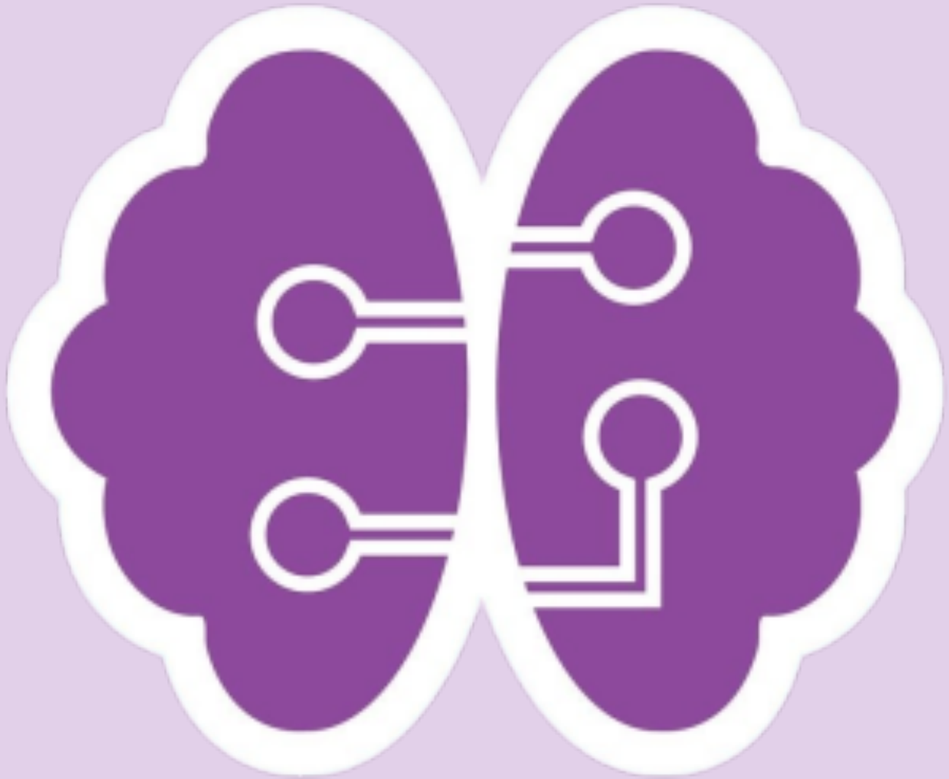


Histology mind maps for midterm

Done by:- TOLEEN MAWAZREH

The file isn't reviewed !!

LECTURE 1

Blood as a connective tissue

Components

- **Blood cells** (several types)
- **Plasma** (extracellular matrix)

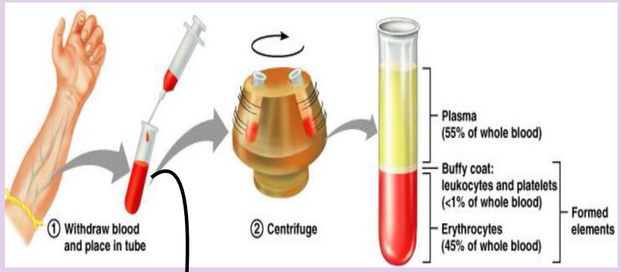
Blood

- PH=7.4
- Is propelled mainly by rhythmic contractions of heart
- About 5-6 Liters of blood in an average adult moves unidirectionally within the closed circulatory system
- Color depends on the amount of oxygen
  - More O2 —> brighter the red
  - Less O2 —> duller the red

Functions of Blood

- Transportation of
  - **nutrients and respiratory gases**
  - **waste products to organs and tissues where they can be recycled or released**
  - **hormones**
  - **immune cells throughout the body**
- Helps in regulating body temperature
- Maintaining of acid-base and osmotic balance

HEMATOCRIT: Ratio of the volume of RBCs to the volume of whole blood
Example: a hematocrit value of 40% means that there are 40 ml of RBCs in 100 ml of whole blood
Normal hematocrit:
Males=40-53%
Females= 36-48%



Collected blood in which clotting is prevented by the addition of anticoagulants (eg, heparin , citrate or EDTA) can be separated by centrifugation into layers that reflect its heterogeneity

Fluid

Components

Living 45%

- RBC Erythrocytes (carry oxygen)
  3.5-5.5 million/mm^3
- WBC Leukocytes (immune)
  4500-11000/mm^3
  - Lymphocytes
  - Neutrophils
  - Monocytes
  - Eosinophils
  - Basophils
- Platelets Thrombocytes (clotting)
  150000-400000/mm^3

Non living (Matrix) 55%

Plasma (pale yellow fluid)

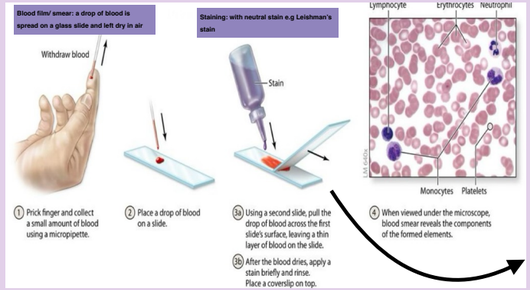
- **Water**
  92% by weight
- **Proteins**
  7% by weight
  ⬇️
  Albumins 58%
  - ✓ The most abundant plasma protein
  - ✓ Is made in the liver
  - ✓ Helps maintain the osmotic pressure in capillaries
  - ✓ Transports steroid hormones and fatty acids

  Globulins 37%
  - **α and β globulins**
    - ✓ Are made mainly by liver
    - ✓ Transport fat soluble vitamins, lipids and iron
  - **γ-globulins (Immunoglobulins (antibodies)**
    secreted by plasma cells

  Fibrinogen 4%
  - ✓ The **largest** plasma protein
  - ✓ Is made in the liver
  - ✓ Important for clot formation

  Regulatory pr. 1%
- **Other solutes**
  1% by weight
  ⬇️
  Electrolytes
  Nutrients
  Respiratory gases
  Waste products

Preparing a blood smear



Blood cells can be studied histologically in smears prepared by spreading a drop of blood in a thin layer on a microscope slide

Polychromatic stains

- Giemsa
- Wright
- **Leishman**
  - **Eosin**, an acidic dye that stains pink to red
  - **Methylene blue**, a basic dye that stains blue to purple
  - Azure dye!! Staining blue to purple

  Dissolved in methyl alcohol (fixative)

Erythrocytes (RBCs)

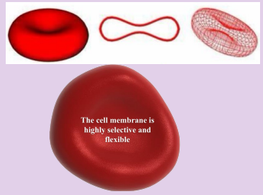
- Small, biconcave discs
- Transport oxygen and CO_2, cytoplasm is full of hemoglobin molecules
- Have no nuclei or organelles
- Pick up O_2 at lung capillaries and release it at body tissue capillaries

During their maturation process, the erythrocytes extrude their nuclei, and the mature RBCs enter the bloodstream, without their nuclei

- Fate: Survive for ~100-120 days in the circulation. Worn out RBCs are removed by macrophages of the spleen, bone marrow and liver.

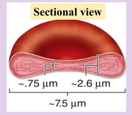
meshwork of proteins

Immediately beneath the plasma membrane is a meshwork of proteins (Spectrin and Ankyrin) forming a cytoskeleton
This submembranous meshwork 1. stabilizes the membrane, 2. maintains the cell shape, and 3. provides the cell elasticity required for passage through capillaries



Normocytic RBCs

Size
6-9 um in diameter (7.5 um)
Thickness
2.6-μm thick at the rim, but only 0.75-μm thick in the center



!!!!! Erythrocytes can be used as a size reference for other cell types

Based on Cell Size (cytometry):

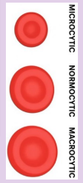
Abnormal sizes

Microcytes (< 6um)
Macrocytes (> 9um)
Anisocytosis (different sizes)

Normocytic: RBCs are of normal size, about 7–8 μm in diameter.

Microcytic: RBCs are smaller than normal (seen in iron deficiency anemia)

Macrocytic: RBCs are larger than normal (seen in vitamin B12 or folate deficiency anemia).



Together, these terms are used to describe and classify anemias

- microcytic hypochromic anemia → in iron deficiency
- macrocytic normochromic anemia → in B12 deficiency

Change from the normal size, shape or staining properties of erythrocytes are important indicator of disease. However, some of these abnormalities may be found in healthy individuals

Based on Hemoglobin Content (color /chromasia):

Normochromic: RBCs have a normal hemoglobin concentration → normal color, normal central pallor (about one-third of the cell).

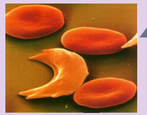
Hypochromic: RBCs have less hemoglobin than normal → appear paler with an abnormally large central pallor (Common in iron deficiency anemia)

Hyperchromic: RBCs have more hemoglobin concentration than normal → cells look denser and darker with absent central pallor (**seen in spherocytosis**).

Abnormal staining

Hypochromia: Denotes a decrease in the intensity of staining Indicates a decreased amount of hemoglobin
Frequently accompanies **microcytosis** ⬇️
Hypochromic microcytic anemia

Abnormal staining

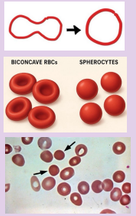


Sickle cell anaemia results from abnormal hemoglobin

Abnormal shapes (Poikilocytosis)

Poikilocytes

- **Spherocytes**
- **Sickle cells** — One of the most sever changes in shape occurs during SICKLING of RBCs in sickle cell anemia where erythrocytes take on the form of crescents
- **Ovalocytes** **Elliptocytes**
- **Dacrocytes** — Teardrop shaped cells



Biconcavity

provides 20-30% greater surface area than a sphere relative to cell volume, facilitating gas exchange

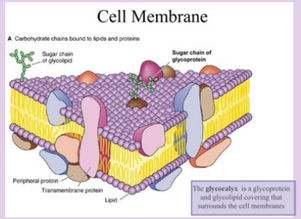
along with the fluidity of the plasma membrane (50% proteins) permits erythrocytes to bend and adapt to the small diameters and irregular turns of capillaries

mutations in genes relating to membrane proteins (mostly Spectrin and Ankyrin) that allow for the erythrocytes to maintain their biconcave shape

Lead to => Hereditary Spherocytosis

Plasma membrane

Erythrocyte consists of an outer plasma membrane enclosing hemoglobin and a limited number of enzymes necessary for maintenance of plasma membrane integrity and gas transport functions



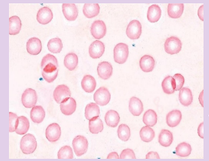
glycoprotein antigens on their external surfaces of the RBCs PM

- A
- B
- AB

There are four common blood groups in the ABO system: O, A, B, and AB. The blood groups are defined by the presence of specific carbohydrate sugars on the surface of red blood cells

Histology

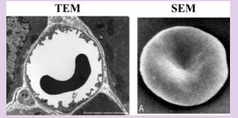
LM:
Blood film stained with Leishman:
Rounded, Non nucleated ,Acidophilic (with pale central area)
—> A zone of central pallor is about 1/3 the size of the RBC



The pale staining of the central region is a result of its biconcave disc shape
Normochromic RBCs

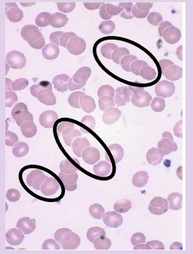
EM:
- Have no nucleus or organelles
- Filled with hemoglobin

Electron dense and homogenous



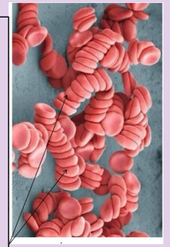
Rouleaux appearance

occurs to some extent in all films



Rouleaux formation:
- RBCs may adhere to one another loosely in stacks called Rouleaux (pile of coins)
- In slow (not in normal) circulation

Due to surface tension caused by their biconcave surface (reversible)



Lecture 2

Erythropoiesis

Production of erythrocytes in the bone marrow, is stimulated by erythropoietin

⬇️

Erythropoietin is produced by the kidneys

⬇️

When RBC count drops, such as during blood loss, the resulting oxygen-deficiency state, hypoxemia, is detected by the kidneys.

