

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ
(وَفَوْقَ كُلِّ ذِي عِلْمٍ عِلْمٌ)



HLS Physiology | MID 2

RBCs

Pt.1



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Red Blood Cells/ Erythrocytes



RBC

RBC structure supports function

- Biconcave disc. (thickness of 2.5 μm at the thickest point and 1 μm or less in the center)
- Diameter is normally 7-8 μm .
- Strong, flexible plasma membrane.
- Lack nucleus and mitochondria.
- Contain oxygen-carrying protein (hemoglobin).
- Key erythrocyte enzymes: glycolytic enzymes and carbonic anhydrase.



- ***RBCs Shape and Measurements:***

- 1) Normal Diameter: The normal diameter of red blood cells ranges from 7 to 8 micrometers.
- 2) Geometric Shape: They take the shape of a biconcave disc.
- 3) Microscopic Appearance (Blood Smear): When examining a blood smear under a light microscope, the shape of the cells shows a "central pallor" why? Because the center is the thinnest part, measuring approximately only 1 micrometer. Being very thin in the center means there is less hemoglobin there, while hemoglobin pigment is distributed at the edges. Under the light microscope, light is reflected so that this central area appears paler and brighter.

- **How does the biconcave shape affect the function of red blood cells and its efficiency?**

- 1) Surface Area: The biconcave shape provides a larger surface area compared to if the cell were spherical at the same volume (less SA), and this larger surface area serves gas diffusion better.
- 2) Distance and Fast Diffusion: Because the center is so thin and close, the diffusion space becomes very short, which in turn provides faster and more efficient diffusion.
- 3) Plasma Membrane: The cell features a strong, flexible, and distinguishable plasma membrane.

- **Practical Application of Flexibility:**

Red blood cells can squeeze themselves and fold to pass inside the tiniest capillaries. As an example mentioned by the doctor: in the spleen, there might be capillaries reaching as narrow as 3 micrometers, while the primary cell diameter is 7 to 8 micrometers. Therefore, the RBC must be flexible enough and have an excess plasma membrane so that it can be deformed and bend itself without causing destruction or rupture.

- **Missing Organelles in RBCs and Their Consequences (Nucleus & Mitochondria):**

Red blood cells do not have a nucleus or mitochondria.

First: Lack of Mitochondria and its Impact:

What would be the consequence on the function if there is no mitochondria? no aerobic respiration, and thus less ATP production.

Do they produce energy at all? If I say: "RBCs they cannot produce ATP", is this statement true or false? The answer: **False!**

The Reason: They are able to produce because they have **anaerobic glycolysis**. They produce energy, but it is not aerobic (they lack mitochondria for aerobic respiration), which leads to less ATP production.

Since the cell lacks a nucleus or massive, highly active machinery to consume huge amounts of energy, the 2 ATP molecules produced from each glucose molecule are completely sufficient (it's fine, it's enough).

Second: Lack of Nucleus and its Impact:

Consequence: A shorter life span for the cell.

No nucleus means no new synthesis for proteins, and therefore no replacement.

Our blood cells may undergo protein oxidation and go through a turn-over stage where each protein has a specific half-life, and due to the lack of renewal or replacement, this causes a shorter life span

RBCs have no nucleus (empty cytoplasm), which provides extra space for the RBCs to be filled with hemoglobin.

Function of Hemoglobin: Hemoglobin acts as an oxygen carrier.

Other Cytoplasmic Enzymes: There are other enzymes present in the cytoplasm, such as glycolytic enzymes and carbonic anhydrase.

RBC

General characteristics

- Oligosaccharides in plasma membrane are responsible for ABO and Rh blood groups.
- 5,200,000/ μL in men; and 4,700,000/ μL in women.

Production = destruction (2 million/ sec).

