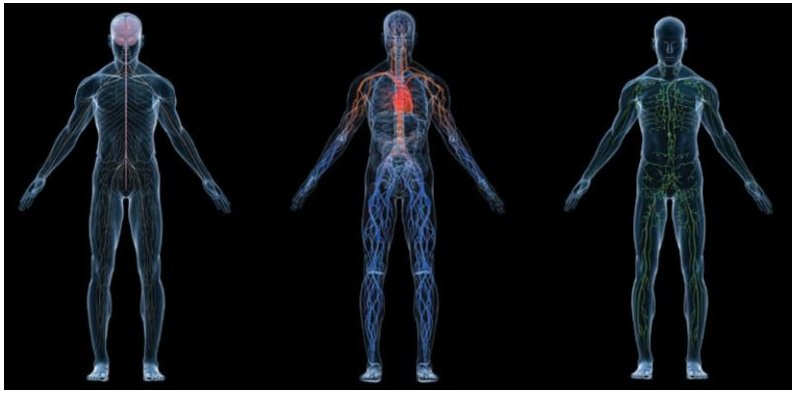
UNIT VI

Chapter 33

GUYTON AND HALL
TEXTBOOK OF MEDICAL PHYSIOLOGY



Introduction: Red Blood Cells, Anemia and Polycythemia

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Learning Objectives

- Identify blood components (formed elements), their main characteristics and functions.
- Understand genesis of blood cells (hematopoiesis)
- Describe regulation red blood cells production
- Identify requirements for erythropoiesis
- Describe red blood cells cycle
- Define abnormalities of red blood cells

Functions of Blood

- Transport

O2, CO2, nutrients, wastes, hormones

- Regulation

pH, temp, Bp, Osm. P, volume

- Protection

Clot, immune, proteins

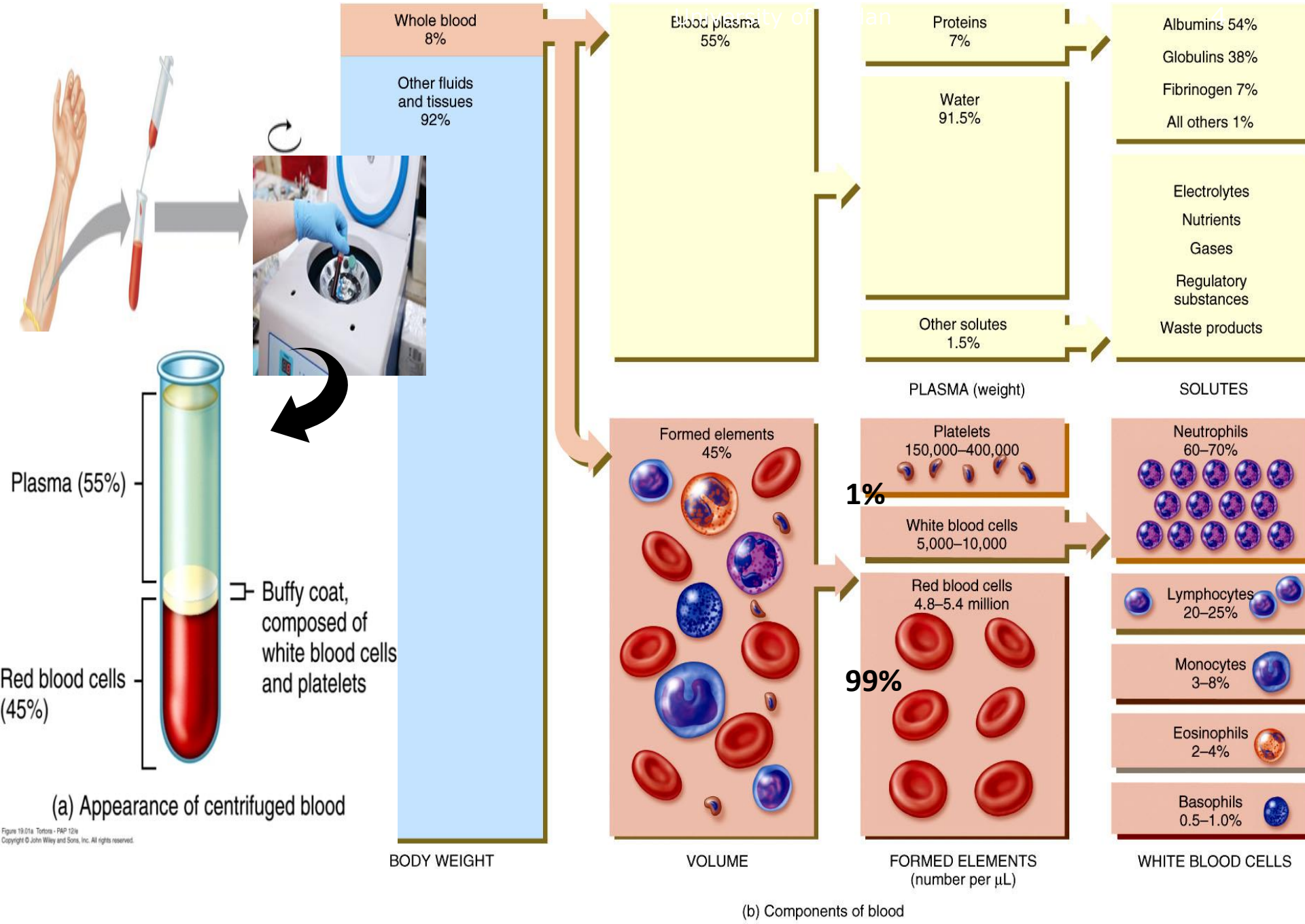


Figure 19.01b Tortora - PAP 12/e

- Blood physical characteristics:
- 38 C
- Viscous sticky
- alkaline pH 7.35-7.45
- Color depends on O2 (bright-dark) red
- 20% of ECF, 8% by weight
- Blood volume: 5-6 males, 4-5 females / Body size

