Hematology

HISTOLOGY

☐ Sheet ☐ Slide ☑ Handout

Number: **2**

Subject: **Lymphoid immune System**

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Price:

Lymphoid (Immune) System

(21)

(organs)

- encapsulated
  - Thymus
  - lymph nodes
  - spleen
- not encapsulated
  - Diffuse L.S
    - MALT
      - mucosa-associated lymph. tissue
      - GIT
      - Resp.
      - urinary

Immune System

- innate
  - Non-specific & composed of
  - (1) complement (a system of blood-born macromolecule)
  - (2) macrophages, Neutrophils } Phagocytose invaders
  - (3) NK cells (Natural Killer cells)
    - Kill
      - tumour cells
      - virally infected cells
      - parasites
- Adaptive immune System
  - deals with specific invaders
  - Reacts with one specific antigen of a pathogen + its ability improves é subsequent exposure
    - Specificity
    - memory
    - self/non self recognition

Adaptive immune system

1. T-lymphocytes
2. B-lymphocytes
3. specialized macrophages APCs (antigen-presenting cells)

→ These cells communicate with each other by signaling molecules (cytokines) released in response to antigens

1+2+3 → all formed in the bone marrow

B cells → become immunocompetent in the bone marrow

T cells → migrate to thymus to become immunocompetent

Bone marrow, Thymus → Primary (central) lymphoid organs

Bustam (22)

After lymphocytes become immunocompetent in the bone marrow or thymus → they migrate to the secondary (peripheral) lymphoid organs: diffuse lymphatic tissue, lymph nodes, spleen

Where they come into contact with antigens

Epitope ?? The region of the antigen that reacts with the Antibody or T-cell receptor (TCR)

= antigenic determinant

Each epitope is a small portion of the antigen molecule & consists of 8-11 hydrophilic amino acids or sugar residues → Large foreign invaders such as Bacteria have SEVERAL EPITOPES → each capable of binding to a different antibody

All lymphocytes in a particular clone have identical cell-surface proteins:
- SIGs (Surface immunoglobulins) in B-cell
- TCRs in the case of T cells

Although the molecular structures of SIGs & TCRs differ → they are functionally equivalent in their ability to recognize & interact with specific epitopes

Both B & T cells are said to be virgin (naive cells) before exposure to antigens → once a virgin cell comes in contact with an antigen → it proliferates to form
- activated cells
- memory cells

Bustrami (23)

Activated cells → also known as **effector cells** are responsible for carrying out an immune response
- derived from B cells → plasma cells (produce & release antibodies)
- » » T cells → either secrete cytokines or destroy foreign cells or altered self-cells

Memory cells
- similar to virgin lymphocyte express either B-cell receptors (SIGs) or TCRs which can interact with specific antigens
- Not directly involved in the immune response during which they are generated
- live for months or years
- have much greater affinity for antigens than do virgin lymphocytes

⇩

formation of memory cells after the first exposure to an antigen → ↑ the size of original clone
a process called **Clonal expansion**

↓

The presence of expanded population of memory cells with increased affinity for the antigen → subsequent exposure to the same antigen induces a secondary response that is
- → much faster
- → longer in duration than the 1ry response
- → more potent

B-lymphocytes

Bustami (24)

- originate & become immunocompetent in bone marrow
- responsible for humorally mediated immune response

↓

During the process of becoming immunocompetent → each B cell produces 50-000 to 100.000 IgM and IgD immunoglobulins (SIGs) & INSERTS THESE IN ITS PLASMA MEMBRANE so that the epitope-binding sites of antibodies face the extracellular space. The Fc region of the antibody is embedded in phospholipid bilayer of the cell membrane by means of 2 proteins Igβ and Igα

↓

When the surface immunoglobulin reacts with its epitope → Igβ & Igα relay the information to the intracellular protein complex with which they are in contact initiating a chain of events that results in activation of the B cell → Undergoes mitosis forming antibody-producing plasma cells & B-memory cells

↓

Because the antibodies produced by plasma cells are released either into the blood or lymph circulation B cell are responsible for humorally mediated immune respone

Class switching !! once IgM is produced → The B cell can produce a different class of immunoglobulin. This ability is determined by the particular cytokines present around the B cell and released by T-Helper cells as a response to the pathogen present

↓

(1) During parasitic worm invasion → T cells release interleukin-4 (IL-4) & IL5 → B cell switch into the form of IgE to elicit mast cell degranulation on the surface of the parasite

T-lymphocytes

originate in the bone marrow & migrate to the thymus to become immunocompetent → they are responsible for cellularly-mediated immune response

Although histologically T cells appear to be identical to B cells → there are important differences between them:

1. T cells have TCRs rather than SIGs on their cell surface
2. T cells recognize only epitopes presented to them by other cells (APCs)
3. T cells respond only to protein antigens
4. T cells perform their functions only at a short distance

Similar to SIGs on B cells, TCRs on the plasmalemma of T cells function as **antigen receptors**

The constant regions of the TCR are membrane-bound and associated with another membrane protein CD_3 forming (TCR-CD_3 complex)

A TCR can recognize an epitope ONLY (1) if the epitope is a polypeptide (composed of amino acids) & (2) if the epitope is bound to a major histocompatibility complex (MHC) molecule such as those in the plasmalemma of an APC → There are 2 classes of these glycoproteins

Class I MHC molecule | **Class II MHC molecule**

Most nucleated cells express MHC I molecules on their surface where as APCs can express both MHC I & MHC II on their plasmalemma (26)

⇓

MHC molecules are unique in each individual (except for identical twins)

↓

To be activated, T cells must recognize Not only the foreign epitope but also the MHC molecule itself → if the T cell recognizes the epitope but not the MHC molecule it does not become stimulated

Hence ⟹ T cells capacity to act against an epitope is MHC restricted

↓

Types of T cells

Bursary

① T-Helper cells 1 and 2 (T_H1 and T_H2)
activated T-helper cells secrete a variety of cytokines which modulate the activity of other lymphoid tissue

In general the cytokines secreted by a T_H1 cells elicit a response against bacterial or viral attack whereas those secreted by T_H2 elicit a response against a parasite (IgE) or mucosal infection (IgA)

② Cytotoxic T cells (CTLs) kills cells that recognize as foreign such as cells transformed by viruses

③ Suppressor T cells repress the immune response by inhibiting the capabilities of other T & B cells

④ T-memory cells → they have immunological memory for a particular epitope

In addition to TCR molecules → T cells express Clusters of differentiation proteins (CD molecules or CD markers) on their plasmalemma → They bind to specific ligands on target cells

(27)

Major Histocompatability molecules (MHC molecules)

↓

Present epitopes of Pathogens to T cells

↓

their importance is to Permit APCs (antigen presenting cells) and cells under viral attack or cells virally transformed to present the epitopes of the invading Pathogens to T cells

These epitopes are short polypeptides that fit into a groove on the surface of MHC molecules

MHC I molecule

↓

function in presenting short polypeptide chains (8-12 amino acids) derived from endogenous proteins

MHC II molecule

Present long polypeptide chains derived from exogenous proteins

Antigen-presenting cells (APCs) – Express both MHC I / II on their plasma membrane

- phagocytose & process antigens → attach their epitopes to MHC II → present this complex to T cells !!
  [T cells can recognize only peptides associated with MHC molecules]
- Most APCs are derived from monocytes & therefore belong to (Mononuclear phagocyte system) → include
  - Macrophages ①
  - dendritic cells ② (e.g. langerhans cells of epidermis)
  - 2 types of non-monocyte derived cells
    - B cells ③
    - epithelial reticular cells of thymus ④
- Similar to T helper cells APCs manufacture & release cytokines → signaling molecules needed to activate target cells

Antigen presenting cells (APCs) process and present exogenous antigens to helper T cells. While B cells can recognize antigen that is free in the extracellular fluid, T cells can only recognize antigen that is complexed (associated) with MHC proteins on the surfaces of plasma membranes. "Presenting" an antigen means that a fragment of the antigen is associated with an MHC protein and inserted in the plasma membrane of the APC; only when an antigen is "presented" in this manner is a T cell able to recognize it (bind with it).

Endogenous Antigens (Host Antigens) Endogenous antigens originate inside the body. Certain proteins on the plasma membranes of virus-infected cells and cancer cells are endogenous antigens. They are complexed with MHC-I proteins and are recognized by cytotoxic T cells.

Exogenous Antigens (Foreign Antigens) Exogenous antigens originate outside the body. The millions of protein molecules present in the external environment that are not produced by the body are all exogenous antigens. They are complexed with MHC-II proteins on the surfaces of antigen presenting cells and are recognized by helper T cells.

TYPES OF ANTIGEN PRESENTING CELLS

There are three basic types of antigen presenting cells:

Macrophages

Macrophages phagocytize and partially digest antigens; then combine antigen fragments with MHC-II proteins and insert the complex into the plasma membrane for presentation to helper T cells. They can also present antigen that is not associated with MHC proteins to B cells.

Dendritic Cells

Dendritic cells trap antigens on their surfaces and present them to T cells or B cells, depending upon the location of the dendritic cell. Dendritic cells have different names depending upon their locations; they are not phagocytic.

Langerhans Cells Langerhans cells are found in the skin epidermis. They trap antigens on their surfaces, then migrate to nearby lymph nodes, where they present the antigens complexed with MHC-II proteins to helper T cells.

Follicular Dendritic Cells Follicular dendritic cells are located in follicles (lymphatic nodules) of lymph nodes and spleen. They process and present antigen that is not associated with MHC proteins to B cells.

Interdigitating Dendritic Cells Interdigitating dendritic cells are located in the regions of lymph nodes and spleen where T cells reside. They process and present antigen complexed with MHC-II proteins to helper T cells.

B Cells

In certain situations B cells can perform the macrophage functions of processing and presenting antigens to helper T cells; they also secrete interleukin-1 (needed to activate the T cells).

