Bone Marrow

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Bone marrow is found in the medullary cavities - the centres of bones. The bone marrow is where circulating blood cells are produced – a process known as **haematopoiesis**. Early on in a human's life, this takes place in many bones, but during development haematopoiesis increasingly centres on flat bones so that by puberty, blood production takes place predominantly in the **sternum**, **vertebrae**, **iliac bones** and **ribs**. Bone marrow undergoing haematopoiesis is coloured red due to the presence of red blood cells, whereas bone marrow that is not undergoing haematopoiesis is yellow. The **red marrow** consists of long trabeculae (beam-like structures) within a sponge-like reticular framework. Spaces around this framework are filled with fat cells, stromal fibroblasts and blood cell precursors. A healthy bone marrow biopsy is shown in **Figure 1**.

During the development of the blood cells, these haematopoietic precursors migrate from the **subendosteal region** (the inner bone surface) towards a central region (**Figure 2**). The matured blood cells exit through a dense network of vascular sinuses.

During haematopoiesis the **haematopoietic stem cells** (**HSC**) divide, and one daughter cell remains in the bone marrow to continue renewing the HSC pool. The other daughter cell will pass through several stages of development (see **Figure 4**) to become a mature blood cell and leave the bone marrow to enter the circulation.

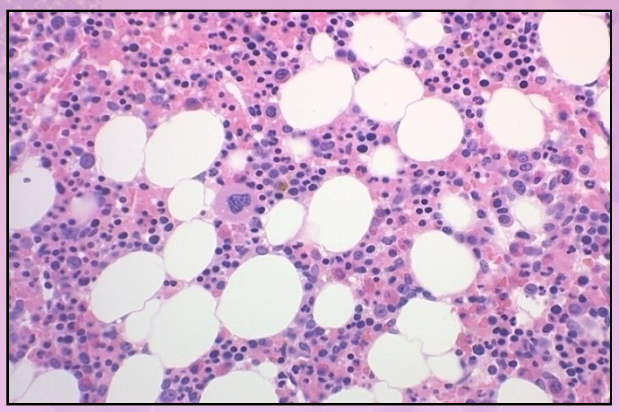

Figure 1. Haematoxylin-Eosin stain of healthy bone marrow (from http://bonemarrowbiopsy.wordpress.com/normal-results/) The haematoxylin has stained the cells' nuclei purple and the eosin has stained the cells' cytoplasm pink. The white patches are fat stored in fat cells.

Mesenchymal stem cells (MSC) are found in the bone marrow cavity and differentiate into a number of stromal lineages such as **chondrocytes** (cartilage generation), **osteoblasts** (bone formation), **adipocytes** (adipose), **myocytes** (muscle), **endothelial cells** and **fibroblasts**.

After leaving the bone marrow and undergoing further development, activated antigen-experienced B cells differentiate into **plasma cells** which return to, and colonise the bone marrow cavity.

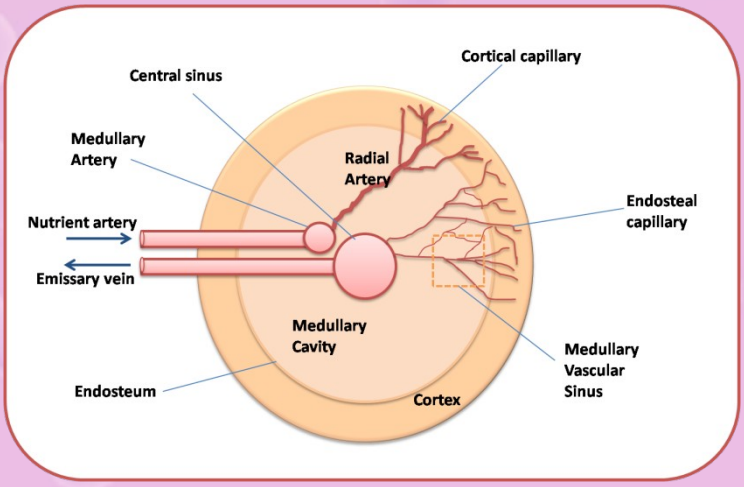

Figure 2. Bone Marrow Morphology
Adapted from Nagasawa *Nat Rev Immunol.* 2006 Feb;6(2):107-16

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Bone Marrow
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The framework of the bone marrow and all the cells present within it, along with their secreted cytokines and cell surface receptors make up a complex microenvironment. Maintenance of this microenvironment is important to promote haematopoiesis, cell development and prevent haematological disorders.