⬇️

The kidneys respond by increasing their erythropoietin secretion, which leads to increased red blood cell production → Polycythemia: an increase in the total number of RBCs (and/or hemoglobin) While Anemia: is a decrease

People living at high altitudes usually have higher RBC count as a response to lower oxygen levels.

Athletes whose demand for oxygen is more elevated, also have higher RBC counts.

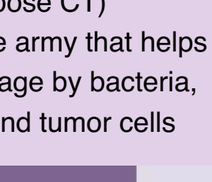
	RBCs (Erythrocytes)	WBCs (Leukocytes)
Types	1 type	5 types
	Not true cells	True cells
Number	Male: 4.5-5.5 million/mm3 female:4-5 million/mm3	4500-11000/mm3
Diameter	6-9um (7.5um)	6-20um
Life span	120 days	Few days-years
Origin and maturation	Bone marrow	Bone marrow and lymphoid tissue
Shape	Biconcave discs	Spherical
Function	Gas exchange	Defense
Motility	Non motile	Motile
	Function exclusively within vascular system	Function mainly OUTSIDE blood vessels in the tissues

Leukocytes

- Originate in the bone marrow and released continuously into the blood
- **Travel** in bloodstream but **function** mainly outside blood vessels (in loose CT)
- Leukocytes form a mobile army that helps protect the body from damage by bacteria, viruses, parasites, toxins and tumor cells

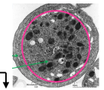
Thrombocytes (Platelets) neither granulocytes nor agranulocytes

- Small non-nucleated cytoplasmic fragments
- Formed by fragmentation of the cytoplasm of megakaryocytes in the bone marrow
- Number: 200,000-400,000/mm3
- Shape: biconvex discs
- Cytoplasm: purple, granular
- Diameter: 2-4 um
- Lifespan about 10 days
- Control the bleeding by plugging the defects in blood vessels and activating blood clotting cascades



In stained blood smears, platelets often appear in clumps

Platelete has 2 Zones



Have thick glycocalyx

Outer pale basophilic (clear) perpheriral zone: hyalomere

Hyalomere: contains cytoskeleton and membranous channels

- Cytoskeletal elements
  - > Microtubule
  - > Actin filaments

Maintain shape and help contractions of platelets and squeezing, clot retraction

Membrane channels

- Open canalicular system
- Dense tubular system

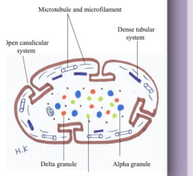
Central dark granular zone: granulomere

Granulomere: contains granules and organelles

Alpha granules: clotting factors, growth factors

Dense (delta) granules: serotonin (absorbed from plasma), ATP, ADP

Lambda granules: lysosomes (aid in clot resorption)



Their main function is to continually monitor the vascular system and detect any damage to the endothelial lining of the vessels. If the endothelial lining breaks, the platelets adhere to the damaged site and initiate a highly complex chemical process that produces a blood clot Thus preventing blood loss

Classification

Depending on the presence or absence of specific granules in their cytoplasm

Cytoplasmic granules

- Specific granules ← Secondary granules
- Non-specific granules → Azurophilic granules, Lysosomes, Primary granules

Granulocytes

- Cytoplasmic granules (containing enzymes or chemicals) ➡️ makes cytoplasm look grainy
- Single multi-lobed nucleus (segmented)
- All are phagocytic; they engulf and consume foreign cells and material
- 3 main types:

Neutrophils

Small granules, pale pink/ salmon pink

Eosinophil

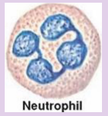
Large granules, Red

Basophils

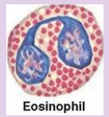
Large granules, blue

Agranulocytes

- Monocytes
- Lymphocytes



Neutrophil



Eosinophil

Basophil

	Neutrophil	Eosinophil	Basophil
Percentage (WBCs)	Most →		Least
Size	12-15um	12-15um	12-15um
Life span	Few days	Few days	Few days
Nucleus	2-5 lobes	2 lobes	Irregular (S-shaped)
Phagocytic activity	Most →		Least
Motility	Most →		Least

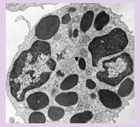
Never Let Monkeys Eat Bananas
Most common to least

Granulocytes

General features of granulocytes
-Spherical in blood stream, irregular in connective tissue
-Highly motile with different shapes due to their amoeboid movement
-Leave blood stream by migrating between the endothelial cells by a process called diapedesis

Basophils

• Rarest leukocyte – might not see these under the microscopes
• Usually have bi-lobed, S-shaped nuclei obscured by the large basophilic granules
• Has large granules that stain dark purple/ blue in basic dyes (basophil = basic loving)
• Granules contain histamine, heparin and eosinophilic chemotactic factor that mediate inflammation in **allergic reactions and parasitic infections**



Both basophils and mast cells have surface receptors for immunoglobulin E (IgE), and secrete their granular components in response to certain antigens and allergens.

IgE

Allergy mechanism

In some individuals a second exposure to a strong allergen, such as that delivered in a bee sting, may produce an intense, adverse systemic response. Basophils and mast cells may rapidly degranulate, producing vasodilation in many organs, a sudden drop in blood pressure, and other effects comprising a potentially lethal condition called Anaphylaxis or anaphylactic shock.

Anaphylaxis or anaphylactic shock.

Basophils account for up to 15% of infiltrating cells in allergic dermatitis and skin allograft rejection

Allergic dermatitis (eczema) is an itchy skin rash that develops when you come into contact with an allergen

Allergic dermatitis

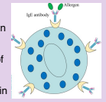
Exposure may be by ingestion, inhalation, injection, or direct contact

First exposure

In some individuals substances such as certain pollen proteins or specific proteins in food are allergenic, that is, elicit production of specific IgE antibodies, which then bind to receptors on mast cells and immigrating basophils.

Second exposure

Upon subsequent exposure, the allergen combines with the receptor-bound IgE molecules, triggering rapid exocytosis of the cytoplasmic granules.
Release of the inflammatory mediators in this manner can result in bronchial asthma, cutaneous hives, rhinitis, conjunctivitis, or allergic gastroenteritis.

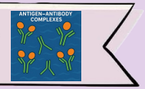


Immediate or type 1 hypersensitivity

Eosinophils

• Usually have bi-lobed nuclei connected by a short "thread" of nuclear material
• Large cytoplasmic granules, which stain red with the acidic eosin dye (eosinophil = eosin loving)
• Help in **ending allergic reactions and in fighting parasitic infections**

Eosinophils have a particular phagocytic affinity for antigen antibody complex



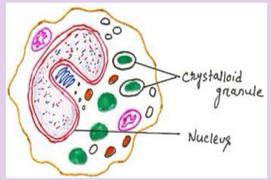
Oval in shape, with flattened crystalloid cores

Parts

Externum (pale): contains histaminase and sulfatase

Internum (dark): contains basic protein to kill parasites

Specific granules (Crystalloid granules)

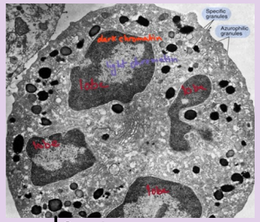


Neutrophils

Different names for neutrophils:
Polymorphs / Pus cells
Myelocytes / Microphages
Cells of acute inflammation

• The most common leukocyte
• 2-5 lobes in nucleus connected by "threads" of nuclear material (polymorphs)
• Light pink cytoplasm
• Called neutrophils because cytoplasm takes up red (acidic) and blue (basic) stains equally
• Specialized for responding to **Bacterial invasions- Acute infections- Acute pyrogenic infections**
• Neutrophils are short-lived cells with a half-life of 6-8 **hours in blood** and a life span of 1-4 **days in connective tissues** before dying by apoptosis

Note: Neutrophils will show increasing segmentation (many segments of the nucleus) as they mature. A normal neutrophil should have 3–5 segments. Hypersegmentation is not normal but occurs in some disorders, most notably vitamin B12 deficiency.



Granules

Specific granules (secondary)
Smaller, more numerous, formed later in development.
- Lysozyme - Lactoferrin (bacteriostatic)
- Collagenase - NADPH oxidase

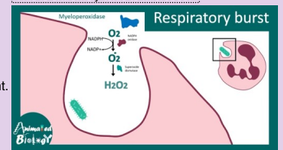
Azurophilic granules (primary)
Larger, formed early in neutrophil development.
- Myeloperoxidase - Acid hydrolase
- Defensins - Protease (eg. Elastase)

Form H_2O_2, HOCL: powerful cytotoxin

The ways of killing

Oxygen-dependent killing:
The neutrophil undergoes a 'respiratory burst' activating NADPH oxidase to produce reactive oxygen species. Hydrogen peroxide is formed, and with the help of myeloperoxidase, it generates hypochlorous acid.

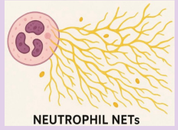
This is extremely toxic to microbes.



Oxygen-independent killing:
Granules inside the neutrophil release enzymes like defensins, lysozyme, and proteases. These proteins break down microbial walls and deprive bacteria of nutrients.

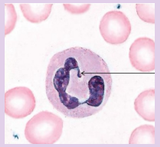
NETs

the Neutrophil Extracellular Trap, or NET. When overwhelmed, a neutrophil can undergo NETosis—a unique cell death where it releases its DNA coated with antimicrobial proteins.
This sticky web traps and kills microbes outside the cell, preventing them from spreading."



Barr body

In females, the inactive X chromosome (Barr body) may appear as a drumstick-like appendage on one of the lobes of the nucleus (about 3% of neutrophils in peripheral blood)



Cells of acute infection

Neutrophils are the first WBCs that leave the blood in large numbers to reach the site of inflammation
Why???
1- The most abundant
2-The most motile
3- Neutrophil chemotactic factors are the first released

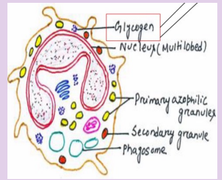
Pus is a viscous, usually yellow collection of fluid.

PUS

Dead neutrophils, bacteria, lysed ECM, and tissue-fluid form a viscous, usually yellow collection of fluid called pus.

Pyogenic is referring to bacterial infections that make pus while **pyrogenic** is producing heat

The ability of neutrophils to survive in an anaerobic environment is highly advantageous, because they can kill bacteria and help clean up debris in poorly oxygenated regions, for example, damaged or necrotic tissue lacking normal microvasculature.