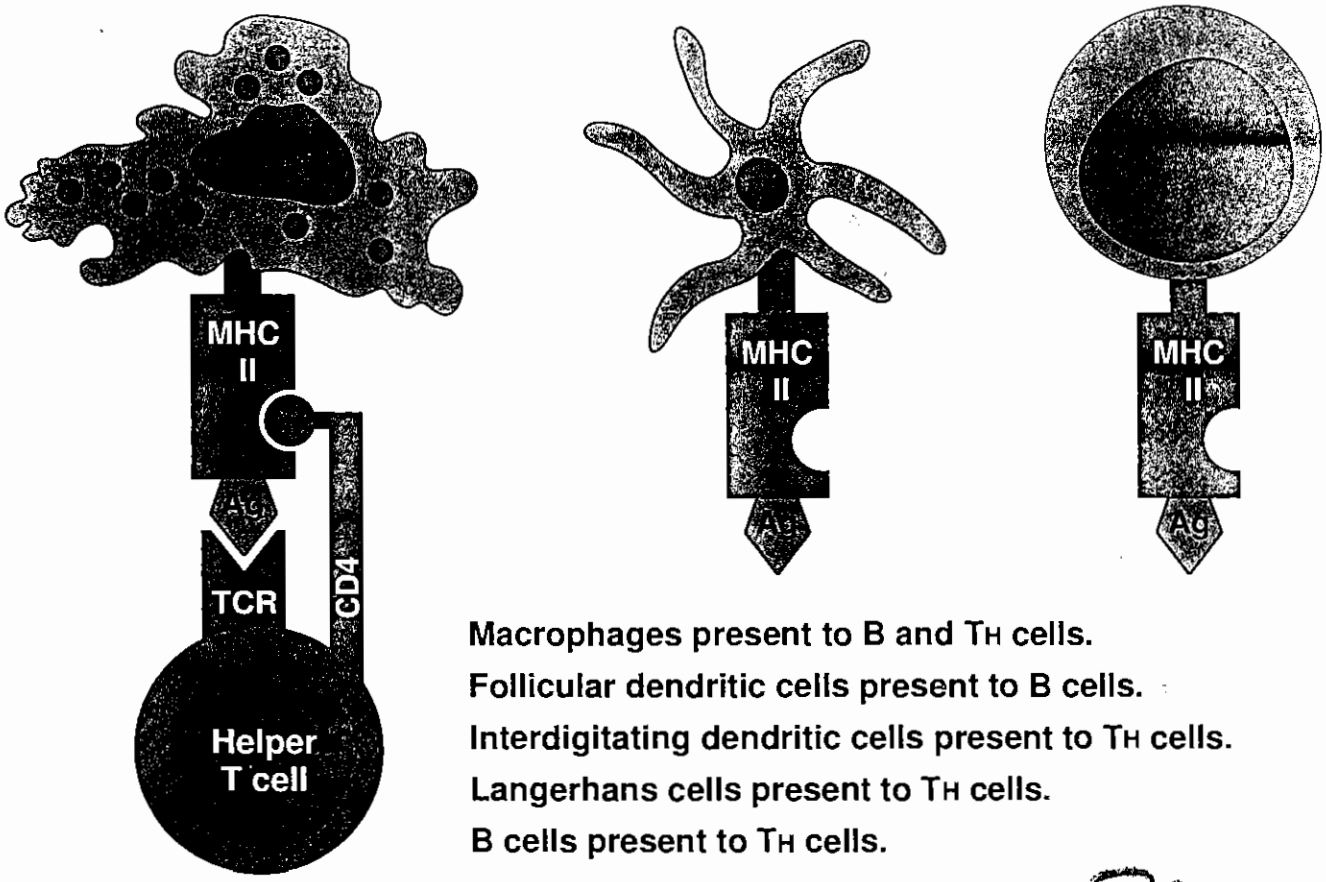
LOCATIONS OF ANTIGEN PRESENTING CELLS

Antigen presenting cells are found in four basic locations: skin epidermis, diffuse lymphatic tissue (mucous membranes of tracts), lymph nodes, and spleen.

ANTIGEN PRESENTING CELLS

Antigen Presenting Cells Process and Present Antigens to Helper T Cells and B Cells.

Macrophage **Dendritic Cell** **B Cell**

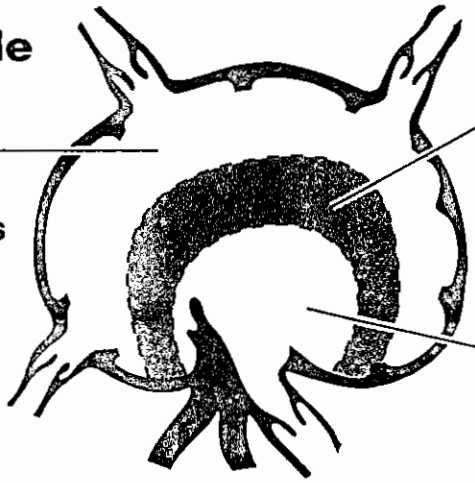


Macrophages present to B and TH cells.
Follicular dendritic cells present to B cells.
Interdigitating dendritic cells present to TH cells.
Langerhans cells present to TH cells.
B cells present to TH cells.