Bone Marrow Disorders

Leukaemias are malignant diseases of the bone marrow and occur during haematopoietic development of either lymphoid lineages in *acute or* **chronic lymphoblastic leukaemia** (**ALL/CLL**) (**Figure 3**); or myeloid lineages in **acute *or* chronic myeloid leukaemia** (**AML/CML***)*.

Myeloproliferative disorders are related to leukaemias in that they are characterised by the overproduction of one type of blood cell and in some cases they may develop into leukaemias. There are three main forms: **essential thrombocythaemia**, **polycythaemia vera** and **myelofibrosis**, in which the overproduced cell types are platelets, red blood cells and fibroblasts, respectively.

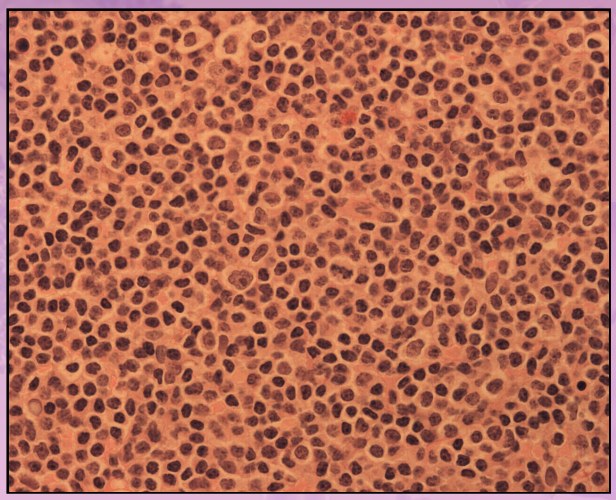

Figure 3. Stain of CLL patient bone marrow showing heavy infiltration of leukaemic cells (from http://bonemarrowbiopsy.wordpress.com)

Myelodysplastic syndromes (**MDS**) are a spectrum of disorders resulting from overproduction of one or more type of blood cell. Some cases transform into AML. **Multiple myeloma** is a malignancy of plasma cells which leads to excessive production of a single paraprotein. **Aplastic anaemia** is characterised by reduced blood production as a result of loss of haematopoietic stem cells and replacement by fat cells.

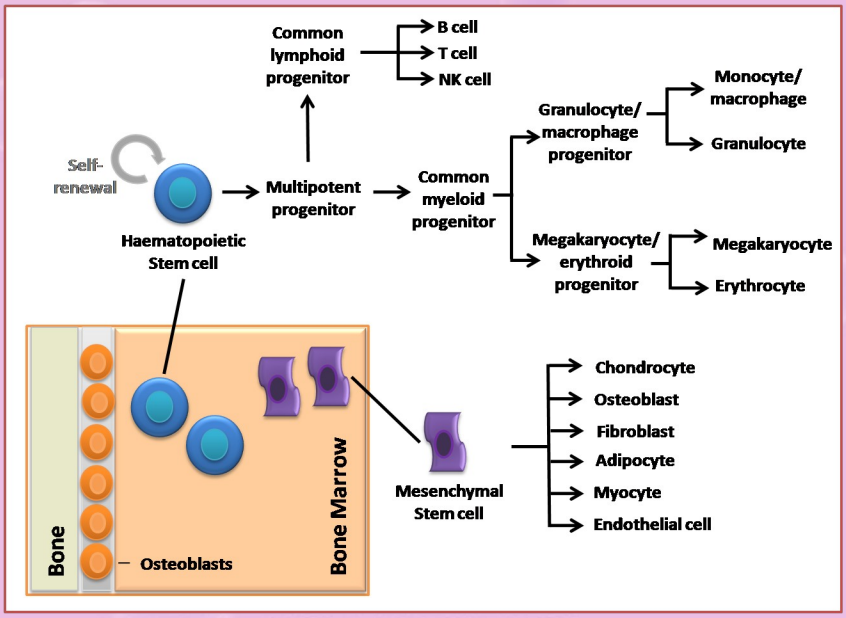

Figure 4. A model for blood and tissue production in Bone Marrow. HSCs (haematopoeitic stem cells) are self-renewing stem cells that can differentiate into any blood cell type. MPPs (multipotent progenitors) still have the potential differentiate into any cell type, but cannot divide continuously so must be renewed by the differentiation of HSCs. CLPs (common lymphoid progenitors) differentiate into lymphoid cell types whereas CMPs (common myeloid progenitors) differentiate into myeloid cells types via the GMP (granulocyte-macrophage progenitor) or MKEP (megakaryocyte-erythrocyte progenitor).

Adapted from Yin, Li *J Clin Invest.* 2006 May;116(5):1195-201