Q15 Briefly outline the production and fate of Red Blood Cells (RBC) (40% of marks). Describe the breakdown of haemoglobin (Hb) (60% of marks) (March 2012)

Erythrocytes (red blood cells) play a vital role in oxygen and carbon dioxide transport through the body.
They make up 40-50% of the blood volume, usual value 4-5 x 10^{12}/L
Biconcave disc shaped
Lifespan 120 days

ERYTHROCYTES – PRODUCTION

- Myeloid progenitor → differentiates into erythroid line
- The erythroid line begins with the proerythroblast, a nucleated cell. As it differentiates into a reticulocyte it decreases in size, gradually losing cytoplasmic organelles and increasing its haemoglobin content
- Reticulocytes then lose their ribosomes to become mature erythrocytes
- The differentiation from stem cell to erythrocyte takes 7-10 days.
- Erythropoietin increases the rate of differentiation of the stem cell. EPO is produced in the corticomedullary cells of the kidney in response to low local oxygen tension
- Haemoglobin (MW 65,000Da) is synthesized in erythroid cells from the proerythroblast stage. It consists of four globin chains, each covalently linked to a haem molecule. Haem is an iron chelated porphyrin ring structure synthesized in the mitochondria from glycine, succinyl CoA and Fe2+.

ERYTHROCYTES - FATE

- RBCs are destroyed after 120 days (this may be due to continual loss of membrane components, accumulation of oxidative products, decreased deformability of the aging cell, leaving it unable to pass through minute fenestrations in the microvasculature)
- 90% are removed by phagocytosis in the liver, spleen and lymph nodes
- 10% hemolyse in the circulation and are then engulfed by circulating macrophages
- Lysosomes within the macrophage breakdown the chemical components of the RBC. Globin is metabolized to amino acids which can be used for protein synthesis
- Iron is removed from haem molecules and either stored in the macrophage or released into the bloodstream where it binds to transferrin and delivered to the bone marrow where it is used to synthesise new hemoglobin
- Haem is metabolized as below

BREAKDOWN OF HB

- Microsomal haem oxygenase converts haem to biliverdin which is then reduced to bilirubin
- Free bilirubin is bound to albumin, leaving only a very small percentage unbound in plasma
- Bilirubin is taken up by the hepatocyte, where the bilirubin binds with intracellular protein; microsomal UDP glucuronyltransferase (UDPGT) is responsible for the conjugation of bilirubin with glucuronide to form bilirubin monoglucuronide.
- Further conjugation to diglucuronide also occurs. Both conjugates of bilirubin are more water soluble thus allowing excretion into the bile canniliculus. The conjugated bilirubin ends up in the gut at the level of the mid duodenum.
- In the gut, intestinal flora hydrolyse and reduce conjugated bilirubin to form urobilinogen (colourless and water soluble). Three things can then happen:
    - Most urobilinogen is oxidized by gut bacteria to form the dark pigment stercobilin, which is egested in the faeces
    - Some is reabsorbed unchanged by the portal system and recycled by the liver
    - The remainder is reabsorbed by the portal system and then excreted in the urine