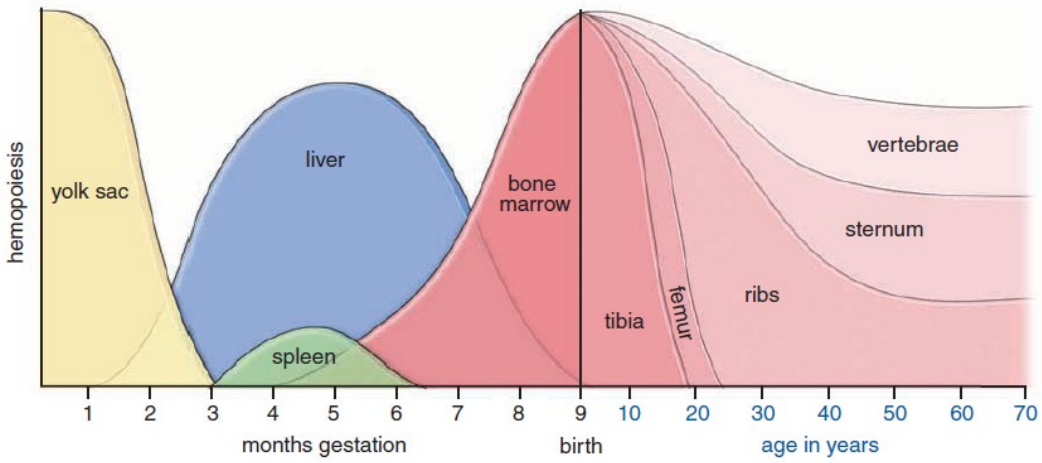
BONE MARROW – Part I

Objectives

- To learn about hemopoiesis.
- To understand the histological and functional characteristics of bone marrow.
- To know the clinical importance of bone marrow examination and bone marrow transplant.
- To learn about haemopoietic stem cells, their progenitors and precursors.

Introduction

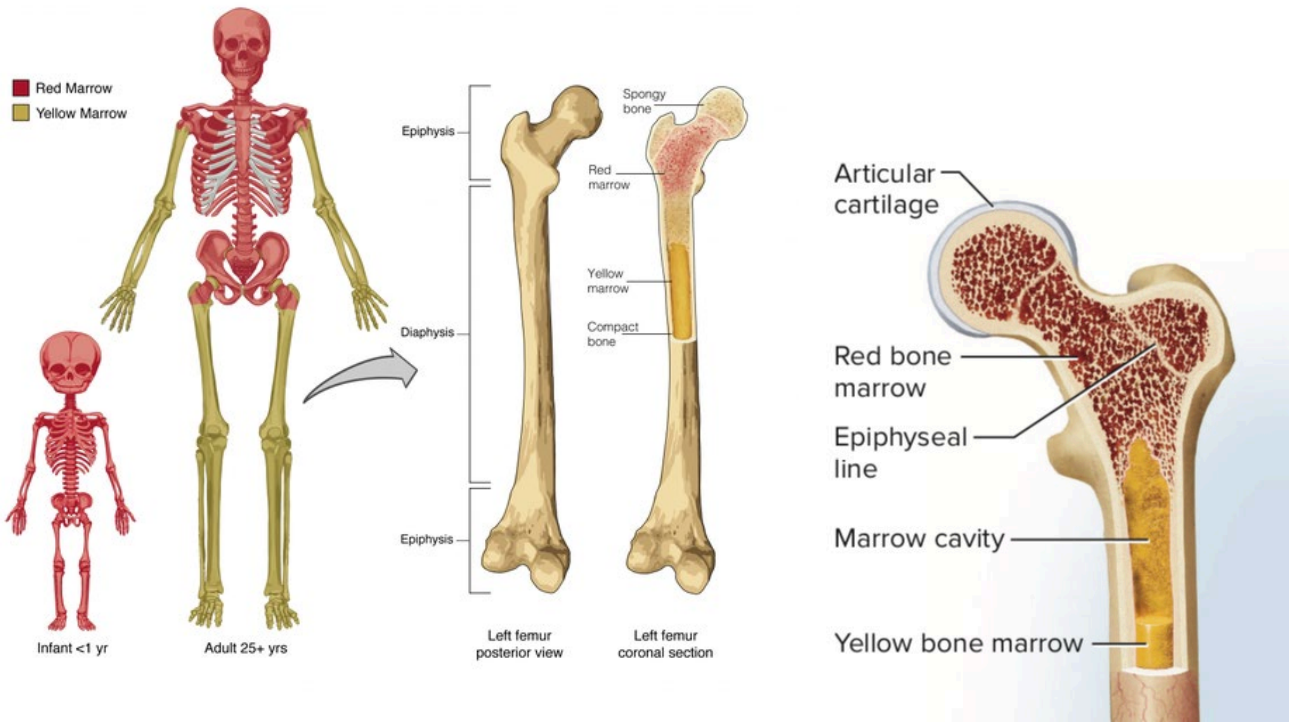
- Mature blood cells have a relatively short life span and must be continuously replaced with new cells from precursors developing during **hemopoiesis** (also called **hematopoiesis);** defined as the process of blood cells formation.
- In the early embryo (first trimester of pregnancy), these blood cells arise in the **yolk sac** mesoderm. In the second trimester, hemopoiesis occurs primarily in the developing **liver,** with the spleen playing a minor role. Bones begin to ossify, and **bone marrow** develops in their medullary cavities, so that in the third trimester marrow of specific bones becomes the major hemopoietic organ.



