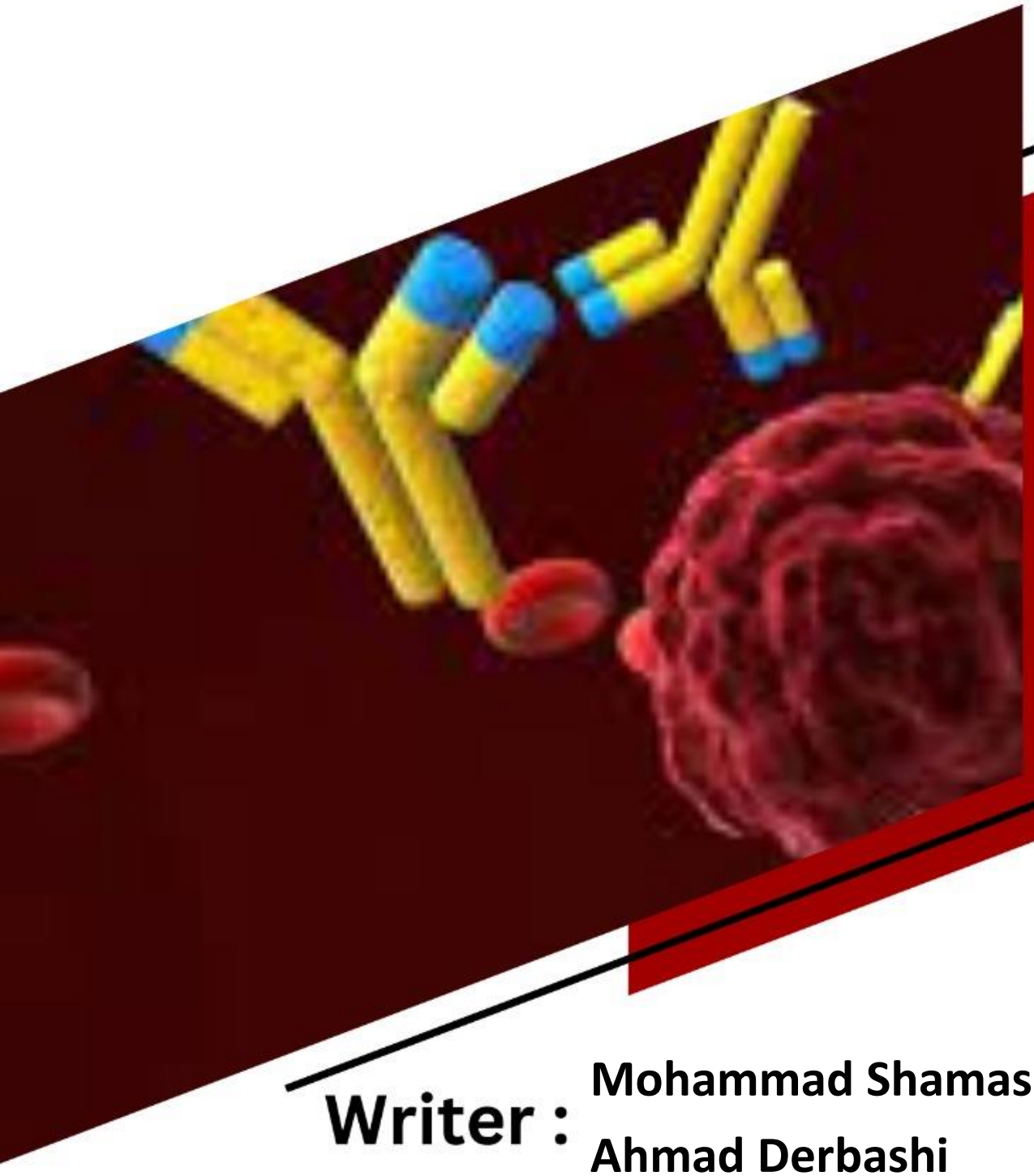
Doctor 021

IMMUNOLOGY

Sheet no. 4



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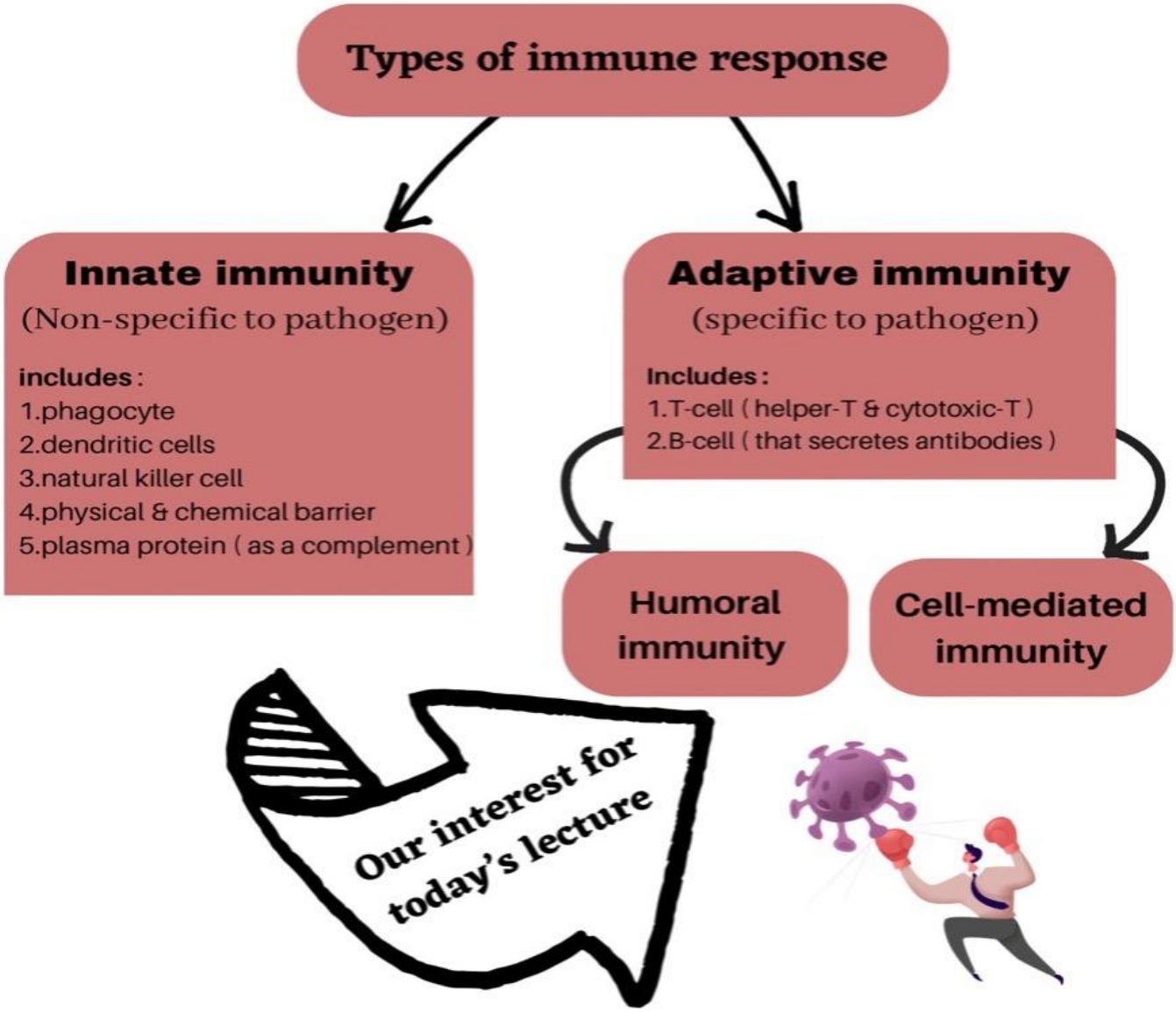
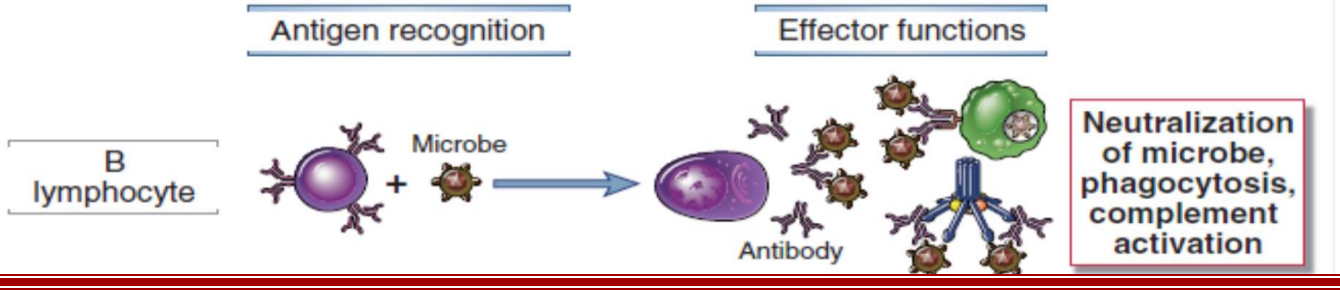


