CELLS OF IMMUNE SYSTEM

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INTRODUCTION

- The immune system is composed of different types of cells. These cells are generally found in the blood, lymph and local secretions.
- They are also scattered in various organs except the central nervous system.
- Few organs in the body are made up of a collection of these cells and such organs are called as **lymphoid organs.**
- The immune system is composed of two types of cells – lymphoid and non-lymphoid cells.

Introduction

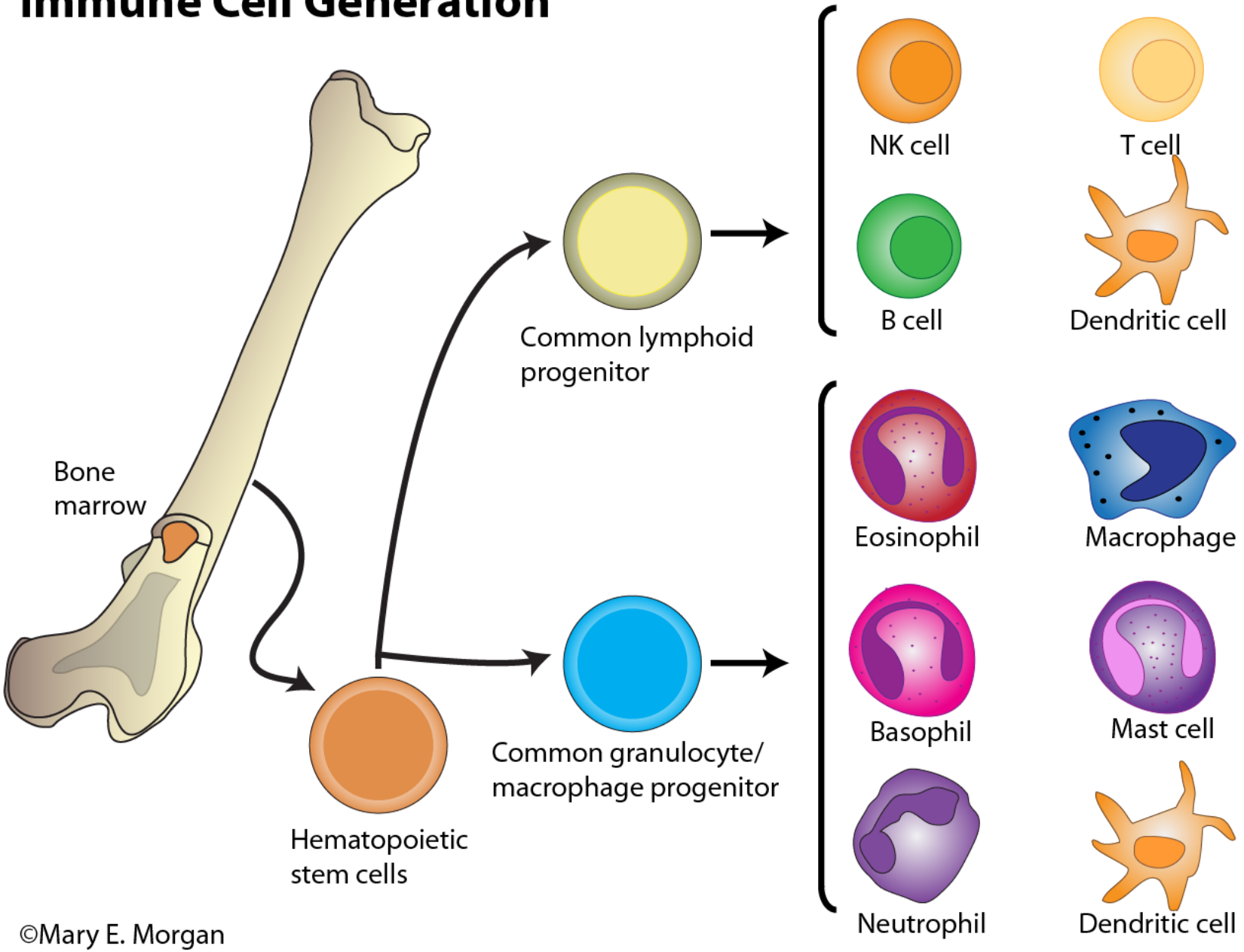
- The lymphoid cells are known as **lymphocytes** and there are three classes of lymphocytes – B-lymphocytes, T-lymphocytes and Natural Killer cells (NK cells).
- The non-lymphoid cells are also called as **accessory cells.** The important accessory cells of immune system are the mononuclear phagocytic cells (Macrophage) and polymorpho- nuclear cells (PMNL). The common PMNL are Neutrophils and Eosinophils.

