HLS

MODIFIED NO. 2

PHYSIOLOGY

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تدقيق: فرح عليان

الدكتور: د.إباء الزيادنة

- Welcome Back !

- المحاضرة بسيطة ان شاء الله، كل معلومة أو صورة تم توضيحها بالتفصيل في الموديفايد
- كل سلايد الشرح الخاص به إما عليه نفسه أو في بوكس منفصل السلايد يلي بعده ، بالتوفيق!!

Color code

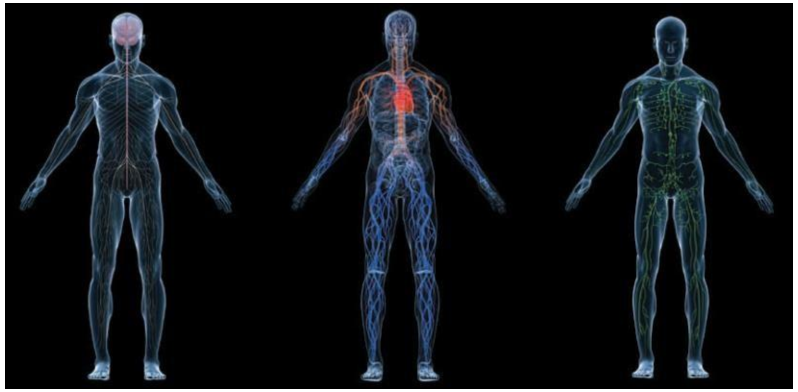
■ (black)	Slides
■ (green)	Doctor
■ (blue)	Additional info
■ (red)	Important

UNIT VI

Chapter 33

GUYTON AND HALL

TEXTBOOK OF MEDICAL PHYSIOLOGY



Introduction: Red Blood Cells, Anemia and Polycythemia

Ebaa M Alzayadneh, PhD

Functions of Red Blood Cells (Erythrocytes)

- **Carry hemoglobin, bearing O_2 to the tissues**

- **Contain carbonic anhydrase, which catalyzes the reaction:**

Carbonic anhydrase increases the rate of this reaction by several thousandfolds (it facilitates the rxn between water and co2)

- $CO_2 + H_2O \longrightarrow H_2CO_3 \longrightarrow$ **H+ + HCO3-**

- **allows large amounts of CO_2 to be carried in solution as HCO_3^-**

HCO_3^- (bicarbonate) increases the solubility of CO_2. Most of the CO_2 in the body is transported in the form of HCO_3^-.

- **Hemoglobin is an excellent acid-base buffer (as is true of most proteins)**
- **buffer = resist changes in PH**

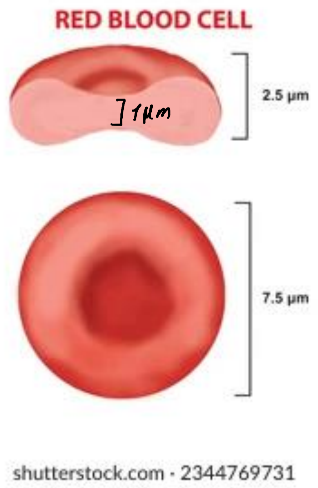
Some notes about hemoglobin:

- It gives the blood its red color.
- It is a protein composed of two α-globulin (alpha) and two β-globulin (beta) chains, along with a heme group. The heme group contains iron, which binds to oxygen, that's why hemoglobin is important in oxygen transport.
- Hemoglobin can carry carbon dioxide (CO_2), but it binds to a different site on the globulin chains rather than competing with oxygen, which binds to the iron in the heme group.
- In some animals, hemoglobin circulates as a free protein and not enclosed in RBCs

How carbon dioxide is transported in the blood stream

1- dissolved gas
2- bicarbonate (most of CO2)
3- bound to hemoglobin

RBC Size and Shape



- **Biconcave discs**
- **Mean 7.8(diameter) x 2.5 microns (thickest) or x 1 micron (center)**
- **Average volume 90-95 micrometers^3**
- **Redundant** (excess) **membranes allows deformation to squeeze through capillaries without being damaged (flexibility and biconcavity allow RBCs to pass through small capillaries, remember that the diameter of the capillaries is smaller than the diameter of RBCs)**

RBCs can change remarkably as the cells squeeze through capillaries. The normal cell has a great excess of cell membrane than is needed to contain its internal contents. deformation does not stretch the membrane greatly and, consequently, does not rupture the cell, as would be the case with many other cells.

** This is does not apply to aged RBCs, they are fragile so they destruct during squeezing and die

RBC Count and Indices

- Don't memorize the numbers

- **Men: 5,200,000 (± 300,000) / mm³ (more)**
- **Women: 4,700,000 (± 300,000) / mm³**
- **RBC counts can be increased at higher altitudes**

  This is a normal physiological response, not a pathological one. At high altitudes, the partial pressure of oxygen is low , requiring more RBCs to transport oxygen effectively throughout the body.

2 million /sec production

due to their short lifespan of 120 days. This high production rate ensures that RBC destruction is balanced, keeping their overall count stable.

- **RBC indices:**

- MCV (Mean cell volume)	90 ± 9 fl = 10^{-15} L
- MCH (Mean Cell Hgb)	32 ± 2 pg
- MCHC (Mean cell Hgb concntration)	33 ± 3 %
- RDW (red cell distribution width)CV	11.6-14.6 %
(SD of MCV/MCV)	39-46 fL

Red cell distribution width (RDW) : is a test measures the differences in the volume and size of your red blood cells
A high RDW means that there's a major difference between the size of your smallest and largest red blood cells. This may be a sign of a medical condition.

