بسم الله الرحمن الرحيم

Physiology

﴿ وَقُل رَّبِّ أَدْخِلْنِي مُدْخَلَ صِدْقٍ وَأَخْرِجْنِي مُخْرَجَ صِدْقٍ وَاجْعَل لِّي مِن لَّدُنكَ سُلْطَانًا نَّصِيرًا ﴾

ربنا آتنا من لدنك رحمة وهيئ لنا من أمرنا رشدًا

MID | Lecture 3

# Erythropoiesis Requirements (Pt.1)


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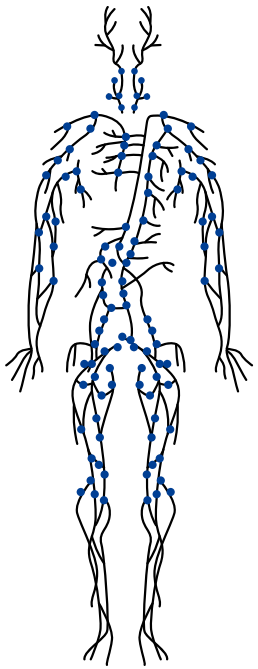


# Erythropoietin (EPO)

- Circulating hormone, mw ~34,000
- Necessary for erythropoiesis in response to hypoxia, so if erythropoietin production is disturbed, hypoxia will not affect erythropoiesis.
- ~90% made in the kidney
- Cells of origin not established, but some references suggest that they are interstitial cells or epithelial tubular cells.


- HIF-1: Hypoxia-induced factor 1 (a transcription factor)

# Erythropoietin (cont'd)

- **Extra-renal hypoxia can stimulate Epo production.**

  In response to hypoxia, extra-renal tissues signal the kidneys to produce erythropoietin; some signaling mediators are the hormones below.

  - **epinephrine, norepinephrine, and some prostaglandins can promote Epo production.**

- **In anephric or in kidney failure → severe anemia (low RBCs) because 90% of Epo is made in the kidneys.**

- **In anephric individuals, 10% residual Epo (mainly from liver), supports 30-50% needed RBC production (not enough).**
  - **Hematocrit (packed cell volume) ~23-25% rather than 40- 45%**

# Response to Hypoxia

- Minutes to hours ⬆ Erythropoietin
- New circulating reticulocytes ~ 3-5 days 
- Erythropoietin (2 roles in erythropoiesis)
  - drives production of proerythroblasts from HSCs
  - accelerates their maturation into RBCs
- Can increase RBC production up to 10-fold
- Erythropoietin remains high until normal tissue oxygenation is restored, which inhibits further Epo production by negative feedback through blocking renal and extra-renal pathways that induce Epo production.

# Formation of Hemoglobin

- Occurs from proerythroblast through reticulocyte stage.
- Reticulocytes retain a small amount of endoplasmic reticulum and mRNA, supporting continued hemoglobin synthesis.
- Mature RBCs do NOT produce new hemoglobin.

