HEMATOLOGY
&LYMPH SYSTEM

Histology sheet

Number	7
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Note: This is handout 5 (page12-30) with notes were mentioned by Dr.Hanan in the lecture (7).

Secondary lymphoid organs are: **lymph nodes, lymph nodules, spleen**, **Peyer's patches** and **mucosa associated lymphoid tissue (MALT**).

The largest secondary lymphoid organ >> lymph nodes

Why isn't the spleen? Because all the lymph nodes in body collectively are larger than the spleen.

Lymph nodes and nodules

Lymph nodes and **nodules** are masses of lymphatic tissue. Nodes and nodules differ with respect to size and location. Nodes are usually larger, 10 to 20mm in length; nodules range from a fraction of a millimeter to several millimeters in length.

Differ in capsulation; lymph nodes are capsulated while nodules are not or partially capsulated. Lymph nodes are found along the lymphatic vessels, while lymph nodules can be found primarily in the submucosa.

Lymph nodes are found in groups along the pathways of lymph vessels, and lymph flows through these nodes on its way to the subclavian veins. Lymph enters the nodes through several afferent lymph vessels and leaves through one or two efferent vessels.

The Function of lymph nodes is filtration of lymph.

The amount of lymph entering the lymph node is more than the amount leaving it, why??

Because the slow passage of lymph, providing more chance to the lymph to be filtered.

As lymph passes through a lymph node, bacteria and other foreign materials are phagocytized

by fixed (stationary) macrophages. Fixed plasma cells (from lymphocytes) produce antibodies to any pathogens in the lymph; these antibodies, as well as lymphocytes and monocytes, will eventually reach the blood.

There are many groups of lymph nodes along all the lymph vessels throughout the body, but three paired groups deserve mention because of their strategic locations. These are the **cervical**, **axillary**, and **inguinal** lymph nodes.

Very important clinically.

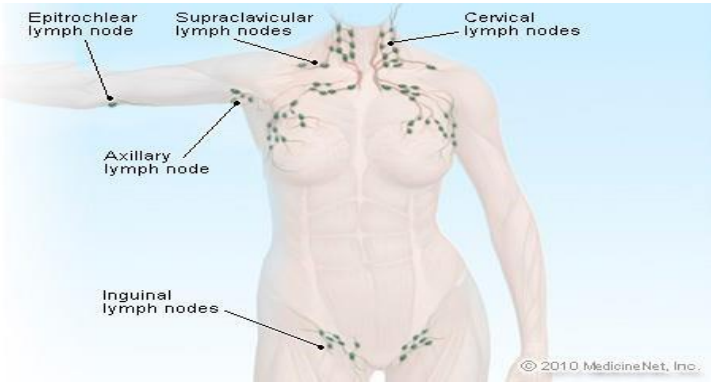
Notice that these are at the junctions of the head and extremities with the trunk of the body. Breaks in the skin, with entry of pathogens, are much more likely to occur in the arms or legs or head rather than in the trunk. If these pathogens get to the lymph, they will be destroyed by the lymph nodes before they get to the trunk, before the lymph is returned to the blood in the subclavian veins.

Lymph can carry cancer cells.

Cancer: malignant tumor that can spread.

Metastasis of cancer: Cancer stem cells (responsible for the growth of the cancer) can be carried by lymph or blood to implant themselves in distant sites.

Metastasis occur by lymph or blood.



Cervical Lymph Nodes

In the head and neck, lymph nodes are arranged in two horizontal rings and two vertical chains on either side of the neck.
The outer, superficial ring consists of the **occipital**, **postauricular, preauricular** (**parotid**), **submandibular**, **sublingual** and **submental** nodes.
The inner, deep ring is formed by clumps of mucosa associated lymphoid tissue (MALT) located primarily in the naso- and oropharynx (**Waldeyer's ring**).
Tonsils

The following describes the main cervical node groups:

HORIZONTAL

The **occipital nodes** are in the superficial group, which includes 3-5 nodes. This group of nodes is localized between the sternocleidomastoid (SCM) and trapezius muscles, at the apex of the posterior triangle. These nodes are superficial to the splenius capitis.

The **deep posterior cervical group** includes 1-3 nodes. This group of nodes is located deep to the splenius capitis and follows the course of the occipital artery. These nodes drain the scalp, the posterior portion of the neck, and the deep muscular layers of the neck.

Enlargement of a lymph node can be due to an infection or cancer.

Enlargement accompanied by wasting and fever with no apparent pain indicates a certain type of cancer is present.

If the enlargement hasn't disappeared after antibiotic >>> should be investigated.

One way of examination the deep lymph nodes is rotation of the head to the opposite side which is the action of SCM that masks the deep cervical lymph nodes.

Post >> behind or posterior to auricle

The **postauricular nodes** vary in number from 2 to 4; they are located in the fibrous portion of the superior attachment of the SCM muscle to the mastoid process. Postauricular nodes drain the posterior parietal scalp and the skin of the mastoid region.

The **preauricular (parotid) nodes** can be divided into intraglandular and extra-glandular groups. The extra-glandular parotid nodes are located outside but adjacent to the parotid gland, where they drain the frontolateral scalp and face, the anterior aspects of the auricle, the external auditory canal, and the buccal mucosa. Embryologically, the lymphatic system develops before the parotid gland, which surrounds the intraglandular nodes as it develops. This explains why the parotid gland contains lymphoid tissue. The intraglandular nodes drain the same regions as the extra-glandular nodes, to which they interconnect and then drain into the upper jugular group of lymph nodes. As many as 20 parotid nodes may be found.

You may find in some references that the extra-glandular nodes are called specifically preauricular lymph nodes and the intraglandular nodes are called parotid lymph nodes.

The **submandibular** nodes are divided into 5 groups: preglandular, postglandular, prevascular, postvascular, and intracapsular. The preglandular and prevascular groups are located anterior to the submandibular gland and facial artery, respectively. The postglandular and postvascular groups are posterior to these structures.

Submandibular nodes are very important because they almost drain the whole face.

Sometimes in tonsillitis, submandibular nodes are enlarged because of drainage from tonsils to submandibular.

Differing from the parotid gland in embryological development, there is no true intraglandular node; however, occasionally, a node has been identified inside the capsule of the gland. The submandibular nodes drain the ipsilateral upper and lower lip, cheek, nose, nasal mucosa, medial canthus, anterior gingiva, anterior tonsillar pillar, soft palate, anterior two thirds of the tongue, and submandibular salivary gland. The efferent vessels drain into the internal jugular nodes.

For the **submental** nodes, 2-8 nodes are located in the soft tissues of the submental triangle between the platysma and mylohyoid muscles. These nodes drain the chin, the middle portion of the lower lip, the anterior gingiva, and the anterior third of the tongue. The efferent vessels drain into both the ipsilateral and contralateral submandibular nodes or into the internal jugular group.

Dental problem in one side of the mouth can cause swelling in both sides because there's crossing in the efferent vessels.