- Hormonal regulation: RAAS, ANP,ADH

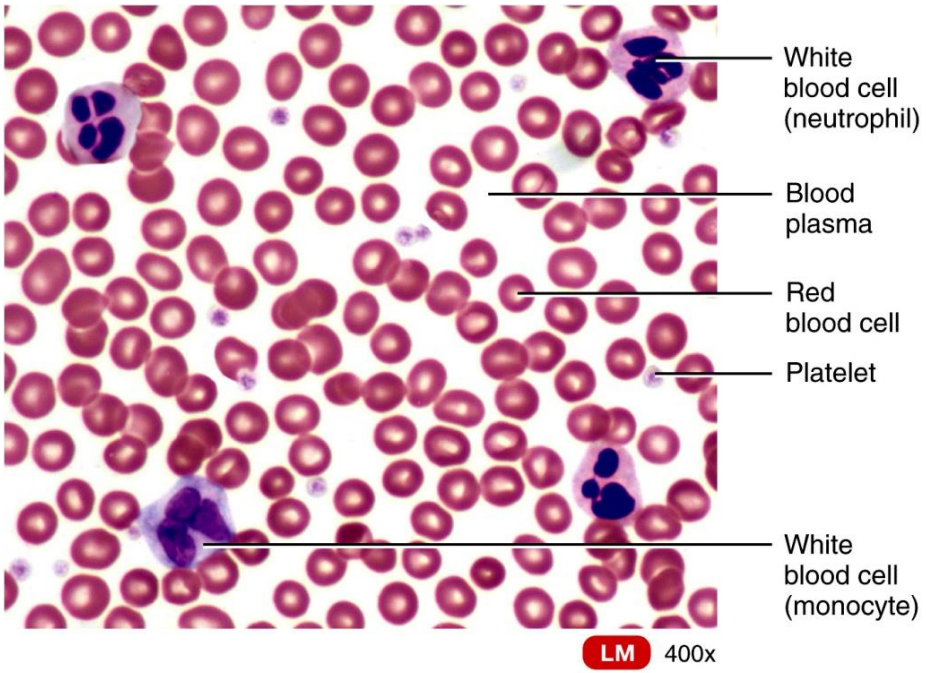
Question

Are all blood sampling tubes the same? And procedures?

Tubes:

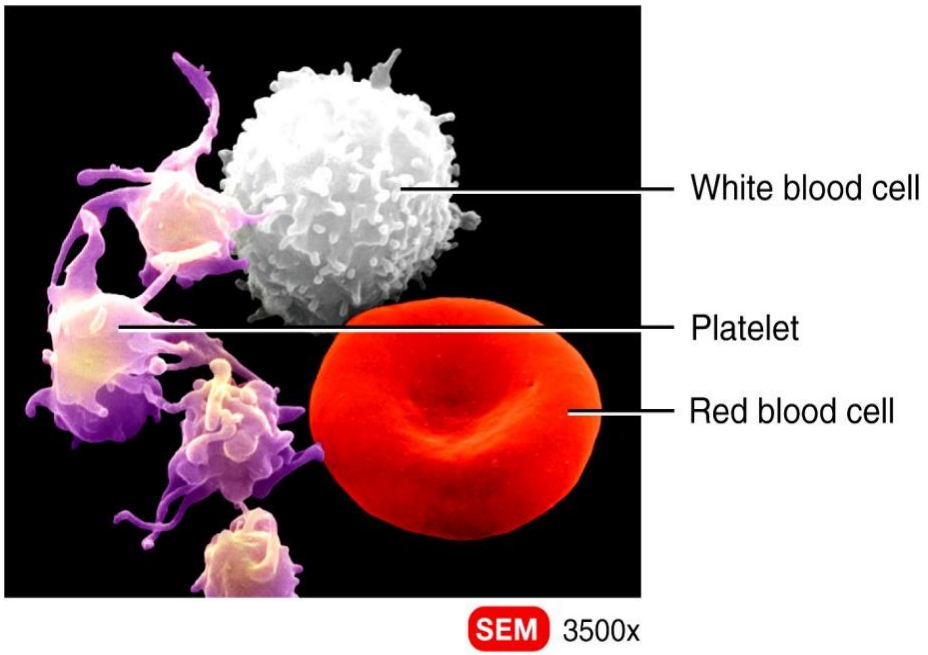
Venipuncture, Finger or heel stick, arterial stick

Formed Elements of Blood



(b)

Figure 19.02b Tortora - PAP 12/e



(a)

Figure 19.02a Tortora - PAP 12/e

Blood : a liquid connective tissue, Extracellular matrix is plasma, cells are suspended,

Interstitial fluid: part of ECF renewed by blood

Functions
Red Blood Cells (Erythrocytes)

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

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

$$CO_2 + H_2O \longrightarrow H_2CO_3$$

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

- **Hemoglobin is an excellent acid-base buffer**

RBC Size and Shape

- **Biconcave discs**
- **Mean 7.8(d) x 2.5 microns (thickest) or x 1 micron (center)**
- **Average volume 90-95 micrometers^3**
- **Redundant membranes allows deformation to squeeze through capillaries**

RBC Count and Indices

- **Men: 5,200,000 (± 300,000) / mm^3**
- **Women: 4,700,000 (± 300,000) / mm^3**

- RBC counts can be increased at higher altitudes

2 million /sec production

- **<u>RBC indices</u>:**
  - **MCV (Mean cell volume) 90 ± 9 fl = 10^{-15} L**
  - **MCH (Mean Cell Hgb) 32 ± 2 pg**
  - **MCHC (Mean cell Hgb conc) 33 ± 3 %**
  - **RDW CV 11.6-14.6 %**