# Shapes of RBC and Hemoglobin

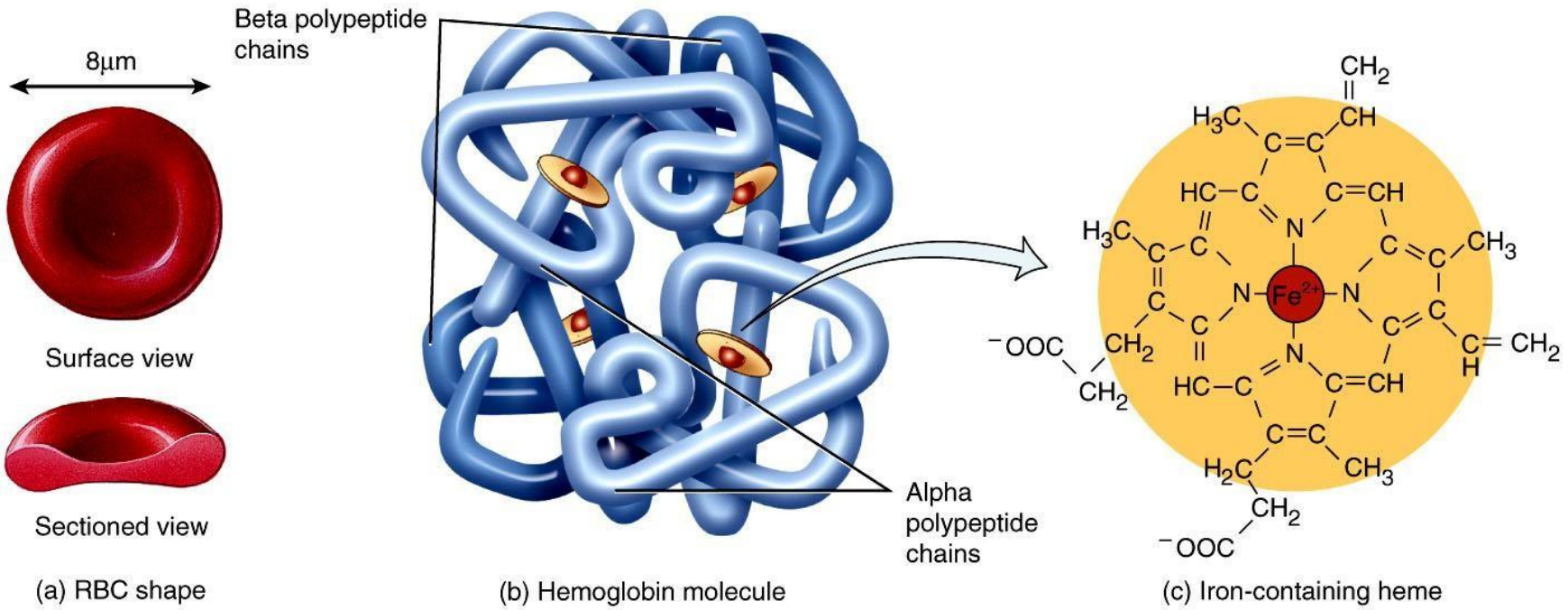
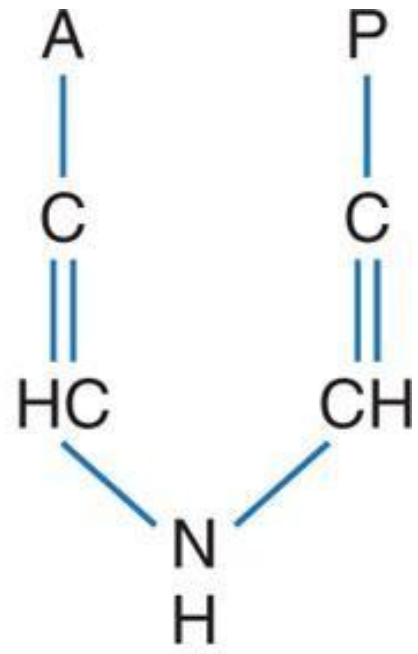



Figure 19.04 Tortora - PAP 12/e



- Similar details as we took in biochemistry – hemoglobin is stored in RBCs, and each hemoglobin molecule has 4 chains, 2 alpha and 2 beta, and each chain has a heme group, which contains one iron atom, which can bind one $O_2$, so each hemoglobin can carry 8 oxygen atoms in the form of 4 molecular oxygens ($O_2$).

# Formation of Hemoglobin

I. 2 succinyl-CoA + 2 glycine → 

(pyrrole)