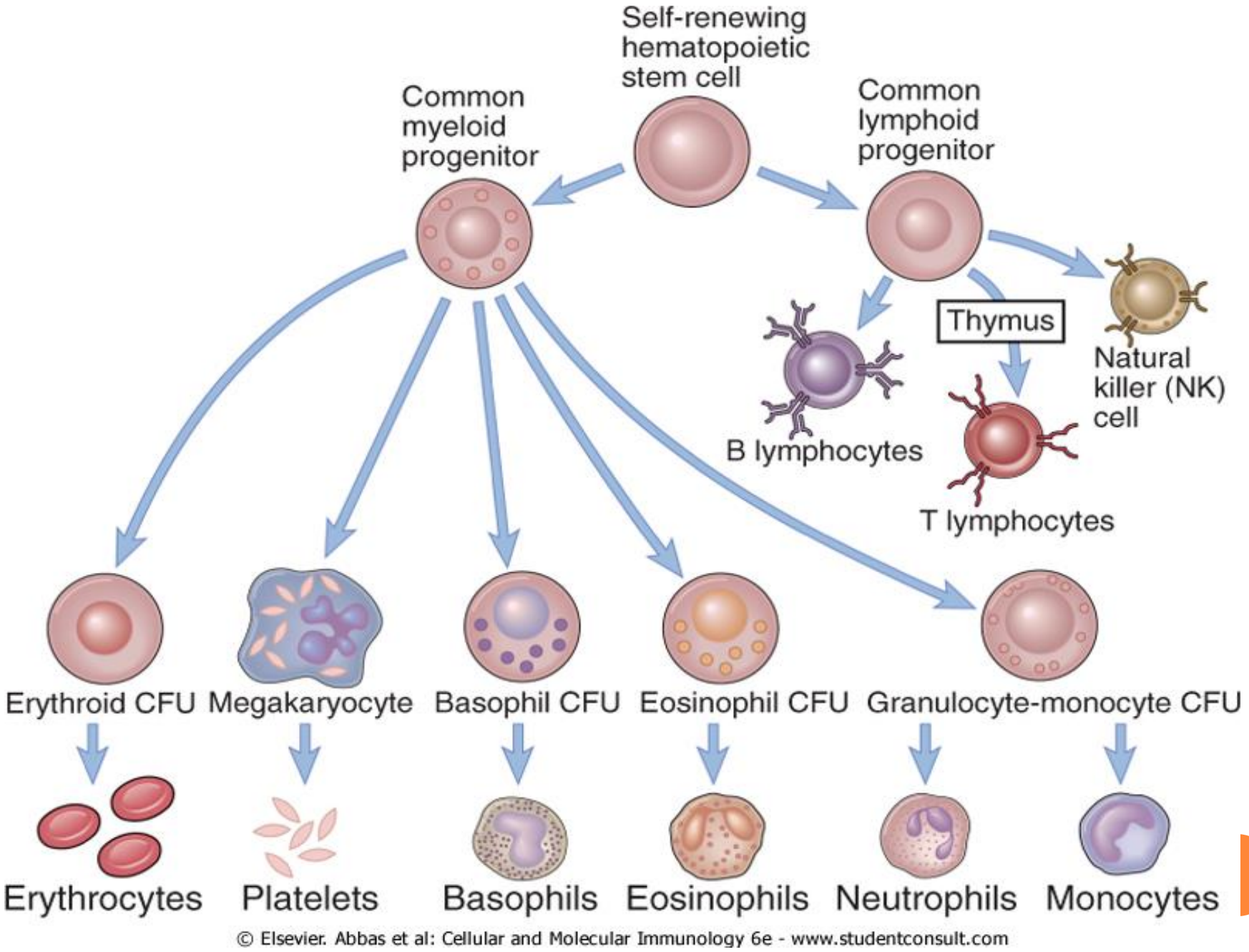
ORIGIN OF CELLS

- All functionally specialized, mature blood cells (red blood cells, granulocytes, Macrophages, dendritic cells, lymphocytes) arise from a single cell type, the **hematopoietic stem cell (HSC)**.
- Early in the process, a multipotent stem cell differentiates along one of the two pathways, giving rise to either a common myeloid progenitor cell (CMP) or a common lymphoid progenitor cell (CLP).

1. **Common myeloid-erythroid progenitor cells (CMP)-**which gives rise to all red blood cells (the erythroid lineage), granulocytes, monocytes, and macrophages (the myeloid lineage)
2. **Common lymphoid progenitor cells (CLP)-**which gives rise to B lymphocytes, T lymphocytes, and NK cells.

Immune Cell Generation





A. LYMPHOCYTES

- The lymphocytes are small, round cells found in blood and lymphoid organs such as thymus, lymph nodes and spleen.
- The diameter of each lymphocyte range from 7-15μm. They have a large and round nucleus that takes the haematoxylin intensely.
- They possess a thin rim of cytoplasm containing mitochondria, free ribosomes and a small Golgi apparatus.

- The surface of few lymphocytes are covered by small projections whereas, the surface is smooth for some lymphocytes.

Classes of lymphocytes:-

- Though lymphocytes are morphologically same, there are distinct subsets that differ functionally and in their protein products.
- The three important classes are B-lymphocytes, T-lymphocytes and NK cells.

- The B-lymphocytes (B cells) are called thus, since they were first shown to mature in an organ in birds called bursa of Fabricius.
- However, in mammals they mature in bone marrow. B cells are the cells in immune system capable of producing antibodies.
- The T-lymphocytes (T cells) arise from bone marrow and matures in thymus.

- The T cells are divided into distinct functional groups called **helper T cells and cytotoxic T cells**.
- The main role of T cells is to regulate immune response against all protein antigens and to produce specific immunity against intracellular antigens.
- Besides these two sub classes of T cells there is also one more sub class called **T suppressor cells** that suppress the immune response.

- The origin and role of T suppressor cells are still controversial. The surface membrane proteins of T cells mainly identify the sub classes.
- The surface membrane proteins are also called as receptors or markers of lymphocytes. The receptors of lymphocytes are identified by CD nomenclature. The T helper cells are identified by presence of CD4 receptor (old name T4 receptor) and cytotoxic T cells are identified by presence of CD8 receptor.

- The third class of lymphocytes NK cells lack surface markers.
- These cells are also referred as null cells.
- They have a large cytoplasm filled with cytoplasmic granules.
- They lyse the virus infected and tumour cells without any antigenic stimulation.

