 weeks) during organogenesis**
  - **Liver (6-30 weeks)**
  - **Spleen (9-28 weeks)**
  - **Bone marrow (28 weeks-adult)**
- HEMOGLOBIN
  - Fetal hemoglobin consists of two alpha subunits and two gamma sitbunils (alpha2 and gamma2)-

HEMOPOIESIS

- **Location**
- **Fetal Life:**
  - *Yolk sac*: early embryonic stage.
  - *Liver and spleen*: main sites during mid-gestation.
- **After Birth:**
  - *Red bone marrow*: primary site in adults (especially in flat bones like sternum, ribs, pelvis, and vertebrae).

- **Types of Hemopoiesis**
- **Erythropoiesis** – formation of red blood cells (RBCs).
- **Leukopoiesis** – formation of white blood cells (WBCs), including:
  - *Granulopoiesis*: neutrophils, eosinophils, basophils.
  - *Monocytopoiesis*: monocytes/macrophages.
  - *Lymphopoiesis*: B and T lymphocytes.
- **Thrombopoiesis** – formation of platelets from megakaryocytes.

- **Hemopoietic cells** (those which produce blood) first **appear in the yolk sac of the 2-week embryo**.

- By **8 weeks**, blood making has **become established in the liver of the embryo,**
-
- By **12-16 weeks the liver** has become the major site of blood cell formation.
- It remains an active hemopoietic site until a **few weeks before birth**.

- The spleen is also active during this period, particularly in the production of lymphoid cells, and the fetal thymus is a transient site for some lymphocytes.

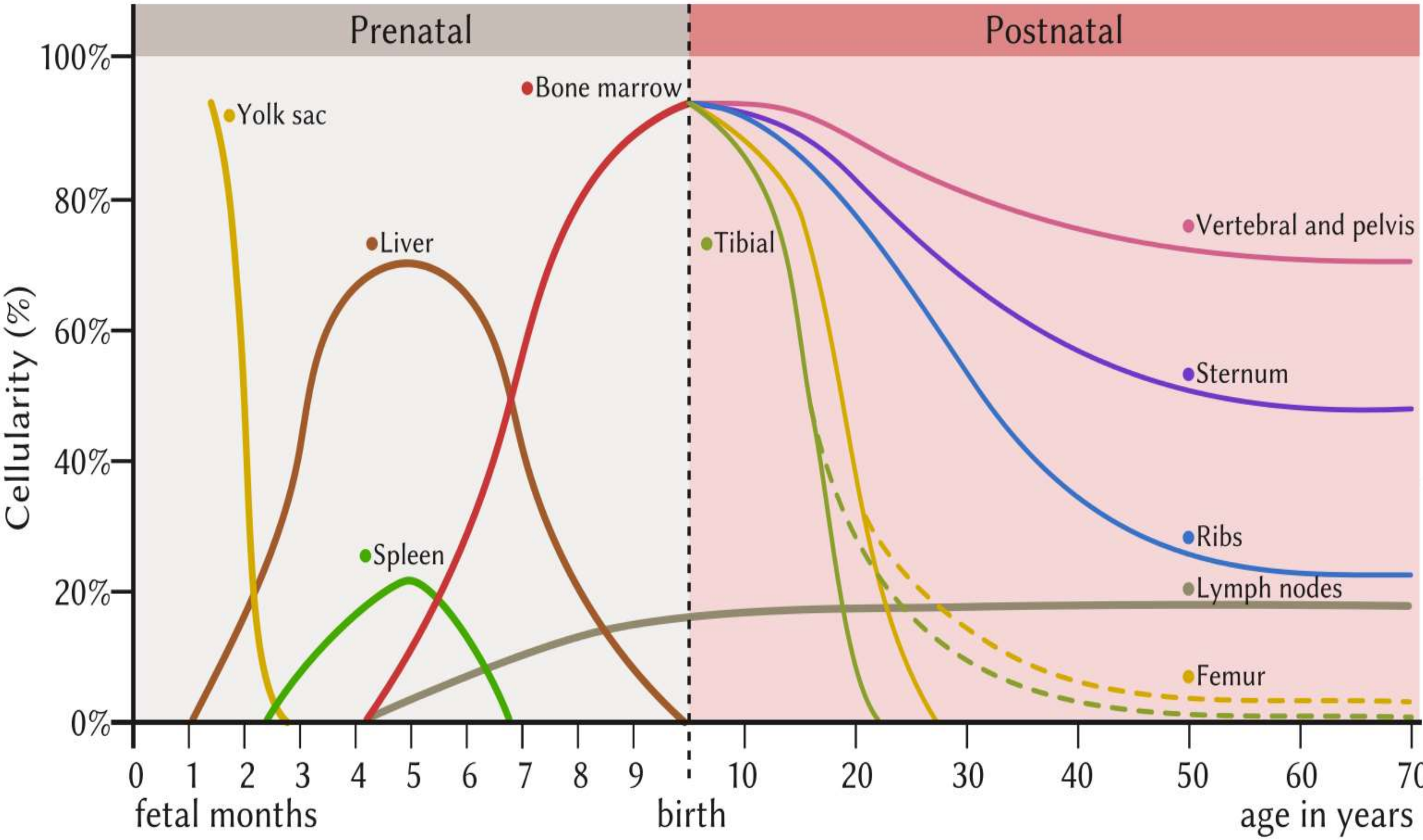
At birth, active blood making red marrow occupies the entire capacity of the bones and continues to do so for the first 2-3 years after birth.

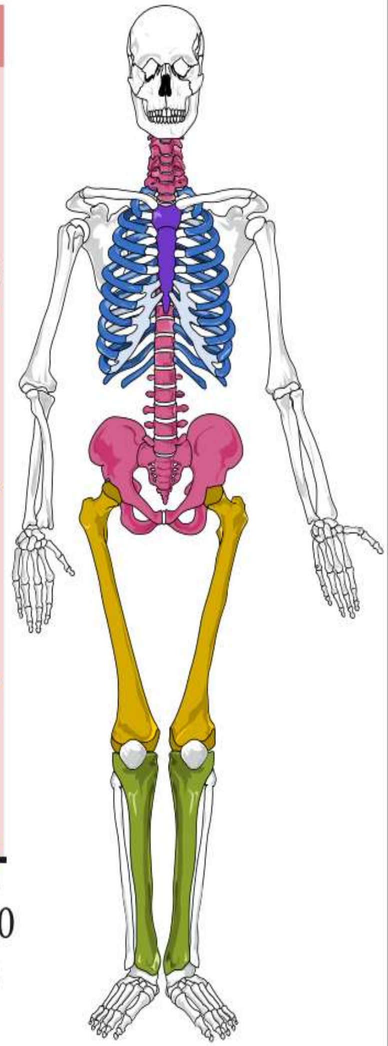
- **The red marrow is then very gradually replaced by inactive, fatty, yellow, lymphoid marrow.**

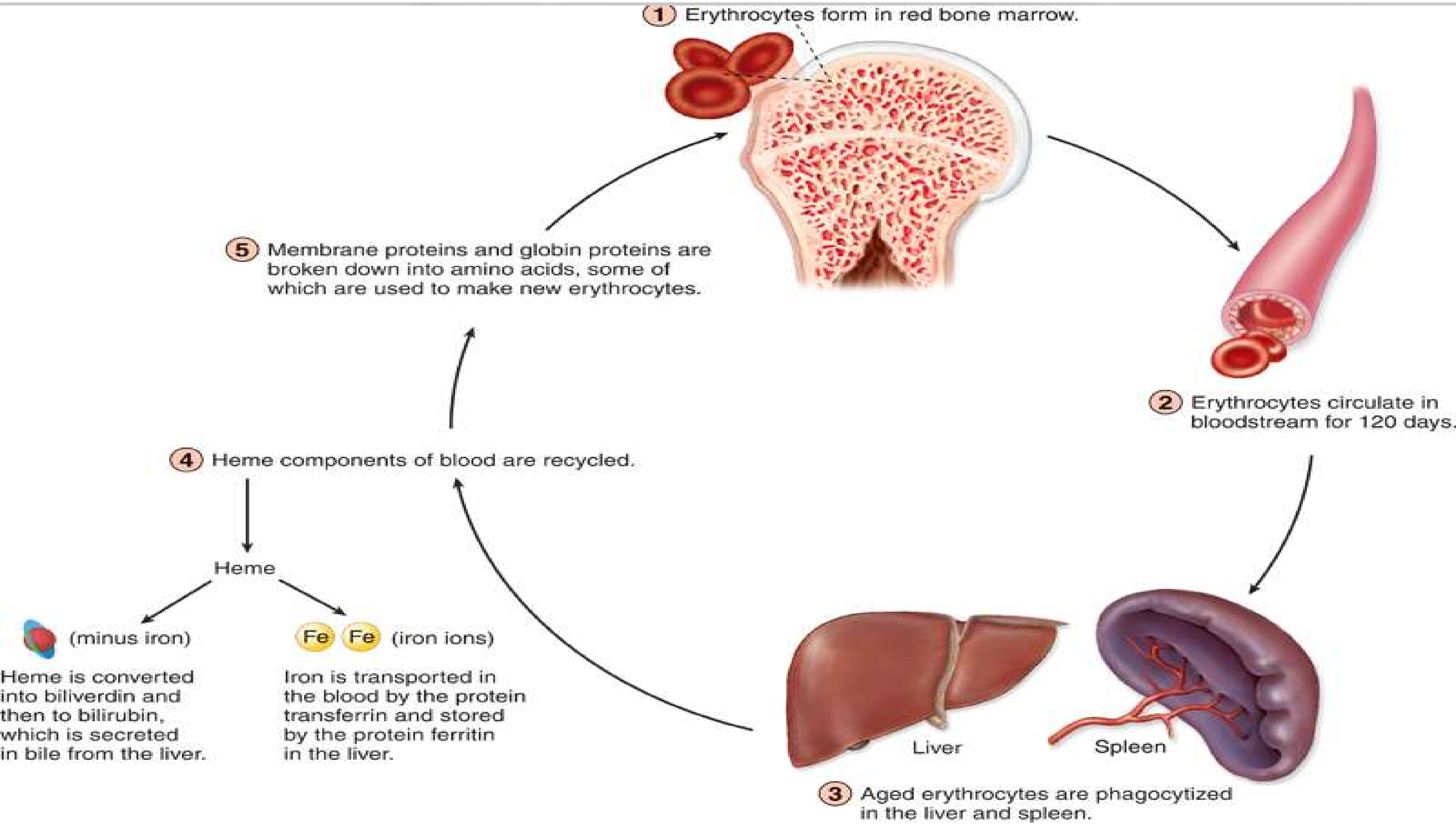
- **The latter begins to develop in the shafts of the long bones and continues until, by 20-22 years, red marrow is present only in the upper ends of the femur and humerus and in the flat bones of the sternum, ribs, cranium, pelvis and vertebra.**

- **However, because of the growth in body and bone size that has occurred during this period, the total amount of active red marrow (approximately 1000-1500 g) is nearly identical in the child and the adult.**

HEMATOPOIESIS•






1 Erythrocytes form in red bone marrow.
2 Erythrocytes circulate in bloodstream for 120 days.
Liver
Spleen
3 Aged erythrocytes are phagocytized in the liver and spleen.
4 Heme components of blood are recycled.
Heme
(minus iron)
Fe Fe (iron ions)
Heme is converted into biliverdin and then to bilirubin, which is secreted in bile from the liver.
Iron is transported in the blood by the protein transferrin and stored by the protein ferritin in the liver.
5 Membrane proteins and globin proteins are broken down into amino acids, some of which are used to make new erythrocytes.

•Pluripotent stem cells: are mesenchymal cells representing less than .

•1% of Red Bone Marrow cells having the ability to develop into several other kinds of cells.

•These further lead to 2 other stem cells known as *Myeloid* and *lymphoid* stem cells.

Myeloid Stem Cells lead to development of:

- *RBCs (erythrocytes)* (CFU-E)
- *Platelets (thrombocytes)*
- *Eosinophils*
- *Neutrophils* (CFU-GM)
- *Basophils*

Of the cell types listed above, all except eosinophils and basophils are produced by intermediate or Progenitor cells before fully developing.

•Lymphoid Stem Cells lead to the development of T and B lymphocytes (T/B cells).

•HGFs (*Hemopoietic Growth factors*) control the production of progenitor cells. Examples include

- *erythropoietin* (EPO)
- *Thrombopoietin* (TPO).

•EPO cells are produced in the kidneys, therefore, renal failure contributes to insufficient production of RBCs.

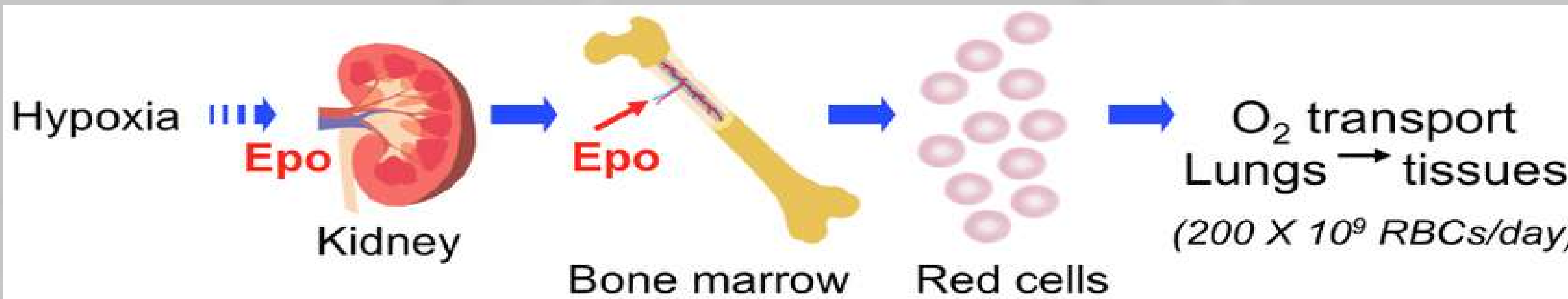
• TPO originates in the liver to promote the synthesis of platelets from Megakaryocytes

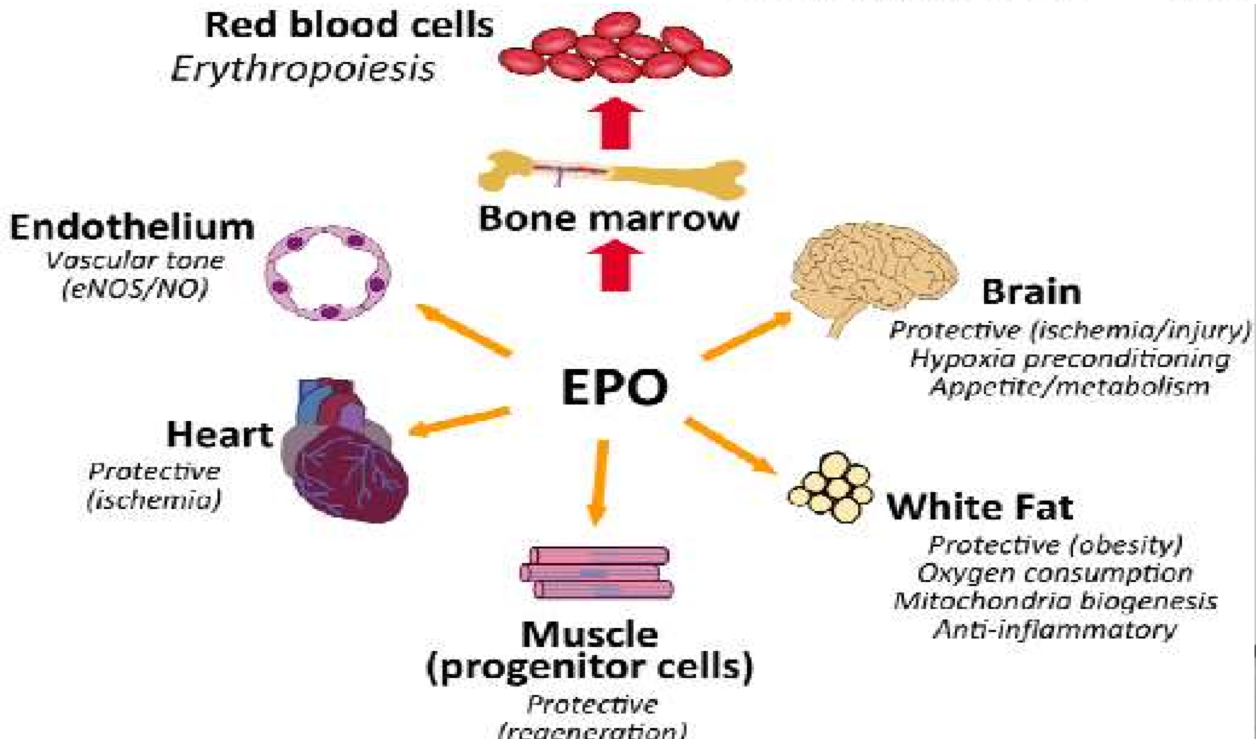
•Cytokines - Typically acting as autocrines/paracrines,

- cytokines are glycoproteins synthesized by RBM cells, leukocytes, macrophages, fibroblasts and endothelial cells.
- They promote the spread of progenitor cells.

•2 Cytokine Families that stimulate production of WBCs:

- *CSFs* (*Colony-Stimulating Factors*)
- *Interleukins*

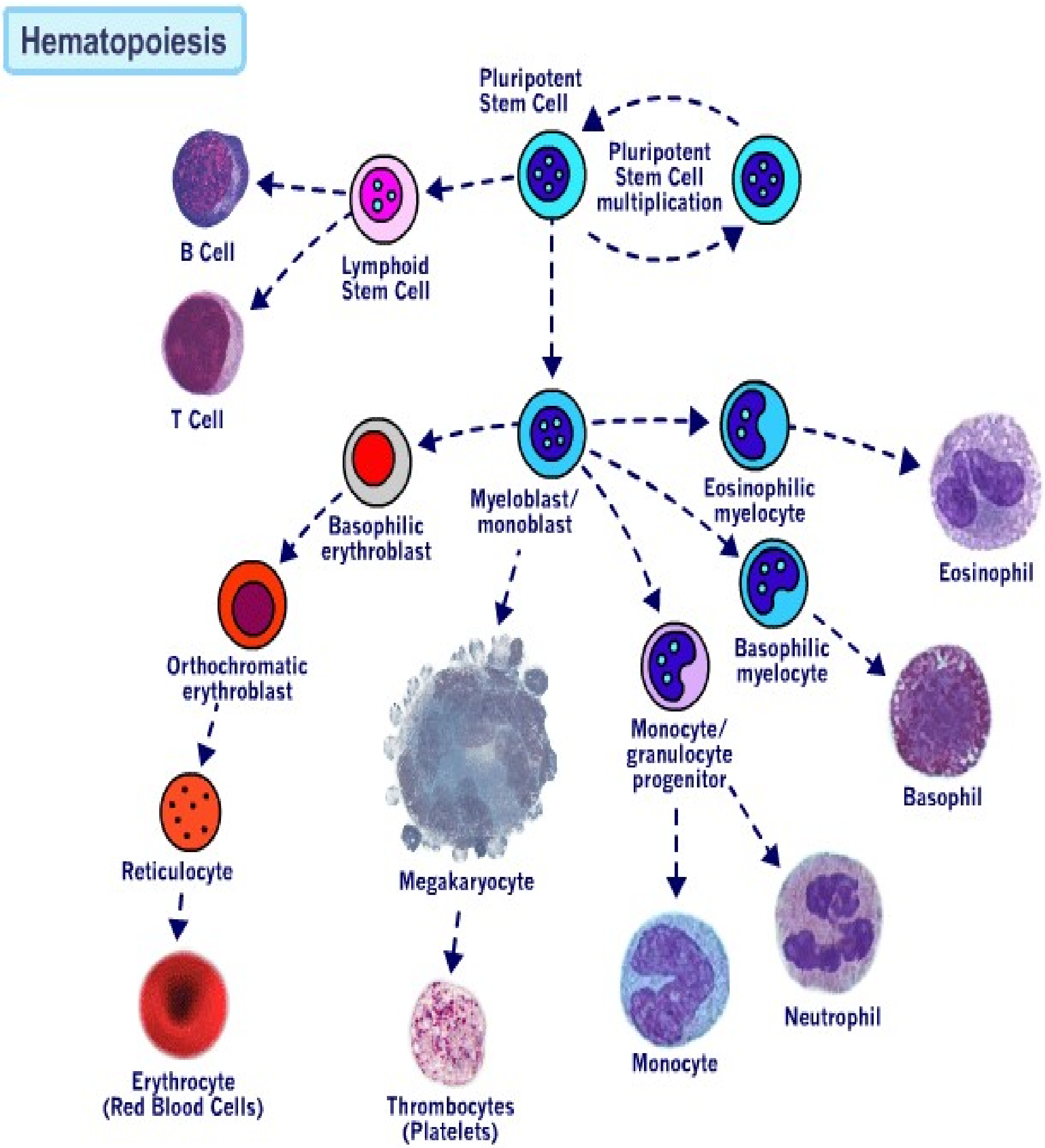


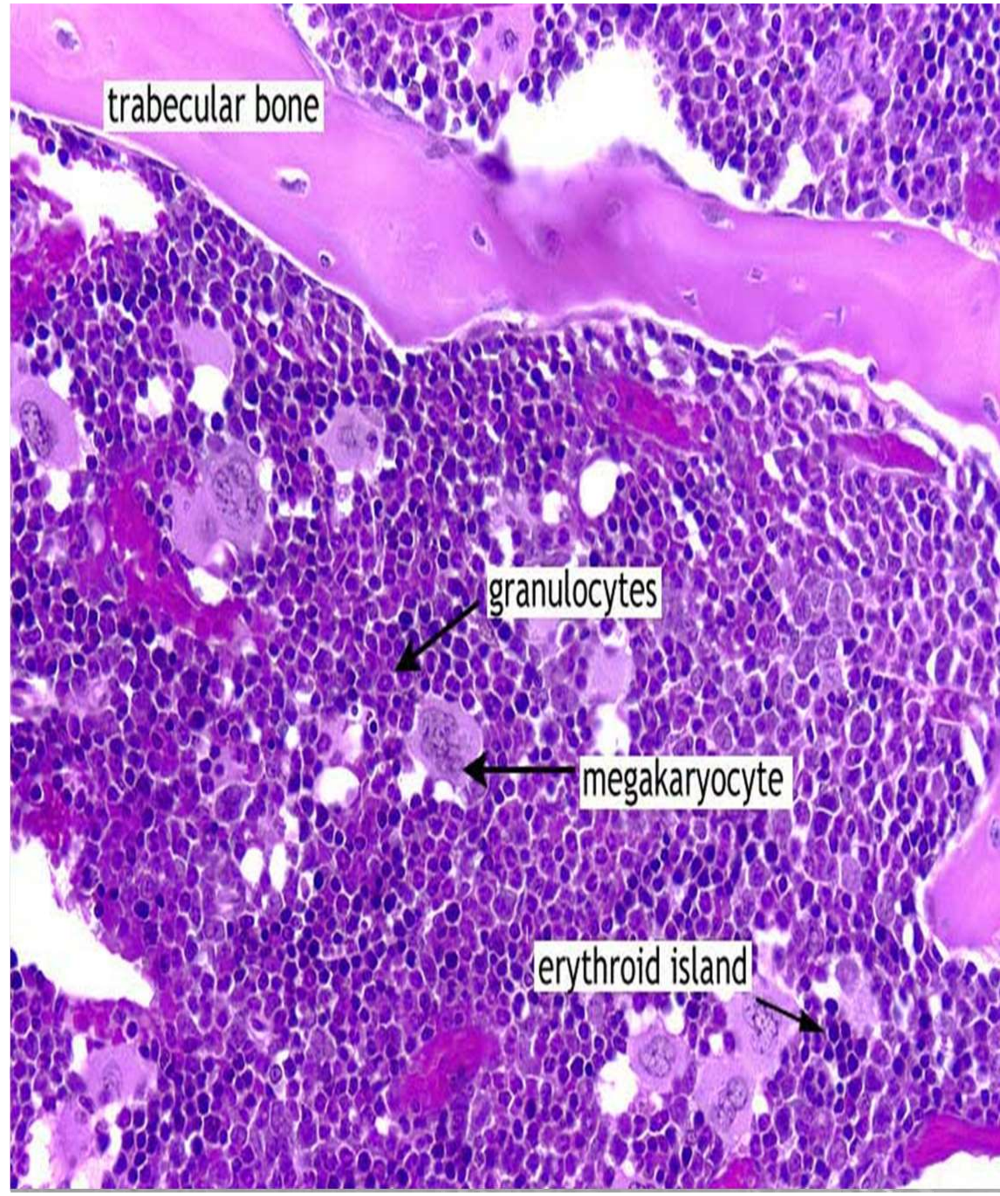


Erythropoietin PRODUCED BY THE KIDNEY , also known as *Epoetin alfa*, to treat

- **Low RBC concentration during end-stage kidney disease.**
- **Patients going through chemotherapy are treated with Granulocytic-Machrophage CSF and Granulocyte CSFs to treat low WBC concentration.**

•Thrombopoietin also produced by the kidneys is used to treat platelet depletion.


Hematopoiesis
Pluripotent Stem Cell
Pluripotent Stem Cell multiplication
B Cell
Lymphoid Stem Cell
T Cell
Basophilic erythroblast
Myeloblast/ monoblast
Eosinophilic myelocyte
Eosinophil
Orthochromatic erythroblast
Basophilic myelocyte
Megakaryocyte
Monocyte/ granulocyte progenitor
Basophil
Reticulocyte
Neutrophil
Monocyte
Erythrocyte (Red Blood Cells)
Thrombocytes (Platelets)


trabecular bone
granulocytes
megakaryocyte
erythroid island

Stem Cell Origin

•All blood cells arise from **hematopoietic stem cells (HSCs)**, which are:

- **Multipotent** (can give rise to all blood cell types).
- Found in the bone marrow.

Differentiation Pathways

HSCs differentiate into:

•**Myeloid stem cells** → RBCs, platelets, monocytes, granulocytes.

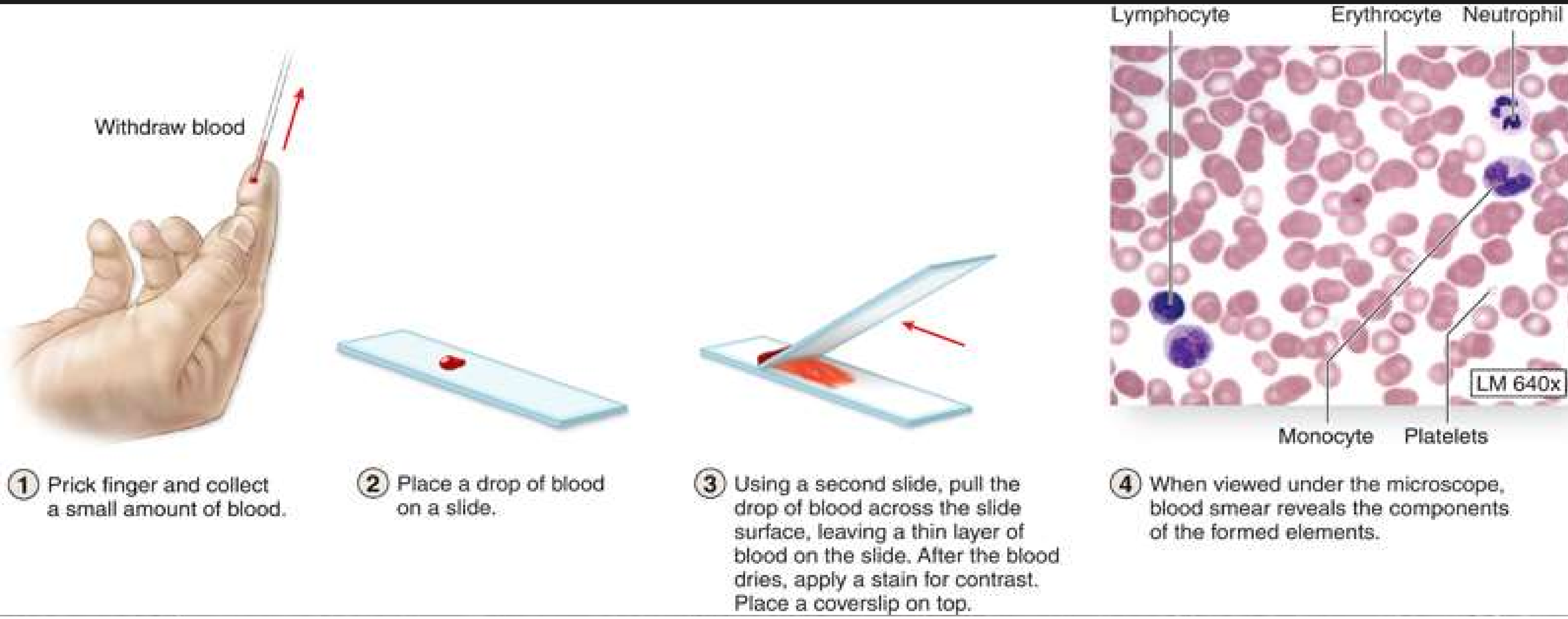
•**Lymphoid stem cells** → B-cells, T-cells, NK cells.

Regulation

•**Controlled by growth factors and cytokines, such as:**

- **Erythropoietin (EPO)** – stimulates RBC production.
- **Thrombopoietin** – stimulates platelet production.
- **Colony-stimulating factors (CSFs)** – stimulate WBC production.

Def and Generality



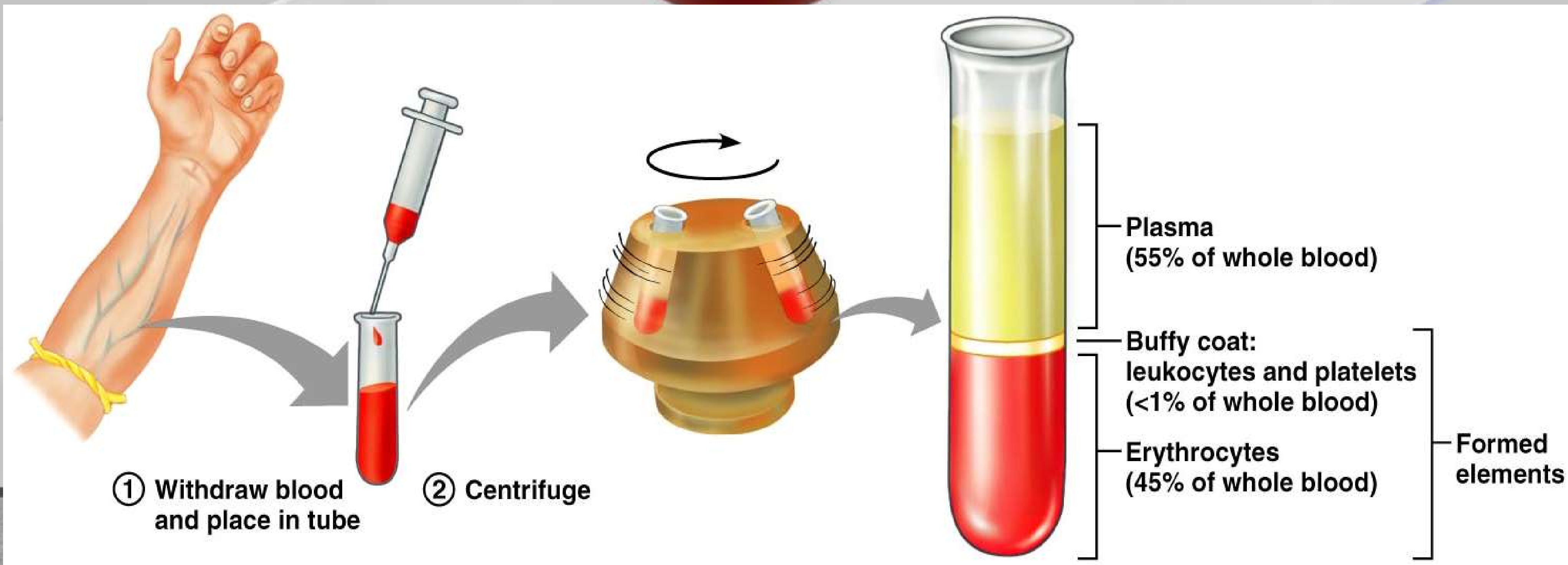
- **Blood is a connective tissue whose matrix is fluid.**
- **It is composed of:**
  - **red corpuscles,**
  - **white cells,**
  - **platelets,**
  - **blood plasma.**
- **It is transported throughout the body within blood vessels veins arteries and white cells within lymphatics and arteries, veins.**

- In human **adults about 5 liter of blood contribute 7-8 % to the body weight of the individual**.
- The contribution of red blood cells (erythrocytes) to the total volume of the blood **(hematocrit) is about 43%.**
- **Erythrocytes are the dominant (99%)** but not the only type of cells in the blood.
- **Erythrocytes, leukocytes and blood platelets = formed elements of the blood**.
- Erythrocytes and blood platelets perform their functions exclusively in the blood stream.
- In contrast, **leukocytes reside only temporarily in the blood.**
- Leukocytes can leave the blood stream through the walls of capillaries and venules and enter either connective or lymphoid tissues.

Components of Whole Blood

Whole blood is a living tissue that circulates through the heart, arteries, veins, and capillaries carrying nourishment, electrolytes, hormones, vitamins, antibodies, heat, and oxygen to the body's tissues.

Whole blood contains red blood cells, white blood cells, and platelets suspended in a fluid called plasma.



