Erythropoiesis L3

- All the circulating blood cells derive from **pluripotent stem cells** in the marrow. They divide into three main types.

    1. Erythropoiesis, is formation of RBC
    2. Leucopoiesis (myelopoiesis) is formation of WBC
    3. Thrombopoiesis is formation of platelets.

Erythron

- Collectively, the progenitors, precursors, and adult red cells make up an organ termed the **erythron**, which arises from pluripotent hematopoietic stem cells. The most numerous are red cells.

1- **Erythropoiesis**

- Erythropoiesis passes from the pluripotent hematopoietic stem cell through the →progenitor cells, →colony-forming unit granulocyte- erythroid, and →burst-forming unit erythroid (BFUE) and →erythroid CFU (CFUE).

- Each committed erythroid stem cell (pronormoblast) may give rise to up to an estimated 16 mature red blood cells, each pronormoblast, usually goes through four cell divisions to produce a total of 16 daughter cells. The normal process of proliferation and maturation lasts from 3 to 5 days, depending on the urgency of red blood cell needs of the circulating blood.

- During that time four mitotic divisions usually occur.

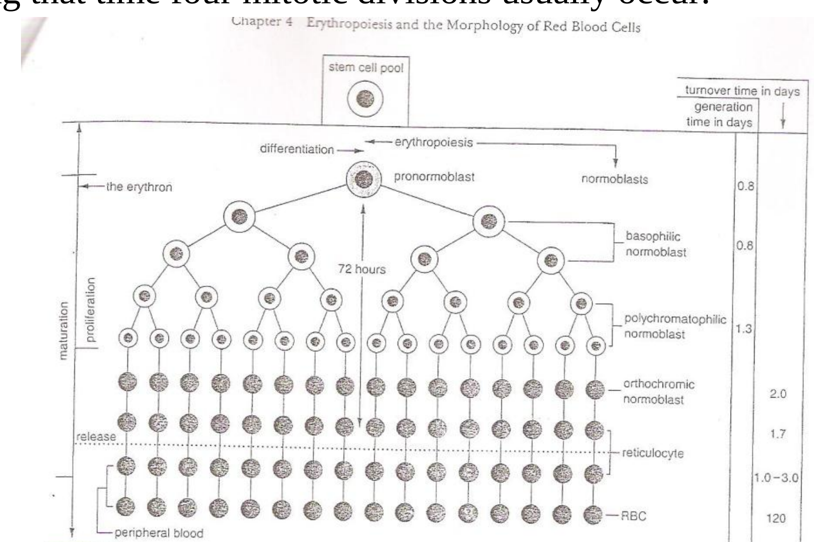
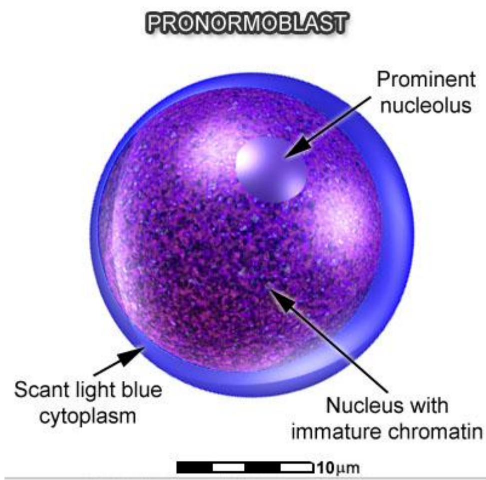


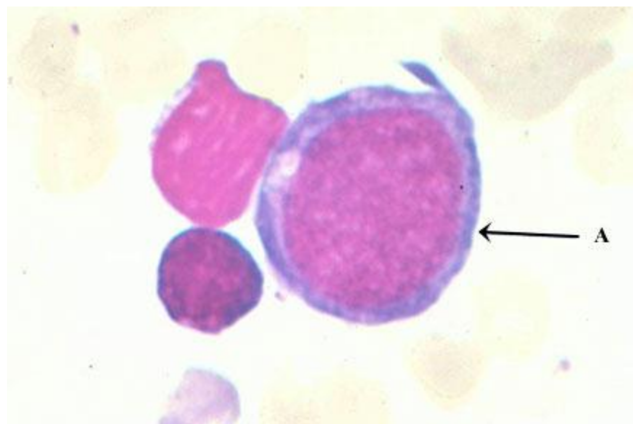
figure 4.1
Erythropoiesis, the development and maturation of the red blood cells.

Stages of Erythrocyte Development

Usually six stages in the development of red blood cells are recognized.