The **sublingual** nodes are located along the collecting trunk of the tongue and sublingual gland and drain the anterior floor of the mouth and ventral surface of the tongue. These nodes subsequently drain into the submandibular or jugular group of nodes.

Sublingual is inside the oral cavity, above the mylohyoid

VERTICAL

-The **retropharyngeal nodes** are divided into a medial and lateral group, located between the pharynx and the prevertebral fascia. The lateral group, located at the level of the atlas near the internal carotid artery, consists of 1-3 nodes, which may extend to the skull base. The medial group extends inferiorly to the postcricoid level. This group drains the posterior region of the nasal cavity, sphenoid and ethmoid sinuses, hard and soft palates, nasopharynx, and posterior pharynx down to the postcricoid area. Management of these nodes must be considered if any malignancy arises from the mentioned drainage areas.

Any cancer arising within the oral cavity could drain into the retropharyngeal lymph nodes and can cause a pushing pressure on the respiratory passages.

Radiation is used to examine these nodes.

-The **anterior cervical nodes** are divided into the anterior jugular chain and the juxtavisceral chain of nodes. The anterior jugular chain nodes follow the anterior jugular vein, located superficial to the strap muscles. These nodes drain the skin and muscles of the anterior portion of the neck, and the efferent vessels empty into the lower internal jugular nodes.

Around the trachea, 2 groups are found:

-The **pretracheal group** consists of nodes between the isthmus of the thyroid gland down to the level of the innominate vein. Varying from 2-12 in number, these nodes drain the region of the thyroid gland and the trachea and receive afferent flow from the prelaryngeal group. The pretracheal efferents empty in the internal jugular group and the anterior superior mediastinal nodes.

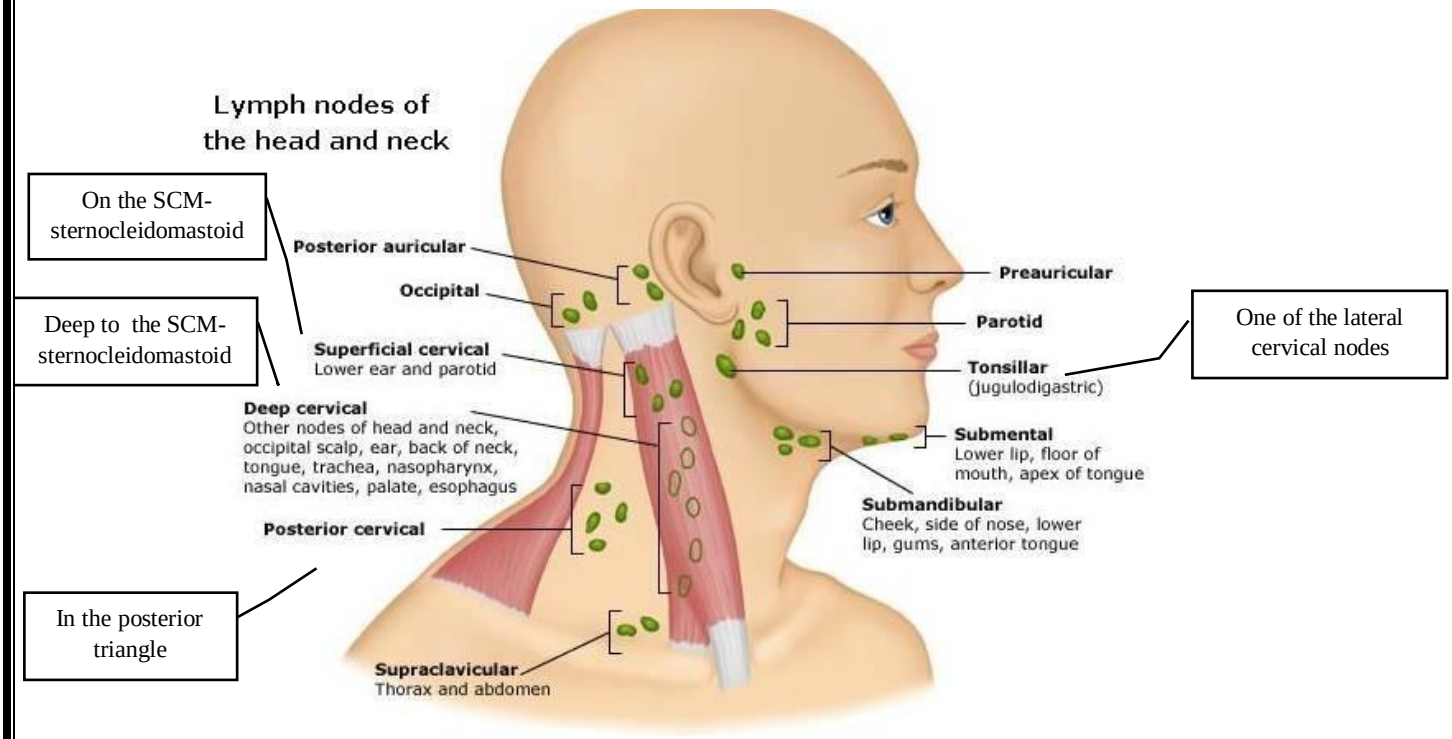
-The **paratracheal** nodes lie near the recurrent laryngeal nerve and drain the thyroid lobes, parathyroid glands, subglottic larynx, trachea, and upper esophagus. The efferent vessels travel to the lower jugular group or directly toward the junction of the internal jugular vein and the subclavian vein. The anterior nodes drain bilaterally because the midline of the neck has no division. Treatment must be planned accordingly when a tumor is located in subjacent draining areas.

-The **lateral cervical nodes** are divided into superficial and deep groups. The superficial group follows the external jugular vein and drains into either the internal jugular or transverse cervical nodes of the deep group.

