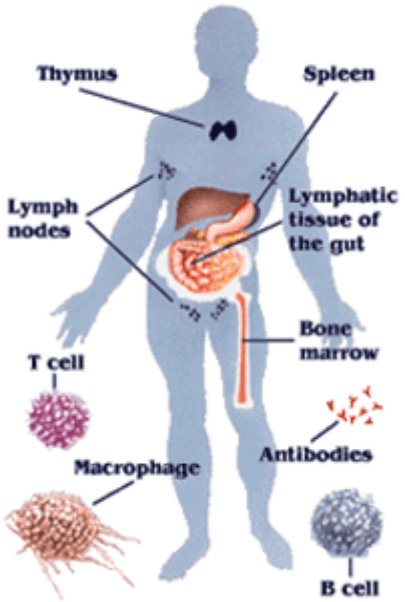
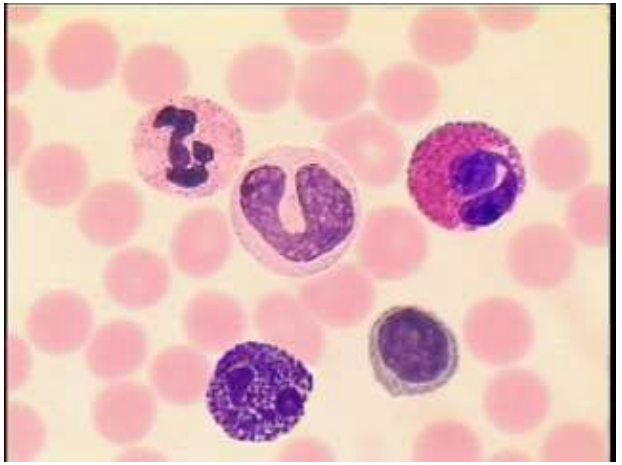
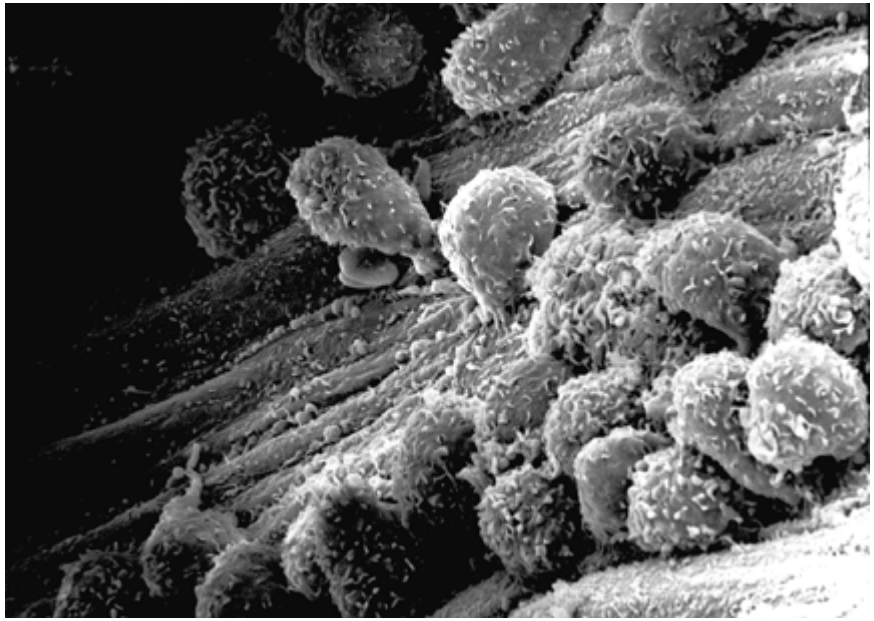
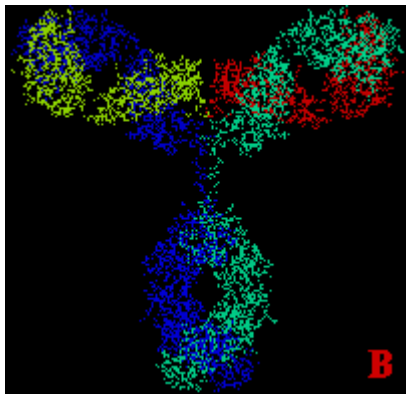




THE IMMUNE SYSTEM





Intro…..

- The immune system consists of various lymphoid organs and tissues
- Along with these organ a vast variety of cell play important roles in the defense mechanism of the body

Learning Objectives

- Lymphoid cells & Lymphoid organ
- Characteristics of T & B cells
- Importance of phagocytic cells
- Human leukocyte antigen(HLA) & HLA complex

The Immune System is the Third Line of Defense Against Infection

Nonspecific defense mechanisms		Specific defense mechanisms (immune system)
First line of defense	Second line of defense	Third line of defense
• Skin • Mucous membranes • Secretions of skin and mucous membranes	• Phagocytic white blood cells • Antimicrobial proteins • The inflammatory response	• Lymphocytes • Antibodies

Lymphoreticular system

Reticuloendothelial system : → Phagocytic cells :

Non specific immunity

concerned with scavenger function of eliminating microorganism & other foreign particles from blood & tissue

Lymphoid components: → lymphocytes

→ plasma cells

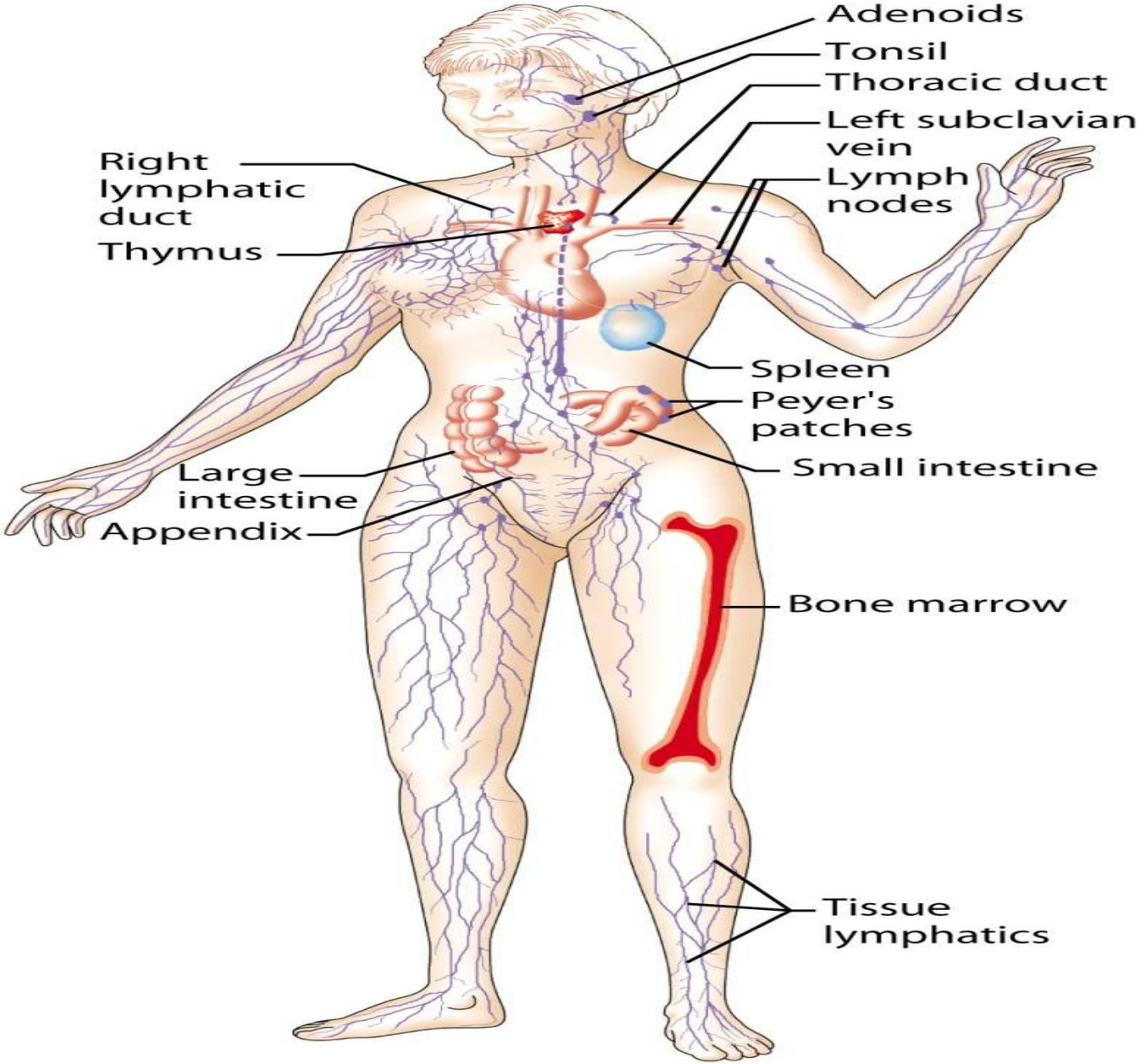
specific immunity

The lymphoid system

- **Lymphoid cells** → Lymphocytes,
  Plasma cells
- **Lymphoid organs**:
  - Central (Primary) lymphoid organs:
    Thymus Bone Marrow
  - Peripheral (Secondary) lymphoid Organs:
    Spleen, lymph nodes, MALT,
    Lymphoid tissues in gut, lungs, liver,
    bone marrow

Organs Of Immune System

- Primary Lymphoid Organs
  - Bone Marrow and Thymus
  - Maturation Site
- Secondary Lymphoid Organs
  - Spleen, lymph nodes,
  - MALT (mucosal associated lymph tissue)
  - GALT (gut associated lymph tissue)
  - Trap antigen, APC, Lymphocyte Proliferation


Adenoids
Tonsil
Thoracic duct
Left subclavian vein
Lymph nodes
Right lymphatic duct
Thymus
Spleen
Peyer's patches
Small intestine
Large intestine
Appendix
Bone marrow
Tissue lymphatics

Duality of Immune System

I. Humoral (Antibody-Mediated) Immunity

- Involves production of antibodies against foreign antigens.
- Antibodies are produced by a subset of lymphocytes called **B cells**.
- B cells that are stimulated will actively secrete antibodies and are called ***plasma cells***.
- Antibodies are found in **extracellular fluids** (blood plasma, lymph, mucus, etc.) and the surface of B cells.
- Defense against bacteria, bacterial toxins, and viruses that circulate freely in body fluids, ***before*** they enter cells.
- Also cause certain reactions against transplanted tissue.

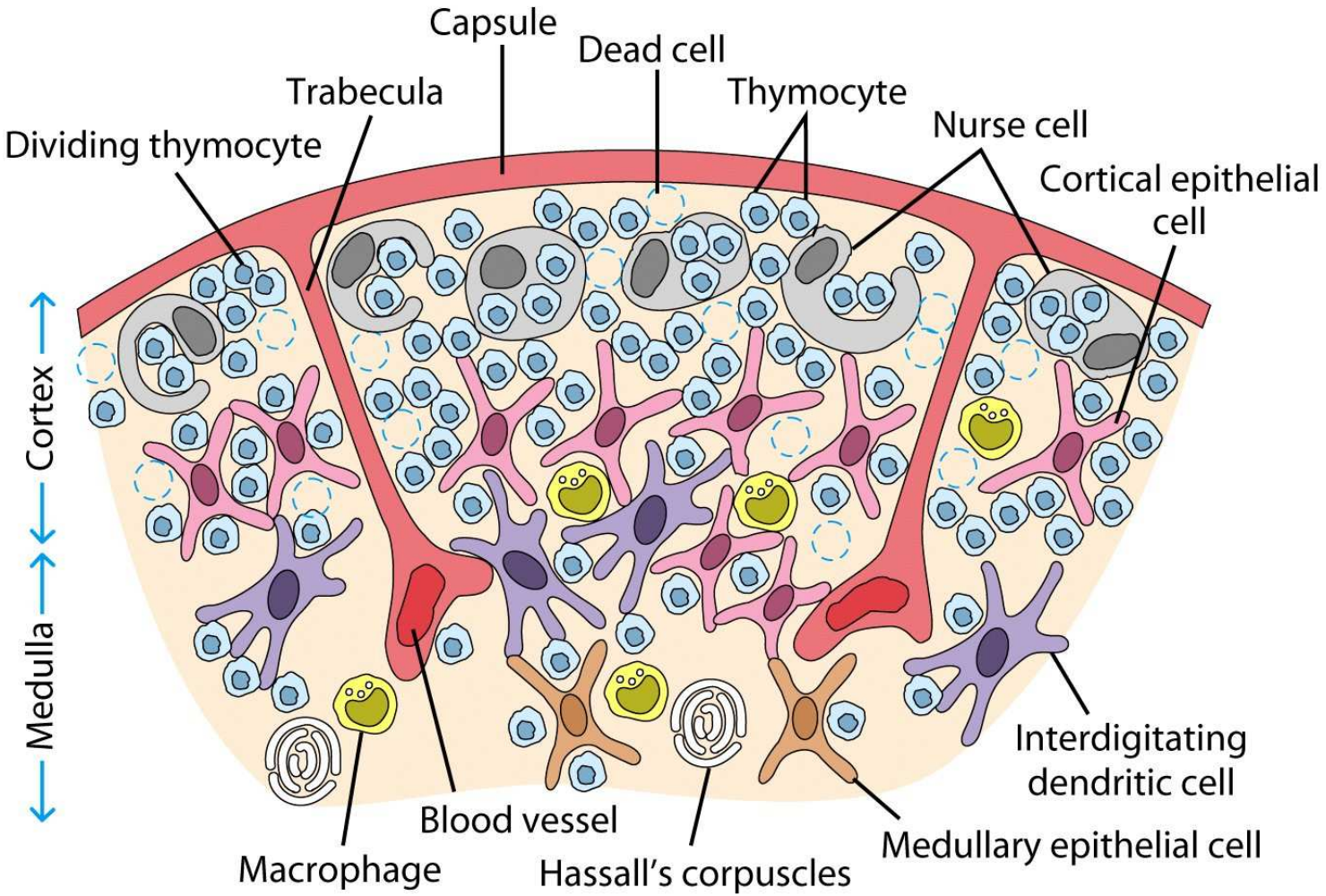
II. Cell Mediated Immunity

- Involves specialized set of lymphocytes called T cells that recognize foreign antigens on the surface of cells, organisms, or tissues:
  - Helper T cells
  - Cytotoxic T cells
- T cells regulate proliferation and activity of other cells of the immune system: B cells, macrophages, neutrophils, etc.
- Defense against:
  - Bacteria and viruses that are inside host cells and are inaccessible to antibodies.
  - Fungi, protozoa, and helminths
  - Cancer cells
  - Transplanted tissue

