HAEMATOPOIESIS

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CELL SYSTEMS

- All blood cells derive from a common **stem cell**.
- Under the influences of local and humoral factors, stem cells differentiate into different cell lines.

- The **Bone Marrow,** which is the major site of haemopoiesis in adult humans, contains cells that represent the stages in the development of the different types of blood cells.

STEM CELLS

- The stem cells are the most important cells in haemopoietic cell production.

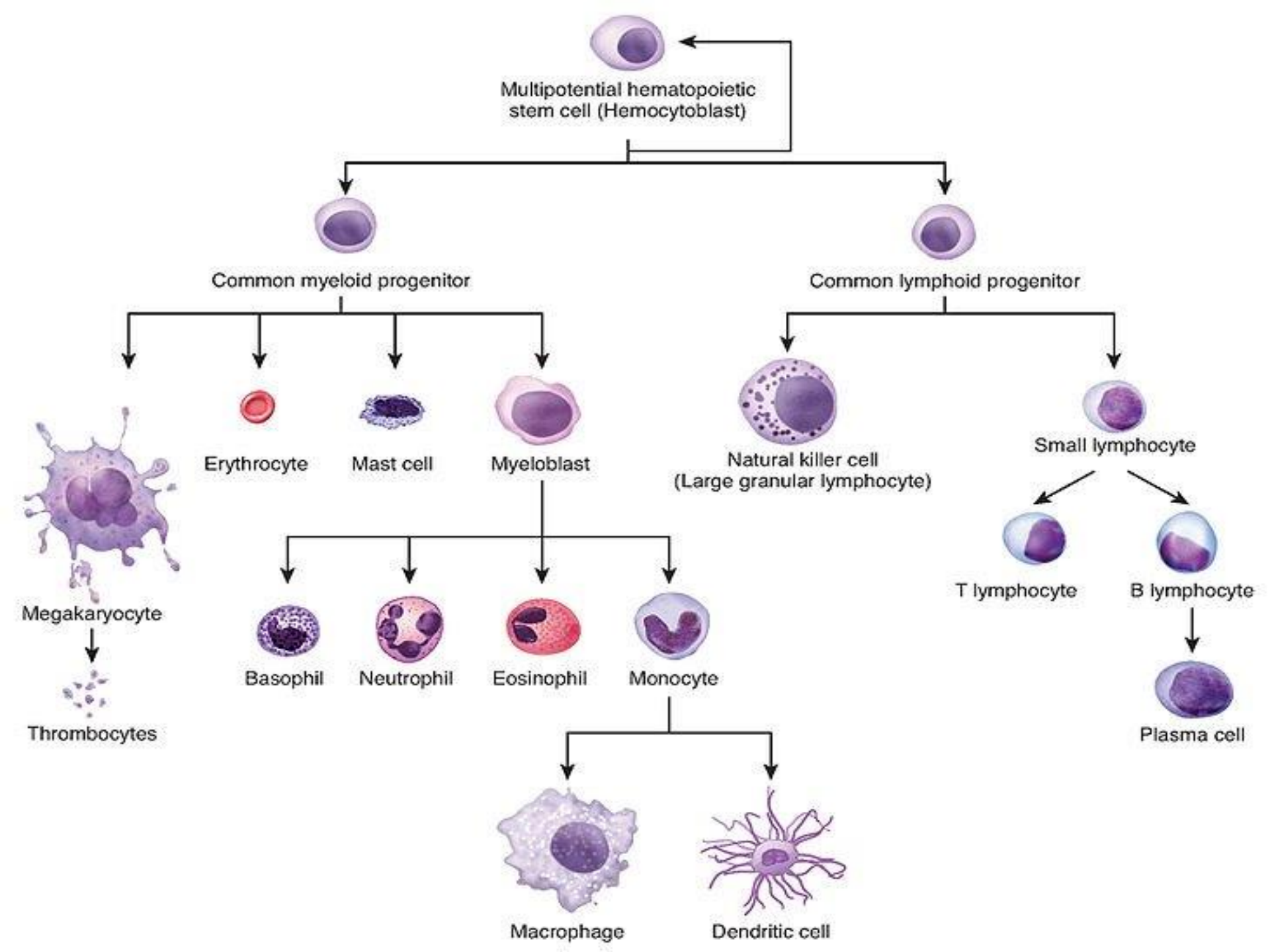
- **Regenerating haemopoiesis** following damage to the haemopoietic system by myelotoxic chemotherapy or after stem cell transplantation.
- This is accomplished by stem cell division, producing new stem cells to maintain the stem cell pool (**stem cell renewal**) and differentiating into progenitor cells of each of the blood cell lineages.