☐ Blood Groups & RBC Count

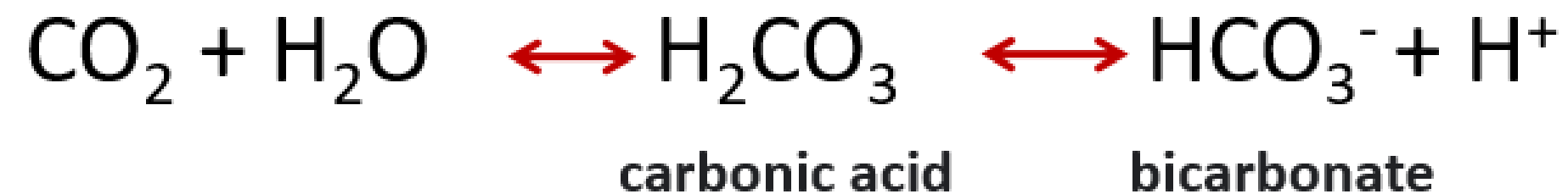
- One of the functions of RBCs is that they determine blood groups. Every person has a blood group different from others, and this is determined by certain oligosaccharides on the surface of the cell membrane.
- Average Count of RBCs: Approximately 5 million per microliter!
- Difference Between Genders: The average count is different between genders; it is higher in males. Reason: The effect of testosterone and the loss of RBCs in females during menstruation.
- To maintain this concentration of RBCs, production must be in equilibrium with destruction (turnover).
- The bone marrow produces about 2 million RBCs per second(erythropoiesis) to maintain balance in the bone marrow and circulation. This is because the count in circulation is 5 million per microliter, not just a total of 5 million.

RBC

Function

RBCs contribute to:

- **Oxygen transport** through hemoglobin.
- **Carbon dioxide transport**, including conversion of CO₂ to bicarbonate.
- **Acid–base buffering**, particularly through hemoglobin.



- **Functions of RBCs (General Overview)**

- 1. Oxygen Transport:**

Mainly the function of hemoglobin inside the RBCs.

- 2. Carbon Dioxide (CO₂) Transport:**

As mentioned, there is an enzyme in the cytoplasm called **carbonic anhydrase**.

Carbonic anhydrase converts water and CO₂ to H₂CO₃. This is a spontaneous reaction, but in the presence of carbonic anhydrase, the reaction becomes faster and more efficient.

We convert CO₂ taken from the tissues into bicarbonate, which is carried throughout the circulation until it gets back to the lungs as CO₂ again and is exhaled.

Is this the only way to carry CO₂?

No, RBCs also help transport CO₂ through hemoglobin. Hemoglobin can carry CO₂ on the globin part (the amino acids part).

This means CO₂ does not compete with oxygen.

In contrast, carbon monoxide (CO) poisoning occurs because CO *does* compete with the oxygen-binding sites on hemoglobin.

- 3. Buffering Function:**

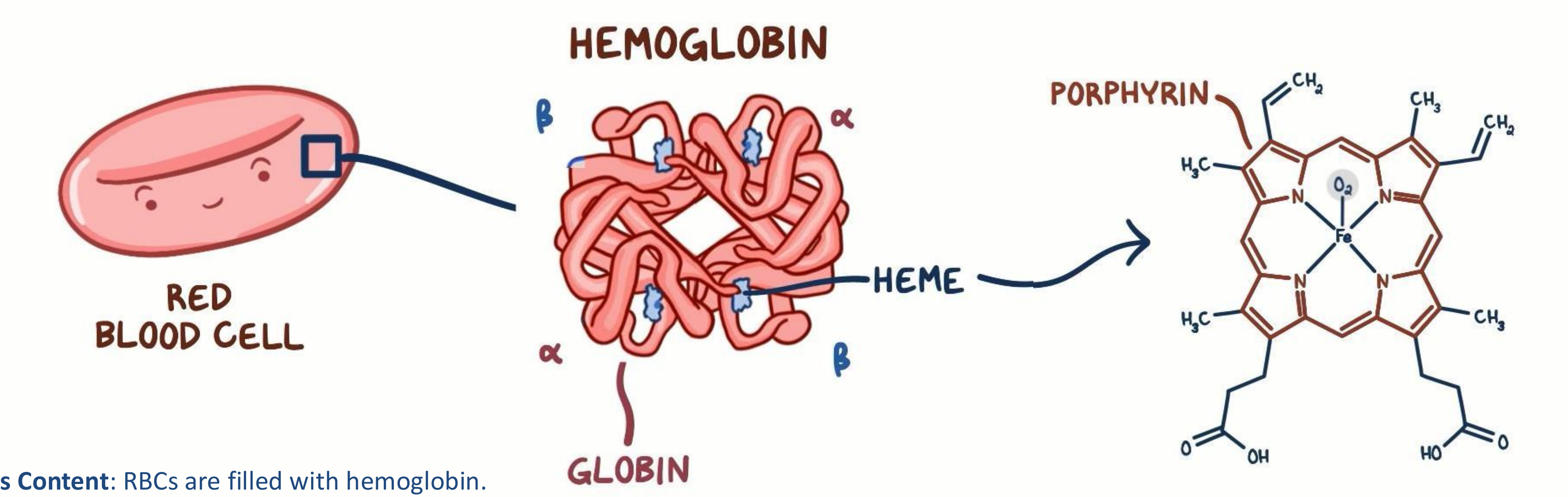
As we previously discussed with plasma, most proteins can act as buffers (acid-base buffering) by donating or accepting hydrogen ions.

