Blood cell formation (Hemopoiesis):

Sites of hemopoiesis:

From 6 weeks to 6 months the liver & spleen are the main organs.

From 7 months of gestation throughout all life the bone marrow is the main site of hemopoiesis.

In infancy all the bone marrow is hemopoietic.

In childhood there is progressive fatty replacement.

In adulthood hemopoietic marrow is confined to central skeleton and proximal ends of femurs and humeri, & even in these areas 50% of marrow consists of fat.

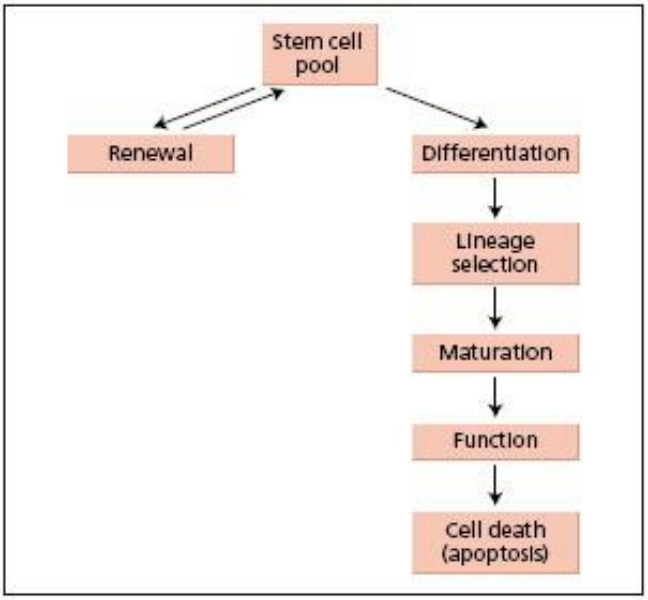
Hemopoietic stem cells & progenitor cells:

The lifelong production of blood cells occurs in haemopoietic tissue. This involves a very high level of cell turnover, demanded by the need to replace mature circulating blood cells at a rapid rate, and is necessitated by the limited lifespan of the mature cells.

Granulocytes survive for only a few hours and erythrocytes for a few months, so that some 10^{13} new cells must be replaced each day to maintain steady-state blood counts. This is equivalent to an annual number of cells approximating the total body weight, but the total bone marrow of an adult human contains around 10^{12} cells only, 10-fold less than daily needs. From these estimates it is clear that the blood cells required for lifelong hemopoiesis cannot be preformed in the body.

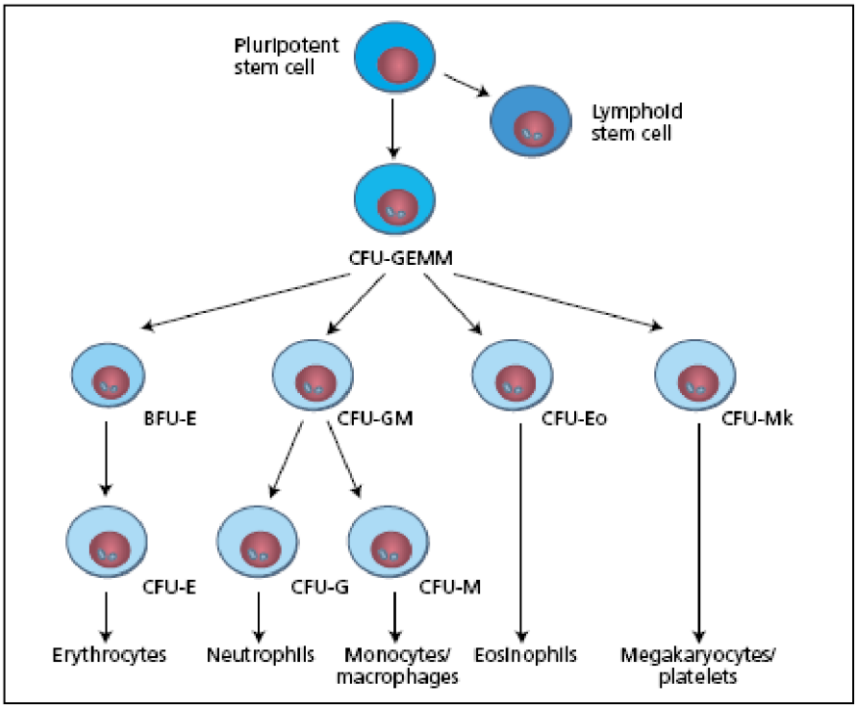
Hemopoiesis starts with a common pluripotent stem cell that can give rise to separate cell lineages. It has the capability of self renewal. It is recognized by being CD34+. They are capable of responding to hemopoietic growth factors with increased production of one specific cell line when the need arises.

Cell differentiation occurs from the stem cell down to erythroid, granulocytic and other lineages via the committed hemopoietic progenitors which are restricted in their developmental potential.



Hemopoietic cell development.

The hemopoietic system is a hierarchy of cells in which multipotent hemopoietic stem cells give rise to lineage-committed progenitor cells, which divide to generate the maturing and mature blood cells.



Hierarchical organization of hemopoiesis.