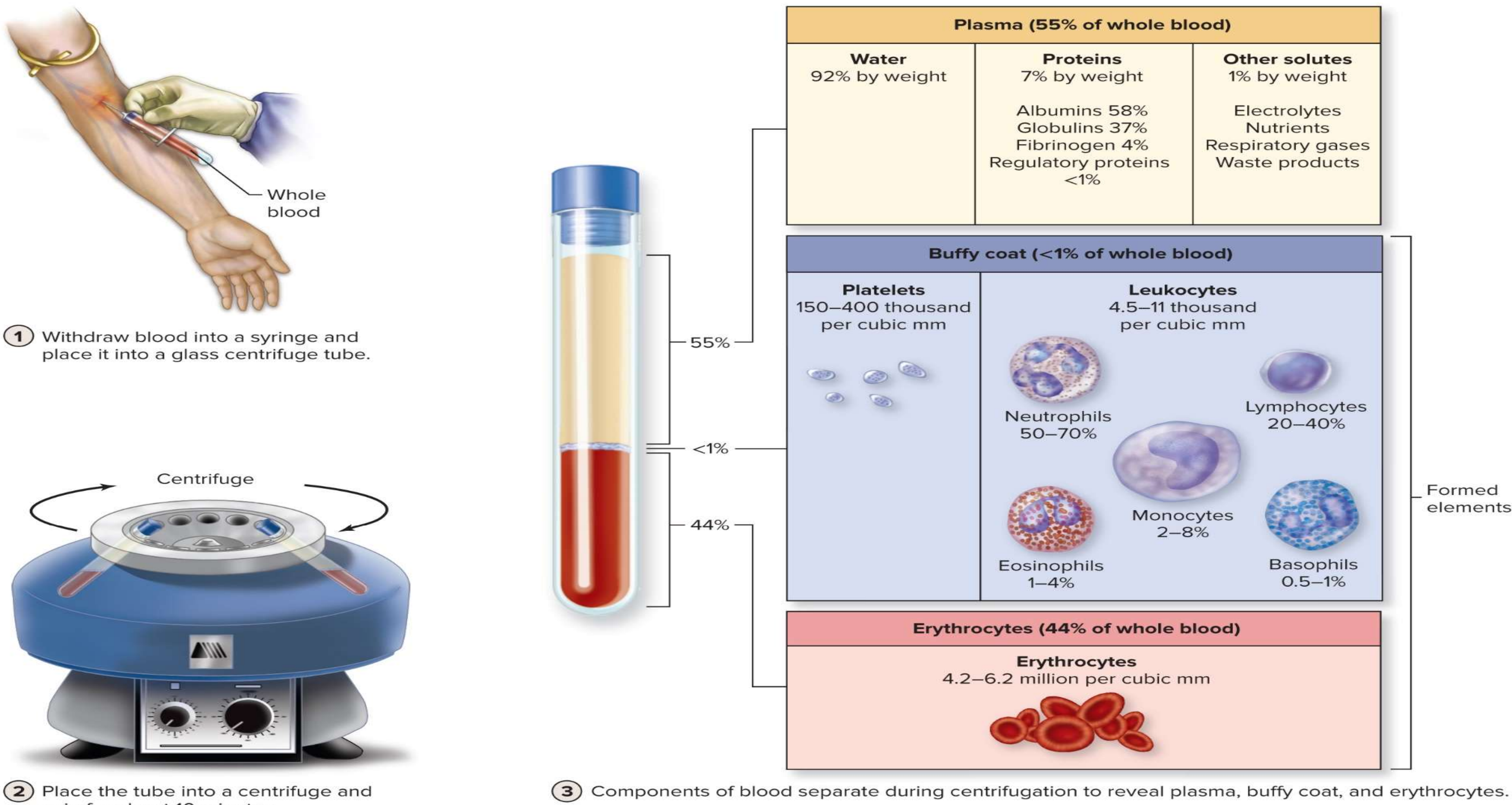
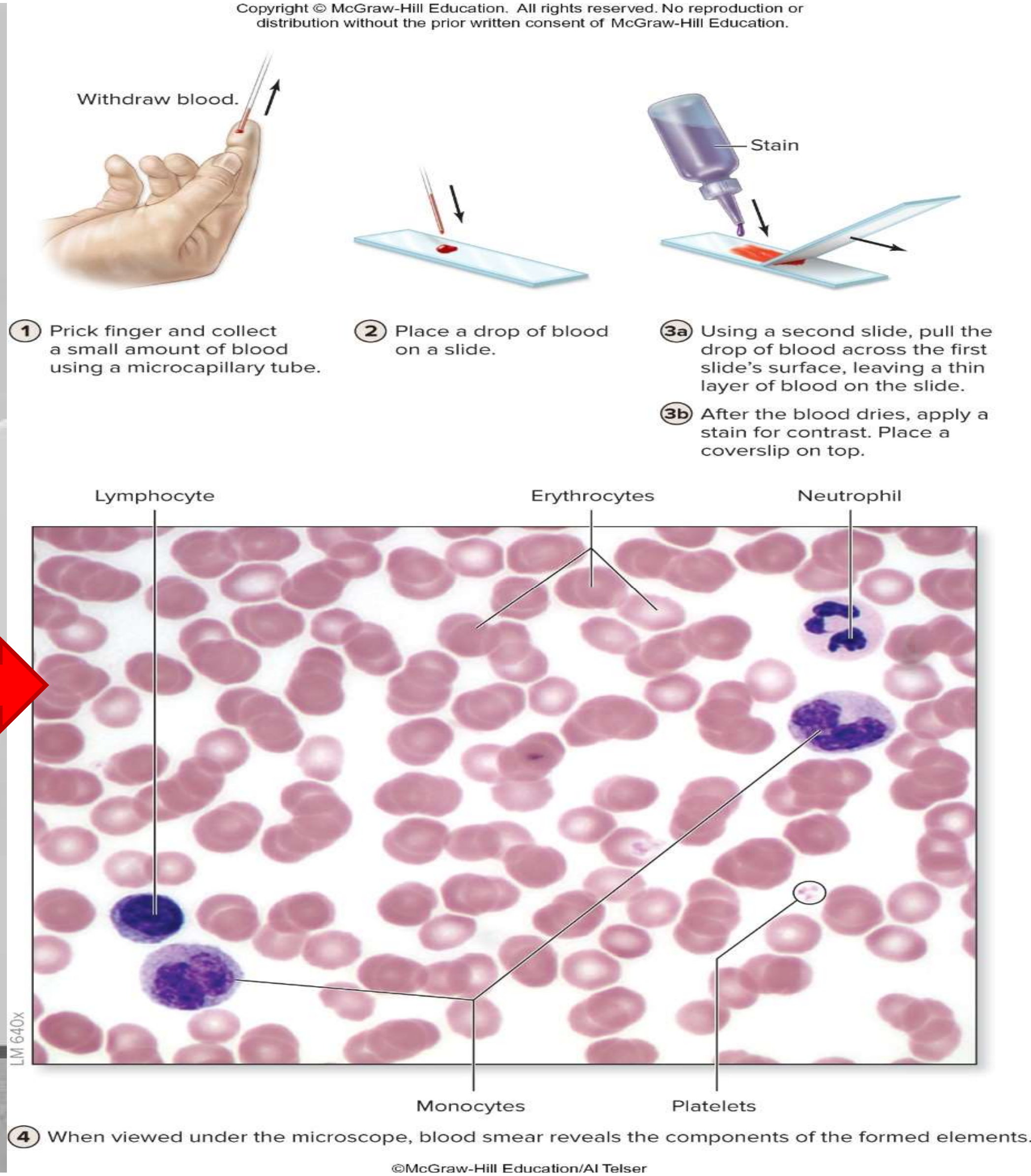
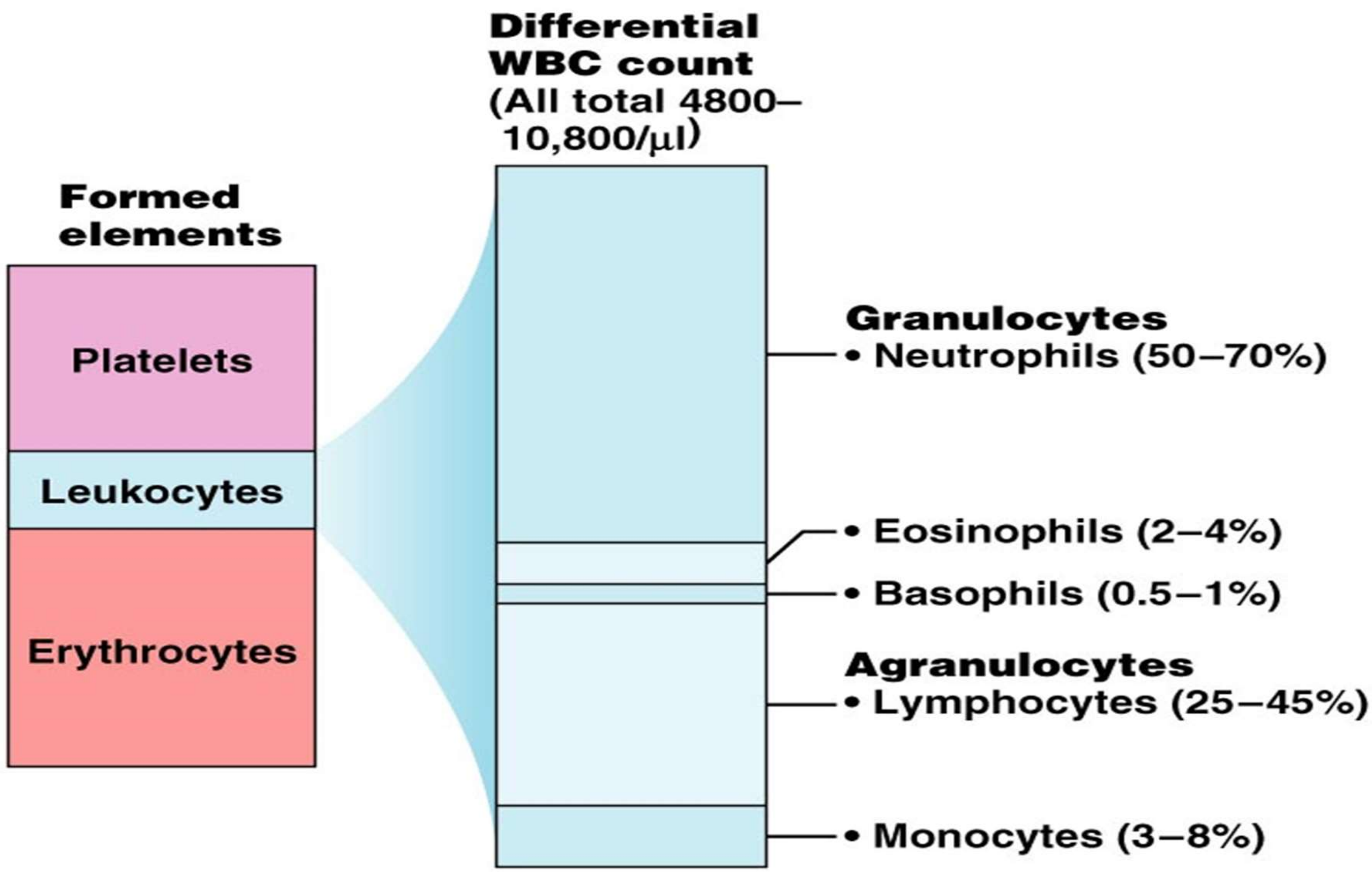

Whole blood
1 Withdraw blood into a syringe and place it into a glass centrifuge tube.
Centrifuge
2 Place the tube into a centrifuge and
55%
<1%
44%
Plasma (55% of whole blood)
Water
92% by weight
Proteins
7% by weight
Albumins 58%
Globulins 37%
Fibrinogen 4%
Regulatory proteins <1%
Other solutes
1% by weight
Electrolytes
Nutrients
Respiratory gases
Waste products
Buffy coat (<1% of whole blood)
Platelets
150–400 thousand per cubic mm
Leukocytes
4.5–11 thousand per cubic mm
Neutrophils 50–70%
Lymphocytes 20–40%
Monocytes 2–8%
Eosinophils 1–4%
Basophils 0.5–1%
Erythrocytes (44% of whole blood)
Erythrocytes
4.2–6.2 million per cubic mm
Formed elements
3 Components of blood separate during centrifugation to reveal plasma, buffy coat, and erythrocytes.

Figure 18.2

Blood smear




Formed elements
Platelets
Leukocytes
Erythrocytes
Differential WBC count (All total 4800–10,800/μl)
Granulocytes
• Neutrophils (50–70%)
• Eosinophils (2–4%)
• Basophils (0.5–1%)
Agranulocytes
• Lymphocytes (25–45%)
• Monocytes (3–8%)

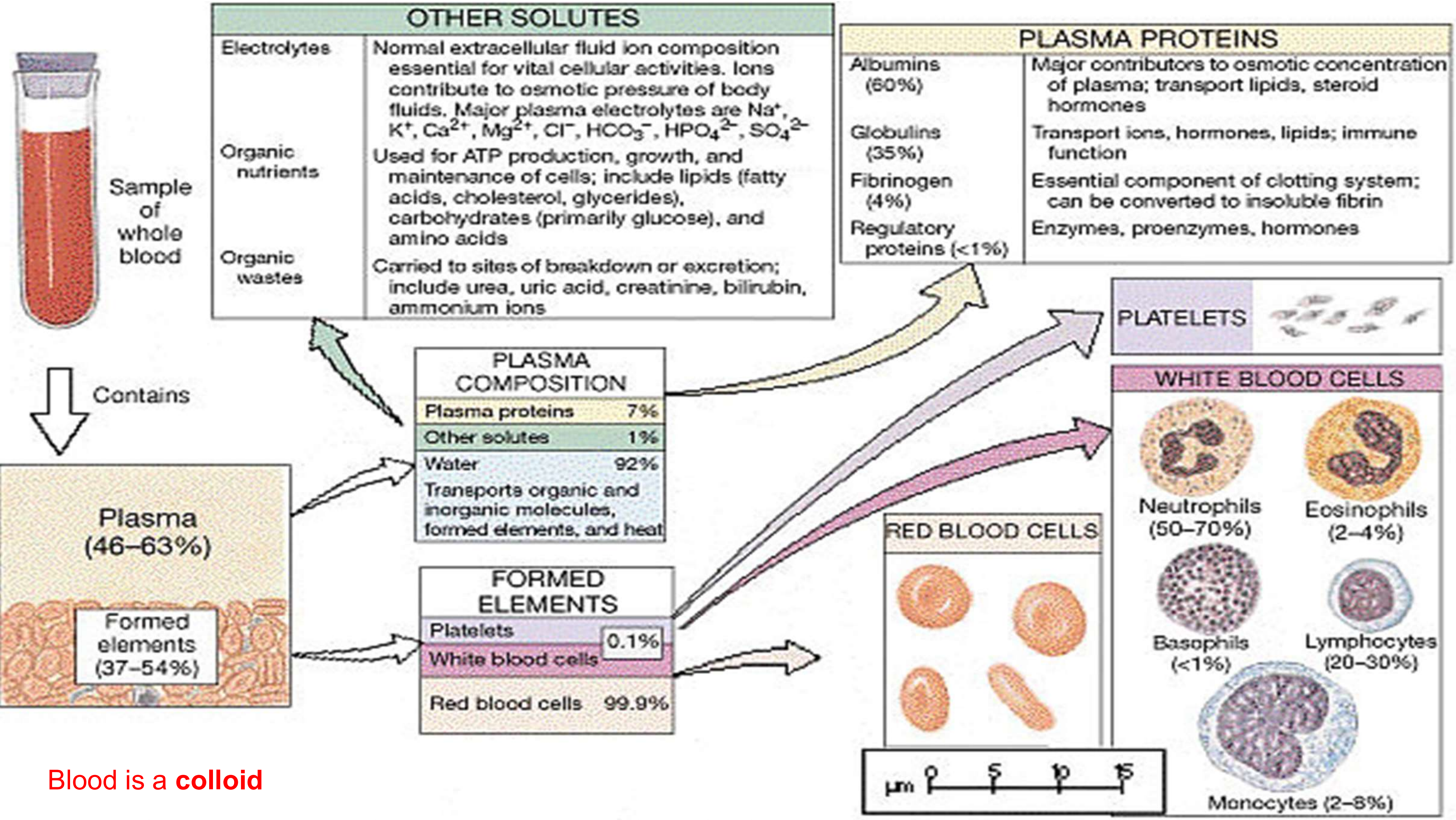
Blood Plasma

- **Blood Plasma - Representing 55% of whole blood**
- **Of plasma, water makes up 91.5%, while 7.5% makes up proteins**

•1% is a mix of other solutes including electrolytes, enzymes, hormones and waste products.

- **Blood plasma contains over 100 solutes, including:**
  - Proteins – albumin, globulins, clotting proteins, and others
  - Lactic acid, urea, creatinine
  - Organic nutrients – glucose, carbohydrates, amino acids
  - Electrolytes – sodium, potassium, calcium, chloride, bicarbonate
  - Respiratory gases – oxygen and carbon dioxide

- **There are 3 basic types of plasma proteins synthesized by hepatocytes (liver cells):**
  - ***Albumins* (54%)**
  - ***Globulins* (38%)**
  - ***Fibrinogen* (7%)**
- **Gamma globulins are also known as *immunoglobulins* or *antibodies*.**
- **bacterial or viral invasion prompts the production of millions of antibodies, which bind to an *antigen* (invader).**



Blood is a **colloid**

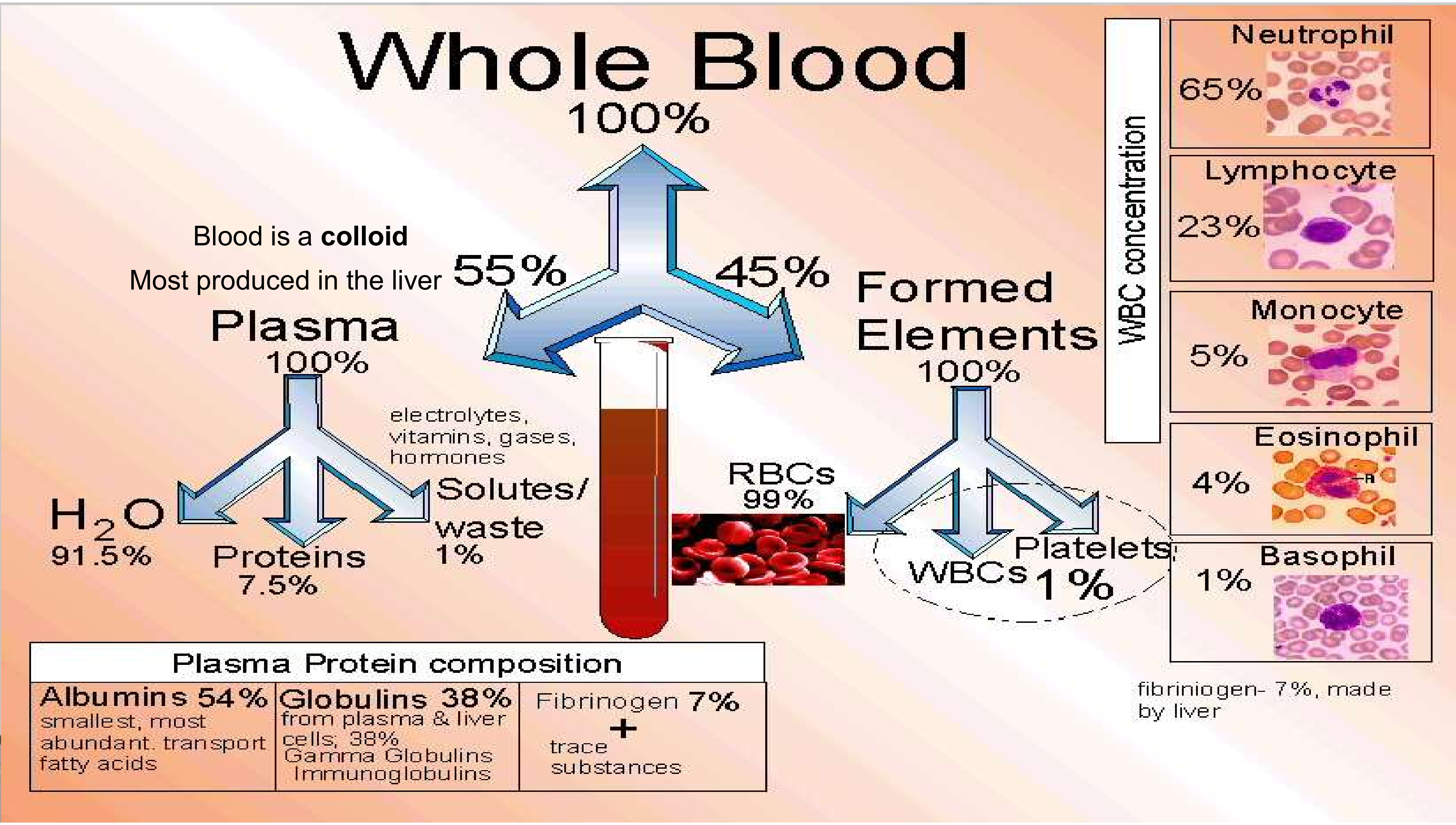

Whole Blood
100%
Blood is a colloid
Most produced in the liver
55%
45%
Plasma
100%
Formed Elements
100%
electrolytes, vitamins, gases, hormones
H_2O
91.5%
Proteins
7.5%
Solutes/ waste
1%
RBCs
99%
WBCs
Platelets
1%
WBC concentration
Neutrophil
65%
Lymphocyte
23%
Monocyte
5%
Eosinophil
4%
Basophil
1%
Plasma Protein composition
Albumins 54%
smallest, most abundant. transport fatty acids
Globulins 38%
from plasma & liver cells; 38%
Gamma Globulins
Immunoglobulins
Fibrinogen 7%
+
trace substances
fibriniogen- 7%, made by liver

Table 18.2 The Composition of Blood Plasma

Plasma Component (Percentage of Plasma)	Functions
Water (~92% of plasma)	The solvent in which formed elements are suspended and proteins and solutes are dissolved
PLASMA PROTEINS (~7% OF PLASMA): All proteins buffer against pH changes.	
Albumin (~58% of plasma proteins)	Exerts osmotic force to retain fluid within the blood Contributes to blood's viscosity Responsible for transport of some ions, lipids (e.g., fatty acids), and hormones
Globulins (~37% of plasma proteins)	Alpha-globulins transport lipids and some metal ions (e.g., copper) Beta-globulins transport iron ions and lipids in blood Gamma-globulins are antibodies that immobilize pathogens
Fibrinogen (~4% of plasma proteins)	Participates in blood coagulation (clotting)
Regulatory proteins (<1% of plasma proteins)	Consists of enzymes and hormones
OTHER SOLUTES (~1% OF BLOOD PLASMA)	
Electrolytes (e.g., sodium, potassium, calcium, chloride, iron, bicarbonate, hydrogen)	Help establish, maintain, and change membrane potentials, maintain pH balance, and regulate osmosis
Nutrients (e.g., amino acids, glucose, cholesterol, vitamins, fatty acids)	Energy source; precursor for synthesizing other molecules
Respiratory gases (oxygen: <2% dissolved in plasma, 98% bound to hemoglobin within erythrocytes, and carbon dioxide: ~7% dissolved in plasma, ~23% bound to hemoglobin within erythrocytes, ~70% converted to HCO_3^-)	Oxygen is needed for aerobic cellular respiration; carbon dioxide is a waste product produced by cells during this process
Wastes (breakdown products of metabolism, such as lactate, creatinine, urea, bilirubin, ammonia)	Waste products serve no function in the blood plasma; rather, they merely are being transported to the liver and kidneys, where they can be removed from the blood

Table 18.3 Common Electrolytes in Arterial Plasma

Electrolytes (Ions)	Normal Ranges (Values)	Function(s)	Substances and Structures That Regulate Electrolyte Blood Level
CATIONS			
Sodium (Na^+)	135–145 milliequivalents per liter (mEq/L)	Neuron and muscle function; fluid balance; cotransporter	Aldosterone, atrial natriuretic peptide (ANP), estrogen, progesterone, glucocorticoids
Potassium (K^+)	3.5–5.0 mEq/L	Neuron and muscle function	Aldosterone, ANP
Calcium (Ca^{2+})	8.4–10.2 milligrams per deciliter (mg/dL)	Hardens bone; release of neurotransmitter; muscle contraction; blood clotting; second messenger	Parathyroid hormone, calcitriol, calcitonin
Hydrogen (H^+)	pH 7.35–7.45	pH balance	Buffering systems—chemicals in blood, kidney, respiratory system
ANIONS			
Chloride (Cl^-)	96–106 mEq/L	Anion bound to sodium; component of gastric acid (HCl); chloride shift	Regulated indirectly through sodium
Bicarbonate (HCO_3^-)	23.1–26.7 mEq/L	pH balance	Dependent upon carbon dioxide and H^+ blood levels
Phosphate (PO_4^{3-})	2.5–4.1 mEq/L	Binds with calcium and deposited in bone	Parathyroid hormone

Table 18.4 Common Molecules Found in Blood Plasma

Molecule	Normal Ranges (Values)	Function
Glucose	Fasting: 70–100 mg/dL; 2 hours after a meal: <145 mg/dL	Fuel molecule for cellular respiration (primary energy source for nervous tissue); tightly regulated by a number of hormones, including insulin and glucagon
Amino acids	Varies, based on specific amino acid being measured	Monomers for synthesizing protein; also regulated by some of the same hormones as glucose
Lactate	4.5–14.4 mg/dL	By-product of glycolysis
Lipids		Molecules that generally do not dissolve in water
Cholesterol	100–200 mg/dL	Plasma membrane component; synthesis of steroid hormones; bile salts
HDL	40–80 mg/dL	Transports lipids to the liver
VLDL/LDL	10–100 mg/dL	Transport lipids from the liver
Triglycerides	30–149 mg/dL	Fuel molecules
Phospholipids	6–12 mg/dL	Molecules that form plasma membrane bilayer

Table 18.5 Characteristics of the Formed Elements

Formed Element	Size (Diameter)	Function	Life Span	Density (Average Number per mm^3 of Blood = µL)
Erythrocytes	7.5 µm	Transport oxygen and carbon dioxide	~120 days	Females: ~4.8 million Males: ~5.4 million
Leukocytes (e.g., neutrophils, eosinophils, basophils, monocytes, and lymphocytes)	1.5 to 3 times larger than an erythrocyte; 11.25–22.5 µm	Initiate immune response; defend against potentially harmful substances	Varies from 12 hours (neutrophils) to years (lymphocytes)	4500–11,000
Platelets	<¼ the size of an erythrocyte; ~2 µm	Participate in hemostasis	~8–10 days	150,000–400,000

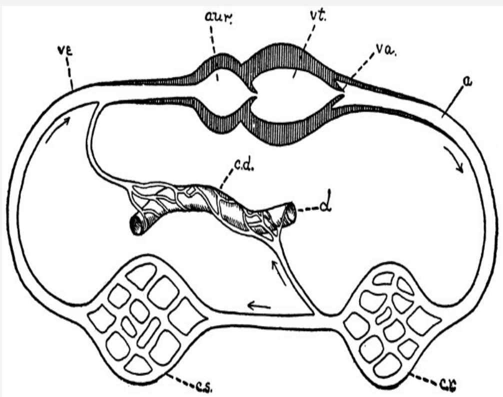
Physical characteristics

- Viscosity 4.5 - 5.5 (where H_2O = 1.0)
- Temperature 100.4F [38 degree Celsius]
- pH 7.35 - 7.45
- Salinity . 85% - .90%
- Volume 5 - 6 liters in males
  4 - 5 liters in females
- Blood accounts for approximately 7-8% of body weight

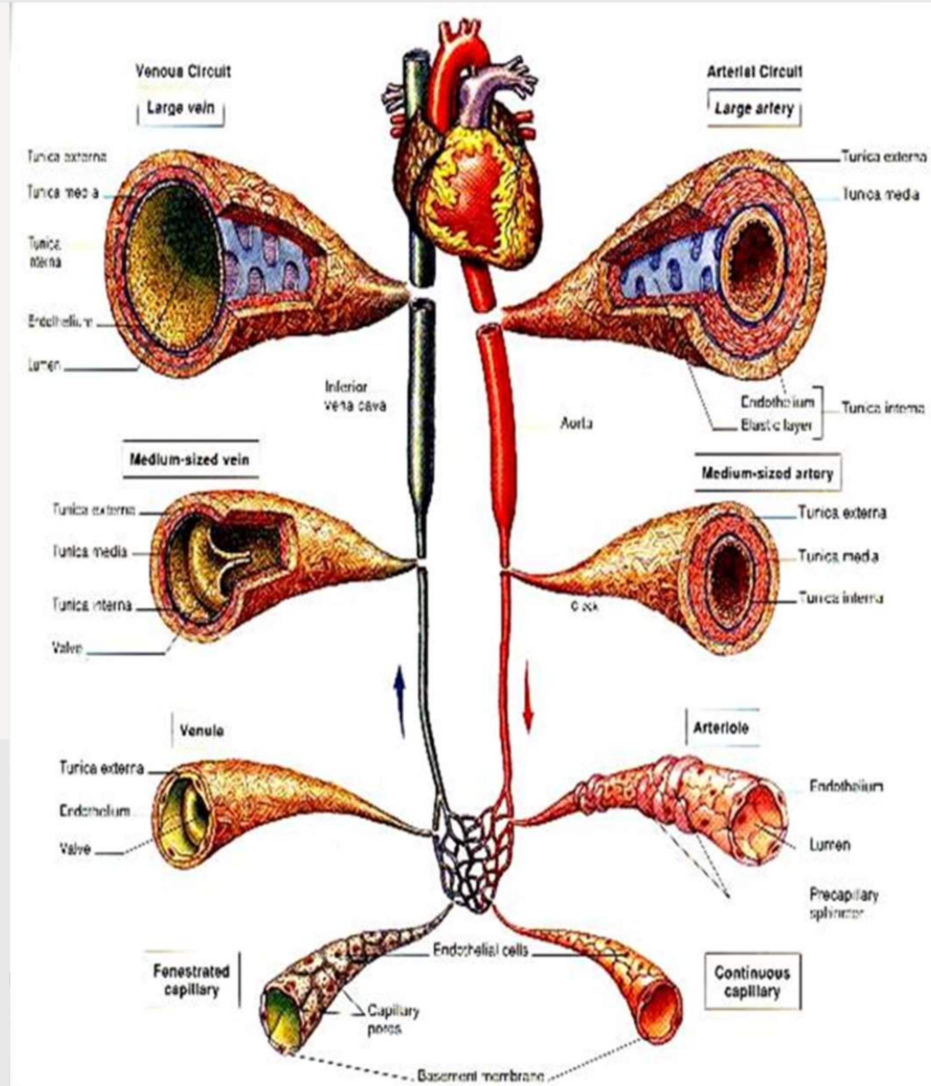
Blood is a sticky, opaque fluid with a metallic taste (iron)
Color varies from scarlet to dark red

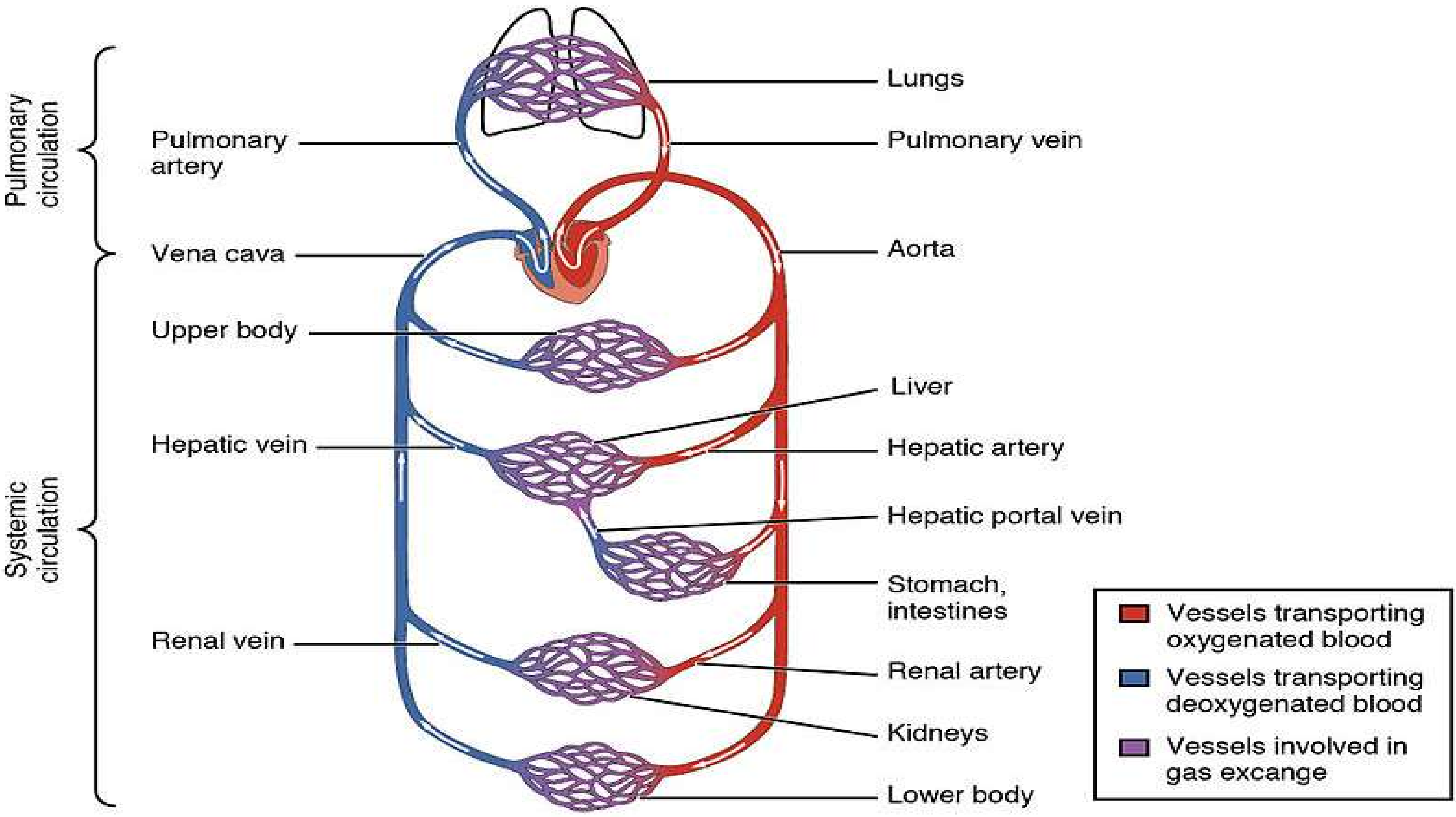
Overview of Blood Circulation

- Blood leaves the heart via arteries that branch repeatedly until they become capillaries
- Oxygen (O_2) and nutrients diffuse across capillary walls and enter tissues
- Carbon dioxide (CO_2) and wastes move from tissues into the blood



- **Oxygen-deficient blood leaves the capillaries and flows in veins to the heart**
- **This blood flows to the lungs where it releases CO_2 and picks up O_2**
- **The oxygen-rich blood returns to the heart**





Pulmonary circulation
Systemic circulation
Lungs
Pulmonary artery
Pulmonary vein
Vena cava
Aorta
Upper body
Liver
Hepatic vein
Hepatic artery
Hepatic portal vein
Stomach, intestines
Renal vein
Renal artery
Kidneys
Lower body
Vessels transporting oxygenated blood
Vessels transporting deoxygenated blood
Vessels involved in gas excange

The volume of blood in an average-sized person (70 kg; 154 lbs) is approximately 5.5 L.