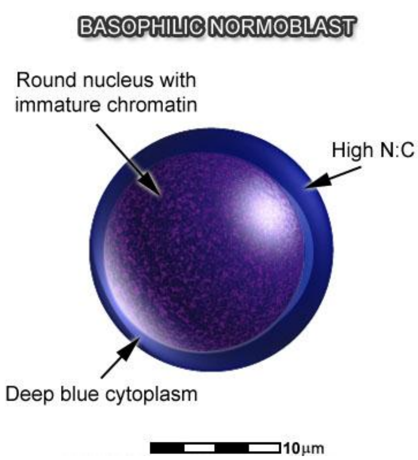
1- **The pronormoblast (or proerythroblast)** is the earliest stage in erythrocyte development. This pronormoblast is a fairly large cell, varying in diameter from 12 to 14 µm. The nucleus is prominent; it contains coarse chromatin and one or more nucleoli. When stained with Wright's stain, the cytoplasm is a deep blue and lacks inclusions and life span 0.8 day.

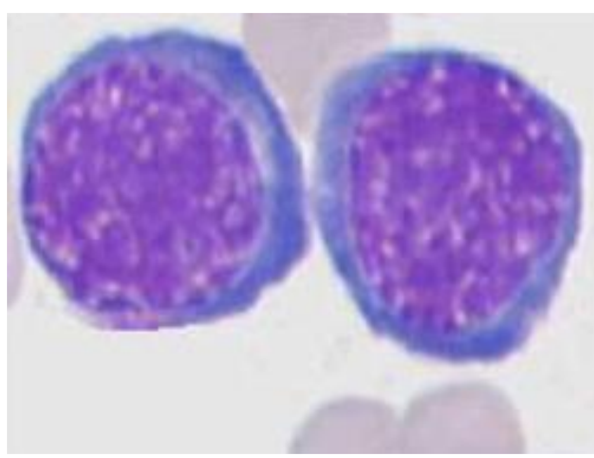




2- Basophilic normoblast (basophilic erythroblast).

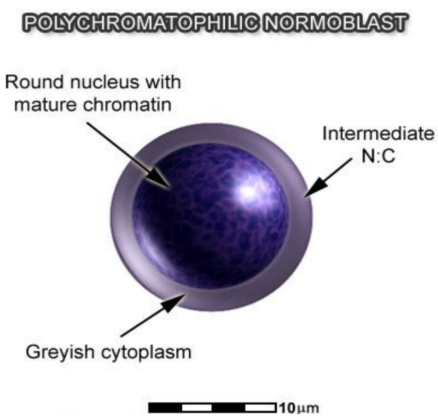
This cell may smaller than the pronormoblast, and the chromatin of the nucleus is coarser. The cytoplasm of the basophilic normoblast also stains a deep blue with Wright's stain and life span 0.8 day. What distinguishes this cell from the pronormoblast is the absence of nucleoli in the nucleus, the absence of nucleoli indicates the presence of a basophilic normoblast

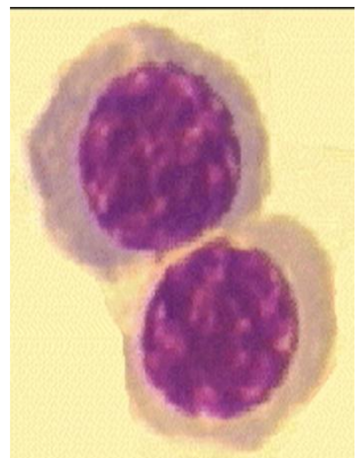




3- Polychromatophilic normoblast (polychromic erythroblast).

- This cell is usually smaller than the previous two cell types, having a diameter of about 10 µm and life span 1.3 days.
- It can be easily distinguished from the basophilic normoblast by two major changes. First, the nucleus! Is much more condensed and stains much darker. Second, the cytoplasm is no longer deep blue but appears much paler and shows a variable mixture of pink and blue, when stained with Wright's stain. This is the stage in which the hemoglobin appears for the first time in the cytoplasm

