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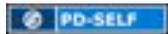
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# Lymphatic Histology

M1 – Immunology Sequence

J. Matthew Velkey, Ph.D.

Winter 2009



# Learning Objectives

Text: Ross, 5<sup>th</sup> ed., pp. 396-441

Atlas: Wheater's, 5<sup>th</sup> ed., pp. 215-233

1. Understand the distinction between PRIMARY and SECONDARY lymphoid organs
2. Be able to describe the organization and function of:
  - Mucosa-associated lymphoid tissue
    - Diffuse and nodular lymphoid tissue, also including regions of extensive lymphoid infiltration such as Peyer's patches, appendix, and tonsils.
  - lymph nodes
  - Spleen
  - Thymus
3. Be able to identify the regions rich in B and T lymphocytes in each organ and explain the cellular processes, relevant to immune functions, that are taking place in these regions.
4. Know the homing patterns of B & T lymphocytes.

# Functions of the Lymphatic System

1. Monitor body surfaces and fluid compartments (e.g. epidermis, mucosae\*, interstitium)
2. React to the presence of potentially harmful antigens recognized as “non-self”
3. Autoimmune diseases (rheumatoid arthritis, type I diabetes, etc.)

Lymphatic System consists of:

A. Cells

1. Lymphocytes (B,T, natural killer)
2. Antigen-presenting cells (dendritic cells, Langerhans' cells & macrophages)

B. Lymphatic “tissue” –diffuse and nodular

C. Lymphatic “organs” (lymph nodes, spleen, thymus)

D. Lymphatic vessels that carry the cells and fluid

\*Mucosae refers to lining tissue of the body cavities, e.g. GI tract, respiratory tract, genitourinary tract

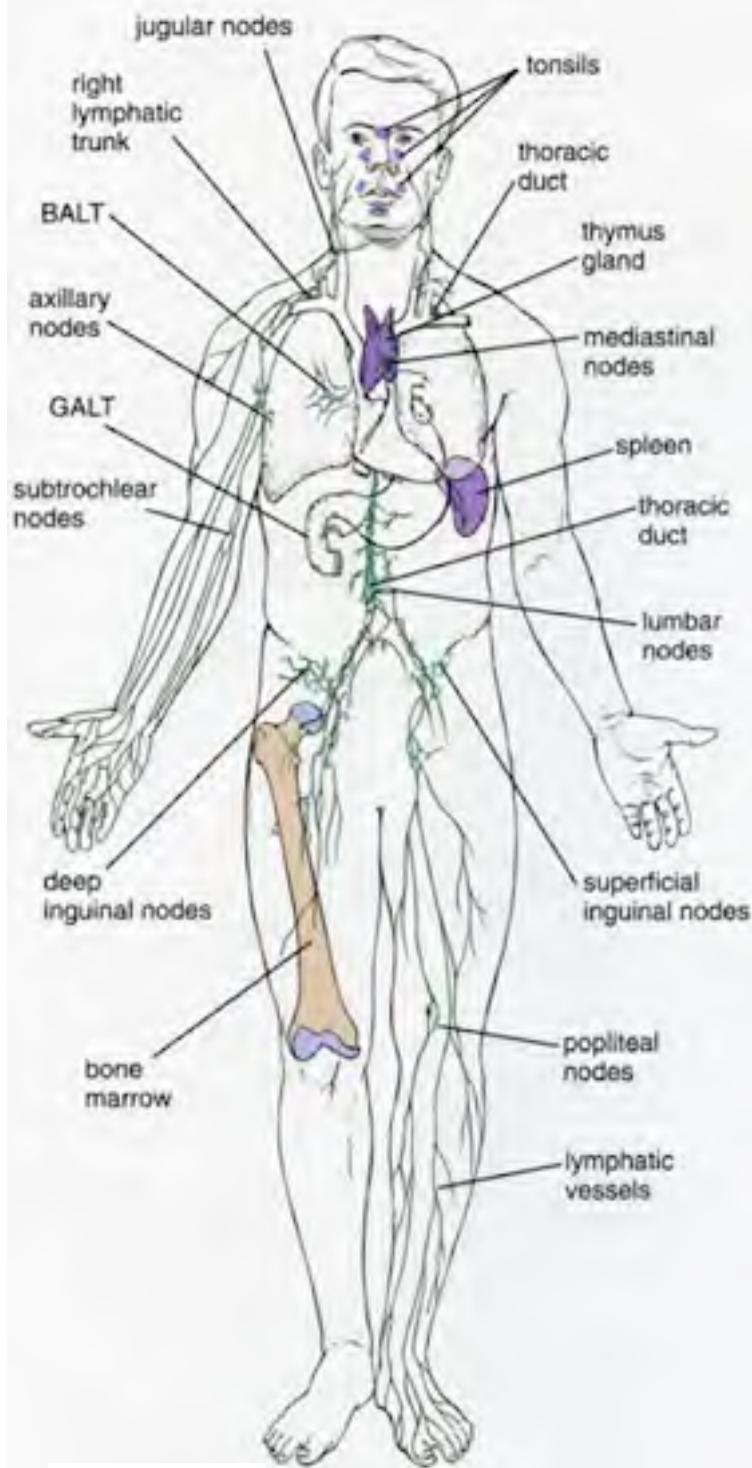
Lymphoid organs are classified as:

## Primary lymphoid organs

- Thymus
- Bone marrow
- Lymphatic nodules of the distal intestinal tract (e.g. ileum and appendix)

## Secondary (effector) lymphoid organs/tissue

- Spleen & lymph nodes (organs)
- Mucosal associated lymphoid tissue (MALT), e.g. lymphocytes and lymphatic nodules in the lamina propria



## Primary Lymphoid Organs:

The bone marrow and the thymus and the Gut-Associated Lymphoid Tissue (e.g. [appendix, terminal ileum](#)) are the initial “education centers” of the immune system

In these organs, lymphocytes (T cells in the thymus, B cells in bone marrow and gut) differentiate into **immunocompetent** cells (i.e. they can recognize “self” vs. “nonself”)

This differentiation is said to be antigen-*independent*

The lymphocytes then enter the blood and lymph to populate:

- epidermis and mucosae
- connective tissue
- secondary lymphoid organs

## Secondary Lymphoid Organs:

The lymph nodes, lymphatic nodules, tonsils, spleen are the secondary “education centers” of the immune system

In these organs, immunocompetent lymphocytes differentiate into immune effector and memory cells that undergo antigen-***dependent*** activation and proliferation in these organs.

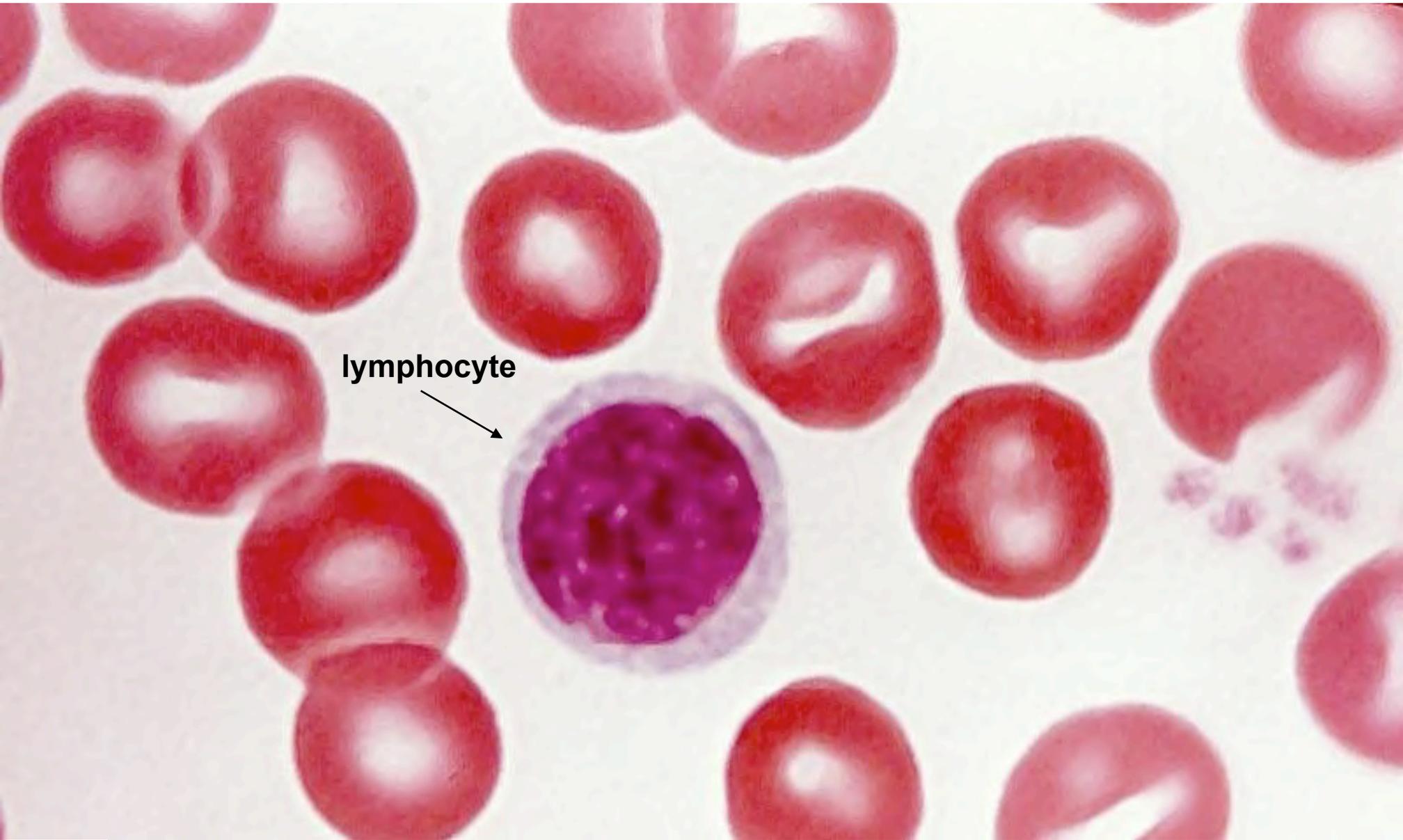
These lymphocytes then carry out their functions in the:

- connective tissue
- secondary lymphoid organs
- mucosal surfaces lining epithelia

They participate in:

- Cell mediated immunity (mostly “cytotoxic” T cells)
- Humoral responses (production of antibody) (B cells, also requires “helper” T cells.

# Lymphocytes in peripheral blood smear



PD-INEL Mizobuti histology slide set

These are B and T-cells that have undergone antigen-INDEPENDENT differentiation and are trafficking through the bloodstream on their way to lymphoid organs/tissue.

# Resting Lymphocyte



# Diapedesis: it's not just for the Normans and the Saxons...

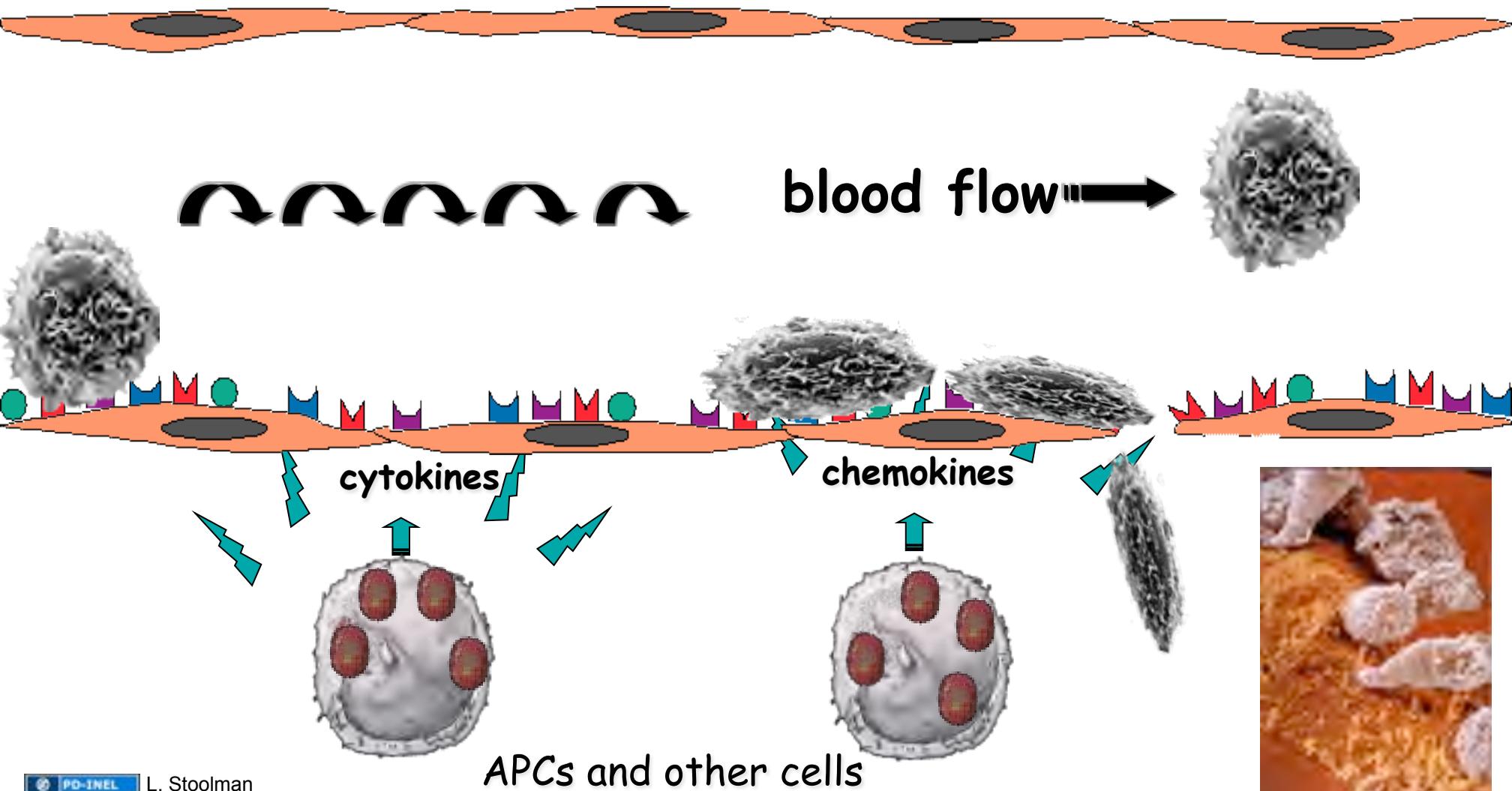
Cytokines and chemokines (along with selectins and integrins) mediate EXTRAvasation of lymphocytes into tissues.

**Tether**

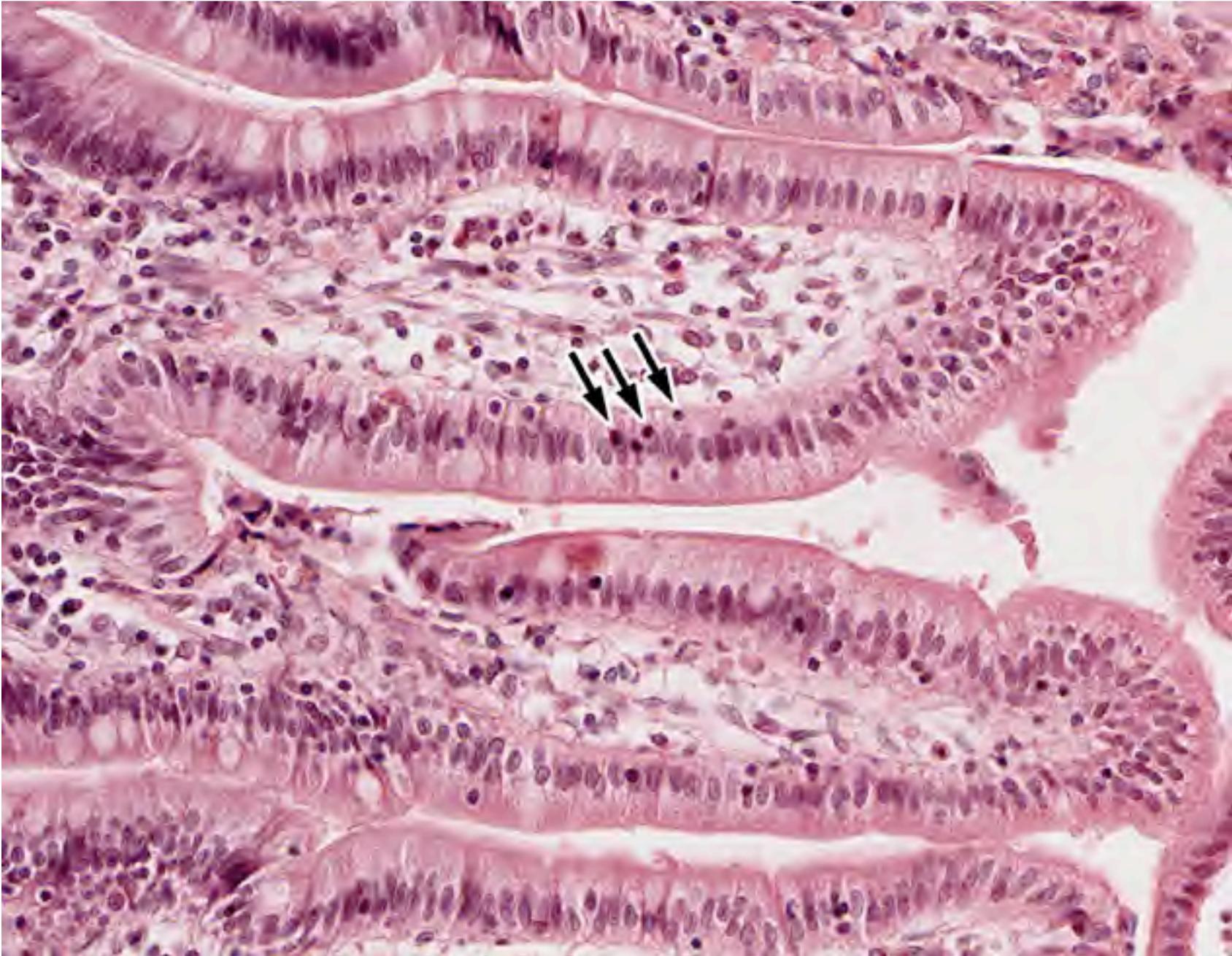
**Roll**

**Arrest**

**Migrate**



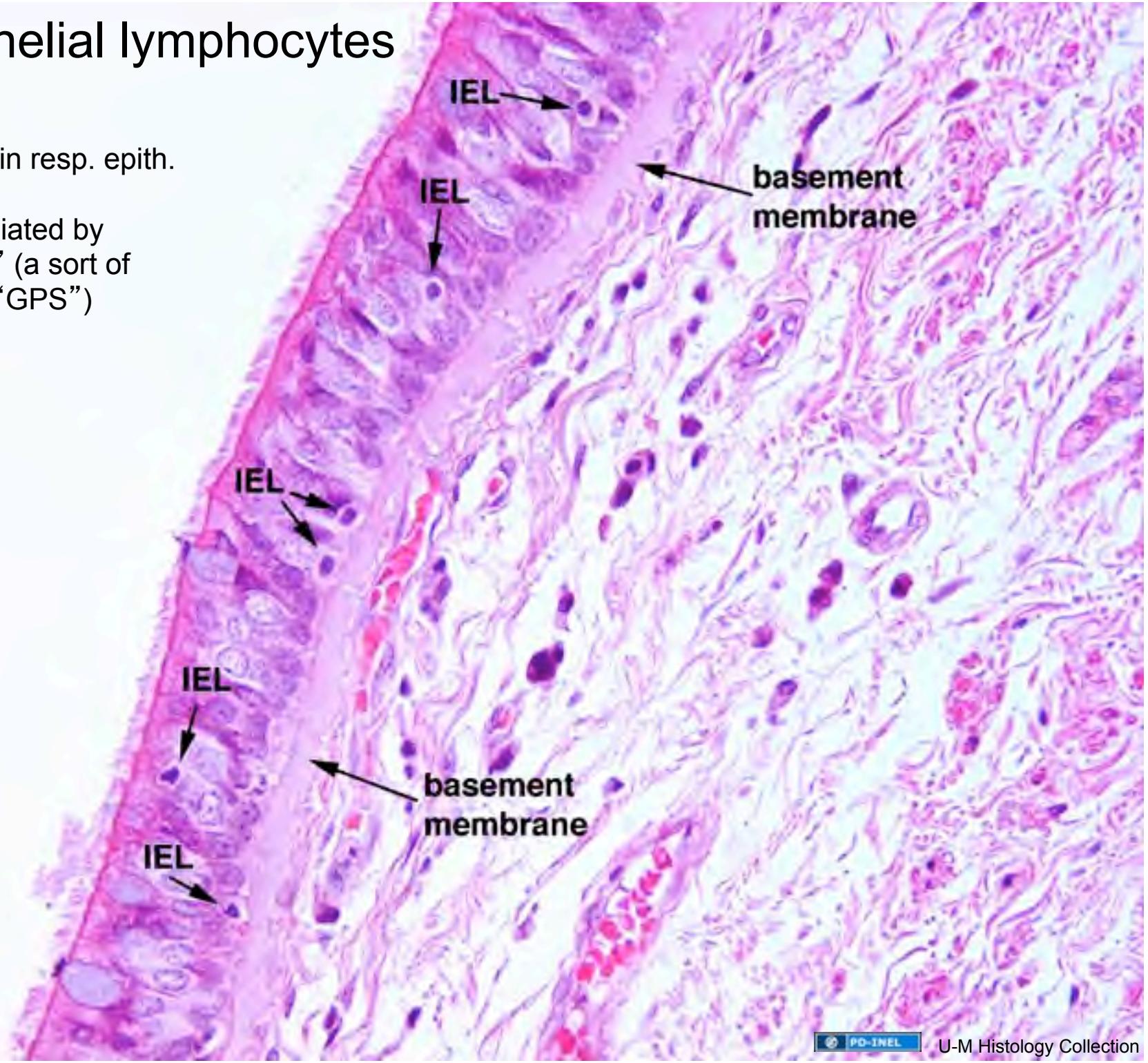
MALT: intraepithelial lymphocytes:  
 $\gamma\delta$ T-cells (neither helper nor cytotoxic): first to see antigens



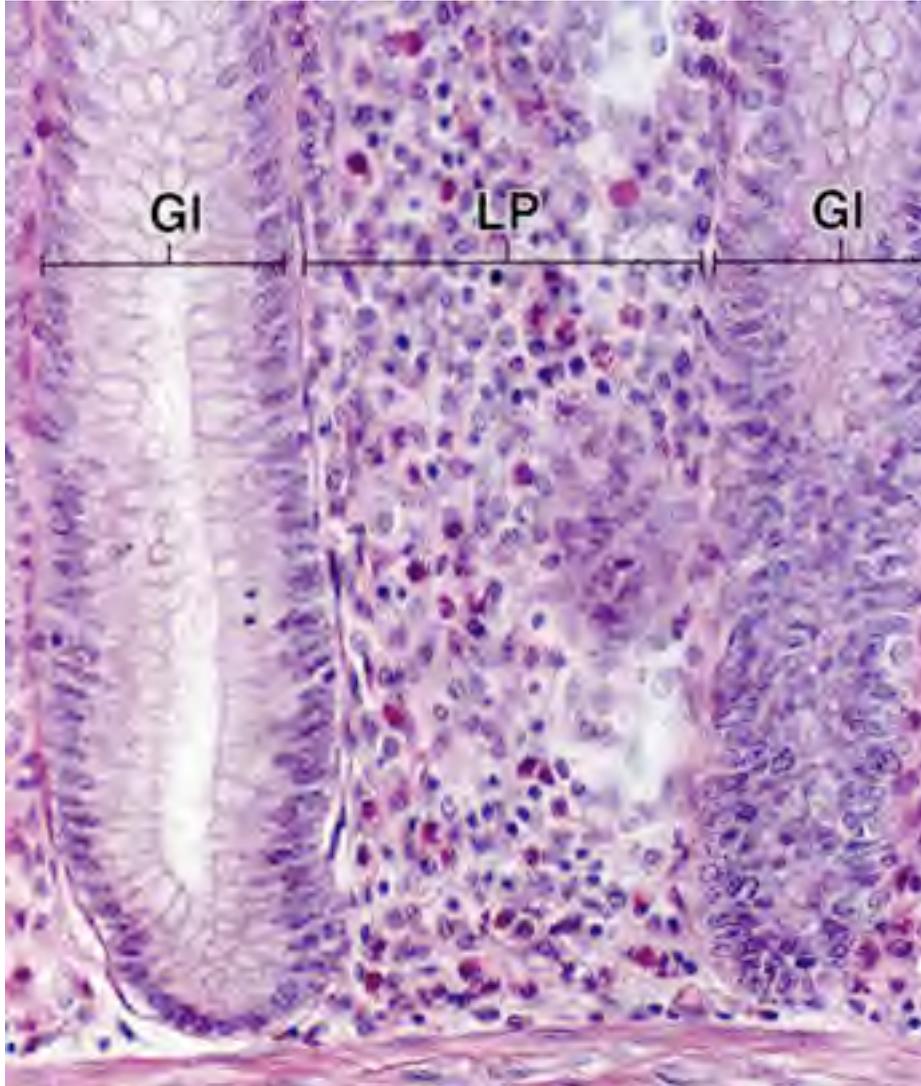
# Intraepithelial lymphocytes

Shown here in resp. epith.

Homing mediated by  
“addressins” (a sort of  
lymphocyte “GPS”)



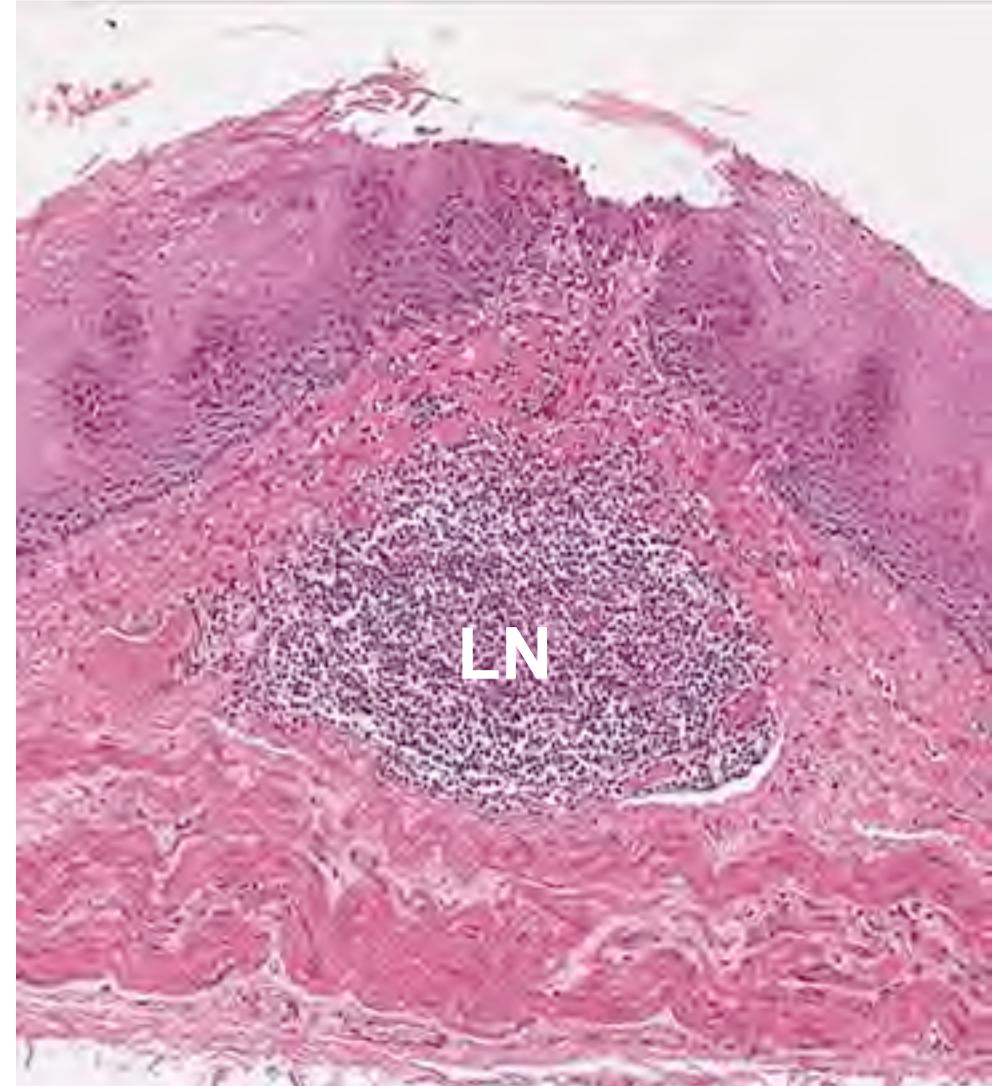
# LYMPHOCYTES IN CONNECTIVE TISSUE: MALT = mucosa-associated lymphoid tissue



PD-INEL Ross and Pawlina, *Histology: A Text and Atlas*

## Diffuse lymphoid tissue

Lamina propria (LP) of gut shown here, but can be found associated with mucosae anywhere in the gut, respiratory, and genitourinary tracts.

