Hematology Physiology

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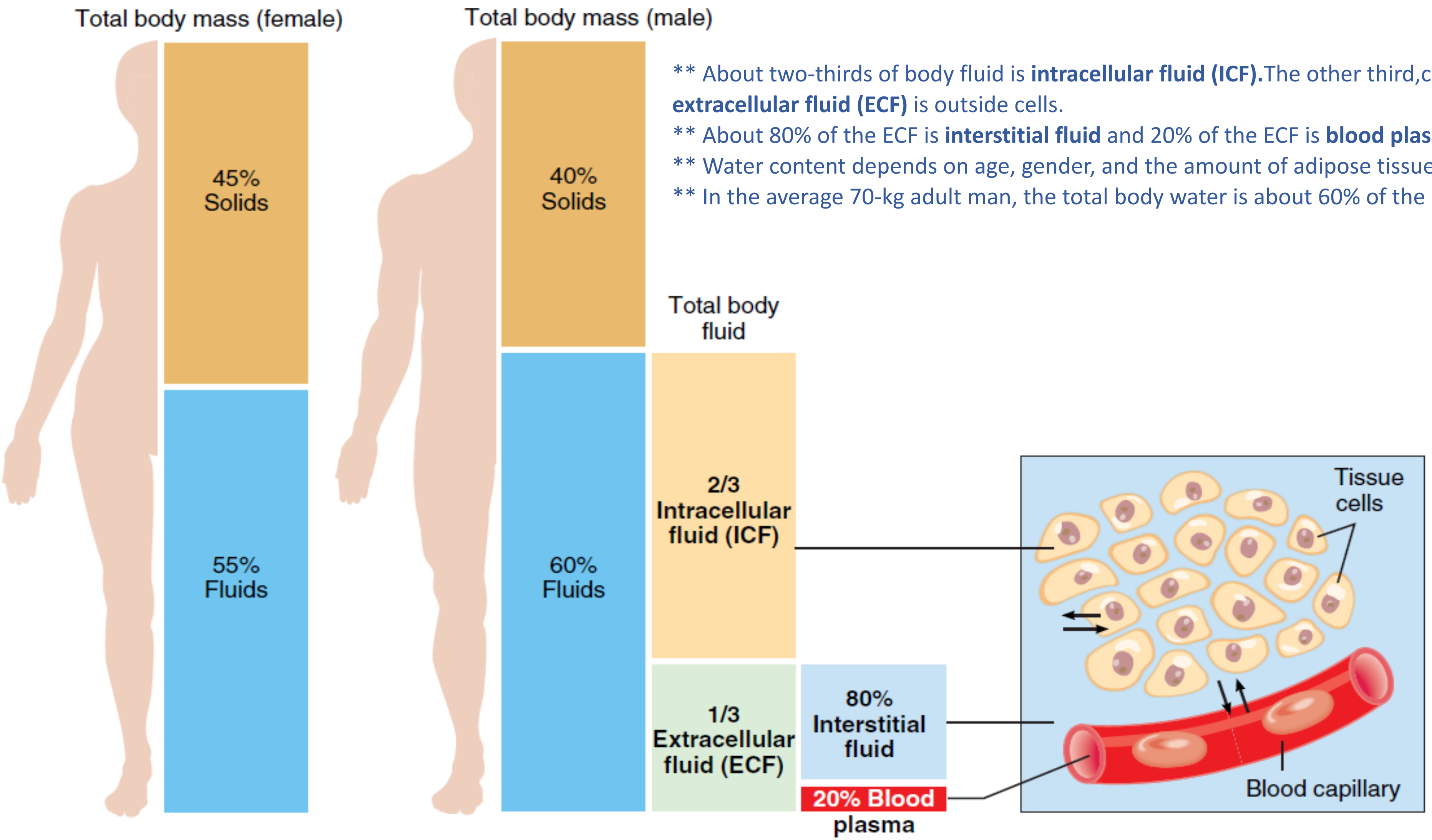
Reference books:

1. Hall, John, E. and Michael E. Hall. Guyton and Hall Textbook of Medical Physiology (14th Edition).
2. Lauralee Sherwood. Human Physiology: From Cells To Systems (9th Edition).
3. Gerard J. Tortora and Bryan Derrickson. Principles Of Human Anatomy & Physiology (15th Edition)

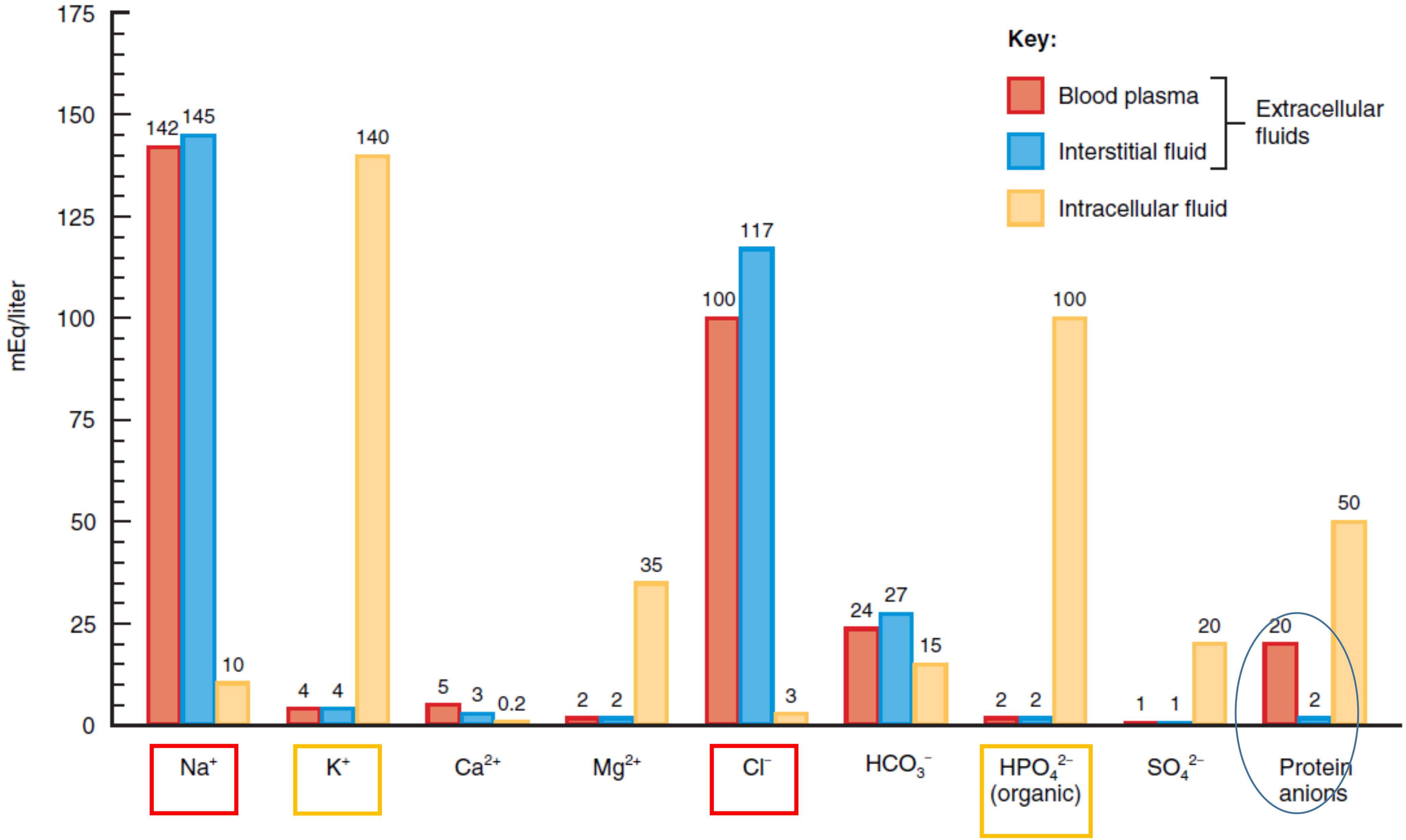
Doctors Notes are either in blue color or have a blue Background



(a) Distribution of body solids and fluids in average lean adult female and male

** About two-thirds of body fluid is **intracellular fluid (ICF).** The other third,called **extracellular fluid (ECF)** is outside cells.
** About 80% of the ECF is **interstitial fluid** and 20% of the ECF is **blood plasma**.
** Water content depends on age, gender, and the amount of adipose tissue present in the body.
** In the average 70-kg adult man, the total body water is about 60% of the body weight (42 L).

Hematology | Body Fluids



**In extracellular fluid, the most abundant cation is Na^+, and the most abundant anion is Cl^-.
**In intracellular fluid, the most abundant cation is K^+, and the most abundant anions are proteins and phosphates.
** By actively transporting Na^+ out of cells and K^+ into cells, sodium–potassium pumps (Na^+–K^+ ATPases) play a major role in maintaining the high intracellular concentration of K^+ and high extracellular concentration of Na^+.
** The chief difference between the two extracellular fluids—blood plasma and interstitial fluid—is that blood plasma contains many protein anions, in contrast to interstitial fluid, which has very few. Because normal capillary membranes are virtually impermeable to proteins, only a few plasma proteins leak out of blood vessels into the interstitial fluid.
This difference in protein concentration is largely responsible for the blood colloid osmotic pressure exerted by blood plasma

Hematology | Body Fluids

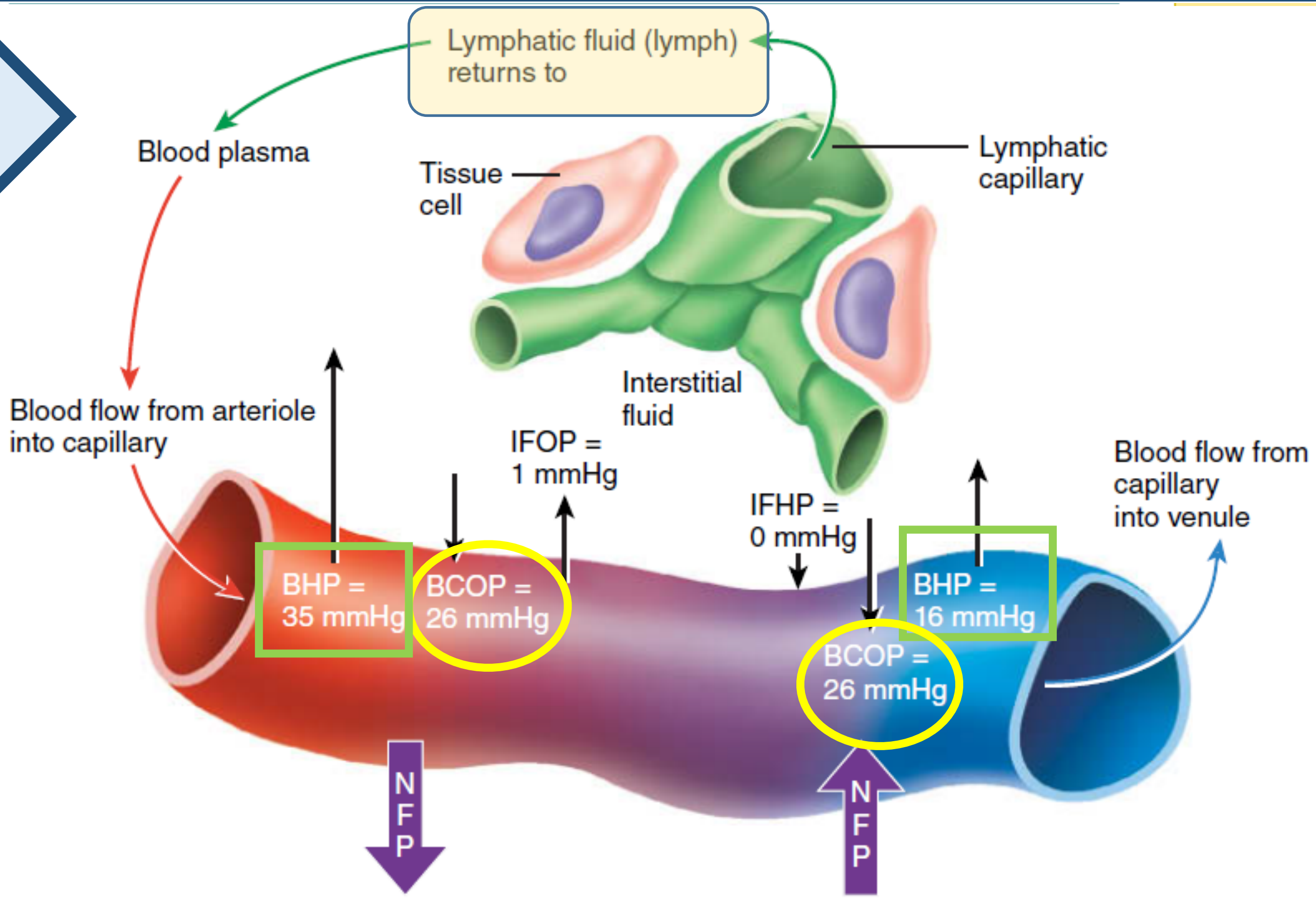
Key:

BHP = Blood hydrostatic pressure
IFHP = Interstitial fluid hydrostatic pressure
BCOP = Blood colloid osmotic pressure
IFOP = Interstitial fluid osmotic pressure
NFP = Net filtration pressure

Blood hydrostatic pressure pushes fluid out of capillaries (filtration)

Blood colloid osmotic pressure pulls fluid into capillaries (reabsorption)

**The processes of filtration, reabsorption, diffusion, and osmosis allow continual exchange of water and solutes among body fluid compartments . Yet the volume of fluid in each compartment remains remarkably stable.



