LYMPHATIC SYSTEM

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MUNI MED
Department of Histology and Embryology

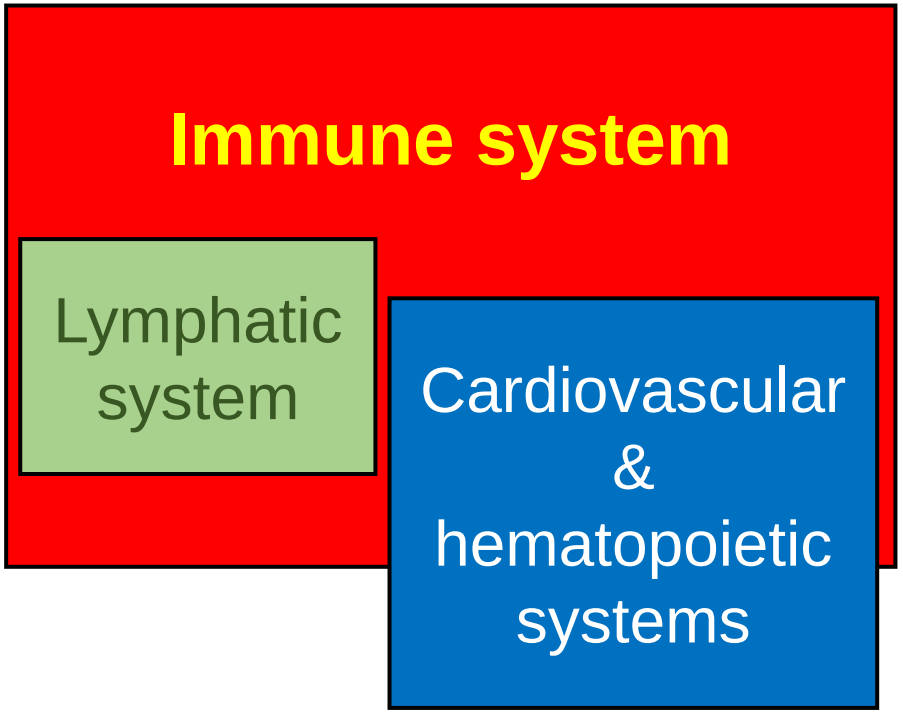
LECTURE CONTENT

- Principles of immune response
  - Innate and acquired immunity
  - Humoral and cellular immunity

Useful for understanding

- Structures essential for functioning of immune system
  - Lymphatic circuitry
  - Lymphatic follicles
  - Lymph nodes
  - Spleen
  - Thymus
  - MALT

Important for our course



- Development of lymphatic system

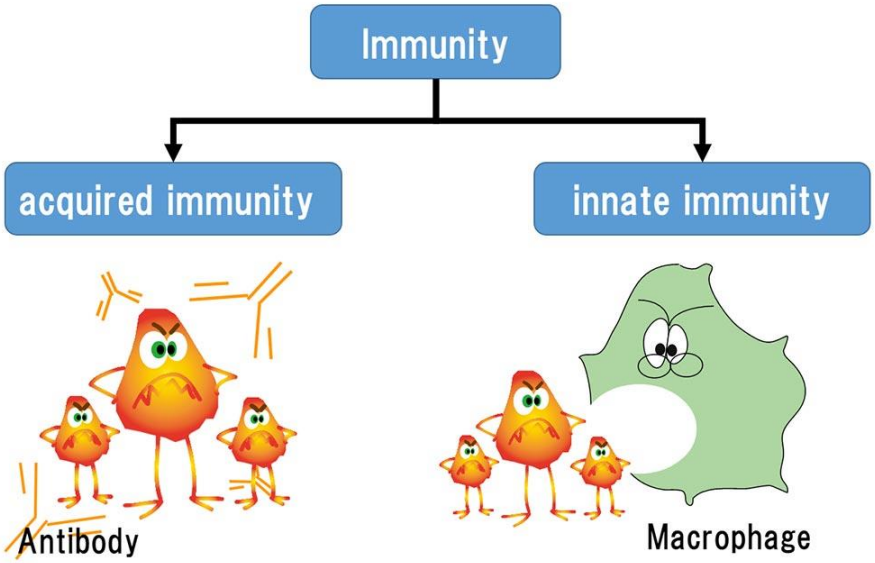
IMMUNE SYSTEM

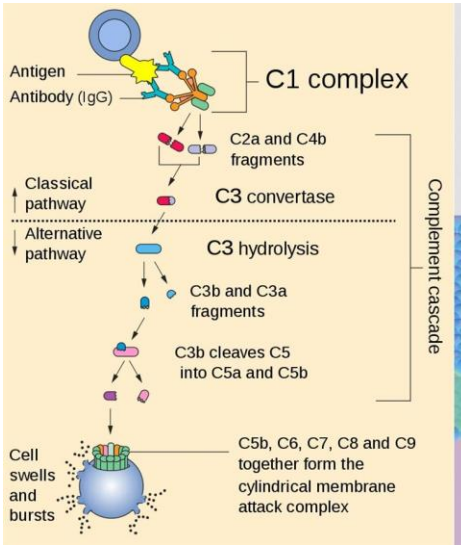
Immunity = self defense

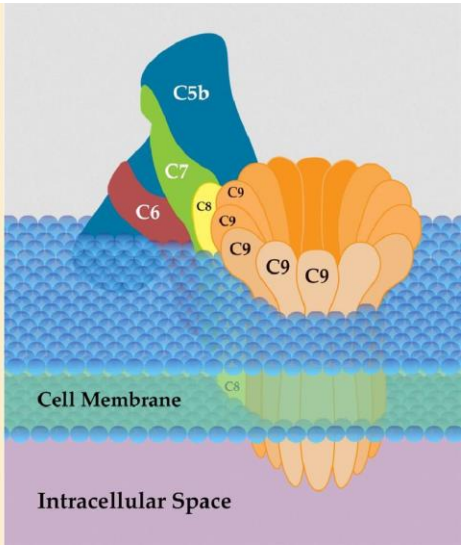
- Epithelial: epithelial barriers equipped with antimicrobial substances
- Innate: complement, macrophages and neutrophils, natural killers
- Acquired: T and B lymphocytes

Clinical relevance?

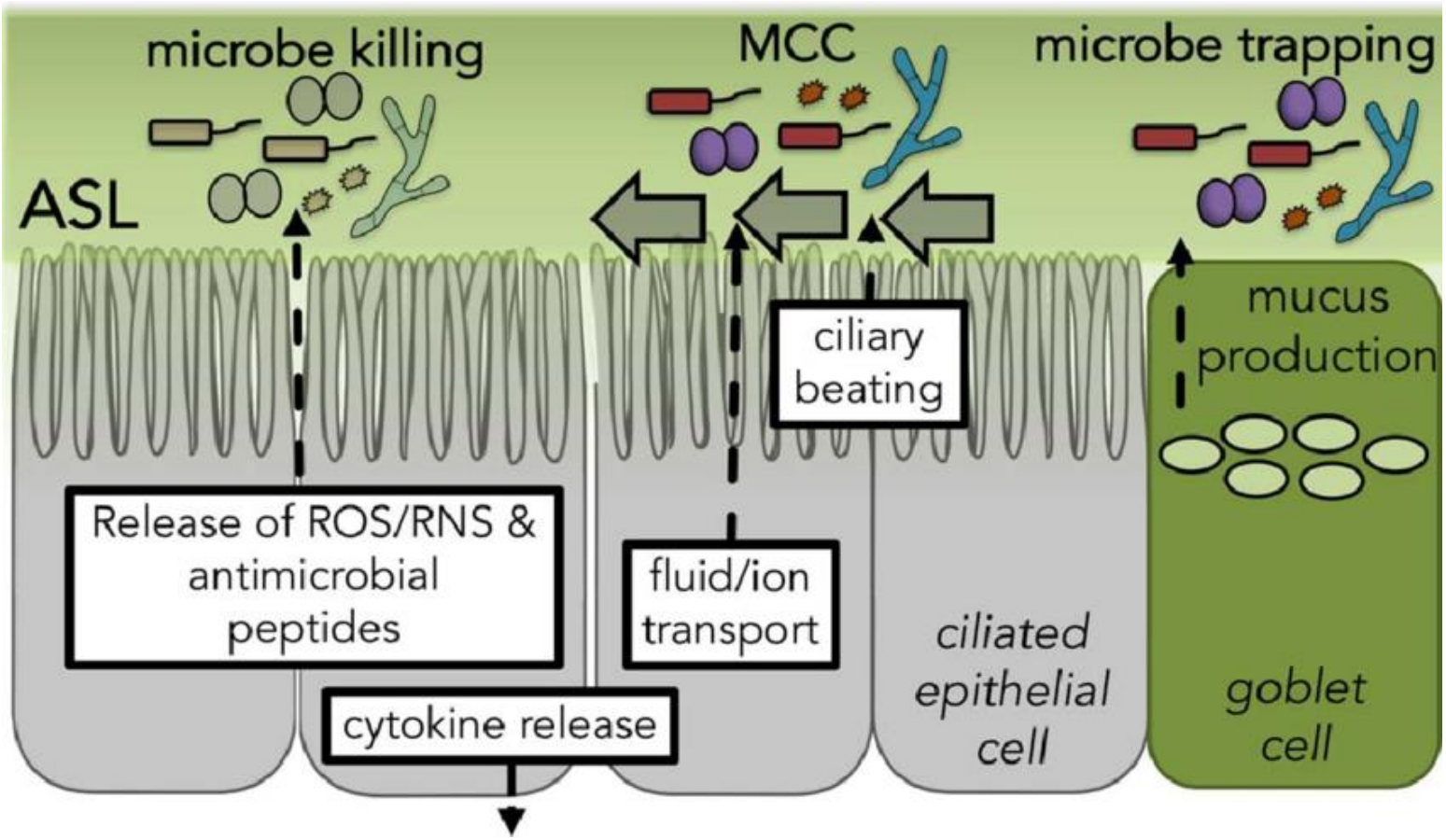
- Autoimmune disorders
- Immunodeficiency





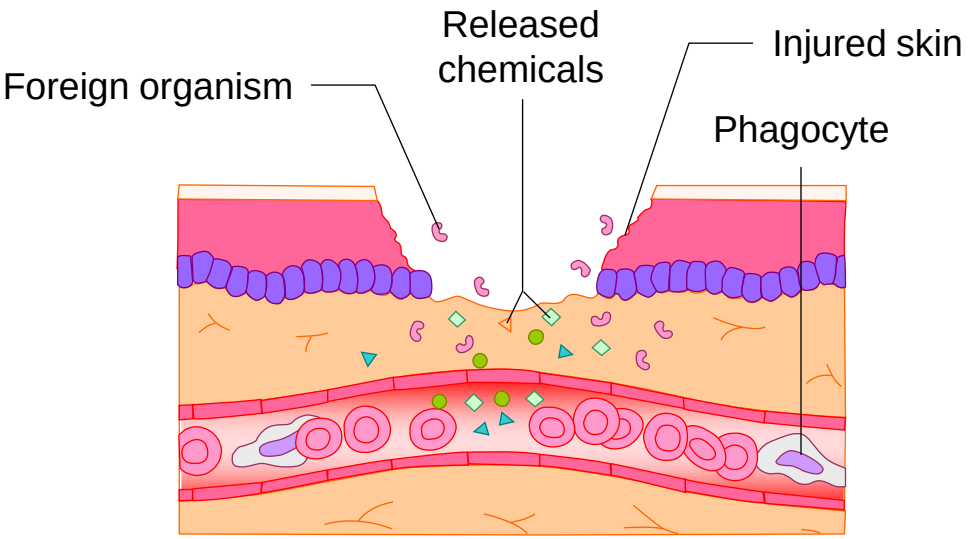


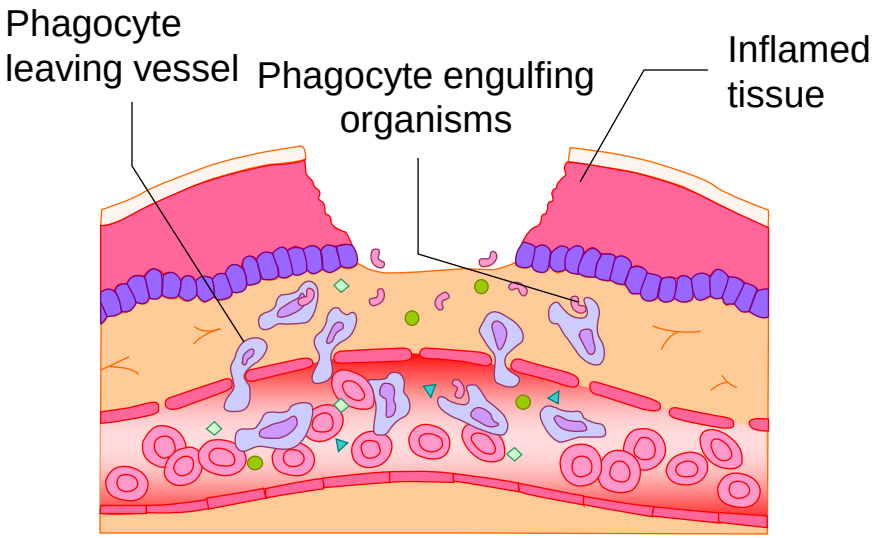
EPITHELIAL IMMUNE RESPONSE



EPITHELIUM OF RESPIRATORY PASSAGES

EPITHELIAL INFLAMMATORY RESPONSE



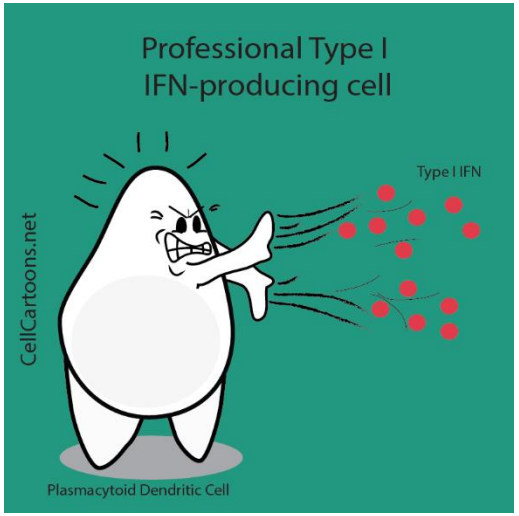


- Chemotaxis and extravasation of leukocytes, mostly neutrophils, monocytes and dendritic cells to the site of inflammation

- Pro-inflammatory cytokines
- interleukins (e.g. IL-1, IL-8)
- TNFa, TGFb
- interferons

- Other signaling molecules
- prostaglandins
- GM-CSF, M-CSF

and many others



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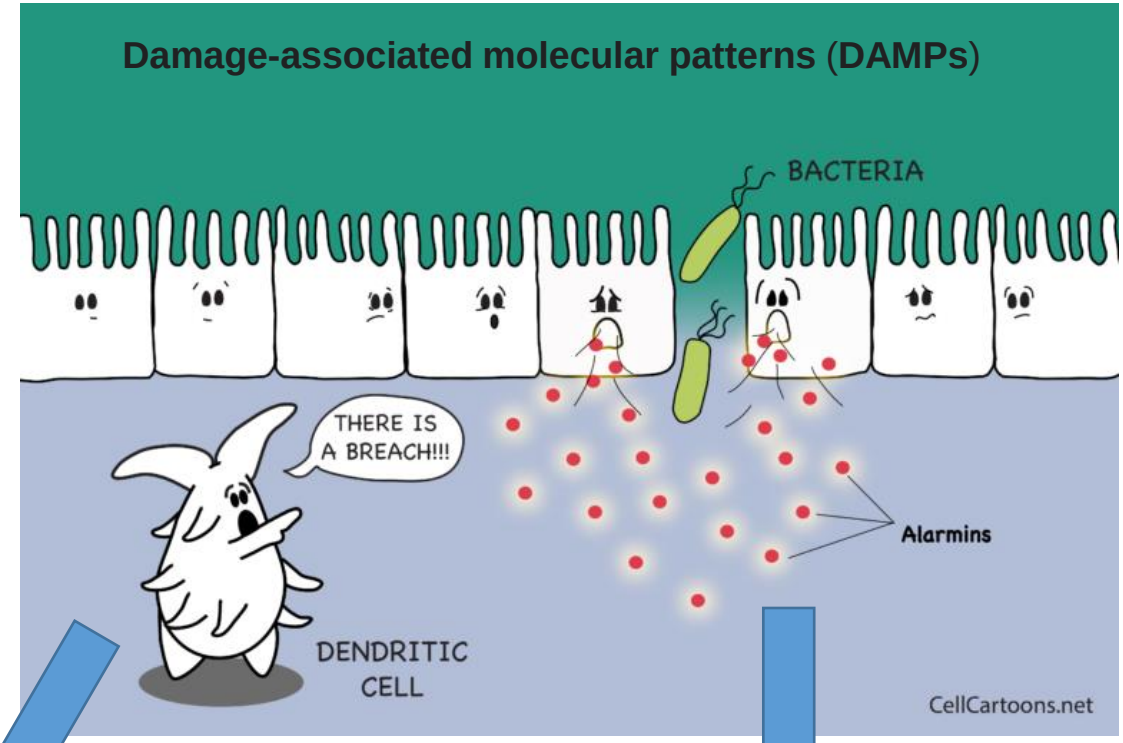
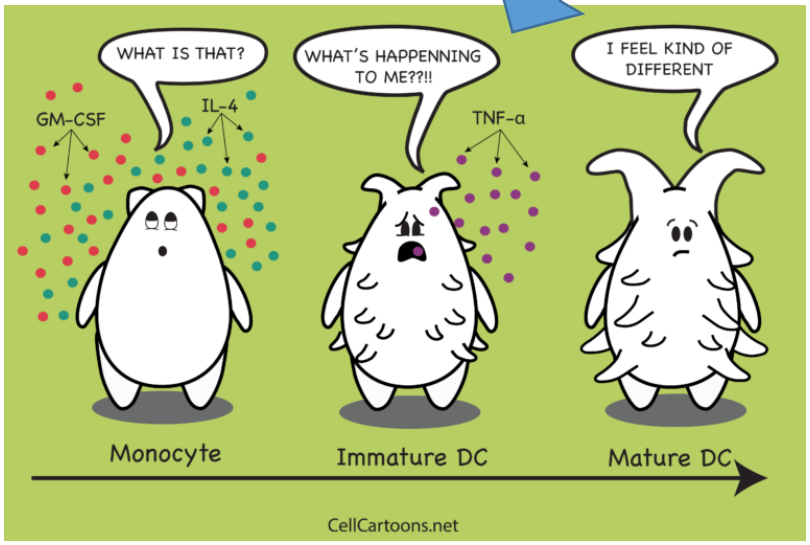
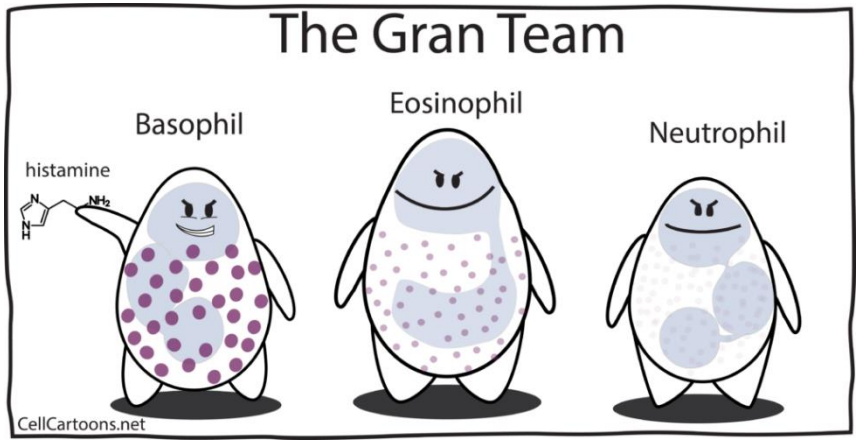
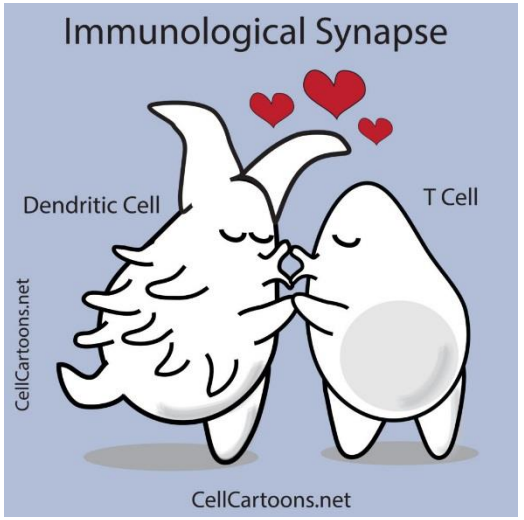




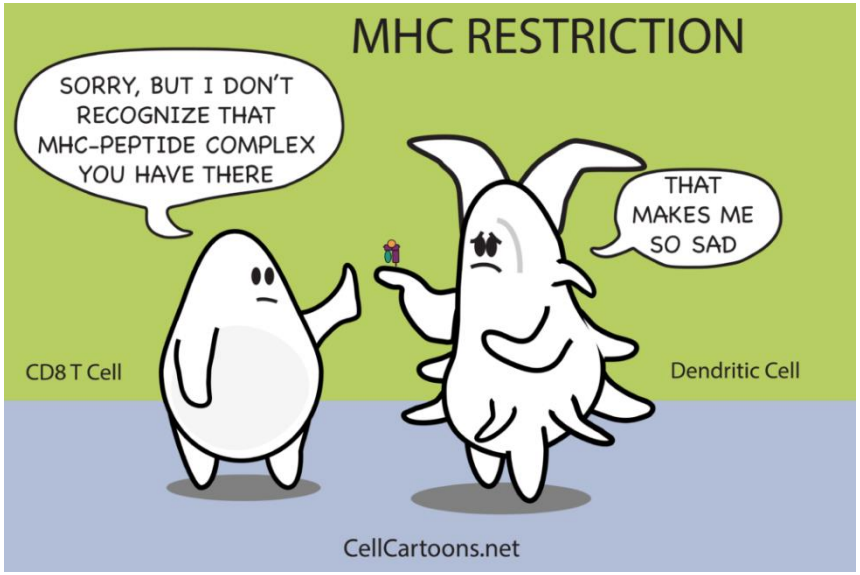


DENDRITIC CELLS

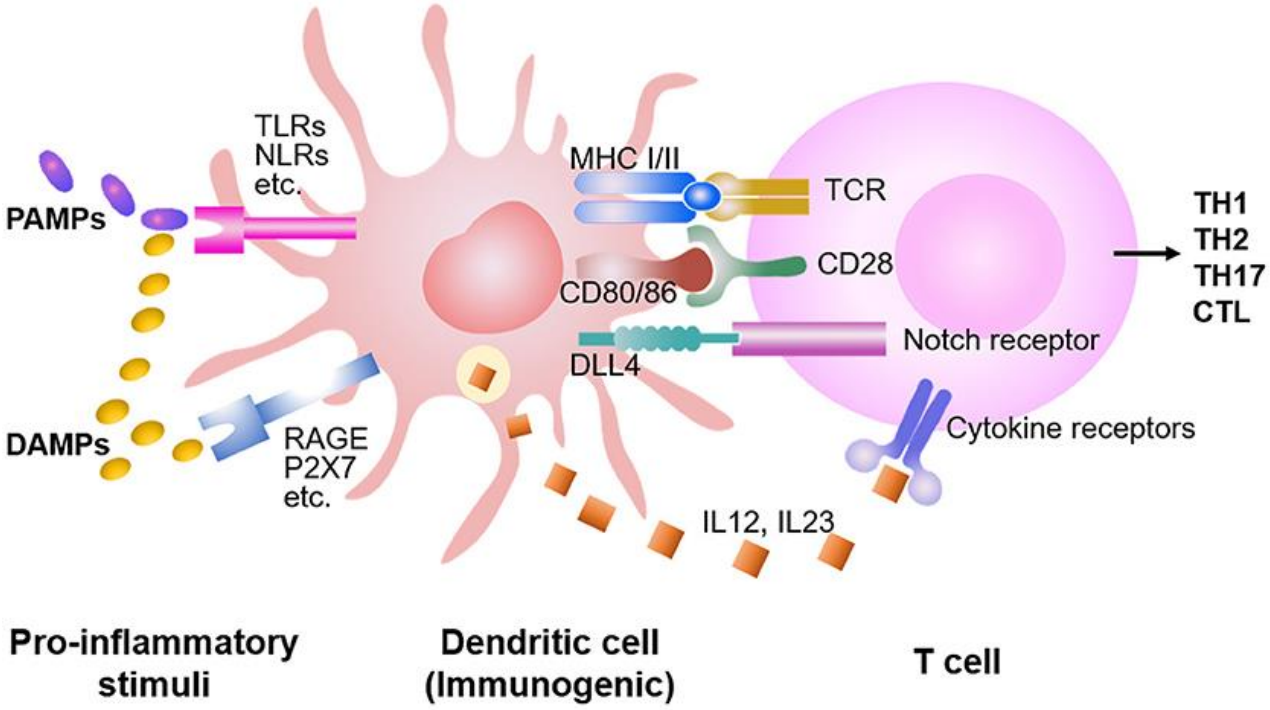
- „professional“ antigen presentation = activation of immune cells with high efficiency
- antigen processing – MHC II
- cytokine production
- component of monocyte-macrophage system
- lymphatic organs, epithelia, connective tissue



- **TCR** recognizing antigen presented in **MHC complex** is eesential for activation of **T-cells**
- **Highly regulated mechanism**
- **MHC restriction**



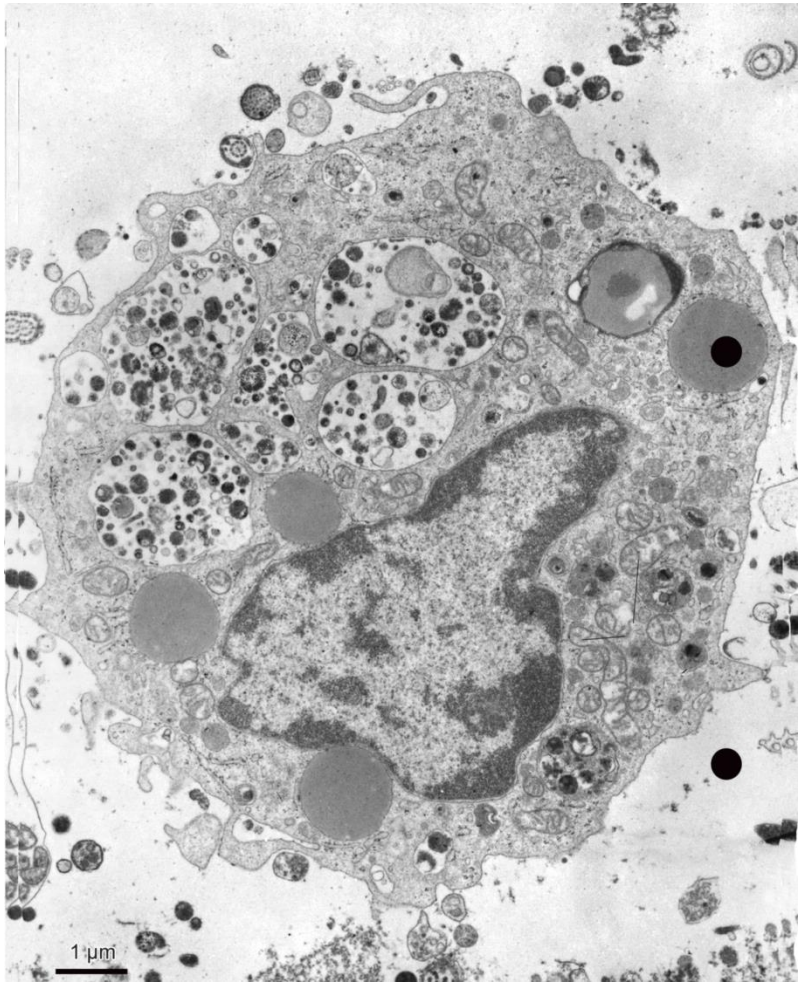
DENDRITIC CELLS



https://doi.org/10.3389/fimmu.2019.00093

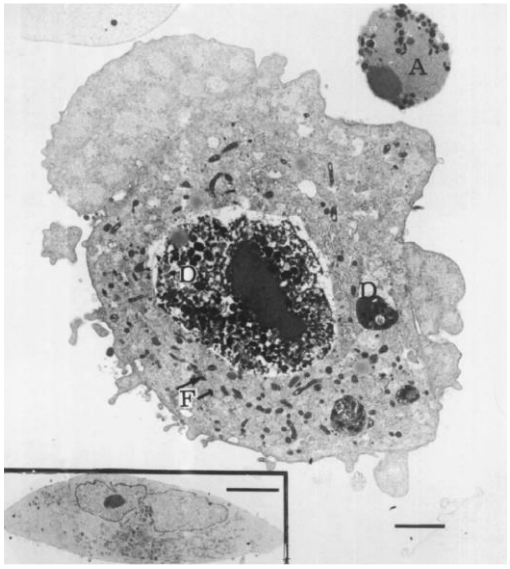
MONOCYTE-MACROPHAGE SYSTEM

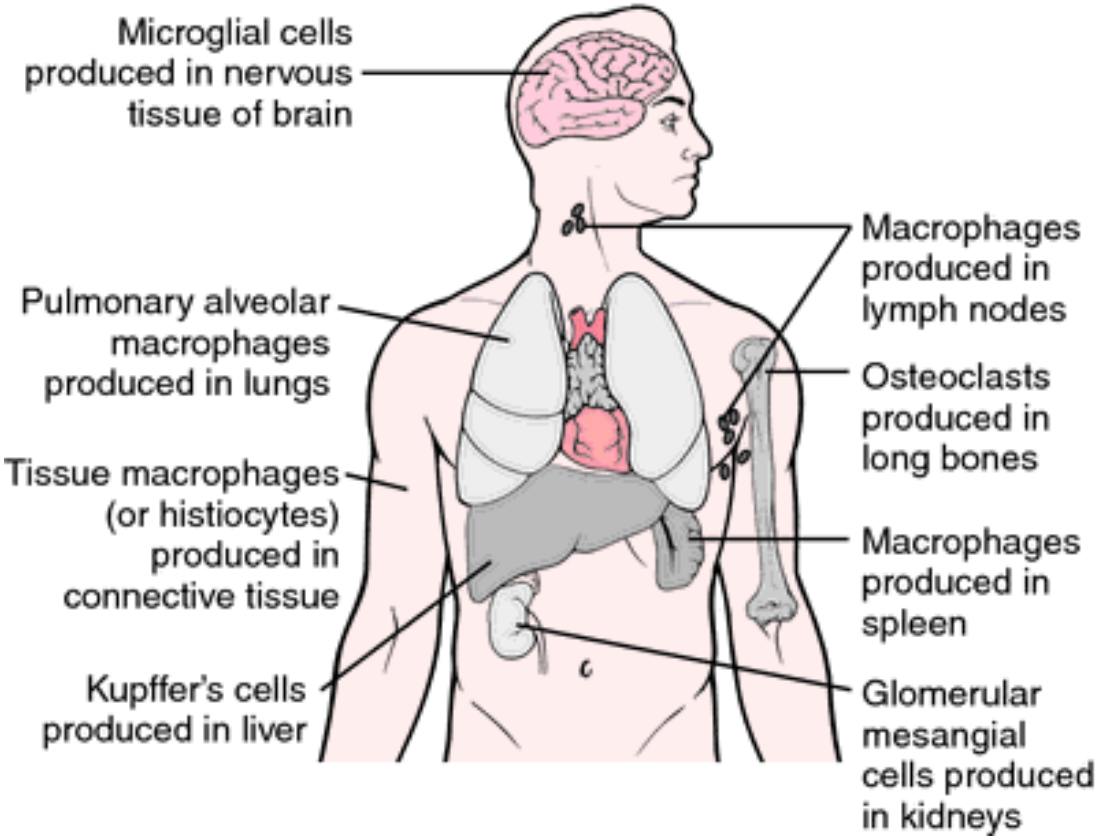
- mononuclear phagocytic system, reticuloendothelial system
- originate in bone marrow: monoblasts → monocytes
- after extravasation → macrophages
- irregular surface (hallmark of phagocytosis)
- numerous lysosomes
- Golgi apparatus and rER
- long-living cells (months)
- phagocytosis (large particles)