- In addition to the haemopoietic system, the bone marrow contains **stromal stem cells** - Mesenchymal stem cells, which are important for constructing the haemopoietic microenvironment.

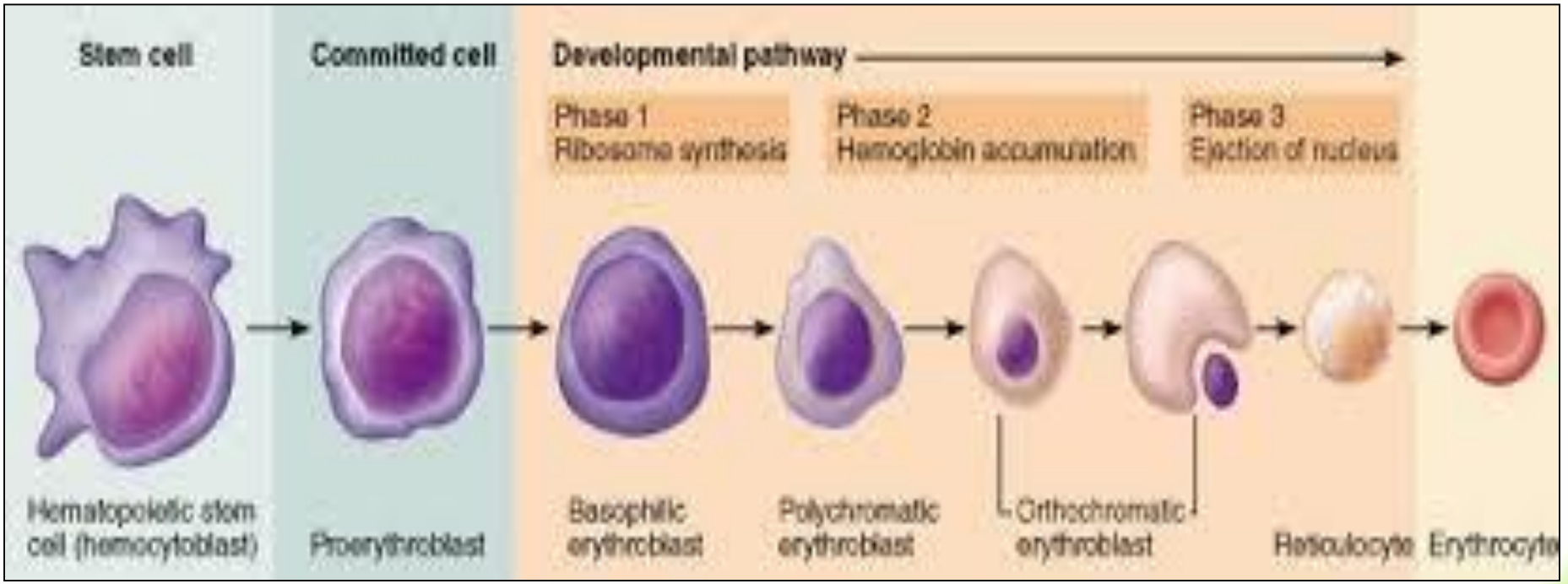
- Damage to the microenvironment, for example by **chemotherapy**, has been implicated in haemopoietic insufficiency after treatment.