RBC

Hemoglobin

RBC

Hemoglobin



RBCs Content: RBCs are filled with hemoglobin.

Adult Hemoglobin Name: In adults, hemoglobin is called Hemoglobin A.

Structure of Hemoglobin A: It is composed of four chains (two alpha chains and two beta chains).

Chain Composition: Each chain contains a heme group.

Heme Group Structure:

It consists of a porphyrin ring. In the center, there is an iron atom (Fe) which can reversibly bind oxygen.

Note: CO₂ can also bind (about 23%) to the globulin part.

RBC

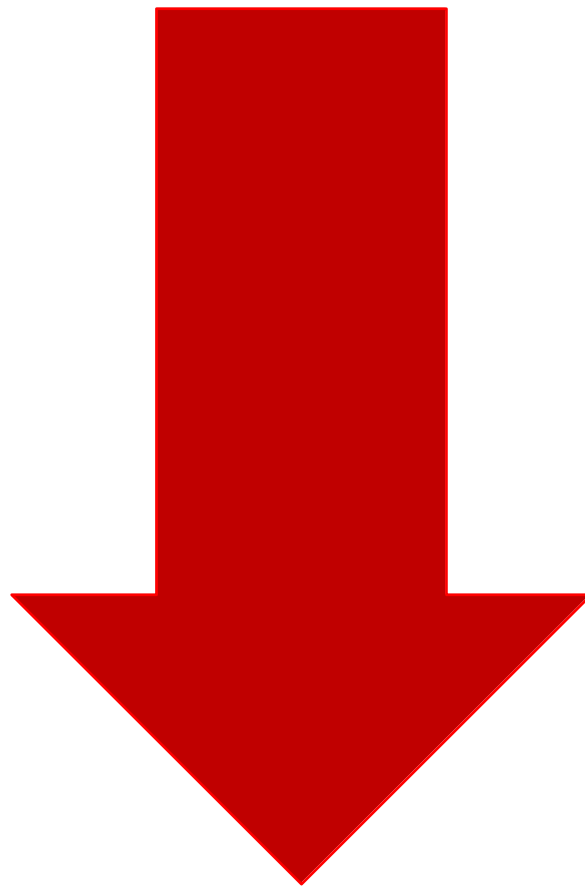
Hemoglobin

- 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).