MONOCYTE-MACROPHAGE SYSTEM

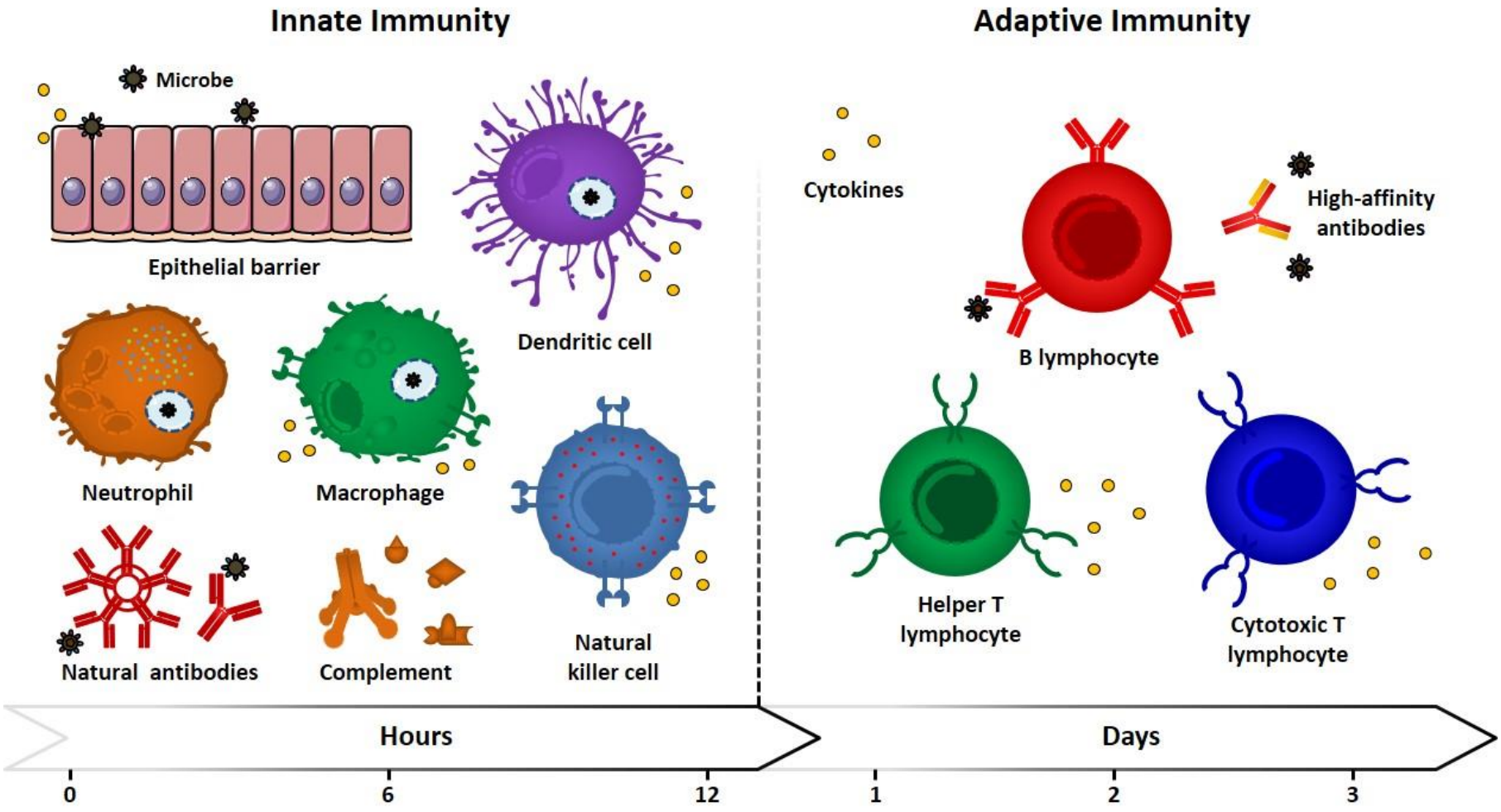
- monocytes (circulation)
- macrophages (histiocytes) of c.t.
- Kupffer cells (liver)
- osteoclasts (bones)
- microglia (CNS)
- alveolar macrophages (lungs)
- macrophages and dendritic cells (lymphatic organs, epithelia, c.t.)
- Langerhans cells (skin)
- mesangial cells (kidney)



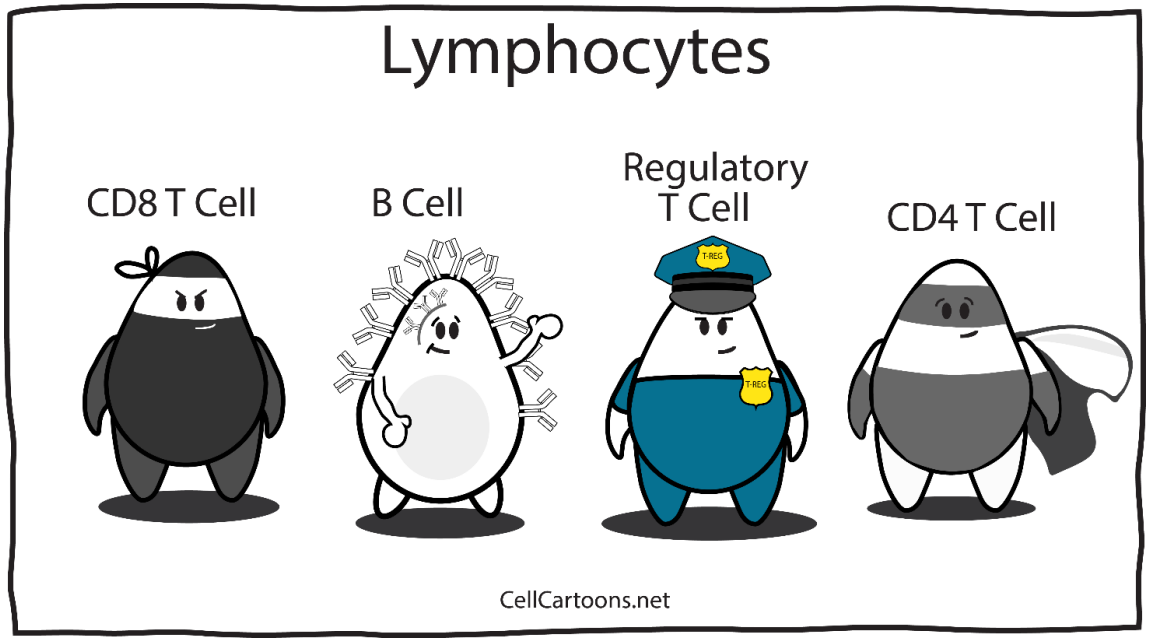


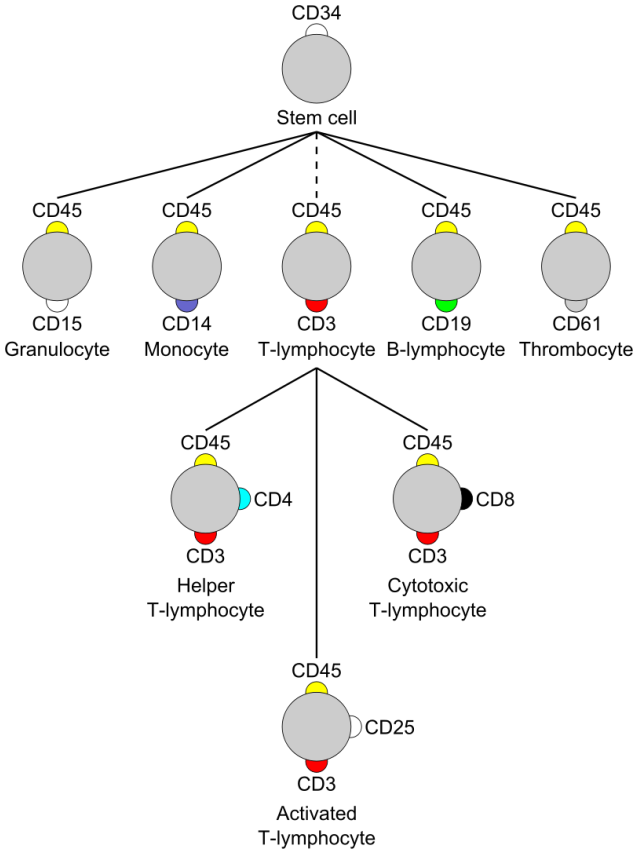
DOI: 10.1038/ki.1992.369

INNATE AND ACQUIRED IMMUNITY



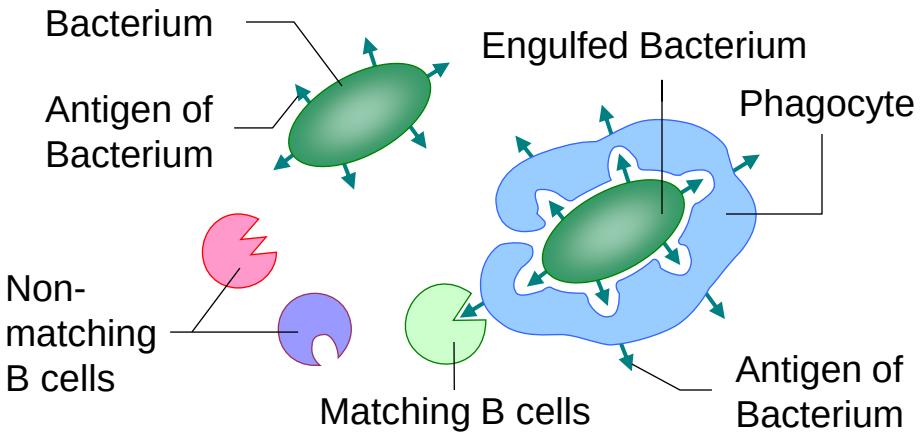
LYMPHOCYTES





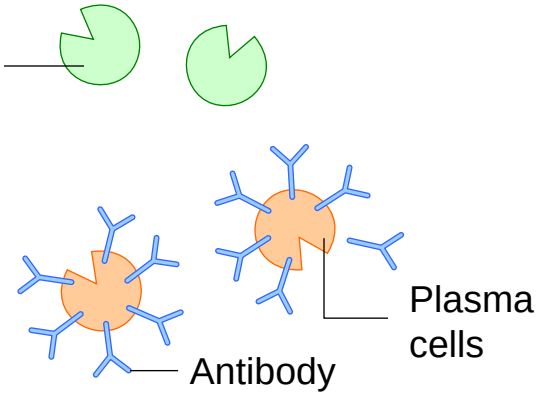
- „Clusters of differentiation“, CD
- Surface molecules constituting immunophenotype
- Molecular signaling regulating immune response
- Clinically relevant in diagnostics and therapy

ANTIBODY (HUMORAL) RESPONSE

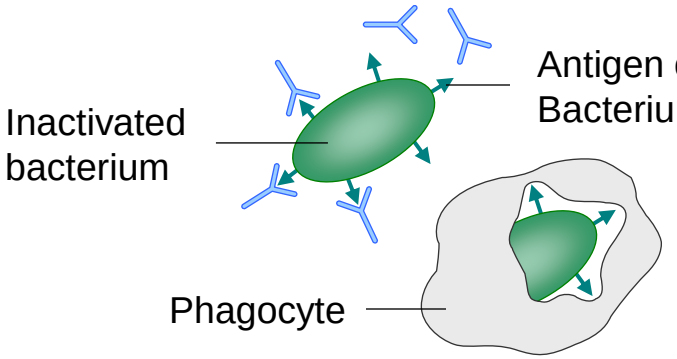


1. Antigen presentation and activation of B-cells

Memory B cell
Second exposure to the same bacteria activates this cell to rapidly produce plasma cells

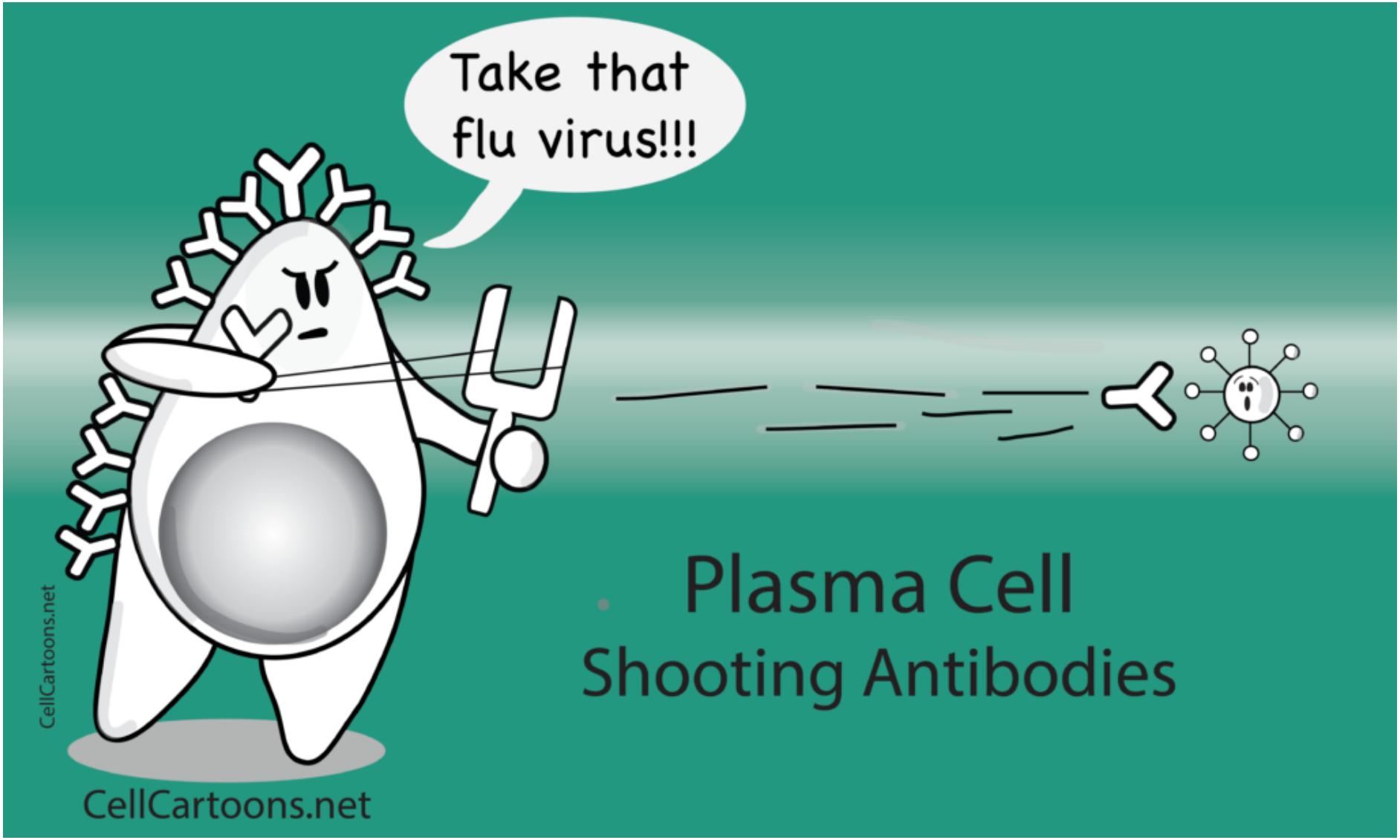


2. Activated B-cells proliferate and expand



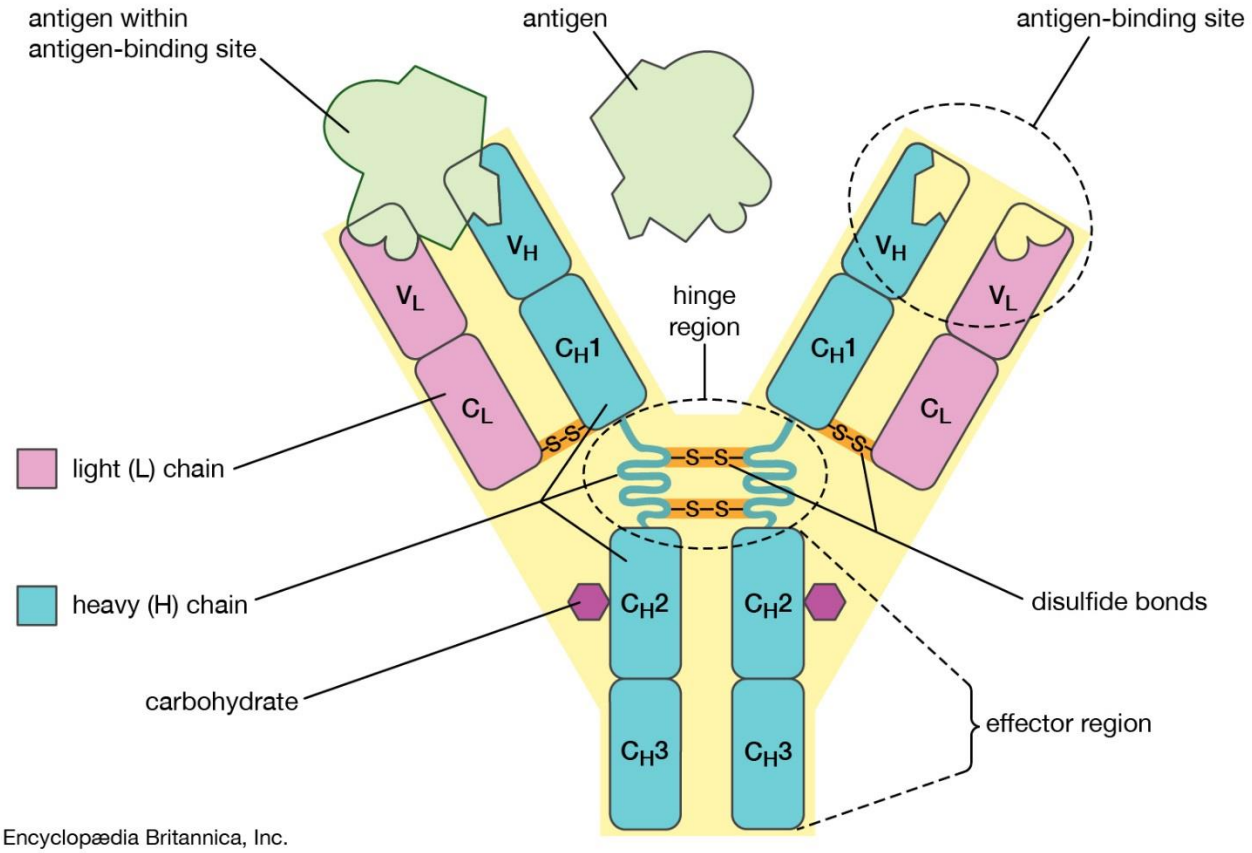
3. Most of B-cells differentiate to plasma cells, some will convert to memory cells

ANTIBODY (HUMORAL) RESPONSE



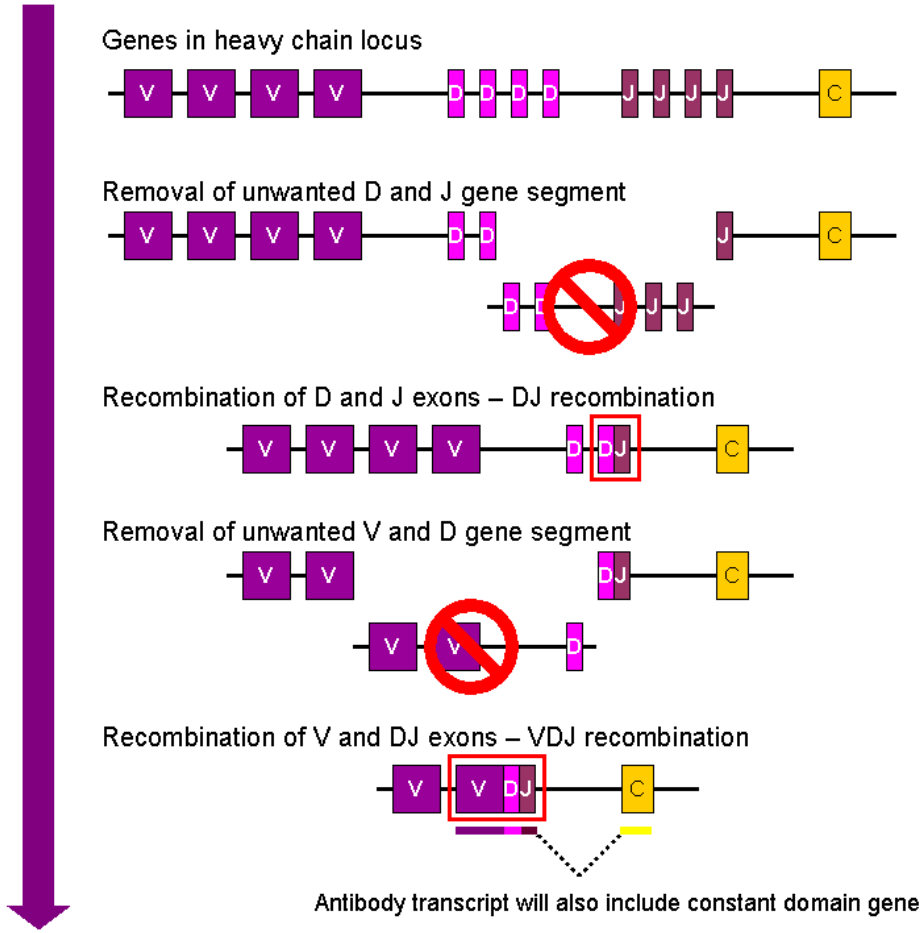
ANTIBODIES

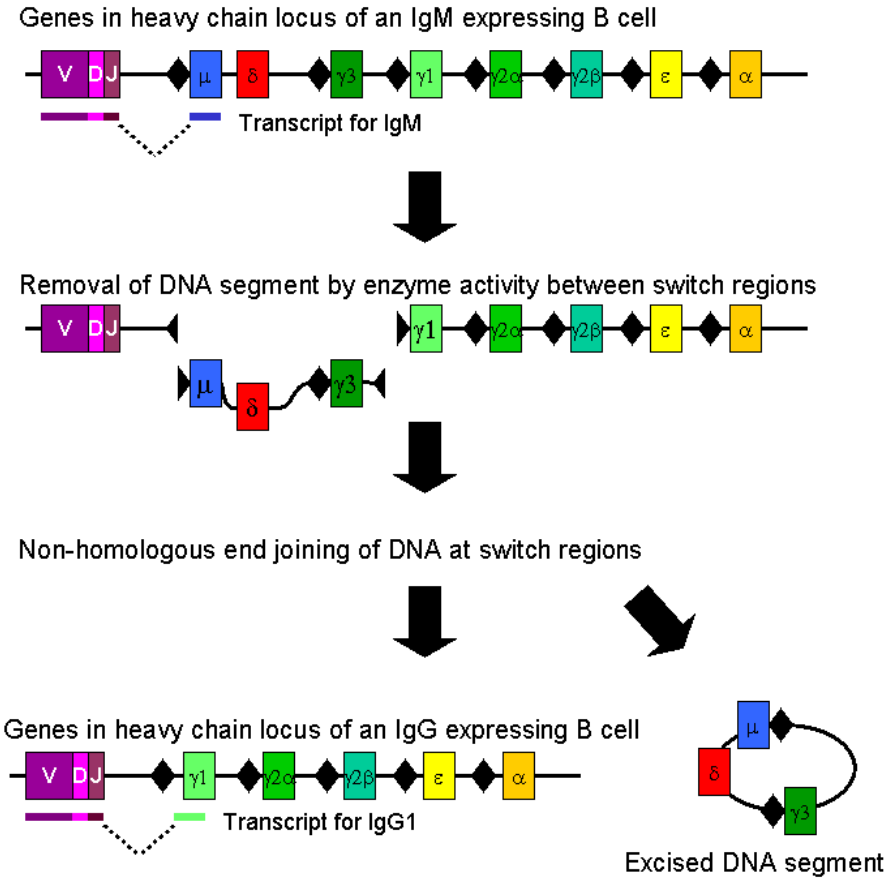
- Immunoglobulins
- Large proteins with defined structure capable of binding antigens
- Variable and constant regions
- Fc region bound by Fc receptor on immune cells



ANTIBODIES

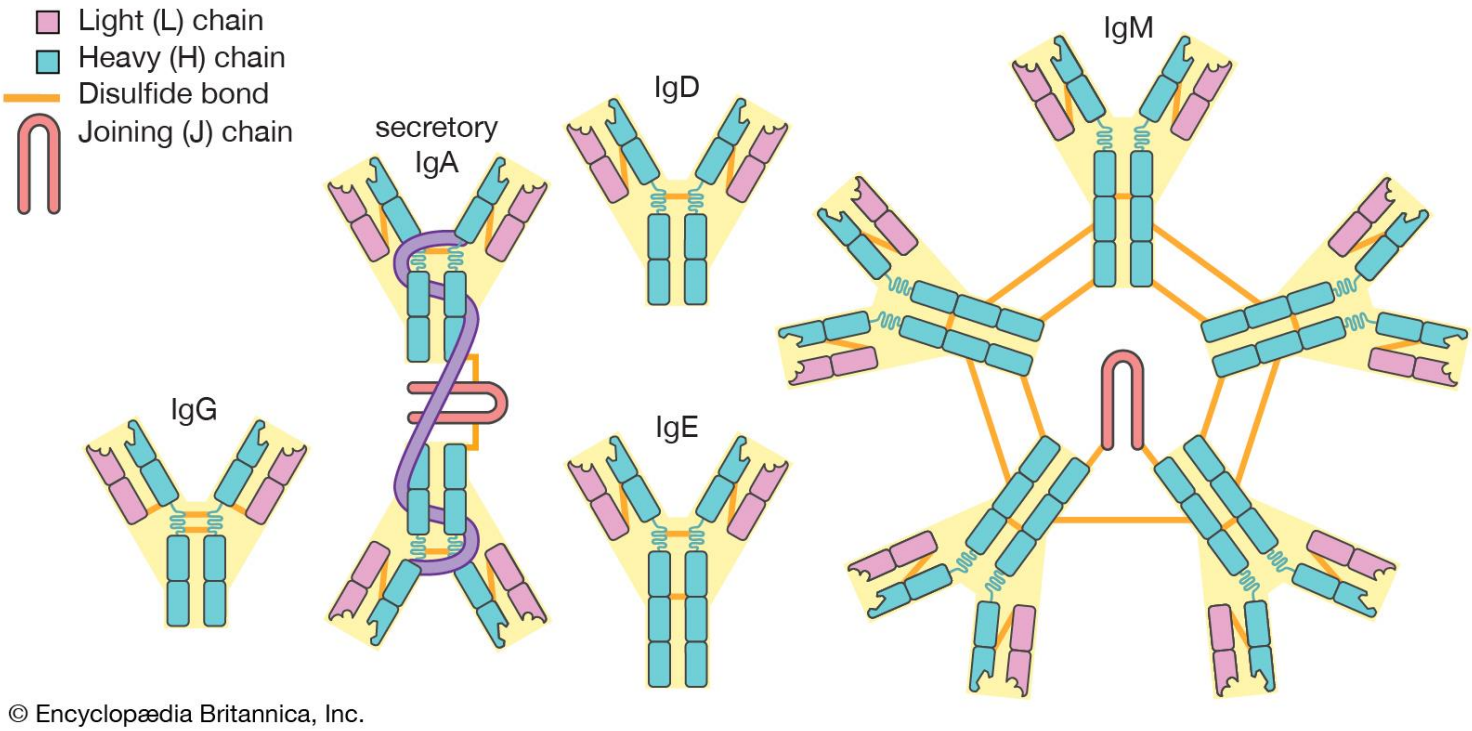
- Genome rearrangements leading to generation of unique antibody transcripts (>**10 billions**)
- V(D)J recombination during development
- Isotype switching





ANTIBODIES

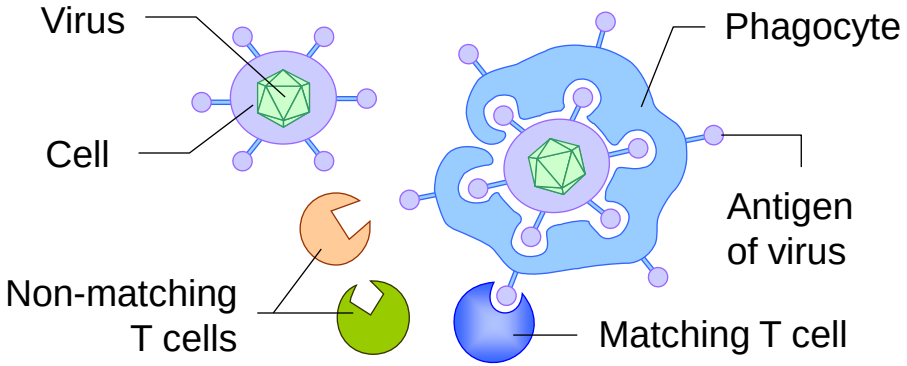
- Five principal classes
  - IgG: most common (>75%), soluble, stable
  - IgA: in exocrine secretions, mucosa
  - IgM: natural immunity, activator of complement
  - IgE: activator of mast cells
  - IgD: B-cells activators



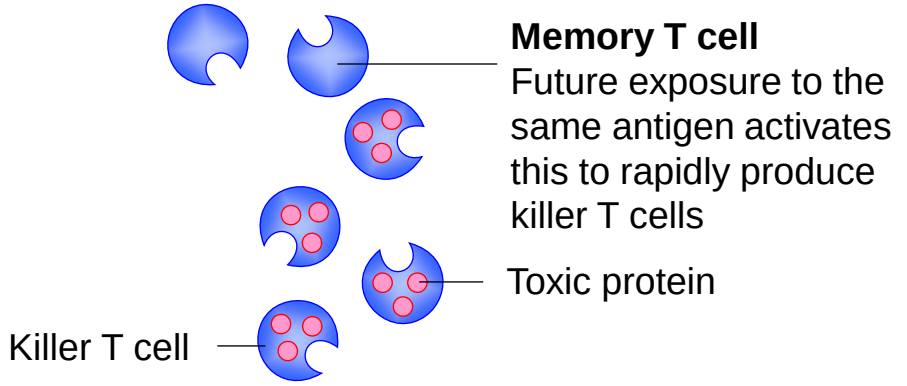
ANTIBODIES

- IgE: activator of mast cells

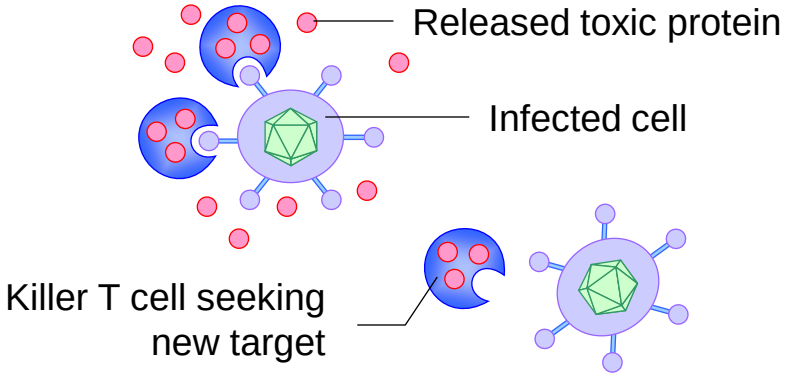
CELLULAR RESPONSE



1. Antigen presentation and activation of T-cells

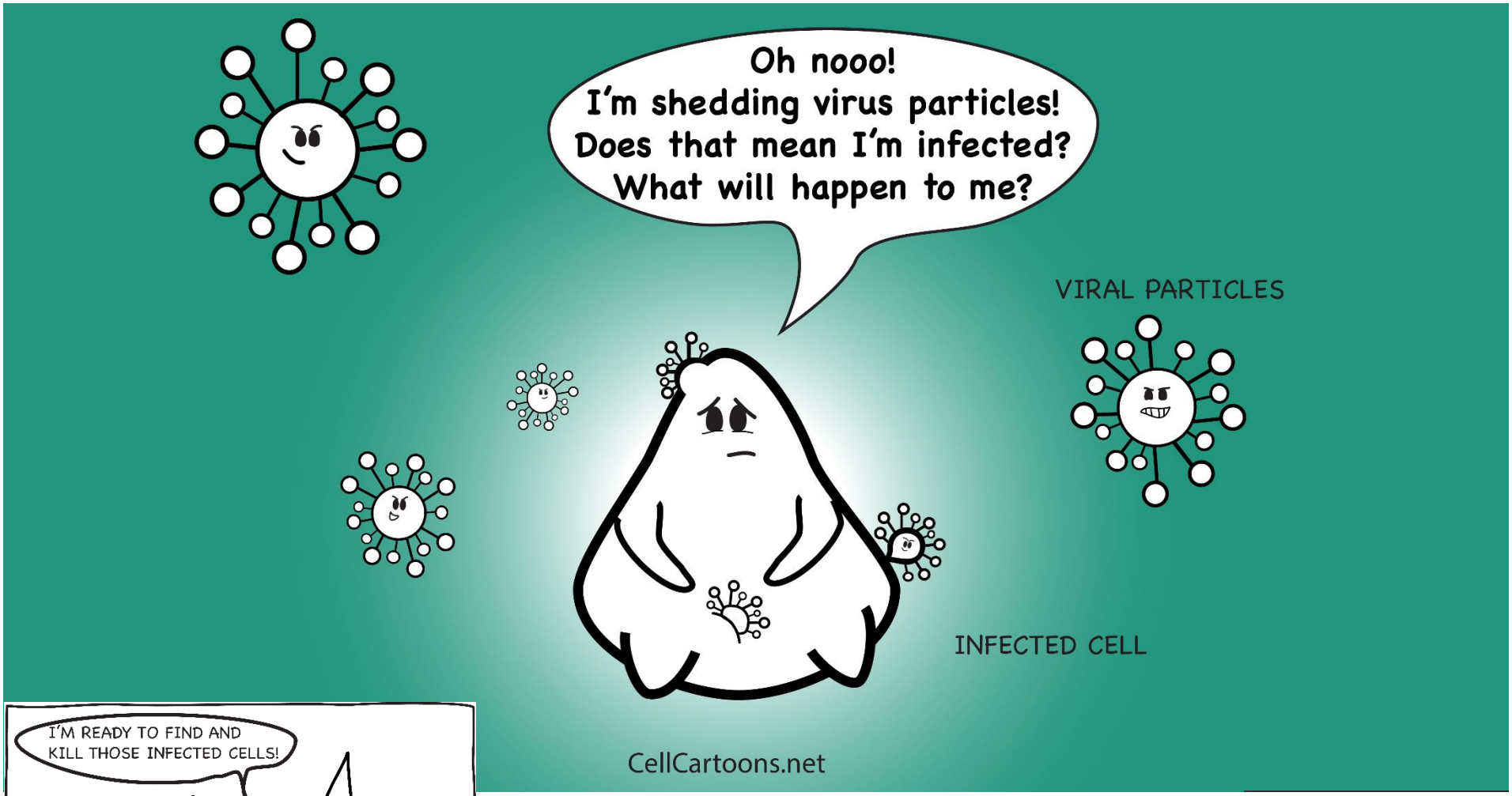


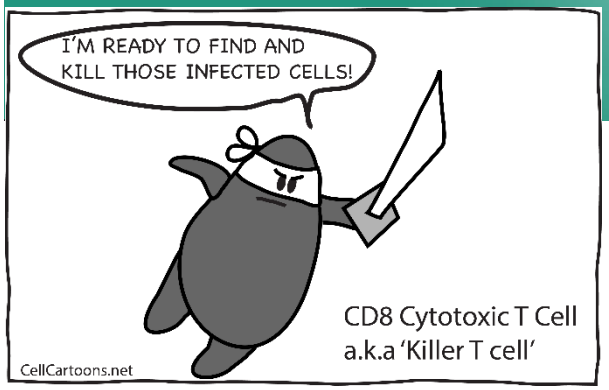
2. T-cells differentiate to cytoxic Tc cells, memory t cells or regulatory cells