LECTURE 3

Agranulocytes

- Single non-lobulated nucleus
- Granules in cytoplasm are too small to see (**nonspecific granules**, azurophilic granules, primary granules, lysosomes)

Monocytes

- Largest leukocytes
- Bluish cytoplasm (frosted glass appearance → Azurophilic granules(lysosomes)) & a large C-shaped nucleus
- Highly motile and phagocytic
- Travel through bloodstream to reach connective tissues, where they transform into macrophages (large phagocytic cells)

Perform 2 functions—> phagocytosis and antigen presentation

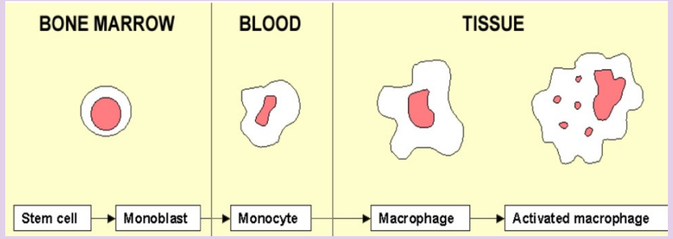
Are precursor cells of macrophages, osteoclasts, microglia, and other cells of the **mononuclear phagocyte system** in connective tissue

All monocyte-derived cells are **antigen-presenting cells**

all characterized by phagocytic activity

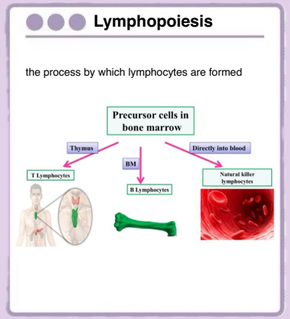
- **Kupffer Cells** — Liver
- **Microglia** — CNS
- **Dust cells** — Lung
- **Osteoclasts** — Bone resorption
- **Langerhans cells** — Epidermis
- **Dendritic cells** — Lymph node, Spleen
- **Macrophages** — Bone marrow, Connective tissue

Monocytes and macrophages are the same cells at different stages of maturation



Morphologic changes occur upon differentiation of monocytes into macrophages:

- The cell increases in diameter more than threefold
- The cell acquires more cytoplasmic granules and vacuoles
- Cell surface receptors increase in number
- The phagocytic activity improves



Lymphocytes

Morphologically lymphocytes can be classified into

Large (9-18 micro m) **Active** lymphocyte

- B lymphocyte
- T helper
- T cytotoxic
- Natural killers

Could be

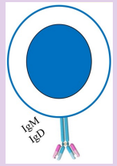
Small (6-9 micro m) **Inactive** lymphocyte

- B lymphocyte
- T helper
- T cytotoxic

Could be

The amount of cytoplasm depends upon state of activity of the lymphocyte
In circulation blood there is predominance of small inactive lymphocytes

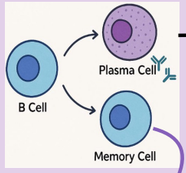
- Smallest leukocytes
- Round nucleus occupies most of cell volume
- Cytoplasm is light clear blue
- Increased numbers are commonly seen in **viral infections**
- Lymphocytes vary in life span according to their specific function, some live for a few days and some live for many years



B Lymphocyte

(Humoral immunity)

– Differentiate into plasma cells
– Secrete antibodies that bind to specific antigens and mark them for destruction by phagocytic cells



Produces antibodies

Memory cells allow a more rapid response if the antigen appears again later which allows a very rapid response upon subsequent exposure to the same antigen. Basis of immunity/vaccination

T Lymphocyte

(Cell mediated immunity)

Has different types, some directly kill foreign or infected cells; others activate phagocytes to destroy microbes

- **T helper (CD4+)** — Help cytotoxic T cells and B cells in their immune functions
- **T cytotoxic (CD8+)** — Kill virus-infected, transplanted and neoplastic cells (**adaptive immunity**)
- **Suppressor T cell (CD8+ or CD4+)** — Suppresses immune response to self Ag; Suppresses immune response of T and B lymphocytes

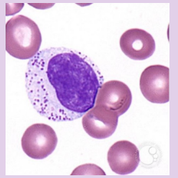
The retrovirus that produces acquired immunodeficiency syndrome (AIDS) infects and rapidly kills helper T cells. Reduction of this key lymphocyte group cripples the patient's immune system rendering them susceptible to opportunistic bacterial, fungal, protozoan, and other infections that usually dealt with easily in immunocompetent individuals.

Suppressor T cells switch off the immune response when the stimulus is removed
Damage to suppressor cells can result in autoimmune disease

Natural killer cells (NULL Lymphocyte)

Kill virus-infected, transplanted and neoplastic cells (**innate immunity**)

Natural killer cells and T cells play a major role in graft rejection



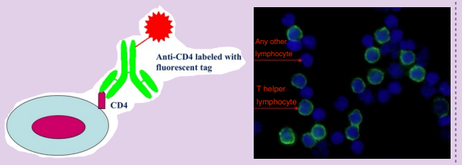
Large granular lymphocytes
Activated lymphocytes

Similar to cytotoxic T cell
But T cell needs activation by MHC molecules while NKC are always large and activated

Natural killer cells don't have a problem with MHC1 molecules, but once it sees a cell without those MHCs it will kill it directly

The small lymphocyte has scanty cytoplasm (contain few organelles but large number of ribosomes)
Account for basophilic cytoplasm

Immunohistochemistry
Direct method



Immunity

Innate immunity:

We are born with innate immunity. It is non-specific, which means that the innate cells are not able to distinguish one type of pathogen from another.

Cells of innate immunity:

- **Neutrophils**
- **Basophils**
- **Eosinophils**
- **Mast cells**
- **Monocytes**
  - macrophages
  - dentritic cells
- **Natural killer cells**

Neutrophils and monocytes are highly phagocytic and engulf microorganisms and cell debris in a **NON-SPECIFIC manner**

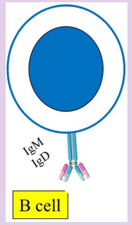
Adaptive (acquired) immunity:

the body's ability to recognize and respond to specific foreign substances (antigens: microbes, parts of microbes, or non-microbial substances, such as pollen)

- T lymphocytes
- B lymphocytes

specific cell surface proteins

Receptors of B cells are immunoglobulins that bind antigens directly



those on T cells react only with antigen on MHC molecules and this requires the additional cell surface proteins CD4 or CD8

MHC=HLA

T lymphocytes are said to be MHC restricted

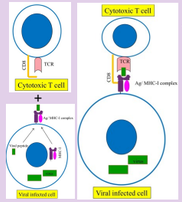
"CD" stands for "cluster of differentiation": are surface molecules that help differentiate one cell type from another

Cell mediated immunity

Cytotoxic CD8 T cells:

Antigen in virus infected, transplanted or neoplastic cells bind to MHC-I molecules

Ag-MHCI complex

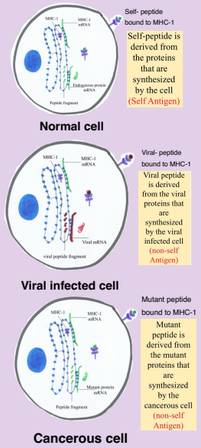


When the Ag- MHC-I complex binds to receptors on cytotoxic CD8 T cells

CD8 T cells Proliferate &Activate

Release Perforins and granzymes (proteases)

Perforins form pores in the cell membrane through which granzymes can enter, inducing apoptosis



The antigens presented by class I peptides are derived from intracellular proteins (cytosolic)

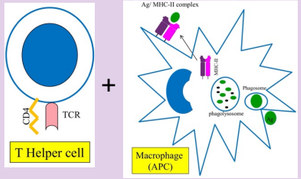
Antigen presenting cells

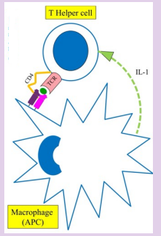
- macrophage
- dendritic cell
- B lymphocyte

Helper CD4 T cells:

When Ag is phagocytosed by antigen presenting cells (APCs) e.g macrophages, dentritic cell and B lymphocytes , It binds to MHC-II molecules

Ag-MHCII complex



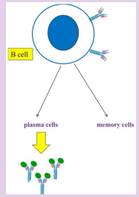


When the Ag- MHCII complex binds to receptors on Helper CD4 T cells

CD4 T cells Proliferate, Activate

Secrete Lymphokines (cytokines) to Stimulate T and B cells

The antigens presented by class II peptides are derived from extracellular proteins



When a B lymphocyte is stimulated by T helper cells

B lymphocytes Proliferate and Activate

Activated B lymphocytes:

1- differentiate into plasma cells (secrete antibodies)

2- differentiate into memory cells

(Rapid response on the 2nd exposure to the same Ag)

Life long immunity (vaccination)

Major histocompatibility complex MHC

Glycoprotein on cell membrane

MHC-I

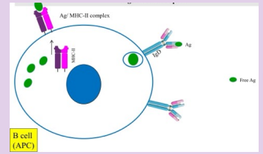
On surface of **all nucleated cells**

Coupled to peptide formed **within the cell**

MHC –II

On surface of **APCs**

Coupled to peptide product of **proteins the cells had ingested** (peptide product of Ag digestion)

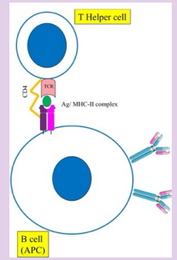


B cells:

When the specific Ag binds to receptors on B cells

receptor-mediated endocytosis and fragments of the Ag bind to MHC-II molecules

Ag-MHCII complex



T Helper cells bind to Ag-MHCII complex on the B cells

Stimulates proliferation and differentiation (activation) of B cells

B cells Proliferate ,Activate

Activated B lymphocytes:

1- differentiate into plasma cells (secrete antibodies)

2- differentiate into memory cells

(Rapid response on the 2nd exposure to the same Ag)

Life long immunity (vaccination)

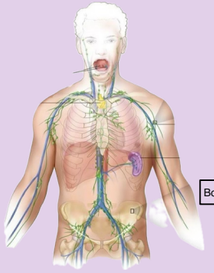
T lymphocytes are specialized to recognize both classes of MHC proteins and the antigens they present

If the MHCs on cells of a tissue graft are not similar to those that T lymphocytes encountered during their development, the grafted cells will induce a strong immune reaction by T cells of the recipient.