Stem cell renewal and differentiation

Stem cells are capable of self-renewal and differentiation when they divide and are responsible for producing all the mature blood cells throughout life.

This means that when steady-state stem cells divide, only 50% of the daughter cells, on average, differentiate, the remaining 50% do not differentiate, but maintain stem cell numbers.

This could be accomplished by asymmetric cell division, so that each dividing stem cell forms one new stem cell and one differentiated cell.

Hemopoietic growth factors:

They are glycoprotein hormones that regulate the proliferation and differentiation of hemopoietic progenitor cells and the function of mature blood cells.

Their biological effect is mediated through specific receptors on target cells. They may act locally or circulate in plasma.

Hemopoietic growth factors share a number of common properties:

- Glycoproteins that act at very low concentrations.
- Act hierarchically.
- Produced by many cell types.
- Affect more than one cell lineage.
- Active on stem/progenitor cells and on functional end cells.
- Synergistic or additive interaction with other growth factors.
- Act on the neoplastic equivalent of the normal cell.
- Multiple actions: proliferation, differentiation, maturation, functional activation and prevention of apoptosis.

Maturing and mature cells:

The maturing and mature hemopoietic cells are recognizable on stained smears of blood or bone marrow. During maturation, the cells maintain some capacity for division that can influence the blood count because each additional division would double the blood count. Eventually, however, the

capacity for cell division is lost because of expulsion of the nucleus (red cells), fragmentation (platelets) or nuclear distortion (polymorphonuclear granulocytes). In contrast, mature lymphocytes have a monomorphic nucleus and retain the ability to divide. The end-products of hemopoietic cell development are cells that are highly specialized for their different functions in the body.

Programmed cell death (Apoptosis):

The final stage in the life of a blood cell is death and disposal by apoptosis. Apoptotic cell death is a mechanism for disposing of unwanted or excess cells, and it occurs widely in biological systems. It ensures the destruction of cells without releasing any lysosomal or granule contents that would cause an inflammatory reaction. Apoptosis involves a complex series of events that culminate in the activation of proteases, fragmentation of DNA and phagocytosis of apoptotic bodies by macrophages.

Red blood cell formation (Erythropoiesis):

Understanding the basic biology of erythropoiesis provides a logical basis for the diagnosis and treatment of the inherited and acquired anemias that are so frequently encountered in clinical practice.

Erythrocytes (Red blood cells, RBC) are the oxygen carriers for all oxygen-dependent metabolic reactions. They are the only blood cells without nuclei, since this allows them to bind and exchange the greatest number of O_2 molecules by carrying haemoglobin (Hb) around the circulation in high concentration (about $640 * 10^6$ hemoglobin molecule in each mature red cell) and in a functional state (reduced form). Their physiological biconcave disk shape with a thick rim provides optimal plasticity (for molding).

The erythrocyte is a complex cell. The membrane is composed of lipids and proteins. The interior of the cell contains metabolic machinery designed to sustain the cell through its 120-day life span and maintain the integrity of hemoglobin function. The only source of energy as ATP is derived from anaerobic glycolysis. The lack of protein synthesis in the mature red cell

means that none of the enzymes in the metabolic pathways can be replaced during the red cell lifespan. Over the 120 days of normal red cell survival, enzyme activities decline contributing to the ageing process of the red cell.

Erythropoiesis: There is a continuous need to renew senescent blood cells that are ultimately lost from the peripheral blood, as throughout adult life approximately 10^{11}-10^{12} senescent red cells must be replaced every day.

In a normal adult, the numbers of circulating red blood cells and their precursors remain more or less constant with a balance between the continuous loss of mature cells by senescence and new red cell production in the marrow. This complex and finely regulated balance is maintained by an oxygen-sensing system that is affected by the red cell mass and responds via the kidney produced erythropoietin (Epo), which, in turn, controls red cell production by binding and signaling to committed erythroid progenitors.

Epo production is mediated by decreased oxygen saturation of hemoglobin, that is, hypoxemia.

Interaction of Epo with its receptor EpoR results in (1) stimulation of erythroid cell division and differentiation, and (2) prevention of erythroid progenitor apoptosis

Erythropoiesis passes from *stem cell* through the progenitor cells CFU_{GEMM} (Colony forming unit granulocyte, erythroid, monocyte and megakaryocyte), and CFU *erythroid* to the first recognizable erythrocyte precursor in the bone marrow, the *pronormoblast*.

The pronormoblast gives rise to a series of progressively smaller *normoblasts* by a number of cell divisions. Normoblasts (nucleated red cells) are not normally present in peripheral blood. They also contain progressively more hemoglobin (which stains pink) in the cytoplasm; the cytoplasm stains paler blue as it loses its RNA and protein synthetic apparatus while nuclear chromatin becomes more condensed.

The nucleus is finely extruded from the late normoblasts within the marrow and *reticulocyte* stage results which still contains some ribosomal RNA and is still able to synthesize hemoglobin. This cell is slightly larger than a mature red cell, spends 1-2 days in the marrow and also circulates in the peripheral blood for 1-2 days before maturing, mainly in the spleen when

RNA is completely removed, then completely pink staining mature *erythrocyte (RBC)* results which is a non-nucleated biconcave disc.