Hemoglobin and Hematocrit

- **280 million /RBC (280 million hemoglobin in one RBC)**
- Hemoglobin is present in red blood cells (RBCs) even though mature RBCs lack a nucleus. This is because the nucleus was present during the early stages of RBC development in the bone marrow. During these stages, the nucleus did the transcription and production of hemoglobin. Once enough hemoglobin is produced, the nucleus degenerates before the cell enters circulation.
- **Normal hemoglobin concentration is 34 g per 100 ml of packed cells**
- **33% of RBC weight**

- **Normal hematocrit ("packed cell volume") is 40-45% (slightly lower in women)**

- This difference is primarily due to hormonal influences and blood loss. Testosterone promotes the production of red blood cells (RBCs), leading to higher hematocrit levels in men. In contrast, estrogen has a suppressive effect on RBC production, contributing to lower levels in women. Additionally, women experience regular blood loss through menstruation, which further reduces their hematocrit levels..

- **Thus normal hemoglobin is 14-15 g per 100 ml of blood((قوة الدم**

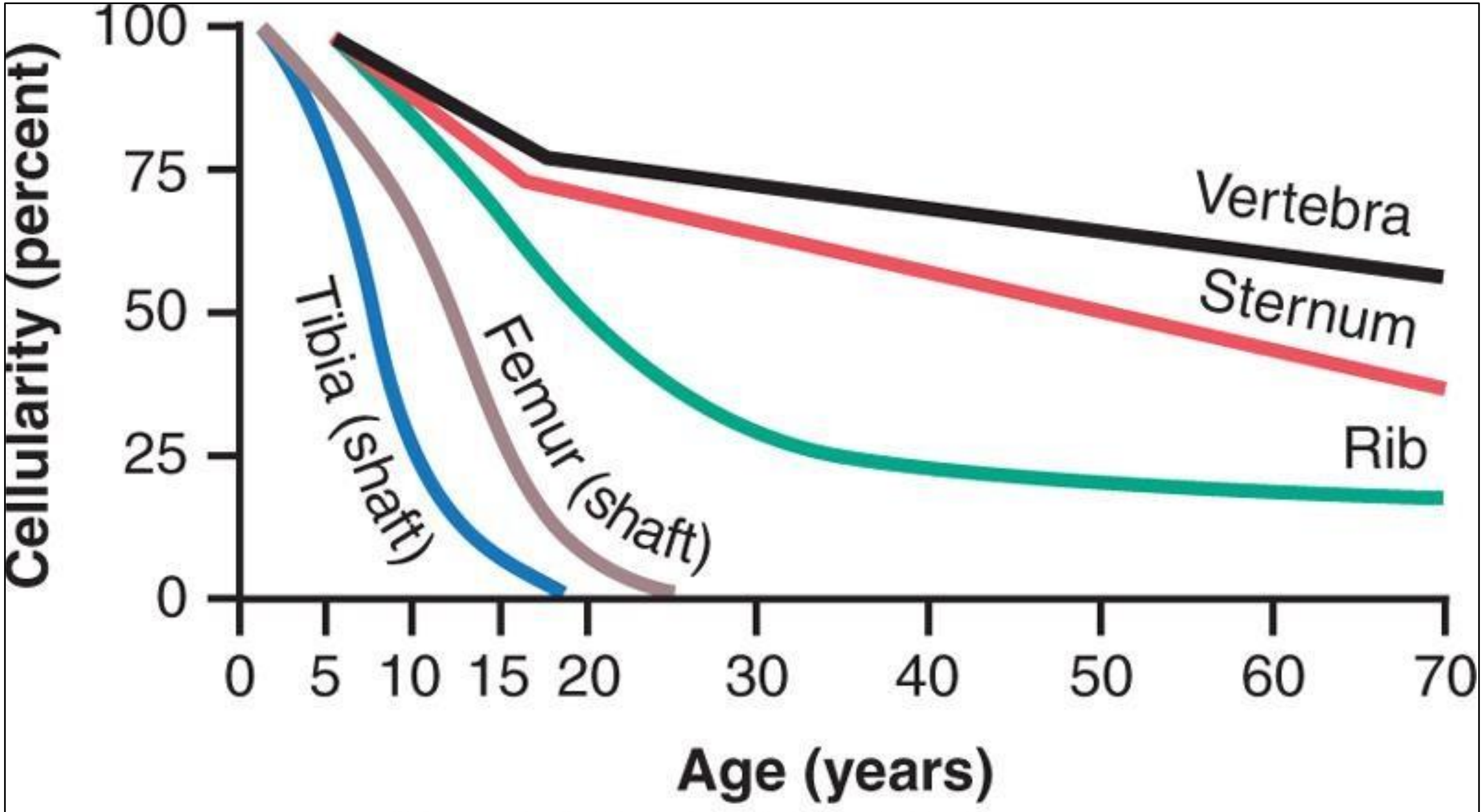
- **O_2 carrying capacity is 1.34 ml / g Hgb, or 19-20 ml O_2 / 100 ml blood**

- **transports 25% CO2**

Sites of Erythropoiesis) the process of RBCs formation)

- **First few weeks of gestation – yolk sac** (notice that the process starts from embryonic life)
- **Mid-trimester – Liver (+ spleen, lymph nodes)**
- **Last month of gestation** (third trimester) **through adulthood – Bone marrow**

Sites of Erythropoiesis by Age



Hall: Guyton and Hall Textbook of Medical Physiology, 12th Edition

As we age, the primary sites of red blood cell (RBC) production change.

Red bone marrow, which produces all blood cell types, is gradually replaced by yellow bone marrow (adipose tissue). This occurs because hematopoietic stem cells in the bone marrow decrease, and mesenchymal stem cells differentiate into adipocytes as part of the aging process.. Consequently, RBC production becomes limited to specific areas..
Mainly the short bones such as vertebrae, sternum, with a decrease in the production at long bones such as tibia, femur.