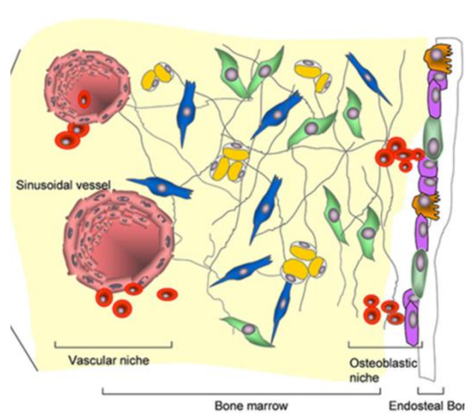




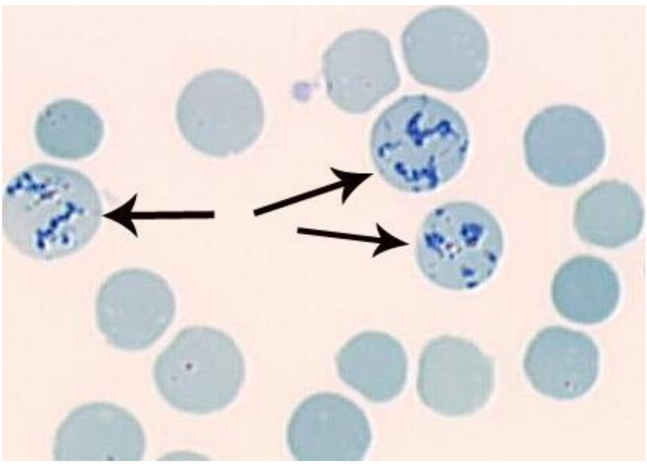
4- Orthochromic normoblast (or pyknotic erythroblast).

It is called "orthochromic" since the cytoplasm is now almost completely pink, and practically all traces of blue have disappeared. The other distinguishing feature of this cell is the shape and size of the nucleus. The nucleus appears as a dense blue-black sphere, is known as a pyknotic nucleus.

At the end of this phase, the nucleus is extruded, and the cell enters the circulation by squeezing itself through an opening in the endothelial lining of the bone marrow sinusoid. The nucleus is then phagocytosed and digested by one of the bone marrow macrophages and life span 2 days.



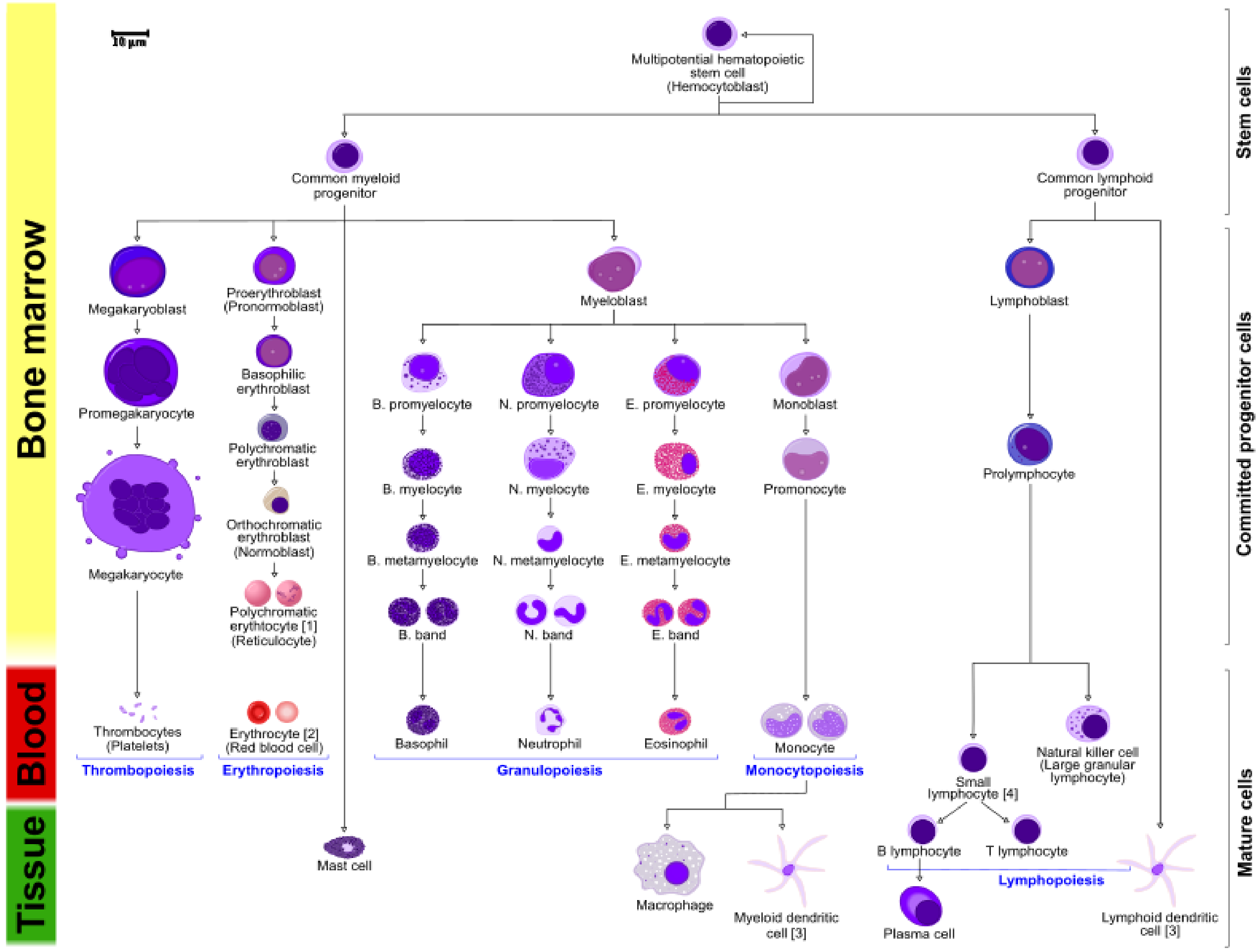
5- Reticulocyte. It is given this name because when stained with supravital dyes, a reticular network of strands can be observed inside the cell. These threads are remnants of RNA strands. This threadlike material disappears in a day or two, and the fell now becomes a fully mature red blood cell. The reticulocyte is slightly larger and less regular in shape than the erythrocyte.

