SCHOOL OF MEDICINE AND HEALTH SCIENCES
DIVISION OF BASIC MEDICAL SCIENCES
DISCIPLINE OF BIOCHEMISTRY AND MOLECULAR BIOLOGY

PBL SEMINAR: REGULATION OF HEMOPOIESIS – AN OVERVIEW

- Hemopoiesis is the synthesis of blood cells, a process that starts in the embryo and continues throughout life
- Red Marrow forms all types of blood cell and is also active in the destruction of Red Blood Cells (RBC)
- Red Marrow is one of the largest and most active organs in the human body, approaching the size of the liver in overall mass, although it is distributed in various parts of the body
- About two-thirds of its (Red Marrow) mass functions in production of White Blood Cells (**Leucopoiesis**), and one-third in Red Cell production (**Erythropoiesis**)
- There are, however, about 700 times as many Red Cells as there are White Cells in Peripheral blood
- Such apparent anomaly reflects the Shorter Life Span and hence greater turnover of WBC in comparison with RBC
- During childhood and adulthood, blood-making sites outside Marrow, such as the Liver, can become active if there is excessive demand as, for example, in severe Haemolytic Anaemia, or following Haemorrhage
- During old age, Red Marrow sites are slowly replaced with Yellow, Inactive Marrow
- Blood cells are made from relatively few "uncommitted" cells, which are capable of mitosis and of differentiation into "committed" precursors of each of the main types of blood cell

Red Blood Cells (Erythrocytes):

- **Erythropoiesis** is the production of RBC
- Mature RBC develops from Hemocytoblasts.
- Development takes about 7 days and involves 3 to 4 Mitotic cell divisions, so that each Stem Cell gives rise to 8 to 16 cells

- Various cell types in Erythrocyte development are characterised by the following:

    - Gradual appearance of Haemoglobin (Hb) and disappearance of Ribonucleic Acid (RNA) in the cell
    - Progressive degeneration of the nucleus, which is eventually extruded from the cell
    - Gradual loss of Cytoplasmic Organelles, for example, Mitochondria
    - Gradual reduction in cell size
    - Young Red Cell is called a **Reticulocyte** because of a network of Ribonucleic acid (Reticulum) present in its Cytoplasm.
    - Reticulum disappears as the RBC matures
    - Reticulocyte normally takes about 4 days to mature into an Erythrocyte
    - Between 2 and 6% of circulating RBC in Neonates are Reticulocytes,
    - Reticulocytes levels drops to less than 2% in Healthy adult,

- Circulating Erythrocytes level is maintained within a narrow range**,** because **Erythropoiesis is a highly regulated process**,
- In "Healthy" individual, a little less that 1.0% of the total RBC is produced per day to replace an equivalent amount that have reached the end of their life span
- Reticulocyte count usually increases considerably in conditions, in which rapid Erythropoiesis occurs, eg., following Haemorrhage or Acute Haemolysis of RBC

What is the effect of Hypoxia on Erythropoiesis?

- **Erythropoiesis is stimulated by Hypoxia (lack of oxygen**)
- Hypoxia does not act directly on the Hemopoietic tissues, but instead stimulates the production of a hormone, **Erythropoietin**
- Erythropoietin then stimulates Hemopoietic tissues to produce RBC

What is Erythropoietin?

- Erythropoietin is a Glycoprotein
- Erythropoietin is formed within the Kidney by the action of a Renal Erythropoietic Factor called **Erythrogenin** on plasma protein, **Erythropoietinogen**
- Erythrogenin is present in the Juxtaglomerular cells of the kidneys and is released into the blood in response to hypoxia in the renal arterial blood supply
- Erythropoietin is inactivated by the Liver and excreted in the urine

What other factors that affect the rate of Erythropoiesis by influencing Erythropoietin production?

- Factors that enhance formation of Erythropoietin, thus promotes Erythropoiesis

These factors include the following:

- Thyroid Hormones (deficiency may cause reduction in Erythropoiesis resulting in anaemia)
- Dysfunction in Anterior Pituitary hormones may cause reduction in Erythropoiesis resulting in anaemia
- Thyroid-Stimulating Hormone (TSH),
- Adrenal Cortical Steroids,
- Adrenocorticotrophic Hormone (ACTH)
- Human Growth hormone
- Variety of tumours produces Erythropoietin

- **Polycythemia** (excess RBC production) is often a feature of Cushing's syndrome (excess Cortisol production).
- Very high doses of steroid hormones can inhibit Erythropoiesis

- Androgens (male hormones) stimulate Erythropoiesis
- Estrogens (female hormones) depress Erythropoietic response, thus together with the effects of Menstrual blood loss, may explain why female tend to have a lower Hb and RBC levels than male

- Plasma levels of Erythropoietin are raised in hypoxic conditions, producing Erythrocytosis (increase in the number of circulating erythrocytes), and the condition is known as **Secondary Polycythemia**

Physiological Secondary Polycythemia is present in:

- Foetus (and residually in the Neonates)
- People living at High Altitude because of relatively low partial pressure of Oxygen in their environment

Secondary polycythemia: Occurs as a result of Tissue Hypoxia in diseases such as:

- Chronic Bronchitis,
- Emphysema and
- Congestive Cardiovascular abnormalities associated with Right-to-Left shunting of blood through the heart, for example, Fallot's tetralogy

Some causes of anaemia:

- Reduction in Hb level due to decrease in the number of circulating RBC and/or in the amount of Hb they contain
- Erythropoietic tissues cannot supply enough normal Erythrocytes to the circulation
- Defective production of Erythropoietin, eg., in Renal disease

Plasma Erythropoietin levels are increased in anaemia caused by:

- Abnormal RBC production,
- Increased destruction of Erythrocytes
- Demand for Oxygen exceeds the capacity of the RBC

- Some dietary requirements are needed for efficient production of RBC

Summary of some dietary requirements needed for adequate RBC production are presented in the Table:

Dietary Element	**Role in red blood cell production**
Protein	Required to make red blood cell proteins and also for the globin part of haemoglobin
Vitamin B_6	Is involved in the biosynthesis of Heme; deficiency has occasionally been associated with anaemia
Vitamin B_{12} and folic acid	Needed for DNA synthesis and are essential in the process of red blood cell formation
Vitamin C	Required for folate metabolism and also facilitates the absorption of iron. Extremely low levels of Vitamin C are needed before any problems occur. Anaemia caused by lack of Vitamin C (scurvy) is now extremely rare.
Iron	Required for the Haem part of haemoglobin