SITES OF HEMATOPOIESIS

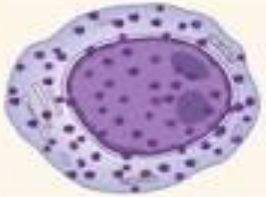
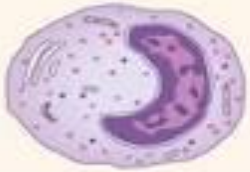
- YOLK SAC
- FETAL LIVER
- BONES
- **Adults** : sternum and pelvis, with small amounts in other bones like the ribs, skull and vertebrae

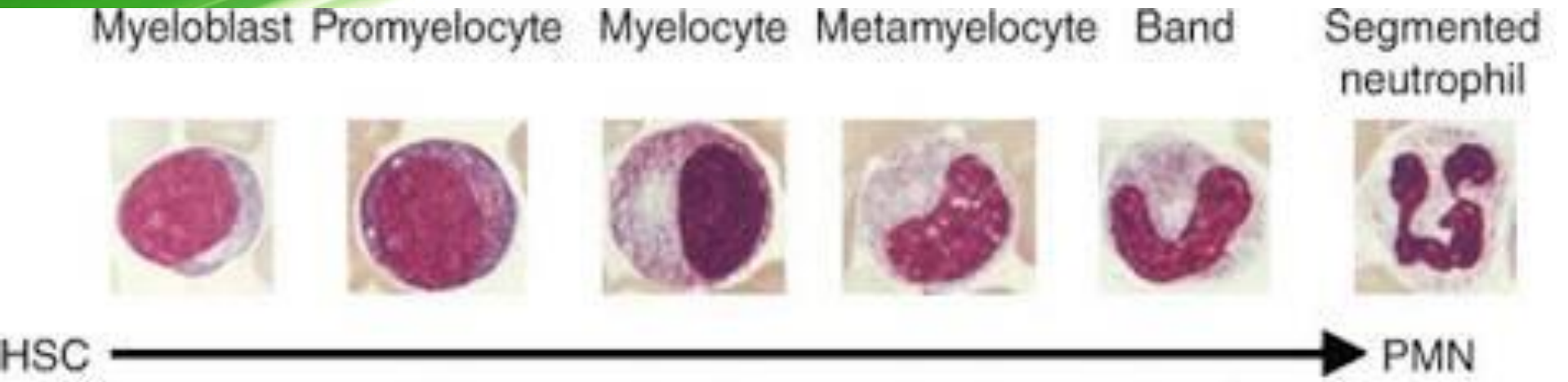

Multipotential hematopoietic stem cell (Hemocytoblast)
Common myeloid progenitor
Common lymphoid progenitor
Erythrocyte
Mast cell
Myeloblast
Natural killer cell (Large granular lymphocyte)
Small lymphocyte
Megakaryocyte
Thrombocytes
Basophil
Neutrophil
Eosinophil
Monocyte
T lymphocyte
B lymphocyte
Plasma cell
Macrophage
Dendritic cell

