Erythropoiesis

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Erythropoiesis

The process of development, differentiation and maturation of red blood cells from primitive stem cells

Objectives

- Sites of erythropoiesis
- Different stages of erythropoiesis
- Features of erythrocyte precursors
- Factors affecting erythropoiesis
  - Erythropoietin
  - Vitamin B_{12} and folate
  - Iron

Sites of erythropoiesis

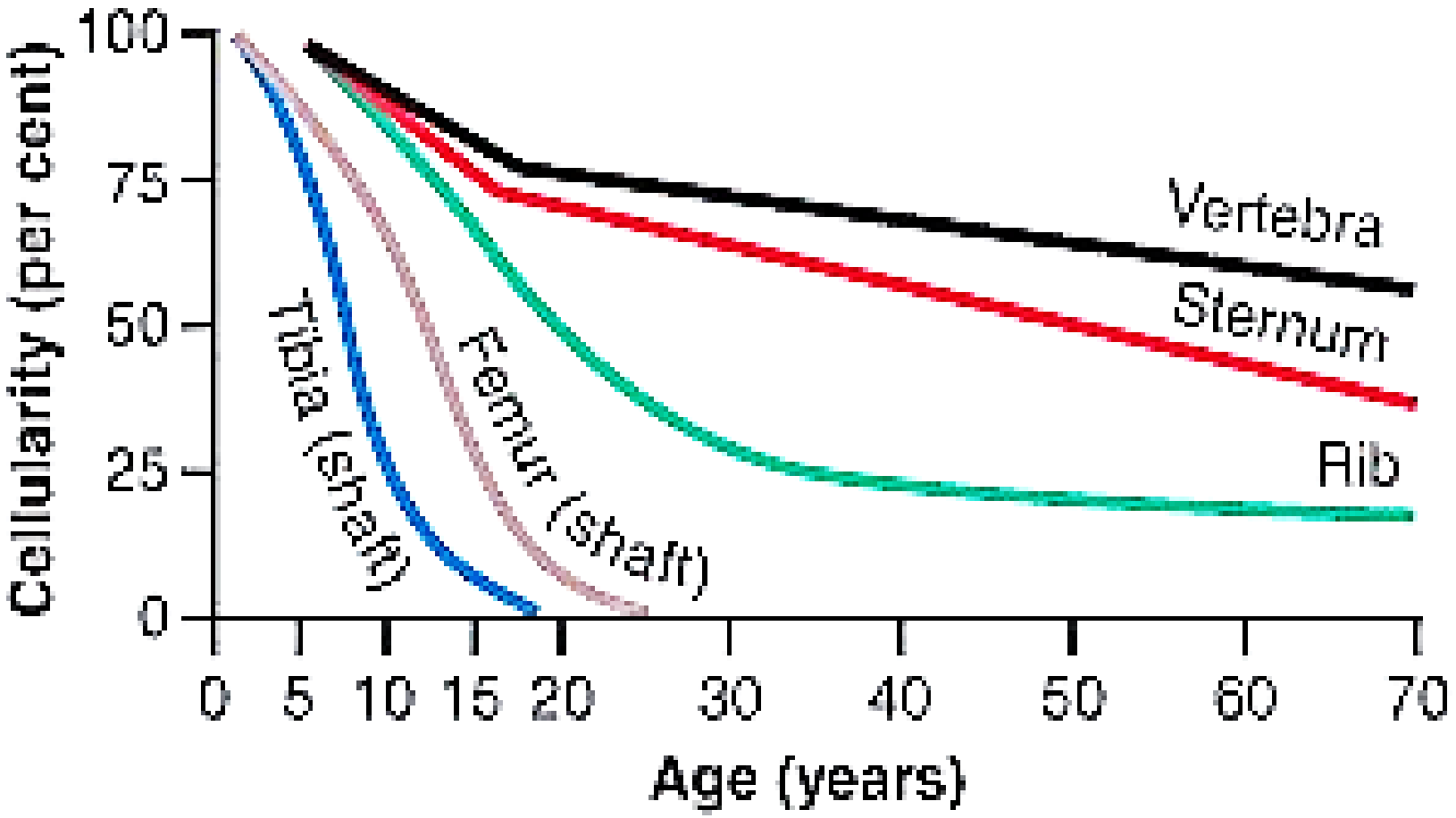
Erythropoiesis during intrauterine life

- Mesoblastic stage
  - Yolk sac and mesothelial layers of the placenta – 3rd week to 3 months
- Hepatic stage
  - At 6 weeks – Liver form blood cells
  - Spleen & lymphoid tissues form blood cells
- Myeloid stage
  - From the third trimester onwards – the bone marrow gradually becomes the principal source of red cell synthesis
  - Last month – RBC produced in bone marrow exclusively

