Problem 1 – Unit 6 – Physiology: Erythropoiesis & Iron Metabolism

- **Sites where erythropoiesis occurs in fetus and adults:**

Fetus	Adults
Early embryonic life (0-2 months: in the yolk sac.	In the bone marrow (sternum, ribs, vertebra, skull, femur)
2-7 months: in the liver.	
5-9 months: in the bone marrow.	

- **Erythropoiesis:**
  PHSC (pluripotential hemopoietic stem cells) ---> **BFU_E** (Burst Forming Unit-Erythroid) ---> **CFU_E** (Colony Forming Unit-Erythroid) ---> **Proerythroblast** (which will start incorporating heme) ---> **Reticulocytes** (which have ribosomal RNA in their cytoplasm, enter the circulation and with 1-2 days will be converted to ---> **mature RBCs** (which have no nucleus no DNA or RNA and are biconcave in shape with a life-span of 120 days.

- **Regulation of eythropoiesis by erythropoietin**:
  When there is hypoxia (caused by different reasons such as low blood volume, anemia, low Hb, poor blood flow caused by cardiac failure, pulmonary diseases…etc) there will be less oxygenation to the renal tissue. This is going to be sensed by HIF-1α (Hypoxia Induced Factor-1α) which will stimulate the peritubular interstitial cells of the kidney to produce the hormone erythropoietin (90% of this hormone is synthesized in the kidneys, 10% is synthesized in the liver). Erythropoietin will bind to its receptors on BFU_E & CFU_E to increase the production of RBCs. Note that HIF-1α will also:
  - Inhibits the release of hepcidin. Normally, hepcidin inhibits ferroportin, so it acts as a down-regulatory mechanism causing iron accumulation in the liver without being used).
  - Facilitates iron transport to the bone marrow (used for heme synthesis).

  Erythropoiesis can be erythropoietin-dependent or erythropoietin-independent (in this case there will still be production of RBCs but in very low amounts. Eventually, this will result in anemia).

- **Requirements for erythropoiesis**:
  - Mg, Fe, Cu, Co (for heme synthesis).
  - Vitamin B_{12} & folic acid (for RBCs maturation). If they are deficient megaloblastic anemia will result (large RBCs with fragile membrane).
  - Vitamin C: needed for the conversion of iron from ferric (Fe^{3+}) to the ferrous form (Fe^{2+}).
  - Amino acids.
  - Hormones: erythropoietin, androgens & thyroxine.

- **Red Blood Cells**:
  They are flexible, biconcave-shaped (with a diameter of 8µm), having no nucleus, no mitochondria, no ER, no DNA or RNA & they live for 120 days. RBCs use 90% of glucose in the anaerobic glycolytic pathway to produce 2ATP + 2 NADH (for each glucose molecule). 10% of glucose will be used in the hexose monophosphate shunt generating NADPH which protects the RBCs membrane from the oxidative damage that would be cause by ROS (Reactive Oxygen Species). RBCs also act as a powerful acid-base buffering system as they have the enzyme carbonic anhydrase. Also their membrane contains aquaporins (water channels) which permits the diffusion of water in & out (this is important for maintain the shape and elasticity of the red blood cells). After 120 days, destruction of RBCs will occur in the reticuloendothelial system (mainly in spleen & liver).

- **Some normal values**:
  - Hematocrit (PCV): the ratio of RBCs to the whole blood volume. It is 40% (in females) & 45% (in males).
  - Hb: 14 (in females) & 15 (in males).