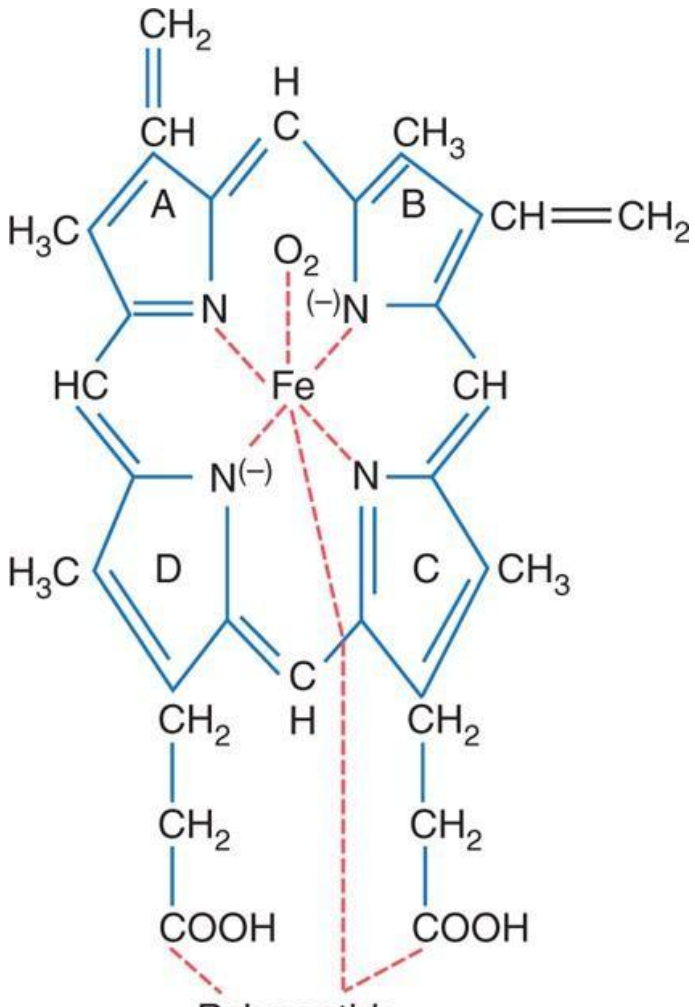
II. 4 pyrrole → protoporphyrin IX

III. protoporphyrin IX + $Fe^{++}$ → heme

IV. heme + polypeptide → hemoglobin chain ($\alpha$ or $\beta$)

V. 2 $\alpha$ chains + 2 $\beta$ chains → hemoglobin A (most common adult form)

# Hemoglobin Structural Units





- Notice the heme group on the left.
- The bond between the oxygen (one of the oxygens of $O_2$) and Fe is a coordinate covalent bond, not an ionic bond.

- Recall chemistry 101:

A coordinate covalent bond is a bond where one atom shares a pair of electrons, and the other atom accepts the pair in a vacant orbital. In this case, $O_2$ is the electron donor and $Fe^{2+}$ (ferrous iron) is the acceptor.

# Types of Globin Chains

- Several types of globin chains resulting from gene duplication – α, β, γ, δ; MW ~ 16,000
- Predominant form in adults is Hemoglobin A, with 2 α and 2 β chains; MW 64,458
- Each globin chain is associated with one heme group containing one atom of iron
- Each of the four iron atoms can bind loosely with one molecule (2 atoms) of oxygen
- Thus, each hemoglobin molecule can transport 8 oxygen atoms.

Clinical Perspective

# Variation in Globin Chains

- **Modest differences in $O_2$ binding affinities; wait for slide 13.**
- **Sickle hemoglobin:**

  **Glutamic acid ⟶ Valine at AA 6**

- **Hemoglobin of homozygous individuals ("SS") forms elongated crystals when exposed to low $O_2$.**
- **The crystals makes RBCs lose their flexibility**