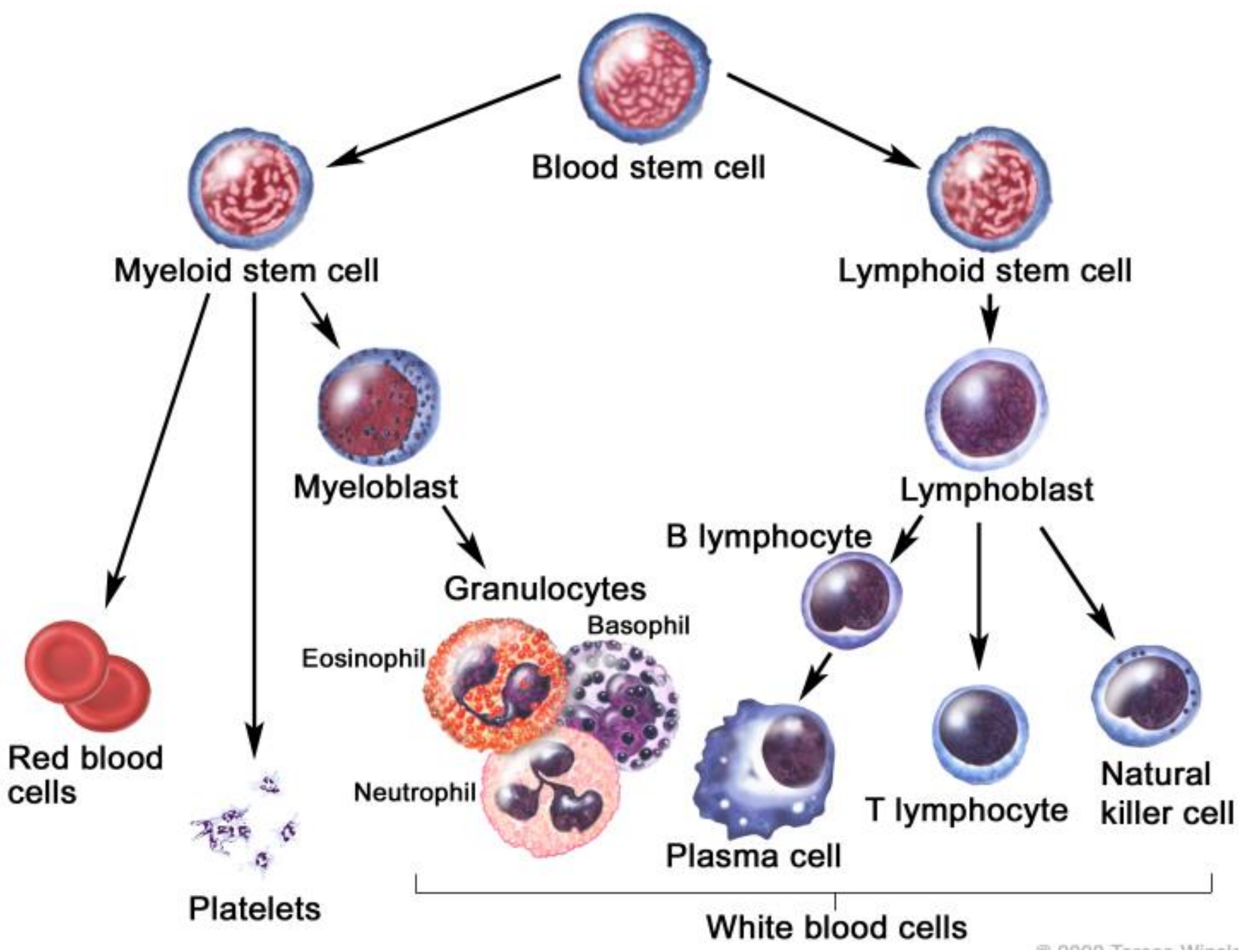
Erythropoiesis after the birth

- The bone marrow of all bones - up to 5 years
- Marrow of the long bones – up to about 20 years
- Marrow of the membranous bones (e.g. Vertebrae, sternum, ribs, ilium) produced most of the red blood cells afterwards
- Even in this bones – marrow becomes less productive with age

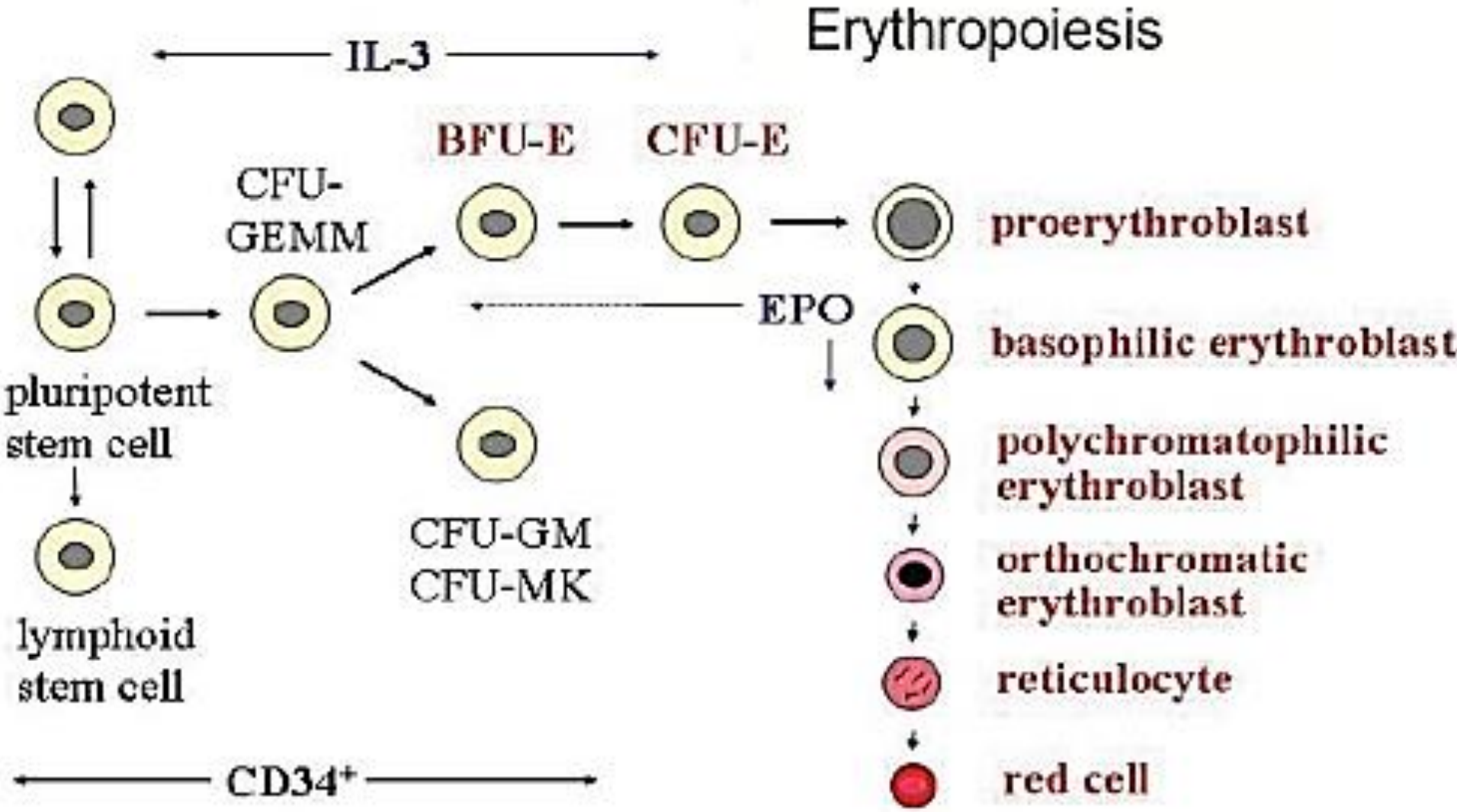
Rate of RBC production in different sites



Precursor cells of RBC


Blood stem cell
Myeloid stem cell
Lymphoid stem cell
Myeloblast
Lymphoblast
B lymphocyte
Granulocytes
Basophil
Eosinophil
Neutrophil
Red blood cells
Platelets
Plasma cell
T lymphocyte
Natural killer cell
White blood cells