If we take the hematocrit to be 45 percent, then

Erythrocyte volume = 0.45 x5.5 L =2.5 L

"Erythrocyte volume" can refer to different but related measurements concerning red blood cells (RBCs), especially in the context of laboratory tests and clinical evaluation.

Since the volume occupied by the leukocytes and platelets is normally negligible, the plasma volume equals the difference between blood volume and erythrocyte volume; therefore, in our average person

Plasma volume = 5.5 L - 2.5 L = 3.0 L

Erythrocyte Volume (Red Blood Cell Volume)

1. Mean Corpuscular Volume (MCV)

•**Definition**: The average volume of a single red blood cell.

•**Normal range**:

- **80–100 femtoliters (fL)** per RBC.

•**Clinical Use**:

- Helps classify **anemias**:
  - **Microcytic** (<80 fL): e.g., iron-deficiency anemia, thalassemia.
  - **Normocytic** (80–100 fL): e.g., acute blood loss, chronic disease.
  - **Macrocytic** (>100 fL): e.g., B12 or folate deficiency.

2. Packed Cell Volume (PCV) / Hematocrit (Hct)

•**Definition**: The proportion of blood volume that is occupied by red blood cells.

•**Normal values**:

- **Men**: 40–54%
- **Women**: 36–48%

•Indicates the **overall volume** taken up by erythrocytes in a given blood sample.

3. Total Red Blood Cell Volume

•Total RBC volume in the body depends on:

- **Total blood volume** (~5 liters in adults)
- **Hematocrit level**

•For example:

If Hct = 45% → Total RBC volume ≈ 0.45 × 5 L = **2.25 liters**

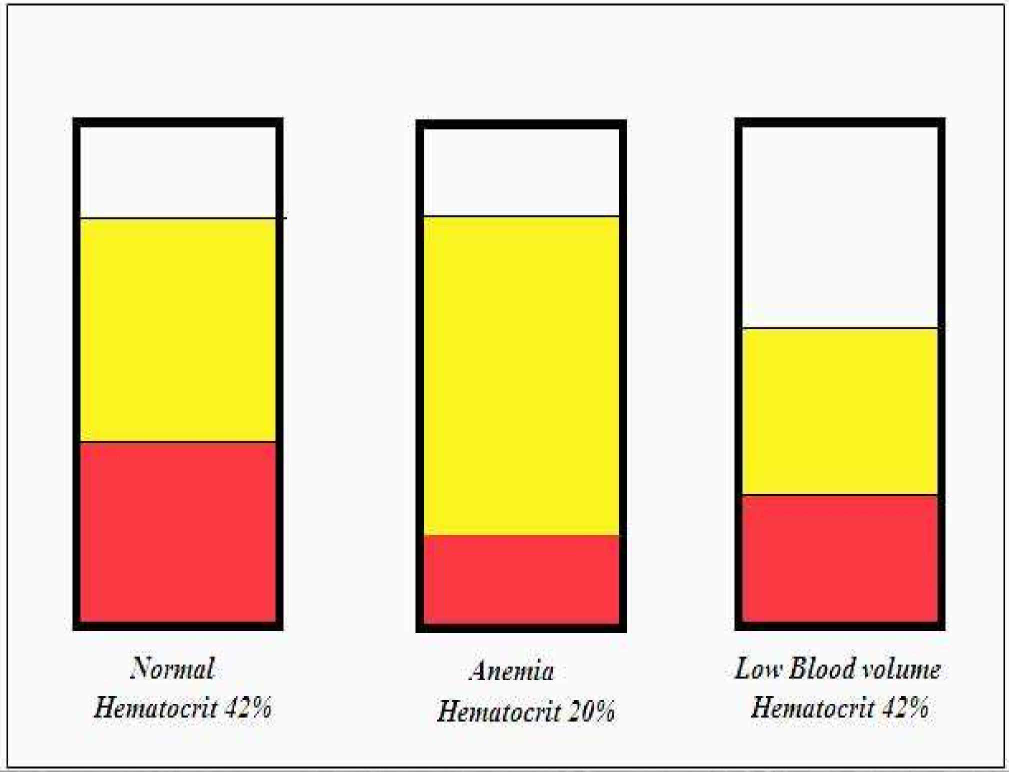
Blood Volume

blood volume refers to the **total amount of blood circulating within the body**, including **plasma** and **formed elements** (red blood cells, white blood cells, and platelets).

- **Blood volume is about 8% of body weight.**
- **1 kg of blood ≈ 1 L of blood**
- **70 kg X 0.08 = 5.6 Kg = 5.6 L**

- **Blood volume (mL)=Body weight (kg)×70 mL/kg**
- **A 70 kg adult → 70 × 70 = 4,900 mL (≈ 5 liters)**

- **45 % is formed elements**
- **55% plasma**



Population	Blood Volume
Adult male	**~5–6 liters**
Adult female	**~4–5 liters**
Newborn	**~80–100 mL/kg**
Child	**~75–80 mL/kg**
Adult (average)	**~70 mL/kg body weight**

Clinical Importance

- **Hypovolemia**: Decreased blood volume (e.g., bleeding, dehydration)
- **Hypervolemia**: Increased blood volume (e.g., fluid overload, heart failure)
- **Shock**: May result from severe hypovolemia
- **Transfusion medicine**: Requires careful estimation of blood volume

Blood Volume versus Plasma Volume

- Blood volume represents the plasma volume plus the volume of RBCs, which is usually expressed as hematocrit (fractional concentration of RBCs).

- The following formula can be utilized to convert plasma volume to blood volume:
  - **Blood volume =** $\dfrac{\text{plasma volume}}{1 - \text{hematocrit}}$

$$\text{Plasma Volume} = \text{Total Blood Volume} \times (1 - \text{Hematocrit})$$

- For example, if the hematocrit is 50% (0.50) and plasma volume = 3 L, then:
  - **Blood volume =** $\dfrac{3L}{1 - 0.5} = 6\ L$
- If the hematocrit is 0.5 (or 50%), the blood is half RBCs and half plasma.
- Therefore, blood volume is double the plasma volume.

- **Blood volume can be estimated by taking 7% of the body weight in kgs. For example, a 70 kg individual has an approximate blood volume of 5.0 L.**

•Blood volume = 5 liters

•Hematocrit = 45% (0.45)

$$\text{Plasma Volume} = 5\text{ L} \times (1 - 0.45) = 2.75\text{ L}$$

Normal Plasma Volume

Population	Plasma Volume Estimate
Adult males	~3.0–3.5 liters
Adult females	~2.5–3.0 liters
General estimate	~55% of total blood volume

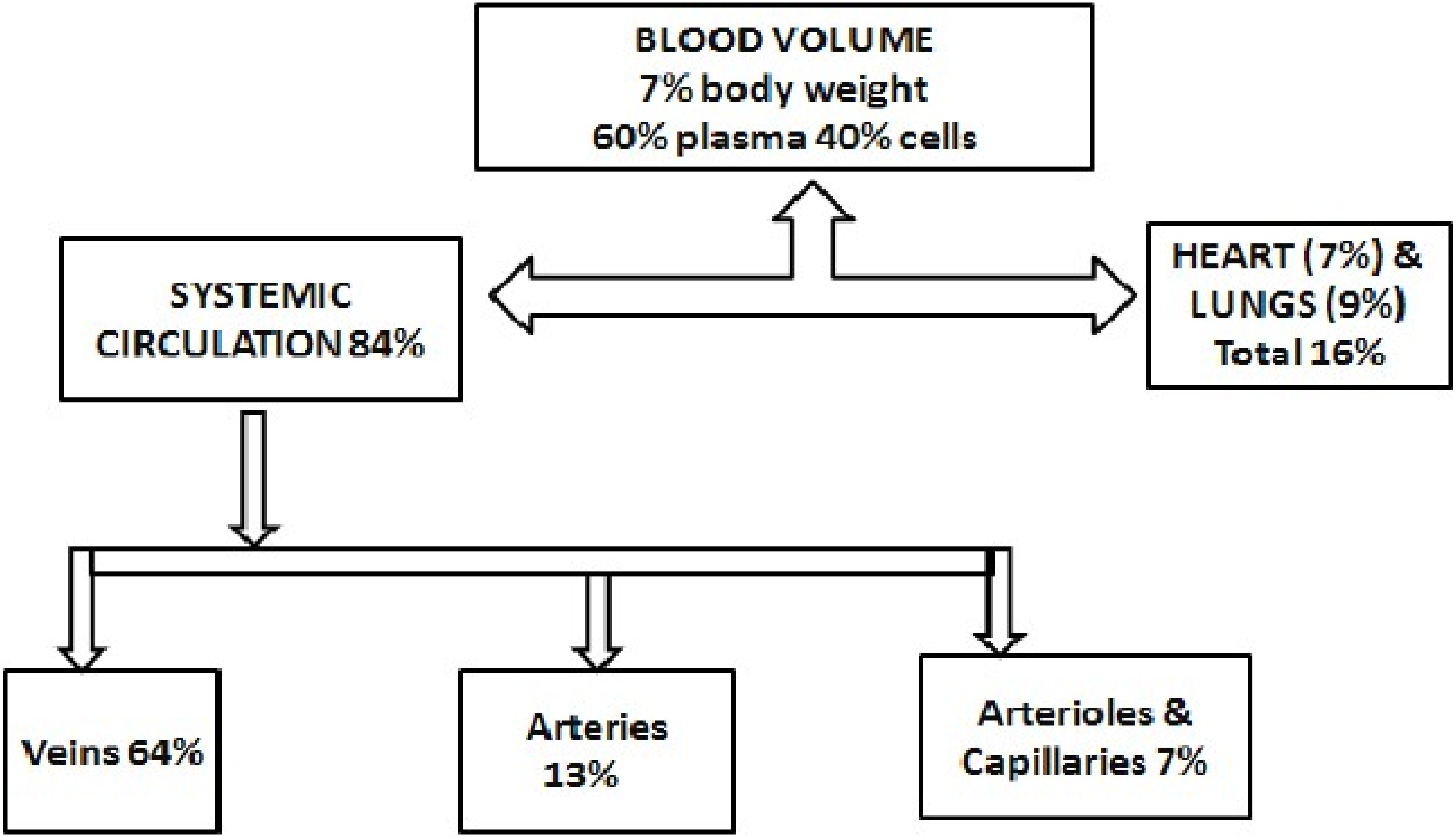
Functions of Plasma

- Transports **hormones**, **nutrients**, and **waste**
- Regulates **pH** and **osmolarity**
- Maintains **blood pressure** and **volume**
- Plays a role in **immunity** and **coagulation**

Composition of Plasma

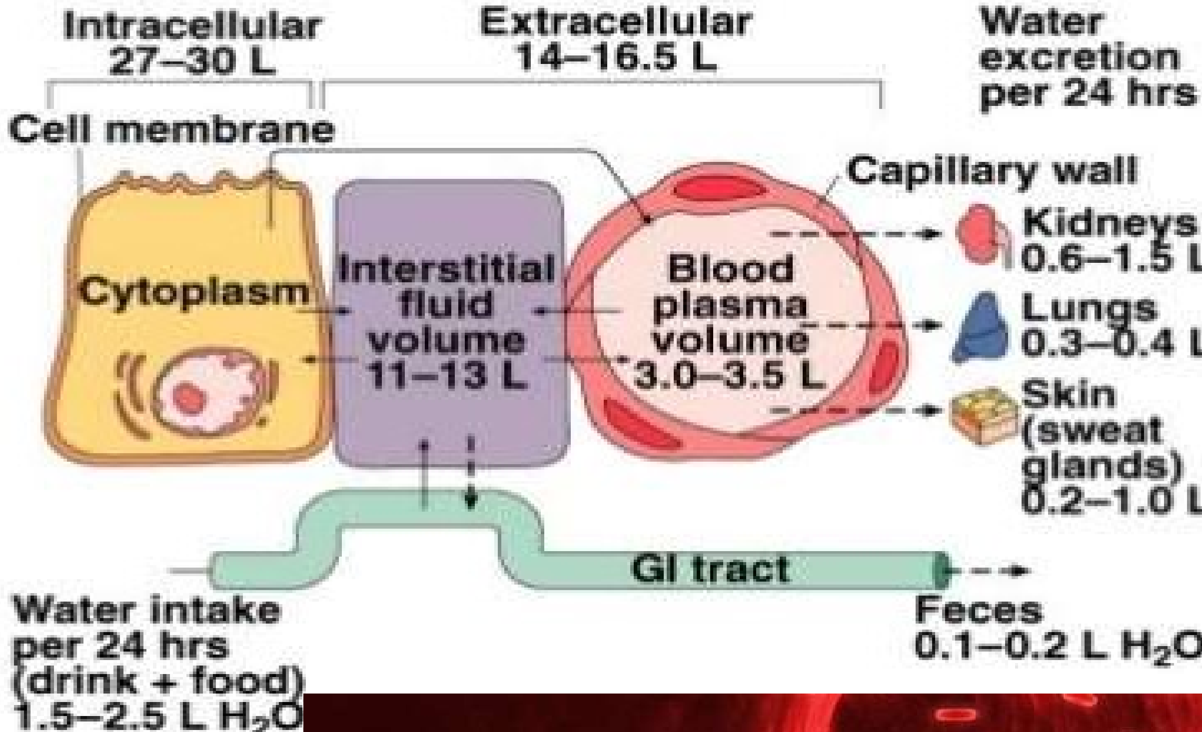
Plasma is about **90–92% water** and contains:

- **Proteins** (6–8%):
  - **Albumin**: maintains oncotic pressure
  - **Globulins**: immune function
  - **Fibrinogen**: blood clotting
- **Electrolytes** (Na^+, K^+, Cl^-, HCO_3^-)
- **Hormones**
- **Nutrients** (glucose, lipids, amino acids)
- **Waste products** (urea, creatinine, bilirubin)


BLOOD VOLUME
7% body weight
60% plasma 40% cells
SYSTEMIC CIRCULATION 84%
HEART (7%) & LUNGS (9%) Total 16%
Veins 64%
Arteries 13%
Arterioles & Capillaries 7%

Blood Volume

- Constitutes small fraction of total body fluid
- 2/3 of body H_2O is inside cells (intracellular compartment)
- 1/3 total body H_2O is in extracellular compartment
  - 80% of this is interstitial fluid; 20% is blood plasma



Total Body Water (TBW) Distribution
Total body water = ~60% of body weight
For a **70 kg adult**:
•**Total Body Water** ≈ 42 liters

Plasma is part of the **ECF**, but **RBCs/WBCs/platelets** are not — they are **cellular**.

Major Fluid Compartments

Compartment	% of Body Weight	Volume (70 kg)
Intracellular Fluid (ICF)	~40%	~28 liters
Extracellular Fluid (ECF)	~20%	~14 liters

Extracellular Fluid (ECF) Subdivisions

Subcompartment	% of ECF	Volume	Notes
Interstitial fluid	~75%	~10.5 L	Fluid between tissue cells
Plasma (intravascular)	~25%	~3.5 L	**Fluid component of blood**

- RBC cytoplasm → **ICF**
- Plasma → **ECF**
- Whole blood = **ICF (in RBCs) + ECF (plasma)**

Where Do Blood Cells Fit In?

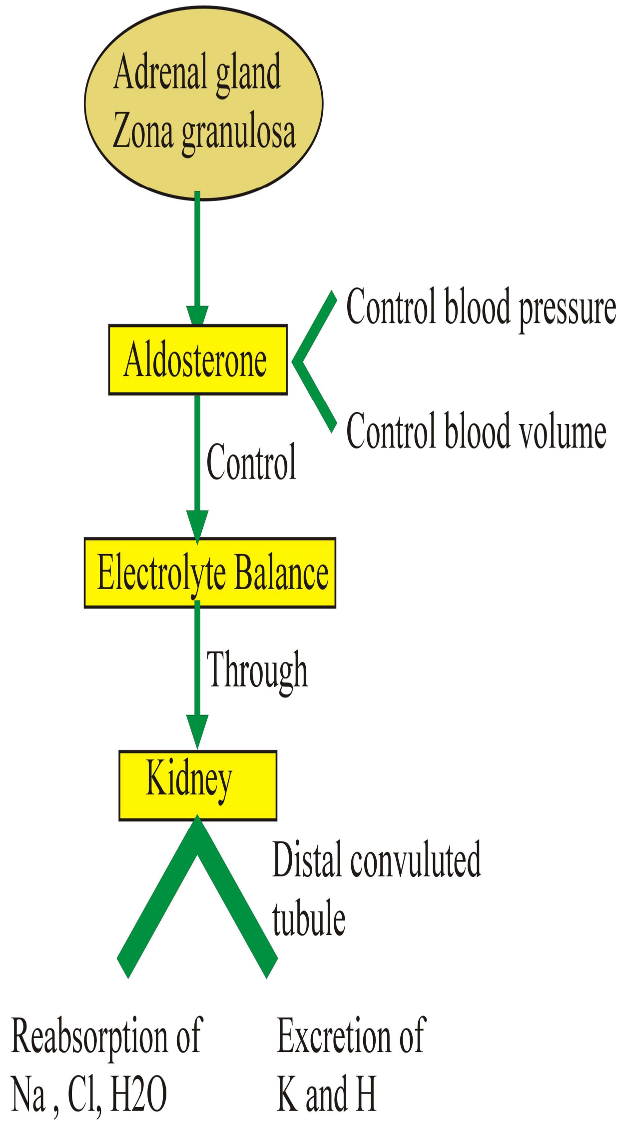
Component	**Category**
Plasma	**Extracellular fluid**
RBCs, WBCs, platelets	**Neither ICF nor ECF** (they're cells **within** the blood)
Inside RBCs	**Intracellular fluid** (within the RBC membrane)

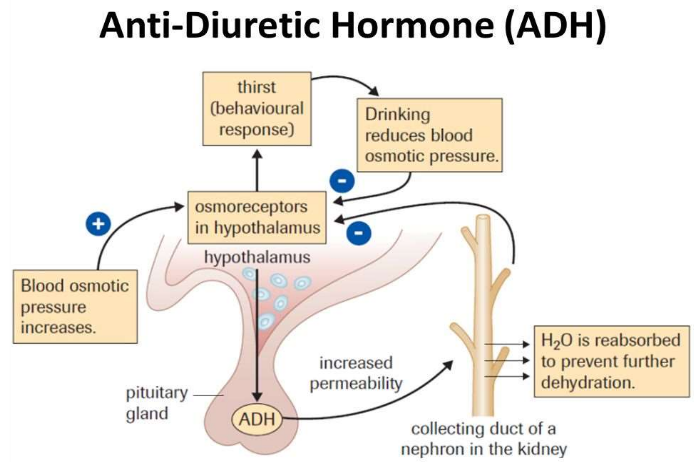
Example: 5L Blood Volume Breakdown

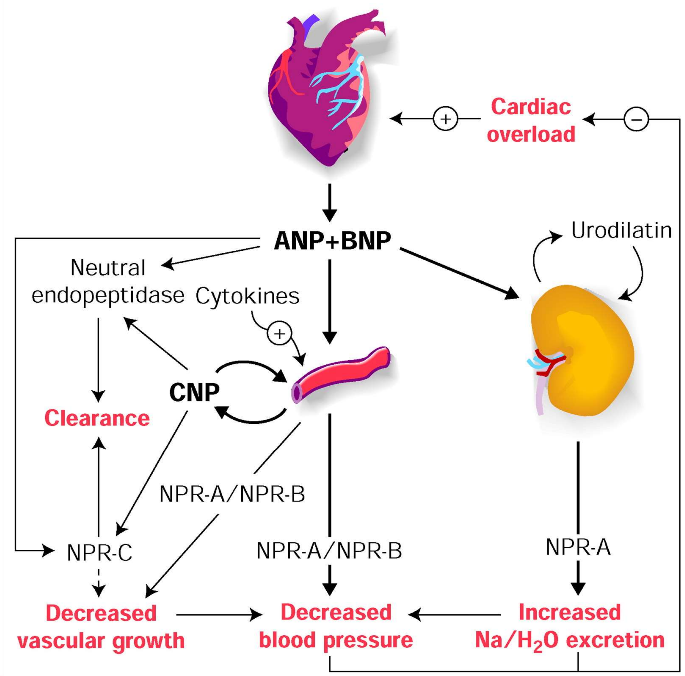
Component	**Category**	**Approx. Volume**	**Fluid Type**
Plasma	ECF	~3.0 L	Extracellular
RBCs (cytoplasm)	ICF	~2.0–2.5 L	Intracellular
WBCs/Platelets	Mixed	<100 mL	Negligible

Body Water Compartment	Fluid Type	Includes
Intracellular (ICF)	Cytoplasmic	RBCs, all body cells
Extracellular (ECF)	Interstitial + Plasma	Blood plasma, CSF, lymph, GI fluids
Blood Plasma	ECF	Carries hormones, electrolytes, nutrients
Blood Cells	Cellular (ICF inside)	RBCs, WBCs, platelets

- **Blood volume and osmotic pressure are regulated by several negative feedback mechanisms.**
- **Those mechanisms of specific interest involve**
    - **aldosterone,**
    - **ADH**
    - ***atrial natriuretic peptide (ANP)***
    - **Kidneys (via RAAS system)**







Regulation of Blood Volume

Blood volume is tightly regulated by various physiological mechanisms to ensure adequate perfusion of tissues and organs.

Key factors and systems involved include:

1. **Renal Regulation**:
   1. **Renin-Angiotensin-Aldosterone System (RAAS)**: Activated in response to decreased blood volume or blood pressure. Renin is released by the kidneys, leading to the production of angiotensin II, which constricts blood vessels and stimulates aldosterone release from the adrenal glands. Aldosterone increases sodium and water reabsorption by the kidneys, expanding blood volume.
   2. **Antidiuretic Hormone (ADH)**: Also known as vasopressin, ADH is released from the posterior pituitary gland in response to increased plasma osmolality or decreased blood volume. It promotes water reabsorption in the kidneys, increasing blood volume.
   3. **Natriuretic Peptides**: Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are released by the heart in response to increased blood volume and pressure. **They promote sodium and water excretion by the kidneys, reducing blood volume.**
2. **Neural Regulation**:
   - **Sympathetic Nervous System**: Activation of the sympathetic nervous system **in response to stress, exercise, or blood loss increases heart rate and constricts blood vessels, maintaining blood pressure and directing blood flow to vital organs.**
3. **Capillary Exchange**:
   - **Starling Forces**: These **include hydrostatic pressure** (pushing fluid out of capillaries) and oncotic pressure (pulling fluid into capillaries). Proper balance between these forces ensures appropriate fluid exchange between blood vessels and tissues, maintaining blood volume.

Clinical Relevance

1.Hypovolemia:

- A decrease in blood volume, which can result from
  - **hemorrhage,**
  - **dehydration,**
  - **severe burns.**
- Symptoms include
  - **low blood pressure,**
  - **tachycardia,**
  - **reduced organ perfusion.**
- Treatment involves fluid resuscitation and addressing the underlying cause.

2. **Hypervolemia**: An increase in blood volume, often due to
   - **heart failure,**
   - **kidney disease,**
   - **excessive fluid intake.**

- Symptoms include high blood pressure, edema, and dyspnea.
- Treatment involves diuretics and managing the underlying condition.

Blood Volume Measurement

1.Indicator Dilution Method: A known amount of a tracer (**such as a dye or radioactive substance)** is injected, and its dilution in the blood is measured to estimate blood volume.

2.Hemoglobin and Hematocrit: Blood tests to measure red blood cell concentration, providing an indirect assessment of blood volume.

colloid osmotic pressure

- known as oncotic pressure.
- Colloid osmotic pressure is the pressure exerted by proteins, **mainly albumin**, in a blood vessel's plasma that tends to pull water into the circulatory system.
- It is a vital part of the body's regulation of fluid balance between blood vessels and surrounding tissues.

- Plasma proteins exert **colloid osmotic pressure**
  - Prevents loss of fluid from blood as it moves through capillaries
    - Helps maintain blood volume and blood pressure
  - Can be decreased with diseases, resulting in fluid loss from blood and tissue swelling
    - E.g., liver diseases that decrease production of plasma proteins
    - E.g., kidney diseases that increase elimination of plasma proteins

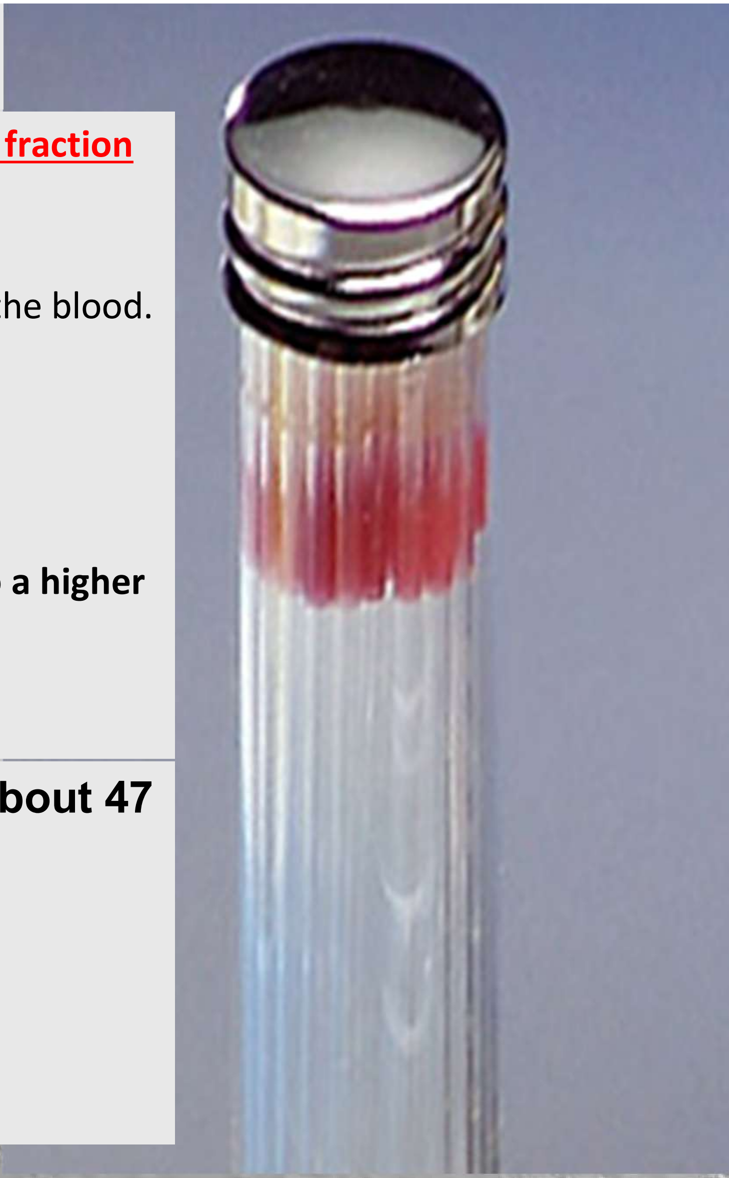
Hematocrit

- **The hematocrit (Ht or HCT) or packed cell volume (PCV) or erythrocyte volume fraction (EVF)** is the proportion of **blood volume that is occupied by red blood cells.**

- The volume of RBCs refers to the amount of space that the RBCs occupy within the blood.

- **Males the average is slightly higher at 47% (40-54%) due to higher levels of testosterone in males. females 38–46%**

- **Testosterone promotes synthesis of EPO (*erythropoietin*), which contributes to a higher RBC count.**

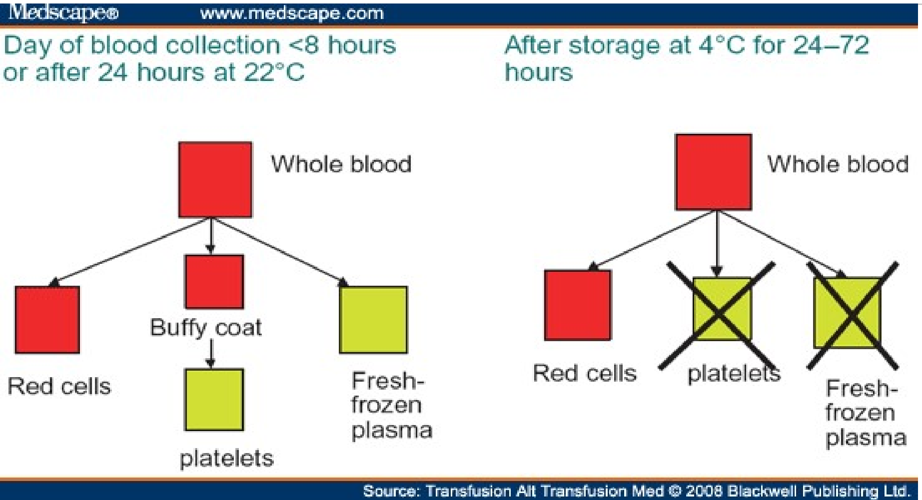


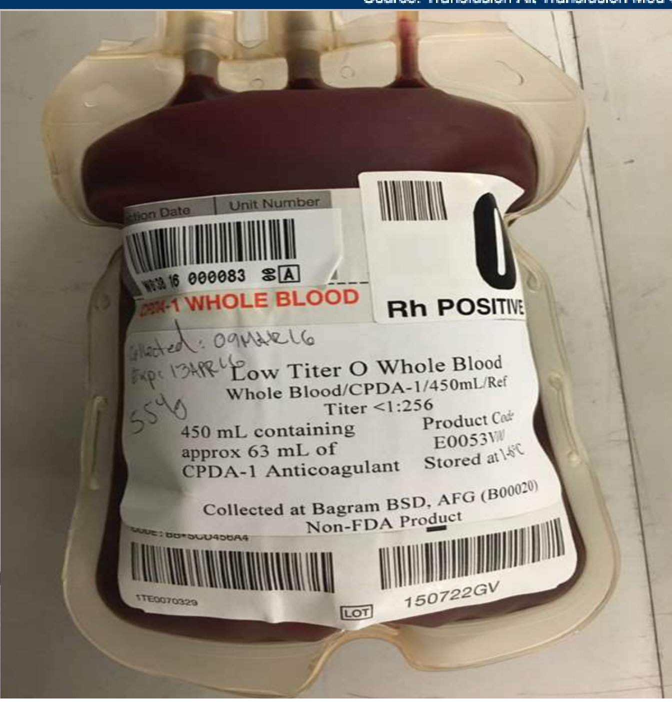
- **At sea level, the hematocrit of a normal adult male averages about 47**
- **which means that 47% of the blood volume is RBCs**
- **while that of a normal adult female is 42.**

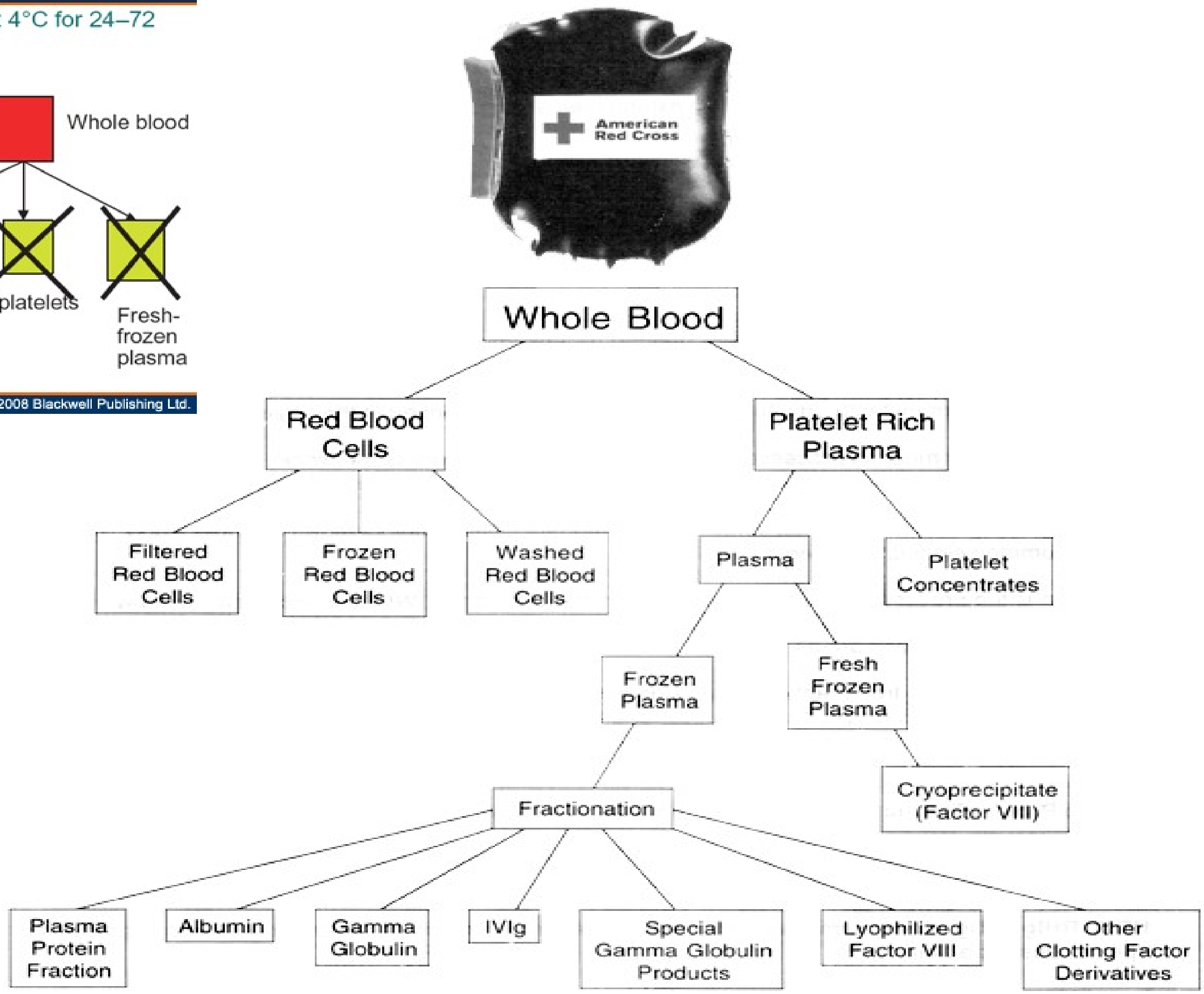
- **Ht=Hbx3**

- The normal ranges for hematocrit are dependent on age and, after adolescence, the sex of the individual.
- The normal ranges are:

- Newborns: 55%-68%
- One (1) week of age: 47%-65%
- One (1) month of age: 37%-49%
- Three (3) months of age: 30%-36%
- One (1) year of age: 29%-41%
- Ten (10) years of age: 36%-40%
- **Adult males: 42%-54%**
- **Adult women: 38%-46%**


Medscape® www.medscape.com
Day of blood collection <8 hours or after 24 hours at 22°C
After storage at 4°C for 24–72 hours
Whole blood
Red cells
Buffy coat
platelets
Fresh-frozen plasma
Whole blood
Red cells
platelets
Fresh-frozen plasma
Source: Transfusion Alt Transfusion Med © 2008 Blackwell Publishing Ltd.


