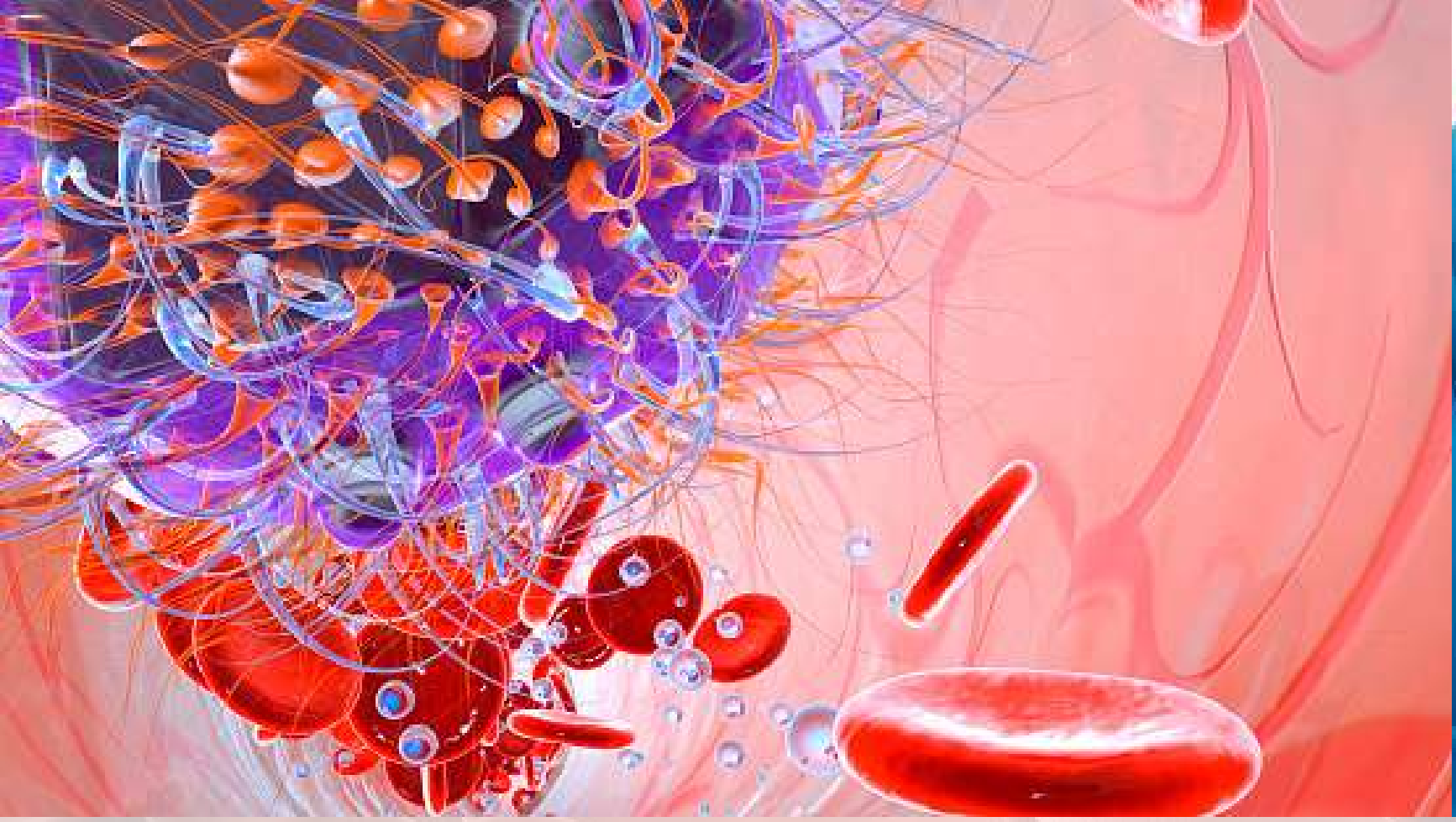


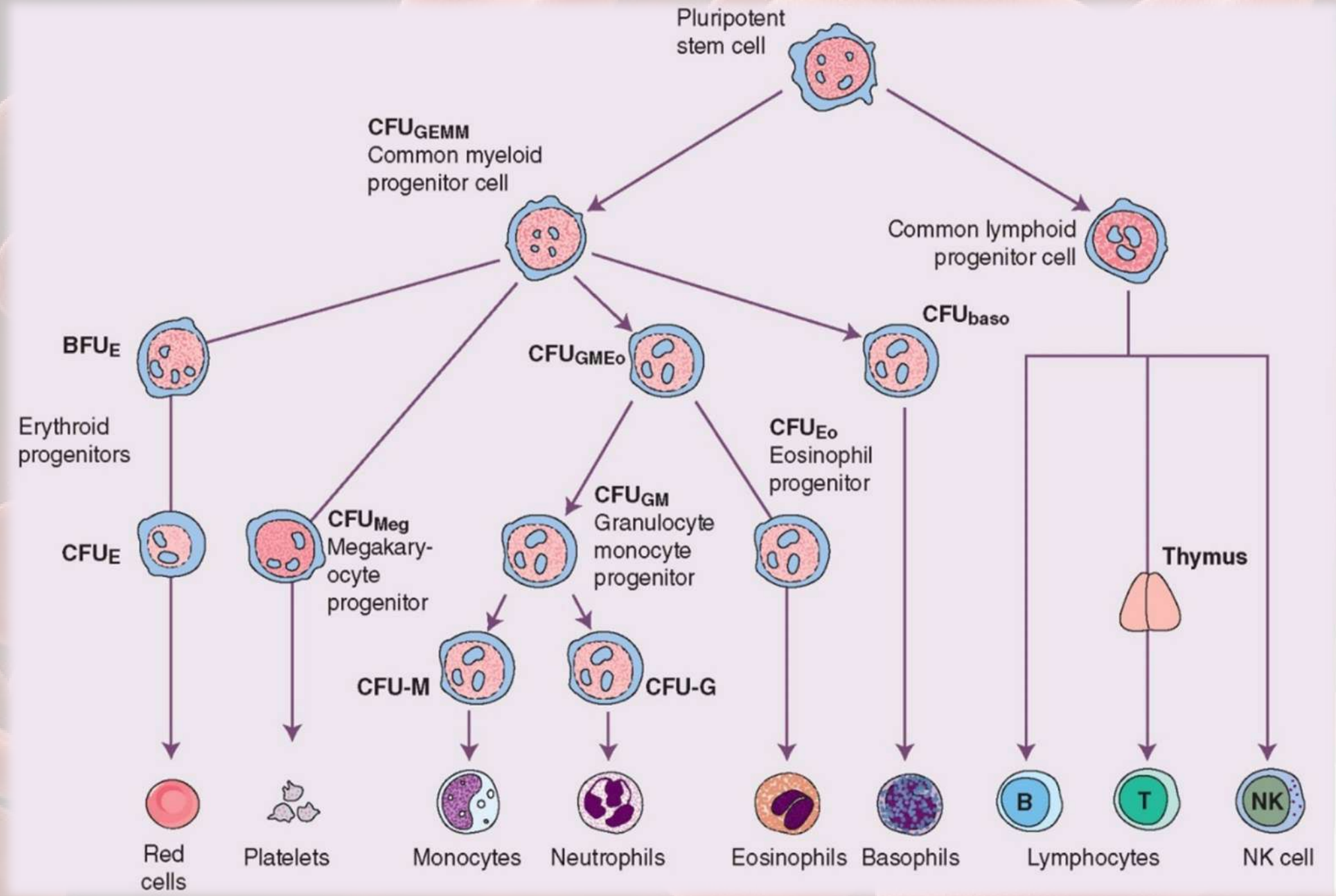
Hematology

"Haematology"

Dr. Abdulsalam A. Al-Ani
4th Year- Under Graduate
Medical College
University of Anbar

HEMOPOIESIS

- Hemopoiesis; formation of blood cells.
- Erythropoiesis; formation of RBCs.
- Myelopoiesis; formation of granulocytes and monocytes.
- Thrombopoiesis (Megakaroypoiesisi); formation of platelets.