(SD of MCV/MCV) 39-46 fL

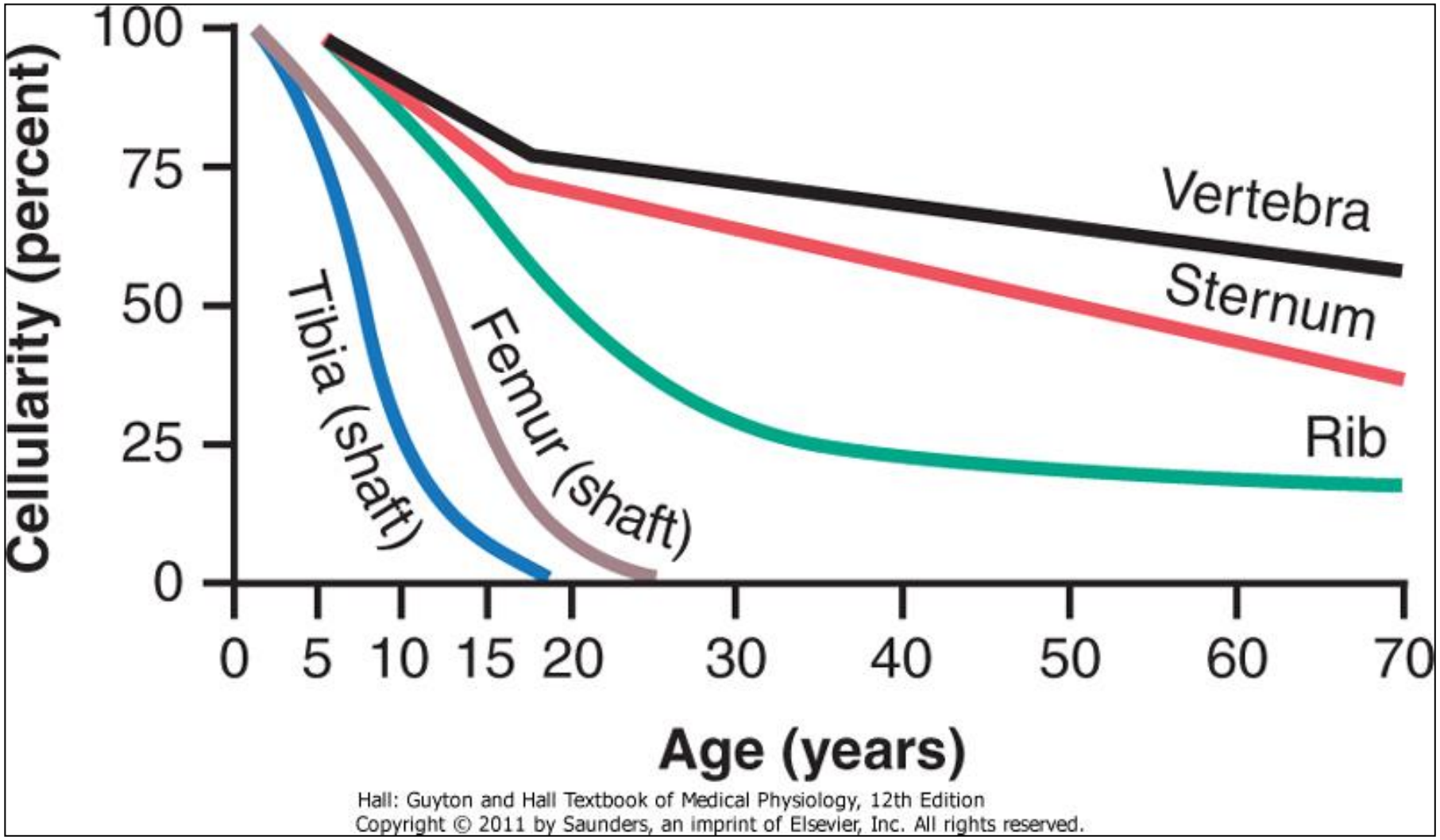
Hemoglobin and Hematocrit

- 280 million /RBC
- 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)
- Thus normal hemoglobin is 14-15 g per 100 ml of blood
- 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

- **First few weeks of gestation – yolk sac**
- **Mid-trimester – Liver (+ spleen, lymph nodes)**
- **Last month of gestation through adulthood – Bone marrow**