Explanation of the graph from the book :
the marrow of essentially all bones produces RBCs until a person is about 5 years old. The marrow of the long bones, except for the proximal portions of the humeri and tibiae, becomes fatty and produces no more RBCs after about the age of 20 years. Beyond this age, most RBCs continue to be produced in the marrow of the membranous bones, such as the vertebrae, sternum, ribs, and ilia. Even in these bones, the marrow becomes less productive as age increases.

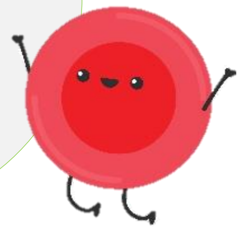
Hematopoiesis:

- **Pluripotent hematopoietic stem cells give rise sequentially to committed stem cells and mature cells**
- **Driven by**
  - **Growth inducers (factors; e.g. *interleukin-3*)**
  - **Differentiation inducers**
- **Hematopoiesis responds to changing conditions**
  - **Hypoxia: erythropoiesis**
  - **Infection / inflammation: WBC production**

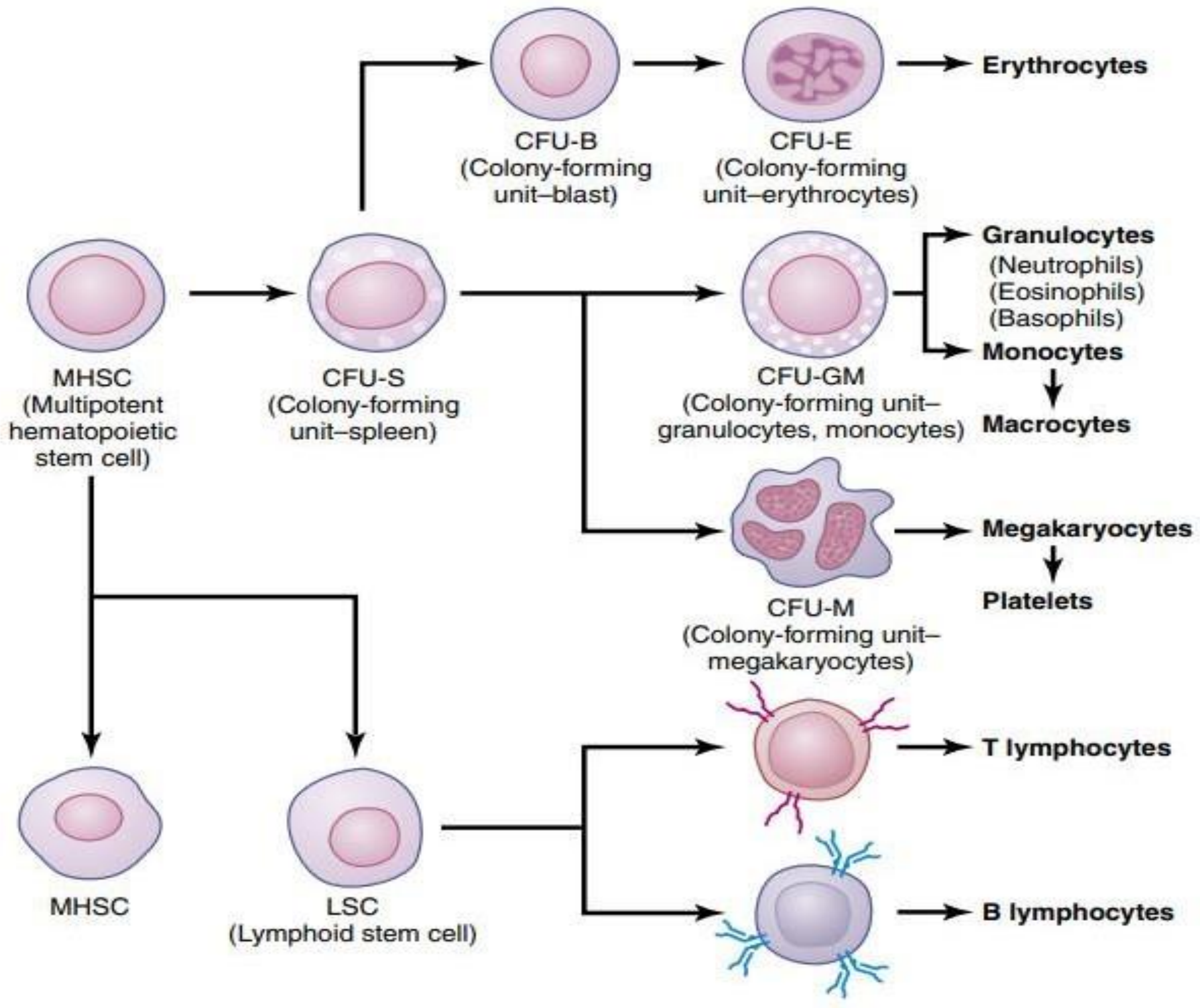
- **Hematology** is the science that studies the components, characteristics, and abnormalities of blood. When using the term **hematopoiesis**, we refer to the formation of all blood components. However, when focusing on **erythropoiesis**, we are specifically addressing the production of red blood cells (RBCs).

- pluripotent hematopoietic stem cells have the potential to differentiate into all types of blood cells (formed elements).
- , **depending on the signals and differentiation factors** they receive. These factors guide the stem cells along the appropriate developmental pathway.
- *IL-3 is a non-specific growth inducer that guides the stem cells along the appropriate developmental pathway.