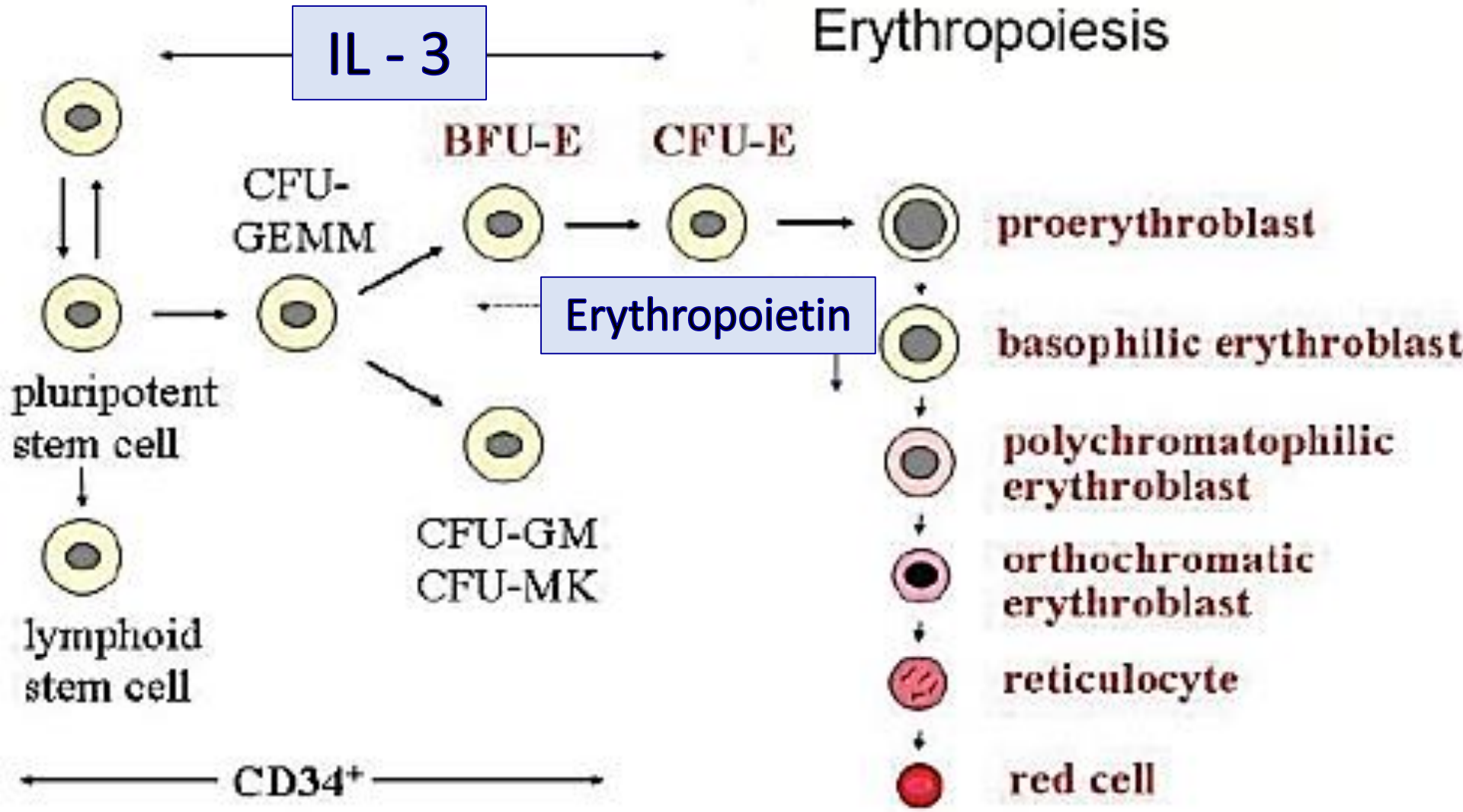
Precursors of RBS



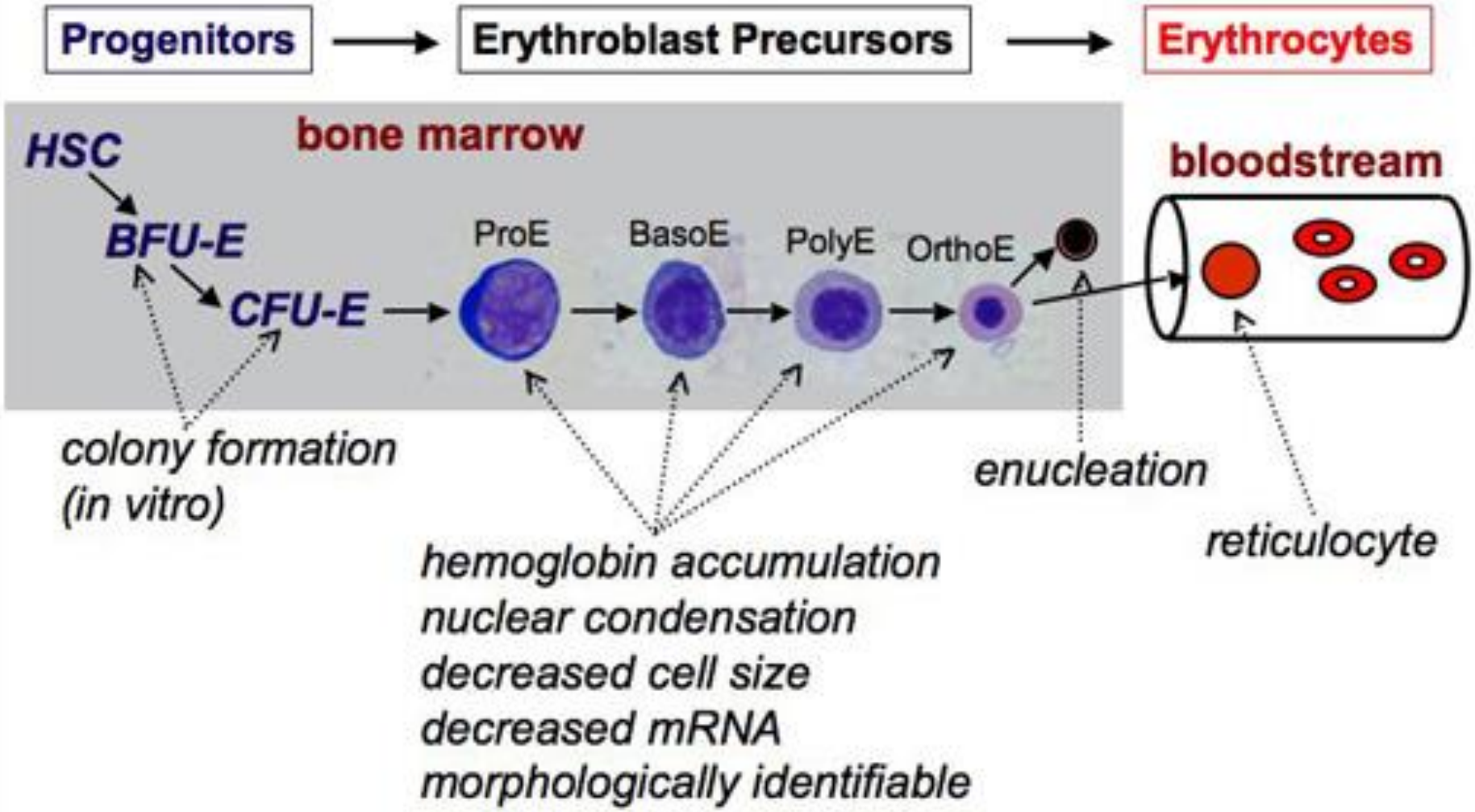
Production of red cells

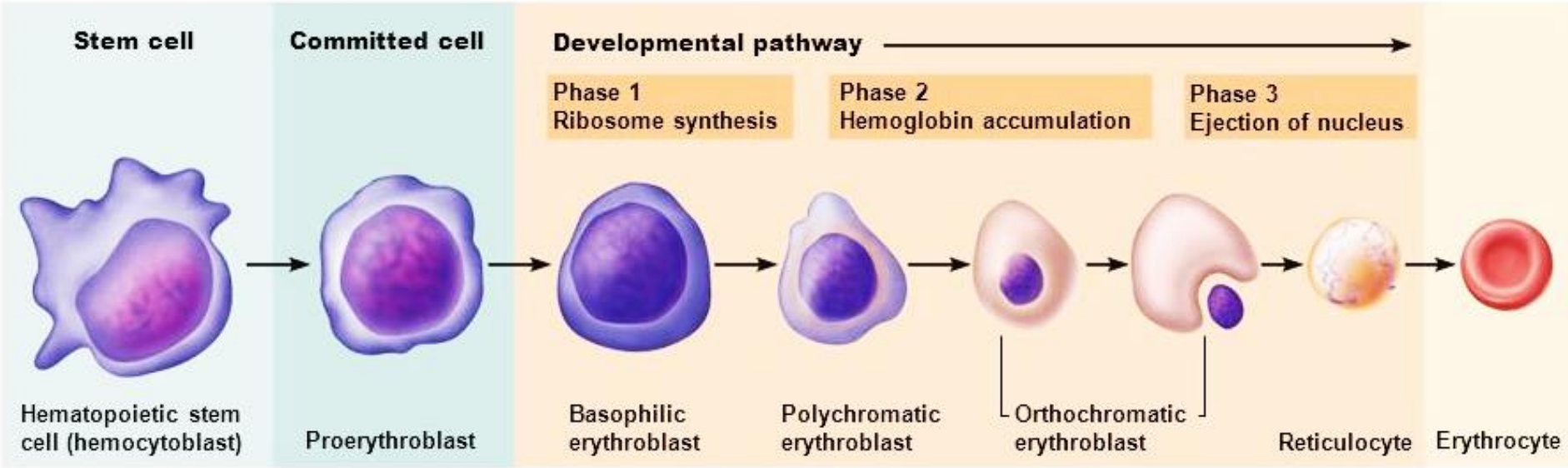
- All blood cells begin their lives in bone marrow from a single type of cell – pluripotential haemopoietic stem cell
- Subsequently the majority of these cells differentiate into committed stem cells
- Committed stem cell which produce RBC – colony forming unit erythrocyte
- Growth and reproduction of RBC is controlled by growth induces and differentiation induces
  - Interleukin - 3