- Throughout childhood and adult life, erythrocytes, granulocytes, monocytes, and platelets continue to form from stem cells located in bone marrow. The origin and maturation of these cells are termed, respectively, **erythropoiesis**, **granulopoiesis, monocytopoiesis,** and **thrombocytopoiesis.**
- **Lymphopoiesis** or lymphocyte development occurs in the bone marrow and in the lymphoid organs to which precursor cells migrate from marrow.

Bone Marrow

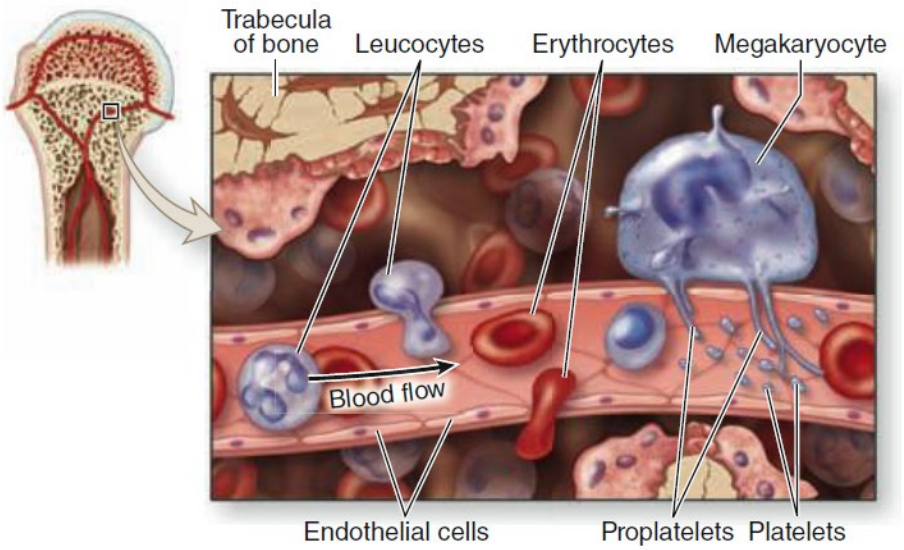
- Bone marrow is a specialized connective tissue found in the medullary canals of long bones and in the small cavities of cancellous bone. There are two types of bone marrow based on their appearance at gross examination:
  1) **Red bone marrow,** whose color is produced by an abundance of blood and hemopoietic cells.
  2) **Yellow bone marrow,** which is filled mostly with adipocytes and few hemopoietic cells.
- In the newborn all bone marrow is red and active in blood cell production, but as the child grows, most of the marrow changes gradually to the yellow variety.
- Under certain conditions, such as severe bleeding or hypoxia, yellow marrow reverts to red.