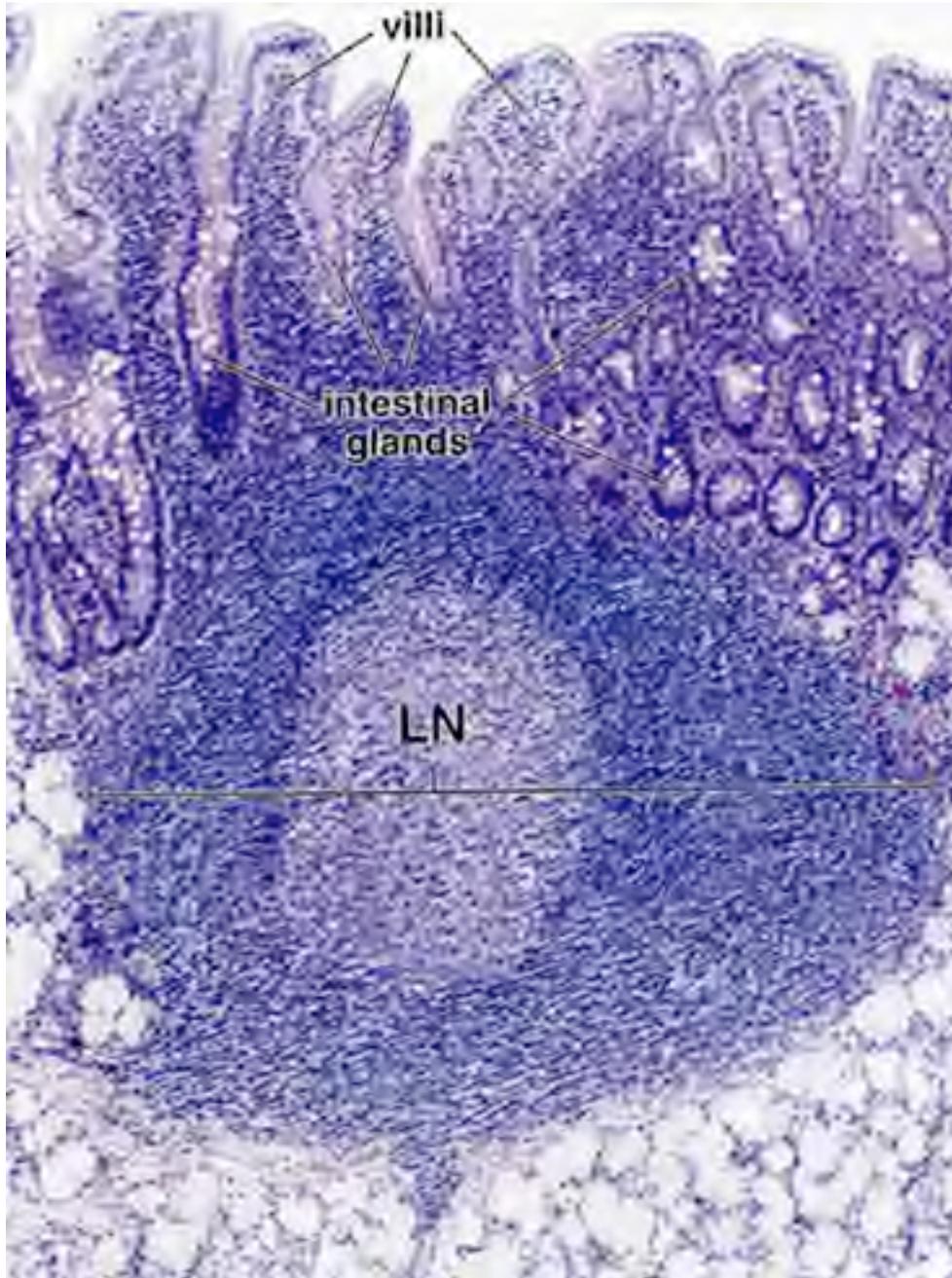


PD-INEL U-M Histology Collection

## Primary lymphatic nodule/follicle (LN)

Aggregation of lymphocytes in lamina propria or submucosa

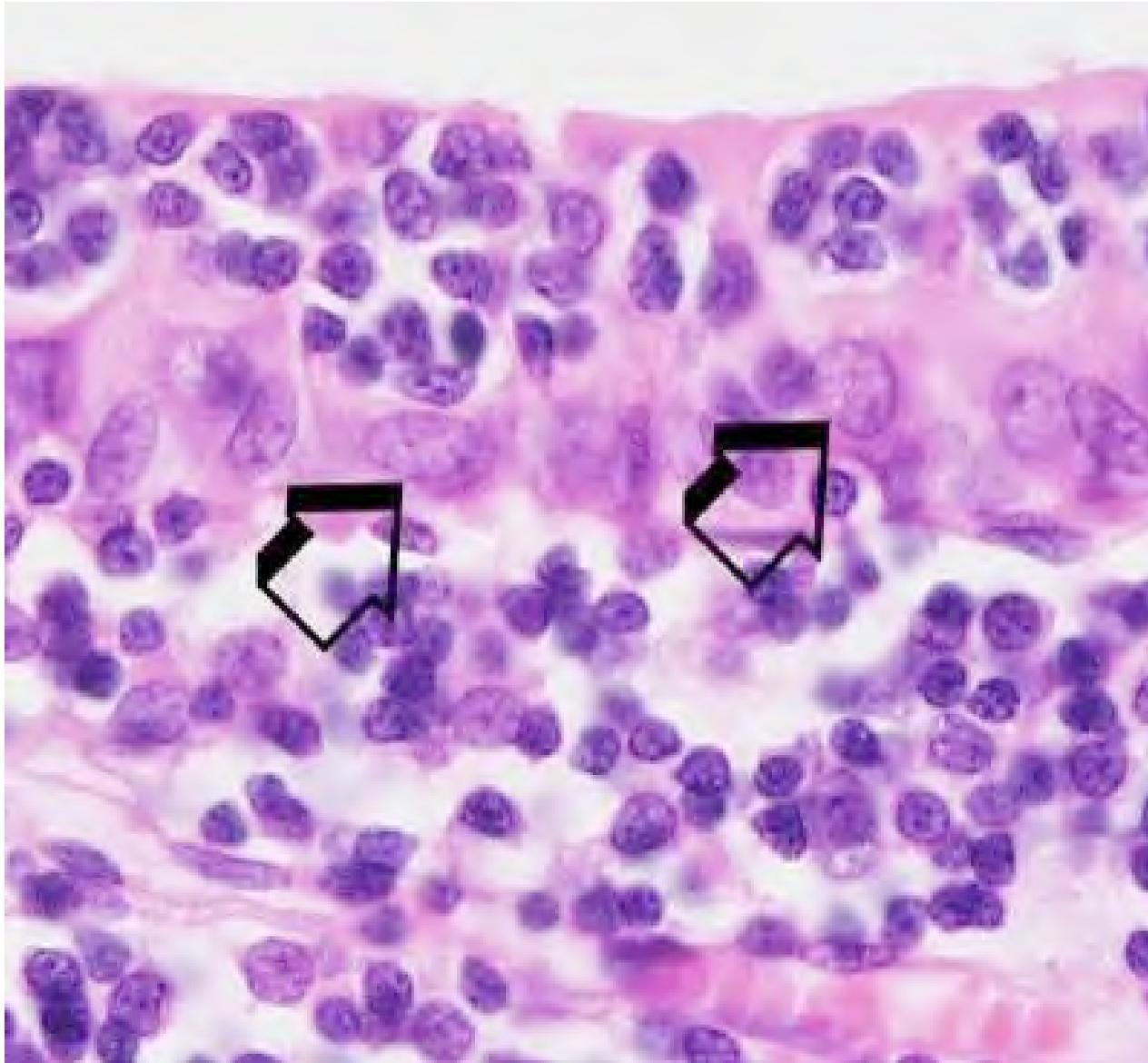
# Secondary follicles/nodules



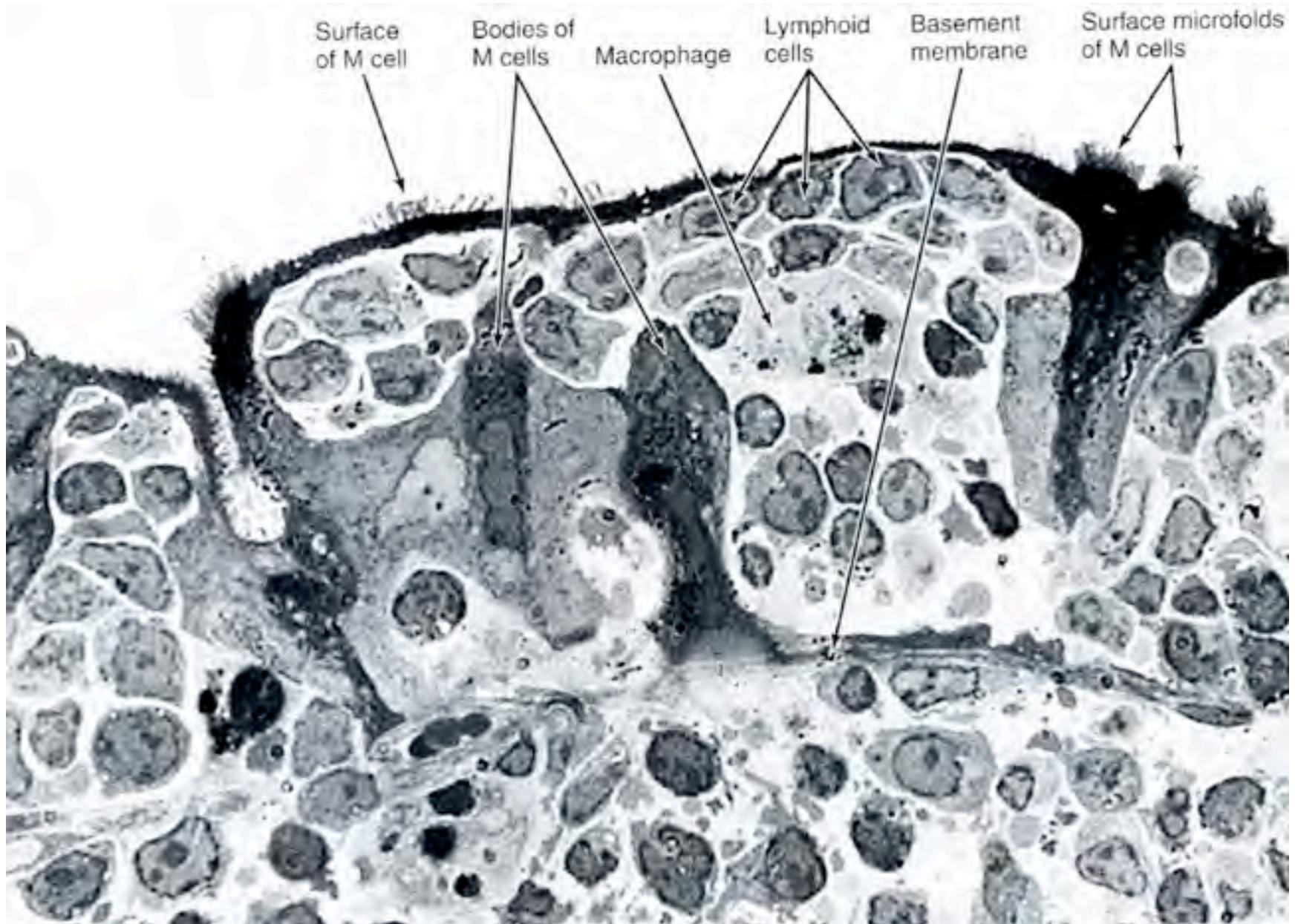
- Contain germinal centers
- Arise when B-lymphocytes are presented with appropriate antigen, receive T-cell help, and then begin proliferating as lymphoblasts
- Lymphoblasts differentiate into plasma cells or memory cells; aberrant lymphoblasts undergo apoptosis.

# Microfold, or “M” CELLS

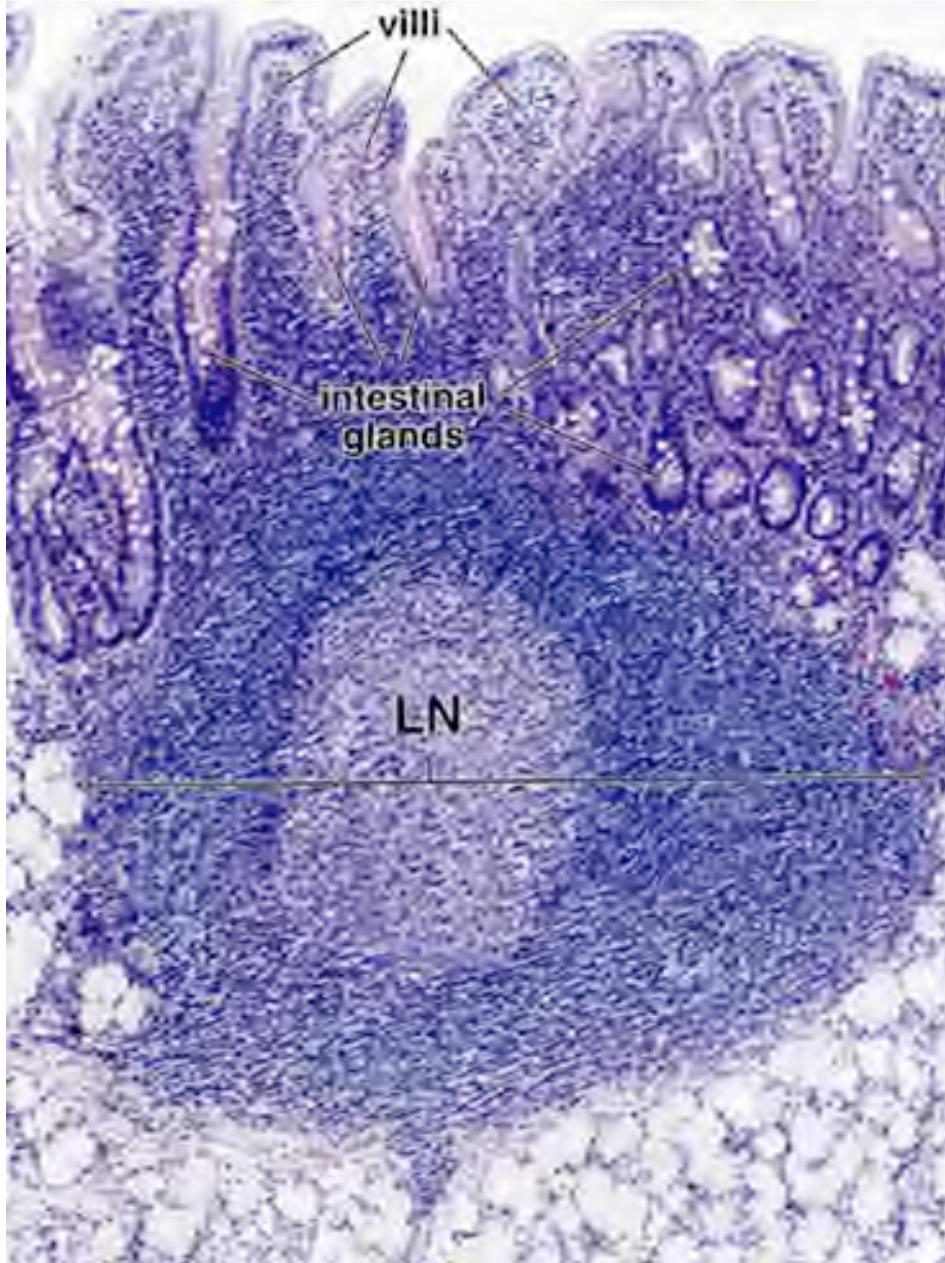
Modified intestinal epithelial cells that assist in antigen presentation by conveying macromolecules from the intestinal lumen to underlying compartments housing lymphocytes and macrophages.



# M cells: TEM



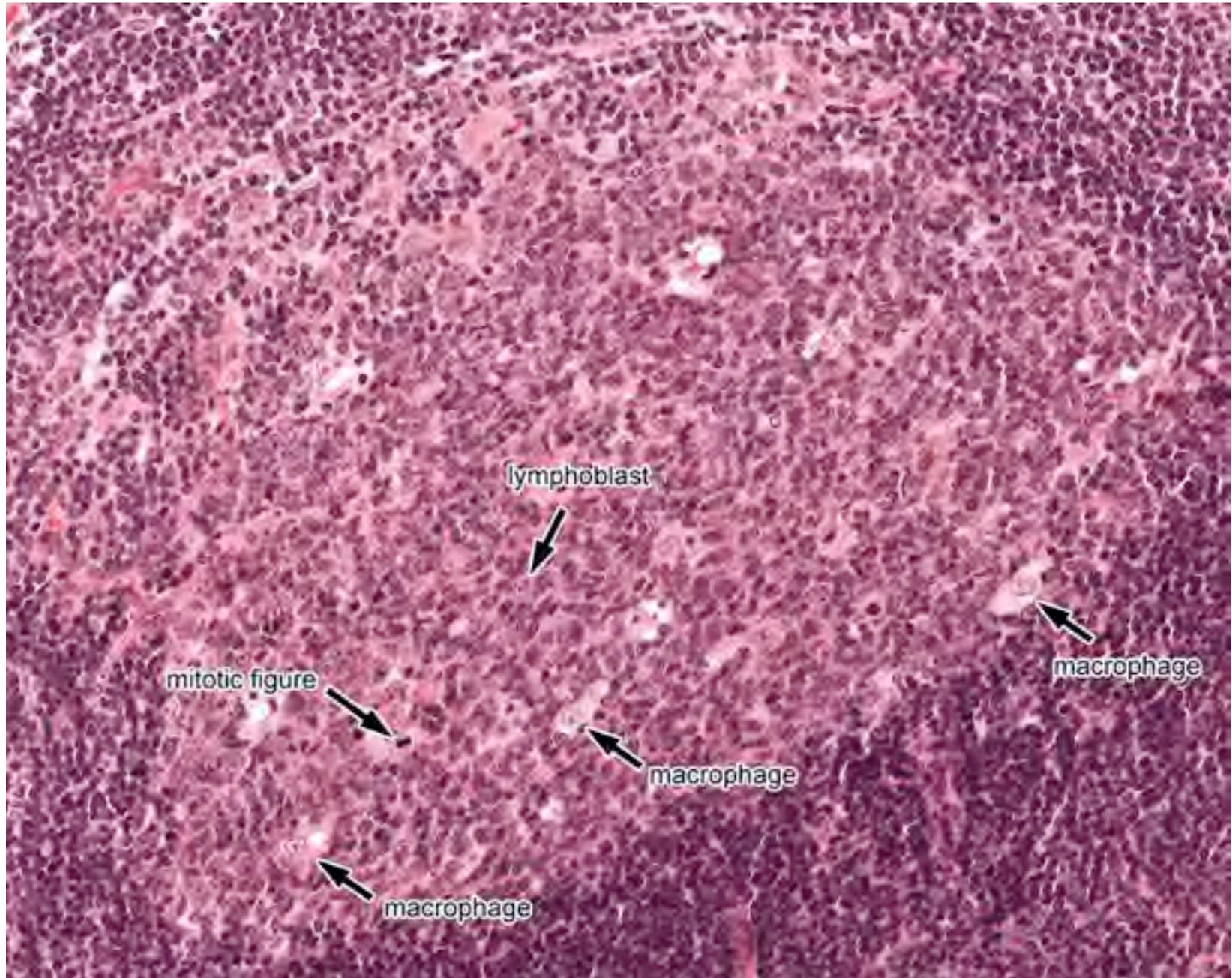
# After antigen presentation and T-cell help, activated B-cells set up germinal centers in secondary follicles



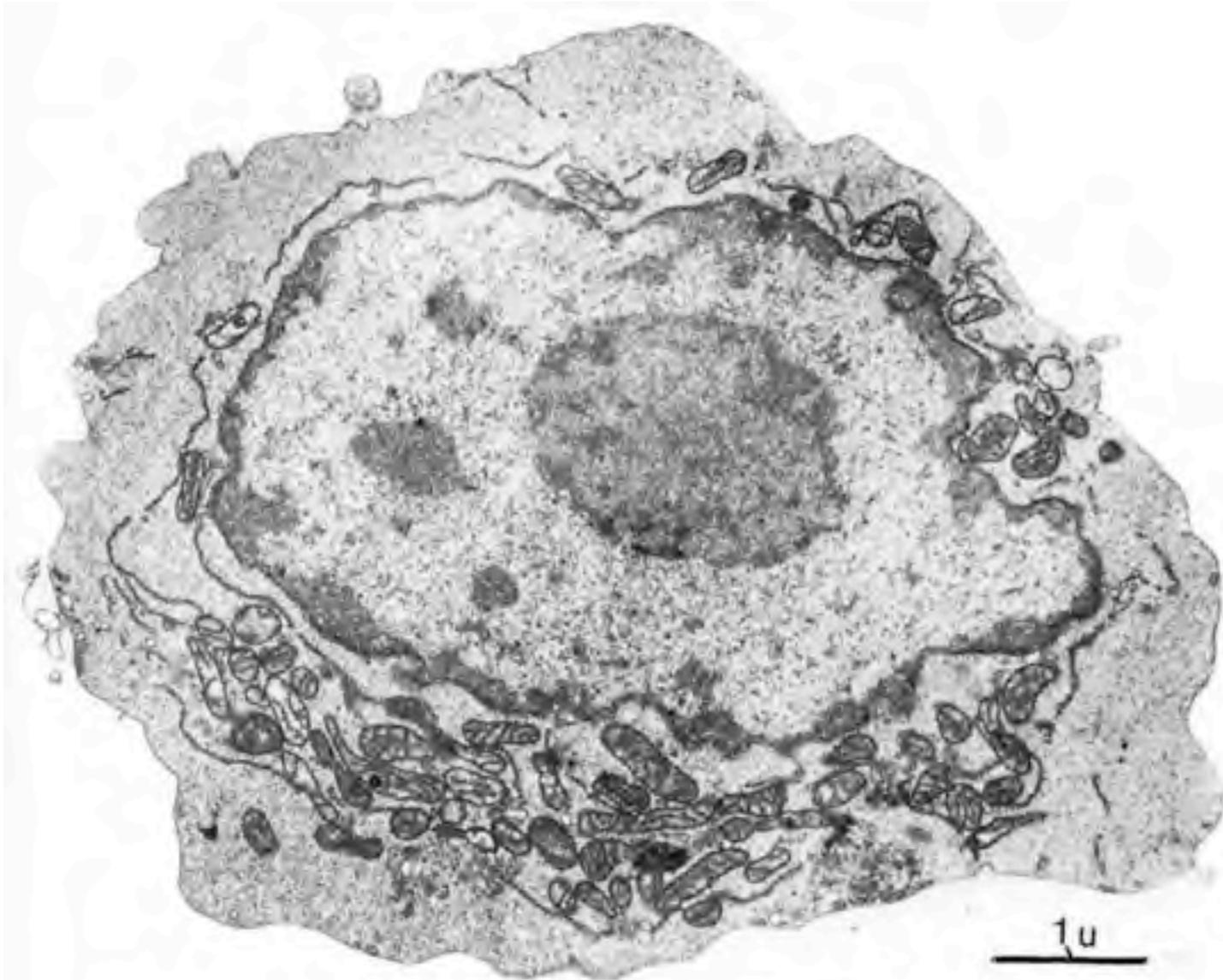
## Secondary follicle germinal centers

- Arise when B-lymphocytes are presented with appropriate antigen, receive T-cell help, and then begin proliferating as lymphoblasts
- Lymphoblasts differentiate into plasma cells or memory cells; aberrant lymphoblasts undergo apoptosis.

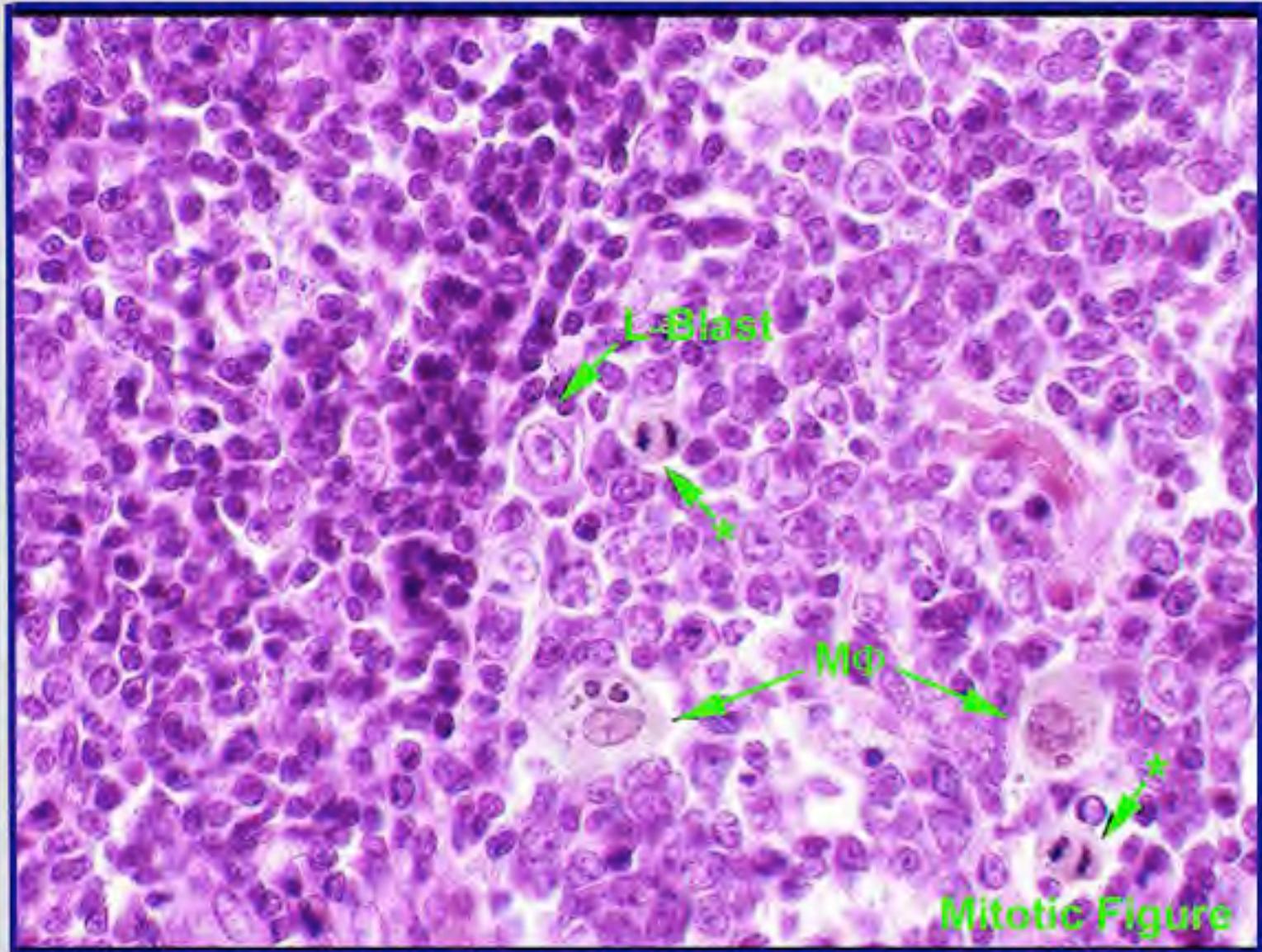
# Germinal center: high magnification



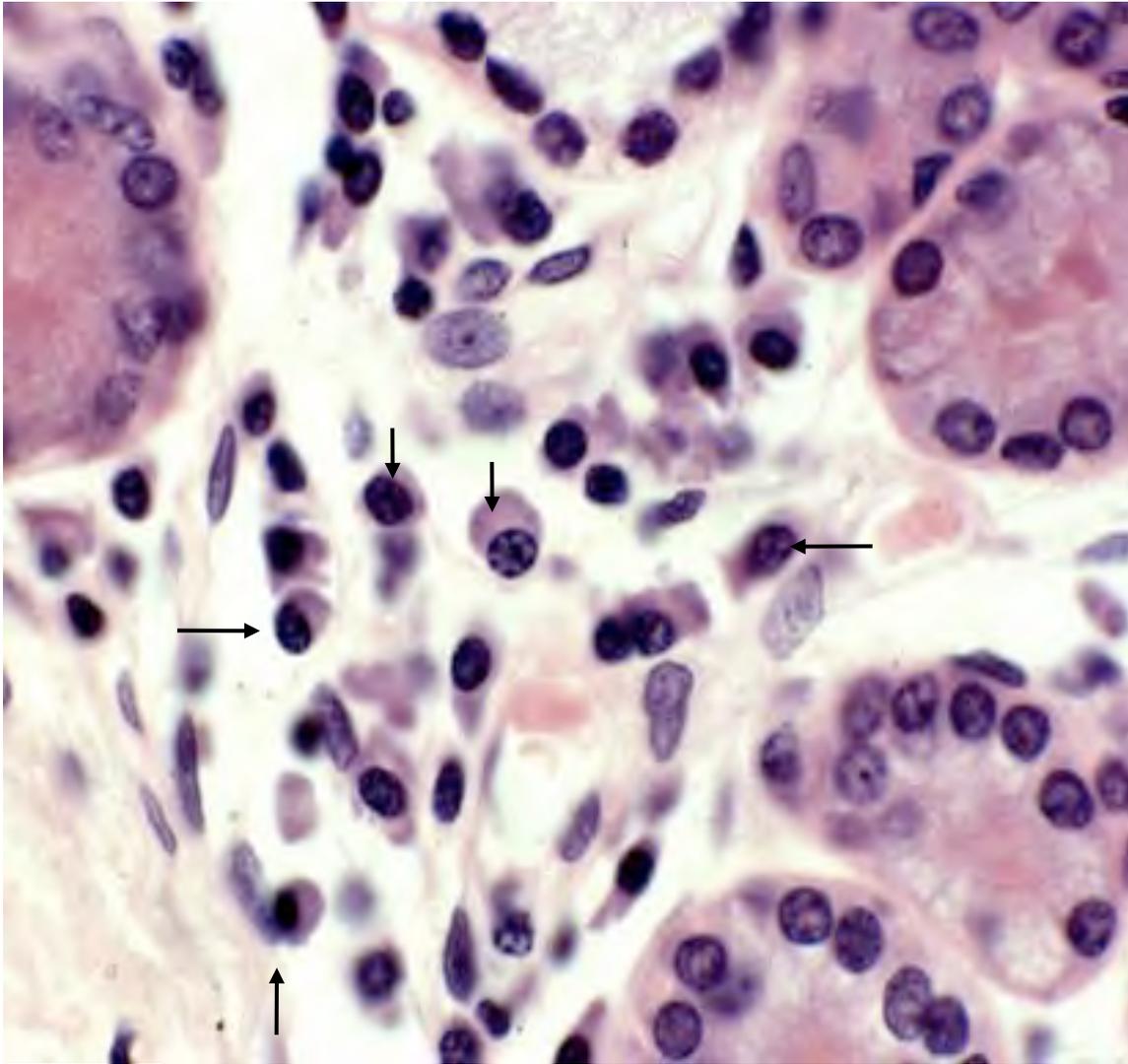
# Lymphoblast viewed by transmission electron microscopy