  - Erythropoietin

Precursors of RBS



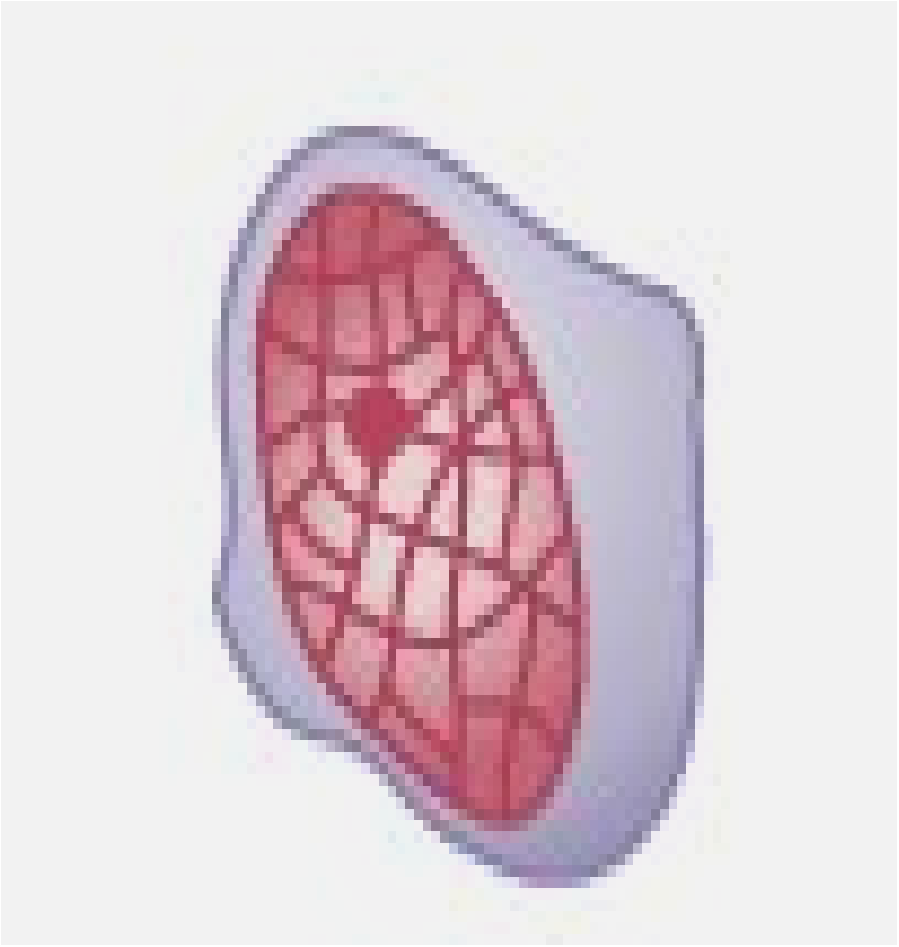
Erythropoiesis




Stem cell
Committed cell
Developmental pathway
Phase 1
Ribosome synthesis
Phase 2
Hemoglobin accumulation
Phase 3
Ejection of nucleus
Hematopoietic stem cell (hemocytoblast)
Proerythroblast
Basophilic erythroblast
Polychromatic erythroblast
Orthochromatic erythroblast
Reticulocyte
Erythrocyte

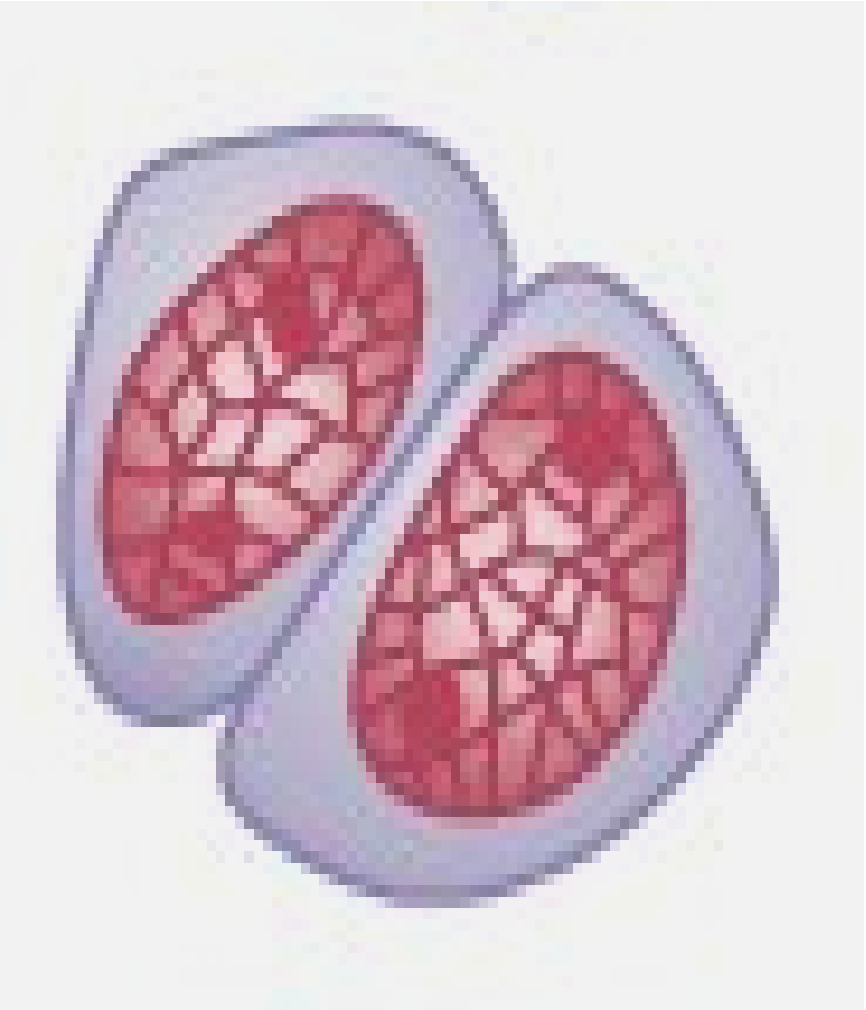
Proerythroblast

- No hemoglobin
- Nucleus 12 micrometers
- Contains nucleoli
- Divides multiple times



