Hematology/ Physiology

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Part 1

Erythropoiesis requirements

Erythropoietin (EPO)

- Circulating hormone, mw ~34,000
- Necessary for erythropoiesis in response to hypoxia
- ~90% made in the kidney
- Cells of origin not established

Hypoxia → *HIF-1* → binds hypoxia

response element → ↑ *Epo* transcription

Erythropoietin (cont'd)

- **Extra-renal hypoxia can stimulate Epo production…**
  - **epinephrine, norepinephrine, and some prostaglandins can promote Epo production**
- **In anephric or in kidney failure; severe anemia ????**
- **In anephric individuals, 10% residual Epo (mainly from liver), supports 30-50% needed RBC production…**
  - **Hematocrit (packed cell volume) ~23-25% rather than 40- 45%**

Response to Hypoxia

- Minutes to hours… ⬆ Erythropoietin
- New circulating reticulocytes…~ 3 days 
- Erythropoietin…
  - 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.

Formation of Hemoglobin

- **Occurs from proerythroblast through reticulocyte stage**
- **Reticulocytes retain a small amount of endoplasmic reticulum and mRNA, supporting continued hemoglobin synthesis**

Shapes of RBC and Hemoglobin

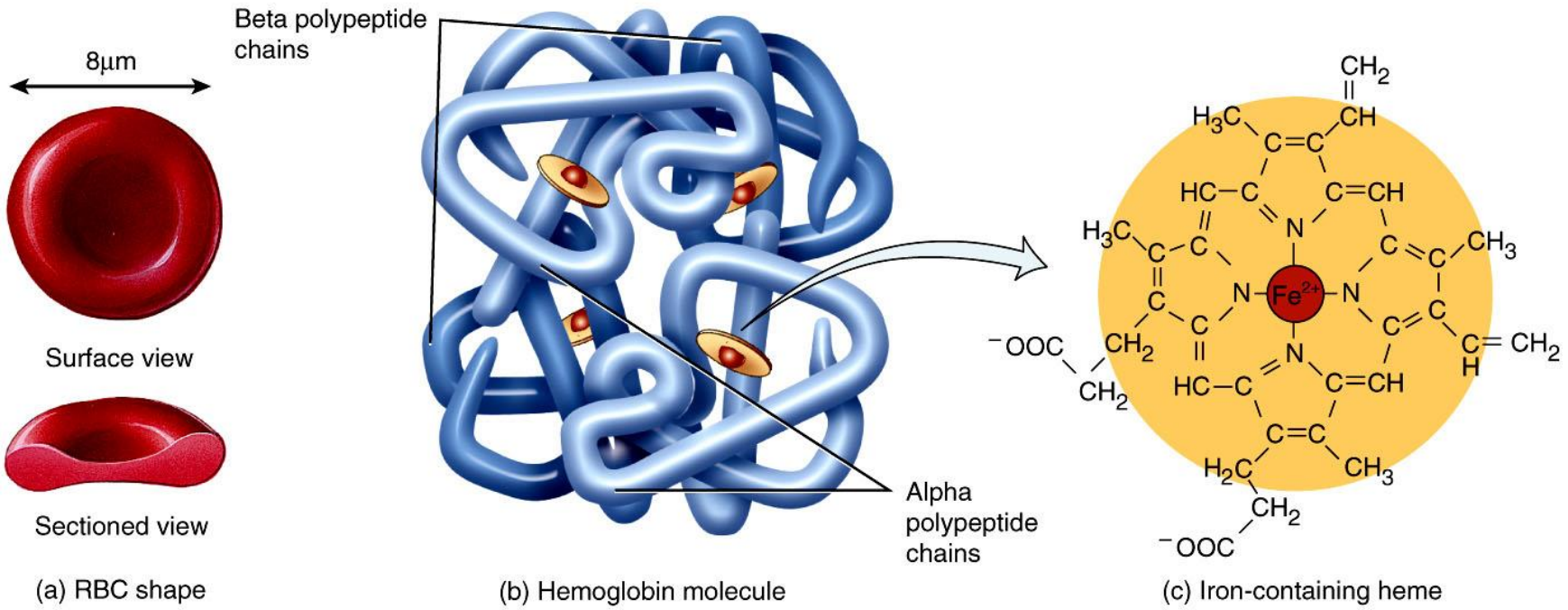
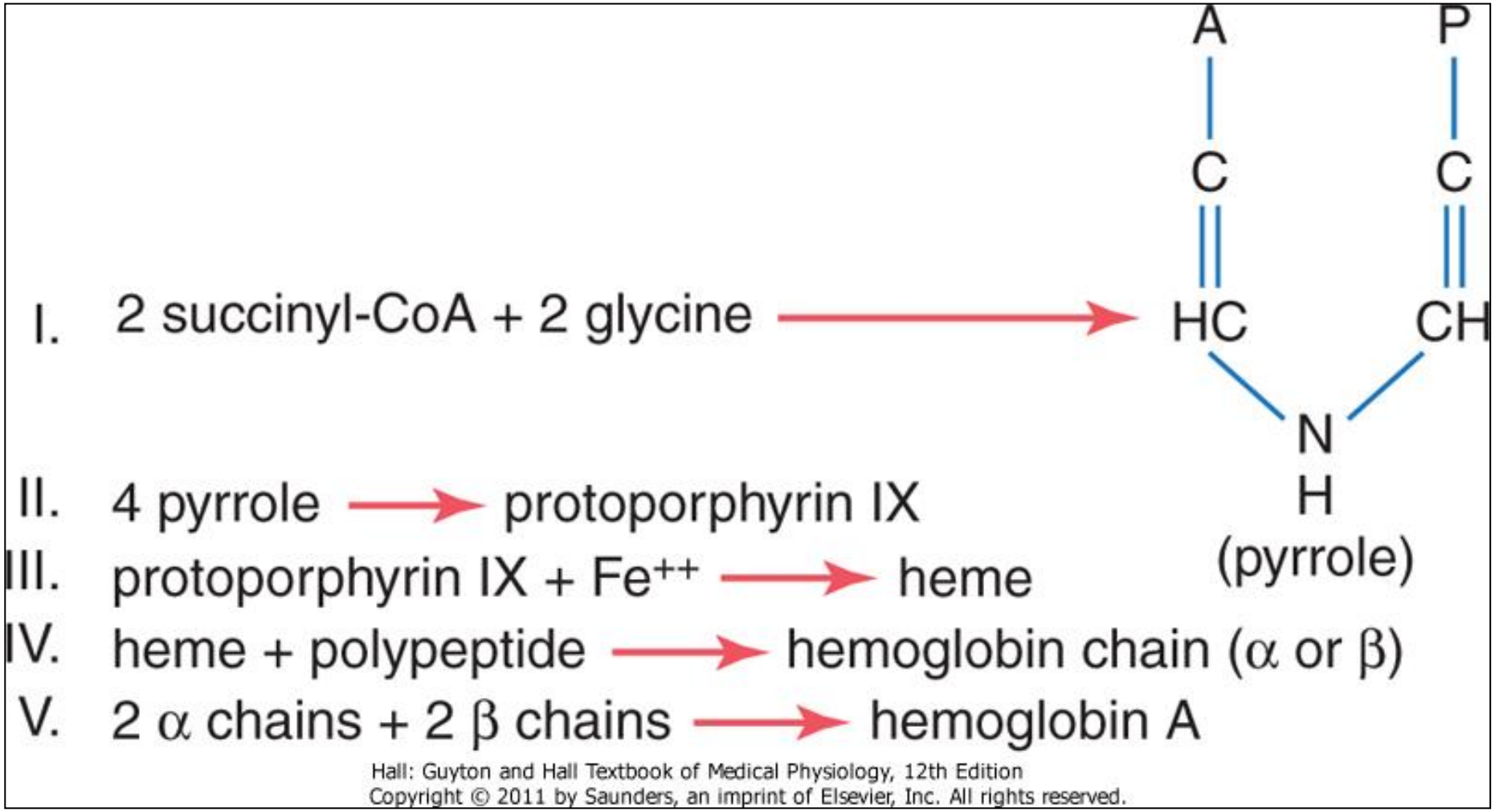
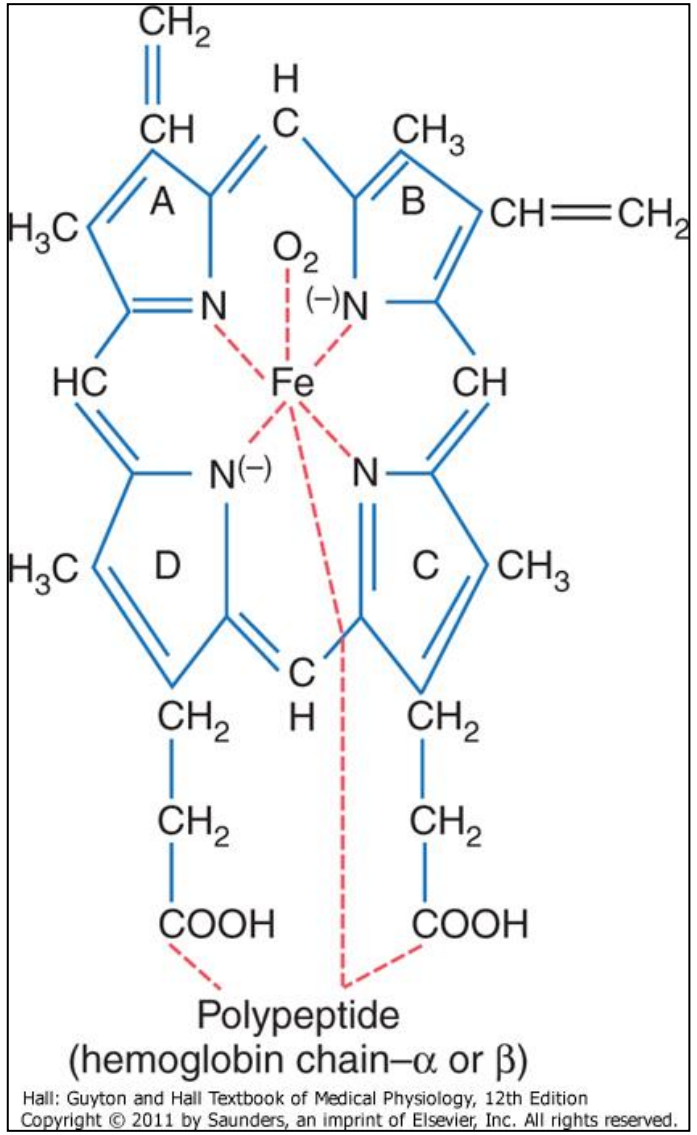