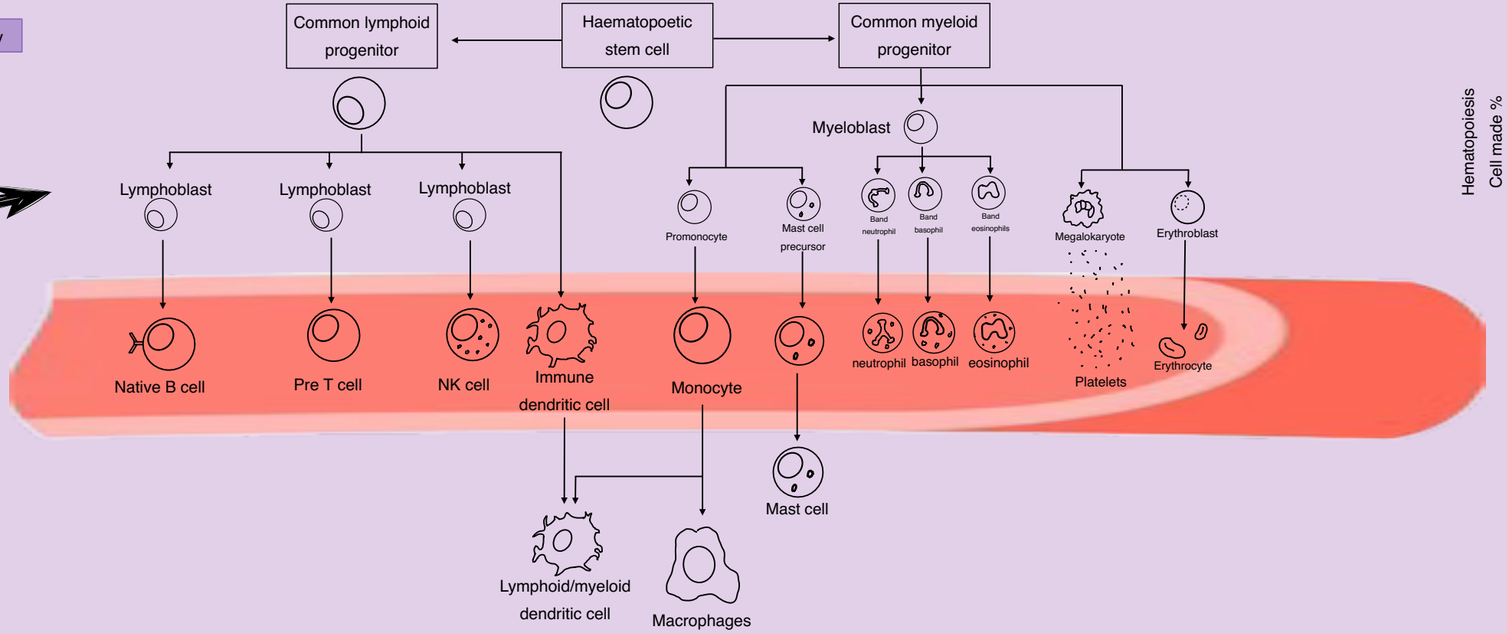
To these lymphocytes, the unfamiliar MHC epitopes on the graft's cells are recognized as markers of "non-self" cells that they must eliminate.

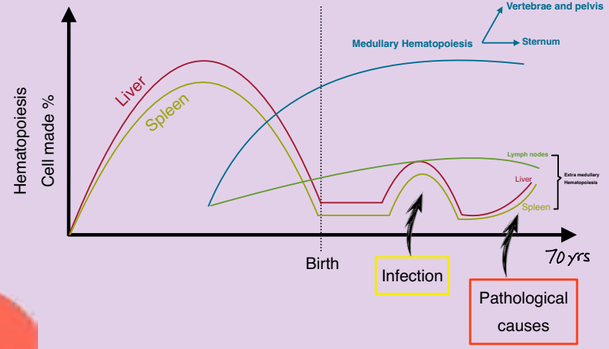
LECTURE 4+5

Additional Summary



Bone marrow



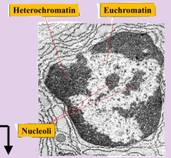


General look before starting …

Nucleus

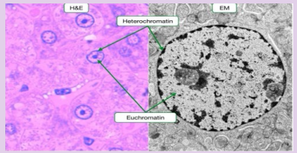
Chromatin

Formed of DNA



Euchromatin
extended active chromatin (pale).

Heterochromatin
condensed inactive chromatin (dark)



Nucleolus

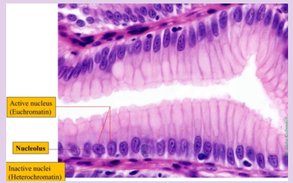
- It is a spherical dark basophilic mass not surrounded by a membrane.
- Usually one.
- Function: formation and assembly of ribosomal RNA (rRNA), which is responsible for protein synthesis in the cytoplasm

Stain of cells

The nucleus stains **blue (basophilic)** using H&E

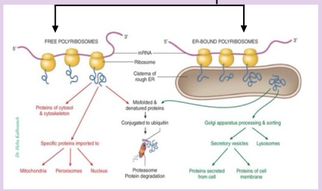
Lightly basophilic: active

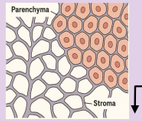
Deeply basophilic and small: inactive



The cytoplasm stains **pink/red (acidophilic)** using H&E

The only organelle (when prominent) produces basophilia in the cytoplasm is **the ribosome**





Parenchyma vs Stroma

The **parenchyma** of an organ consists of that tissue which conducts the specific function of the organ and which usually comprises the bulk of the organ

Ex

The parenchyma of the heart is muscle tissue (cardiac muscle cells)

Stroma is everything else -- connective tissue, blood vessels, nerves, ducts. It is made up of all the parts without specific functions of the organ

Ex

The nerves, intrinsic blood vessels, and connective tissue of the heart comprise the stroma.

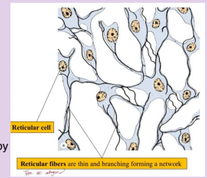
Reticular connective tissue

Consists of

- reticular cells (modified fibroblasts)
- the network of reticular fibers formed by them

- Forms the structural framework (stroma) in which the cells of the organ are suspended
- found In the liver, bone marrow, lymph nodes and spleen

(**Reticulo-Endothelial organs**)



Types of capillaries

Continuous capillaries

- ✓ Are most common
- ✓ Endothelium forms solid lining
- ✓ Adjacent cells are held together with tight junctions
- ✓ Found in most organs

Fenestrated capillaries

- ✓ Endothelium contains pores (fenestrations)
- ✓ Found wherever active capillary absorption or filtrate formation occurs
- ✓ Found in endocrine glands, small intestine, and kidney

Sinusoidal capillaries

- ✓ Exhibit wide diameters with wide gaps between endothelial cells
- ✓ Basement membrane incomplete or absent
- ✓ Allow large molecules (proteins and blood cells) to pass between the blood and surrounding tissues
- ✓Found in liver, spleen, and bone marrow

Blood Cell Formation (Hematopoiesis)

Mature blood cells have a relatively short life span and must be continuously replaced with new cells from precursors developing during hemopoiesis/ hematopoiesis (Gr. haima, blood + poiesis, a making).

Medullary hematopoiesis
all blood cells originate in bone marrow

Extramedullary hematopoiesis
hematopoiesis that occurs in organs other than bone marrow.

Occurs during:
- fetal development
- normal immune responses
- pathological circumstances

Location of Hematopoiesis

Early embryo	Second trimester	Third trimester	After birth
Yolk sac mesoderm	Developing liver and spleen	Bone marrow	Bone marrow

Bone marrow

The yellow marrow — Under certain conditions (severe bleeding or hypoxia), yellow marrow reverts to red

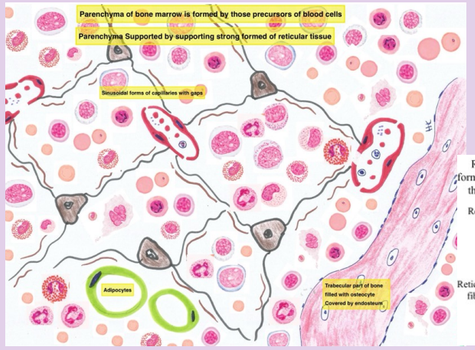
The red bone marrow
is a highly cellular structure that is located in the medullary cavities of the bone

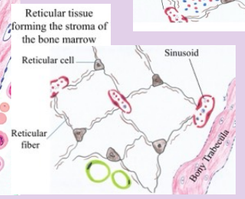
consists of:
- Hemopoietic stem cells (the origin of different blood cells)
- numerous macrophages
- sinusoidal capillaries
- reticular tissue

As the individual ages and becomes an adult

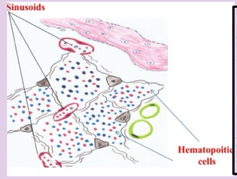
the axial skeleton
the red marrow is found primarily in the axial skeleton (flat bones of the skull, sternum and ribs, vertebrae, and pelvic bones)

The remaining bones
primarily the long bones in the limbs of the body, gradually accumulate fat, and their marrow becomes yellow. Consequently, they lose the hemopoietic functions.

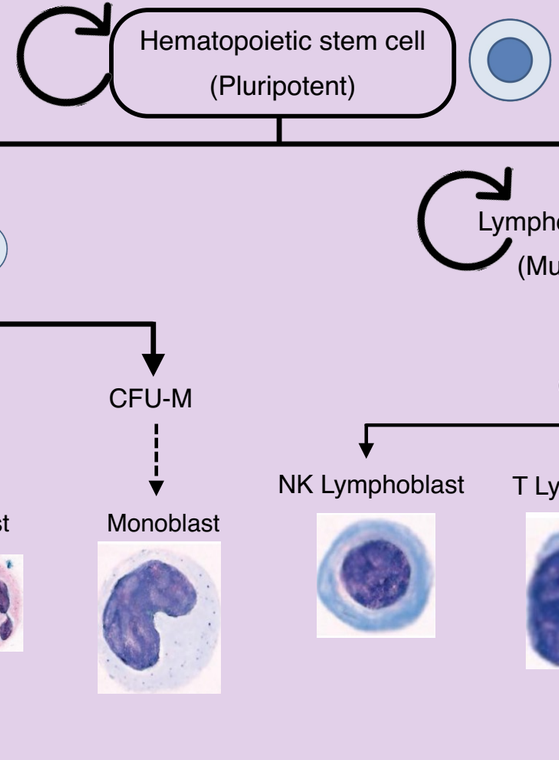




Between the hematopoitetic cells run the **sinusoids**, which have discontinuous endothelium, through which newly differentiated blood cells and platelets enter the circulation

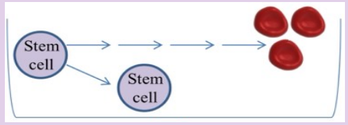


Red marrow is also a site where older, defective erythrocytes undergo phagocytosis by macrophages, which then reprocess heme-bound iron for delivery to the differentiating erythrocytes.



Capability of renewal

Stem cells are capable of asymmetric division and self-renewal.



Every time the stem cell multiplies, it will give two cells, one differentiate into mature RBCs and the other cell add to the original population

Precursor cells produce only mature blood cells

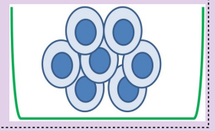
All Erythroblasts multiply and differentiate into mature RBCs (erythrocytes) and no erythroblasts are left in the end

Morphologically

Stem cells and progenitor cells cannot be morphologically distinguished and resemble large lymphocytes

Precursor cells gradually assume the morphologic characteristics of the mature, functional cell types they will become morphologically distinguished and resemble large lymphocytes

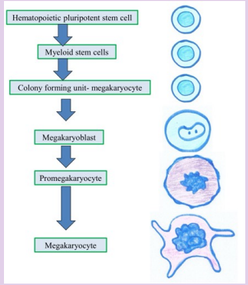
The progenitor cells for blood cells are often called colony-forming units (CFUs), because they give rise to colonies of only one cell type when cultured in vitro or injected into a spleen.