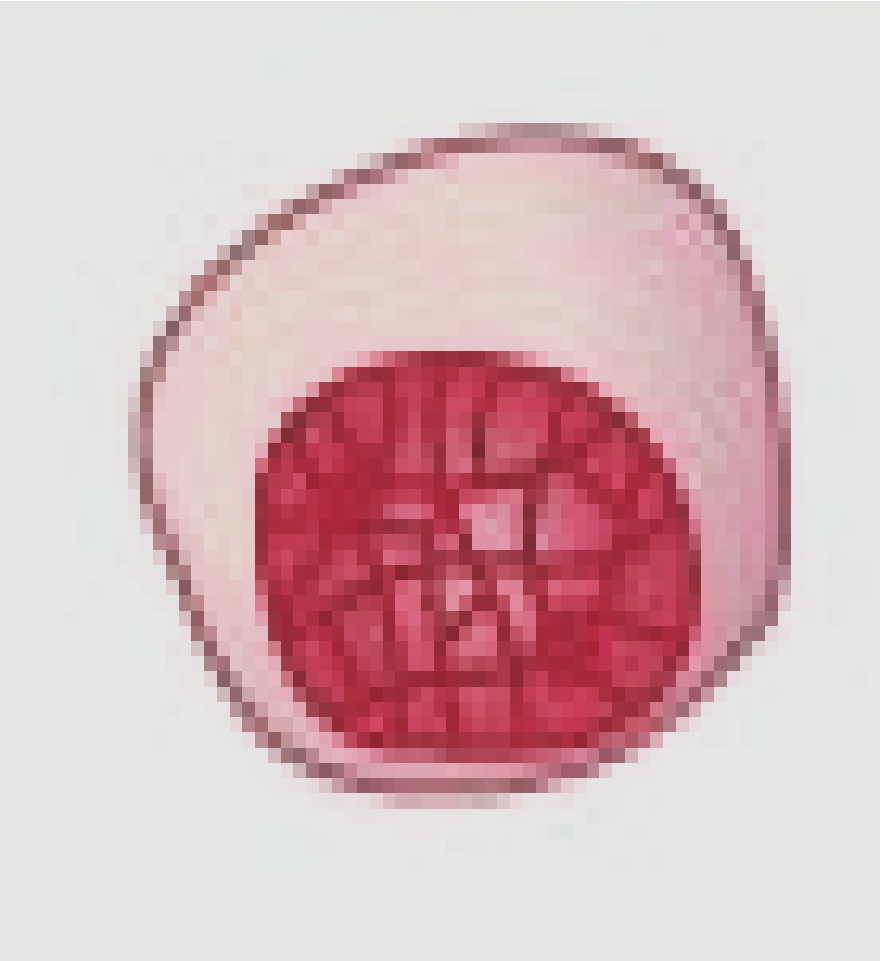
Basophilic erythroblast

- Early normoblast
- Nucleoli disappear
- Show mitosis
- Cytoplasm deep blue
  - Increase in RNA
- Hemoglobin starts appearing – Little Hb



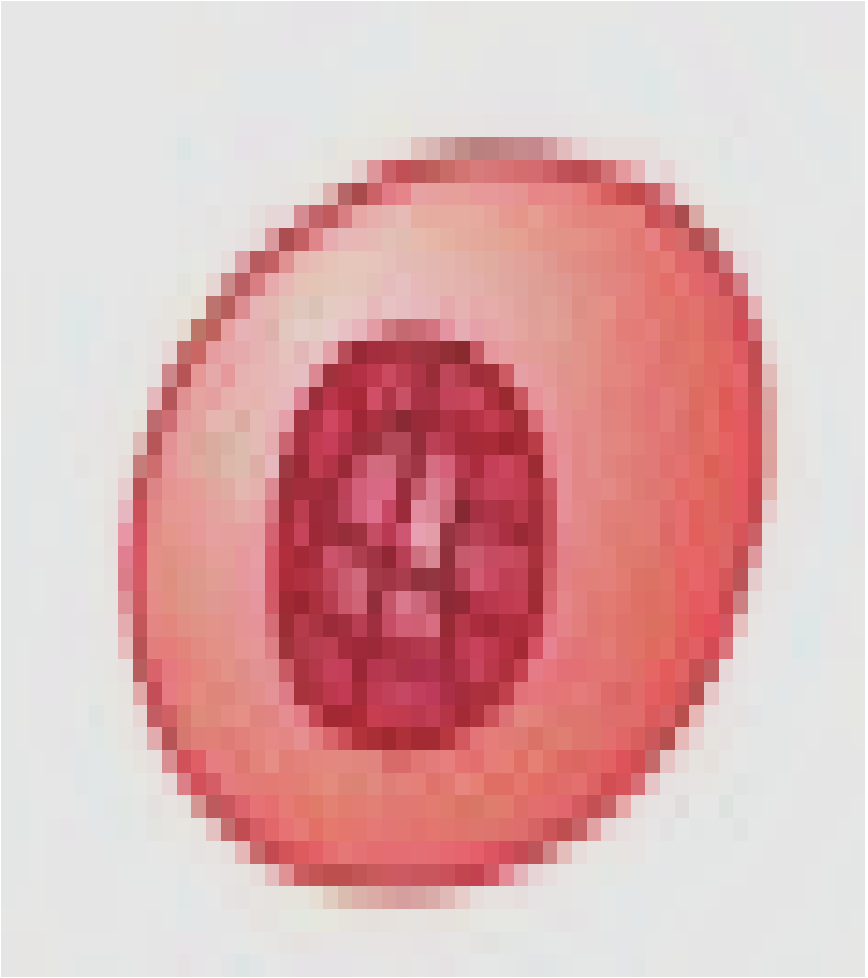
Polychromatophilic erythroblast

- Late normoblast
- Nucleus smaller
- Coarse chromatin
- Hemoglobin increase
  - Eosinophil Stain
- RNA – Basophil stain