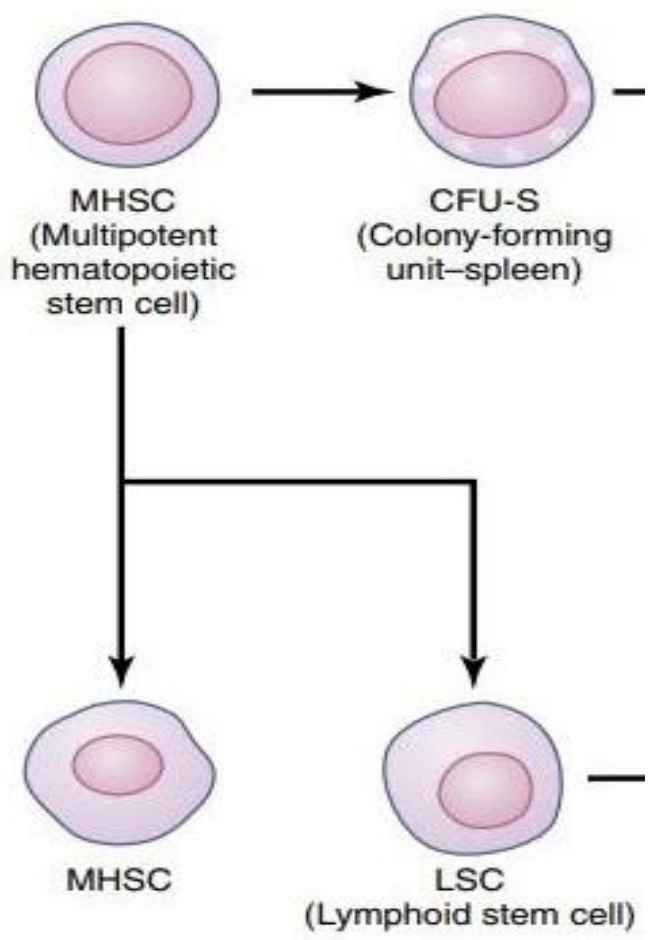
- stem cells should undergo proliferation to increase in number. Also, These cells are present since birth, and their reproduction continues throughout life, as there is a need for constant replenishment due to cell turnover. Differentiation factors determine the fate of each stem cell, guiding them along specific pathways.
- **Hematopoiesis** does not occur at a constant rate; it varies based on physiological conditions. For example, at high altitudes, where the oxygen level is low , the body increases the production of red blood cells (RBCs) to optimize oxygen delivery to tissues.



Blood Cell Lineages



Formation of the mul-
blood cells from the
potent hematopoietic
e bone marrow.

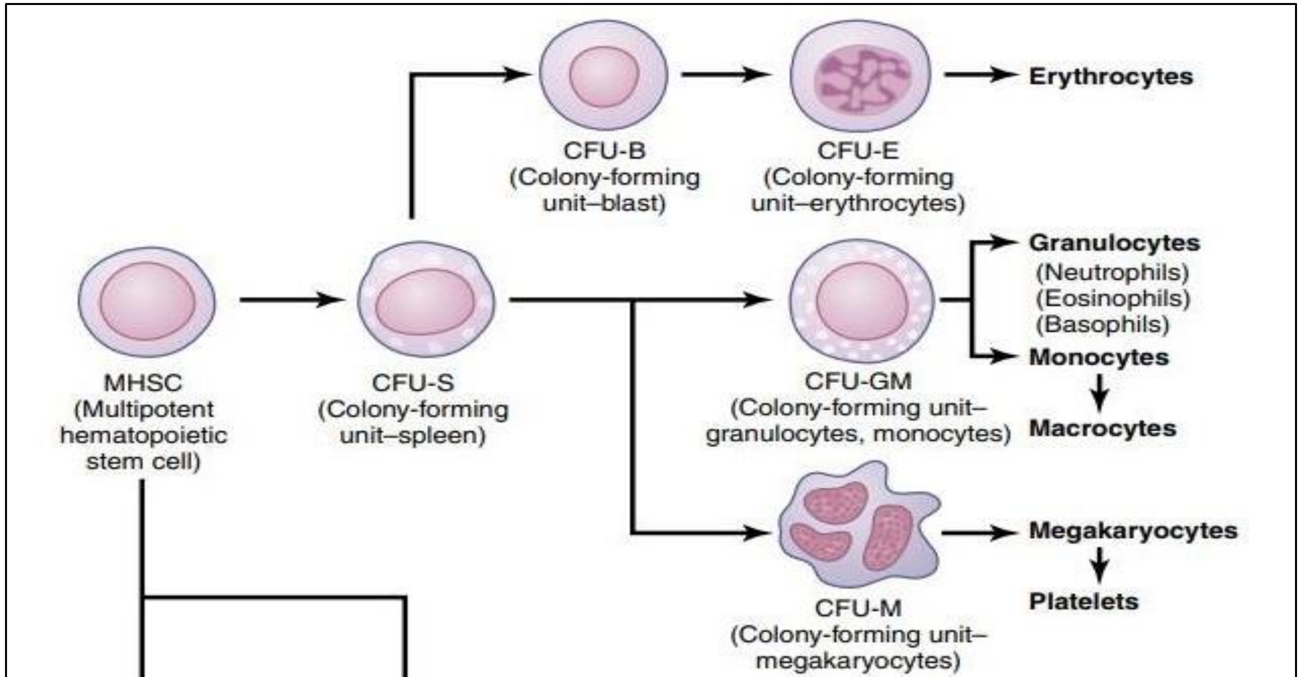


🎯 Our story begins with **(MHSC)**, which can be thought of as the "grandfather"👴 of all blood cells. These cells must undergo proliferation to maintain their population 👧👶
as they are essential for generating various blood cell types.
Over time, MHSCs will differentiate into either
1.**lymphoid stem cells** or