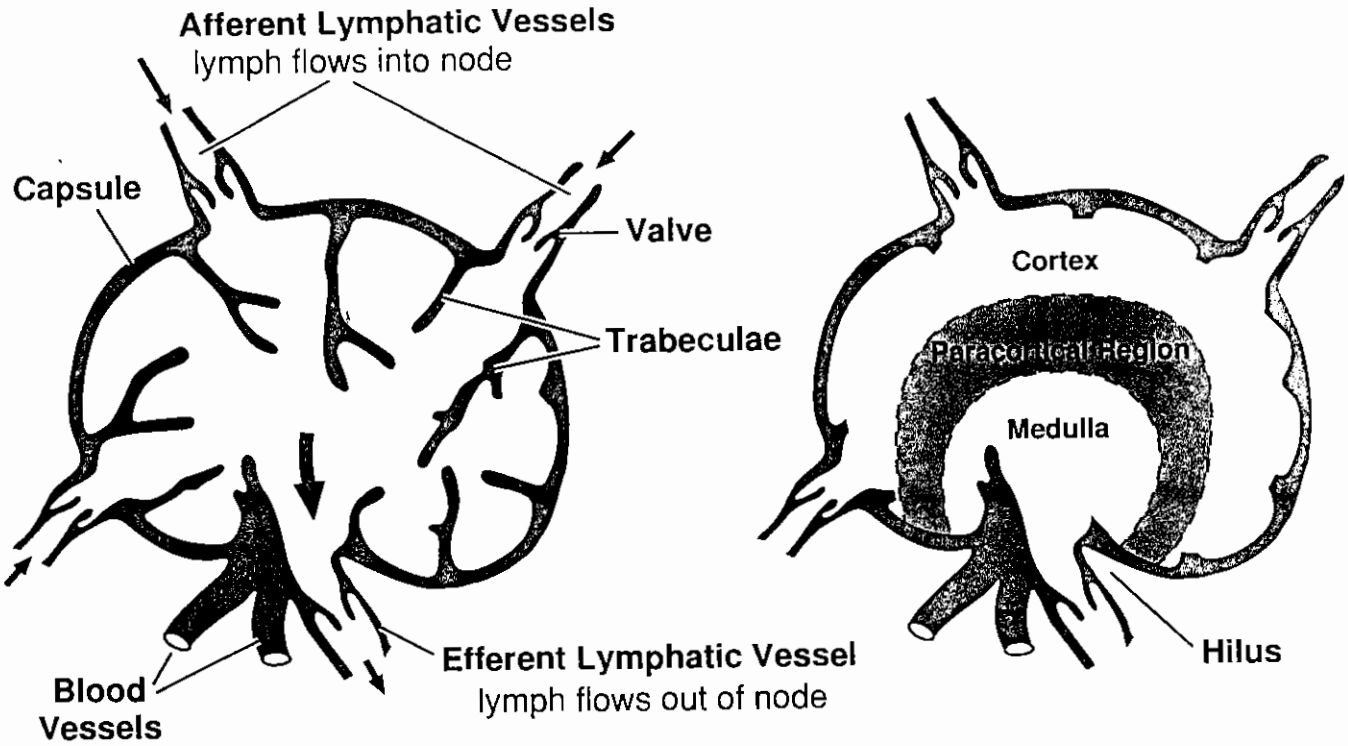
Locations of Antigen Presenting Cells

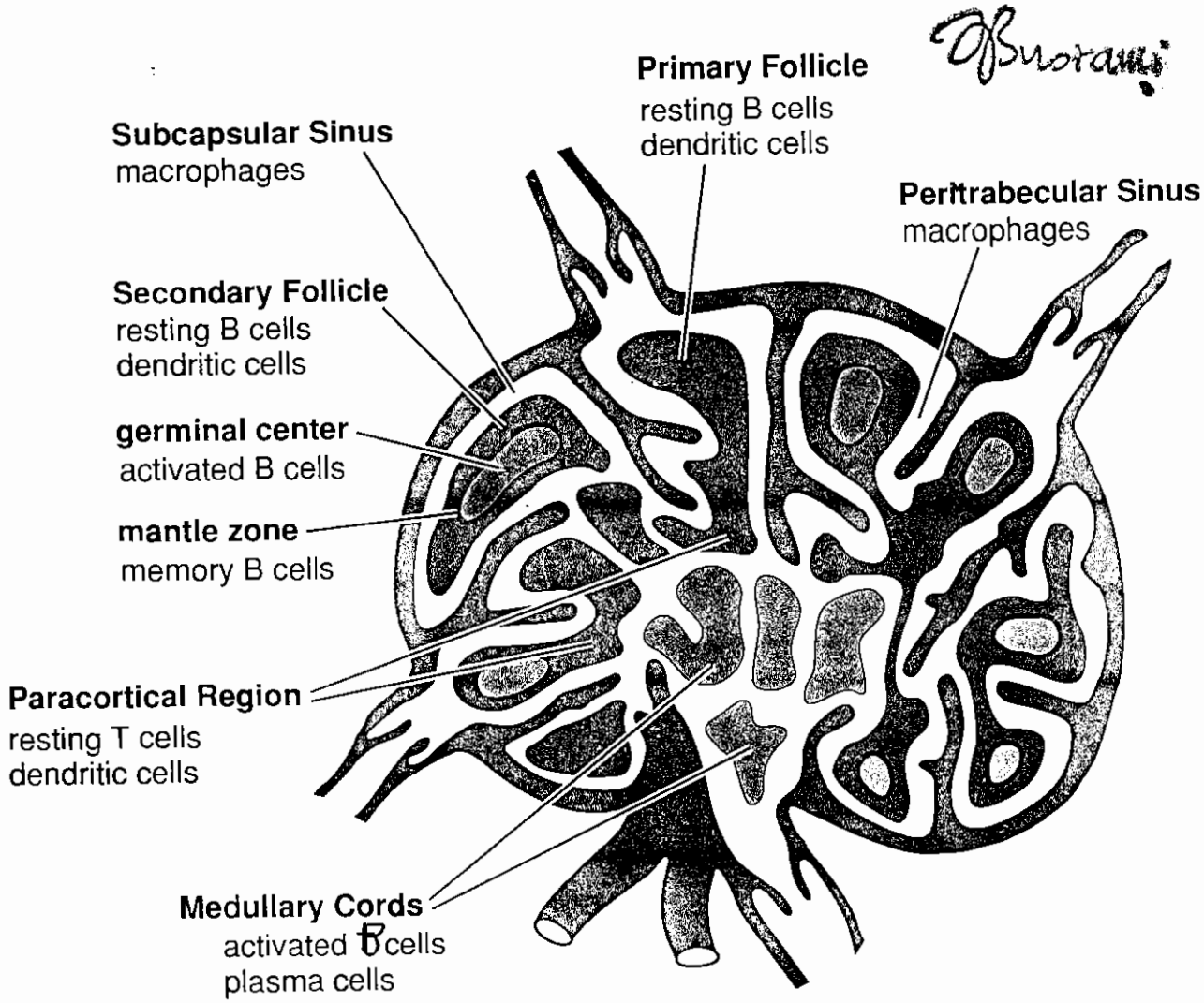
Macrophages are found in many tissues of the body. Dendritic cells are found in the skin (Langerhans cells) and in lymphatic tissues (follicular dendritic cells and interdigitating dendritic cells). B cells are found in lymphatic tissues.

Lymph Node



LYMPH NODE


Afferent Lymphatic Vessels
lymph flows into node
Capsule
Valve
Trabeculae
Blood Vessels
Efferent Lymphatic Vessel
lymph flows out of node
Cortex
Paracortical Region
Medulla
Hilus


Primary Follicle
resting B cells
dendritic cells
Subcapsular Sinus
macrophages
Peritrabecular Sinus
macrophages
Secondary Follicle
resting B cells
dendritic cells
germinal center
activated B cells
mantle zone
memory B cells
Paracortical Region
resting T cells
dendritic cells
Medullary Cords
activated B cells
plasma cells

LYMPHATIC TISSUES / Lymph Nodes

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STRUCTURE

Lymph nodes are spherical or kidney-shaped. A depression called the *hilus* (or hilum), where arteries and nerves enter and veins exit, is located on the concave side. Lymph nodes are found throughout the body along the course of lymphatic vessels. They are abundant under the arms, in the groin area, along the great vessels of the neck, and in the thorax and abdomen. Lymph nodes are covered by a *capsule* of dense connective tissue; extensions of the capsule called *trabeculae* form partitions within the lymph nodes. A network of reticular fibers ensheathed by *reticular cells* extends throughout the node; mature (immunocompetent) B cells and T cells are suspended throughout.

CORTEX

The cortex is the outer region of a lymph node directly beneath the capsule.

Sinuses Sinuses are irregular spaces through which the lymph percolates. The subcapsular sinus is the space between the capsule and the cortex; the peritrabecular sinuses surround the trabeculae. Macrophages span the sinuses; they phagocytize and destroy foreign materials (antigens) suspended in the lymph. Over 99% of the antigens entering a lymph node are destroyed by macrophages.

Primary Follicle Aggregation of B cells and follicular dendritic cells.

Resting (inactive) B Cells Most of the cells in primary follicles are resting (inactive) B cells. Follicular dendritic cells trap antigens encountered in the lymph and present them to B cells.

Secondary Follicle (contains a germinal center) When activated by antigens, 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.

Activated B Cells Activated B cells enlarge, divide mitotically, and differentiate into plasma cells and memory B cells. Memory cells are found in the mantle zone (outer border of secondary follicle). Some B cells do not differentiate into plasma cells; they become memory B cells. Memory cells flow with the lymph and re-enter the blood circulatory system.

PARACORTICAL REGION

The paracortical region is between the cortex and the medulla.

Resting (inactive) T Cells Resting T cells reside in the paracortical region. Interdigitating dendritic cells in the paracortical region trap antigens and present them to T cells.

MEDULLA

The medulla is the innermost portion of a lymph node adjacent to the hilus.

Medullary Sinuses The lymph from cortical sinuses passes through the medullary sinuses and then exits the lymph node via the efferent lymphatic vessels.

Activated B Cells and Plasma Cells Medullary cords (regions of densely packed lymphocytes) are composed of activated B cells and plasma cells.

FUNCTION

Nodes filter the lymph, removing foreign material and microorganisms (bacteria). All lymph is filtered by at least one lymph node before it returns to the blood. Antibody-mediated and cell-mediated immune responses occur in the lymph nodes.

Lymph nodes → serve as FILTERS for removal of bacteria & other foreign substances

Most prevalent in the neck, in the axilla, groin, body cavities

→ Their Parenchyma is composed of collections of T & B lymphocytes, APCs & macrophages

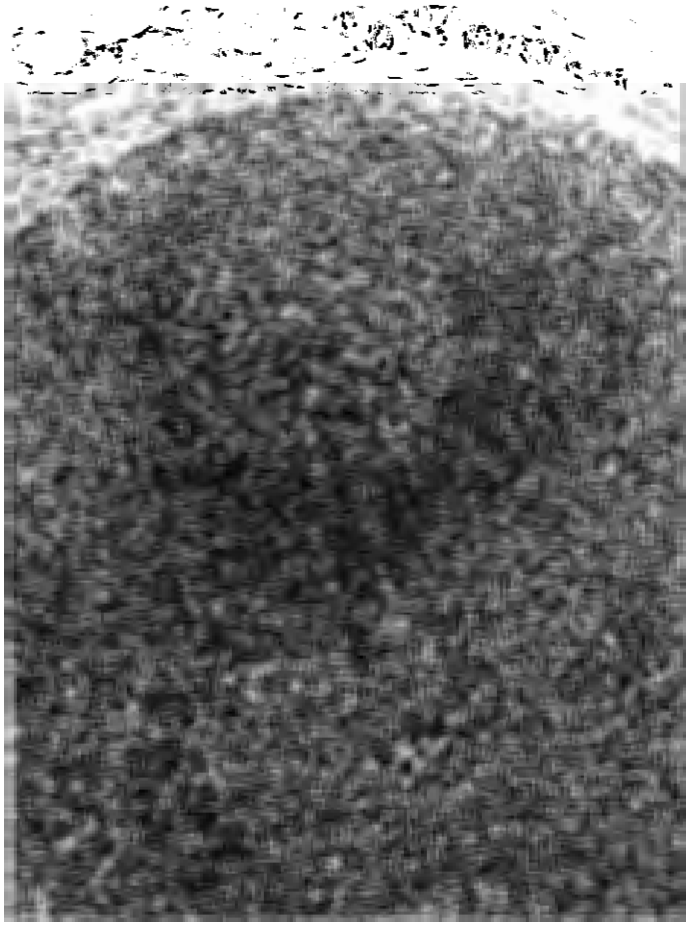

Figure 12–8 Photomicrograph of the lymph node cortex (×132).

← Lymphoid nodules (follicle)
2 types < 1ry, 2ry (have germinal centre)

CORTEX of lymph node

The capsule sends trabeculae that divide the outer region of the cortex into incomplete compartments that extends into the hilum

↓

Suspended from the capsule & trabeculae is three-dimensional network of reticular C-T (cells & fibres) that forms the stroma of lymph node

↓

The incomplete compartments within the cortex house primary lymphoid nodules which are spherical aggregates of B lymphocytes → Both < virgin B cell, B memory cells > entering or leaving the lymph node

Secondary lymphoid nodules (follicles) → have pale centres (germinal centres)

- form only in response to exposure to antigens
- sites of B memory cell & plasma cell generation
- outer region → dense accumulation of small lymphocytes that are migrating away from their site of origin within the secondary nodule

Lymph nodes < filter lymph
act as sites for antigen recognition

↓

Filter → As lymph enters the lymph node → FLOW RATE IS REDUCED

↓

give the macrophage in the sinuses more time to phagocytose foreign particulate matter (99% are removed)

* Lymph nodes also function as sites of antigen recognition !!

