The Formed Elements

1. **Red Blood Cells (RBCs) or Erythrocytes**

- RBCs are biconcave disc-shaped, non-motile and non-nucleated blood cells.
- Their interior is packed with Hb, which gives the RBCs a bright red colour.
- The predominance of RBCs in turn gives blood the characteristic red colour.
- Their unique shape increases the surface area to facilitate the exchange of oxygen (O_2) and carbon dioxide (CO_2).

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Red blood cells cont'd

- Their membranes are flexible, but also rigid.
- This allows RBCs to change shape while passing through capillaries, further increasing the available surface area.
- There are about 5.4 million RBCs in men and 4.8 million RBCs per µL of blood in women.
- Each RBC is about 7.5 µm in diameter and 2 µm thick, and contains 29 pg of Hb.

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Red blood cells cont'd

- **Functions of RBCs**

  a) The transport of O_2 from the lungs to the body tissues and CO_2 from the body tissues back to the lungs.

  b) The synthesis of bicarbonate, which acts as a buffer.

  This function is possible because of the presence of the enzyme carbonic anhydrase which catalyses

  - the formation of carbonic acid from water and CO_2, followed by the dissociation of the acid into H+ and HCO_3-

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Erythropoiesis

- Erythropoiesis: is the synthesis or formation of RBCs.
- It is part of a bigger process of *hematopoiesis*, which is the synthesis of the blood cells, including the WBCs and megakaryocytes.
- The sites of synthesis change with developmental stage.

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Erythropoiesis cont'd

- During early fetal development, it occurs in the blood vessels of the yolk sac membranes.
- Later in embryonic development, it shifts to the liver, spleen and lymph nodes.
- In the late gestation and after birth, it occurs in the bone marrow throughout the skeleton.

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Erythropoiesis cont'd

- In adult life, the red marrow of long bones which were active in the younger ages becomes replaced by the fat tissues.
- The red marrow of the membranous bones such as the sternum, the ribs, the vertebrae and the pelvic bones

- then take over the functions of erythropoiesis.

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The Process of erythropoiesis

- All blood cells arise from the primitive pluripotent haematopoietic stem cells (PHSC)

- found in the bone marrow, which have originated from vessels of the embryonic yolk sac.

- After development of liver, spleen and bone marrow, the PHSCs migrate into their sinusoids, and transform into committed stem cells (CSCs).

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The Process of erythropoiesis cont'd

- The committed stem cells are destined to differentiate into different stem cell lines, known as colony forming units (CFUs).
- The colony forming units eventually form hemocytoblasts which establish haematopoietic activity.
- The CFUs that are destined to form RBCs are known as the colony forming unit-erythrocytes (CFU-Es).

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The process of erythropoiesis cont'd

- Their differentiation then proceeds from the proerythroblasts through the following sequential stages:
- Rubriblasts (early basophilic erythroblasts/normoblasts) to
- Prorubricyte (intermediate polychromatic erythroblasts/normoblasts), then to
- Metarubricytes (late pyknotic orthochromatic erythroblasts/normoblasts), and to
- reticulocyte (basophilic erythrocyte) and finally the mature RBCs.

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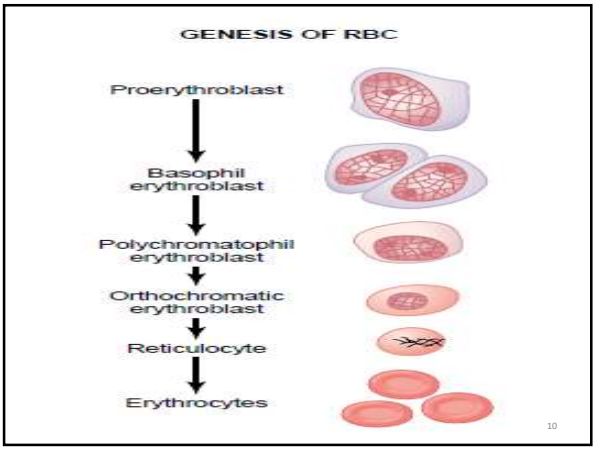

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The process of erythropoiesis cont'd

- The stages can be distinguished using special histological staining of smears/films of bone marrow aspirate.
- Development of RBCs is accompanied by the following changes:
  - Progressive decrease in size and nucleus of the developing cells; ends up in total loss of the nucleus before mature RBCs are released.

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Development changes of RBCs

- Accumulation of Hb with progressive disappearance of the cytoplasm, which stains blue due to abundant RNA in early stages, but becomes reddish due to Hb.

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The process of erythropoiesis cont'd

1. Proerythroblast (Megaloblast)

- Proerythroblast or megaloblast is the first cell derived from CFU-E.
- It is very large in size with a diameter of about 20 µm.
- Its nucleus is large and occupies the cell almost completely.

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Proerythroblast cont'd

- The nucleus has two or more nucleoli and a reticular network.
- Proerythroblast does not contain hemoglobin.
- The cytoplasm is basophilic in nature.

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Proerythroblast cont'd

- Proerythroblast multiplies several times and finally forms the cell of next stage called early erythroblast.
- Synthesis of hemoglobin starts in this stage (early erythroblast).
- However, appearance of hemoglobin occurs only in intermediate erythroblast.