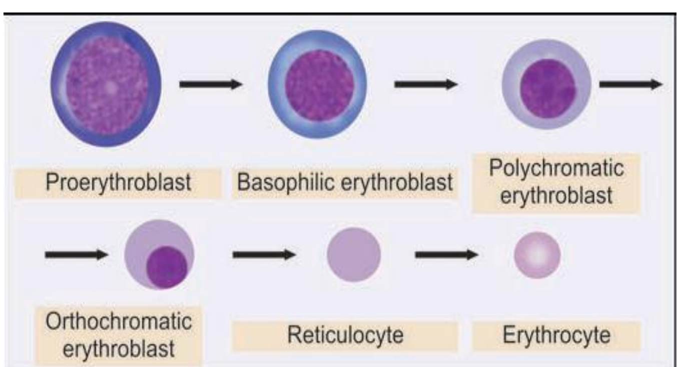


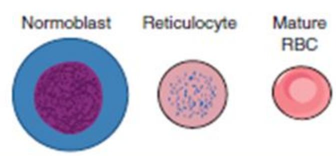
5- **Erythrocyte.** The maturation of a reticulocyte to an adult erythrocyte takes about 24 to 48 hours.
   - In the course of maturation, the ribosomes and mitochondria disappear, and the cell loses its capacity for hemoglobin synthesis and oxidative metabolism.
   - The maturing red blood cell enters the circulation as a reticulocyte.
   - life span 120 days

Q/ **what is the importance of the reticulocyte level in the blood?**

The reticulocyte level of the blood is the most common clinical index used to measure erythropoietic activity. Under normal conditions approximately 1% of the red blood cells need to be replacing each day.







	Normoblast	Reticulocyte	Mature RBC
Nuclear DNA	Yes	No	No
RNA in cytoplasm	Yes	Yes	No
In marrow	Yes	Yes	Yes
In blood	No	Yes	Yes

Figure 2.4 Comparison of the DNA and RNA content, and marrow and peripheral blood distribution, of the erythroblast (normoblast), reticulocyte and mature red blood cell (RBC).

Figure 1.7: Stages in the formation of a mature red cell. With each stage, cell size and nuclear size become smaller, chromatin clumping increases, and ultimately nucleus is extruded. Color of cytoplasm gradually changes from basophilic to orange-red.

Regulation of Erythropoiesis

Red Blood Cell Production

- The rate of new red blood cell (RBC) production varies according to the rate of

1- Red blood cell destruction and

2- Tissue oxygen requirements.

- A decrease in the oxygen content of hemoglobin (pulmonary dysfunction) ,
- the hemoglobin level (anemia) , or
- the hemoglobin affinity for oxygen will stimulate an increased production of erythropoietin by renal interstitial cells, initiate transcription of erythropoietin by a single gene on chromosome 7.
- Erythropoietin then travels to the marrow, where it binds to a specific receptor (EPOR) on the surface of committed erythroid precursors. Within hours, there is a detectable increase in (DNA) synthesis.
- This is followed by proliferation and maturation of committed stem cells to produce an increased number of new red blood cells.
- The full marrow response takes several days. Given a sustained increase in erythropoietin stimulation, a rise in the reticulocyte index will not occur for 4-5 days and a detectable increase in hematocrit will take a week or more.