Erythropoiesis



Granulopoiesis

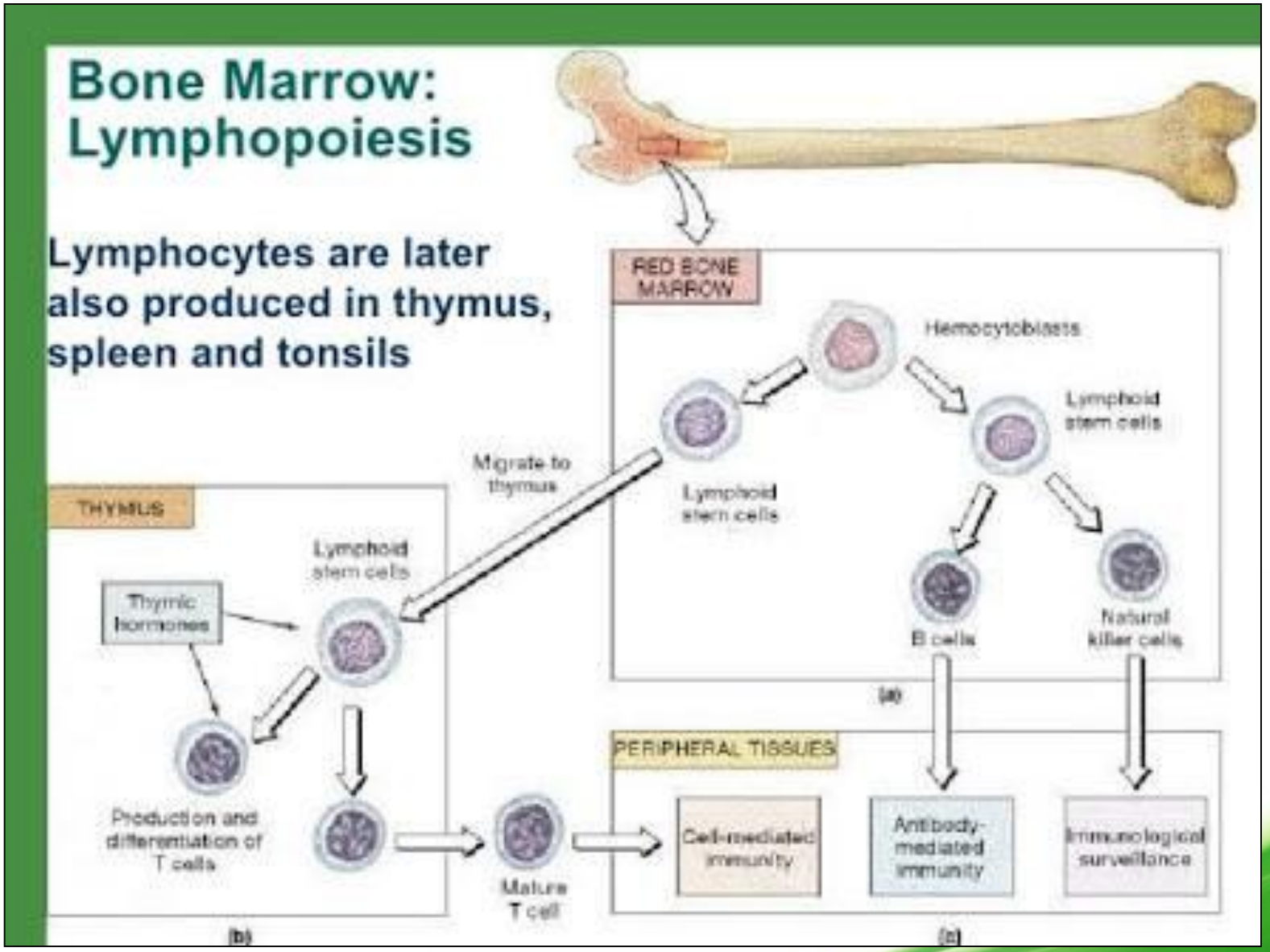
	**Myeloblast** Large round nucleus Fine chromatin One or more nucleoli Blue cytoplasm – no granules
	**Promyelocyte** Azurophilic granules in cytoplasm and over nucleus
	**Myelocyte** Nucleus round to ovoid Chromatin coarser Nucleoli not seen Few azurophilic granules Small pink specific granules in cytoplasm
	**Metamyelocyte (Band)** Nucleus indented Chromatin coarse Only specific granules
	**Neutrophil (Granulocyte)** Segmented nucleus Clumped chromatin Pink cytoplasm