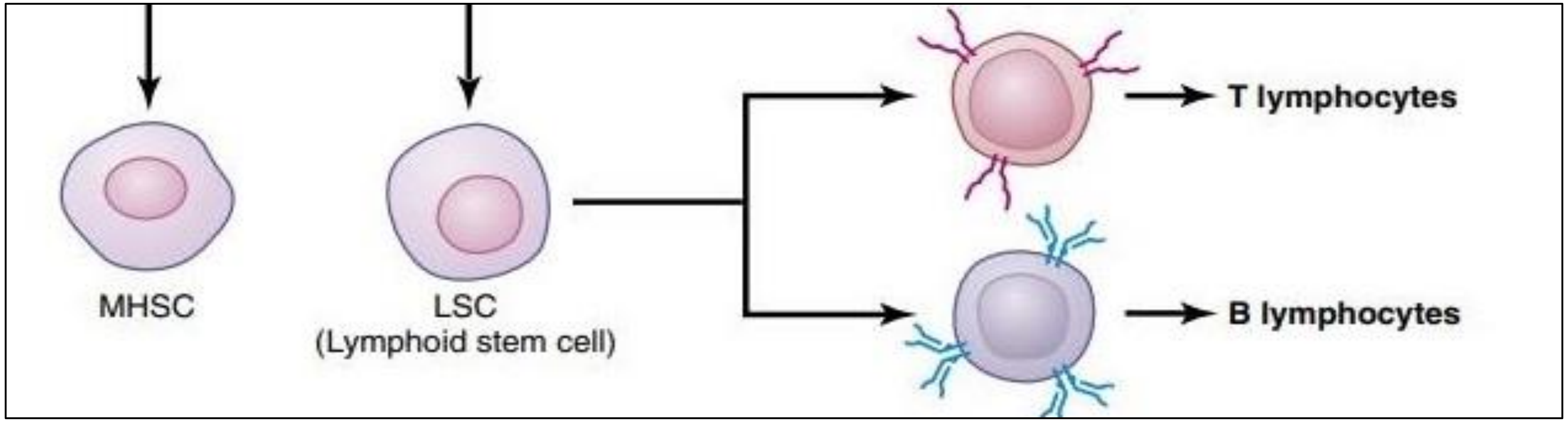
2. **CFU-S (myeloid stem cells)** . The key difference between these two lies in the specific types of cells they give rise to, which can be identified using certain staining markers.

CFU-S can also differentiate into either **Granulocyte-Monocyte** Progenitors **(GM)** or **megakaryocyte CFU-M** , a large cell that fragments into **platelets**. or **Colony-Forming Unit-Blast (CFU-B)** cells which becomes then CFU-E. This CFU-E, will further differentiates into **erythrocytes** (red blood cells), but not immediately, though this follows a specific sequence that we will discuss in the next few slides .

The **GM lineage** gives rise to **granulocytes**, which include neutrophils, basophils, and eosinophils, all of which contain granules that can be observed under a light microscope. GM progenitors can also differentiate into **monocytes**, which lack granules and eventually mature into **macrophages**. 🥳



- On the other hand, the lymphoid lineage is distinct from the CFU-S pathway and gives rise to different cell types, such as T cells, B cells .. depending on specific growth and differentiation factors.🧬