3. Cytotoxic Tc eliminate abnormal cells

CELLULAR RESPONSE

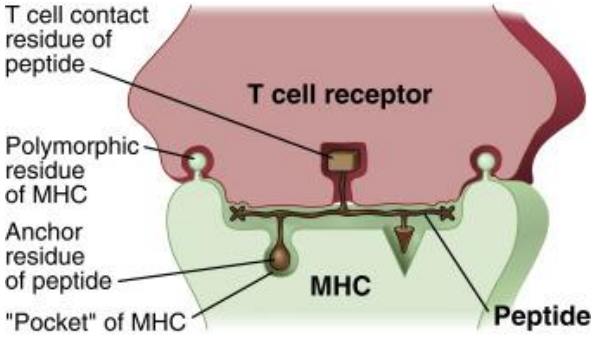


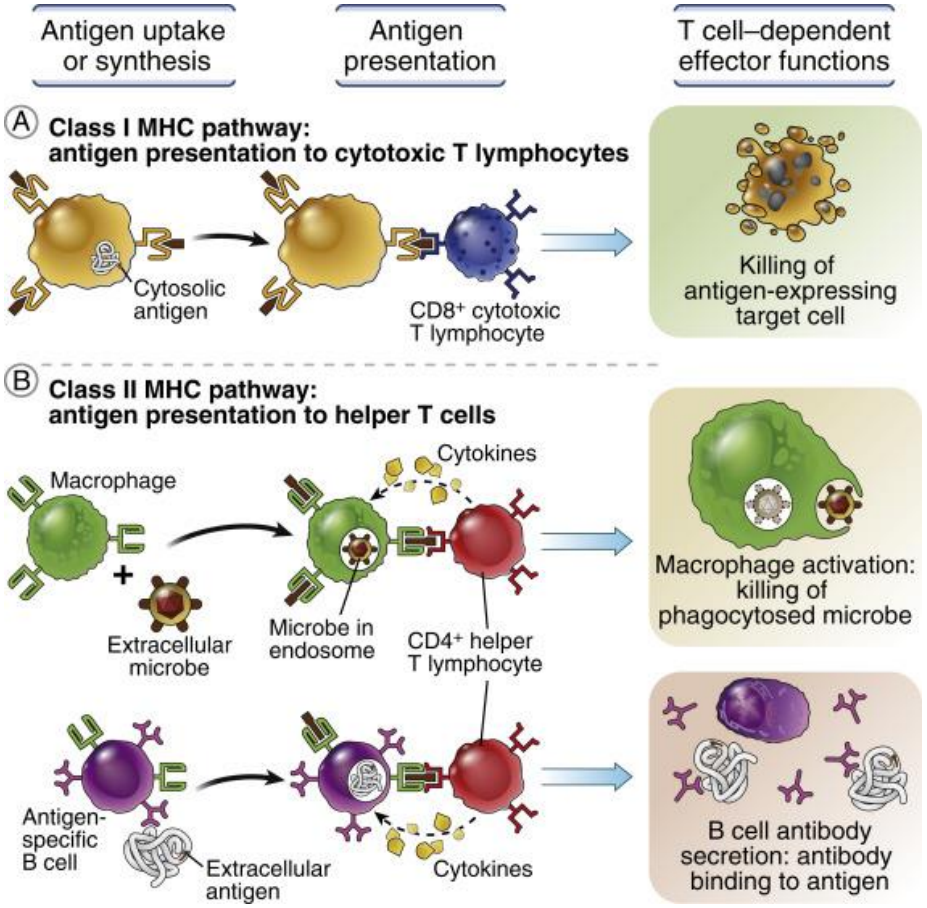


MHC PROTEINS

- Major histocompatibility complex
- Activation or attenuation of T-cell response
- Peptide display

- MHC I: all nucleated cells and platelets
- MHC II: antigen presenting cells
- (MHC III: structurally similar ti MHC I and II, but with rather unknown function in immune respone)





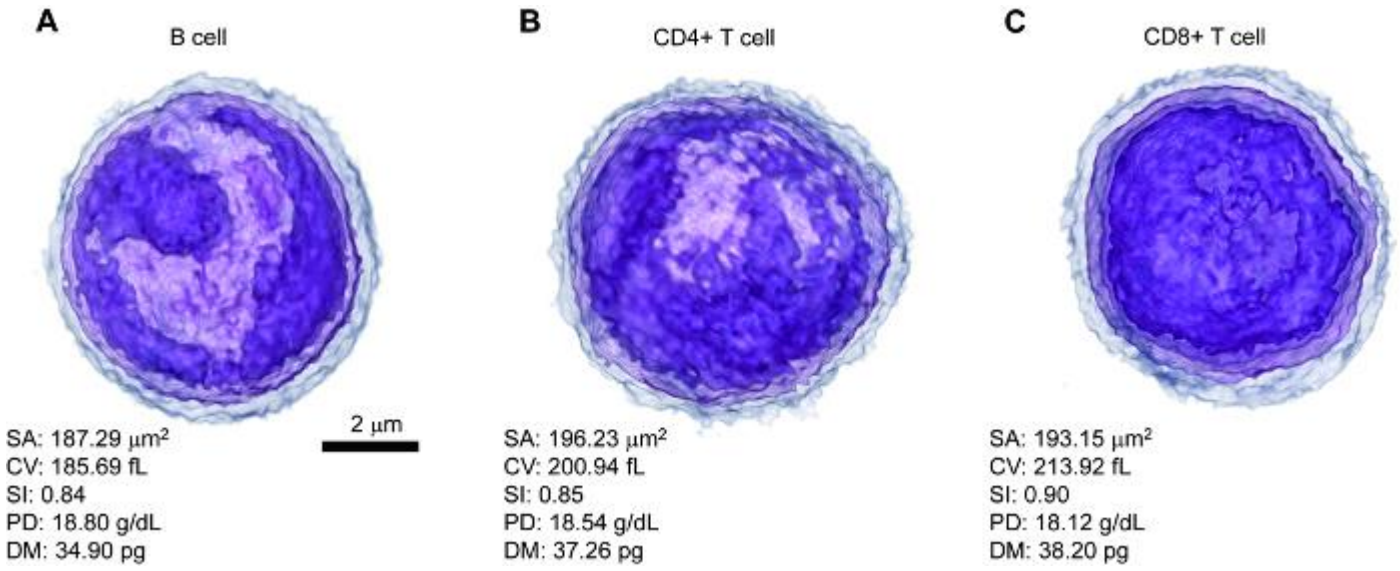
B- AND T- LYMPHOCYTES IN HUMAN BODY

T-lymphocytes

- paracortical zone of lymph nodes
- white pulp of spleen (periarteriolar lymphatic sheath, PALS)
- interfollicular regions in other lymphatic organs (tonsils)

B-lymphocytes

- lymphatic follicles and medullary cords of lymph nodes
- spleen follicles and marginal zone of white pulp
- lymphatic follicles in other organs



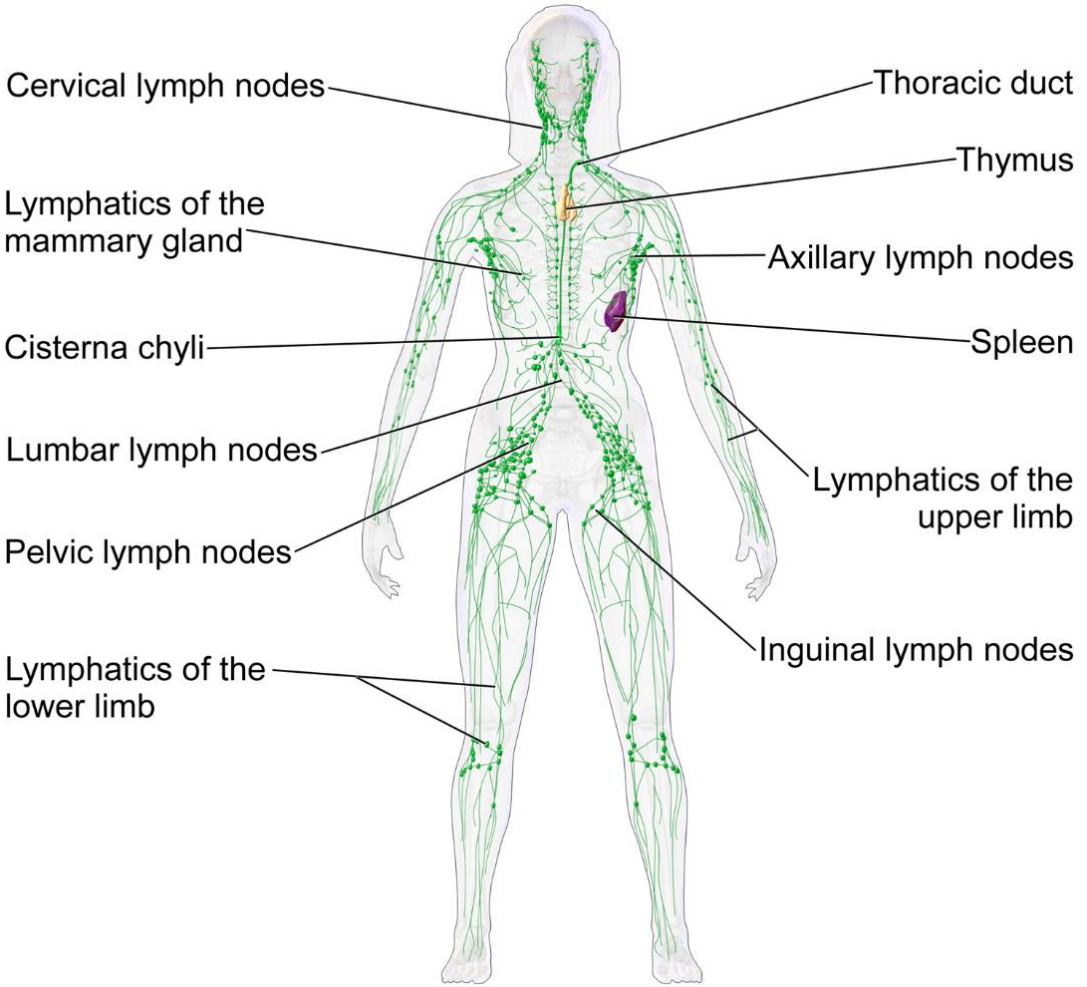
doi: 10.3791/58305

ACQUIRED IMMUNITY

Histology:

- **Leukocytes**
  - Lymphocytes
  - Antigen presenting cells

- **Lymphatic organs**



LYMPHATIC ORGANS

Development of lymphocytes and APC:

Primary lymphatic organs

- bone marrow
- thymus

Secondary lymphatic organs

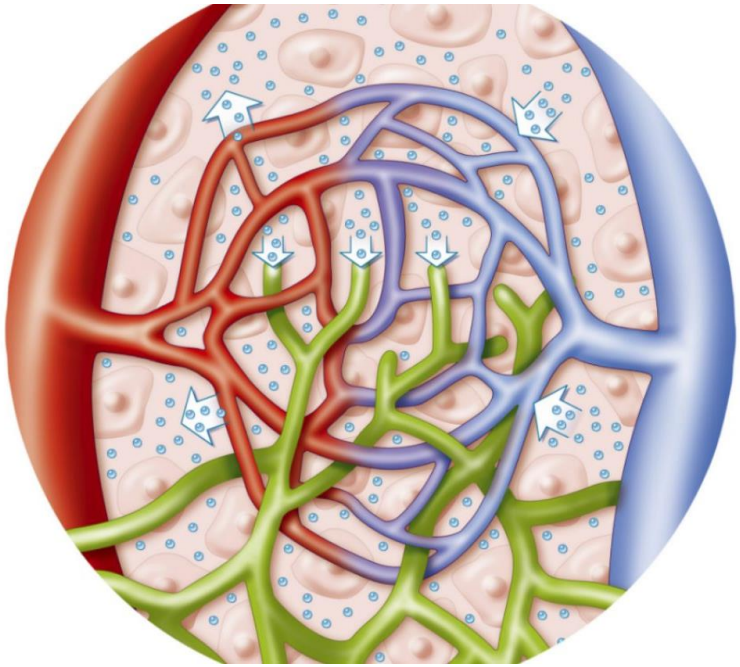
- lymph nodes
- spleen
- MALT including tonsils and appendix

Tissues

- blood
- lymph
- epithelia
- connective tissues

LYMPHATIC CIRCULATION

Lymph vessels



Histology

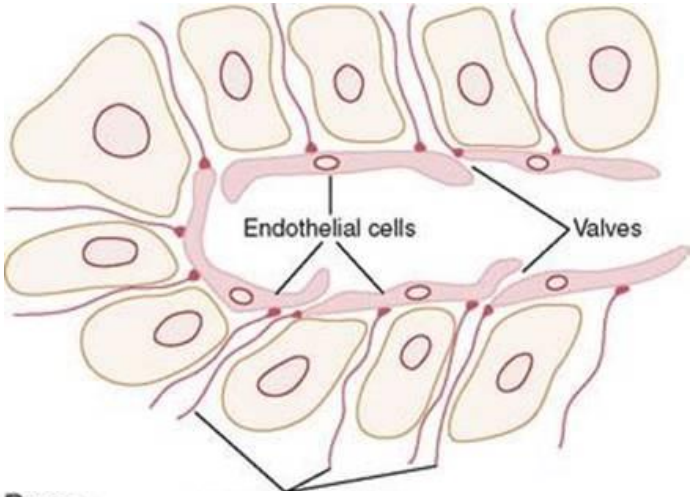
- <u>Lymph capillaries</u>
- Thin walled, blunt ended vessels with irregular lamina basalis
- Anchoring filaments, tiny valves
- <u>Lymph vessels</u>
- T. intima – endothelium and subendothelial c.t.
- T. media - few layers of smooth muscle cells
- T. adventitia - collagen c.t.
- Similar to small veins
- Valves derived from t. intima
- Open to d. thoracicus and d. lymphaticus dx. → v. subclavia (at v. jugularis int.)

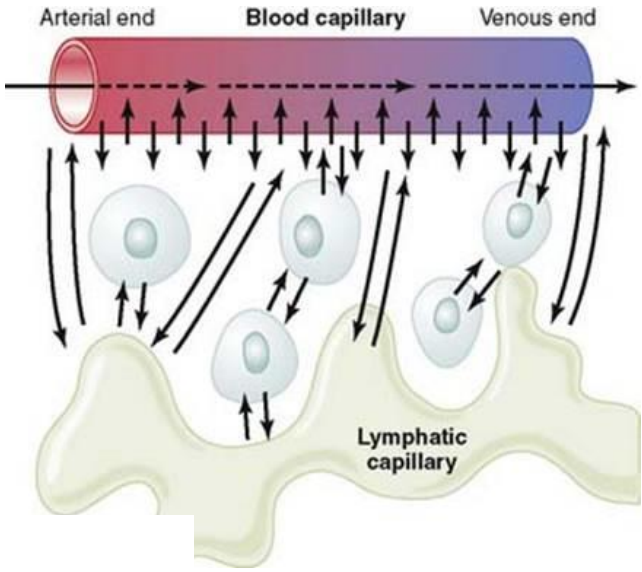
Function

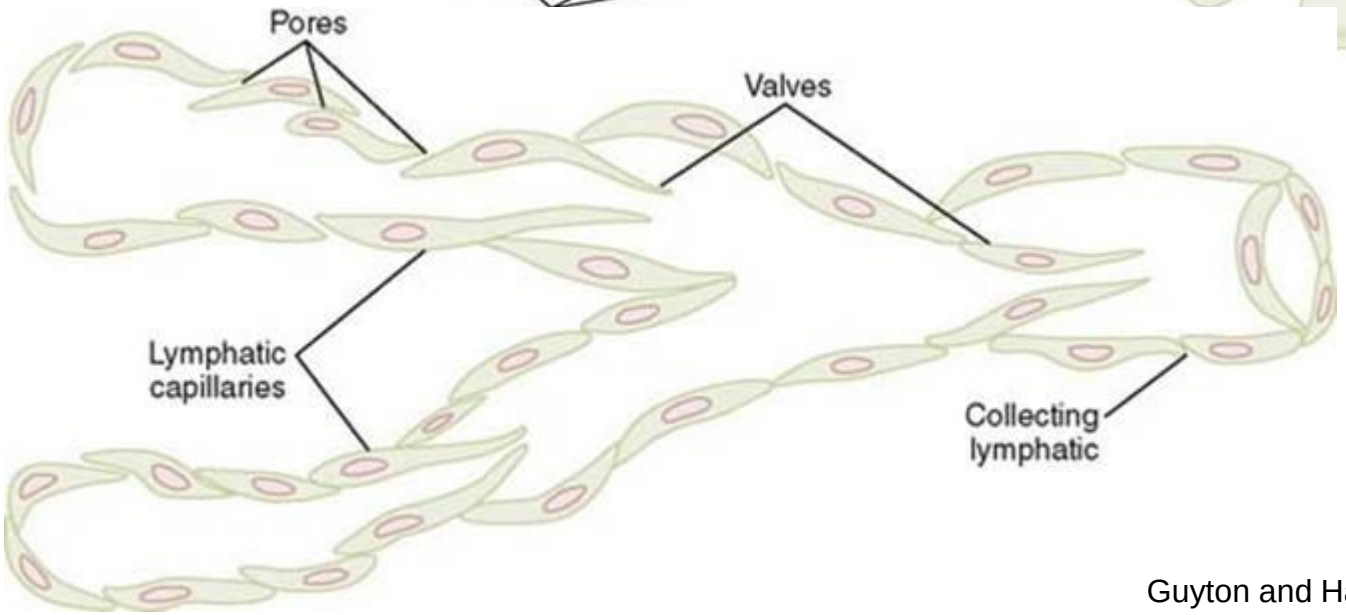
- Collect interstitial fluid
- Microenvironment for lymphocyte development and maturation
- Lipid transport (chylomicrons)

LYMPHATIC CIRCULATION

Lymph capillaries



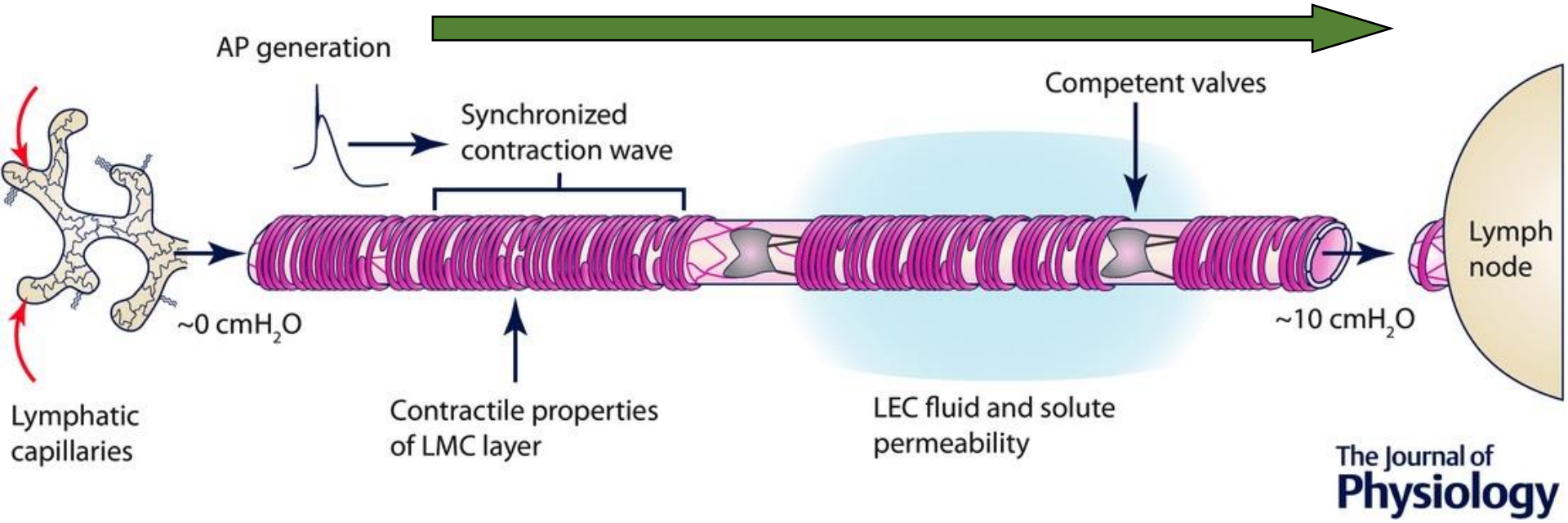




Guyton and Hall Textbook of Medical Physiology

LYMPHATIC CIRCULATION

Lymph flow is unidirectional



The Journal of Physiology

https://doi.org/10.1113/JP272088

Lymph composition

- Contains similar concentration of ions to plasma, but lower levels of proteins
- Lipid-rich lymph from intestine - chylus
- Immune cells
- Volume in the circulation ca. 1L (2-2.5L new lymph from interstitial fluid per day)

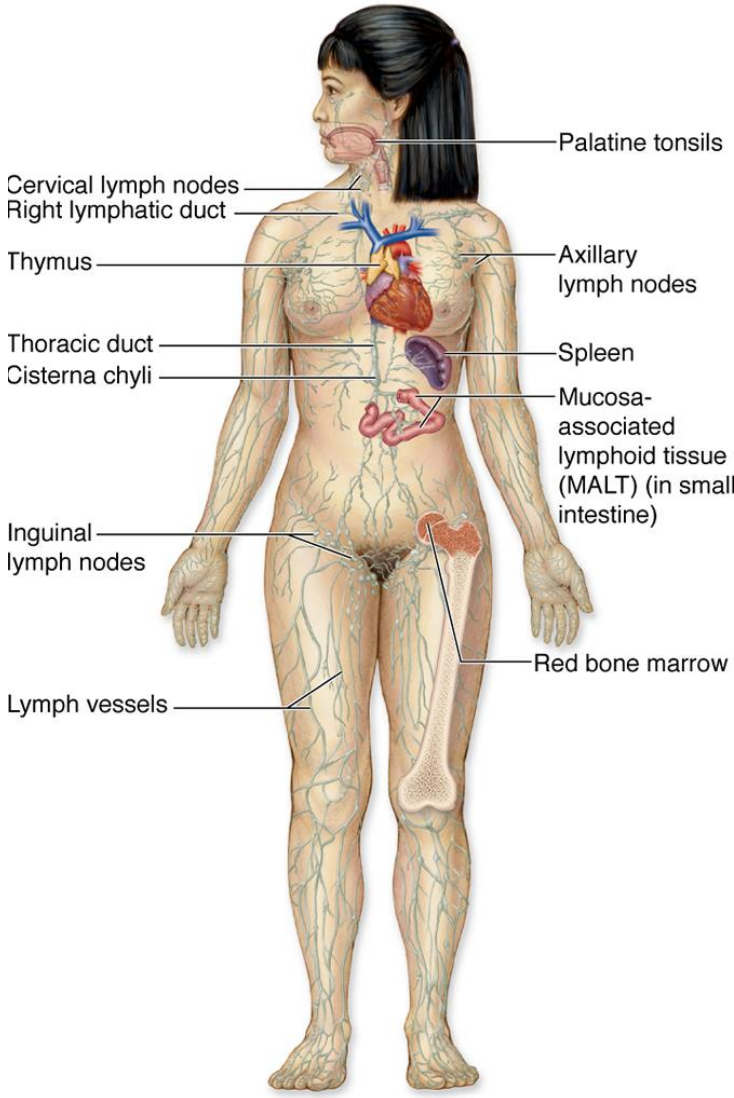
LYMPHATIC ORGANS

central:

- thymus
- bone marrow

peripheral:

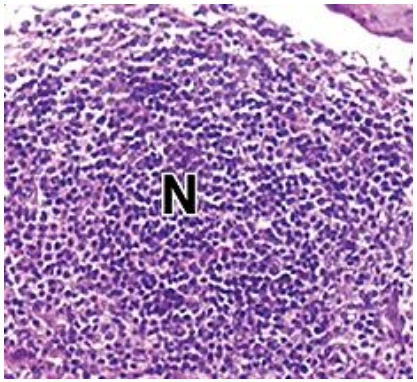
- encapsulated – lymph node, spleen
- mucosa associated lymphoid tissue – MALT
  - tonsils (partially encapsulated)
  - lymphatic follicles in mucosa of hollow organs



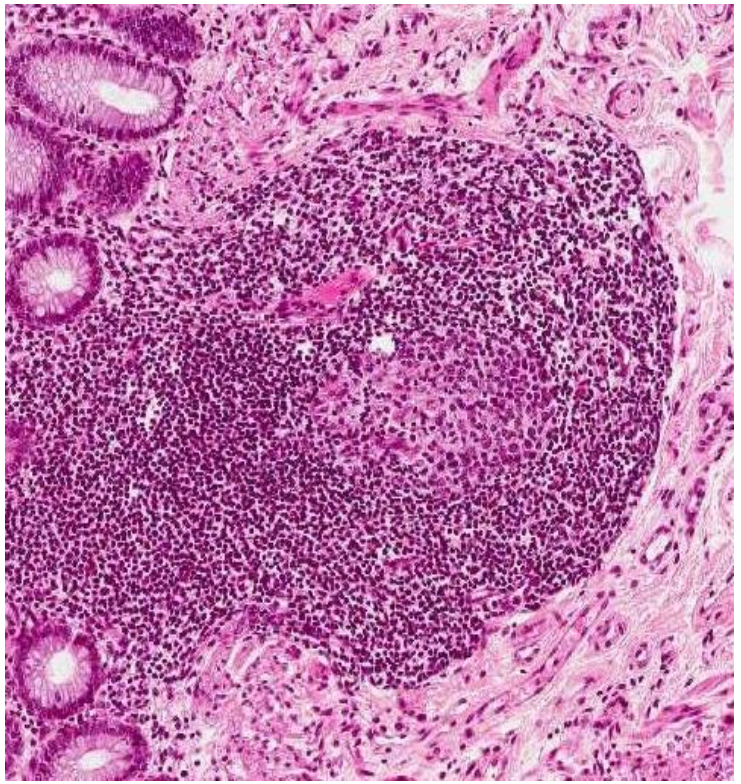
Mescher

LYMPHATIC FOLLICLE

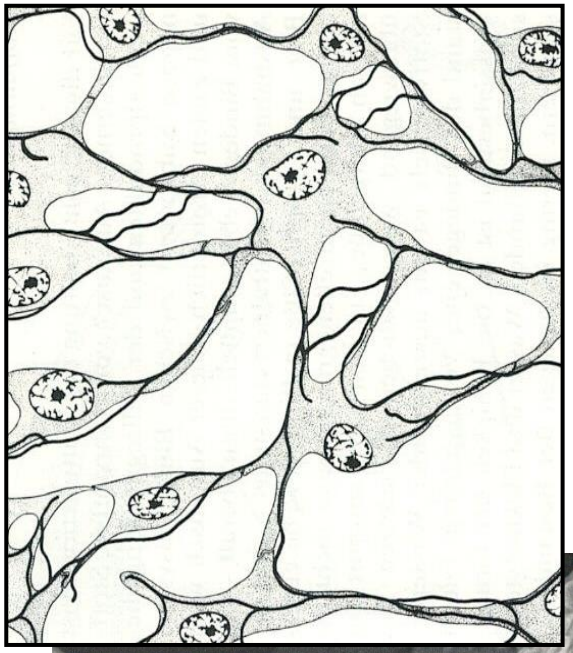
Folliculus, nodulus lymphaticus

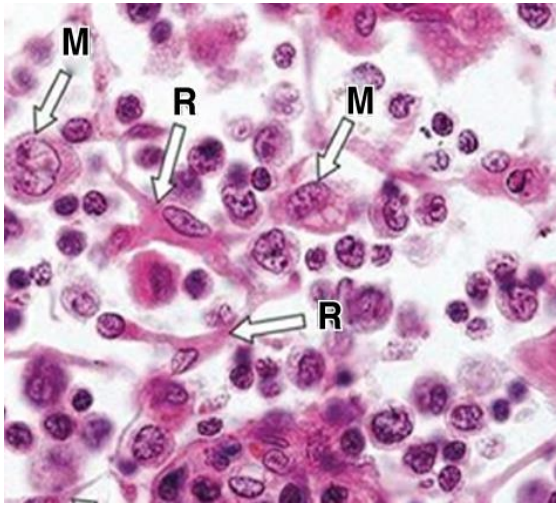


- non-encapsulated aggregates of reticular connective tissue and lymphocytes
- peripheral lymphatic organs
- mucosa of hollow organs (GIT, respiratory, urinary, reproductive system)
- **primary** – prior any contact with antigen
- **secondary** – stimulated by antigen
  - pale germinative center
  - dark mantle zone