Central Lymphoid organs

- **Thymus**
- Develops from epithelium of third and fourth pharyngeal pouches at about sixth week of gestation, reaches maximum size just before birth
- Primary function to produce thymic lymphocytes
- Major site for lymphocyte proliferation

Thymus


Capsule
Dead cell
Trabecula
Thymocyte
Dividing thymocyte
Nurse cell
Cortical epithelial cell
Cortex
Medulla
Interdigitating dendritic cell
Blood vessel
Medullary epithelial cell
Macrophage
Hassall's corpuscles

- In the thymus lymphocytes acquire new surface antigen (Thy antigens), are called Thymus dependent lymphocytes(T cells)
- Lymphocytes proliferation in thymus is not dependent on antigenic stimulation
- The thymus confers immunological competence on these cells during their stay in the organ
- Majority of proliferate lymphocytes die in thymus and only 1% migrate to secondary lymphoid organ

- T cells circulate through blood & lymphatics in man.
- T lymphocytes are responsible for cell mediated immunity
- T lymphocytes selectively seeded into certain areas of peripheral lymphatic tissue, being found in the white pulp of spleen, around central arteriole &in the Para cortical areas of lymph nodes (Thymus dependent)

Bone Marrow

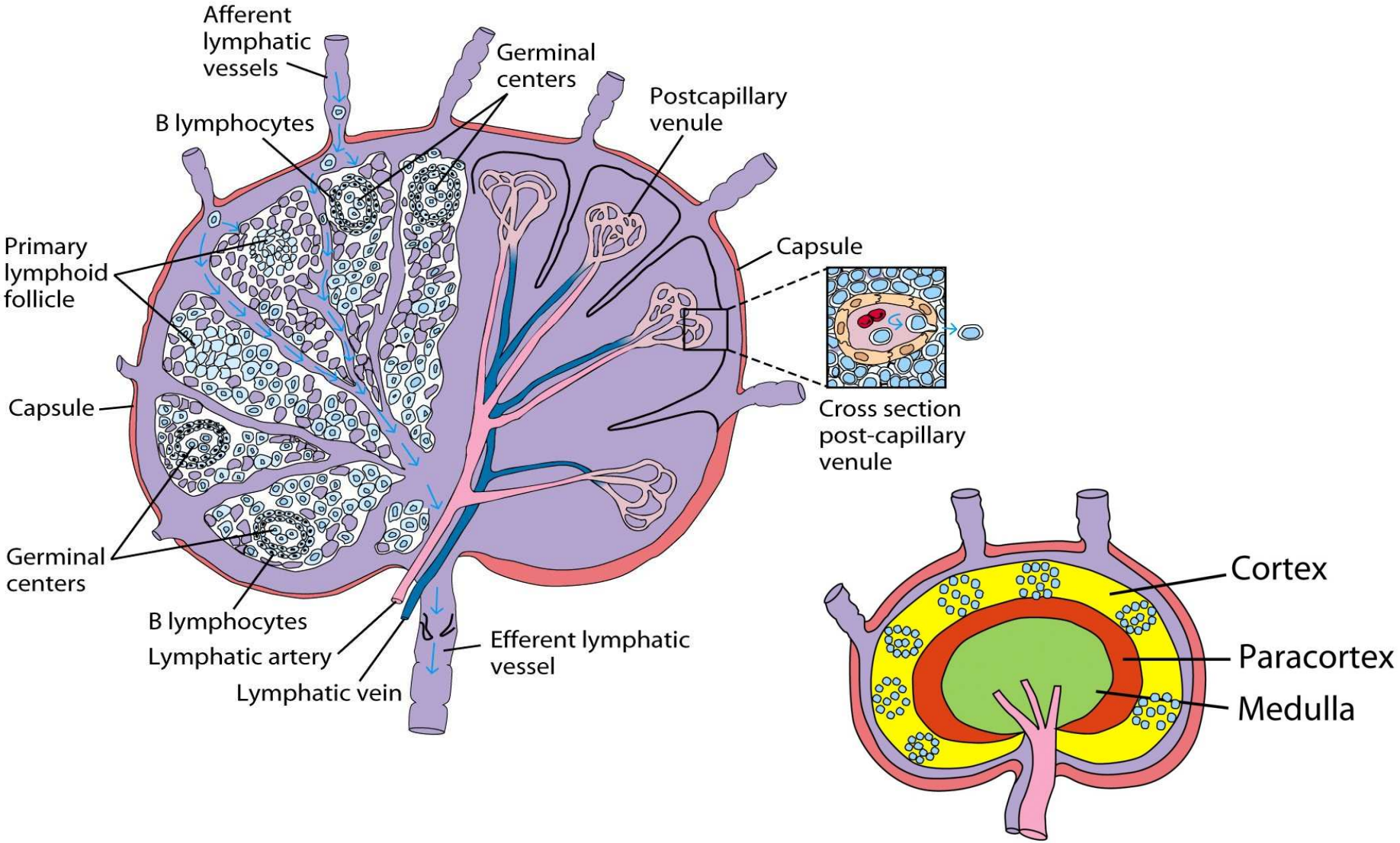
- Some lymphoid cells develop and mature within Bone marrow : B cells
- In birds Bursa of Fabricius : equivalents to bone marrow
- Site for stem cell proliferation , origin for Pre B cells , B lymphocytes
- Following antigenic stimulation B cells transform into plasma cells & secrete antibodies. Full immunocompetence is attained only after the 1st decade of life

Peripheral lymphoid organ

- **Lymph node**: round bodies placed along the course of lymphatic vessels
- Outer cortex & inner medulla, paracortical areas lies between cortical follicles and base of medullary cords
- Cortex contains primary lymphoid follicles

  (accumulation of lymphocytes) within which secondary follicles (germinal centre) develop during antigenic stimulation

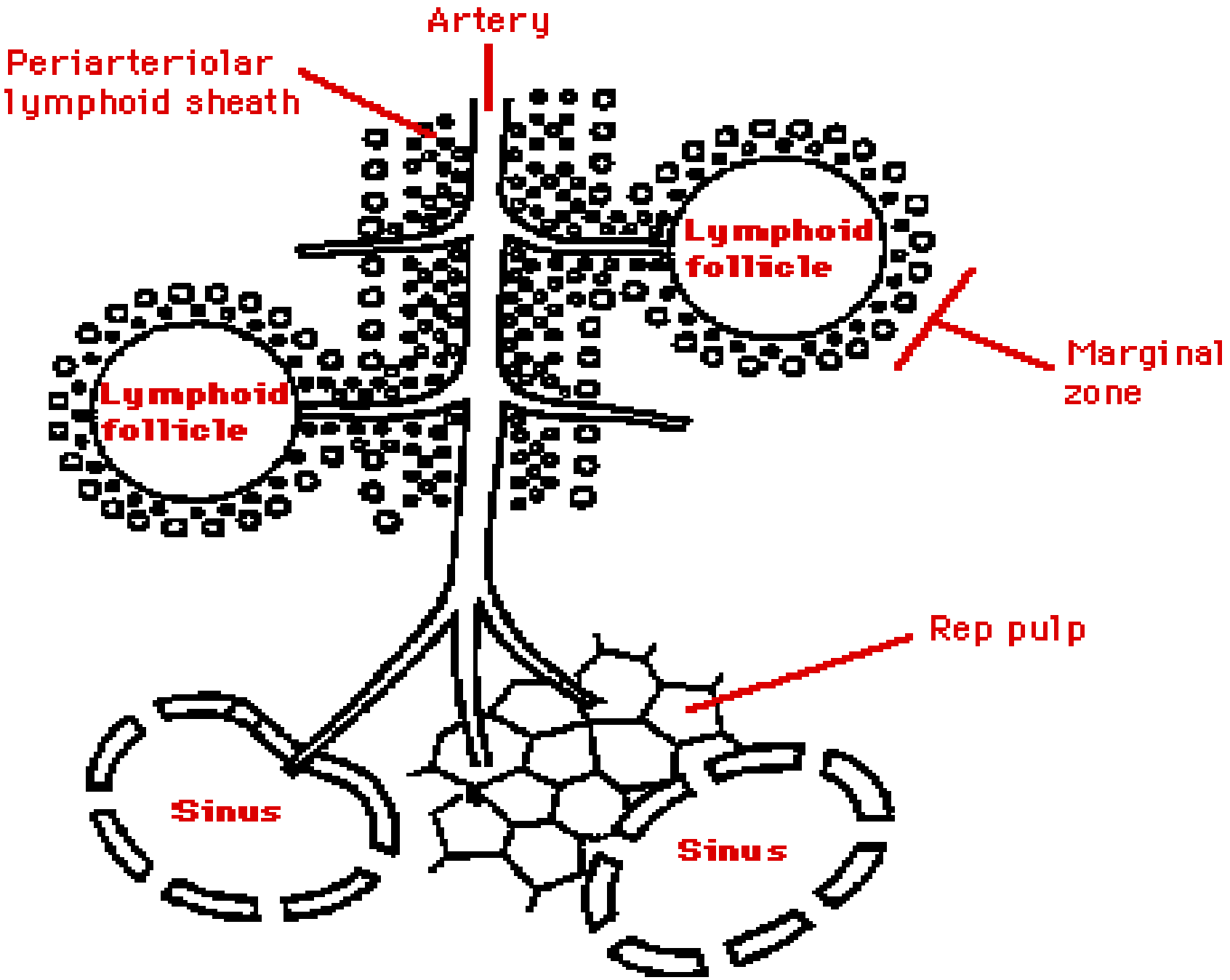
Lymph Node

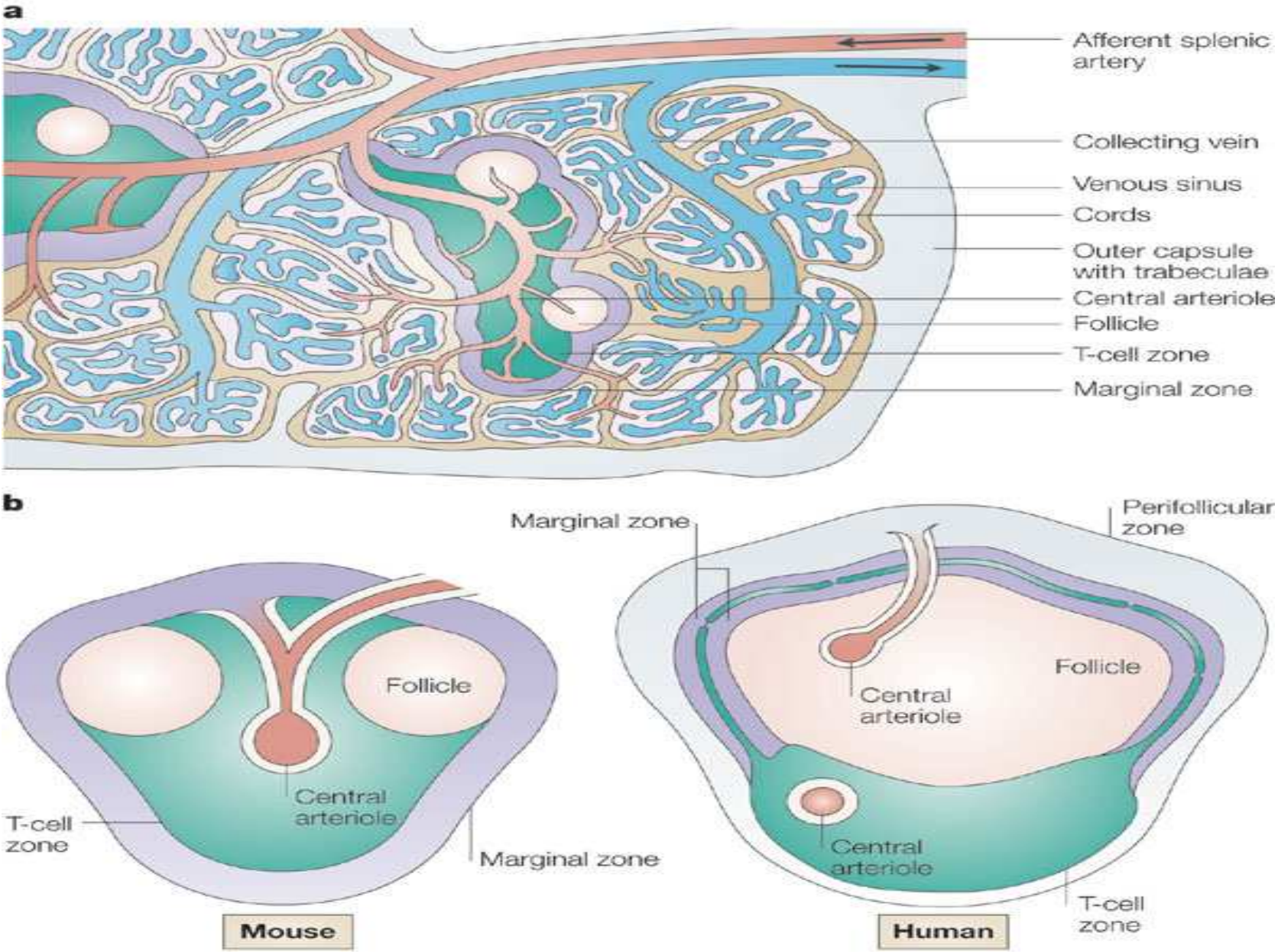

Afferent lymphatic vessels
Germinal centers
Postcapillary venule
B lymphocytes
Primary lymphoid follicle
Capsule
Capsule
Cross section post-capillary venule
Germinal centers
B lymphocytes
Lymphatic artery
Lymphatic vein
Efferent lymphatic vessel
Cortex
Paracortex
Medulla