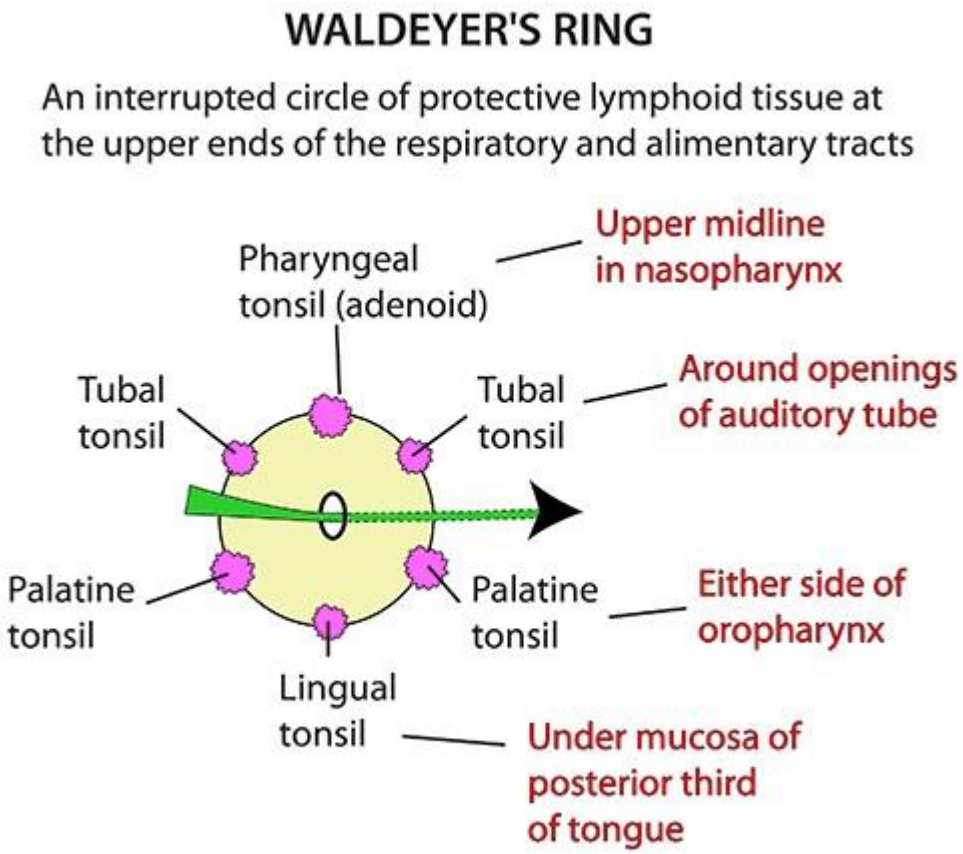
-The **deep group** forms a triangle bordeed by the internal jugular nodes, the spinal accessory nodes, and the transverse cervical nodes. The transverse cervical nodes, forming the base of the triangle, follow the transverse cervical

vessels and may contain as many as 12 nodes. These nodes receive drainage from the spinal accessory group and from collecting trunks of the skin of the neck and upper chest. The spinal accessory chain follows the nerve of the same name and may account for as many as 20 nodes. This chain receives lymph from the occipital, postauricular, and suprascapular nodes and from the posterior aspect of the scalp, nape of the neck, lateral aspect of the neck, and the shoulder.

-The **internal jugular chain** consists of a large system covering the anterior and lateral aspects of the internal jugular vein, extending broadly from the digastric muscle superiorly to the subclavian vein inferiorly. As many as 30 of these nodes may exist, and they have been arbitrarily divided into upper, middle, and lower groups. The efferent of these nodes eventually pass into the venous system via the thoracic duct on the left and multiple lymphatic channels on the right. These nodes drain all the other groups mentioned.



The palatine tonsils, nasopharyngeal tonsil (adenoid) and lingual tonsil constitute the major part of **Waldeyer's ring**, with the tubal tonsils (around the auditory tube) and lateral pharyngeal bands as less prominent components. The lymphoid tissue of Waldeyer's ring is located at the gateway of the respiratory and alimentary tract and belongs to the mucosa-associated lymphoid tissue (MALT). As tonsils (details discussed below) are the first site of encounter with inhaled and ingested micro-organisms, they are considered the first line of defense against exogenous aggressors. The generation of B cells in the germinal centers of the tonsil is one of the most essential tonsillar functions.



Axillary Lymph Nodes

The lymph nodes of the axillary region are responsible for the lymphatic drainage of a large section of human anatomy. Due to this arrangement and duty, they have a particular clinical relevance. This is particularly evident with breast cancer, where axillary lymph node status, with regards to cancer, defines the treatment algorithm and approach. There are 20-30 lymph nodes divided into five groups; Anterior (pectoral), posterior (subscapular), lateral (humeral), central, and apical.

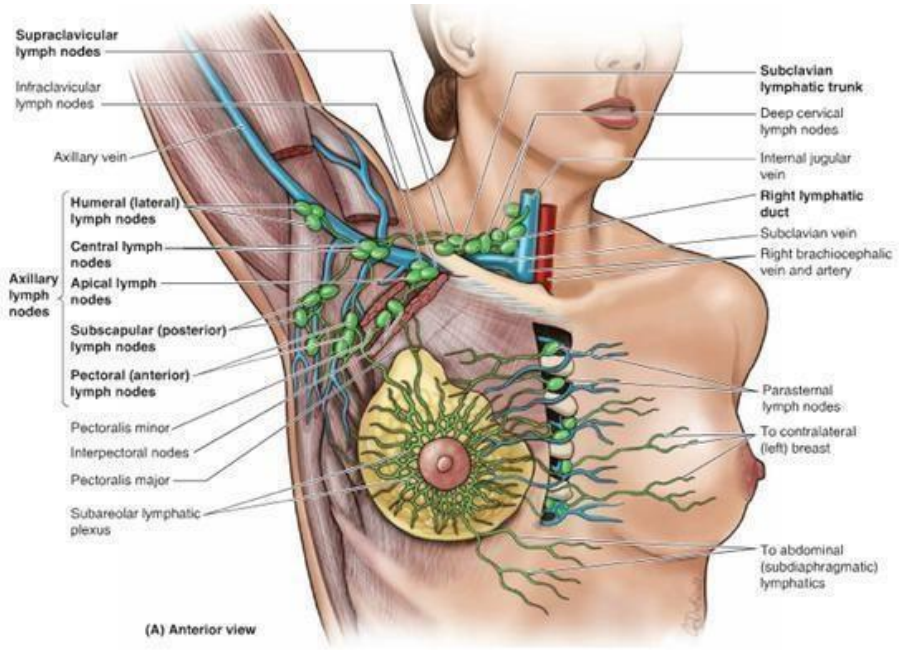
The **anterior (pectoral) group** is located across the inferior border of the pectoralis minor muscle and the superior border of the pectoralis major muscle. There are usually 4-5 large nodes. The lymph flows from the anterolateral aspect of the abdominal wall superior to the level of the umbilicus and the lateral quadrants of the breast. It conveys the lymph to more central nodes.

The **posterior (subscapular) group** consists of 6-7 nodes that can be found anterior to the subscapularis muscle and receives superficial lymph vessels located more commonly within the upper portion of the back and posterior neck. However, these can receive lymph from as far inferior as the superior border of the iliac crests.

The **lateral (humeral) group** is a group of 4-6 nodes that can be found against the axillary vein. The vast majority of the lymph vessels of the upper limb flow into this group. The superficial group of nodes however, drains the lateral aspect of the upper limb and flows into the infraclavicular nodes.

The **central group** consists of 3-4 nodes, and is found at the base and centrally located in the axilla. These nodes are interspersed amongst the adipose (fat) of the region. These are the most important group of nodes in terms of drainage because these receive lymph flow from the three groups of nodes mentioned above (anterior, posterior, and lateral).