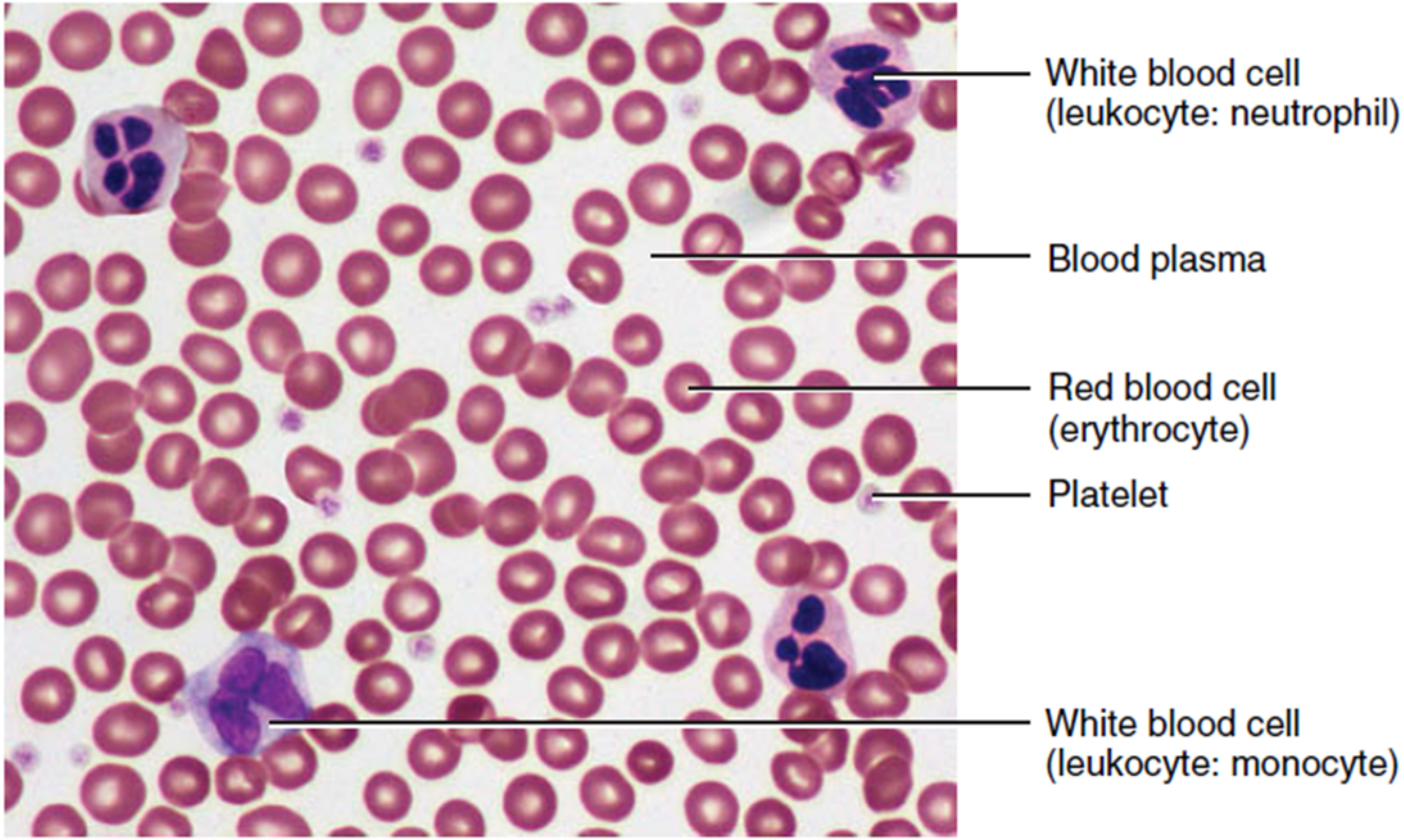
Net filtration pressure (NFP) = (BHP + IFOP) − (BCOP + IFHP)

Pressures promoting filtration | Pressures promoting reabsorption

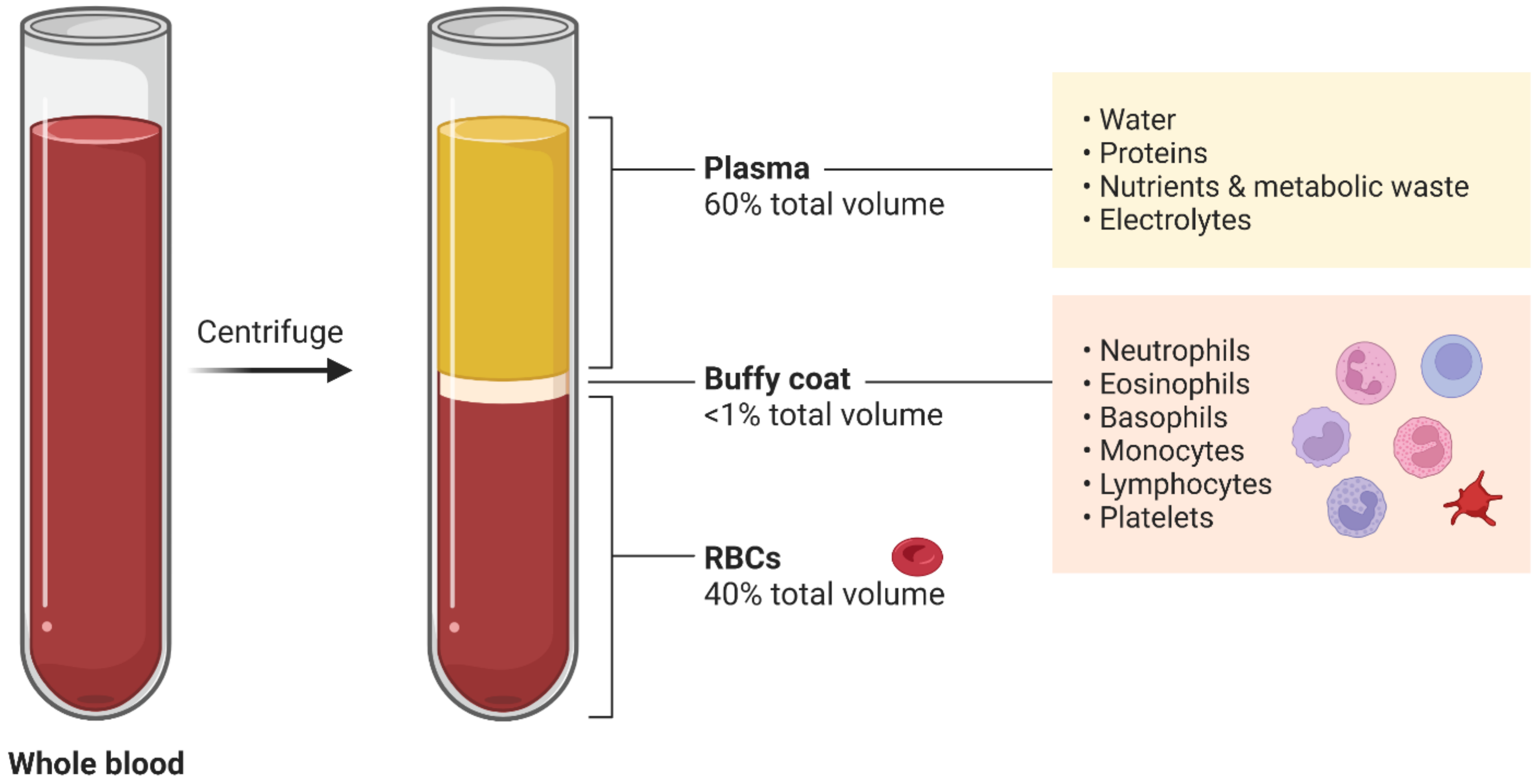
	Arterial end	Venous end
	NFP = (35 + 1) – (26 + 0) = 10 mmHg	**NFP** = (16 + 1) – (26 + 0) = –9 mmHg
Result	Net filtration	Net reabsorption

- **The average blood volume of adults is about 7% of body weight, or about 5 liters.**
- **Blood is connective tissue.**
- **Blood is denser and more viscous (thicker) than water.**
- **The temperature of blood is 38°C.**
- **Slightly alkaline pH ranging from 7.35 to 7.45 (average = 7.4).**
- **The color saturated (O_2)→ bright red**

  unsaturated (O_2) → dark red


White blood cell
(leukocyte: neutrophil)
Blood plasma
Red blood cell
(erythrocyte)
Platelet
White blood cell
(leukocyte: monocyte)

Hematology | Blood and its components



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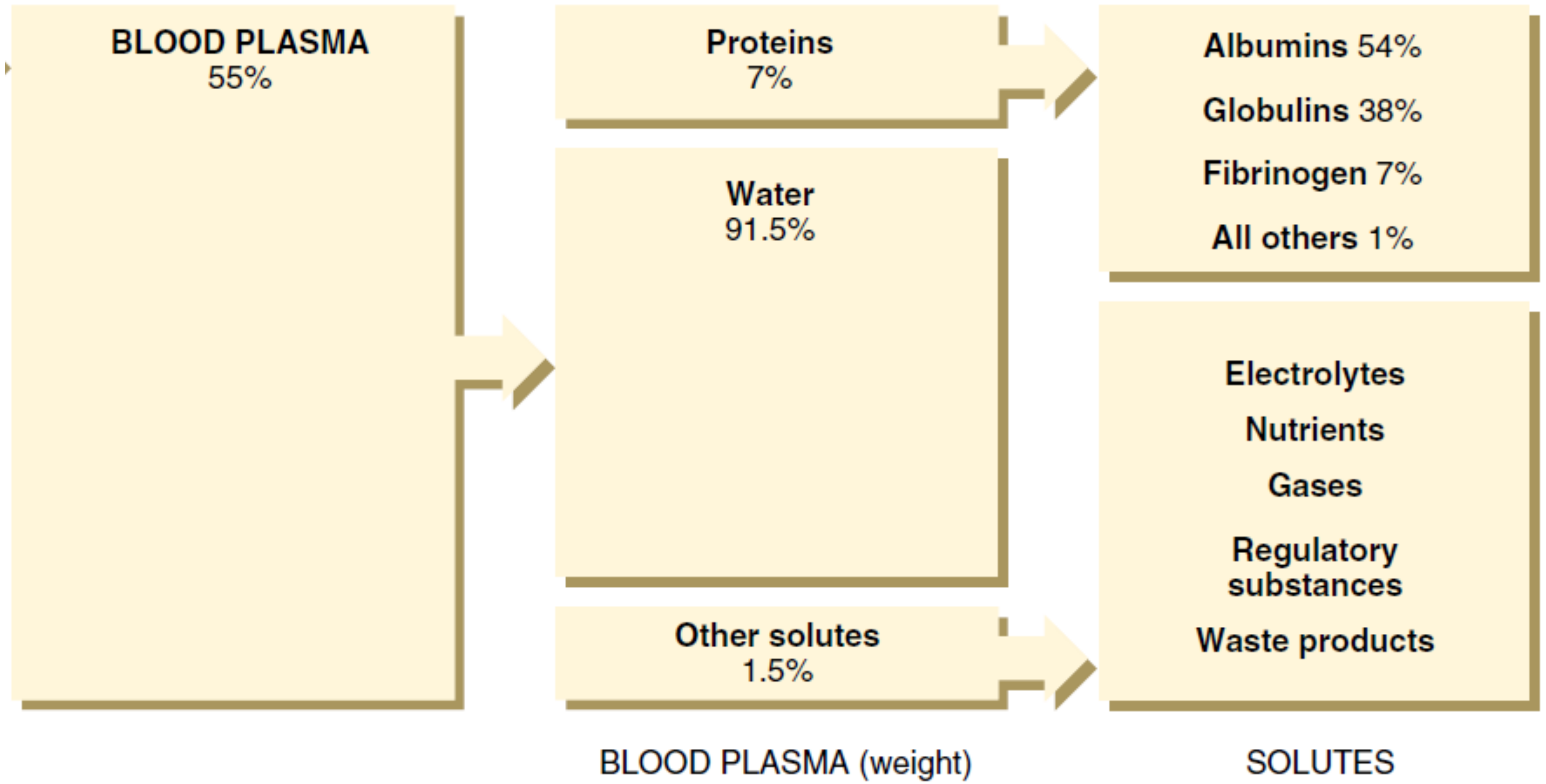