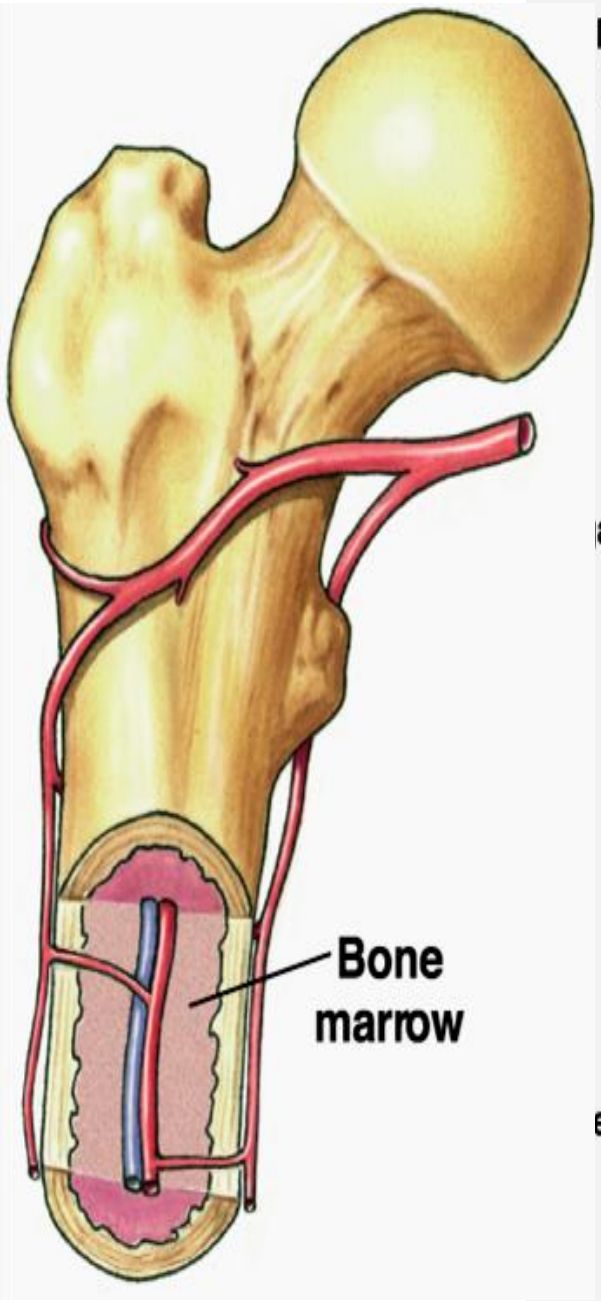
Orthochromatic Erythroblast

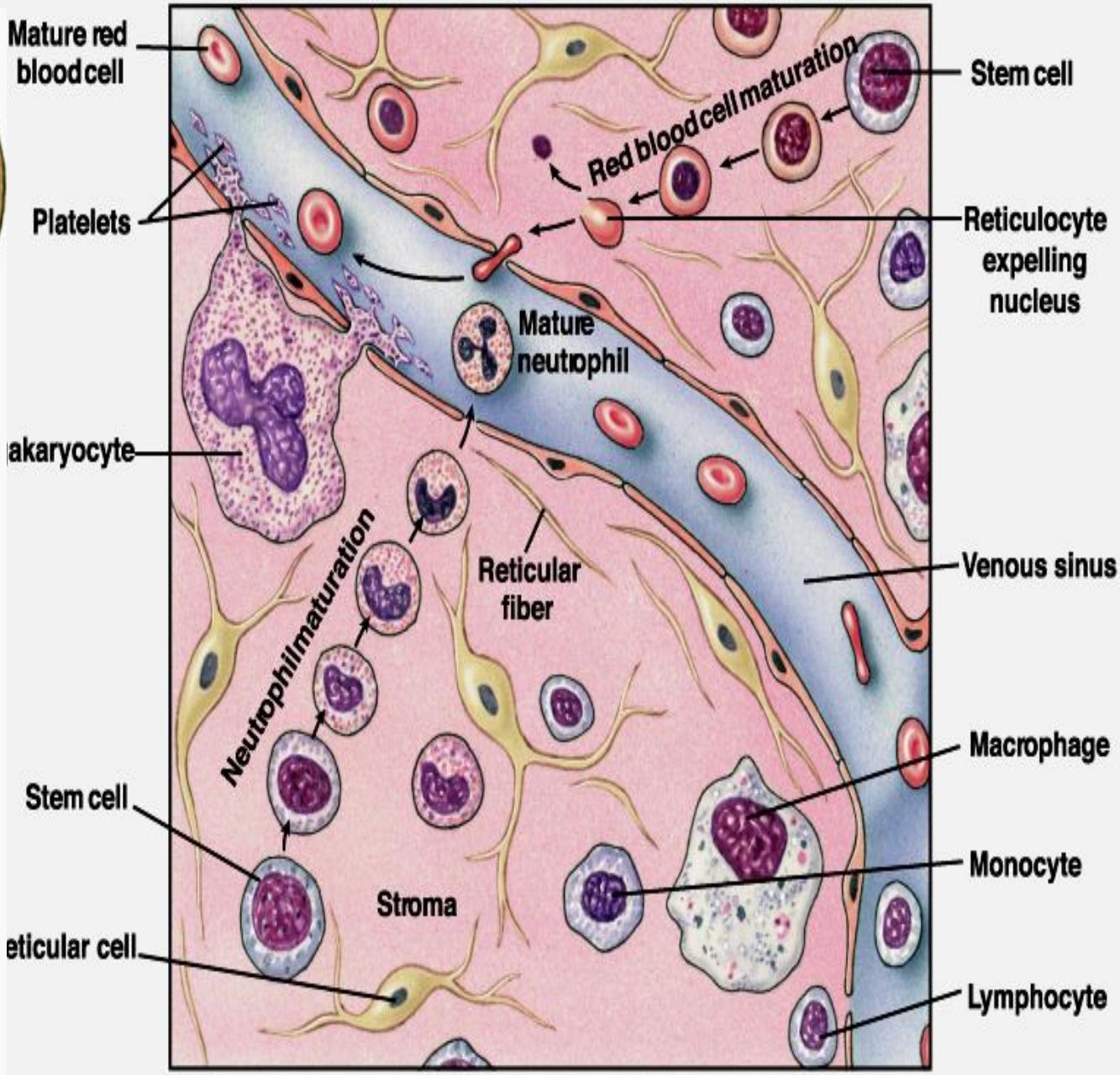
- Normoblast
- Nucleus smaller
  - Pyknosis
- Nuclear lysis and
- Nuclear extrusion