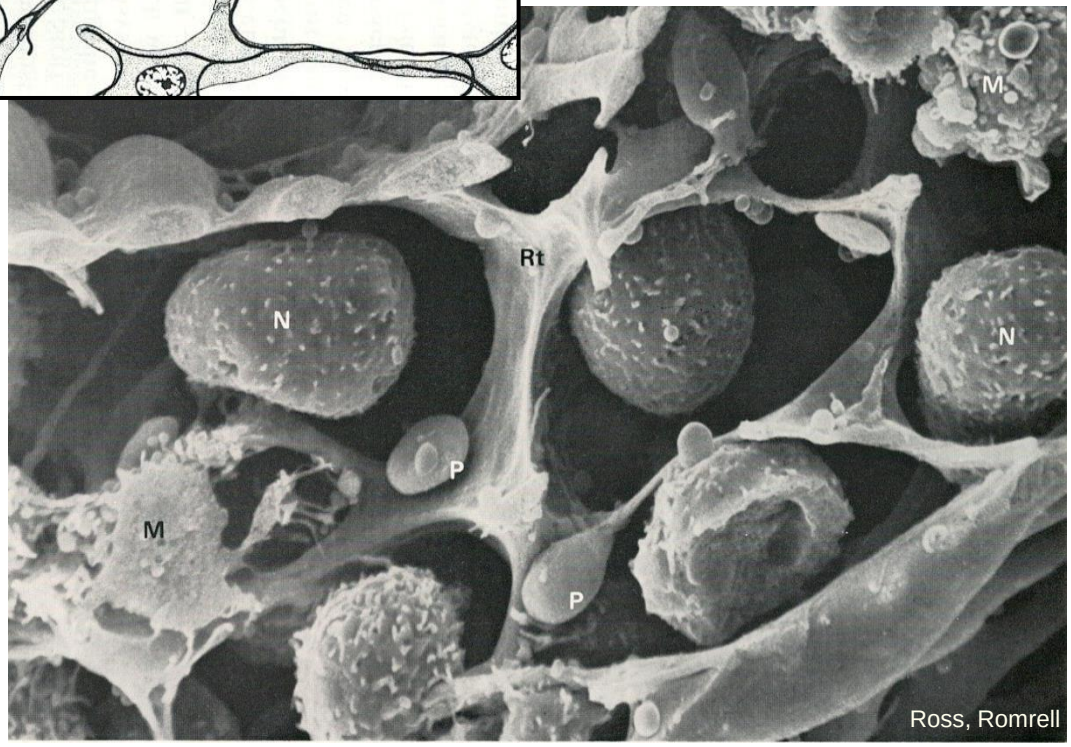
LYMPHATIC (LYMPHORETICULAR) TISSUE



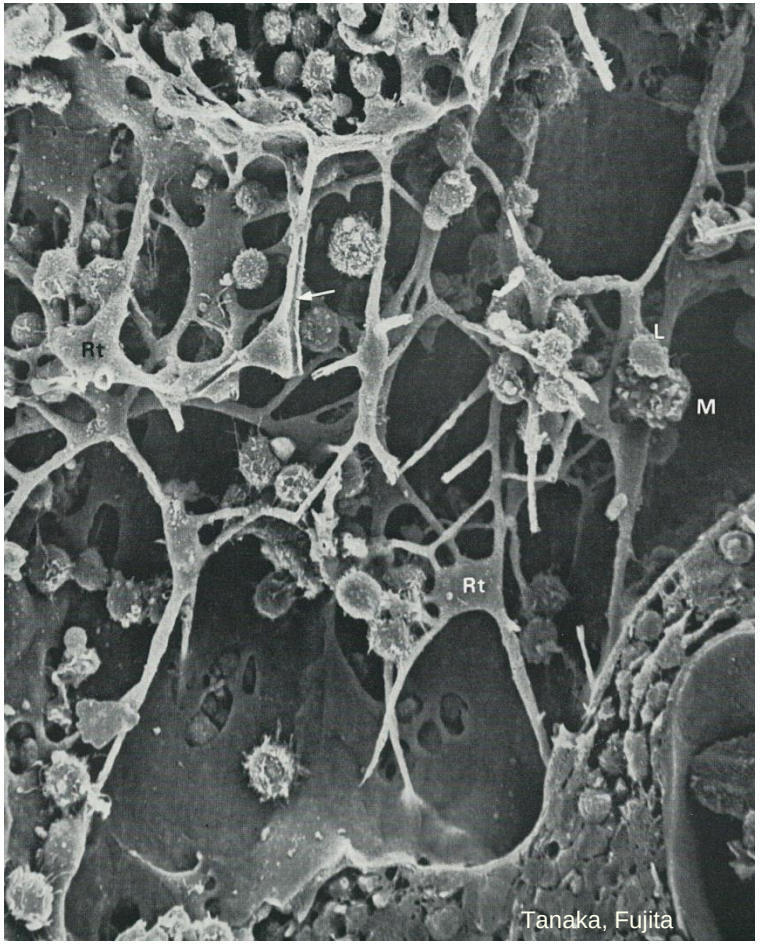


Mescher

- reticular connective tissue + lymphocytes



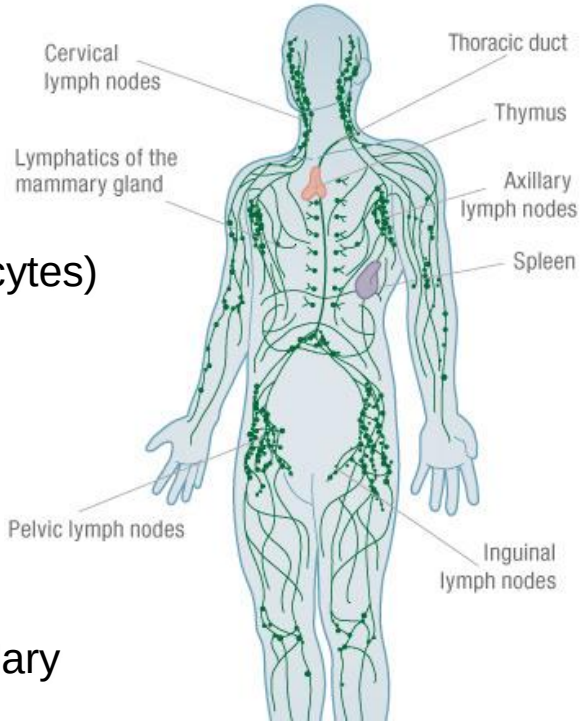
Ross, Romrell

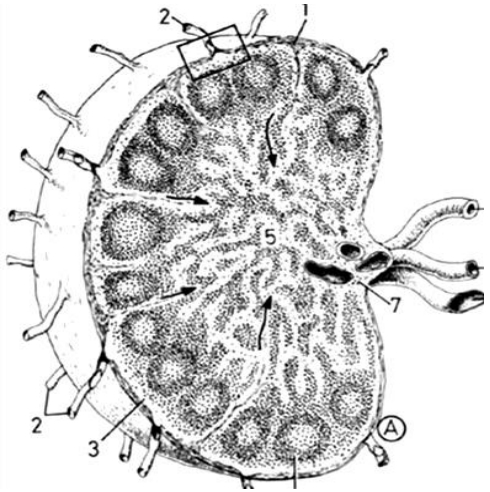


Tanaka, Fujita

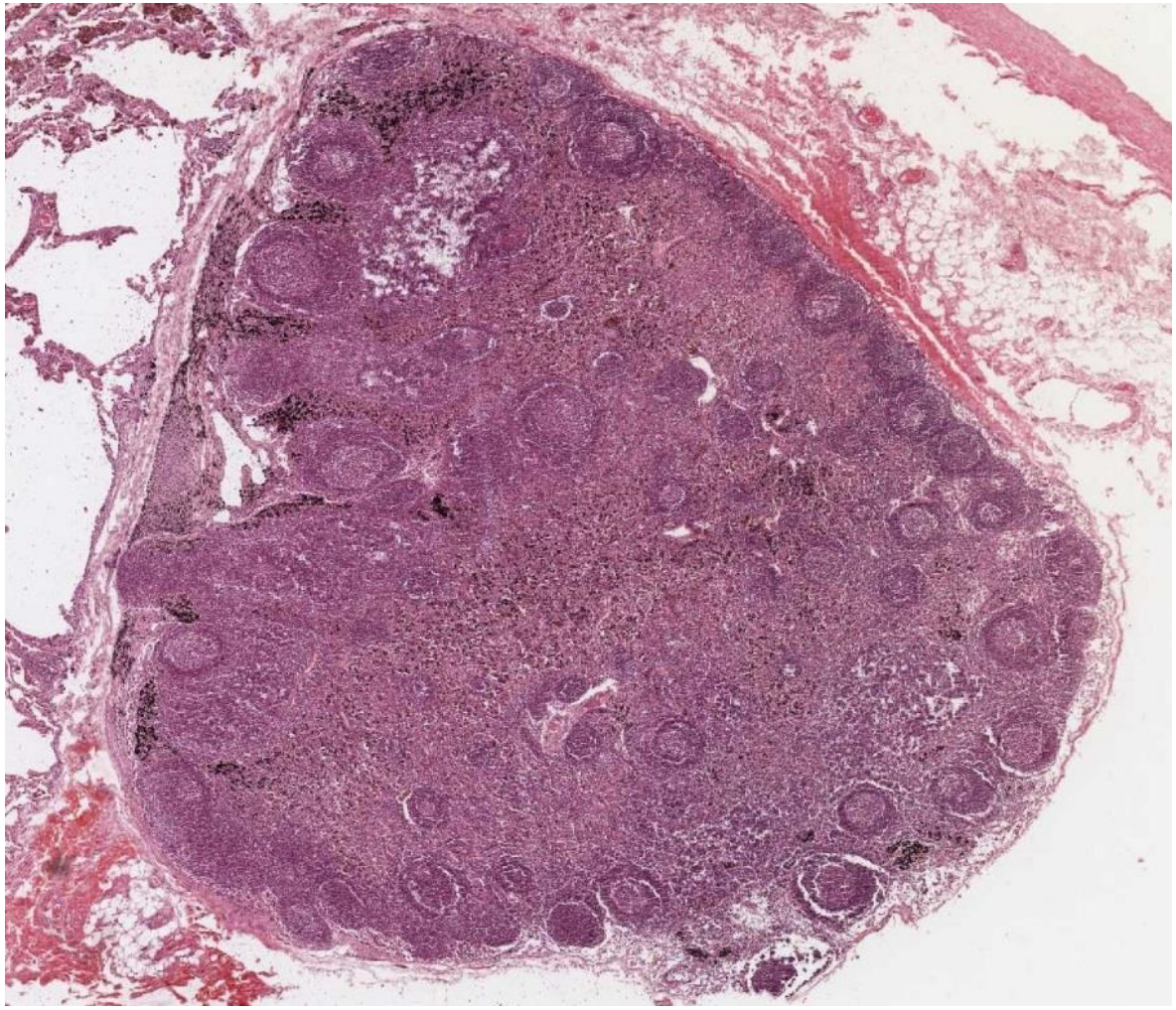
LYMPH NODE (nodus lymphaticus, lymphonodus)

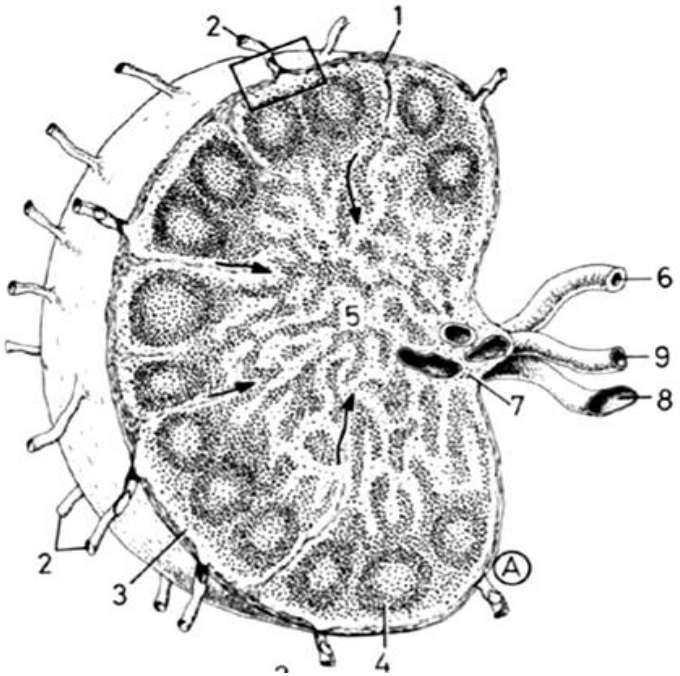
- C.t. capsule containing *hilus* with vessels
- parenchyma = lymphoreticular tissue (reticular c.t. and lymphocytes)
  - **cortex** (lymphatic follcicles and sinuses) (B-cells)
  - **medulla** (cords and sinuses) (B-cells)
- paracortical region (T-cells)
- **sinuses**: subcapsular (marginal), perifolicullar (cortical), medullary
- *Littoral cells* – lining of sinuses, phagocytosis

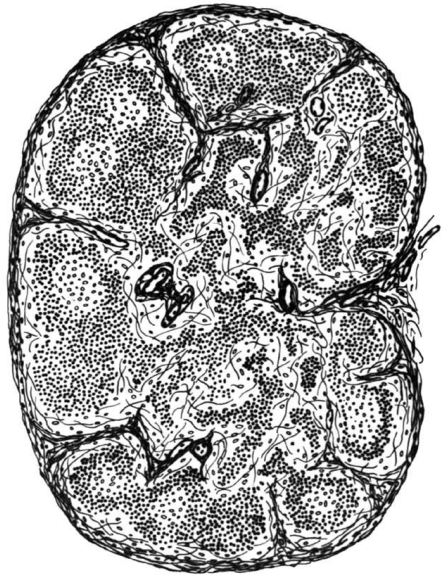




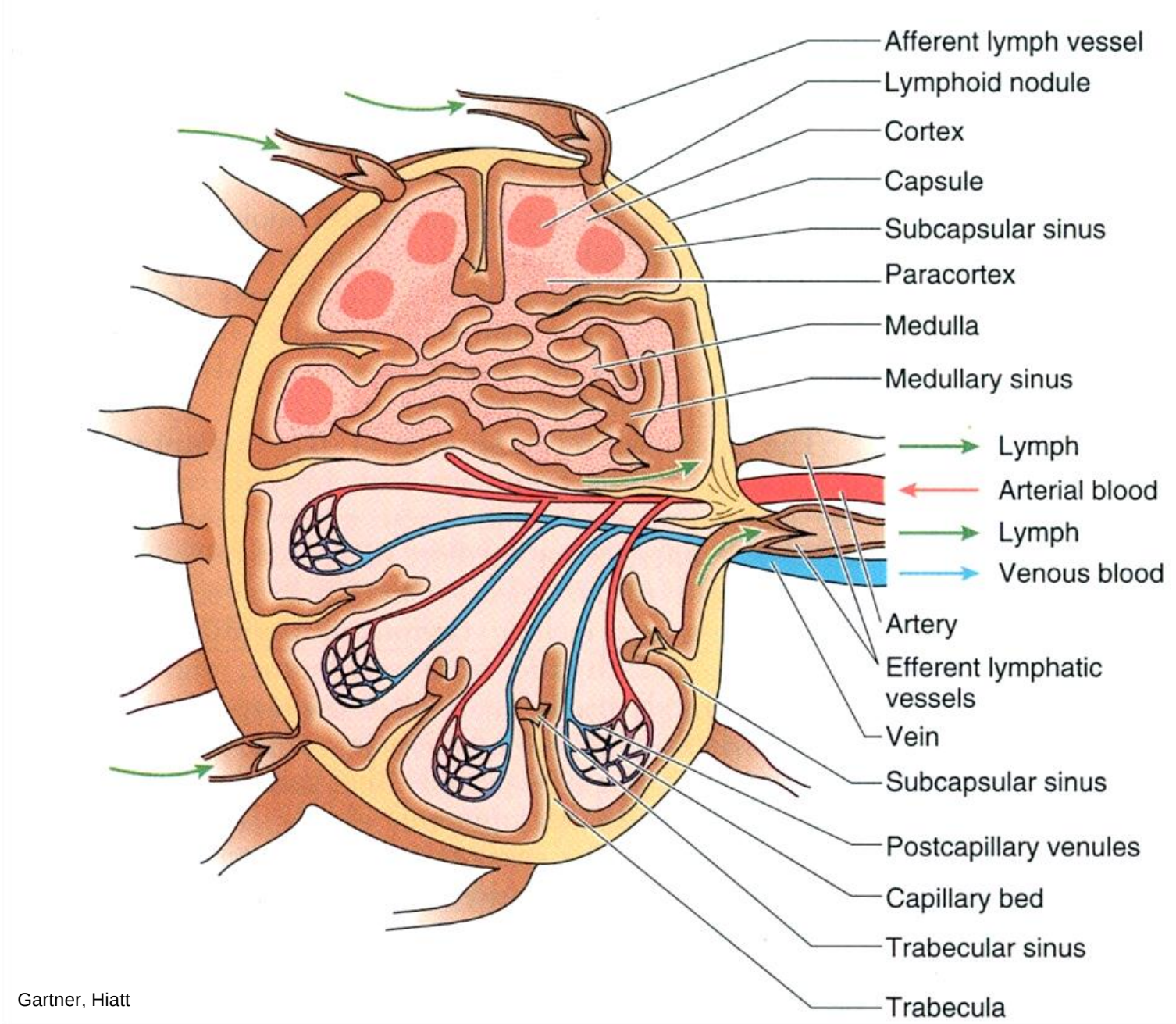
LYMPH NODE (NODUS LYMPHATICUS, LYMPHONODUS)





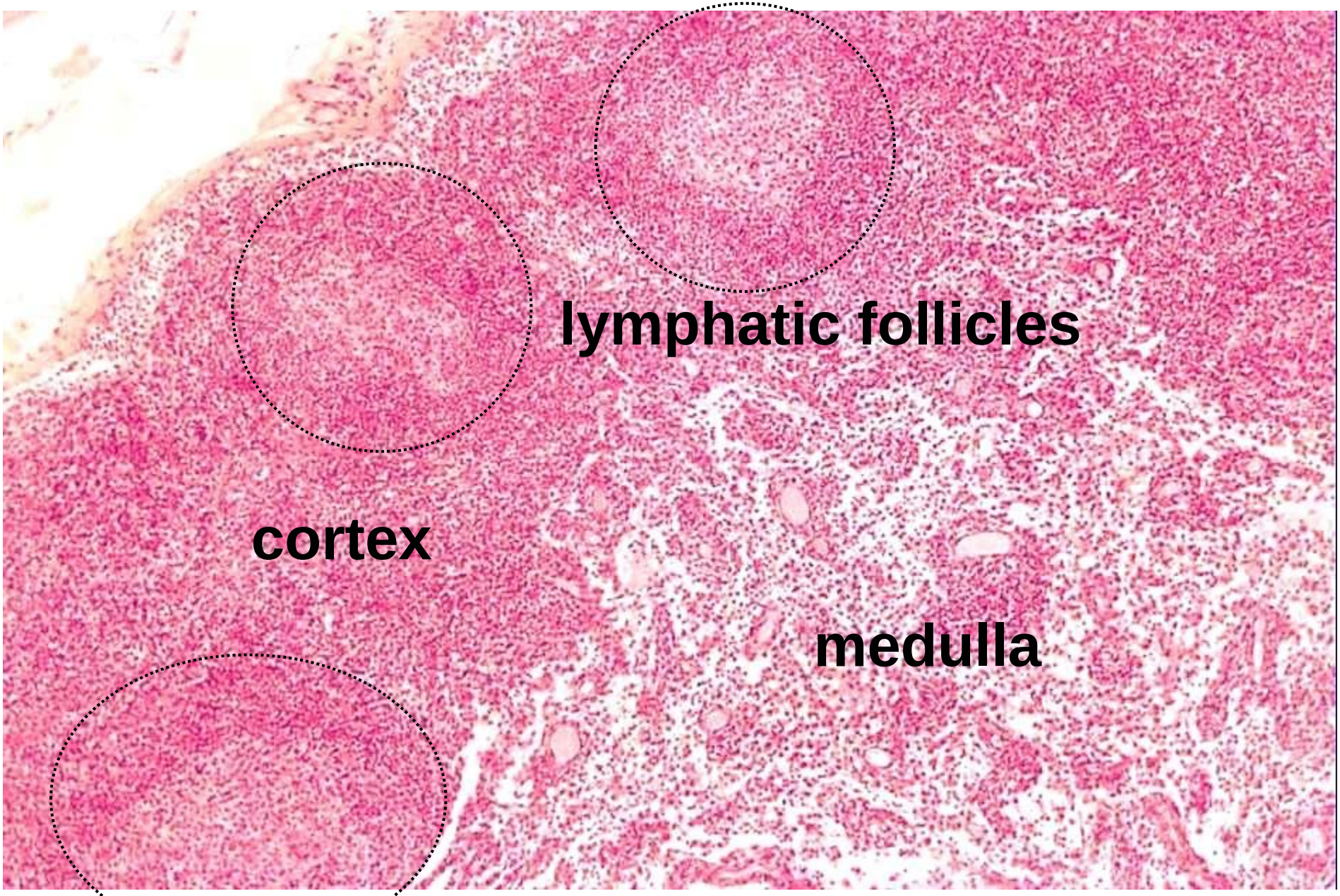


LYMPH NODE CIRCULATION (BLOOD AND LYMPH)



Gartner, Hiatt

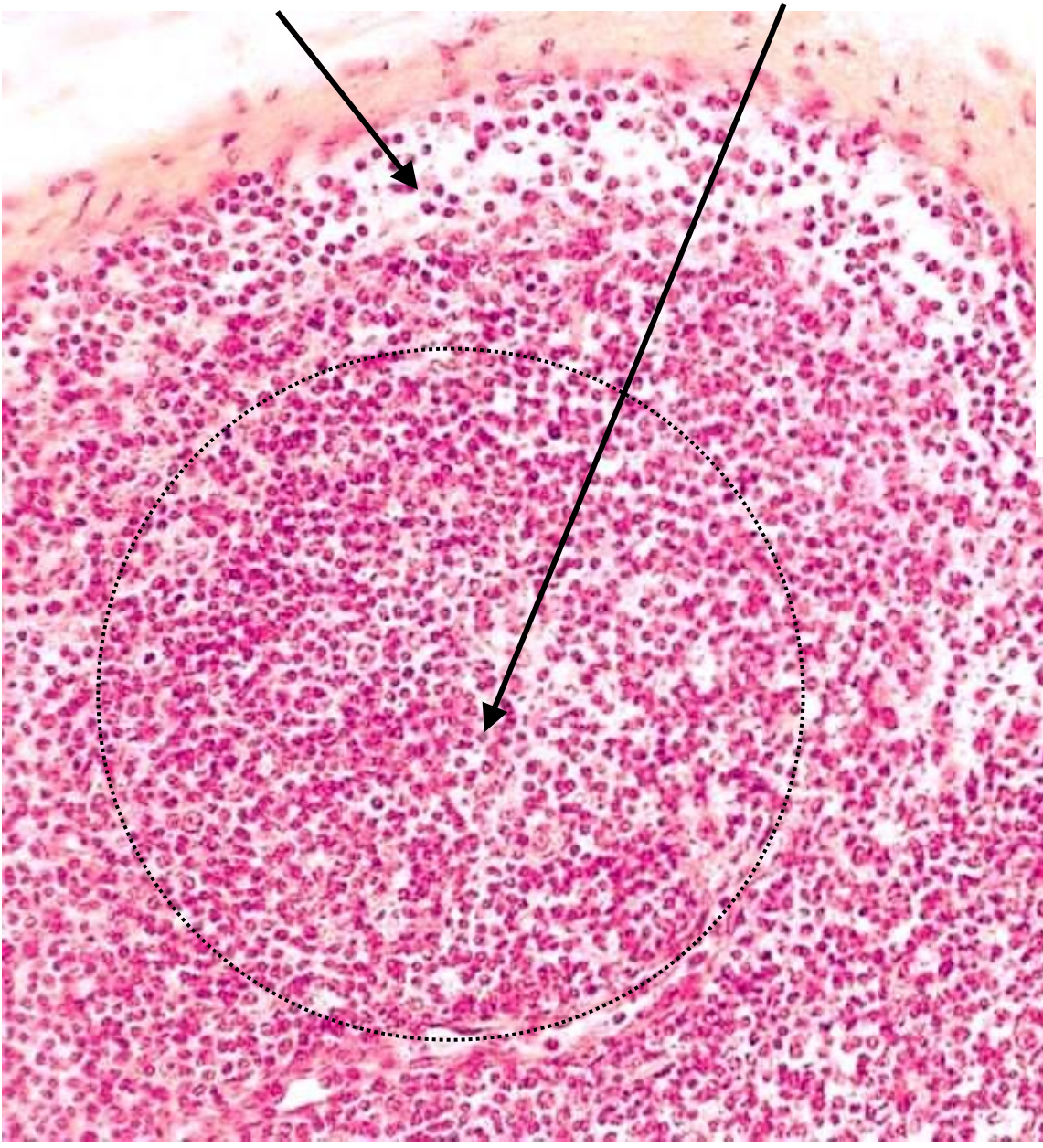
LYMPH NODE (NODUS LYMPHATICUS, LYMPHONODUS)

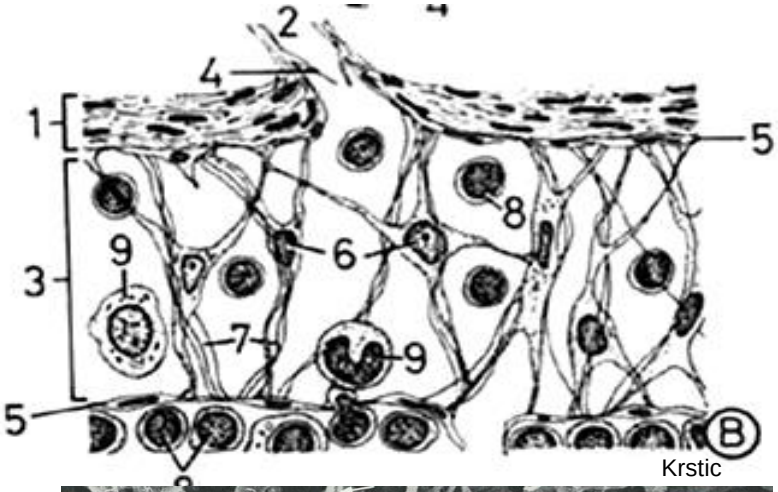


LYMPH NODE (NODUS LYMPHATICUS, LYMPHONODUS)

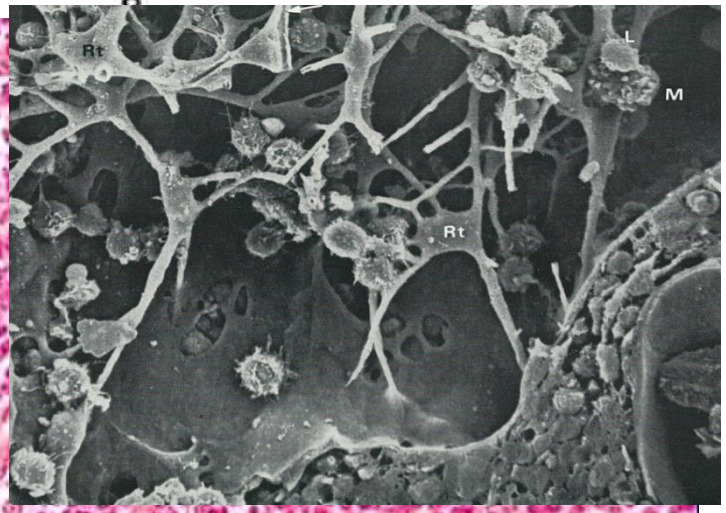
subcapsular sinus

lymphatic follicle

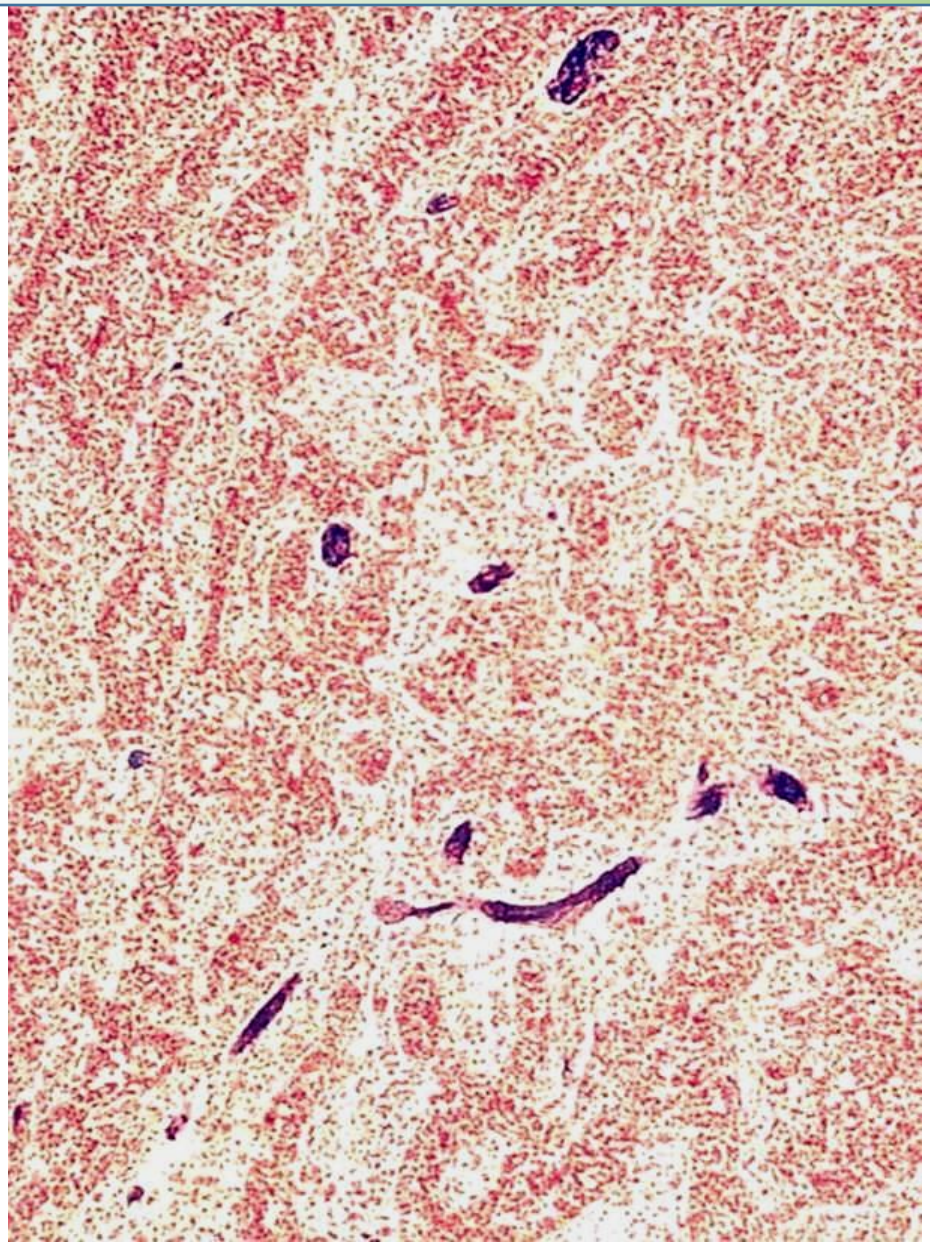




Krstic

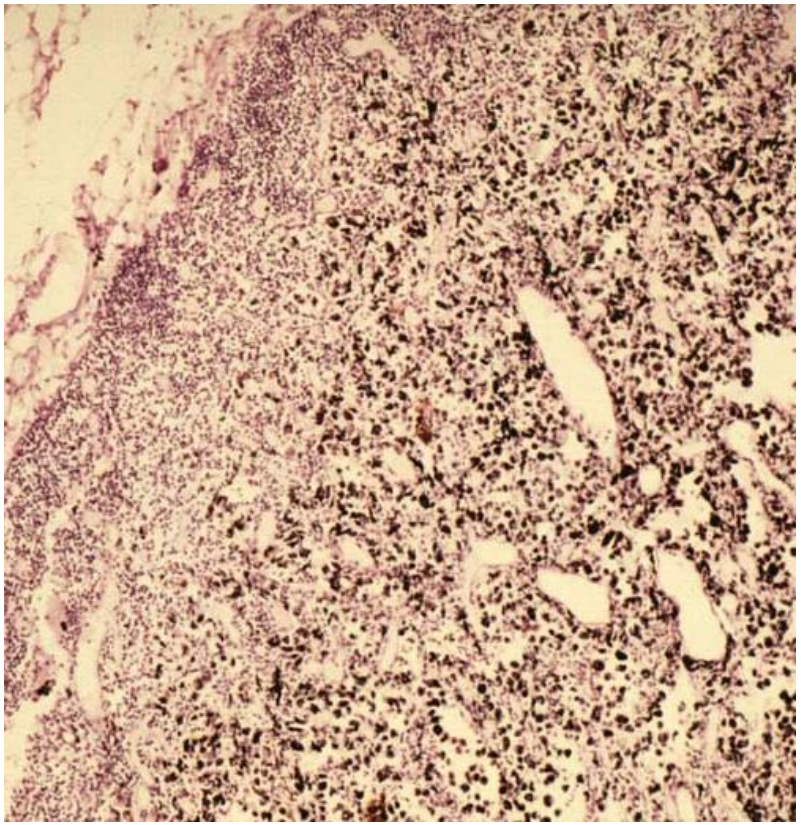


LYMPH NODE MEDULLA

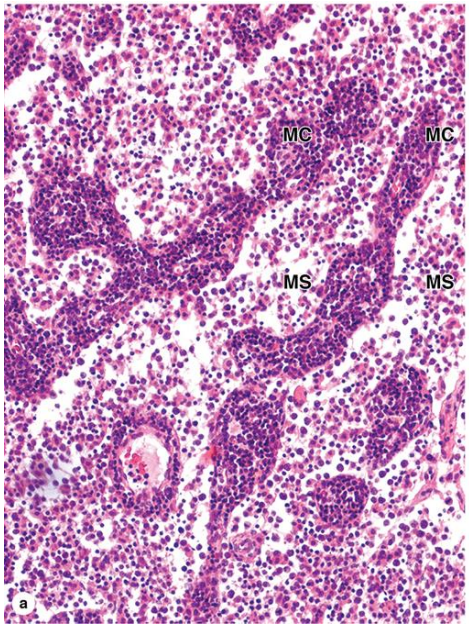


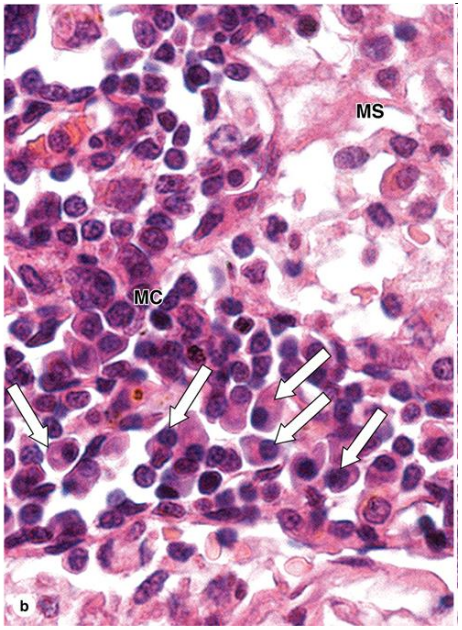
Medullary cords and sinuses

Lymph node from lung hilus with dust (carbon) deposites



LYMPH NODE MEDULLA

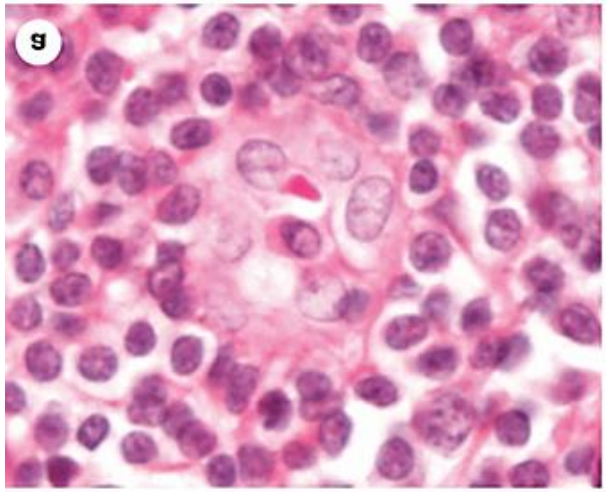


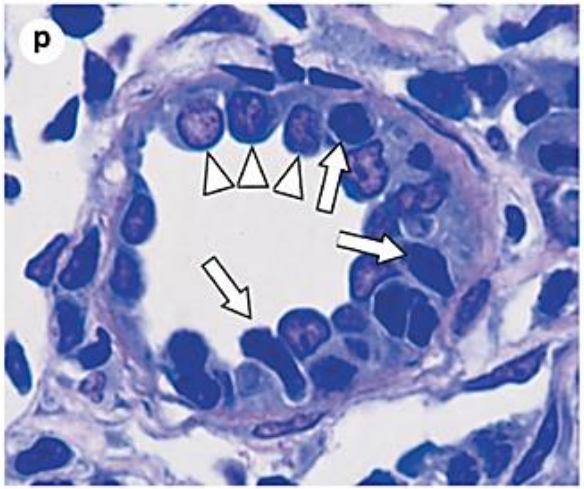


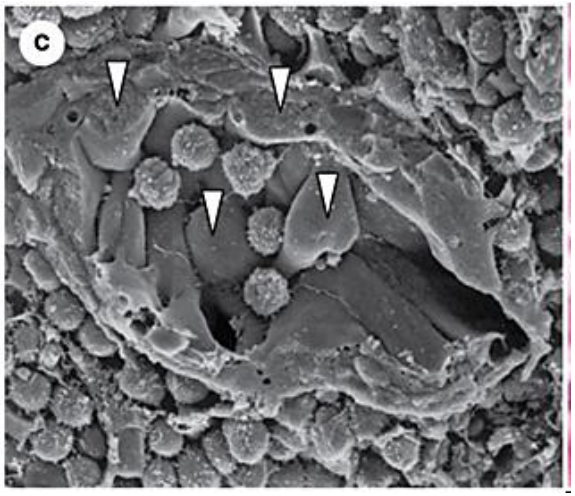
Mescher

Medullary cords and sinuses

- Plasma cells in medullary cords
- High endothelium post-capillary venules – extravasation of leukocytes from blood to lymph node parenchyma