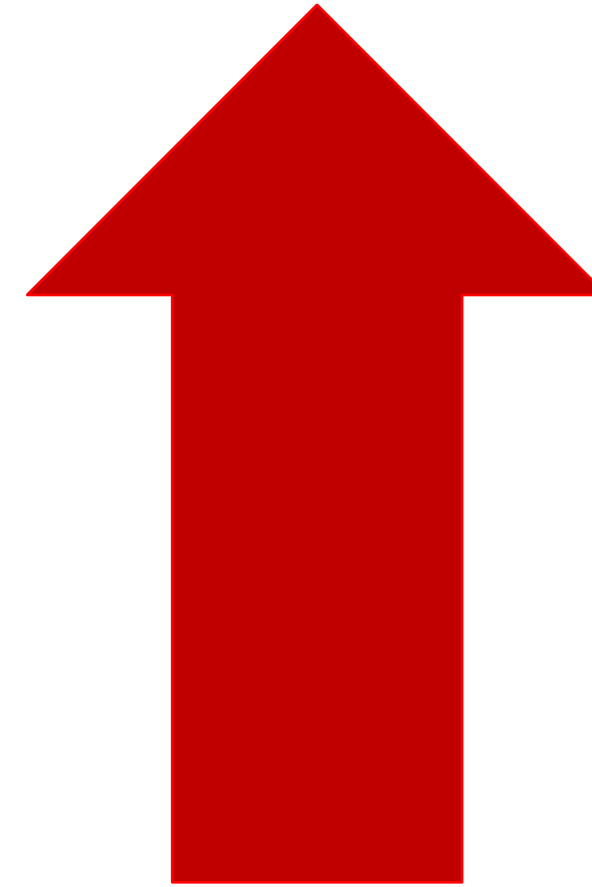
RBC

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

- **Definition of Hemoglobin Count:** When people talk about the "strength of blood" or hemoglobin count, it is actually a measurement of **hemoglobin concentration in the whole blood**.

- **Normal Averages:**

The average is about **14 grams per deciliter (g/dL)** in females, and it is higher in males (units are very important: **g/dL**). This is similar to other RBC parameters.

- **Interpretation of Lab Tests (Anemia & Polycythemia)**

Diagnosing Anemia:

Based on this laboratory test/hemoglobin concentration, if a female's blood hemoglobin is **11 g/dL**, we describe her as "**anemic**".

We cannot say anything else definitively other than that she is *probably* anemic.

As mentioned at the beginning of the lecture, **anemia is not a diagnosis**.

Diagnosing Polycythemia:

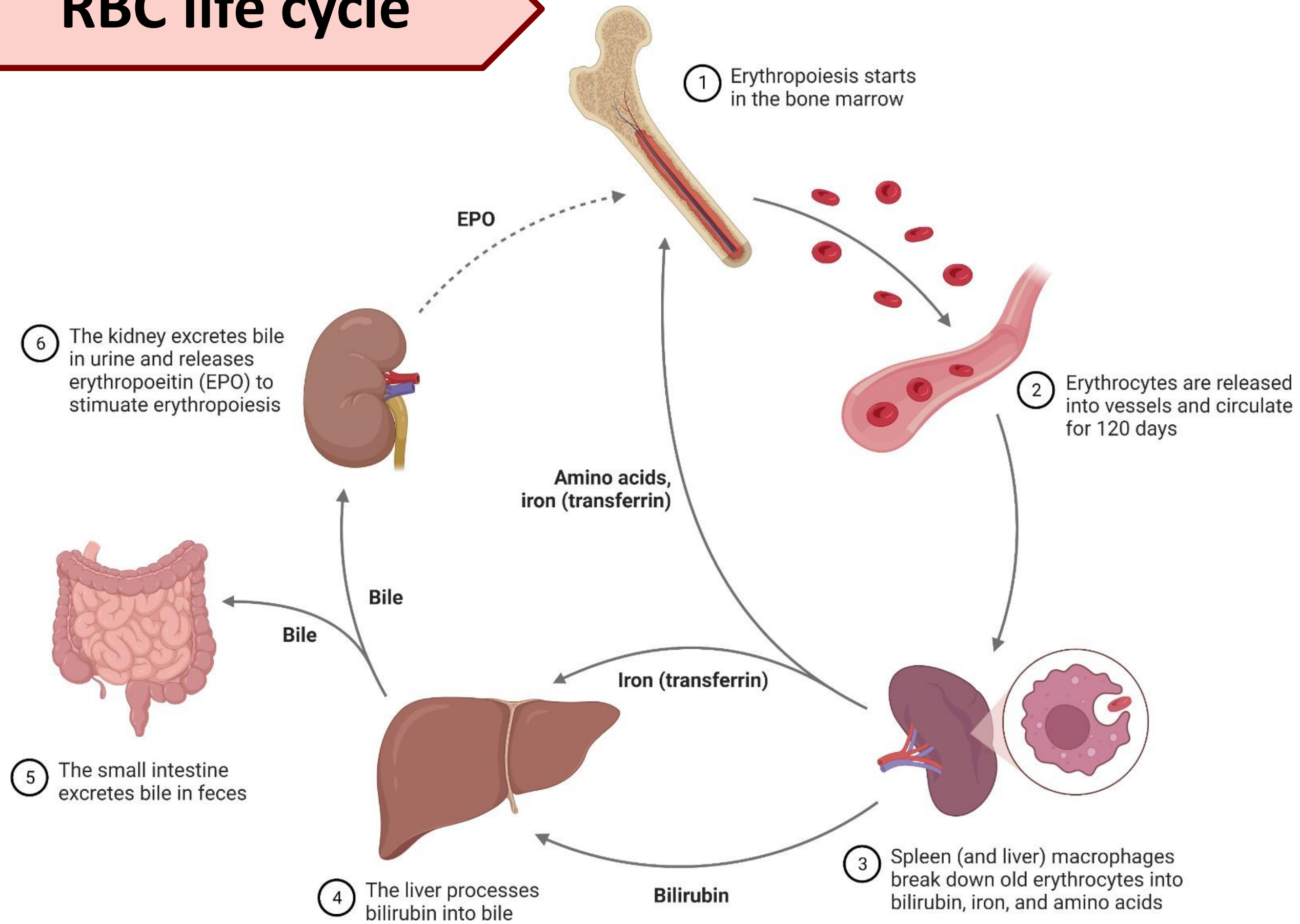
On the other hand, an **increased level of hemoglobin** reflects fully polycythemia.