Sites of Erythropoiesis by Age



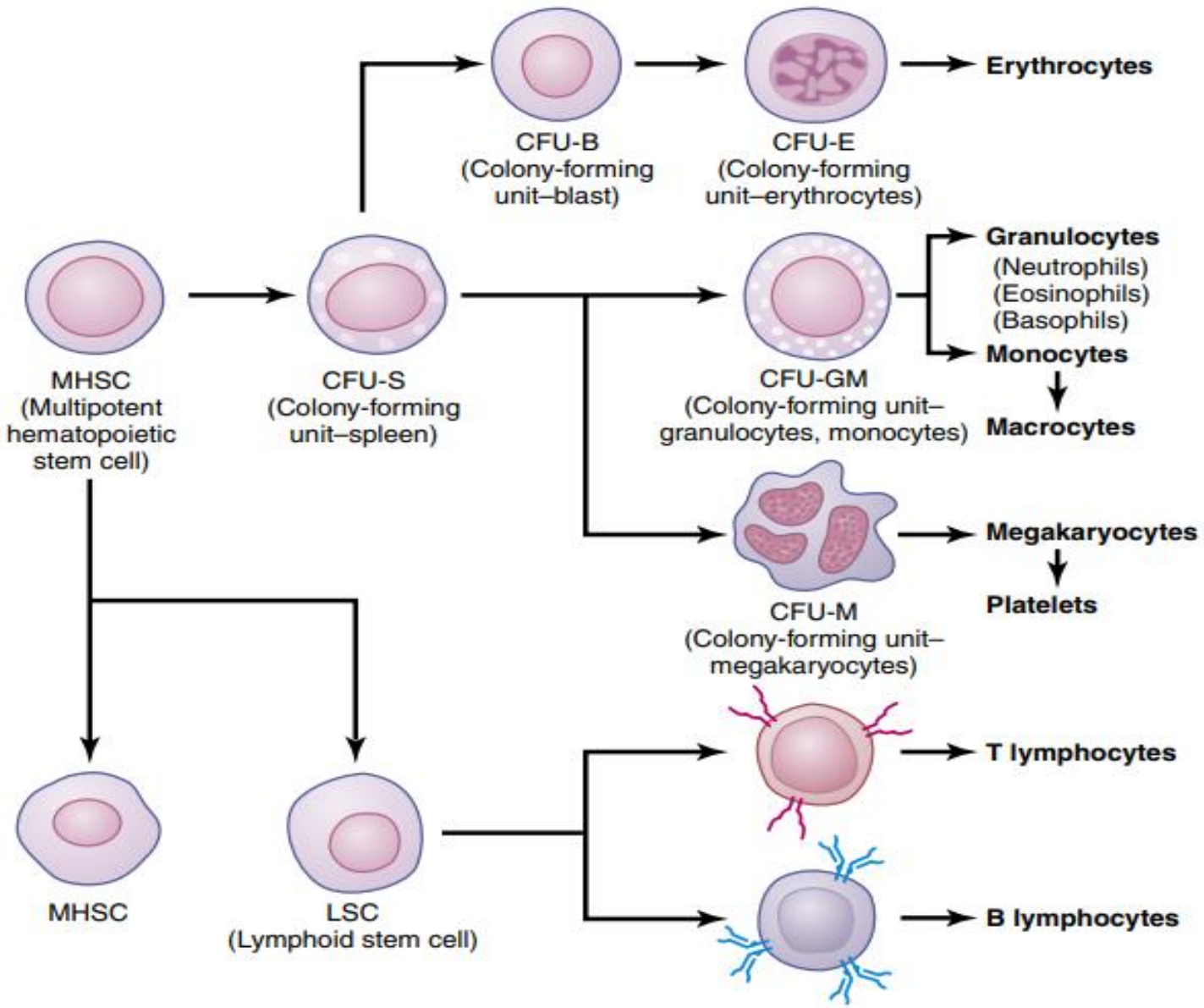
Hematopoiesis

- **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**

Blood Cell Lineages



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

Erythropoiesis and Anemia

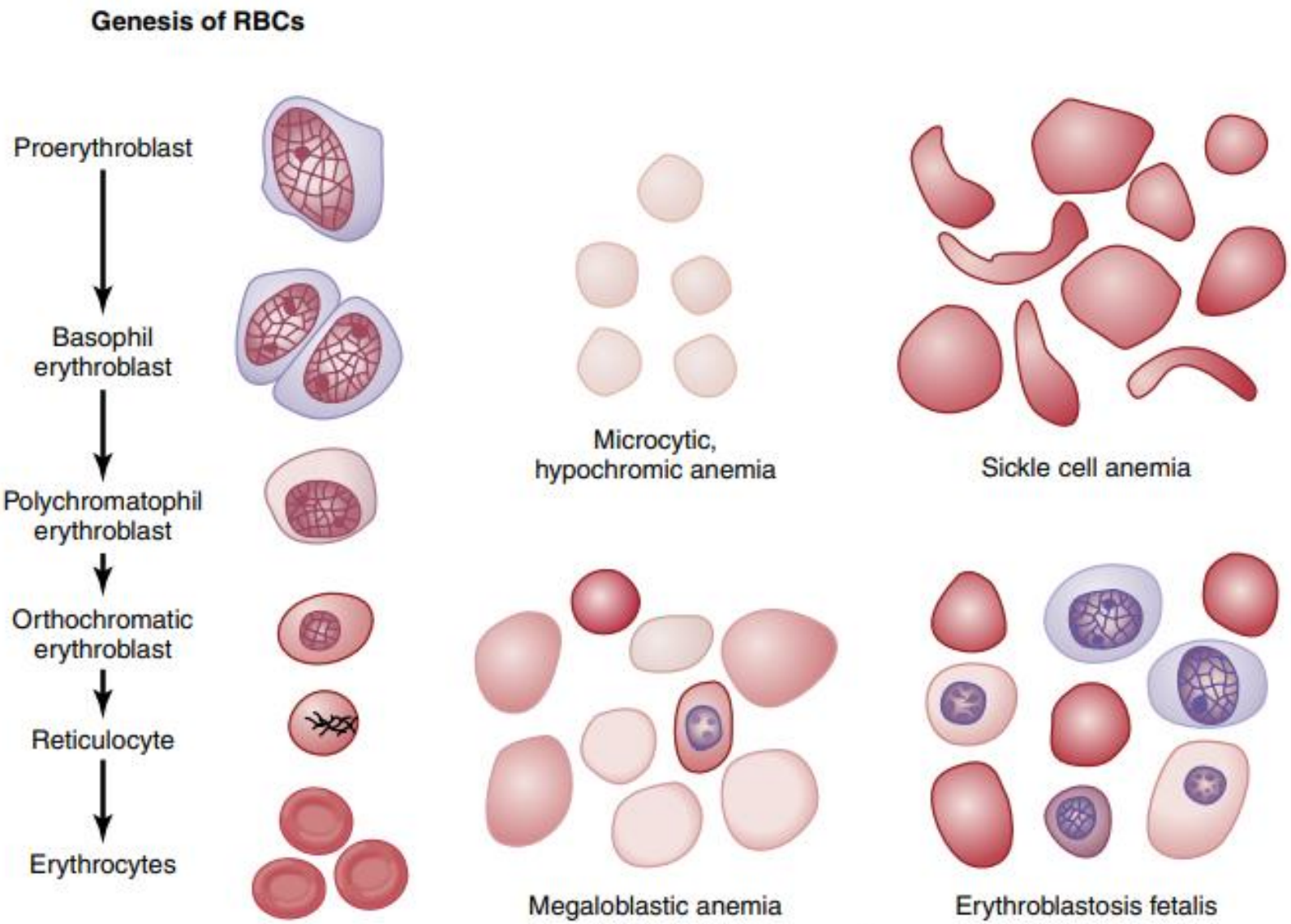


Figure 33-3. Genesis of normal red blood cells (RBCs) and characteristics of RBCs in different types of anemias.