- The follicles contain proliferating lymphocytes & dendritic macrophage which capture & process the antigen
- The cortical follicles & medullary cords contains B lymphocytes & called Bursa dependant areas.
- The paracortical areas which contain T lymphocytes are called Thymus dependent areas.
- Lymph nodes are filter for lymph, phagocytes foreign particles, help in proliferation and circulation of T & B Lymphocytes, enlarge on antigenic stimulation

Spleen

- Largest lymphoid organ
- Contains two distinct areas : white & red pulps
- Periaterial lymphoid collection in the white pulp called Malphigian corpuscles
- Germinal centers develop within white pulp following antigenic stimulation .
- B lymphocyte areas : Perifollicular regions, germinal centers and mantle layer
- T lymphocytes areas : lymphatic sheath surrounding the central arteriole


Artery
Periarteriolar
lymphoid sheath
Lymphoid
follicle
Lymphoid
follicle
Marginal
zone
Rep pulp
Sinus
Sinus

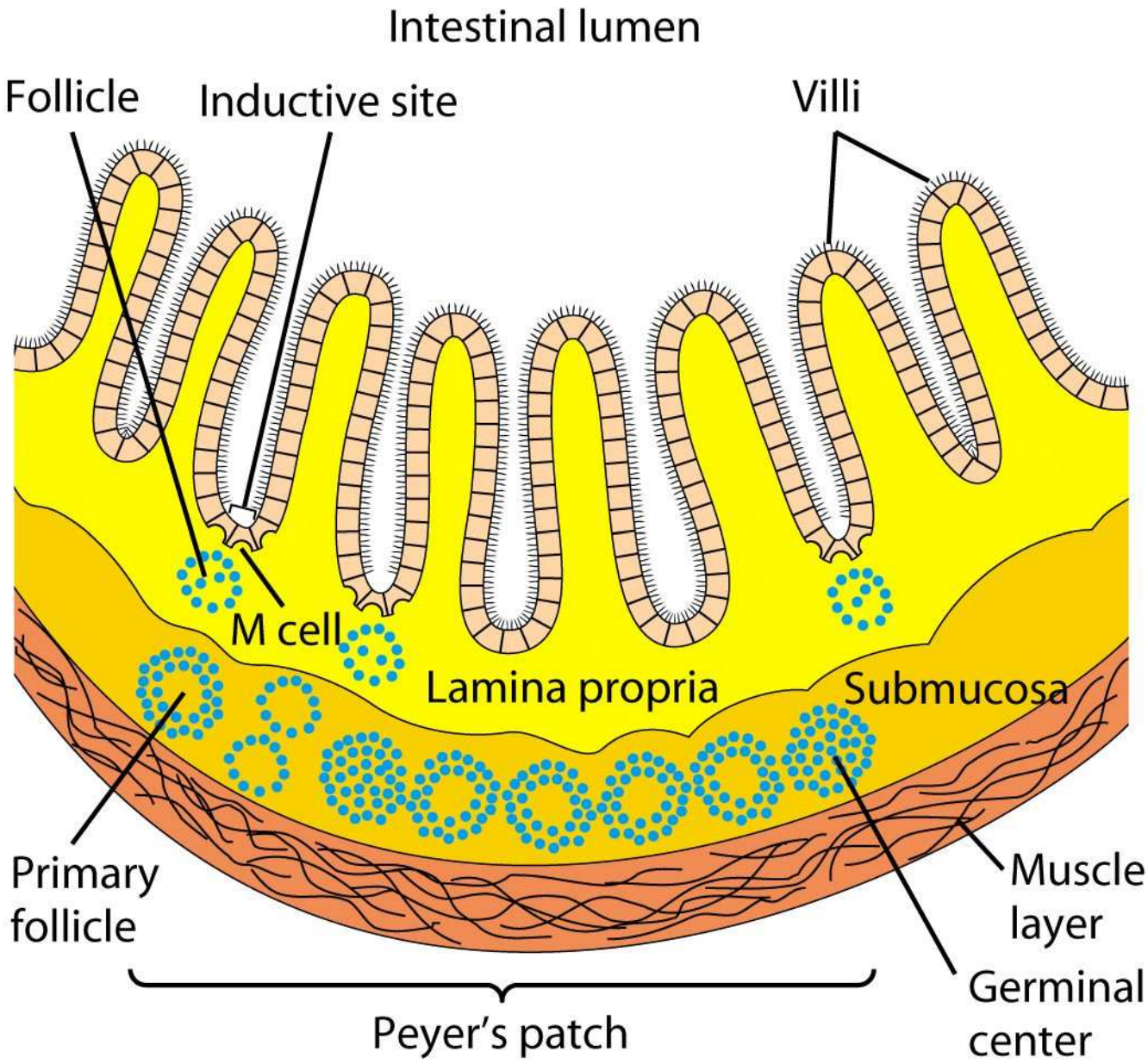


Nature Reviews | Immunology

- Serves as the grave yard for blood cells
- Systemic filter for trapping circulating blood borne foreign particles.
- Immunological function is primarily directed against blood borne antigens

Mucosa Associated Lymphoid tissue s(MALT)

- The sub epithelial accumulation of lymphoid tissue protects the mucosa of alimentary, respiratory & genitourinary tract.
- GALT – Gut associated lymphoid tissue
- BALT – Bronchus associated lymphoid tissue
- MALT contains both T & B cells as well as phagocytes
- Predominant Immunoglobulin is secretory IgA


Intestinal lumen
Follicle
Inductive site
Villi
M cell
Lamina propria
Submucosa
Primary follicle
Muscle layer
Germinal center
Peyer's patch

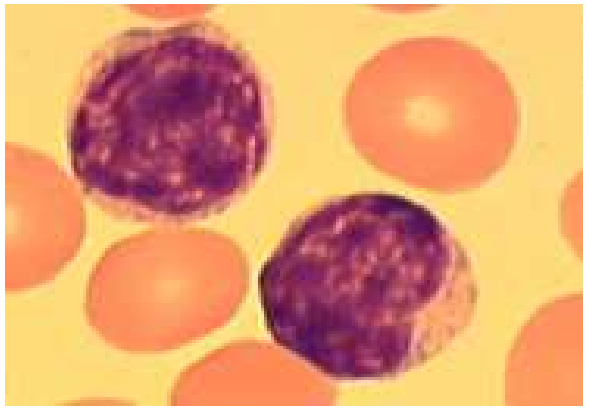
Cells of lymphoreticular cells

- Consist of structural cells & immunologically competent cells
- Structural cells include reticulum cells, endothelial cells & fibroblasts
- Immunologically competent cells include lymphocyte, plasma cells & macrophage

Lymphoid cells

- Lymphocytes are the only cells in the body capable of specifically recognizing and distinguishing different antigenic determinants
- Responsible for adaptive immune response, specificity and memory
- 3 types
  - B lymphocytes
  - T lymphocytes
  - Natural killer cells

Lymphocytes



- Small round cells, constitute 20 – 45% of leucocytes population in peripheral blood
- Produce antibodies
- B-cells mature in bone marrow then concentrate in lymph nodes and spleen
- T-cells mature in thymus
- B and T cells mature then circulate in the blood and lymph
- Circulation ensures they come into contact with pathogens and each other

- Newly formed lymphocytes are all alike
  - But they later develop into B cells or T cells, depending on where they continue their maturation

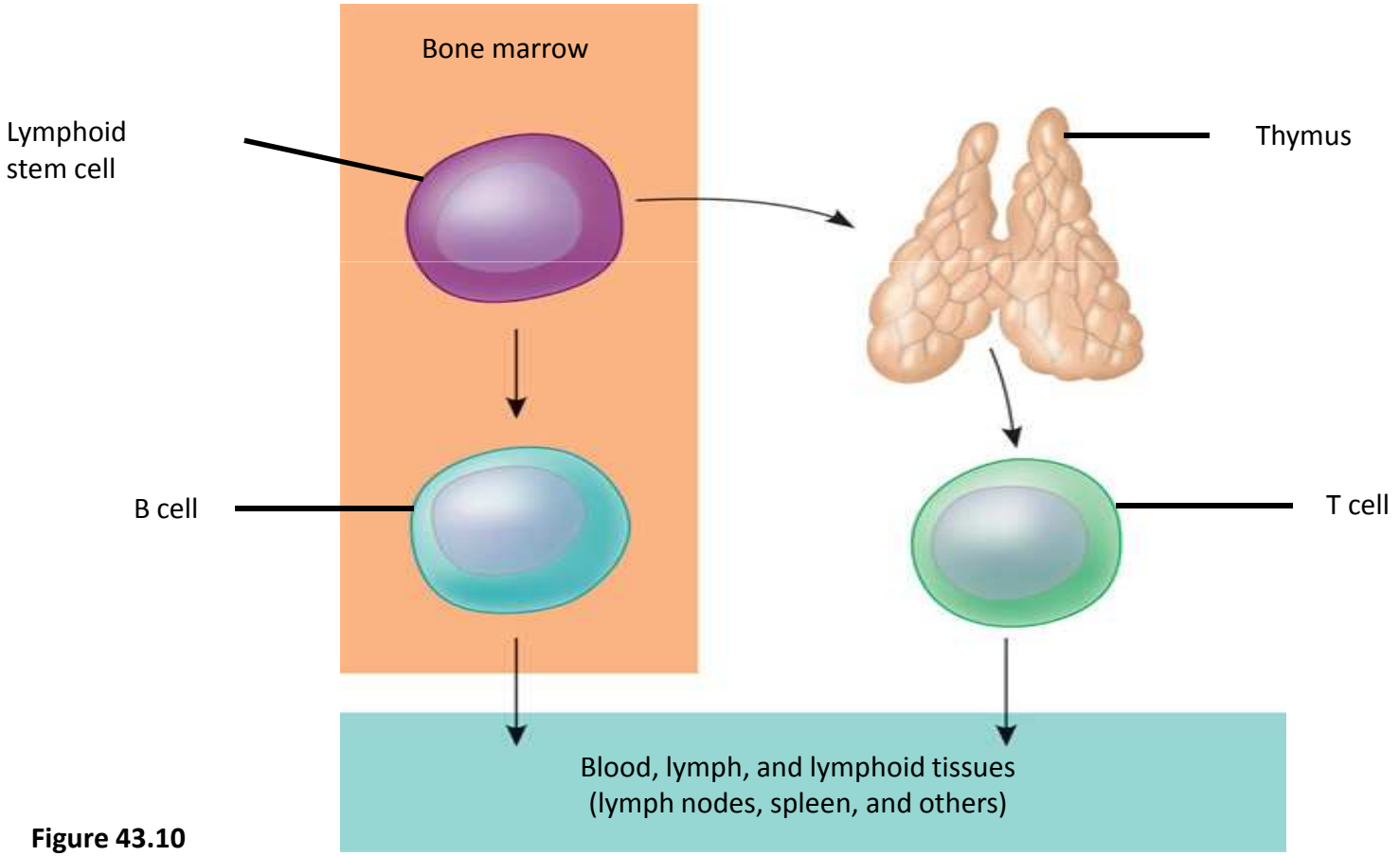


Figure 43.10

- Lymphocyte recirculation: lymphopoesis occurs at three places. The lymphocytes of these three sites mix together in the process known as lymphocyte recirculation.
- Immunologically competent cells
- Naive cells: recognition of antigen, storage of immunological memory, immune response to antigen