↓

Because ① APCs that contact antigens migrate to the nearest lymph node & present their epitope-MHC complex to lymphocytes ② antigens percolating in the lymph node are trapped by Follicular dendritic cells and lymphocytes that are in the lymph node or migrate into lymph node recognize antigen

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⇓

If an antigen is recognized → B cell become activated
→ B cell migrates to a Primary lymphoid nodule & proliferates → forming germinal centre → 1ry nodule becomes 2ry nodule → Newly formed cells differentiate into < B memory cell, plasma cell } leave the cortex & form medullary cords

→ about 10% of newly formed plasma cells stay in the medulla & release antibodies into medullary sinuses
→ the remainder plasma cells enter sinuses & go to bone marrow → produce antibodies

→ Some B memory cells stay in 1ry lymph nodules of the cortex
→ Most → leave the node into other 2ry lymphatic organs → if there is second exposure to same antigen → memory cells provide potent Secondary Response

Paracortex → region of lymph node between the cortex & medulla

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→ houses mostly T cells

→ is thymus-dependant zone of lymph node

APCs < Langerhans cells from skin / dendritic cells from mucosa } migrate to Paracortical region of lymph node to present their epitope-MHC II complex to T Helper cells

when activated, they proliferate increasing the width of the paracortex

Newly formed T cells migrate to the medulla → leave the lymph node (efferent L. vessels) & proceed to area of antigenic activity

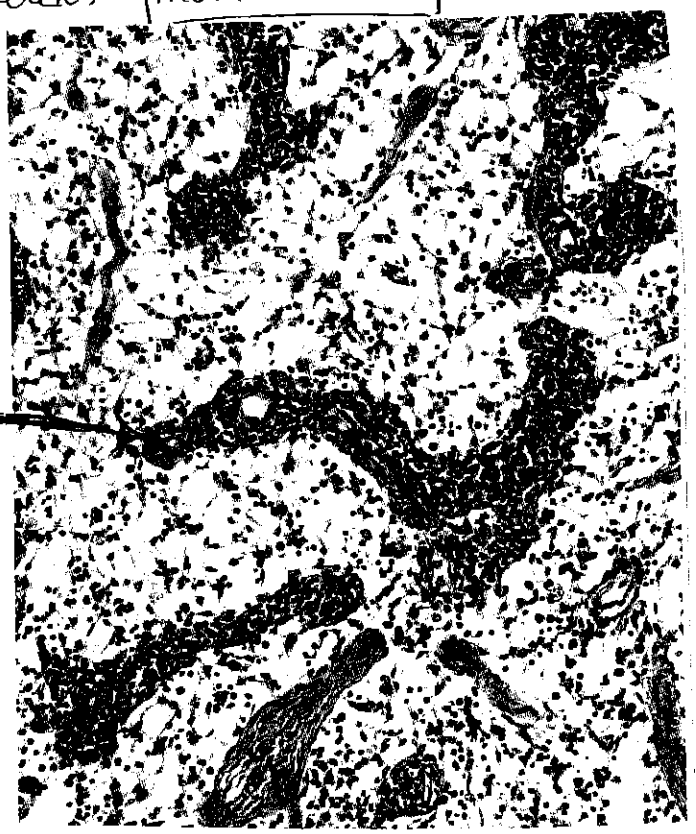
High endothelial venules (HEVs) = ⟨Post-Capillary venules⟩

→ located in the paracortex

→ lymphocytes leave the blood by migrating between the (diapedesis) cuboidal !! cells of this unusual endothelium & enter the substance of lymph node → B cells migrate to the outer cortex whereas most T cells remain in the paracortex

Medulla of lymph node

→ composed of large tortuous lymph sinuses surrounded by lymphoid cells that are organized in clusters known as medullary cords → contain B lymphocytes & some plasma cells



Lymphocyte Recirculation

(34)B

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(lymphocyte homing)

- serves critical functions in adaptive immune response → ① It enables the limited number of lymphocytes in an individual that are specific for a particular antigen to search for that antigen throughout the body. ② It ensures that particular lymphocytes are delivered to particular tissue e.g Recirculation of naive lymphocyte differ from those of effector and memory lymphocytes → specifically naive lymphocytes recirculate through peripheral lymphoid organ and effector lymphocyte migrate to peripheral tissues at sites of infection & inflammation

↓

The process of lymphocyte recirculation is regulated by ADHESION MOLECULES ON LYMPHOCYTES called HOMING RECEPTORS & their ligands on vascular endothelial cells called ADRESSINS

↓

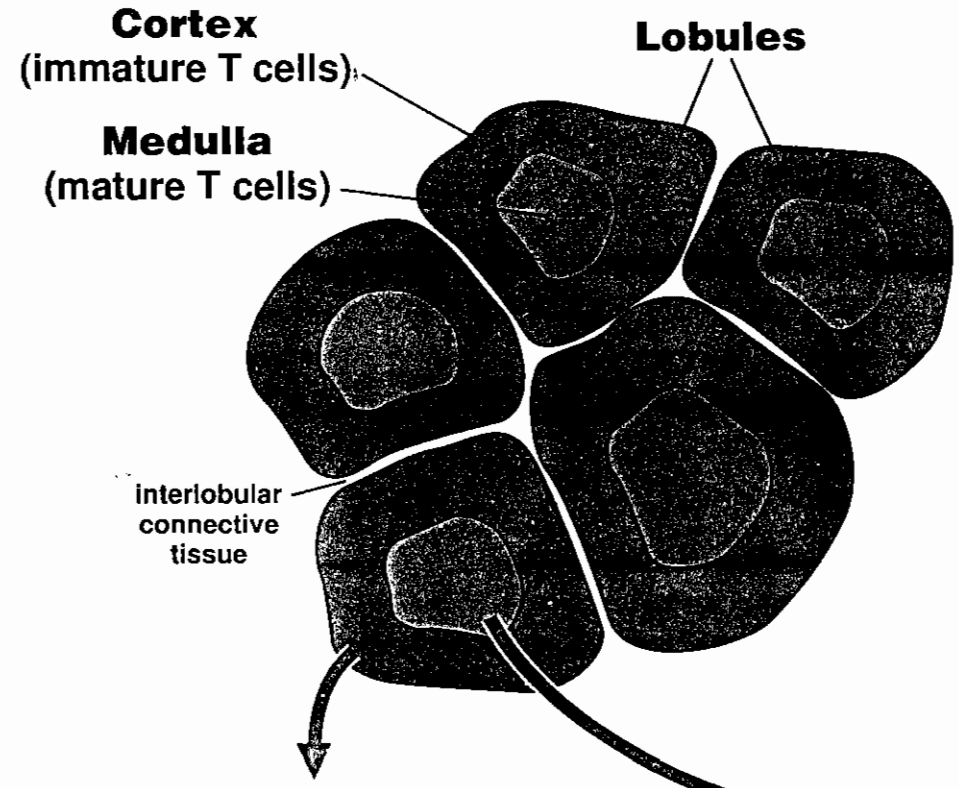
Why naive T cells migrate preferentially to lymph node ??? This process is largely mediated by binding of L-Selectin on the T-cell to peripheral lymph nodes addressins on high endothelial post-capillary venules in lymph nodes

The effector and memory T cells that are generated by antigen stimulation of naive T cells Exit the lymph node → they have decreased L-selectin expression but increased expression of integrins

THYMUS GLAND

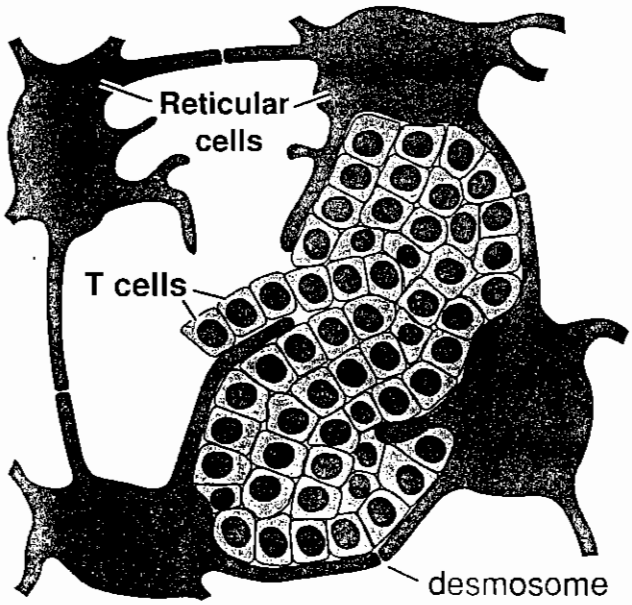
Immature T Cells : Immature T cells migrate from the bone marrow via the blood to the thymus, where they mature.

Mature T Cells : Mature T cells migrate from the thymus to specific regions in the lymph nodes and the spleen, where they reside.



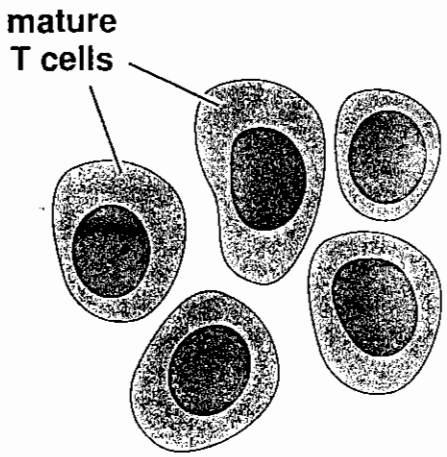
Cortex

In the cortex of a lobule, reticular cells envelop groups of T cells that are multiplying and maturing.



Medulla

As T cells mature, they migrate to the medulla. Fully mature T cells leave the medulla via venules and efferent lymphatic vessels.



LYMPHATIC TISSUES / Thymus Gland

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STRUCTURE

The thymus is a soft structure consisting of two lobes (bilobed). It is located in the chest (thorax) anterior to the great vessels of the heart and posterior to the upper part of the sternum.

It reaches its maximum size at puberty. At birth the thymus weighs about 15 grams; by puberty (age 13) it weighs 30 – 40 grams; after puberty it atrophies, and in old age weighs about 15 grams again.

Capsule A capsule consisting of connective tissue envelops the thymus.
Septa Extensions of the capsule called septa form partial partitions that separate the tissues of the thymus into regions called lobules.
Lobules Each lobule has an outer region called the cortex and an inner region called the medulla.