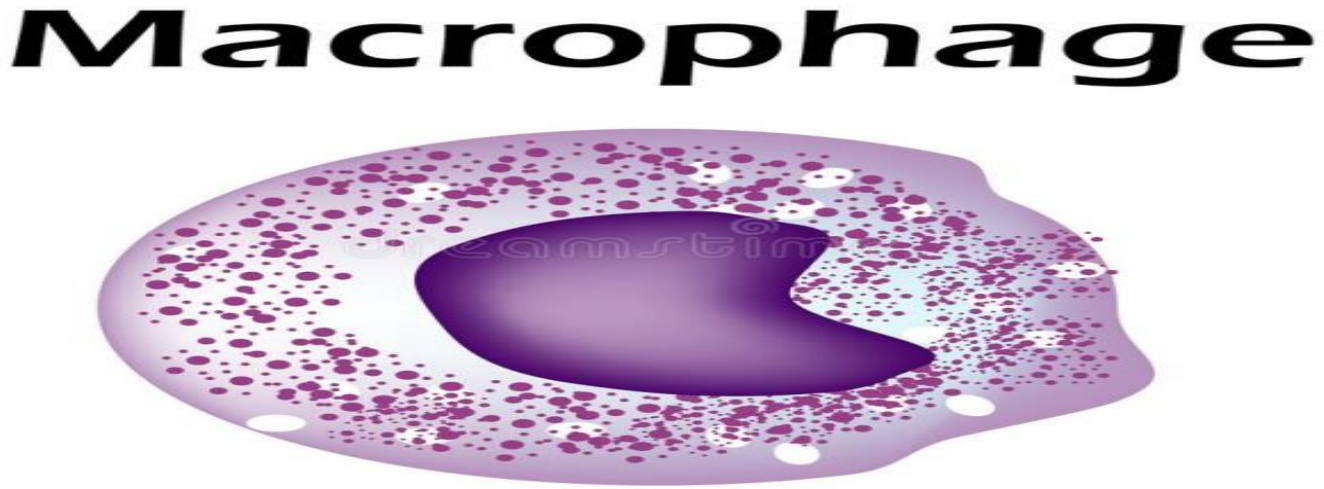
- From the lymphoid stem cell pre B and Pre T cell arise. The pre B cells develop into B cells and pre T cells develop into T cells.
- Upon antigens stimulation, the B cells differentiate into memory B cells and plasma cells. Where as the T cells differentiates into cytotoxic T cells, helper T cells and memory T cells.

Identifying features of T and B cells

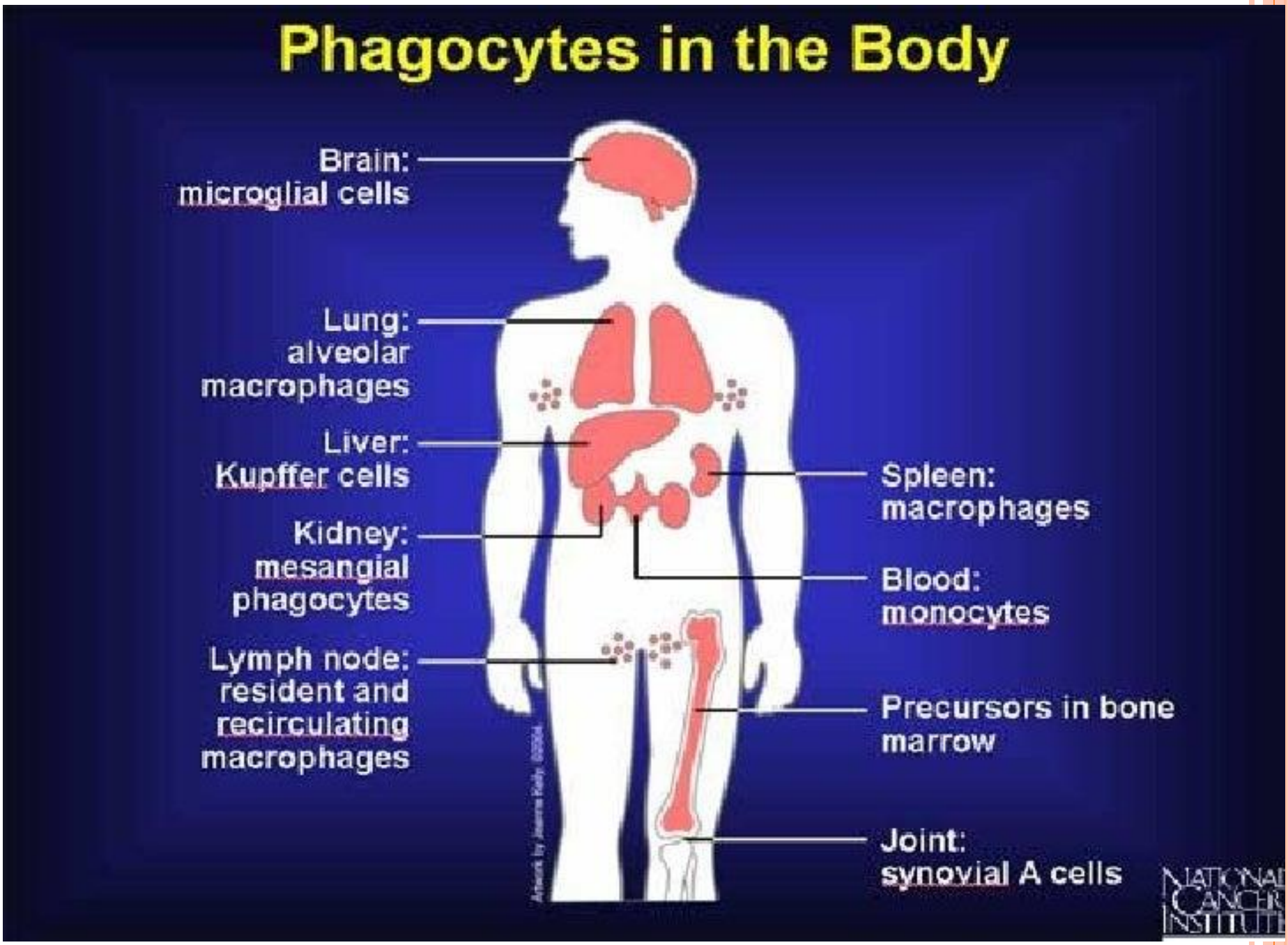
S.No	Property	B cells	T cells
1.	Site of development	Bone marrow, bursa, Peyer's patches,Lymph node cortex.	Thymus
2.	Distribution	Splenic Follicles	Spleen periarticular sheath
3.	Circulate	No	Yes
4.	Antigen receptors	BCR	TCR
5.	Important surface antigens	Immunoglobulins	CD2, CD3, CD4, CD8
6.	Antigens recognised	Free foreign proteins	Processed foreign proteins on MHC
7.	Tolerance induction	Difficult	Easy
8.	Progeny cells	Plasma cells, memory cells	Helper T cell, cytotoxic cells
9.	Secreted proteins	Immunoglobulins	Cytokines