Blood Cell Formation (Hematopoiesis)

Erythropoiesis
the process which produces erythrocytes

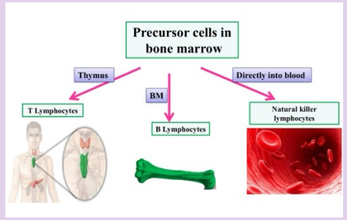
Granulopoiesis
the process which produces granulocytes



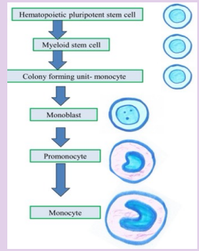
Thrombopoiesis
the process which produces thrombocytes

Lymphopoiesis
the process which produces lymphocytes

Lymphopoiesis occurs in the marrow and in the lymphoid organs to which precursor cells migrate from marrow.



Monocytopoiesis
the process which produces monocytes



Distribution of RBCs and WBCs in

peripheral blood

RBCs —> in 1 ul of peripheral blood —> 5 million/ul

WBCs —> in 1 ul of peripheral blood —> 4500-11000/ul

bone marrow

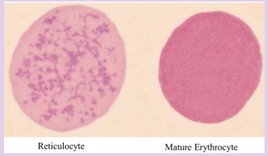
Myeloid: Erythroid 3:1

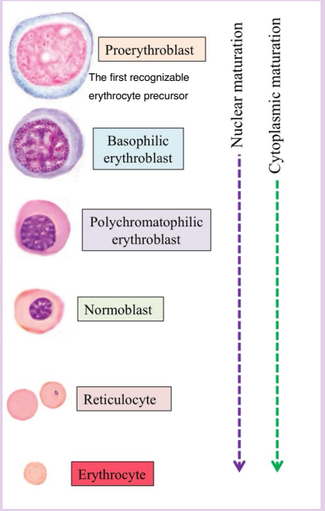
Why?! As it should be the opposite? Due to the life span, WBCs die within 2-5 days after eliminating infection, so there should be compensation of this loss, so bone marrow produce them in larger numbers

Erythropoiesis (red cell formation)

- Takes about 1 week
- Rate is controled by the hormone erythropoietin (secreted by the kidney cells) and the availability of iron, folic acid, vitamen B12, protein precursors

- Normally, only about 1% of all red blood cells in the bloodstream are reticulocytes
- They circulate for about 1-2 days before developing into mature red blood cells
- An increase in reticulocytes ---- blood loss (hemorrhage)

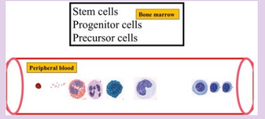




Stage	Cell size مش مطلوب	Nucleus	Cytoplasm	Notes
Proerythroblast	Largest cell (17um)	Large pale nucleus with prominent nucleolus	Pale basophilic cytoplasm	
Basophilic erythroblast	The cell becomes smaller (15um)	smaller and darker	Deeply basophilic cytoplasm (high in ribosomes)	
Polychromatophilic erythroblast	The cell becomes smaller (13um)	smaller and darker	Cytoplasm becomes violet	Takes basic (ribosomes) and acidic stains (Hb)
Normoblast **Orthochromatic erythroblast**	The cell becomes smaller (11um)	smaller, darker and eccentric to be expelled outside	Cytoplasm is acidophilic (Hb)	**The nucleus is extruded at this stage**
Reticulocyte	Immature erythrocyte but slightly larger (9um)	No nucleus	Cytoplasm is acidophilic (Hb) but contains remnants of ribosomes forming reticulum	Can be stained by supravital stains (brilliant cresyl blue)
Erythrocyte				

Stages of differentiation are characterized by:
1- Decreasing cell size
2- Progressive loss of organelles

Presence of free ribosomes at early stages
⇩
Accounts for the marked cytoplasmic basophilia **(blue)**
3- Progressive increase in hemoglobin content
⇩
Accounts for increasing eosinophilia **(pink/red)**



White blood cell abnormalities

In peripheral blood

Increased numbers of white cells appear in the peripheral blood in a variety of disorders and provide a useful clue to the underlying disease.

- considerable and sustained increase of **circulating neutrophils** in bacterial infection
- An increase of **circulating eosinophils** in parasitic infection and some allergies

In bone marrow

Suppression of these cells on bone marrow
⇩
Hypoplastic bone marrow
Aplastic anemia
(pancytopenia)

Malignant proliferation of these cells inside bone marrow
Leukaemia
⇩
Vast number of white cells and their precursors (many of which spell over into the blood)
Leukemia is classified according to the cell line involved (granulocytic, monocytic, lymphocytic)

Clinical applications

Bone marrow Apirate or biobsy
Needed to diagnose disorders like aplastic anemia or leukemia

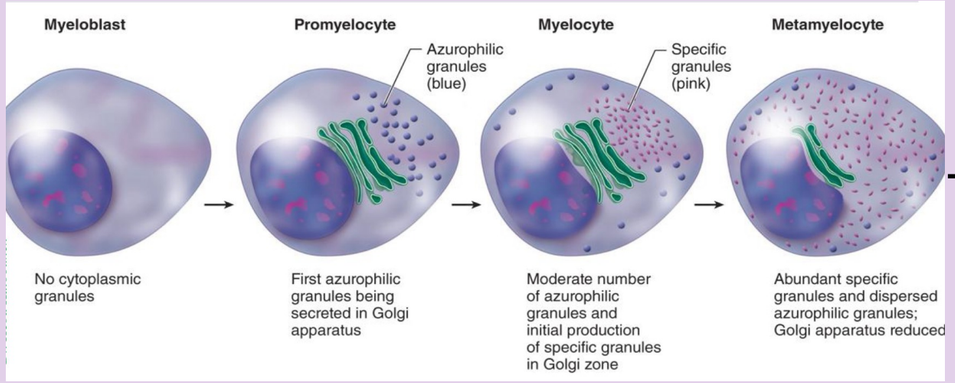
Bone marrow transplantation
In bone marrow diseases like leukemia, hematopoietic stem cells taken from a donor are infused into the same or another person

Blood Cell Formation (Hematopoiesis)

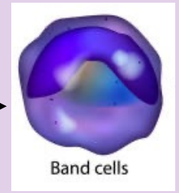
- Erythropoiesis
- Granulopoiesis
- Thrombopoiesis
- Lymphopoiesis
- Monocytopoiesis

Granulopoiesis (Neutrophils, Eosinophils and Basophils formation)

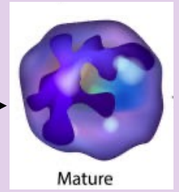
Neutrophilic band cells (important CLINICALLY)
Their percentage does not exceed 5% in peripheral blood
The appearance of large numbers of immature neutrophils (band cells) in the blood, sometimes called a “shift to the left,” is clinically significant, usually indicating a **bacterial infection**.
This means that the bone marrow has been signaled to release more neutrophils and increase production of neutrophils



Band cell (stab cell)

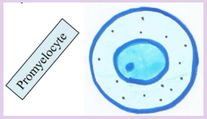


Mature cell

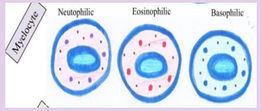


The first recognizable precursor

- The largest (20um)
- Azurophilic granules start to appear



3 types
- The cell becomes smaller
- The nucleus becomes smaller and darker
- Specific granules start to appear

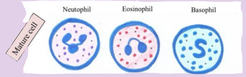


3 types
- **Cannot divide**
- Undergoes metamorphosis
- Nucleus becomes indented (kidney shaped)
- Specific granules increase in number

3 types
- Nucleus becomes curved rod in shape

Band cell is **almost** a mature neutrophil, just doesn’t have a segmented nucleus yet

Mature cells



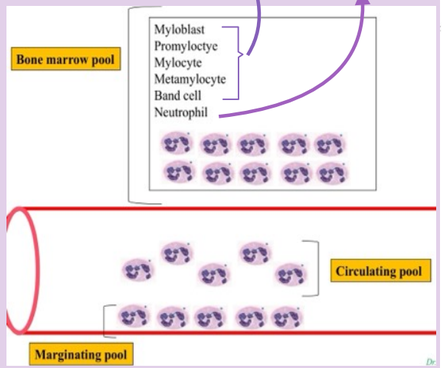
Cells can divide

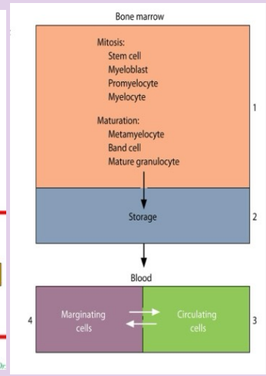
Changes in the number of neutrophils in the blood must be evaluated by taking all their compartments into consideration.

Pools of neutrophils

four functionally and anatomically defined compartments for Developing and maturation of neutrophils

- **The granulopoietic compartment in active marrow**
- **Storage as mature cells in marrow until release**
- **The circulating population**
- **A population undergoing margination**
- **Inflamed connective tissues**





Margination is a process in which neutrophils adhere loosely and accumulate transiently along the endothelial surface in venules and small veins.
Note: Margination of neutrophils in some organs can persist for several hours and is not always followed by the cells’ emigration from the microvasculature.

form a fifth terminal compartment for neutrophils, where the cells reside for a few days and then die by apoptosis, regardless of whether they have performed their major function of bacterial phagocytosis.

Neutrophilia

an increase in the number of **circulating neutrophils**

Could be due to

- **increase in granulopoiesis**
- **Intense muscular activity**
- **the administration of epinephrine**
- **glucocorticoids (adrenal hormones) such as cortisone**

can cause neutrophils in the marginating compartment to move into the circulating compartment, producing neutrophilia even though granulopoiesis has not increased

increase the mitotic activity of neutrophil precursors and this also increases the blood count of neutrophils.

LECTURE 5

Lymphatic system

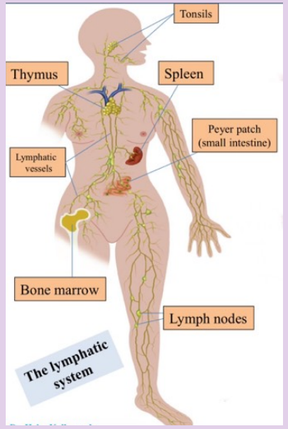
Components

lymphatic fluid
Lymph is a colorless fluid that floats in the lymphatic vessels. It is similar in composition to blood plasma

lymphatic vessels
thin vessels that accompany arteries and veins throughout the body and transport lymph.

lymphatic tissue
specialized form of reticular connective tissue that is composed of masses of lymphocytes.
- occur alone as lymph nodules (follicles)
- organized into various lymphatic organs.

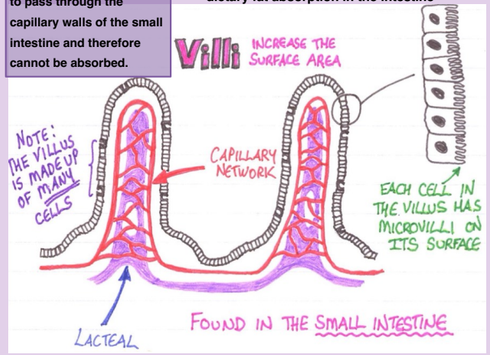
lymphatic organs
include the lymph nodes, spleen, thymus, and red bone marrow



functions
- Drain excess interstitial fluid from the tissues and return to blood stream
- Initiate an immune response against disease by producing and transporting lymphocytes
- Transport dietary lipids absorbed by the gastrointestinal tract into the blood

Some lipids are too large to pass through the capillary walls of the small intestine and therefore cannot be absorbed.

lymphatic system is used, for example, for dietary fat absorption in the intestine



The lymphatic capillaries within the small intestine, known as ***lacteals***, can absorb these large lipid molecules and transport them into the venous circulation via the thoracic duct. Lymph containing these lipids becomes a creamy white color and is referred to as **chyle**.