Cortex

Epithelial Reticular Cells The cortex has a spongelike texture and consists of a network of epithelial reticular cells bound together by desmosomes. Dense granules in the cytoplasm of these cells secrete hormones that promote the differentiation of T cells. Epithelial reticular cells envelop groups of T cells in the process of mitotic division and maturation; they also surround all blood vessels in the cortex, providing a blood-thymus barrier that prevents antigens in the blood from making contact with the developing T cells.

Immature T Cells T cells in various stages of differentiation and maturation reside in the spaces between the reticular cells of the cortex.

Macrophages Many macrophages are present. They phagocytize many of the T cells developing in the cortex of lobules. Macrophages reside in the spaces between capillaries and the epithelial reticular cells that cover the capillaries.

Medulla

Mature T Cells As T cells mature, characteristic surface antigens appear on the outer surfaces of their plasma membranes. The mature T cells migrate to the medulla. They leave the medulla via blood vessels and migrate to specific regions of the lymph nodes (paracortical zone) and spleen (periarteriolar sheaths of the white pulp).

FUNCTION

The thymus is colonized by immature T cells originating in the bone marrow. These cells develop into mature T cells, which are released into the circulation. The mature T cells travel via the blood to the lymph nodes, spleen, and diffuse lymphatic tissues, where they reside and are responsible for cell-mediated immune responses.

The Cortex of the thymus → appears darker histologically than does the medulla because of the presence of a large number of T lymphocytes (thymocytes)

⇓

Immunologically incompetent T cells leave the bone marrow, and migrate to the periphery of the thymic cortex where they undergo extensive proliferation & instruction to become immunocompetent T cells

↓

In addition to T lymphocytes the cortex contains macrophages and epithelial reticular cells

→ derived from the endoderm of the 3rd pharyngeal pouch

→ 3 types are present in the cortex < Type I, " II, " III

and 2 types in the medulla < " IV, " V

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The 3 types of epithelial reticular cells completely isolate the thymic cortex and thus prevent developing T cells from contacting foreign antigens

⇓

→ Type II & III cells
→ Bone marrow derived interdigitating cells (APCs)

} → Present Self-antigens, MHC I & MHC II molecules to the developing T cells

⇓

Developing T lymphocytes whose TCRs Recognize self proteins or whose CD4 or CD8 molecules Cannot recognize MHC I / MHC II

⇒ Undergo apoptosis before they leave the cortex

↓

98% of developing T cells die in the cortex and phagocytosed by resident macrophages

The surviving cells → enter medulla of thymus as Virgin (naive) T lymphocytes & from there (or from cortico-medullary junction) they are distributed to secondary lymphoid organs via the vascular system

To function properly Your T lymphocytes

1. must be able to recognize your own MHC Proteins
   a process known as Self-Recognition
2. they must lack reactivity to peptide fragments from your own proteins
   a process known as Self tolerance

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Self recognition → by a process of Positive selection

Some maturing T-cells Express T-cell receptors (TCRs) that interact with Self-MHC proteins on epith. cells in the thymic cortex → Because of this interaction the T-cells can recognize the MHC part of the antigen-MHC complex → these cells survive

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Self tolerance → develops by a process of Negative selection

T cells interact with dendritic cells at the junction of the cortex and medulla of thymus → In this process T cells with receptors that Recognize self-peptide fragments are eliminated or inactivated.

⇓

The T cells selected to survive do not respond to self antigens

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Negative selection occurs via : < Deletion / anergy

Deletion → self reacting T cells undergo apoptosis and die

Anergy → they remain alive but unresponsive to antigen stimulation

The epithelial reticular cells of the thymus produce several hormones that are necessary for the maturation of T cells ← Paracrine hormones (acting at short range) released into blood stream

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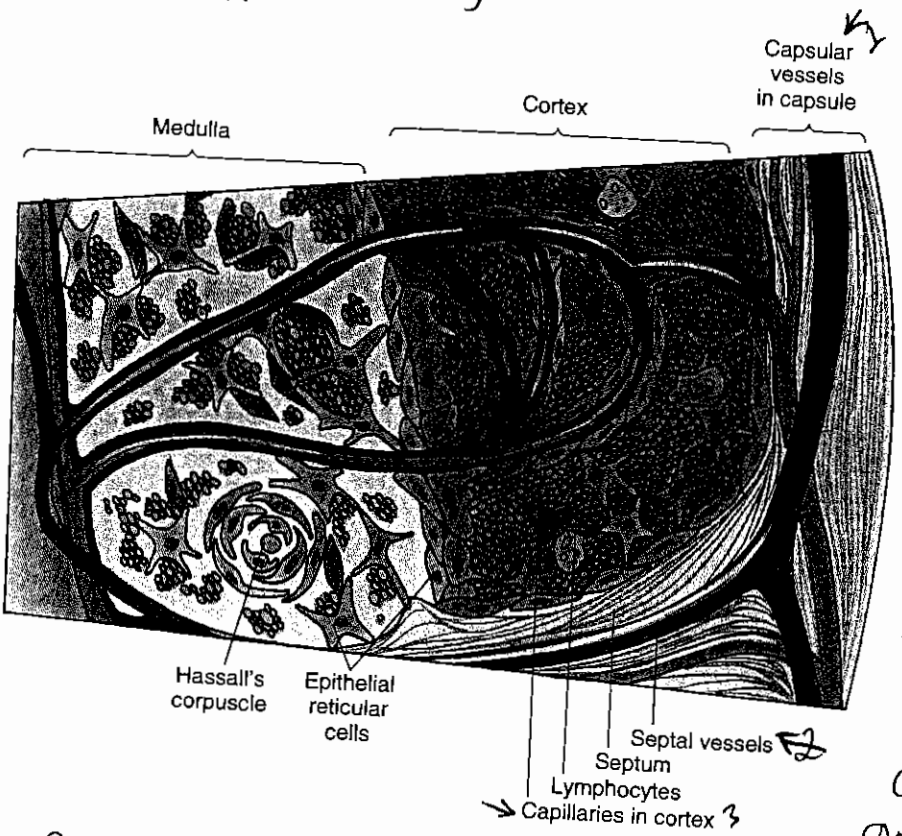
→ These hormones include: Thymosin, thymulin, thymopoietin, thymic humoral factor

- they facilitate T-cell proliferation and the expression of their surface markers
- hormones from extrathymic sources especially: gonads, pituitary, thyroid, suprarenal influence T cell maturation

↓ e.g

⟨Adrenocorticosteroids in the thymic cortex → decrease T-cell numbers⟩

Observation



Vascular supply

Thymus receives numerous small arteries → distributed throughout the organ via the trabeculae between adjacent lobules

↓

Branches of these vessels do not enter the cortex directly, instead from the trabeculae they enter the corticomedullary junction where they form capillaries that penetrate the cortex

↓

Capillaries of the cortex are of continuous type

⊕ thick basal lamina

⊕ invested by: a collar of connective tissue & a sheath of type I epithelial reticular cells

⇩

Together form Blood-thymus barrier

Blood-thymus barrier

The developing T cells of the cortex are protected from contacting blood-born macromolecules. However self-molecules are permitted to cross blood thymus barrier (probably controlled by epithelial reticular cells) → possibly to eliminate those T cells that are programmed against self-antigens

Thymic corpuscles (Hassall's bodies) → 20 - 100 μm

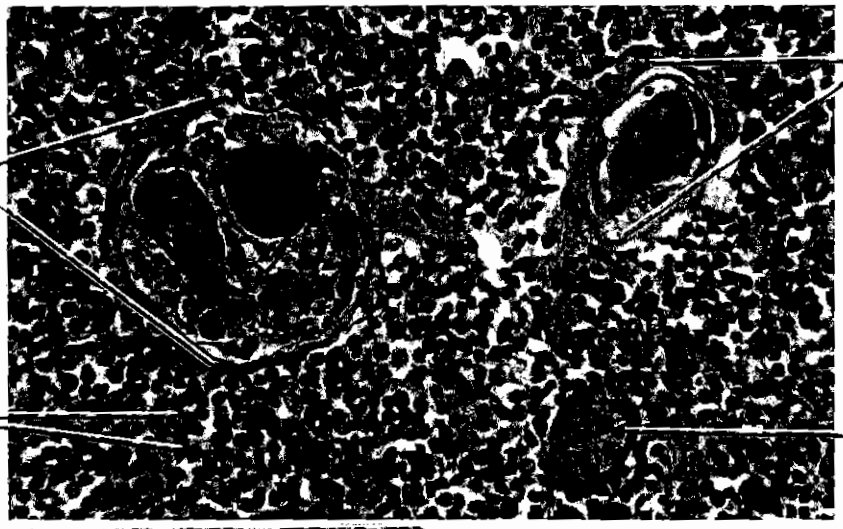
prominent feature of the thymic medulla

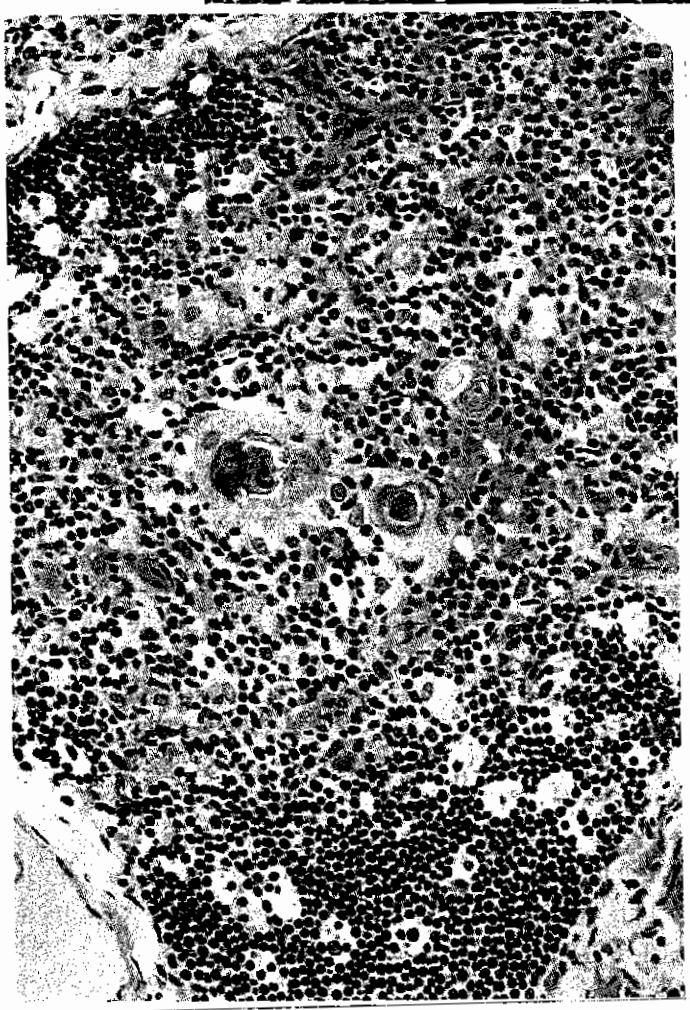
(39)

consists of ~~flattened epithelial reticular cells~~ wrapped about one another in concentric lamellation

cells are joined by numerous desmosomes & those at the centre show degeneration

function ? unknown ? degenerated structure !!