# Germinal Center--Lymphoblasts and Macrophages

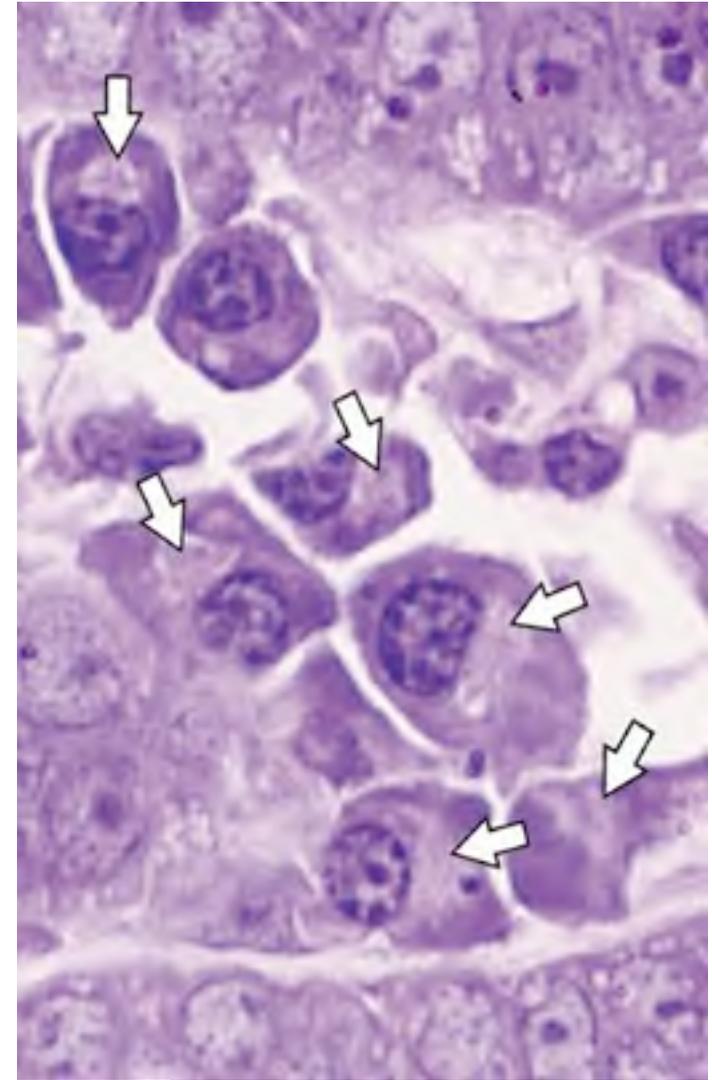


# Plasma Cells are mature B lymphocytes



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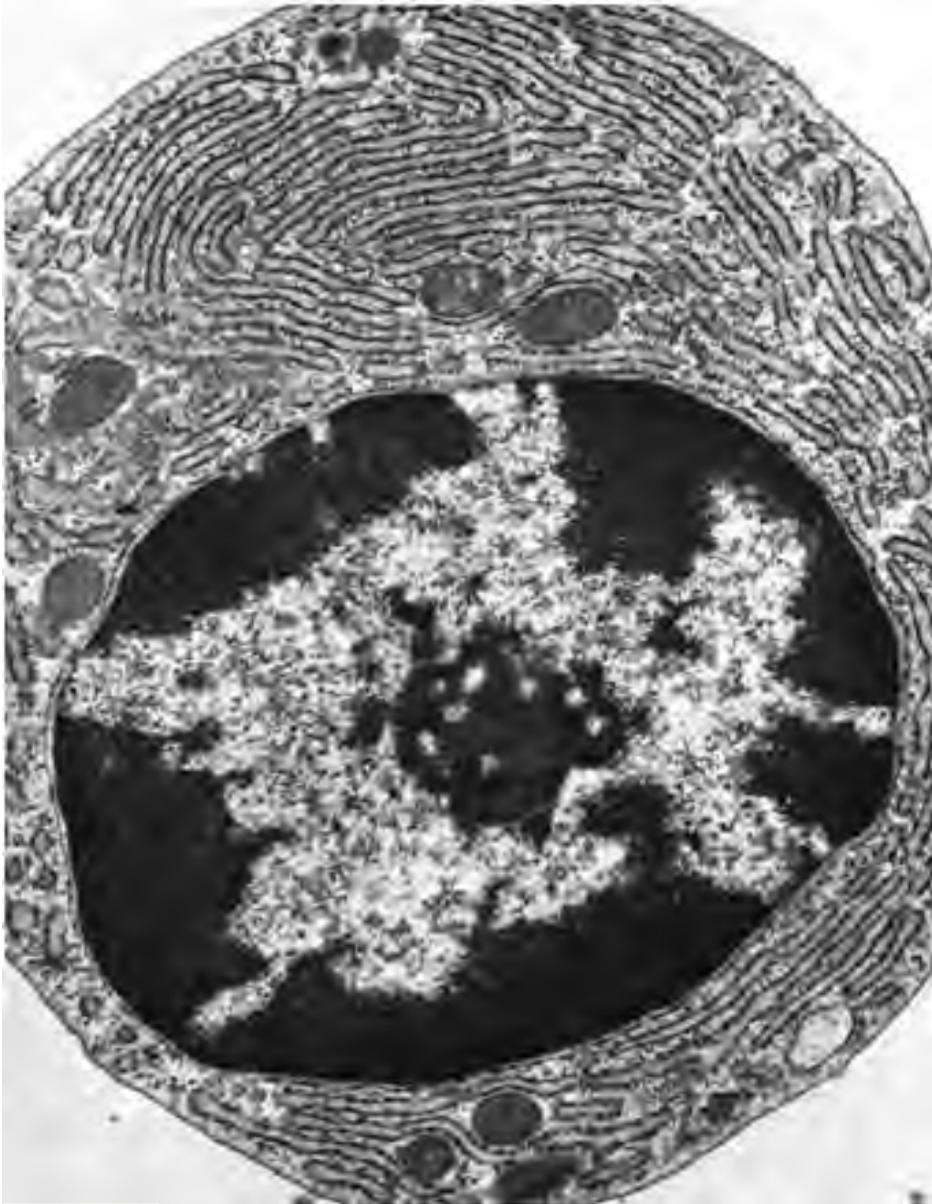
Black arrows indicate several plasma cells



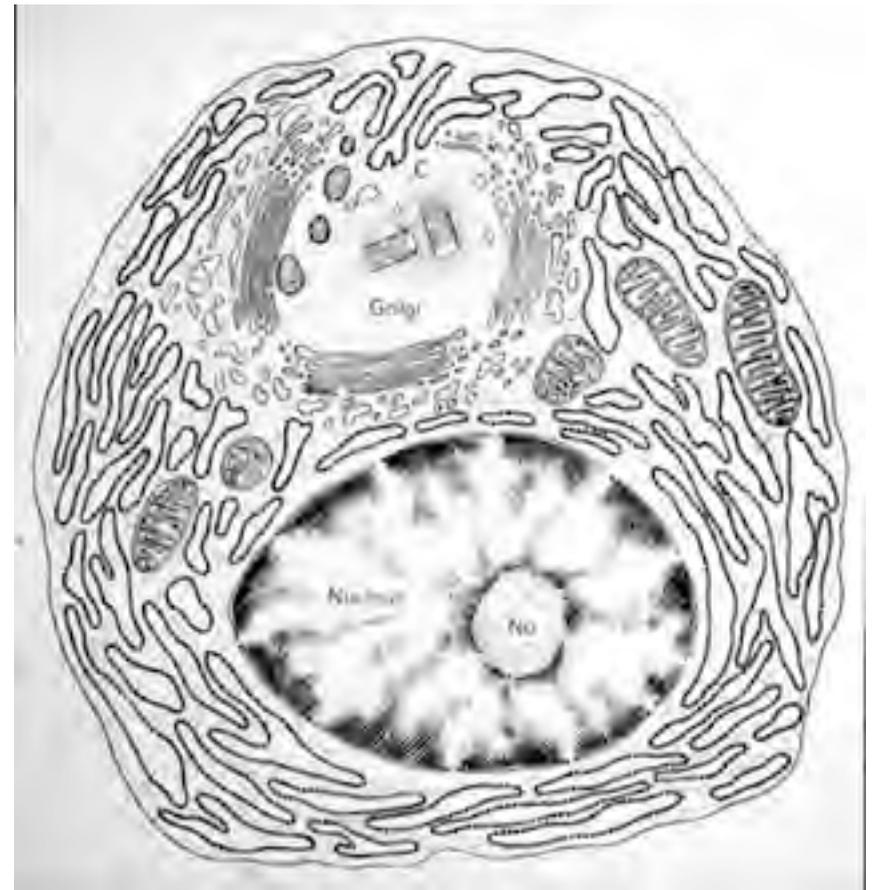
PD-INEL Junquiera and Carneiro. Basic Histology. Tenth Ed. 2003

White arrows = Golgi regions

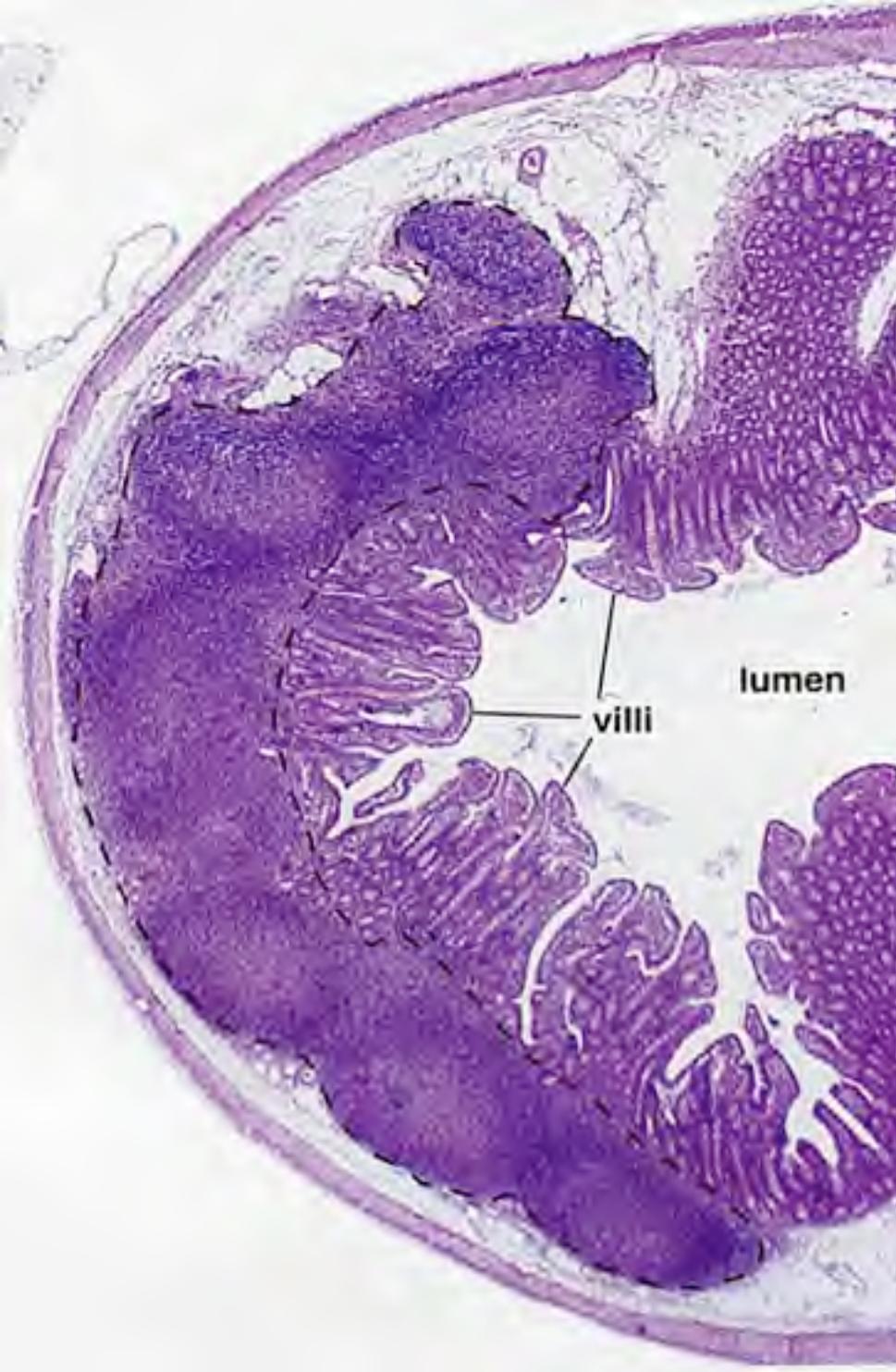
# EM of Plasma Cells



PO-INEL Source Undetermined



PO-INEL Source Undetermined



**So, associated with just about any mucosa (GI, respiratory, genitourinary), you may see:**

- Intraepithelial lymphocytes (T-cells)
- Diffuse lymphoid tissue:
  - B-cells
  - T-cells
  - APCs
- Primary nodules
- Secondary nodules
  - Germinal center with lymphoblasts and mphages

# Regions of extensive lymphoid infiltration: Peyer's patches

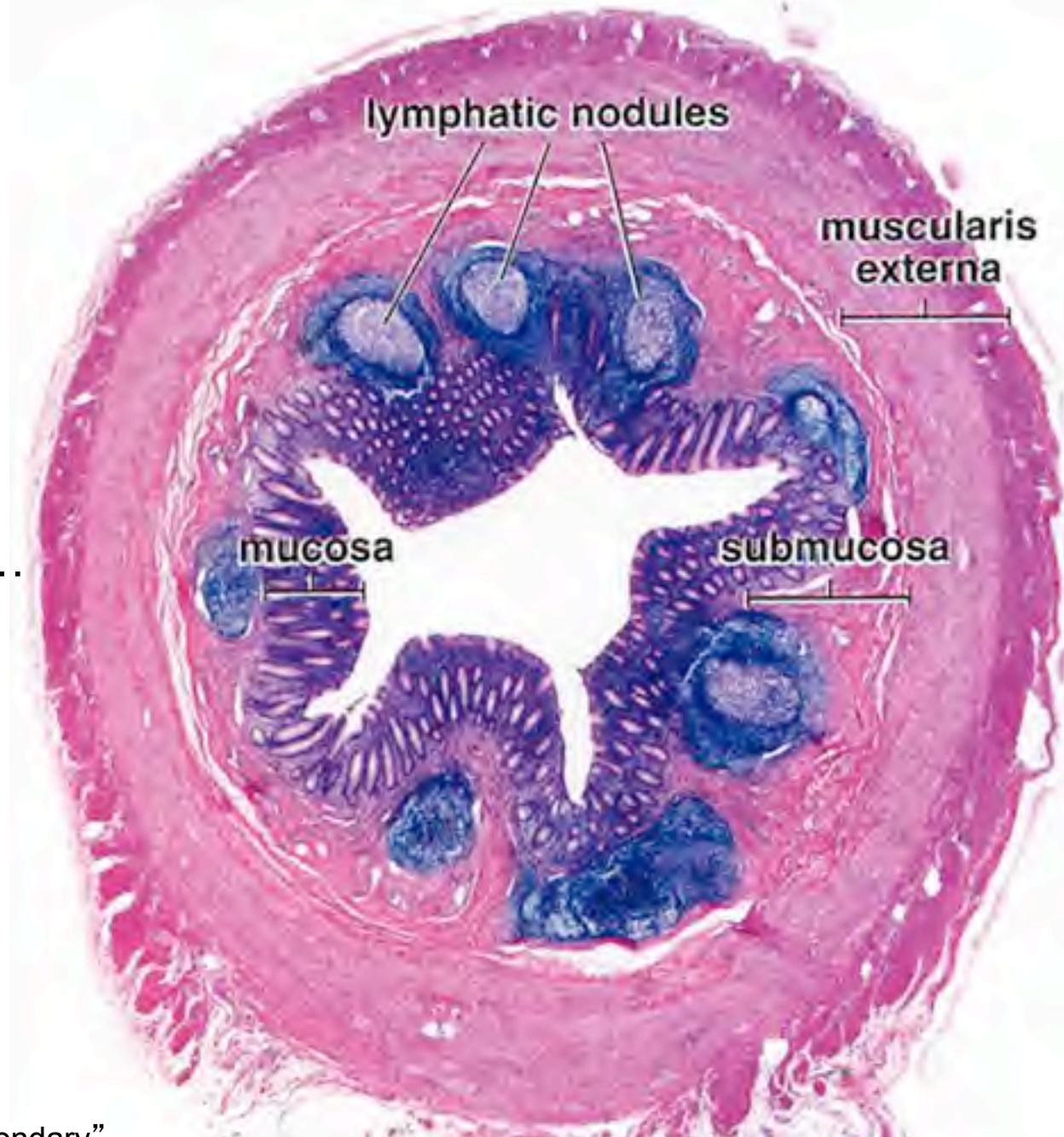


Aggregates of lymphoid follicles in the ileum.

# Appendix

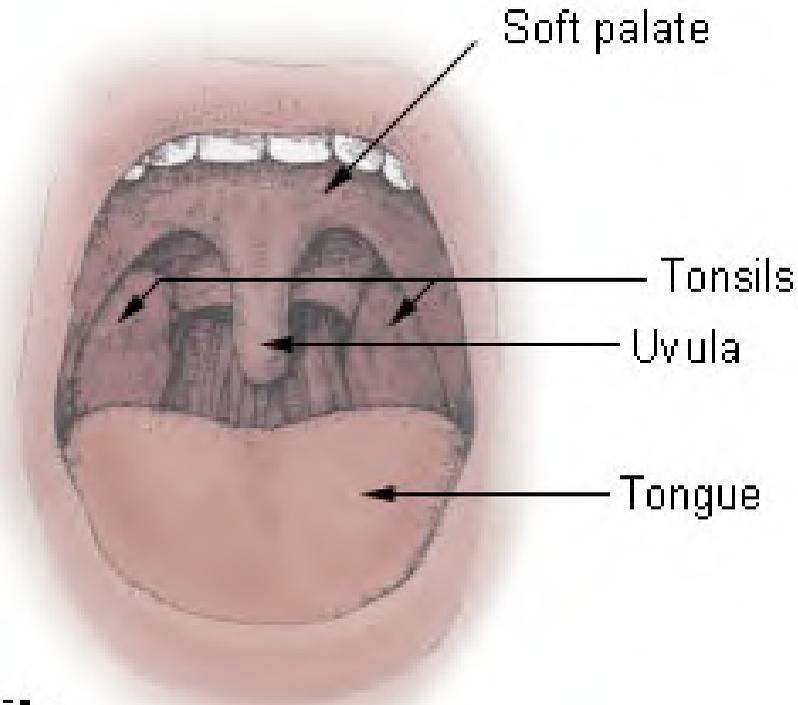
Blind sac extending from the caecum

- primary and secondary follicles in lamina propria and submucosa
- So, clearly a [secondary lymphoid organ](#)...
- However, also a site of antigen-INDEPENDENT differentiation (similar to Bursa of Fabricius in birds)
- So, also a [primary lymphoid organ](#)



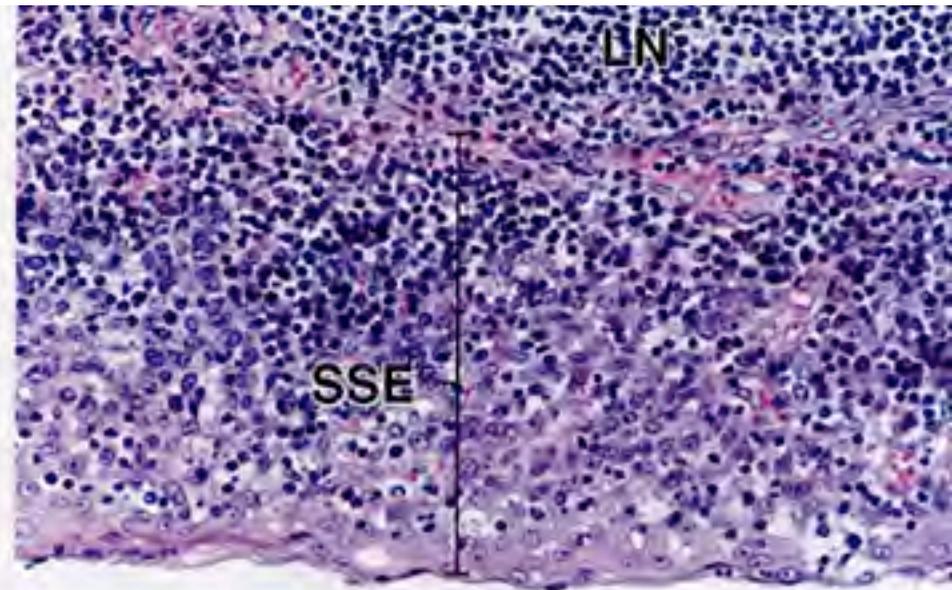
Sorry about the various “primary” and “secondary” nomenclature; that’s just the way it is...

# Tonsils: MALT of the oropharynx



## Tonsils

# TONSILS



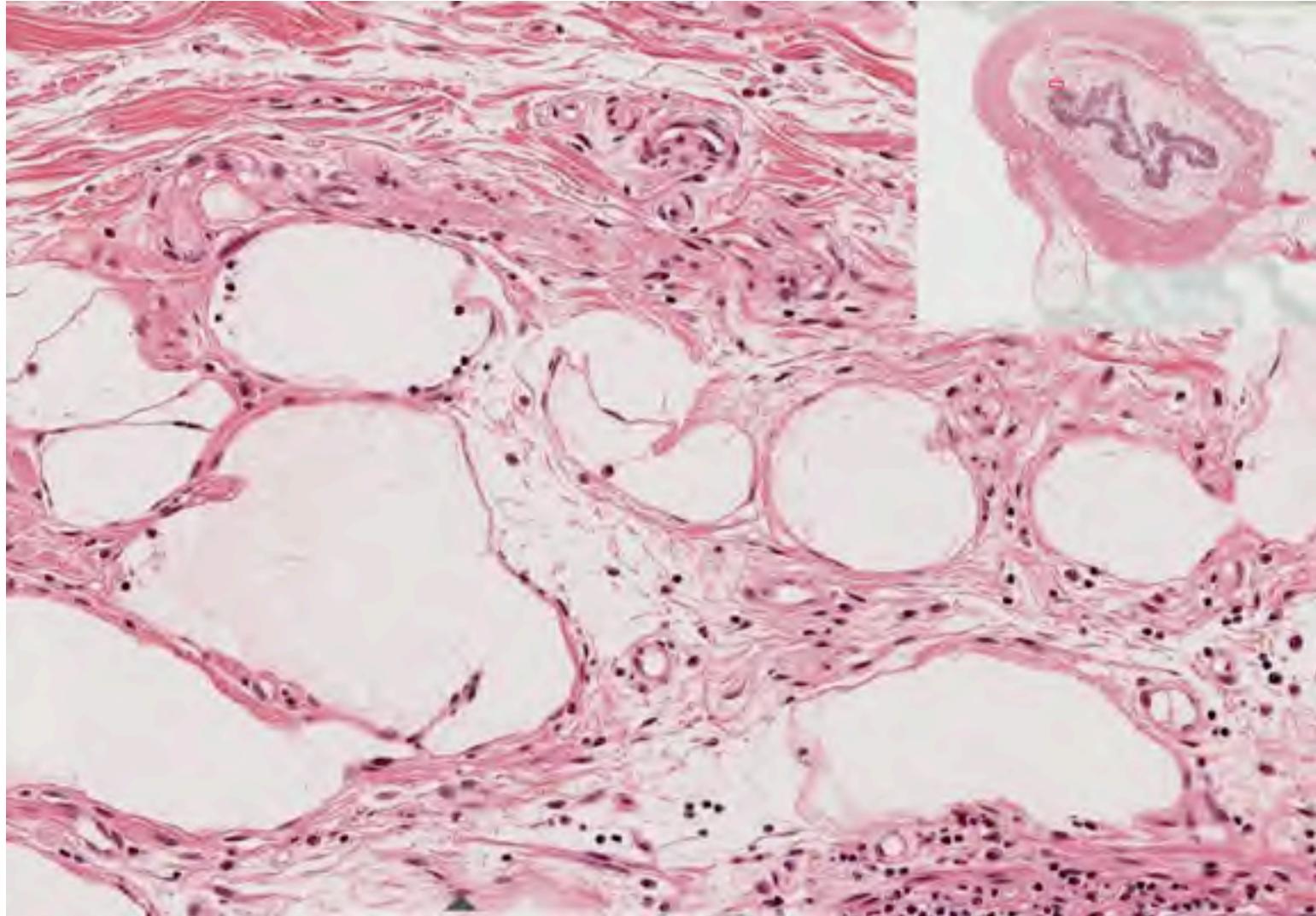
PD-INEL Ross and Pawlina, *Histology: A Text and Atlas*

The palatine tonsils are paired structures made of dense accumulations of lymphatic tissue located in the mucous membrane of the junction of the oropharynx and oral cavity. The tonsils dip down into the underlying CT, forming crypts. There are also lingual tonsils and pharyngeal tonsils (under the roof of the nasopharynx and around the opening of the Eustachian tubes). **Key features: crypts, abundant nodules, stratified squamous epithelium**

# Wanderlust:

lymphocytes don't just stay in one place

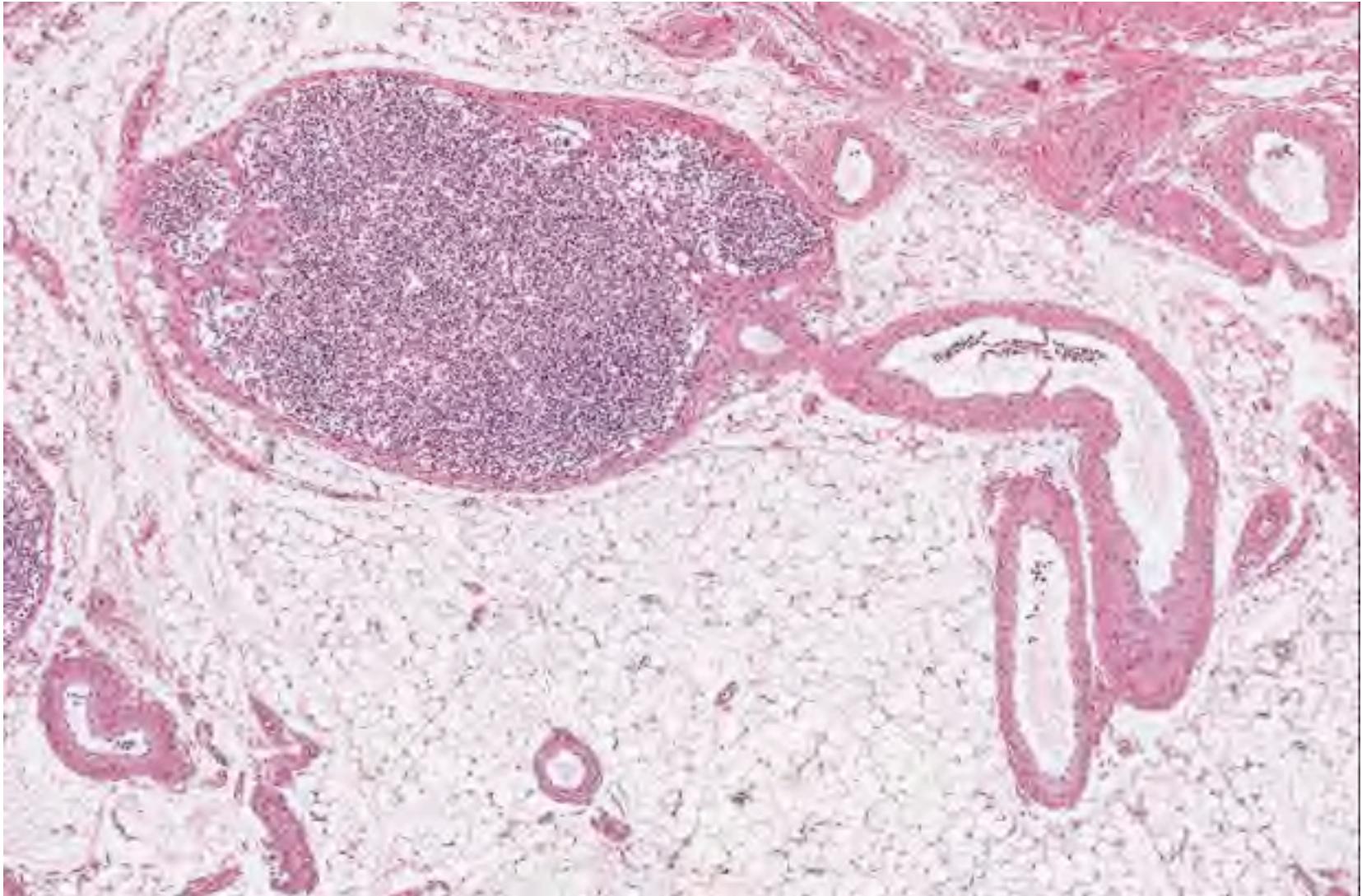
From the MALT, lymphocytes can squeeze into lymph vessels...



..go through larger lymphatic channels in the mesentery...