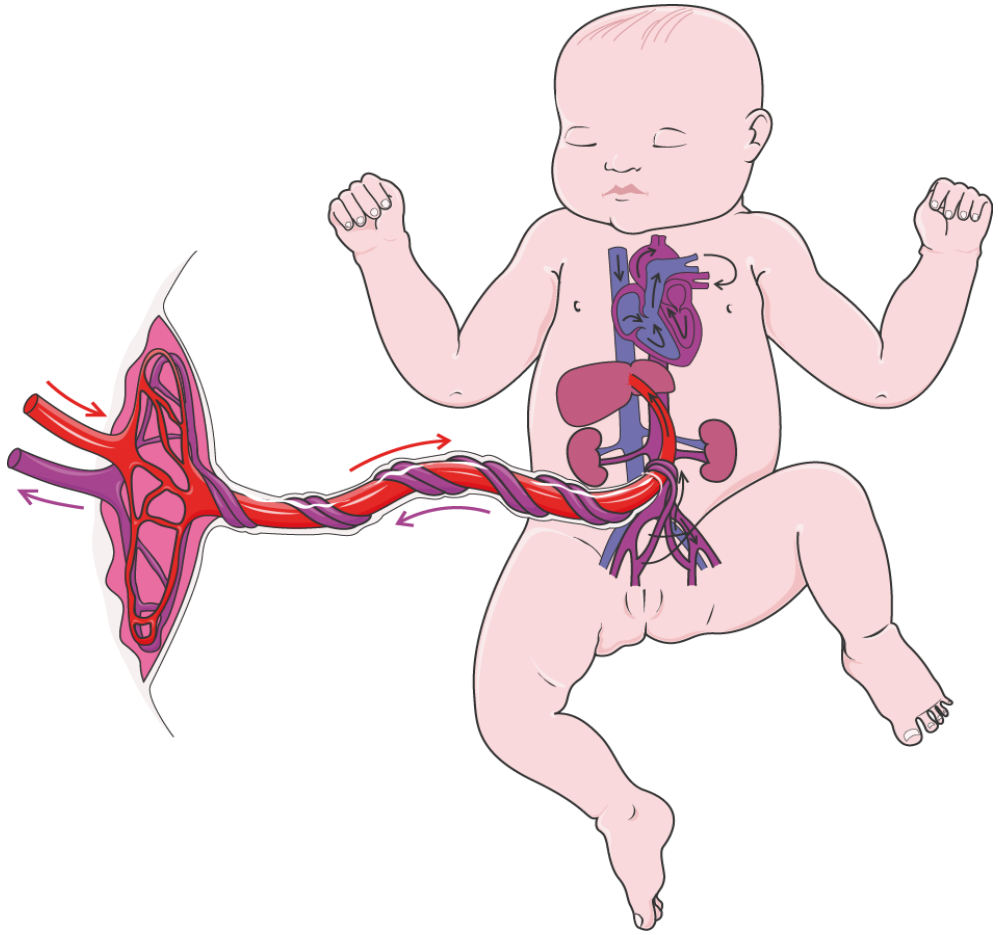
  **⟶ hemolysis, vascular occlusion**

# Oxygen Binding to Hemoglobin

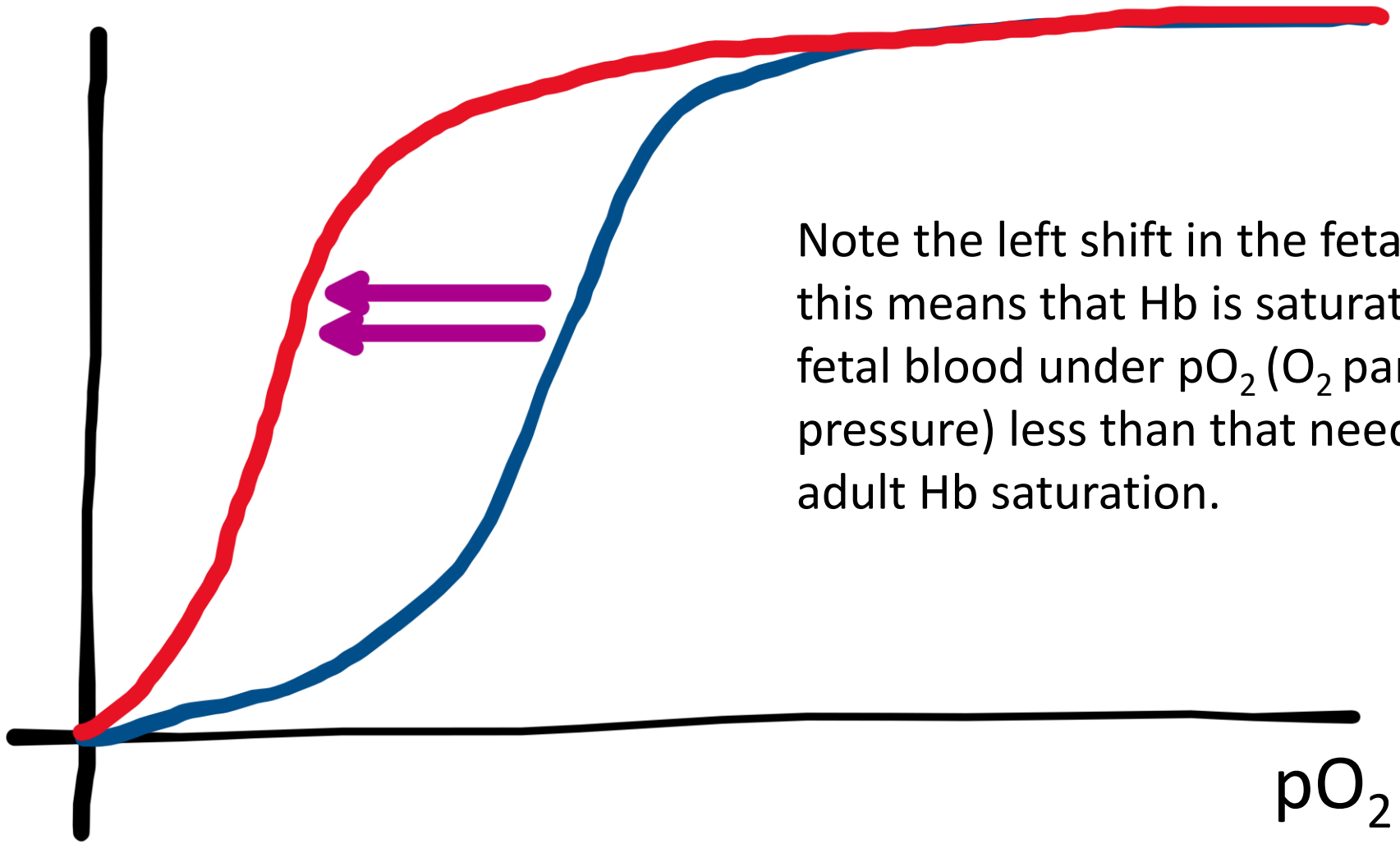
- **Must be loosely bound – binding in settings of higher $O_2$ concentration, releasing in settings of lower concentration.**
- **Binds loosely with one of the coordination bonds of iron.**
- **Carried as molecular oxygen (not as ionic oxygen).**