On the basis of surface antigenic determinants

- Surface antigens on T cells (markers)
- Previously designated as T1 to T11
- CD Markers: Cluster of differentiation

more than 150 CD markers have been identified.CD2, CD3,CD4,CD5,CD8

Difference between T &B cells

Feature	T cells	B cells
Location 1.Periheral blood 2.Lymphe node 3.Spleen 4.Thoracic duct 5.Thymus	 65-85% 60-75% 25- 45% 80-90% 96%	 15-25% 30- 35% 55-60% 10-20% Negligible
Thymus specific antigen	+	_
CD3 receptor	+	--
Surface immunoglobulin	--	+
Receptor for Fc fragment of IgG	--	+
SRBC rosette	+	--
EAC rosette	--	+
Numerous microvilli on surface	--	+
Blast transformation with 1) anti-CD3 2) Anti Ig 3) PHA 4) Concavalin A 5) Endotoxin	 + -- + + --	 -- + -- -- +

T lymphocytes

- Classified into different subpopulation

(1) On the basis of functions: Regulatory cells, Effector cells

(2) On the basis of surface antigenic determinants

T cell maturation

- Pro T cell - CD7
- CD2(thymus)
- CD3(cytoplasm) → pre T cell
- TCR → αβ
  γδ

Ag recognition unit

- Immature T cell - CD 7,2,1,4,8 + TCR
- CD1 lose -- CD4 & CD8 with αβ
- CD4 (helper/inducer cell) B cell differentiation
  Stimulate CD8, produce lymphokines
- CD8(suppressor/cytotoxic cells) inhibit Bcell
  Ab synthesis and act as cytotoxic
  effector cells

Regulatory T cells

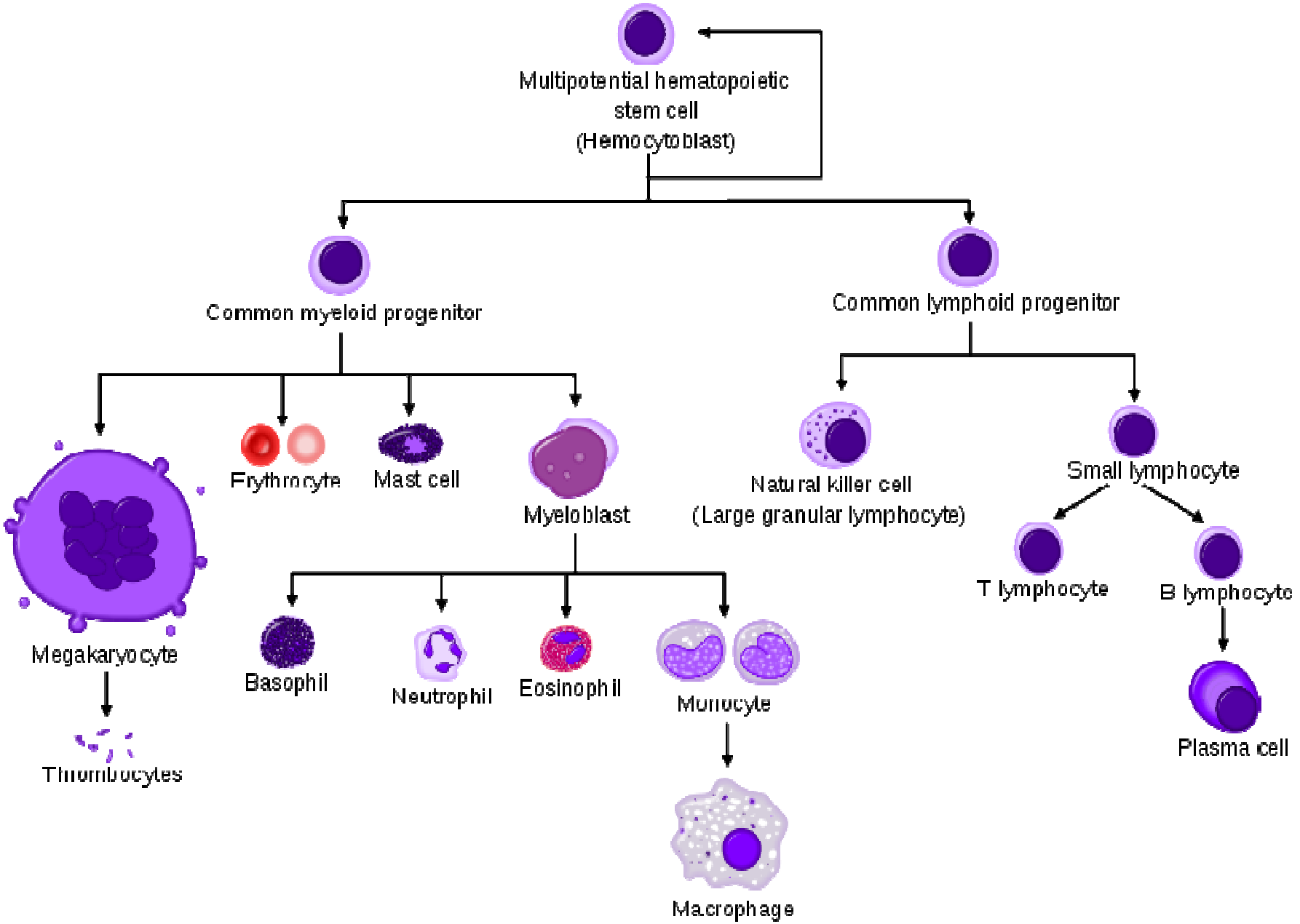
- T helper(CD4) cells: Th1 & Th2

  Th1 cells: produces interferon gamma & interleukin-2 activates macrophages & T cells – cell mediate immunity

  Th2 cells : produces interleukin-4,5,6 & interact with B lymphocytes to develop into plasma cells - Ab (AMI)

* T suppressor (CD8)cells: Block immune response by their action on T helper or B cells

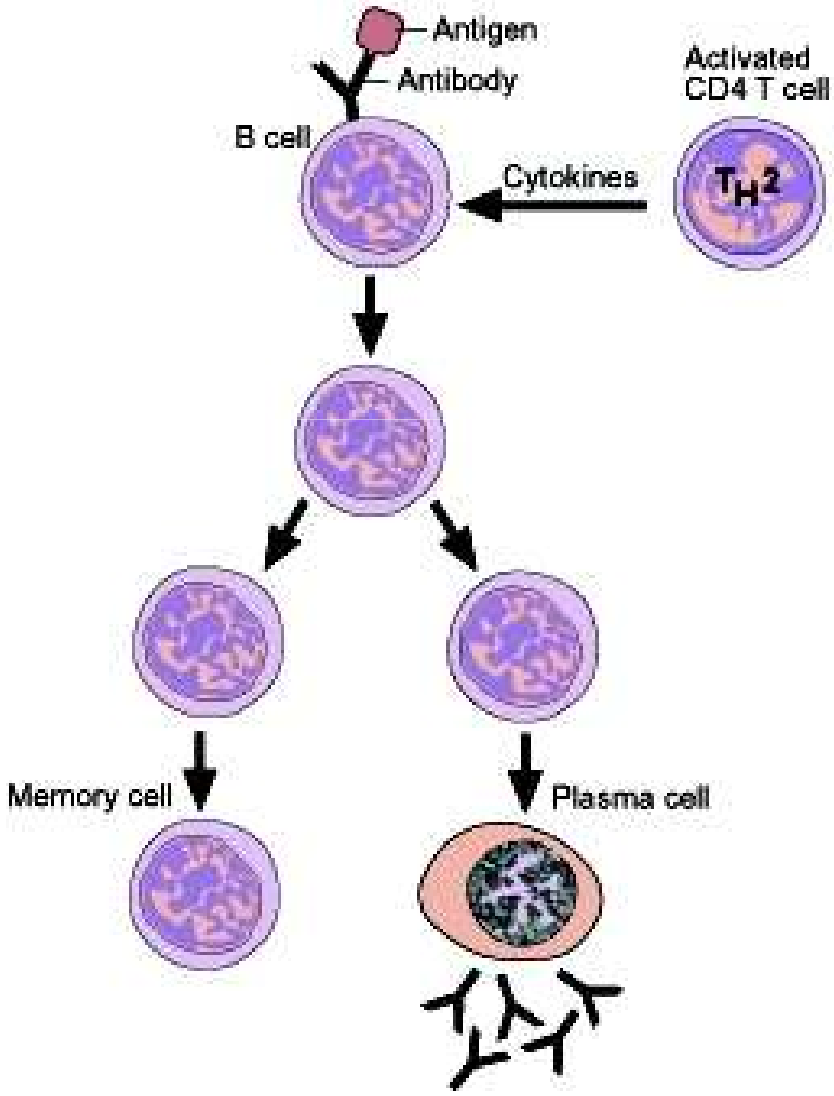
- T cell - suppressor/cytotoxic cells
- Memmory cells


Multipotential hematopoietic stem cell (Hemocytoblast)
Common myeloid progenitor
Common lymphoid progenitor
Megakaryocyte
Thrombocytes
Erythrocyte
Mast cell
Myeloblast
Basophil
Neutrophil
Eosinophil
Monocyte
Macrophage
Natural killer cell (Large granular lymphocyte)
Small lymphocyte
T lymphocyte
B lymphocyte
Plasma cell

Effector cells

- Cytotoxic cells(Tc): lyses specific target cells e.g. virally infected cells, tumor cells.
- Delayed type hypersensitivity(DTH) cells
- Mixed lymphocyte reactivity(MLR) cells

B -Lymphocytes



B -Lymphocytes

- Some activated B cells → PLASMA CELLS
  these produce lots of antibodies.
- The antibodies travel to the blood, lymph, lining of gut and lungs.
- The number of plasma cells goes down after a few weeks
- Antibodies stay in the blood longer but eventually their numbers go down too.

B -Lymphocytes

- Some activated B cells → MEMORY CELLS.
- Memory cells divide rapidly as soon as the antigen is reintroduced.
- There are many more memory cells than there were clone cells.
- When the pathogen/infection infects again it is destroyed before any symptoms show.

Null cells

- Killer cells : possess surface receptor for Fc portion of IgG, capable of killing target cells sensitised with IgG,

  Responsible for ADCC
- Natural killer cells(NK cells): Large granular lymphocytes, Cytolytic for virally transformed target cells, certain tumor cells.
- Lymphocyte Activated Killer cells(LAK cells): NK cells treated with Interleukin2, cytotoxic to tumour cells

Natural killer cells (NK cells)

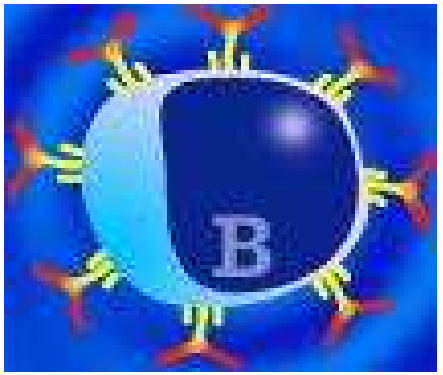
- instead of attacking the invaders, they attack the body's own cells that have become infected by viruses
- they also attack potential cancer cells, often before they form tumors
- they bind to cells using an antibody "bridge", then kill it by secreting a chemical (perforin) that makes holes in the cell membrane of the target cell.
- With enough holes, the cell will die, because water rushing inside the cell will induce osmotic swelling, and an influx of calcium may trigger apoptosis.

B -Lymphocytes

- There are 10 million different B-lymphocytes, each of which make a different antibody.
- The huge variety is caused by genes coding for abs changing slightly during development.
- There are a small group of clones of each type of B-lymphocyte

B -Lymphocytes

- At the clone stage antibodies do not leave the B-cells.
- The Abs are embedded in the plasma membrane of the cell and are called antibody receptors.



- When the receptors in the membrane recognise and antigen on the surface of the pathogen the B-cell divides rapidly.
- The antigens are presented to the B-cells by macrophages

Myeloid cells

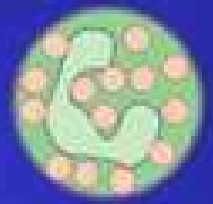
- Cell populations that are specialized to capture microbial and other antigens, display them to lymphocytes, and provide signals that stimulate the proliferation and differentiation of lymphocytes
- Cells of this type includes :
  - Granulocytes
  - Macrophages
  - Mast cells
  - Dendritic cells

Phagocytic cells

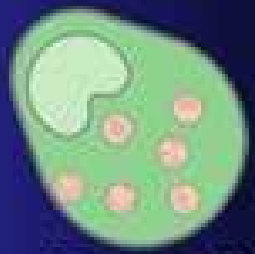
- Macrophages : Blood macrophage, Tissue Macrophage
- Function: Phagocytosis, Specific immune response, antitumour activity & Graft rejection
- Microphages :Neutrophils, Eosinophils, Basophils