BLOOD PLASMA
55%
Proteins
7%
Water
91.5%
Other solutes
1.5%
Albumins 54%
Globulins 38%
Fibrinogen 7%
All others 1%
Electrolytes
Nutrients
Gases
Regulatory substances
Waste products
BLOOD PLASMA (weight)
SOLUTES

1. Establishment of colloid osmotic pressure.
2. Responsible for plasma's capacity buffer changes in pH.

Albumin

Nonspecifically binds substances that are poorly soluble in plasma (bilirubin)

Fibrinogen

Is an inactive precursor for a clot's fibrin meshwork

Globulins

α & β

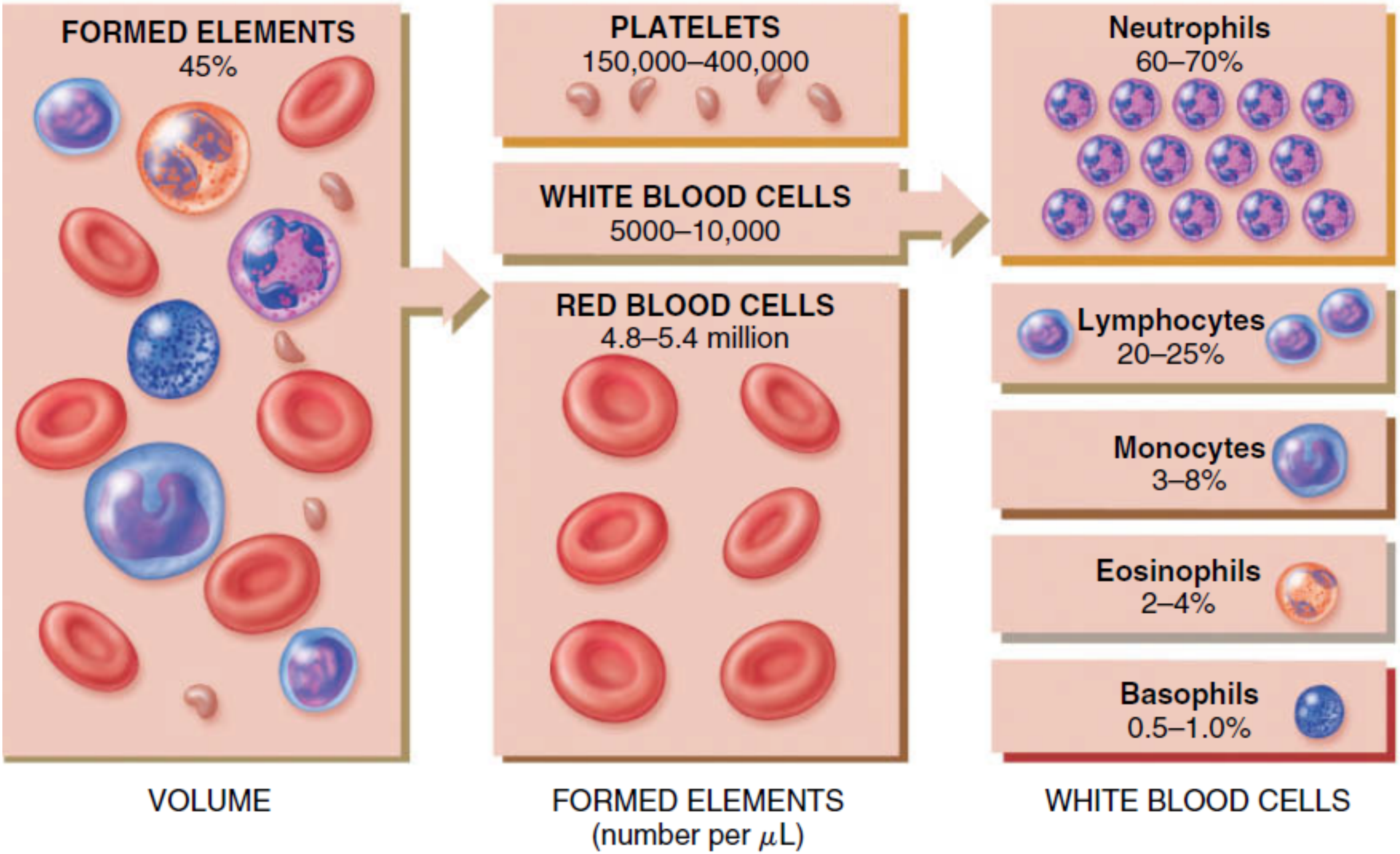
- Specifically bind poorly water-soluble substances (thyroid hormone, cholesterol, and iron).
- Involved in blood-clotting.
- Angiotensinogen.

γ

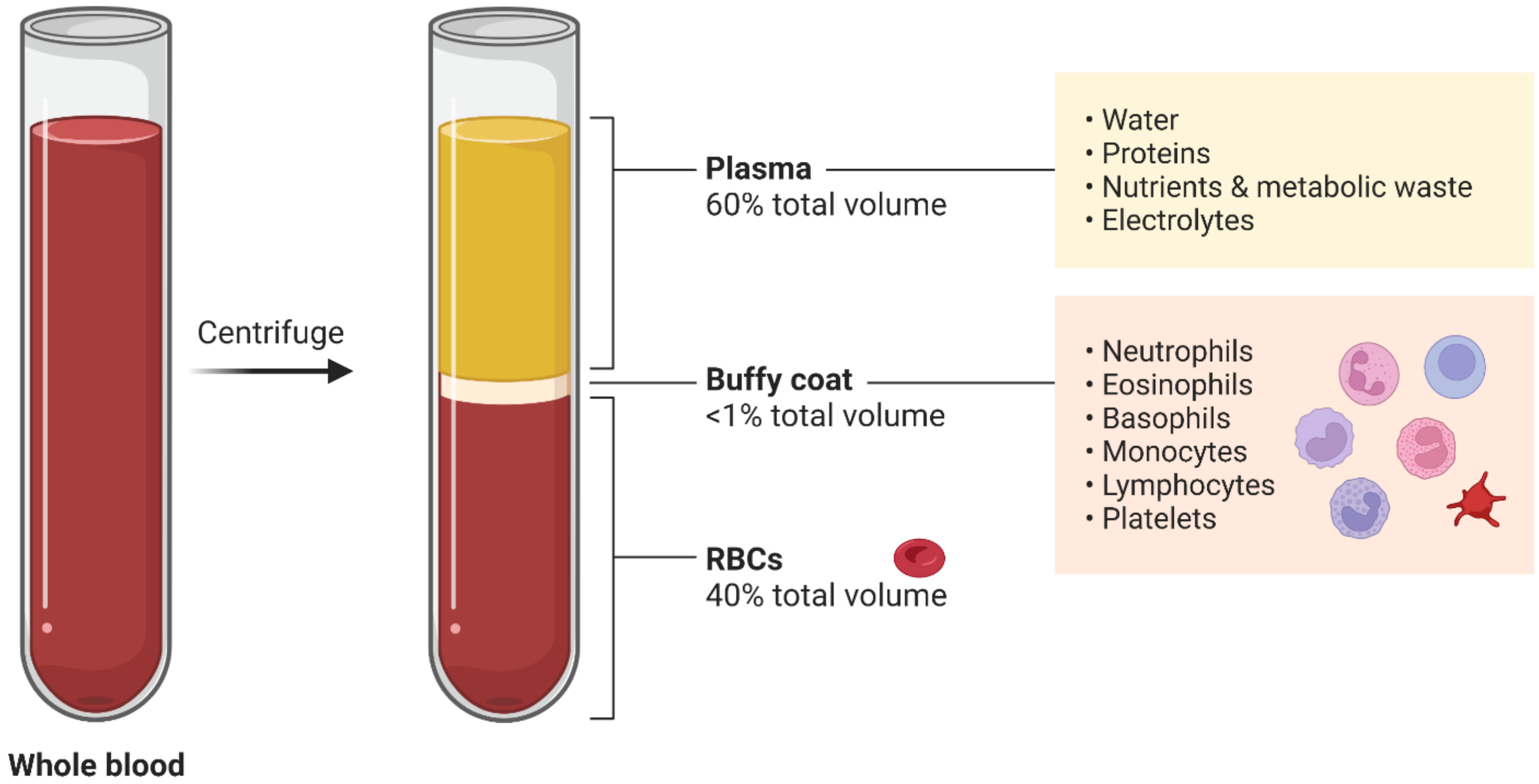
Antibodies/ immunoglobulins.
Body's defense mechanism.

Plasma proteins are synthesized by the liver, with the exception of antibodies, which are produced by lymphocytes, one of the types of white blood cells.

Hematology — Blood and its components



Hematology | Packed Red Cell Volume



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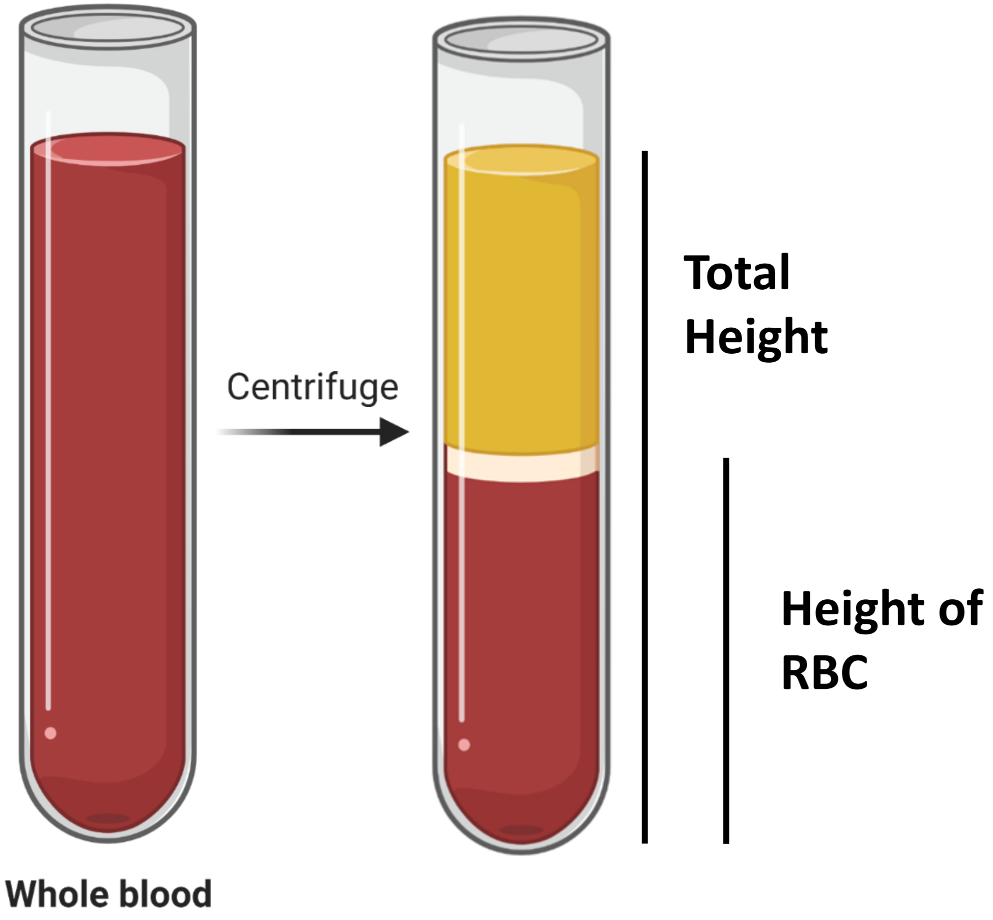
Hematology | Hematocrit

- Hematocrit/ Packed Red Cell Volume
- Adult males: 40–54% (avg = 47%).
- Adult females: 38–46% (avg = 42%)

$$\text{Hematocrit} = \frac{\text{Height of RBCs}}{\text{Total height}} \times 100\%$$

Concentration!!