- **Causes of Anemia**

Anemia can be caused by two main physiological factors (which can occur together or separately):

1. Decreased number of RBCs.
2. Decreased amount of hemoglobin inside the RBCs

RBC life cycle



- **RBCs Life Cycle & Erythropoiesis:**
 - Site of Production:** The process of **erythropoiesis** takes place in the **bone marrow**.
 - Circulation and Lifespan:** RBCs leave the bone marrow into the circulation. The lifespan of RBCs is approximately **120 days** (around 100 to 120 days).
 - Destruction (The Spleen):**

Once they become old enough, they undergo destruction, mainly in the **spleen**.
 - Bone Marrow Location Detail (Shaft):**

Regarding erythropoiesis and the bone marrow, if we look at the shaft: red bone marrow is found in the shaft (at least under the age of 5 years old, when red bone marrow is extensively present there).
 - How the Spleen Identifies Aged RBCs (Filtering Criteria):**
 - Plasma Membrane Integrity:** In the spleen, there are tiny, tiny capillaries. If RBCs are deformed, or have become old enough that they lack the enzymes or proteins suitable to maintain ions, electrolytes, and the integrity of the plasma membrane, once they pass through these tiny capillaries, their membrane undergoes **rupture**.
 - Alternatively, they might already have an **abnormal shape** as they exit the bone marrow (e.g., sphere or abnormal shape).
 - In the spleen, macrophages phagocytize and cause degradation of these aged or ruptured RBCs.



- **Breakdown of RBC Products**

Hemoglobin Breakdown:

Hemoglobin is composed of **protein (globulin)** and **heme**.

Globulin Part:

We degrade globulin into **amino acids**, which can be recycled and reused by the body.

Heme Part:

Heme consists of a **porphyrin ring** and **iron (Fe)**.

Iron (Fe) Fate:

Iron is **not** excreted in the urine.

There is only a slight shedding through the Gastrointestinal (GI) tract.

Iron is one of the minerals/ions where the body controls its level via **absorption** rather than excretion. In females, there are menstrual cycles, but once iron enters the body (and since there are no regular menstrual cycles like in males), tiny amounts leave the body only through GI shedding.

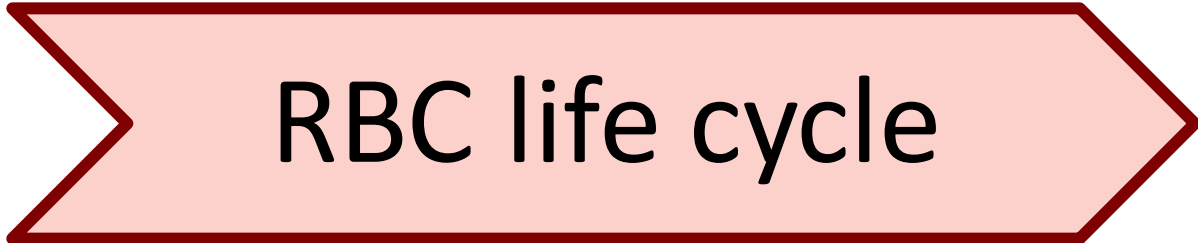
Therefore, since iron is not excreted in the urine, it is **reused** in erythropoiesis or stored with ferritin in the body.