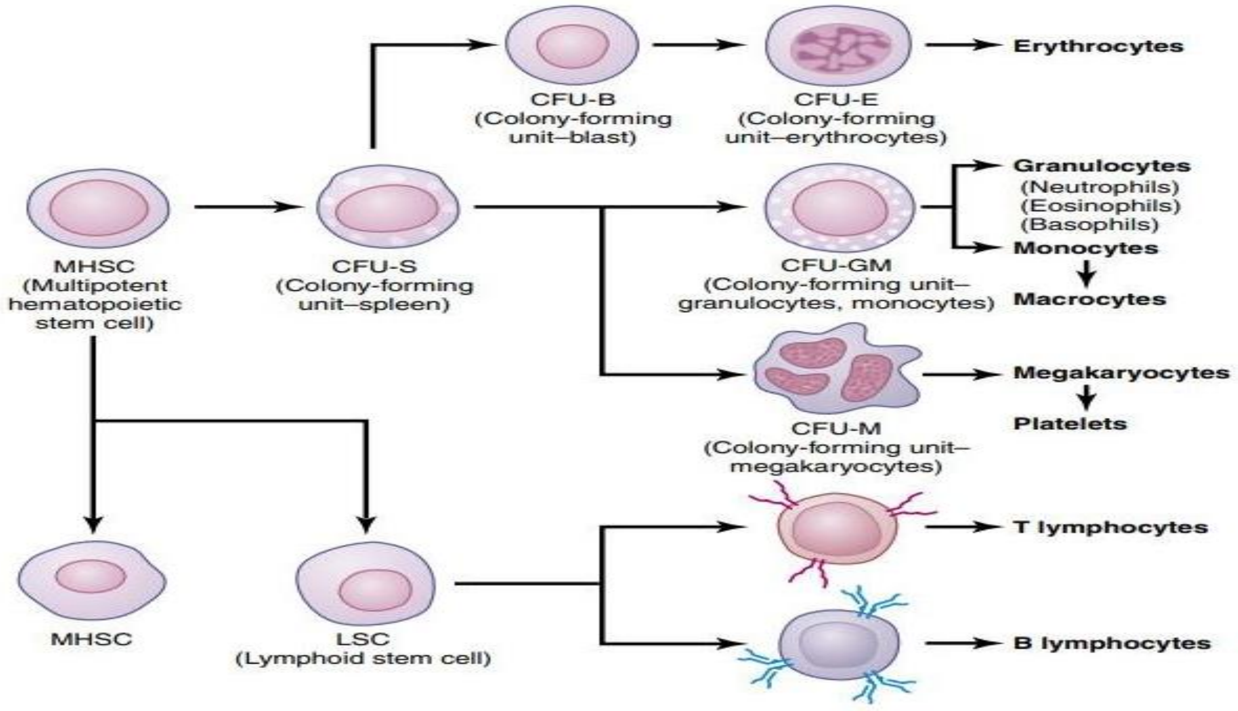


Let's revise our story again 👆🧐

The process of hematopoiesis begins with **Multipotent Hematopoietic Stem Cells (MHSC)**, which proliferate to maintain their population. These stem cells differentiate into two main lineages: **lymphoid stem cells** and **(CFU-S)**

- **CFU-S** gives rise to **granulocytes** (neutrophils, basophils, eosinophils), **monocytes** (which become macrophages), **megakaryocytes** (which produce platelets), and **erythrocytes** (red blood cells).
- **Lymphoid stem cells** differentiate into immune cells like **T cells**, **B cell.**

This process is regulated by specific growth factors and differentiation signals, allowing the body to adjust blood cell production based on its needs, such as during low oxygen conditions or immune responses.



Erythropoiesis and Anemia

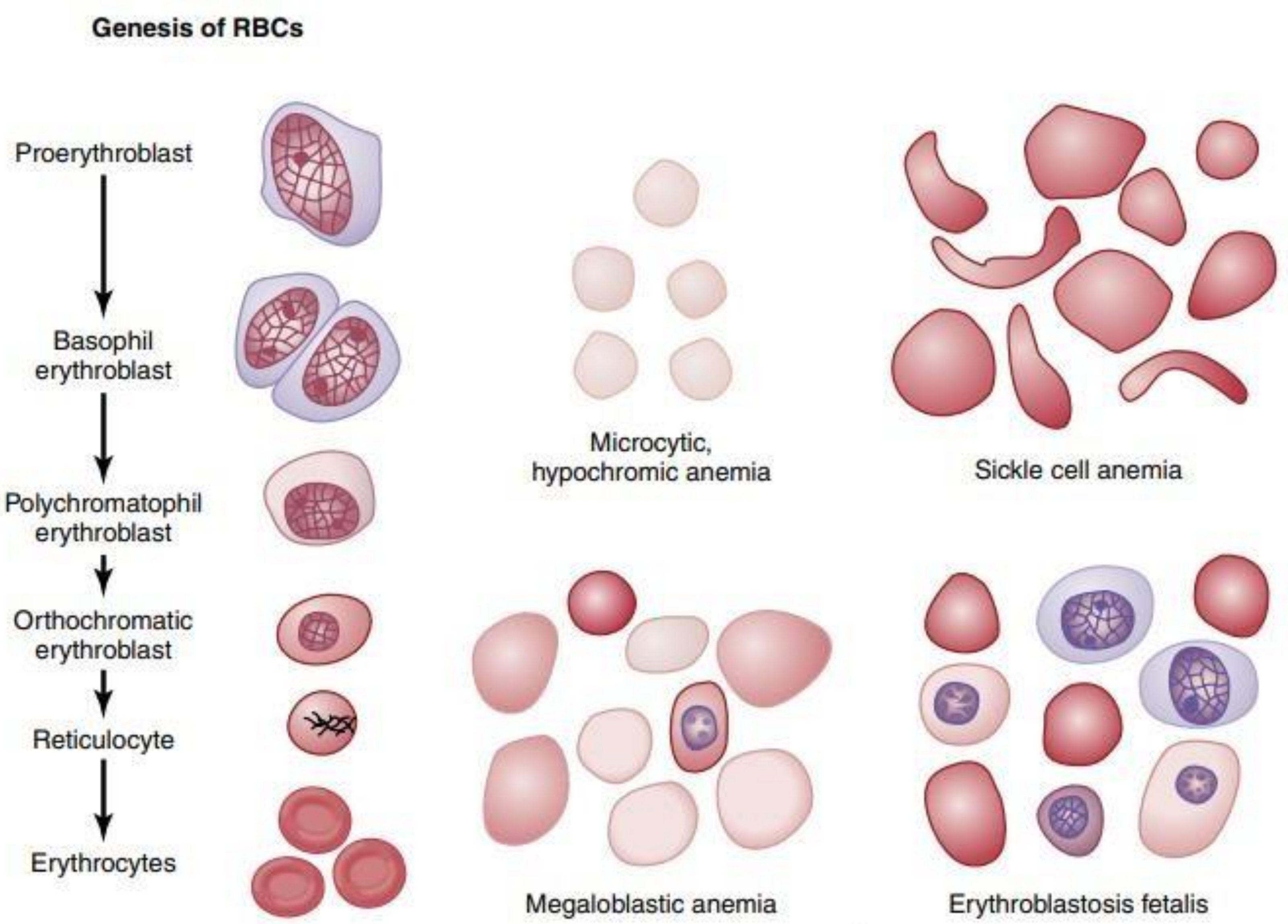


Figure 33-3. Genesis of normal red blood cells (RBCs) and characteristics of RBCs in different types of anemias.

Let's focus on **erythropoiesis (look at the prev. Pic at left side while reading)**

Proerythroblast: The process begins with a proerythroblast, which differentiates into a **basophilic erythroblast**. It's important to note that the term "basophilic" here refers to the bluish color due to basic staining and does not refer to basophils, a type of (WBC).
Then **polychromatophilic erythroblast** and **orthochromatic erythroblast** stages (these two the Dr only mentioned their names without further details) then **reticulocyte**

but what happens to RBC while maturation?

