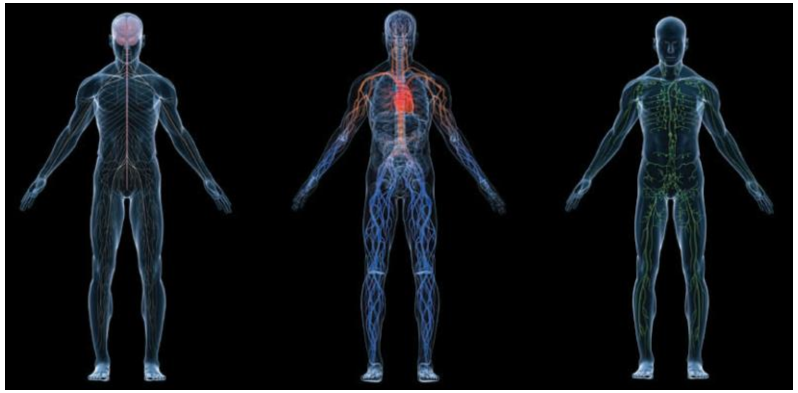
UNIT VI

Chapter 33

GUYTON AND HALL
TEXTBOOK OF **MEDICAL PHYSIOLOGY**



Introduction: Red Blood Cells, Anemia and Polycythemia

Lect 2

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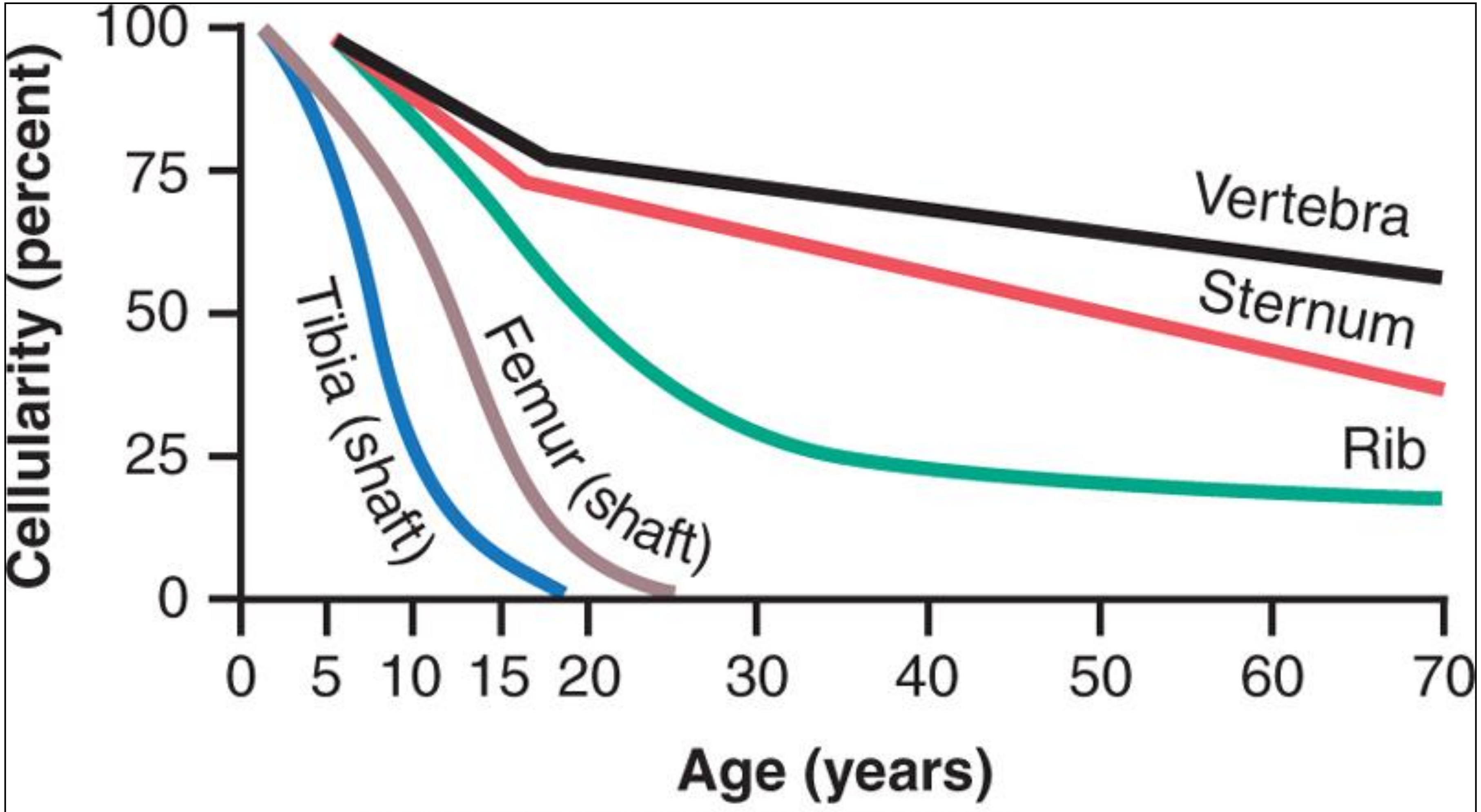
Sites of Erythropoiesis