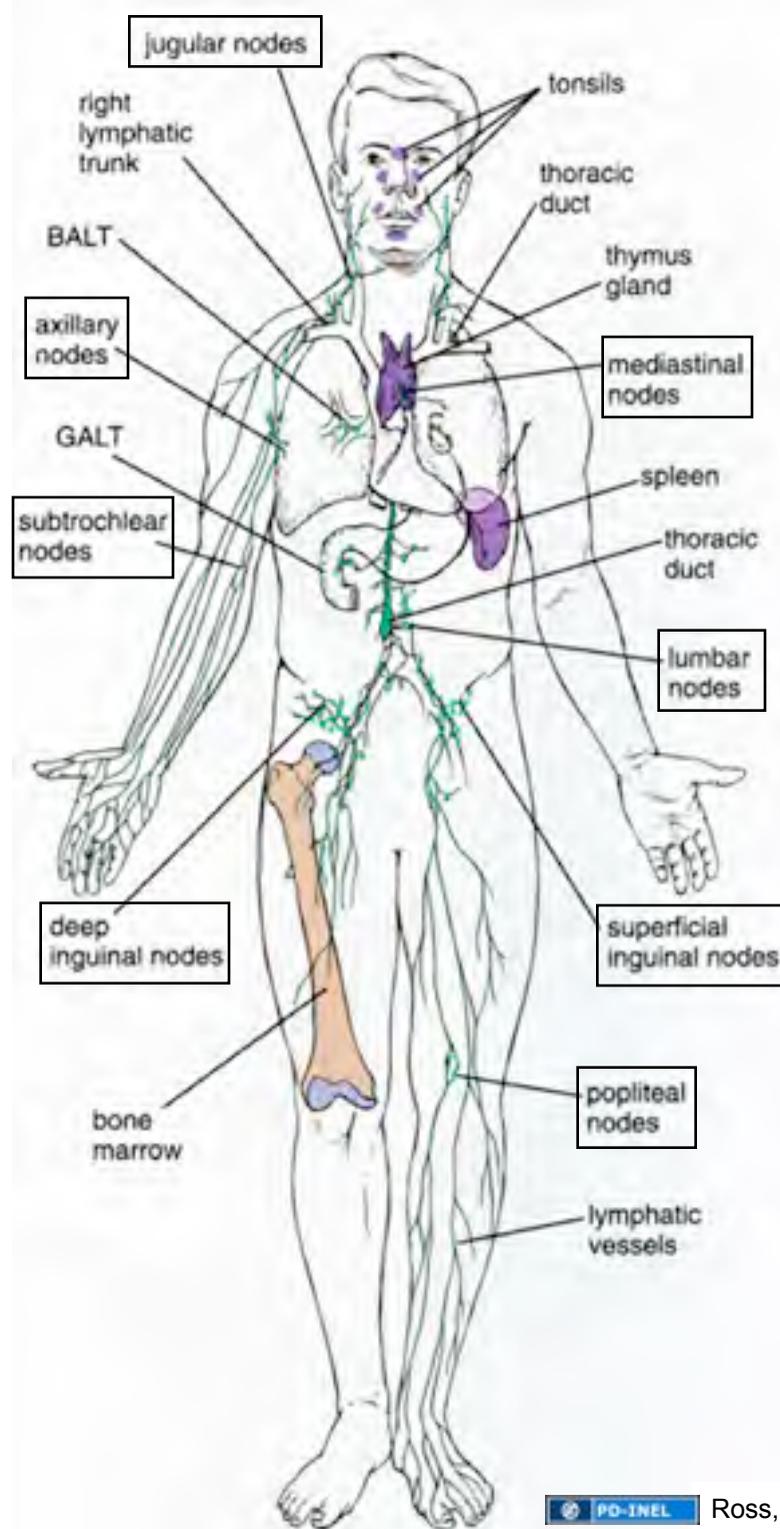
..and end up at a LYMPH NODE.



# Lymph Nodes

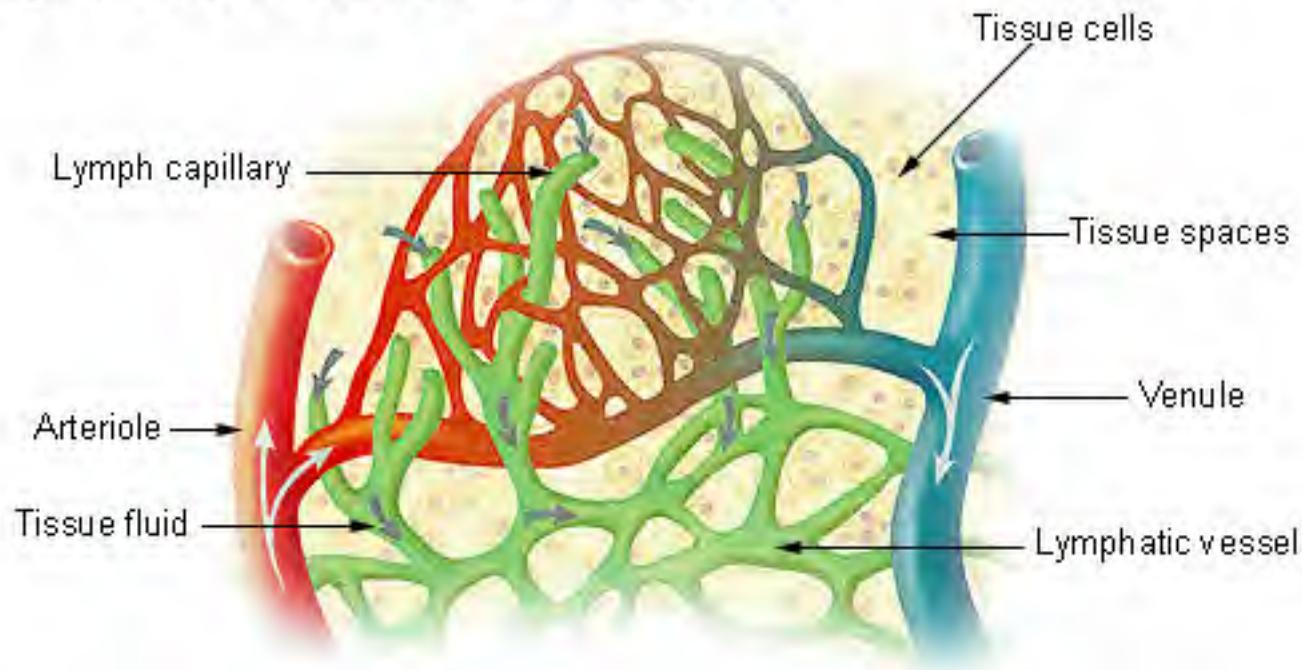
Main functions:

1. Filter lymph, thereby promoting lymphocyte contact with antigen
2. Provides necessary microenvironment for antigen-dependent differentiation

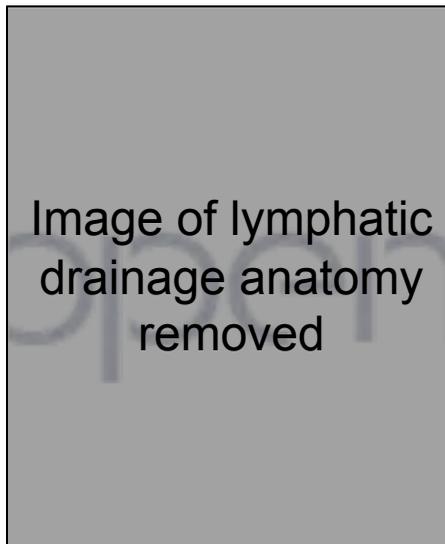


Lymphoid circulation in the body takes place in both the blood stream and the **lymphatic vessels**, a separate vessel system that carries cells of the lymphoid system and their products (cytokines, antibodies, etc.).

### Lymph Capillaries in the Tissue Spaces



# Lymphatic drainage: anatomy



Original Image: <http://health-tune-ups.com/wp-content/uploads/2009/04/cdr533339-750.jpg>

# Lymph node structure

Image of lymph  
node structure  
removed

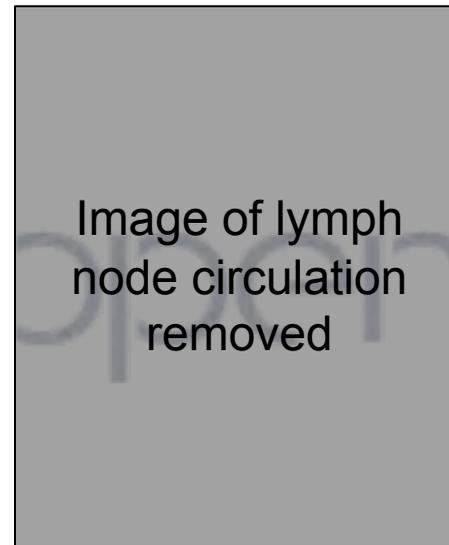
Original Image: [http://academic.kellogg.cc.mi.us/herbrandsonc/bio201\\_McKinley/f24-10a\\_lymph\\_node\\_and\\_\\_c.jpg](http://academic.kellogg.cc.mi.us/herbrandsonc/bio201_McKinley/f24-10a_lymph_node_and__c.jpg)



# Lymphatic Circulation Through a Lymph Node

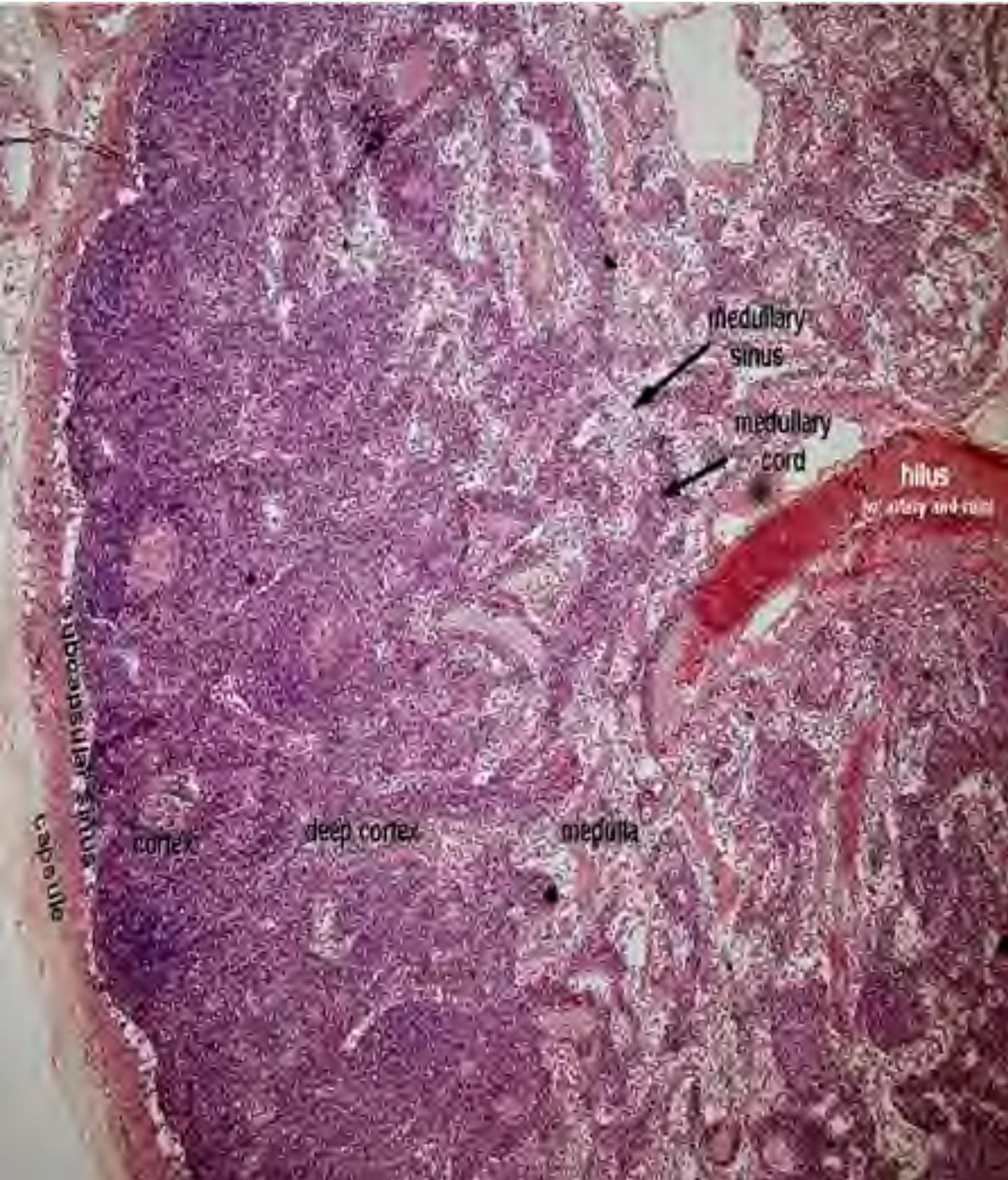
## Lymph nodes filter lymph

1. Afferent lymphatic vessels drain lymph into the Subcapsular Sinus
2. Lymph then passes to the Trabecular sinuses
3. From there, the lymph goes to the Medullary sinuses.
4. Lymphocytes and macrophages pass easily between these sinuses and the tissue of the lymph node.
5. Macrophages in sinuses monitor the fluids. Macs phagocytose the antigenic material and present it to T- and B-cells



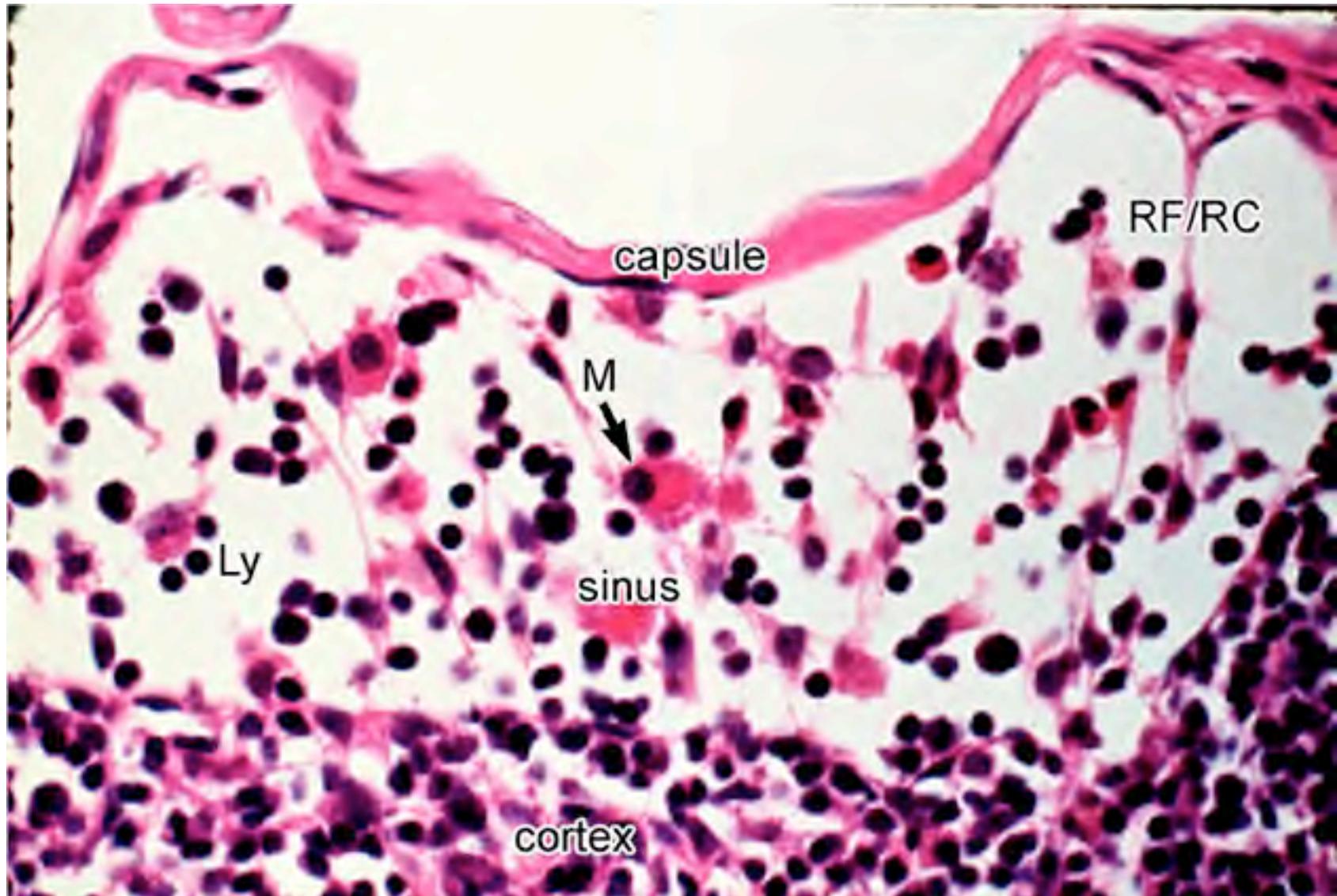
Original Image: [http://human.freescience.org/images/lllu\\_lymph\\_node\\_structure.png](http://human.freescience.org/images/lllu_lymph_node_structure.png)

# Lymph Node Structure



- **Capsule & subcapsular sinus**
- **Trabeculae & trabecular sinuses**  
sinuses contain lymph, macrophages, and reticular cells
- **Cortex:**
  - superficial cortex (B-cells)
    - primary follicles/nodules
    - secondary follicles/nodules (i.e. with germinal centers)
  - “deep” cortex (T-cells, dendritic cells)
- **Medulla:**
  - medullary cords (B-cells, plasma cells)
  - medullary sinuses (lymph, more macrophages, plasma cells, and reticular cells)

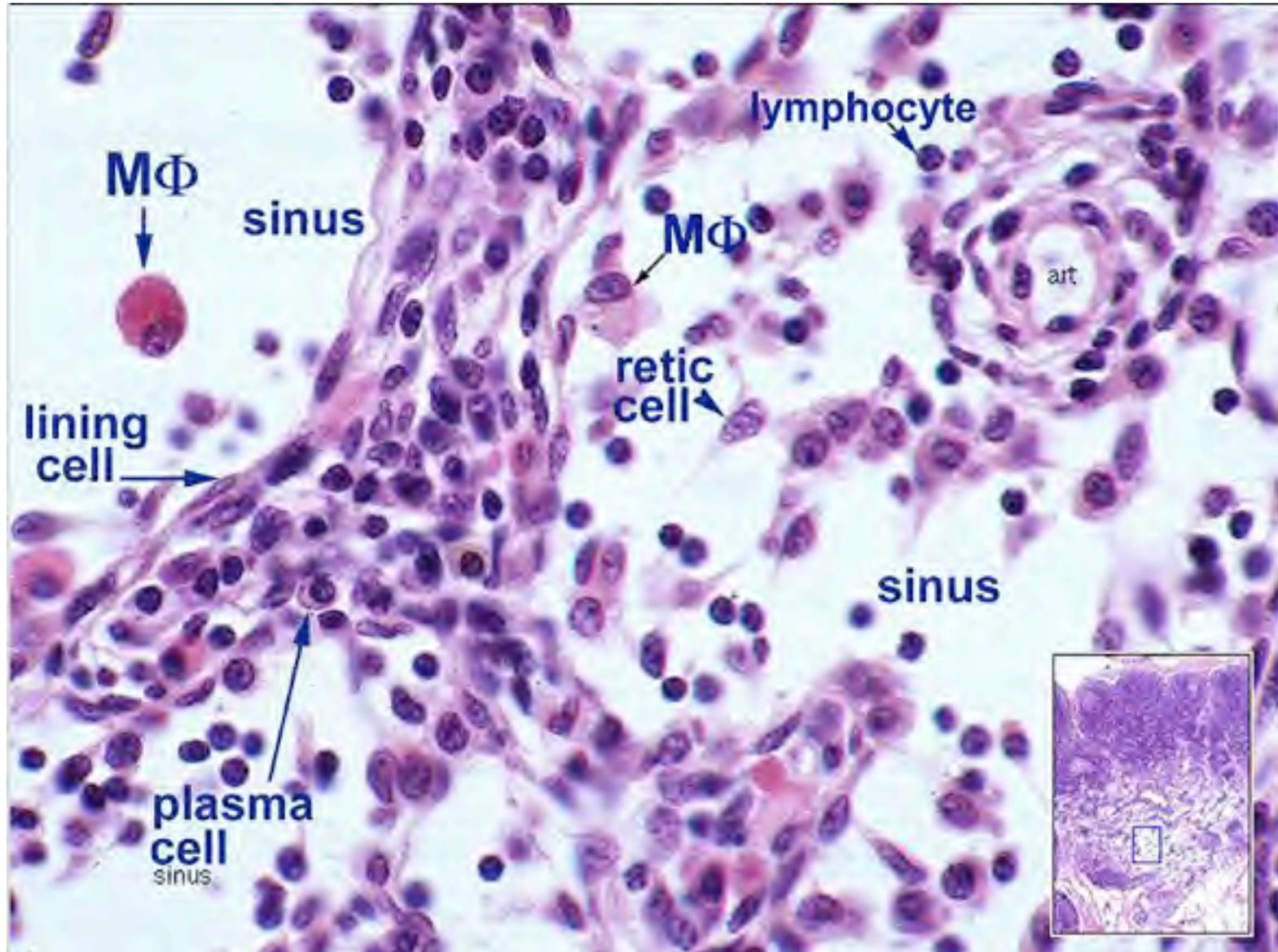
# High magnification view of a sinus (subcapsular sinus shown here)



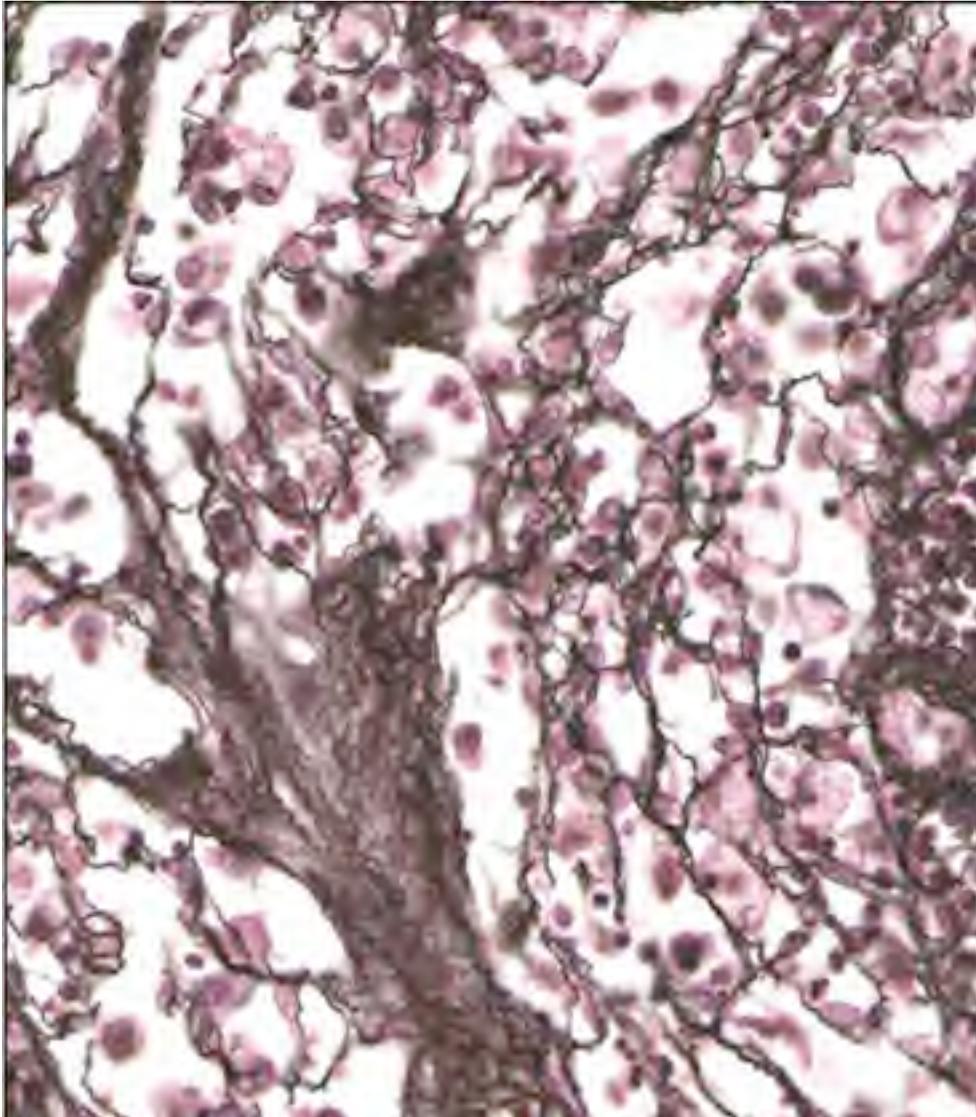
PD-INEL U-M Histology Collection

M=macrophage, Ly=lymphocytes, RF/RC=reticular fiber (and associated reticular cell)

From the sub-capsular sinus, lymph percolates through trabecular sinuses, and finally into medullary sinuses



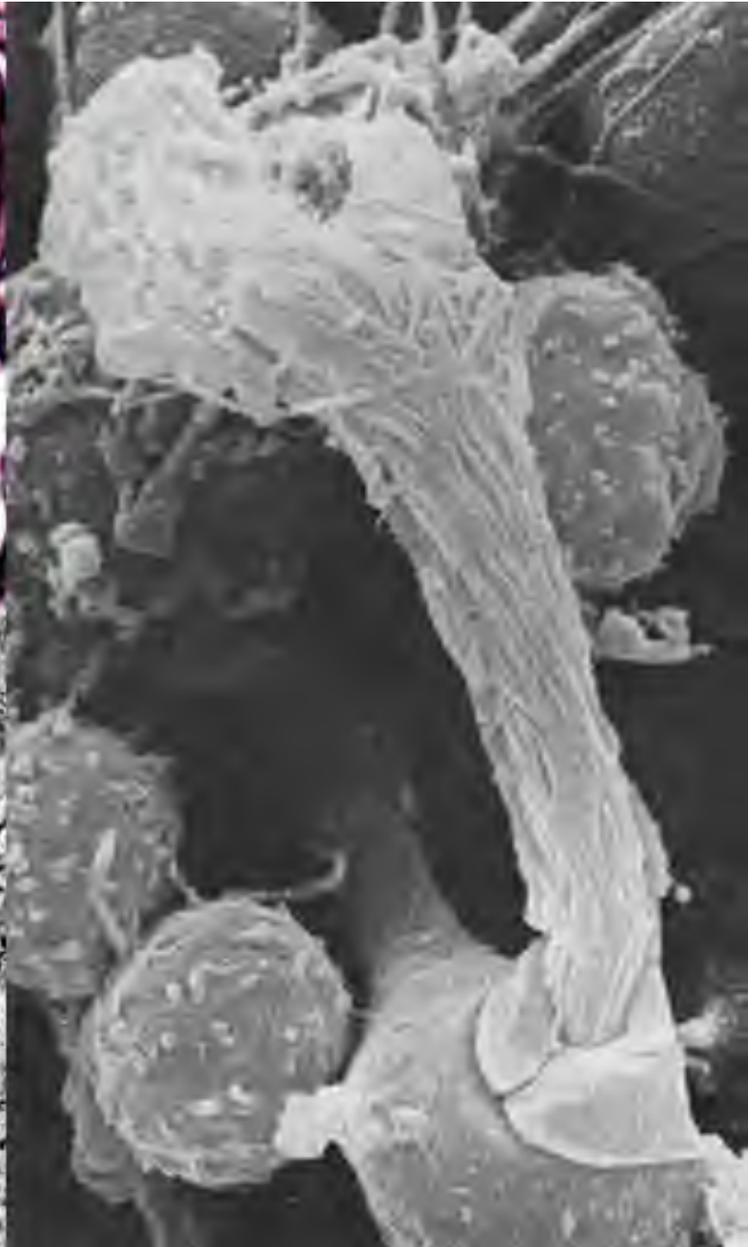
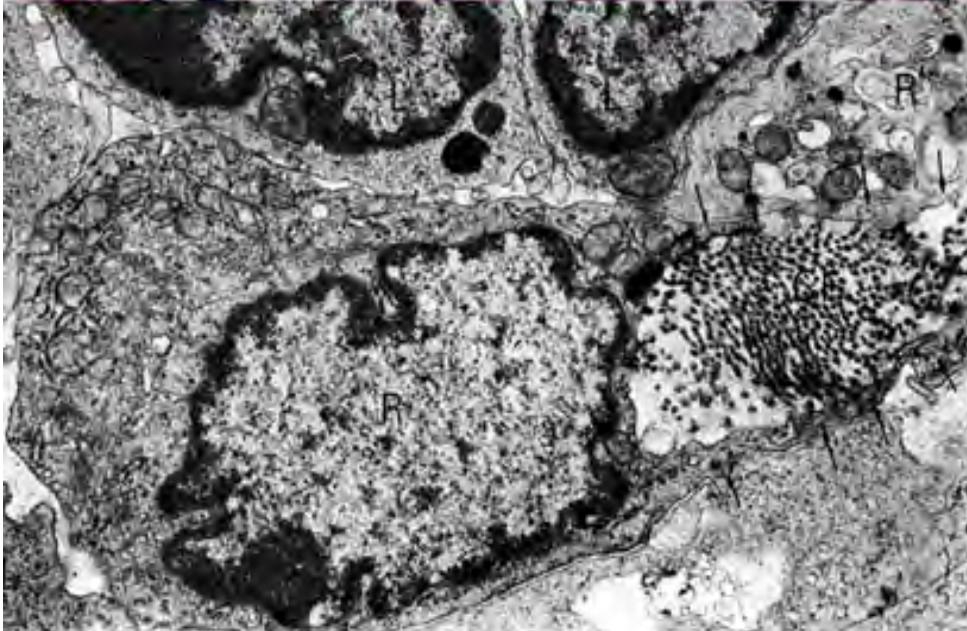
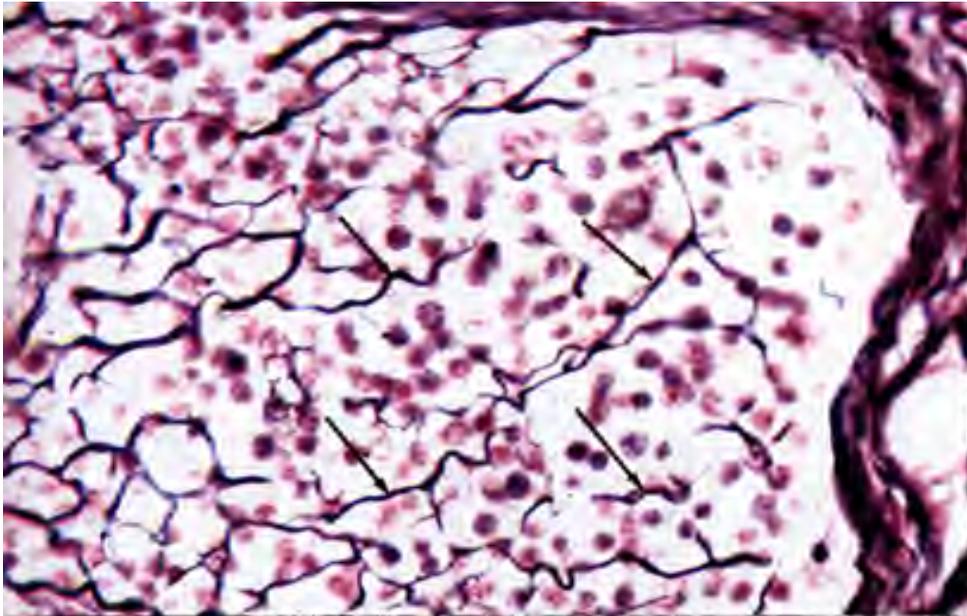
# Reticular (Reticulin) Fibers