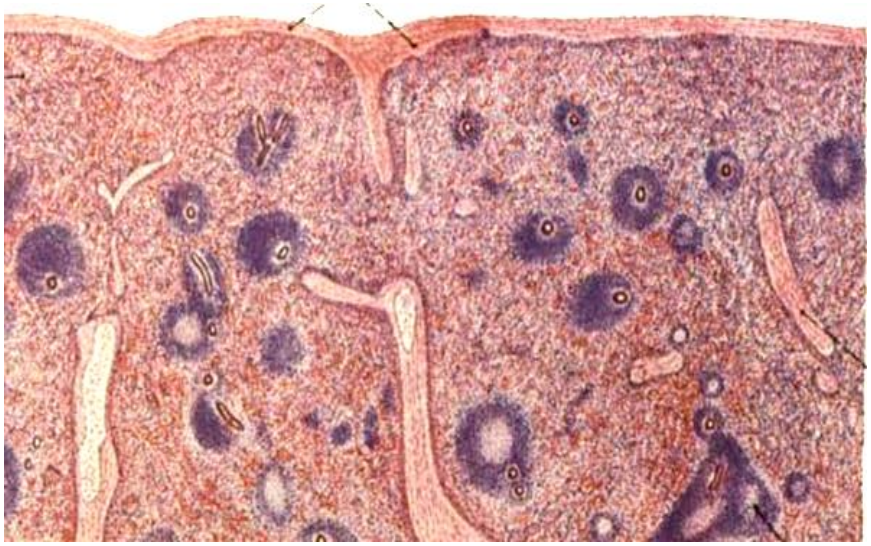


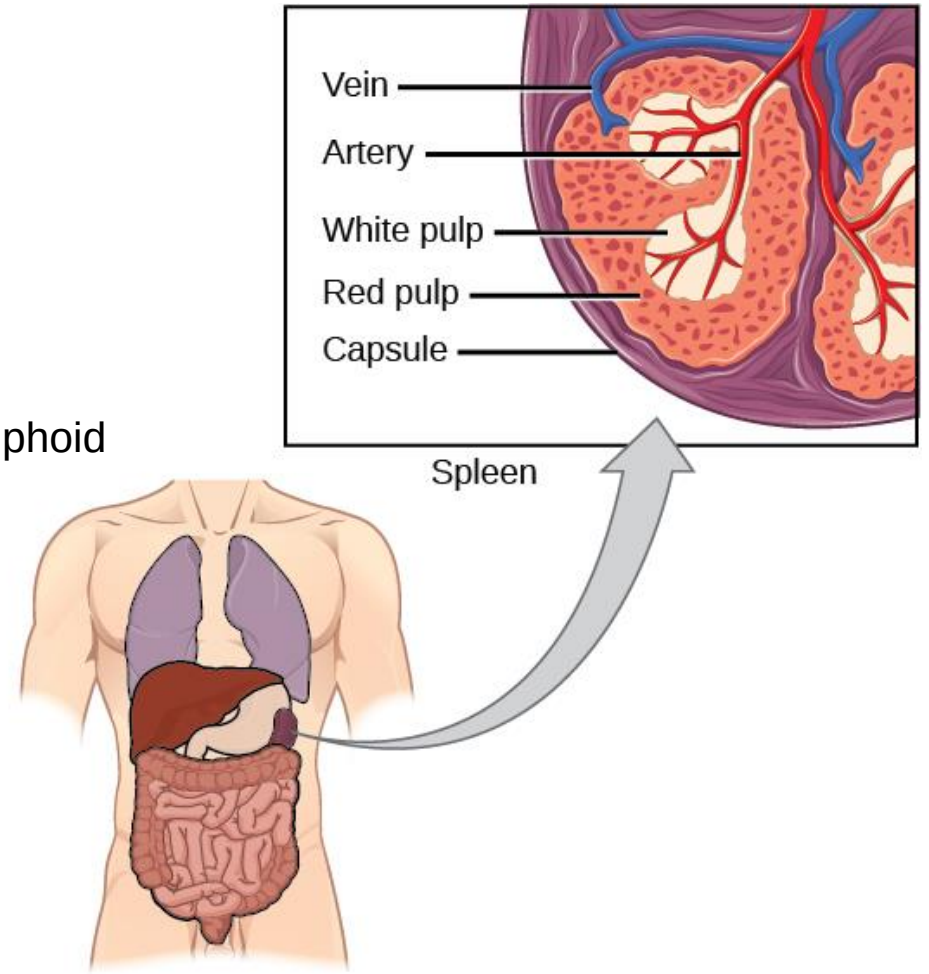




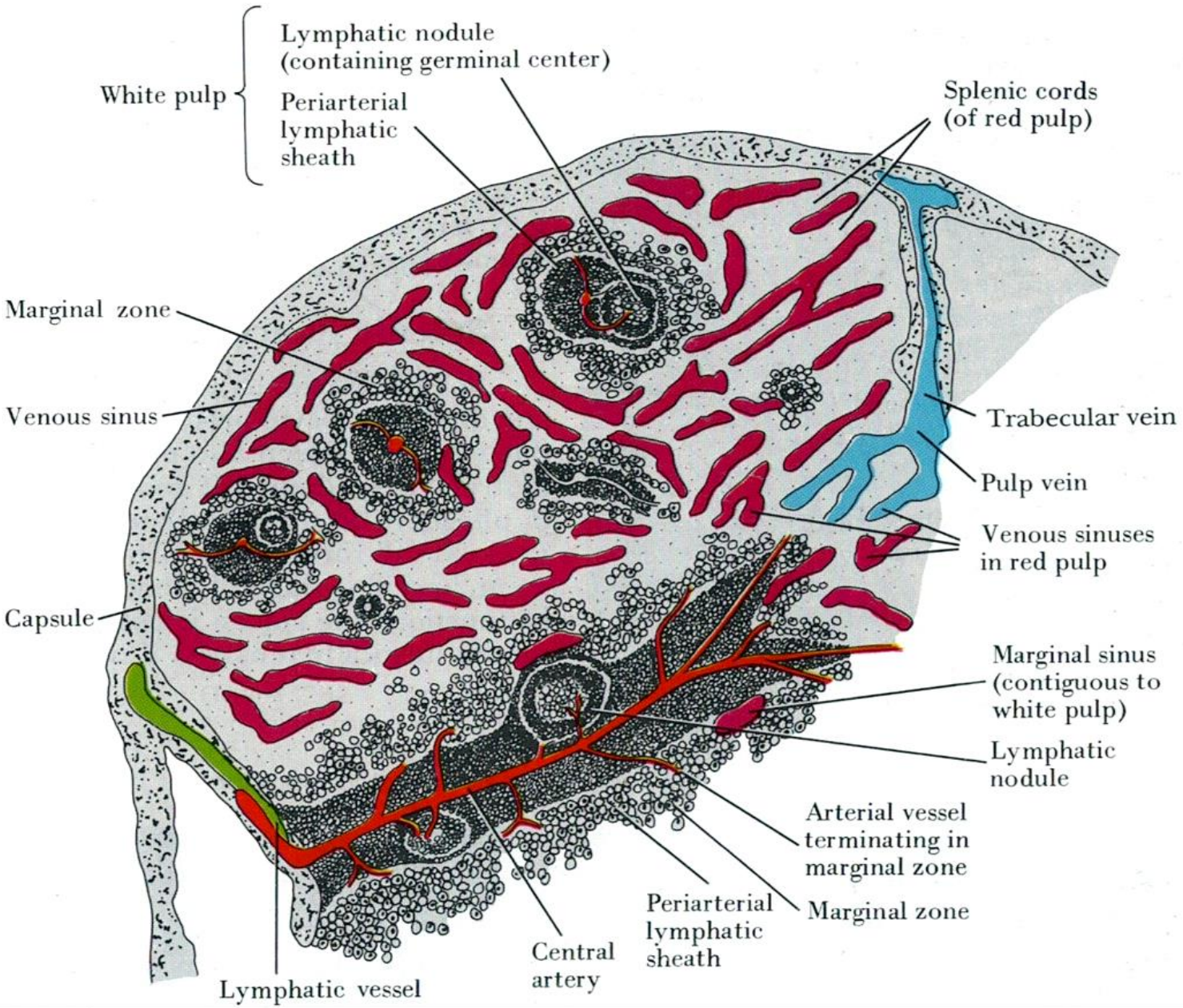
SPLEEN (LIEN)

- C.t. capsule and trabecules
- Parenchyma = pulp
- **white** (lymphoid)
  - periarteriolar lymphatic sheath - PALS
  - Malpighian bodies - follicles)
- **red** (non-lymphoid)
  - cords of Billroth
  - venous sinuses
- **marginal zone** between lymphoid and non-lymphoid regions in the spleen



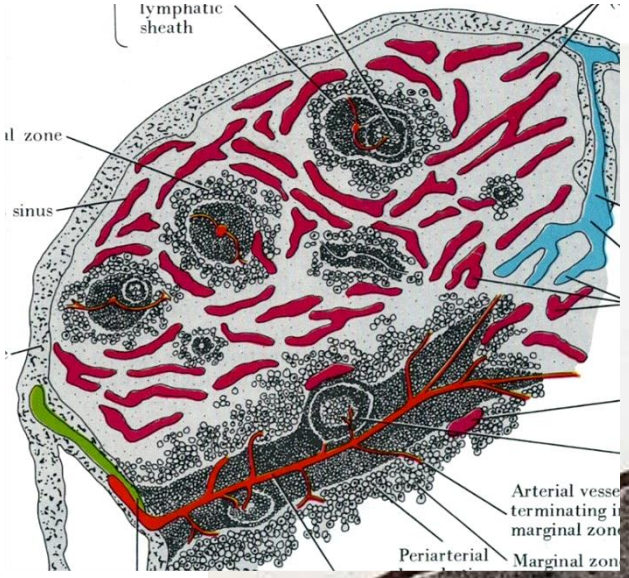


SPLEEN (LIEN)

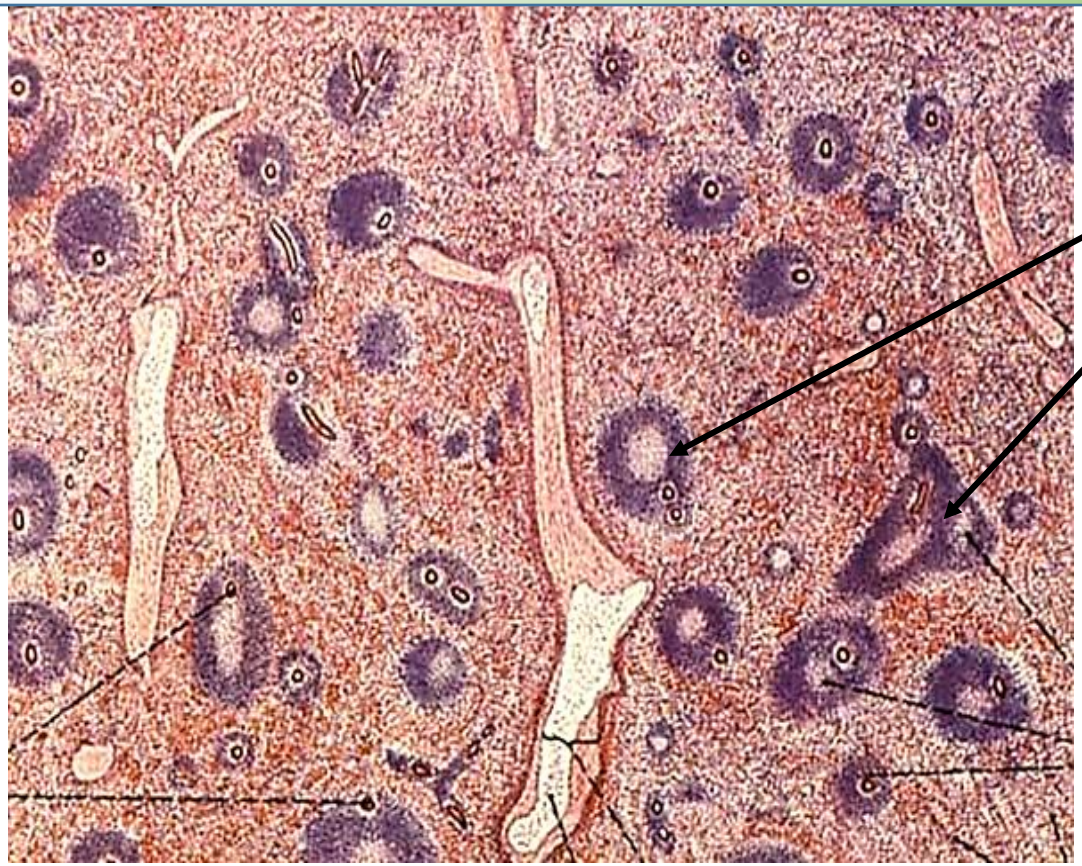


Ross, Romrell

SPLEEN (LIEN)

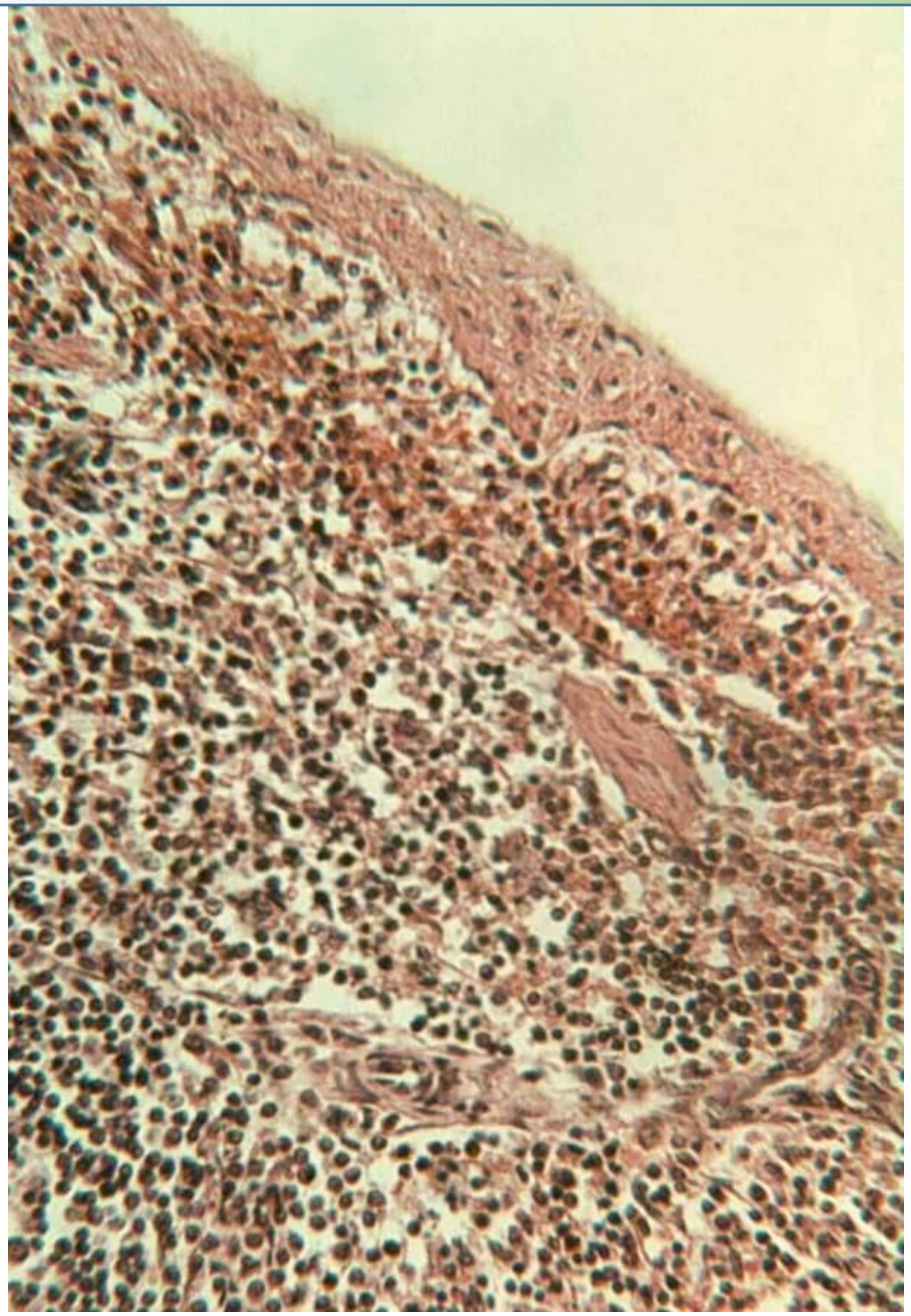

lymphatic
sheath
l zone
sinus
Arterial vesse
terminating i
marginal zon
Periarterial
Marginal zon

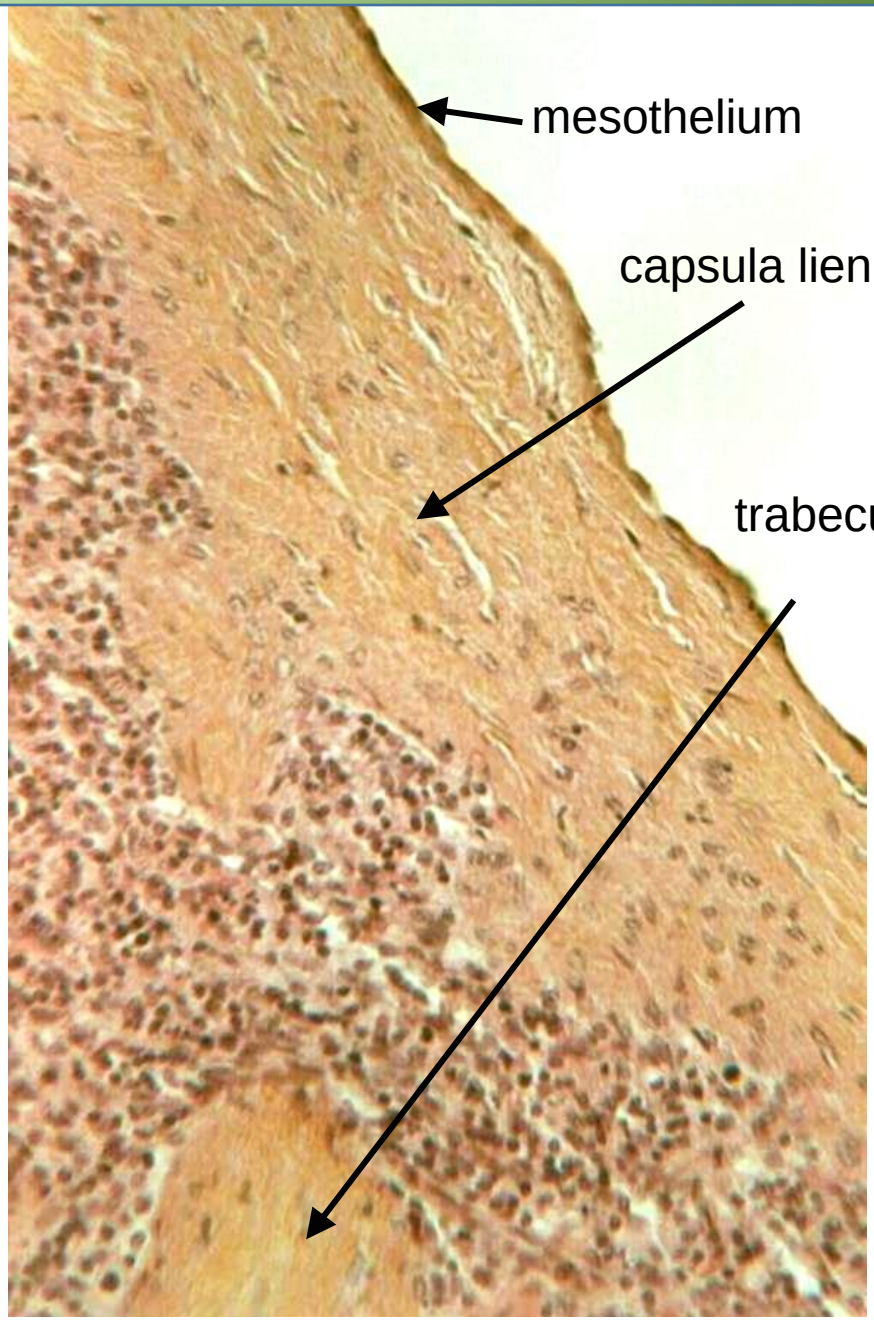
SPLEEN (LIEN)



Sobotta

SPLEEN (LIEN)





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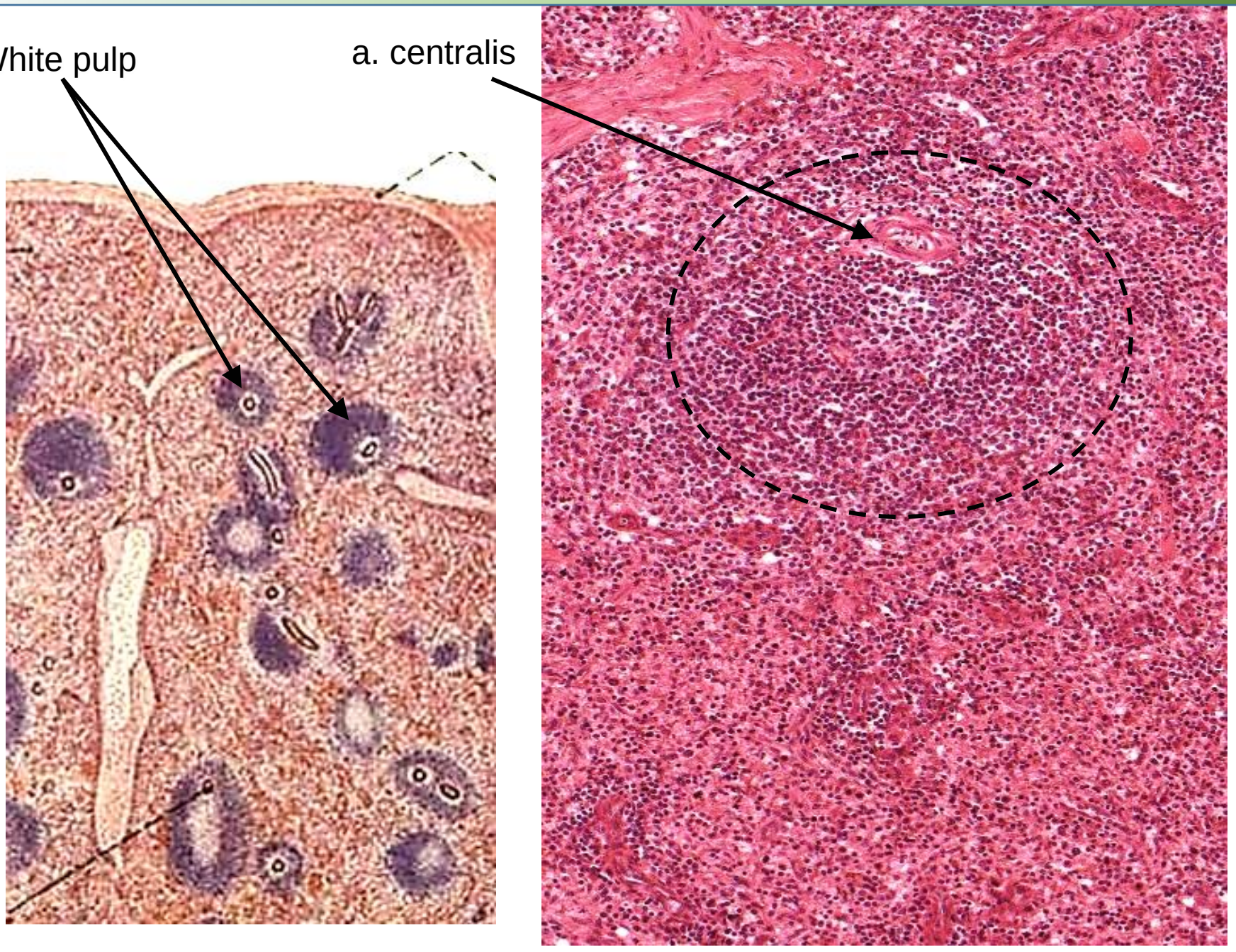

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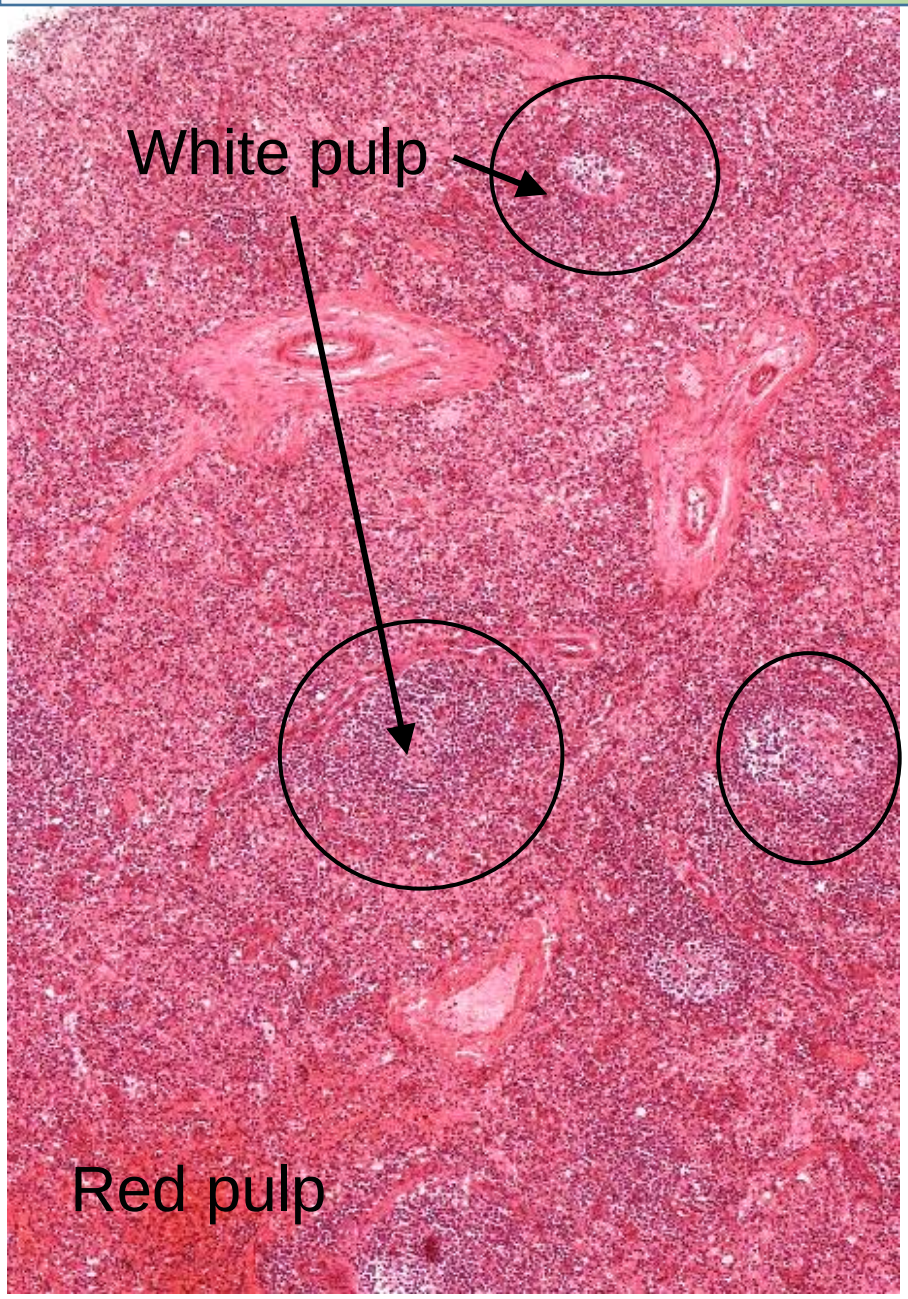
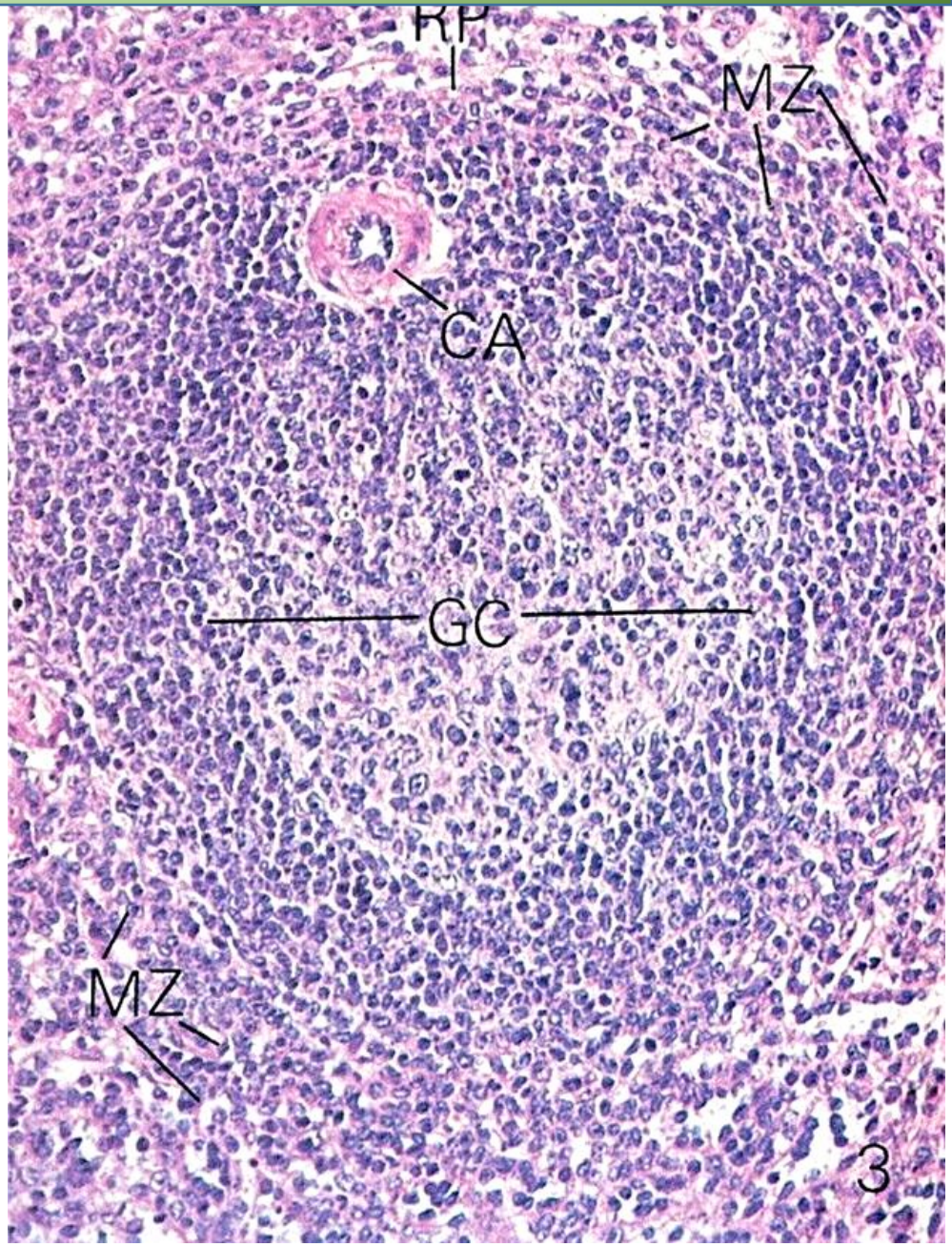
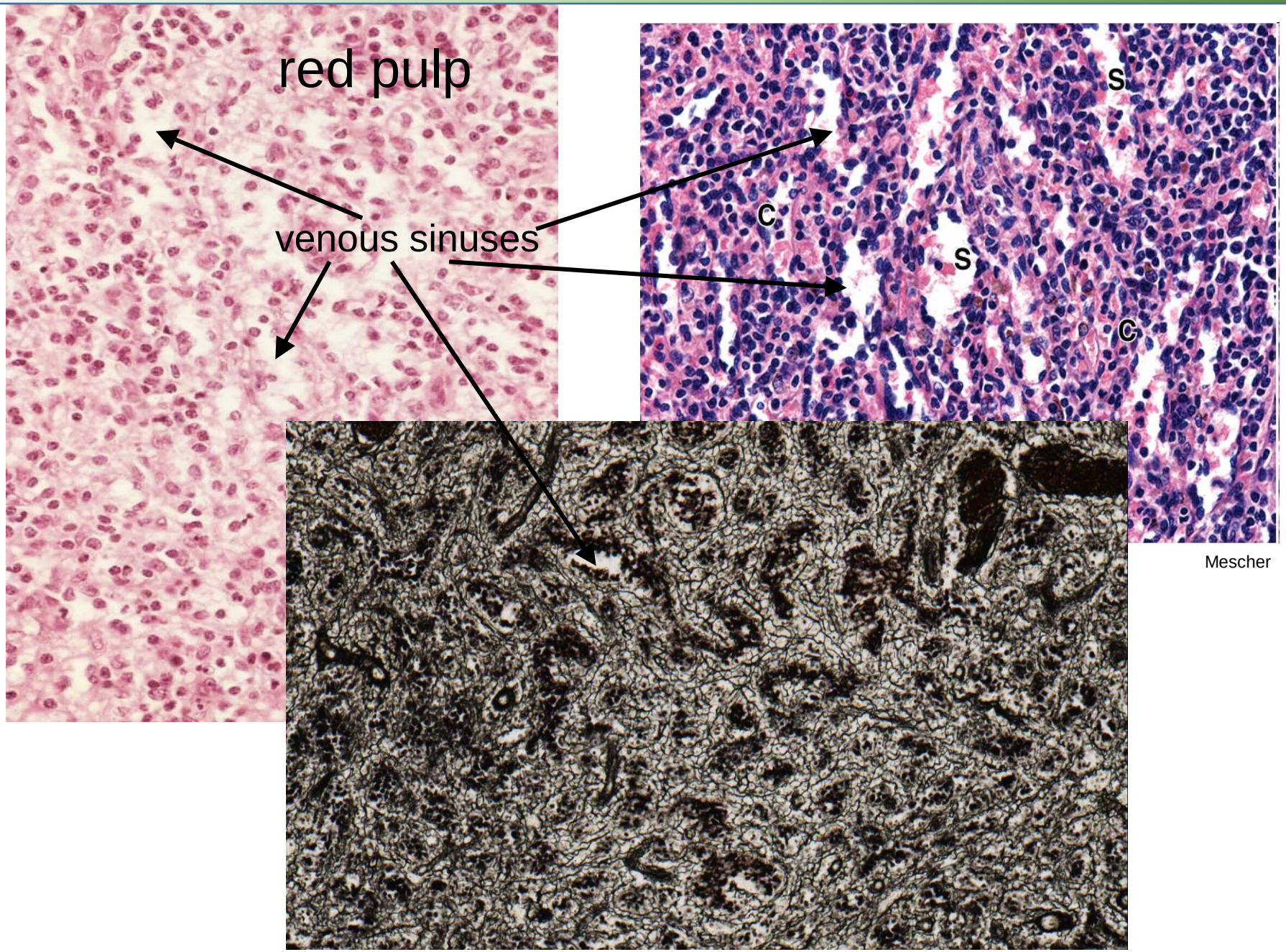