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.**

Tissue O_2 and Erythropoietin

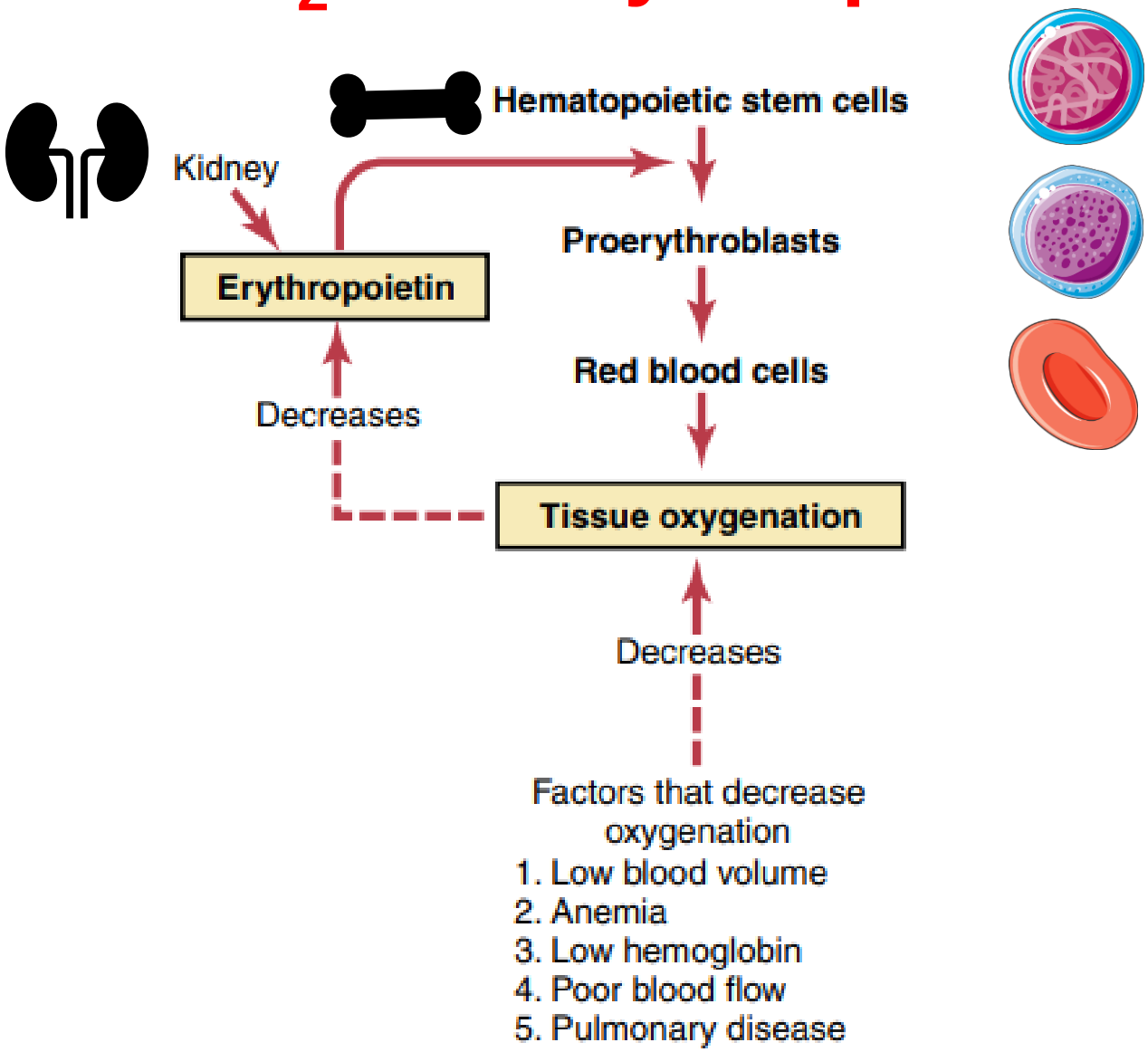


Figure 33-4. Function of the erythropoietin mechanism to increase production of red blood cells when tissue oxygenation decreases.

Clinical
Perspective

Compensatory Polycythemia

- **Sustained hypoxia can result in red cell mass above the usual normal range…**
  - **Prolonged stay at high altitude**
  - **Lung disease**
  - **Heart failure**

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.**

Vitamin B_{12} and Folic Acid

- **Rapid, large-scale cellular proliferation requires optimal nutrition**
- **Cell proliferation requires DNA replication**
- **Vitamin B_{12} and folate both are needed to make thymidine triphosphate (thus, DNA)**
- **Abnormal DNA replication causes failure of nuclear maturation and cell division…**

➡ ***maturation failure*** ➡ ***large, irregular, fragile "macrocytes"***

Pernicious Anemia

- **Failure to absorb vitamin B_{12}**
- **Atrophic gastric mucosa…**
  - **Failure to produce *intrinsic factor***
- **Intrinsic factor binds to vitamin B_{12}**
  - **Protects it from digestion**
  - **Binds to receptors in the ileum**
  - **Mediates transport by pinocytosis**
- **Vitamin B_{12} - stored in liver, released as needed**
- **Usual stores: 1 – 3 mg Daily needs: 1 – 3 µg**
- **Thus normal stores are adequate for 3 – 4 years**

Clinical Perspective

Folic Acid Deficiency

- **Folic acid is present in green vegetables, some fruits, and meats**
- **Destroyed during cooking**
- **Subject to dietary deficiencies**
- **May also be deficient in cases of intestinal malabsorption**
- **Maturation failure may reflect combined B_{12} and folate deficiency**