Phagocytes and Their Relatives

Monocyte



Eosinophil

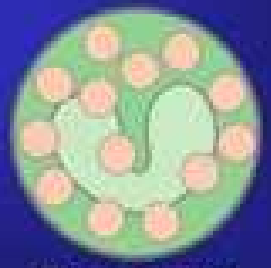


Mast cell

Macrophage

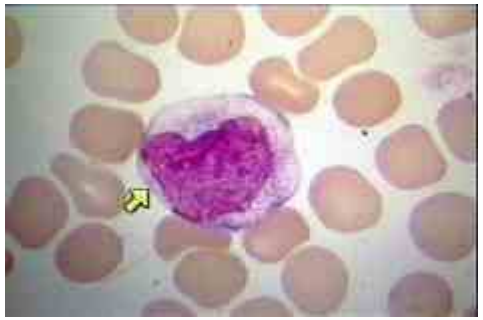
Dendritic cell

Neutrophil



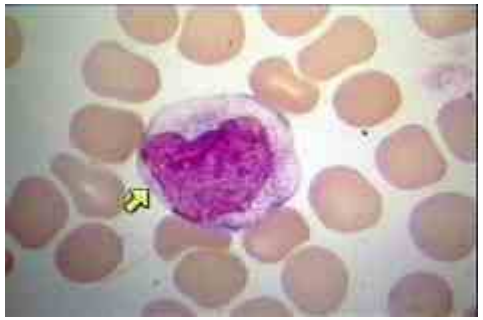
Basophil

Macrophages

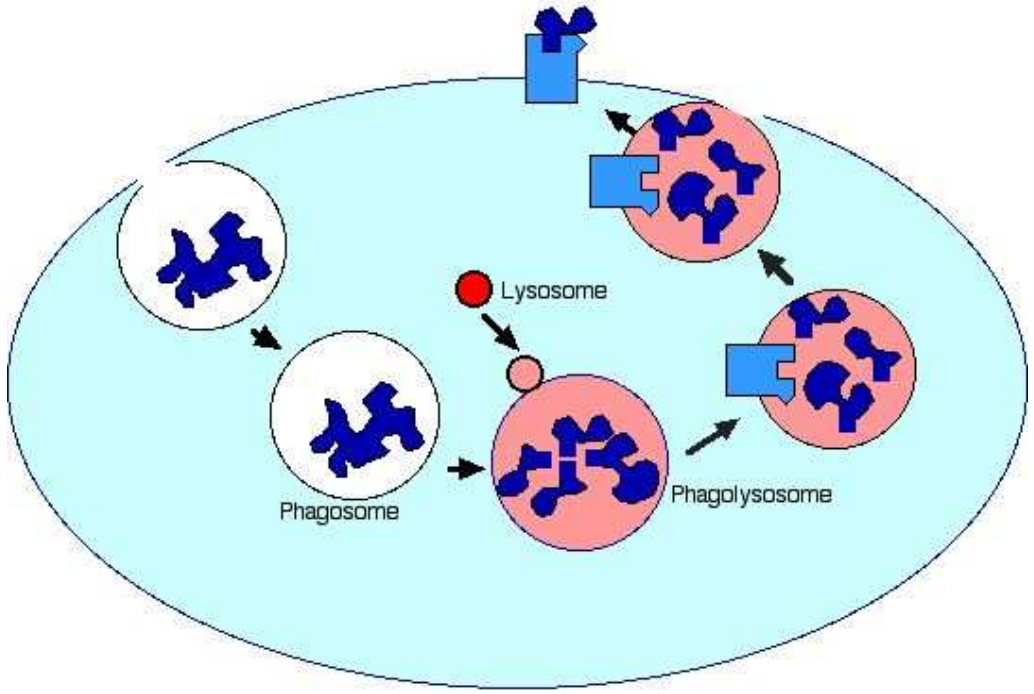


- Larger than neutrophils.
- Found in the organs, not the blood.
- Made in bone marrow as monocytes, called macrophages once they reach organs.
- Long lived
- **Initiate** immune responses as they display antigens from the pathogens to the lymphocytes.

Macrophages

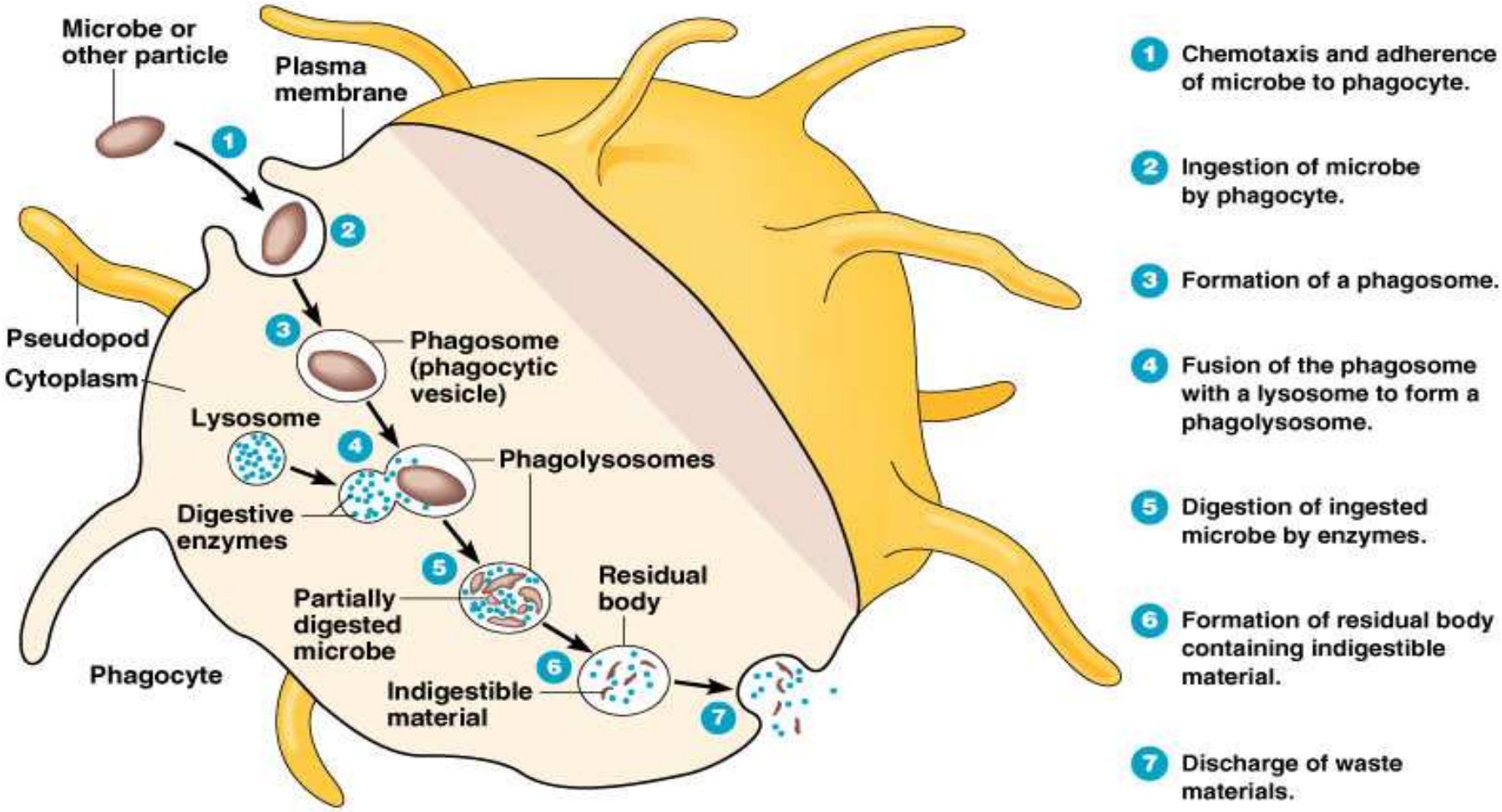


Antigen Presentation



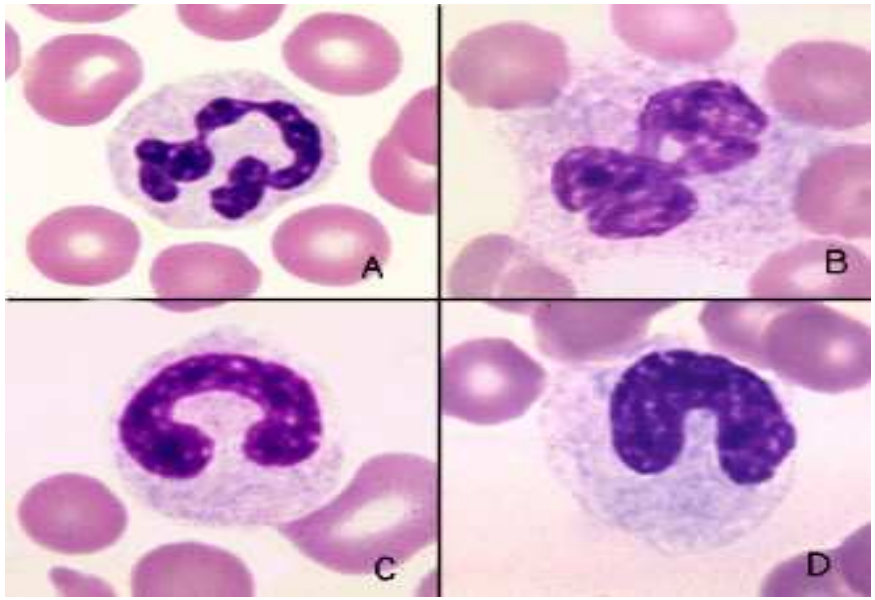
Macrophage ("Big Eater" = big phagocyte)