WHOLE BLOOD
Rh POSITIVE
Low Titer O Whole Blood
Whole Blood/CPDA-1/450mL/Ref
Titer <1:256
450 mL containing approx 63 mL of CPDA-1 Anticoagulant
Product Code E0053
Collected at Bagram BSD, AFG (B00020)
Non-FDA Product
150722GV


American Red Cross
Whole Blood
Red Blood Cells
Platelet Rich Plasma
Filtered Red Blood Cells
Frozen Red Blood Cells
Washed Red Blood Cells
Plasma
Platelet Concentrates
Frozen Plasma
Fresh Frozen Plasma
Cryoprecipitate (Factor VIII)
Fractionation
Plasma Protein Fraction
Albumin
Gamma Globulin
IVIg
Special Gamma Globulin Products
Lyophilized Factor VIII
Other Clotting Factor Derivatives

BLOOD PRODUCTS

- Blood-cells products
  - whole blood
  - packed red blood cells
  - leukocyte-poor (reduced) red cells
  - washed red blood cells
  - random-donor platelets concentrates
  - single-donor platelets concentrates [human leukocyte antigens(HLA)-matched platelets]
  - irradiated blood products (red blood cells and platelets concentrates)- after exposure 20 to 40 Gy
  - leukocyte (granulocyte) concentrates
- Plasma products
  - fresh-frozen plasma (FFP)
  - cryoprecipitate
  - factor concentrates (VIII, IX)
  - albumin
  - immune globulins

Functions of Blood

- **Primary**
  - Transportation
  - Exchange
- **Secondary**
  - Immunity
  - Thermoregulation
  - Fluid volume balance
  - pH balance

Distribution

- **Blood transports:**
  - Oxygen (co2) from the lungs and nutrients from the digestive tract
  - Metabolic wastes from cells to the lungs and kidneys for elimination
  - Hormones from endocrine glands to target organs

Regulation

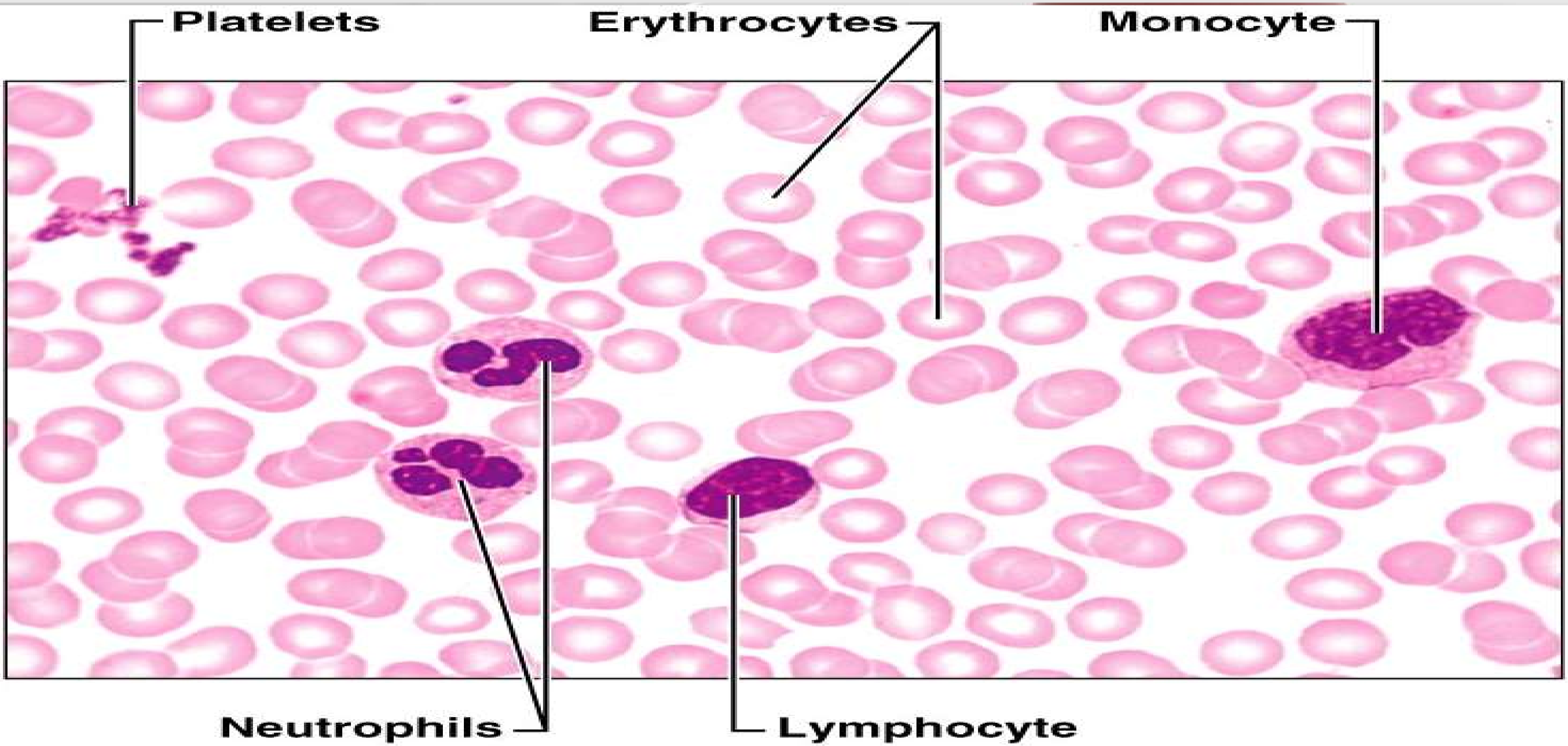
- Blood maintains:
  - Appropriate body temperature by absorbing and distributing heat
  - Normal pH in body tissues using buffer systems
  - Adequate fluid volume in the circulatory system

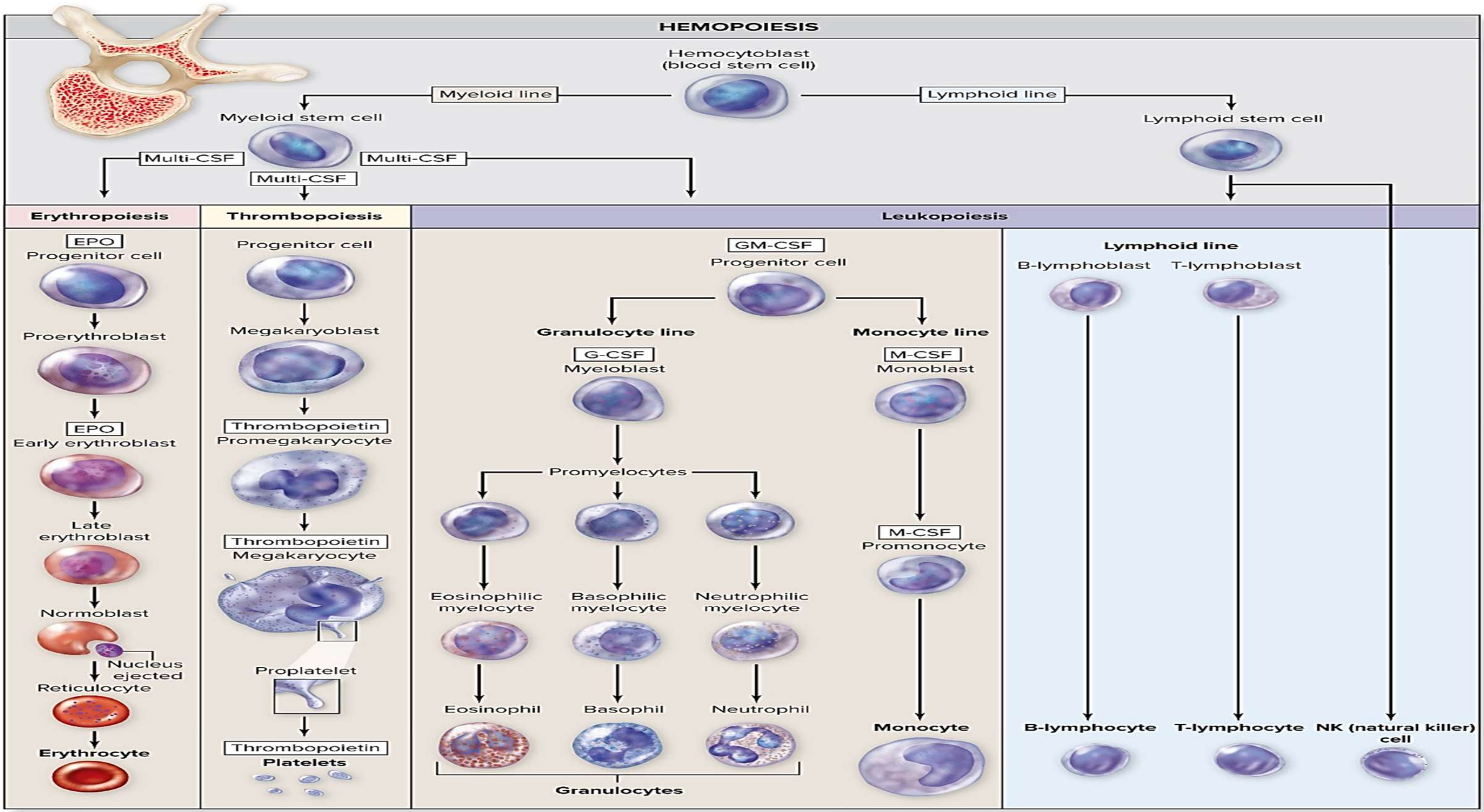
Protection

- **Blood prevents blood loss by:**
  - Activating plasma proteins and platelets
  - Initiating clot formation when a vessel is broken

- **Blood prevents infection by:**
  - Synthesizing and utilizing antibodies
  - Activating complement proteins
  - Activating WBCs to defend the body against foreign invaders

Components of Whole Blood



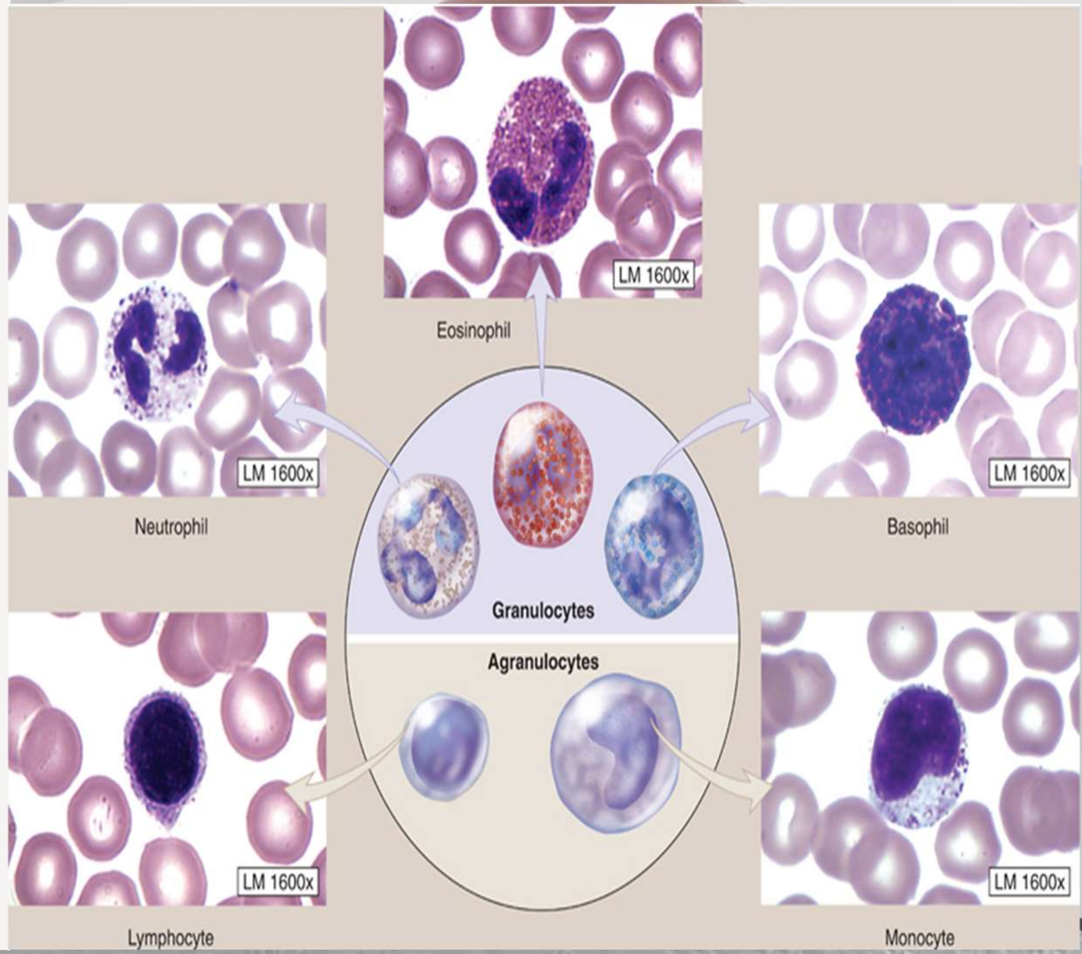

HEMOPOIESIS
Hemocytoblast
(blood stem cell)
Myeloid line
Lymphoid line
Myeloid stem cell
Lymphoid stem cell
Multi-CSF
Multi-CSF
Multi-CSF
Erythropoiesis
Thrombopoiesis
Leukopoiesis
EPO
Progenitor cell
Proerythroblast
EPO
Early erythroblast
Late
erythroblast
Normoblast
Nucleus
ejected
Reticulocyte
Erythrocyte
Progenitor cell
Megakaryoblast
Thrombopoietin
Promegakaryocyte
Thrombopoietin
Megakaryocyte
Proplatelet
Thrombopoietin
Platelets
GM-CSF
Progenitor cell
Granulocyte line
Monocyte line
G-CSF
Myeloblast
M-CSF
Monoblast
Promyelocytes
M-CSF
Promonocyte
Eosinophilic
myelocyte
Basophilic
myelocyte
Neutrophilic
myelocyte
Eosinophil
Basophil
Neutrophil
Monocyte
Granulocytes
Lymphoid line
B-lymphoblast
T-lymphoblast
B-lymphocyte
T-lymphocyte
NK (natural killer)
cell

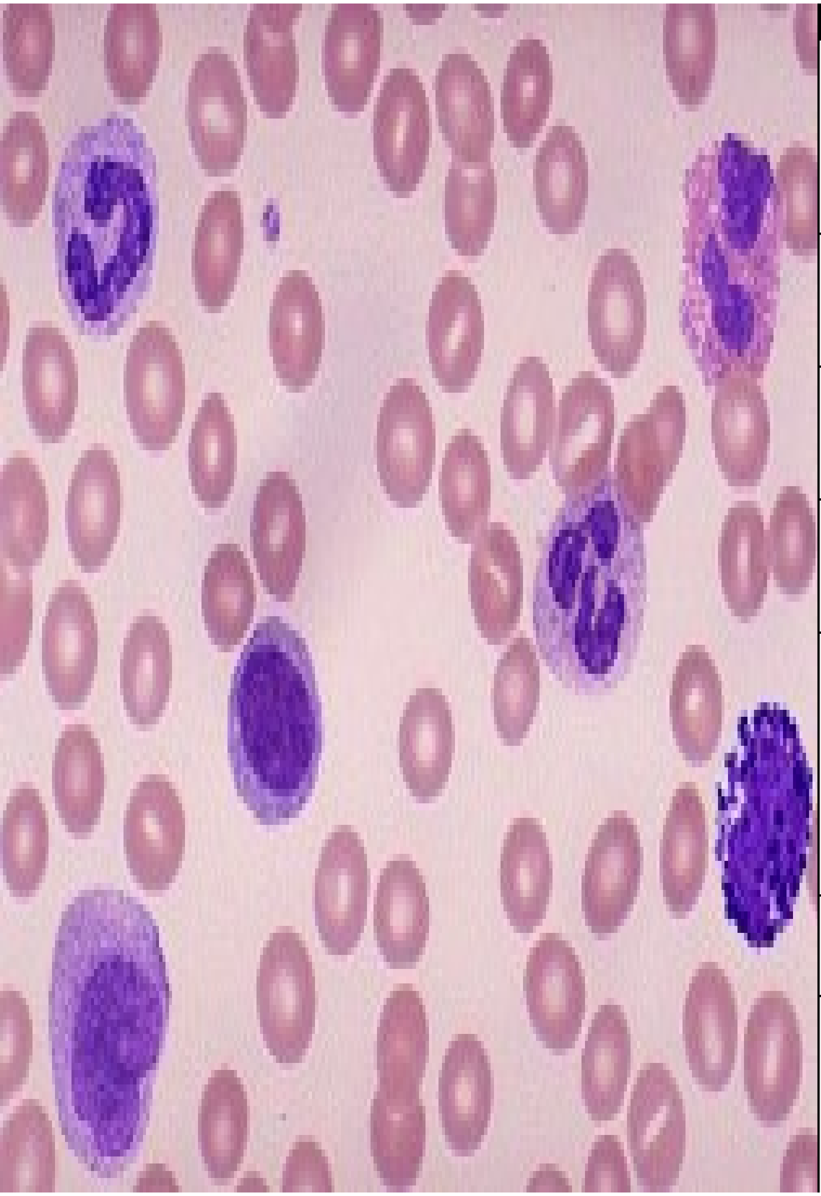
Formed Elements

- Erythrocytes, leukocytes, and platelets make up the formed elements
  - Only WBCs are complete cells
  - RBCs have no nuclei or organelles, and platelets are just cell fragments

- Most formed elements survive in the bloodstream for only a few days

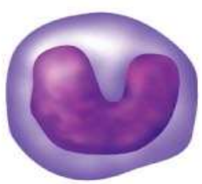
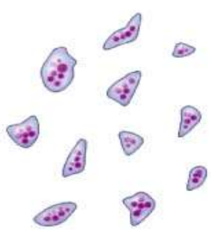
- Most blood cells do not divide but are renewed by cells in bone marrow



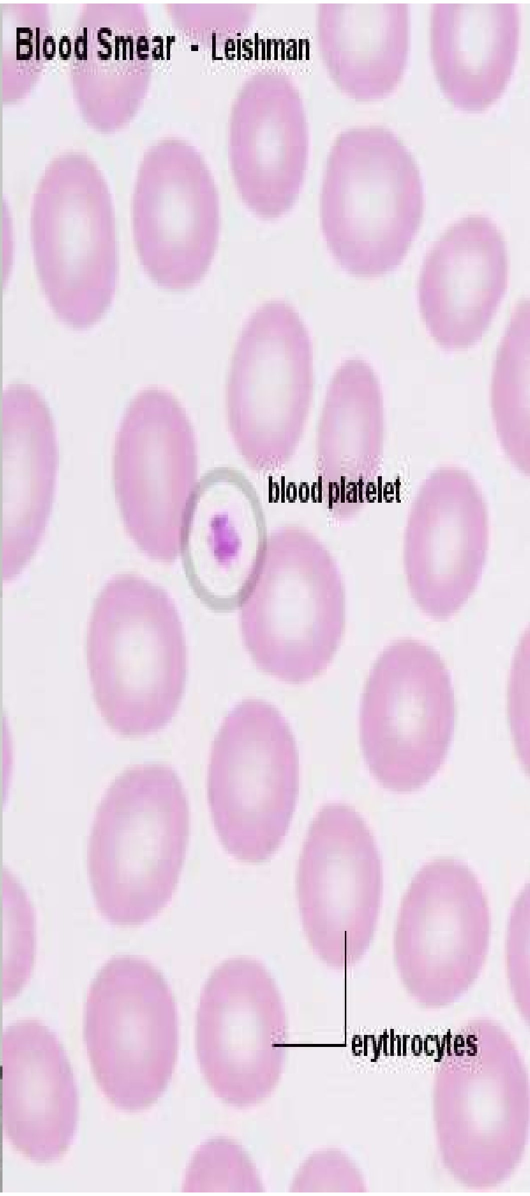


Name	Concentration	Characteristics	Functions
Erythrocytes (RBCs)	4.8 Million/microliter in females 5.4 Million/microliter in males	Biconcave disc no nucleus 120 day lifespan	Transports oxygen and carbon dioxide
Neutrophils	60% - 70% WBC concentration	Has 2-5 lobes joined by chromatin with a fine, pale granular cytoplasm	Phagocytosis. Uses lysozyme, super oxides and peroxides to destroy antigens.
Eosinophils	2% - 4% WBC concentration	has 2 - 3 lobes with large red/orange granules.	Responds to histamine in allergic reactions. Phagocytosis. destroys parasitic worms.
Basophils	0.5% - 1% WBC concentration	2 lobes with large, deep blue/purple granules	Intensify inflammatory response by liberating heparin, histamine and seratonin
Lymphocytes	20% - 25% WBC concentration	T/B cells. Cytoplasm forms ring around nucleus	Mediates immune response. B cells become plasma cells that form antibodies. T cells attack viruses, cancer cells and transplanted tissue cells.
Monocytes	3% - 8% WBC concentration	kidney-shaped nucleus with blue/gray cytoplasm	Becomes machrophage before phagocytosis
Thrombocytes (Platelets)	150,000 - 400,000/microliter	cells fragments, no nucleus	Forms platelet plug in hemostasis, and releases chemicals to promote vascular spasms and blood clotting.

TABLE 17.2 Summary of Formed Elements of the Blood (continued)

CELL TYPE	ILLUSTRATION	DESCRIPTION*	CELLS/µl (mm^3) OF BLOOD	DURATION OF DEVELOPMENT (D) AND LIFE SPAN (LS)	FUNCTION
Leukocytes (white blood cells, WBCs)		Spherical, nucleated cells	4800–10,800		
Agranulocytes					
▪ Lymphocyte		Nucleus spherical or indented; pale blue cytoplasm; diameter 5–17 µm	1500–3000	D: days to weeks LS: hours to years	Mount immune response by direct cell attack or via antibodies
▪ Monocyte		Nucleus U or kidney shaped; gray-blue cytoplasm; diameter 14–24 µm	100–700	D: 2–3 days LS: months	Phagocytosis; develop into macrophages in the tissues
Platelets		Discoid cytoplasmic fragments containing granules; stain deep purple; diameter 2–4 µm	150,000–400,000	D: 4–5 days LS: 5–10 days	Seal small tears in blood vessels; instrumental in blood clotting

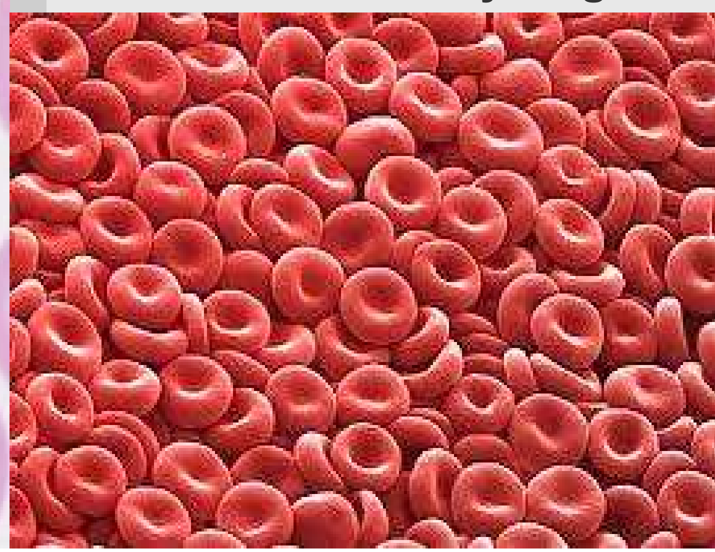
*Appearance when stained with Wright's stain.



Erythrocytes

Life cycle

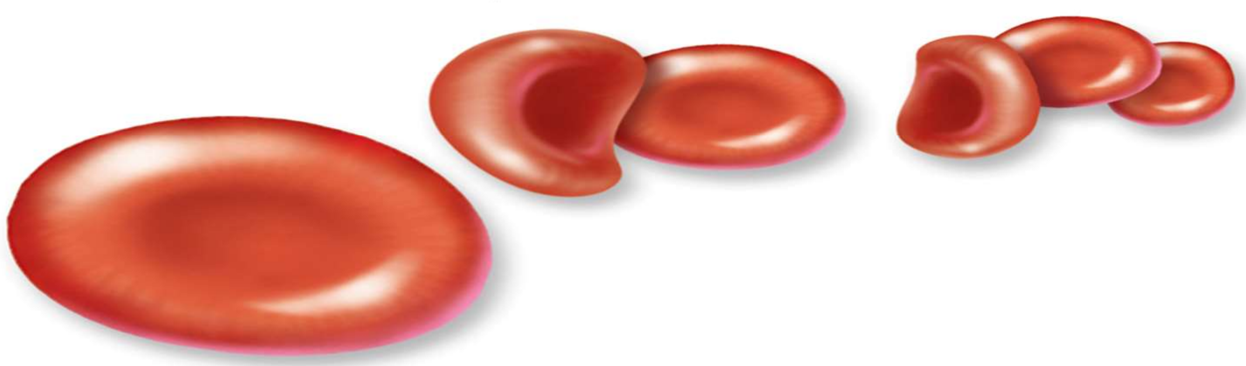
1. Erythropoiesis
    a. negative - feedback regulation
        1. erythropoietin
2. 120 days ---> destruction
3. recycling bilirubin; jaundice



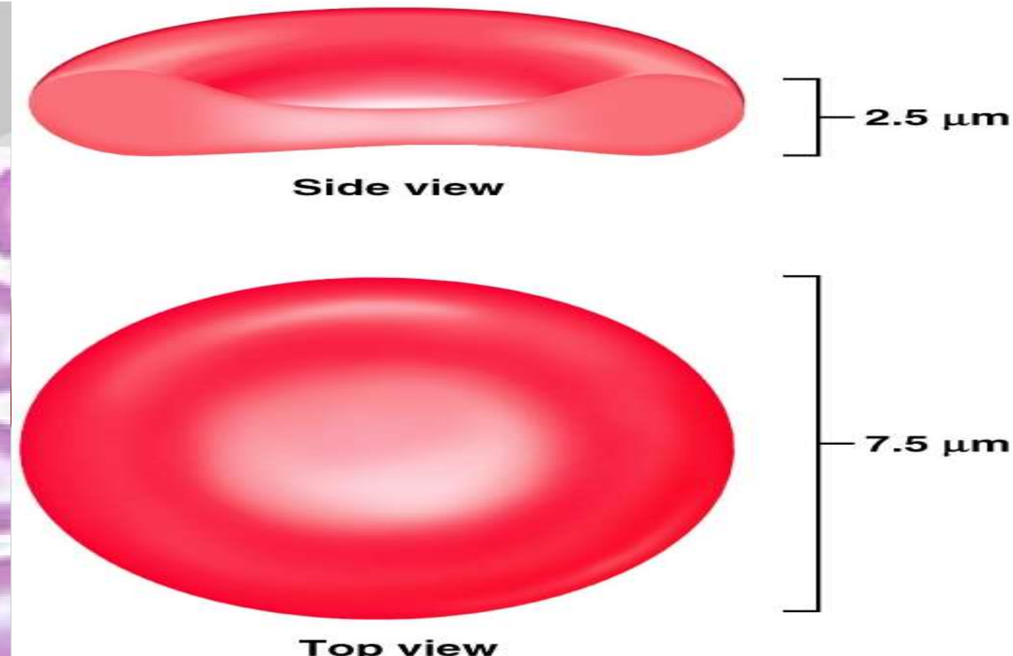
Erythrocytes (RBCs)

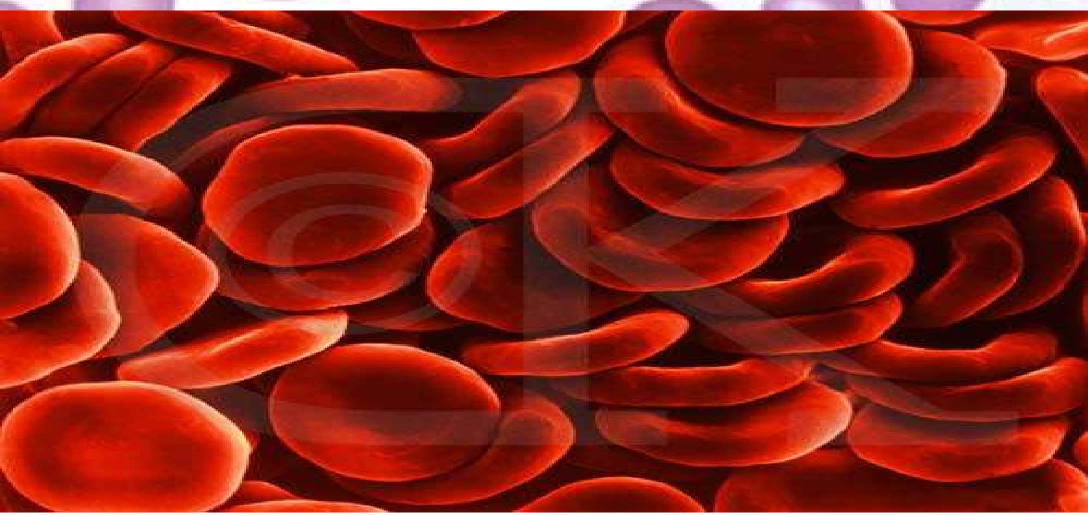
- Erythrocytes are an example of the complementarity of structure and function
- **Structural characteristics contribute to its gas transport function**
  - **Biconcave** shape has a huge surface area relative to volume
  - Erythrocytes are more than **97% hemoglobin**
  - **ATP is generated anaerobically**, so the erythrocytes do not consume the oxygen they transport

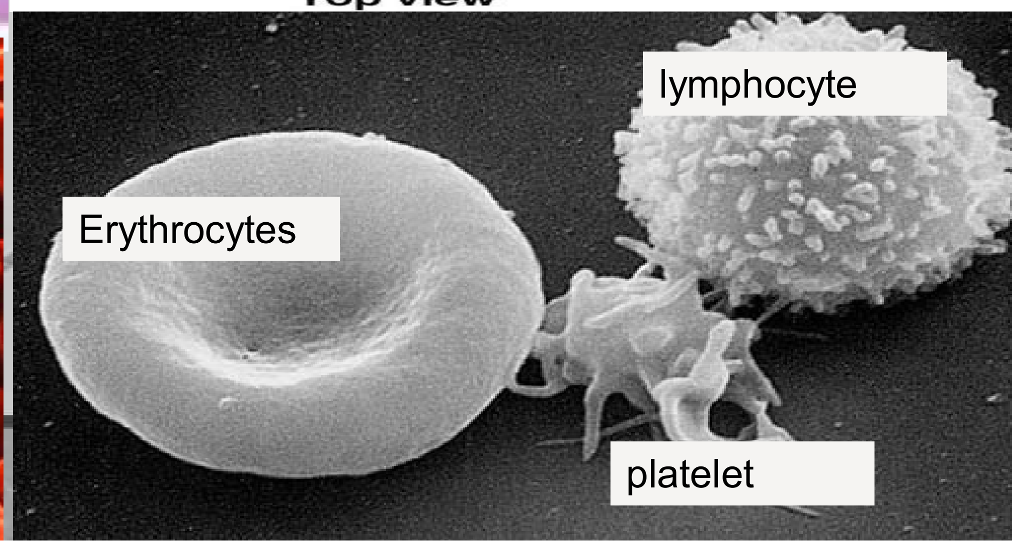
- Biconcave discs
- anucleate
- essentially no organelles
- Filled with hemoglobin (Hb), a protein that functions in gas transport
- Contain the plasma membrane protein **spectrin** and other proteins that:
  - Give erythrocytes their flexibility
  - Allow them to change shape as necessary

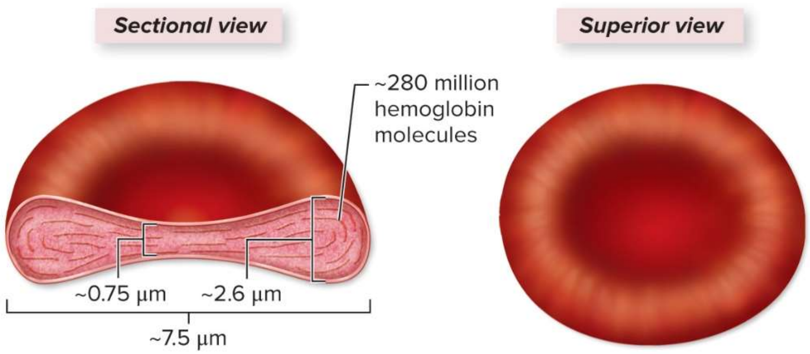


Erythrocytes (RBCs)

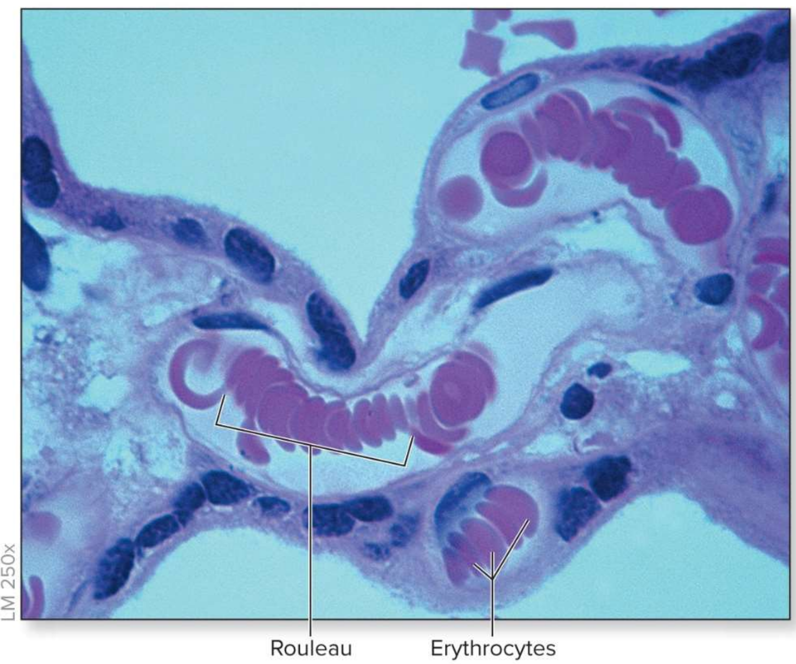








(a) Erythrocyte structure



(b) Erythrocyte rouleau in a blood vessel

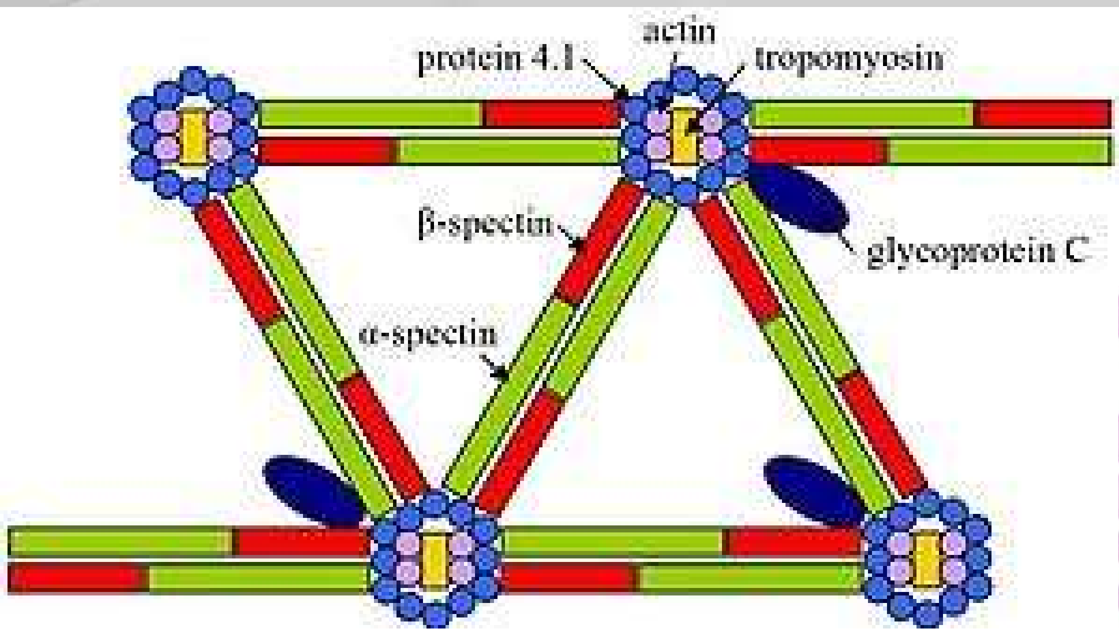
Spectrin is a **cytoskeletal protein** critical for maintaining the **shape, flexibility, and integrity** of red blood cells (RBCs).