- 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

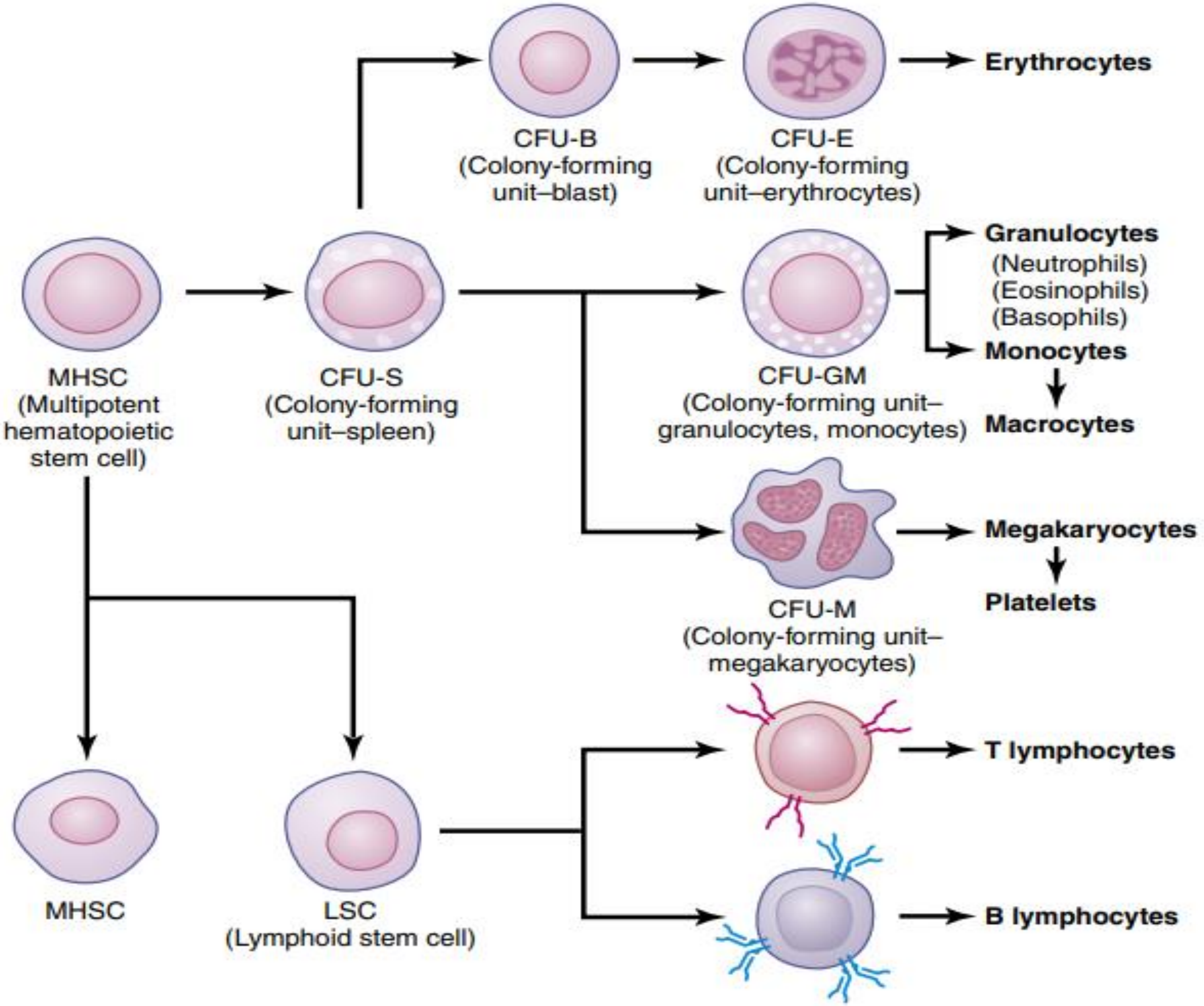


Hall: Guyton and Hall Textbook of Medical Physiology, 12th Edition