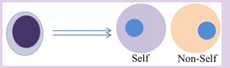
Lymphatic Organs

Lymphocytes can be found throughout the body, however, they **aggregate in places** where they are most likely to come into contact with pathogens.

Primary lymphatic organs
Bone marrow.

Thymus gland.

Are sites of Lymphocyte production, maturation, ***selection***

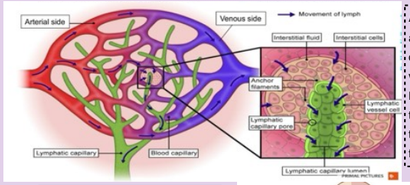


Secondary lymphatic organs
- Diffuse lymphatic tissue (lymphatic nodules).
- Spleen.
- Lymph nodes.

Are sites to encounter pathogens and become activated

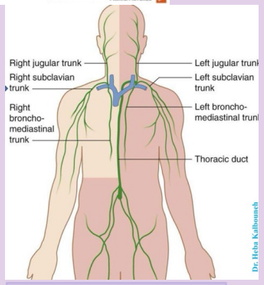
The tissues of the body are supplied by blood capillaries that bring oxygen-rich blood and remove carbon dioxide-rich blood.
Fluid similar to blood plasma, called interstitial fluid, leaches from these vessels into the surrounding tissue.

Lymphatic capillaries are made of overlapping endothelial cells with **large gaps**.
The overlapping flaps function as **a one-way valve**.



Around 20 liters of fluid leaves the arterial capillaries every day, but only 17 liters of fluid returns to the venous capillaries.
lymphatic vessels function to drain this excess fluid (3L) from the tissues as lymph and return this fluid to the blood.

Lymphatic vessels begin as "porous" blind-ended lymphatic capillaries in tissues of the body and converge to form a number of larger vessels, which ultimately connect with large veins in the root of the neck.



Lymph returns back to the big veins (venous angle: the junction between subclavian and internal jugular veins) through the Thoracic duct and Right lymphatic duct.

Lymph flow is enabled by the same forces that facilitate blood flow in the veins. It goes from lymphatic capillaries to larger and larger lymphatic vessels and eventually drains into the bloodstream. On the way, it passes through a number of lymph nodes, which serve as filters, cleansing the fluid before it reaches the bloodstream.

When fluid accumulates in the tissue
↓
interstitial pressure increases pushing the flaps inward
↓
opening the gaps between cells, allowing fluid to flow in
↓
pressure inside the capillary increases
↓
the endothelial cells are pressed outward, closing the gaps, thus preventing backflow.

Unlike blood capillaries, the gaps in lymphatic capillaries are so large that they allow bacteria and immune cells (ex. Macrophages/ dendritic cells) to enter. This makes the lymphatic system a useful way for large particles to reach the bloodstream.

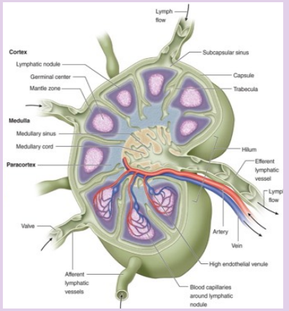
Lymph nodes

✓ Are kidney-shaped small encapsulated bodies located along the course of lymphatic vessels (Approximately 600 lymph nodes)
✓ All lymph is filtered by at least one lymph node before it returns to the blood
✓ Lymph nodes congregate around blood vessels in clusters and are usually named according to the vessel or location that they are associated with.

Consists of
- Reticular tissue forms the stroma of the lymph node
- Immunocompetent B cells and T cells are suspended throughout the lymph node

Lymph nodes are production sites of antibodies and activated lymphocytes

Functions
- Nodes filter the lymph, removing foreign material and microorganisms.
- Antibody- mediated and cell-mediated immune responses occur in the lymph nodes



Lymph node enlargement
- in cases of lymphoma (painless lymphadenopathy)
- infection (painful)

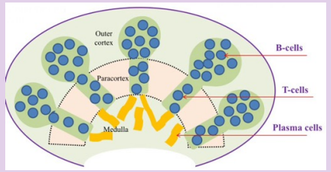
Lymph nodes

covered by → a ***capsule*** of dense connective tissue, and have capsular extensions called the trabeculae, which provide support for blood vessels entering into the nodes.
When lymph nodes become enlarged, the capsule is stretched and becomes painful

consists of

outer cortex

- highly cellular part of the lymph node
- Contains lymphatic follicles
- Receives lymph from **afferent vessels**



Other cells in the lymph node:
Macrophages
Dendritic cells
Follicular dendritic cells
Reticular cells

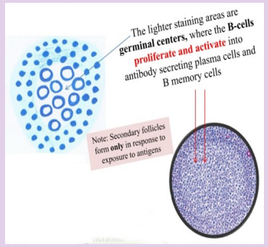
- **inner paracortex**
  contains mostly T-cells
- **outer cortex**
  has lymphatic follicles that mostly contain B-cells

Primary follicles
lymphoid follicles without a germinal center. (virgin B cells)

As B cells in lymphatic follicle are stimulated, they differentiate into plasma cells. Plasma cells move to medulla (medullary cords)

Secondary follicles
lymphoid follicles with a germinal center.
Sites for B memory cell and plasma cell generation

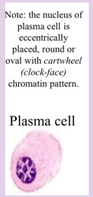
When activated by antigens (and T helper cells),
⬇
B cells migrate to the center of the follicle, forming a germinal center. Germinal centers are the central regions of secondary follicles where activated B cells are proliferating (dividing by mitosis) and differentiating into plasma cells and memory B cells. When stimulated by antigens, lymph nodes enlarge due to the formation of germinal centers and B cell proliferation



inner medulla

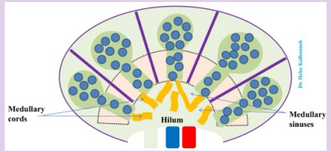
- No follicles
- Forms sinuses that lead to **efferent vessels** at the hilum

contain mostly **plasma cells**



composed of

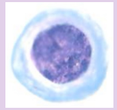
- **medullary cords**
  Separated by
- **medullary sinuses**
  converge at
- **the hilum**
  slight indentation on one side of the node. Here, an artery, vein, and an efferent lymphatic vessel enter and leave the node.



Lymphocytes

Small
(6-9 micro m)
Inactive lymphocyte
Darkly stained cell

Large
(9-18 micro m)
Active lymphocyte
Lightly stained cell



Other cells in the lymph node

- **Macrophages**
- **Dendritic cells**
- **Follicular dendritic cells**
- **Reticular cells**

Monocytes derived cells

	Macrophage	Dendritic cell	Follicular dendritic cell
Phagocytosis	Most phagocytic	Moderately phagocytic	X
Antigen presenting (via MHC-II)	Moderate Ag-presenter	Very powerful Ag-presenter	X
Location in lymph node	Cortex and medulla	Cortex and medulla	Outer cortex

Are antigen HOLDING cells
Holds the Ag for long time

Macrophages and Dendritic cells capture antigen within tissues and transport antigen to secondary lymphoid tissue

Lymphocytes can enter lymphoid tissues in two ways

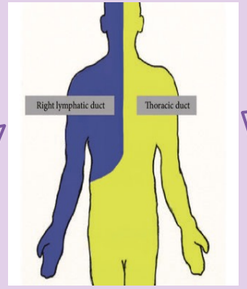
consists of

Direct entry into lymph nodes via afferent lymphatics

Entry from blood capillaries across specialized endothelial cells present in the postcapillary venules (High Endothelial Venules= HEV) within the paracortex of the lymph node

Lymphatic trunks and ducts

All lymphatic vessels coalesce to form larger trunks which eventually converge to form the right lymphatic duct and the thoracic duct



Right lymphatic duct
- Is formed by right jugular + + right subclavian trunks
- Drains lymph from the upper right quadrant of the body (the right side of the head and neck, the right side of the thorax and the right upper limb)
- Empties into the junction where right internal jugular vein joins the right subclavian vein (**Rt venous angle**)

Thoracic duct (Left lymphatic duct)
- Is larger and drains lymph from the rest of the body
- Originates in the abdomen as ***cisterna chyli***
- Passes through the diaphragm at the aortic aperture
- Empties into the junction where left internal jugular vein joins the left subclavian vein (**Lt venous angle**)

Cisterna chyli is a dilated sac at the lower end of the thoracic duct (anterior to the bodies of L1 and L2) formed by confluence of the right and left lumbar trunks and the intestinal trunk

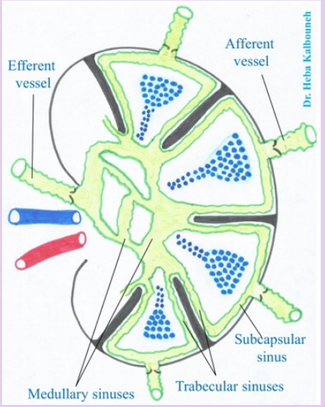
Sinuses are irregular spaces through which the lymph percolates
All the lymphatic sinuses are lined by a discontinuous layer of simple squamous endothelium

Lymph, containing micro-organisms, soluble antigens and antigen presenting cells

Efferent vessels

The lymph is removed from the medullary sinus via one or two efferent lymphatic vessels that leave the lymph node at the hilum. Valves in the vessels prevent lymph from flowing in the wrong direction.

Efferent lymph contains lots of activated T-lymphocytes, activated B-lymphocytes, plasma cells and antibodies.



Afferent vessels

Many afferent lymphatic vessels enter the lymph node at different points over its convex surface, each containing valves to prevent backflow of lymph.

Subcapsular sinuses

Each afferent vessel empties into the subcapsular sinus

Trabecular sinuses

a continuation of the subcapsular sinuses that follow the trabeculae and drain into the medullary sinuses.

Medullary sinuses

Found separating the cords. The medullary sinuses converge at the hilum into the efferent lymphatic vessel.

Lymph slows down when it passes in lymph nodes.

LECTURE 6

Spleen

- ✓ an oval-shaped intraperitoneal organ
- ✓ Has a notched anterior border.
- ✓ lies high on the upper left portion of the abdomen, just beneath the diaphragm, behind the stomach and above the left kidney
- ✓ the **largest of the lymphoid organs**

Functions

- **Filtration of blood** (defense against blood-borne antigens)
- The main site of **old RBCs destruction**.
- **Production** site **of antibodies and activated lymphocytes** (which are delivered directly into the blood)

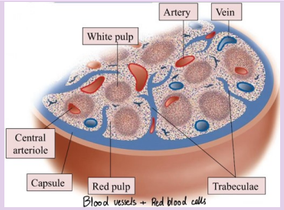
The spleen is covered by a ***capsule*** of dense connective tissue

have

capsular extensions called the ***trabeculae***

have

Large trabeculae **originate at the hilum**, on the medial surface of the spleen, and carry branches of the splenic artery, vein, lymphatics, and nerves into the spleen

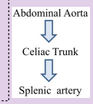


Spleen

The splenic artery

the largest branch of the celiac artery. It has a tortuous course as it runs along the upper border of the pancreas. The splenic artery then divides into about six branches, which enter the spleen at the hilum

supplies the spleen as well as large parts of the stomach and pancreas



The splenic vein

leaves the hilum and runs behind the tail and the body of the pancreas. Behind the neck of the pancreas, the splenic vein joins the superior mesenteric vein to form the portal vein

In cases of portal hypertension, spleen often enlarges from venous congestion.