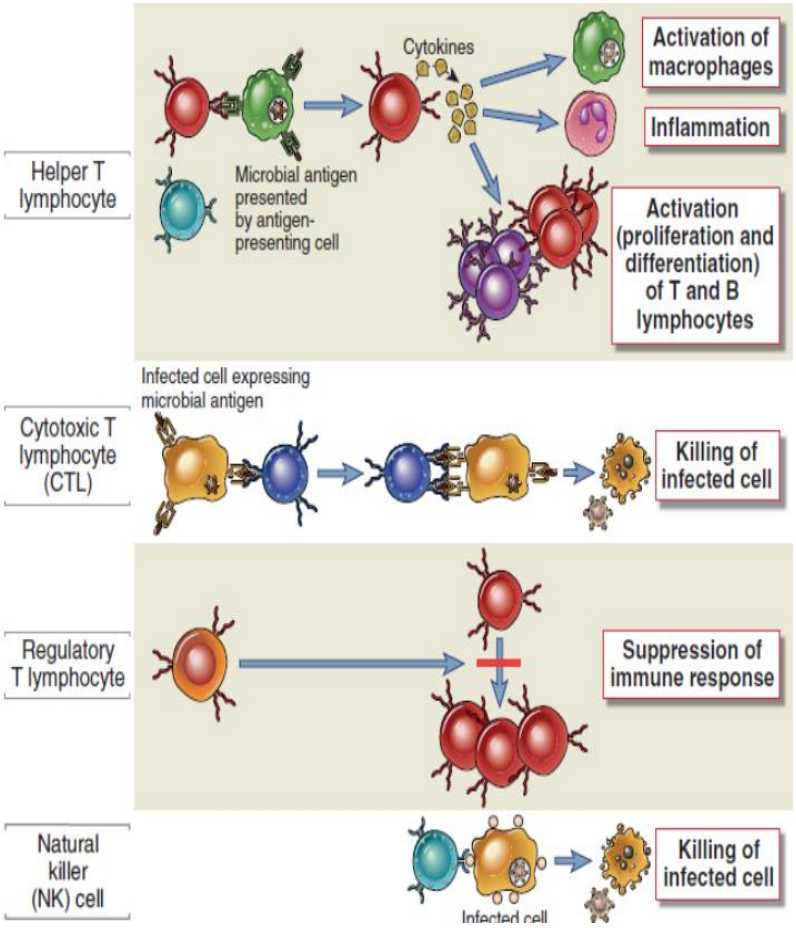
TYPES OF ADAPTIVE IMMUNITY:

1- Humoral immunity is mediated by molecules in the blood and mucosal secretions, called antibodies, which are produced by cells called B lymphocytes.

(humoral ; related to body fluid)



2- Cell-mediated immunity is mediated by T lymphocytes. Viruses and some bacteria, survive and proliferate inside phagocytes and other host cells, where they are inaccessible to circulating antibodies. Defense against such infections is a function of cell mediated immunity, which promotes the destruction of microbes residing in phagocytes or the killing of infected cells to eliminate reservoirs of infection.



(Through the action of perforin , granzymes enter the cytoplasm of the target cells and their serine protease function triggers the caspase cascade , which eventually lead to apoptosis (programmed cell death).

Cytotoxin-T cells way of killing infected cells

Remember:

-Perforin is a pore-forming protein, which forms pores in the plasma membrane of the infected cells .

-Granzymes is a family of structurally related serine proteases stored within the cytotoxic granules of cytotoxic lymphocytes .

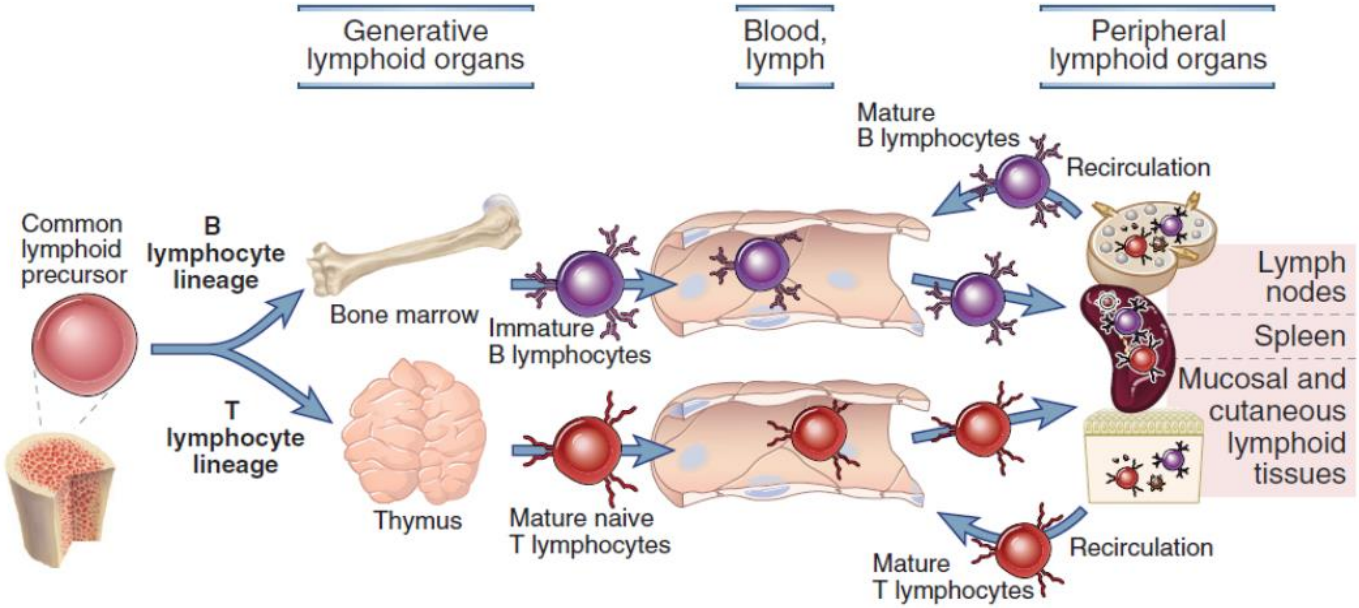
(The main difference between humoral & cell-mediated immunity **is** that in the humoral immunity , antibodies (which are produced by B cells) are accessible to the microbes & pathogens , while in (cell-mediated) the antibodies can not catch the antigens because they exist (and survive) in the infected cells , so in this case T cells kill the infected cells) .