B. MONONUCLEAR PHAGOCYTIC SYSTEM – MACROPHAGES

- One of the four important cells that constitute the immune system is the macrophage. The other three being B cells, T cells and NK cells.



- The phagocytic cells can be divided into two distinct groups based on the morphology of nucleus into mononuclear (macrophages and their precursor monocytes) and polymorphonuclear (neutrophils and eosinophils) cells.
- Of the two groups, the macrophages are considered as powerful phagocytic cells and are referred as **big eaters** or **garbage collectors.**


Phagocytes in the Body
Brain: microglial cells
Lung: alveolar macrophages
Liver: Kupffer cells
Kidney: mesangial phagocytes
Lymph node: resident and recirculating macrophages
Spleen: macrophages
Blood: monocytes
Precursors in bone marrow
Joint: synovial A cells
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3. Development of macrophages: Macrophages develop from a myelomonocytic stem cell through monoblast, promonocyte and monocyte till they reach structurally developed final stage called macrophage.

- The development of monocyte from promonocyte is stimulated by few factors called colony-stimulating factors.
- Before becoming macrophages they remain in the blood stream as monocyte for a period of time.

4. Characteristics of macrophages:

Macrophages have important characteristics that determine its role in the immune response. The characteristics are as follows.

- They are mononuclear cells.
- They show peroxidase and estrase activity.
- They bear specific receptors for antibody and complement.
- They have strong phagocytic properties

The characteristics are as follows.

- They are stimulated into active state by stimulation.
- They have varied secretory property.
- They can adhere to glass or plastic surface whereas T cells and B cells cannot adhere.

Surface markers of macrophages: The macrophages are characterized by presence of Fc receptors like (CD16, CD32, CD64), complement receptors (C11b, CD35), interleukin receptor (CD25), transport receptor (CD71) and Class I and II MHC molecules. The most important CD marker of macrophages is CD68, which is otherwise called as **macrosialin.**

Functions of macrophages:

1. **Phagocytosis:** The primary function of macrophage is phagocytosis.

- They are potent phagocytic cells and can kill any foreign substance like microbe, carbon particles etc.
- They are also capable of doing repeated phagocytosis, which is not common among other phagocytic cells.
- The actual mechanism of macrophage-mediated phagocytosis is by **receptor-mediated endocytosis** followed by lysosomal enzyme degradation.

2. Antigen presentation:

- Macrophages break the antigen into different epitopesand present them to helper T cells via MHC II molecules on their surface.
- Helper T cells will accept epitopes only when presented by MHC II on macrophages.
- This step is essential for stimulating specific immune response. Hence, they are known as antigen presenting cells (APC).

3. Secretory property:

They are strong secretory cells that secrete over 100 important substances. These substances play important role in lymphocyte differentiation, effector capability etc.

4. Activation:

Certain agents stimulate macrophages and convert them from accessory cells to effector cells.

This process is called activation of macrophages and the macrophages are referred as activated macrophages.

- In normal conditions, the macrophages remain in circulation as monocytes or resting macrophages.
- When they reach the site of inflammatory response they possess enhanced phagocytic property with expression of Fc and complement receptors.
- At this stage the macrophages are referred as **inflammatory macrophages.** These inflammatory macrophages are further stimulated by certain substances like interferon into **activated macrophages.**

- The activated macrophages are bigger in size, increased mobility, and increased expression of Fc and complement receptors, increased lysosomal activity, increased MHC II expression and increased ability to kill bacteria.
- In certain chronic infections or in case of foreign substances remaining in body for a long time, a large number of macrophages accumulate at the site around the material and resemble epithelial cells.

- These accumulated cells are called as **epitheloid cells.** These cells may fuse to form multinucleated giant cells. Giant cell formation is seen when the particle to be ingested too big for a single cell.

5. **Regulation of immune response:** The exact regulatory mechanisms are not clear. But macrophages through monokines control T cell proliferation.

6. Wound healing: Apart from phagocytosis, macrophages also help in wound healing. Macrophages secrete proteases that help in breakdown of connective tissue and regulate the production of collagenase by fibroblasts and help in formation of blood vessels. Thus it helps in wound healing.