Hematology › Hematocrit

**The hematocrit is the fraction of the blood composed of red blood cells, as determined by centrifuging blood in a "hematocrit tube" until the cells become tightly packed in the bottom of the tube.
**The hormone testosterone stimulates synthesis of erythropoietin that in turn stimulates production of RBCs.
** Lower values in women during their reproductive years also may be due to excessive loss of blood during menstruation
**Expansion of plasma volume in a pregnant woman reduces the hematocrit, whereas her total red cell volume also increases but less than plasma volume.
** Higher in dehydration.
** HCT values are slightly less than PCV because there is no trapped plasma in an automated hematocrit calculation, as can occur with spun, packed cell values.

Polycythemia

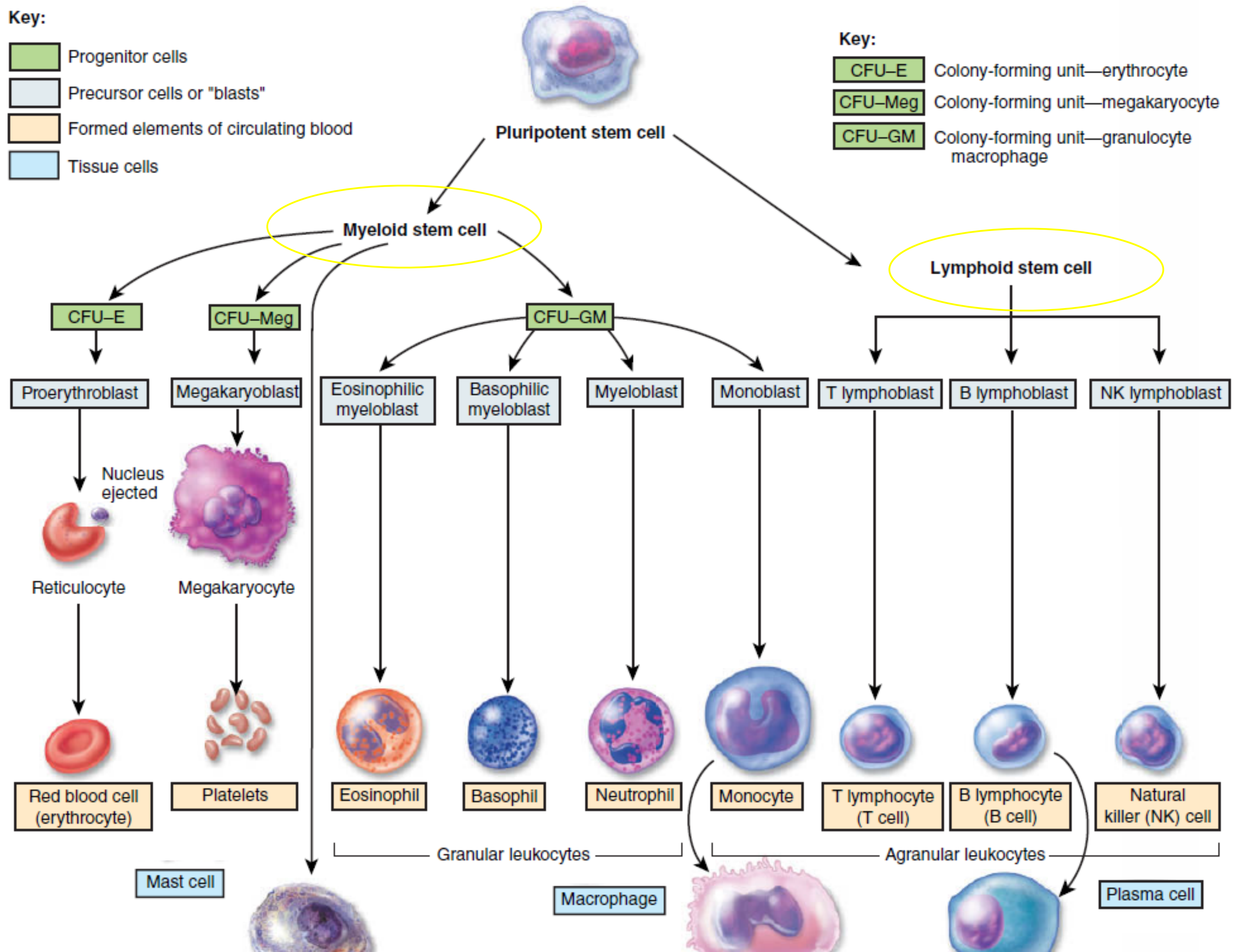
Anemia

Hematology | **Principle roles of the blood**

Transportation	• Gases, nutrients, hormones, waste products.
Regulation	• pH, body temperature, water content (osmotic pressure)
Protection	• Clotting, white blood cells,antibodies

Hemopoiesis (formation of blood cells)

Early fetal life	Occurs in the yolk sac of an embryo and later in the liver, spleen, thymus, and lymph nodes of a fetus.
last 3 gestational months- death	*Red bone marrow becomes the primary site of hemopoiesis in the, and continues as the source of blood cells after birth and throughout life. *axial skeleton, pectoral and pelvic girdles, and the proximal epiphyses of the humerus and femur.


Key:
Progenitor cells
Precursor cells or "blasts"
Formed elements of circulating blood
Tissue cells
Pluripotent stem cell
Key:
CFU–E Colony-forming unit—erythrocyte
CFU–Meg Colony-forming unit—megakaryocyte
CFU–GM Colony-forming unit—granulocyte macrophage
Myeloid stem cell
Lymphoid stem cell
CFU–E
CFU–Meg
CFU–GM
Proerythroblast
Megakaryoblast
Eosinophilic myeloblast
Basophilic myeloblast
Myeloblast
Monoblast
T lymphoblast
B lymphoblast
NK lymphoblast
Nucleus ejected
Reticulocyte
Megakaryocyte
Red blood cell (erythrocyte)
Platelets
Eosinophil
Basophil
Neutrophil
Monocyte
T lymphocyte (T cell)
B lymphocyte (B cell)
Natural killer (NK) cell
Granular leukocytes
Agranular leukocytes
Mast cell
Macrophage
Plasma cell

Hemopoiesis (formation of blood cells)

**pluripotent hematopoietic stem cells: constitute a population of adult stem cells found in bone marrow that are multipotent and able to self-renew.

**The intermediate-stage cells are very much like the pluripotential stem cells, even though they have already become committed to a particular line of cells and are called *committed stem cells (CFU).* The different committed stem cells, when grown in culture, will produce colonies of specific types of blood cells.

**Growth and reproduction of the different stem cells are controlled by multiple proteins called *growth inducers.* One of the growth inducers is *interleukin-3,* promotes growth and reproduction of virtually all the different types of committed stem cells.

Hemopoiesis (formation of blood cells)

- Stem cells in bone marrow
  - Reproduce themselves
  - Proliferate and differentiate
- Formed elements do not divide once they leave red bone marrow
  - Exception is lymphocytes

Hemopoiesis (formation of blood cells)

- ✓ **Myeloid stem cells**
  - **Give rise to red blood cells, platelets, monocytes, neutrophils, eosinophils and basophils**
- ✓ **Lymphoid stem cells** give rise to
  - **Lymphocytes and natural killer cells**

- ✓ **Hemopoietic growth factors regulate differentiation and proliferation**
  - **Erythropoietin – RBCs**
  - **Thrombopoietin – platelets**
  - **Colony-stimulating factors (CSFs) and interleukins – WBCs**

Red Blood Cells/ Erythrocytes

RBC — General characteristics

- **Biconcave disc.**
- **Diameter is normally 8 μm.**
- **Strong, flexible plasma membrane.**
- **Lack nucleus and other organelles**
- **Lack mitochondria.**
- **Key erythrocyte enzymes: glycolytic enzymes and carbonic anhydrase.**
- **Contain oxygen-carrying protein (hemoglobin).**

** The biconcave shape provides a larger surface area for diffusion of O2 from the plasma across the membrane into the erythrocyte than a spherical cell of the same volume would. Also, the thinness of the cell enables O2 to diffuse rapidly between the exterior and innermost regions of the cell.

**A second structural feature that facilitates RBCs' transport function is their flexible membrane (in great excess). Red blood cells, whose diameter is normally 8 um, can deform amazingly as they squeeze through capillaries. Because they are extremely pliant, RBCs can travel through the narrow, tortuous capillaries to deliver their O2 cargo at the tissue level without rupturing in the process.

The third and most important anatomic feature that enables RBCs to transport O2 is the hemoglobin they contain.

Cannot synthesize new components – no nucleus

RBC

General characteristics

- Oligosaccharides in plasma membrane are responsible for ABO and Rh blood groups.
- 5,200,000/ mm^3 in men; and 4,700,000/ mm^3 in women.
- Production = destruction (2 million/ sec).

RBC Function

- **Oxygen and CO_2 transport (hemoglobin).**
- **Contain a large quantity of carbonic anhydrase → increasing the rate of this reaction several thousand folds.**
- **Responsible for most of the acid-base buffering power of whole blood (hemoglobin).**

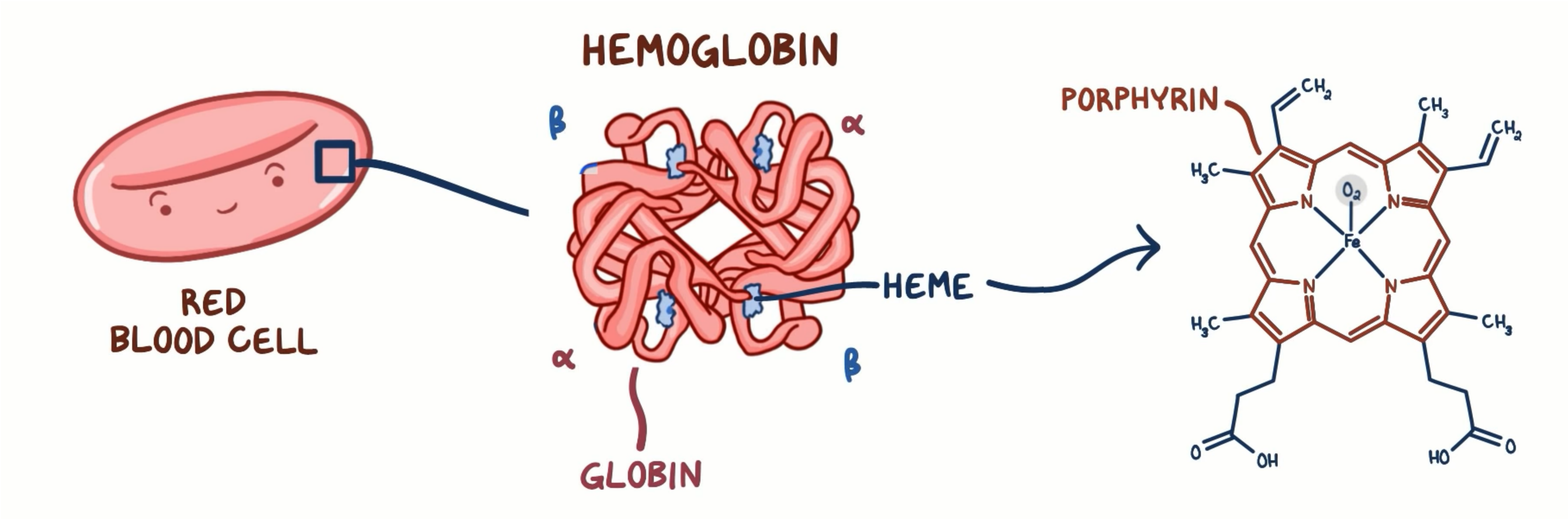
$$CO_2 + H_2O \leftrightarrow \underset{\text{carbonic acid}}{H_2CO_3} \leftrightarrow \underset{\text{bicarbonate}}{HCO_3^-} + H^+$$

** Erythrocytes contribute to CO2 transport in two ways—by means of its carriage on hemoglobin and its carbonic anhydrase–induced conversion to HCO3-.