MATURATION OF LYMPHOCYTES:

Lymphocytes develop from bone marrow stem cells and mature in the generative lymphoid organs (bone marrow for B cells and thymus for T cells) and then circulate through the blood to secondary lymphoid organs (lymph nodes, spleen, regional lymphoid tissues such as mucosa-associated lymphoid tissues) . Fully mature T cells leave the thymus , but immature B cells leave the bone marrow and complete their maturation in secondary lymphoid organs. (We will talk about these organs later on)

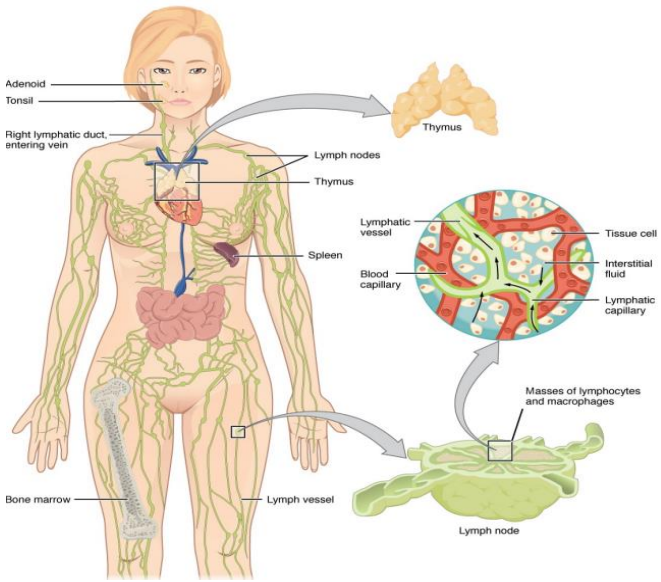
Naive lymphocytes (lymphocytes that haven't encountred antigens yet , may respond to foreign antigens in these secondary lymphoid tissues , or return by lymphatic drainage to the blood and recirculate through other secondary lymphoid organs .

Naive lymphocytes are called this until they meet their first antigen & get activated



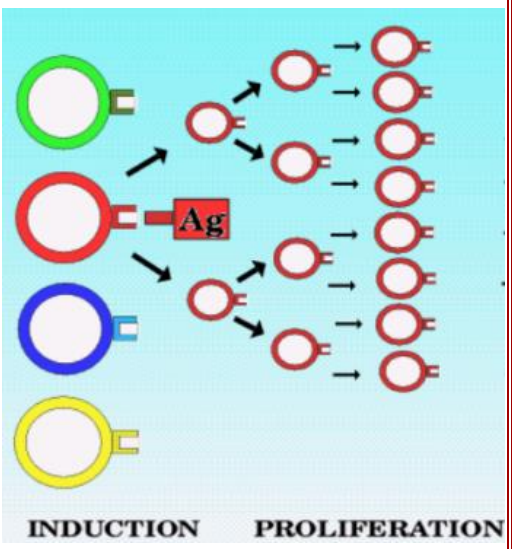
The total number of lymphocytes in a healthy adult about 5 × 1011. Of these:

- ~2% are in the blood .
- ~10% in the bone marrow .
- ~15% in the mucosal lymphoid tissues of the gastrointestinal and respiratory tract . (in these places there is a high probability of meeting an antigen)



•~65% in lymphoid organs (mainly the lymph nodes and spleen).

-Lymphocytes, the unique cells of adaptive immunity, are the only cells in the body that express clonally distributed antigen receptors, each with a fine specificity for a different antigenic determinant.



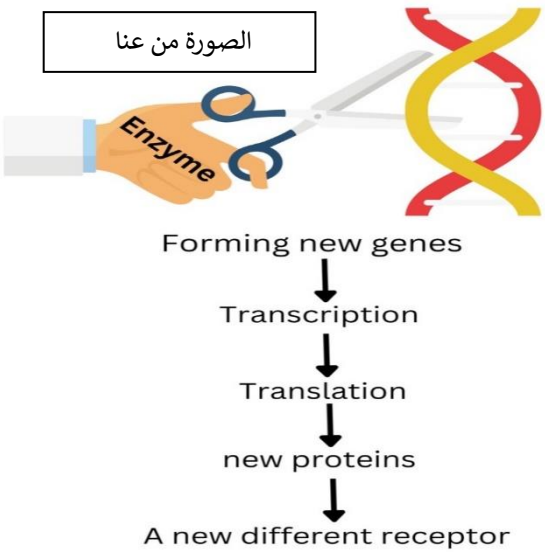
-Each clone of lymphocytes consists of the progeny of one cell and expresses antigen receptors with a single specificity.

-There are millions of lymphocyte clones in the body, enabling the organism to recognize and respond to millions of foreign antigens.

Now, How the enormously diverse repertoire of antigen receptors (millions) , and therefore specificities , is generated from a small number of genes for these receptors in the germline ?

Its due to Gene recombination.

-Genes encoding the antigen receptors of lymphocytes are formed by recombination of DNA segments during the maturation of these cells. There is a random aspect to these somatic recombination events that results in the generation of millions of different receptor genes and a highly diverse repertoire of antigen specificities among different clones of lymphocytes.



(Splicing and recombination of gene segments in different ways leads to translate new proteins which make the new receptors, so the lymphocyte has it specific receptor, and when activated it proliferates to produce colonies. so next time when it faces the same antigen there will be faster response (adaptive immune) .

-In contrast with most organs, such as the heart, which does the same job throughout life, the immune system needs to adapt to an environment that is always changing. This problem is solved by investing in strategies that exploit the power of random change itself.

-Using randomness in this way creates waste (because we will have useless lymphocytes with receptors bind to no antigens) but preserves responsiveness (immune system will response to probably all antigens in life).

Adaptive immunity does not mean that when the body is exposed to new antigen, it starts forming receptors for the first time specifically for this antigen, **THE BODY ALREADY HAS**, but it increases the number for next times, to have a very fast response.

Tonegawa's Nobel Prize work elucidated the genetic mechanism of the adaptive immune system, which had been the central question of immunology for over 100 years. Prior to Tonegawa's discovery, one early idea to explain the adaptive immune system suggested that each gene produces one protein; however, there are under 19,000 genes in the human body which nonetheless can produce millions of antibodies.