1.Organelle Degradation: As it matures, its **nucleus begins to degrade**, along with the **endoplasmic reticulum (ER)** and **Golgi apparatus**. This is a crucial step because these organelles consume oxygen and produce proteins, which would interfere with the primary function of RBCs (carrying oxygen). By eliminating these organelles, the cell becomes more efficient in oxygen transport.

2.Hemoglobin Production: Before the nucleus degrades, the cell produces **hemoglobin** and the necessary **enzymes**. These are synthesized while the nucleus is still present, ensuring that the RBC has all the components required for its oxygen-carrying function.

Reticulocyte Stage: Once the cell is nearly mature, it enters the bloodstream from the **red bone marrow** as a **reticulocyte**, which still contains remnants of the ER and a few organelles but no nucleus. Within 1–2 days, these remaining organelles degrade, and the cell becomes a fully mature **erythrocyte**.

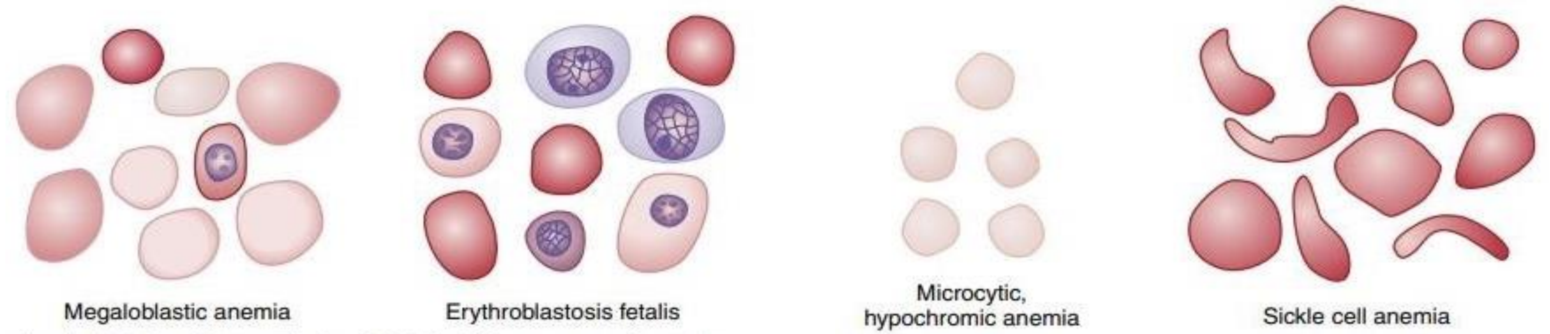
RBC Abnormalities: Different abnormalities can affect RBCs:

1. **Hypochromic** and **microcytic anemia** indicate lower hemoglobin concentration and smaller RBC size, respectively.
2. **Sickle cell anemia** is characterized by misshapen RBCs.
3. **Megaloblastic anemia** is a type of anemia caused by impaired DNA synthesis, often due to deficiencies in vitamin B12 or folate. It leads to the production of abnormally large, immature red blood cells (megaloblasts).
4. **Erythroblastosis fetalis** is a condition where a mother's immune system attacks the red blood cells of her fetus due to blood group incompatibility, typically when the mother is Rh-negative and the fetus is Rh-positive, causing severe anemia in the fetus.

الأزرق هو كلام اضافي سيتم شرحه لاحقًا بالباثو

👉**المختصر**:

The shape and size of RBCs can aid in the differential diagnosis of various conditions, and Dr. said that you'll learn more about these abnormalities in pathology course.



od cells (RBCs) and characteristics of RBCs in different types of anemias.

Regulation of Red Cell Production

- **Red blood cell mass is regulated within a relatively narrow range to…**
  - **Maintain adequate oxygen carrying capacity**
  - **Avoid excessive blood viscosity**

- **If the bone marrow is damaged or if demand for erythropoiesis is extreme, other parts of the bone marrow may become hyperplastic, or *extramedullary hematopoiesis* may occur.**

💡 The mass of red blood cells (RBCs) must remain within a narrow range to maintain proper function. If RBC numbers increase excessively, it leads to higher blood viscosity, which increases resistance within blood vessels. To make it simpler, compare the flow of water to a more viscous fluid in blood vessels(such as honey🍯) .. higher viscosity creates more resistance against the vessel walls. This increases the workload on the heart, which must pump harder to push the thicker blood through the circulatory system, potentially leading to cardiac hypertrophy .

⛔ To prevent this, the body uses a negative feedback mechanism that maintains RBC homeostasis. Similarly, white blood cells (WBCs) are regulated. For example, during an allergic reaction, basophils increase, and during parasitic infections, eosinophils increase. The production of WBCs depends on various factors, and specific conditions will trigger the synthesis of certain WBC types. The rate of production is not constant, and a single stem cell can differentiate into multiple cell types depending on signals.

If part of the bone marrow is damaged due to factors like radiation, fractures, or medications, other regions of the bone marrow will compensate to maintain blood cell production. In response to low oxygen levels (hypoxia), the kidneys secrete **erythropoietin**, with a smaller contribution from the liver. Under normal conditions, this hormone is released in small amounts to support RBC production. However, in cases of severe hypoxia, such as at high altitudes or in respiratory conditions, erythropoietin levels increase significantly, stimulating more RBC production to improve oxygenation. This process is regulated by negative feedback to restore normal oxygen levels.
Bone marrow hyperplasia could happen. Also, extramedullary hematopoiesis may occur, where blood cell production happens outside the bone marrow in response to severe conditions. Similar feedback mechanisms regulate WBC production, with different factors influencing WBC types depending on the body's needs.