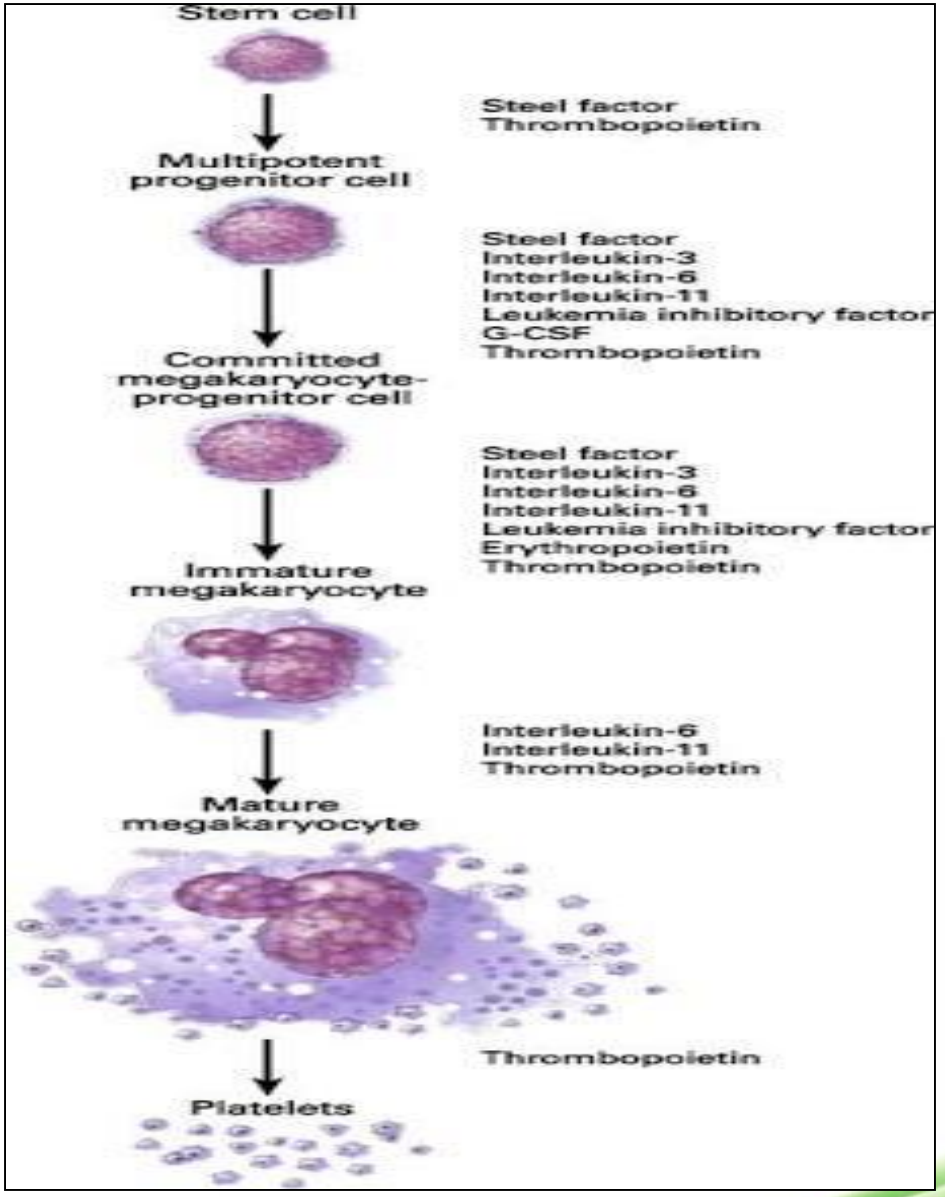
- Phagocytosis
- Chemotaxis
- Acquisition of respiratory burst
- O_2 independent killing

Source: Jon C. Aster, H. Franklin Bunn:
Pathophysiology of Blood Disorders, Second Edition
www.hemonc.mhmedical.com

Lymphopoiesis



Thrombopoiesis



HEMOGLOBIN STRUCTURE AND METABOLISM

- Hemoglobin is the **iron-containing oxygen-transport metalloprotein** in the red cells of the blood in mammals and other animals.

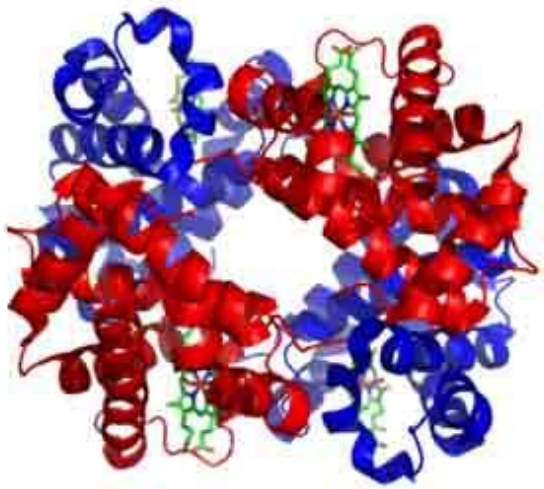
- Haemoglobin is the main constituent of the red cell and accounts for nearly 90% of the dry weight of RBCs.