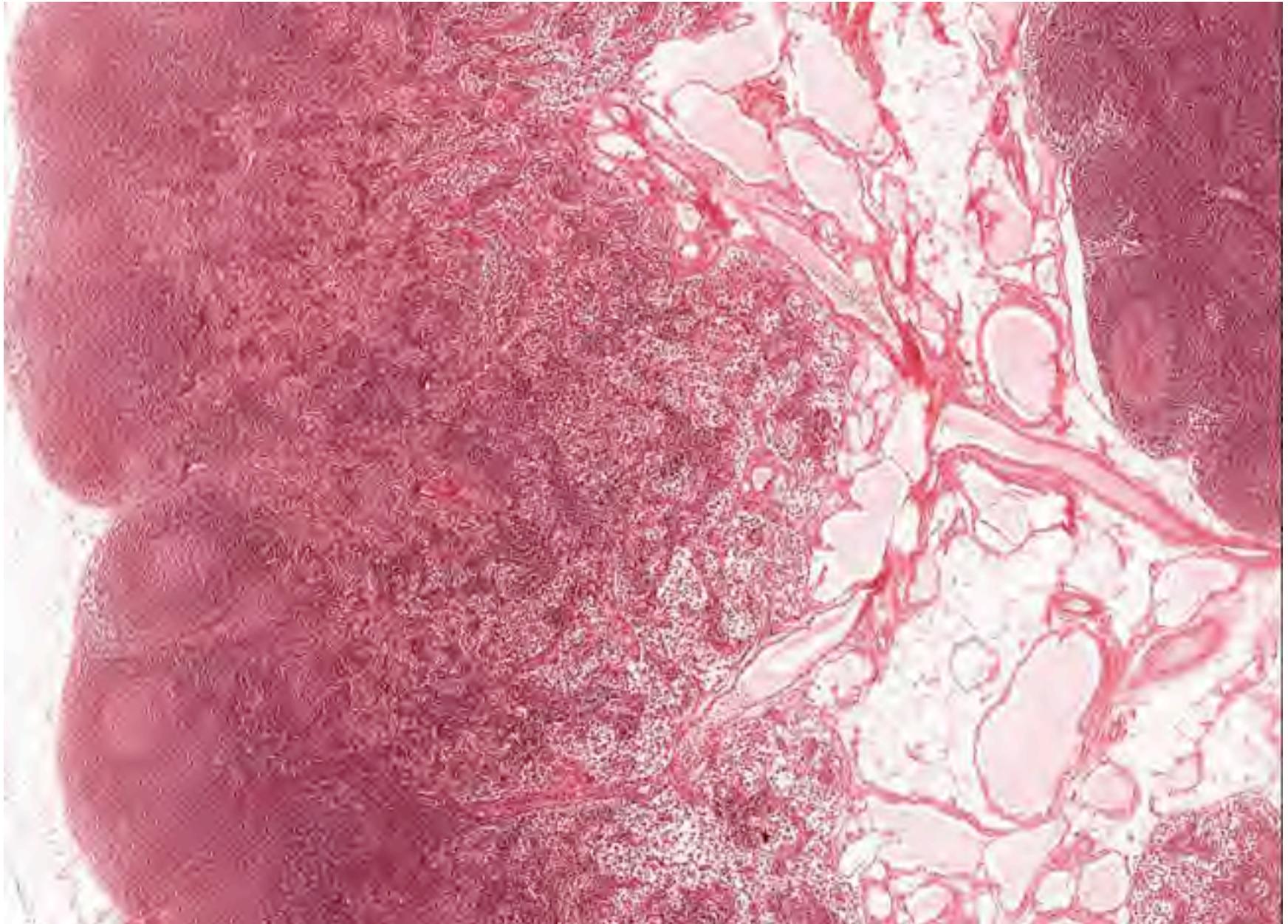
- **Form a delicate supporting framework** for highly cellular tissues (endocrine glands, lymph nodes, liver, bone marrow, spleen, smooth muscle).
- **Composed mainly of Type III collagen**, with a carbohydrate moiety that reduces  $\text{Ag}^+$  to metallic silver = **argyrophilic**
- **Special stain**: silver impregnation to visualize.
- **Thinner than type I collagen** (Type III fibrils are 30-40 nm diameter; type I fibrils are ~200 nm diameter)

# Reticular Fibers (type III collagen)

made by reticular cells (specialized fibroblasts)

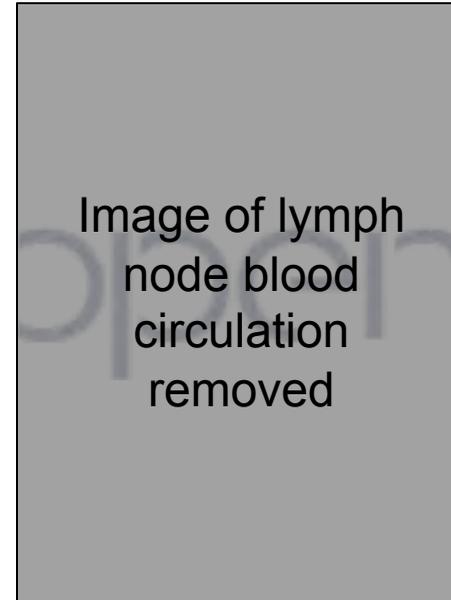


Medullary sinuses drain into EFFERENT lymphatics that exit from the hilum of the lymph node



# Blood Circulation Through a Lymph Node

1. Blood enters through an artery at the hilus
2. Arterioles branch from hilar artery to feed into capillary beds
3. Capillary beds are drained by high endothelial venules\*
4. HEVs drain into hilar vein



Original Image: Ross, fig. 14.18

\*HEVs are sites where lymphocytes can leave blood stream to enter the lymph node tissue bed.

# Slide 27, lymph node, H&E, 10x obj.

medulla

deep cortex

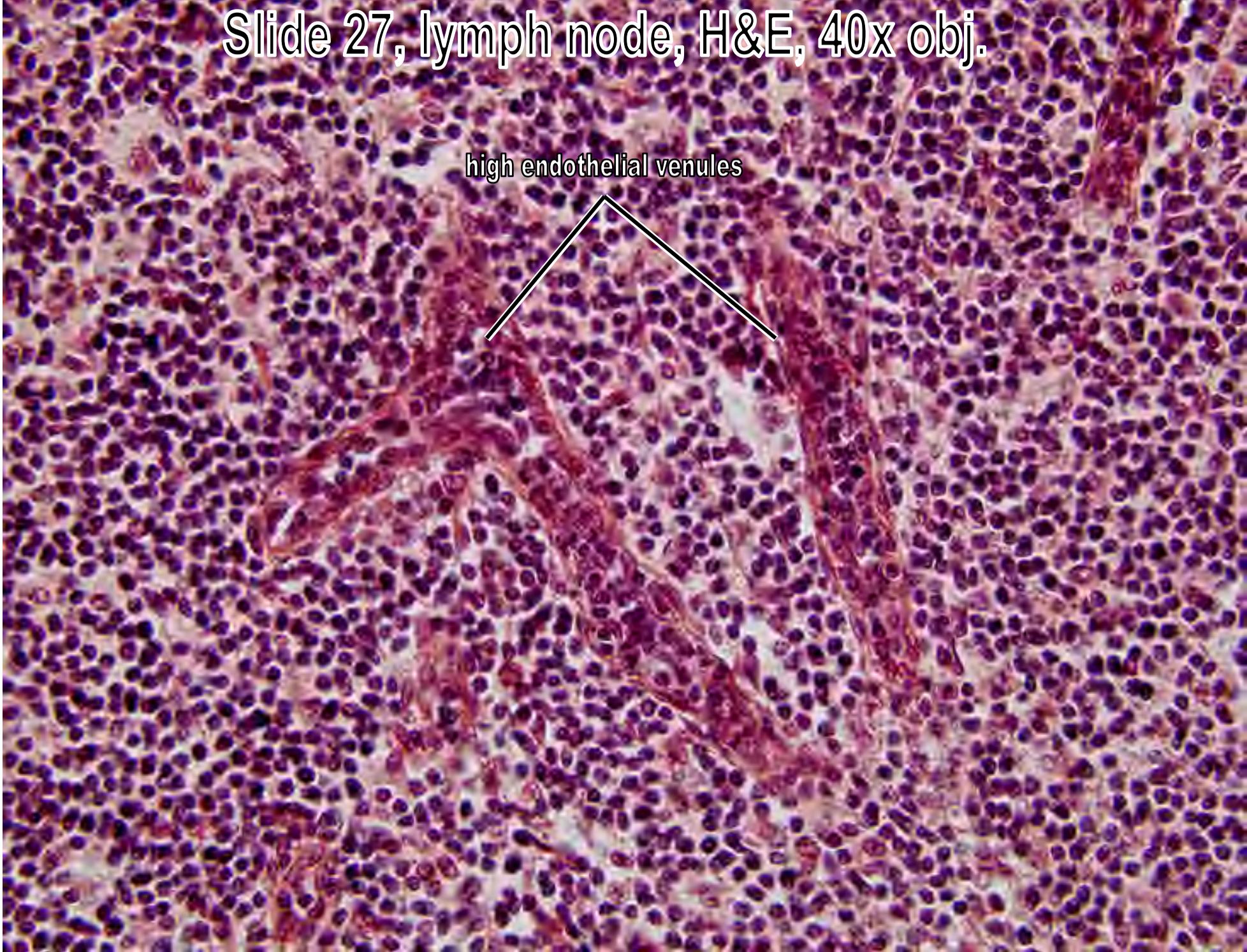
high endothelial venules

cortex

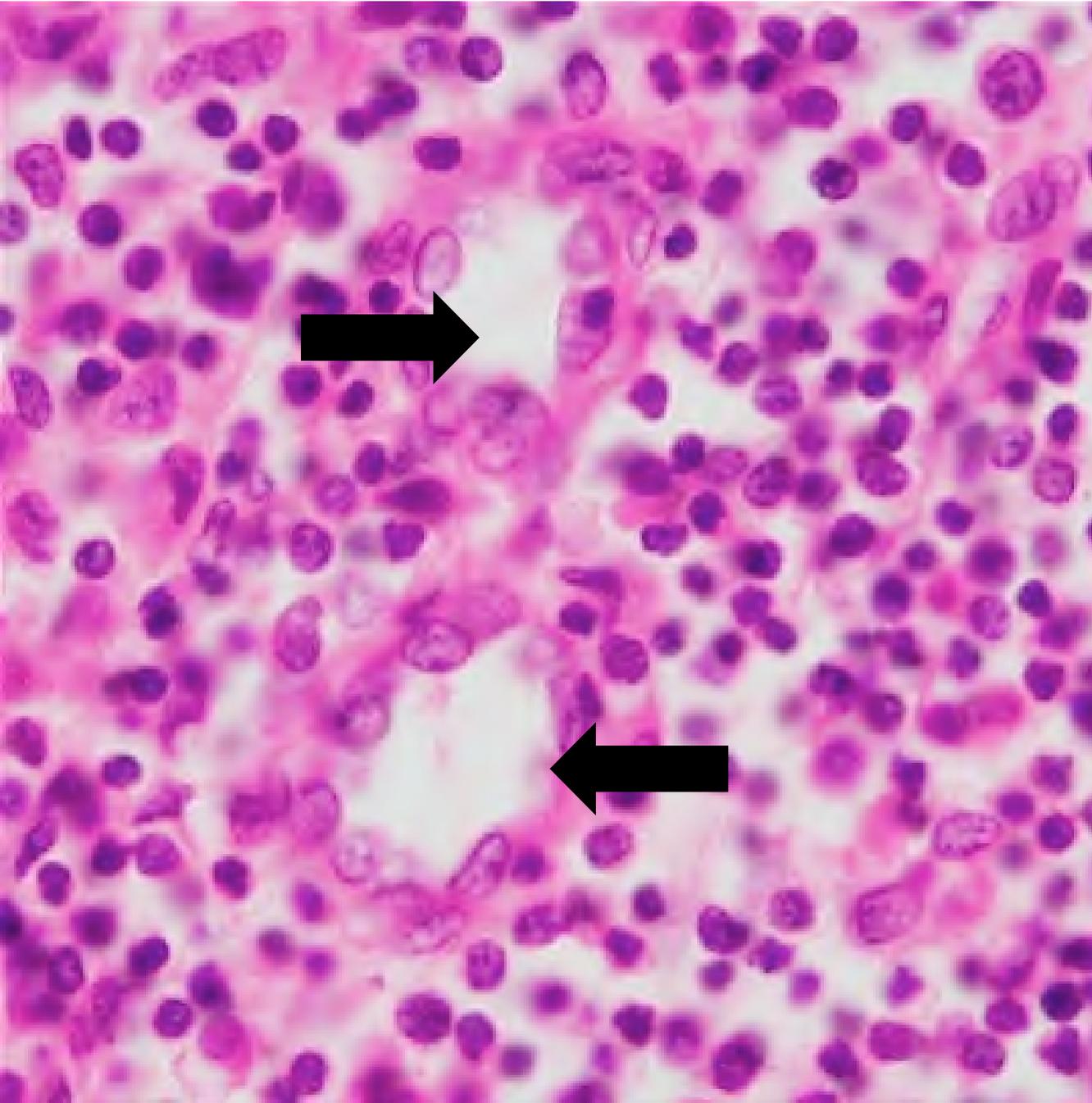
capsule

# Slide 27, lymph node, H&E, 40x obj.

high endothelial venules



# High Endothelial Venules

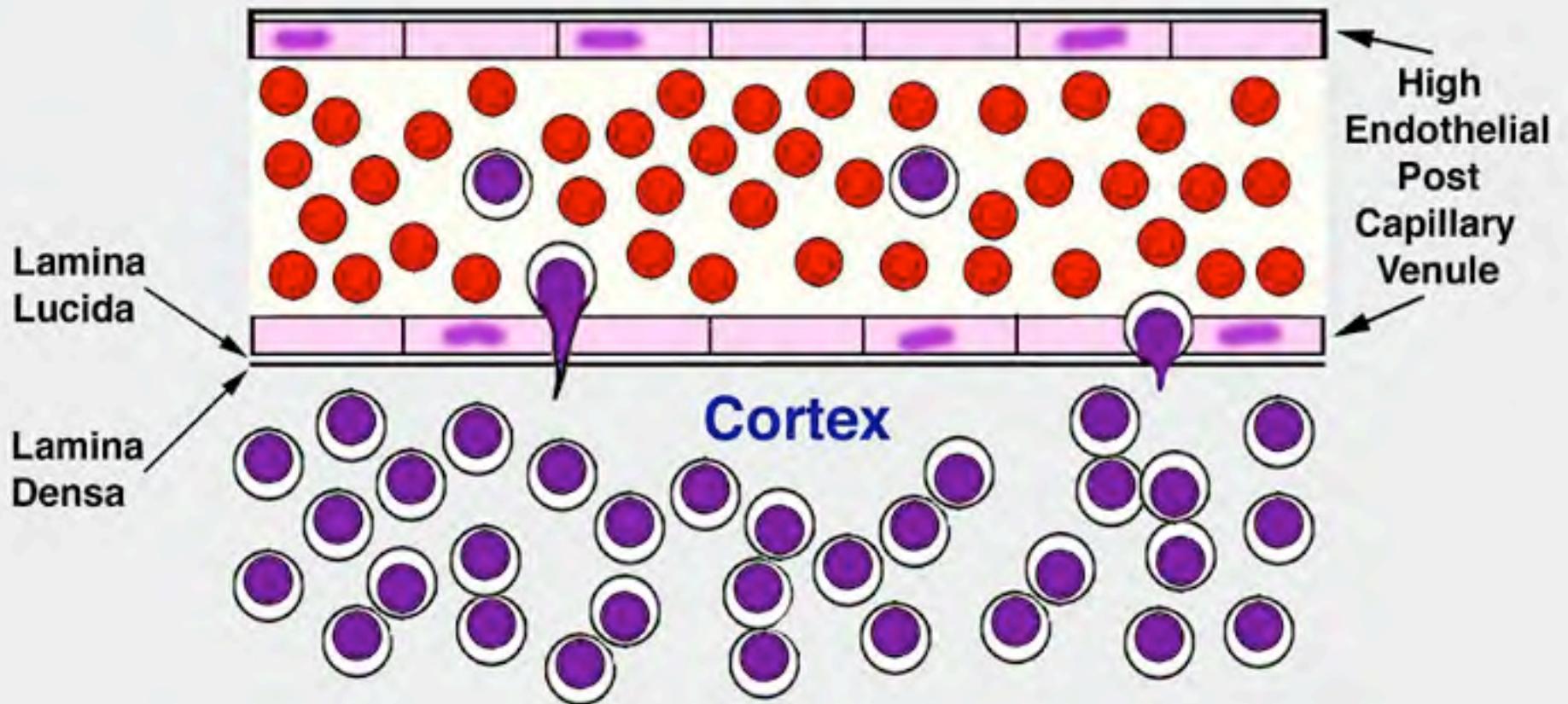


Site of:

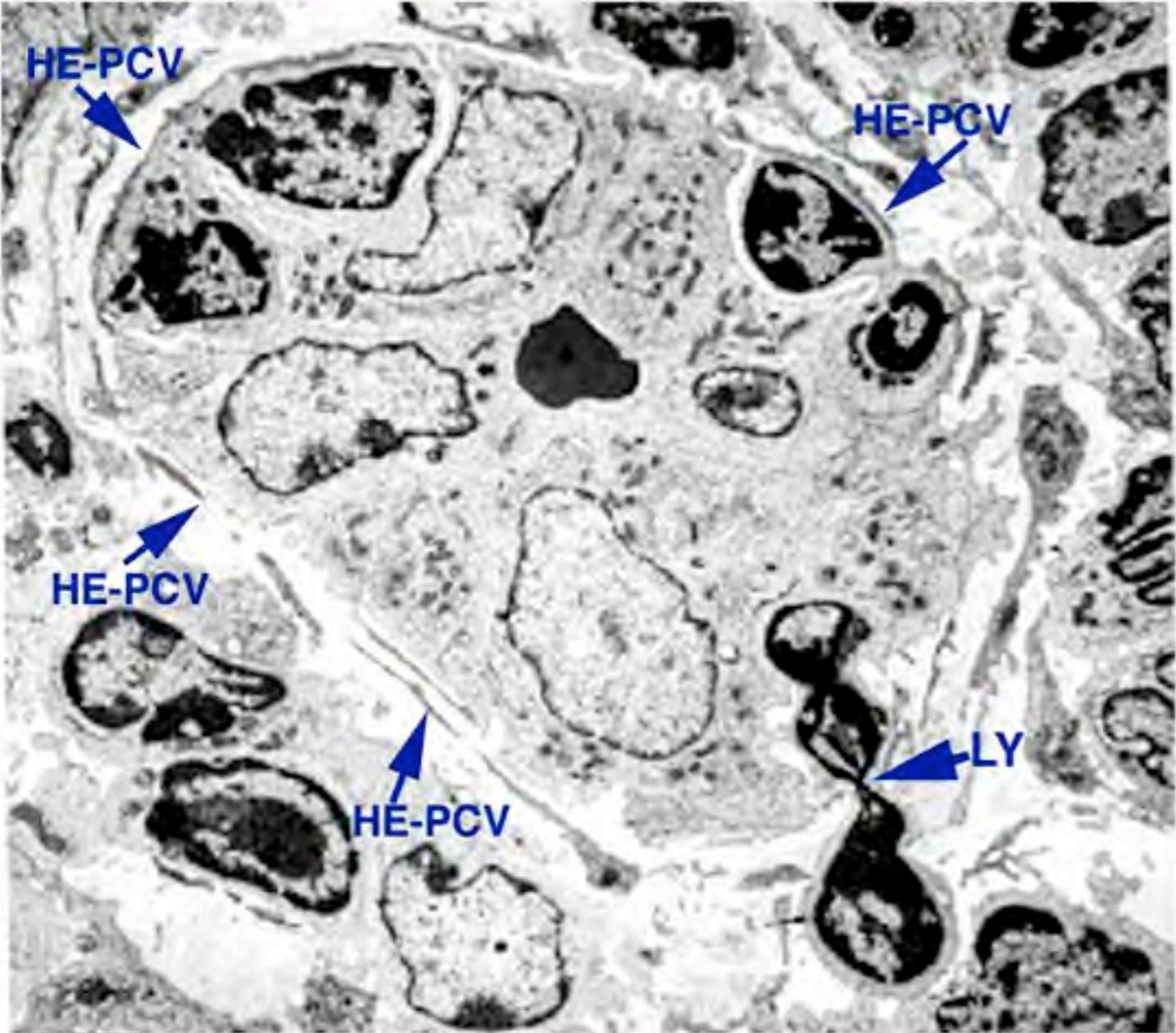
- Fluid absorption (via aquaporin-1 channels), which causes lymph flow
- EXIT of lymphocytes from bloodstream via diapedesis

# Lymphocyte Homing -

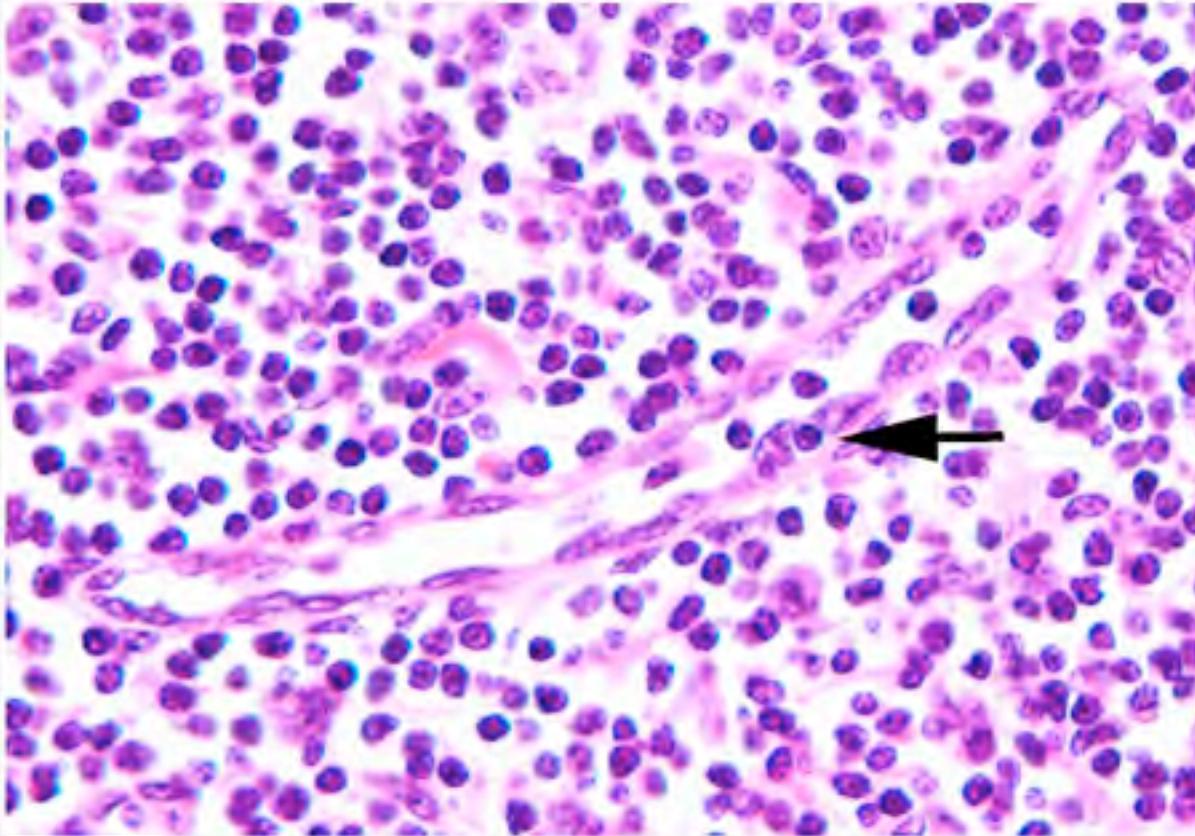
## Extravasation by T and B Cells in the High Endothelial Postcapillary Venules of the Lymph Node Cortex



# Lymphocyte Homing

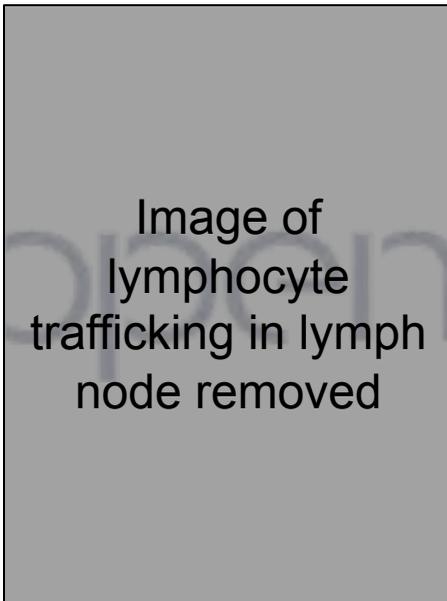


## Lymphocyte Homing in the High Endothelial Postcapillary Venule



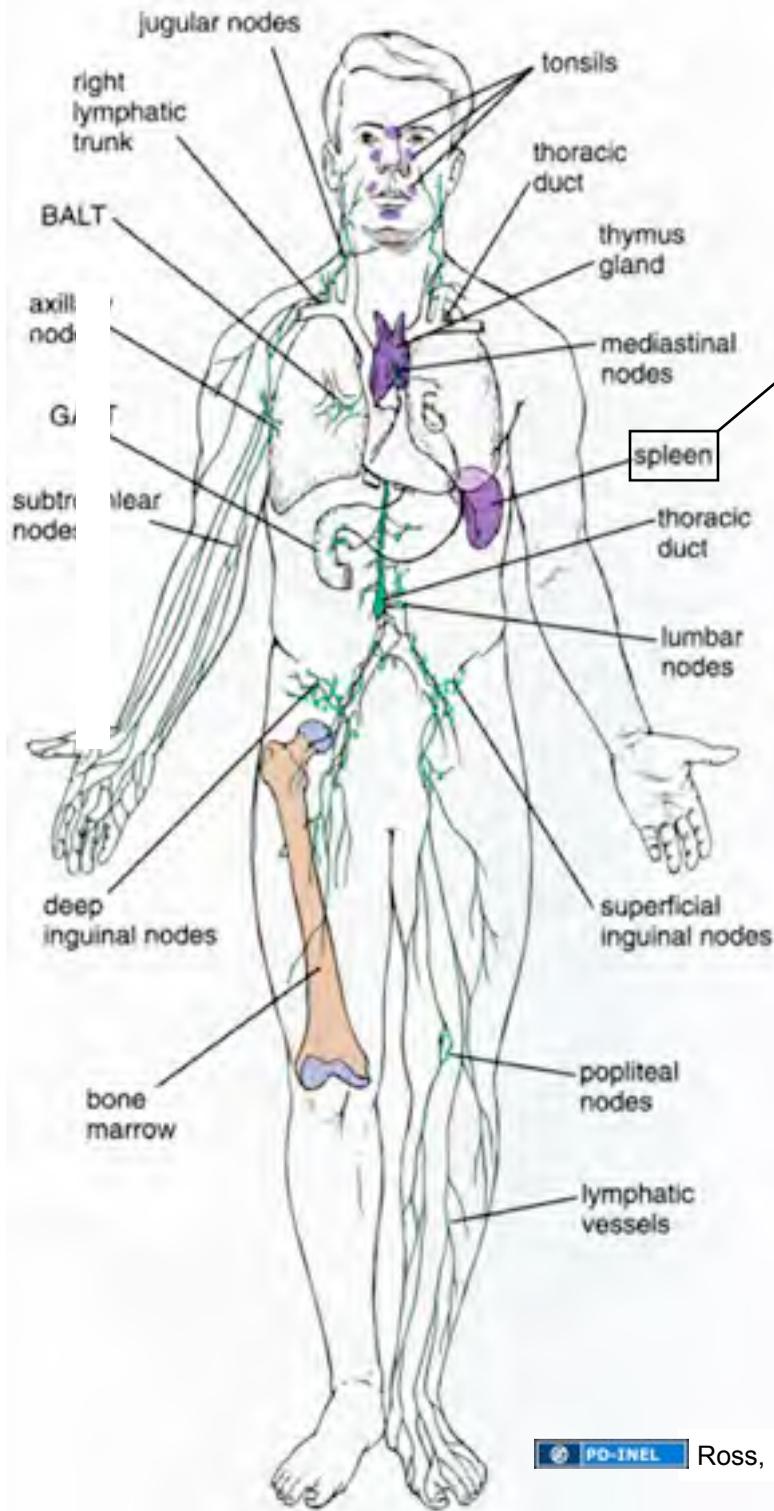
PO-INEL Source Undetermined

# Summary of lymphocyte traffic in a lymph node



- Solvent drag caused by HEV fluid transport draws lymph in via afferent vessels
  - **~10% of lymphocytes enter this way; mostly memory cells**
- HEV endothelial cells express selectins and other receptors for antigen-primed lymphocytes that stimulate them to EXIT bloodstream via diapedesis
  - **~90% enter this way; mostly naïve lymphocytes**
- **T-cells** move to deep cortex; **B-cells** migrate to superficial cortex; differentiated **plasma cells** move to medullary cords and secrete IgG into lymph
- Lymphocytes may leave lymph node via EFFERENT lymph vessels (can rejoin bloodstream via thoracic duct, jugular vein, etc.)