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

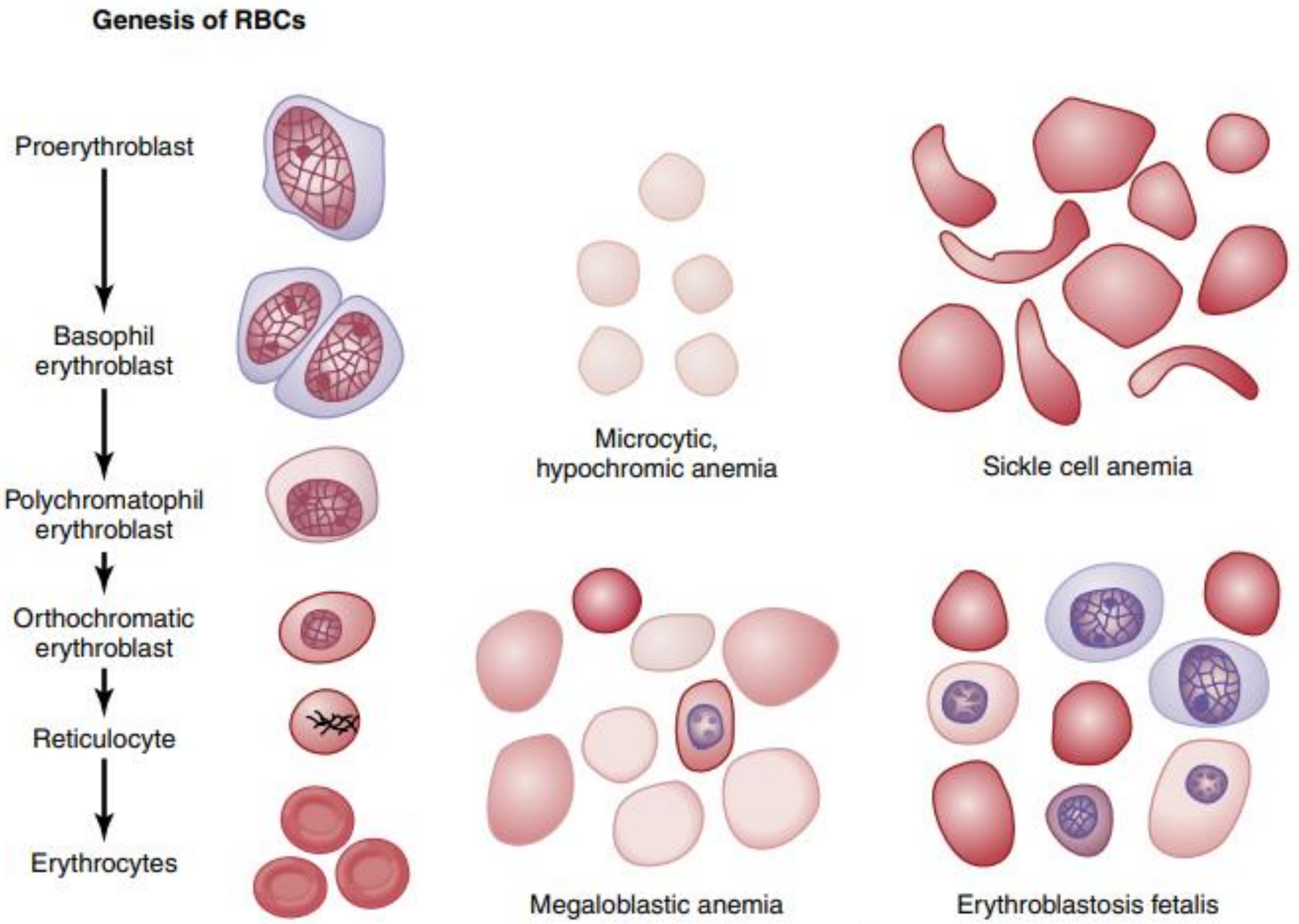


Figure 33-3. Genesis of normal red blood cells (RBCs) and characteristics of RBCs in different types of anemias.