- It imparts red color to the erythrocytes.

- The main function of red cells is to carry O2 to the tissues and return CO2 from the tissues to the lungs - This function is carried out by haemoglobin present in the red cells.

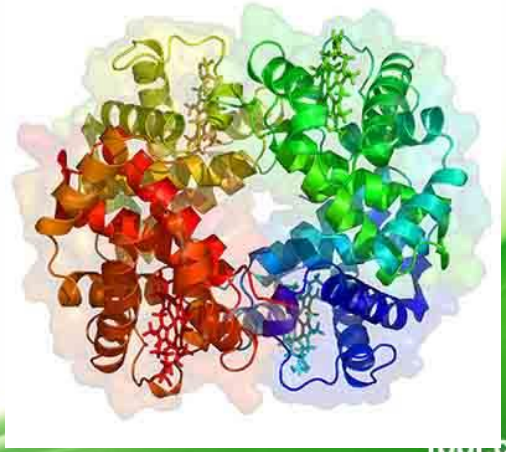
3-D STRUCTURE OF HEMOGLOBIN MOLECULE

- Tetramer of 5.0 x 5.5 x 6.4 nm.
- Molecular weight of 64,000 daltons.
- Two pairs of unlike globin polypeptide chains.
- A heme moity



HAEM SYNTHESIS

- Haem synthesis occurs mainly in the mitochondria of **normoblasts**.
- 60-70% of hemoglobin is synthesized in normboblasts.
- 30-35% is synthesized at the reticulocyte stage.



- Haem is synthesized from glycine and succinyl Co-A which is a by product of <u>citric acid cycle.</u>

- **Glycine + Succinyl Co-A**

↓

↓

↓

(tetrapyrrole made up of 4 pyrrole rings A, B, C, D Protoporphyrin IX)

Fe2+ ↓ **Haem synthase**

Haem

Proto-porphyrin IX
(tetra-pyrrole ring)

+

Fe 2+

=

Haem

(IRON PROTO-PORPHYRIN)

SYNTHESIS OF GLOBIN

- Each globin molecule in an adult is made up of **2α** and **2β chains**.

- α chain – **141 amino-acids**
- β chain - **146 amino-acids**

- Synthesis of α and β chains occurs in **normoblasts** similar to protein synthesis from individual amino acids like in other cells.

- Each globin chain bears a **haem** group whose **central iron atom** is the site at which oxygen attaches to haemoglobin.

HEMOGLOBIN STRUCTURE

Structural complexity of hemoglobin

- The structure of the hemoglobin molecule may be viewed at four levels of organizational complexity.

- Primary
- Secondary
- Tertiary
- quaternary

- The basic arrangement of linked amino acids forming four polypeptide chains, each attached to a haem molecule, is the **primary structure**.

- 2 α chains + 2 β chains

  +

- HAEM with each chain.

- Each chain is arranged in a series of eight helical segments joined by short non-helical segments.

- Eighty percent of the total length of each chain is in helical conformation, and this is referred to as the **secondary structure**.