TABLE 2–2 Lymphocyte Classes

Class	Functions	Antigen Receptor and Specificity	Selected Phenotype Markers	Percentage of Total Lymphocytes (Human)		
				Blood	Lymph Node	Spleen
αβ T lymphocytes						
$CD4^+$ helper T lymphocytes	B cell differentiation (humoral immunity) Macrophage activation (cell-mediated immunity) Stimulation of inflammation	αβ heterodimers Diverse specificities for peptide–class II MHC complexes	$CD3^+$, $CD4^+$, $CD8^-$	50-60*	50-60	50-60
$CD8^+$ cytotoxic T lymphocytes	Killing of cells infected with viruses or intracellular bacteria; rejection of allografts	αβ heterodimers Diverse specificities for peptide–class I MHC complexes	$CD3^+$, $CD4^+$, $CD8^-$	20-25	15-20	10-15
Regulatory T cells	Suppress function of other T cells (regulation of immune responses, maintenance of self-tolerance)	αβ heterodimers Unresolved	$CD3^+$, $CD4^+$, $CD25^+$ (most common, but other phenotypes as well)	Rare	10	10
γδ T lymphocytes	Helper and cytotoxic functions (innate immunity)	γδ heterodimers Limited specificities for peptide and nonpeptide antigens	$CD3^+$, $CD4^+$, and CD8 variable			
B lymphocytes	Antibody production (humoral immunity)	Surface antibody Diverse specificities for all types of molecules	Fc receptors; class II MHC; CD19, CD21	10-15	20-25	40-45
Natural killer cells	Cytotoxic killing of virus-infected or damaged cells (innate immunity)	Various activating and inhibitory receptors Limited specificities for MHC or MHC-like molecules	CD16 (Fc receptor for IgG)	10	Rare	10
NKT cells	Suppress or activate innate and adaptive immune responses	αβ heterodimers Limited specificity for glycolipid-CD1 complexes	CD16 (Fc receptor for IgG); CD3	10	Rare	10

*In most cases, the ratio of $CD4^+CD8^-$ to $CD8^+CD4^-$ is about 2:1.
IgG, immunoglobulin G; MHC, major histocompatibility complex.

TISSUES OF THE IMMUNE SYSTEM

-Lymphocytes and APCs are localized and concentrated in anatomically defined tissues or organs, which are also the sites where foreign antigens are

transported and concentrated.
The role of these sites is to optimize the cellular interactions necessary for antigen recognition and lymphocyte activation in adaptive immune response.

These lymphoid tissues are classified as:

1-Generative organs, also called primary or central lymphoid organs , where lymphocytes first express antigen receptors and attain phenotypic and functional maturity.
2-Peripheral organs , also called secondary lymphoid organs , where lymphocyte responses to foreign antigens are initiated and develop.

GENERATIVE ORGANS , (PRIMARY LYMPHOID ORGANS)

A-Bone marrow: The bone marrow is the site of generation of most mature circulating blood cells, including red cells, granulocytes, and monocytes, and the site of early events in B cell maturation.

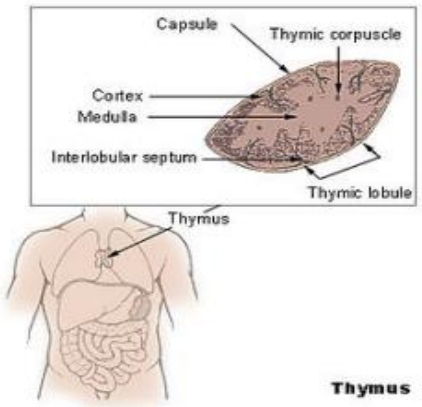
-The generation of all blood cells, called hematopoiesis occurs initially, during fetal development, in blood islands of the yolk sac and the para-aortic mesenchyme, then shifts to the liver between the third and fourth months of gestation, and gradually shifts again to the bone marrow.

-At birth, hematopoiesis takes place mainly in the bones throughout the skeleton, but it becomes restricted increasingly to the marrow of the flat bones. (as growing up hematopoiesis takes place in long bones then in flat bones in adults)

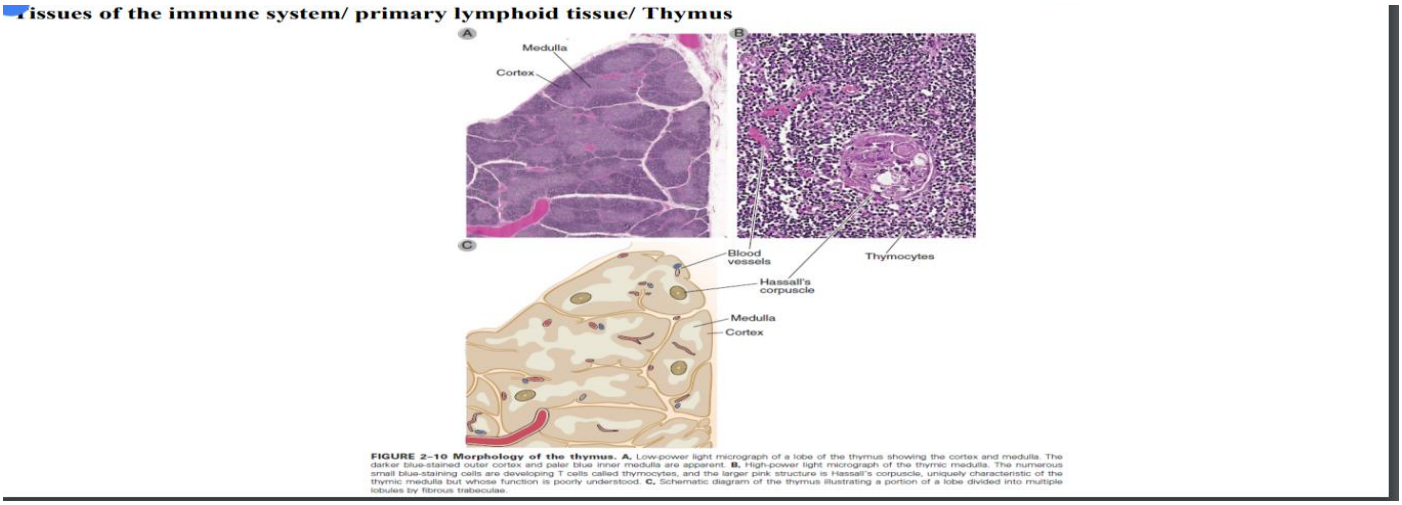
B-Thymus: The thymus is the site of T cell maturation. The thymus is a bilobed organ situated in the anterior mediastinum. Each lobe is divided into multiple lobules by fibrous septa, and each lobule consists of an outer cortex and an inner medulla. (Thymus is right behind the sternum)

-A subset of epithelial cells found only in the medulla, called thymic medullary epithelial cells (often abbreviated as TMEC), play a special role in presenting self-antigens to developing T cells and causing their deletion. (TMEC have special genes that can express different self-antigens (same self-antigens

produced by brain, liver, etc..) , and when T cells interact with them they get killed , thus no T cells will attack our self-antigens throughout our body).