Blood flow through the spleen

Each central arteriole eventually leaves the white pulp and enters the red pulp, losing its sheath of lymphocytes and branching

→ **penicillar arterioles** several short straight penicillar arterioles that continue as terminal capillaries.

→ **Terminal capillaries** (Sheathed capillaries) Some of these terminal capillaries are sheathed with APCs for additional immune surveillance of blood

→ **Splenic sinusoids**

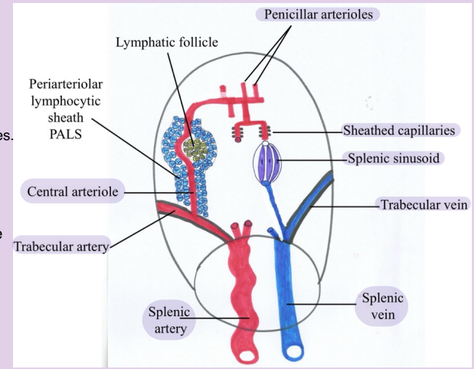
→ **Trabecular veins**

→ **Splenic vein**

Central arterioles Are branches of trabecular arteries entering the white pulp. They are surrounded by a sheath of lymphocytes.

Trabecular arteries Follow the course of trabeculae

Splenic artery Divides into trabecular arteries as it enters the hilum

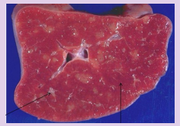


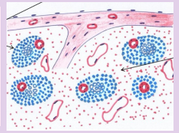
Spleen

Stroma

Reticular tissue (reticular fibers and reticular cells)

parenchyma





White pulp

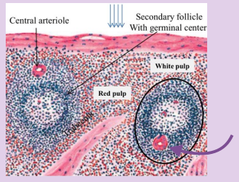
lymphoid tissue

which appears white on gross examination (**collection of both B and T lymphocytes**)

Constituting 25% of the spleen, the white pulp is responsible for the immunological (lymphatic) function of the spleen.

Function: The lymphocytes and APCs monitor the blood for foreign antigens and respond in a similar way to those in the lymph nodes.

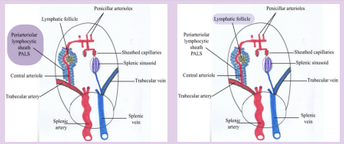
contains



When the lymphatic sheath expands to incorporate the follicles, the central arteriole is displaced to one side and acquires an eccentric position in the follicle but is still called the central arteriole (Follicular arteriole).

Periarteriolar lymphatic sheaths (PALS)

tightly packed **T cells** arranged in cylindrical sheaths around central arterioles



Lymphoid follicles

spherical aggregations of **B cells** scattered throughout the PALS

These follicles have the same structural organization as those found in lymph nodes

- **Primary (unstimulated) follicles** contain resting (inactive) B cells
- **Secondary (stimulated) follicles** contain activated B cells in a central region (germinal center)

Splenic nodules (Malpighian corpuscles)

Production of antibodies and activated lymphocytes (which are delivered directly into the blood)

Marginal zone sinuses

Red pulp

which appears red on gross examination (**blood filled**)

Constituting 75% of the spleen, the red pulp is responsible for the hematological (circulatory) function of the spleen.

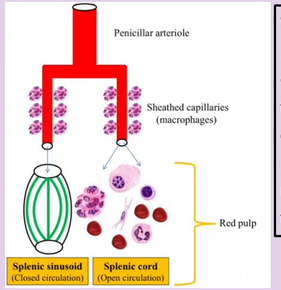
contains

Splenic cords (Billroth's cords): consist of all cells between the sinusoids in the red pulp (reticular cells, macrophages, plasma cells, lymphocytes, RBCs, platelets, other leukocytes)

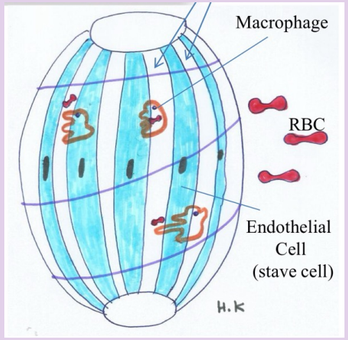
Splenic sinusoids: blood- filled spaces located throughout the red pulp. They have large, dilated, irregular lumens and large pores (spaces between the endothelial cells)

Function: Destruction of worn-out RBCs and platelets

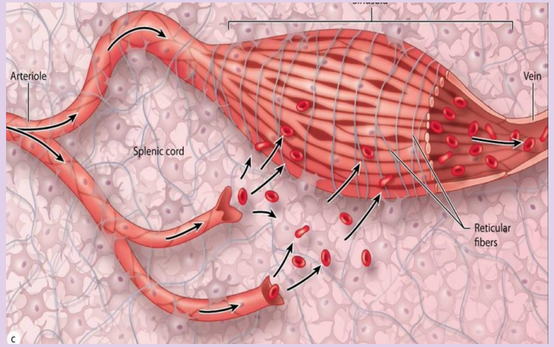
Red pulp



When B cells in the primary follicles are exposed to Antigen, they proliferate and differentiate to plasma cells and move toward the red pulp.



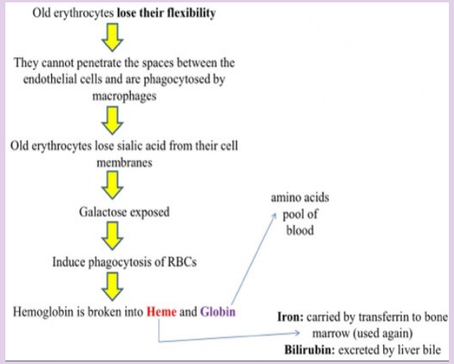
wide gaps between endothelial cells which allow for movement of entire cells **from cords => to sinuses**



1. The endothelial cells (stave cells) are elongated, fusiform cells that lie parallel to the long axis of the vessel
2. The cells lie side by side around the vessel but not joined by any type of intercellular junctions
3. The endothelial cells are supported by highly discontinuous basal lamina (forms bars and encircles the sinusoid)

all the formed elements of blood must reenter the vasculature by passing through narrow slits between the stave cells into the sinusoids. These small openings present no obstacle to platelets, to the motile leukocytes, or to thin flexible erythrocytes

stiff or swollen RBCs at their normal life span of 120 days are blocked from passing between the stave cells and undergo selective removal by macrophages
Bcz Deformed or less pliable RBCs ***cannot squeeze effectively*** from the cord into the sinus and upon their mechanical fragmentation are removed by resident macrophages (lie just next to the sinusoids)

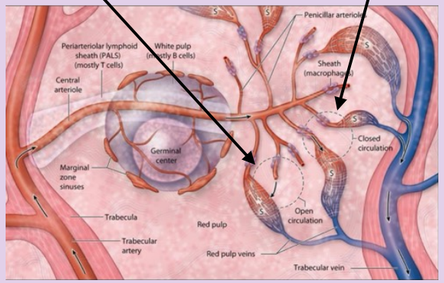


After surgical removal of the spleen (splenectomy), **the number of abnormal erythrocytes in the circulation increases** although most such cells are then removed by macrophages in sinusoids of the bone marrow and liver.

Blood flow through the splenic red pulp can take either of two routes:

Open circulation:
the capillaries open into the spaces of the red pulp (splenic cords) and then the blood returns to the venous system through the wall of the splenic sinusoids

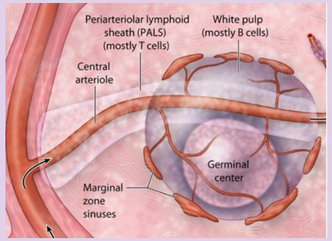
Closed circulation:
the capillaries open directly into the splenic sinusoids (blood is enclosed by endothelium)



Marginal zone sinuses

- Located between the white and the red pulp
- The spaces between these sinuses are wide (2-3um)

It is here the blood- borne antigens and particulate matter have their first free access to the parenchyma of the spleen



events occur at the marginal zone:

1- **APCs sample the material travelling in blood searching for antigens**
2- **Macrophages attack microorganisms present in the blood**
Lymphocytes come into contact with APCs, if they recognize their Ag-MHC complex, the lymphocytes initiate immune response within the white pulp
3- **The circulating B and T cells leave the blood stream to enter the preferred location within the white pulp**

- T cells: PALS
- B cells: lymphatic follicles

Functions of the spleen

circulatory functions

Blood cell production
During the fetal life, blood cells are produced in the spleen

Blood storage
A small quantity of blood is stored in the ***sinusoids*** of the red pulp

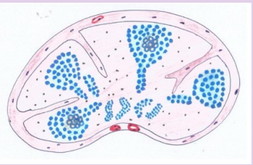
RBC destruction
Most worn-out or damaged red blood cells are destroyed in the spleen (some in the liver and bone marrow). They are phagocytized by macrophages

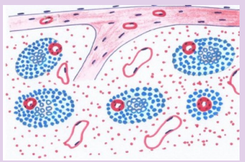
lymphatic functions

Defense mechanism
- Macrophages phagocytize microbes that have penetrated the blood.
- Antigens in the blood activate B and T cells residing in the spleen, triggering immune response
- Production of antibodies and activated lymphocytes (which are delivered directly into the blood)

Lymph node vs spleen

Lymph node	Spleen
Multiple, small	Single, large
Along the course of lymphatic vessels	Intra-abdominal
Filters lymph	Filters blood
Covered by fascia	Covered by peritoneum
Has afferent vessels	No afferent vessels
Cortex and medulla	White pulp and red pulp
Contains Lymphatic sinuses	Contains Blood sinuses





LECTURE 7

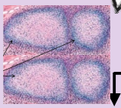
Diffuse lymphatic tissue (lymphatic nodules)

- Is formed by aggregations of lymphatic tissue
- Is found in various **mucosal sites of the body**

inner lining of the
- digestive tract
- respiratory tract
- genitourinary tract

a common site of invasion by pathogens because their lumens open to the external environment.

therefore be referred to as



Mucosa-Associated Lymphatic Tissue (MALT)

These aggregations are not encapsulated
=> Collectively the MALT is one of the largest lymphoid organs, containing up to 70% of all the body's immune cells.

found in
- Palatine tonsils
- Lingual tonsils
- Pharyngeal tonsils
- Gut-associated lymphoid tissue (GALT)
- Bronchus-associated lymphatic tissue (BALT)

populated by
- T cells
- B cells
- Plasma cells
- APCs

Each of which is well situated to encounter antigens passing through the mucosal epithelium

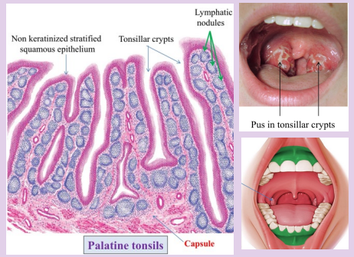
Tonsils

are large, irregular masses of lymphoid tissue
Function of tonsils: Protect the body from inhaled and ingested pathogens.