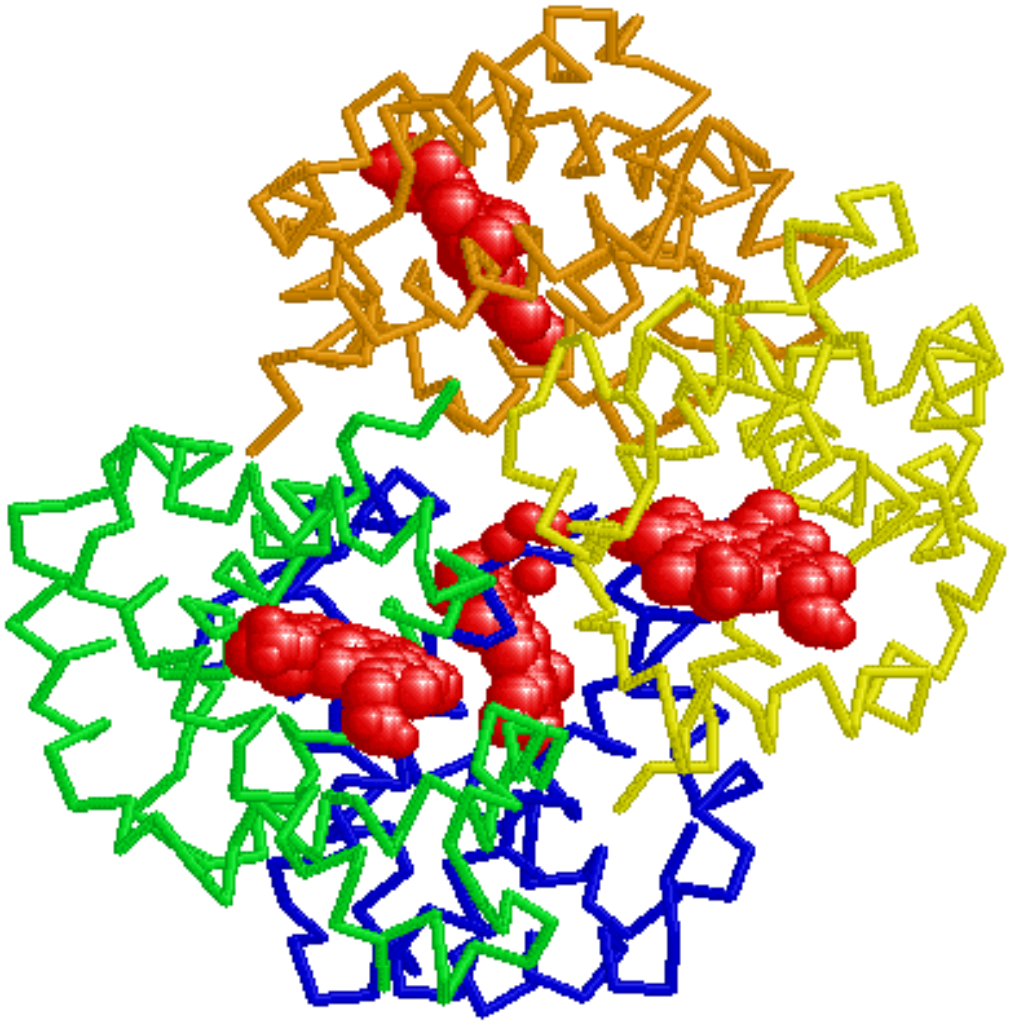
- The folding of each coiled chain into a specific three-dimensional configuration is the **tertiary structure**.

- (Globin chains + Haem) -- helical --folding

=

Tertiary structure

- The four folded chains **fit closely** together to form a **compact tetrameric molecule** known as the **quaternary structure**.



Human Haemoglobins

Types of Hb.	Structure	% of (N) Hemolysate	Increased in
HbA_1	$\alpha_2\beta_2$	92.5	
HbA_2	$\alpha_2\delta_2$	2.5	β Thalassemia
HbA_{1C}	α_2 (β-N-glucose)$_2$	3 – 6	D.M.
HbF	$\alpha_2\gamma_2$	< 1.0	Fetal red cells
HbH	β_4		
HbBart's	γ_4	0	α-Thalassemia

Physiological aspects

- The extent to which oxygen is released from haemoglobin in tissue capillaries is influenced by :
- Nature of **globin chain**
- **pH**
- **concentration of 2, 3, diphosphoglycerate** within the RBCs.

- Normal **adult haemoglobin A_1** has lower affinity for O_2 than fetal haemoglobin and thus releases a greater porportion of bound oxygen at the partial pressure of the oxygen of tissue capillaries.