← Lobule of the thymus

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LYMPHATIC TISSUES / Spleen

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INTRODUCTION

Size, Shape, and Location

The spleen is the largest of the lymphatic organs—about 5 inches long. It is located in the upper left portion of the abdominal cavity, just beneath the diaphragm and adjacent to the 10th rib. Its shape resembles a large lymph node. The spleen filters the blood (as lymph nodes filter lymph).

Basic Structures

Capsule The spleen is surrounded by a capsule of dense connective tissue.

Hilum The hilum is a depression on the medial surface; nerves and arteries enter the spleen here; veins and lymphatic vessels exit here.

Trabeculae Extensions of the capsule called trabeculae form partitions within the spleen.

Pulp The tissue inside the spleen is called the splenic pulp or parenchyma. It is divided into white pulp (lymphatic tissue) and red pulp (rich in blood).

Blood Circulation

Splenic Artery The splenic artery divides into trabecular arteries as it enters the hilum.

Trabecular Arteries These branches of the splenic artery follow the course of trabeculae.

Central Arteries When trabecular arteries enter the white pulp they are called central arteries. They are surrounded by a sheath of lymphocytes. Arterioles branching from the central arteries carry blood to marginal zone sinuses and to sinusoids in the red pulp.

SPLENIC PULP

White Pulp

Periarteriolar Lymphatic Sheaths (PALS) The white pulp consists of lymphatic tissue arranged in cylindrical sheaths (periarteriolar lymphatic sheaths) around central arteries. T cells are found in greatest concentrations in the region closest to the central arteries.

Follicles (also called splenic nodules) Spherical clusters of B cells called follicles are scattered throughout the PALS. Primary (unstimulated) follicles contain resting (inactive) B cells; secondary (stimulated) follicles contain activated B cells in a central region called the germinal center. These follicles have the same structural organization as those found in lymph nodes.

Marginal Zone The marginal zone is the region between the white and red pulp. It is composed primarily of macrophages and dendritic cells.

Red Pulp

The red pulp is mainly concerned with the destruction of worn-out red blood cells. It consists of splenic cords and sinusoids.

Splenic Cords (Billroth's Cords) Splenic cords consist of all cells between the sinusoids in the red pulp: reticular cells, macrophages, monocytes, lymphocytes, plasma cells, granulocytes, red blood cells, and platelets.

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

FUNCTIONS

Blood Cell Production Lymphocytes produced in white pulp migrate to red pulp sinuses. During the fetal phase of development, granulocytes and erythrocytes are produced.

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 bone marrow). They are phagocytized by macrophages.

Defense Mechanisms Macrophages phagocytize microbes that have penetrated the blood. Antigens in the blood activate B and T cells residing in the spleen, triggering immune responses.

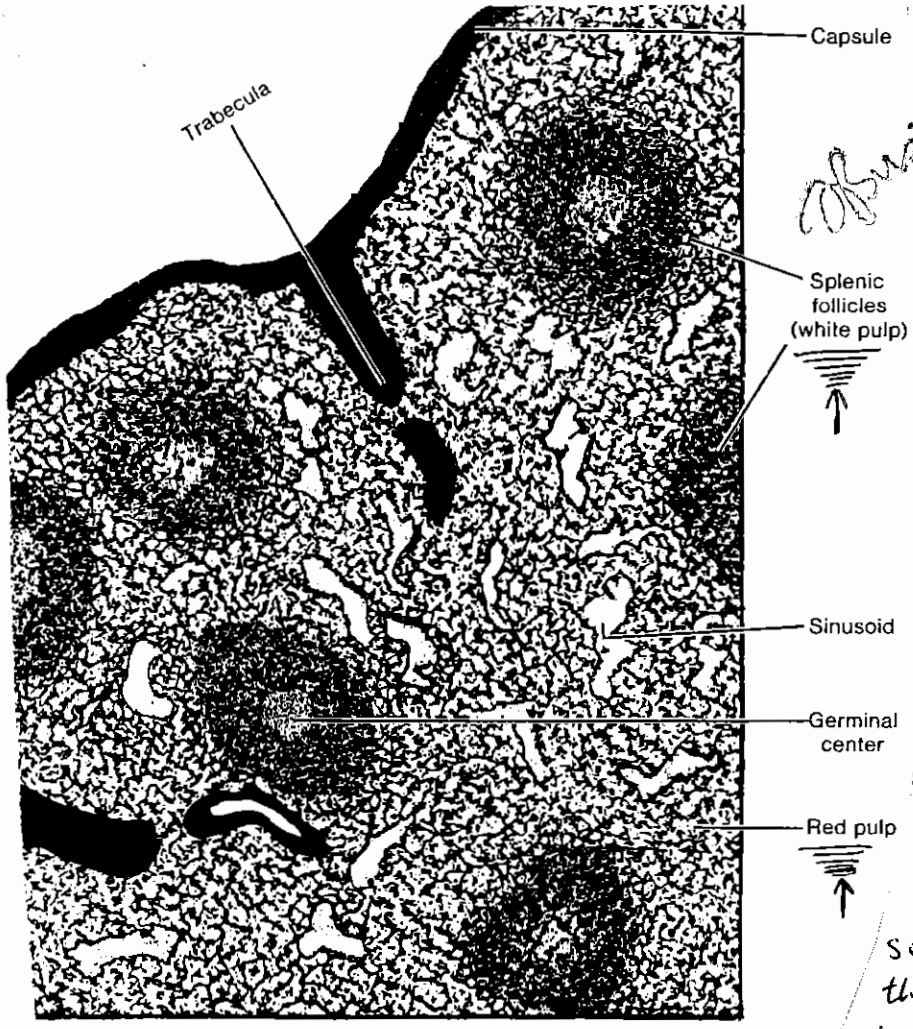


Figure 12-3 General structure of the spleen.

SPLeen

(4)

Unlike lymph nodes the spleen:

1. has NO afferent lymphatics
2. has NO lymphatic sinus system
3. its lymphatic tissue is NOT arranged into a cortex and medulla.

⇩

The spleen is surrounded by a capsule (dense C-T.) which sends out trabeculae that divide the Parenchyma or splenic pulp into incomplete compartments.

* The spaces between the trabeculae are filled with reticular network of fibres and associated reticular cells.
* The substance of the spleen is referred to as SPLENIC PULP

A. White pulp associated with the arterial supply to the spleen and forms the PERIARTERIAL LYMPHATIC SHEATHS that extend about the arteries where these leave the trabeculae to enter the splenic pulp. The SHEATHS have the structure of DIFFUSE LYMPHATIC TISSUE (small lymphocytes make up the bulk of the cells in the sheath and most of these are T-cells). Here and there along the course of the sheath ⇒ the lymphatic tissue EXPANDS to incorporate NODULAR LYMPHATIC TISSUE which resemble the cortical nodules of lymph nodes and represent accumulation of B-cells. Many of the nodules contain germinal centres. The lymphatic nodules of the spleen have been called splenic follicles or Malpighian corpuscles.

* Marginal zone? The loose lymphatic tissue between the lymphatic nodules and the red pulp. It contains few lymphocytes but many macrophages (+ plasma cells)

The Structure of the spleen is built around its blood supply.