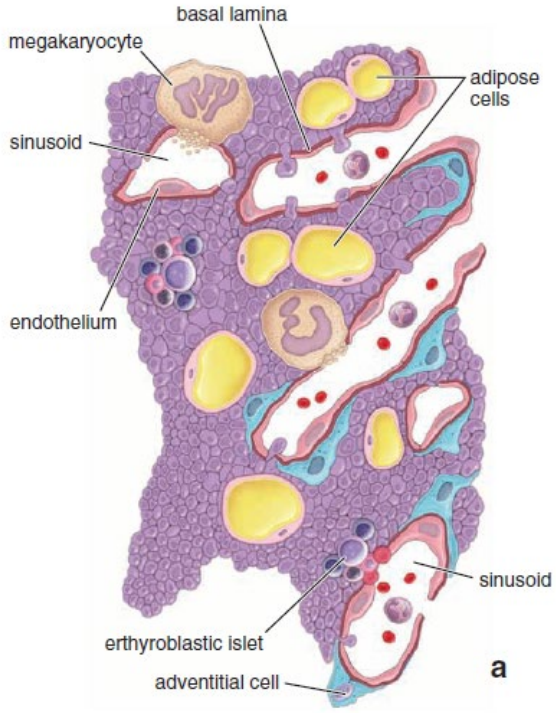
- Red bone marrow contains:
  A. a reticular connective tissue **stroma** (Gr. *stroma,* bed),
  B. **hemopoietic cords** or **islands** of cells, and
  C. **sinusoidal capillaries (sinusoids).**
- The stroma is a meshwork of specialized fibroblastic cells called **stromal cells** (also called **reticular or adventitial cells)** and a delicate web of reticular fibers supporting the hemopoietic cells and macrophages. In addition, there is collagen type I, proteoglycans, fibronectin, and laminin.

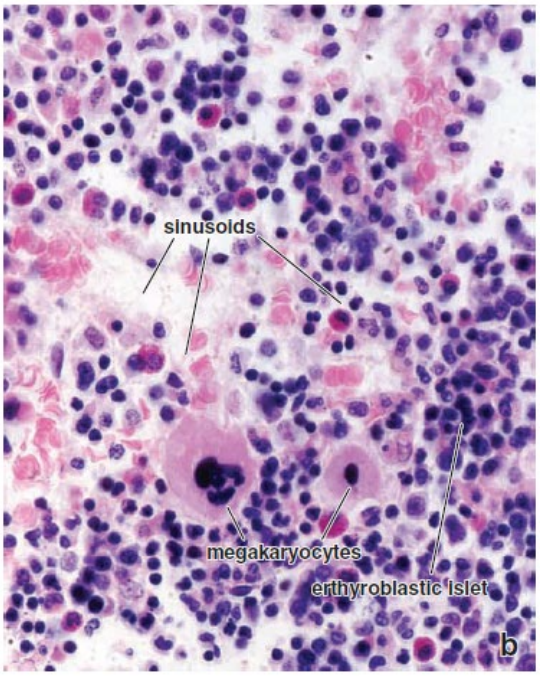
- The hematopoietic niche in marrow includes the stroma, osteoblasts, and megakaryocytes.
- Between the hematopoietic cords run the sinusoids, which have discontinuous endothelium, through which newly differentiated blood cells and platelets enter the circulation.
- The bone marrow sinusoids provide the barrier between the hemopoietic compartment and the peripheral circulation.

- The sinusoid of red bone marrow is a unique vascular unit. It arises from blood vessels that supply the cortical bone tissue at the corticomedullary junction.
- The sinusoid wall consists of an endothelial lining, a discontinuous basement membrane, and an incomplete covering of adventitial cells. The endothelium is a simple squamous epithelium.