Ross, Romrell

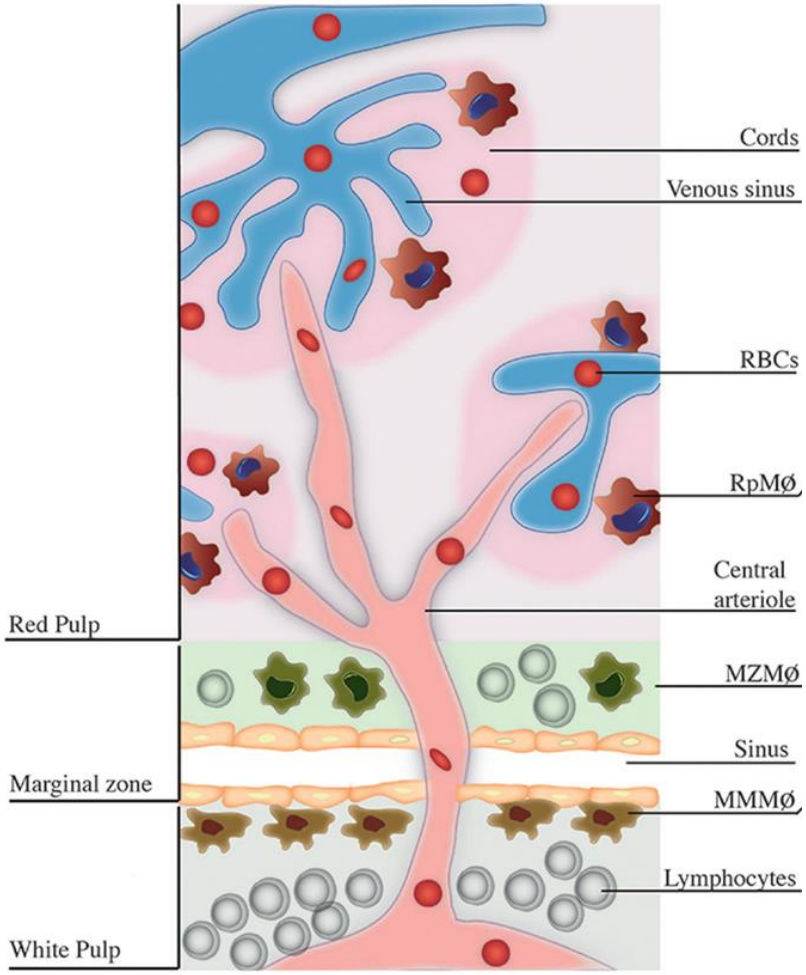
SPLEEN (LIEN)

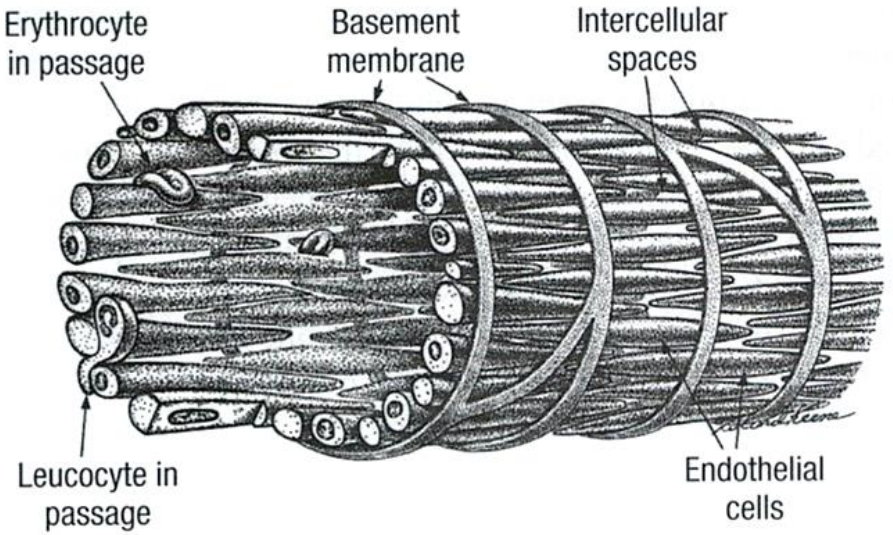


Mescher

SPLEEN (LIEN)

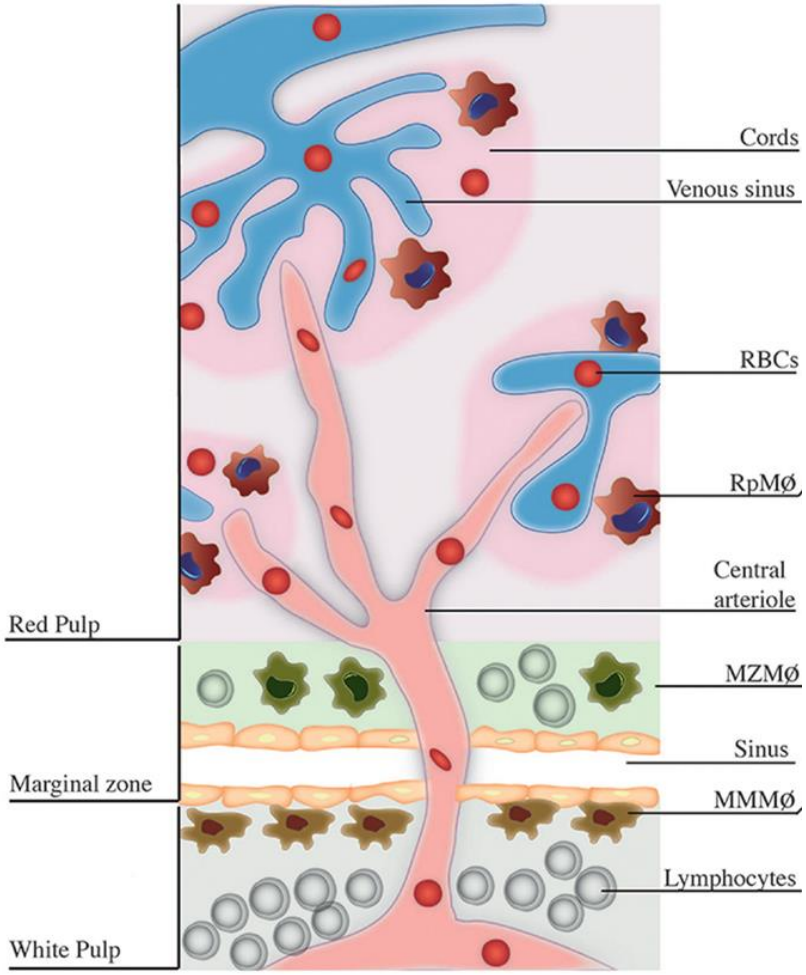
- Venous sinuses of red pulp
- Removal of abnormal erythrocytes

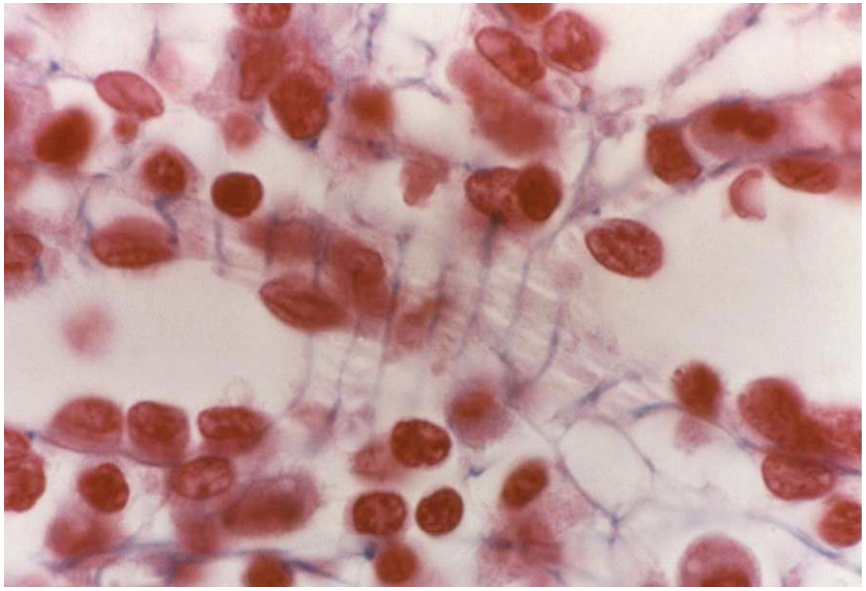




SPLEEN (LIEN)

- Venous sinuses of red pulp
- Removal of abnormal erythrocytes



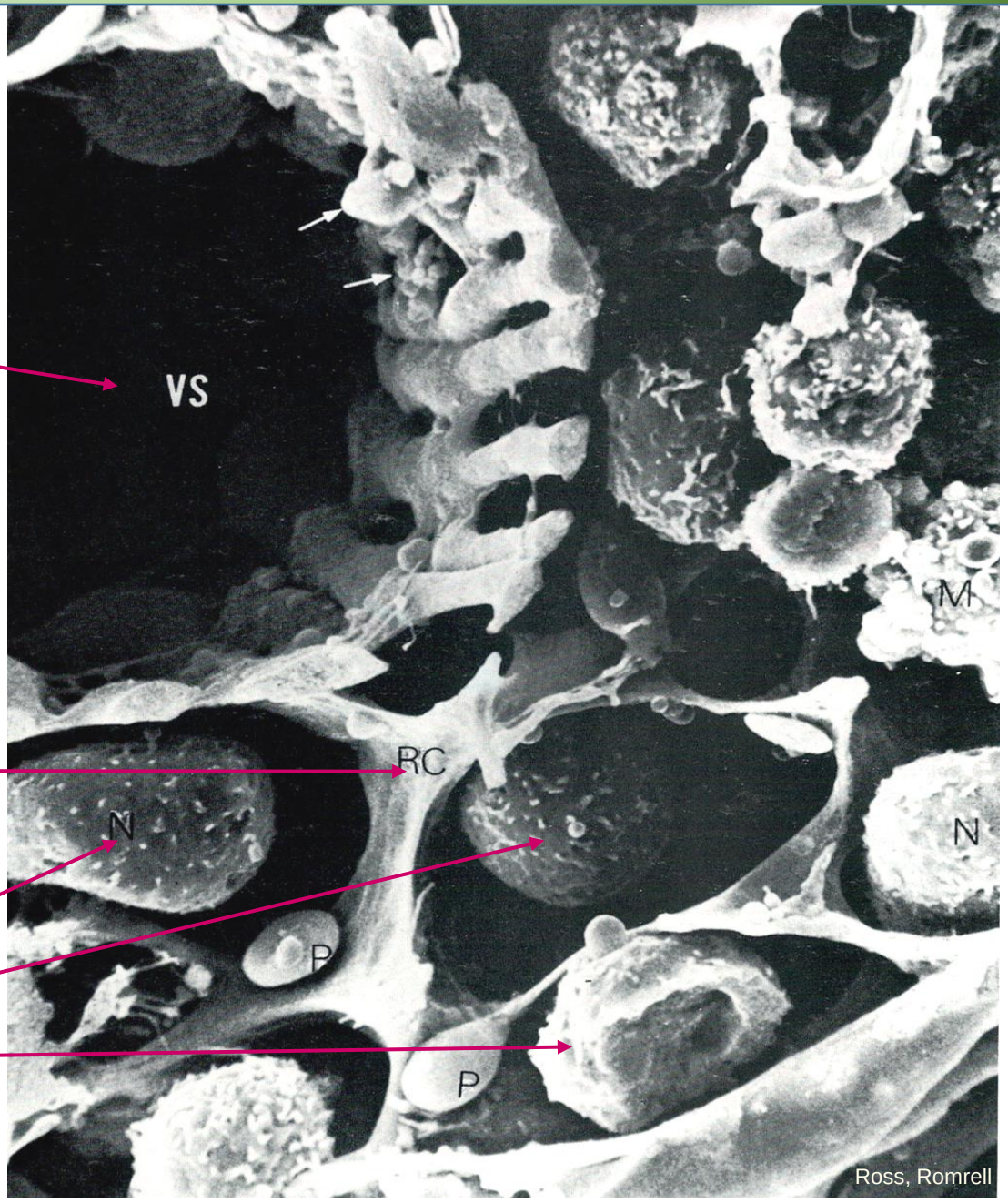


SPLEEN (LIEN)

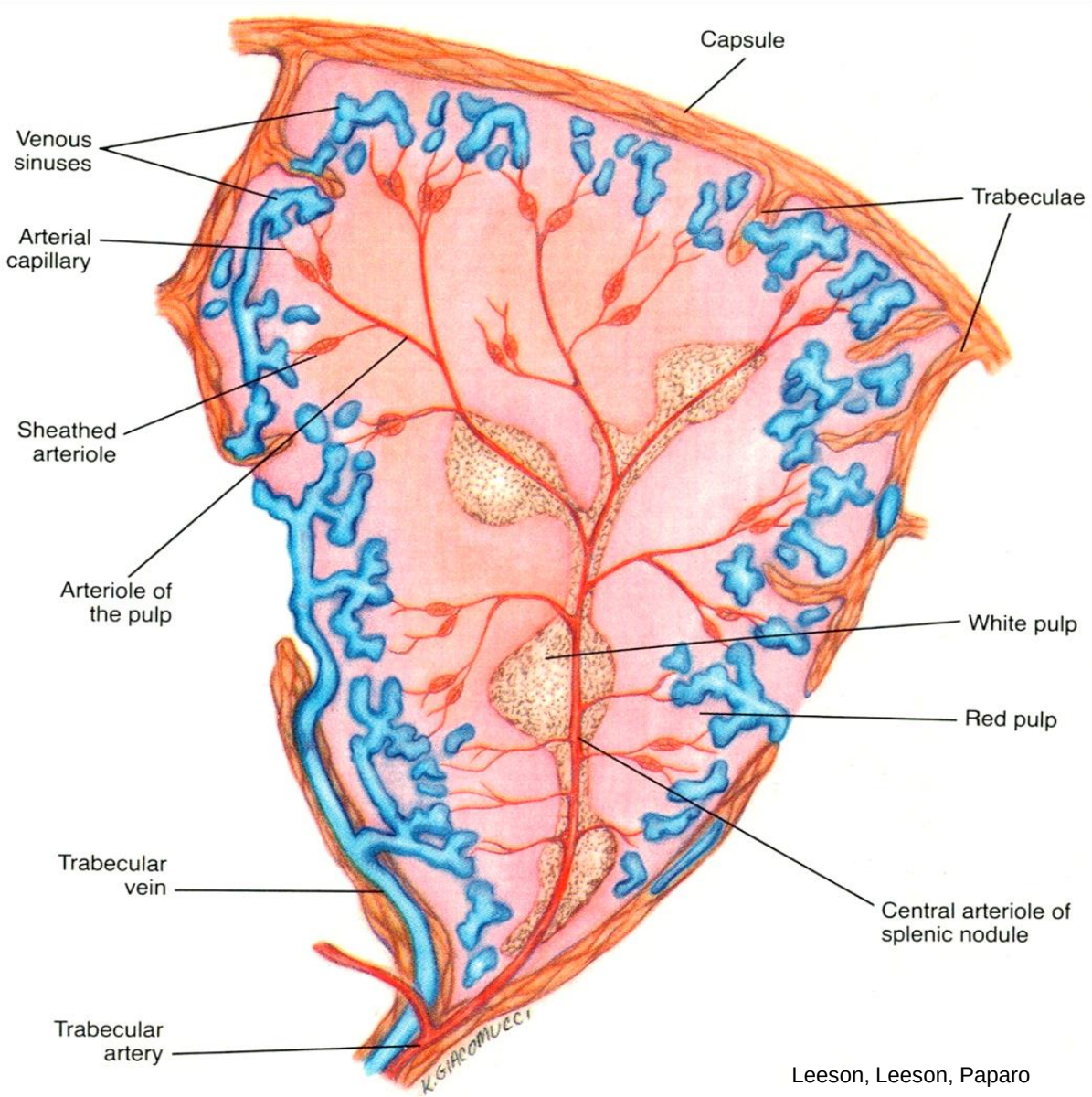
Venous sinus

Reticular cell

Cells in circulation



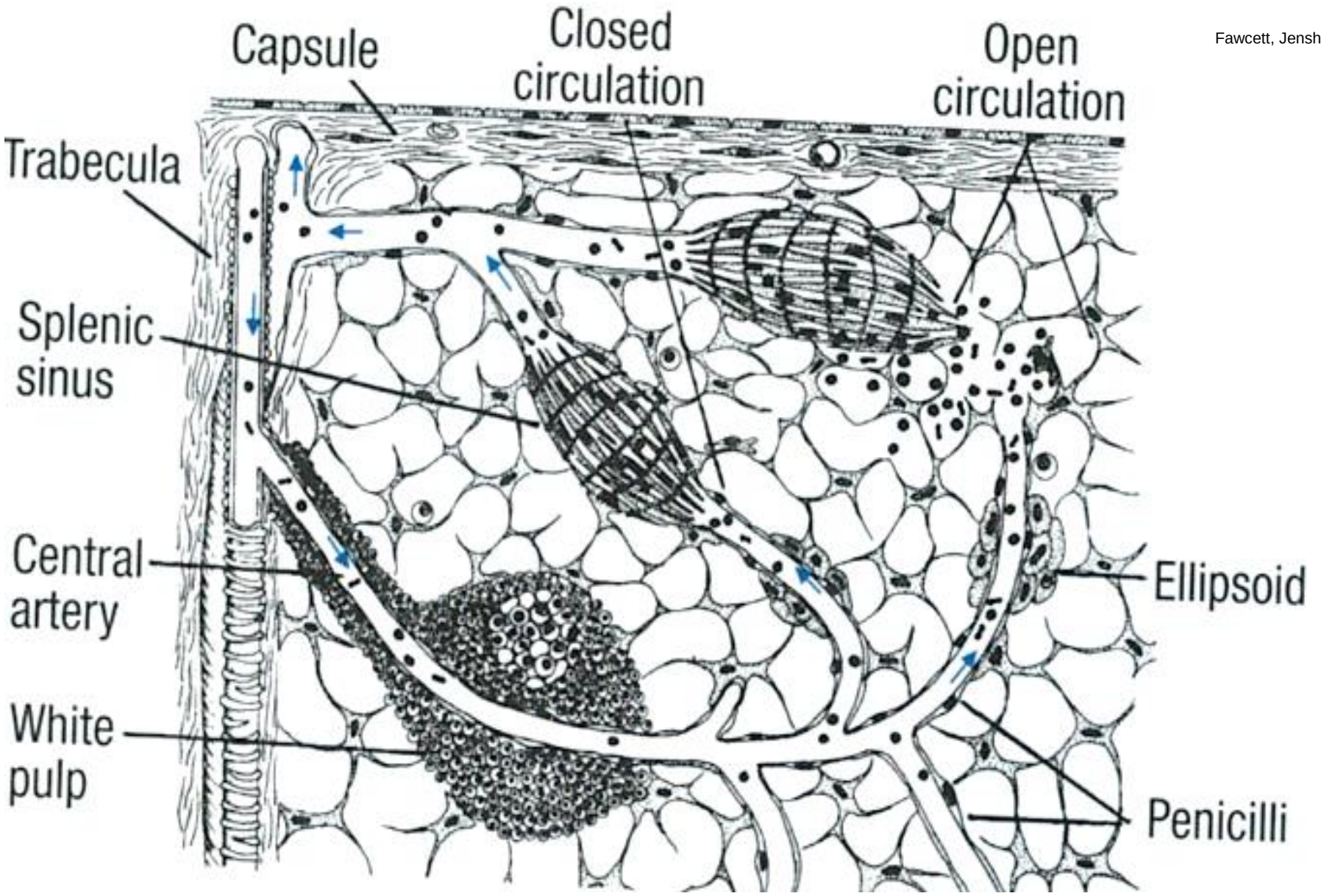
SPLEEN BLOOD CIRCULATION



- a. lienalis
- aa. trabeculares
- aa. centrales
- arteriolae penicillatae
- *(arteriole of the pulp, sheated arteriole)*
- venous sinuses
- veins of the pulp
- vv. trabeculares
- v. lienalis

Leeson, Leeson, Paparo

SPLEEN – OPEN AND CLOSED CIRCULATION

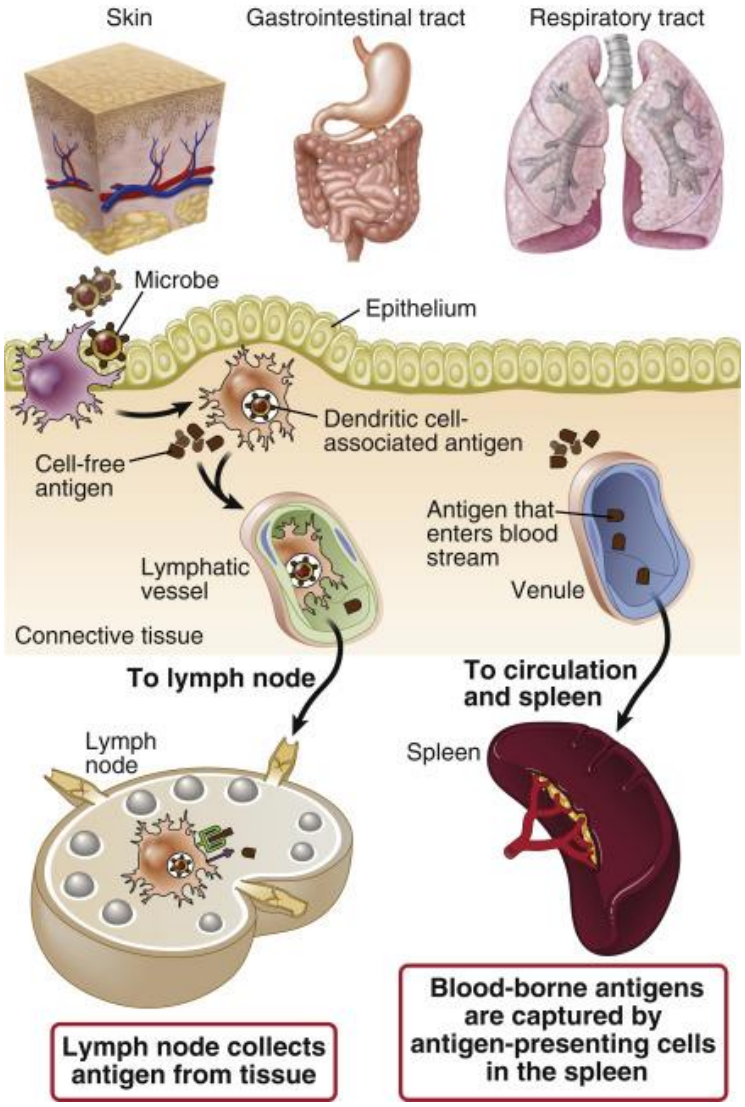


Fawcett, Jensh

SPLEEN AND LYMPH NODE IN ANTIGEN RECOGNITION

Lymph node

Spleen

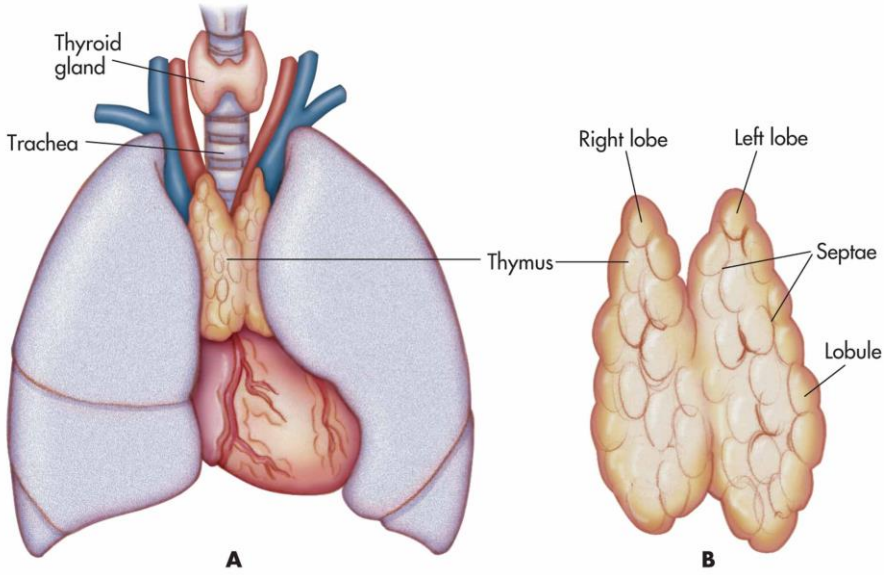


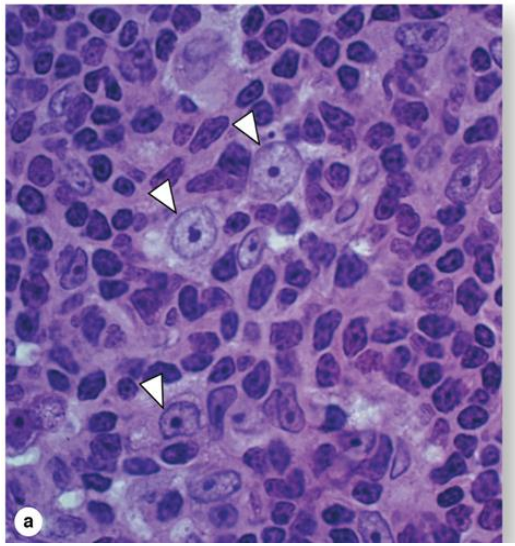
Lymph filter

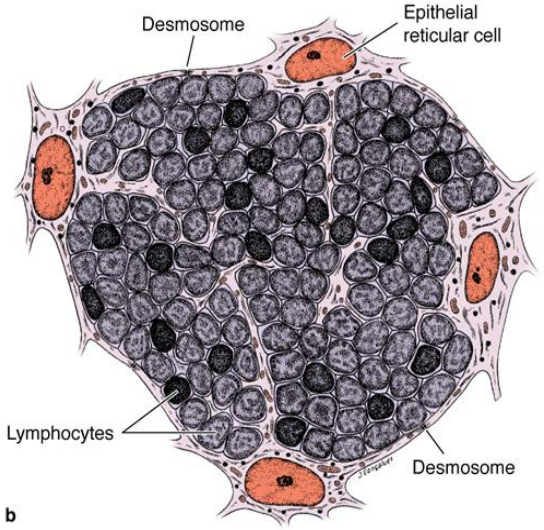
Blood filter

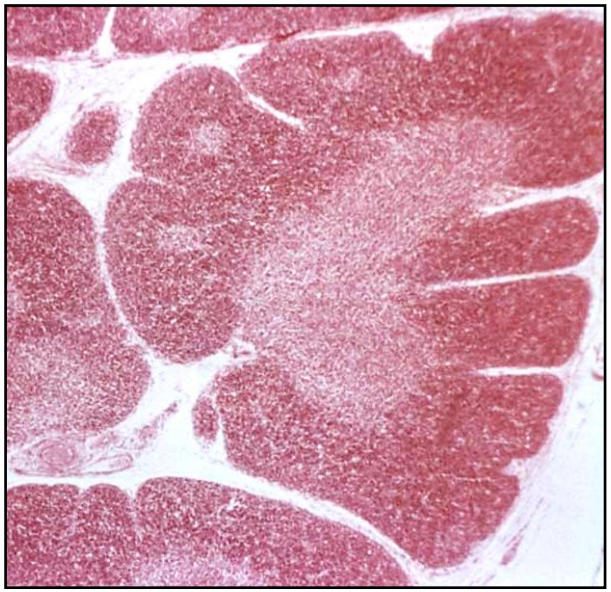
THYMUS

- c.t. capsule
- parenchyma: cortex and medulla
- epithelial reticulum and T-cells
- Hassal bodies



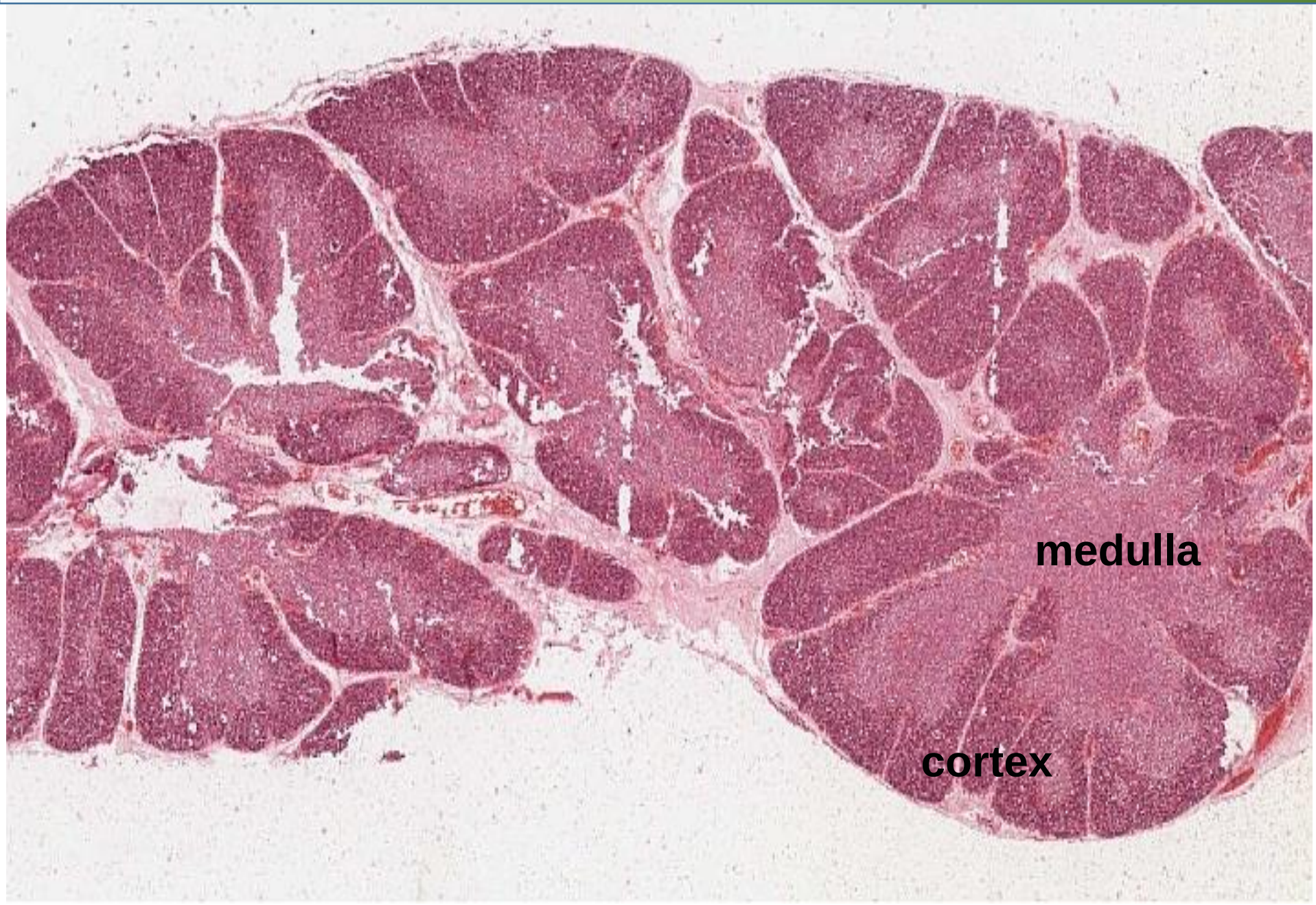






Mescher

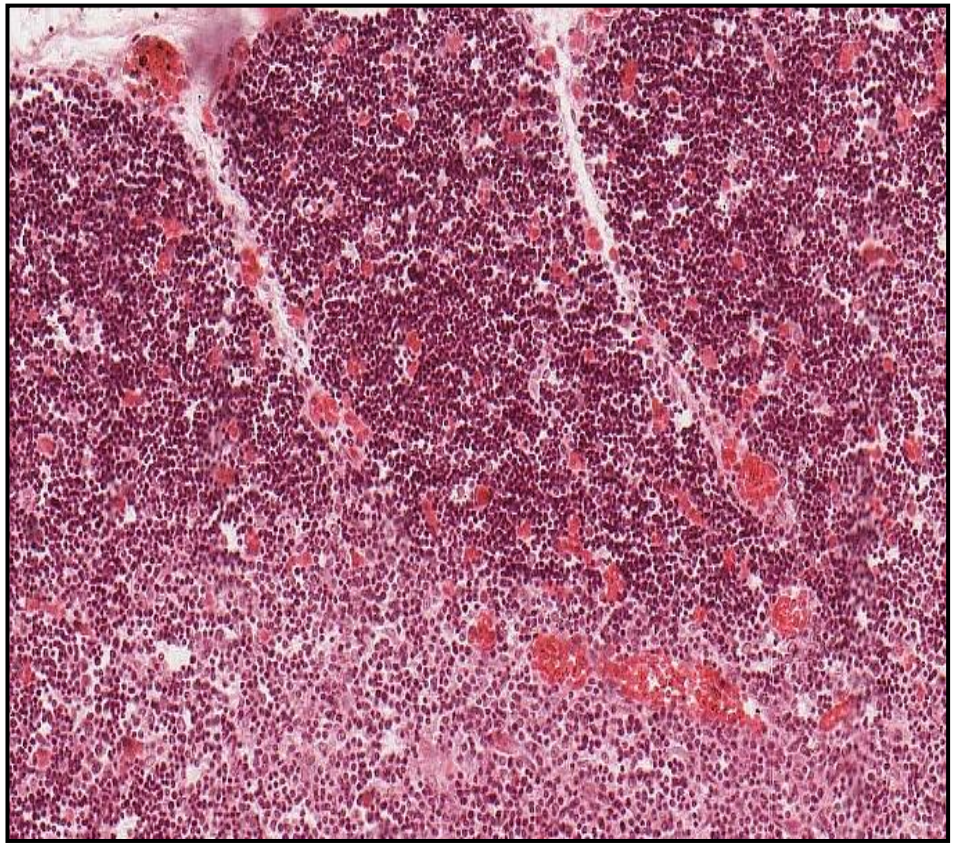
THYMUS (YOUNG)