Figure 19.04 Tortora - PAP 12/e

Formation of Hemoglobin



Hemoglobin Structural Units



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**
- **Sickle hemoglobin:**
  Glutamic acid ➡ Valine at AA 6
- **Hemoglobin of homozygous individuals ("SS") forms elongated crystals when exposed to low O_2**

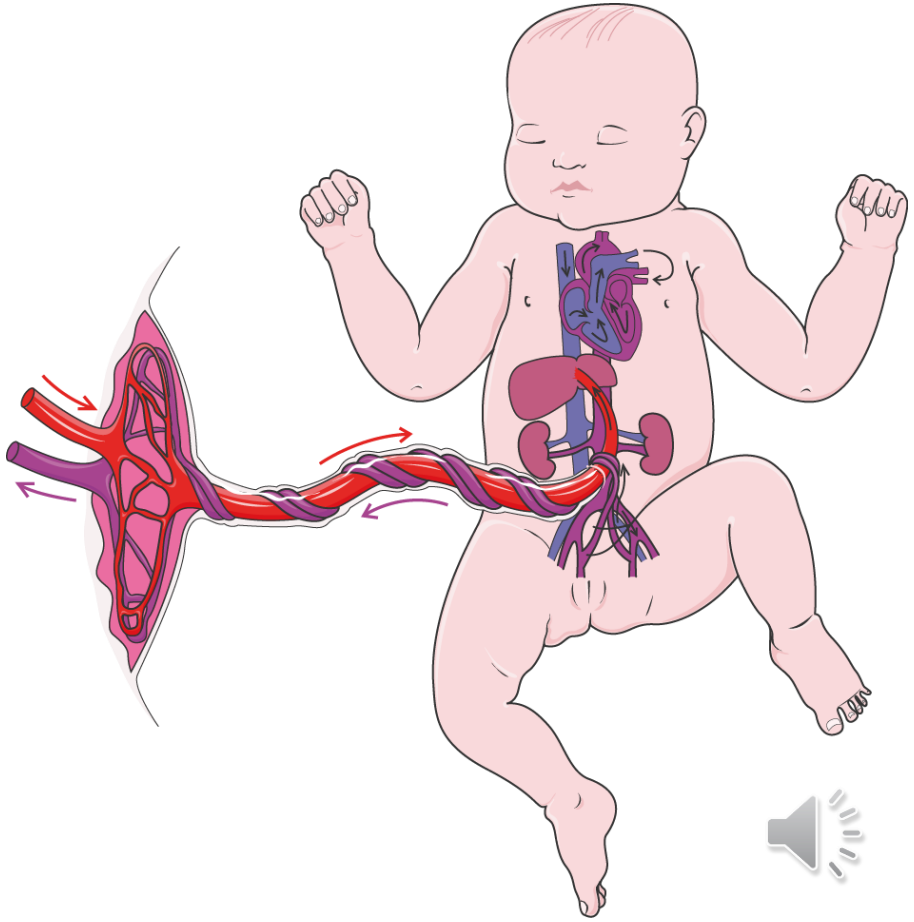
  ➡ hemolysis, vascular occlusion