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

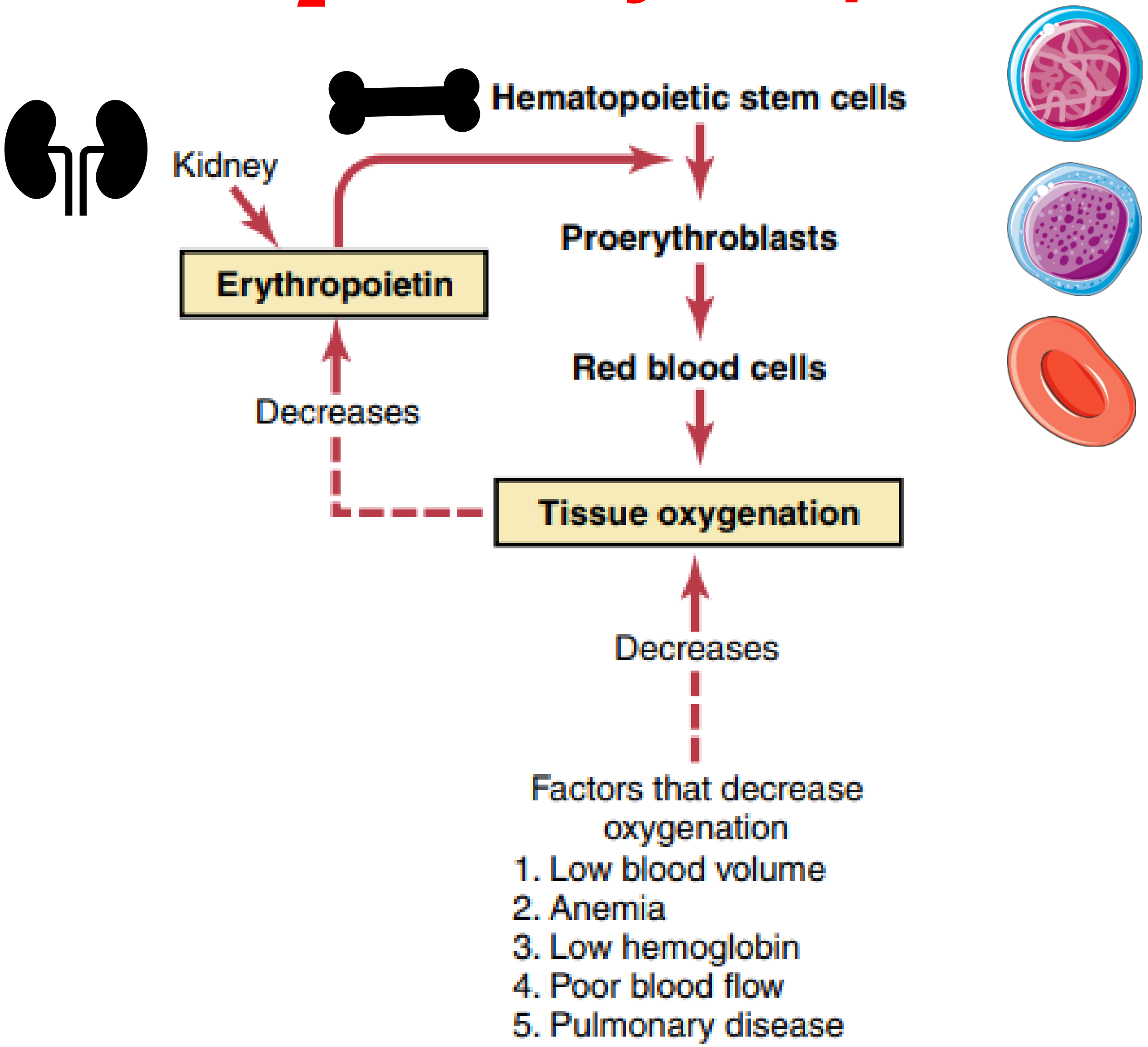


Figure 33-4. Function of the erythropoietin mechanism to increase production of red blood cells when tissue oxygenation decreases.

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)

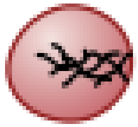
- Circulating hormone, mw ~34,000
- Necessary for erythropoiesis in response to hypoxia
- ~90% made in the kidney
- Cells of origin not established

Hypoxia $\longrightarrow$ *HIF-1* $\longrightarrow$ binds hypoxia response element $\longrightarrow$ $\uparrow$ *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"*

Clinical Perspective

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