Palatine tonsils

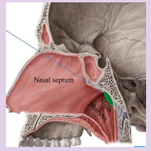
Are located at the lateral wall of oropharynx, between the glossopalatine and pharyngopalatine arches (two masses)
- Are covered by stratified squamous epithelium.
- The surface area of each is enlarged with 10-20 tonsillar crypts (deep invaginations)
- Many lymphoid nodules around the crypts
- Has an underlying capsule (partial capsule)

Acute inflammation of these tonsils causes ***tonsillitis***.

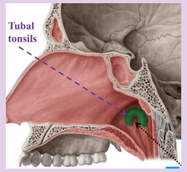


Pharyngeal tonsils

Are located in the posterior wall of the nasopharynx.
Pharyngeal tonsils are covered by ciliated pseudostratified
columnar epithelium (respiratory epithelium)
It is most prominent in children, but begins to atrophy from the age of seven.
Hypertrophied regions of pharyngeal tonsils resulting from chronic inflammation are called ***adenoids***.

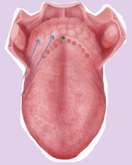


Tubal tonsils



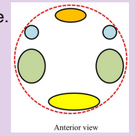
Lingual tonsils

Are located on the posterior 1/3 of the tongue



Waldeyer's tonsillar ring

ringed arrangement of lymphoid tissue
In the nasopharynx, oropharynx, and base of the tongue.



Adenoids

Excessive hypertrophy of the lymphoid tissue, usually associated with infection, causes the ***pharyngeal tonsils*** to become enlarged

Clinical picture

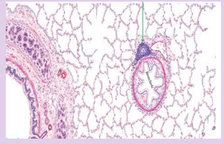
Marked hypertrophy blocks the posterior nasal openings and causes the patient to ***snore loudly*** at night and to breathe through the open mouth. The close relationship of the infected lymphoid tissue to the auditory tube may be the cause of ***recurrent otitis media***.

Treatment

Adenoidectomy is the treatment of choice for hypertrophied adenoids with infection

Bronchus-associated lymphoid tissue (GALT)

- Is located in the mucosa of the bronchioles.
- Function:
  Protects the body from inhaled pathogens.



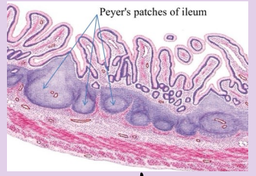
Gut-associated lymphoid tissue (GALT)

located in the mucosa of the intestine.
- By their ability to transport luminal antigens and bacteria, PPs can be considered as the ***immune sensors of the intestine***.

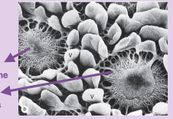
Function
Protects the body from ingested pathogens

Examples

Peyer's patches of ileum



With the surface epithelial cells removed, scanning electron microscopy (SEM) shows typical **basement membrane** over ***the villi (V)*** but reveals a highly porous covering over lymphoid nodules of the Peyer patch.



Peyer's patch and M cells

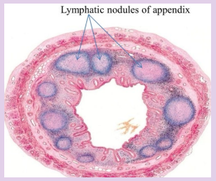
antigens in the gut lumen are bound by ***M cells*** and undergo transcytosis into their intraepithelial pockets

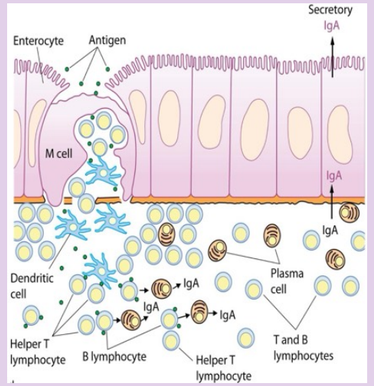
dendritic cells take up the antigen, process it, and present it to ***T helper cells***

B lymphocytes stimulated by the ***Th cells*** differentiate into ***plasma cells*** secreting IgA antibodies

The IgA is transported into the gut lumen where it binds its antigen on the surface of microorganisms, neutralizing potentially harmful invaders before they penetrate the mucosa.

Lymphatic nodules of appendix





LECTURE 8

Thymus

✓ The thymus is a bi-lobed gland located in the anterior mediastinum, posterior to the sternum and anterior to the trachea.

✓ It is **large in the newborn** and young child From puberty onwards, it gradually **becomes replaced by fat**

Fully formed and functional at birth, the thymus remains large and very active in T-cell production until puberty during which it normally undergoes involution, with **decreasing lymphoid tissue mass and cellularity** and reduced T cell output

=> may be involved with the decline of immune function in the elderly

Double function

As gland part of the endocrine system
Secreting thymic **hormones**

- Thymosin
- Thymopoietin
- Thymotaxin

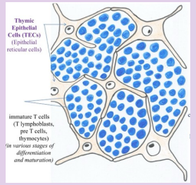
Those 2 hormones are necessary for differentiation and proliferation of T cells

a chemotactic peptide that attracts the migration of T lymphoblasts from bone marrow to thymus

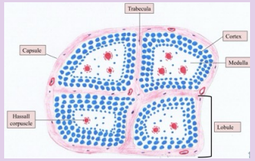
As a primary lymphatic organ
For production and maturation of T-lymphocytes

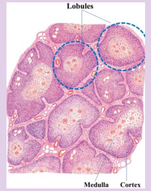
Double embryonic origin

Endoderm
Originates from the embryo's **third** pair of pharyngeal pouches
⬇
unique thymic epithelial cell



Mesoderm
Hematopoietic origin
Immature T lymphocytes (T lymphoblasts) circulating from the bone marrow to invade and proliferate in thymus during its development.





consists of

a connective tissue capsule that extends septa, dividing the organ into many incomplete ***lobules***.

Each lobule has

outer darkly basophilic cortex

The cortex contains

- Immature T cells (T lymphoblasts , thymocytes) (in various stages of differentiation and maturation)
- Macrophages
- Unique thymic epithelial cells (TECs)

The staining differences reflect the much greater density of lymphocytes in the cortex than the medulla

As T cells mature, they migrate to the medulla

more lightly stained medulla

The cortex contains

- Fewer and more **mature** lymphocytes.
- Macrophages
- Dendritic cells (APCs)
- Unique thymic epithelial cells (TECs)
- Large aggregates of TECs called **Hassall corpuscles**
  - are unique to the thymic medulla
  - Up to 100 µm in diameter
  - Are concentric aggregates of squamous cells with central keratinization (acidophilic)
  - Tend to grow larger with age

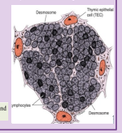
Develop from endoderm

Epithelial reticular cells

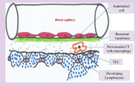
- Form a ***stroma*** to which macrophages and developing lymphocytes attach instead of reticular fibers
- Envelop groups of T cells that are multiplying and maturing (in cortex)
- Act as APCs, expressing MHC class II and MHC class I molecules (in cortex)
- Express many specialized proteins specific to cells of other organs, tissue specific antigens (in medulla)
- Secrete hormones that promote the differentiation of T cells (endocrine thymus)
- Line the capsule and septa and surround all blood vessels in the cortex

called **Nursing Cells**

They form sheets for cells deep to the capsule, around septa and blood vessels, to isolate developing T lymphocytes in the cortex from contact with antigens (present in the blood), while they are programmed



Form a **blood-thymus barrier** preventing antigens in the blood from making contact with the developing T cells (in cortex)



Within the thymus

immature T-cells
- develop
- differentiate
- multiply

gaining their antigen specificity and immune tolerance to the body's own tissues

selection

Only about 2% of all developing T lymphocytes pass both the positive and negative selection tests and survive to exit the thymus as **immunocompetent T cells.**

Fully mature T cells (immunocompetent T-cells) leave the medulla via venules and efferent lymphatic vessels

They migrate from the thymus to specific regions in the

- nodes (paracortex)
- the spleen
- diffuse lymphatic tissues

they reside and are responsible for ***cell-mediated immune responses***

Because of the constant mobility of lymphocytes and APCs, **the cellular locations and microscopic details of lymphoid organs differ from one day to the next**. However, the relative **percentages** of T and B lymphocytes in these compartments are **relatively steady**

Lymphocytes in the marrow and thymus of a newborn infant not yet exposed to antigens are immunocompetent but naïve (not yet exposed to antigens). After circulating to the various secondary lymphoid structures, lymphocytes are exposed to antigens on APCs and become activated, proliferating to produce a clone of lymphocytes all able to recognize that antigen

Advantages of lymphocyte recirculation

- Lymphocyte recirculation enables the limited number of naïve lymphocytes in an individual that are specific for a particular antigen to search for that antigen throughout the body
- It ensures that particular lymphocytes are delivered to particular tissue

Recirculation of naïve lymphocytes:
recirculate through secondary lymphoid organs

Recirculation of activated lymphocytes:
migrate to peripheral tissues at sites of infection

Ex.

If you have a viral infection in your oral cavity, this infection spreads to lymph nodes draining the oral cavity, and lymphocytes in these lymph nodes develop an immune response against this virus.
Then the activated lymphocytes leave the lymph node and circulate in the lymph and then blood..
They will go to every lymph node in your body and settle there
⬇
The whole body is prepared against this virus,, the whole body is tuned up for the next infection with the same virus

After maturation in primary lymphoid organs

B and T cells circulate to

the peripheral secondary lymphoid organs (the MALT, the lymph nodes, and the spleen)

Lymphocytes do not stay long in the lymphoid organs; they continuously recirculate through the body in connective tissues, blood, and lymph.

If no antigen is present
lymphocytes routinely enter and leave secondary lymphoid tissues

If antigen enters the secondary lymphoid tissue
Lymphocyte proliferation in response to antigen occurs within the lymphoid tissue.
After several days, antigen-activated lymphocytes begin leaving the lymphoid tissue.

Positive selection

Immature T cells arriving in the thymus do not yet express CD4, CD8, or a TCR.

These cells populate the cortex and begin to proliferate and express TCR proteins, CD4 and CD8

TECs in the cortex present the developing T cells with peptides on both MHC class I and class II molecules

This interaction determines **whether the newly made TCR proteins** of these cells **are functional**.
A cell's survival depends on whether its TCRs can recognize and bind MHC molecules properly (positive selection)
=> 80% of the developing T cells die in the cortex (undergo ***apoptosis***) and are removed by the macrophages

Depending on which class of MHC they interacted with

- become either helper T cell

- become either cytotoxic T cell

negative selection

The surviving cells (T cells with functional TCRs) ***enter medulla***
In the medulla, T cells encounter antigens presented on both TECs and dendritic cells

Self-antigens presented here are those from proteins specific for many tissues other than the thymus (tissue specific antigens)

Here the focus is on removing T cells whose TCRs bind self-antigens
A cell's survival depends on a cell not binding to MHC molecules with self-antigens (negative selection)

T cells that bind MHCs containing self antigens undergo apoptosis and are removed by the macrophages (if survive autoimmune response!!!)