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

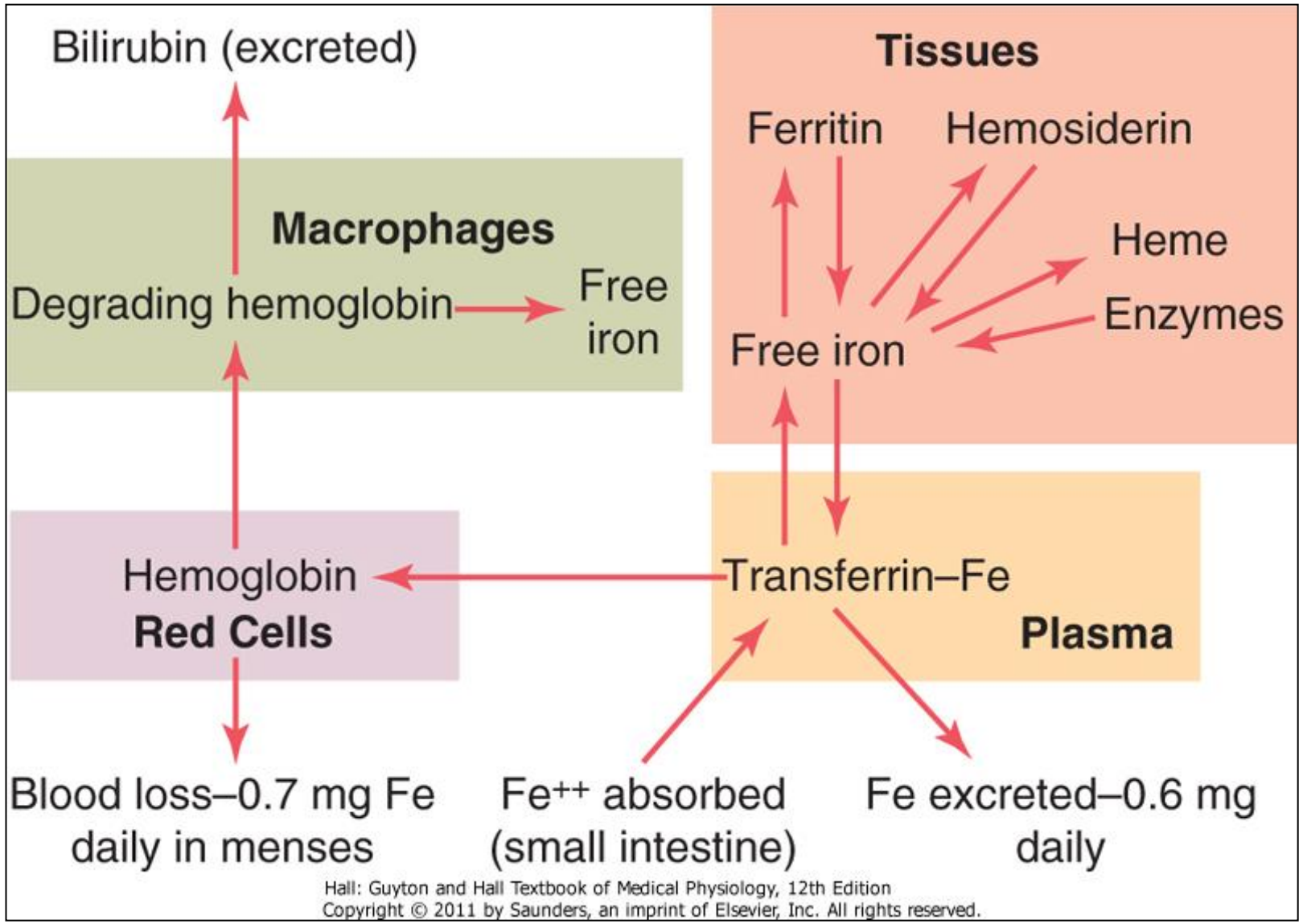
- Fetal hemoglobin is a principal oxygen carrier in blood in fetus and neonates
- It has higher affinity to oxygen and the OHD curve is shifted to the left. (efficient extraction of oxygen from mothers circulation)
- It is composed of 2 alpha and 2 gamma subunits