It's part of the **membrane skeleton** beneath the plasma membrane, especially important in **erythrocytes**, which undergo constant mechanical stress in circulation.

Function in Red Blood Cells

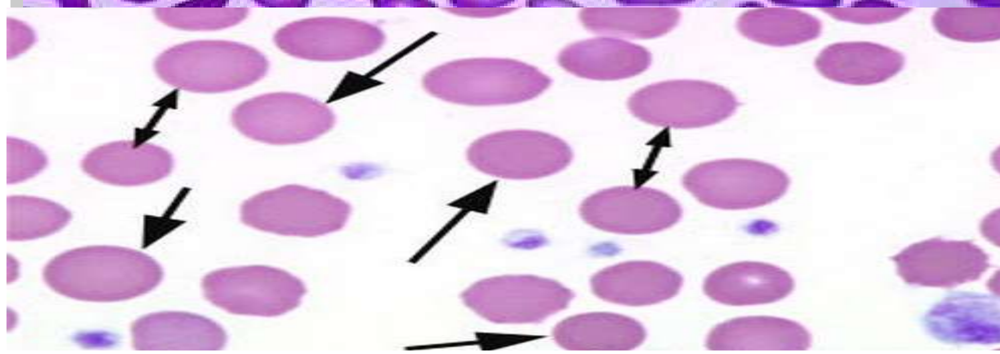
Function	Importance
Maintains biconcave shape	Allows high surface area for gas exchange
Provides elasticity	Enables RBCs to squeeze through capillaries
Anchors membrane proteins	Stabilizes the plasma membrane
Prevents hemolysis	Maintains membrane cohesion under stress

A schematic diagram of **spectrin** and other cytoskeletal molecules

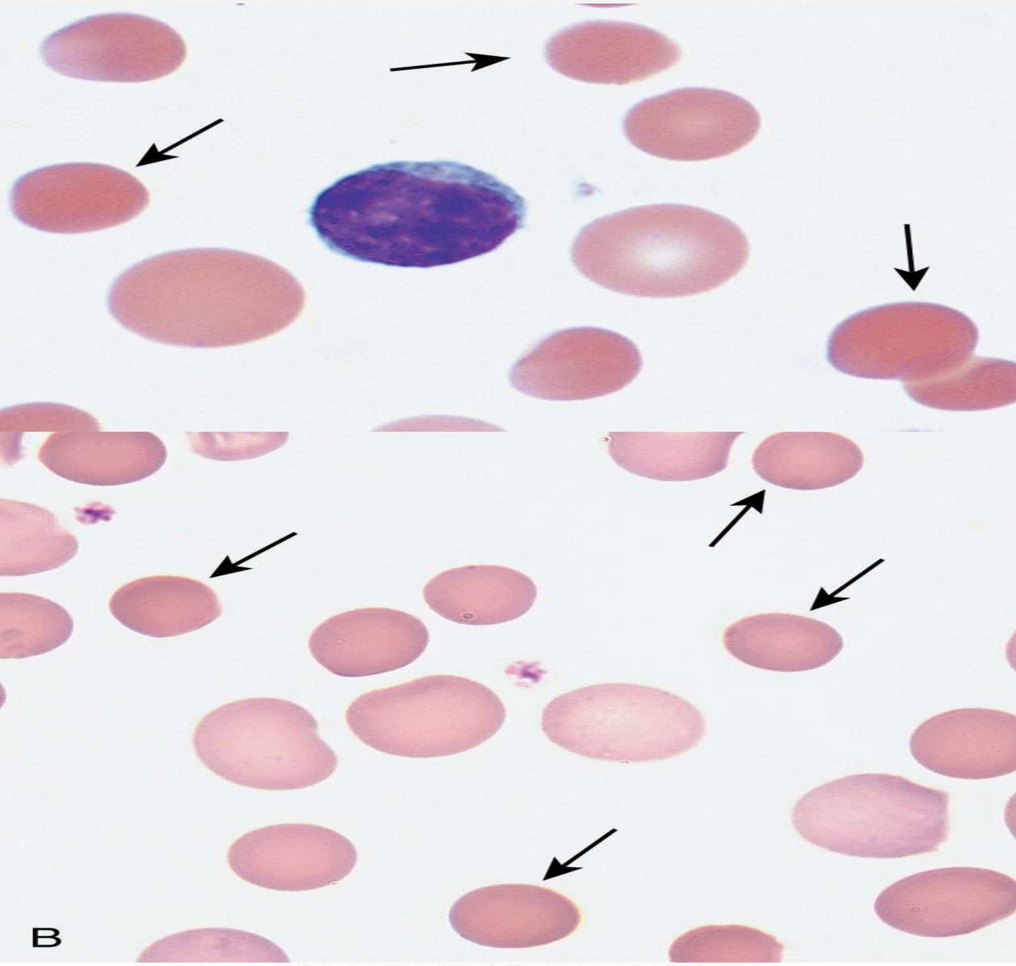


The erythrocyte model demonstrates the importance of the spectrin cytoskeleton in that mutations in spectrin commonly cause hereditary defects of the erythrocyte, including

- **hereditary elliptocytosis**
- **Hereditary spherocytosis**



Spherocytes



Graphics accessed http://evolvels.elsevier.com/

hereditary elliptocytosis

Hemopoiesis [1]

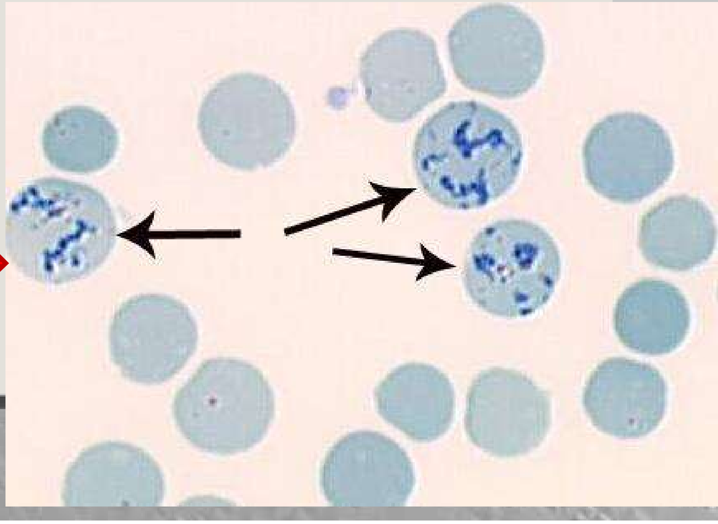
Hemopoiesis: production of formed elements

- Occurs in **red bone marrow** of certain bones
- **Hemocytoblasts:** stem cells
  - Pluripotent: can differentiate into many types of cells
  - Produce two different lines: myeloid line and lymphoid line
  - **Myeloid line** forms erythrocytes, all leukocytes except lymphocytes, and megakaryocytes (cells that produce platelets)
  - **Lymphoid line** forms only lymphocytes

Colony-stimulating factors (CSFs) stimulate hemopoiesis

Erythropoesis-Brief

- **Bone marrow**
  - Pluripotent stem cells
  - Chemical regulation
    - **Cytokines**
    - **Erythroid specific growth factor**
    - **Erythropoietin (EPO)**
  - Life span
    - Reticulocyte- 4 days
    - RBC –120 days



Production of Erythrocytes

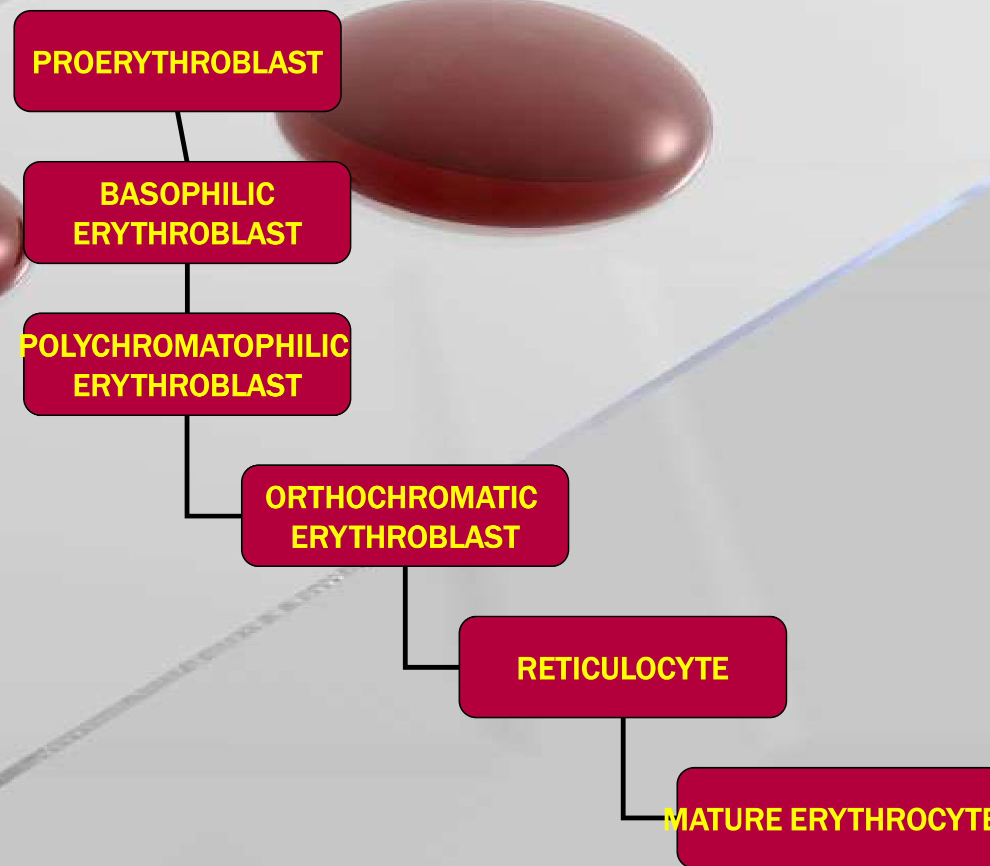
- **Hematopoiesis** – blood cell formation
- Hematopoiesis occurs in the red bone marrow of the:
  - Axial skeleton and girdles
  - Epiphyses of the humerus and femur
- **Hemocytoblasts** give rise to all formed elements

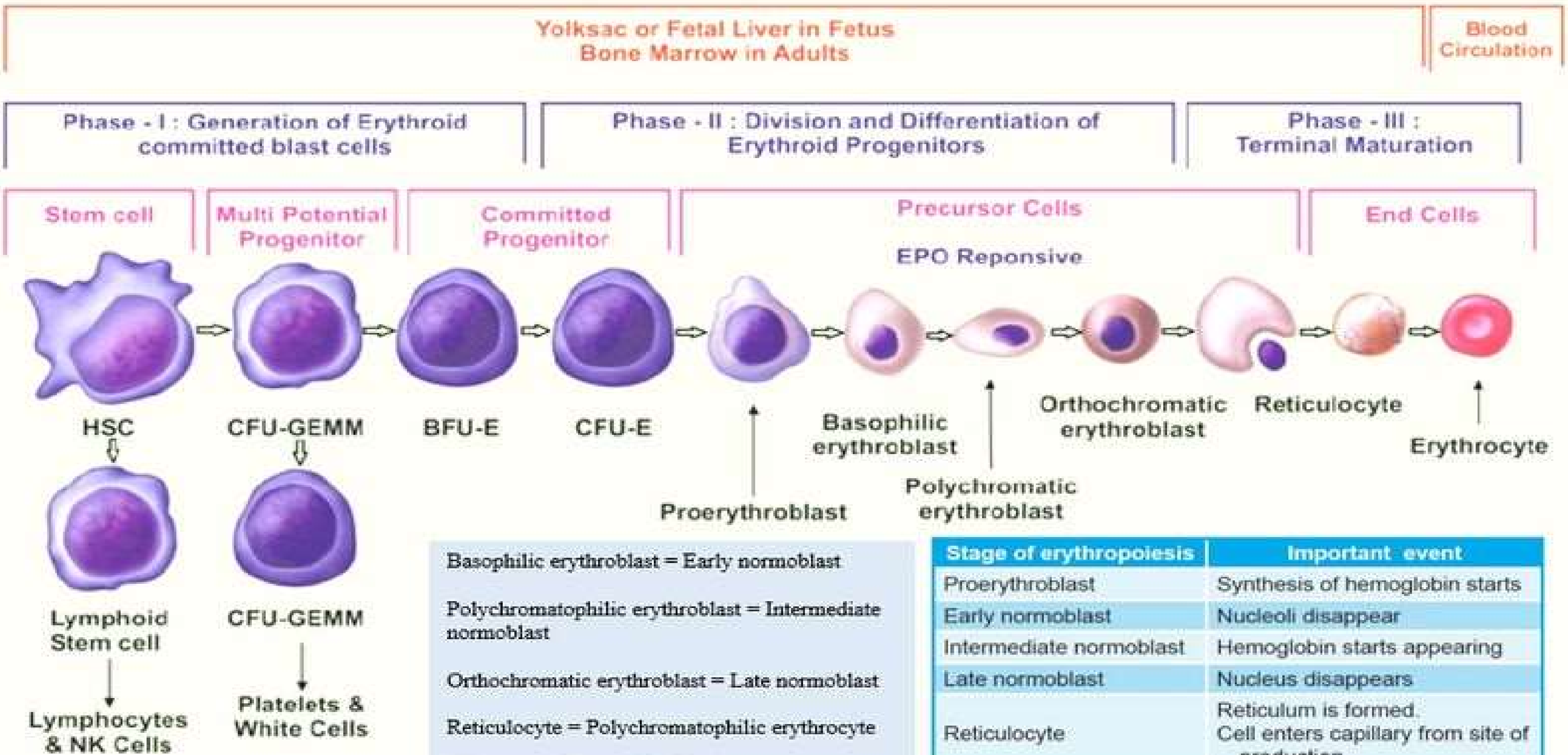
ERYTHROPOIESIS: SITES/PHASES

- **INTRAUTERINE LIFE:**
  - **INTRAVASCULAR PHASE: Upto 3rd month of Intra Uterine Life.**
    - **Endothelial cells = = = RBCs**
  - **HEPATIC PHASE: 3rd to 5th month IUL**
    - **Liver & Spleen**
    - **nRBCs from Mesenchymal cells.**
  - **MYELOID PHASE: From 5th month of IUL onwards.**
- **POST NATAL LIFE:**
  - **CHILDREN:**
    - **Predominantly Red Bone Marrow of skeleton:**
      - **Axial &**
      - **Appendicular.**
  - **ADULTS:**
    - **Red Bone Marrow of Axial Skeleton.**

Production of Erythrocytes: Erythropoiesis

- A **hemocytoblast is transformed into a proerythroblast**
- Proerythroblasts develop into early erythroblasts
- **The developmental pathway consists of three phases**
  - ***1 – ribosome synthesis in early erythroblasts***
  - ***2 – Hb accumulation in late erythroblasts and normoblasts***
  - ***3 – ejection of the nucleus from normoblasts and formation of reticulocytes***
- Reticulocytes then become mature erythrocytes





Basophilic erythroblast = Early normoblast

Polychromatophilic erythroblast = Intermediate normoblast

Orthochromatic erythroblast = Late normoblast

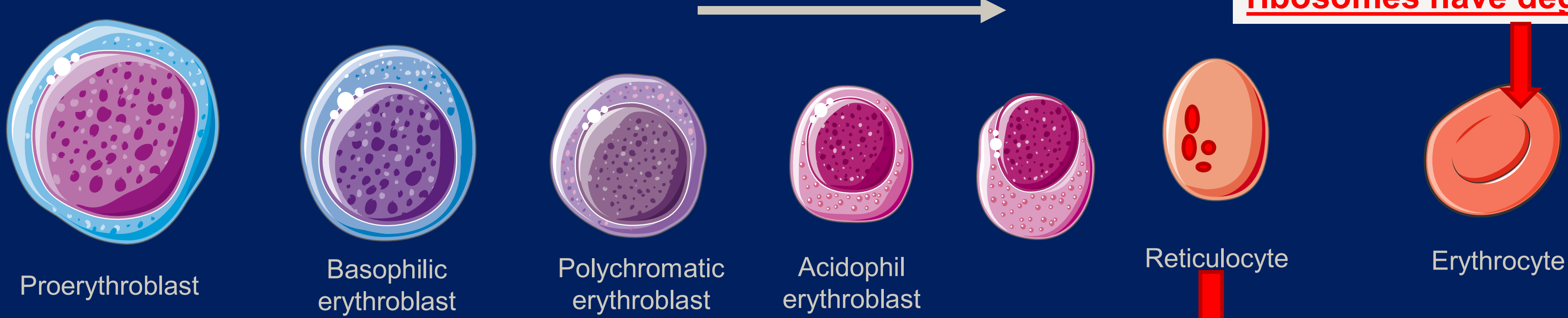
Reticulocyte = Polychromatophilic erythrocyte

Ribosome = Basophilic (Blue)
Hemoglobin = Acidophilic (Pink)

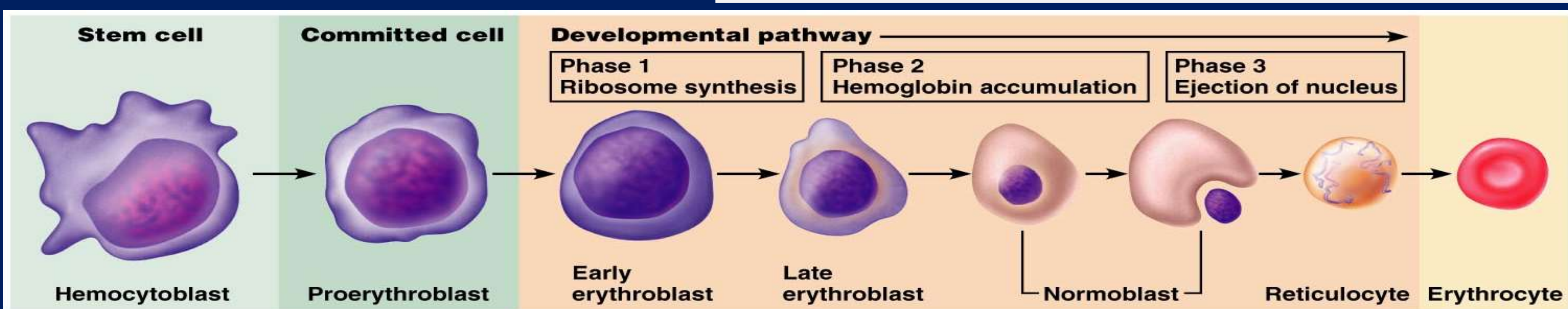
Stage of erythropoiesis	Important event
Proerythroblast	Synthesis of hemoglobin starts
Early normoblast	Nucleoli disappear
Intermediate normoblast	Hemoglobin starts appearing
Late normoblast	Nucleus disappears
Reticulocyte	Reticulum is formed. Cell enters capillary from site of production
Matured RBC	Reticulum disappears Cell attains biconcavity

Erythropoiesis

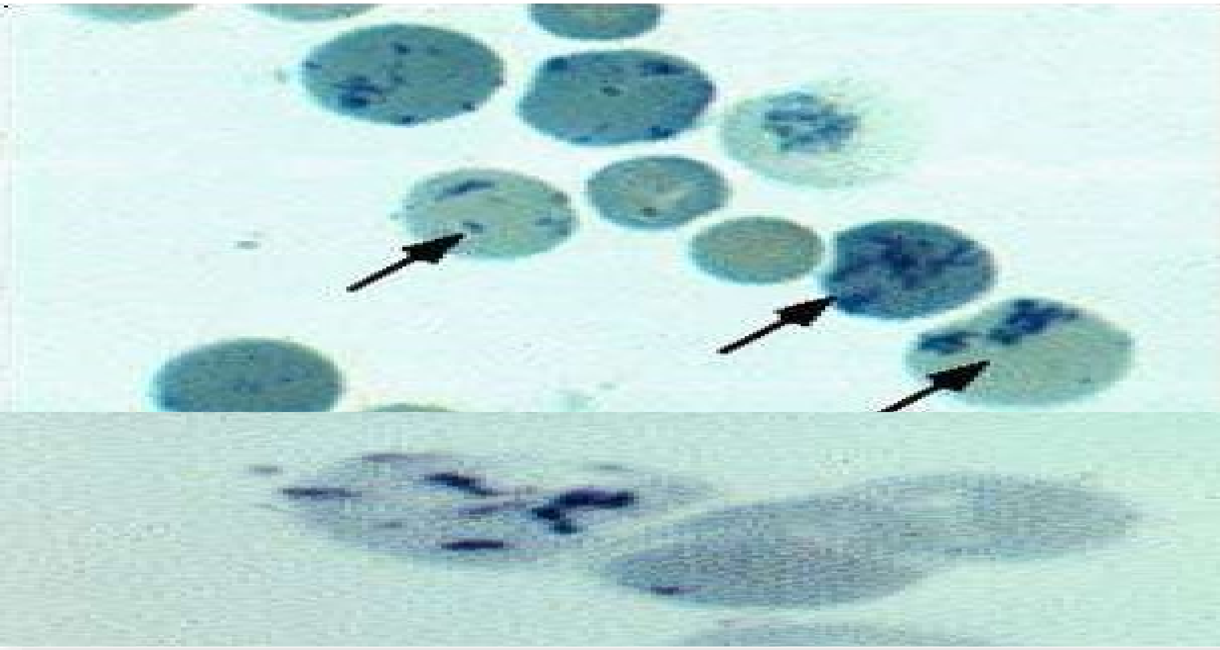
ribosomes have degenerated

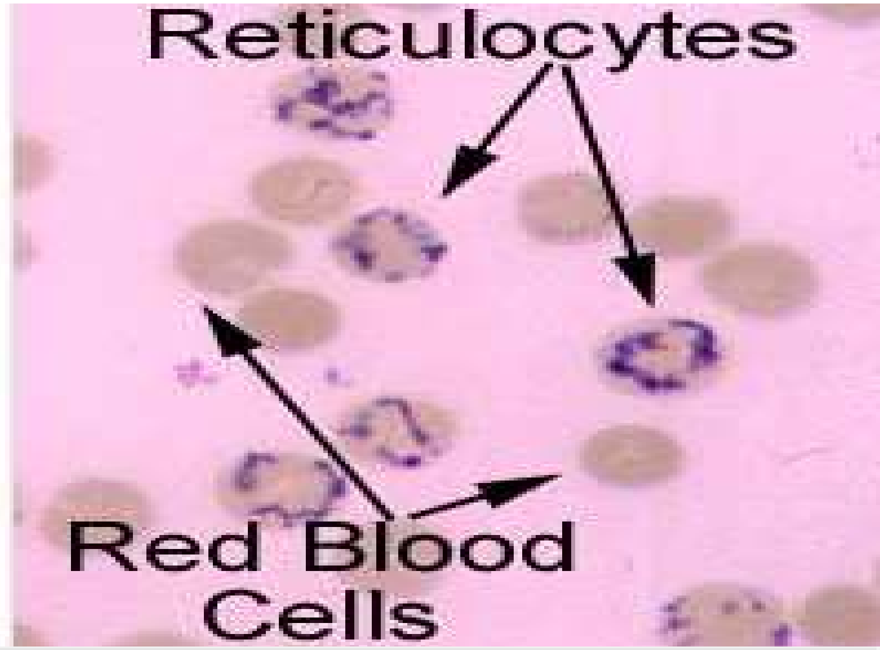


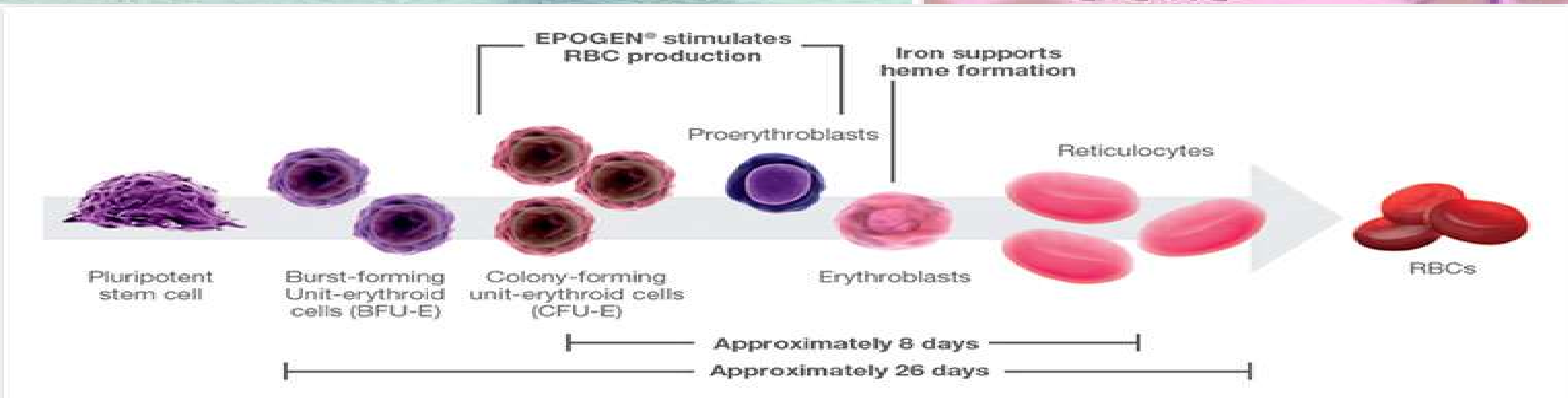
lacks organelles except ribosomes that make hemoglobin

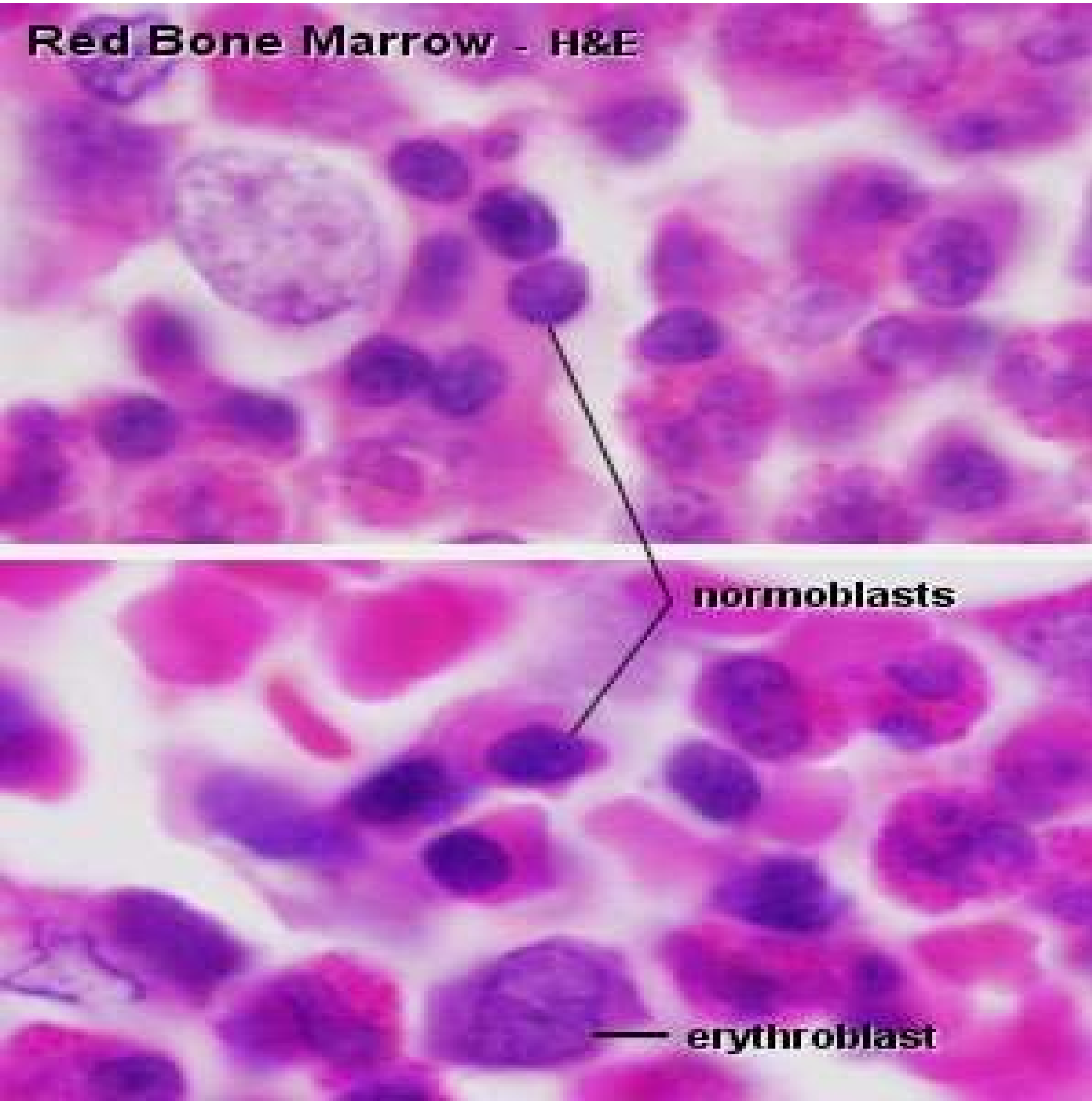


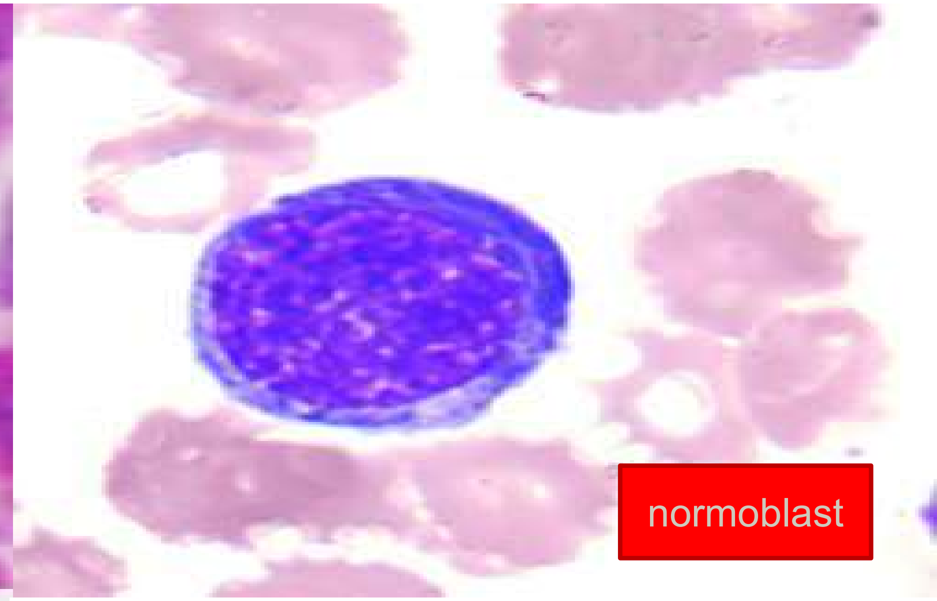
- **Erythropoiesis:** red blood cell production
  - Process requires iron, B vitamins, amino acids
  - Begins with **myeloid stem cell—**responds to multi-CSF
  - Forms progenitor cell
  - Forms **proerythroblast—**a large nucleated cell
  - Becomes **erythroblast—**smaller, produces hemoglobin
  - Becomes **normoblast—**still smaller, more hemoglobin, anucleate
  - Becomes **reticulocyte—**lacks organelles except ribosomes that make hemoglobin
  - Becomes erythrocyte—ribosomes have degenerated