⇓ (42)

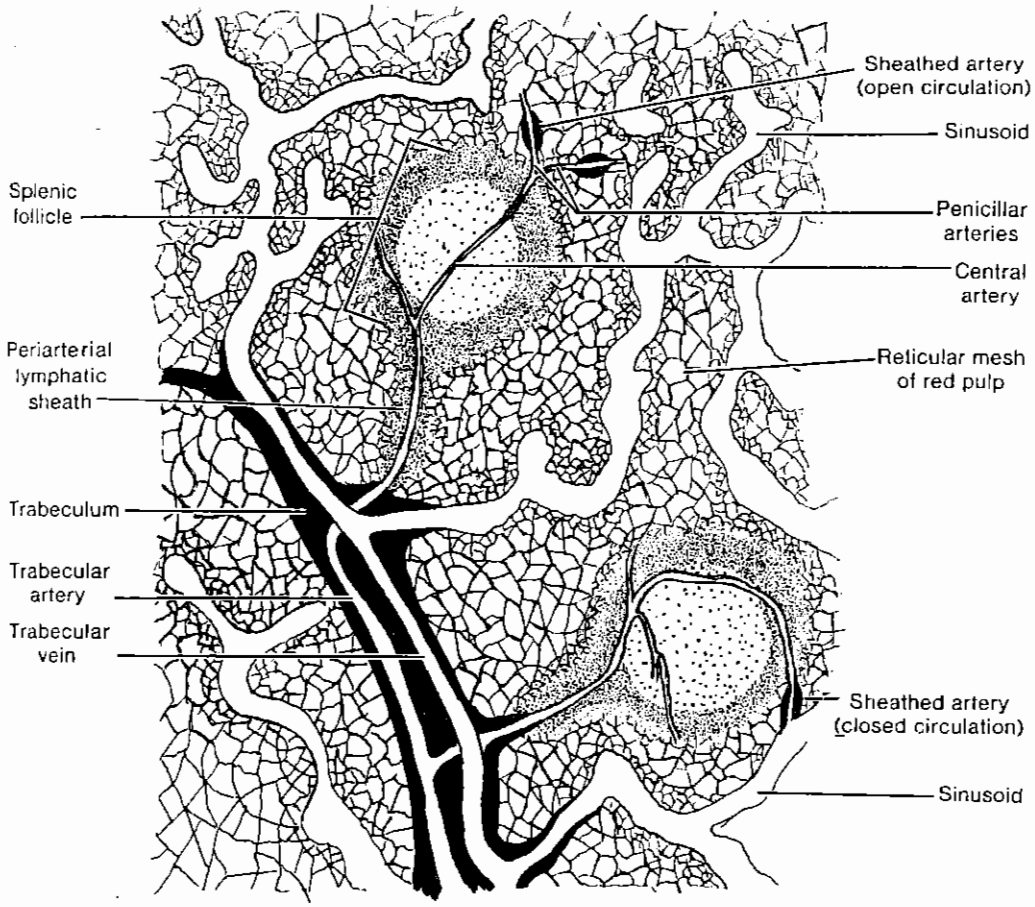


Figure 12-5 Blood supply of the spleen.

Bhusrami

Splenic artery (enters at hilum) → Provide branches that pass within the trabeculae into the interior of the organ → These trabecular arteries branch repeatedly and ultimately emerge from trabeculae as → central arteries

↓

immediately surrounded by periarterial lymphatic sheath (PALS) (T-lymphocytes)

⇐ When the sheath expands to form nodules

↓

central artery is displaced to one side and acquires an eccentric position in the nodule

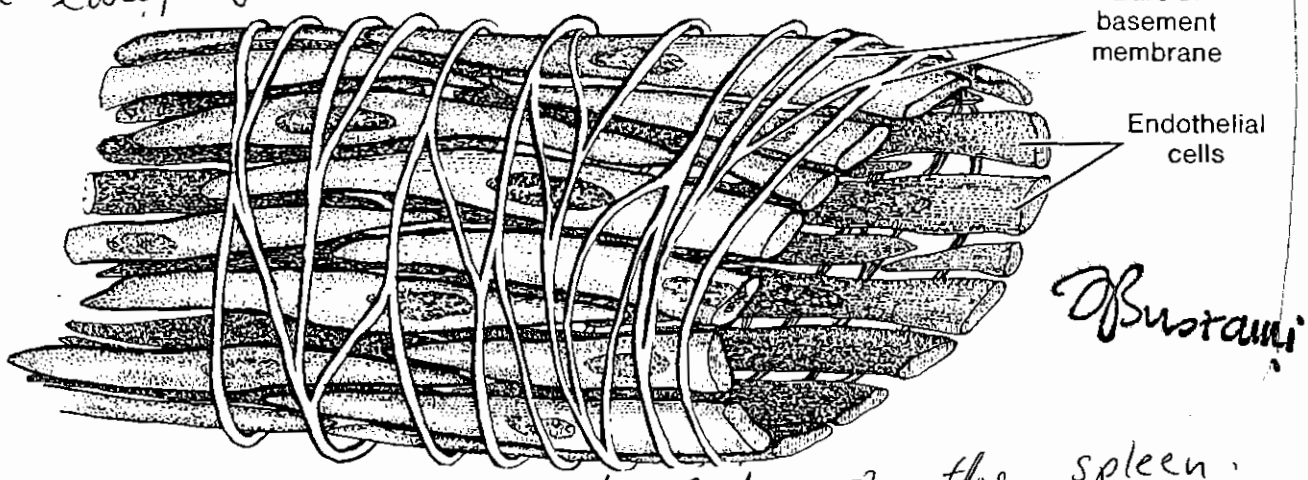
* Central artery ← supplies capillaries ∴ to lymphatic sheath continue to branch and its terminal narrow part divided into several short, straight PENICILLAR ARTERIES (some show thickening of their walls and called sheathed capillaries)

open circulation theory: the capillaries open into the spaces of the red pulp of the splenic cords and then return to the venous system through the wall of the splenic sinusoids

The closed theory holds that the capillaries open directly into the venous sinusoids

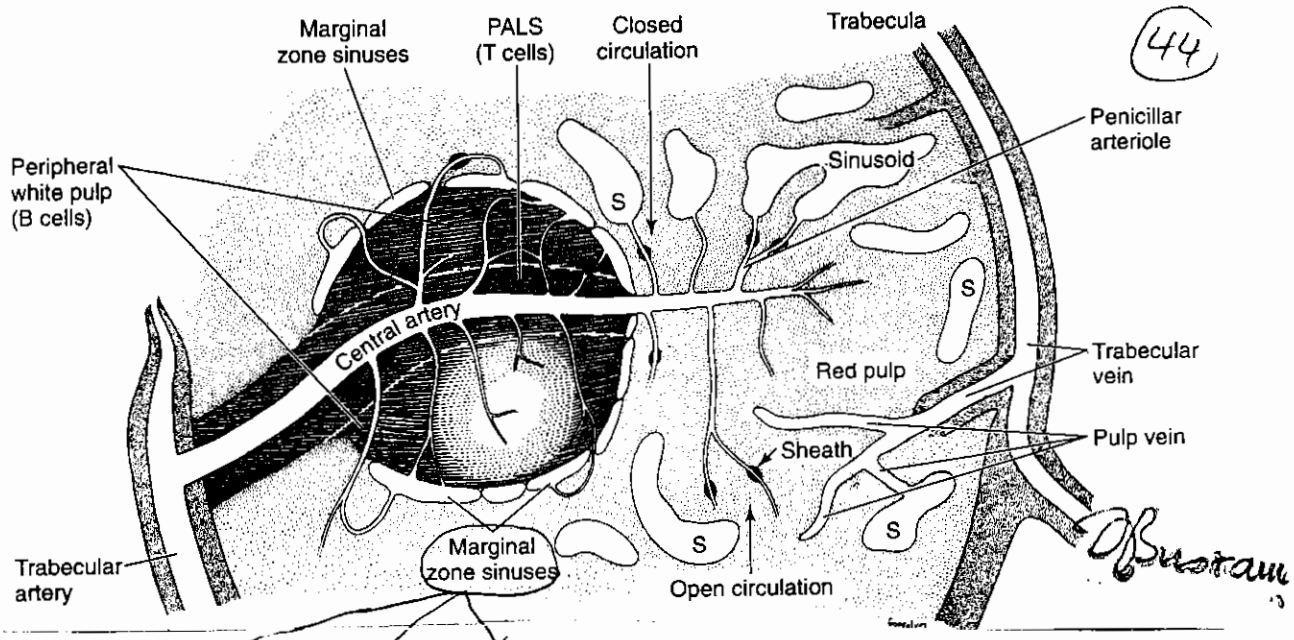
* Plasma cells of the spleen → they are descendants of activated B-lymphocytes (i.e lymphocytes exposed to antigens) which proliferate and differentiate and move towards the red pulp. Hence, the plasma cells of the spleen are found in it marginal zone and red pulp. (2) (43)

The Red Pulp: Associated with the venous system of the spleen. It consists of large thin-walled sinuses filled with blood and thin plates or cords of lymphoid tissue → the splenic cords (of Billroth) wedged between the sinuses. In addition to all circulating blood cells, these cords contain many macrophages which destroy senile RBCs and granulocytes. Postnatally → the red pulp is a storage depot for red blood cells while in the early fetus it is a temporary site of hemopoiesis.



Sinusoids of the red pulp of the spleen:

1. The endothelial cells are elongated fusiform elements that lie parallel to the long axis of the vessel.
2. The cells lie side by side around the vessel but are NOT joined by any type of intercellular junctions
3. outside the endothelium → the wall is supported by a basement membrane which is NOT continuous but which forms widely-spaced thick bars that encircle the sinusoids



Because the spaces between the endothelial cells of these sinuses may be as wide as 2 to 3 μm, it is here that blood-borne cells, antigens, and particulate matter have their first free access to the parenchyma of the spleen. Thus, the following events occur at the marginal zone:

1. APCs sample the material traveling in blood, searching for antigens.
2. Macrophages attack microorganisms present in the blood.
3. The circulating pool of T and B lymphocytes leaves the bloodstream to enter its preferred locations within the white pulp.
4. Lymphocytes come into contact with the interdigitating dendritic cells; if they recognize their epitope–MHC complex, the lymphocytes initiate an immune response within the white pulp.
5. B cells recognize and react to thymus-independent antigens (such as polysaccharides of bacterial cell walls).