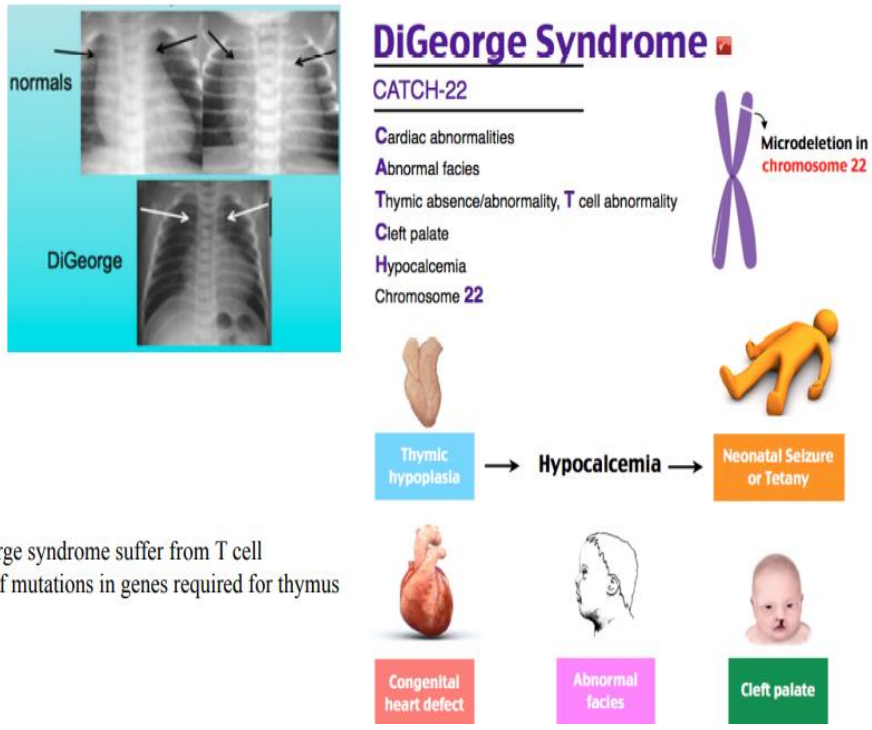


-Maturation in the thymus begins in the cortex, and as thymocytes mature, they migrate toward the medulla, so that the medulla contains mostly mature T cells.



NOTE: By the early teens, the thymus begins to atrophy and thymic stroma is mostly replaced by adipose (fat) tissue.

These 2 slides are talking about the absence of thymus.



Humans with DiGeorge syndrome suffer from T cell deficiency because of mutations in genes required for thymus development.

Nude mice lack thymus and hair (good model to study the absence of T cells).

In the "nude" mouse strain, which has been widely used in immunology research, a mutation in the gene encoding a transcription factor causes a failure of differentiation of certain types of epithelial cells that are required for normal development of the thymus and hair follicles. Consequently, these mice lack T cells and hair.

PERIPHERAL ORGANS, (SECONDARY LYMPHOID ORGANS)

The lymphatic system, which consists of specialized vessels that drain fluid from tissues into and out of lymph nodes and then into the blood, is essential for tissue fluid homeostasis and immune responses .

The lymphatic system collects microbial antigens from their portals of entry and delivers them to lymph nodes, where they can stimulate adaptive immune responses. (It collects the antigen or could be antigen binding to APC's cell).

Microbes/ antigens, Dendritic cells, and inflammatory mediators reach lymph nodes from the tissue.

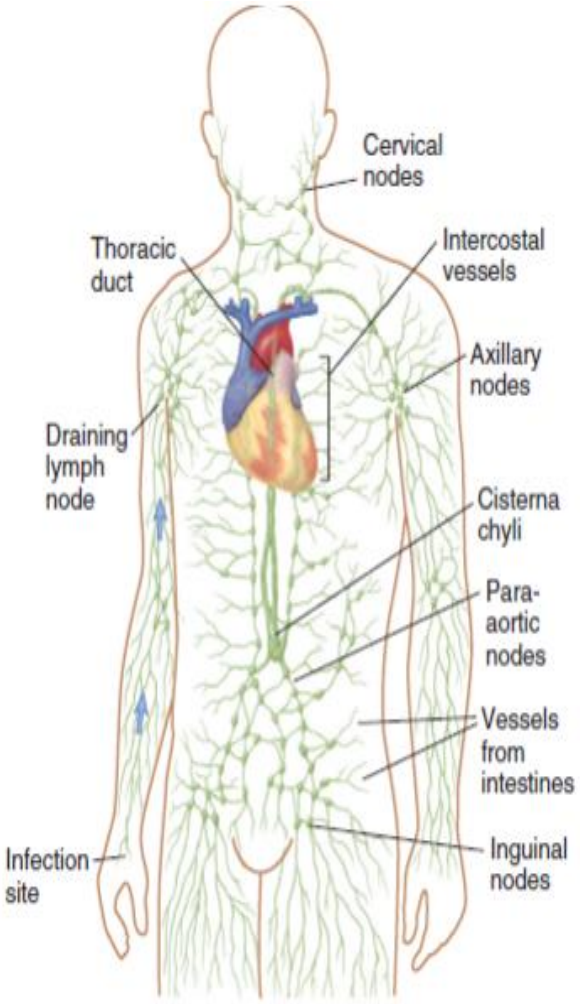
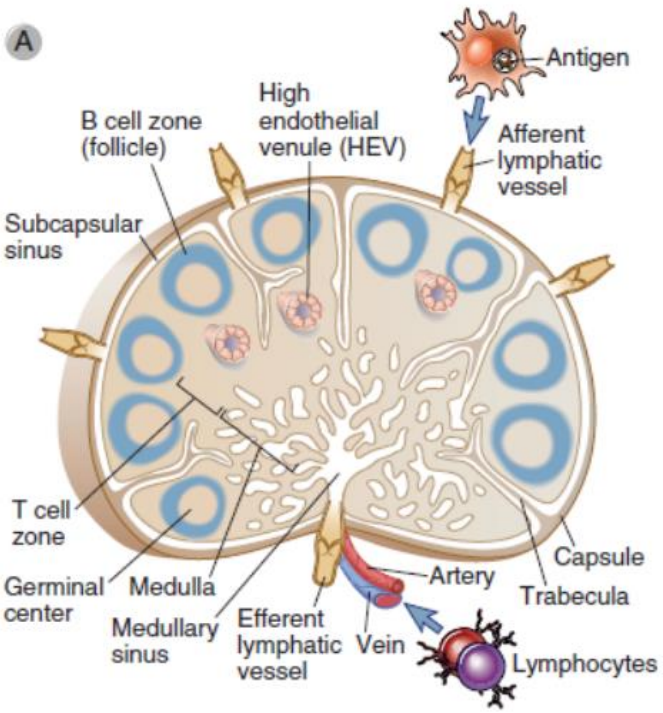


FIGURE 2-11 The lymphatic system. The major lymphatic vessels, which drain into the inferior vena cava (and superior vena cava, not shown), and collections of lymph nodes are illustrated. Antigens are captured from a site of infection and the draining lymph node to which these antigens are transported and where the immune response is initiated.

1.Lymph nodes are encapsulated, vascularized secondary lymphoid organs with anatomic features that favor the initiation of adaptive immune responses to antigens carried from tissues by lymphatics.