Reticulocytes
Red Blood
Cells


EPOGEN® stimulates
RBC production
Iron supports
heme formation
Proerythroblasts
Reticulocytes
Pluripotent
stem cell
Burst-forming
Unit-erythroid
cells (BFU-E)
Colony-forming
unit-erythroid cells
(CFU-E)
Erythroblasts
RBCs
Approximately 8 days
Approximately 26 days


Red Bone Marrow - H&E
normoblasts
erythroblast


normoblast

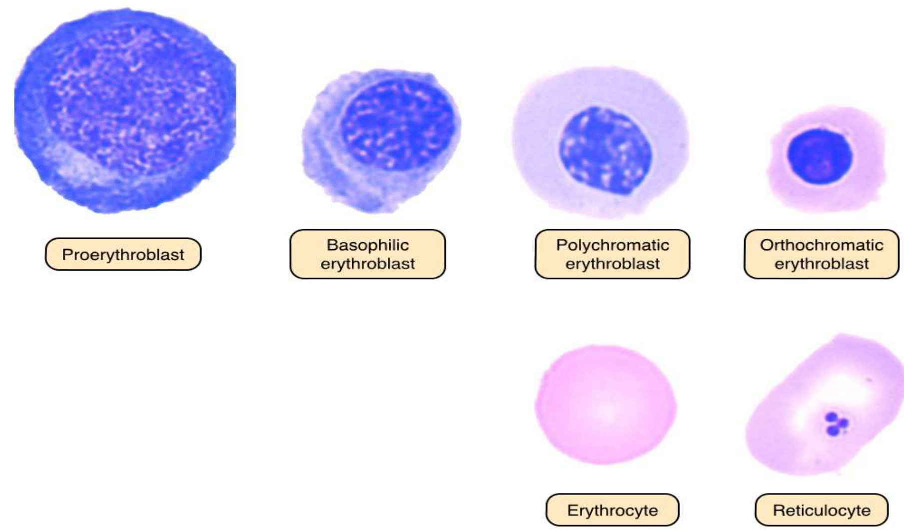
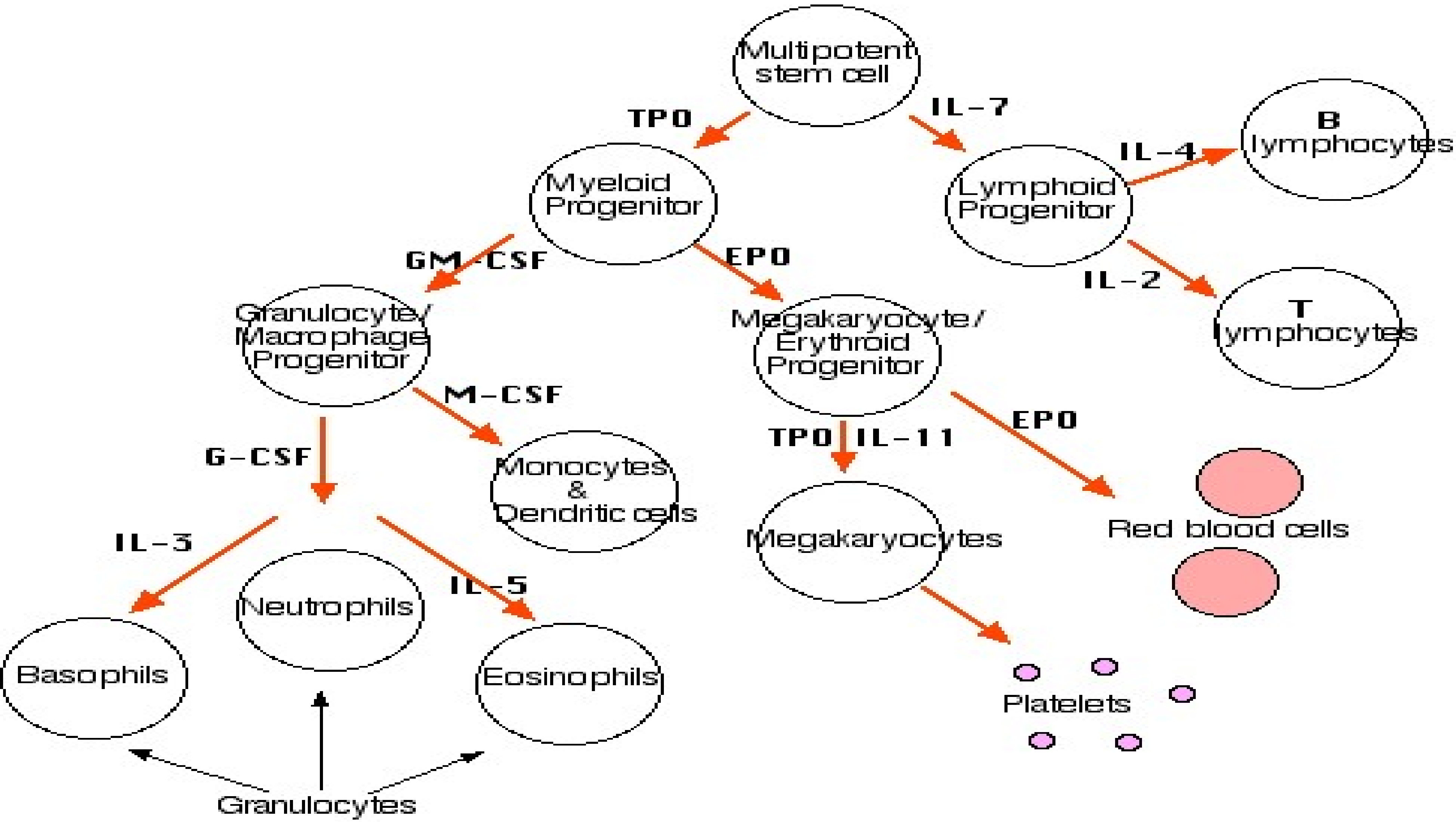

Proerythroblast
Basophilic erythroblast
Polychromatic erythroblast
Orthochromatic erythroblast
Erythrocyte
Reticulocyte

Table 18.6 Substances That Influence Hemopoiesis

Substance	Growth Factor or Hormone	Function
Multi-colony-stimulating factor (multi-CSF)	Growth factor	Increases the formation of erythrocytes, granulocytes, monocytes, and platelets from myeloid stem cells
Granulocyte-macrophage colony-stimulating factor (GM-CSF)	Growth factor	Accelerates the formation of all granulocytes and monocytes from their progenitor cells
Granulocyte colony-stimulating factor (G-CSF)	Growth factor	Stimulates the formation of granulocytes from myeloblast cells
Macrophage colony-stimulating factor (M-CSF)	Growth factor	Stimulates the production of monocytes from monoblasts
Thrombopoietin	Growth factor	Stimulates both the production of megakaryocytes in the bone marrow and the subsequent formation of platelets
Erythropoietin (EPO)	Hormone (produced primarily by the kidneys)	Increases the rate of production and maturation of erythrocyte progenitor and erythroblast cells



Multipotent stem cell
TPO
IL-7
Myeloid Progenitor
Lymphoid Progenitor
IL-4
B lymphocytes
IL-2
T lymphocytes
GM-CSF
EPO
Granulocyte/ Macrophage Progenitor
Megakaryocyte/ Erythroid Progenitor
M-CSF
G-CSF
TPO IL-11
EPO
Monocytes & Dendritic cells
Megakaryocytes
Red blood cells
IL-3
IL-5
Neutrophils
Basophils
Eosinophils
Platelets
Granulocytes

FACTORS REGULATING ERYTHROPOIESIS

- **SINGLE MOST IMPORTANT REGULATOR: "TISSUE OXYGENATION"**
- **BURST PROMOTING ACTIVITY**
- **ERYTHROPOIETIN**
- **IRON**
- **VITAMINS:**
  - **Vitamin B_{12}**
  - **Folic Acid**
- **MISCELLANEOUS**

- Circulating erythrocytes – the number remains constant and reflects a balance between RBC production and destruction
  - **Too few RBCs leads to tissue hypoxia**
  - **Too many RBCs causes undesirable blood viscosity**

- Erythropoiesis is hormonally controlled and depends on adequate supplies **of iron, amino acids, and B vitamins**

Hormonal Control of Erythropoiesis

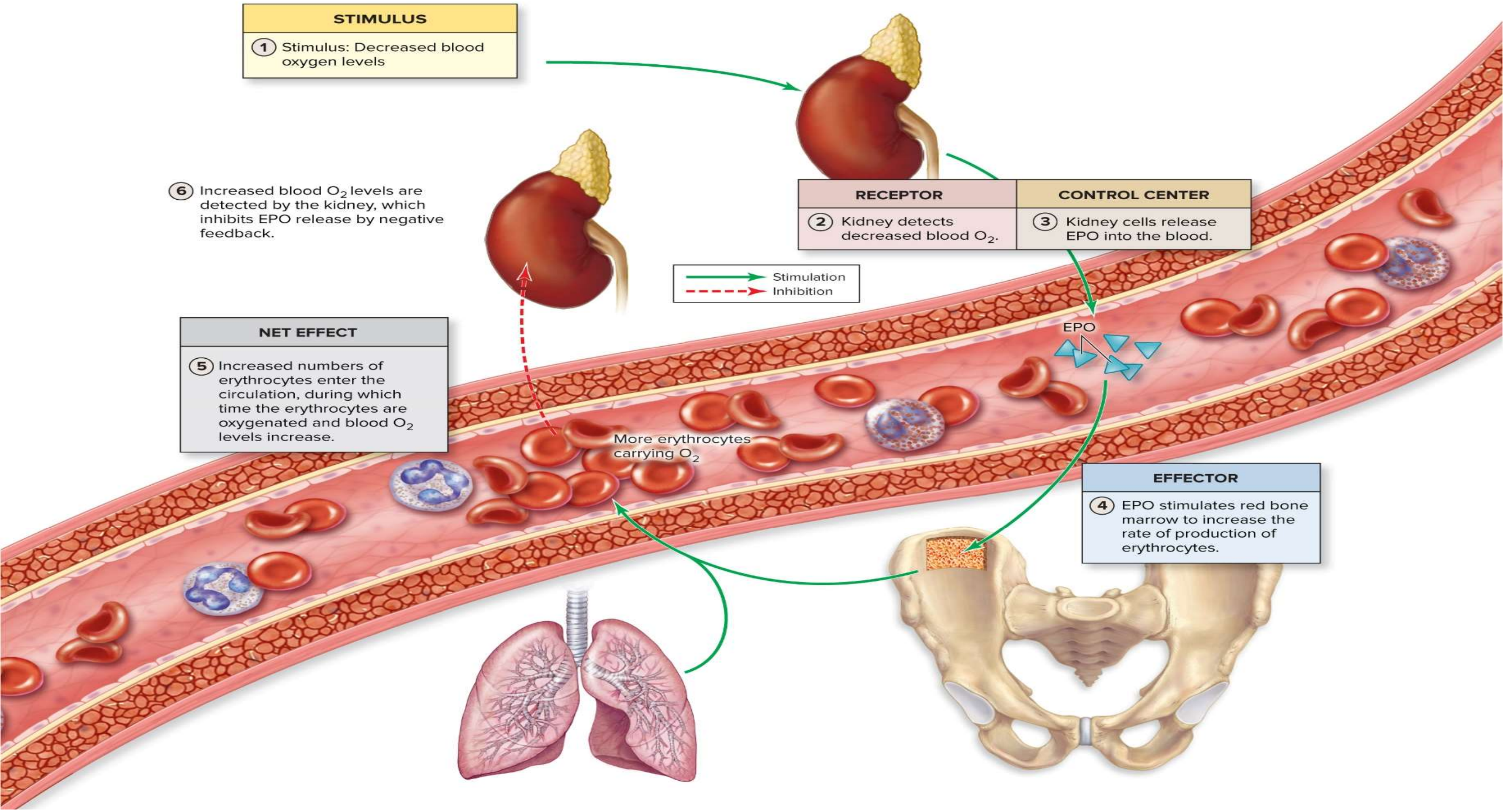
- **Erythropoietin (EPO) release by the kidneys is triggered by:**
  - **Hypoxia due to decreased RBCs**
  - **Decreased oxygen availability**
  - **Increased tissue demand for oxygen**

- **Enhanced erythropoiesis increases the**:
  - **RBC count in circulating blood**
  - **Oxygen carrying ability of the blood**

Erythrocytes 4

Erythropoietin (EPO) controls erythropoiesis **Acts mainly on CFU – E.**

- **Hormone produced primarily in the kidneys (a little in liver)**
- Secretion is stimulated by a decrease in blood oxygen
  - Red marrow myeloid cells respond to EPO by making more erythrocytes and releasing them into circulation
- The erythrocytes increase blood's oxygen carrying capacity
  - The increase in blood oxygen inhibits EPO release (negative feedback)
- Testosterone stimulates EPO production in kidney
  - Therefore males have higher erythrocyte count, higher hematocrit
- Environmental factors such as altitude influence EPO levels
  - Low oxygen levels at high altitude stimulate EPO production


STIMULUS
1 Stimulus: Decreased blood oxygen levels
RECEPTOR
2 Kidney detects decreased blood O_2.
CONTROL CENTER
3 Kidney cells release EPO into the blood.
Stimulation
Inhibition
EPO
EFFECTOR
4 EPO stimulates red bone marrow to increase the rate of production of erythrocytes.
NET EFFECT
5 Increased numbers of erythrocytes enter the circulation, during which time the erythrocytes are oxygenated and blood O_2 levels increase.
More erythrocytes carrying O_2
6 Increased blood O_2 levels are detected by the kidney, which inhibits EPO release by negative feedback.

Erythropoietin Mechanism

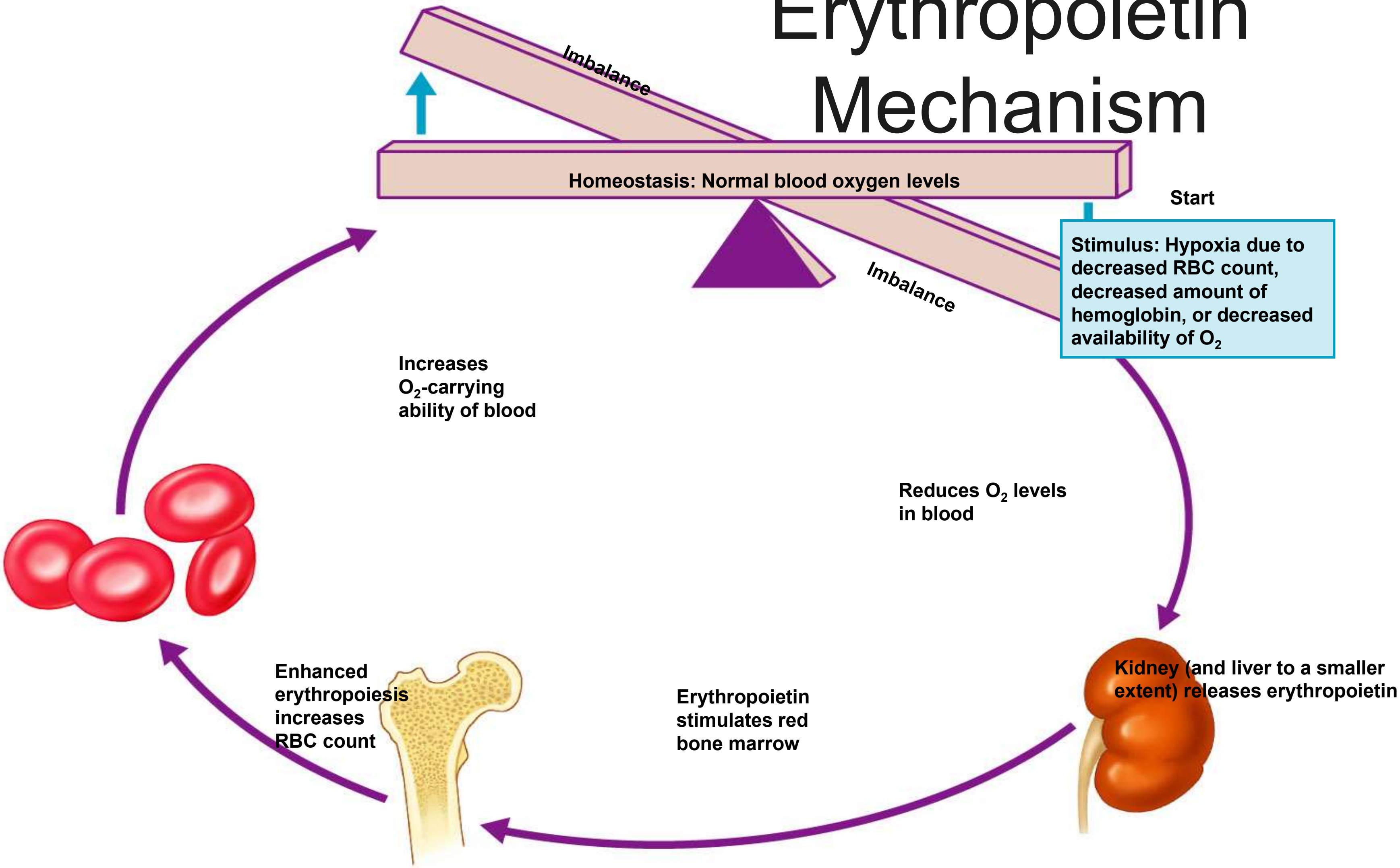
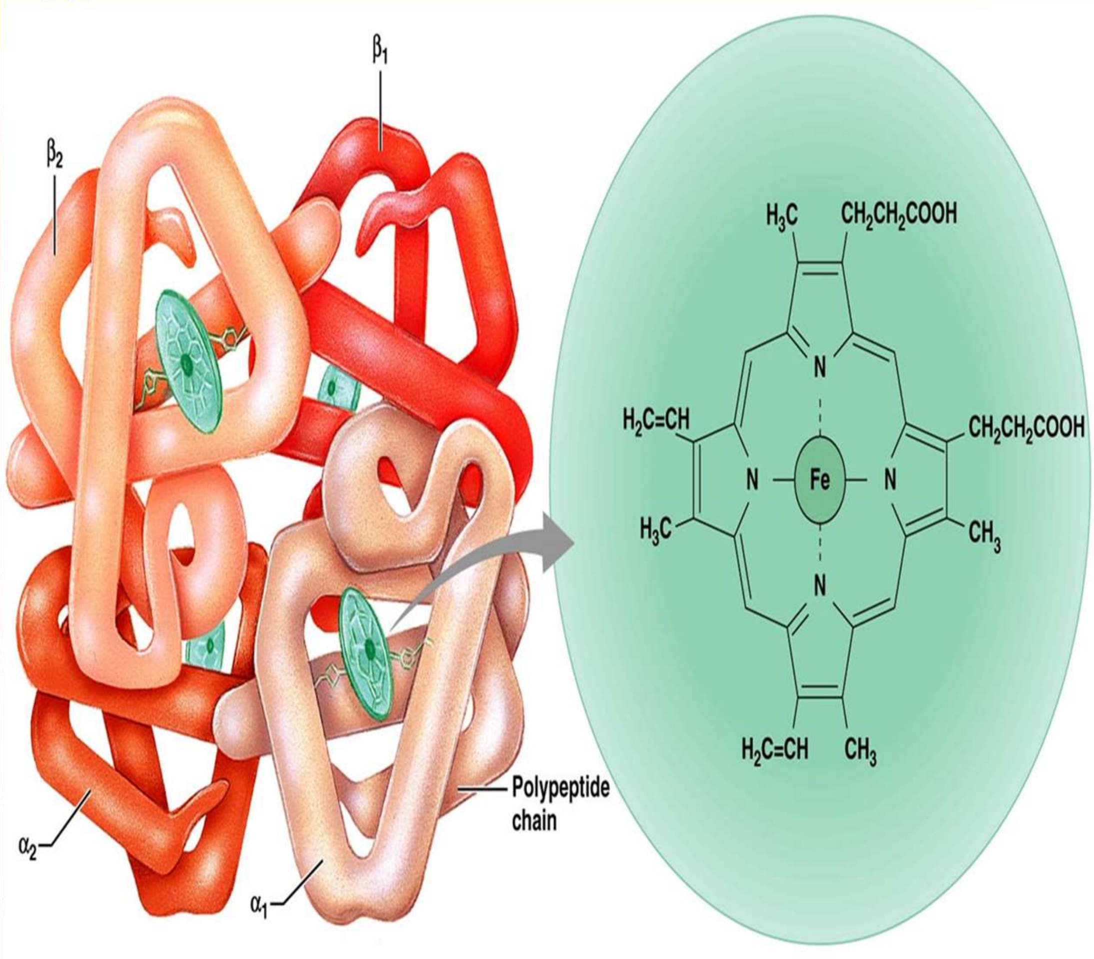


Figure 17.6

Hemoglobin

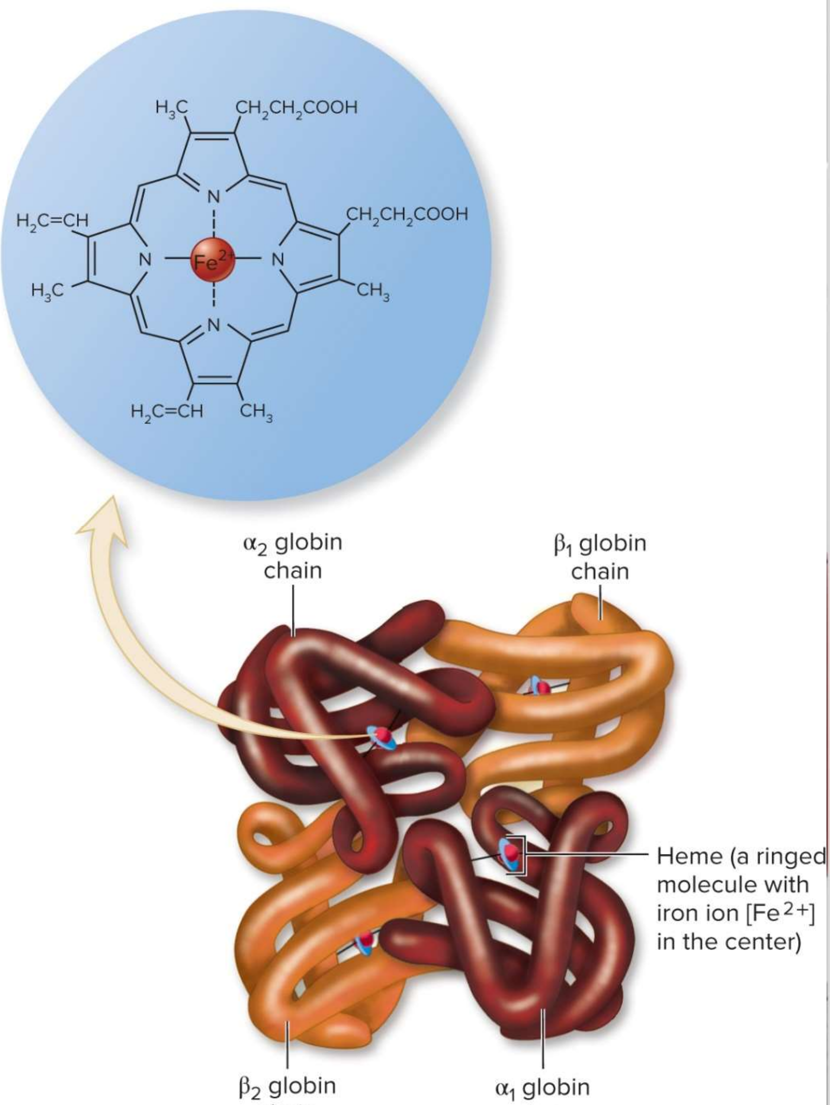
•**Type**: Tetrameric protein (4 subunits)

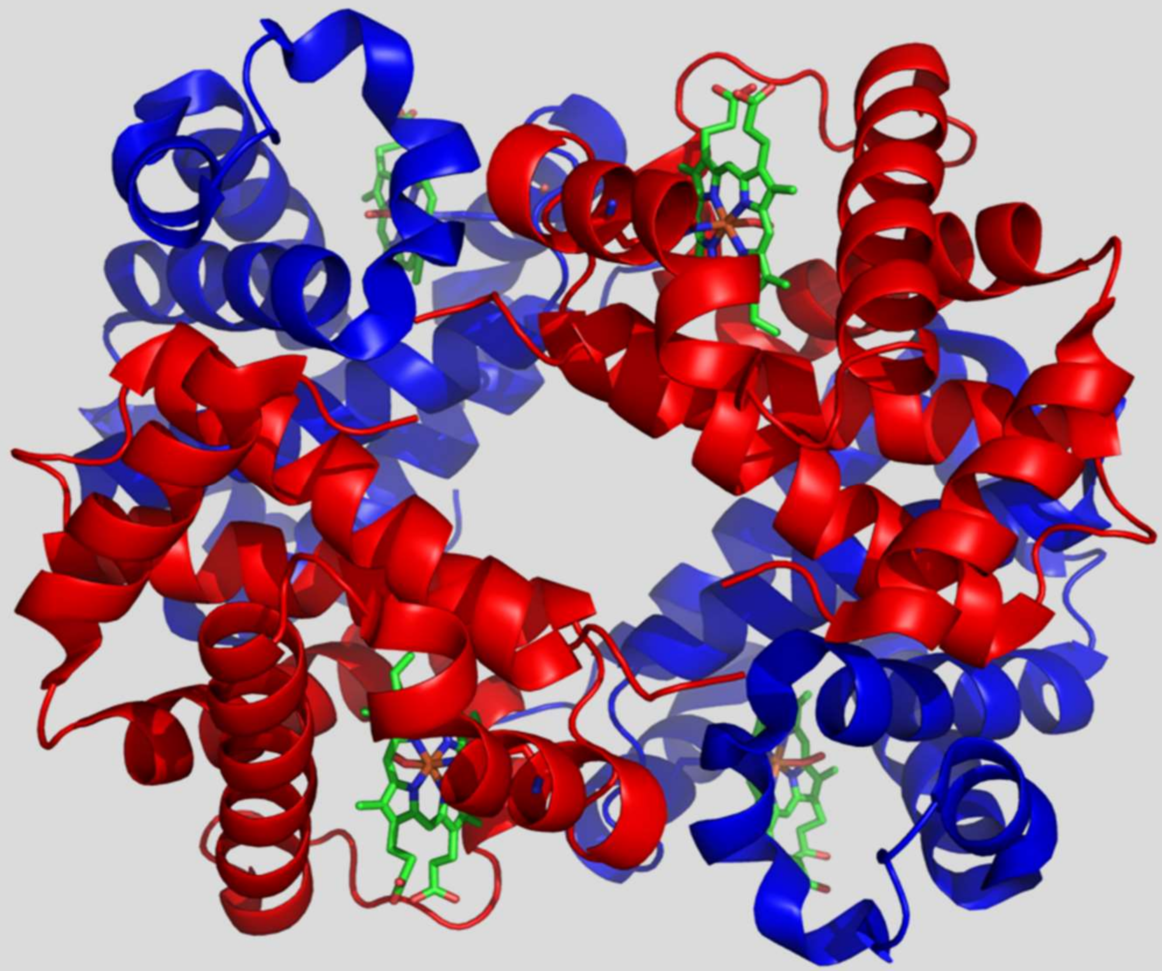
•**Subunits**: 2 alpha (α) and 2 beta (β) chains in adult hemoglobin (HbA)
•**Heme group**: Each subunit contains one heme group with an iron (Fe^{2+}) ion that binds oxygen
•**Binding Capacity**: One hemoglobin molecule can carry up to **4 oxygen molecules (O_2)**



(a) Hemoglobin (b) Iron-containing heme group

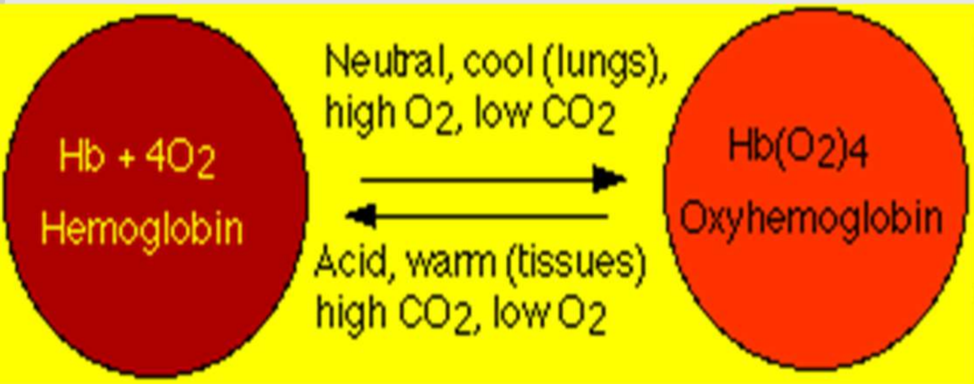
Types of Hemoglobin
•**HbA (Adult)**: $\alpha_2\beta_2$ – most common in adults
•**HbF (Fetal)**: $\alpha_2\gamma_2$ – higher oxygen affinity, predominant in fetuses
•**HbA2**: $\alpha_2\delta_2$ – minor adult component
•**Abnormal forms**: e.g., **HbS** in sickle cell disease, **HbC**, **HbE**


H_3C
CH_2CH_2COOH
$H_2C{=}CH$
CH_2CH_2COOH
Fe^{2+}
H_3C
CH_3
$H_2C{=}CH$
CH_3
α_2 globin chain
β_1 globin chain
Heme (a ringed molecule with iron ion [Fe^{2+}] in the center)
β_2 globin
α_1 globin



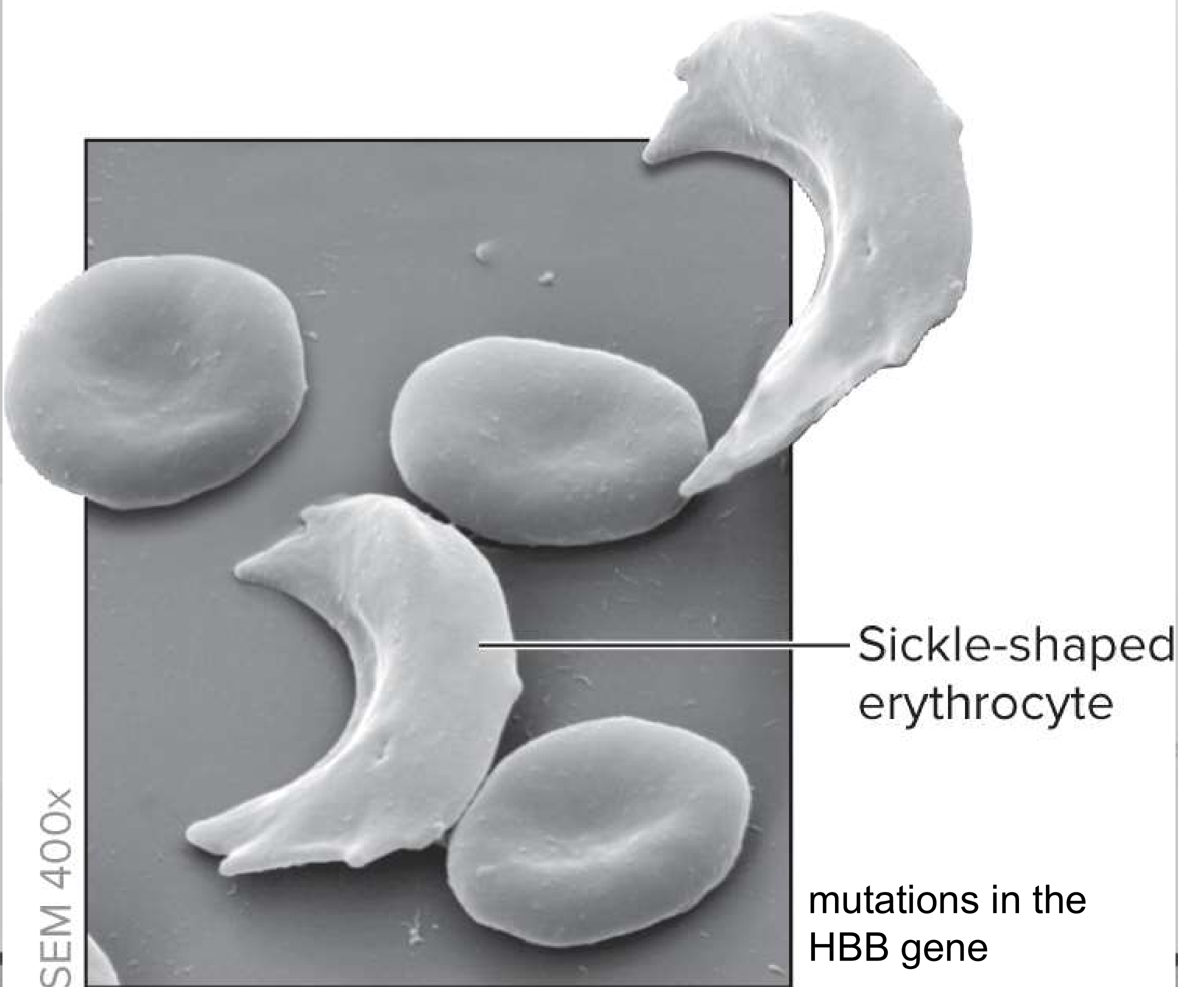
Hemoglobin (Hb)

- **Oxyhemoglobin** – Hb bound to oxygen
  - Oxygen loading takes place in the lungs
- **Deoxyhemoglobin** – Hb after oxygen diffuses into tissues (reduced Hb)
- **Carbaminohemoglobin** – Hb bound to carbon dioxide
  - Carbon dioxide loading takes place in the tissues



- **Men: 13.5 to 16.5 g/dl**
- **Women: 12.1 to 15.1 g/dl**
- **Children: 11 to 16 g/dl**
- **Pregnant women: 11 to 12 g/dl**

Name of Hemoglobin	Subunit Structure	Time of Expression
Hemoglobin Portland	$\zeta_2\gamma_2$	Embryonic
Hemoglobin Gower I	$\zeta_2\varepsilon_2$	Embryonic
Hemoglobin Gower II	$\alpha_2\varepsilon_2$	Embryonic
Hemoglobin F	$\alpha_2\gamma_2$	Fetal
Hemoglobin Barts	γ_4	Fetal (pathologic Hb secondary to absence of all 4 α globulin genes; fatal in utero)
Hemoglobin A_2	$\alpha_2\delta_2$	Minor adult hemoglobin
Hemoglobin A	$\alpha_2\beta_2$	Major adult hemoglobin



mutations in the HBB gene

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- The specific mutation results in the production of an abnormal form of hemoglobin known as hemoglobin S.