Phagocytosis



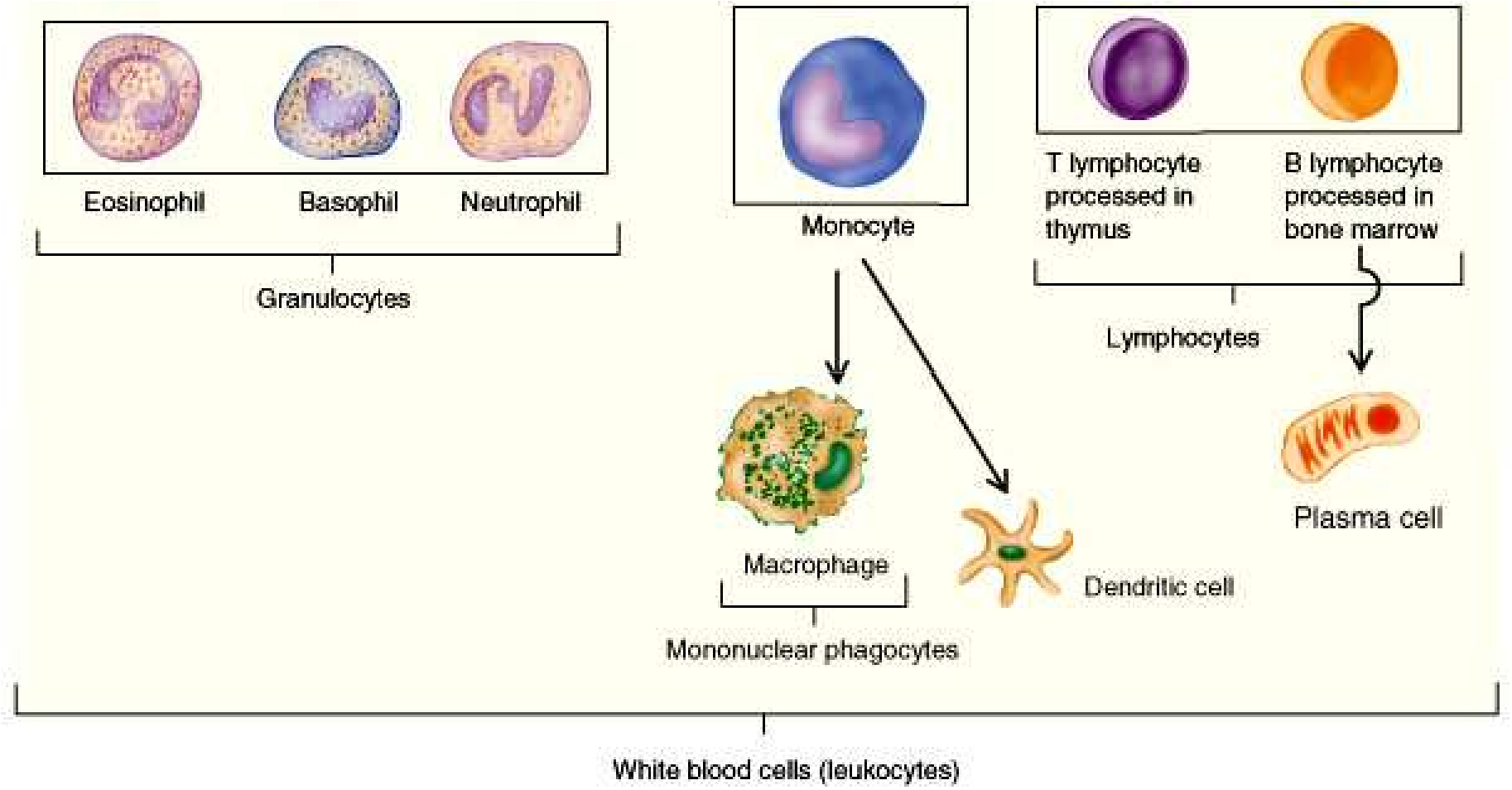
(a) Phases of phagocytosis

Neutrophils

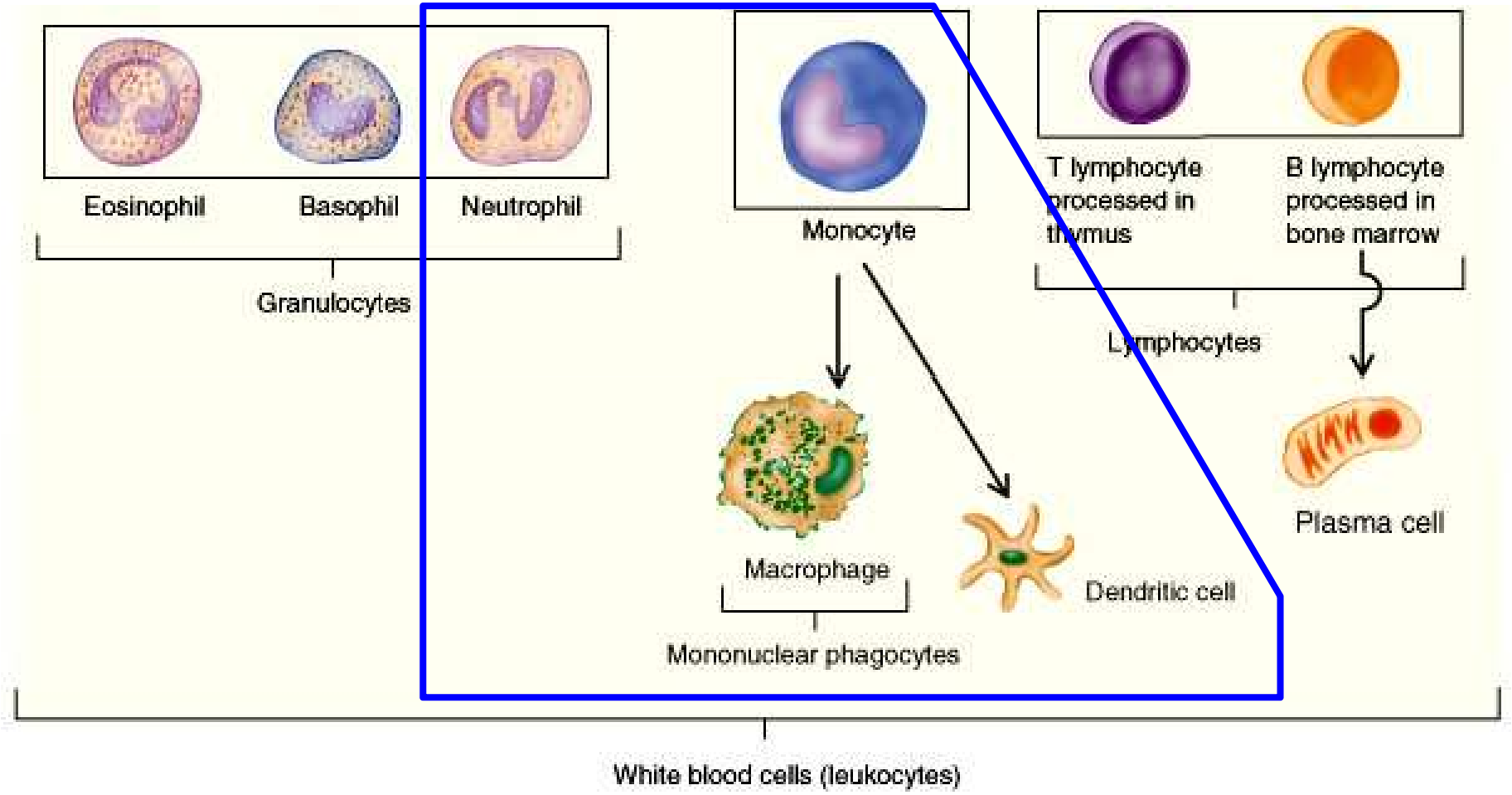


- 60% of WBCs
- ‘Patrol tissues’ as they squeeze out of the capillaries.
- Large numbers are released during infections
- Short lived – die after digesting bacteria
- Dead neutrophils make up a large proportion of puss.

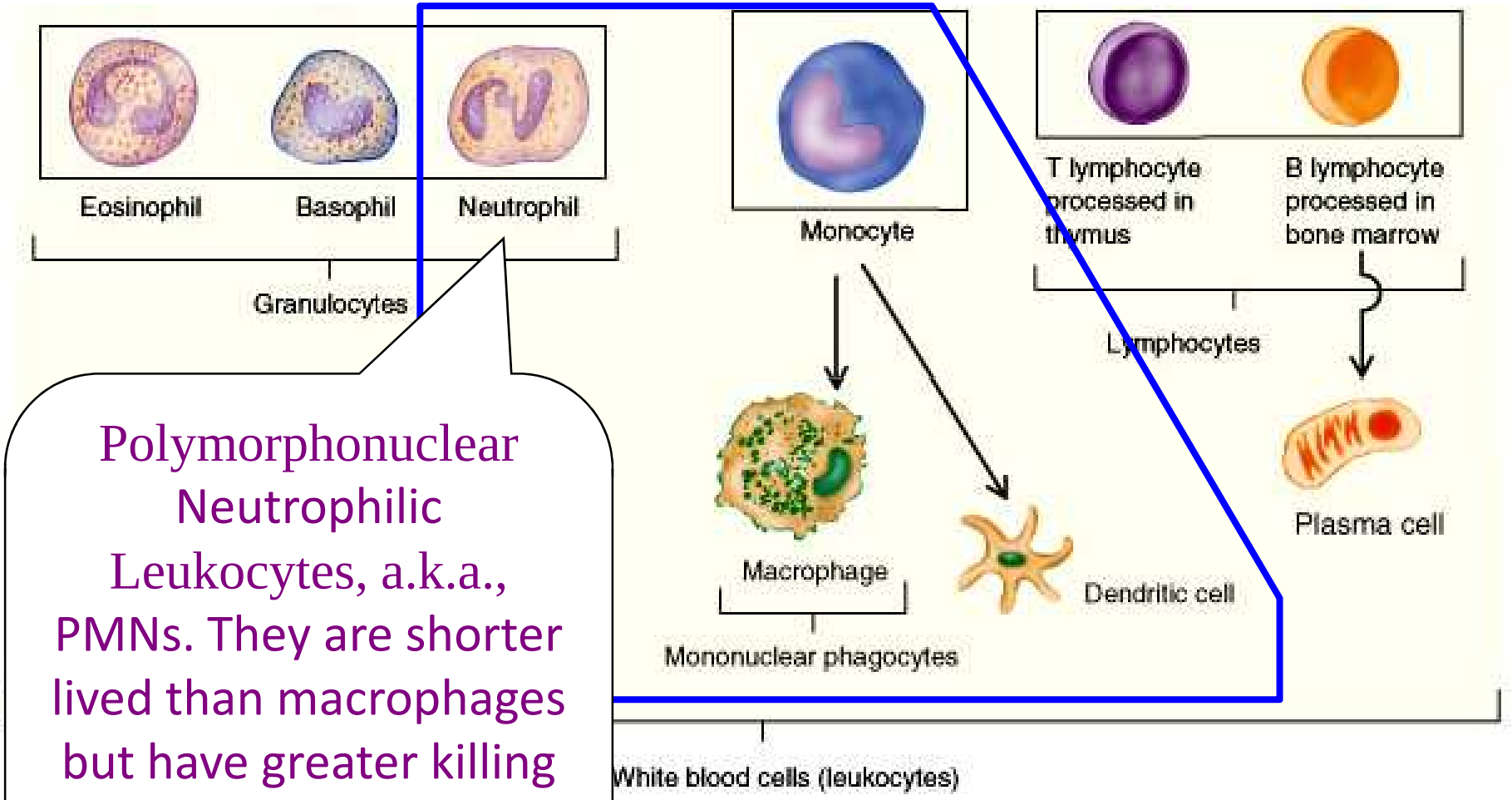
Leukocytes = White Blood Cells



Phagocytic Leukocytes

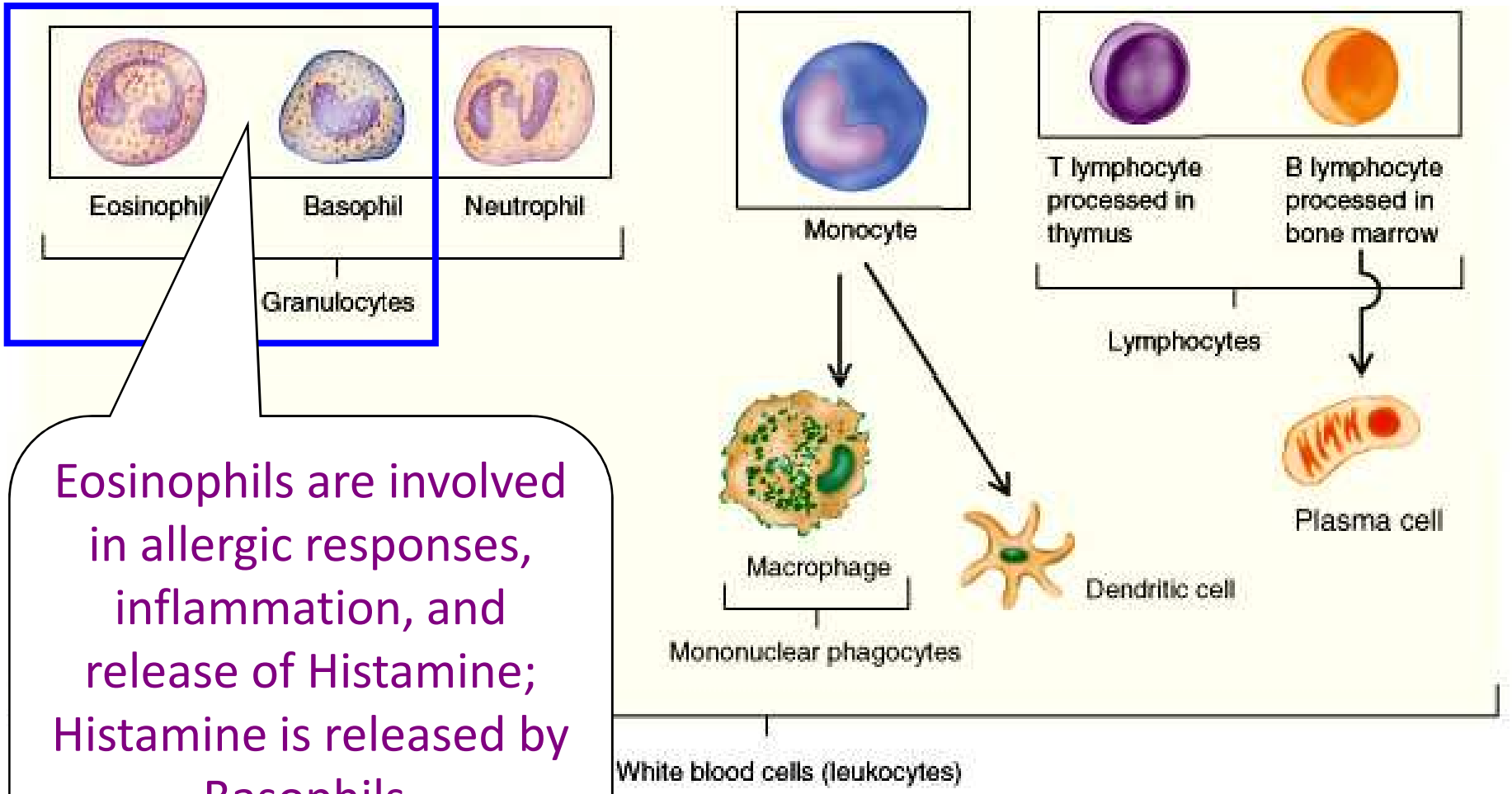


PMNs



Polymorphonuclear Neutrophilic Leukocytes, a.k.a., PMNs. They are shorter lived than macrophages but have greater killing power.

Non-Phagocytic Granulocytes



Eosinophils are involved in allergic responses, inflammation, and release of Histamine; Histamine is released by Basophils.