- The **adventitial cells** produce reticular fibers and also play a role in stimulating the differentiation of developing progenitor cells into blood cells by secreting several cytokines (e.g., CSFs, IL-5, IL-7).
- When blood cells formation and the passage of mature blood cells into the sinusoids are active, adventitial cells and the basal lamina become displaced by mature blood cells as they approach the endothelium to enter the sinusoid from the bone marrow cavity.





Red Bone Marrow

- Active bone marrow is called **red bone marrow** and consists of cords of hemopoietic cells that contain predominately developing blood cells and megakaryocytes. The cords also contain macrophages, mast cells, and some adipose cells.
- Although the cords of hemopoietic tissue appear to be unorganized, specific types of blood cells develop in nests or clusters:
  1) Each nest in which erythrocytes develop contains a macrophage. These nests are located near the sinusoid wall.
  2) Megakaryocytes are also located adjacent to the sinusoid wall, and they discharge their platelets directly into the sinusoid through apertures in the endothelium.
  3) Granulocytes develop in cell nests farther from the sinusoid wall. When mature, the granulocyte migrates to the sinusoid and enters the bloodstream.

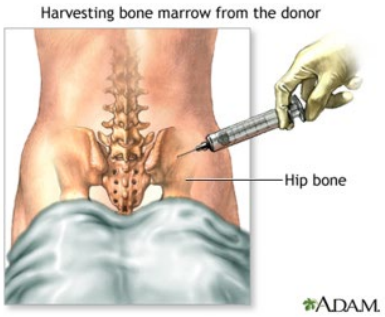
Yellow Bone Marrow

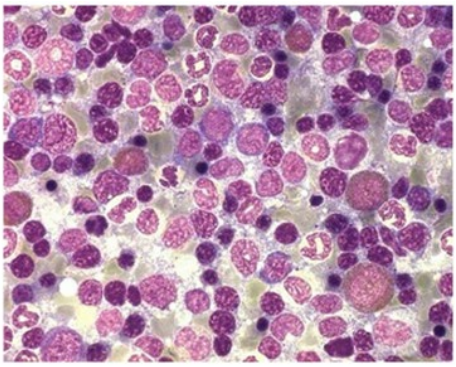
- Inactive bone marrow is called **yellow bone marrow**. It contains predominately adipose cells, giving it the appearance of adipose tissue.
- It is the chief form of bone marrow in the medullary cavity of adult bones that are no longer hemopoietically active, such as the long bones of the arms, legs, fingers, and toes. In these bones, the red bone marrow has been replaced completely by fat.
- Even in hemopoietically active bone marrow in adult humans—such as that in the ribs, vertebrae, pelvis, and shoulder girdle—about half of the bone marrow space is occupied by adipose tissue and half by hemopoietic tissue.
- The yellow bone marrow retains its hemopoietic potential, however, and when necessary, as after severe loss of blood, it can revert to red bone marrow.
- The mechanism by which yellow marrow can convert back to red marrow include:
  1) extension of the hemopoietic tissue into the yellow bone marrow and,
  2) repopulation of the yellow bone marrow by circulating hemopoietic stem cells.