**The red blood cells contain a large quantity of carbonic anhydrase, an enzyme that catalyzes the reversible reaction between carbon dioxide (CO_2) and water to form carbonic acid (H_2CO_3), increasing the rate of this reaction several thousandfold. The rapidity of this reaction makes it possible for the water of the blood to transport enormous quantities of CO_2 in the form of bicarbonate ion (HCO_3^-) from the tissues to the lungs, where it is reconverted to CO_2 and expelled into the atmosphere as a body waste product.

**The hemoglobin in the cells is an excellent acid-base buffer (as is true of most proteins), so the red blood cells are responsible for most of the acid-base buffering power of whole blood.

RBC › Hemoglobin



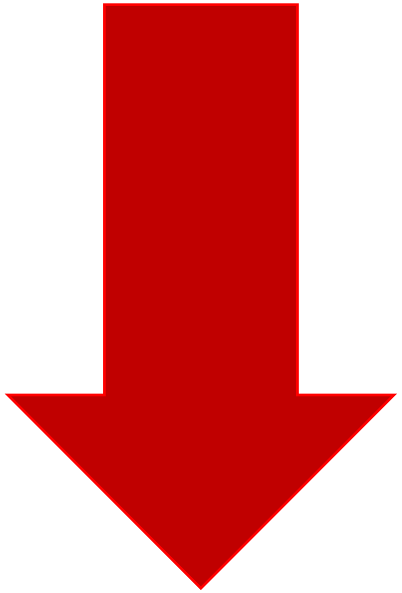
** Hemoglobin is a pigment (that is, it is naturally colored).
** Because of its iron content, it appears reddish when combined with O2 and bluish when deoxygenated.

RBC › Hemoglobin

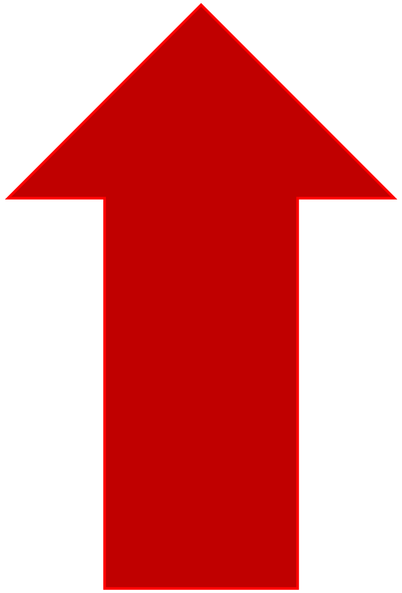
- The different types of chains are designated alpha chains, beta chains, gamma chains, and delta chains.
- The most common form of hemoglobin in the ADULT HUMAN, hemoglobin A, is a combination of two alpha chains and two beta chains.
- Iron ion can combine reversibly with one oxygen molecule
- Also transports 23% of total carbon dioxide (Combines with amino acids of globin).

RBC › Hemoglobin

- **Normal blood hemoglobin content is ~14.0 g/dL in the adult female and ~15.5 g/dL in the adult male.**



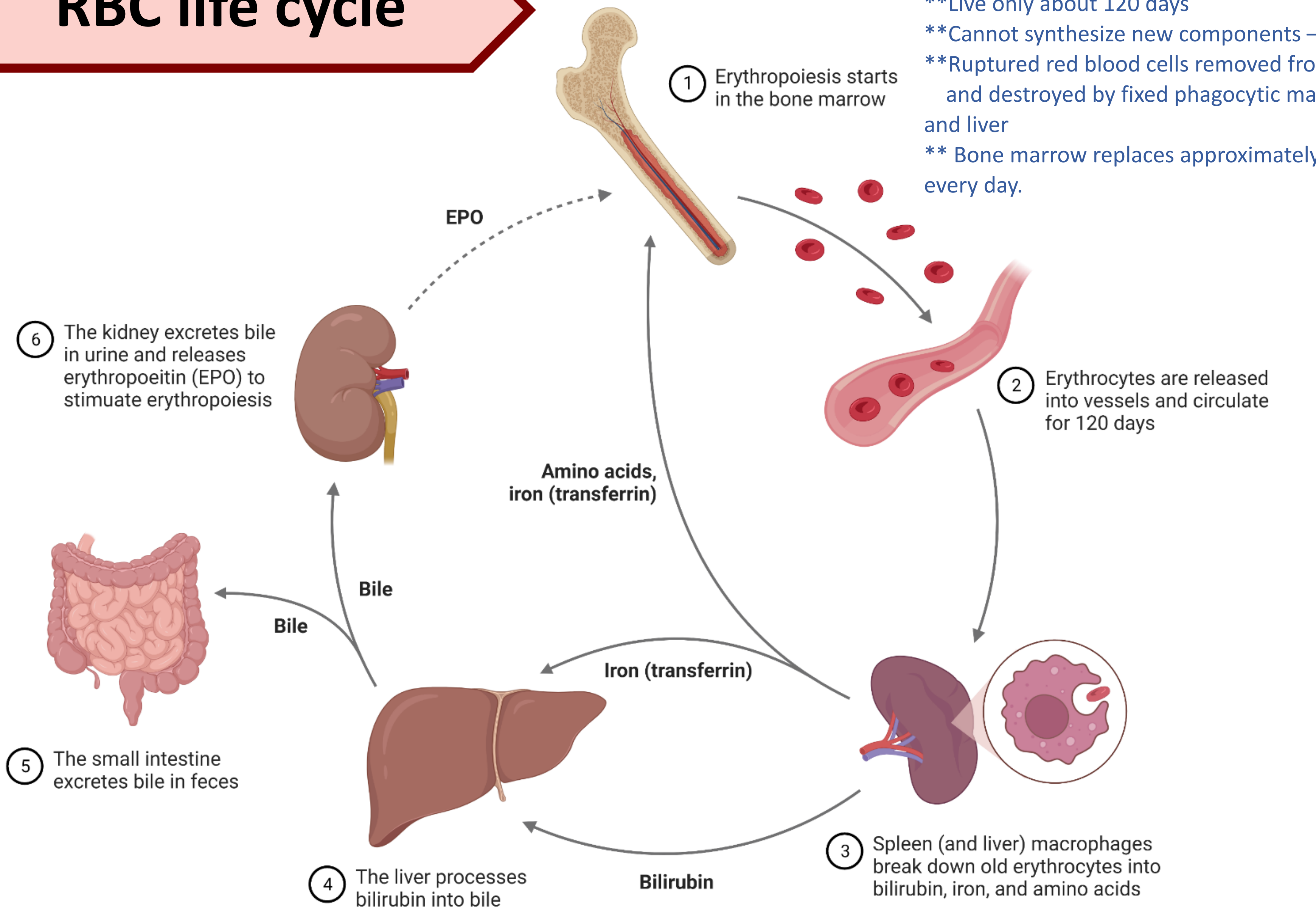
Anemia



polycythemia

RBC | RBC life cycle

**Live only about 120 days
**Cannot synthesize new components – no nucleus
**Ruptured red blood cells removed from circulation and destroyed by fixed phagocytic macrophages in spleen and liver
** Bone marrow replaces approximately 1% of the adult RBC every day.



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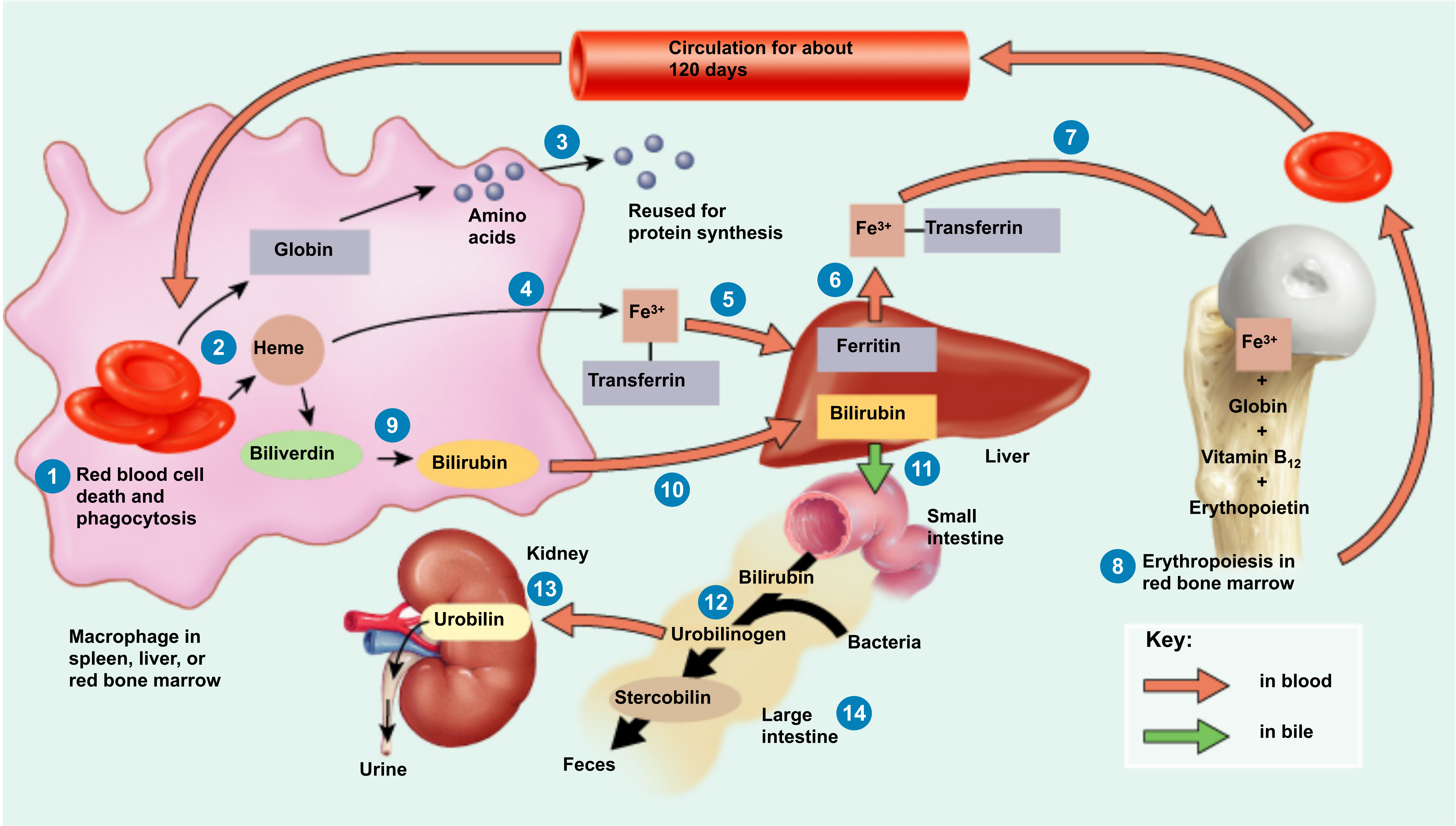


Circulation for about 120 days
3
Amino acids
Reused for protein synthesis
7
Globin
4
Fe^{3+}
5
6
Fe^{3+}
Transferrin
2
Heme
Transferrin
Ferritin
Fe^{3+}
+
Globin
+
Vitamin B_{12}
+
Erythopoietin
9
Biliverdin
Bilirubin
Bilirubin
11
Liver
1
Red blood cell death and phagocytosis
10
Small intestine
Kidney
Bilirubin
8
Erythropoiesis in red bone marrow
13
12
Urobilin
Urobilinogen
Bacteria
Macrophage in spleen, liver, or red bone marrow
Stercobilin
Large intestine
14
Urine
Feces
Key:
in blood
in bile

- Once the red cell membrane becomes fragile, the cell ruptures during passage through some tight spot of the circulation.
- Many of the red cells self-destruct in the spleen, where they squeeze through the red pulp of the spleen.
- Once the RBC membrane becomes fragile, the cell ruptures during passage through some tight spot of the circulation. Many of the RBCs self-destruct in the spleen, where they squeeze through the red pulp of the spleen. There, the spaces between the structural trabeculae of the red pulp, through which most of the cells must pass, are only 3 micrometers wide, in comparison with the 8-micrometer diameter of the RBC.
- Red blood cells burst and release their hemoglobin.
- The macrophages release iron from the hemoglobin and pass it back into the blood, to be carried by transferrin.
- Porphyrin is converted into the bile pigment *bilirubin.* Which is later removed from the body by secretion through the liver into the bile.