Follicles are the B cell zones. They are in the lymph node cortex and are organized around FDCs, which have processes that interdigitate to form a dense reticular network. While T-cells in the parafollicular cortex.

The anatomic segregation of B and T lymphocytes in distinct areas of the node is dependent on cytokines that are secreted by lymph node stromal cells in each area and that direct the migration of the lymphocytes, The type of cytokines that determine where B and T cells reside in the node are called **chemokines** (chemoattractant cytokines) , which bind to chemokine receptors on the lymphocytes.

The B and T lymphocytes that came from the bone marrow and thymus respectively via blood vessels and reach the cortex through HEV (high endothelial vessel, a type of blood vessel). Depending on specific chemokines, they will reside in their anatomical locations within the lymph node: -

B cells ---> B cells follicle which has follicular dendritic cells.

T cells ---> Parafollicular area.

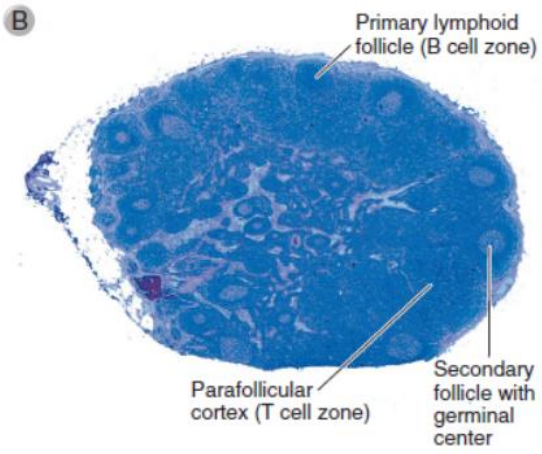
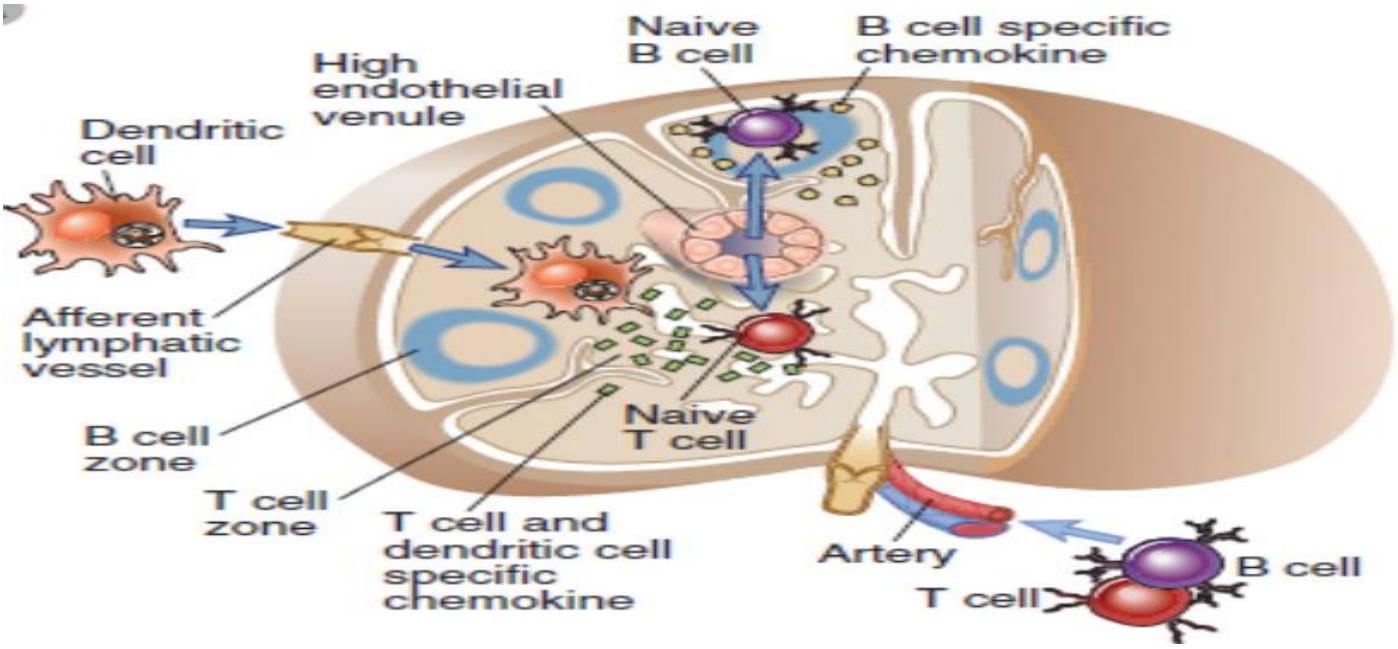
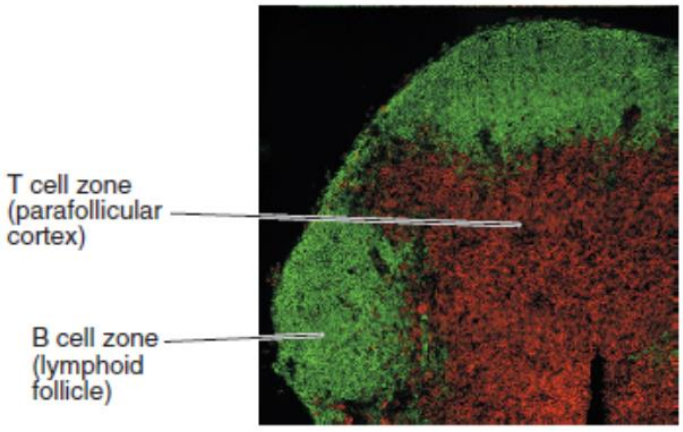


FIGURE 2–12 Morphology of a lymph node. A, Schematic diagram of a lymph node illustrating the T cell–rich and B cell–rich zones and the routes of entry of lymphocytes and antigen (shown captured by a dendritic cell). **B,** Light micrograph of a lymph node illustrating the T cell and B cell zones. *(Courtesy of Dr. James Gulizia, Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts.)*



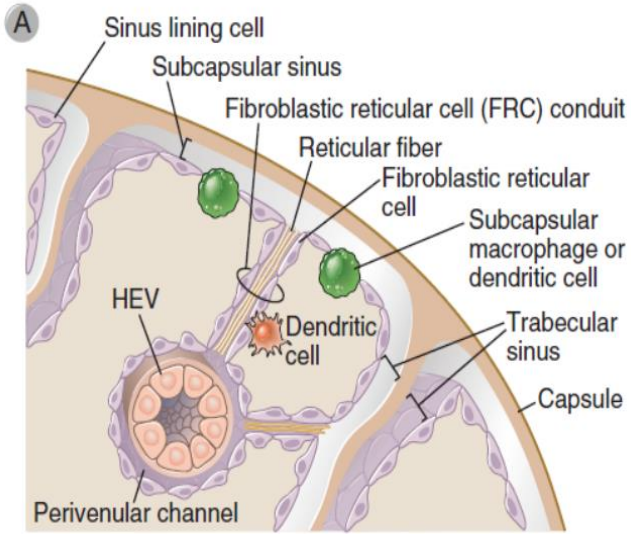
The anatomic segregation of T and B cells ensures that each lymphocyte population is in close contact with the appropriate APCs, that is, T cells with dendritic cells and B cells with FDCs.