Bone Marrow Examination

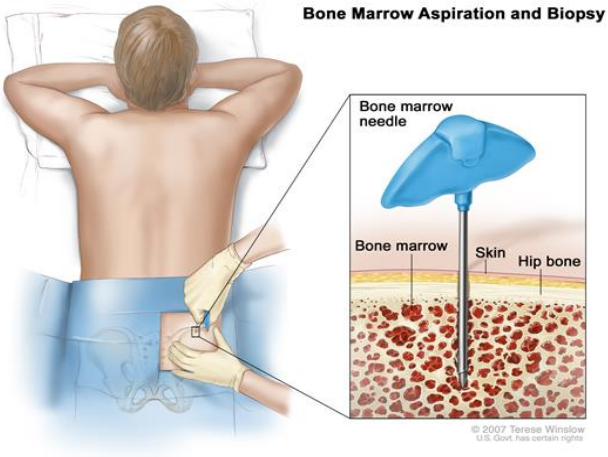
- Examination of bone marrow is essential for the diagnosis of bone marrow disorders. This is done by two methods; **bone marrow aspirate** and **bone marrow core needle biopsy**; which are complementary and provide a comprehensive evaluation of the bone marrow.
- There are several indications for **bone marrow examination**:
  1) unexplained anaemia (low erythrocyte counts),
  2) abnormal peripheral blood smear morphology,
  3) diagnosis and staging of hematological malignant disorders (e.g., leukemia), and
  4) suspected bone marrow metastases.

- In **bone marrow aspiration**, the aspirate is spread as a smear on a glass slide and the specimen is examined with the microscope to examine individual cell morphology.





- In **bone marrow core biopsy**, the core biopsy specimen obtained in this procedure provides <u>for analysis of bone marrow architecture</u> and processed for routine H&E slide preparation.



<u>Clinical Notes</u>

Bone marrow cellularity *is one of the most important factors in evaluating the function of the bone marrow. The assessment of bone marrow cellularity represents the ratio of hemopoietic cells to adipocytes, which varies normally with the age of the patient (a young child has about 80% cellularity while a 75 years old man has about 30%). The most reliable evaluation of cellularity is obtained from the microscopic examination of a bone marrow biopsy that preserves the organization of the marrow. Bone marrow could be* ***normocellular***, ***hypocellular*** *(e.g. aplastic anaemia or after chemotherapy) or* ***hypercellular*** *(e.g. hematopoietic cells tumors).*

Bone Marrow Transplant

- A **bone marrow transplant** is the replacement of cancerous or abnormal red bone marrow with healthy red bone marrow in order to establish normal blood cell counts.
- In patients with cancer or certain genetic diseases, the defective red bone marrow is destroyed by high doses of chemotherapy and whole-body radiation just before the transplant takes place. These treatments kill the cancer cells and destroy the patient's immune system in order to decrease the chance of transplant rejection.

- Healthy red bone marrow for transplanting may be supplied by a donor or by the patient when the underlying disease is inactive, as when leukemia is in remission.

Uses of Bone Marrow Transplant:

Bone marrow transplants have been used to treat aplastic anemia, certain types of leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, thalassemia, sickle-cell disease, breast cancer, ovarian cancer, testicular cancer, and hemolytic anemia.

Problems associated with Bone Marrow Transplant:

- **Increase risk of infection** because the recipient's white blood cells have been completely destroyed by chemotherapy and radiation (It takes about 2–3 weeks for transplanted bone marrow to produce enough white blood cells to protect against infection).
- The transplanted red bone marrow may produce T lymphocytes that attack the recipient's tissues, a reaction called **graft-versus-host disease**. Similarly, any of the recipient's T cells that survived the chemotherapy and radiation can attack donor transplant cells.
- **The patients must take immunosuppressive drugs for life**. Because these drugs reduce the level of immune system activity, they increase the risk of infection. Immunosuppressive drugs also have side effects such as fever, muscle aches, headache, nausea, fatigue, depression, high blood pressure, and kidney and liver damage.