Factors Influencing Erythropoietin Level

- Factors Influencing Erythropoietin Level Although the erythropoietin response is primarily a function of

  1- the severity of anemia or hypoxia,

  2- The erythroid marrow mass

  3- Inflammatory cytokines play a role in regulating erythropoietin production. Including: IL-3 (interleukin- 1), IL-3, IL-4, IL-6, Tumor Necrosis Factor (TNF- a) Platelet-Derived growth factor (PDC1F), Transforming Growth Factor B .

4- Therefore, with aplastic anemia, extremely high levels of serum erythropoietin reflect both an increased production and a decreased clearance. And therefore, a higher serum level

5- In contrast, with chronic hemolytic anemias, the expansion of marrow erythroid precursors results in a more rapid clearance of erythropoietin from circulation and, therefore, a lower serum level.

6- Two other factors, angiotensin II and insulin-like growth factor-I (IGF- 1)

7- Finally, direct suppression of the erythroid marrow response is seen in patients receiving certain drugs (chemotherapeutic agents, cyclosporin A, and theophylline) or who are infected with human immunodeficiency virus (HIV) .

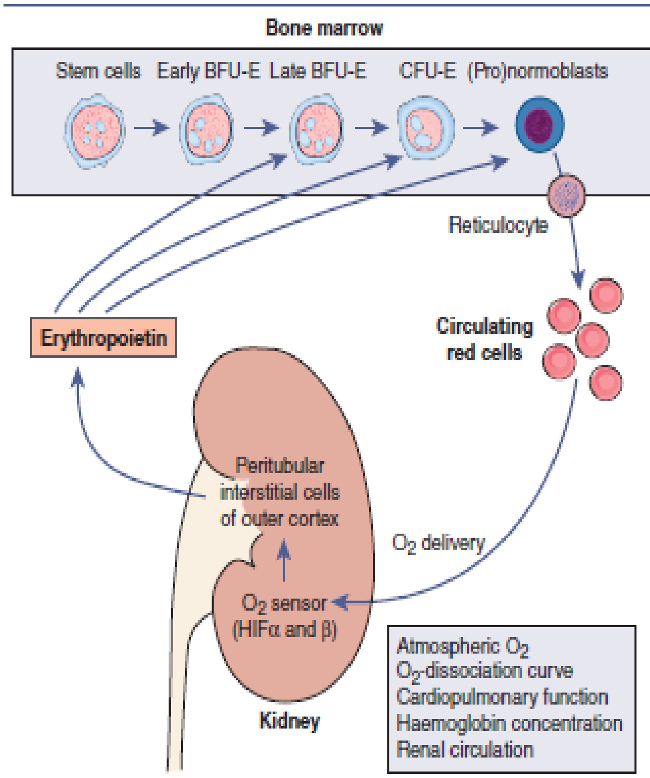
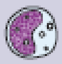


Figure 2.5 The production of erythropoietin by the kidney in response to its oxygen (O_2) supply. Erythropoietin stimulates erythropoiesis and so increases O_2 delivery. BFU_E, erythroid burst-forming unit; CFU_E, erythroid colony-forming unit. Hypoxia induces hypoxia inducible factors (HIFs) α and β, which stimulate erythropoietin production. Von-Hippel–Lindau (VHL) protein breaks down HIFs. PHD2 (prolyl hydroxylase) hydroxylates HIF-1α allowing VHL binding to HIFs. Mutations in VHL, PHD2 or HIF-1α underlie congenital polycythaemia (see p. 171).

Table 2.1 The blood cells.				
Cell	**Diameter (μm)**	**Lifespan in blood**	**Number**	**Function**
Red cells 	6–8	120 days	Male: $4.5–6.5 \times 10^{12}$/L Female: $3.9–5.6 \times 10^{12}$/L	Oxygen and carbon dioxide transport
Platelets 	0.5–3.0	10 days	$140–400 \times 10^{9}$/L	Haemostasis
Phagocytes				
Neutrophils 	12–15	6–10 h	$1.8–7.5 \times 10^{9}$/L	Protection from bacteria, fungi
Monocytes 	12–20	20-40 h	$0.2–0.8 \times 10^{9}$/L	Protection from bacteria, fungi
Eosinophils 	12–15	Days	$0.04–0.44 \times 10^{9}$/L	Protection against parasites
Basophils 	12–15	Days	$0.01–0.1 \times 10^{9}$/L	
Lymphocytes  B T	7–9 (resting) 12–20 (active)	Weeks or years	$1.5–3.5 \times 10^{9}$/L	B-cells: immunoglobulin synthesis T-cells: protection against viruses; immune functions