Porphyrin Ring Fate:

The porphyrin ring is converted into **bilirubin**, which gets secreted into the bile, and finally, the final-final product is excreted in the feces or urine.

Once the cell membrane undergoes degradation and destruction, this is the pathway.

RBC



What happens to RBC components?

Component	Main fate
Globin	Breakdown to amino acids for reuse
Iron	Recovery and reuse in erythropoiesis or storage
Heme pigment remainder	Conversion to bilirubin and hepatic processing
Cell membrane	Macrophage degradation and recycling

RBC

Erythropoiesis

close to the Hemopoiesis which is formation of blood cells .
while Erythropoiesis is formation of red blood cells .

- 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.

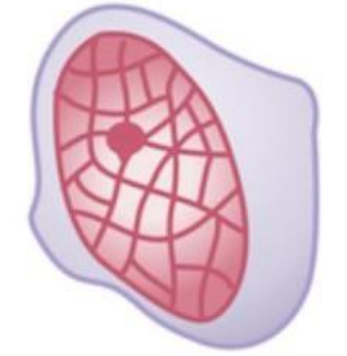
it is remnant of ribosomal RNA ,Golgi apparatus and some organelles .

Reticulocyte it can be found, or release in circulation ; however it is a low Percentage (1-2 %) of normal RBCs in circulation.

NOTE : BONE MARROW RELEASE RETICULOCYTE AND AFTER 1-2 DAYS IT WILL BE FULL MATURE RBCs IN THE CIRCULATION.

Genesis of RBCs

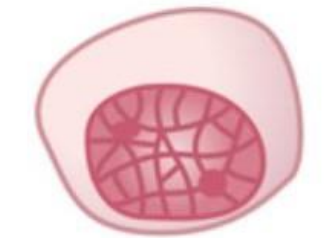
Proerythroblast



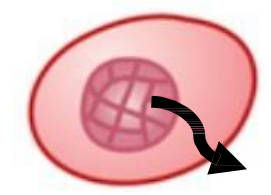
Basophil erythroblast



Polychromatophil erythroblast



Orthochromatic erythroblast

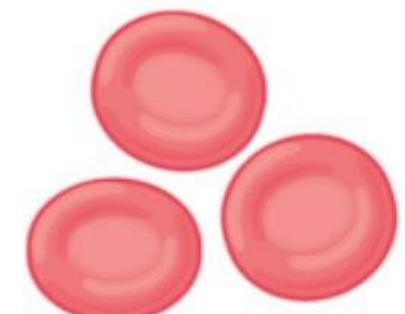


Nucleus exocytosis

Reticulocyte



Erythrocytes



what is the difference between proerythroblast and Fully mature Erythrocytes(RBCs):

1. **Presence of Nucleus:** The proerythroblast contains a nucleus, while mature RBCs lack a nucleus.
 2. **Shape:** The proerythroblast has a spherical/irregular shape, while the mature erythrocyte is biconcave in shape.
 3. **Proliferation:** The proerythroblast can replicate its DNA and proliferate because it has a nucleus, while RBCs cannot replicate because they lack a nucleus.
 4. **Differentiation:** The erythrocyte is fully differentiated.
 5. **Size:** The proerythroblast is a big cell, while the erythrocyte is a small cell.
 6. **Color (reflecting hemoglobin):** The proerythroblast is dark blue because it lacks hemoglobin, while the erythrocyte is red because it is full of hemoglobin. Hemoglobin synthesis starts in the polychromatophilic erythroblast stage.
 7. **Organelles:** The proerythroblast has organelles, while the erythrocyte does not.
 8. **Site:** We can see the proerythroblast in the bone marrow, while the erythrocyte is in circulation.
- The stage just before a fully mature erythrocyte is called the **reticulocyte**.
 - The formation of a reticulocyte is the next step following **nucleus exocytosis** (which means the disappearing of the nucleus).
 - It is called a **reticulocyte** because under the microscope, some basophilic material appears to make a network inside the cytoplasm.