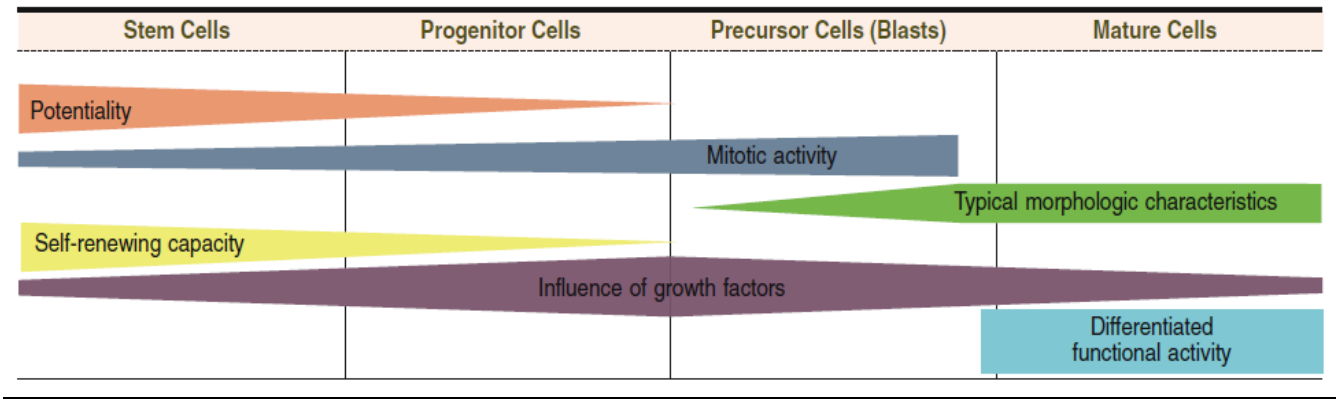
Hemopoietic Stem Cells

- All blood cells arise from a single type of pluripotent **hemopoietic stem cell** in the bone marrow that can give rise to all the blood cell types.
- These pluripotent stem cells are rare, proliferate slowly and give rise to two major lineages of progenitor cells with restricted potentials (committed to produce specific blood cells):
    1) one for **lymphoid cells** (lymphocytes) and,
    2) another for **myeloid cells** (granulocytes, monocytes, erythrocytes, and megakaryocytes) that develop in bone marrow.
- The lymphoid cells migrate from the bone marrow to the thymus or the lymph nodes, spleen, and other lymphoid structures, where they proliferate and differentiate.

Progenitor & Precursor Cells

- The **progenitor cells** for blood cells are often called **colony- forming units (CFUs),** because they give rise to colonies of certain cell type.
- There are four major types of progenitor cells/CFUs:
    1) Erythroid lineage of erythrocytes
    2) Thrombocytic lineage of megakaryocytes for platelet formation
    3) Granulocyte-monocyte lineage of all three granulocytes and monocytes
    4) Lymphoid lineage of B lymphocytes, T lymphocytes, and natural killer cells

- Each progenitor cell lineage produces **precursor cells** (or **blasts**) that gradually assume the morphologic characteristics of the mature, functional cell types they will become.
- In contrast, stem and progenitor cells cannot be morphologically distinguished and simply resemble large lymphocytes.
- While stem cells divide at a rate only sufficient to maintain their relatively small population, progenitor and precursor cells divide more rapidly, producing large numbers of differentiated, mature cells.



- Hemopoiesis depends on a microenvironment, or **niche**, with specific endocrine, paracrine, and juxtacrine factors. These requirements are provided largely by the local cells and ECM of the hemopoietic organs, which together create the niches in which stem cells are maintained and progenitor cells develop.

- Hemopoietic growth factors, often called **colony- stimulating factors (CSF)**, are glycoproteins that stimulate proliferation of progenitor and precursor cells and promote cell differentiation and maturation within specific lineages.

Clinical Notes

Hemopoietic growth factors made available through recombinant DNA technology hold great potential for medical uses when a person's natural ability to form new blood cells is diminished or defective. They are used clinically to increase marrow cellularity and blood cell counts in patients with conditions such as severe anaemia or during chemo- or radiotherapy, which lower white blood cell counts (leukopenia). Such cytokines may also increase the efficiency of marrow transplants by enhancing cell proliferation, enhance host defences in patients with infectious and immunodeficient diseases, and improve treatment of some parasitic diseases.

Disclaimer

The material in this lecture is taken from the following textbooks:

Janquira' Basic histology, 15th edition, 2019.

Histology: A text and atlas with Correlated Cell and Molecular Biology, 7th edition, 2017.