- Granulocytes are group of blood leukocytes that are characterized by presence of number of cytoplasmic granule.
- Granulocytes are composed of three distinct populations of cells called **neutrophils, eosinophils**and **basophils.**
- This classification is based on the ability of the cytoplasmic granules to take up stains and the cell's function.

- The granules of neutrophils do not take any stain, eosinophils take acidic dye like eosin and basophils take basic dye haematoxylin.
- These blood leukocytes are called **inflammatory cells** since they play an important role in inflammatory processes, innate immunity and in removal of dead tissues.

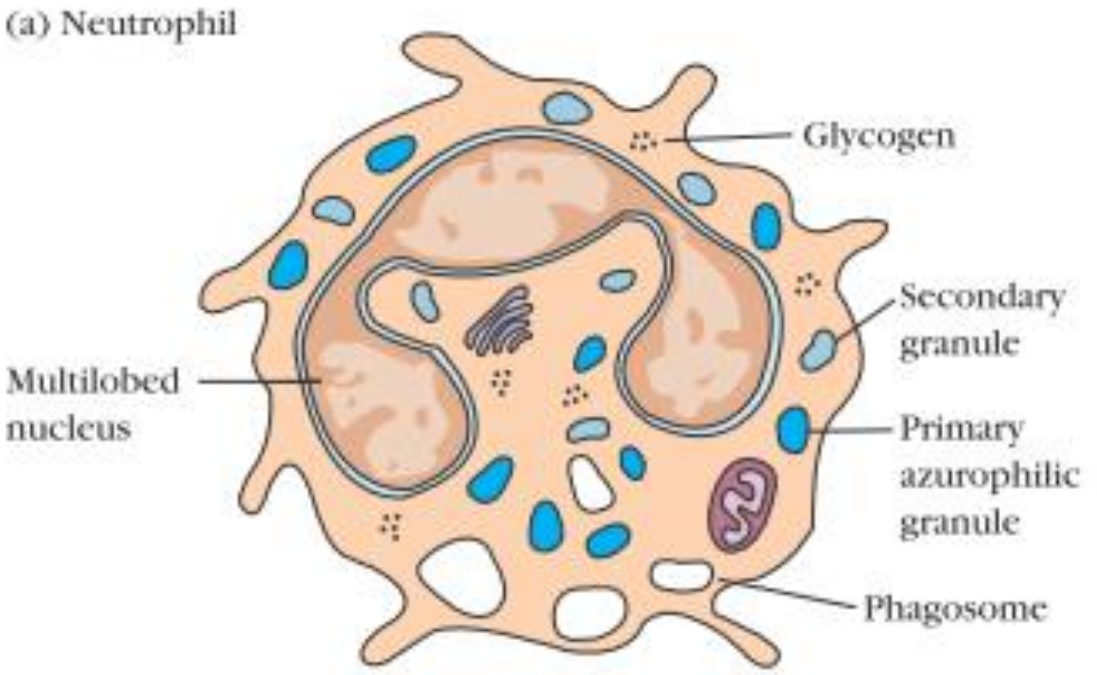
- Besides these functions, they also have effector functions in specific immune response.
- The granulocytes neutrophils and eosinophils constitute the polymorphonuclear phagocytic system.
- They are called so since the nucleus is multi-lobulated.
- The granulocytes originate from myeloid stem cells, which in turn originate from pleuripotent stem cells.

1. NEUTROPHILS

- This is the major cell type of granulocytes. They are formed in bone marrow and arrive at blood stream within 12 hours. They have a very short life span of just few days.
- The percentage of neutrophils in blood circulation among animals varies widely.
- It is 60-70% in carnivores, 20-30% in ruminants and 50% in horses. Their presence in circulation indicates a mild infection.

Morphology:

- They are round cells with a diameter of 12µm.
- The cytoplasm is granular with a central sausage or segmented nucleus.



Morphology:

- The cytoplasmic granules are of two types primary and secondary granules.
- The primary granules are rich in bactericidal enzymes such as myeloperoxidase and lysozyme etc. and secondary granules contain lysozyme, collagenase and iron binding protein lactoferrin.