The **apical group** (4-5 nodes) lies at the apex of the axilla and is located at the lateral border of the first rib. It is also referred to as the subclavicular group. This group receives efferent lymph vessels from the other axillary group of nodes. The apical group of nodes then drains into the subclavian lymph trunk. The drainage is different on the left and right sides. The left side axillary



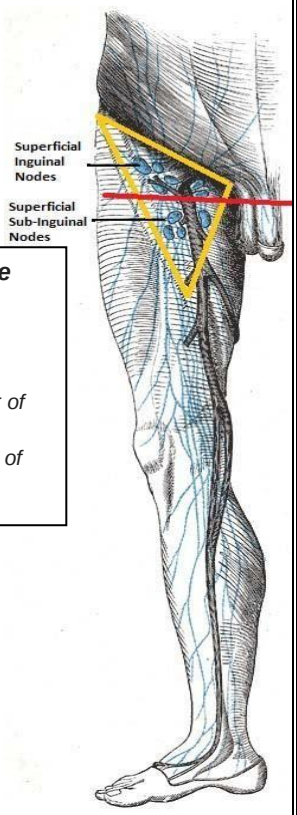
drainage flows into the thoracic duct, whereas on the right side the drainage is into the right lymphatic trunk.

Medial side of breast is drained into parasternal lymph nodes.

Most commonly and easily detected breast cancers are found in the lateral aspect of the breast.

Cancers that are found in lateral aspect of breast are more manageable than medial cancers because cancers in medial side are not easily discovered and their metastasis is fast and easy (their drainage is across the midline) .

Inguinal Lymph Nodes (we worry about them in males -prostate cancer –but mostly the cancer is discovered before swelling of the inguinal lymph nodes. Most of times, they swell because of infection in the visceral area of pelvis.**)**



Boundaries of the Femoral Triangle

- Superior boundary = *inguinal ligament*
- Lateral boundary = *medial border of sartorius muscle*
- Medial boundary = *medial border of adductor longus muscle*

The inguinal nodes are found in the upper aspect of the **femoral triangle** and are around 20 in number. They are subdivided into 2 groups determined by their position relative to a horizontal line drawn at the level of termination of the great saphenous vein. Those below this line are the **sub-inguinal nodes** (consisting of a deep and superficial set) and those above are the **superficial inguinal nodes.**

The **superficial inguinal nodes** form a line directly below the **inguinal ligament** and receive lymph from the penis, scrotum, perineum, buttock and abdominal wall.

The s**uperficial sub-inguinal nodes** are located on each side of the proximal section of the great saphenous vein. They receive afferent input primarily from the superficial lymphatic vessels of the lower leg.

The **deep sub-inguinal nodes** are often found in one to three in number and are most commonly found on the medial aspect of the femoral vein. The afferent supply to these nodes is from the deep lymphatic trunks of the thigh which accompany the femoral vessels.

Lymph nodules are small masses of lymphatic tissue found just beneath the epithelium of all mucous membranes.

The body systems lined with mucous membranes are those that have openings to the external environment: the respiratory, digestive, urinary, and reproductive tracts. You can probably see that these are also strategic locations for lymph nodules, because any natural body opening is a possible portal of entry for pathogens. For example, if bacteria in inhaled air get through the epithelium of the trachea, lymph nodules with their macrophages are in position to destroy these bacteria before they get to the blood.

Some of the lymph nodules have specific names. Those of the small intestine are called **Peyer's patches**, and those of the pharynx are called **tonsils**. The palatine tonsils are on the lateral walls of the pharynx, the adenoid (pharyngeal tonsil) is on the posterior wall, and the lingual tonsils are those on the base of the tongue. The tonsils, therefore, form a ring of lymphatic tissue around the pharynx, which is a common pathway for food and air and for the pathogens they contain.

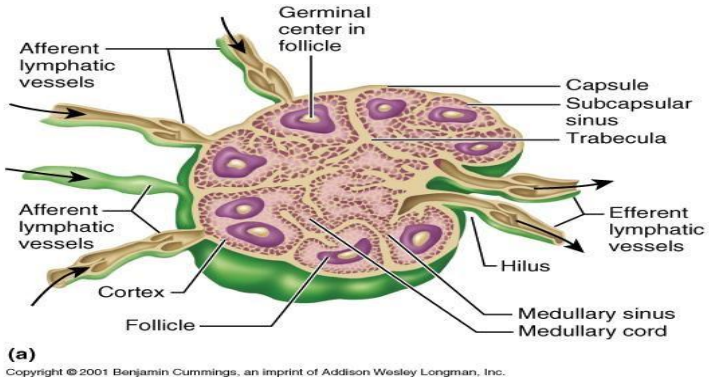
Histology of lymph nodes

The nodes are covered by a **capsule** of dense fibrous connective tissue, and have capsular extensions, of connective tissue, called the **trabeculae**, which provide support for blood vessels entering into the nodes.
Lymph, containing micro-organisms, soluble antigens, antigen presenting cells, and a few B-cells, enters the lymph node via **afferent lymphatic** vessels which enter the **subcapsular sinus**.

It then runs through **cortical sinuses** into **medullary sinuses** and leaves through the **efferent lymphatic vessels**, at the **Hilium** as **efferent** lymph.

This contains lots of T-lymphocytes, B-lymphocytes, plasma cells and antibody.

All the **sinuses** are lined by a discontinuous layer of simple squamous endothelium, and they also contain lymphocytes and macrophages. Reticular fibers provide additional support to the matrix/stroma.



The **cortex** is divided into an outer and an inner cortex (**paracortex**).

The **outer cortex** has lymphatic nodules that mostly contain B-cells. Small lymphocytes sit in the spaces between the reticular fiber meshwork in the cortex. The lighter staining

Cortex is divided into outer cortex that contains naïve B cells and inner paracortex that contains naïve T cells.

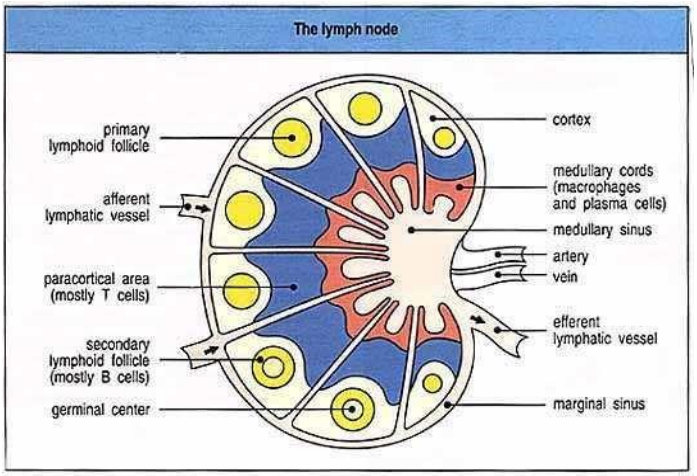
Mature B cells are found in the medulla

areas are **germinal centers,** where the **B-cells proliferate** into antibody secreting plasma cells. **Macrophages** are also present in these regions, together with **dendritic cells**, and some **T-cells**. Both the macrophages, and the dendritic cells trap antigens and present them on their surfaces to B-cells.

The **inner cortex** contains mostly T-cells.

The **deep cortical**, and **medullary cords** contain B-cells and plasma cells.

Most of the lymphocytes enter the lymph nodes via blood vessels, and about 10% enter through the lymph.