Spleen → (1) filters the blood
(2) forms lymphoid cells
(3) eliminates or inactivates blood-born antigens
(4) destroys aged platelets & erythrocytes
(5) participates in haemopoiesis

(1) As a filter: Macrophages at marginal sinuses & red pulp phagocytose blood-born antigens, bacteria & other foreign particulate matter

(2) Source of lymphoid cells
Lymphoid cells are formed in the white pulp in response to an antigenic challenge → B memory cells & plasma cells are formed in lymphoid NODULE where as T cells of various subtypes are formed in PALS

Newly formed B & T cells → enter the marginal sinus & migrate & forms part of circulating pool of lymphocytes

(3) Some plasma cells may stay in the marginal zone, produce antibodies into marginal sinus. Most plasma cells migrate to bone marrow & release their antibodies

(4) Bacteria become opsonized & eliminated by macrophages & neutrophils

Macrophages
- Kill aged platelets
- Monitor erythrocytes as they migrate from splenic cords Between the endothelial cells → into the sinuses

⇓

Old erythrocytes lose their flexibility (as do erythrocytes infected by the malarial parasites)

⇓

they cannot penetrate the spaces between the endothelial cells & are → Phagocytosed by macrophages

↓

Lose sialic acid from their cell membranes

↓

galactose exposed → induce Phagocytosis of RBCs

↓

Hemoglobin broken into
- heme
- globin

↓

globin → aminoacids pool of blood

heme
- iron → carried by transferrin to bone marrow (used again)
- bilirubin → excreted by liver bile

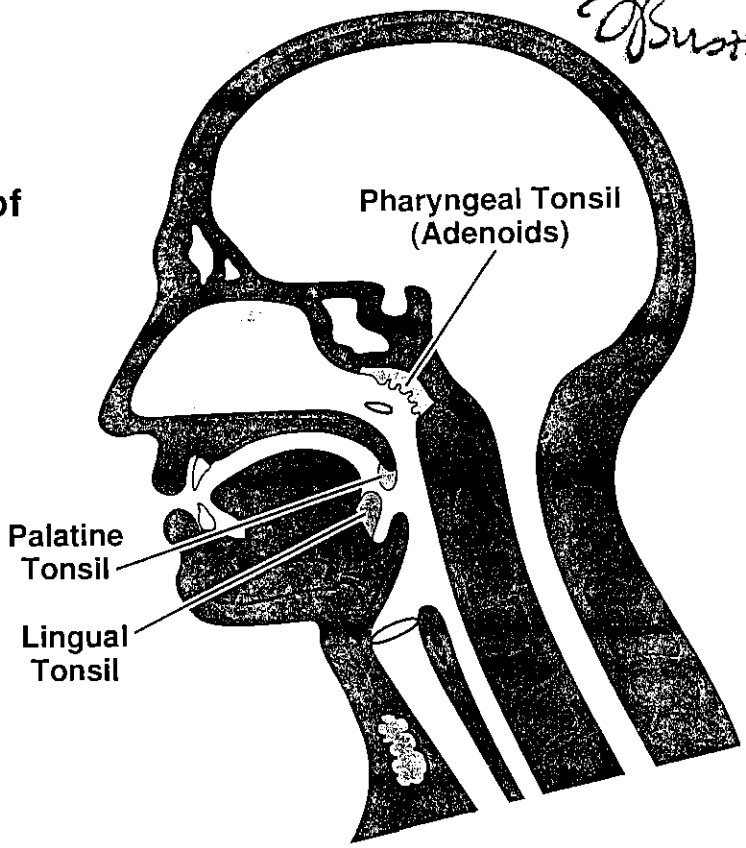
DIFFUSE LYMPHATIC TISSUE

When lymphatic tissue is not enclosed by a capsule, it is called diffuse or unencapsulated lymphatic tissue.
Unencapsulated lymphatic nodules are found isolated or aggregated in the lining of the digestive, respiratory, urinary, and reproductive tracts.

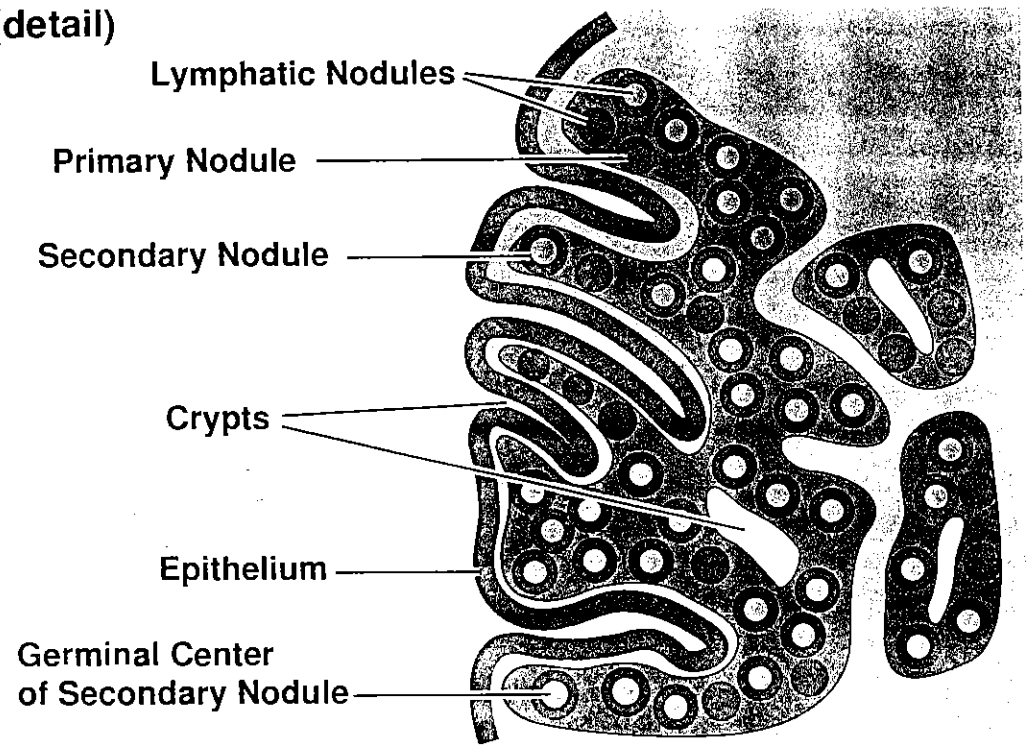
Tonsils

Tonsils are aggregations of large lymphatic nodules embedded in the mucous membranes of the throat.

They form a ring of lymphatic tissue at the junction of the mouth cavity and pharynx (throat).



Tonsil (detail)



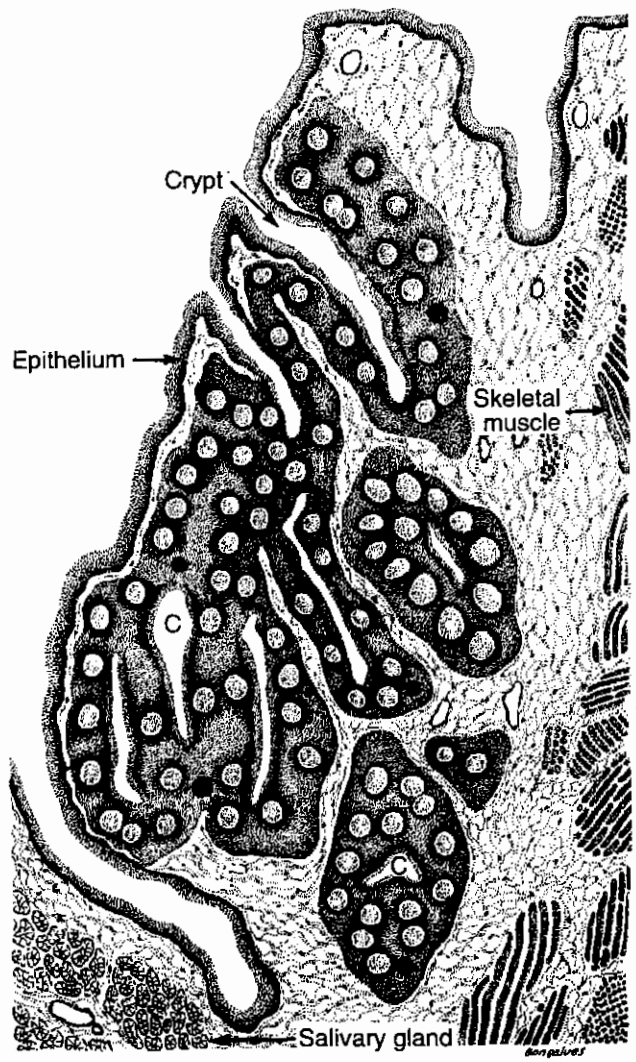


Figure 14–26. Palatine tonsil. Numerous lymphoid nodules can be seen near the stratified squamous epithelium of the oropharynx. The light areas in the lymphoid tissue are germinal centers. Note the sections through the epithelial crypts (C).

Palatine tonsil
- at lateral wall of OROPHARYNX

→ Stratified epith.
↓ deep to it
a band of lymphoid tissue with lymphatic nodules

→ Crypts → filled with desquamated epith.

→ incomplete capsule (between tonsil & pharyngeal wall)

Pharyngeal tonsil (Adenoid) at the junction of roof + post. wall of nasopharynx

→ epith. → ciliated pseudostratified (Resp. epith.)

→ contain diffuse lymphoid tissue & L. Nodules

- NO crypts
- thin capsule

Lingual tonsils :- smaller & more numerous than palatine + pharyngeal
- at base of tongue
- covered by strat. sq. epith.

Each tonsil → single crypt → opening of acc. saliv. gland.

To function properly Your T lymphocytes

① must be able to recognize your own MHC Proteins

a process known as Self-Recognition

② they must lack reactivity to peptide fragments from your own proteins

a process known as Self tolerance

Dr Bustami

Self recognition → by a process of Positive selection

Some maturing T-cells Express T-cell receptors (TCRs) that interact with Self-MHC proteins on epith. cells in the thymic cortex → Because of this interaction the T-cells can recognize the MHC part of the antigen-MHC complex → these cells survive

Self tolerance → develops by a process of Negative selection

T cells interact with dendritic cells at the junction of the cortex and medulla of thymus → In this process T cells with receptors that Recognize self-peptide fragments are eliminated or inactivated

⇓

The T cells selected to survive do not respond to self antigens

Negative selection occurs via : Deletion / anergy

Deletion → self reacting T cells undergo apoptosis and die

Anergy → they remain alive but unresponsive to antigen stimulation