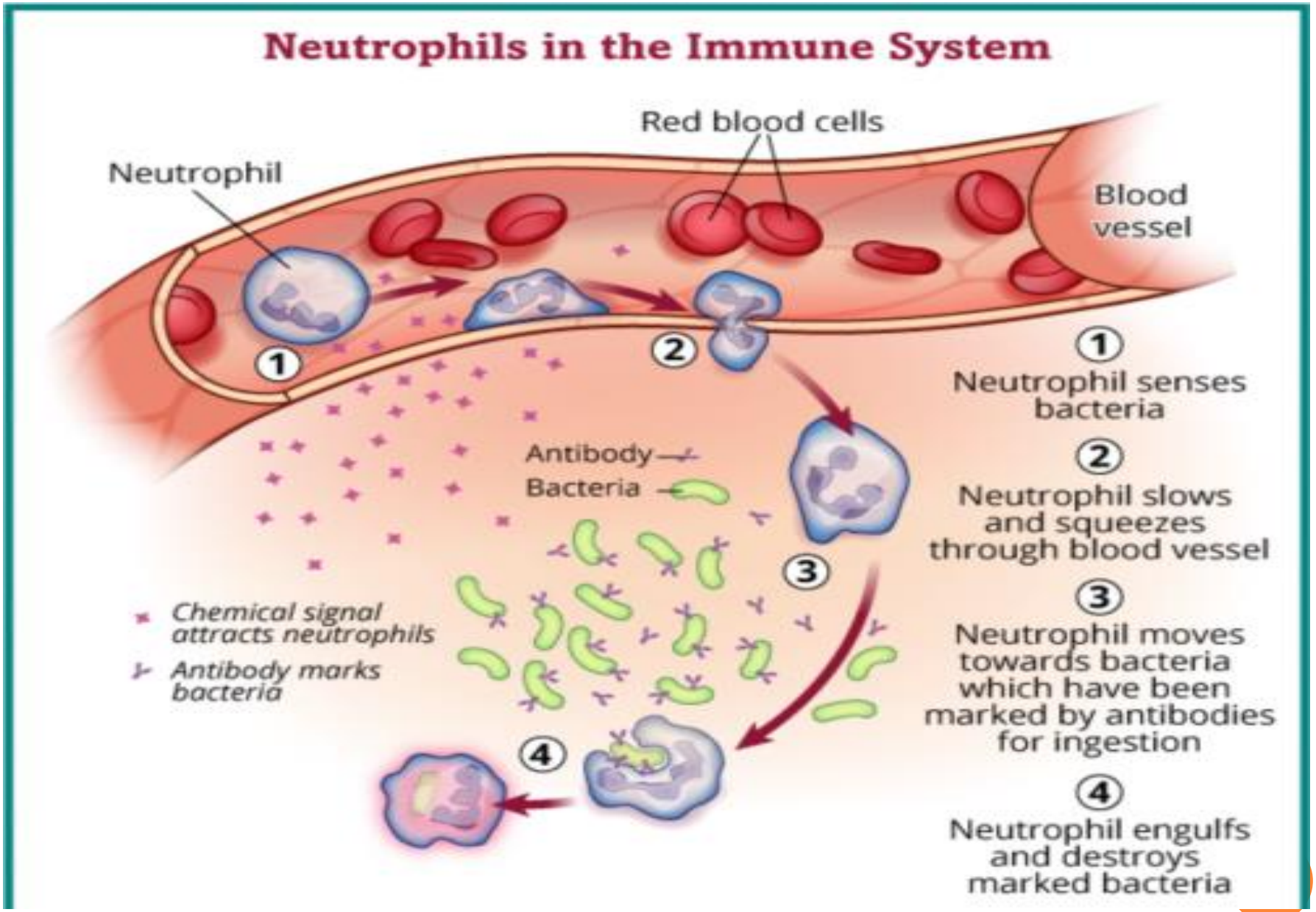
- The cytoplasm also contains a small Golgi apparatus, few mitochondrion and very few ribosomes or rough endoplasmic reticulum. The neutrophils are characterized by inability of the cells to divide and perform protein synthesis
- **Surface receptors:** The neutrophils have cell adhesion molecules (CD11a/CD18, CD11c/CD18), complement receptors (CD35, CD11b/CD18) and Fc receptor (CD32) on their surface

- The cell adhesion molecules or neutrophils are called integrins. There are three types of integrins. Integrins are mixture of two receptors CD11 and CD18.

Functions: The main function of neutrophils is **phagocytosis**. They also have effector function in specific immune response.

Neutrophils can phagocytose only bacteria. Unlike macrophage they cannot perform repeated phagocytosis.

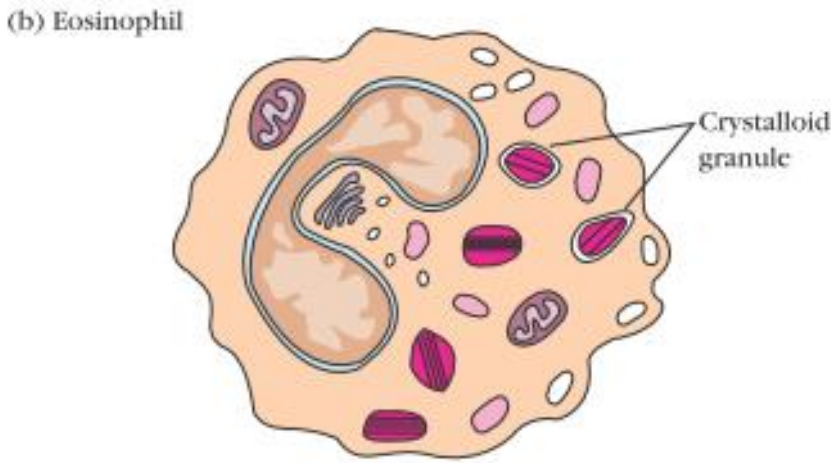
- A neutrophil can do only one phagocytosis. At the end of phagocytosis neutrophills are also killed.
- However, they secrete certain substances that in turn attract macrophages to the site.
- Neutrophils also have receptors for Fc portion of antibodies (CD32) and for complement protein C3b (CD35) on their surface.


Neutrophils in the Immune System
Red blood cells
Neutrophil
Blood vessel
1
2
3
4
Antibody
Bacteria
Chemical signal attracts neutrophils
Antibody marks bacteria
1 Neutrophil senses bacteria
2 Neutrophil slows and squeezes through blood vessel
3 Neutrophil moves towards bacteria which have been marked by antibodies for ingestion
4 Neutrophil engulfs and destroys marked bacteria

- Hence, an antigen neutralised by and antibody or antigen covered with C3b can be taken by neutrophils.
- Thus the antigen antibody complex formed is removed from this system. This process is called **opsonisation** and antibodies and C3b are referred as **opsonin**.

2. EOSINOPHILS

- This is the second major type of granulocytes.
- It is called so since the granules in the cytoplasm take eosin dye and appears pink.
- They are formed in the bone marrow and then they reach spleen where they mature.



- After maturation, they leave for blood stream where they remain for a shorter time (half life 30 minutes). Subsequently they migrate in to tissues where they remain relatively for a longer period (half life 12 days)
- In contrast to neutrophils, the percentage of eosinophils is only 2% for dogs and 10% for cattle.
- They are bigger than neutrophils and contain a bi-lobed nucleus.