Pluripotent stem cell
CFUGEMM Common myeloid progenitor cell
Common lymphoid progenitor cell
BFUE
CFUbaso
CFUGMEo
Erythroid progenitors
CFUEo Eosinophil progenitor
CFUGM Granulocyte monocyte progenitor
CFUE
CFUMeg Megakary-ocyte progenitor
Thymus
CFU-M
CFU-G
B
T
NK
Red cells
Platelets
Monocytes
Neutrophils
Eosinophils
Basophils
Lymphocytes
NK cell

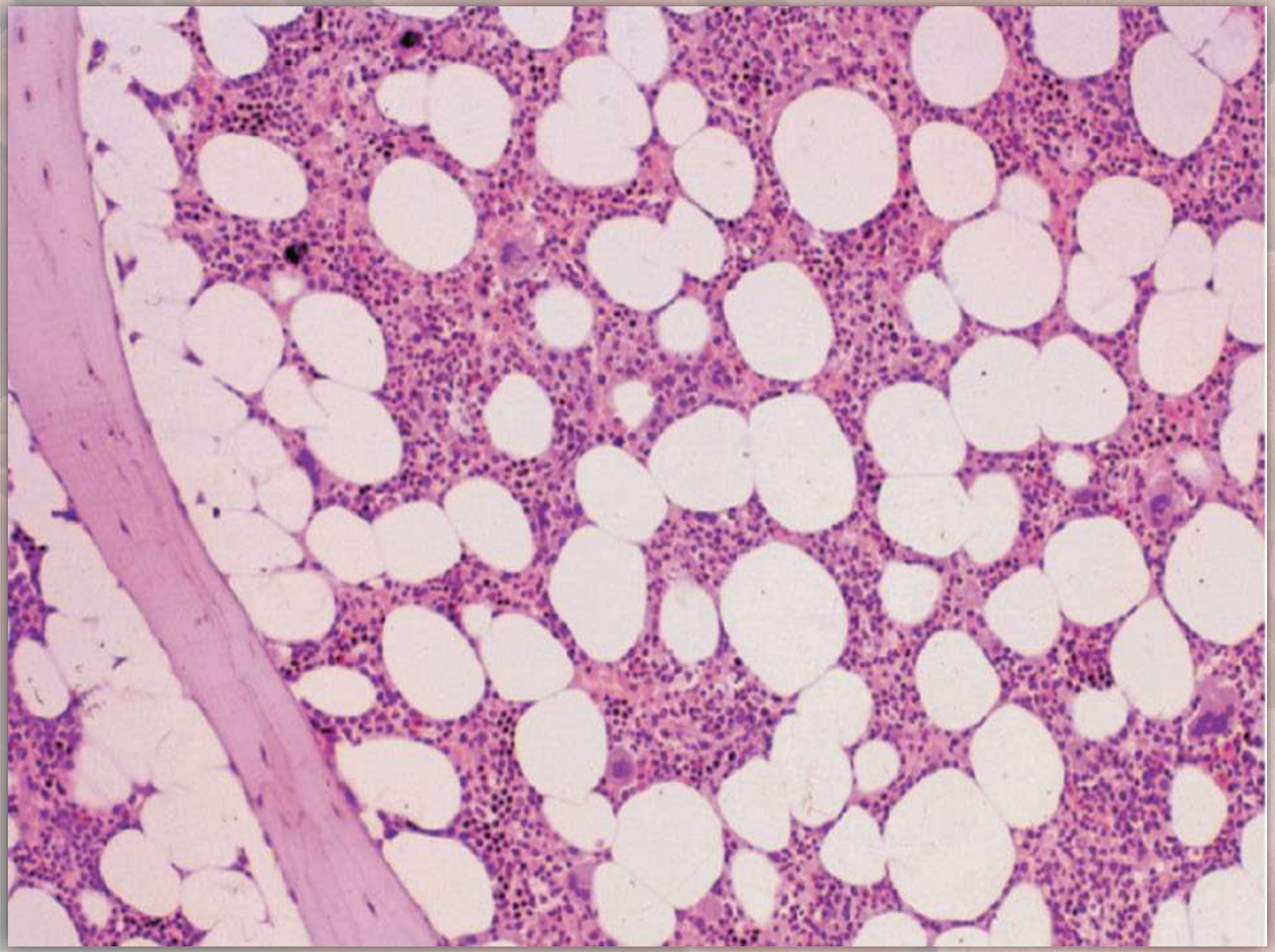
❖ Site of Haemopoiesis:

- In the **first few weeks of gestation** (pregnancy), the yolk sac is the main site of hemopoiesis on the dorsal aorta termed the AGM (aorta-gonads-mesonephros) region. These precursors of endothelial and hemopoietic cells (hemangioblasts) are seed the liver, spleen and bone marrow.
- From **6 weeks until 6–7 months of fetal life** the liver and spleen are the major hemopoietic.
- The bone marrow is the most important site **from 6 to 7 months** of fetal life.
- During **normal childhood and adult life** the marrow is the only source of new blood cells.

- In **infancy** all the bone marrow is hemopoietic, with the progressive fatty replacement of marrow throughout the long bones so that in adult life hemopoietic marrow is confined to the central skeleton and proximal ends of the femurs and humeri.
- The **liver and spleen** can resume their fetal hemopoietic role called ***'extramedullary haemopoiesis'***.

Fetus	0–2 months (yolk sac) 2–7 months (liver, spleen) 5–9 months (bone marrow)
Infants	Bone marrow (practically all bones)
Adults	Bone marrow; Vertebrae, ribs, sternum, skull, sacrum and pelvis, proximal ends of femur

Bone Marrow Trephine Biopsy in the Intertrabecular Tissue



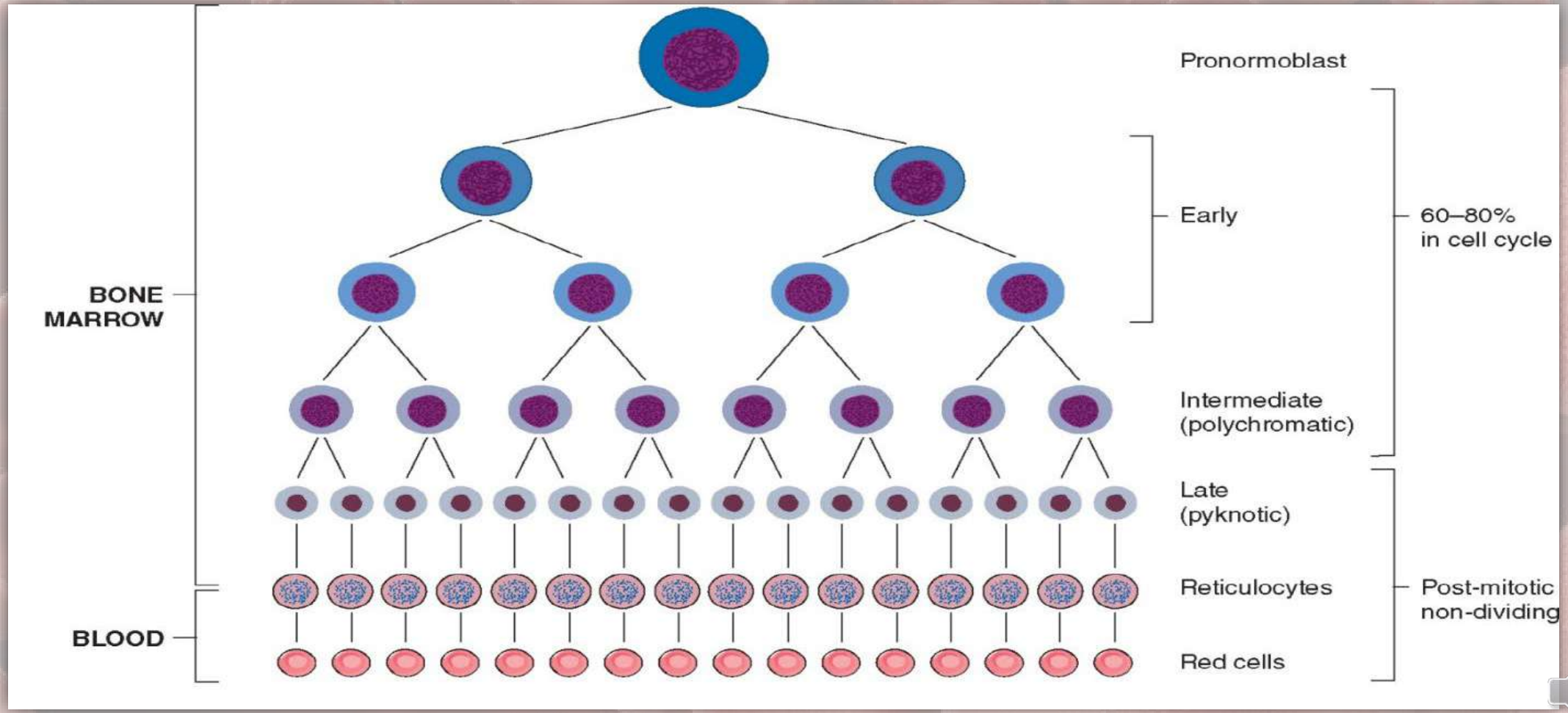
Hemopoietic Stem Cells:

- Undifferentiated (unspecialized) cells capable of renewing themselves through cell division "***self-renewal***", with its ability when induced to become tissue- or organ-specific cells with special functions ***"specialization"***.
- Hemopoietic stem cell (HSC), a very rare cell in the **peripheral blood** and of about 1:20 million bone marrow nucleated cells.
- Can give rise to more than 10^6 mature blood cells after 20 cell divisions.
- More in the BM because of the suitable environment for survival, renewal and differentiation. Under the control of a complicated mechanism HSCs move from and to BM leading to, what is called mobilization and homing processes.
- The stem cells are found in **many organs**, which can generate different types of tissues. This is one of the recent revolution in its uses for the treatment of a different disease (neurons, liver, type1 diabetes, muscles …etc).