- A **fall in pH increases oxygen dissociation** by reducing the affinity of oxyhaemoglobin for O_2 and phenomenon, known as **Bohr effect**, enhances the release of oxygen from erythrocytes at the lower pH existing in tissue capillaries where oxygen is required.

- The affinity for oxygen of adult haemoglobin A_1 also decreases with **increasing concentration of intra-cellular 2, 3 DPG**. A rise in 2-3 DPG concentration occurs in anemia and hypoxia and thereby enhances the delivery of oxygen to the tissues.

BLOOD HAEMOGLOBIN LEVELS

- Men - 15.5 ± 2.5 g/dl
- Women - 14.0 ± 2.5 g/dl
- Full term/ cord blood - 16.5 ± 3.0 g/dl
- Children, 1 year - 12.0 ± 1.0 g/dl
- Children, 10-12 year - 13.0 ± 1.5 g/dl

PHYSIOLOGICAL VARIATION

- **Diurnal variation:** Slightly higher in the morning than in the evening.
- Assumption of the **horizontal posture** is associated with relatively rapid fall in haemoglobin level ….. Relative increase in plasma volume due to redistribution of tissue fluid.
- **Day to day variation in women** (0.8 – 3 g/dl).
- Fall in level during **pregnancy**.

- Decreased levels of hemoglobin, with or without an absolute decrease of red blood cells, leads to symptoms of **anemia.**

- Anemia has many different causes, iron deficiency and its resultant iron deficiency anemia are the most common causes in the world.

- Mutations in the gene for the haemoglobin protein result in a group of hereditary diseases termed the hemoglobinopathies, the most common members of which are **sickle-cell disease** and **thalassaemia.**

GLYCOSYLATION OF HAEMOGLOBIN → HbA_{1C}

- Several substances undergo non-enzymatic linkage to hemoglobin in circulating erythocytes. The most important is glucose, which becomes covalently bound to hemoglobin in amounts that parallel the blood glucose concentration.

- **The proportion of hemoglobin present as glycosylated hemoglobin A1C can consequently be employed as an index of the average blood glucose level over the preceding few weeks in patients with diabetes mellitus**.

- Normal vlaue of HbA_{1C}: **6 – 8%**

HAEMOGLOBIN DERIVATIVES

- The two physiologic haemoglobins, the oxyhaemoglobin and the reduced haemoglobin are readily converted into a series of compounds through the action of acids, alkalies, oxidizing and reducing substances, heat, and other agents.

- METHEMOGLOBIN
- SULFHEMOGLOBIN
- CARBOXYHEMOGLOBIN

METHEMOGLOBIN

- (Hemiglobin-Hi) - iron in the heme group is in the Fe3+ state, not the Fe2+ of normal hemoglobin.
- The polypeptide chains are not altered.
- Methemoglobin is unable to carry oxygen.
- It is chocolate-brown in color.

Sign and Symptoms

- Cyanosis
- Mental deficiency - Headache
- Polycythaemia
- Dyspnoea
- Chocholate brown blood

Methemoglobinemia in infants

- In children, this condition is known as blue baby syndrome, attributed primarily to excessive nitrate intake from drinking well water.

SULFHEMOGLOBIN

- SHb - **Greenish derivative**, is a curious compound in which the iron is in the ferrous state but the oxygen affinity is about 100 times lower than that of normal haemoglobin.

Causes: Treatment with –

- Sulphonamides, Phenacetin
- Clostridium Welchi infection

CARBOXYHEMOGLOBIN

- Results from binding of CO to the heme iron. CO binds to hemoglobin with a higher affinity than oxygen – **200 times more strongly**. As a result, CO destroys hemoglobin's ability to transport and release oxygen throughout the body. If exposed to too much CO for too long, a person will likely die due to the lack of oxygen transported to the brain.
- The symptoms of CO poisoning results from tissue oxygen deprivation, like:
  - **Dizziness**
  - **Headache**
  - **Loss of consciousness**

Thanks