# The Spleen



Filters the blood

Destroys old red blood cells

Serves as an immune organ

Divided into **Red Pulp** (RBC/  
hemoglobin recycling)

**White Pulp** (responsible for  
immune functions)

## Immune Functions Of the Spleen

- Monitoring antigens in blood
- Proliferation of lymphocytes
- Production of humoral antibodies

## Hematopoietic Functions Of the Spleen

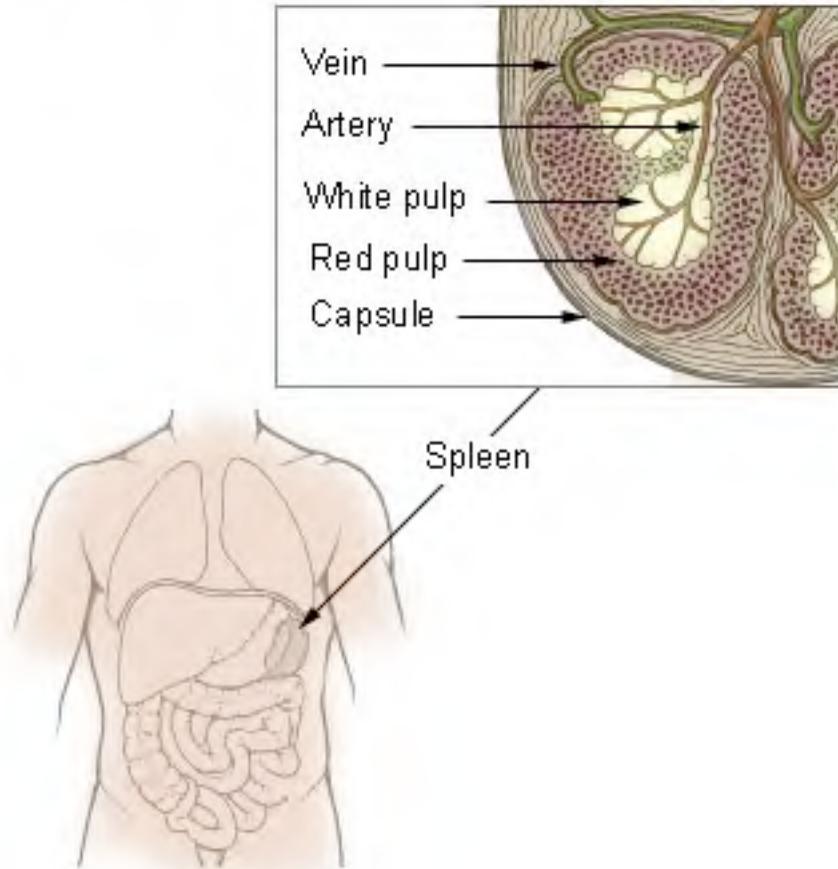
- Formation of blood cells in fetal life
- Removal and destruction of RBCs & platelets
- Retrieval of iron from RBC hemoglobin
- Storage of RBCs and platelets (more so in non-human species)

# Spleen: anatomy



# Spleen: anatomy

## Spleen



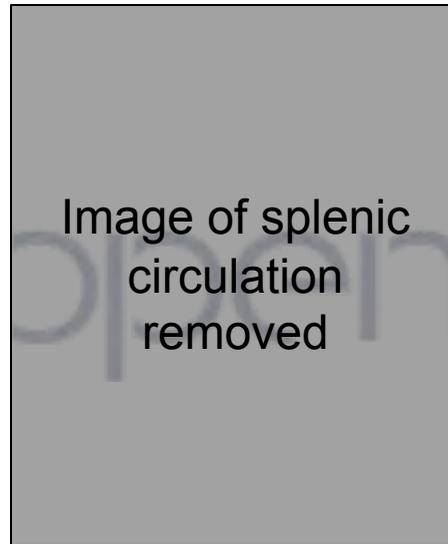
# ORGANIZATION OF THE SPLEEN



# Splenic Circulation

1. Blood enters via splenic artery at hilus
2. Splenic artery branches into trabecular arteries (which travel within connective tissue trabeculae).
3. Trabecular arteries give off branches known as central arteries which leave the trabecula and enter the substance of the spleen (covered by a peri-arterial lymphatic sheath).
4. Central arteries branch into penicillar arterioles that piece through the lymphatic sheath and spill into splenic cords.
5. Blood percolates through splenic cords and across walls of splenic sinuses.
6. Splenic sinuses drain into pulp veins.
7. Pulp veins drain into trabecular veins.
8. Trabecular veins drain into splenic vein at the hilus.

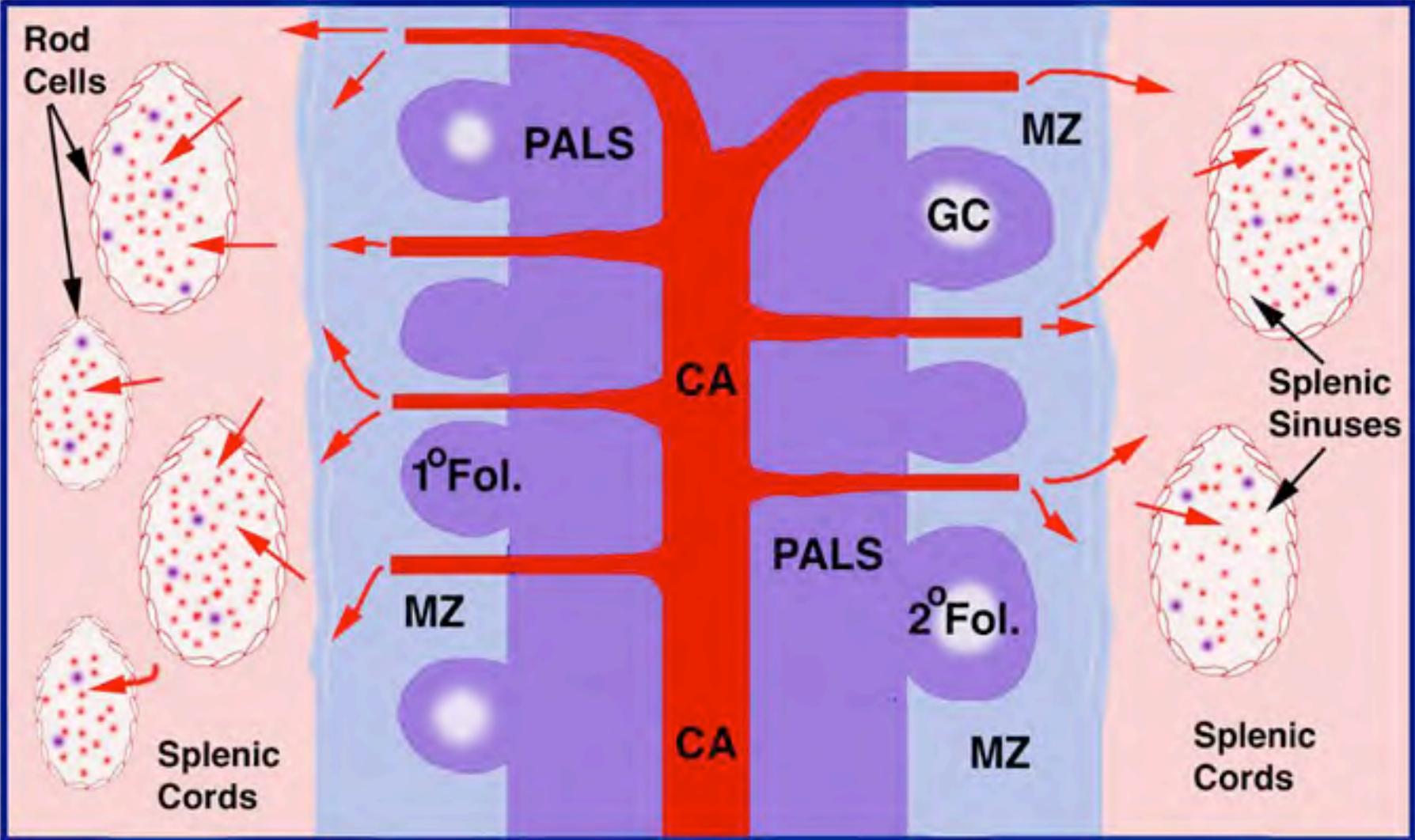
Circulation in the human spleen is primarily “OPEN:” blood pours into the red pulp, percolates through red pulp cords, and re-enters the bloodstream at splenic sinuses



Original Image: <http://www.mc.vanderbilt.edu/histology/images/histology/lymph/display/lymph20015.jpg>

NOTE: NO afferent lymph vessels –not necessary because lymphocytes can easily enter splenic parenchyma via “open” circulation pattern.

# Splenic Circulation



# Organization of the spleen: white pulp and red pulp

White pulp: lymphatic aggregations around “central” arteries:

periarterial lymphatic sheath (PALS): T-cells

lymph nodules: B-cells

Red pulp: cords and sinuses



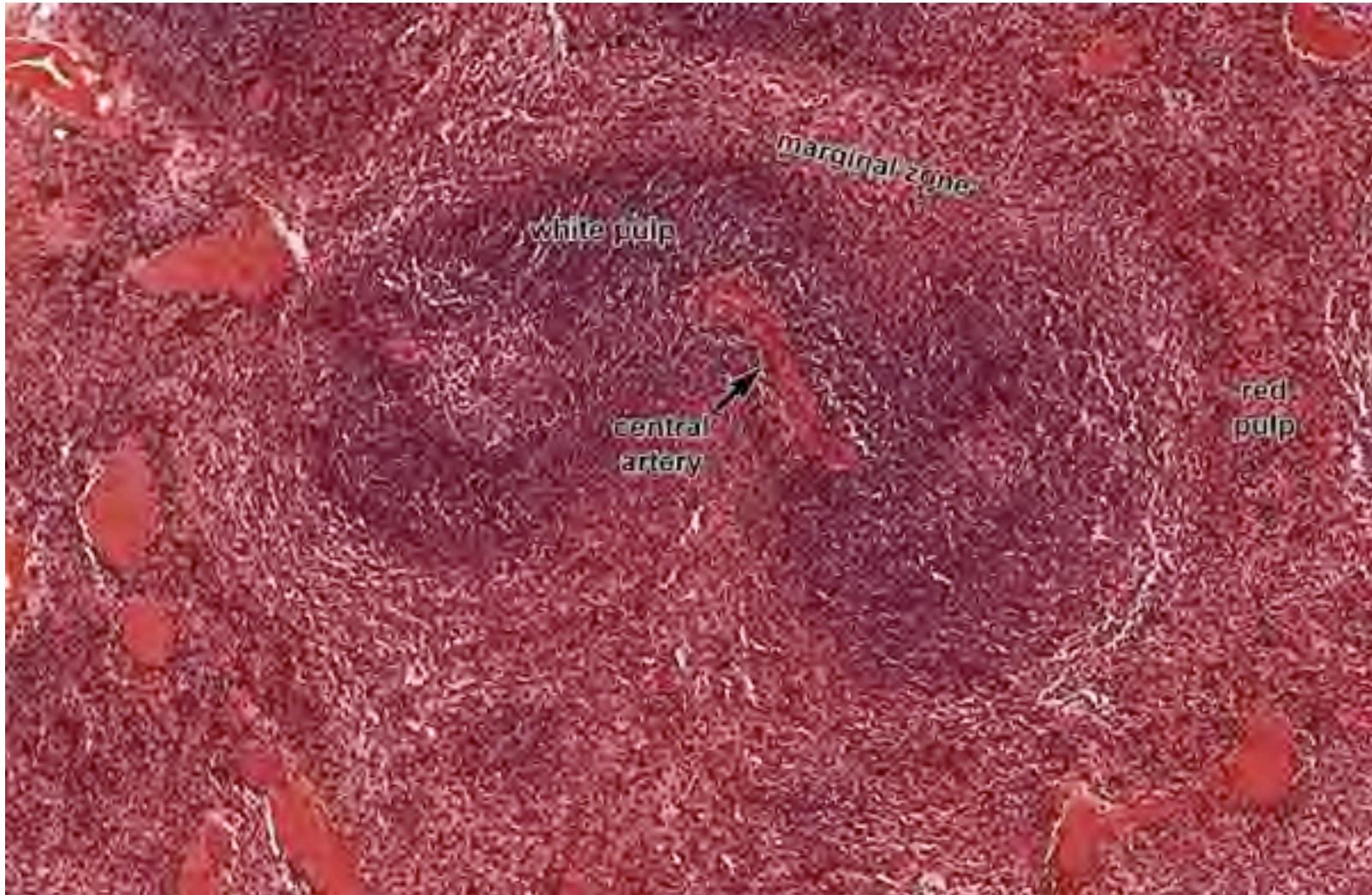
# White pulp function

Blood and antigens pour into red pulp (more on that later)

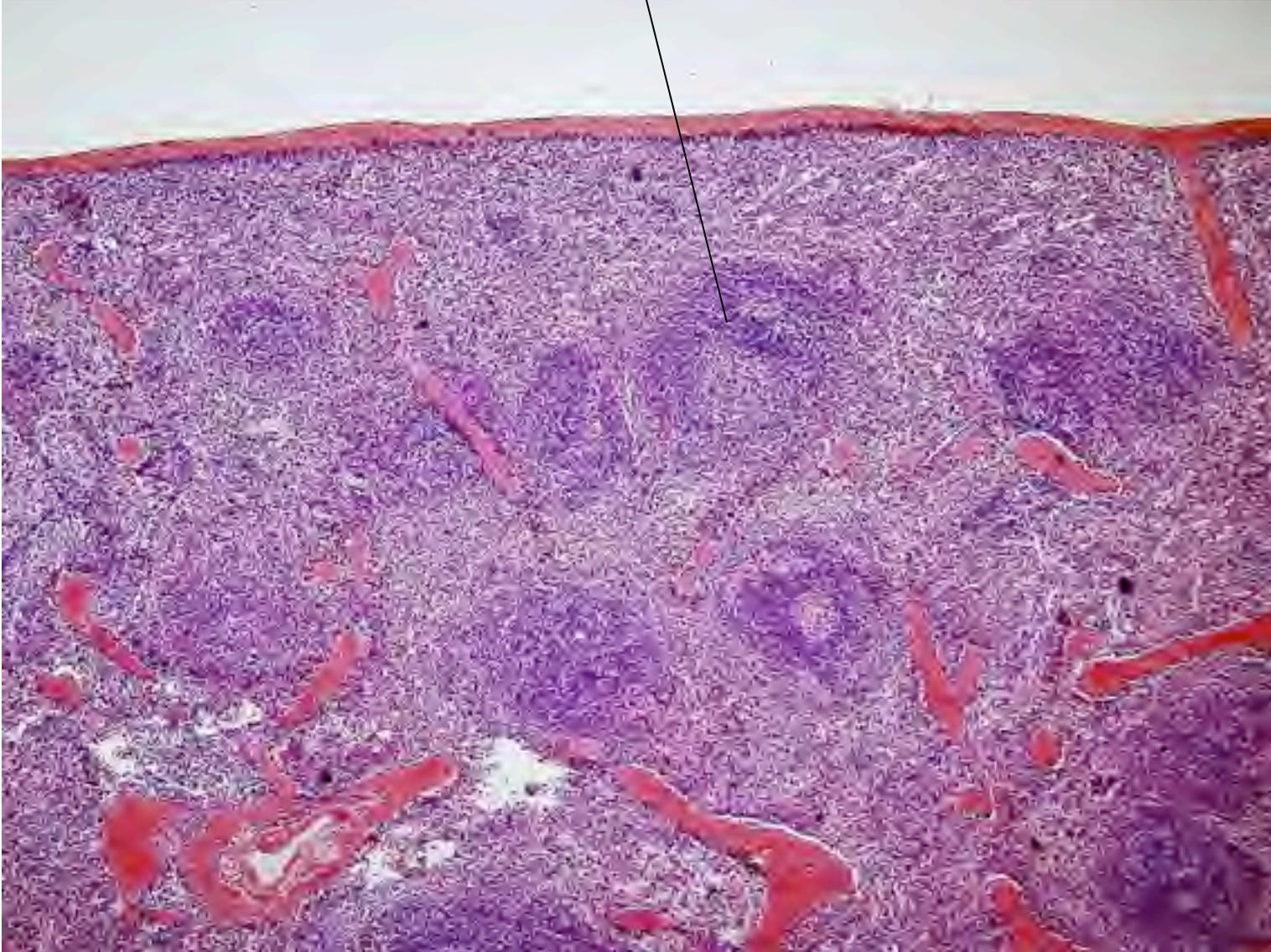
Antigen presentation takes place in MARGINAL ZONE

T-cells (from PALS) provide “help” to activate mphages and B-cells

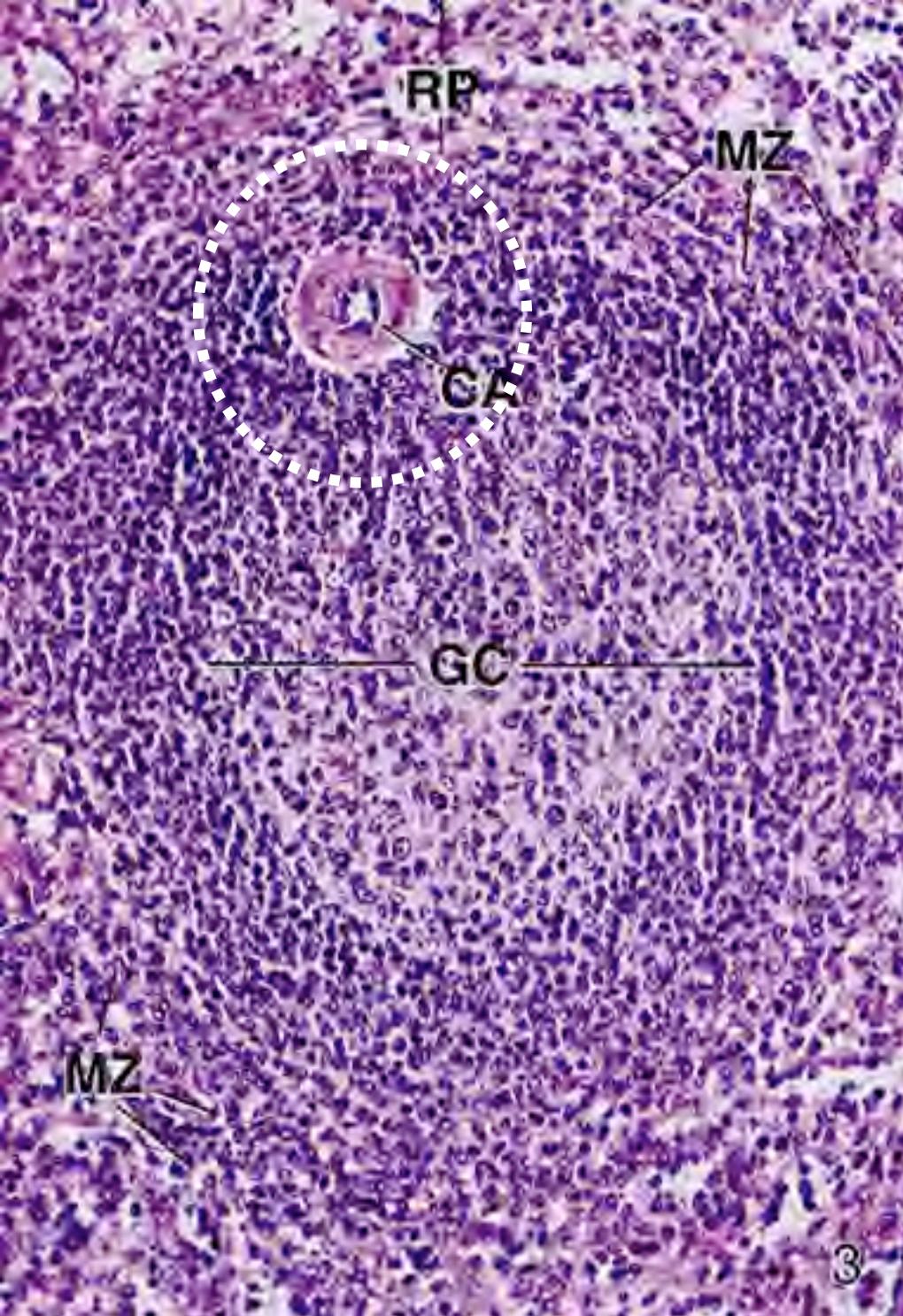
- activated mphages stimulated to destroy ingested material (e.g. bacteria)
- activated B-cells set up proliferative germinal centers



As the body is exposed to antigens and the immune system mounts an immune response in the form of antibody production, lymph nodules (w/ germinal centers) appear in the white pulp of the spleen.



# PALS w/ secondary follicle



Shown here with “central” artery cut in cross section –note that the CA has been pushed off to the side by the rapid expansion of cells in the germinal center (GC)

RP= red pulp

MZ= marginal zone (antigen presentation)

dashed circle = T-cell rich zone

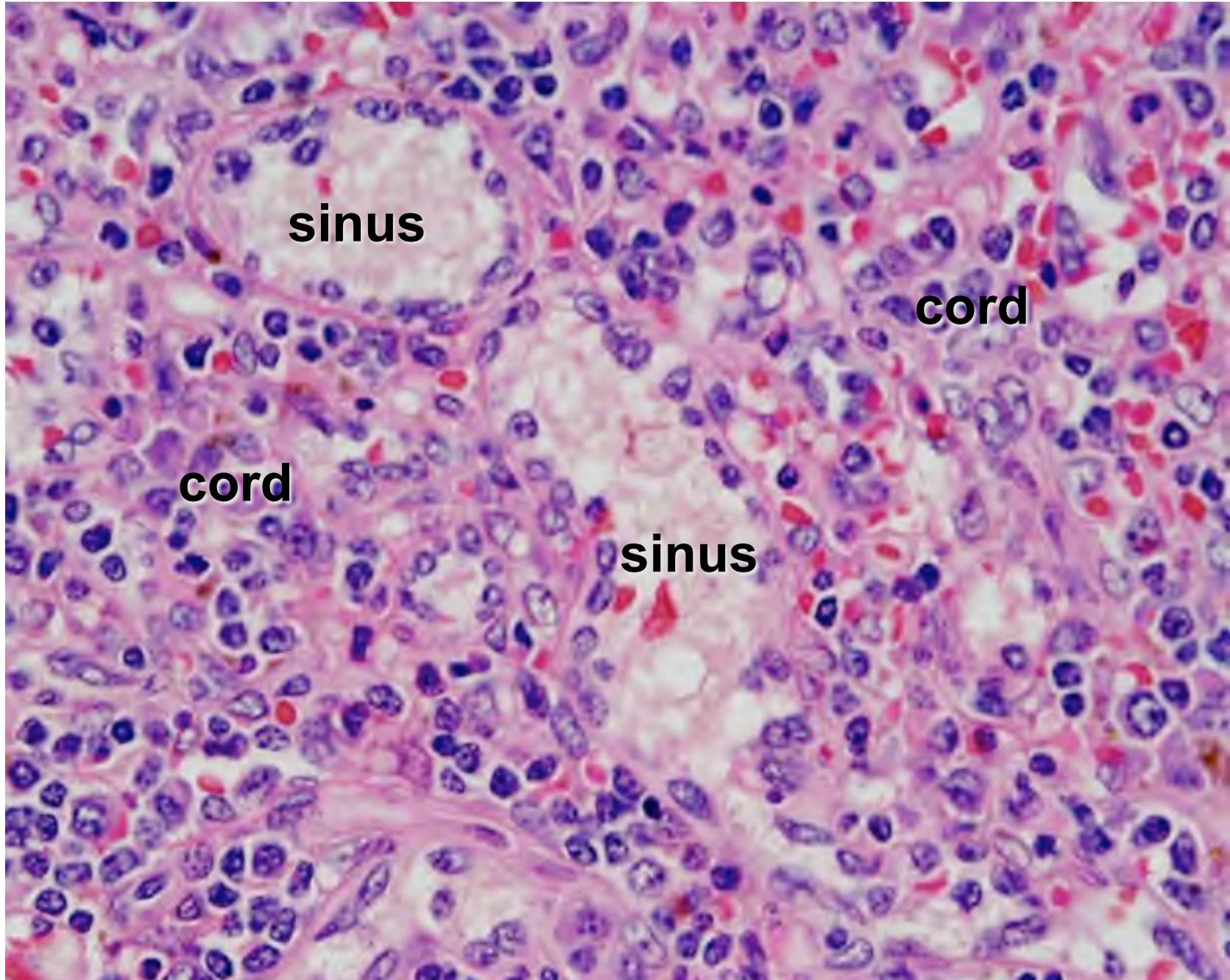


## Scanning EM of a Splenic Sinus (SS) and Cord of Billroth

The cords contain, RBCs, neutrophils (N), macrophages (M), blood platelets (P)

A reticular cell framework (RC) supports the cord. The sinus is bounded by the epithelial cells that form the basket-like structure of the sinus (VS)

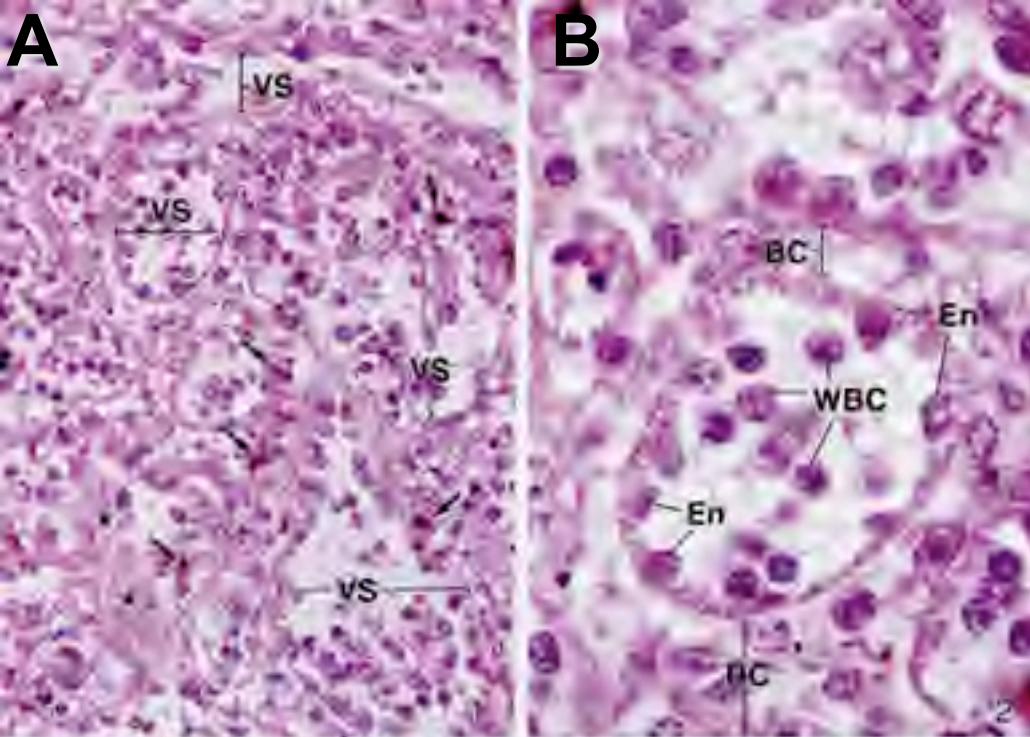
# Spleen (red pulp) at high power (40x)





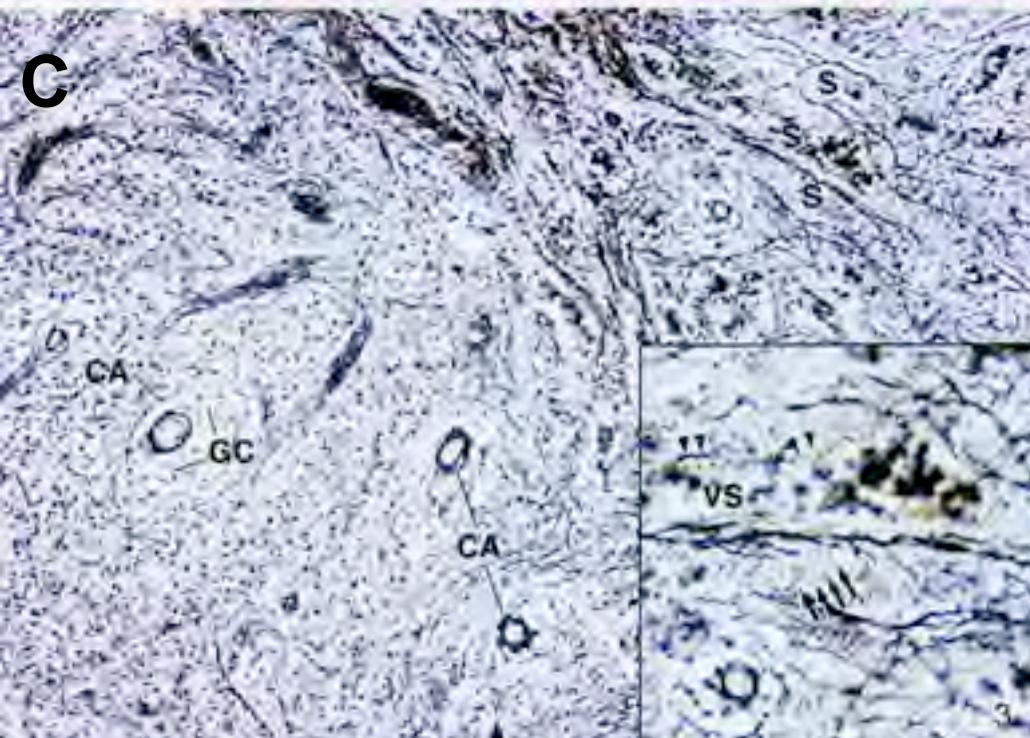
## Percolation of blood into splenic sinuses

Here, you are inside the sinus looking through to the cord, where both a macrophage (M) and a neutrophil (N) are outside the sinus. Note that the endothelial cells have a rodlike appearance.