Exam question:

In the outer cortex, the B Cells are found in follicles; some of them contain germinal center>> secondary lymphoid follicles, while if the follicles don't contain germinal centers >> primary lymphoid follicles.

Germinal centers: B cells that have exposed to antigen and start proliferating.

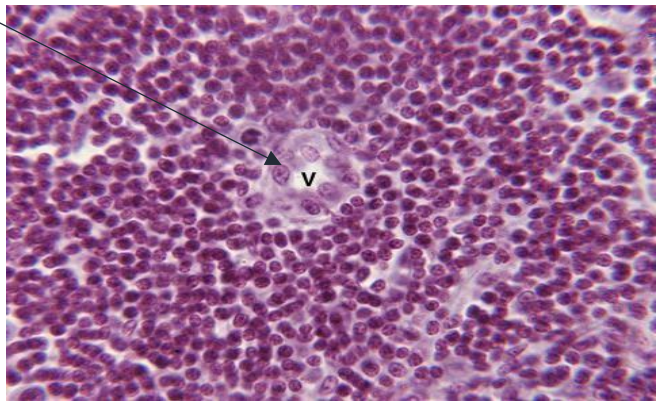
Mature dendritic cells are in the lymph nodes whereas immature dendritic cells are in the tissues where they detect the antigens and proceed to the lymph nodes where they become mature though the influence of growth factors and present the antigens to T-cells.

The structure of the post-capillary venule, in the deep cortex (paracortex) is unusual in that it is not lined by simple squamous epithelium, but by a simple cuboidal epithelium. These are called high endothelial venules (HEVs). Lymphocytes recognize and adhere to these endothelial cells, and squeeze through them into the deep cortical regions of the nodes. This region of the lymph has lots of T-cells, as well as the antigen presenting dendritic cells.

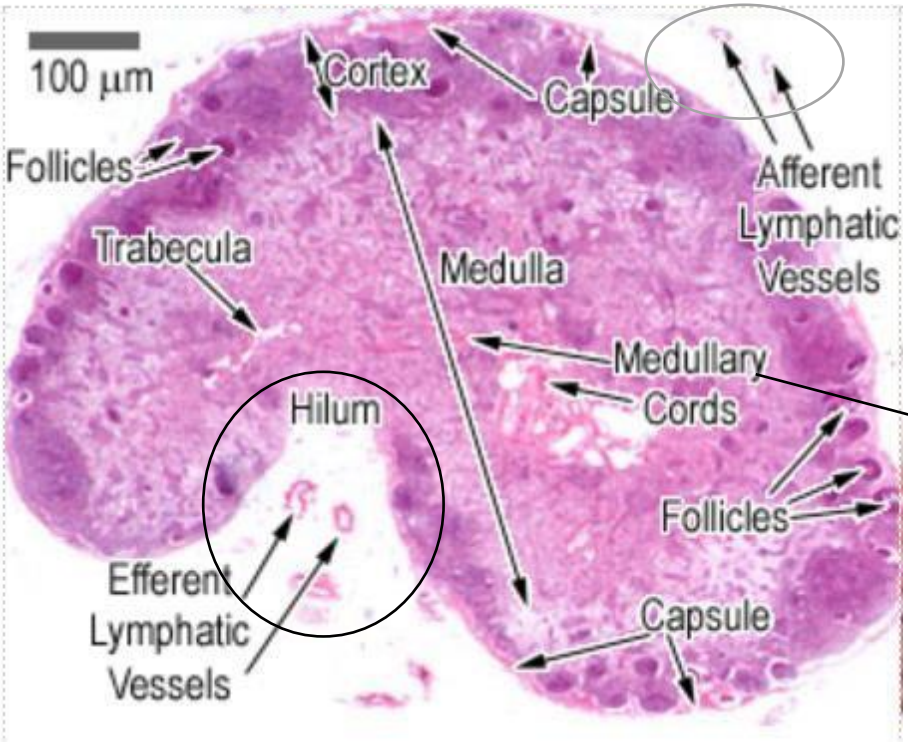
T-cells entering here become activated in the cortex, between lymphoid follicles.

Postcapillary Venules: they are unique in the lymph nodes because of their endothelial lining which is composed of cuboidal HEVs, high endothelial venules.

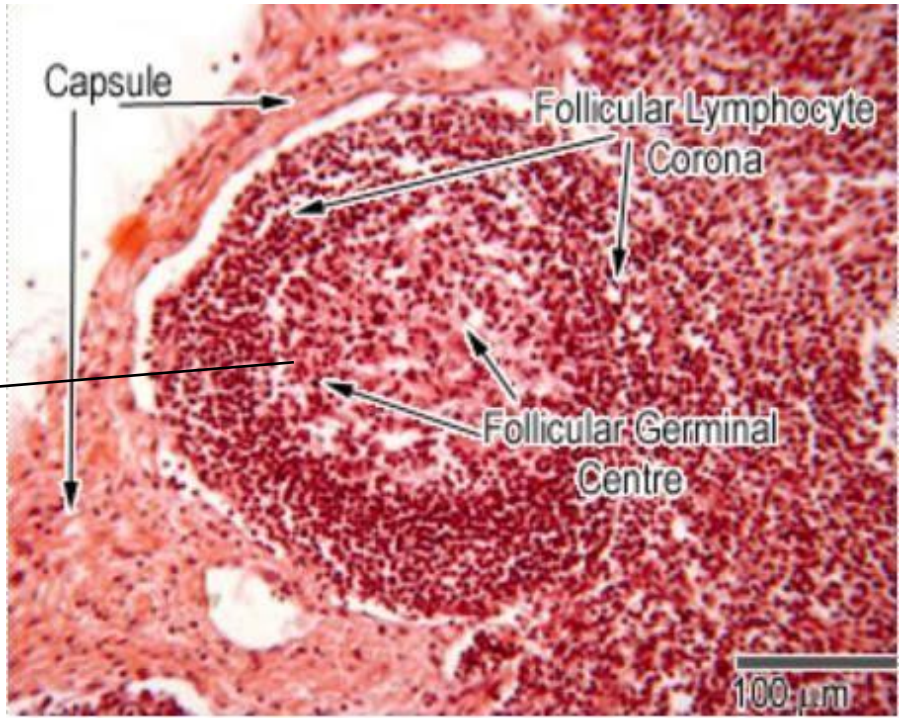
Function of HEVs: lymphocytes which have undergone maturation would **mainly** leave the lymph nodes through the blood, specifically through the HEVs.