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

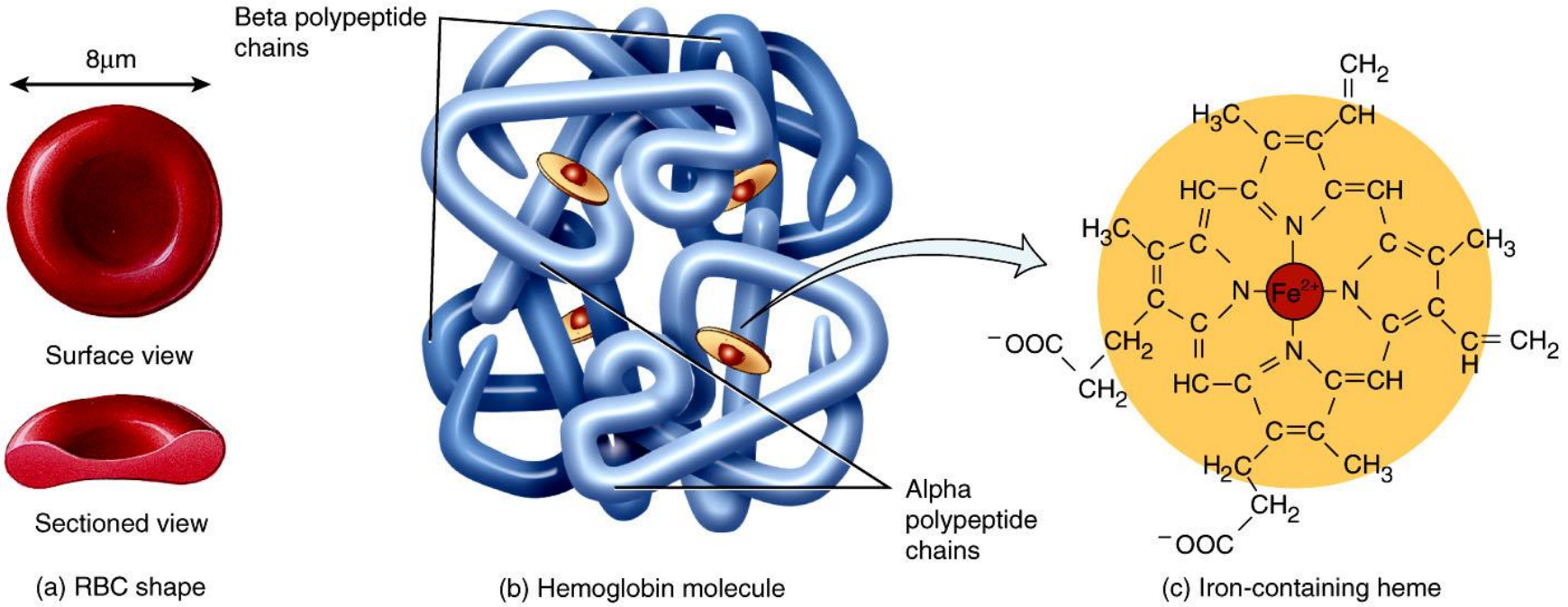
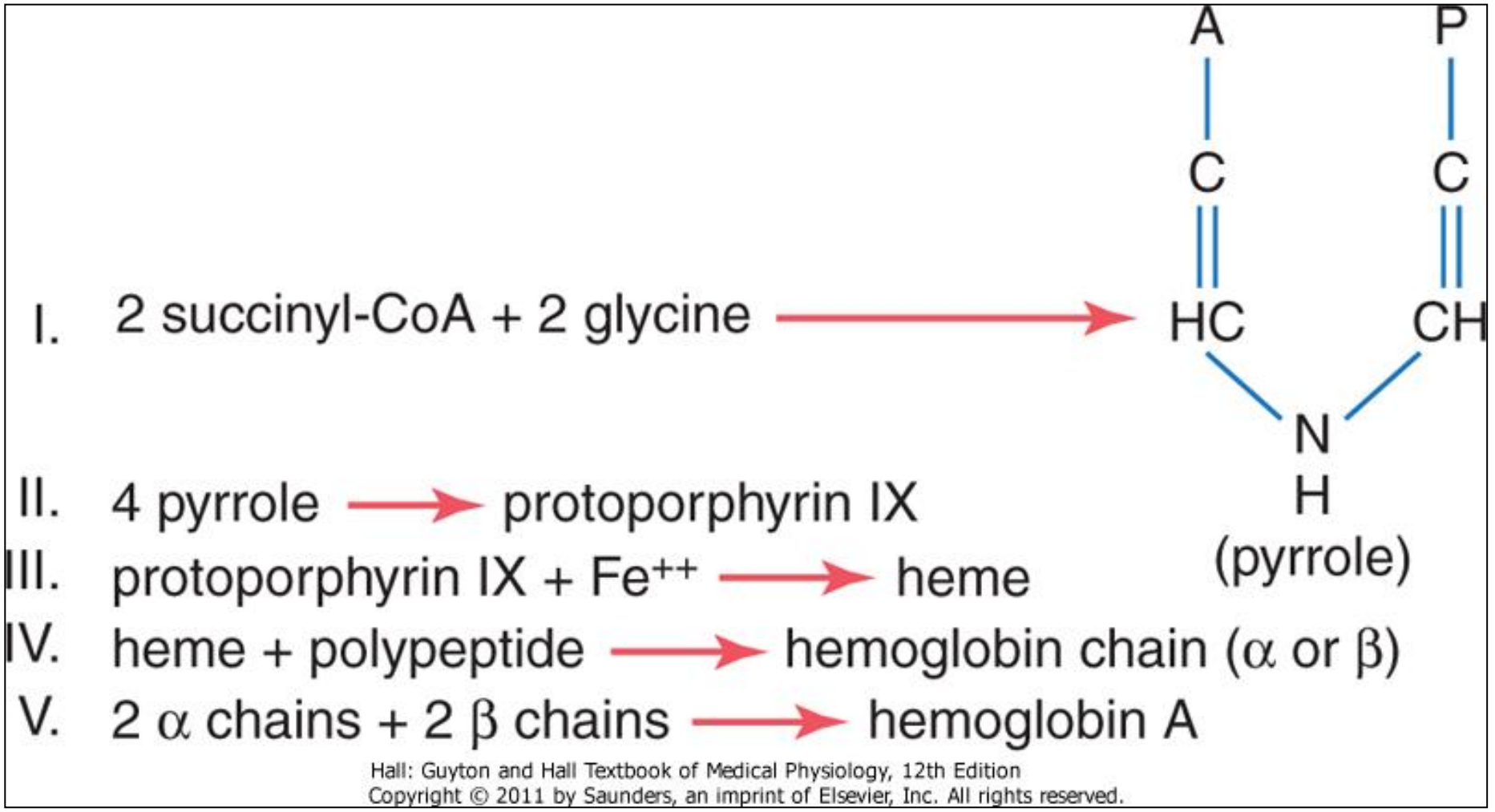
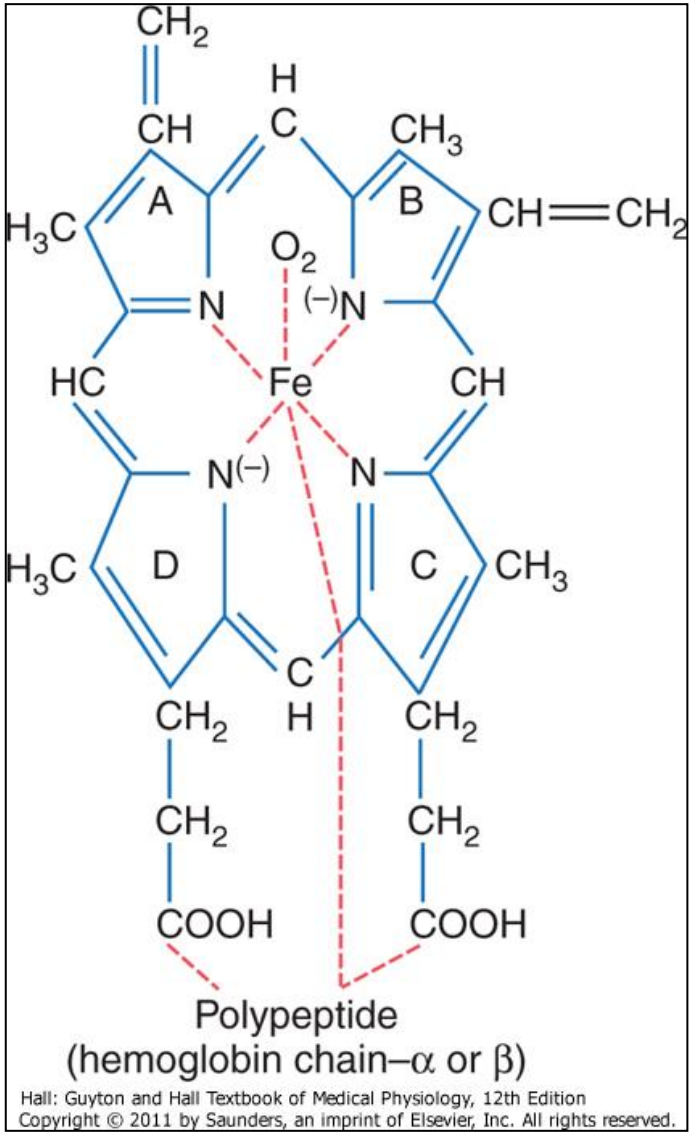