Mast cells/ Basophils

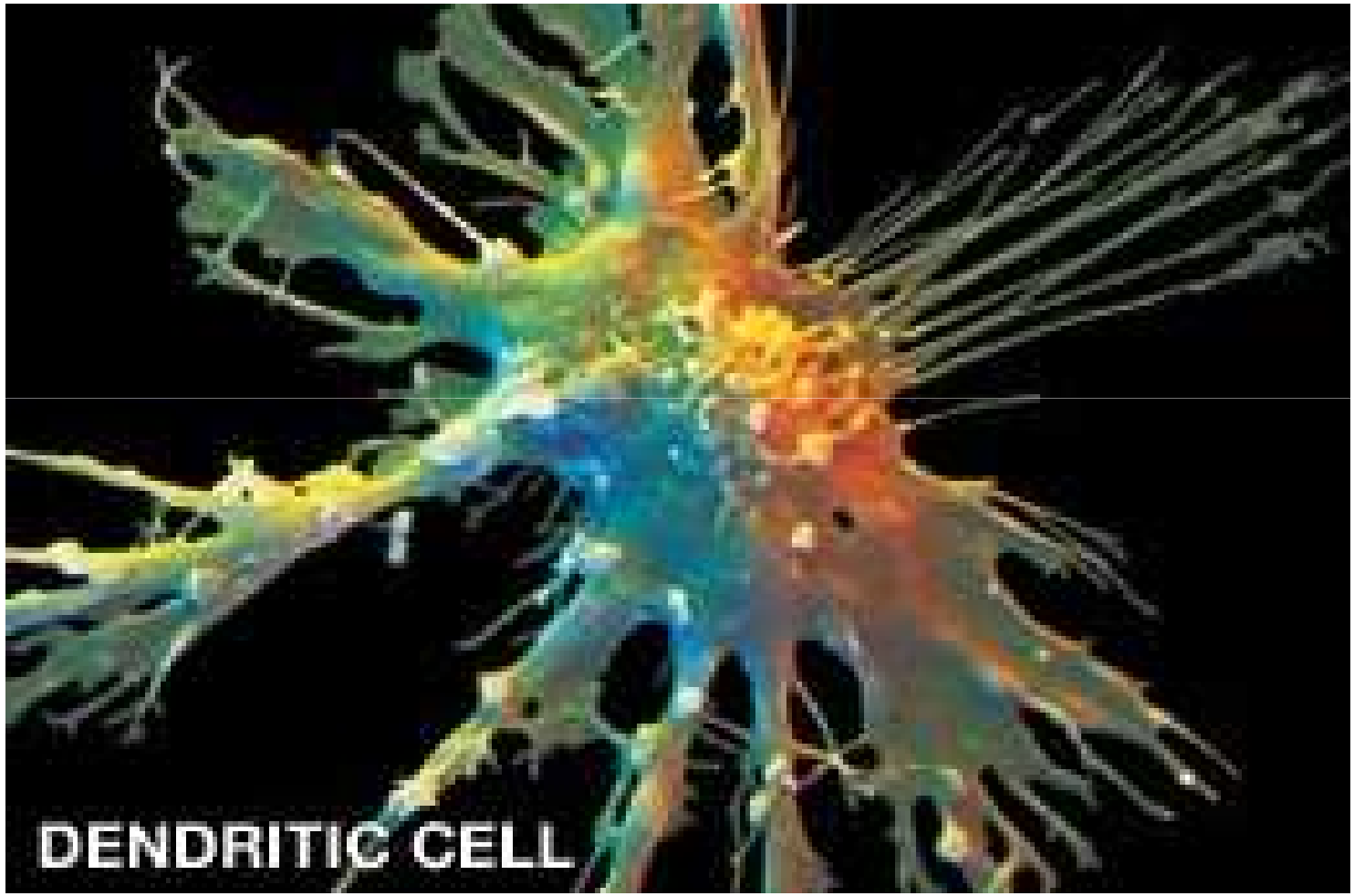
- are found in tissues like the skin, near blood vessels.
- are activated after antigen binds to a specific type of antibody called IgE that is attached to receptors on the mast cell.
- activated mast cells release substances that contribute to inflammation, such as histamine.
- mast cells are important in allergic responses but are also part of the innate immune response, helping to protect from infection.

- Dendritic cells : derived from bone marrow, possess MHC class II antigens, present in peripheral blood & peripheral lymphoid organ involved in the presentation of antigens to T cells during immune response

Dendritic Cells

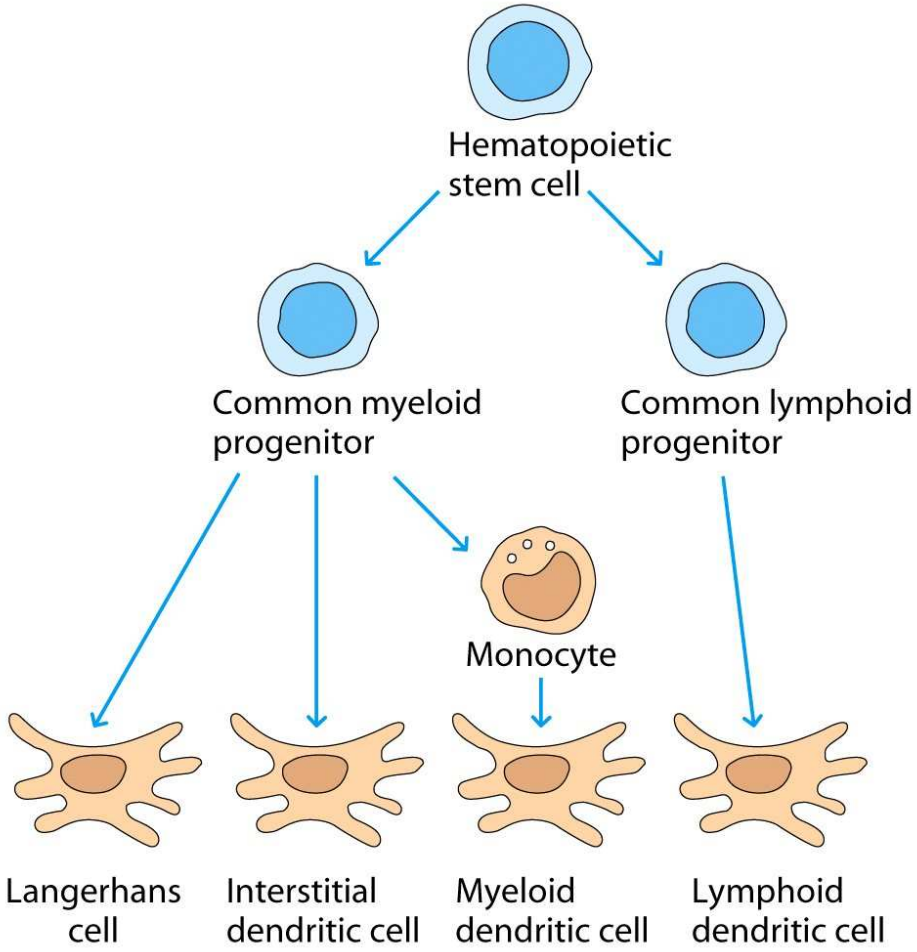
- Professional APCs
- Several Types
  - Langerhans (LC) found in skin
  - Circuilating DCs
    - Myeloid (MDC1 and MDC2)
    - Plasmacytoid
- Interstitial DCs, populate organs such as heart, lungs, liver, intestines
- Interdigitating DCs, T-cell areas of lymph nodes and Thymic medulla

Dendritic Cells



http:www.coleypharma.com

Developmental Pathway of DCs



Key Cells & Overview of their Function in Immune Defense

	Basophils and Mast Cells	*Neutrophils*	*Eosinophils*	*Monocytes and Macrophages*	*Lymphocytes and Plasma Cells*	*Dendritic Cells*
						
% of WBCs in blood	*Rare*	*50–70%*	*1–3%*	*1–6%*	*20–35%*	*NA*
Subtypes and nicknames		Called "polys" or "segs" Immature forms called "bands" or "stabs"		Called the mononuclear phagocyte system	B lymphocytes, Plasma cells T lymphocytes Cytotoxic T cells Helper T cells Natural killer cells Memory cells	Also called Langerhans cells, veiled cells
Primary function(s)	Release chemicals that mediate inflammation and allergic responses	Ingest and destroy invaders	Destroy invaders, particularly antibody-coated parasites	Ingest and destroy invaders Antigen presentation	Specific responses to invaders, including antibody production	Recognize pathogens and activate other immune cells by antigen presentation in lymph nodes
Classifications		*Phagocytes*				
		Granulocytes				
			Cytotoxic cells		*Cytotoxic cells (some types)*	
					Antigen-presenting cells	

Figure 24-4: Cells of the immune system

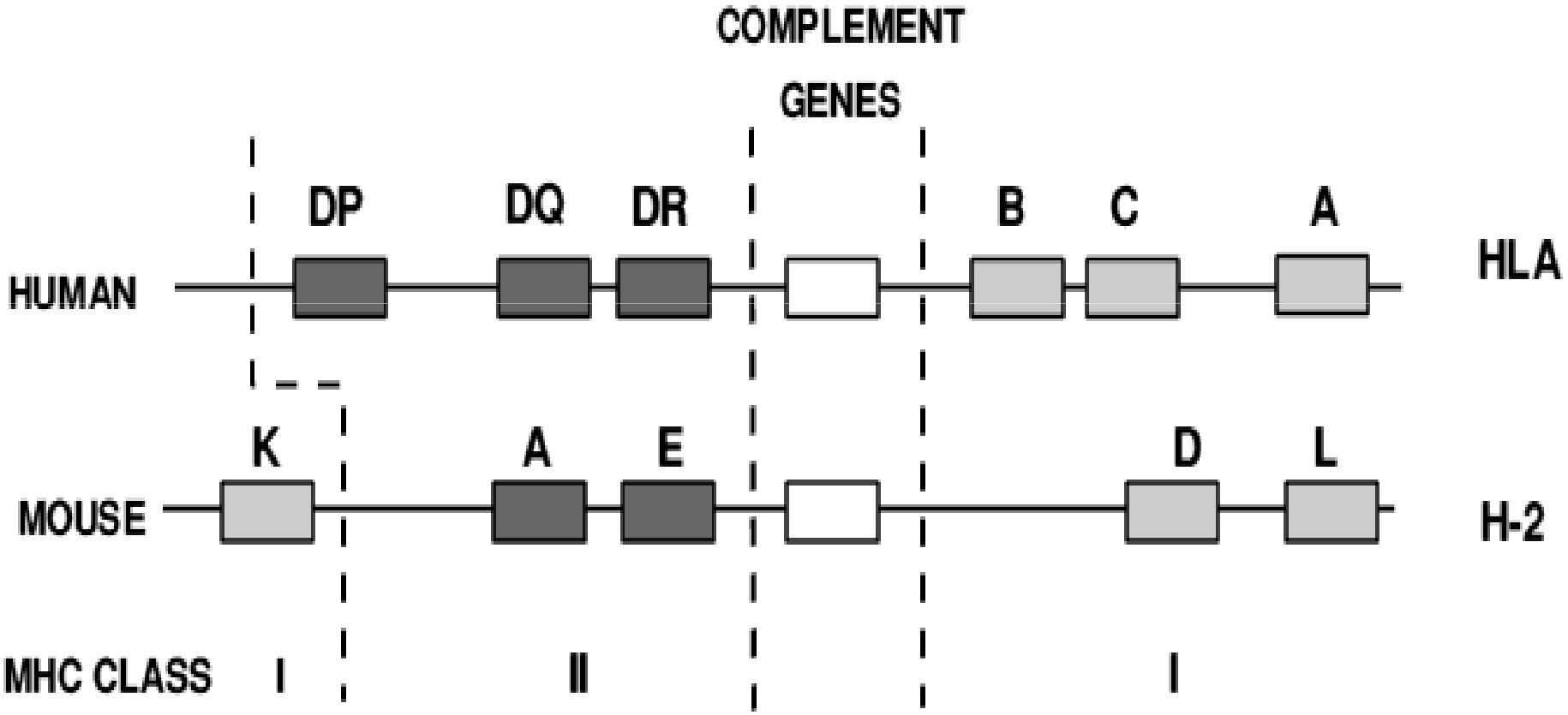
Major Histocompatibility Complex(MHC)

- Allograft
- Gorer(1930) identified the antigen responsible for allograft rejection in inbred mice & discover the Major histocompatibility complex , identified two blood group antigen. Antigen 1& 2
- H2 antigen : major histocompatible antigen
- MHC in humans: HLA complex
- Major transplantation antigen of man include Blood group, HLA system

The HLA complex

- HIstocompatibilty antigens means cell surface antigen that evoke immune response to an incompatible host resulting in allograft rejection. These alloantigen are present on surface of leucocytes in man & are called human leukocyte antigen(HLA) & sets of genes coding for them is name HLA complex.
- The HLA complex of genes is located on short arm of chromosome 6 & is grouped in three classes.

MHC genes on Chromosome 6

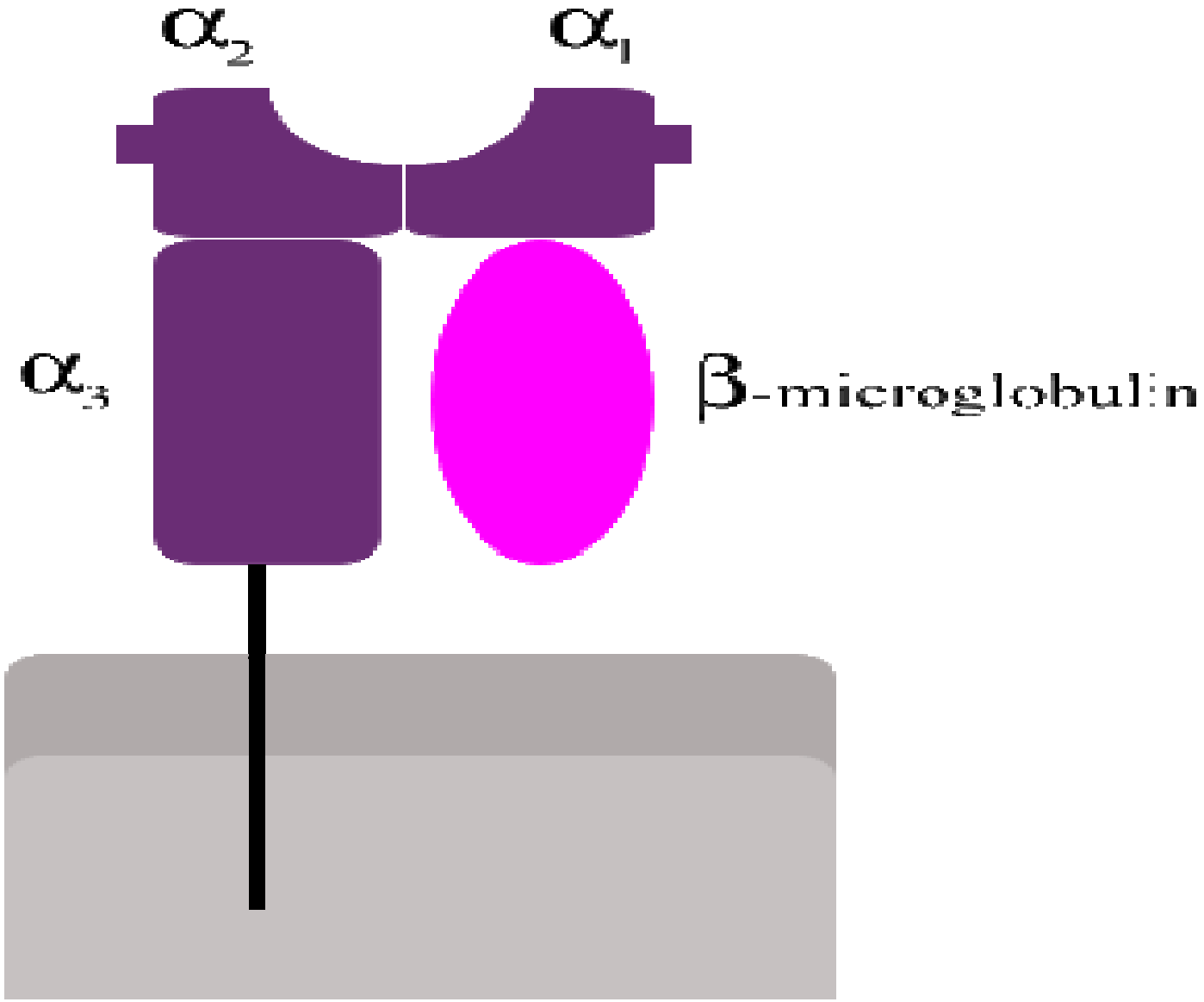


- Class1 (HLA-A,B,C) –
  determine histocompatibility and
  acceptance / rejection of allograft
- Class2 (HLA-DP,DQ,DR) –
  regulate the immune response
- Class3 (Complement loci encode for c2,c4 and
  factor B of complement system).