Longitudinal section

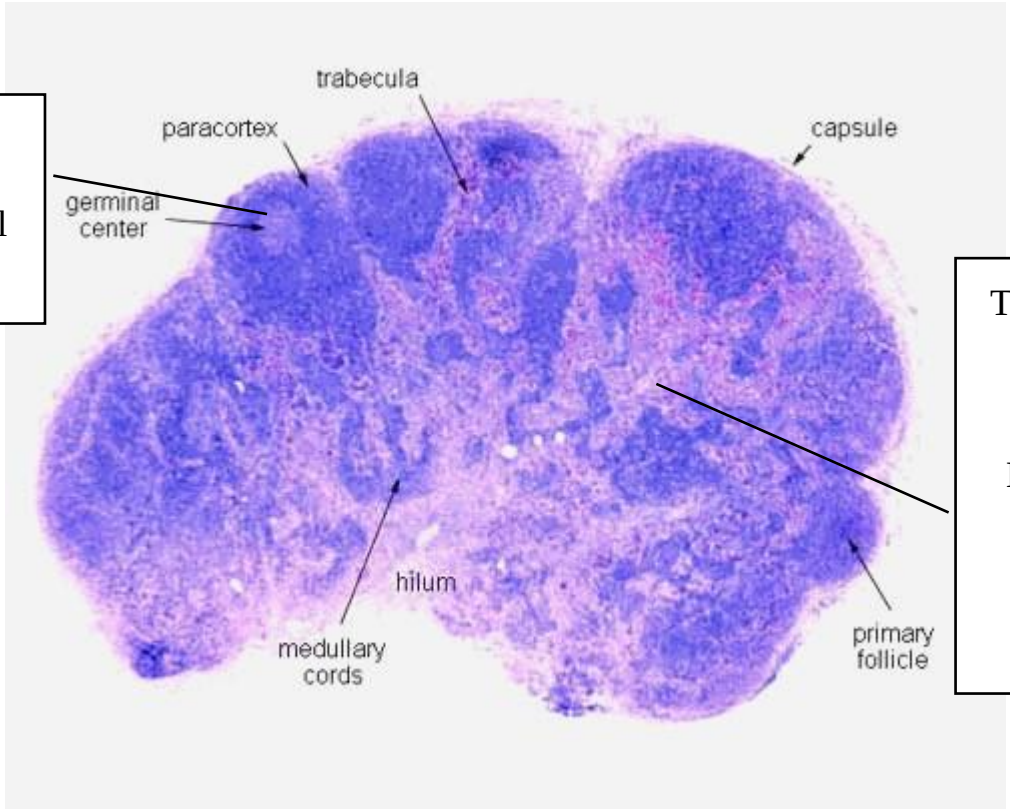


Mature B cells are arranged in cords to leave the medulla



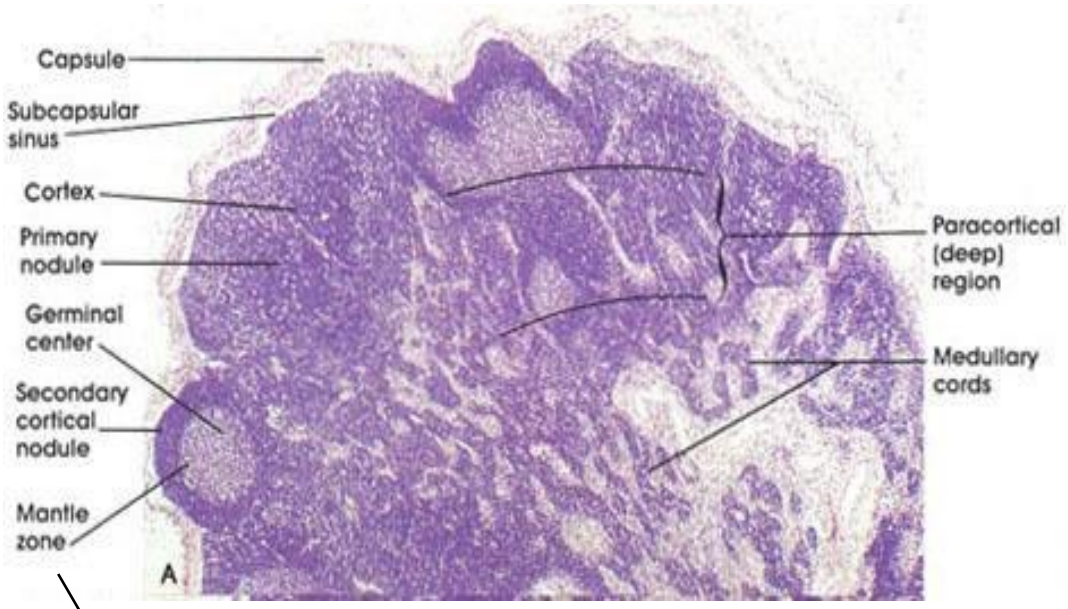
Secondary lymphoid follicles

Light stained germinal center



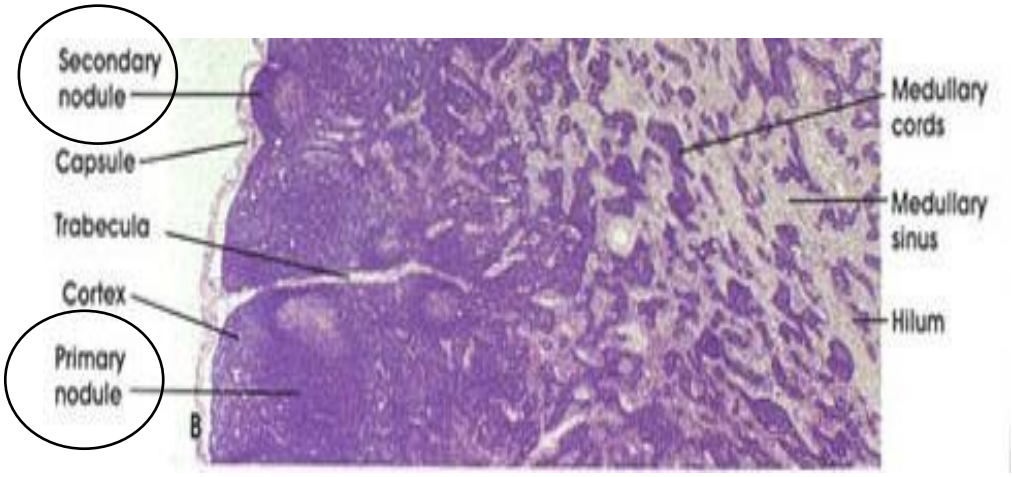
The medulla is lightly stained

Medullary cords are heavily stained



We talked about it in histology of the spleen

Lining of follicles

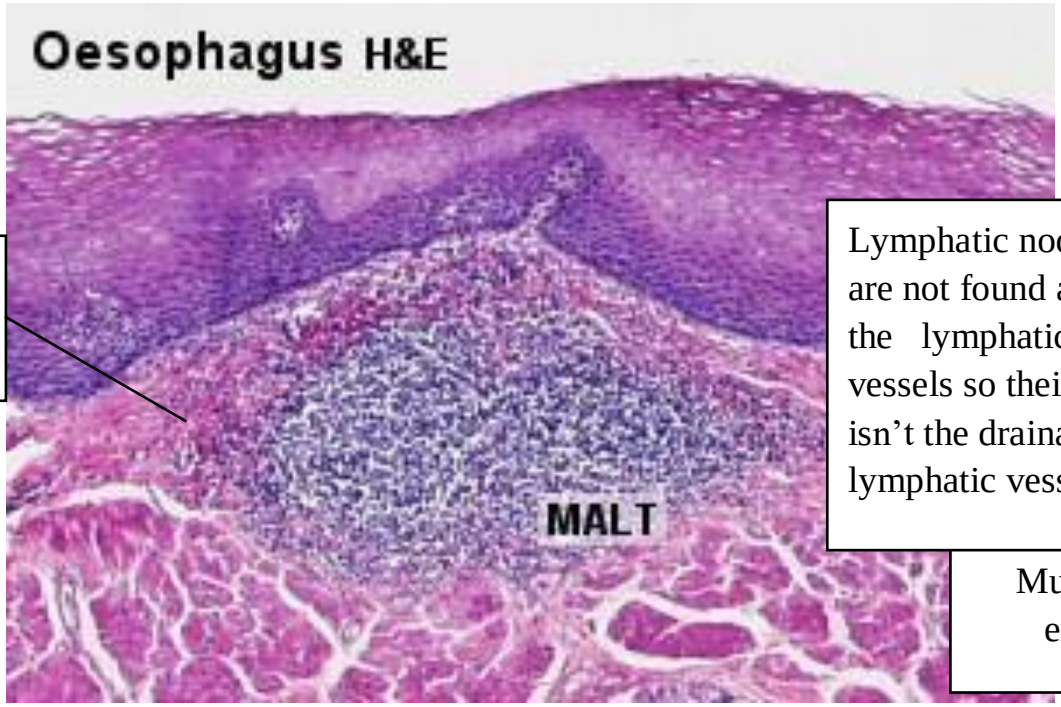


Mucosa-Associated Lymphoid Tissue

The mucosal lining of the alimentary canal and airways is in many ways specialized to facilitate the exchange of substances between the external environment and the body. Unfortunately, these specialization do not just apply e.g. to components of the digested food but also pathogens. This is combined with excellent living conditions for bacteria in parts of the alimentary canal - in particular the ileum and the colon. Lymphoid tissue located beneath the mucosal epithelia, *mucosa-associated lymphoid tissue* (MALT), protects the body against pathogens that may enter the body via the mucosa. The importance of this task is reflected in the mass of the MALT, which corresponds to the combined mass of the other lymphoid organs and tissues.