How much production maintains the pool?

$5 \times 10^6 \text{ RBCs}/\mu\text{L} \times 5 \times 10^6 \mu\text{L blood}$

$\approx 25 \times 10^{12}$ circulating RBCs

$25 \times 10^{12} \div 120 \text{ days} \div 86,400 \text{ seconds/day}$

≈ 2.4 million RBCs replaced each second

≈ 208 billion RBCs/day"

A large circulating population requires continuous renewal.

- EPO 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.
- Negative feedback balances production with destruction.

- **Regulation of Erythropoiesis**

Importance of Regulation: Erythropoiesis is highly regulated because the number of RBCs in circulation must remain within the normal range (5×10^6 RBCs/uL).

If RBCs decline, there will be a problem delivering oxygen to tissues.

If RBCs increase, it will negatively affect blood viscosity and blood flow.

- **Erythropoietin (EPO)**

Definition: A glycoprotein hormone produced by the kidneys.

Function: It travels to the bone marrow to stimulate the synthesis, proliferation, and differentiation of proerythroblasts into fully mature RBCs.

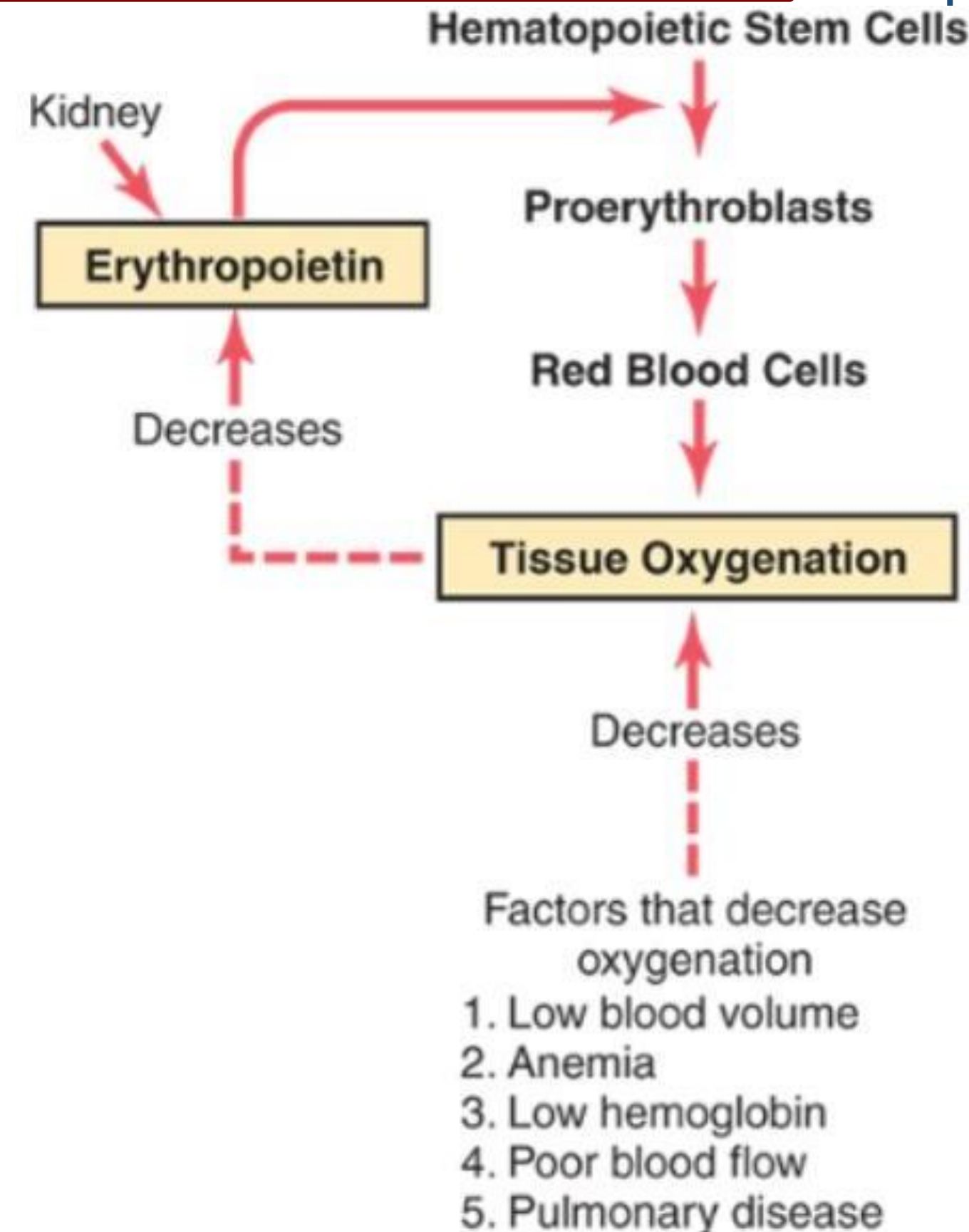
Control of Secretion: EPO secretion is controlled by **hypoxia**, which is defined as low oxygen delivered to tissues.