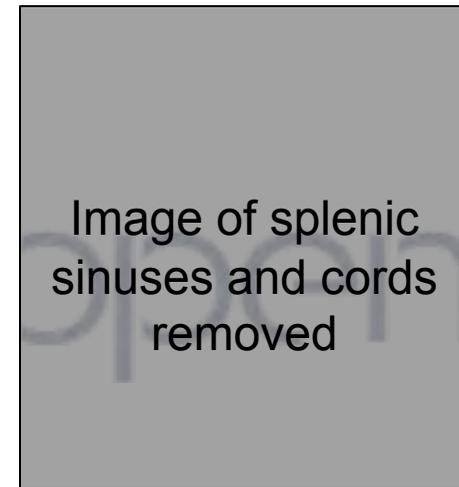


# Splenic sinuses and cords

- A. red pulp
- B. higher mag of venous sinus and cords of Billroth
- C. silver-stained section
- D. diagram



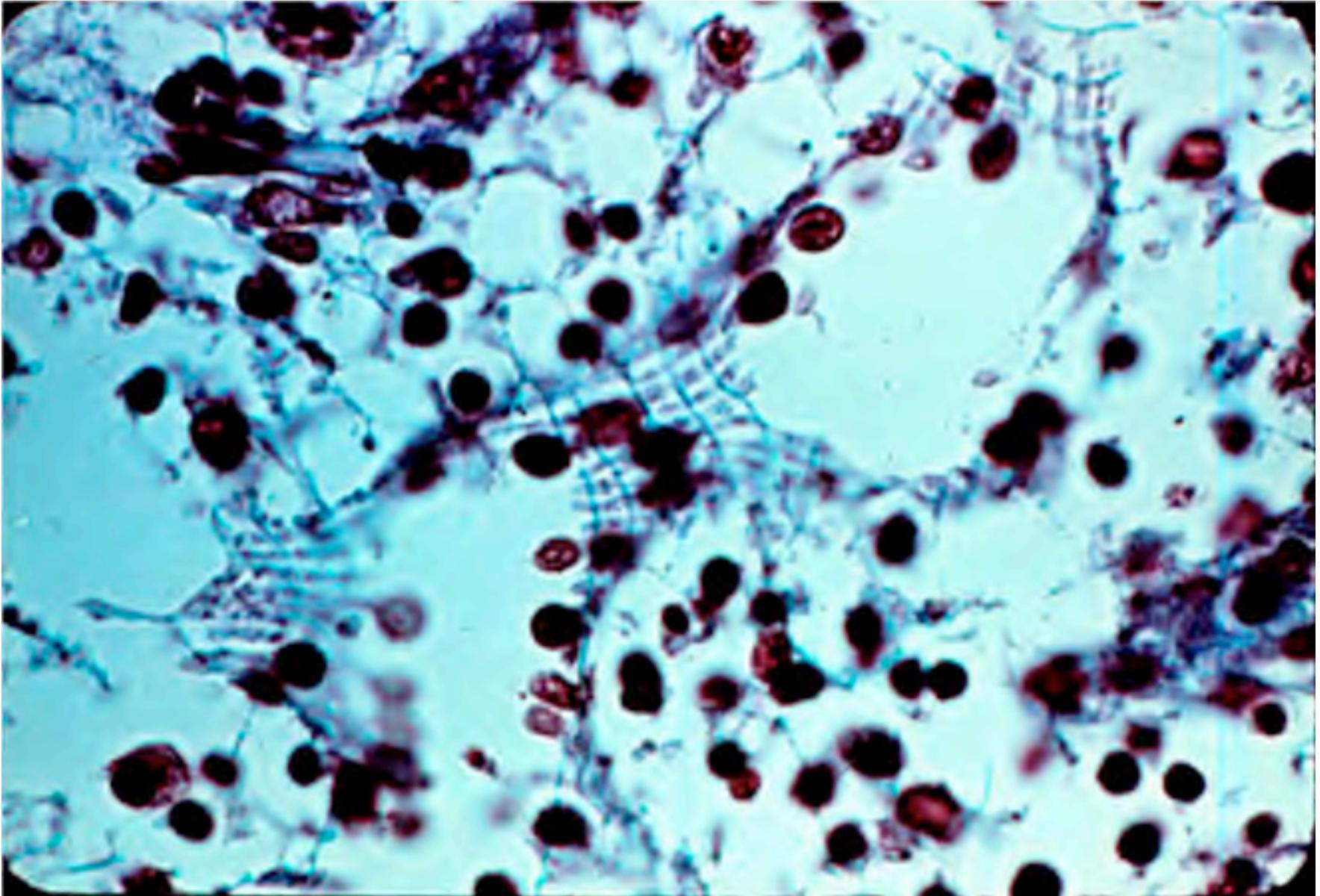
discontinuous basement membrane



**D**

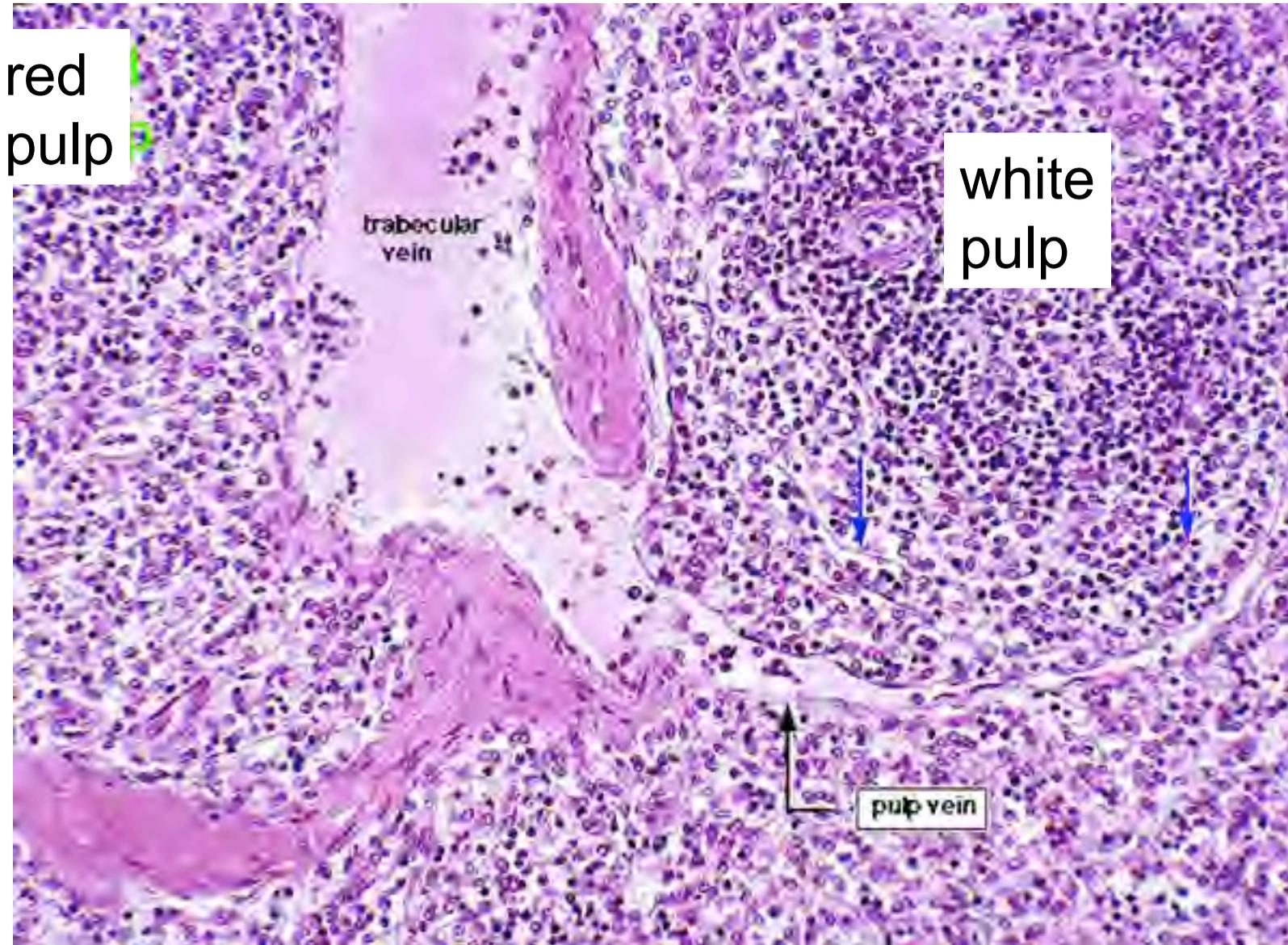
Original Image: <http://immuneweb.xxmu.edu.cn/Lymphoid%20System.files/UntiHE20.jpeg>

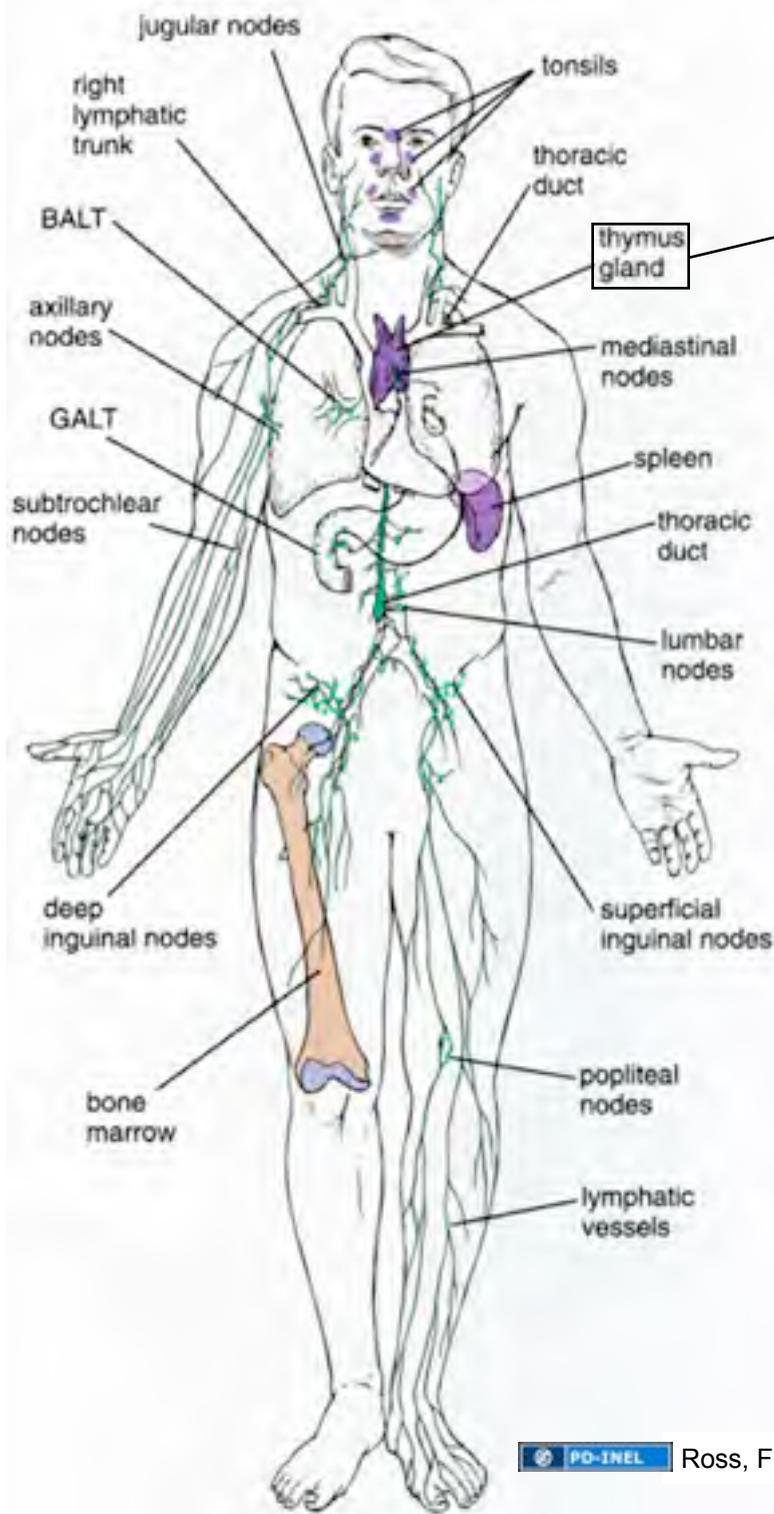
# SPLEEN: venous sinus showing rodlike endothelial cells



# SPLenic CIRCULATION

Sinuses drain into splenic pulp veins, which, in turn, drain into trabecular veins. Trabecular veins travel within trabeculae and drain into splenic vein at the hilus.





# The Thymus

T-cell education

Self vs. nonself distinctions

Cell-mediated immune functions

Populates effector organs

Lymph nodes

Lymphatic nodules

Spleen

Tonsils

# The Thymus is a Primary Lymphoid (Immune) Organ Responsible For the Education of T-Cells

Located over the great vessels of the heart in the area of the body called the mediastinum

Develops from an invagination of EPITHELIUM of the 3<sup>rd</sup> pharyngeal pouch, so an endodermal organ.

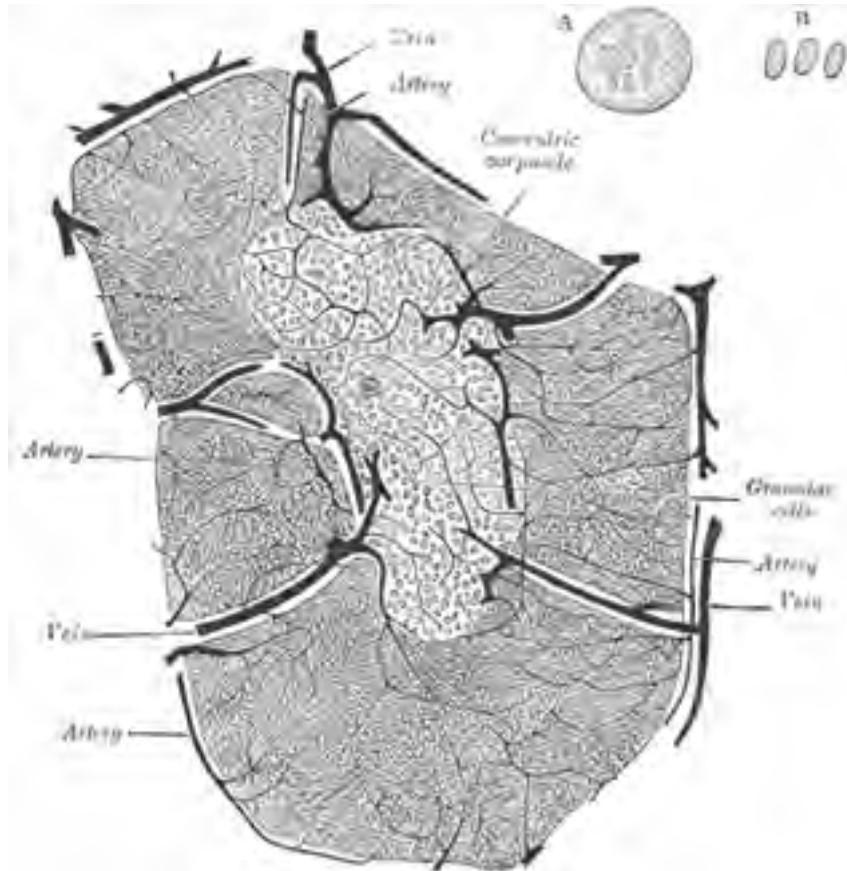
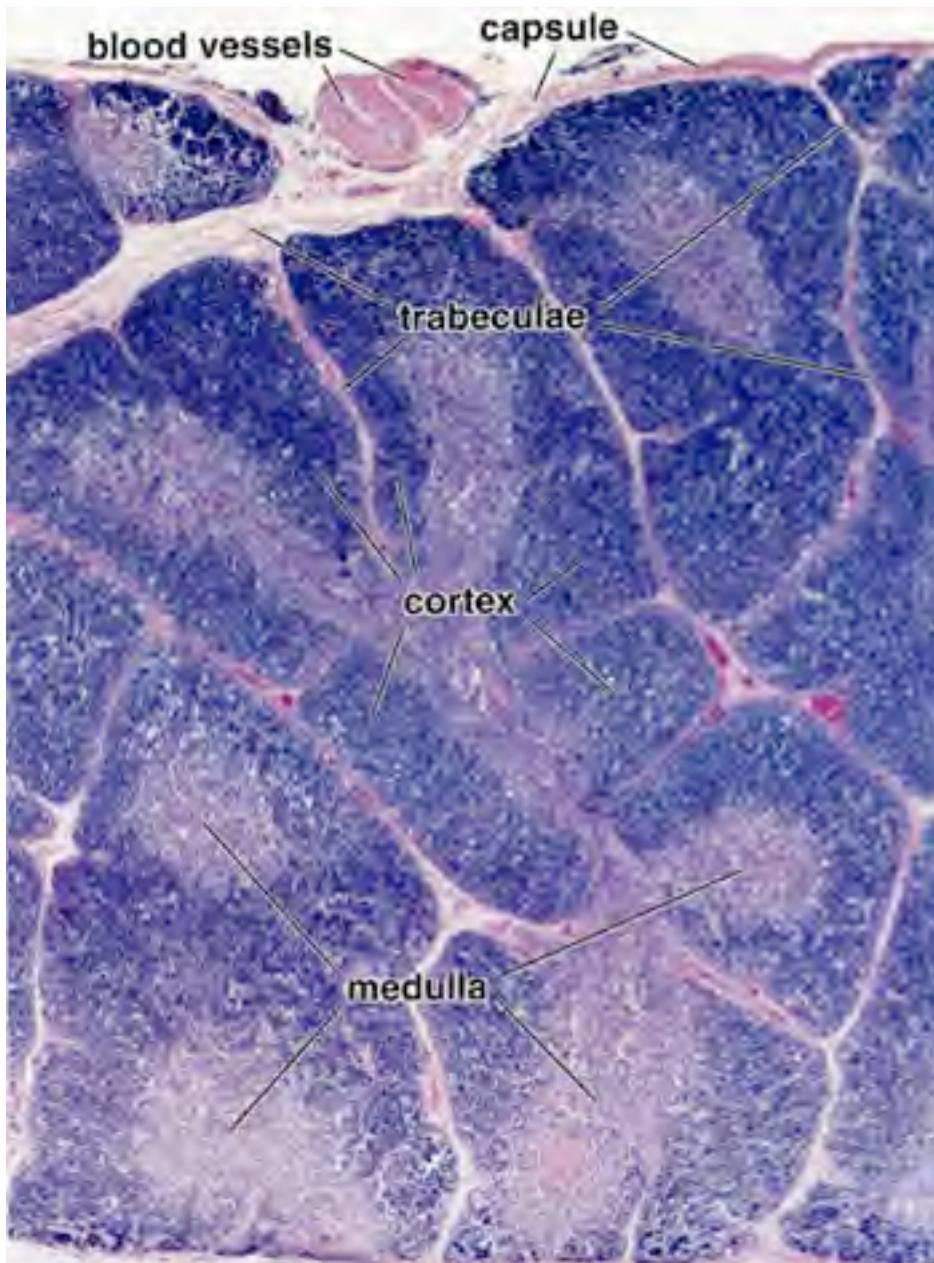
Specialized epithelial cells (called epithioreticular cells) that are joined to one another by long processes with desmosomes on the extremities of the cells (like starfish joined together at the tips) make up the bag-like support for:

Lymphocytes that, when the organ is young, fill this “bag”.

NOTE: There are generally no B cells in the Thymus.

# The Young Thymus

Surrounded by a CT capsule; cortex has a lot of lymphocytes, fewer in the medulla  
THERE ARE NO GERMINAL CENTERS IN THE THYMUS!



PD-EXP Gray's Anatomy

# Thymic Cortex and Medulla

## Thymic (or Hassall's) Corpuscles

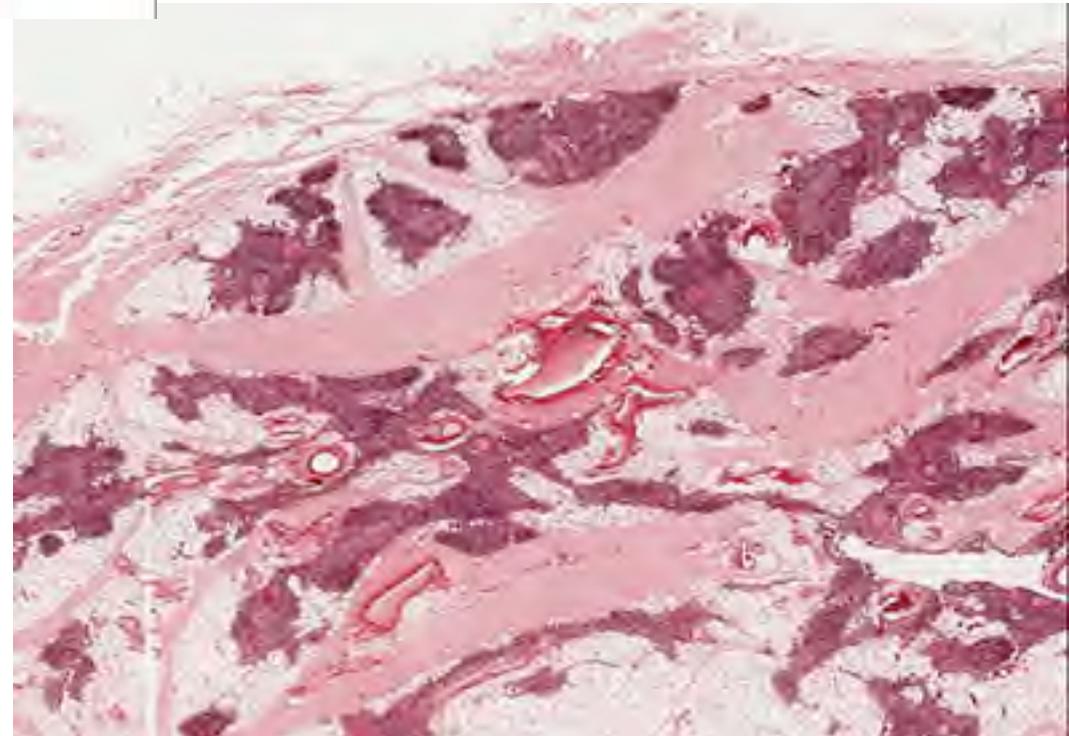




The Thymus undergoes a process called **THYMIC INVOLUTION**, as T cells leave the thymus to populate other lymphoid effector organs, the organ shrinks, leaving only the epithelioreticular cells

PD-INEL U-M Histology Collection

The young thymus



Thymus at puberty

PD-INEL U-M Histology Collection

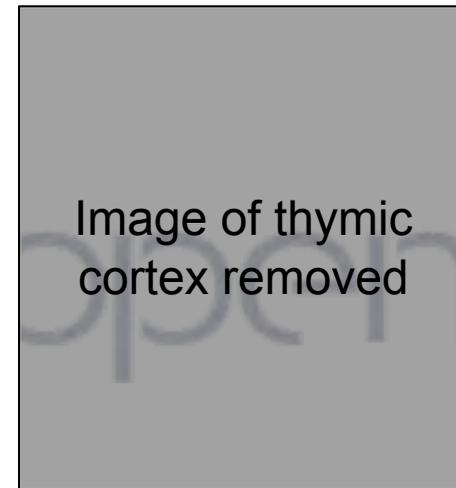
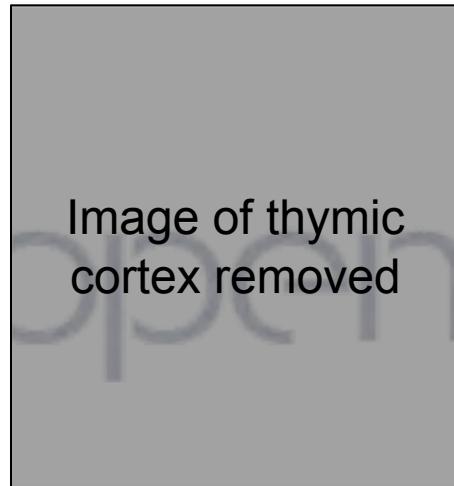
# Overview of T-cell “education”



Original Image: <http://www.nature.com/nri/journal/v6/n2/images/nri1781-f4.jpg>

1. Naïve T-cells enter medulla via diapedesis across venules
2. Pass into cortex to undergo **POSITIVE** selection:
  - Presented with MHC molecules **and** self or non-self antigens by ERCs
  - T-cells that recognize MHCs **and** self/non-self antigens “pass” this selection process and survive (those that don’t undergo apoptosis)
3. Move into medulla to undergo **NEGATIVE** selection:
  - T-cells that recognize **SELF** antigens displayed by self MHCs (i.e. are :autoreactive”) are eliminated
4. Differentiate into helper (CD4+) or cytotoxic (CD8+) T-cells and leave medulla via diapedesis across venules

**Arterioles & capillaries in the thymic cortex are ensheathed by epithelioreticular cells forming a blood-thymus barrier.**



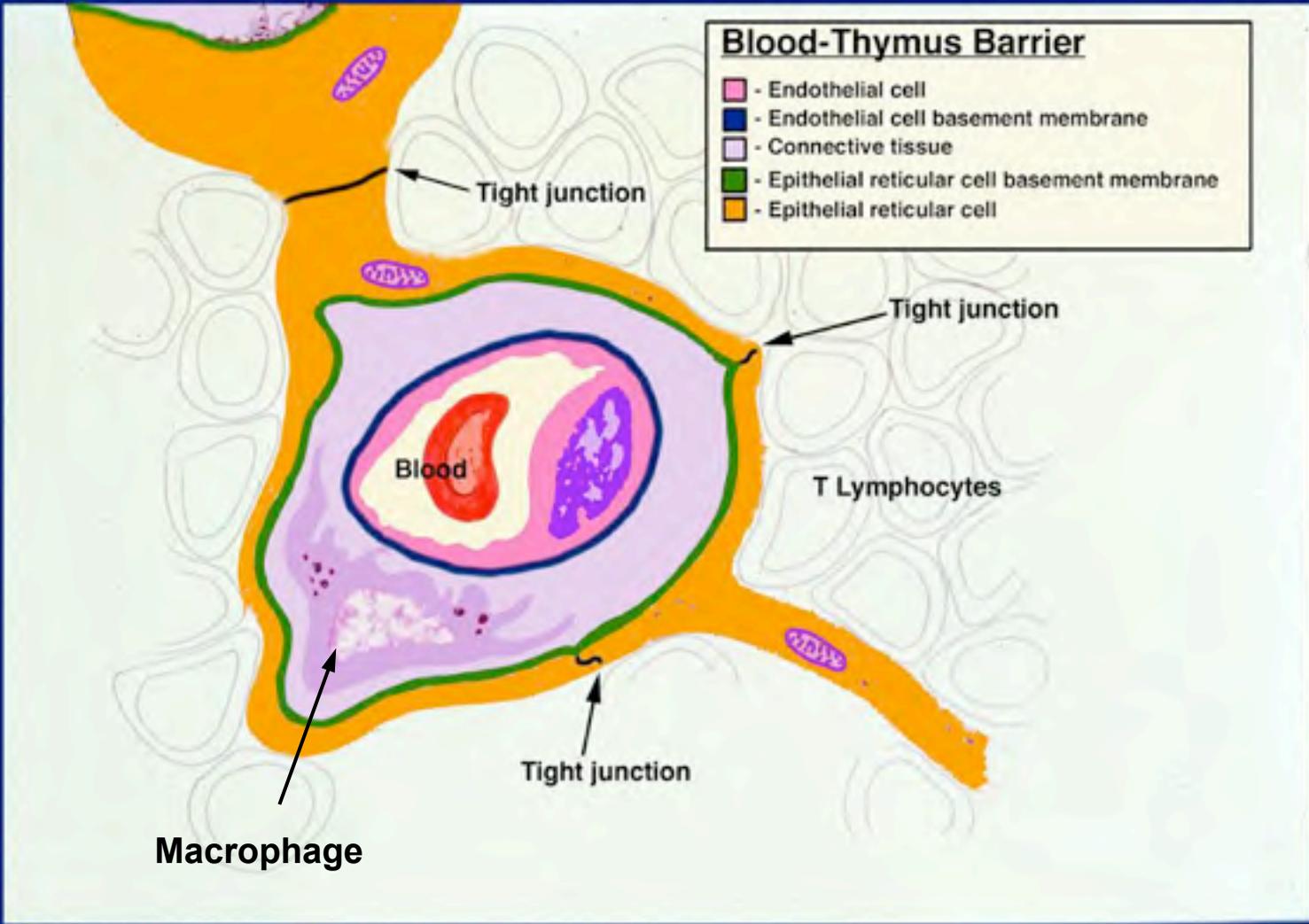
# Blood-Thymus Barrier

Education of T-cells must occur in a very controlled environment such that antigens are **ONLY** presented by epithelial reticular cells.