Breakdown products recycled

- Globin's amino acids reused
- Iron reused
- Non-iron heme ends as yellow pigment urobilin in urine or brown pigment stercobilin in feces

RBC Erythropoiesis

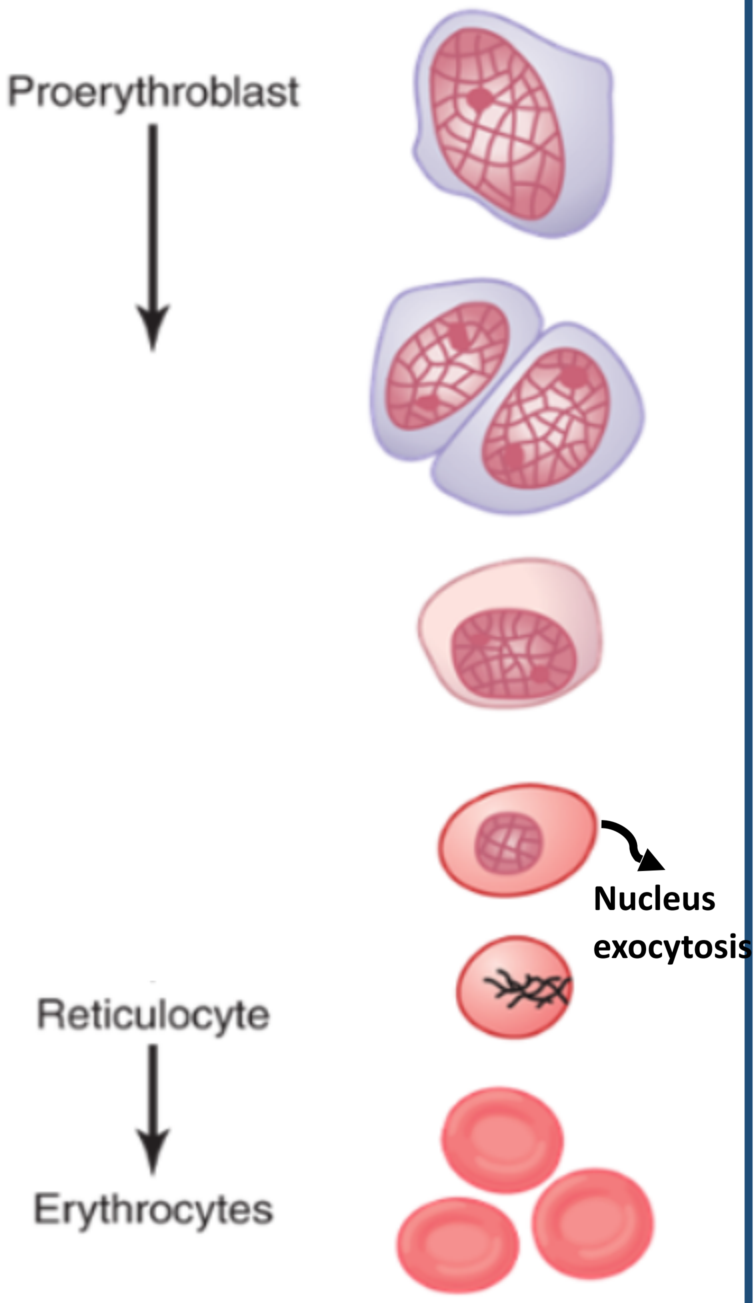
- **Starts in red bone marrow with proerythroblast.**

- **Cell near the end of development ejects nucleus and becomes a reticulocyte which develop into mature RBC within 1-2 days.**

- **The remaining basophilic material in the reticulocyte normally disappears within 1 to 2 days, and the cell is then a mature erythrocyte.**

**Changes: Hemoglobin accumulation, nuclear condensation, reabsorption of the endoplasmic reticulum.

** When reticulocytes leave the bone marrow and pass into the blood stream, they continue to form minute quantities of hemoglobin for another day or so until they become mature erythrocytes.



RBC → Reticulocyte count

<2% in normal adult

$$\text{Reticulocyte count} = \frac{\text{Number of reticulocyte}}{\text{Number of RBCs}} \times 100\%$$

Importance: Reticulocytes count help in diagnosis and typing of anemia

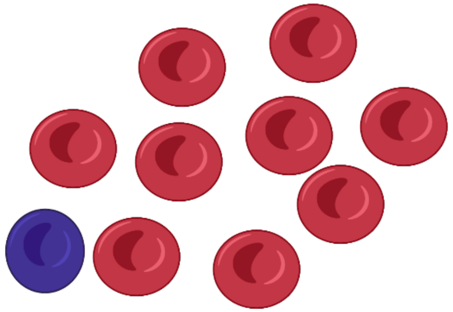
Decreased

Aplastic anemia

** In the state of anemia, reticulocyte % is not a true reflection of reticulocyte production.
** A correction factor must not be applied to overestimate marrow production because each reticulocyte is released into whole blood containing few RBCs, which means low Hct, thus increasing the percentage.

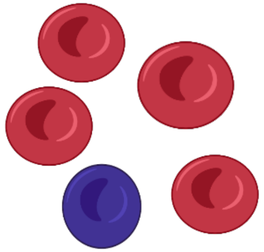
Increased

Hemolytic anemia
Post hemorrhage



Retic = 1%

Hct = 45



Retic = 2%

Hct = 22.5

$$\text{Corrected reticulocyte count} = \text{Reticulocyte count} \times \frac{\text{Actual Hct}}{\text{Normal Hct}}$$

$$= 1\% \times \frac{45}{45}$$

= 1%

$$= 2\% \times \frac{22.5}{45}$$

= 1%

RBC — Vitamins requirement

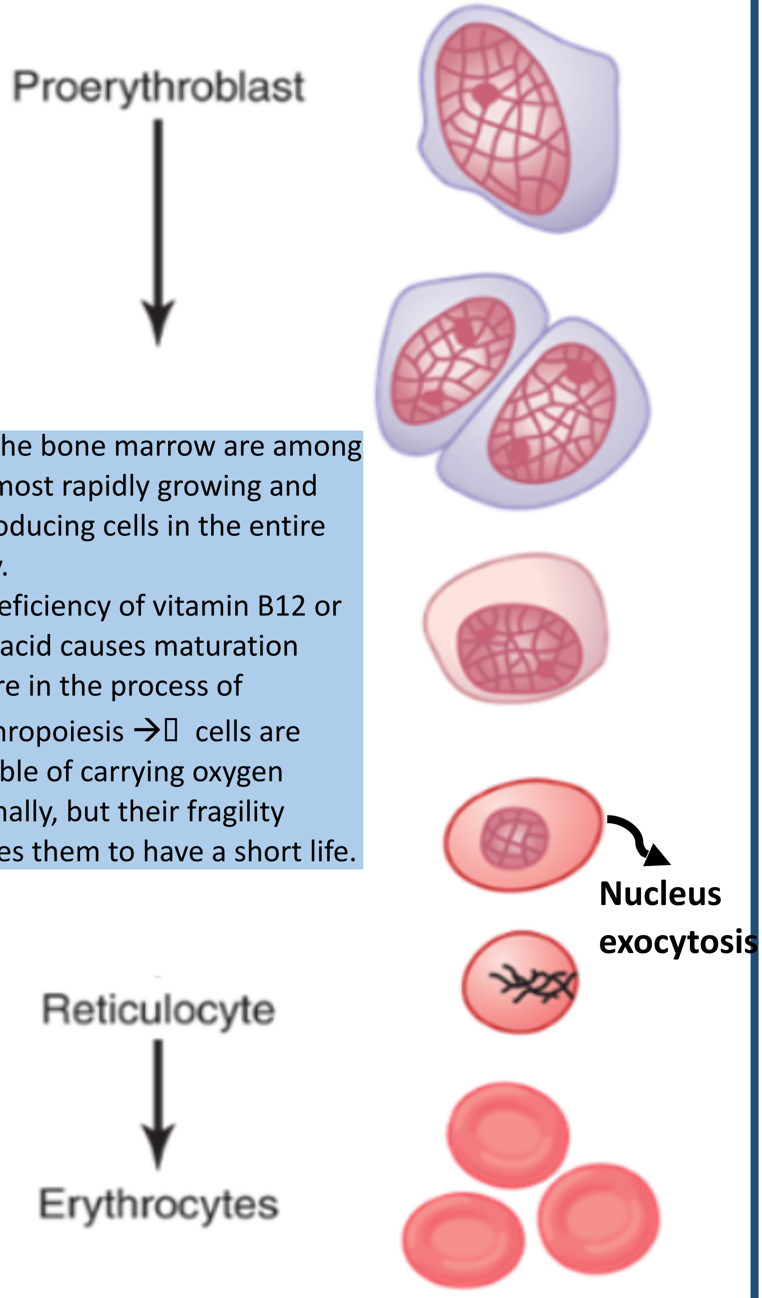
- Maturation of red blood cells requires vitamin B_{12} (Cyanocobalamin) and folic acid.
- Both of these are essential for the synthesis of DNA (formation of thymidine triphosphate).

- lack of either vitamin B_{12} or folic acid causes:

  **abnormal and diminished DNA and, consequently, failure of nuclear maturation and cell division.

  ** production of larger red cells called macrocytes and the cell itself has a flimsy irregular membrane.

** The bone marrow are among the most rapidly growing and reproducing cells in the entire body.
** Deficiency of vitamin B12 or folic acid causes maturation failure in the process of erythropoiesis → cells are capable of carrying oxygen normally, but their fragility causes them to have a short life.



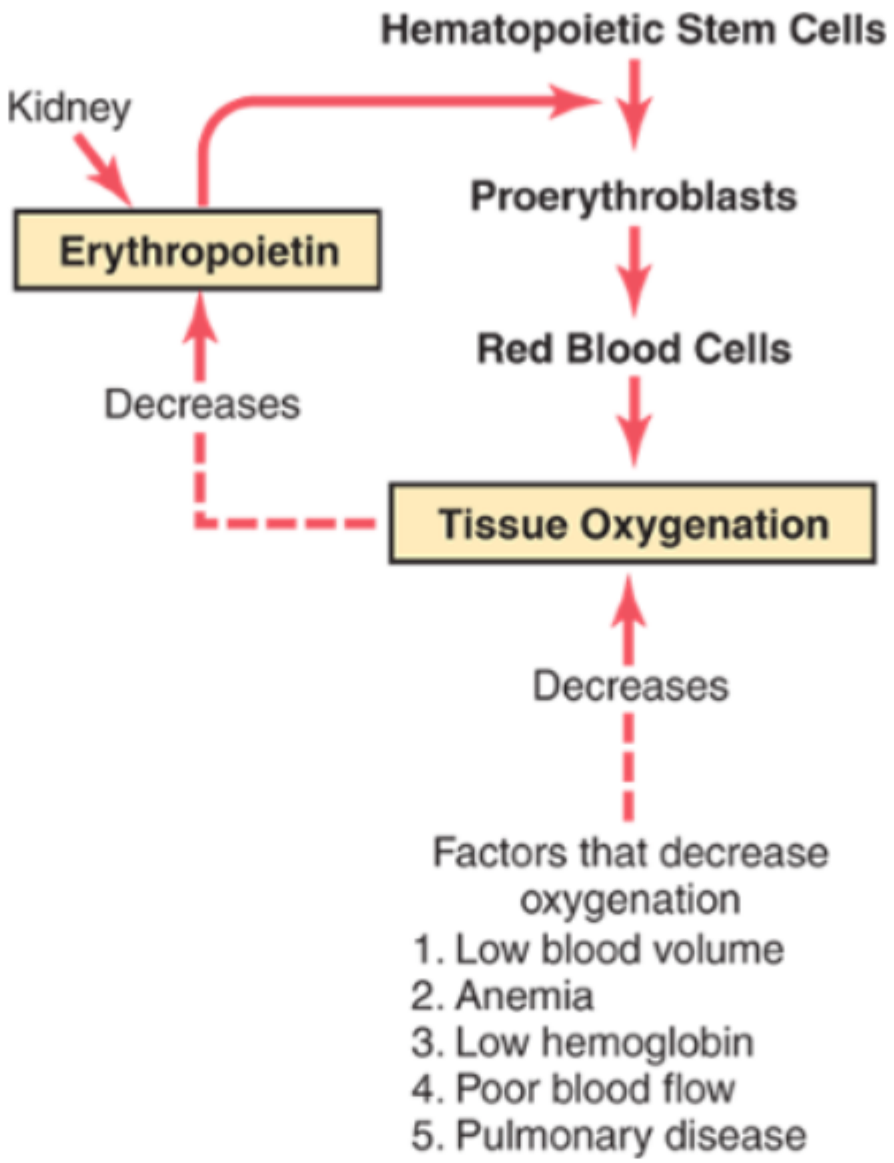
RBC ❯ Regulation of Erythropoiesis_ Erythropoietin (EPO)

- **Negative feedback balances production with destruction.**
- **Is a glycoprotein that normally formed in the kidneys (90%); the remainder is formed mainly in the liver.**
- **It is essential to stimulate the production of proerythroblasts from hematopoietic stem cells in the bone marrow.**
- **EPO causes these cells to pass more rapidly through the different erythroblastic stages.**

RBC — Regulation of Erythropoiesis_ Erythropoietin (EPO)

- **Hypoxia causes a marked increase in erythropoietin production.**

- **With renal failure, EPO release slows and RBC production is inadequate. This leads to a decreased hematocrit.**



- **P.s. Hypoxia is insufficient O_2 at the cellular level**

RBC | Regulation of Erythropoiesis_ Erythropoietin (EPO)

Because O_2 transport in the blood is the erythrocytes' main function, you might logically suspect that the primary stimulus for increased erythrocyte production would be reduced O_2 delivery to the tissues. You would be correct, but low O_2 levels do not stimulate erythropoiesis by acting directly on the red marrow. Instead, reduced O_2 delivery to the kidneys stimulates them to secrete the hormone **erythropoietin (EPO) into the blood, and this hormone in turn stimulates erythropoiesis by the red marrow.