- The next generation from the HSC, called **multipotent progenitor** cells (MPP), which give rise to common; myeloid (CMP) and lymphoid progenitor (CLP) cells.
- **CMP** giving rise to more specialized one for the production of mature blood cells by; erythropoiesis (production of RBCs), myelopoiesis (production of neutrophils, eosinophils, basophils and monocytes) and thrombopoiesis (production of platelets).
- **CLP** giving rise to lymphocyte cells (T and B).
- The regulation of proliferation and differentiation of the hemopoietic progenitor cells (HSCs) and the function of the mature cells are under the control of different hemopoietic growth factors (glycoprotein hormones). The effect of these GFs are mediated through specific receptor on target cells.

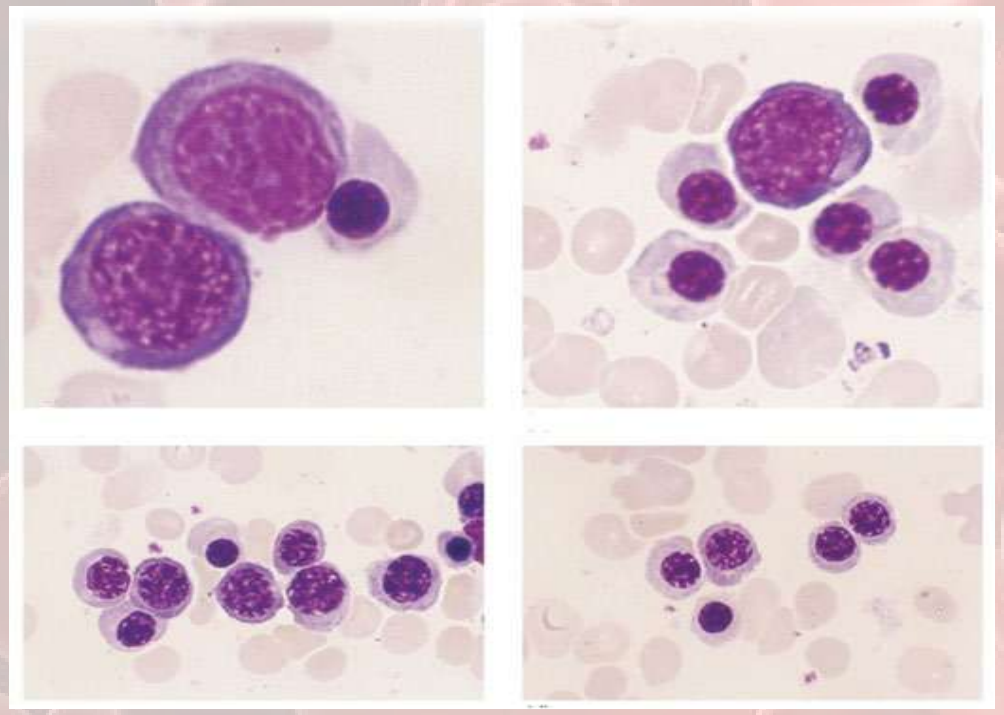
❖ Erythropoiesis;

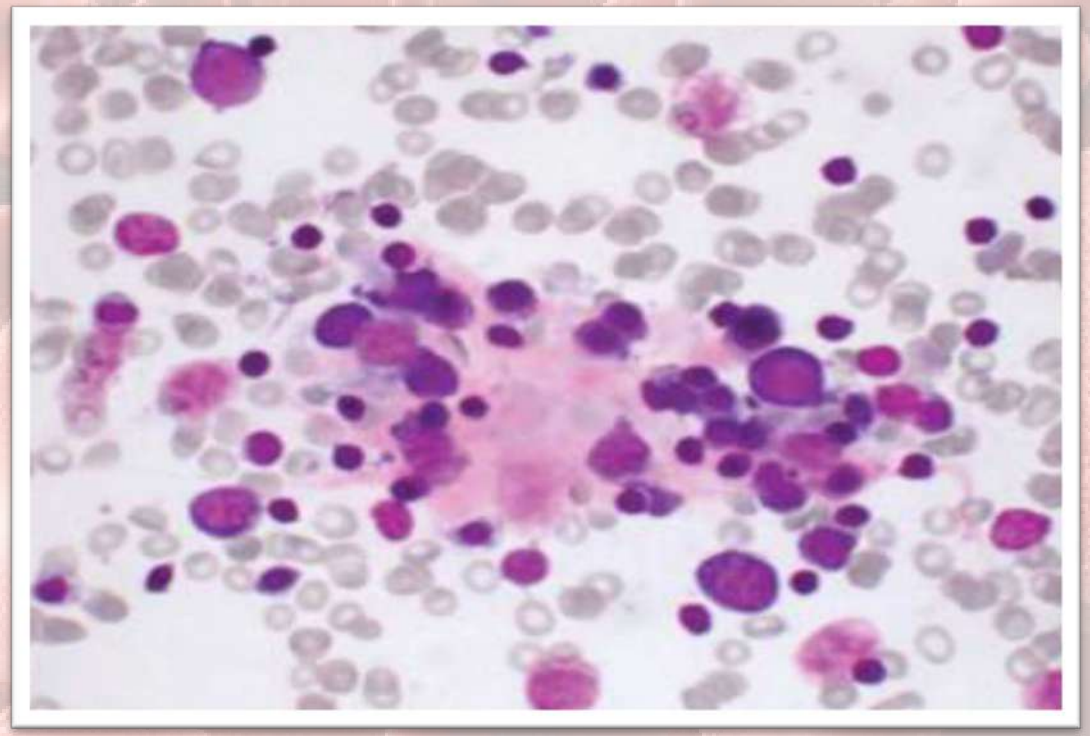
- Formation of red blood cells (RBCs) occur by a complex regulated process, leading to a proximately 10^{12} new erythrocytes per day.



Amplification and maturation of RBCs

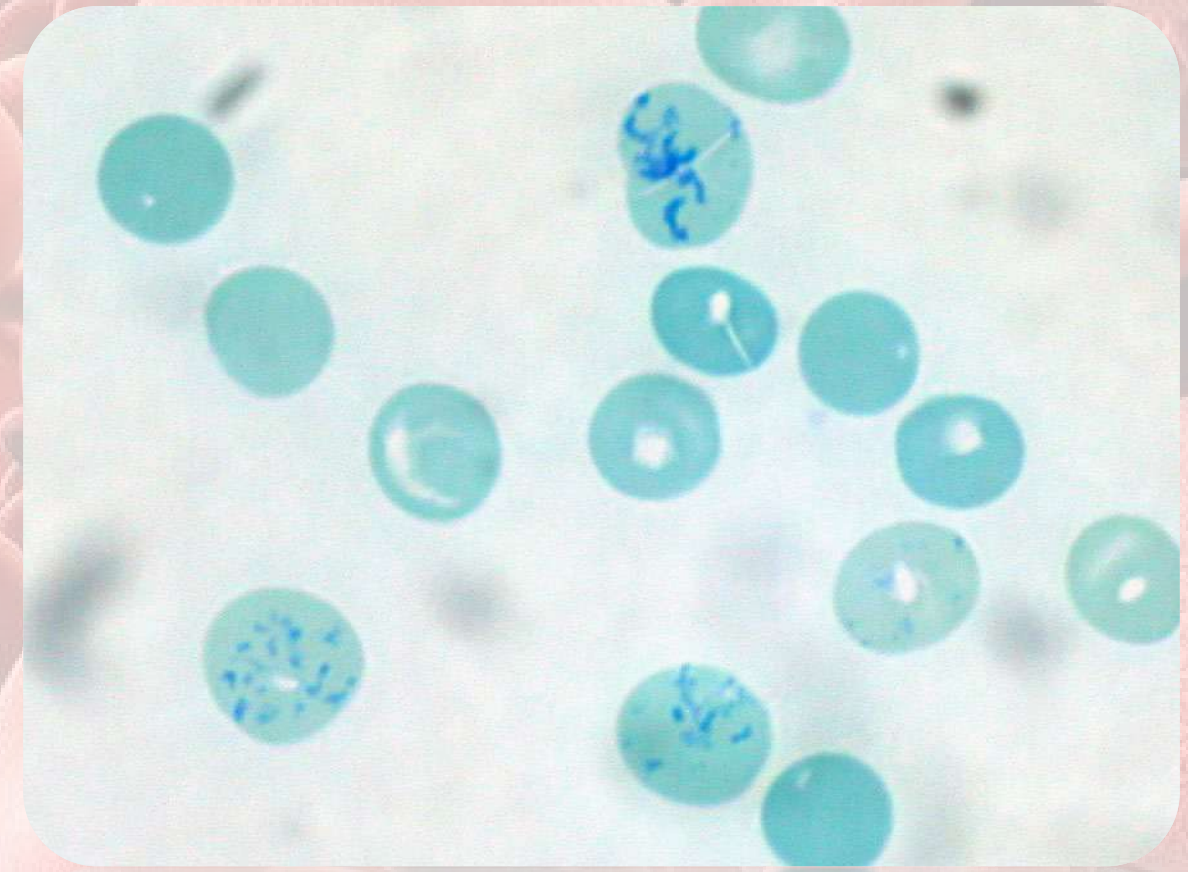
- The first recognizable erythrocyte precursor called pronormoblast, then progressively to smaller basophilic, early polychromatic and finally late polychromatic/orthochromatic normoblasts.