THYMUS (CORTEX)

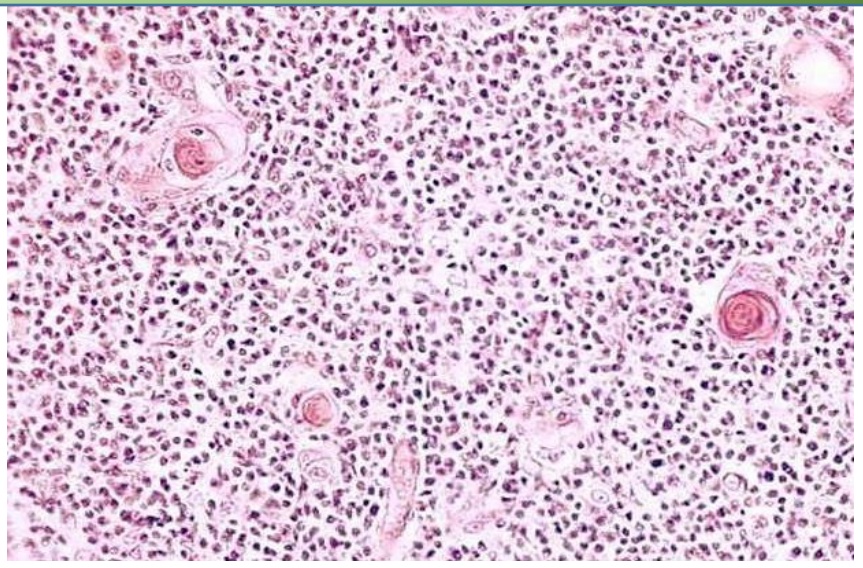
Cortex:

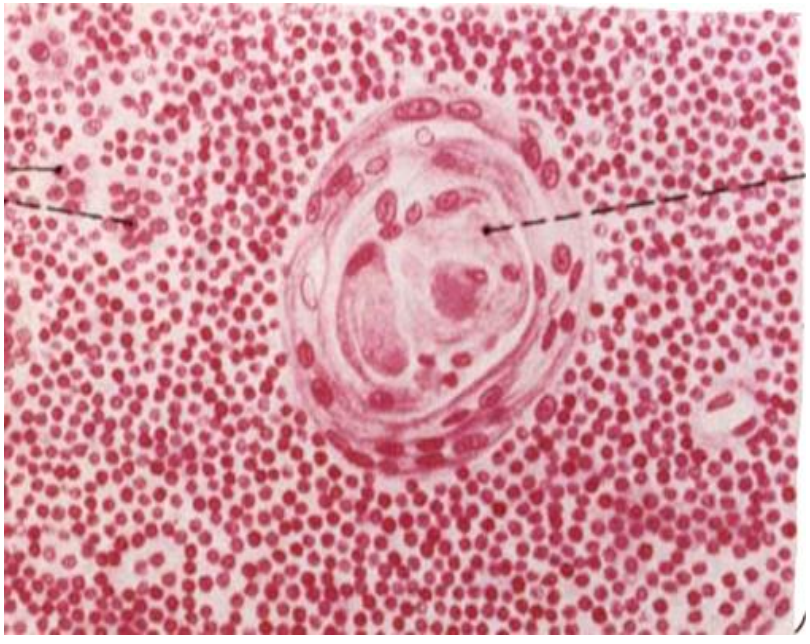
- T-cell proliferation, acquisition of **immunocompetence**
- **positive selection** (functional TCR → survival)
- **hemato-thymic barrier** (endothelium + basal lamina + cell of cytoreticulum)
- prevents premature contact with antigens



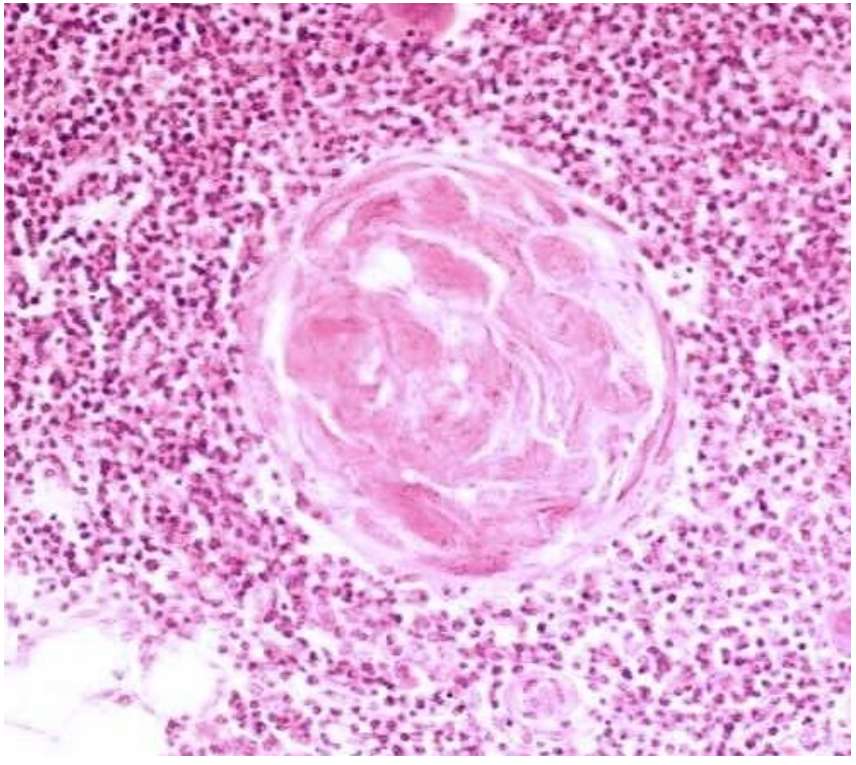
THYMUS (MEDULLA)

- **negative selection**
- prevention of autoimmune reaction
- overal survival 2-3%
- cytoreticulum
- hemato-thymic barrier absent



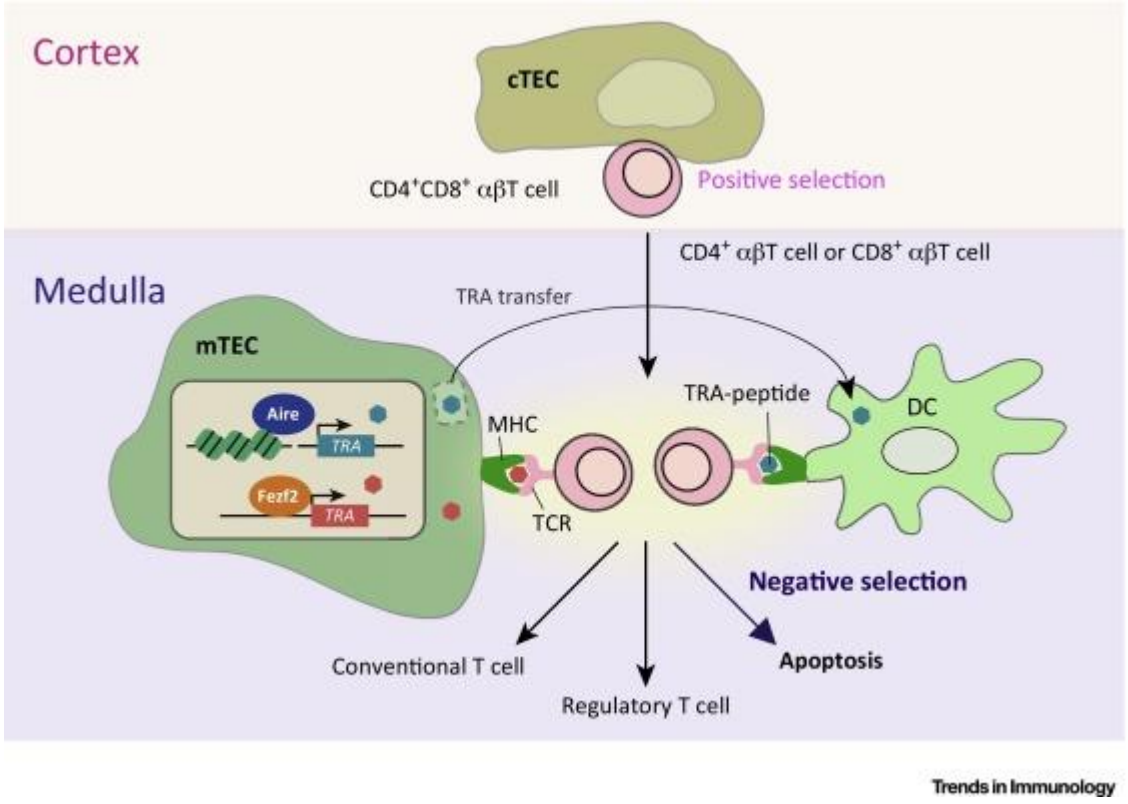


Hassal bodies in medulla

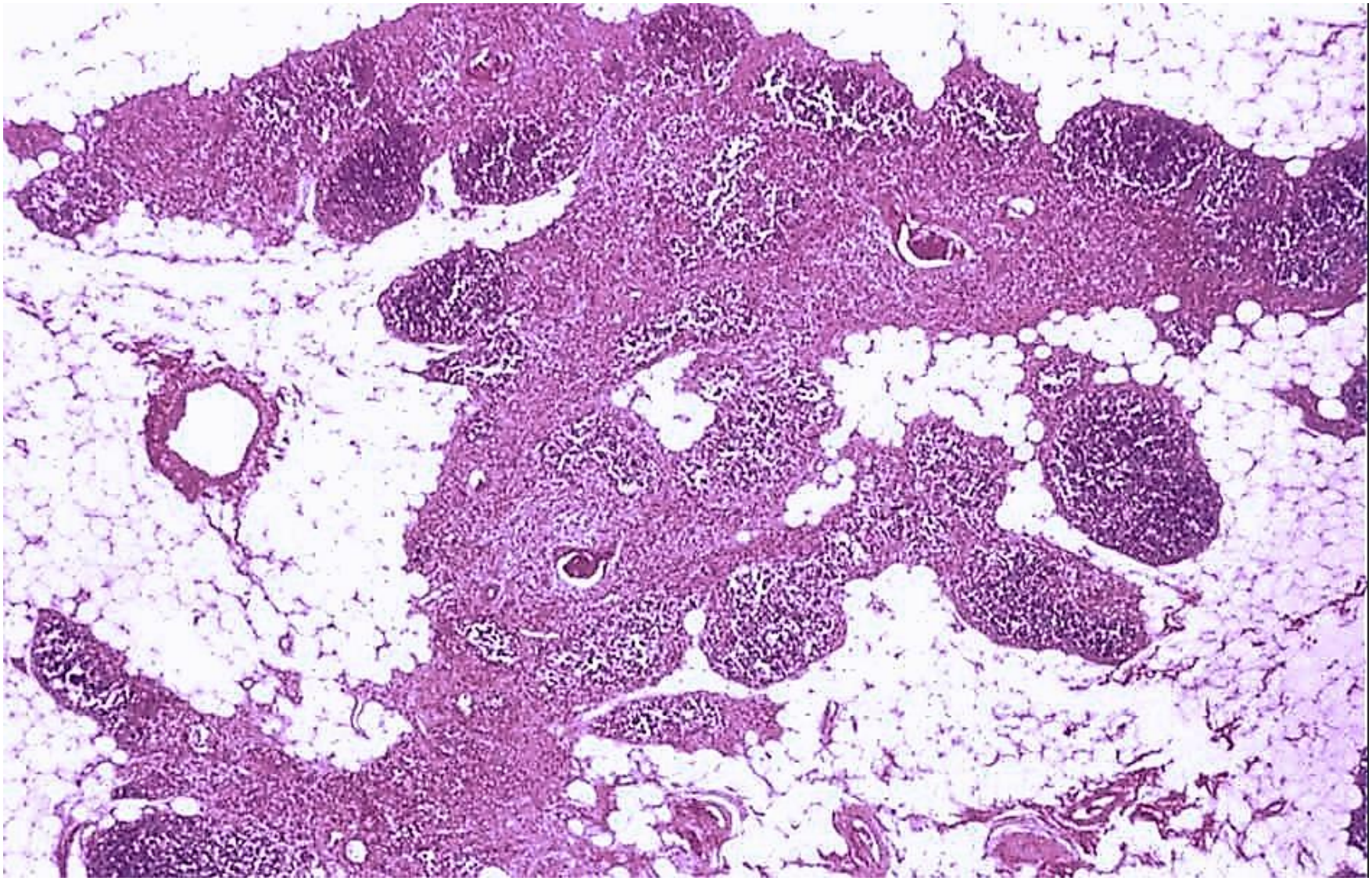


T-CELL SELECTION

- positive: CD4+ CD8+
- tissue-restricted antigens (TRAs)



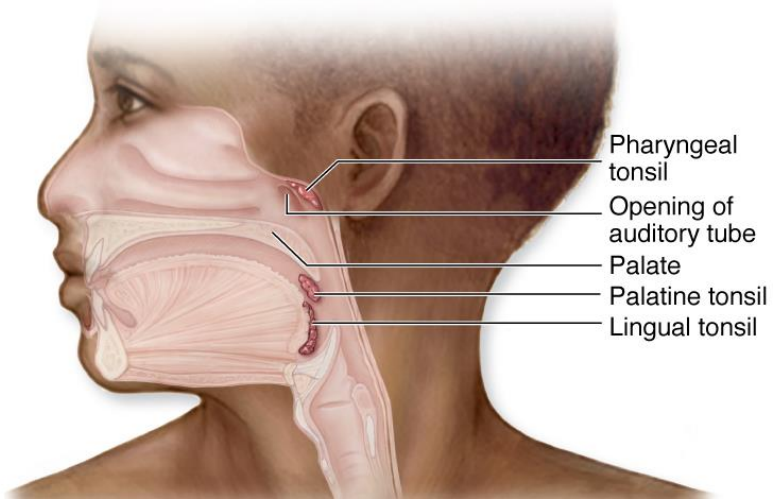
THYMUS (INVOLUTION)

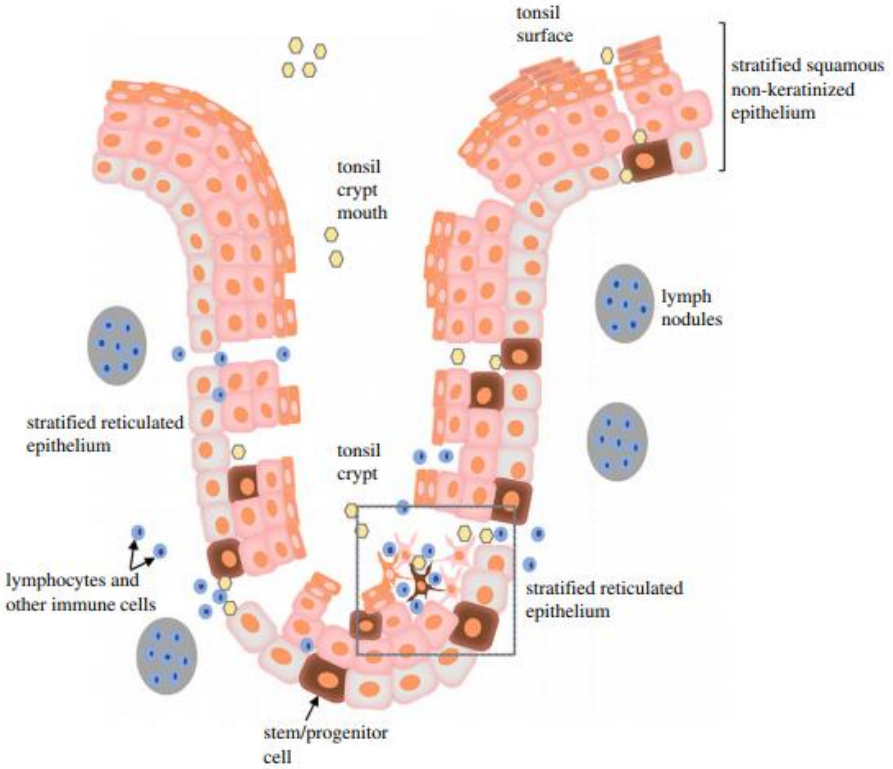


TONSILS

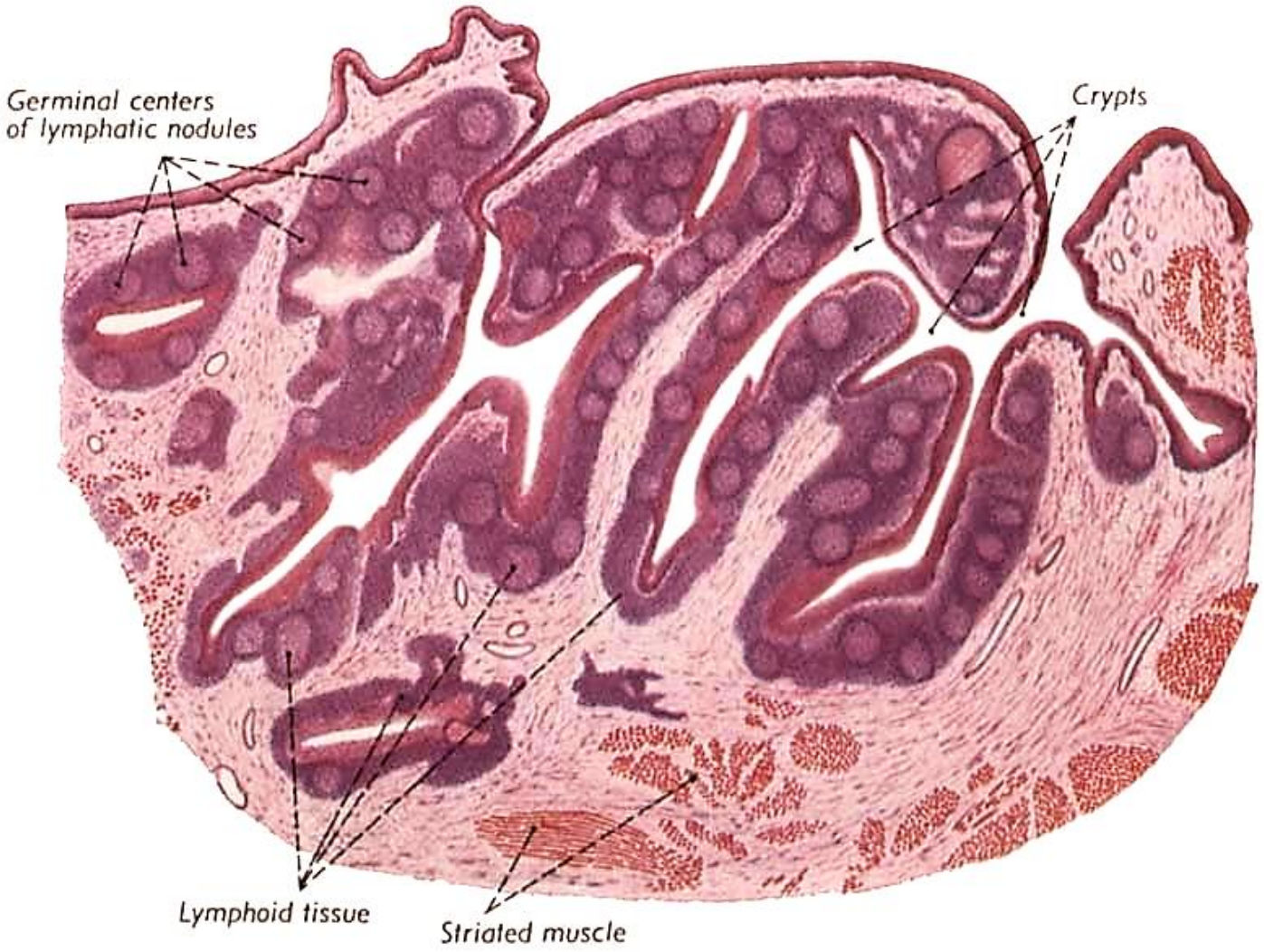
- incomplete encapsulation by connective tissue
- aggregations of lymphatic tissue (follicles) covered by epithelium of crypt
- crypts – deep and branched invaginations lined by epithelium
- reticulated epithelium

- **t. palatina** – stratified squamous e.
- **t. lingualis** – stratified squamous e.
- **t. pharyngea** – pseudostratified columnar e.
- **t. tubaria** – pseudostratified columnar e.