- **Causes of Hypoxia**

1. **Anemia:** Fewer RBCs available to carry oxygen.
2. **Low environmental oxygen:** Reduced oxygen levels in the air itself.
3. **High oxygen demand:** Increased metabolic demand (e.g., in athletes).
4. **Lung diseases:** Impaired gas exchange in the lungs.
5. **Smoking:** Reduced oxygen-carrying capacity of the blood.
6. **Impaired circulation:** Problems with or reduced blood flow.

- **Mechanism / Pathway of EPO Production:**
 - If any cause of hypoxia occurs (leading to low tissue oxygenation):
 1. The **kidney** detects the lack of oxygen via tissue sensors.
 2. **Hypoxia-Inducible Factor (HIF)** is activated.
 3. HIF acts on the nucleus to synthesize new RNA/mRNA.
 4. The mRNA is translated to produce **erythropoietin (EPO)**.
 5. EPO enters the circulation and travels to the bone marrow to stimulate erythropoiesis.

- 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



What stimulates the EPO response?

- **Anemia or blood loss:** less hemoglobin available to carry oxygen.
- **Low blood oxygen:** for example, at high altitude or with lung disease.
- **Reduced kidney blood flow:** less oxygen delivered to kidney tissue.

The shared signal is inadequate oxygen availability to renal tissue.

Erythropoiesis REQUIRE important vitamins:

□ Role of Vitamin B12 and Folic Acid :

- **Importance:** Vitamin B12 and folic acid are essential for DNA synthesis and replication.
 - **Deficiency / Impairment:** If there is a problem with DNA synthesis and replication during RBC production:
 - 1) The cytoplasm continues to grow larger and larger.
 - 2) However, the nucleus is unable to replicate and divide its DNA.
 - 3) This creates an abnormally large cell called a **megaloblast**, which has a weak/fragile membrane, leading to damaged or ineffective erythropoiesis.
- ✓ If these cells enter circulation, they are larger than normal and are called **macrocytes**.

RBC

Vitamins requirement

- Maturation of red blood cells requires vitamin B₁₂ (Cyanocobalamin) and folic acid.
- Both of these are essential for the synthesis of DNA (formation of thymidine triphosphate).
- lack of either vitamin B₁₂ or folic acid causes: abnormal and diminished DNA → failure of nuclear maturation and cell division → production of larger red cells called **macrocytes**, the cell itself has a flimsy irregular membrane → short life span

Proerythroblast



Nucleus
exocytosis



Reticulocyte



Erythrocytes



Check your understanding

Which finding best fits untreated B12-related maturation failure?

A. High effective RBC output despite anemia

B. Inadequate reticulocyte response with abnormal large RBCs

C. Isolated loss of plasma volume

D. Immediate normalization of RBC mass after EPO rises.

Ans: B

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اللهم انفعنا بما علّمتنا، وعلمنا ما ينفعنا، وزدنا علمًا، ووفّقنا لما تحب
وترضى، واجعل هذا العلم حُجَّةً لنا لا علينا، وانفع بنا عبادك،
واكتب لنا الأجر والتوفيق في كل خطوة. ♡

اللَّهُمَّ

انْفَعْنَا بِالْعِلْمِ

وَزَيِّنَا بِالْحِلْمِ

وَحَلِّنَا بِالتَّقْوَى

وَكَرِّمْنَا بِالْعَافِيَةِ

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