- This abnormal hemoglobin can cause red blood cells to become rigid and shaped like a crescent or sickle, leading to various health complications.

Some forms of SCD (sickle cell disease) include:
•Hemoglobin SS (HbSS)
•Hemoglobin SC (HbSC)
•Hemoglobin Sβ0 thalassemia (HbS-beta0 thalassemia)
•Hemoglobin Sβ+ thalassemia (HbS-beta+ thalassemia)
•Hemoglobin SD (HbSD)
•Hemoglobin SE (HbSE)

Clinical Significance

▼ Low Hemoglobin (Anemia):

- **Causes**: Iron deficiency, chronic disease, bone marrow disorders, bleeding, hemolysis
- **Symptoms**: Fatigue, pallor, shortness of breath, tachycardia

▲ High Hemoglobin (Polycythemia):

- **Causes**: Dehydration, smoking, high altitude, polycythemia vera
- **Risks**: Clot formation, stroke, hypertension

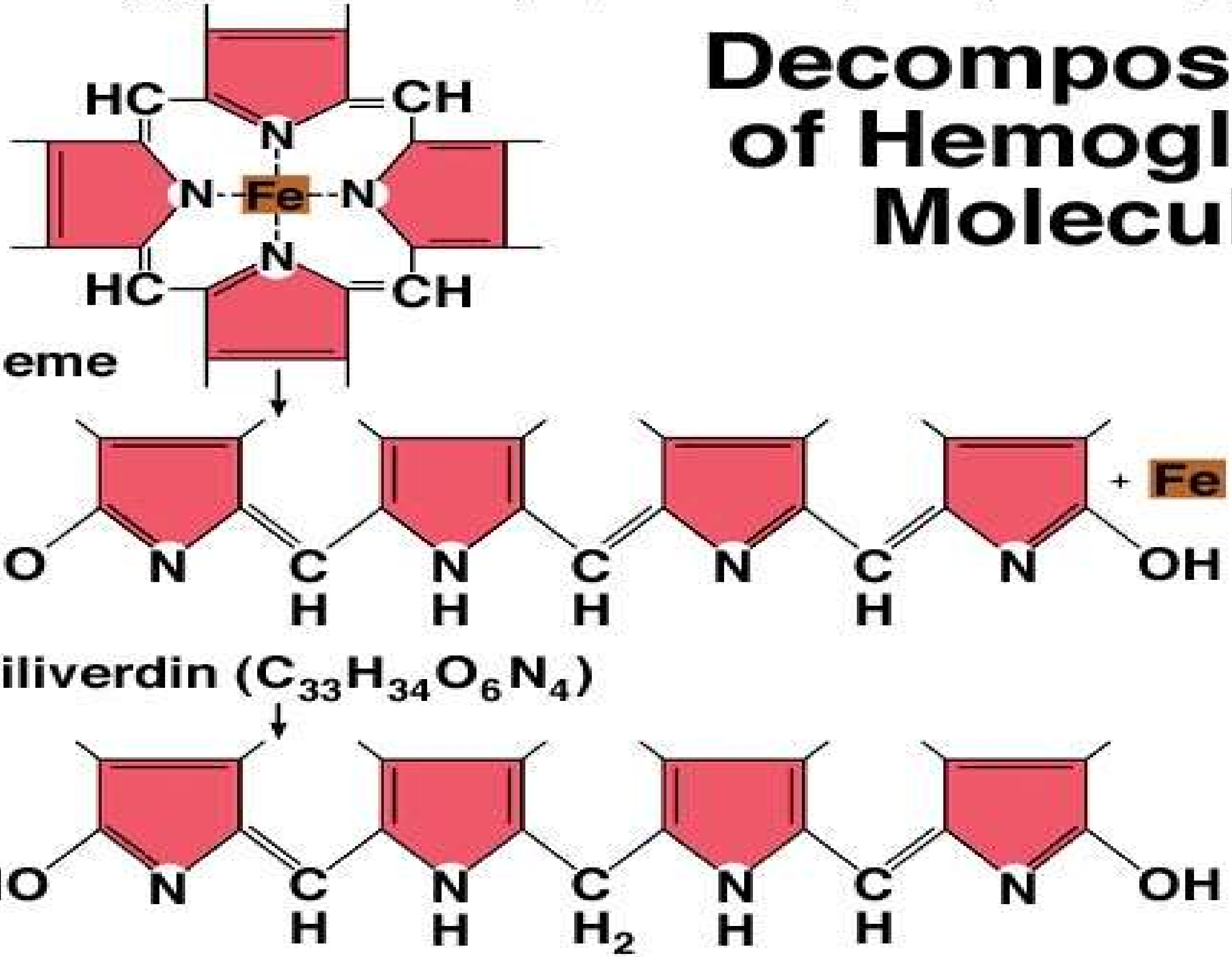
Diagnostic Tests

- **Complete Blood Count (CBC)** – measures hemoglobin, hematocrit, and RBCs
- **Hemoglobin electrophoresis** – identifies abnormal types (e.g., HbS, HbC)
- **Pulse oximetry** – indirect measure of oxygen saturation

Erythrocyte Function

- RBCs are dedicated to **respiratory gas transport**
- **Hb reversibly binds with oxygen and most oxygen in the blood is bound to Hb**
- **Hb is composed of the protein globin, made up of two alpha and two beta chains, each bound to a heme group**
- **Each heme group bears an atom of iron, which can bind to one oxygen molecule**
- **Each Hb molecule can transport four molecules of oxygen**

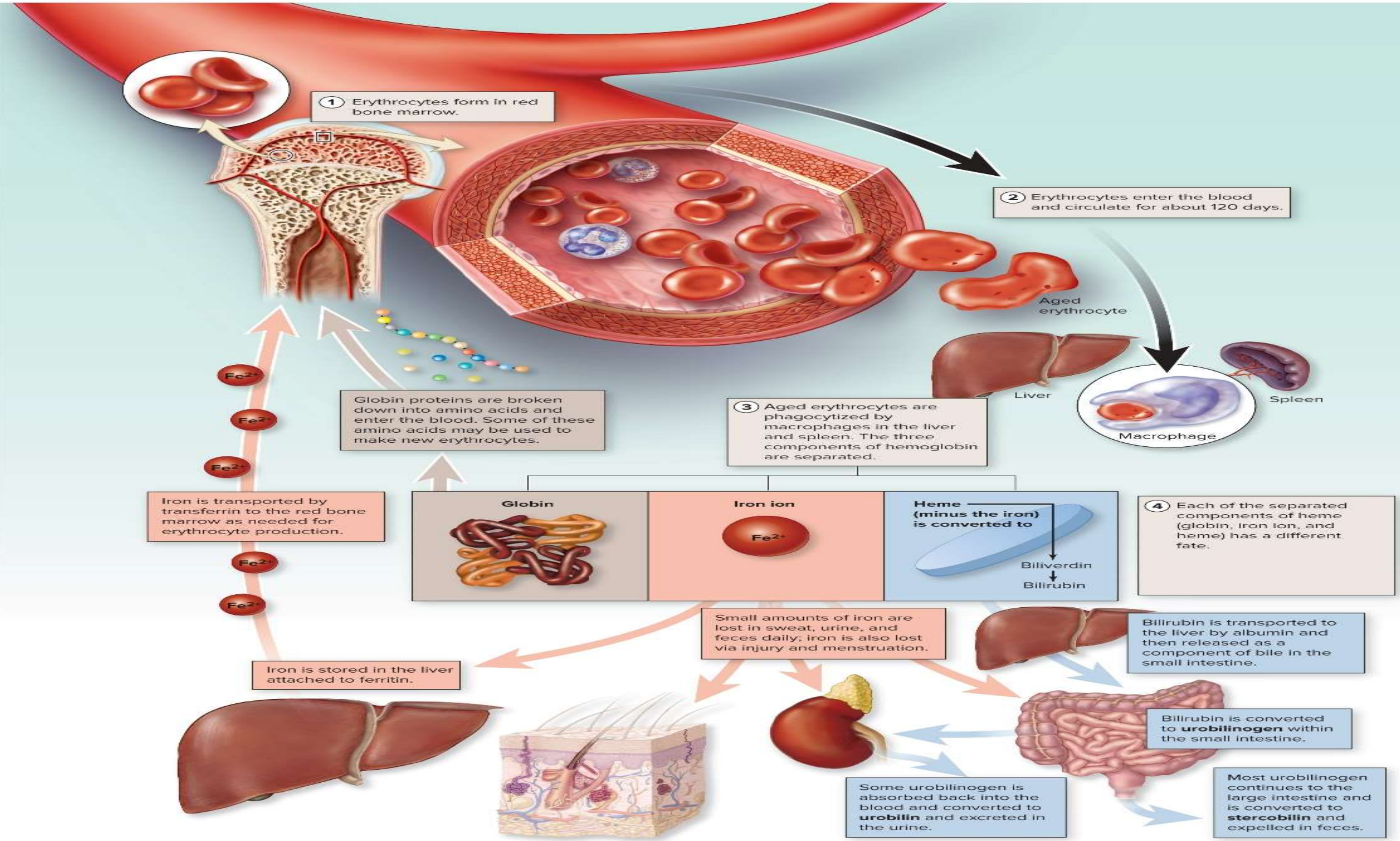
Decomposition of Hemoglobin Molecule



Heme

Biliverdin ($C_{33}H_{34}O_6N_4$)

Bilirubin ($C_{33}H_{36}O_6N_4$)


1 Erythrocytes form in red bone marrow.
2 Erythrocytes enter the blood and circulate for about 120 days.
Aged erythrocyte
Liver
Spleen
Macrophage
3 Aged erythrocytes are phagocytized by macrophages in the liver and spleen. The three components of hemoglobin are separated.
Globin proteins are broken down into amino acids and enter the blood. Some of these amino acids may be used to make new erythrocytes.
Fe2+
Iron is transported by transferrin to the red bone marrow as needed for erythrocyte production.
Globin
Iron ion
Heme (minus the iron) is converted to
Biliverdin
Bilirubin
4 Each of the separated components of heme (globin, iron ion, and heme) has a different fate.
Small amounts of iron are lost in sweat, urine, and feces daily; iron is also lost via injury and menstruation.
Iron is stored in the liver attached to ferritin.
Bilirubin is transported to the liver by albumin and then released as a component of bile in the small intestine.
Bilirubin is converted to urobilinogen within the small intestine.
Some urobilinogen is absorbed back into the blood and converted to urobilin and excreted in the urine.
Most urobilinogen continues to the large intestine and is converted to stercobilin and expelled in feces.

Mean Corpuscular Volume (MCV)

- The MCV is the average or mean volume of a single red blood cell expressed in cubic micrometers (μm3 or femtoliters).

- *Formula* $$MCV = \frac{Hct \times 10}{[RBC]}$$
- *For example*

The common causes of microcytic and hypochromic anemia (decreased MCV and MCH) like thalassemia, iron deficiency

- PCV = 45% RBC count = 5.0 million/mm3 = Packed cell volume (PCV) in 100 ml blood =hematocrit
- MCV = 45 10 5× 90mm3
- Normal range = 74 – 95 μm3

Mean Corpuscular Hemoglobin (MCH)

- Both mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) reflect the average hemoglobin content of red blood cells

$$\boxed{MCH} = \frac{\text{Hb (g/dL)} \times 10}{\text{RBC count (millions/mm}^3\text{)}}$$

labpedia.net

$$\boxed{MCHC} = \frac{\text{Hb (g/dL)} \times 100}{\text{Hct}}$$

labpedia.net

Mean Corpuscular Hemoglobin Concentration (MCHC)

The MCHC represents the relationship between the red cell volume and its degree or percentage saturation with hemoglobin, that is, how many parts or volumes of a red cell are occupied by Hb.

BLOOD INDICES

MCV

Mean corpuscular volume

is a measure of the average volume of a single red blood corpuscle

$$MCV = \frac{HCT}{RBC\ count} \times 10 = \ldots\ldots\ FL$$

76 : 95

MCH

Mean Hemoglobin volume

The average amount of hemoglobin per red blood cell by the red blood cell count

$$MCH = \frac{Hb}{RBC\ count} \times 10 = \ldots\ldots\ Pg.$$

27 : 34

MCHC

Mean Hemoglobin Concentration

The average concentration of hemoglobin per unit volume of red blood cells

$$MCH = \frac{Hb}{HCT} \times 100 = \ldots\ldots\ \%.$$

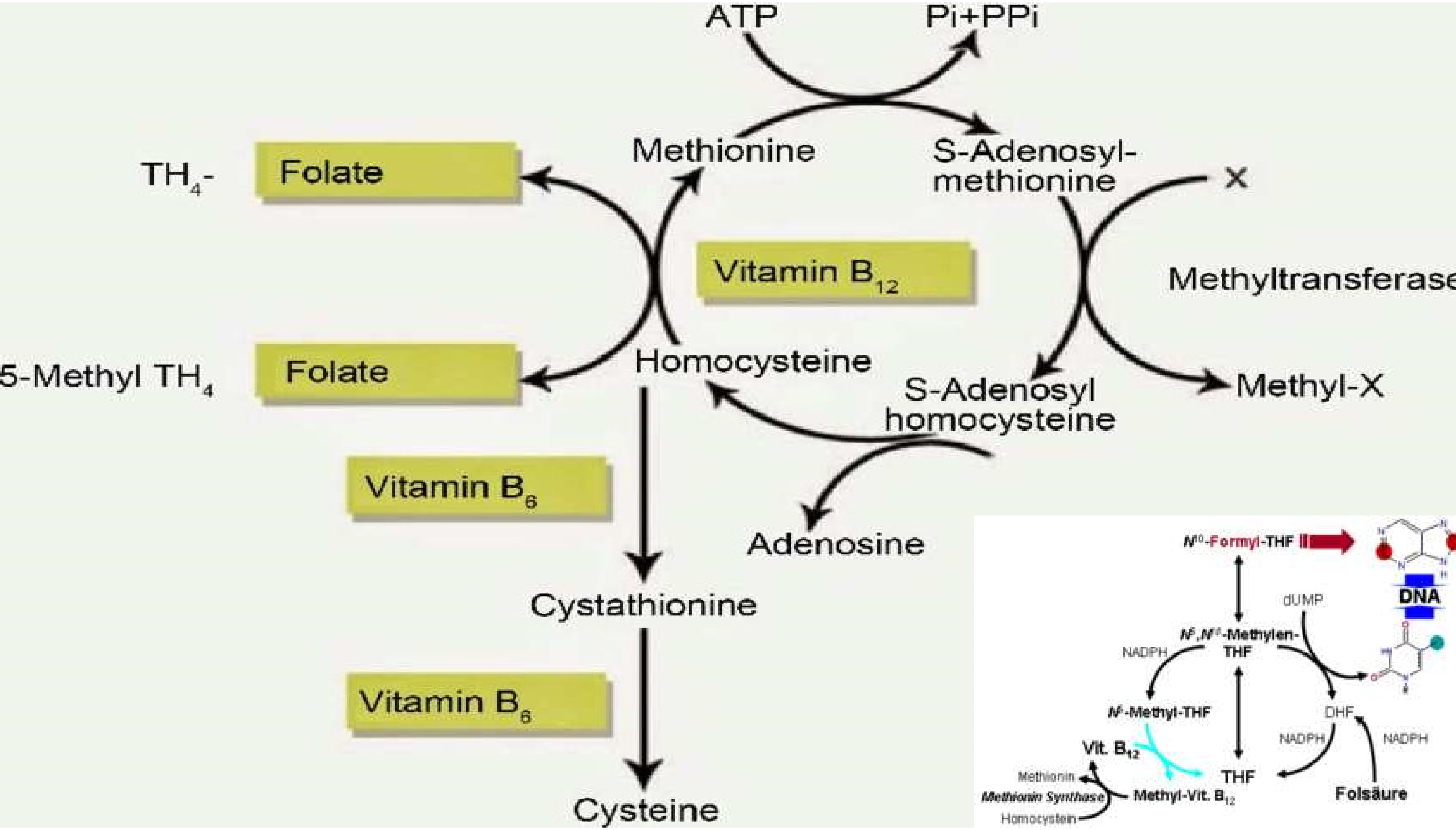
32 : 39

VITAMINS

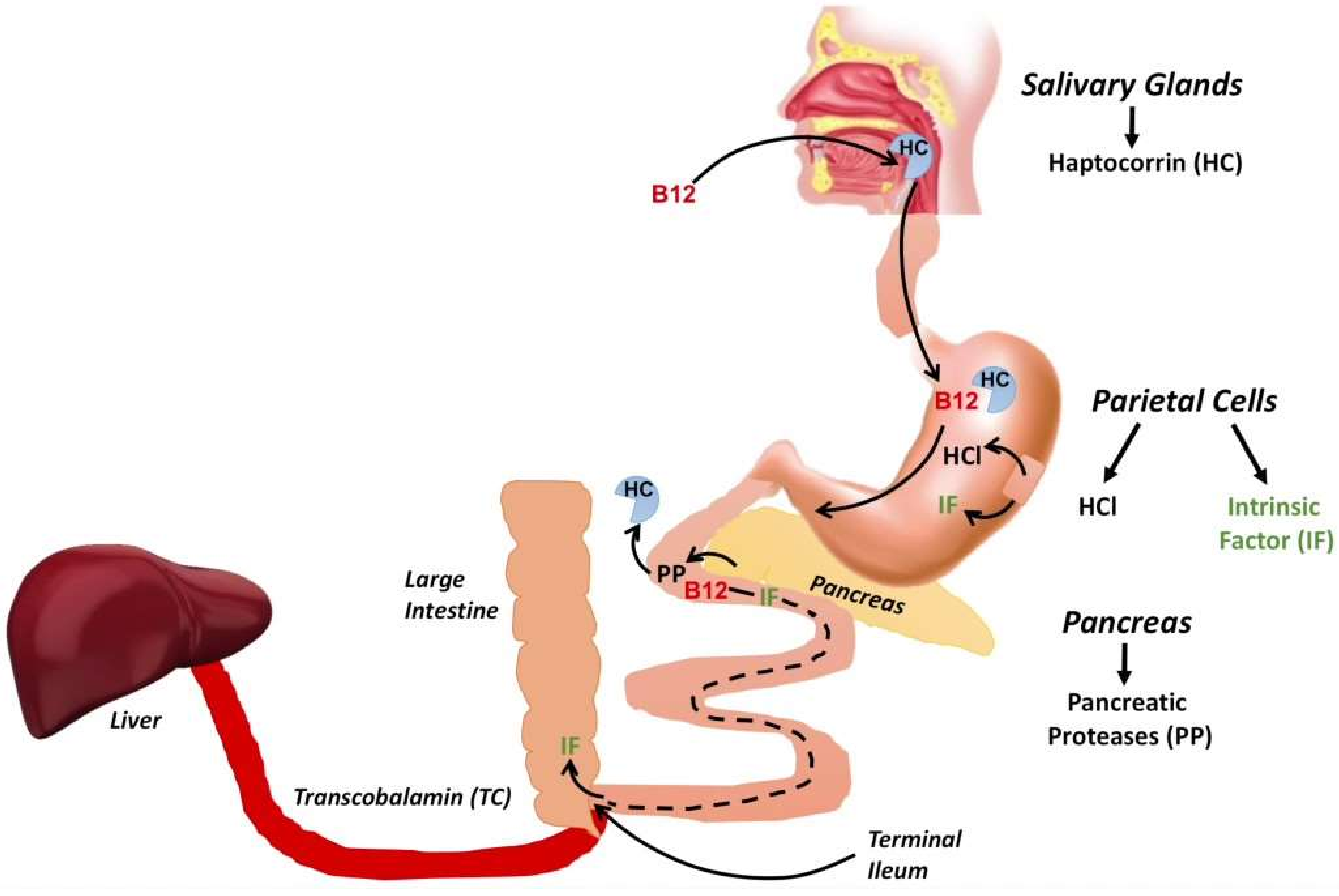
- B_{12}: Cyanocobalamine & Folic Acid:[dna formation]
  - Is also called Extrinsic Factor of Castle.
  - Needs the Intrinsic Factor from the Gastric juice for absorption from Small Intestine.
  - Deficiency causes Pernicious (When IF is missing) or Megaloblastic Anemia.
  - Stimulates Erythropoiesis
  - Is found in meat & diary products.

Iron functions

- **Oxygen carriers**
  - hemoglobin
- **Oxygen storage**
  - Myoglobin
- **Energy Production**
  - Cytochromes (oxidative phosphorylation)
  - Krebs cycle enzymes
- **Other**
  - Liver detoxification (cytochrome p450)



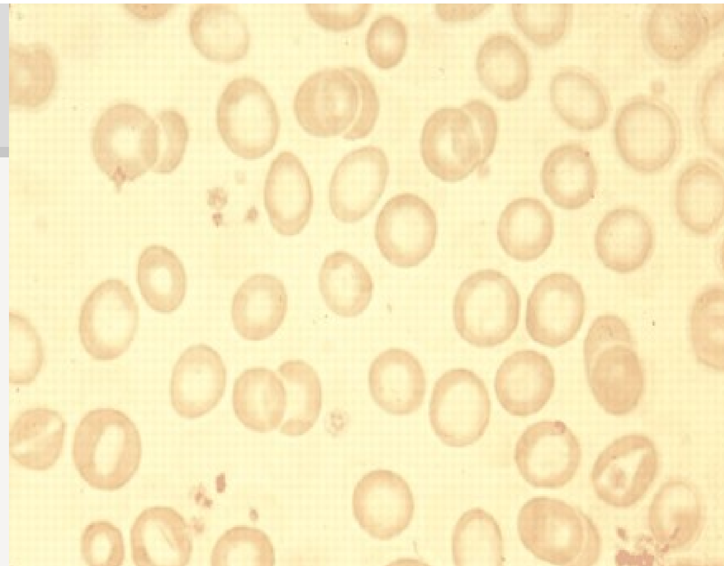
ATP
Pi+PPi
Methionine
S-Adenosyl-
methionine
X
TH_4-
Folate
Vitamin B_{12}
Methyltransferase
5-Methyl TH_4
Folate
Homocysteine
S-Adenosyl
homocysteine
Methyl-X
Vitamin B_6
Adenosine
Cystathionine
Vitamin B_6
Cysteine
N^{10}-Formyl-THF
DNA
dUMP
N^5,N^{10}-Methylen-
THF
NADPH
N^5-Methyl-THF
DHF
NADPH
NADPH
Vit. B_{12}
THF
Methionin
Methionin Synthase
Methyl-Vit. B_{12}
Folsäure
Homocystein

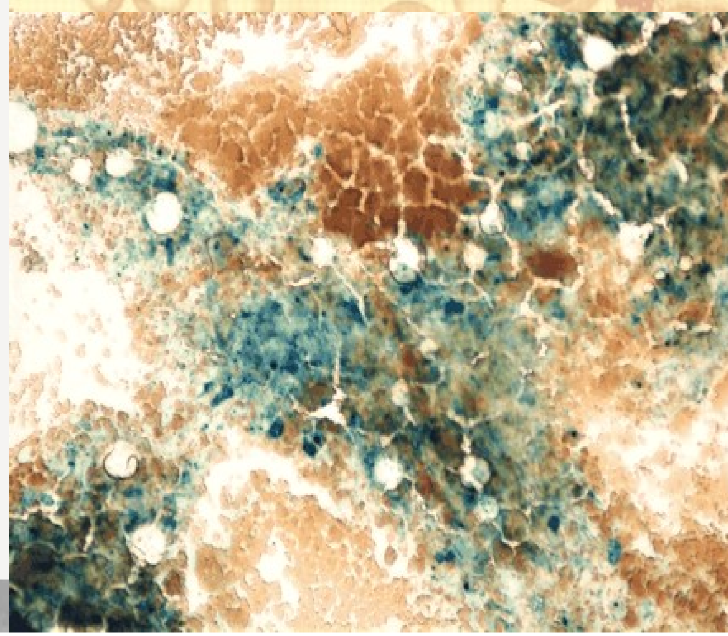


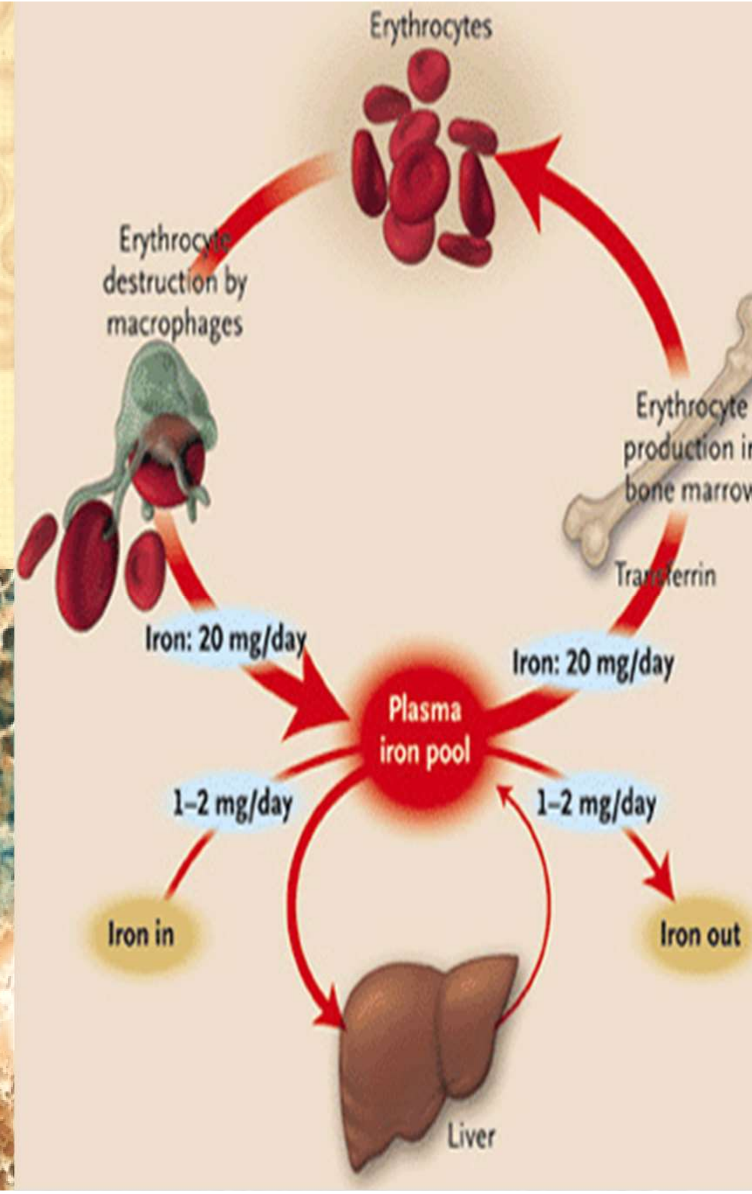
Salivary Glands
Haptocorrin (HC)
HC
B12
B12
HC
Parietal Cells
HCl
HCl
Intrinsic Factor (IF)
IF
HC
PP
B12
IF
Pancreas
Pancreas
Pancreatic Proteases (PP)
Large Intestine
Liver
IF
Transcobalamin (TC)
Terminal Ileum

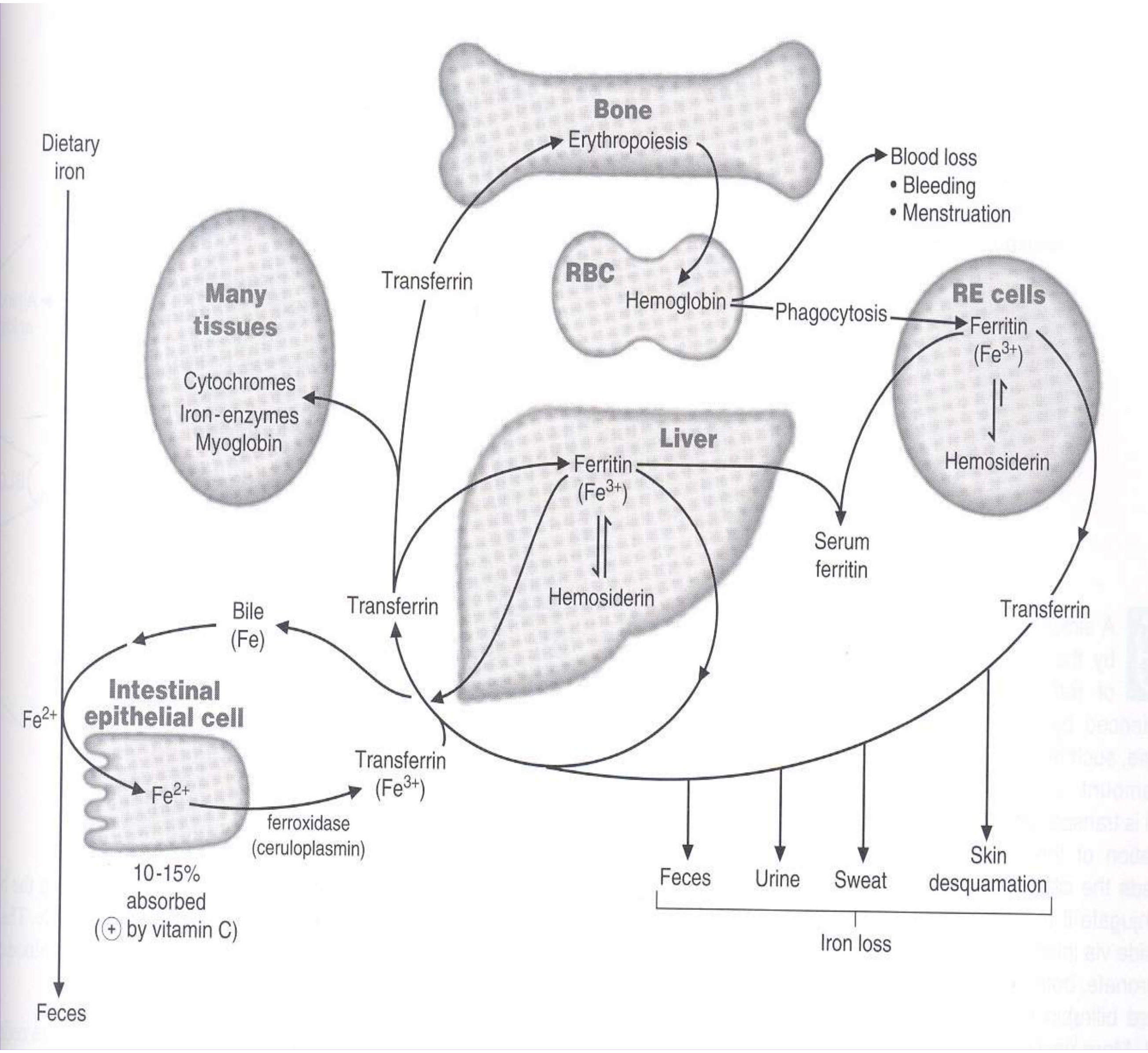
IRON

- **Essential for the synthesis of Hemoglobin.**
- **Deficiency causes Microcytic, Hypochromic Anemia.**
- **The MCV, Color Index & MCH are low.**