Left; Erythroblasts (Normoblasts; NRBCs) in varying stages of development. The earlier cells are larger, with more basophilic cytoplasm and a more open nuclear chromatin pattern. The cytoplasm of the later cells is more eosinophilic as a result of hemoglobin formation maturation. Right; An erythroblastic island with its central macrophage surrounded by erythroid progenitors at various stages of differentiation.

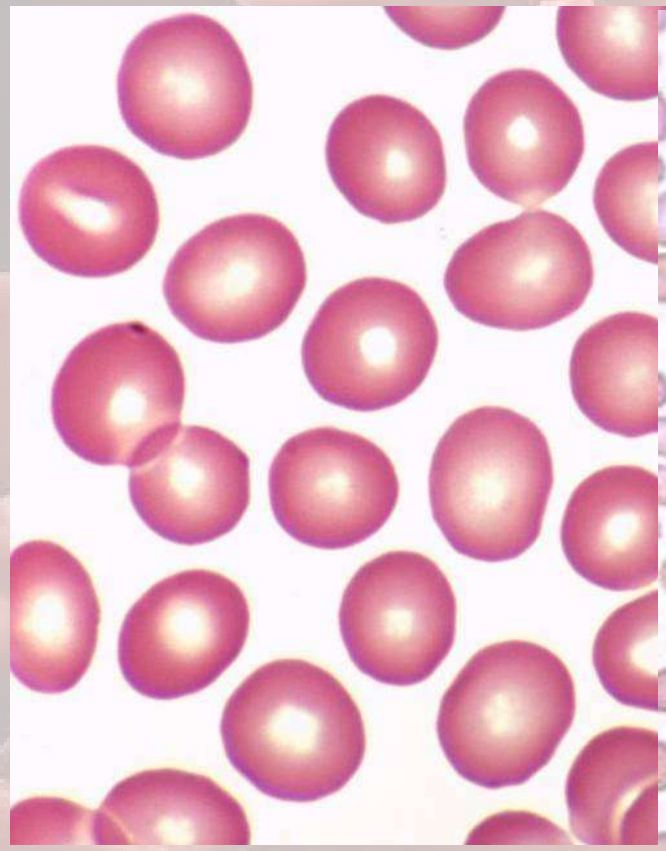
- **Reticulocytes** form when the nucleus extruded with formation of mature erythrocytes. They are called reticulocytes because of a reticular (mesh-like) network of the residual RNA that becomes visible under a microscope with certain stains such as new methylene blue and Romanowsky stain.

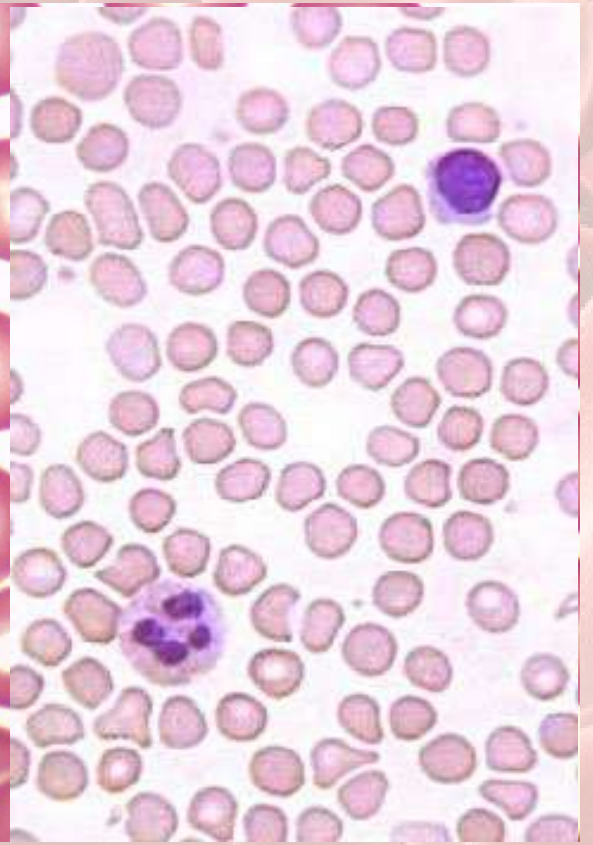


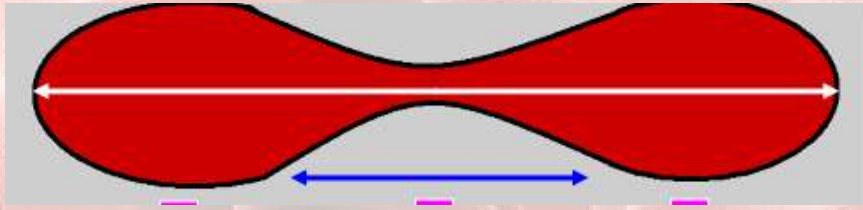
Supravital staining (methylene blue or brilliant cresyl blue), which stained the of a smear from a patient with hemolysis. The reticulocytes are the cells with the dark blue dots and curved linear structures (reticulum) in the cytoplasm.

- The mature non-nucleated RBC is a completely pink-staining with biconcave disc have a diameter of 6 - 8 μm.
- On a peripheral blood smear, normal RBCs are disc-shaped with a pale-staining central area called the central pallor.
- When judging red cell size on a blood smear, the classic rule is to compare them to the nucleus of a small normal lymphocyte. The normal lymphocyte nucleus has an approximate diameter of 8 μm.
- It spend about 120 days in the circulating blood.

Normal Red Blood Cells







Biconcave disc
Diameter : 7 ~ 8 μm
Central pallor occupy 1/3 rd of total
Size: approx. the same as nucleus of mature lymphocyte

❖ Erythropoietin Hormone (EPo):

- The main regulating factor for the erythropoiesis. It is a glycosylated polypetide. EPo mainly produced in the kidney (90%), and the rest 10% mainly produced by the liver.
- Normal concentration of; 9.1–30.8 iu/l.
- Affected by;

1. O2 concentration in the blood (atmospheric O2 or defective cardiac or pulmonary functions).
2. Damages affected renal blood circulation.
3. Polycythemia, chronic inflammatory disorders and certain neoplasia.
4. In pregnancy, it's usually higher than normal.

❖ Recombinant Epo;

Used in anemias caused by:

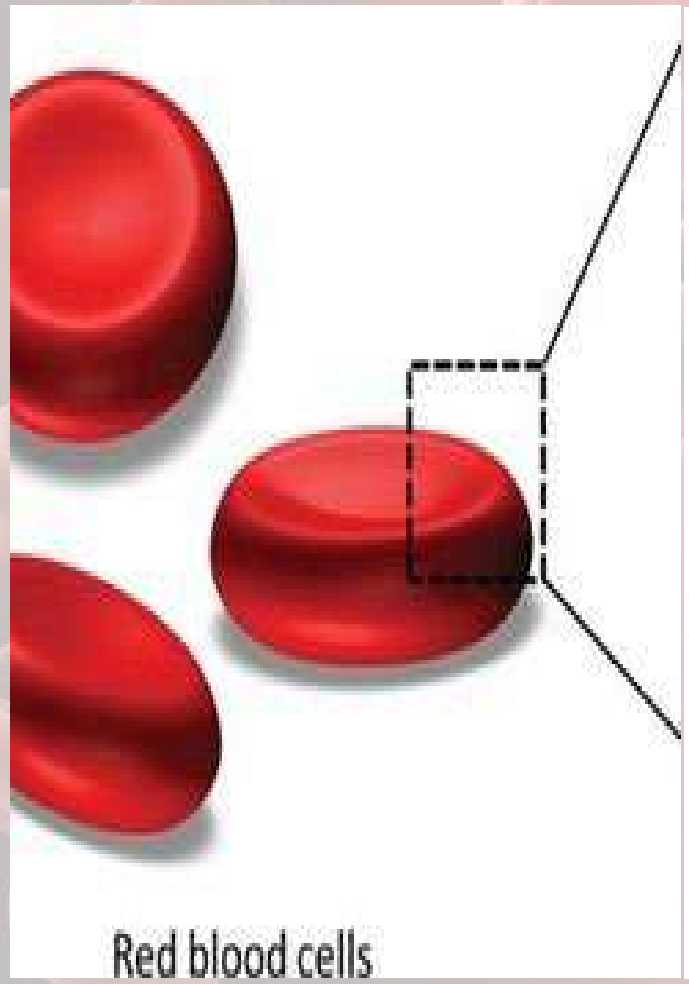
1. Chronic renal diseases.
2. Chronic inflammatory diseases (RA).
3. Myelodysplastic syndrome (MDS).
4. Prematurity.
5. Malignancy or chemotherapy.