****Tissue Oxygenation—Essential Regulator of Red Blood Cell Production**

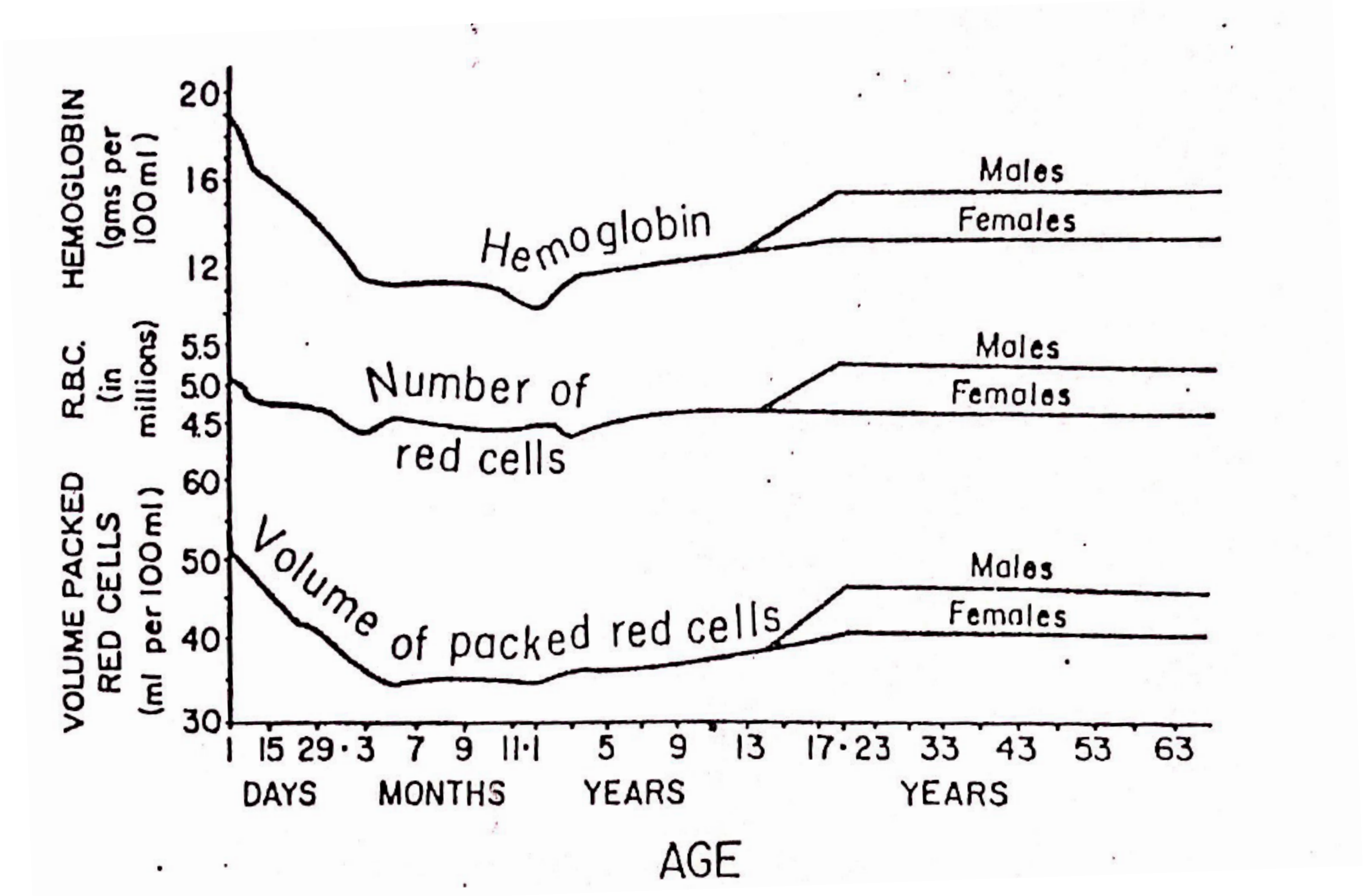
Conditions that decrease the quantity of oxygen transported to the tissues ordinarily increase the rate of RBC production.

*when a person becomes **extremely anemic** as a result of hemorrhage or any other condition, the bone marrow begins to produce large quantities of RBCs. RBCs.

*At very **high altitudes**, where the quantity of oxygen in the air is greatly decreased, insufficient oxygen is transported to the tissues, and RBC production is greatly increased. In this case, it is not the concentration of RBCs in the blood that controls RBC production but the amount of oxygen transported to the tissues in relation to tissue demand for oxygen.

*Various diseases of the circulation **that decrease tissue blood flow**, particularly those that cause **failure of oxygen absorption** by the blood as it passes through the lungs, can also increase the rate of RBC production. This result is especially apparent in **prolonged cardiac failure and in many lung diseases**.

RBC › RBCs parameters



**Factor contributing to decline in hematological parameters in the newborn was due to decrease in blood erythropoietin concentration soon after birth, reducing the erythropoietic rate. Also, transient hemolysis is high during the first days or week after.

**Decrease in hemoglobin level between older men and women may be the result of decrease androgen level in older men and decrease in estrogen levels in older women.

**Iron deficiency and anemia of chronic disease have usually been responsible for low hemoglobin level in majority of asymptomatic elderly people.

RBC

RBCs parameters

RBC count ($10^6/\mu L$ blood)
Hematocrit (%)
Hemoglobin (g/dL blood)
Mean red cell volume, MCV (fL/cell)
Mean red cell hemoglobin, MCH (pg/cell)
Mean cell hemoglobin concentration, MCHC (g/dL RBCs)
Red cell distribution width, RDW (%)

Mean cell volume (fL/cell)

- Is the average volume (size) of the RBCs.
- It can be measured, as it is in automated cell counters, or calculated:

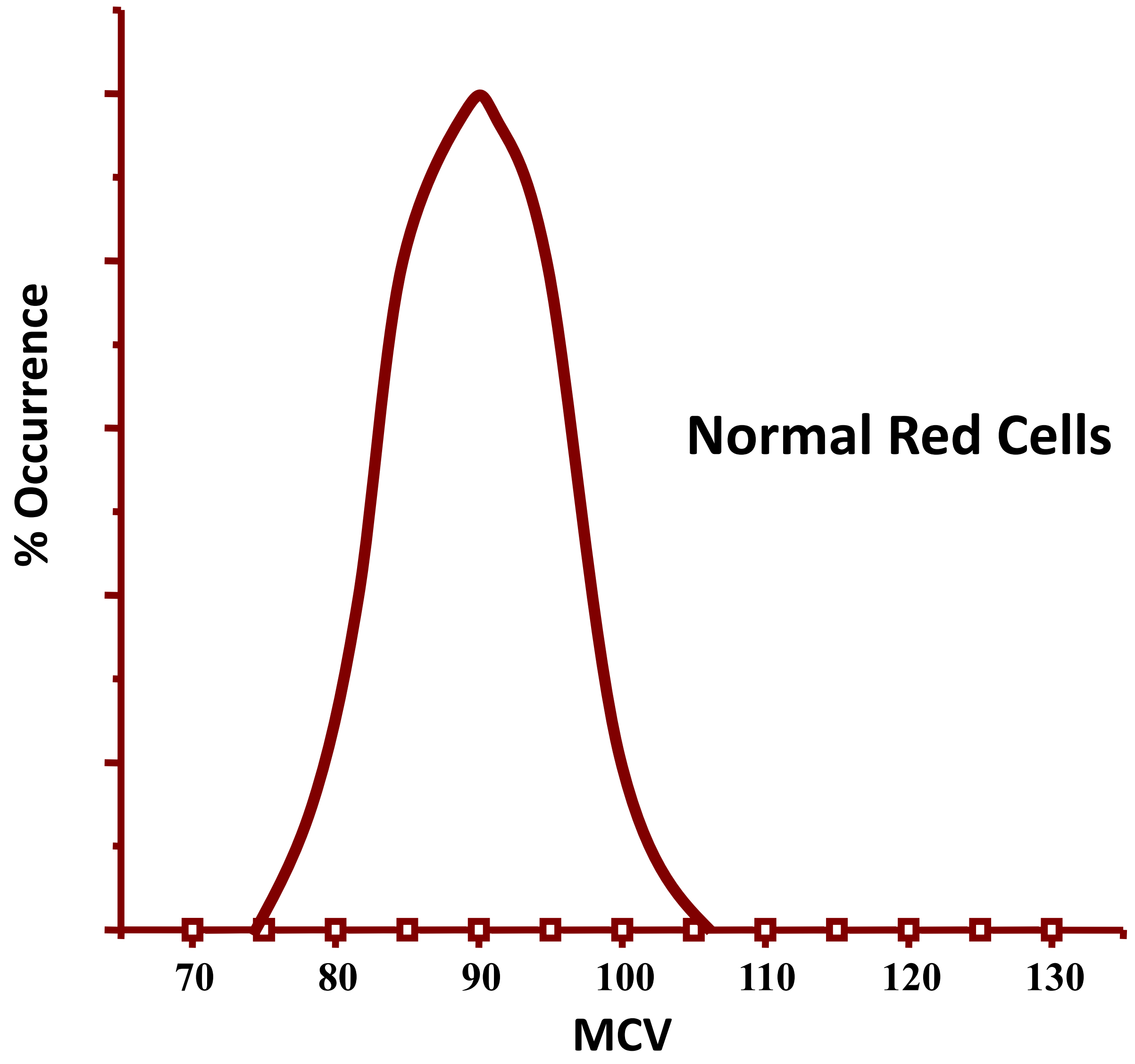
$$= \frac{\text{Hct [\%] x 10}}{\text{RBC count [in millions/}\mu\text{L]}}$$

Macrocytic (>100)