Reticulocyte

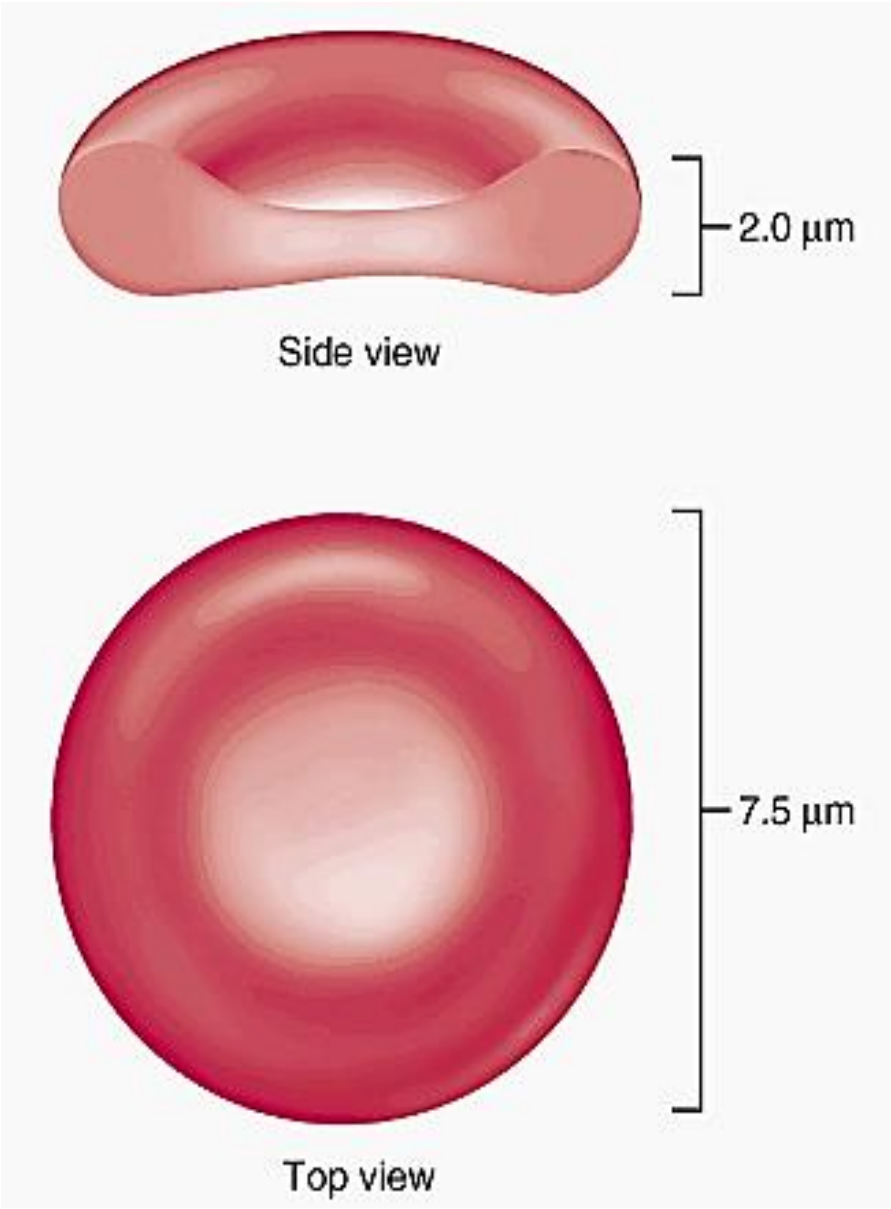
- Remnant of basophilic materials (ER, GA & Few Mitochondria)
- Synthesize Hb
- Young RBCs (34% Hb)
- Pass from BM to blood by diapedesis through the pores of capillary membrane
- Short life span in blood
- Remaining basophilic materials disappear in 1-2 days – mature RBC
- Less than 1 % of Red Cells in peripheral blood


Bone marrow


Mature red blood cell
Platelets
akaryocyte
Stem cell
eticular cell
Red blood cell maturation
Stem cell
Reticulocyte expelling nucleus
Mature neutrophil
Neutrophil maturation
Reticular fiber
Stroma
Venous sinus
Macrophage
Monocyte
Lymphocyte

Mature erythrocytes

- Round, biconcave, disc shaped
- Smooth contours
- Diameter 7.8 μm.
- Normally no variation in size and shape.
- Stain with EOSIN.
  - More stain at periphery
- Can deform easily.



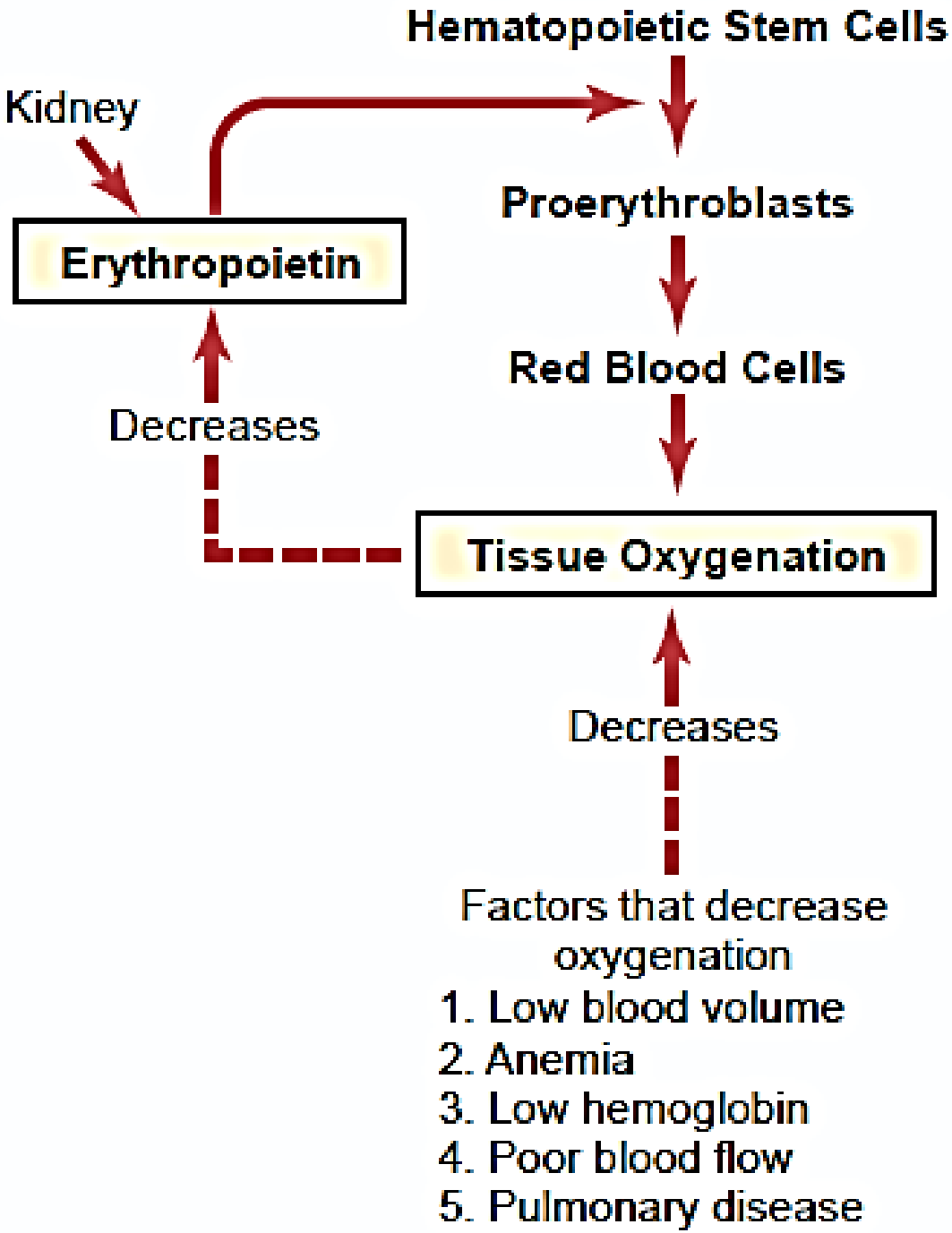
Mature erythrocytes cont..