# Fetal hemoglobin

- Fetal hemoglobin is a principal oxygen carrier in blood in fetus and neonates.
- It has higher affinity to oxygen and the OHD curve is shifted to the left. (efficient extraction of oxygen from the mother's circulation).
- It is composed of 2 alpha and 2 gamma (not beta) subunits.



# OHD curve (extra slide)




- **Adult**
- **Fetal**

Note the left shift in the fetal curve; this means that Hb is saturated in fetal blood under $pO_2$ ($O_2$ partial pressure) less than that needed for adult Hb saturation.

# Iron Metabolism

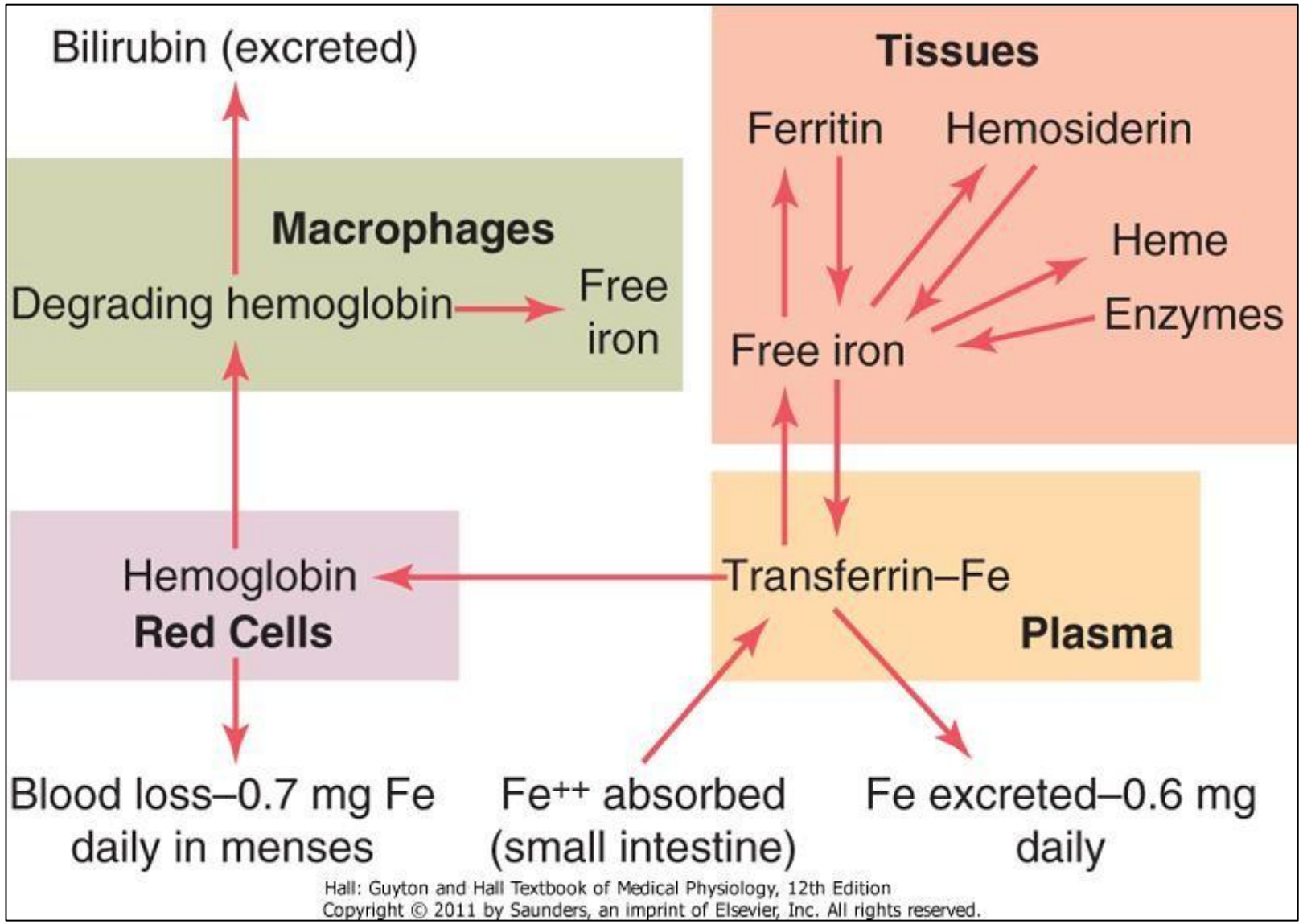
- Iron is a key component of hemoglobin, myoglobin, and multiple oxidation enzymes (cytochromes, cytochrome oxidase, peroxidase, catalase)
- Thus, iron stores are critically regulated
- Total body iron ~ 4 – 5 g
  - 65% in hemoglobin in RBCs
  - 4% in myoglobin in muscle cells
  - 1% in intracellular heme compounds
  - 0.1% associated with circulating transferrin
  - 15 – 30% stored mainly as ferritin in RES

- Transferrin is a specialized protein that transports iron in plasma

RES: Reticuloendothelial system

# Iron Transport and Metabolism

Explanation in the next slide



# Iron transport and metabolism

## 1. Forms of Iron in Tissues

Iron is present in tissues bound to the storage protein **ferritin**.
When ferritin becomes saturated, the excess iron binds to **hemosiderin** (seen as clusters of iron inside cells).
Iron can also be bound to **heme** in various cells and enzymes.

## 2. Iron in the Blood

**Free iron** outside cells must be bound to **transferrin**.
This iron is continuously renewed by **hemoglobin** that breaks down during the RBC life cycle.