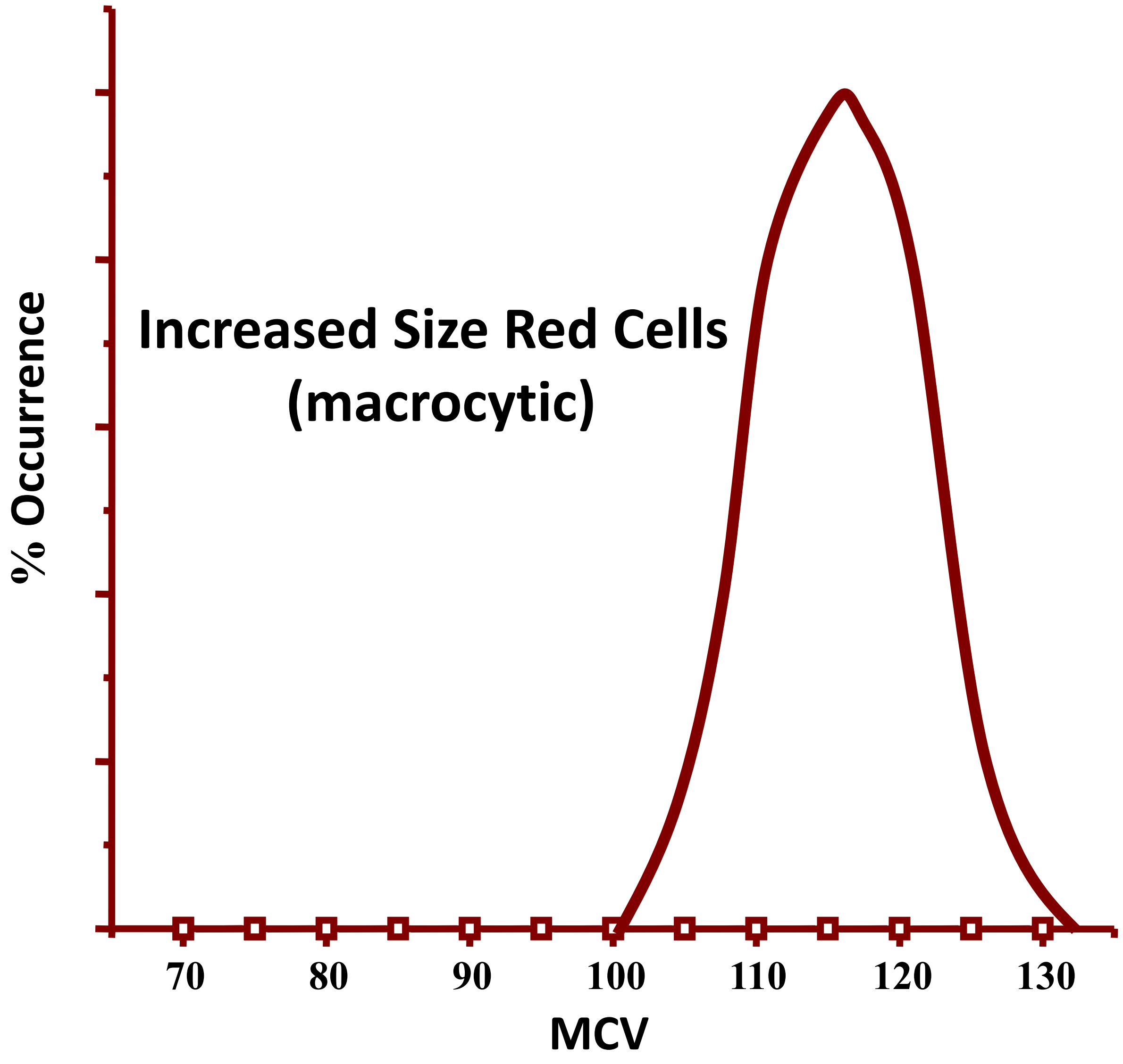
Normocytic (80-100)

Microcytic (<80)

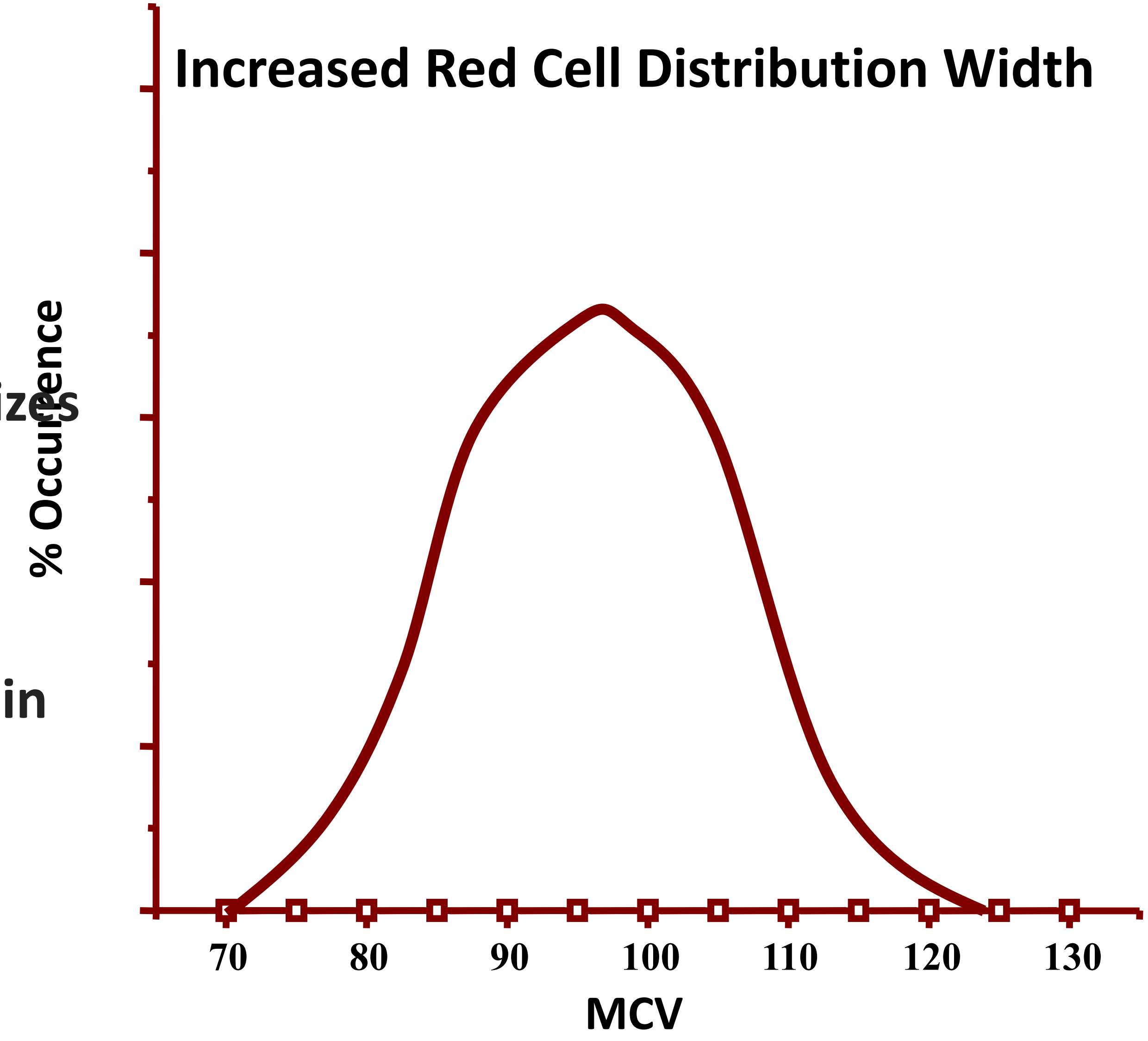
RBC > RBCs parameters > Distribution of RBCs sizes



RBC › RBCs parameters › Distribution of RBCs sizes



- Measurement of RBC size variation (anisocytosis).
- RDW = [standard deviation/MCV] x 100.
- A high RDW → large variation in RBC sizes
- A low RDW → more homogeneous population of RBCs.
- A high RDW can be seen in a number of anemias, including iron deficiency, vitamin B12 or folate deficiency.



Mean cell hemoglobin concentration (pg/ cell)

- Is the average hemoglobin content in a RBC.

$$= \frac{\text{Hemoglobin [g/dL] x 10}}{\text{RBC count [in millions/}\mu\text{L]}}$$

- **A low MCH is typically reflected in an enlarged area of central pallor in RBCs on the peripheral blood smear (greater than one-third of the RBC diameter)**

Normochromic (30-34)

Hypochromic (<30)

Mean cell hemoglobin concentration (g/dL RBC)

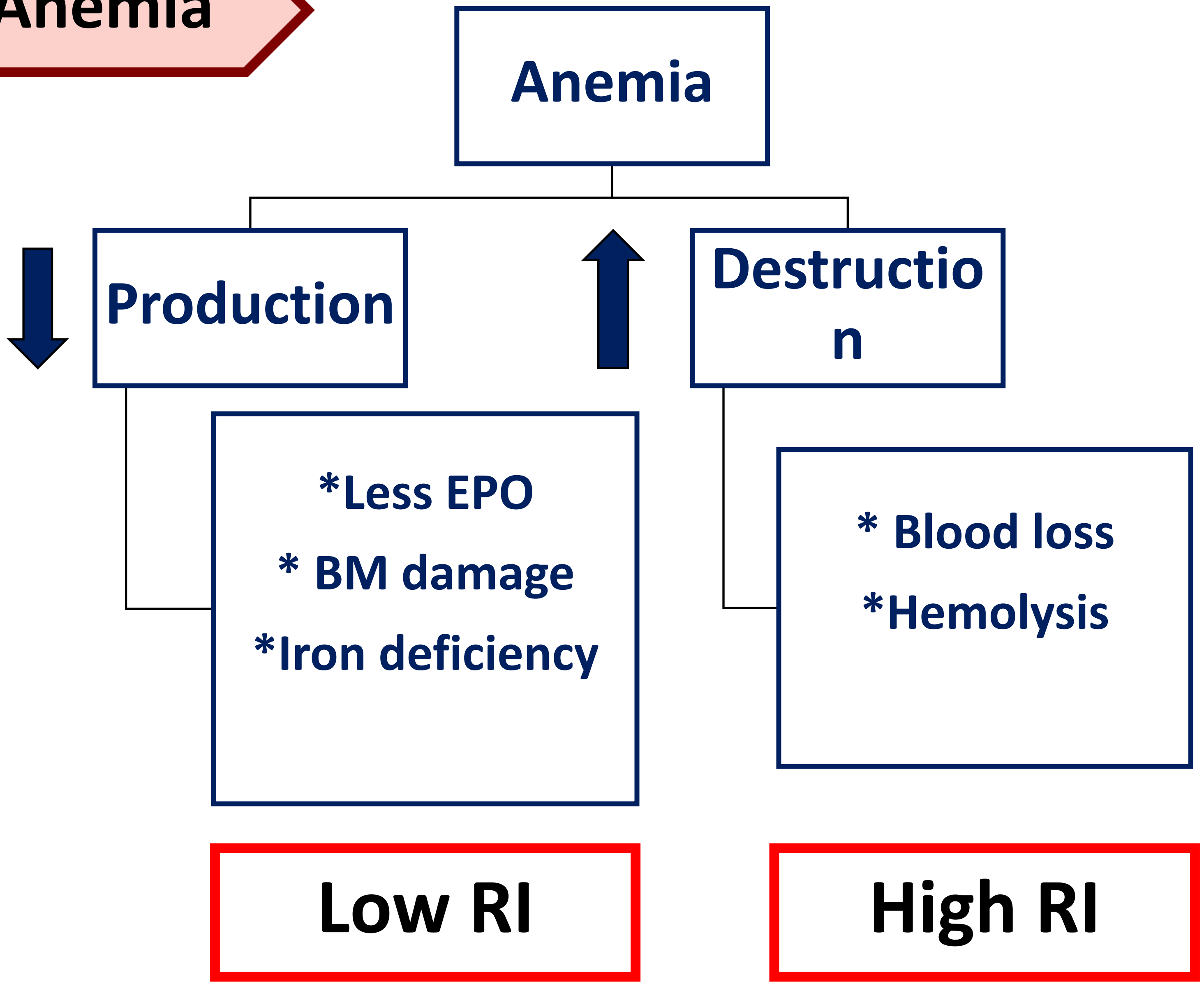
- Is the average hemoglobin concentration per RBC.

$$= \frac{\text{Hemoglobin [g/dL]} \times 100}{\text{Hct [\%]}}$$

MCHC=MCH/MCV

Normochromic (30-36)

Hypochromic (<30)


Anemia
Production
Destructio
n
*Less EPO
* BM damage
*Iron deficiency
* Blood loss
*Hemolysis
Low RI
High RI

RBC

Anemia classification

MCV < 80 fl

Microcytic Anemia

Iron Deficiency
Chronic disease
Thalassemia

MCV 80-100 fl

Normocytic Anemia

Elevated reticulocyte

Acute blood loss
Hemolysis

Normal or low reticulocyte

Kidney disease
Bone marrow Disorder

MCV >100 fl

Macrocytic Anemia

Vitamin B12
Folate

RBC — Anemia classification

MCV	Hb Content (MCH)	Causes
Normocytic	Normochromic	Bone marrow failure, renal disease, hemolytic anemia
Macrocytic	Normochromic	vitamin B_{12}, folic acid deficiency
Microcytic	Hypochromic	Iron deficiency, chronic diseases, Thalassemia

Effects of Anemia on Function of the Circulatory System

- **Blood viscosity is decreased.**
- **This decreases the resistance to blood flow in the peripheral blood vessels.**
- **Greater quantities of blood return to the heart.**
- **Increased cardiac output.**

- ***<u>Thus, one of the major effects of anemia is greatly increased cardiac output, as well as increased pumping workload on the heart</u>.***