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The process of erythropoiesis cont'd

2. Early erythroblast

- The early erythroblast is little smaller than proerythroblast with a diameter of about 15 µm.
- In the nucleus, the nucleoli disappear.
- Condensation (closely packed together) of chromatin network occurs & the condensed network becomes dense (crowded closely together).
- The cytoplasm is basophilic in nature.

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The process of erythropoiesis cont'd

3. Intermediate erythroblast

- Cell is smaller than the early erythroblast with a diameter of 10 to 12 µm.
- The nucleus is still present.
- But, the chromatin network shows further condensation.

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Intermediate erythroblast cont'd

- The hemoglobin starts appearing.
- Cytoplasm is basophilic.
- Because of the presence of hemoglobin, it stains with both acidic as well as basic stains.

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The process of erythropoiesis cont'd

4. Late erythroblast

- Diameter of the cell decreases further to about 8 to 10 µm.
- Nucleus becomes very small with very much condensed (closely packed together) chromatin network.
- Quantity of hemoglobin increases & the cytoplasm becomes almost acidophilic.

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Late erythroblast cont'd

- In the final stage of late erythroblast just before it passes to next stage, the nucleus disintegrates and disappears.

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The process of erythropoiesis cont'd

5. Reticulocyte

- This is the immature RBC, slightly larger than matured RBC.
- The cytoplasm contains the reticular network, which is formed by remnants of disintegrated organelles.
- Reticulocyte is basophilic due to the presence of remnants of disintegrated Golgi apparatus, mitochondria and other organelles of cytoplasm.

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Reticulocyte cont'd

- During this stage, the cells enter the blood capillaries through capillary membrane from site of production by diapedesis.

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The process of erythropoiesis cont'd

6. Matured Erythrocyte

- Reticular network disappears and the cell becomes the matured RBC and attains the biconcave shape.
- The cell decreases in size to 7.2 µm diameter.
- The matured RBC is with hemoglobin but without nucleus.
- It requires 7 days for the development and maturation of RBC from proerythroblast.

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Requirements for erythropoiesis

- Formation of RBCs is one of the most active anabolic processes in the body.
- About 2 x 10^{11} RBCs are replaced by the bone marrow in 24 hrs.
- The process requires a number of dietary factors, also known as erythropoietic factors:
- The following are essential for erythropoiesis:

Amino acids

- Required for formation of globin, a component of the Hb molecule.

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Requirements for erythropoiesis cont'd

Mineral nutrients

Fe^{2+}: is the active component of heme.

- Men have 35-90 mmol (2-5g) of iron in the body, while women have 48 mmol., of which 60-70% is in Hb & 4-5% in myoglobin.
- The rest is stored as ferritin or hemosiderin in hepatocytes and macrophages of the spleen, liver & bone marrow.

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Mineral nutrients cont'd

Cu^{2+}: acts as a catalyst in Vitamin B_{12} metabolism and Hb synthesis

Co: is a component of vitamin B_{12}.

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Requirements for erythropoiesis cont'd

Vitamins

- **Vitamin B_{12} (cyanocobolamine):** synthesized by bacteria from Cobalt
- It is also derived from foods of animal origin.
- Intrinsic factor, a glycoprotein from the small intestines is required for its absorption.
- The vitamin is required for RNA and DNA synthesis; and maturation of RBCs.

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Vitamins cont'd

- **Folic acid (pteroglutamic acid):** RNA and DNA synthesis.
- **Vitamin B6 (Pyridoxine):** a cofactor for synthesis of heme.
- **Other vitamins**: thiamine, riboflavin, biotin are co-enzymes in the various stages of RBC production.

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Control of erythropoiesis

- The hormone **Erythropoietin** (erythrocyte maturation factor), is the primary stimulant of erythropoiesis.
- It is produced by the **kidneys** (85%), and to a lesser extent the liver (15%),
- It is produced by action of the enzyme **erythrogenin**, a circulating plasma protein made in the **liver.**

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Control of erythropoiesis cont'd

- Erythropoietin is produced in response to inadequate oxygen supply to the tissues.
- This may be caused by low oxygen concentration in the atmosphere (high altitude), defective RBCs or anaemia (shortage of RBCs).

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Control of erythropoiesis cont'd

- The primary effect of erythropoietin is to stimulate the committed stem cells,

- the rubriblasts, the pro-rubricytes and the rubricytes to increase their mitotic activity.

- This will lead to more rapid production and release of RBCs into the circulation.

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Control of erythropoiesis cont'd

- Over-stimulation of erythropoiesis may result into release of immature RBCs into the circulation.
- Other hormones which enhance erythropoiesis are: corticosteroids, androgens, growth hormone &thyroxin.
- All these are believed to increase the sensitivity of the precursor cells to erythropoietin.

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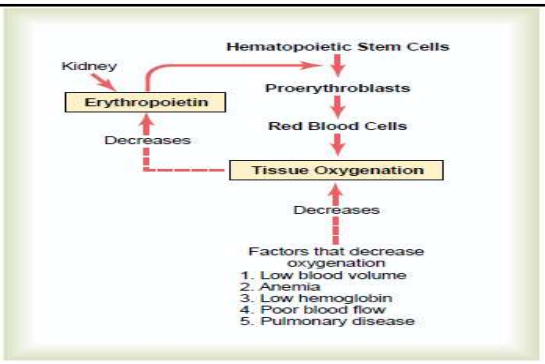

Figure 32–4

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

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