- The cytoplasm consists of two types of granules - small primary granule and crystalloid granules.
- The small primary granules contain **arylsulfatase, eosinophil peroxidase** and **acid phosphatase.**
- The crystalloid granules contain four major proteins – major basic protein (MBP), eosinophilic cationic protein (ECP), eosinophil peroxidase (EPO) and eosinophil derived neurotoxin (EDN).

- In a crystalloid granule, the MBP is arranged as core and remaining proteins are arranged as matrix proteins.
- The cell membrane is characterized by the presence of large amount of lysophospholipase.

Surface receptors:

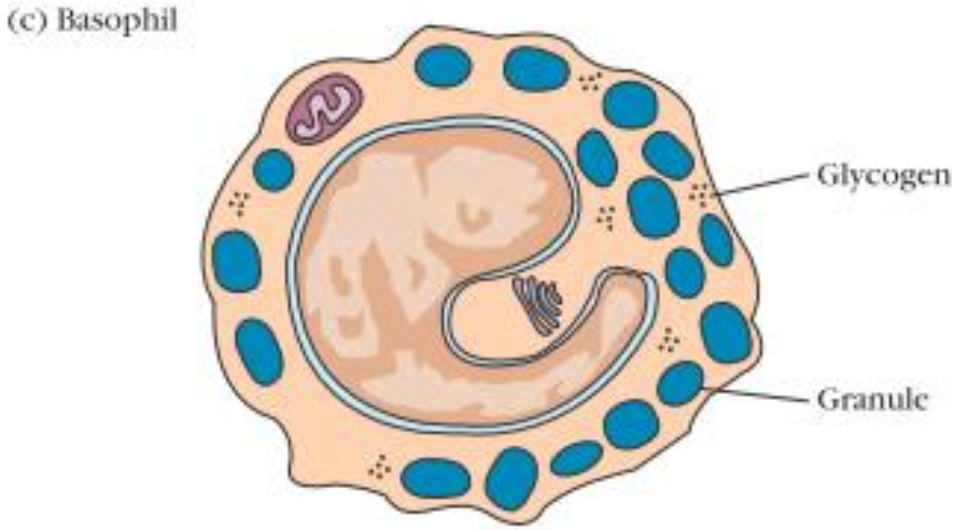
- Eosinophils possess receptors for Fc portion of antibodies (CD16 and CD32) and complement proteins(CD35 and CD23).
- They also possess receptors for IgE.

A condition that affects eosinophilia

- **Eosinopenia:**. Ex:- Cushing's syndrome and sepsis are common causes of Eosinopenia.
- **Eosinophilia:-**. Alcohol intoxication, allergies, gastrointestinal disorder, leukemia, overproduction of cortisol, and parasitic infection are causes of eosinophilia condition.

3. BASOPHILS

- They are less important type of granulocytes.
- They are called so since the granules in the cytoplasm take basophilic dyes like haematoxylin.

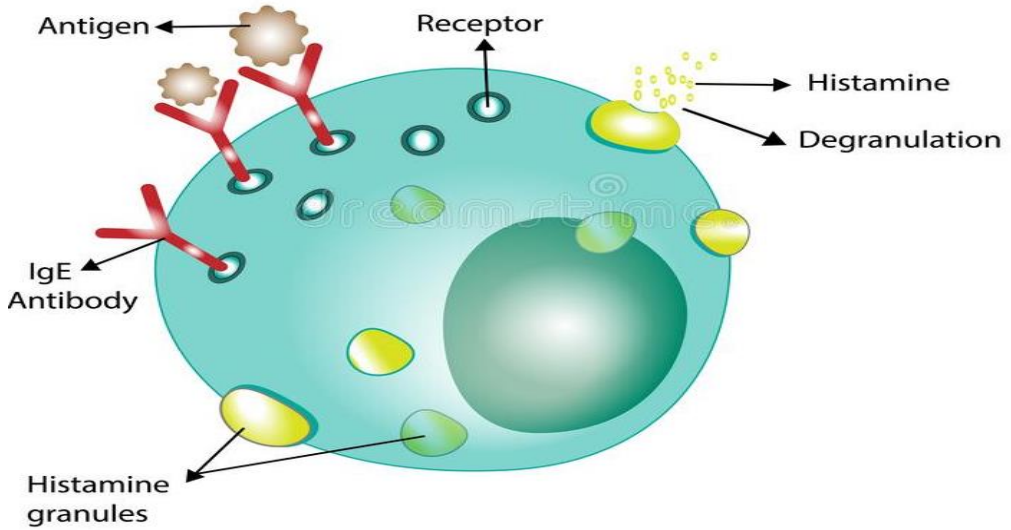


- They constitute only 0.5% of the blood cells.
- They are not normally found in extravascular tissues.
- They migrate into the tissue upon stimulation by the lymphocytes.
- The granules are rich in vasoactive amines like histamine and serotonin.
- They also possess surface receptors for IgE.
- Hence, inside the tissue, they stimulate inflammatory response along with mast cells and eosinophils.

4. Mast cells

- Mast cells are formed in the bone marrow.
- They are released from the bone marrow into the blood as undifferentiated cells, and when they enter the tissues they then mature.
- Mast cells can be found in a wide variety of tissues, including the skin, connective tissues of various organs, and mucosal epithelial tissue of the respiratory, genitourinary, and digestive tracts.

- Like circulating basophils, these cells have large numbers of cytoplasmic granules that contain histamine and other pharmacologically active substances.
- Mast cells, together with blood basophils, play an important role in the development of allergies.