To ensure that no other cells or free antigens are present, there is a very tight **BLOOD-THYMUS BARRIER** consisting of:

1. The blood capillary wall
  - endothelial cells
  - endothelial cell basal laminae
  - pericytes
2. Perivascular connective tissue
  - type III collagen
  - macrophages
3. Epithelioreticular cell layer
  - basal lamina of the epithelial reticular cells (type I ERCs)
  - epithelial reticular cells

(NOTE: T-cells can enter thymus **ONLY** via bloodstream – **NO AFFERENT LYMPH VESSELS!**)

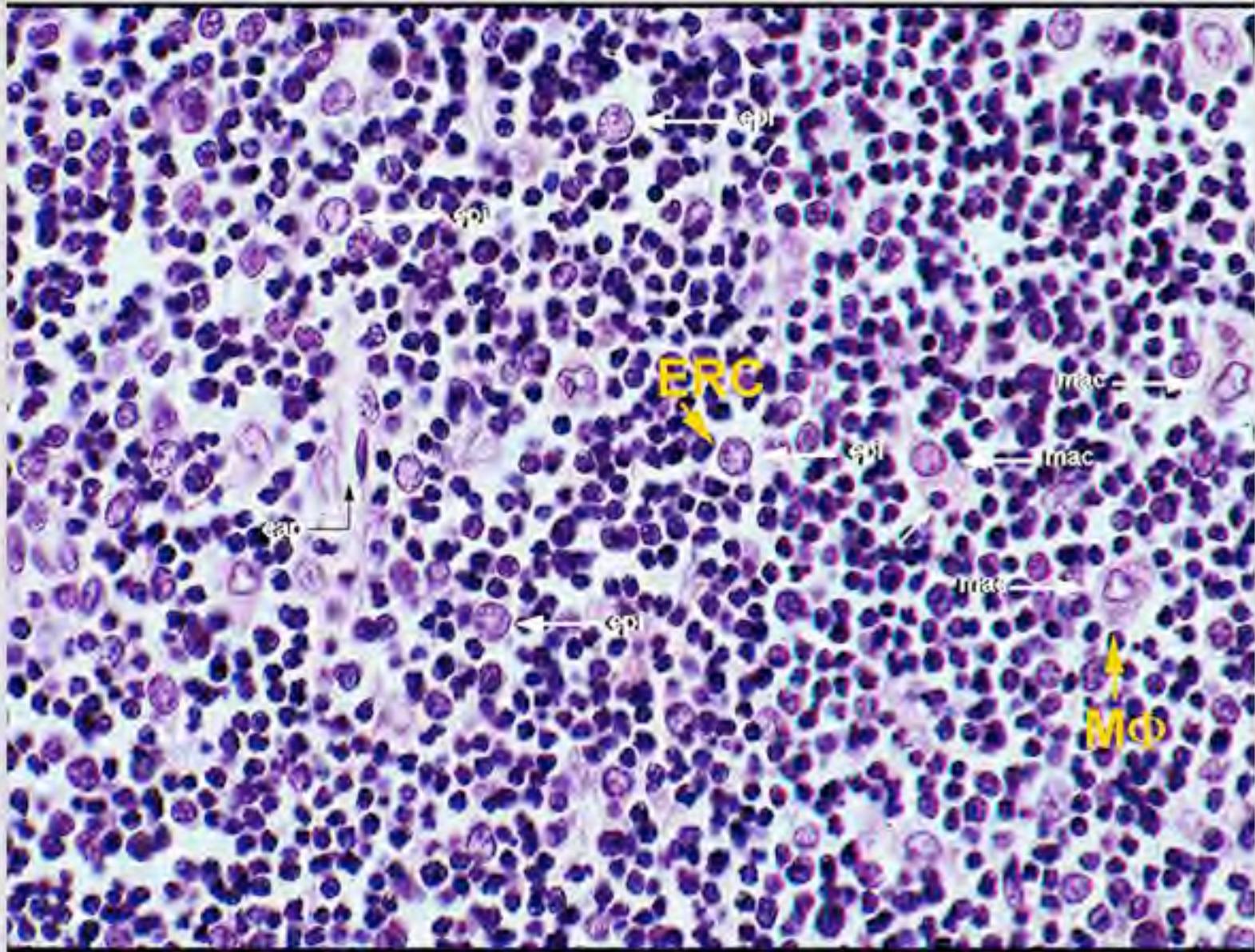


# Thymic Cortex and Medulla

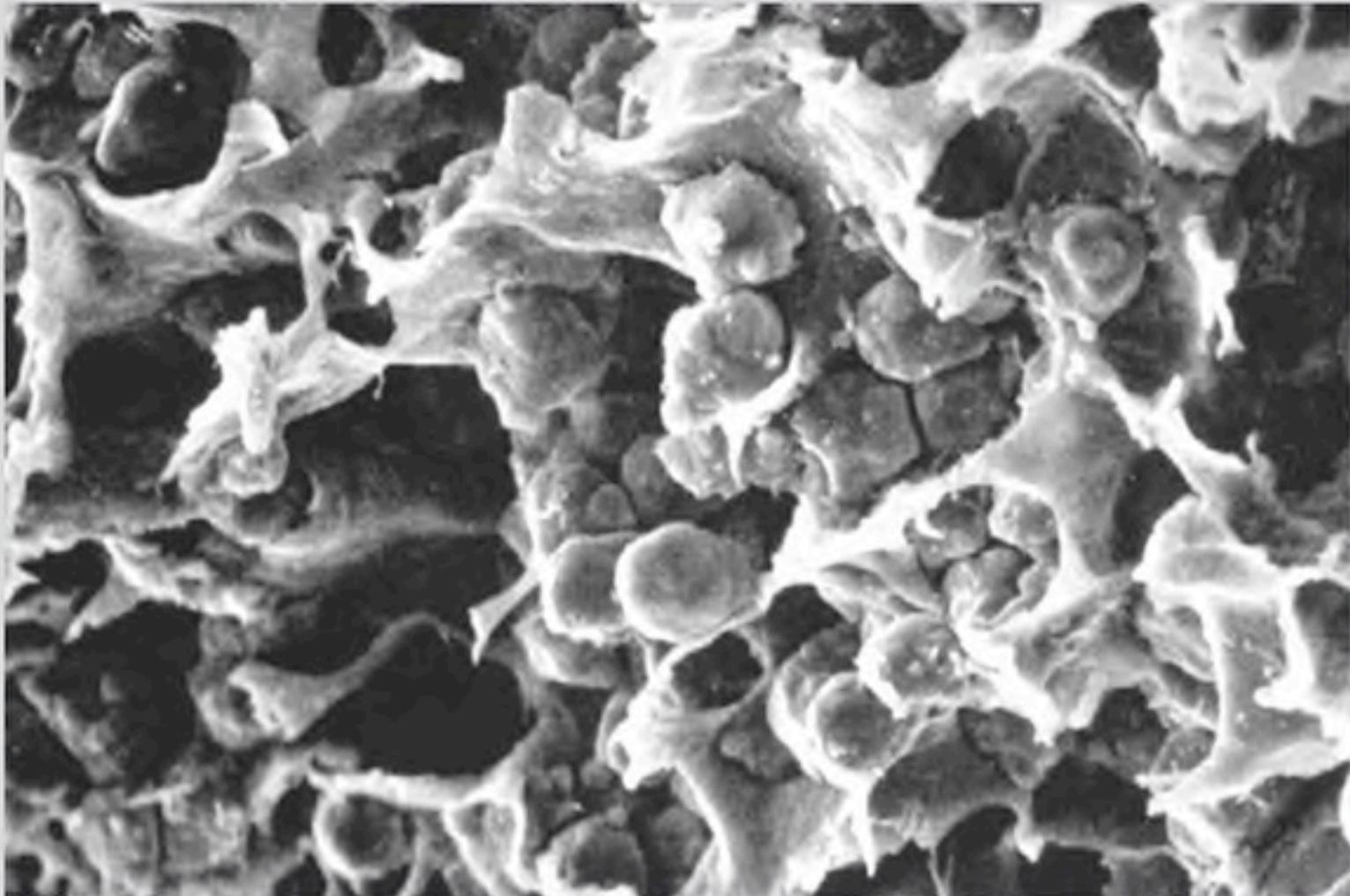
## Thymic (or Hassall's) Corpuscles



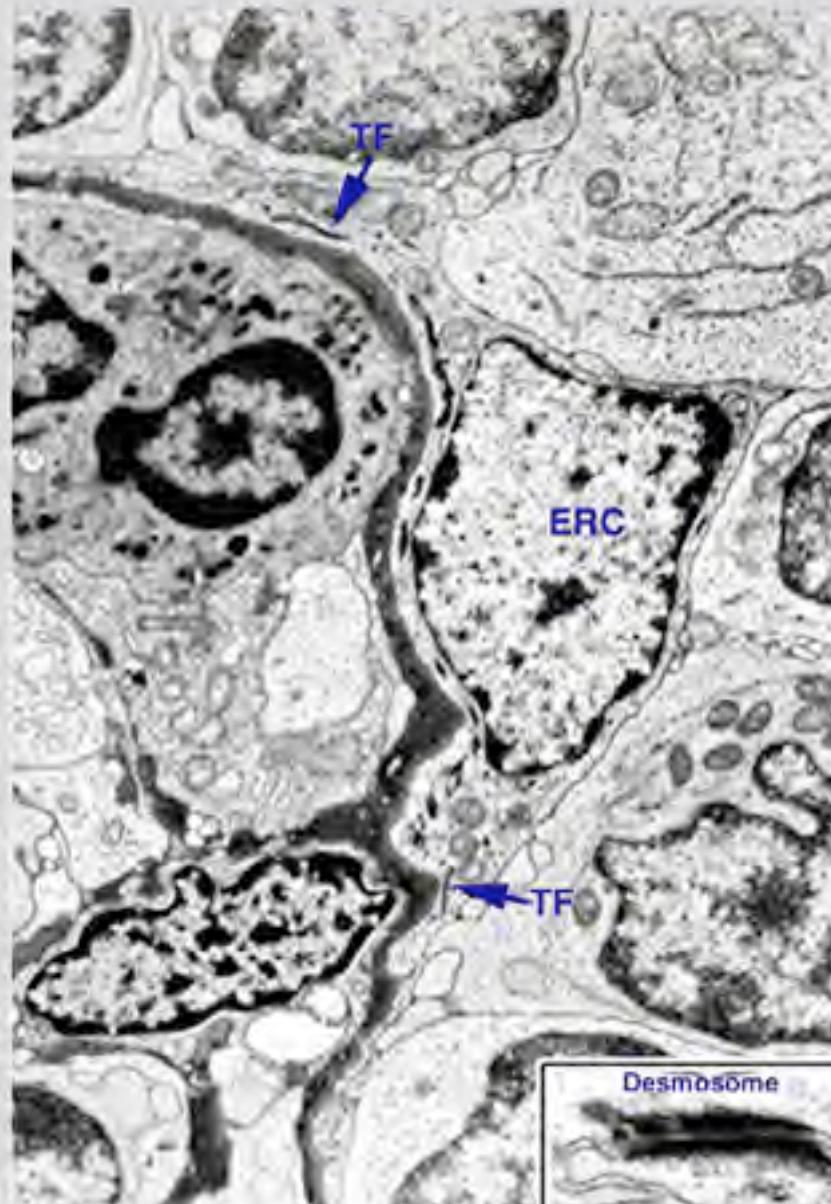
# Thymic Epithelial Reticular Cells and Macrophages



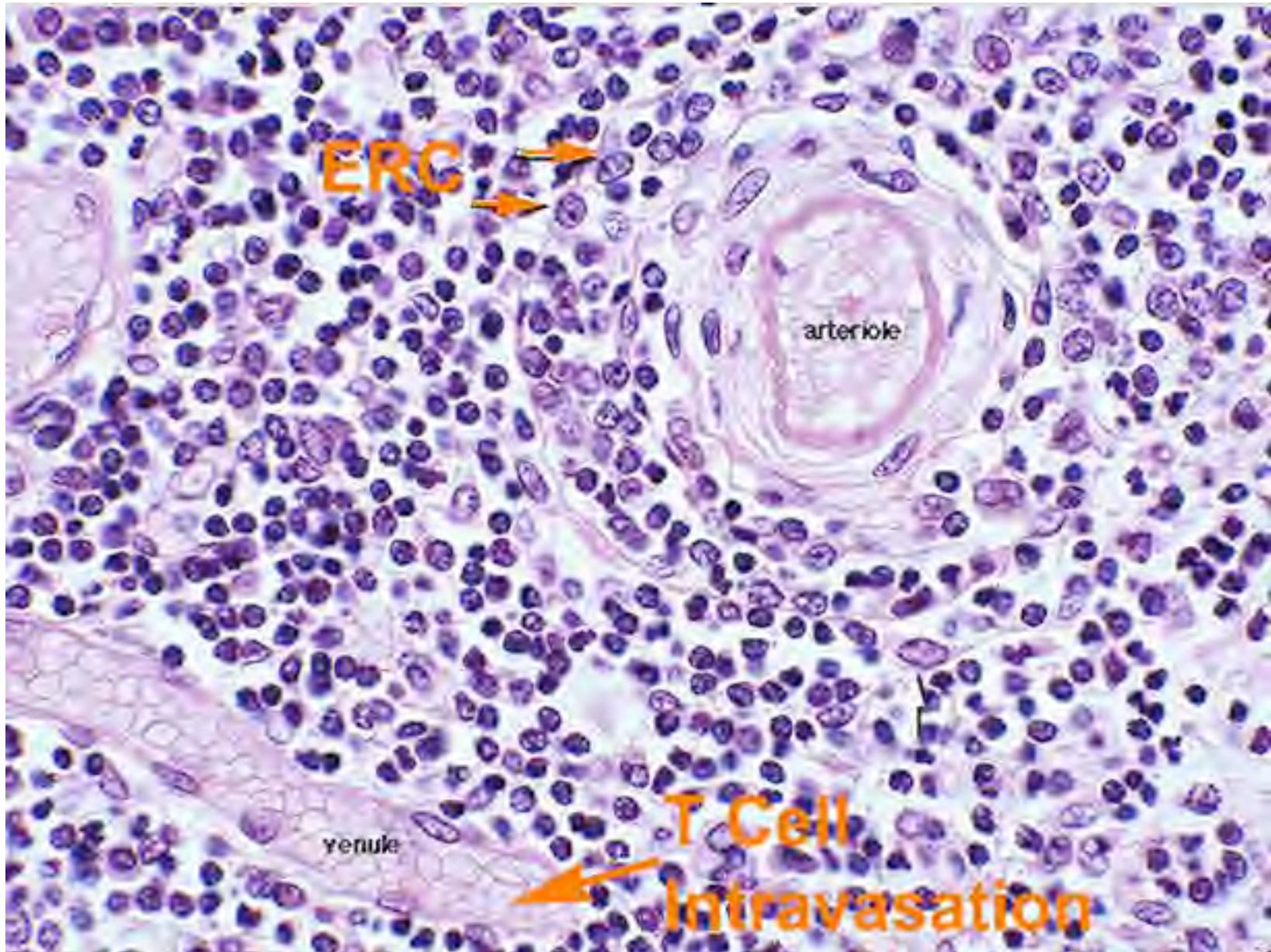
## Thymocytes Differentiating in the Cytoplasmic Folds of Epithelial Reticular Cells



## Formation of Tight Junctions Tonofilaments, and Desmosomes by Thymic Epithelial Reticular Cells



# High mag view of medulla

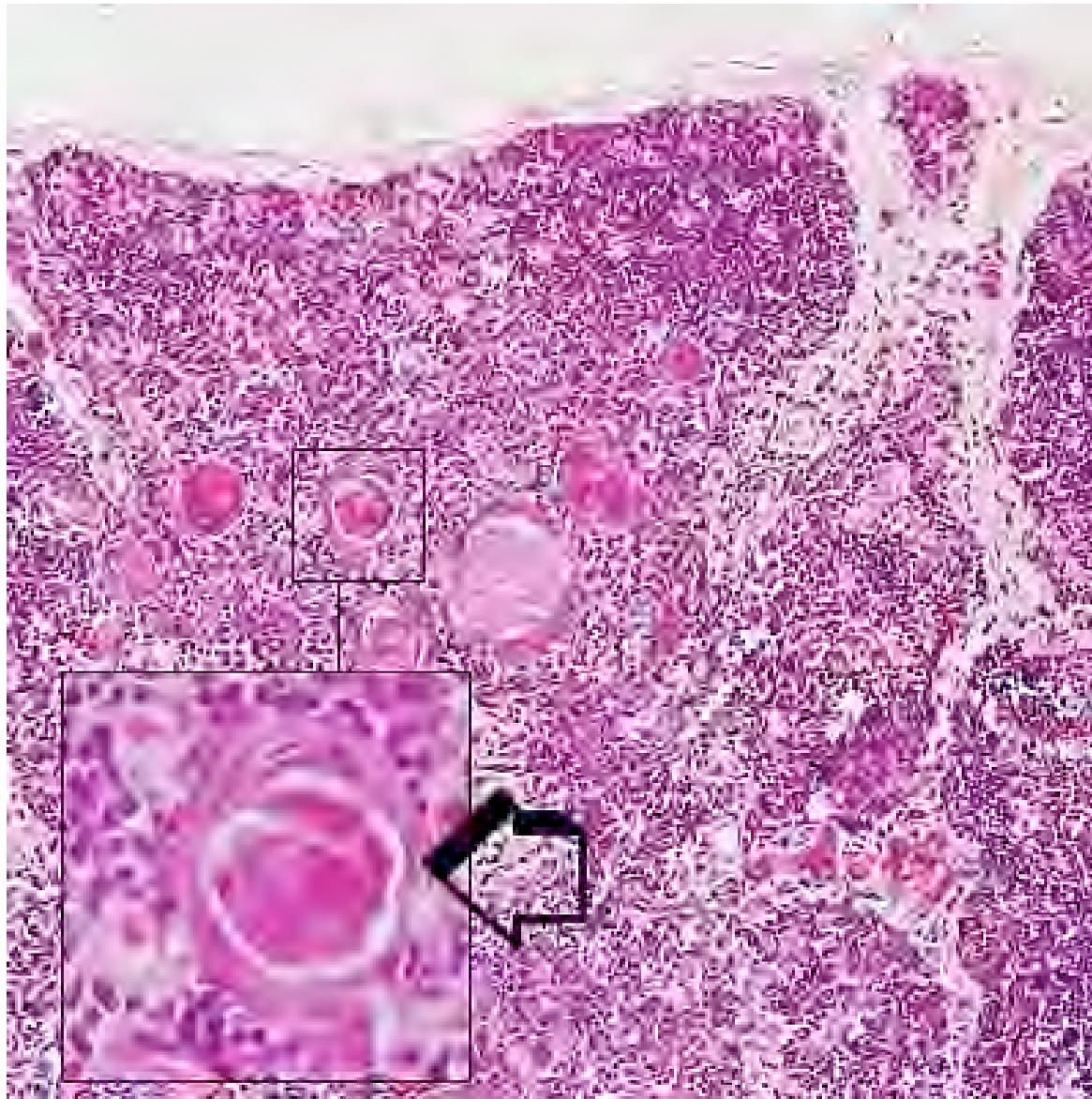


PD-INEL Source Undetermined

T-cells that survive selection process allowed to cross venule endothelium (INTRAVasation) to enter circulation.

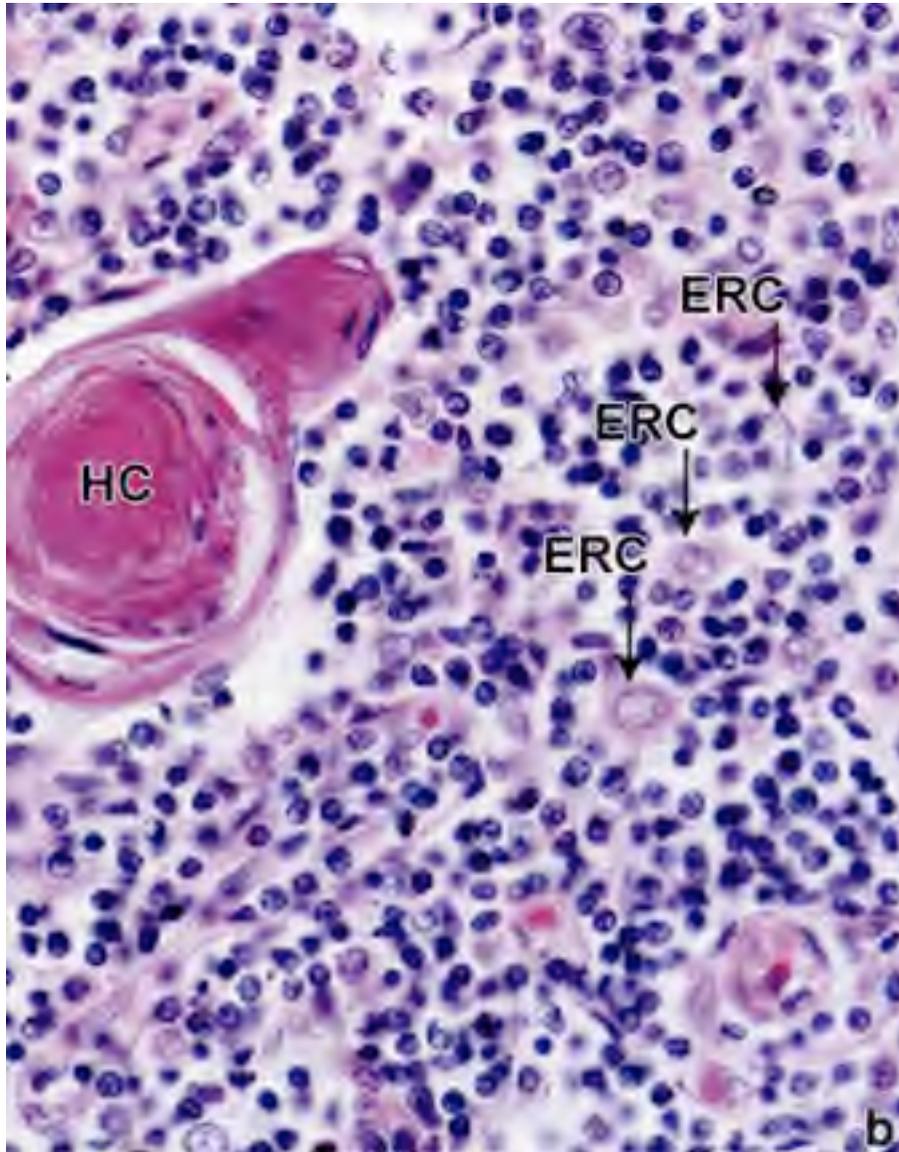
# Hassall's corpuscles

Type VI ERCs; function not very well known, but produce interleukins (such as IL-4 and IL-7) and so likely influence T-cell differentiation

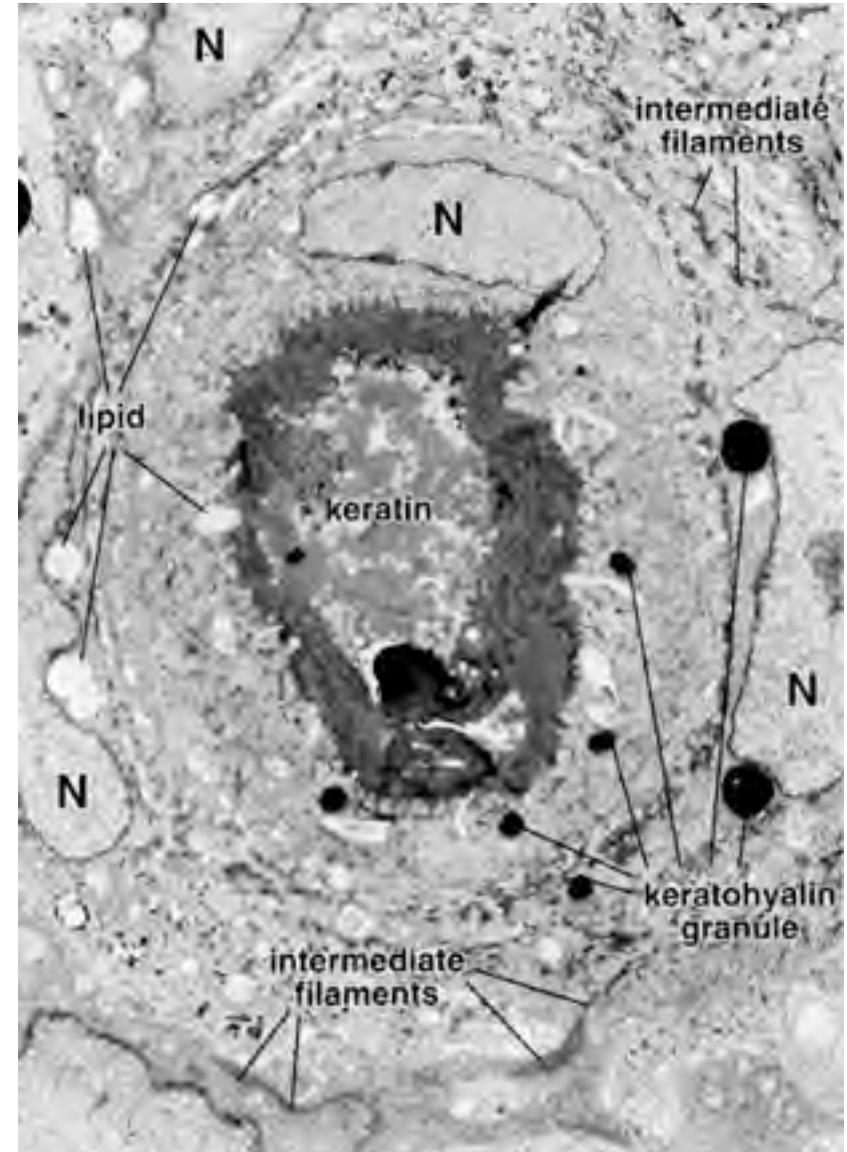


In the medulla, epithelioreticular cells form onionized structures called Hassall's corpuscles –quite prevalent in older thymus

LM view



EM view



	<u>Lymph Node</u>	<u>Splenic White Pulp</u>	<u>Thymus</u>
Follicles -	✓	✓	—
Germinal Centers -	✓	✓	—
Efferent Lymphatics -	✓	✓	✓
Afferent Lymphatics -	✓	—	—
Supporting Meshwork -	Reticular Cells/Fibers	Reticular Cells/Fibers	Epithelial Reticular Cells

# Additional Source Information

for more information see: <http://open.umich.edu/wiki/CitationPolicy>

Slide 6: Ross, Fig. 14.1

Slide 9: Mizobuti histology slide set

Slide 10: Source Undetermined

Slide 11: Dr. Lloyd Stoolman

Slide 12: U-M Histology Collection

Slide 13: U-M Histology Collection

Slide 14: Ross and Pawlina, *Histology: A Text and Atlas*; U-M Histology Collection

Slide 15: Ross and Pawlina, *Histology: A Text and Atlas*

Slide 16: Source Undetermined

Slide 17: Source Undetermined

Slide 18: Ross and Pawlina, *Histology: A Text and Atlas*

Slide 19: U-M Histology Collection. Slide 175.

Slide 20: Source Undetermined

Slide 21: Source Undetermined

Slide 22: U-M Histology Collection; Junquiera and Carneiro. Basic Histology. Tenth Ed. 2003

Slide 23: Source Undetermined; Source Undetermined

Slide 24: Source Undetermined

Slide 25: Ross and Pawlina, *Histology: A Text and Atlas*

Slide 26: Source Undetermined

Slide 27: United States Federal Government

Slide 28: Ross and Pawlina, *Histology: A Text and Atlas*

Slide 29: Dr. S.K. Kim

Slide 30: U-M Histology Collection

Slide 31: U-M Histology Collection

Slide 32: Ross, Fig. 14.1

Slide 33: United States Federal Government

Slide 34: Original Image from <http://health-tune-ups.com/wp-content/uploads/2009/04/cdr533339-750.jpg>

Slide 35: Original Image: [http://academic.kellogg.cc.mi.us/herbrandsonc/bio201\\_McKinley/f24-10a\\_lymph\\_node\\_and\\_c.jpg](http://academic.kellogg.cc.mi.us/herbrandsonc/bio201_McKinley/f24-10a_lymph_node_and_c.jpg); Ross Textbook of Histology

Slide 36: Original Image: [http://human.freescience.org/images/lllu\\_lymph\\_node\\_structure.png](http://human.freescience.org/images/lllu_lymph_node_structure.png)

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Slide 39: U-M Histology Collection  
Slide 40: Source Undetermined  
Slide 41: Ross and Pawlina, *Histology: A Text and Atlas*; Source Undetermined (Rest of Images)  
Slide 42: U-M Histology Collection  
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Slide 45: U-M Histology Collection  
Slide 46: Source Undetermined  
Slide 47: Source undetermined  
Slide 48: Source Undetermined  
Slide 49: Source Undetermined  
Slide 51: Ross, fig. 14.18  
Slide 53: Gray's Anatomy  
Slide 54: Cancer.gov, [Wikipedia, http://commons.wikimedia.org/wiki/File:Illu\\_spleen.jpg](http://commons.wikimedia.org/wiki/File:Illu_spleen.jpg)  
Slide 55: Ross 14.29  
Slide 57: Original Image: <http://www.mc.vanderbilt.edu/histology/images/histology/lymph/display/lymph20015.jpg>  
Slide 58: Wheater's, Functional Histology, Fifth Edition, 2006  
Slide 59: U-M Histology Collection  
Slide 60: U-M Histology Collection  
Slide 61: U-M Histology Collection  
Slide 62: Ross. Plate 35-3  
Slide 63: Ross 14.30a  
Slide 64: U-M Histology Collection  
Slide 65: Ross and Pawlina, *Histology: A Text and Atlas*; Source Undetermined  
Slide 66: Ross and Pawlina. Plate 36. Figure 1, 2, 3.; Original Image  
<http://immuneweb.xmu.edu.cn/Lymphoid%20System.files/UntiHE20.jpeg>  
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Slide 69: Ross Fig. 14.1  
Slide 71: Ross and Pawlina, *Histology: A Text and Atlas*; Gray's Anatomy  
Slide 72: Source Undetermined  
Slide 73: U-M Histology Collection; U-M Histology Collection  
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