Figure 19.04 Tortora - PAP 12/e

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

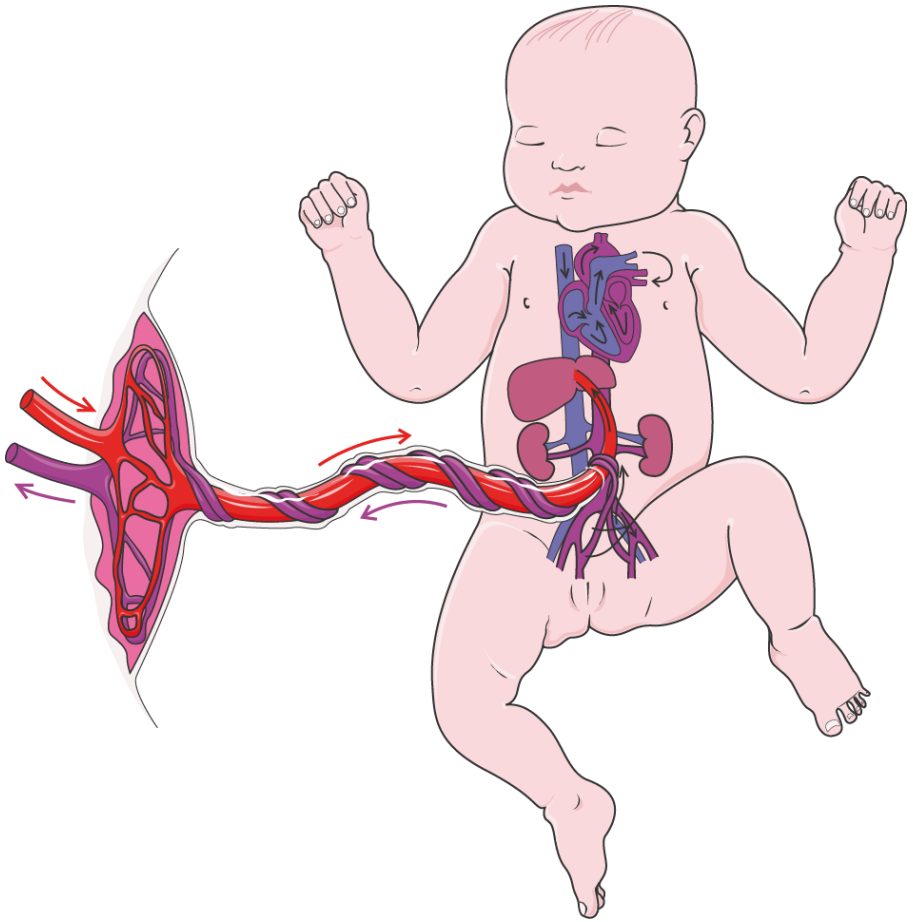
- **Modest differences in O_2 binding affinities**
- **Sickle hemoglobin:**
  Glutamic acid ➡ Valine at AA 6
- **Hemoglobin of homozygous individuals ("SS") forms elongated crystals when exposed to low O_2**