## 3. Breakdown of Hemoglobin

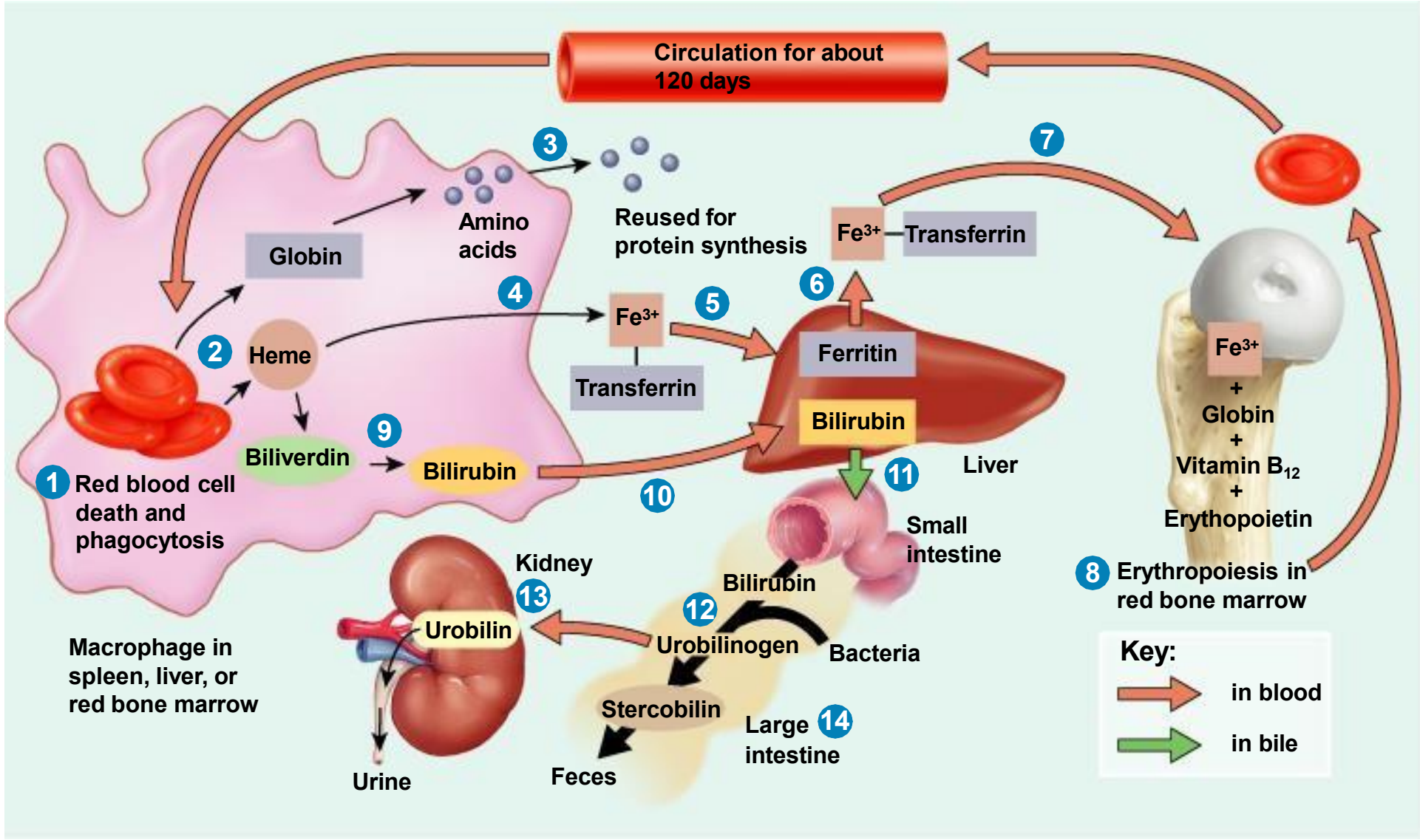
When **hemoglobin** is degraded from aged RBCs in the **bone marrow, spleen, or liver**,
free iron released from it is carried in **plasma** to where it should be used or stored.

## 4. Iron Loss and Absorption

Around **0.6 mg** of iron is excreted daily through the **GI system**.
In females, about **0.7 mg** is lost during **menses**.
**Iron absorption** from the diet occurs in the **small intestine**, and only the needed amount is absorbed. The rest is excreted.

Explanation in the next couple of slides

# Formation and Destruction of RBC's



# RBC Breakdown and Iron Recycling

**1. Destruction of Aged RBCs**
Aged and damaged RBCs in the **spleen, liver, or bone marrow** are **engulfed by macrophages**.
In the **liver**, these macrophages are known as **Kupffer cells**.

**2. Reuse of Hemoglobin Components**
After being **phagocytosed**, the components related to **hemoglobin** are **reused**.

**3. Breakdown of the Globin Part**
The **globin** portion is **converted into amino acids**, which are **reused for protein synthesis**.

**4. Handling of the Heme Part (Iron Transport)**
The **iron** from the heme is **transported by transferrin**, a protein responsible for iron transport.
Iron remains **bound to transferrin in the plasma** during transport.

**5. Iron Storage in the Liver**
Iron transported by **transferrin** can be **taken up by the liver** and **stored in ferritin**, the main iron-storage protein.

**6 & 7. Iron Release and Erythropoiesis**
When there is a **need for new RBC or hemoglobin production**,
**Iron** is **released from ferritin** and transported by **transferrin** to the **bone marrow**.
In the **bone marrow**, **iron**, **amino acids**, **vitamin B12**, **folic acid**, and **erythropoietin (EPO)** are all used for **erythropoiesis** (new RBC formation).