Class1 MHC Antigen

- Class 1 HLA genes are located furthest from the Centromere which are designated by HLA-A to HLA-F;of these HLA-A HLA-B and HLA – C are best studied.
- MHC antigens are found on the surface of all nucleated cells,abundantly on lymphoid cells and sparsely on cells of liver,lungs and kidney.
- The CD8 cells are specific for MHC 1 antigen.

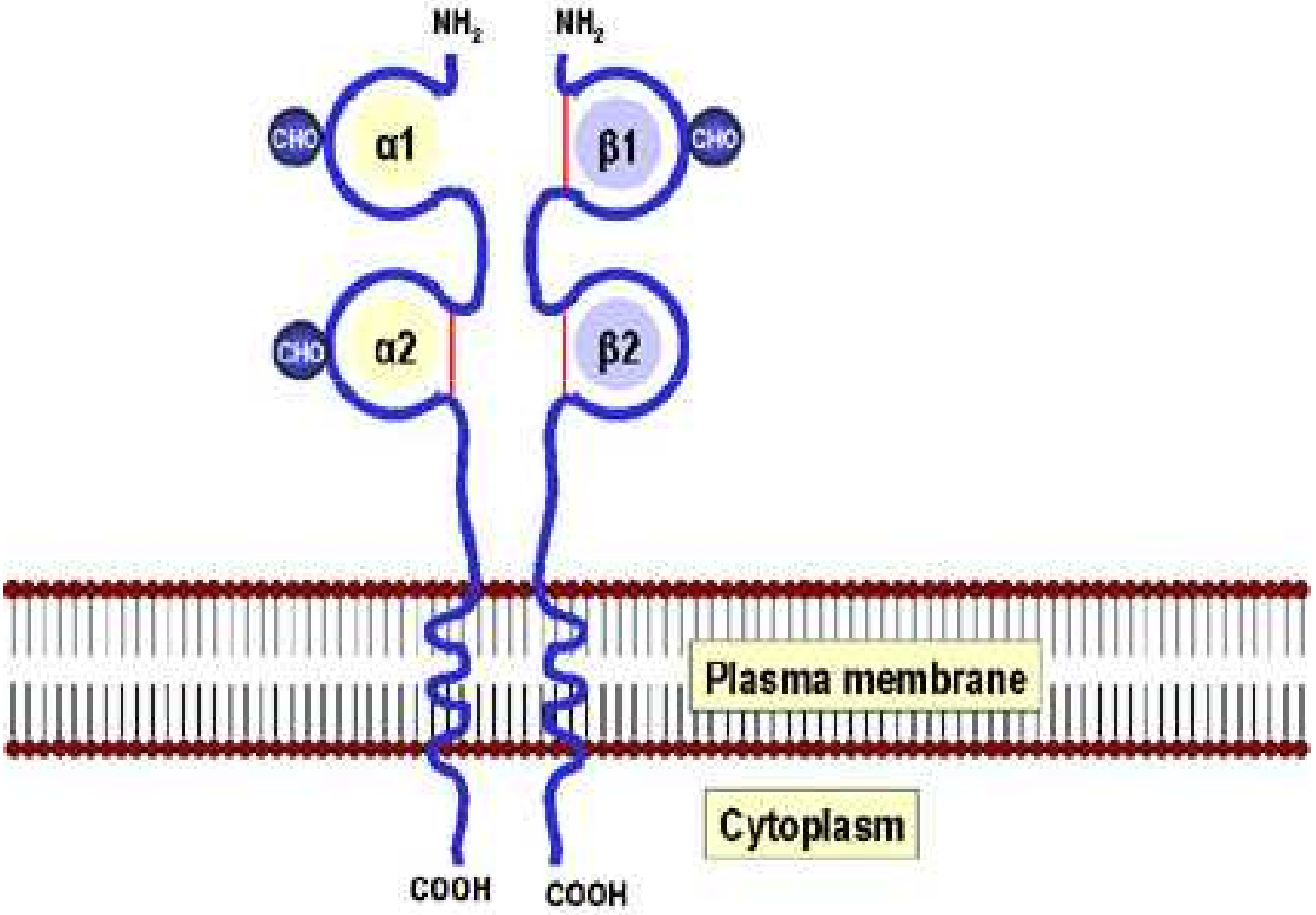
MHC class 1 molecule



Class2 MHC Antigen

- MHC class 2 genes have 3 major subregions,DP,DQ and DR and code for class 2 molecules.
- Class 2 molecules distribution limited to the antigen presenting cells.
- In man they are principally found on the surface of macrophages,monocytes,B lymphocytes and CD4 T lymphocytes.

MHC Class II molecule



HLA typing

- Indications of HLA typing :
- The HLA antigens are widely distributed in tissues except RBCs which contain only ABH antigens.
- HLA system is very useful in tissue typing and matching prior to transplantation.
- It has got application in paternity determination.
- HLA B27 is associated with ankylosing spondylitis.

HLA Typing

- Class 1 are detected by complement dependent cytotoxic reaction.
- Class 2 antigens are identified by mixed leukocyte reaction.
- Preformed cytotoxic antibodies in patient’s serum is tested by mixing with donor’s lymphocytes and complement.cytotoxic or cytolytic effect on donor’s lymphocytes indicates that recipient’s serum is reactive against the graft.

MHC Restriction

- T cell respond to processed antigen on macrophages only when they are presented self with MHC antigen
- Cytotoxic T cells- Class 1 MHC antigen
- Helper T cells – Class 2 MHC antigen

- Class I MHC molecules, found on almost all nucleated cells of the body
  - Display peptide antigens to cytotoxic T cells

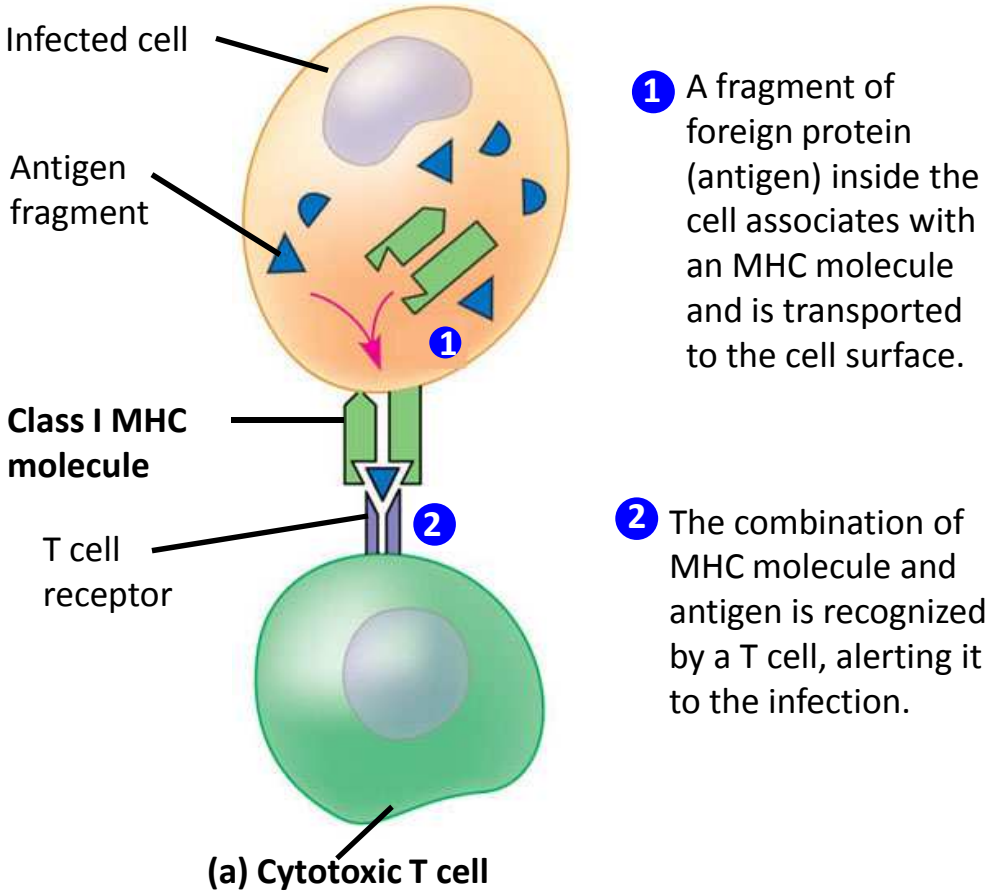


Figure 43.9a

- Class II MHC molecules, located mainly on dendritic cells, macrophages, and B cells
  - Display antigens to helper T cells

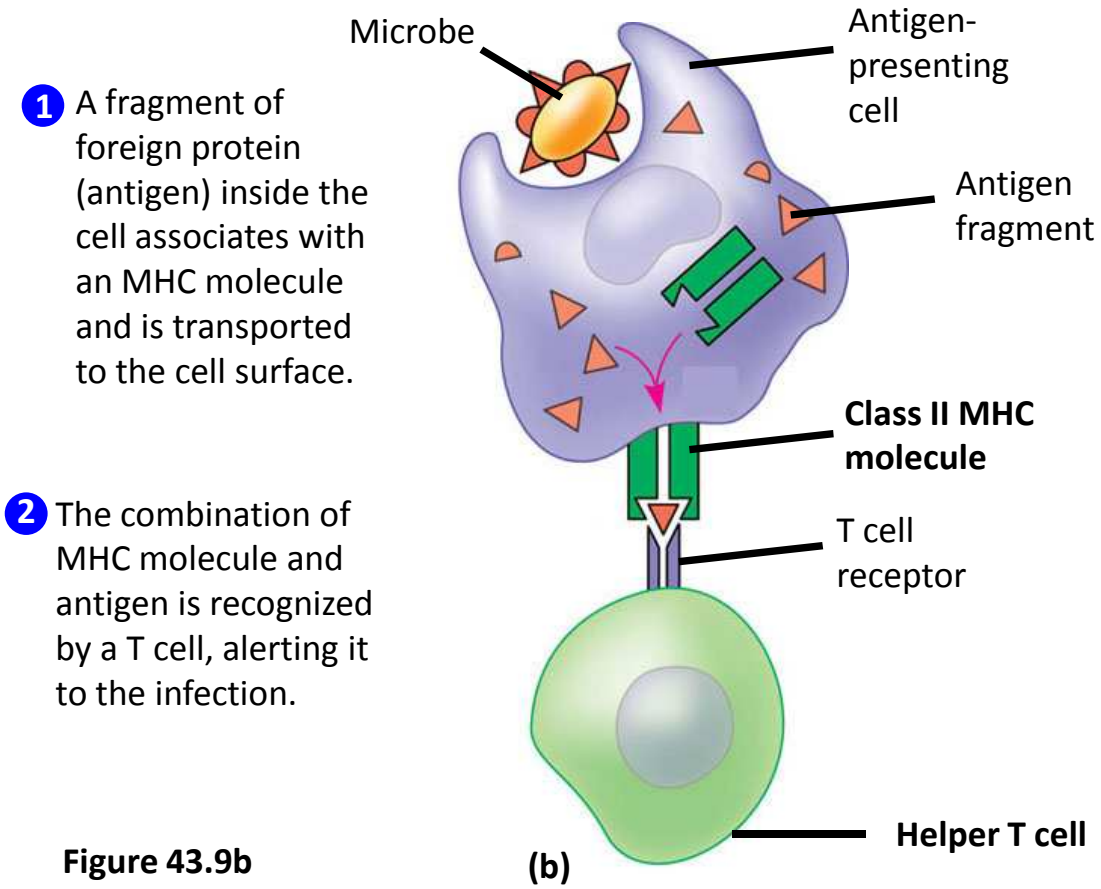


Figure 43.9b

Thank You