The task that the immune cells of the MALT have to accomplish is different from that of other parts of the immune system. We do need a defense against pathogens, but it would not be a good idea to mount an immune response against components of the food. Immune cell activation therefore differs between the MALT and other lymphoid tissues.
This difference is mediated by different receptors expressed by immune cells of the MALT and by different substances which they release upon contact with an antigen. Because of their specific functions, immune cells of the MALT do not mingle with other immune cells. Epithelial cells of the vessels supplying the MALT express specific receptors which are recognized by MALT immune cells and allow their homing to the MALT during recirculation. Lastly, MALT plasma cells produce a secretable form of antibodies, immunoglobulin type A dimers, which can be taken up by epithelial cells and then released onto the epithelial surface.

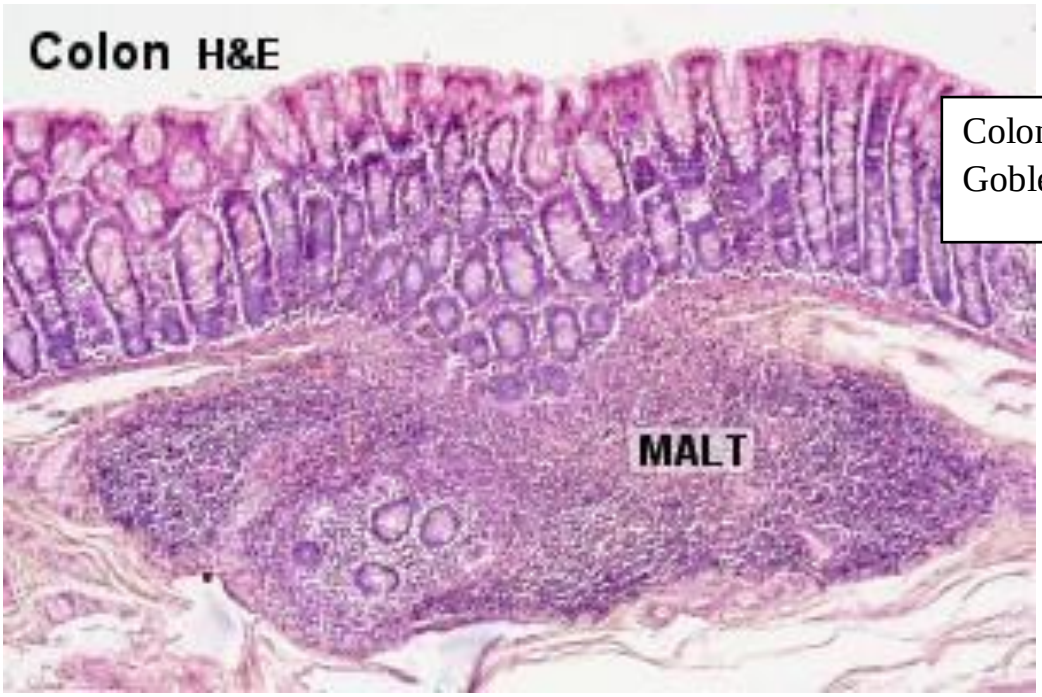
Specialization of MALT immune cells occur at the molecular level. In routine histological preparations, immune cells of the MALT look pretty much like immune cells of other lymphoid tissues.



submucosa

Lymphatic nodules are not found along the lymphatic vessels so their job isn't the drainage of lymphatic vessels.