  ➡ 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)**

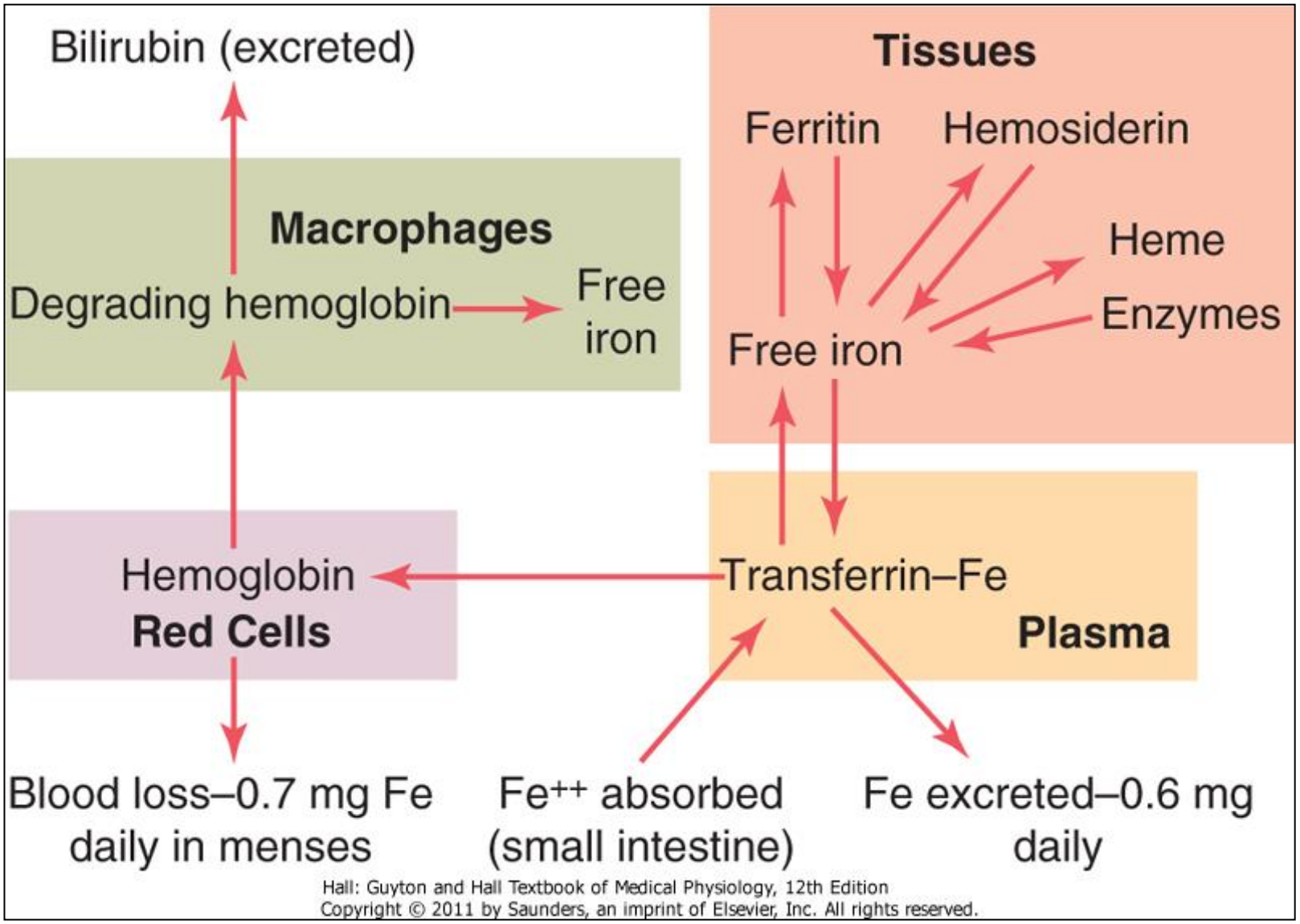
Fetal hemoglobin



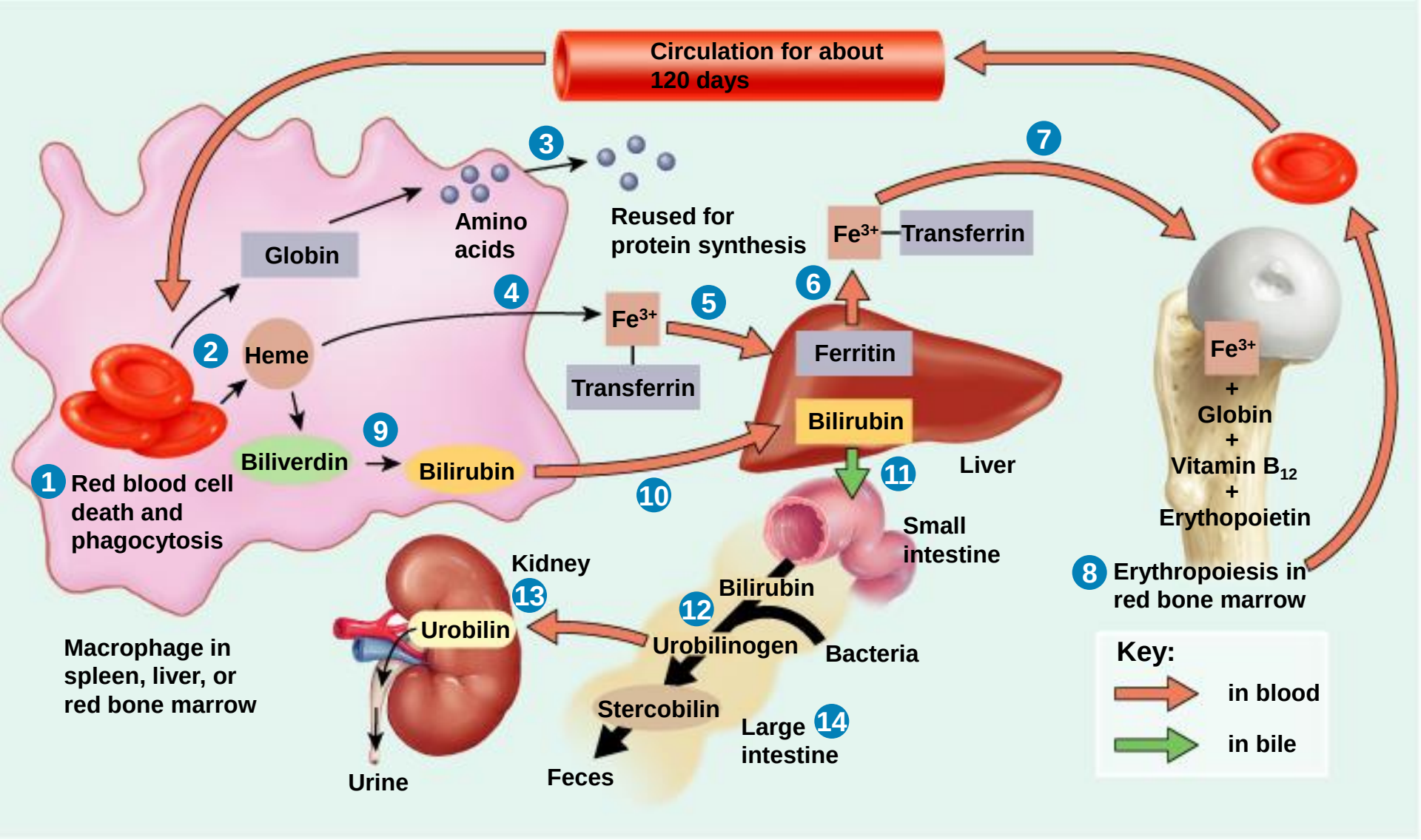
Iron Metabolism

- **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**

Clinical Perspective

Anemias (Reduced Hgb in Blood)

- **Blood loss (acute, chronic)**

- **After hemorrhage…**
  - **Fluid volume restored in 1 – 3 days**
  - **RBC concentration restored in 3-6 weeks**

- **Chronic blood loss can lead to iron deficiency, with hypochromic, microcytic anemia.**

Clinical Perspective

Aplastic Anemia

- **Bone marrow failure caused by…**
  - **Radiation**
  - **Chemotherapy**
  - **Chemical toxins**
  - **Auto-immune**
  - ***Idiopathic***
- **Supported by transfusions or treated by bone marrow transplantation**

Clinical Perspective

Megaloblastic Anemia

- **Deficiency of Vitamin B_{12} and / or Folic Acid**
  - **Pernicious anemia**
  - **Dietary deficiency**
  - **Malabsorption**
- **Impairs DNA replication, causing maturation failure**
- **Formation of large, fragile cells with bizarre shapes, which rupture easily, potentially causing profound anemia**

Clinical
Perspective

Hemolytic Anemia

- **Hereditary conditions causing fragility**
  - **Hereditary spherocytosis**
  - **Sickle cell anemia**

- **Immune-mediated destruction**
  - **Erythroblastosis fetalis**

Clinical
Perspective

Circulatory Effects of Anemia

- **Anemia**
  - **Decreased viscosity**
  - **Decreased O_2 - carrying capacity**

➡ **Increased cardiac output**

- **Markedly decreased exercise capacity**

Clinical Perspective

Secondary (RBC ↑ ~30%; 6-7 million/mm³)

- - Chronic hypoxemia (heart or lung disease)
- - *Physiologic polycythemia*
  - - Living at 14 - 17,000 feet
  - - Markedly enhanced exercise capacity at altitude

Polycythemia Vera

- Clonal abnormality causing excessive proliferation
- Usually all lineages
- 7- 8 million RBCs / mm³; Hematocrit 60-70%
- Blood volume increased almost two-fold
- Hyperviscosity, up to 3-fold normal (10 x water)

Clinical
Perspective

Polycythemia & Circulation

- **Increased viscosity decreases venous return**
- **Increased blood volume increases venous return**
- **2/3 normotensive, 1/3 hypertensive**
- **The subpapillary venous plexus under the skin becomes engorged with slow-moving, de-saturated blood, producing a ruddy complexion with a bluish tint to the skin**