The diagram (in the right) shows this demarcation by immunofluorescent microscopy.



where the antigen goes depends on its molecular weight:

Viruses and other high molecular-weight antigens are taken up by sinus macrophages and presented to cortical B lymphocytes.



Low-molecular-weight soluble antigens are transported to resident dendritic cells that extend processes and capture and pinocytose soluble

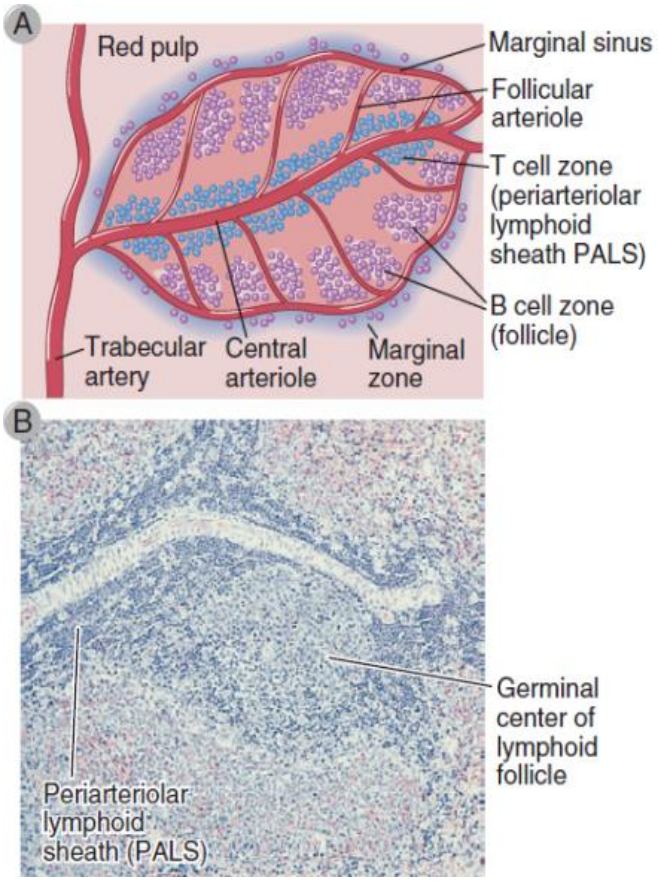
antigens. The contribution of this pathway of antigen delivery may be important for initial T cell immune responses to some microbial antigens, but larger and sustained responses require delivery of antigens to the node by tissue dendritic cells.

All antigens in TISSUES have been presented to lymph nodes. However, some antigens still manage to enter directly to the blood stream. Eliminating them is the role of the second organ of peripheral type, which is :

2- spleen

The spleen is a highly vascularized organ whose major functions are to remove aging and damaged blood cells and particles (such as immune complexes and opsonized microbes) from the circulation and to initiate adaptive immune responses to blood-borne antigens.

The splenic parenchyma (the spleen's functioning tissue) is anatomically and functionally divided into **the red pulp**, composed mainly of blood-filled vascular sinusoids, and the lymphocyte-rich **white pulp**.



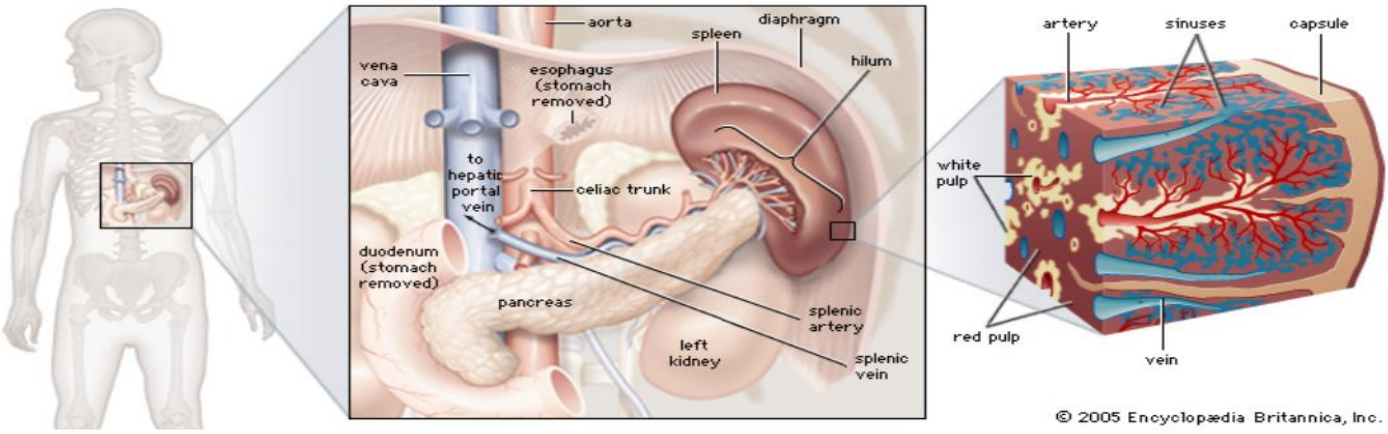
Blood enters the spleen through a single splenic artery, which pierces the capsule at the hilum and divides into progressively smaller branches that remain surrounded by protective and supporting fibrous trabeculae.

The red pulp macrophages serve as an important filter for the blood, removing microbes, damaged cells.

The function of the white pulp is to promote adaptive immune responses to blood-borne antigens.