Muscularis externa



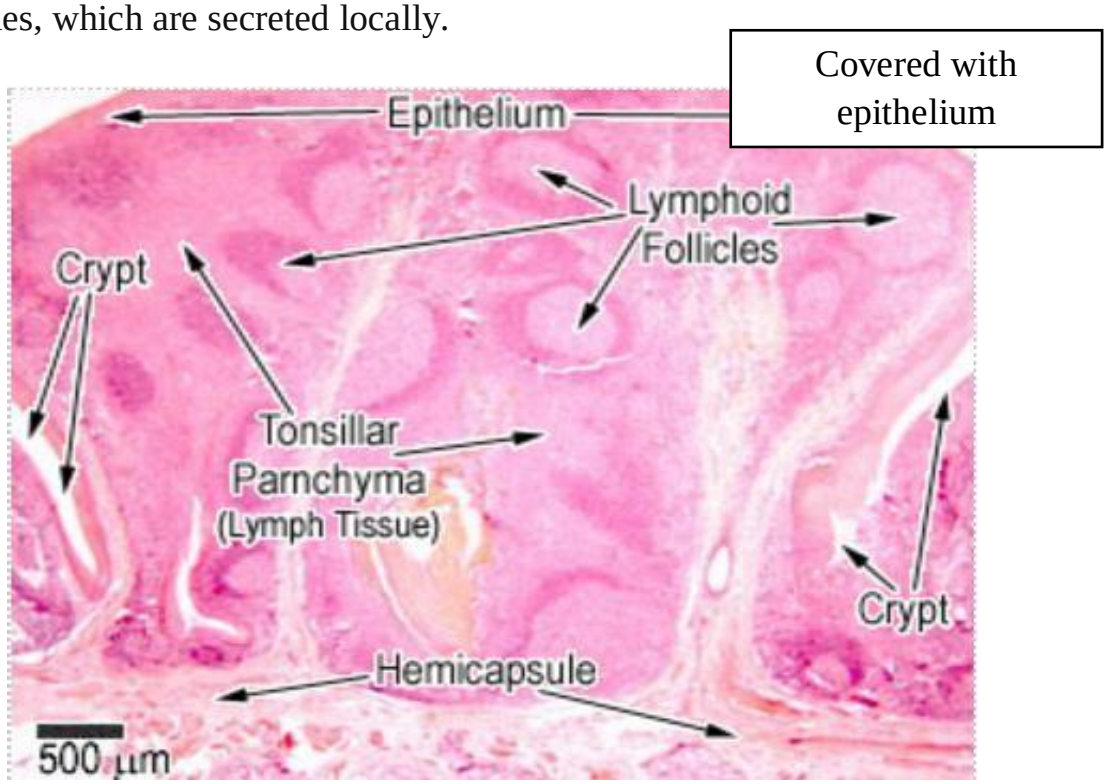
Colon >> from Goblet cells

Often MALT consists of small accumulations of lymphoid cells or one to a few lymph follicles beneath the epithelium and possibly extending into the submucosa. The tonsils and Peyer's patches are large accumulations of lymphoid tissue with associated specializations of the epithelium.

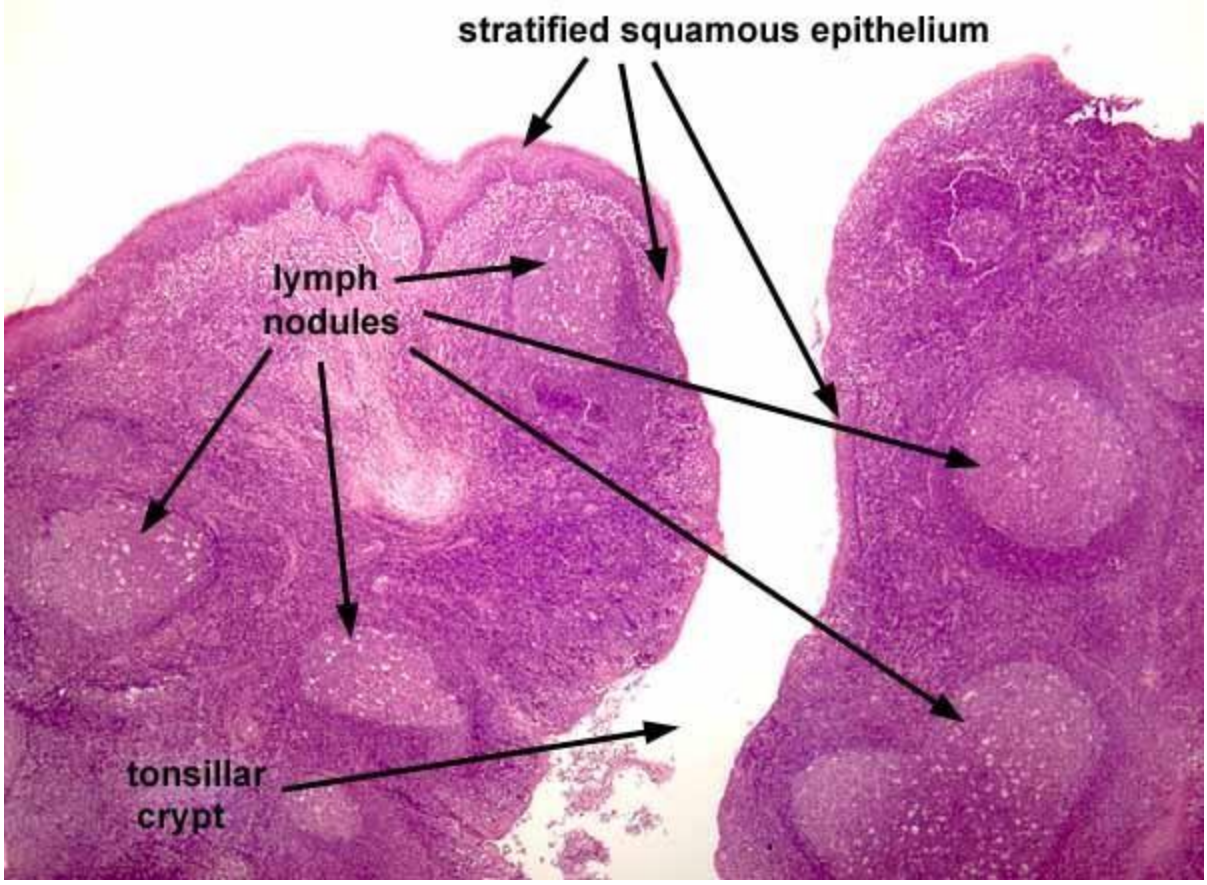
Histology of Tonsils

Tonsils are large non-encapsulated (or partially encapsulated*) masses of lymphoid tissue, that lie in the walls of the pharynx and nasopharynx and at the base of the tongue.
The **luminal surface** of the tonsils is covered with a stratified squamous epithelium (in common with the oral epithelia).

The tonsils have many invaginations which form **blind crypts.**
Below the epithelium, there are many lymphoid follicles beneath which have germinal centers like the lymph nodes.
The epithelial cells are able to phagocytose bacteria, and transfer them to macrophages, which then present the foreign antigens to B-cells, which are activated (with the help of T cells). The activated cells mostly secrete IgA type antibodies, which are secreted locally.



*Tonsils have a hemi-capsule, as part of them are covered by a capsule and the other part is covered by mucosa.



Histology of Peyer's patches

Small accumulations of lymphocytes or solitary lymph follicles are found scattered in beneath the epithelium throughout the gastrointestinal tract. However, the most prominent accumulations occur in the ileum and appendix in the form of Peyer's patches. In the ileum, they form dome-shaped protrusions into the lumen. Beneath the epithelial lining of the domes, Peyer's patches extend from the lamina propria to the submucosa. Within Peyer's patches, lymph follicles with germinal centers are typically located deep in the submucosa.

The epithelium in contact with the lymphoid tissue is specialised to facilitate the contact of antigens with cells of the immune system. The epithelium appears columnar and contains cells with deeply invaginated basal surfaces - *microfold cells or M-cells*. Immune system cells can enter these invaginations (intraepithelial pockets) where they are exposed to materials which have been endocytosed by the epithelial cells and then released into the invaginations.

Goblet cells are rare or absent in the epithelium which covers the domes.