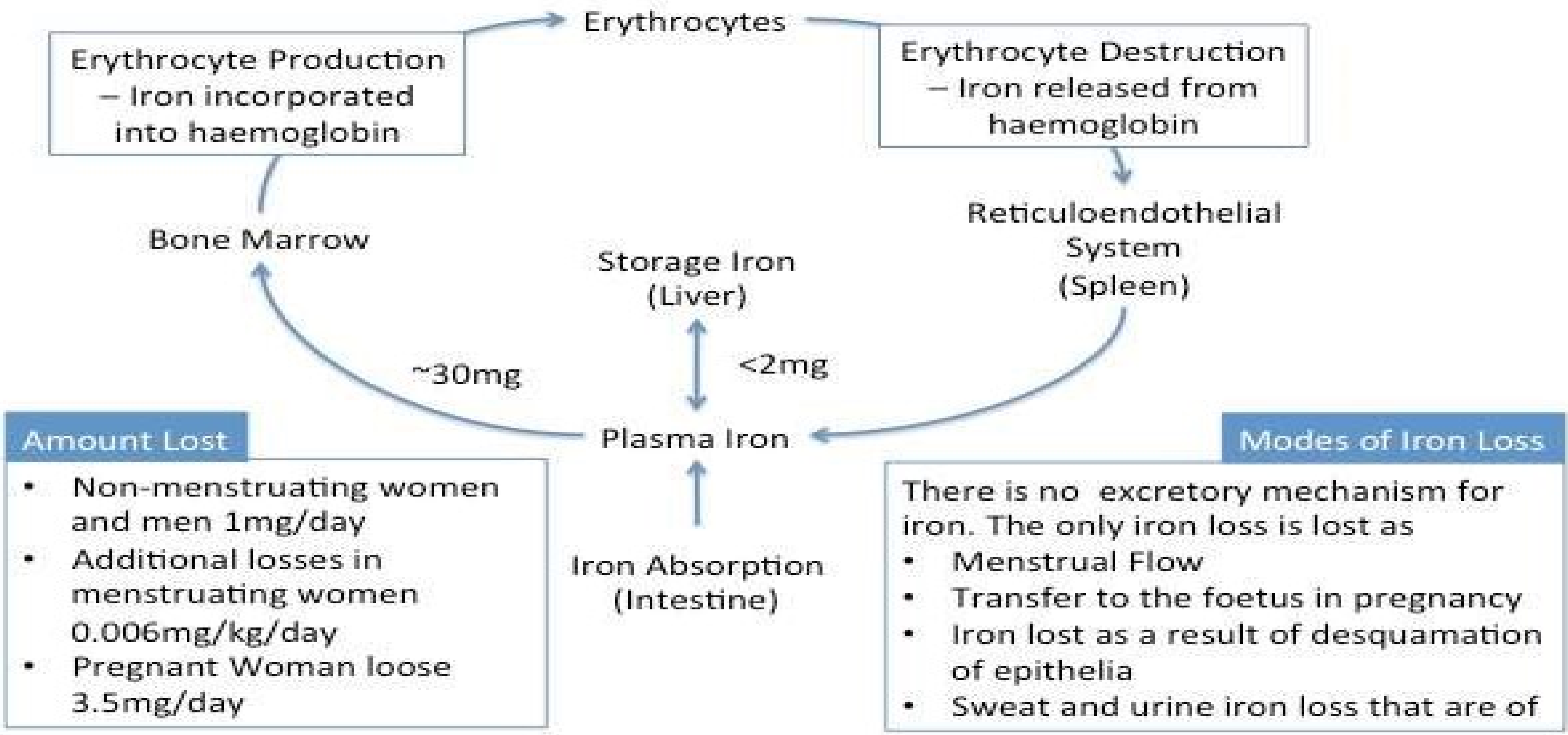


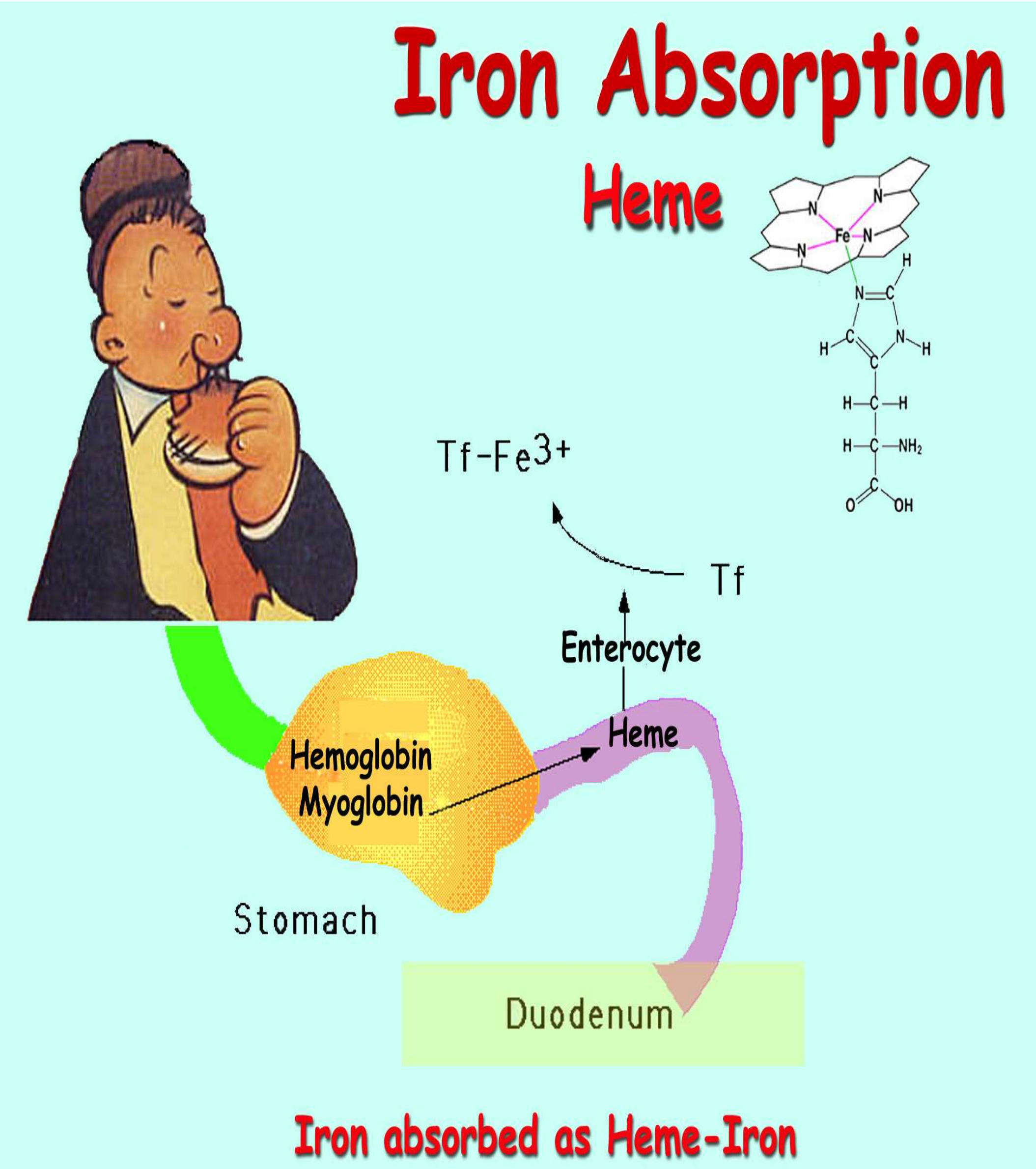


Iron Distribution

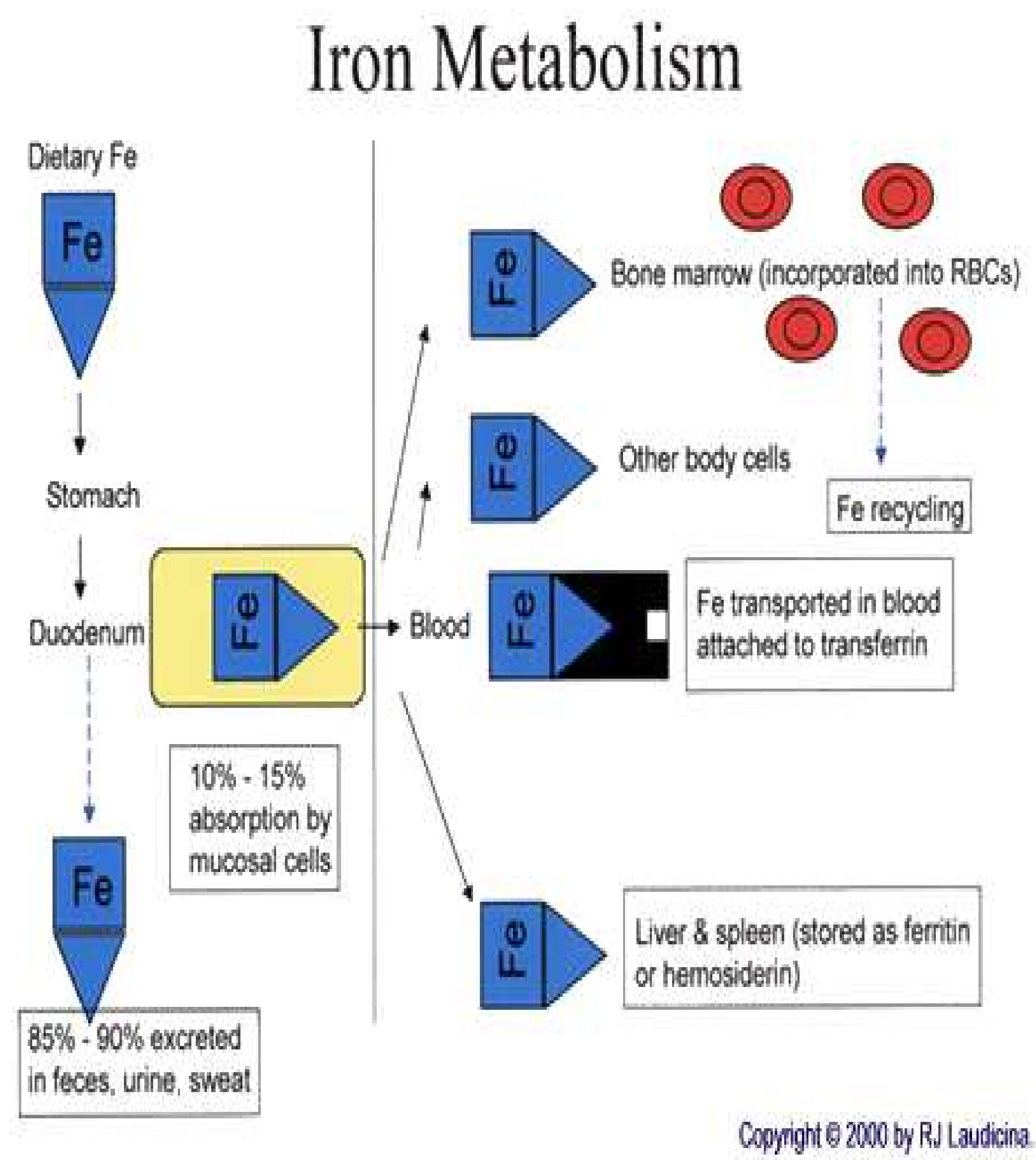
- **35 – 45 mg / kg iron in adult male body**
- **Total approx 4 g**
  - **Red cell mass as hemoglobin - 50%**
  - **Muscles as myoglobin – 7%**
  - **Storage as ferritin - 30%**
    - **Bone marrow (7%)**
    - **Reticulo-endothelial cells (7%)**
    - **Liver (25%)**
  - **Other Heme proteins - 5%**
    - **Cytochromes, myoglobin, others**
  - **In Serum - 0.1%**

The Iron Cycle





Iron Absorption
Heme
Fe
N
H
NH2
OH
Tf-Fe3+
Tf
Enterocyte
Heme
Hemoglobin
Myoglobin
Stomach
Duodenum
Iron absorbed as Heme-Iron



Iron Metabolism
Dietary Fe
Fe
Stomach
Duodenum
Blood
Bone marrow (incorporated into RBCs)
Other body cells
Fe recycling
Fe transported in blood attached to transferrin
10% - 15% absorption by mucosal cells
Liver & spleen (stored as ferritin or hemosiderin)
85% - 90% excreted in feces, urine, sweat
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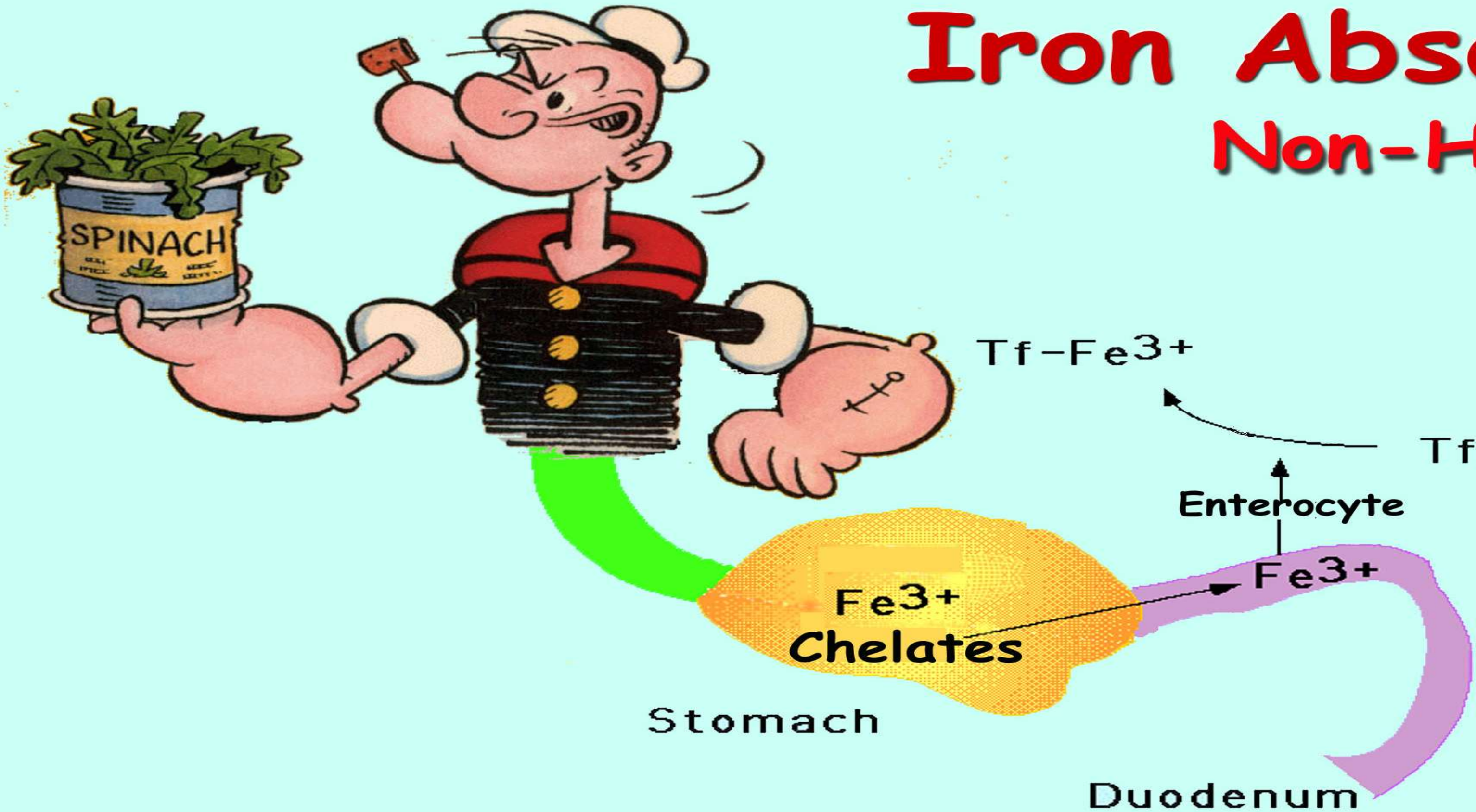
Iron Absorption

Non-Heme



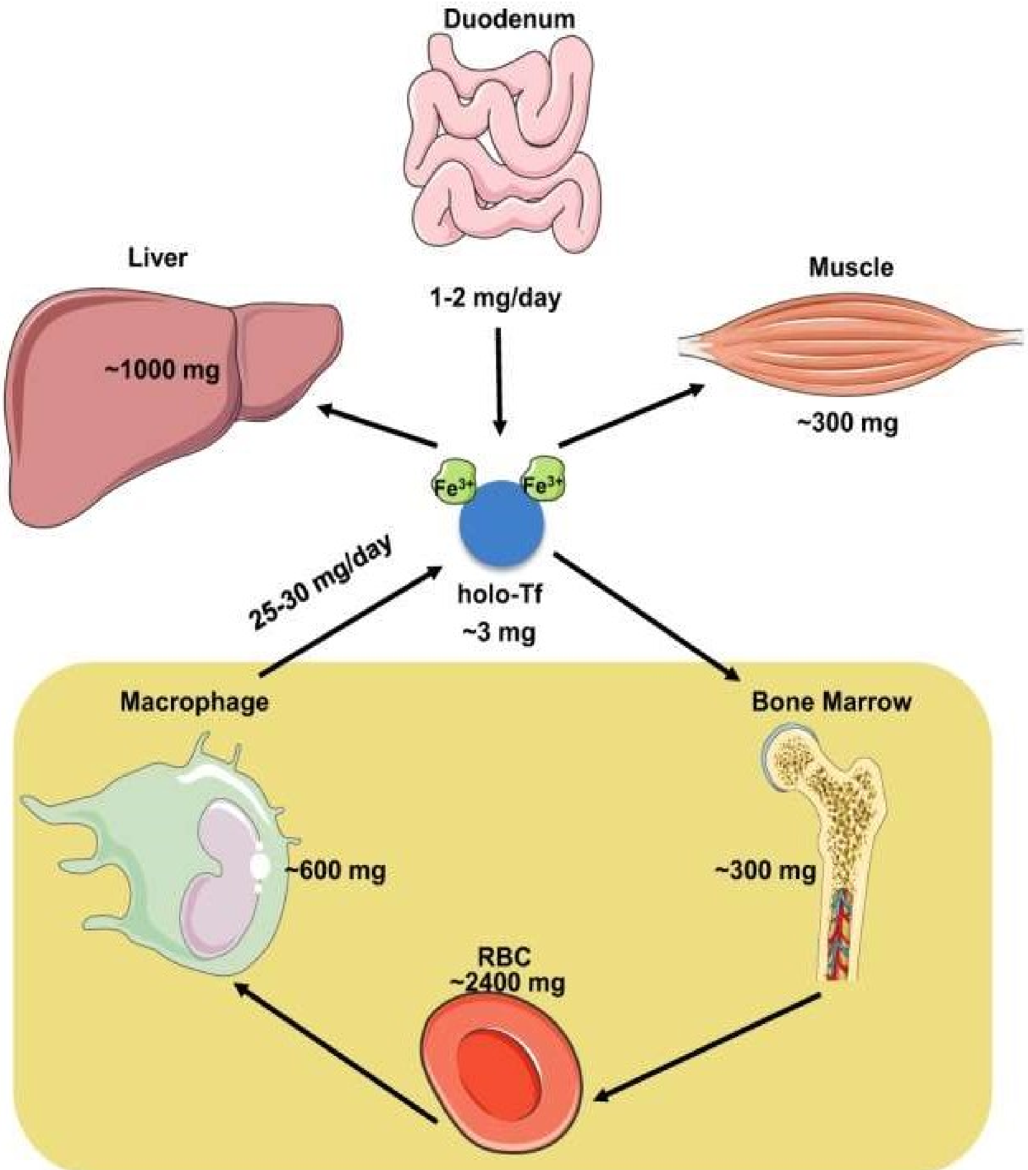
Factors That Influence Iron Absorption

Physical State (bioavailability): heme > Fe2+ > Fe3+

Inhibitors: phytates, tannins, soil clay, antacids, iron overload

Competitors: cobalt, lead, strontium, manganese, zinc

Facilitators: ascorbate, citrate, amino acids, iron deficiency



- Iron from hemoglobin transported by **transferrin** protein to liver
  - Bound to storage proteins: **ferritin, hemosiderin**
  - Most is bound to ferritin and stored in liver and spleen
  - Transported to red bone marrow as needed for erythrocyte production

Iron Transport in Blood

- Red cells
  - As hemoglobin
  - Cannot be exchanged
- Plasma
  - Bound to Transferrin
  - Carries iron between body locations
  - eg between gut, liver, bone marrow, macrophages
  - Iron taken up into cells by transferrin receptors

Transferrin

- Synthesised in the liver.
- Each molecule binds can bind two Fe^{3+} molecules (oxidised)
- Contains 95% of serum Fe.
- Usually about 30% saturated with Fe.
- Production decreased in iron overload.
- Production increased in iron deficiency.
- Measured in blood as a marker of iron status.

Transferrin Testing

- A routine blood test used for iron status
- Also known as TIBC (total iron binding capacity)
- *High levels*:
  - Low body iron stores.
- *Low levels:*
  - High body iron stores.
- *Other conditions*
  - Increase: high oestrogen states (pregnancy, OCP)
  - Decrease: malnutrition, chronic liver disease, chronic disease (eg malignancy), protein-losing states, congenital deficiency, neonates, acute phase (negative reactant).

Dietary Requirements of Erythropoiesis

- **Erythropoiesis requires:**
  - Proteins, lipids, and carbohydrates
  - Iron, vitamin B_{12}, and folic acid

- The body stores iron in Hb (65%), **the liver, spleen, and bone marrow**

- Intracellular iron is stored in protein-iron complexes such as **ferritin and hemosiderin**

- Circulating iron is loosely bound to the transport protein transferrin

Regulation of Erythropoiesis

Stimulates

ERYTHROPOIETIN

Decreases

CFU - E

Proerythroblasts

Mature Erythrocytes

Tissue Oxygenation

Factors decreasing:

- Hypovolemia
  - » Anemia
- Poor blood flow
- Pulmonary Disease

An example of a Negative feed back mechanism

Fate and Destruction of Erythrocytes

- **The life span** of an erythrocyte is **100–120 days**
- Old RBCs become rigid and fragile, and their Hb begins to degenerate
- Dying RBCs are engulfed by macrophages
- Heme and globin are separated and the iron is salvaged for reuse
- Heme is degraded to a yellow pigment called ***bilirubin***
- The **liver secretes bilirubin into the intestines as bile**
- The intestines metabolize it into urobilinogen
- This degraded pigment leaves the body in feces, in a pigment called stercobilin

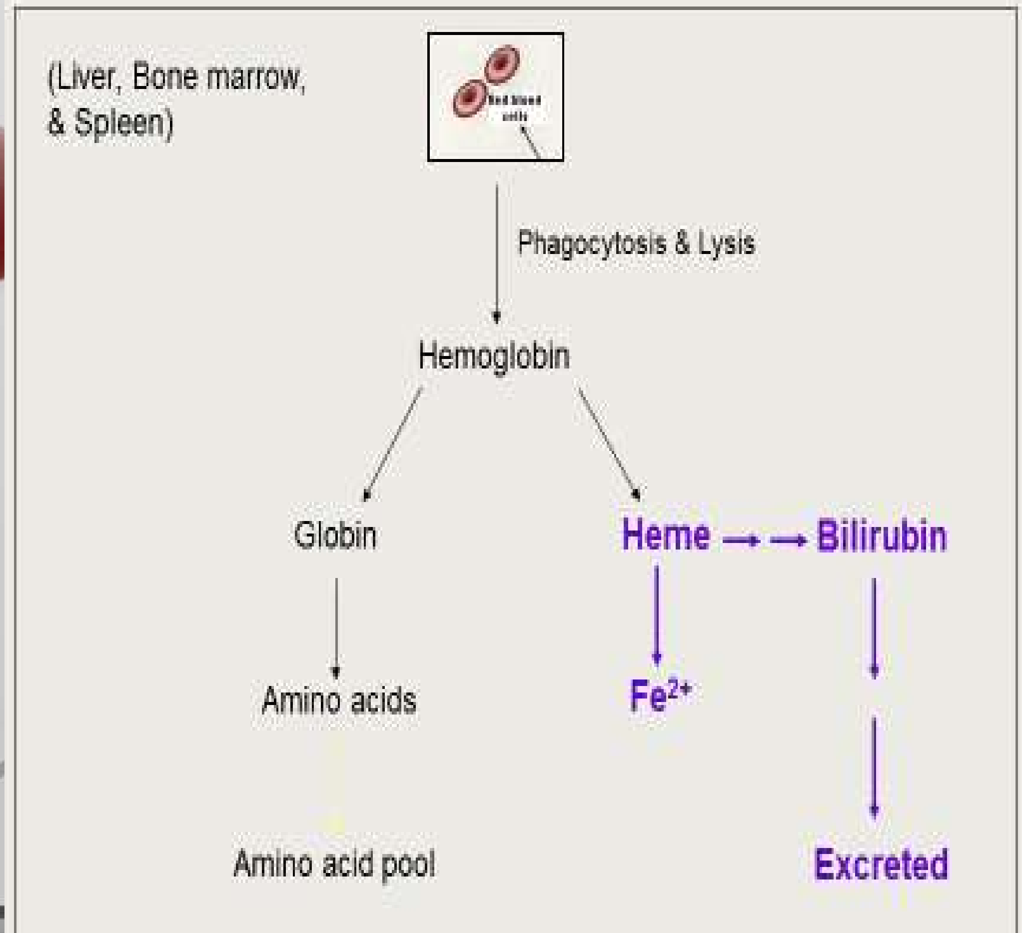
- 75% is derived from RBCs

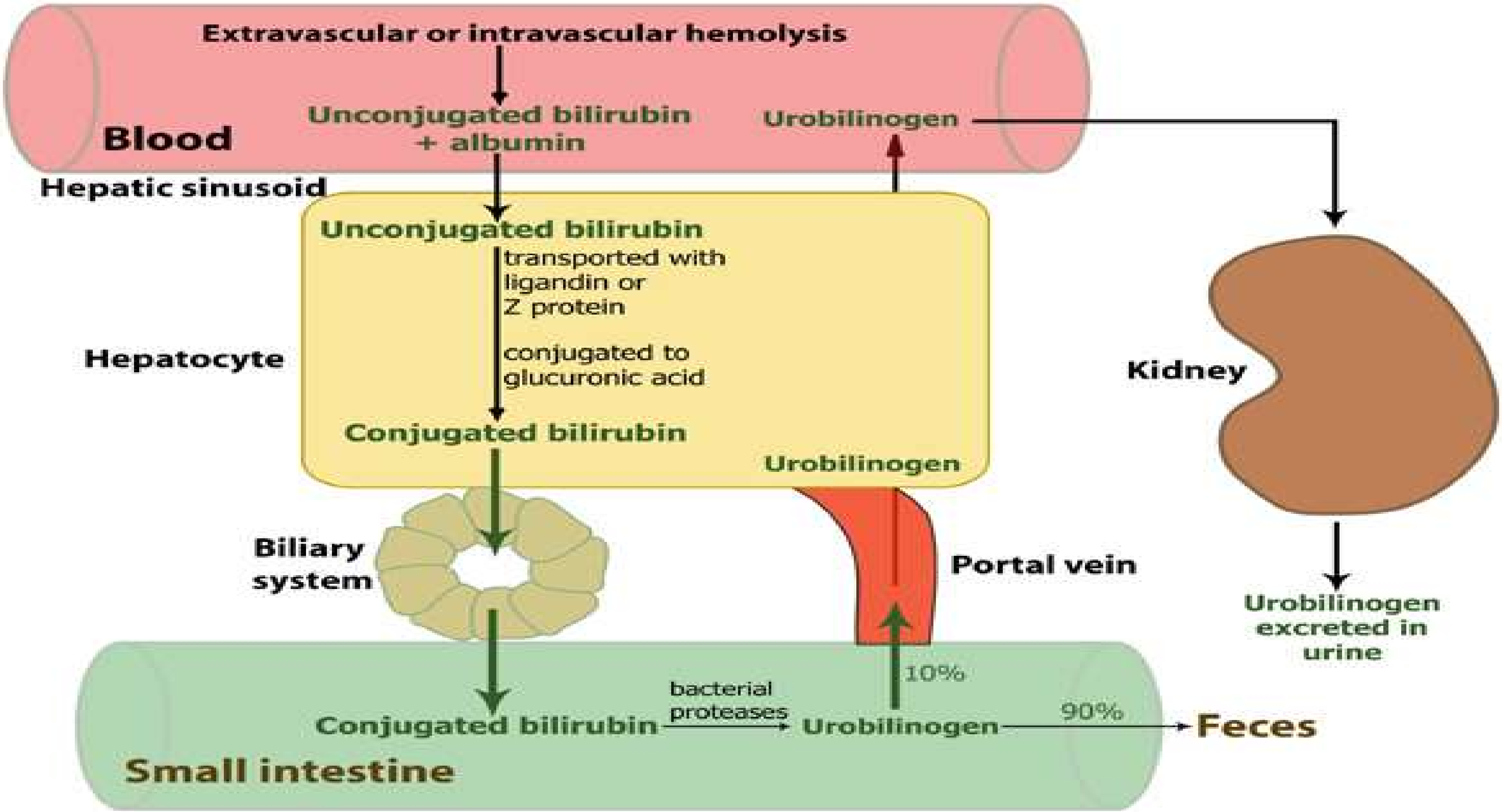
- In normal adults this results in a daily load of 250-300 mg of bilirubin

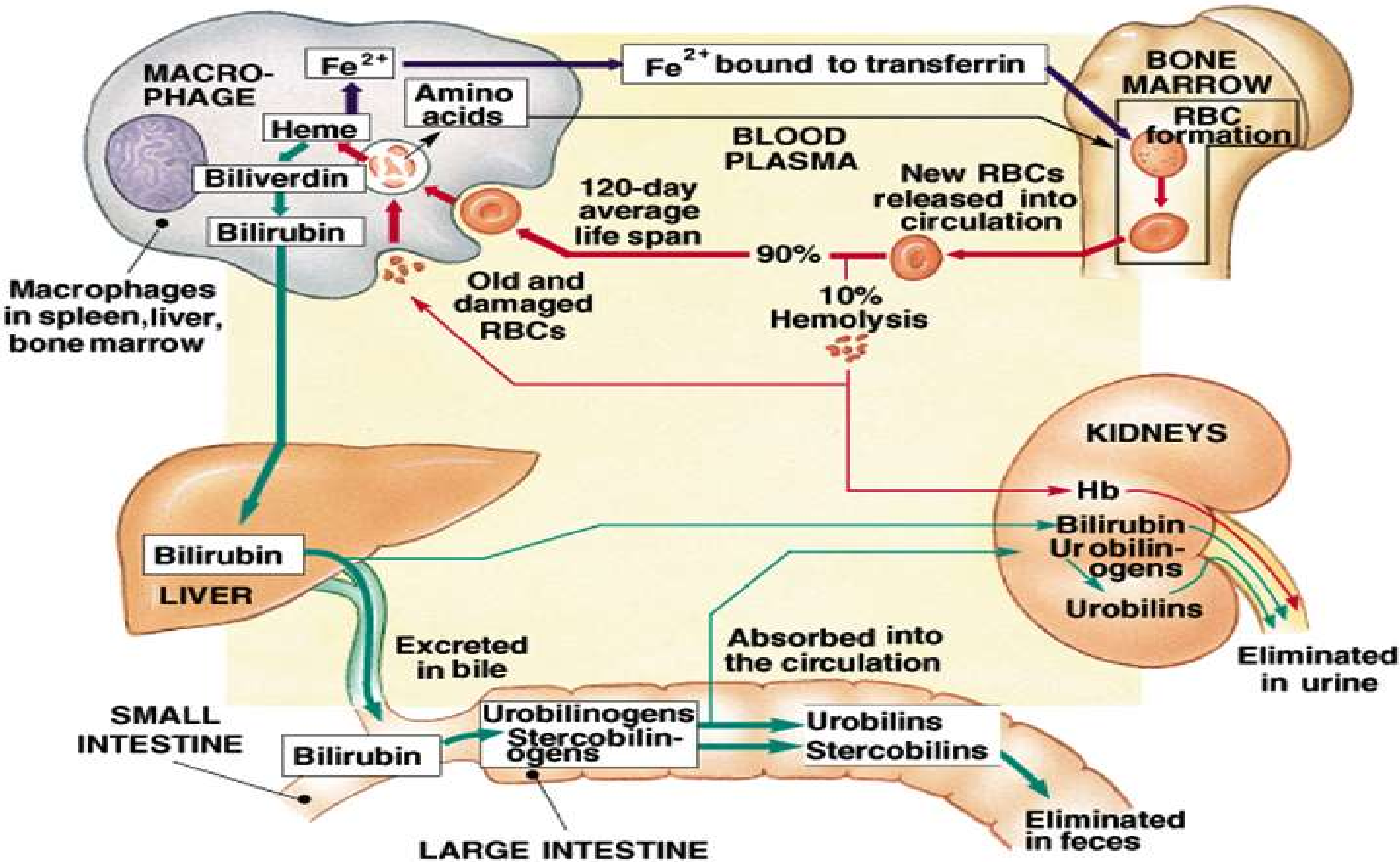
- Normal plasma concentrations are less then 1 mg/dL

- Hydrophobic – transported by albumin to the liver for further metabolism prior to its excretion

Extravascular Pathway for RBC Destruction




Extravascular or intravascular hemolysis
Unconjugated bilirubin + albumin
Urobilinogen
Blood
Hepatic sinusoid
Unconjugated bilirubin
transported with ligandin or Z protein
conjugated to glucuronic acid
Hepatocyte
Conjugated bilirubin
Urobilinogen
Kidney
Biliary system
Portal vein
Urobilinogen excreted in urine
10%
bacterial proteases
90%
Conjugated bilirubin
Urobilinogen
Feces
Small intestine



MACRO-PHAGE
Fe^{2+}
Fe^{2+} bound to transferrin
BONE MARROW
RBC formation
Amino acids
Heme
Biliverdin
Bilirubin
BLOOD PLASMA
New RBCs released into circulation
120-day average life span
90%
10% Hemolysis
Old and damaged RBCs
Macrophages in spleen, liver, bone marrow
KIDNEYS
Hb
Bilirubin
Urobilinogens
Urobilins
Eliminated in urine
Bilirubin
LIVER
Excreted in bile
Absorbed into the circulation
SMALL INTESTINE
Bilirubin
Urobilinogens
Stercobilinogens
Urobilins
Stercobilins
Eliminated in feces
LARGE INTESTINE

Handling of Free (Intravascular) Hemoglobin

Purposes:

1. Scavenge iron
2. Prevent major iron losses
3. Complex free heme (very toxic)

- Haptoglobin: hemoglobin-haptoglobin complex is readily metabolized in the liver and spleen forming an iron-globin complex and bilirubin. Prevents loss of iron in urine.
- Hemopexin: binds free heme. The heme-hemopexin complex is taken up by the liver and the iron is stored bound to ferritin.
- Methemalbumin: complex of oxidized heme and albumin.

Clinical View: Blood Doping

Used by some athletes to enhance performance

One method, self donation of erythrocytes

- Blood removal prior to competition increases EPO production
- Erythrocytes transfused back prior to competition

Second method: pharmaceutical EPO

Dangers

- ***Increased blood viscosity***
- ***Heart required to work harder***
- ***May cause permanent cardiovascular damage***
- ***Banned from athletic competition***

Clinical View: Anemia

Either the percentage of erythrocytes is lower than normal or the oxygen-carrying capacity is reduced

- Symptoms: lethargy, shortness of breath, pallor, palpitations
- Types:
  - **Aplastic anemia** – defective red marrow due to poisons, toxins, radiation
  - **Congenital hemolytic anemia** – genetic defect; erythrocytes destroyed
  - **Erythroblastic anemia** – large numbers of immature cells due to abnormal accelerated cell maturation
  - **Hemorrhagic anemia** – due to blood loss
  - **Pernicious anemia** – failure to absorb vitamin B12 due to lack of intrinsic factor
  - **Sickle-cell disease** – genetic defect; abnormal hemoglobin
- Some cases can be treated by pharmaceutical EPO

Development and Aging of Blood₂

Aging and blood

- Older red bone marrow replaced with fat as individuals age
- Older individuals more likely to become anemic
- May produce fewer and less active leukocytes
- Certain types of leukemia more prevalent in elderly

Role of Metabolic Pathways

Pathway	Enzymes	Role	Problems
EMP Embden–Meyerhof–Parnas most common type of glycolysis	**Phosphofructokinase** **Pyruvate kinase (PK)**	**Produce ATP** **RBC Shape (ion pumps)**	**Hemolytic Anemia** **PK Deficiency**
HMS **hexose monophosphate shunt** **metabolic pathway parallel to glycolysis**	**Glutathione Reductase** **G6PD**	**NADPH Production** **OXY-METH HB Balance**	**Hemolytic Anemias**
RLB	**DPG Synthetase**	**2,3-DPG Production** **HB Oxygen Affinity**	**Hypoxia**
MHBR Methemoglobin Reductase	**Methemoglobin reductase**	**Protects HB from Oxidation via NADH**	**Hemolytic Anemia** **Hypoxia**