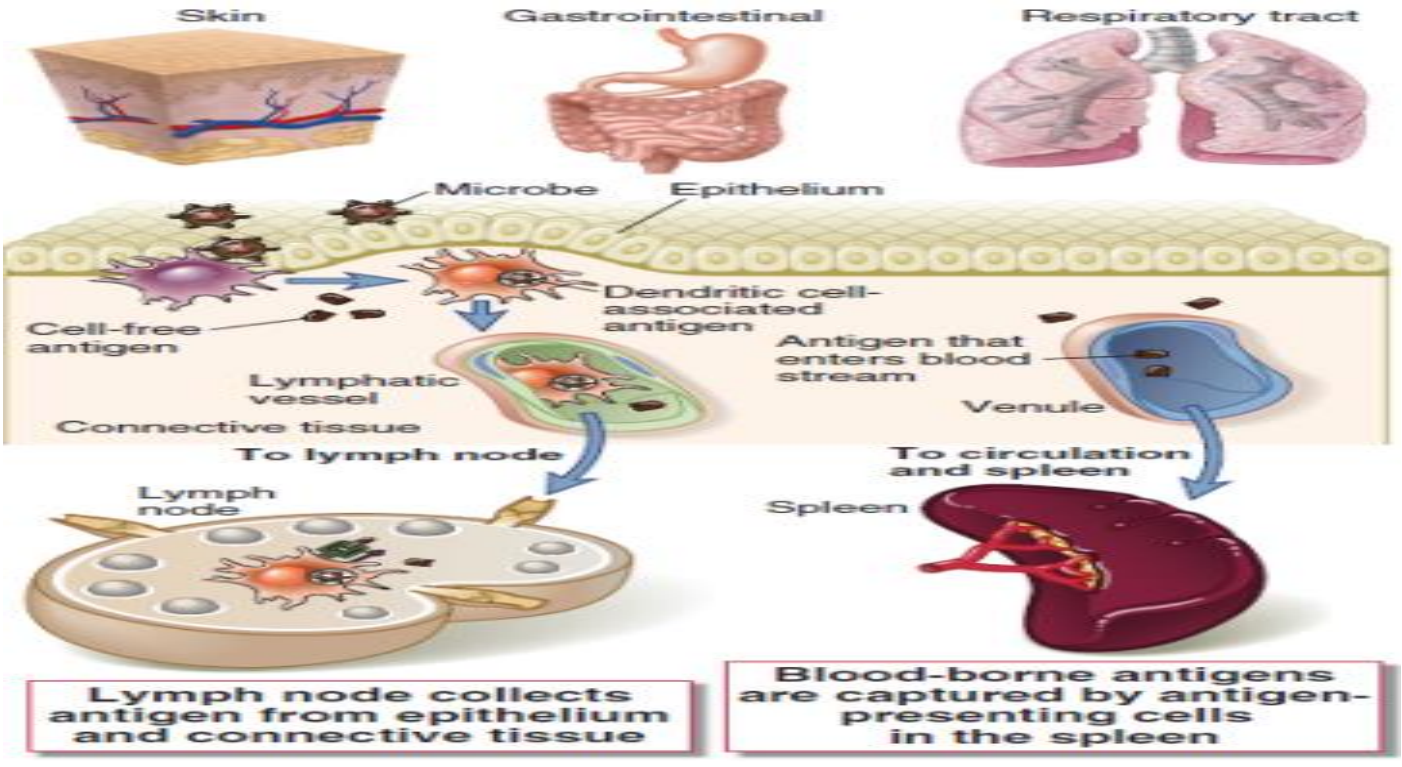
The white pulp is organized around central arteries, which are branches of the splenic artery distinct from the branches that form the vascular sinusoids. Several smaller branches of each central artery pass through the lymphocyte-rich area and drain into a marginal sinus.

A region of specialized cells surrounding the marginal sinus, called **the marginal zone**, forms the boundary between the red and white pulp.

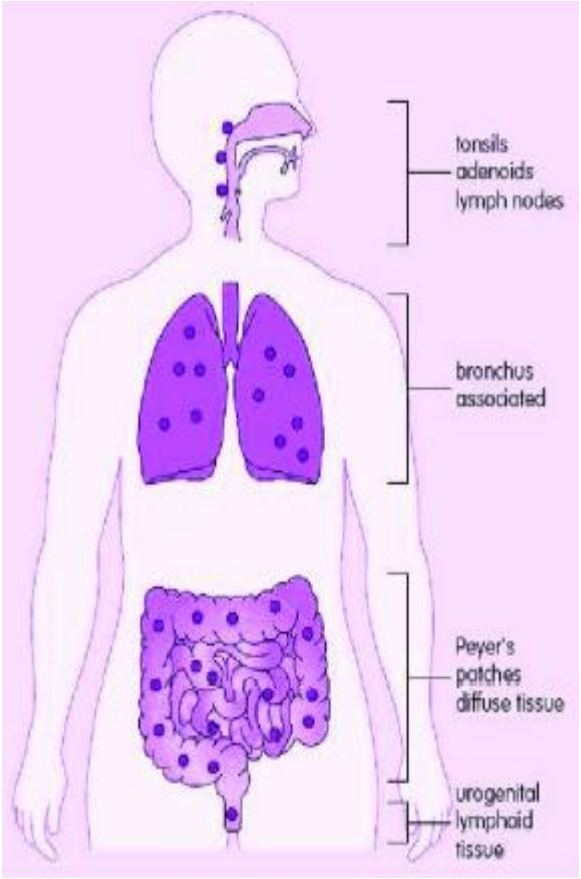


The spleen weighs about 150 g in adults and is in the left upper quadrant of the abdomen.

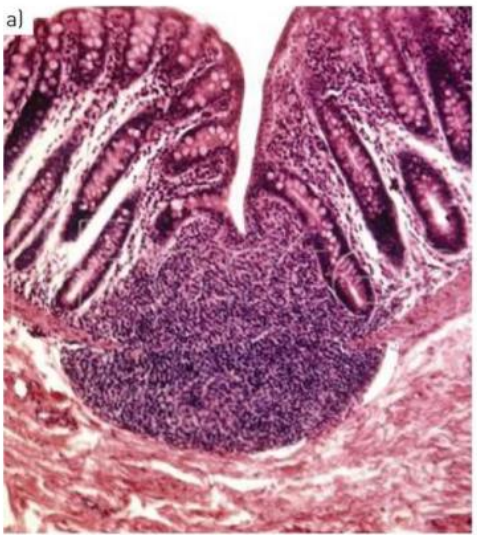
Individuals lacking a spleen are highly susceptible to infections with encapsulate.

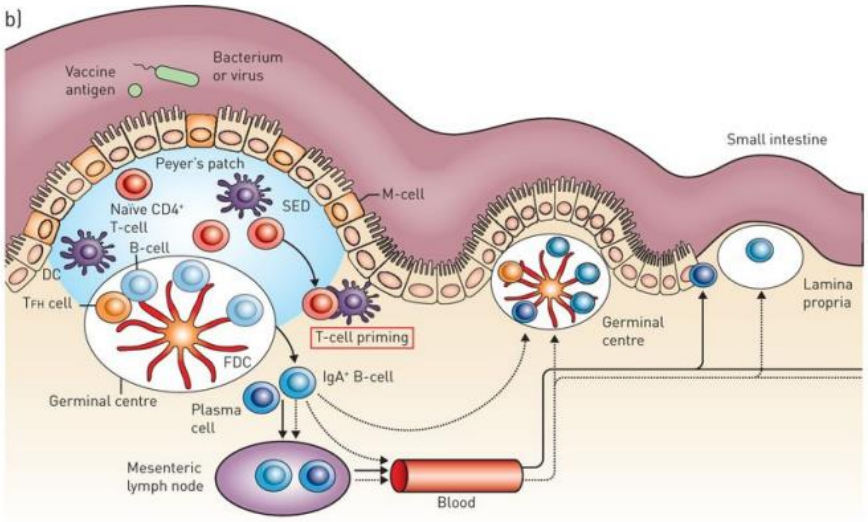


3. Regional Immune Systems, each major epithelial barrier of the body, including the skin, gastrointestinal mucosa, and bronchial mucosa, has its own system of lymph nodes, non-encapsulated lymphoid structures, and diffusely distributed immune cells, which work in coordinated ways to provide specialized immune responses against the pathogens that enter at those barriers.



Mucosa-associated lymphoid tissue (MALT) is involved in immune responses to ingested and inhaled antigens and microbes.





Normal small intestine histology with Peyer's patches. Initiation of the immune response in the gut : antigens are taken up by microfold (M)-cells and process to the resident dendritic cells (DCs) in Peyer's patches. T-follicular helper (TFH) cells interact with B-cells and follicular dendritic cells (FDC) thus forming a germinal center. Antigen specific plasma cells and memory B-cells are generated and migrate through the blood and mesenteric lymph nodes.