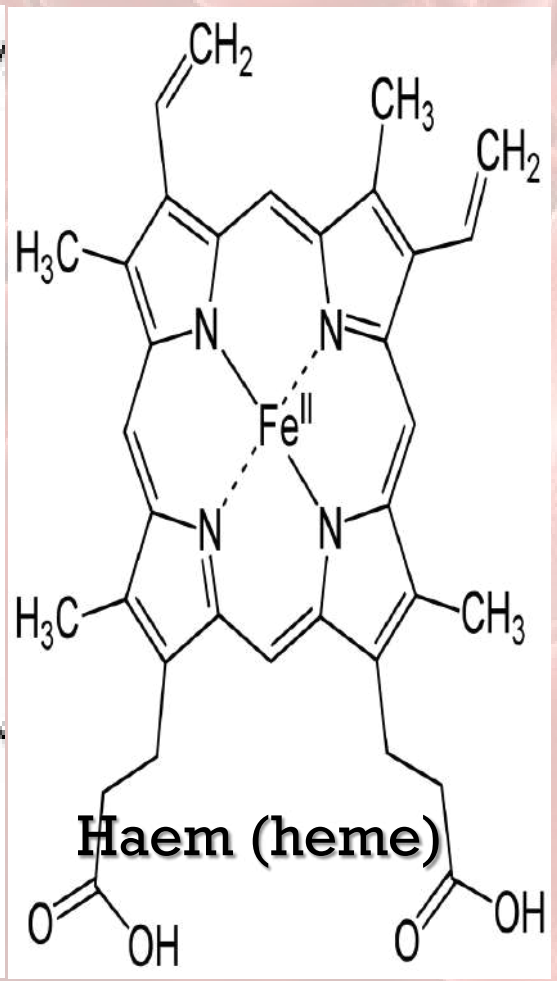
❑ Hemoglobin (Hb):

- A specialized protein of red pigments give the blood its colour and responsible for the gaseous exchange of O2 and CO2 in the body tissues.
- It is synthesized in the cell by ribosomal and mitochondrial reactions for globin and hem respectively.
- The type of Hb depends on the globin chain. In addition to α; β, γ and δ for Hb A (α and β), F (α and γ) and A_2 (α and δ) respectively.

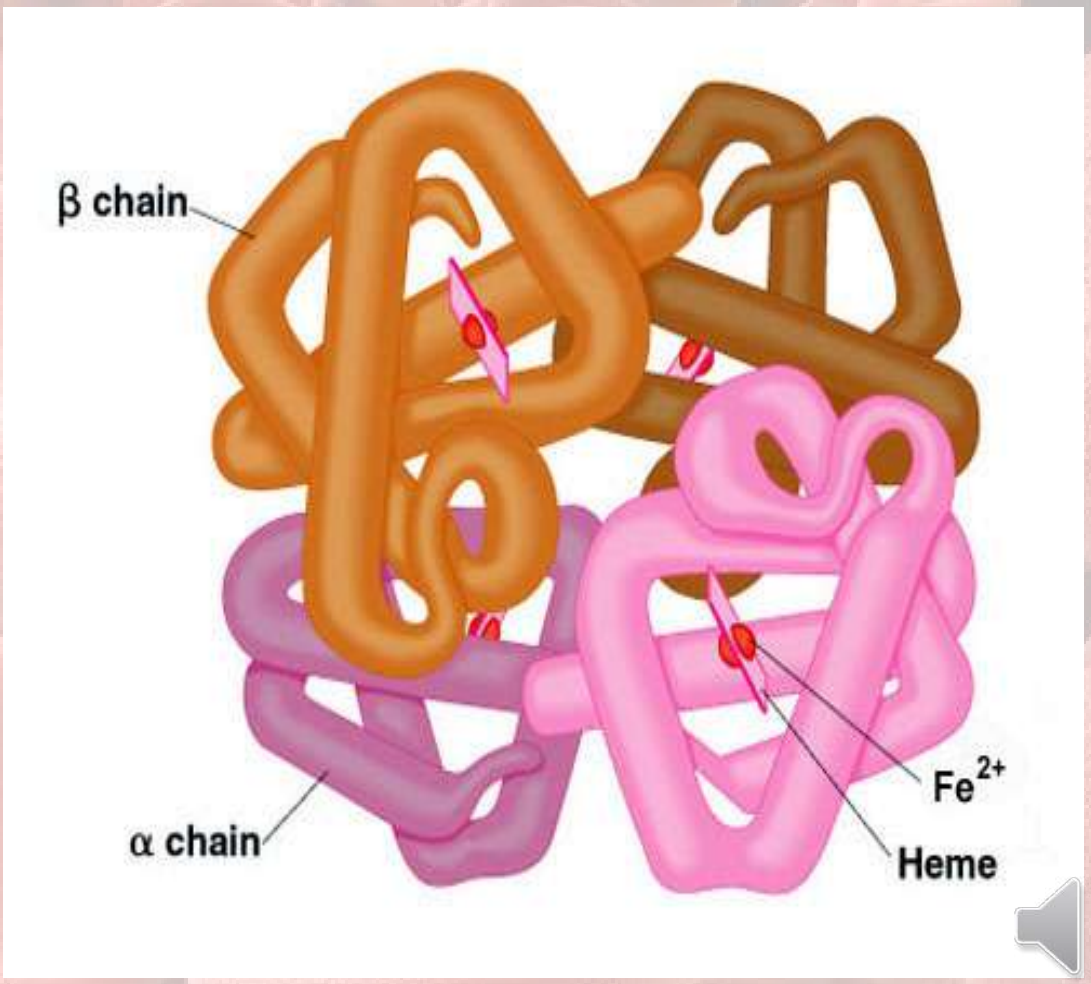
	Hb A	Hb F	Hb A2
Structure	$\alpha_2\beta_2$	$\alpha_2\gamma_2$	$\alpha_2\delta_2$
Normal (%)	96–98%	0.5–0.8%	1.5–3.2%

- Each hemoglobin molecule consists of four iron-containing parts (heme); protoporphyrin with iron core in ferrous (Fe^{+2}) form and four polypeptide chains (globin).





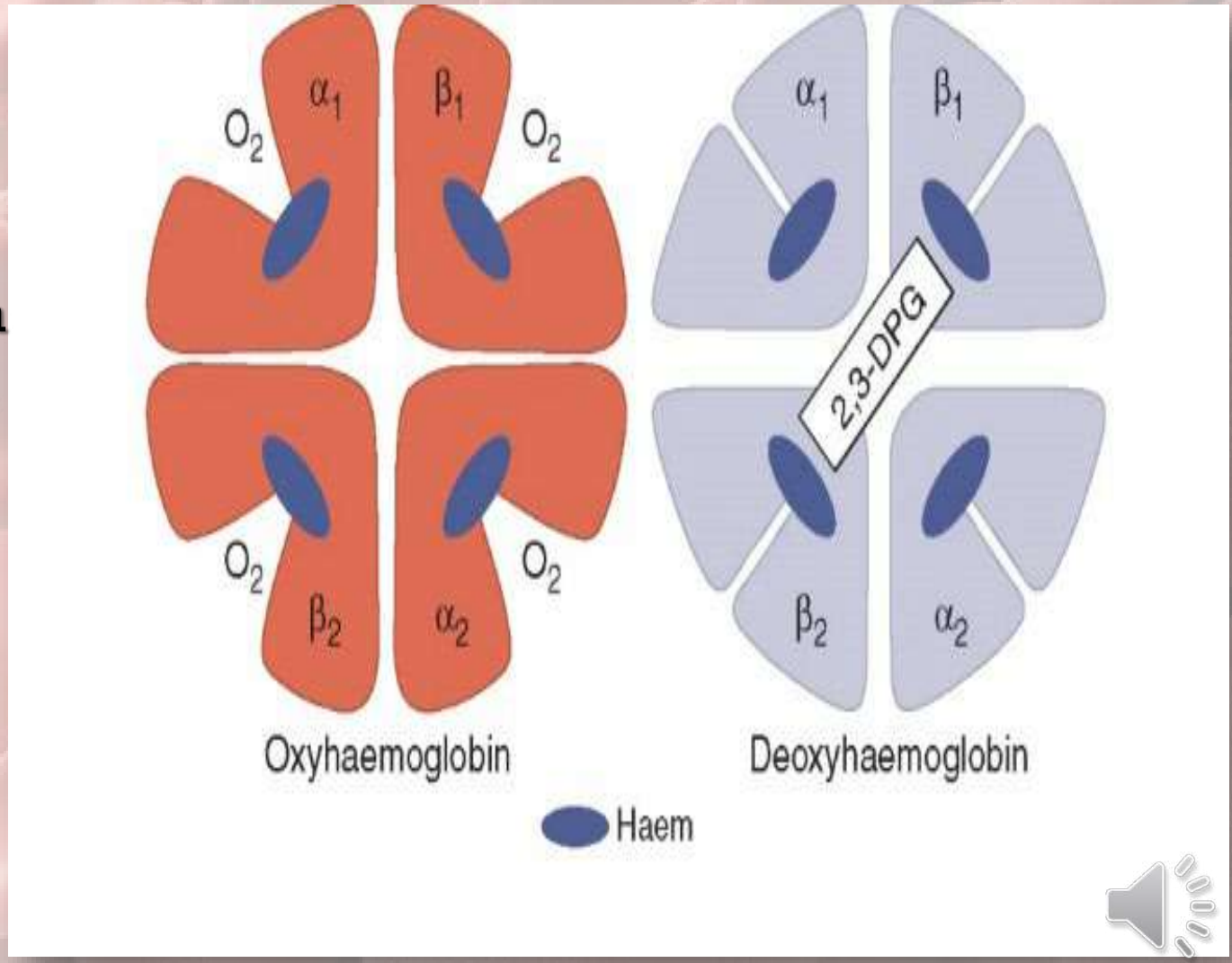
Haem (heme)



❑ Hb Function:

- The function of oxygen transfer performed by RBCs Hb, between lungs and tissues.