- Negative surface charge.
- Bag of fluid with dissolved substances and hemoglobin
- Membrane –
  - Outer glycoprotein coat
  - Lipid bilayer (PL 55%,Cholesterol 45%)
- Inner protein molecules - cytoskeleton
  - Spectrin, Actin, Ankyrin etc.
- No sub cellular particles

Mature erythrocytes cont..

- Remains remarkably constant although there are some variations.
- MALE : $5.2 \pm 0.3 \times 10^6$ /uL.
- FEMALE : $4.7 \pm 0.3 \times 10^6$ /uL.
- Life span : 120 ± 30 Days.

Regulation of erythropoiesis


Hematopoietic Stem Cells
Kidney
Proerythroblasts
Erythropoietin
Red Blood Cells
Decreases
Tissue Oxygenation
Decreases
Factors that decrease oxygenation
1. Low blood volume
2. Anemia
3. Low hemoglobin
4. Poor blood flow
5. Pulmonary disease

Regulation of erythropoiesis

- Tissue oxygenation in the main regulator of RBC production
- Hypoxia increases erythropoietin secretion from the kidney
- Erythropoietin stimulates RBC production
- In absence of erythropoietin, hypoxia has no effect on RBC production
- Erythropoietin secretion also stimulated by androgens, catecolamines and prostaglandin

Erythropoietin

- A glycoprotein
- 90% synthesized in the kidneys. Remainder in the liver
- Main effect is to stimulate production of pro-erythroblasts from haemopoietic stem cells
- In addition, it helps to cells pass rapidly through different erythroblastic stages – increase speed of transition and promote early release of reticulocytes

Other factors needed for RBC synthesis

- Nutritional requirements
  - Vitamin B_{12} and folate
    - Both needed for DNA synthesis and therefore for nuclear maturation and cell division
  - Vitamin C
  - Amino acids
  - Copper, cobalt, zinc, manganese, nickel
  - Iron - Needed for Hb synthesis in RBC

Other hormones

- Androgens, thyroid, cortisol & growth hormones

Conditions which increase RBC production

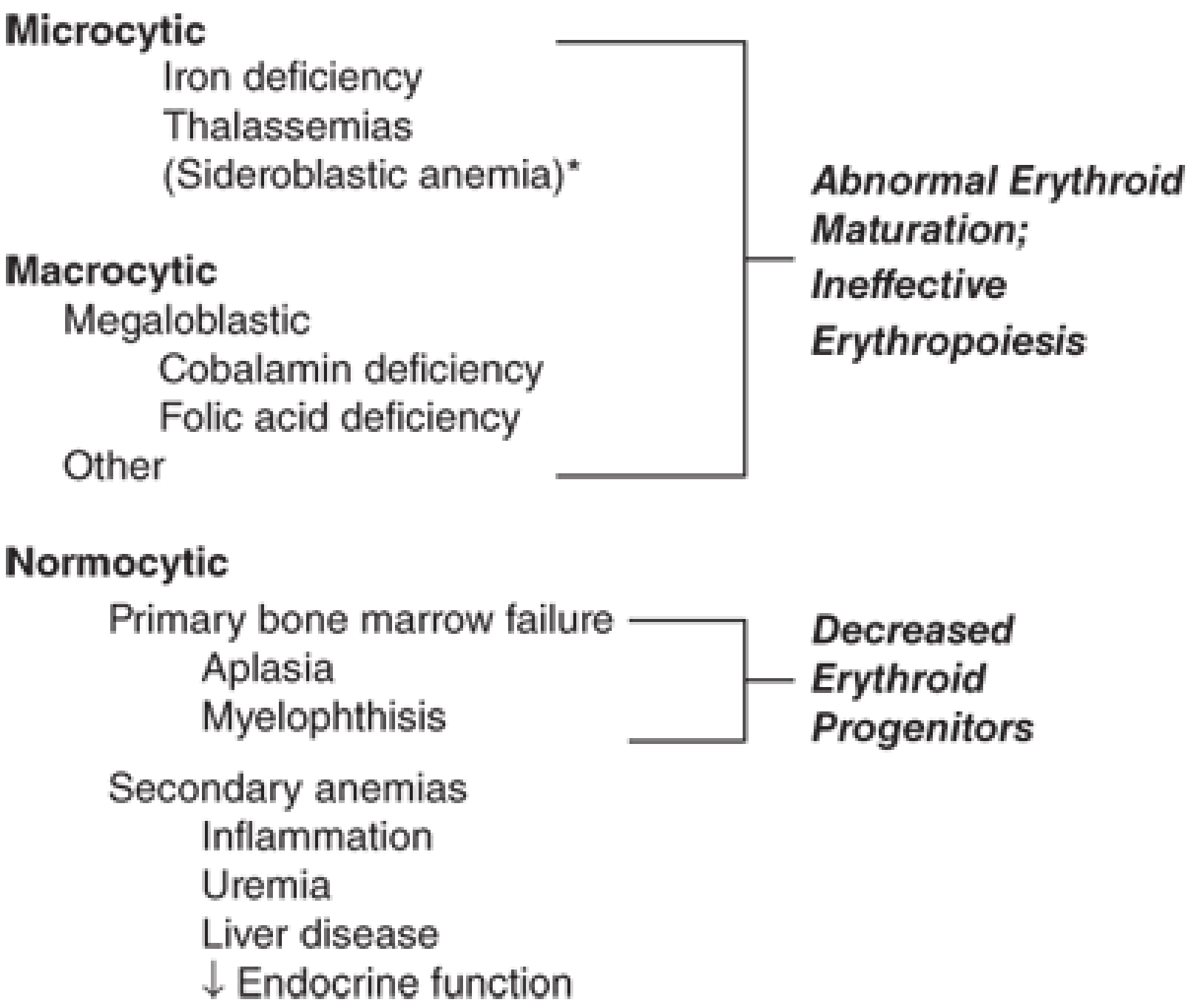
- Anaemia
- High altitude
- Hypoxic lung disease
- Cyanotic heart disease
- Decreased blood flow
  - E.g. cardiac failure
- Increased erythropoietin

Polycythemia

- Polycythemia Vera – primary
- Secondary Polycythemia
  - Appropriate to erythropoietin production
    - High altitude
    - COPD
    - Obesity
  - Inappropriate to erythropoietin production
    - Tumors – RCC, HCC, uterine leiomyoma
    - Renal ischemia
  - Familial Polycythemia

Conditions decreasing RBC production

- Bone marrow failure
  - E.g. Radiation therapy, bone marrow tumours etc.
  - When a major portion of marrow is destroyed, remaining bone marrow becomes hyperplastic attempting to supply enough RBC
- Nutritional deficiencies – e.g. B_{12} and folate
- Decreased erythropoietin
  - E.g. chronic renal failure
- Poisons
  - E.g. lead


Microcytic
Iron deficiency
Thalassemias
(Sideroblastic anemia)*
Macrocytic
Megaloblastic
Cobalamin deficiency
Folic acid deficiency
Other
Abnormal Erythroid Maturation; Ineffective Erythropoiesis
Normocytic
Primary bone marrow failure
Aplasia
Myelophthisis
Secondary anemias
Inflammation
Uremia
Liver disease
↓ Endocrine function
Decreased Erythroid Progenitors