If u still did not get the point, it’s okay, we will repeat it in more details after a while. 😎🎯

Tissue O_2 and Erythropoietin

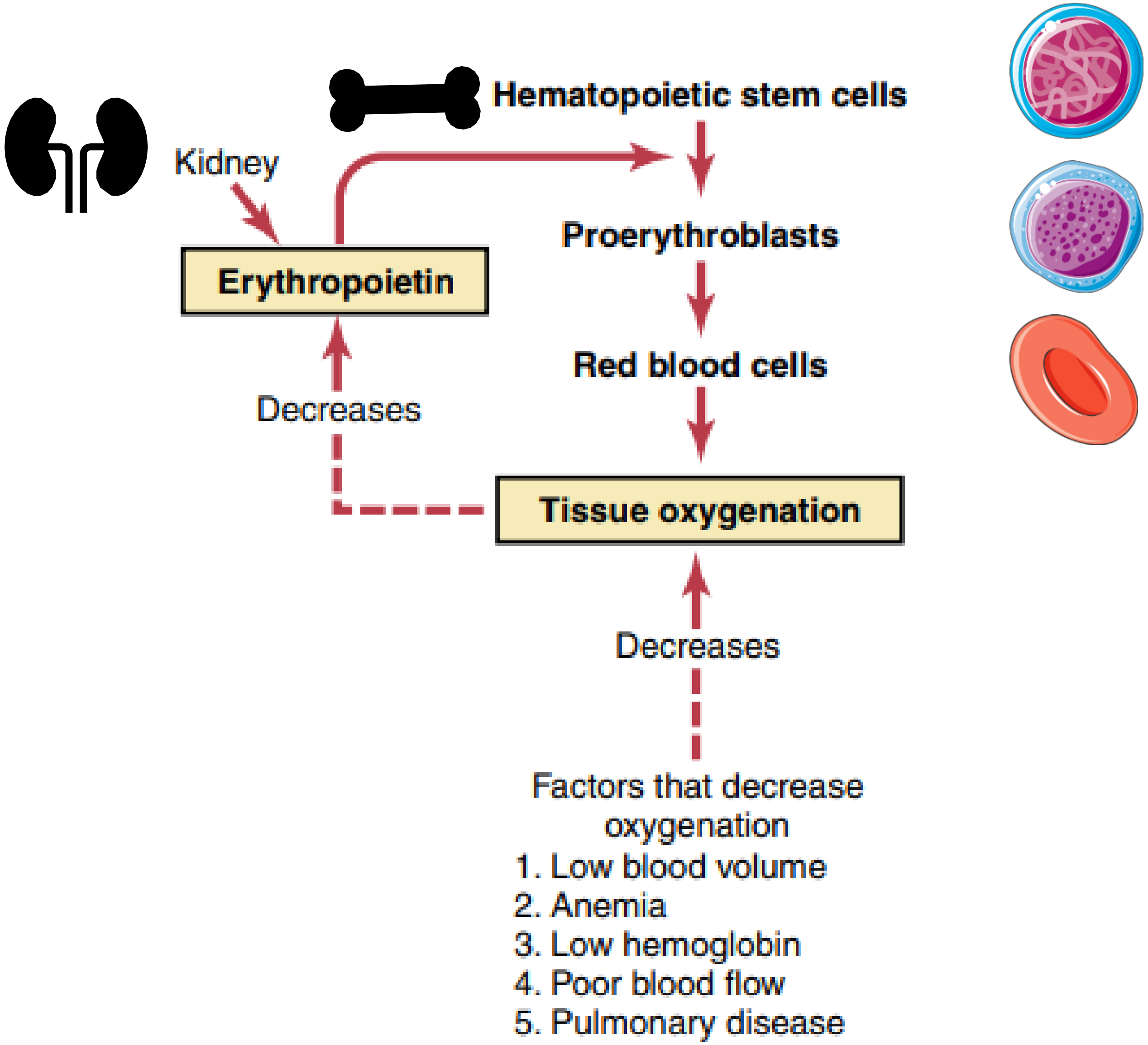


Figure 33-4. Function of the erythropoietin mechanism to increase production of red blood cells when tissue oxygenation decreases.

. When the red blood cell **(RBC) count drops** below the normal range (typically less than 4.5 million cells per microliter), and **oxygen levels fall** below normal (hypoxia), **various factors can be the cause of this**, such as low blood volume (hemorrhage), anemia, reduced hemoglobin production or poor blood flow, which can occur due to conditions like atherosclerosis. Also, pulmonary diseases, or congestive heart failure. All these factors result in decreased oxygen delivery to tissues.

In response to hypoxia, the body triggers the production of erythropoietin (**EPO**), a hormone produced primarily by the **kidneys**. EPO **stimulates** the bone marrow stem cells **to produce more proerythroblasts**, which eventually mature into red blood cells. **As the number of red blood cells increases, tissue oxygenation improves.**

Once normal oxygen levels are restored, **a negative feedback** mechanism reduces EPO production, preventing excessive red blood cell formation.

سُورَةُ النَّجْمِ

بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

وَأَنَّ سَعْيَهُ سَوْفَ يُرَىٰ ٤٠

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2	10 12	pluripotent stem cells in the bone marrow differentiate into adipose tissue as part of the aging process. **depending on the signals and differentiation factors (like IL-3)**	because hematopoietic stem cells in the bone marrow decrease, and mesenchymal stem cells differentiate into adipocytes as part of the aging process. ***IL-3** is a non-specific growth inducer that guides the stem cells along the appropriate developmental pathway.
V2→V3	7	2 million	280 million

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!