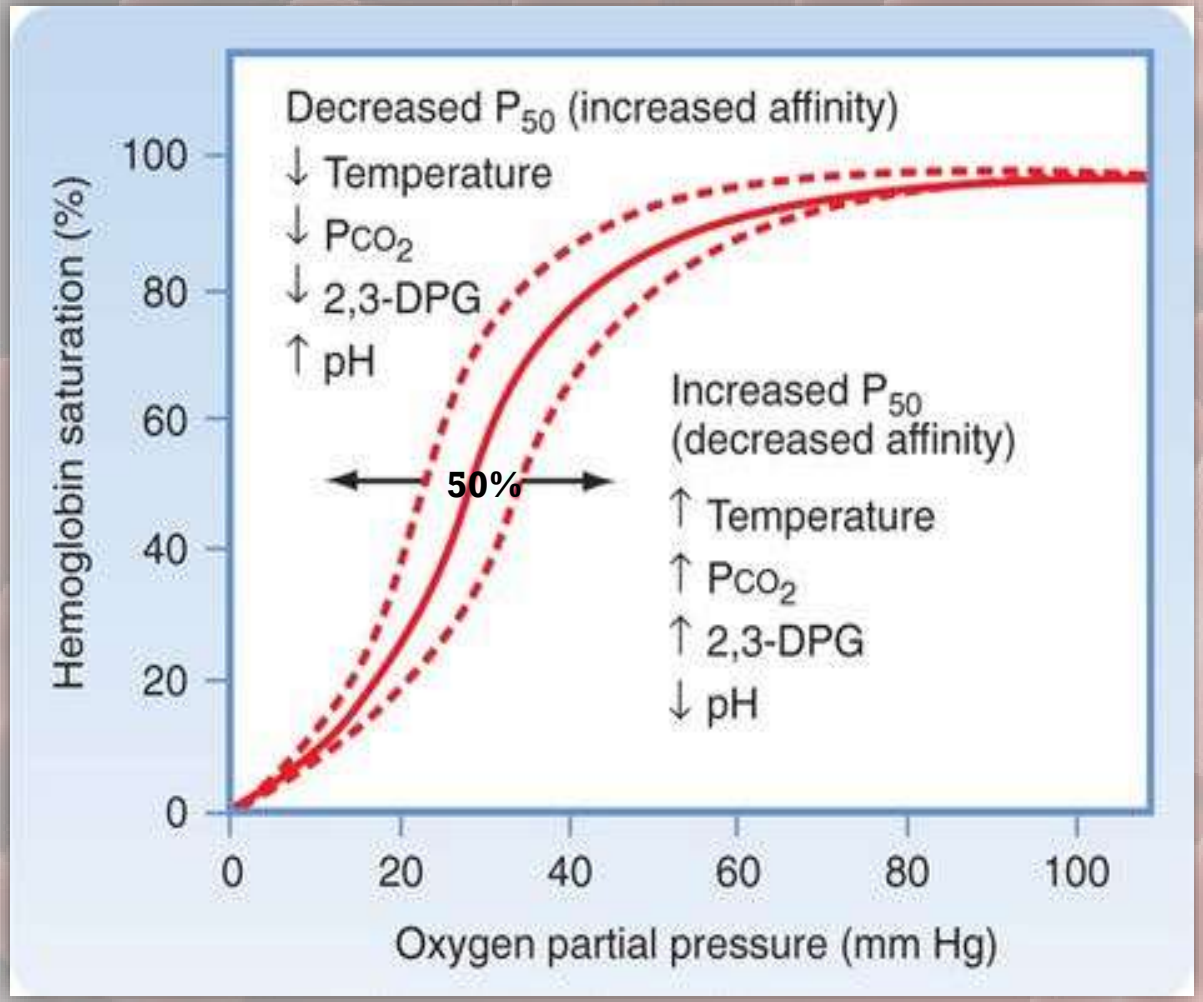
- The process of oxygenation and deoxygenation of the Hb molecule occurred by the sliding of the globin chains in presence of Hem molecule and 2,3-DPG.

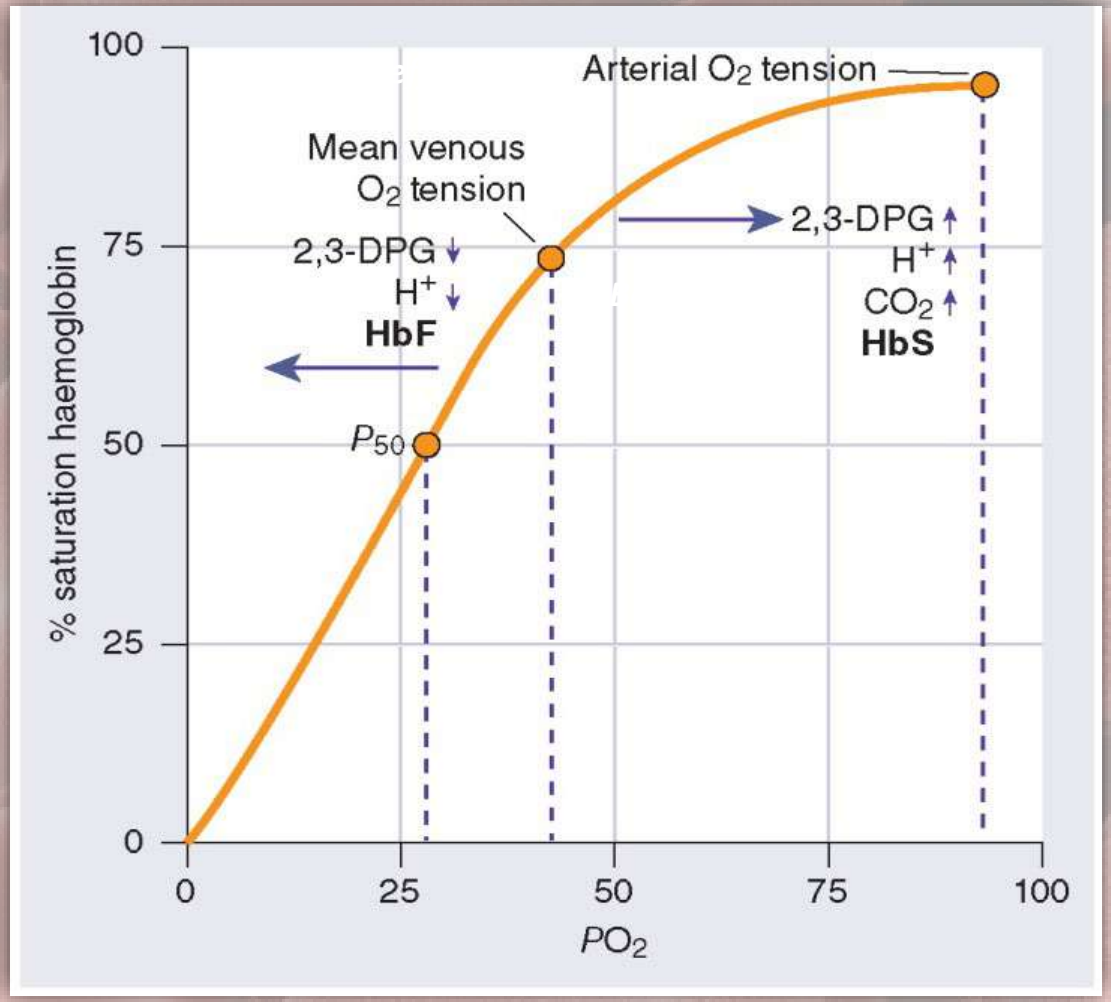


- The exchange of O_2 and CO_2 in the arterial and venous blood in a form of what's called; Hb Oxygen dissociation curve.
- There is certain factors affecting this curve including physiological and pathological causes;

1. H^+, Temp., CO_2 and 2,3-diphosphoglycerate (2,3-DPG), and Hb type (eg; S an F)
2. Partial pressure of oxygen in the blood at which the hemoglobin is 50% saturated, typically about 26.6 mmHg (3.5 kPa) for a healthy person, known as P_{50}

Hemoglobin Oxygen Dissociation Curve





❑ ANEMIA:

Reduction in the haemoglobin concentration of the blood **below** normal level for **age and sex** .

- The Normal values can vary between laboratories. WHO values for anemia, would be less than 13.0 g/dL in adult males and less than 12.0 g/dL and 11.0 g/dL in adult non-pregnant and pregnant females respectively.
- Newborn infants have a high haemoglobin level, and 14.0 g/dL considered as the lower level.
- Usually associated with reduction in packed cell volume (PCV), but sometimes not. In certain conditions with the changes of plasma volume can lead to reduced or increased Hb level normal red cell and Hb mass.
- In hemorrhage although, there is a blood loss but Hb may show normal level during the first day.