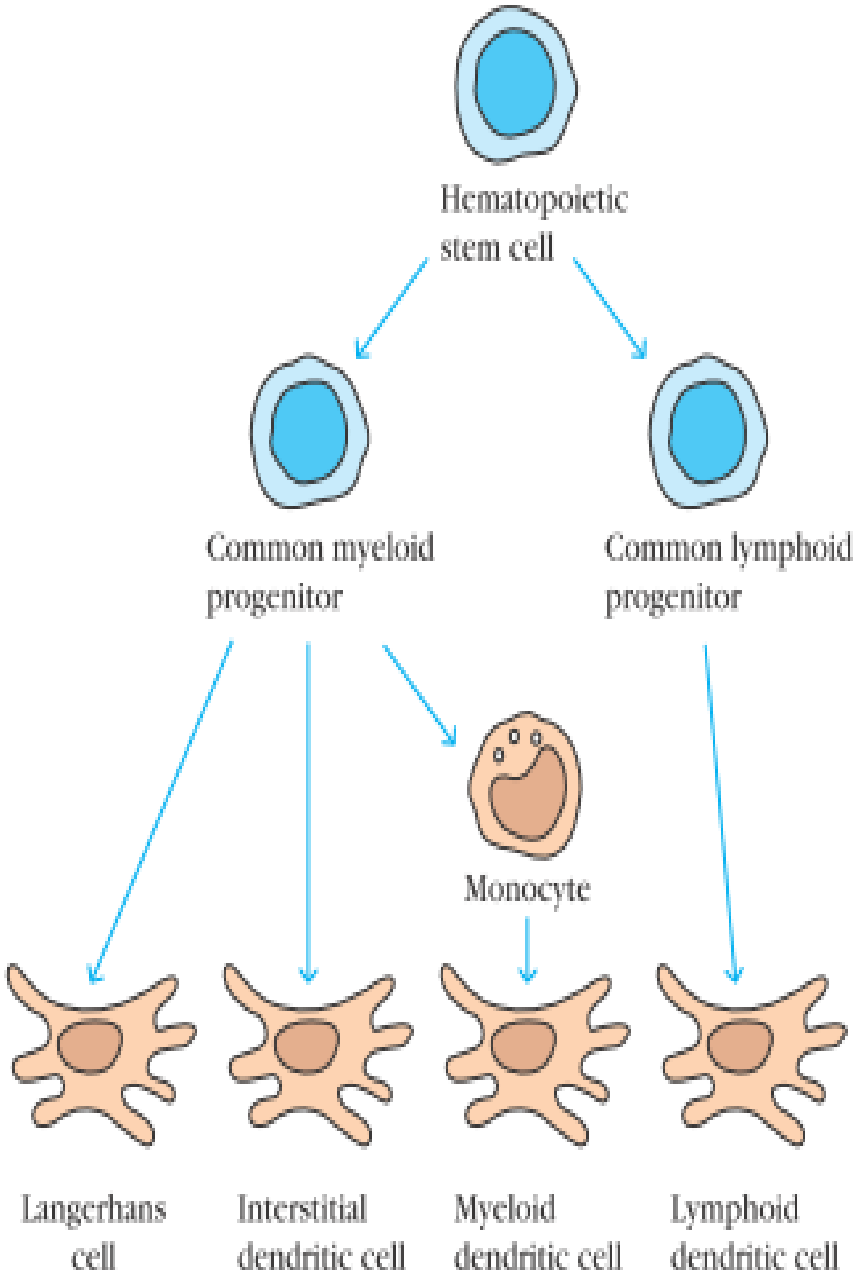


5. DENDRITIC CELLS

- They are accessory cells and play important roles in the induction of immune responses.
- Dendritic cells are population of specialised mononuclear cells that are positioned at the possible places of antigen entry into the body.
- They are poorly phagocytic cells. However, their main role is to present the antigen to lymphocytes for its effective removal from the system.

Morphology: The cells are characterized by lobulated nuclei, clear cytoplasm and filamentous cytoplasmic processes called dendrites.

- The cytoplasm is filled with a special granule (cytoplasmic organelle) called **Birbeck granules.**
- There are many different types of dendritic cells with different properties and functions.



- Dendritic cells arise from both the myeloid and lymphoid lineages.
- The myeloid pathway that gives rise to the monocyte/macrophage cell type also gives rise to dendritic cells.
- Some dendritic cells also arise from the lymphoid lineage.

- There are many types of dendritic cells, although most mature dendritic cells have the same major function, the presentation of antigen to T_H cells.
- Four types of dendritic cells are known: Langerhans cells, interstitial dendritic cells, myeloid cells, and lymphoid dendritic cells.
- Each arises from hematopoietic stem cells via different pathways and in different locations.
- However, they all constitutively express high levels of both class II MHC

- Immature or precursor forms of each of these types of dendritic cells acquire antigen by phagocytosis or endocytosis; the antigen is processed, and mature dendritic cells present it to T_H cells.
- Following microbial invasion or during inflammation, mature and immature forms of Langerhans cells and interstitial dendritic cells migrate into draining lymph nodes, where they make the critical presentation of antigen to T_H cells that is required for the initiation of responses by those key cells.

- Another type of dendritic cell, the follicular dendritic cell does not arise in bone marrow and has a different function from the antigen-presenting dendritic cells described above.
- Follicular dendritic cells do not express class II MHC molecules and therefore do not function as antigen presenting cells for T_H-cell activation.
- These dendritic cells were named for their exclusive location in organized structures of the lymph node called lymph follicles

Thank You

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