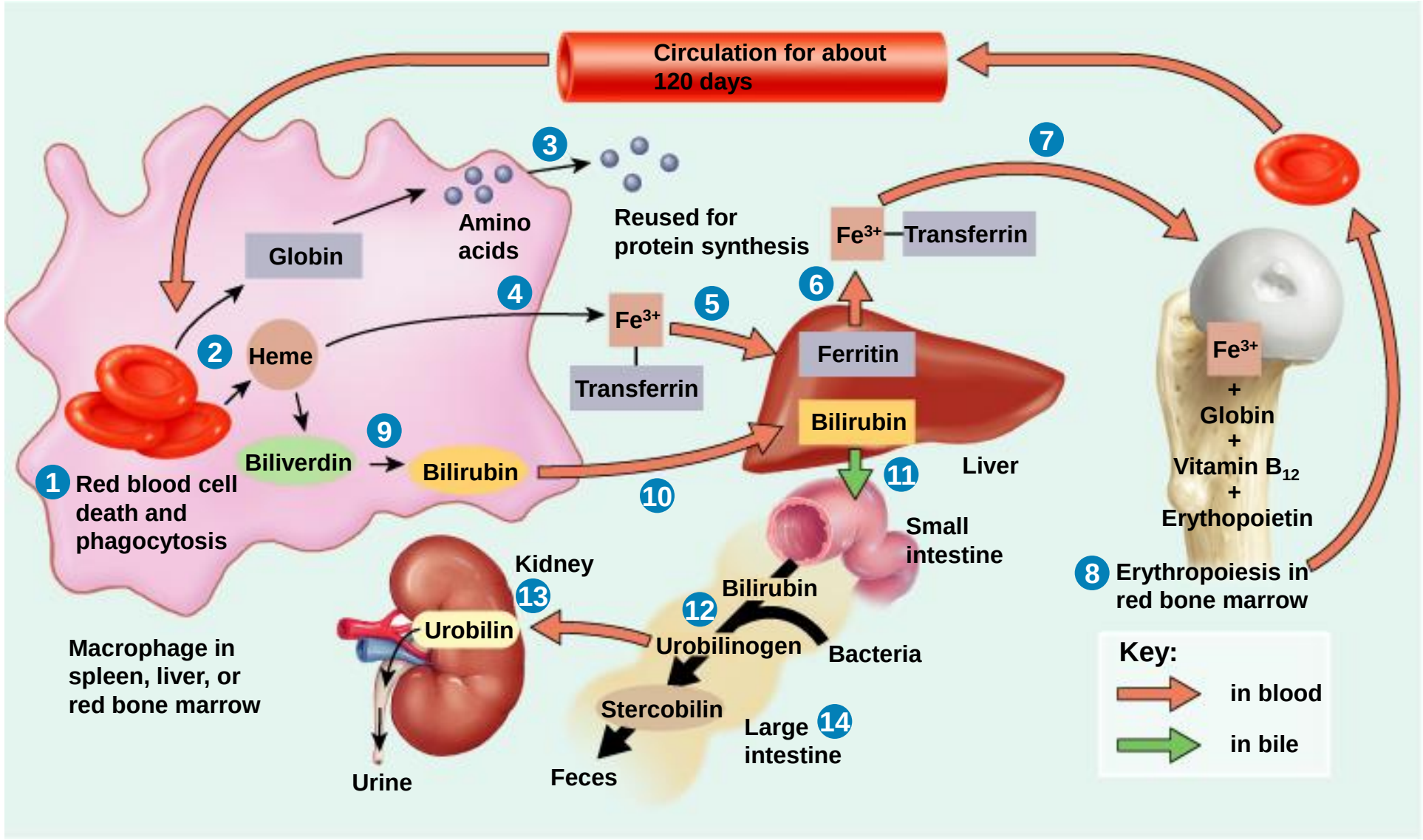
Iron Metabolism

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

Iron Transport and Metabolism



Formation and Destruction of RBC's



Iron Absorption, Transport & Storage

- **Absorbed from small intestine, combines with *apotransferrin* ⟶ *transferrin* (transport iron)**
- **Iron can be released to any cell**
- **RBC precursors have transferrin receptors and actively accumulate iron**
- **Particularly in hepatocytes and reticulo-endothelial cells, iron combines with *apoferritin* ⟶ *ferritin* (MW 460,000)**
- **Ferritin is variably saturated (storage iron)**
- ***Hemosiderin* is quite insoluble excess iron**

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 for incorporation into heme.**
- **Deficiency of transferrin can result in severe *hypochromic* anemia.**
- **Hemoglobin released from senescent RBCs is ingested by macrophages and stored as ferritin.**

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 to become *transferrin***
- **Binds to *transferrin receptors* on intestinal epithelium**
- **Transcytosed into the blood as plasma transferrin**
- **Maximal absorption of a few mg per day, modulated over 5 – 6-fold range based on body stores**

RBC Senescence & Destruction

- **RBC life span is ~120 days**
- **Though lacking a nucleus, mitochondria, and endoplasmic reticulum, RBCs have enzymes that can metabolize glucose 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, 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