Normal Hb values for Adults

	Male	Female
Hemoglobin (g/dL)	13.0–17.0	12.0–15.0
Hematocrit (PCV) (%)	40–50	36–46
Red cell count ($\times 10^{12}$/L)	4.5–6.5	3.9–5.6
Mean cell haemoglobin (MCH) (pg)	27–32	
Mean cell volume (MCV) (fL)	83–100	
Mean cell haemoglobin concentration (MCHC) (g/dL)	31–35	

WHO's Hemoglobin Thresholds Used to Define Anemia*

Age or gender group	*Hb threshold (gm/dL)*	*Hb threshold (mmol/L)@*
Children 0.5–5.0 yrs)	*11.0*	*6.8*
Children (5–12 yrs)	*11.5*	*7.1*
Teens (12–15 yrs)	*12.0*	*7.4*
Women, non-pregnant (>15yrs)	*12.0*	*7.4*
Women, pregnant	*11.0*	*6.8*
Men (>15yrs)	*13.0*	*8.1*

** at sea level, @ 1 gm/dL = 0.6206 mmol/L)*

The lower limits of Hb concentration according to the age and sex

❖ Classification of Anemias

1- **Etiological** (Underlying cause);

A- Bone Marrow defect;

- Hypoproliferative of the marrow.

- Maturation Defects of erythropoiesis.

B- Peripheral blood defect;

- Hemolytic Anemias.

- External Blood Loss.

2- **Morphological**; Most appropriate classification

➢ Morphological Classification of Anemias

- Most appropriate classification, depending on RBC indices (Absolute values)
- Mean Corpuscular Volume (MCV); 83 - 100 femtolitre (fL = μm3) (10^{-15} L), and it's the most important RBC index

$$MCV = \frac{\text{hematocrit}(\%) \times 10}{\text{RBC count}(\text{millions} / \text{mm}^3 \text{ blood})}$$

MCV= Hematocrit (PCV) % x 10 / RBCs count (millions/mm3)

- Mean Corpuscular Hemoglobin (MCH); 27 – 32 picogram (pg) (10^{-15} Kg) which correlates linearly with MCV.

MCH=(Hb x 10)/RBC count. ±

- Mean Corpuscular Hemoglobin Concentration (MCHC); 31 - 35% (gm/dL)

MCHC= Hb (gm/dL) x 100 / hematocrit (PCV) %

$$MCHC = \frac{\text{hemoglobin}(g / 100ml) \times 100}{\text{hematocrit}(\%)}$$

❖ According to morphological classification of anemias:

1- **Microcytic, Hypochromic;** MCV < 83 fl

2- **Normocytic, Normochromic;** MCV 83-100 fl

3- **Macrocytic;** MCV > 100 fl

❖ Microcytic, Hypochromic

1- Iron deficiency.

2- Minor Thalassaemias .

3- 25% of Chronic diseases (75% usually normocytic).

4- Sideroblastic Anemias.

* Hereditary

* Acquired (May give macrocytic)

5- Lead poisoning.

❖ Normocytic, Normochromic

1- Acute blood loss.

2- Hemolysis.

3- 75% of Chronic diseases (25% microcytic).

4- Hypersplenism.

5- Bone Marrow Failure.

6- Hydremia of Pregnancy (dilutional).

❖ Macrocytic

1- Megaloblastic Anemias.

2- Chemotherapy.

3- Reticulocytosis.

4- Aplastic Anemias.

5- Hypothyroidism.

6- Sideroblastic Anemias (Acquired).

7- Myelodysplasias; eg; MDS.

➢ Clinical Features:

Presence or absence depends on;

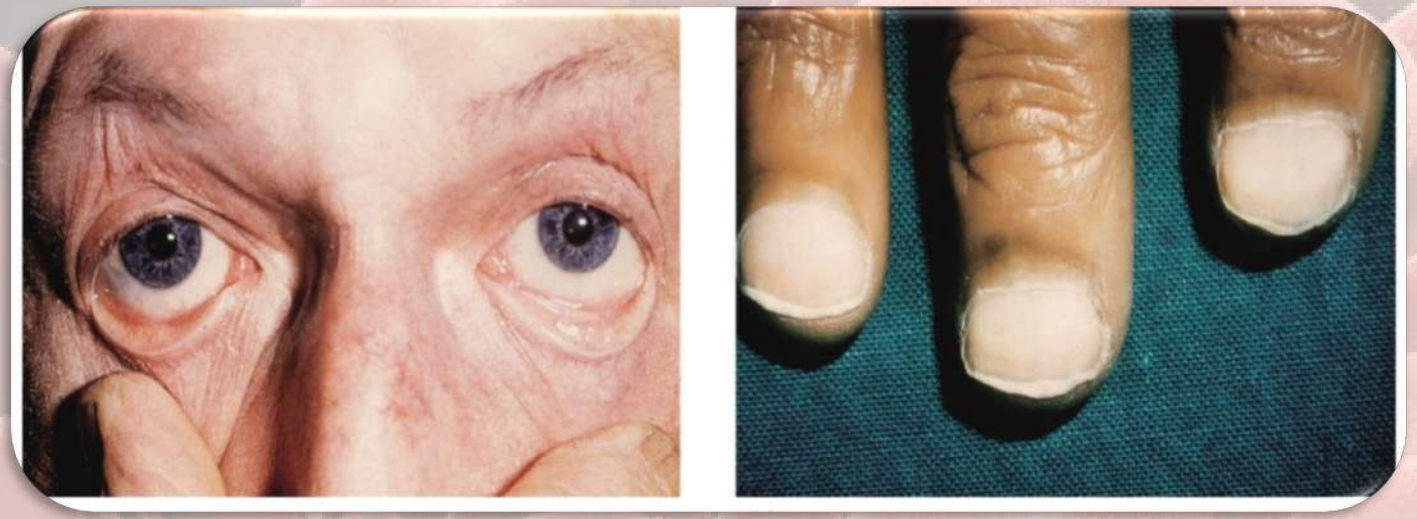
1. **Onset**; rapidly progressed anemia can cause to more apparent symptoms than the gradual one. This due to the cardiac compensation and Hb O_2 dissociation curve.
2. **Severity**; usually Hb level of less than 9-10 g/dL shows the sign and symptoms.
3. **Age**; young usually tolerate more than old, because the better cardiac pump can compensate the low Hb level.
4. **Hb O_2 dissociation curve**; either due to the 2,3-DPG or Hb type.

❖ Symptoms;

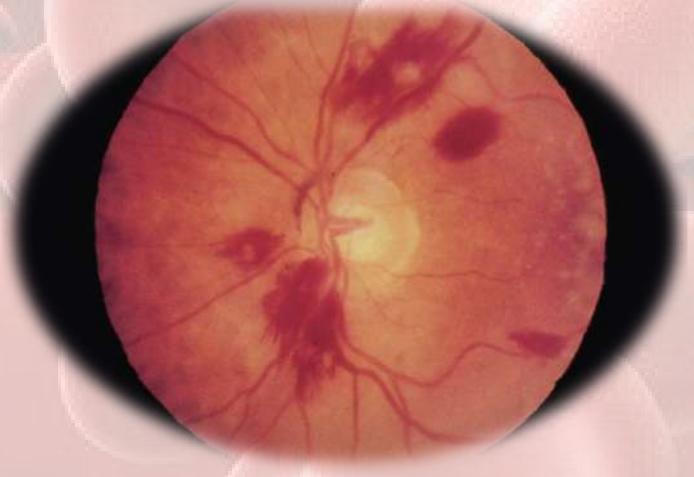
- Hypoxia; shortness of breath, generalized weakness, lethargy, tachycardia and palpitation.
- Cardiac; angina pectoris, and heart failure.
- Others; Intermittent claudication and visual disturbance (retinal hemorrhage).

❖ Signs;

- Pallor (conjunctival mucous membrane and nail bed).
- Hyperdynamic circulation; tachycardia, bounding pulse, cardiomegaly and systolic murmur.
- Heart failure; of congestive type with fluid retention.
- Fundoscopic (Ophthalmoscopic) examination; retinal hemorrhage (sever cases).
- Specific; according to the type; Koilonychia (iron deficiency anemia), jaundice (hemolytic or megaloblastic), leg ulcers (sickle cell) or bone deformities (thalassemia).



Marked pallor of conjunctiva and nail bed in sever anemia



Retinal hemorrhage in a patient with sever anemia

➢ Laboratory findings:

❖**Low Hb level.**

❖**RBCs indices;** according to MCV and MCH divided;

1. Hypochromic microcytic
2. Normochromic normocytic
3. Macrocytic

❖ **Leukocyte and platelets count:**

- In cases of pancytopenia, due to aplastic anemia, metastatic bone infiltration or hypersplenism.
- High count in hyperactive marrow (Hemorrhage, hemolysis).
- Neutrophilia in bacterial infections.