# RBC Breakdown and Iron Recycling

**8. RBC Life Cycle**
Each **RBC circulates for about 120 days**, then is **engulfed again by macrophages**, repeating the same cycle.

**Fate of the Heme (Non-Iron Part)**

**9. Conversion of Heme to Biliverdin and Bilirubin**
After **iron** is removed, the remaining part of the **heme** is converted to **biliverdin**, then to **bilirubin** inside the macrophage.

**10. Transport of Bilirubin**
**Bilirubin** is transported through the **blood to the liver**.

**11. Excretion of Bilirubin**
In the **liver**, bilirubin is **excreted with bile** into the **duodenum**.

**12. Conversion in the Intestine**
In the **small intestine**, bilirubin is **converted by bacteria** into **urobilinogen**.
Urobilinogen is further converted to **stercobilin**, which gives **feces** their **brown color**.

**13. Urobilin Formation and Urinary Excretion**
Some **urobilinogen** is reabsorbed into the blood and **excreted in urine as urobilin**, giving **urine** its **yellow color**.

# Iron Absorption, Transport & Storage

- **Absorbed from small intestine, combines with**

***apotransferrin*** ⟶ ***transferrin*** **(transport iron)**

- **Iron can be released to any cell for intracellular use.**

- **RBC precursors have transferrin receptors and actively accumulate iron because iron is essential for erythropoiesis, especially for hemoglobin synthesis.**

- **Particularly in hepatocytes and reticulo-endothelial cells, iron combines with *apoferritin* ⟶ *ferritin***
  **(Large protein: MW 460,000)**
  - When apoferritin binds iron, it is called ferritin.

- **Ferritin is variably saturated (storage iron)**
  - Sometimes it is fully saturated, other times only partially.

- ***Hemosiderin* is quite insoluble excess iron over the capacity of ferritin.**
  - The clusters of iron can be apparent under LM as a pigment called hemosiderin, while ferritin can only be seen with an EM.

# Iron Exchange

- When iron in the plasma is low, iron is released from ferritin and bound to transferrin for transport.
- It is delivered to the bone marrow, bound by transferrin receptors on erythroblasts, internalized, and delivered directly to the mitochondria (the place of heme production) for incorporation into heme.
- Deficiency of transferrin or apotransferrin can result in severe *hypochromic* anemia due to lack of iron.
- Hemoglobin released from senescent RBCs is ingested by macrophages and stored as ferritin in the liver.

# Iron Balance

- Daily iron loss of ~ 0.6 mg/day in men (GI) or ~1.3 mg/day in women (GI and menses)
- Iron is absorbed throughout the small intestine
- Liver secretes ***apotransferrin*** into the bile, which binds with free iron and some iron compounds present in meals (e.g, myoglobin in meat) to become ***transferrin***
- Iron binds to transferrin and the complex binds to ***transferrin receptors*** on intestinal epithelium

The doc. said iron binds to transferrin receptors, but it is the complex that binds.

- Transcytosed into the blood as plasma transferrin
- Maximal absorption of a few mg per day (5-6mg), modulated over 5 – 6-fold range based on body stores

More iron needed = more absorption
Less iron needed = less absorption

# RBC Senescence & Destruction

- RBC life span is ~120 days
- Though lacking a nucleus, mitochondria, and endoplasmic reticulum, RBCs have enzymes that can metabolize glucose anaerobically and make small amounts of ATP. These enzymes…
  - Maintain membrane pliability
  - Support ion transport
  - Keep iron in the ferrous form (rather than ferric)
  - Inhibit protein oxidation
- As enzymes deplete with age, RBCs become fragile and rupture in small passages of the RES, often in the spleen.

# Degradation of Hemoglobin

- When RBCs rupture, hemoglobin is phagocytosed by macrophages, particularly in the liver and spleen
- Iron is released back to transferrin in the blood to support erythropoiesis or be stored as ferritin
- Macrophages convert the porphyrin portion, stepwise, into bilirubin, which is released into the blood and secreted by the liver into the bile

# Physiology Quiz 3

# For any feedback, scan the code or click on it.

Corrections from previous versions:

| Versions | Slide # and Place of Error | Before Correction | After Correction |
|---|---|---|---|
| V0 → V1 | | | |
| V1 → V2 | | | |