❖ **Reticulocyte count:**

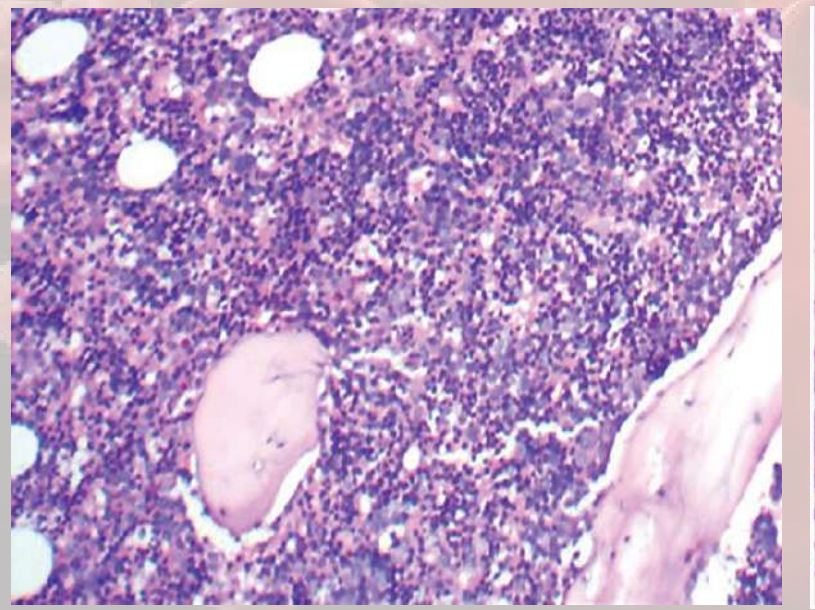
- Give rise to macrocytosis.
- High in cases of hemolysis or hemorrhage.
- Low in hypoplastic marrow or ineffective erythropoiesis and in cases of low erythropoietin stimulation.
- Follow up for the response of the erythropoiesis.

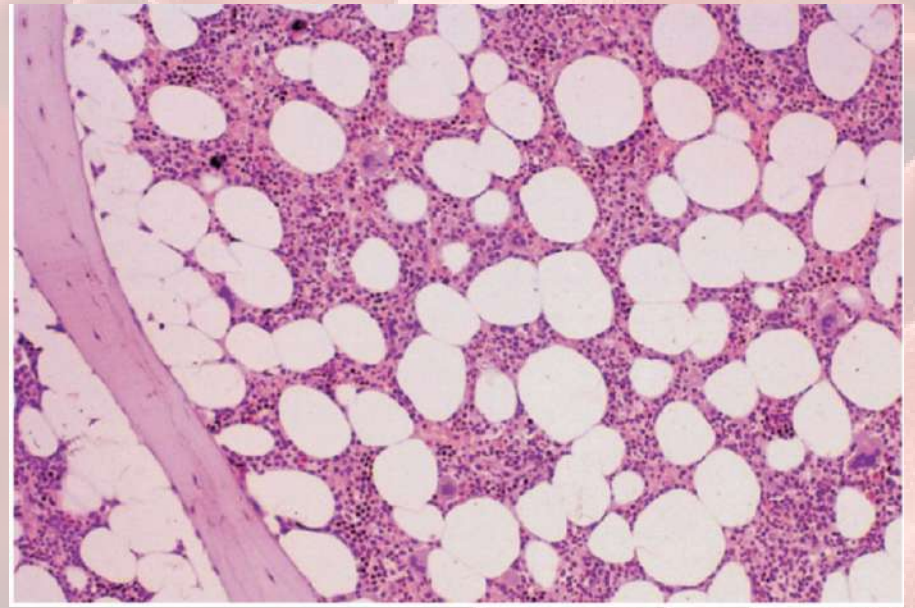
❖ Blood Film:

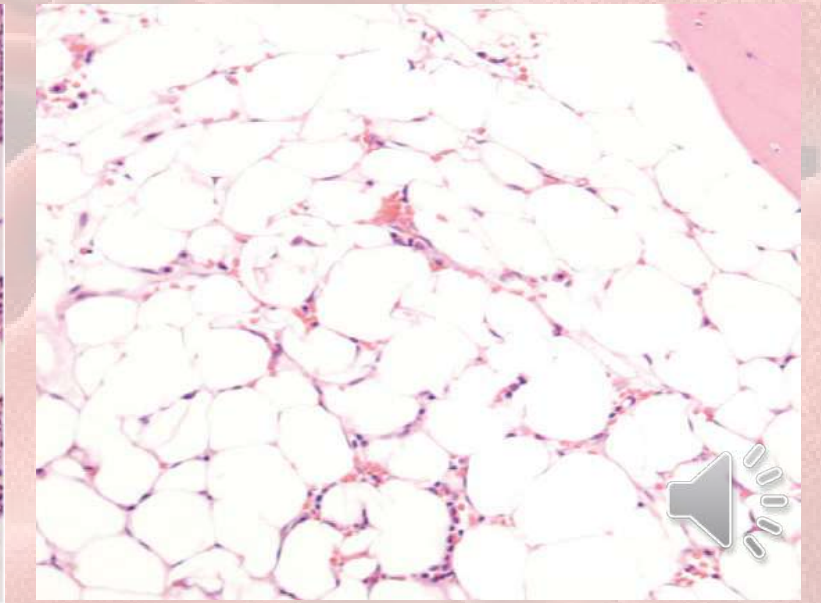
- For each anemia Bd film is essential for the diagnosis of its type.
- RBCs morphology, dimorphic (mixed) anemia may shows normal MCV, abnormal cells with inclusions.
- WBCs and platelets may show certain abnormalities.

❖ Bone marrow (aspirate and/or trephine biopsy)

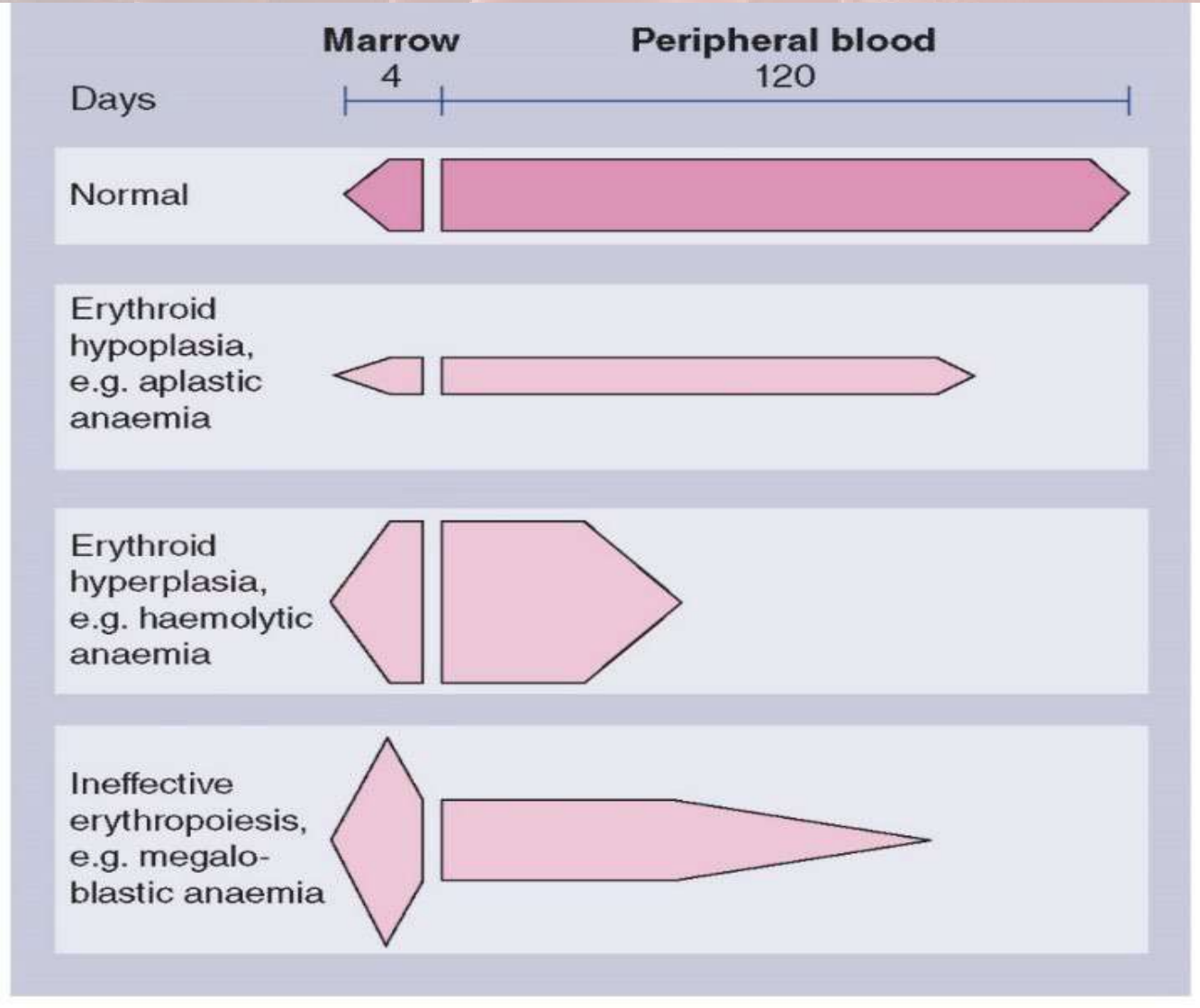
- Hypoplastic marrow (cellularity).
- Infiltration by leukemia, multiple myeloma or secondary.
- Abnormal maturation of the cell lines.
- Iron stain for the its storage or erythroid (siderotic).
- Biopsy useful in cases of diluted aspirate or assessment of the fibrosis or abnormal marrow infiltration.







Erythropoiesis and Rec Cell Mass

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