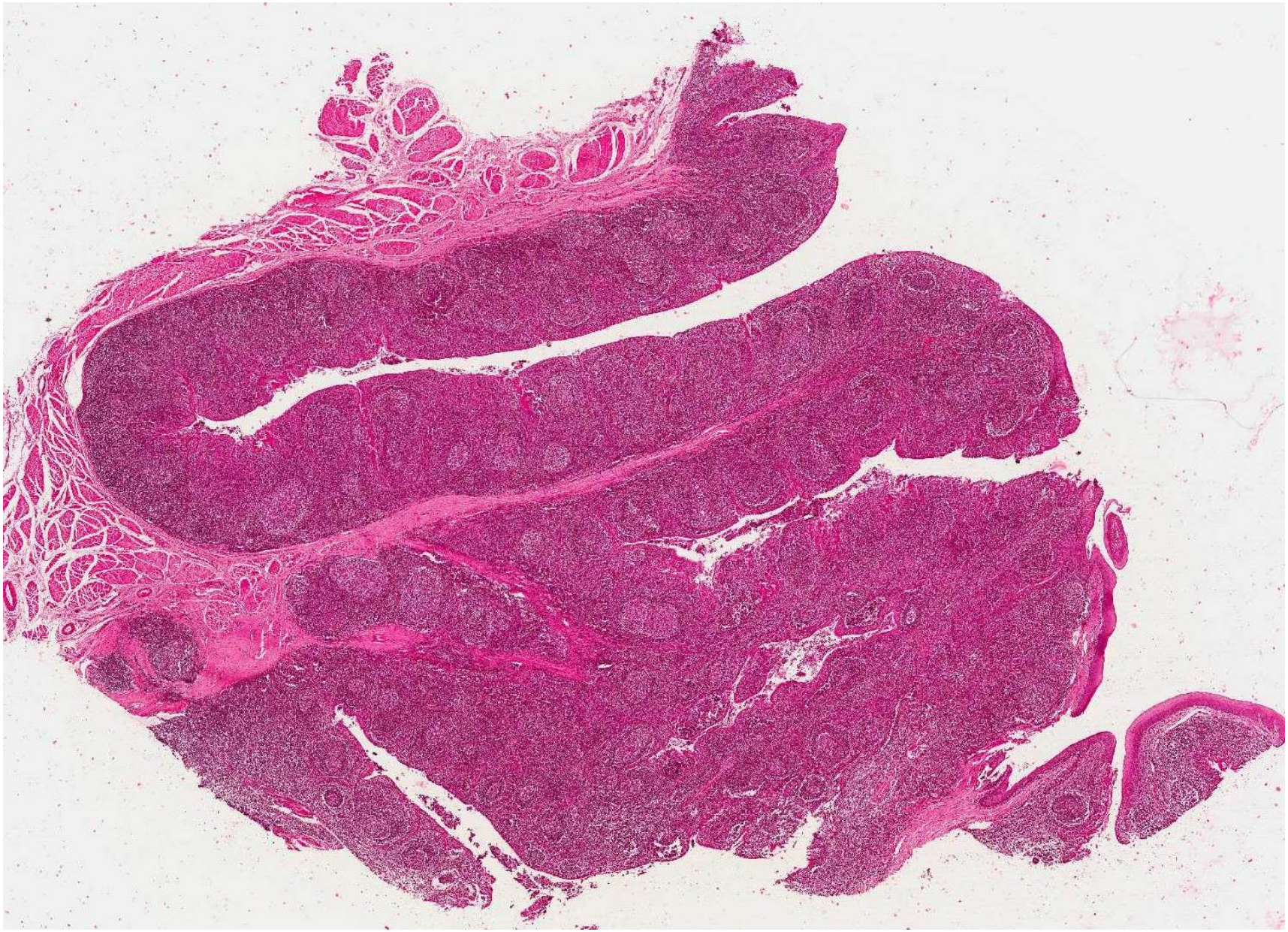


TONSILLA PALATINA

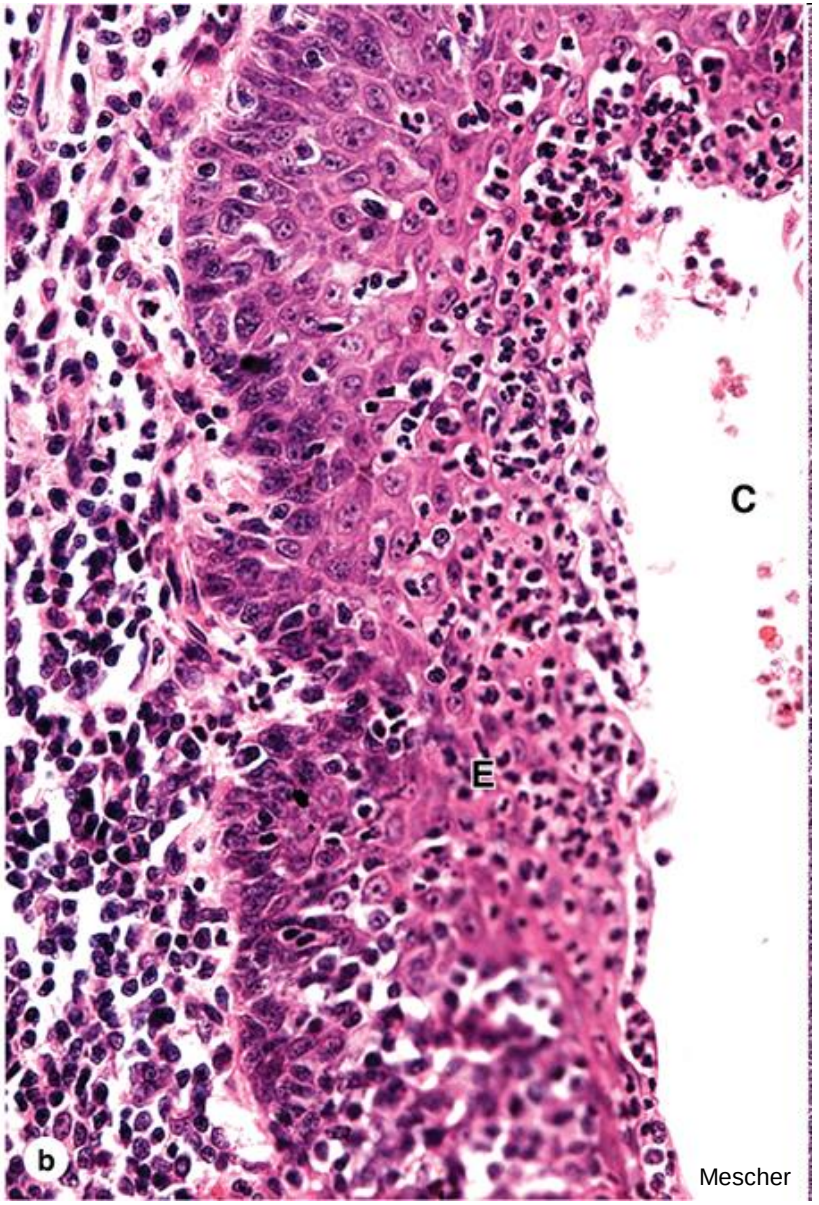


Sobotta

TONSILLA PALATINA

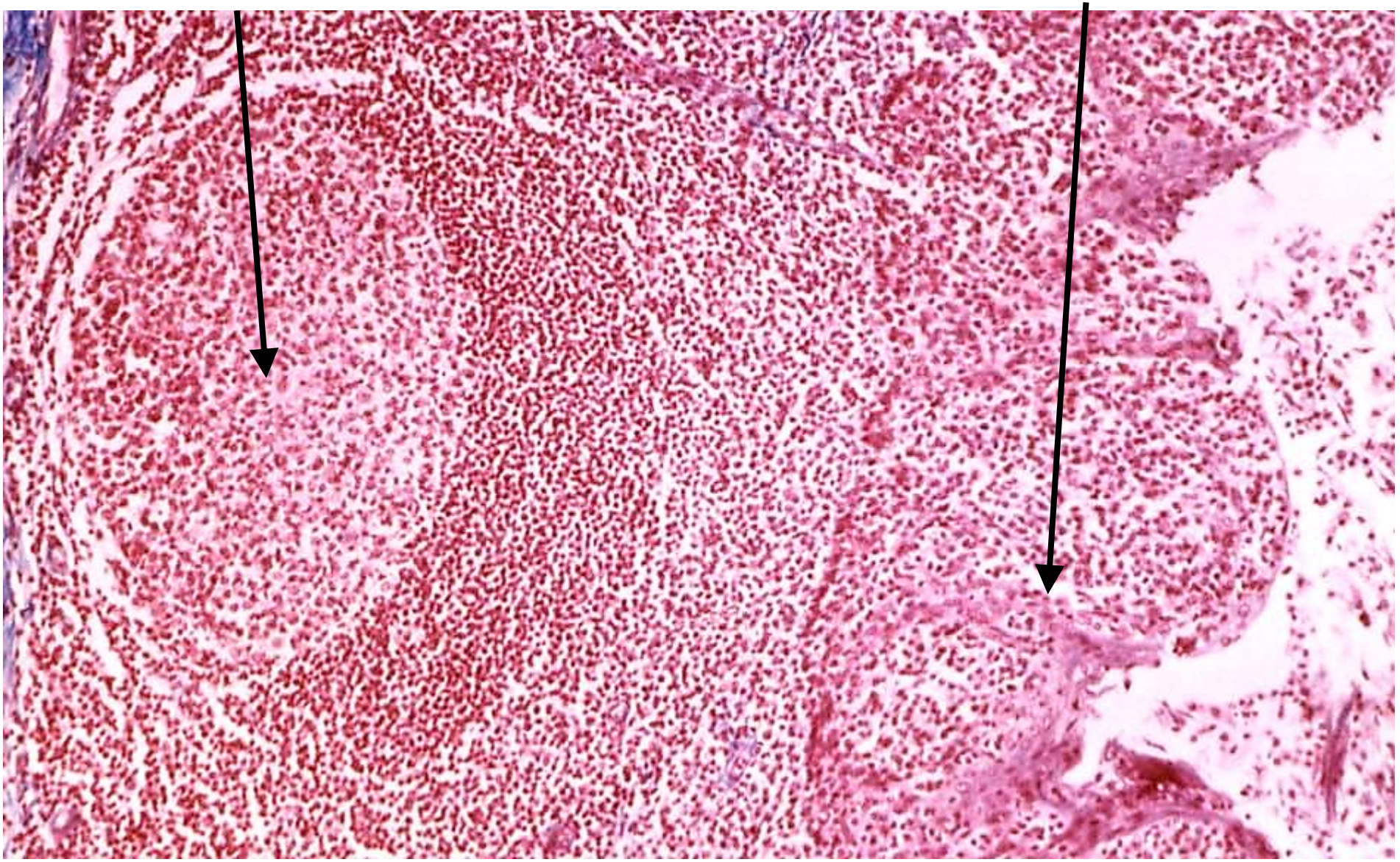


TONSILLA PALATINA

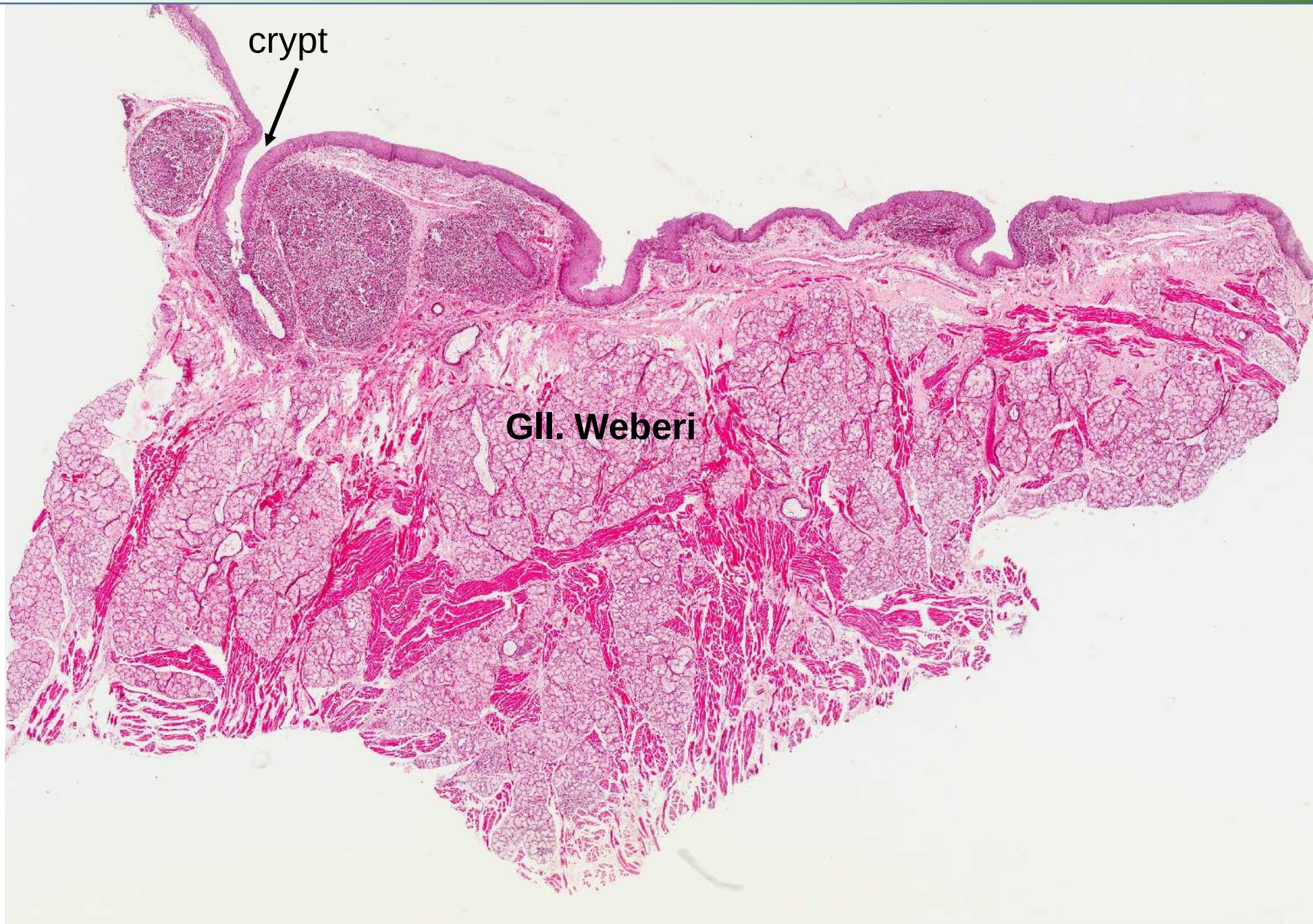


Mescher

TONSILLA PALATINA



TONSILLA LINGUALIS



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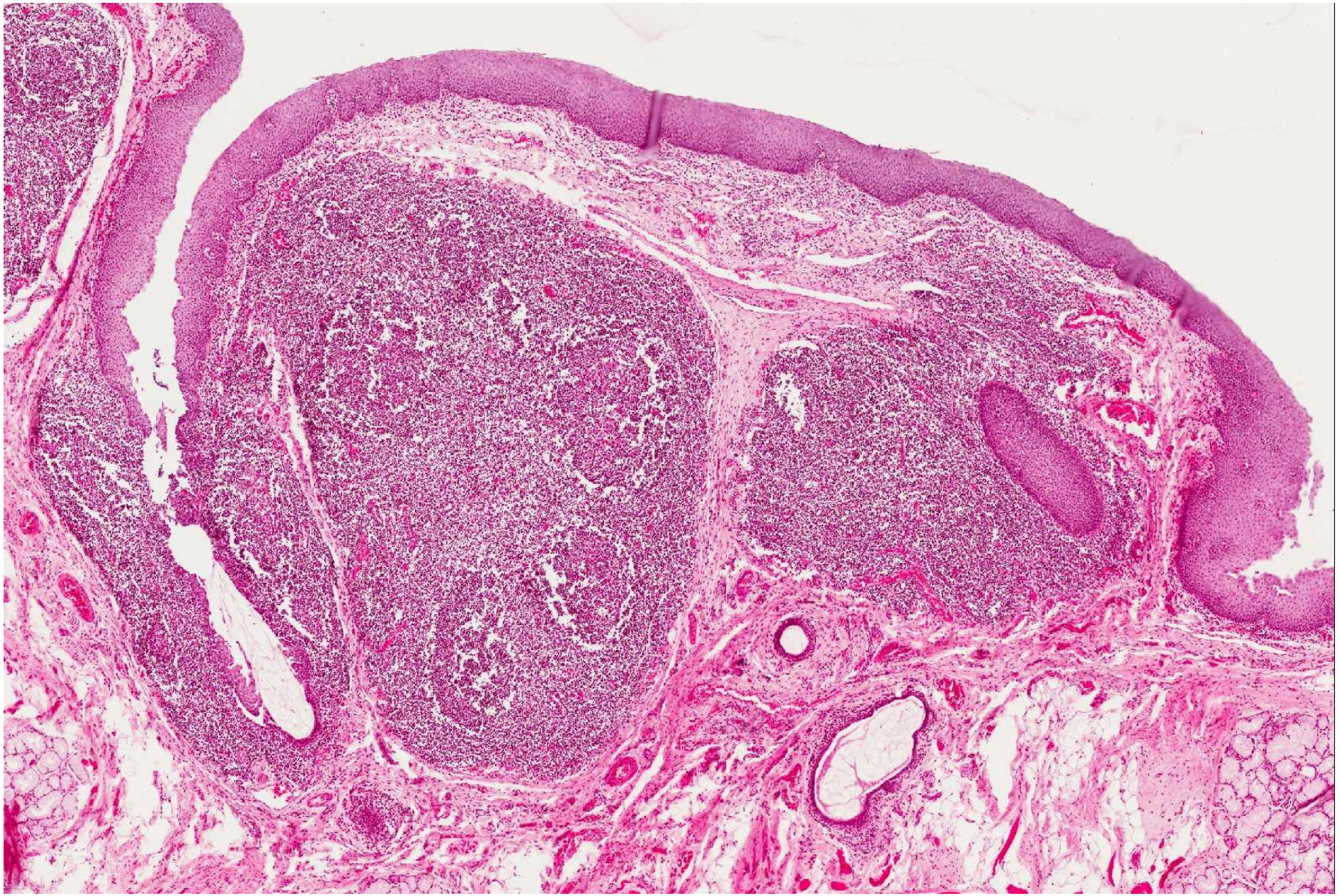

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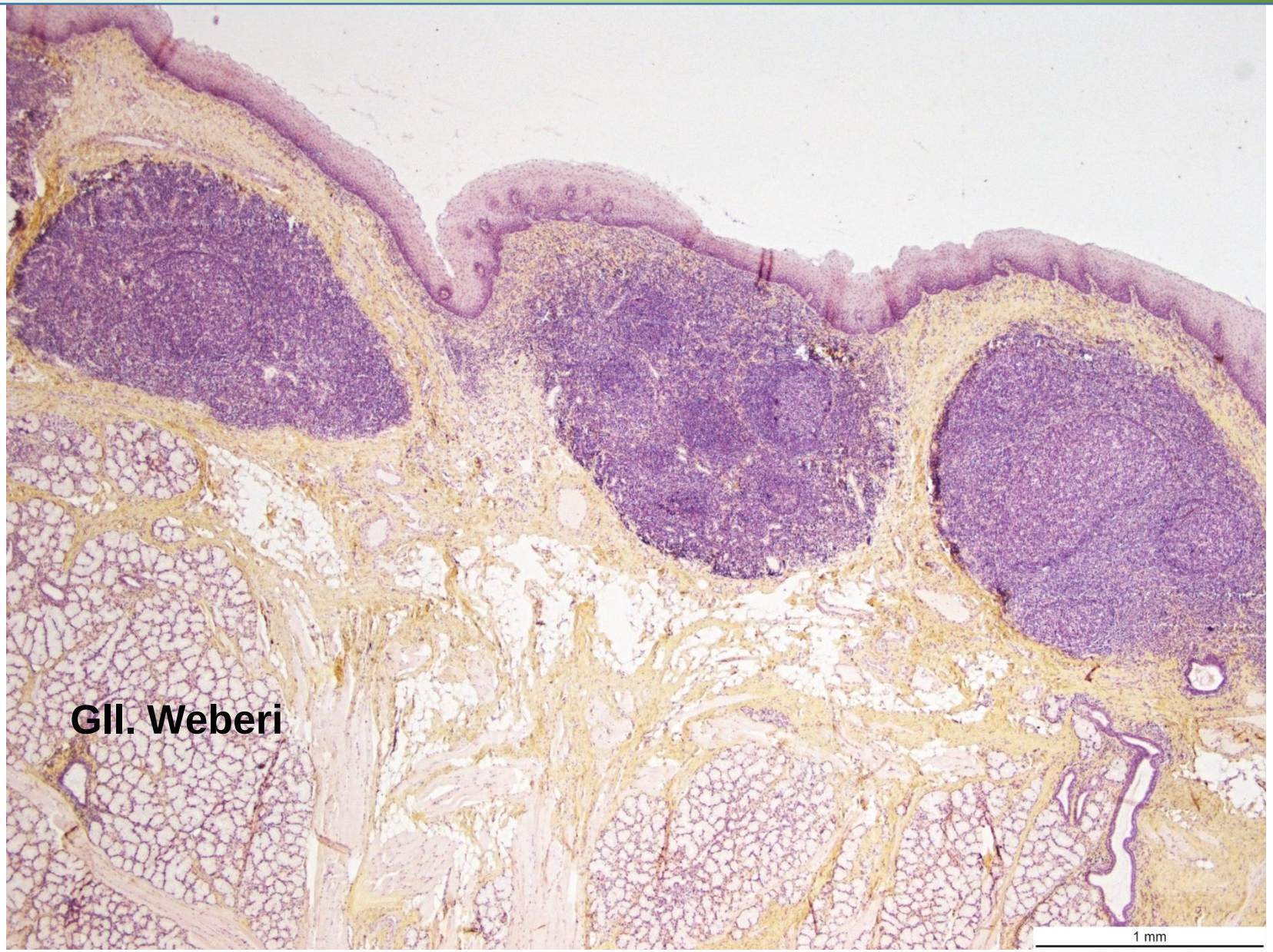
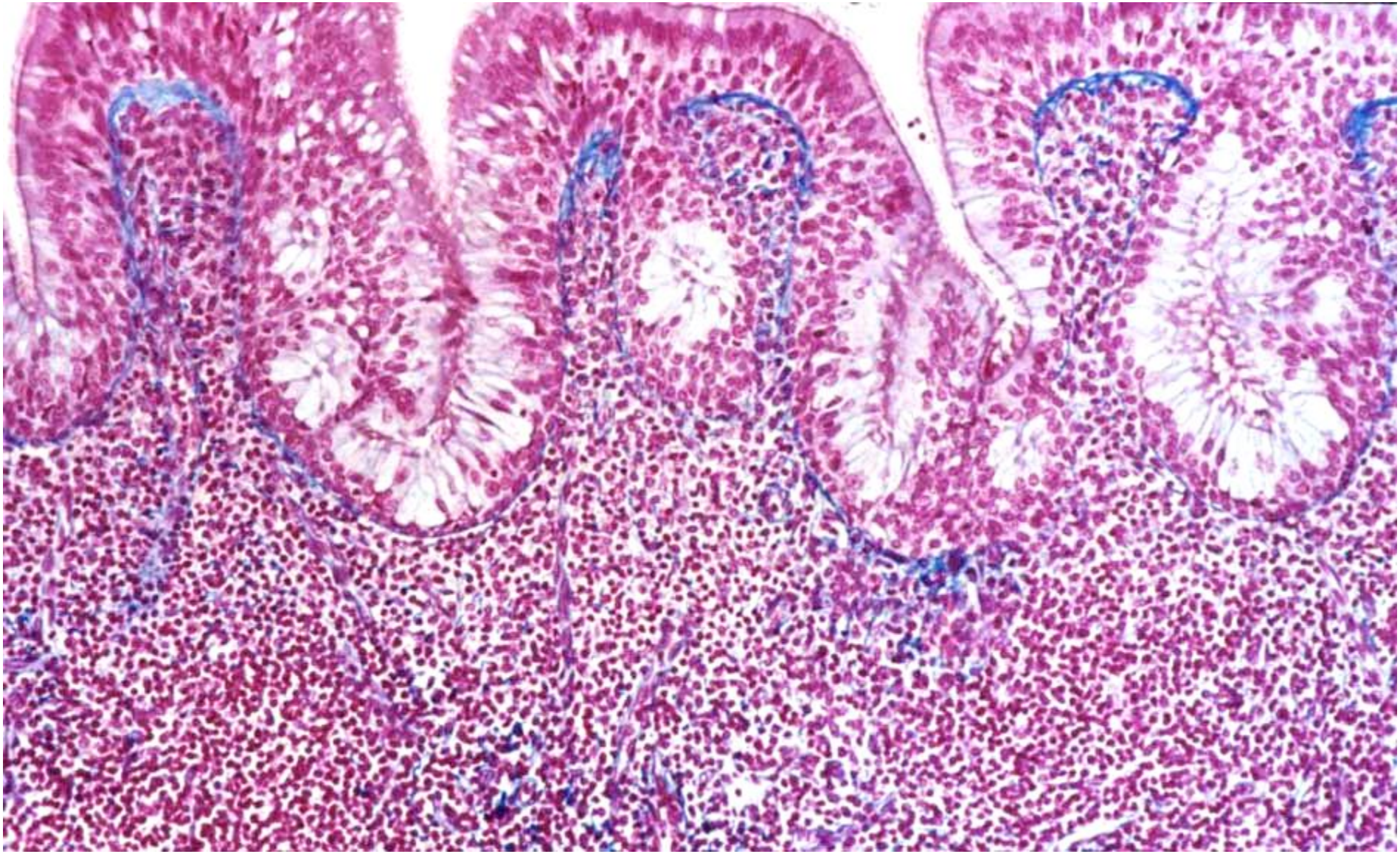
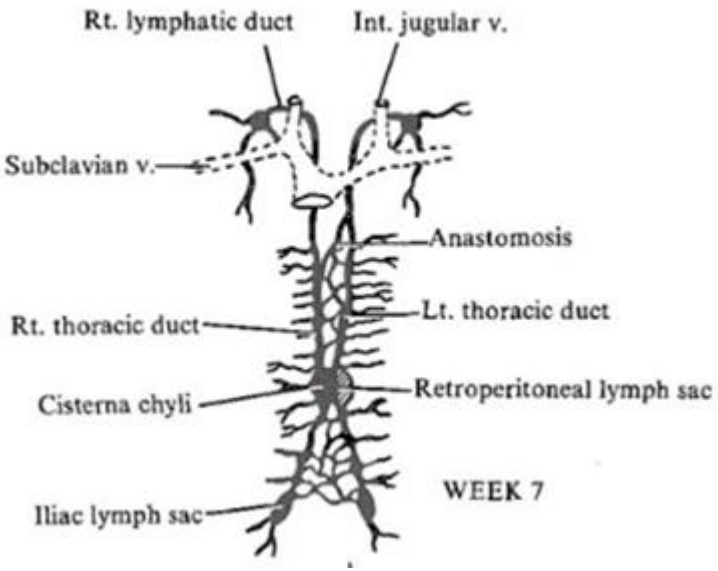


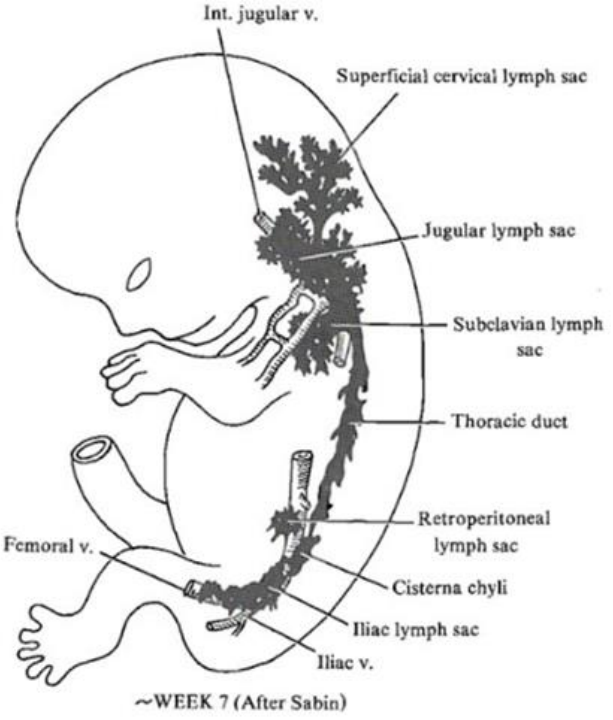
TONSILLA PHARYNGEA



DEVELOPMENT OF LYMPHATIC SYSTEM

- development starts at week 5
- origin unclear, presumably from mesenchyme or as outgrowths of primitive endothelium





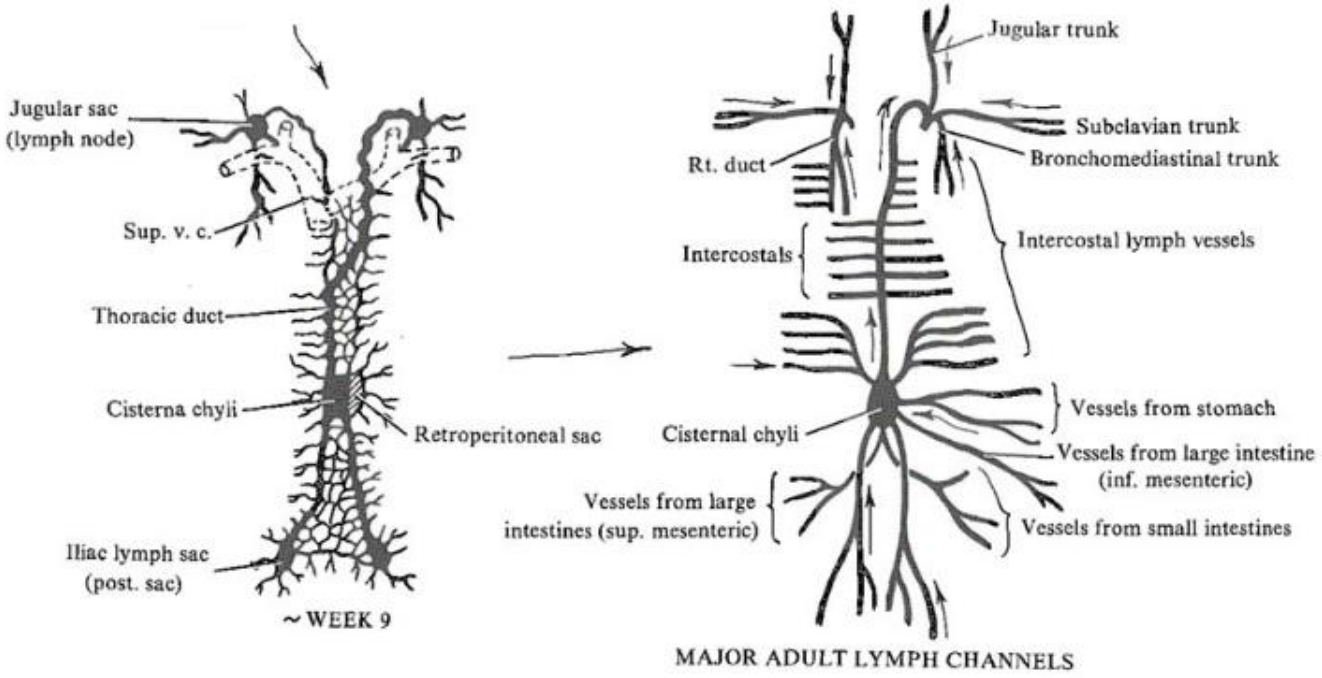
- **Week 6-9**, six primary lymph sacs from local dilatations

1. **Two** jugular (junction of the subclavian veins with the v. precardinales (→ v. jugularis int.)
2. **Two** iliac lymph sacs near the junction of the iliac veins with the v. postcardinales
3. **Single** retroperitoneal lymph sac
4. **Single** cisterna chyli dorsal to the retroperitoneal lymph sac

DEVELOPMENT OF LYMPHATIC SYSTEM

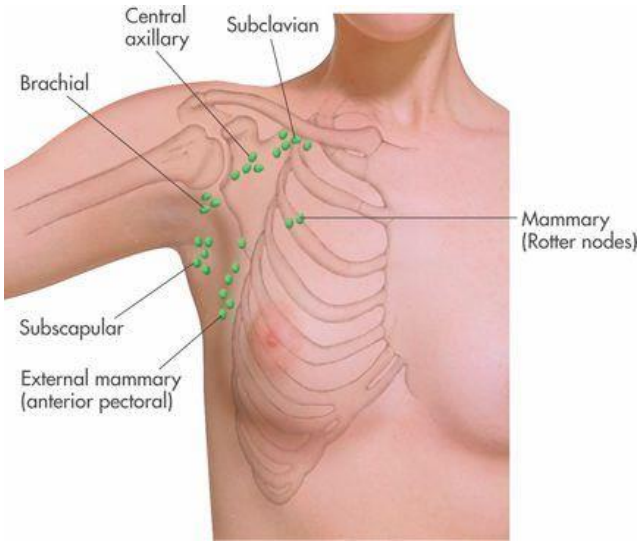
- **Lymph vessels grow from lymph sacs**
  - jugular: head, neck, thorax, upper limbs
  - iliac: trunk, lower limbs from iliac
  - retroperitoneal and cisterna chyli: intestine

- **Development of lymphatic ducts**
  - left and right thoracic duct connecting c. chyli and jugular sacs
  - anastomoses
  - D. thoracicus: caudal part of right thoracic duct, cranial part of left thoracic duct
  - D. lymhaticus dx.: cranial part of right thoracic duct



DEVELOPMENT OF LYMPHATIC SYSTEM

- **Development of lymph nodes**
  - lymph sacs (except for c. chyli) are invaded by mesenchymal cells and constitute apparent clusters of lymph nodes
  - B-cell compartments (follicles) develop around birth, lack germinative centers (naive)
  - lymph nodes develop along lymph vessels by similar mechanism



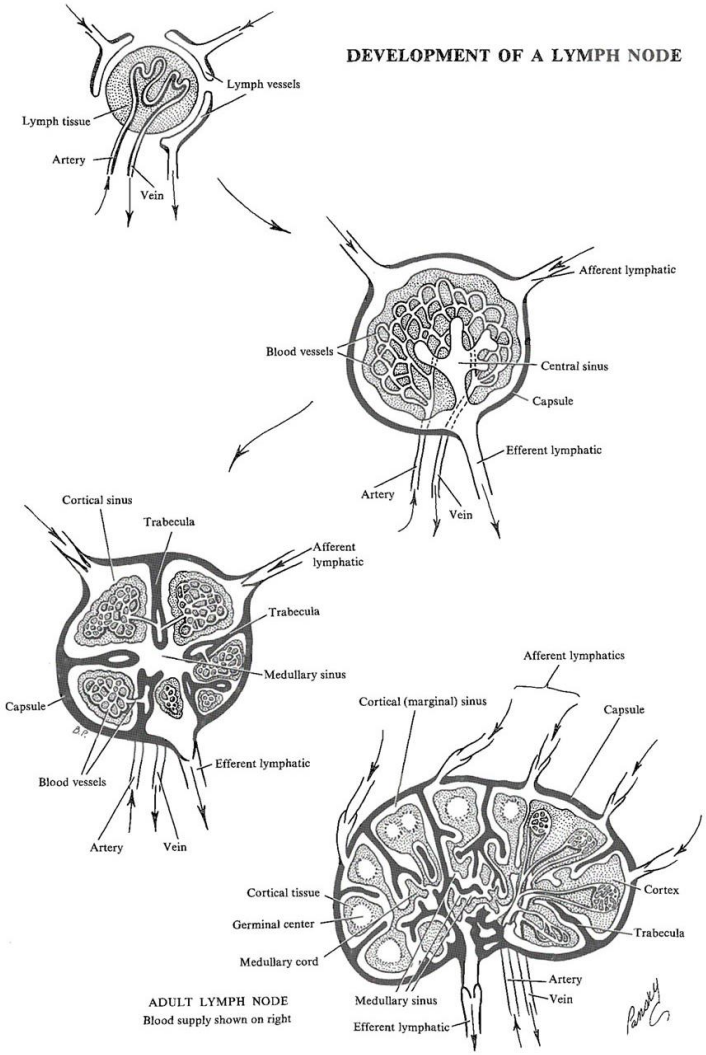
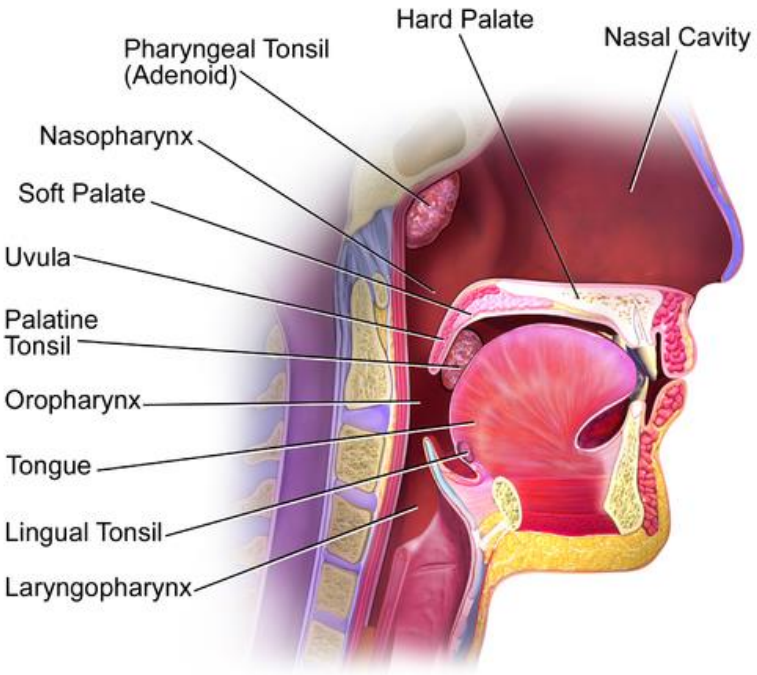


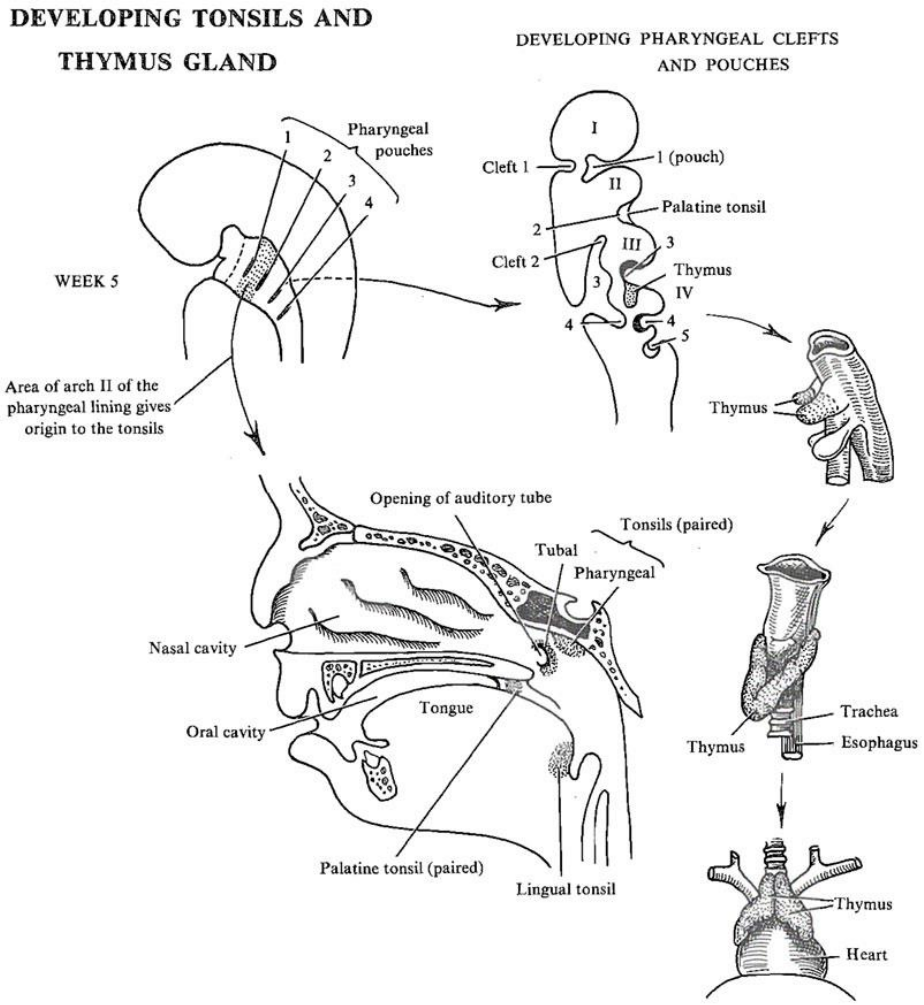
FIGURE 55. **Development of a lymph node.**

DEVELOPMENT OF TONSILS AND THYMUS

- **Tonsilla palatina**
  - second pharyngeal pouch (fossa)
- **Tonsilla pharyngea, tubaria and lingualis**
  - aggregation of lymph nodules in the nasopharynx, by opening of tuba auditiva or lingual root
- **Thymus**
  - third pharyngeal pouch

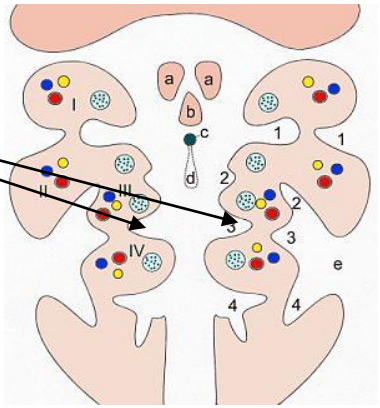


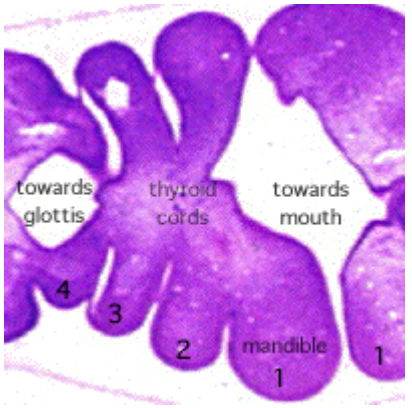
Tonsils and Throat

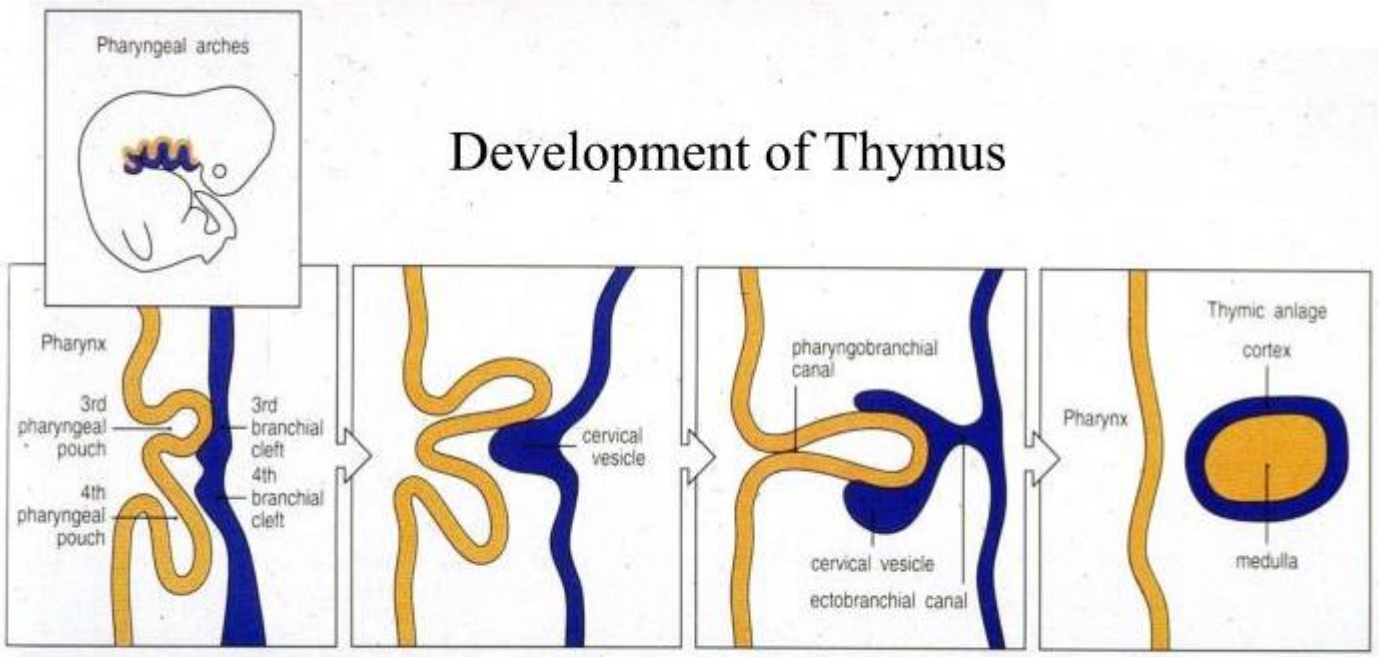


DEVELOPMENT OF THYMUS

- **Thymus**
  - third pharyngeal pouch

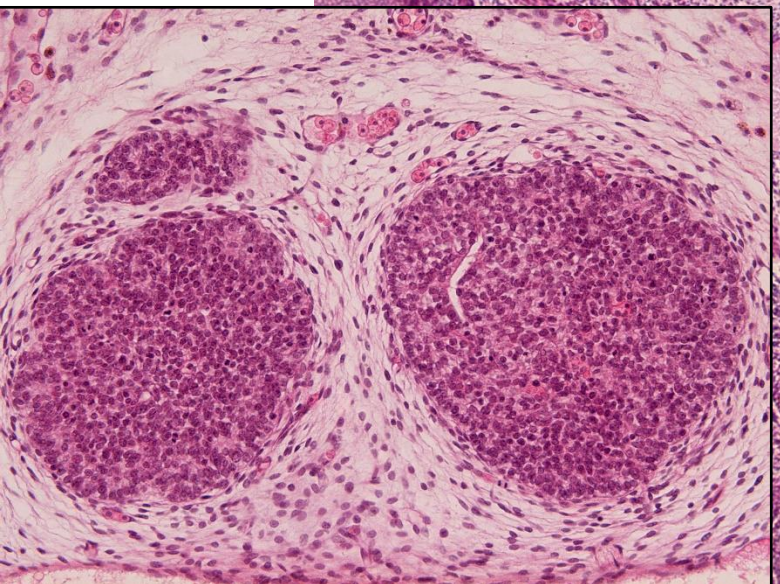


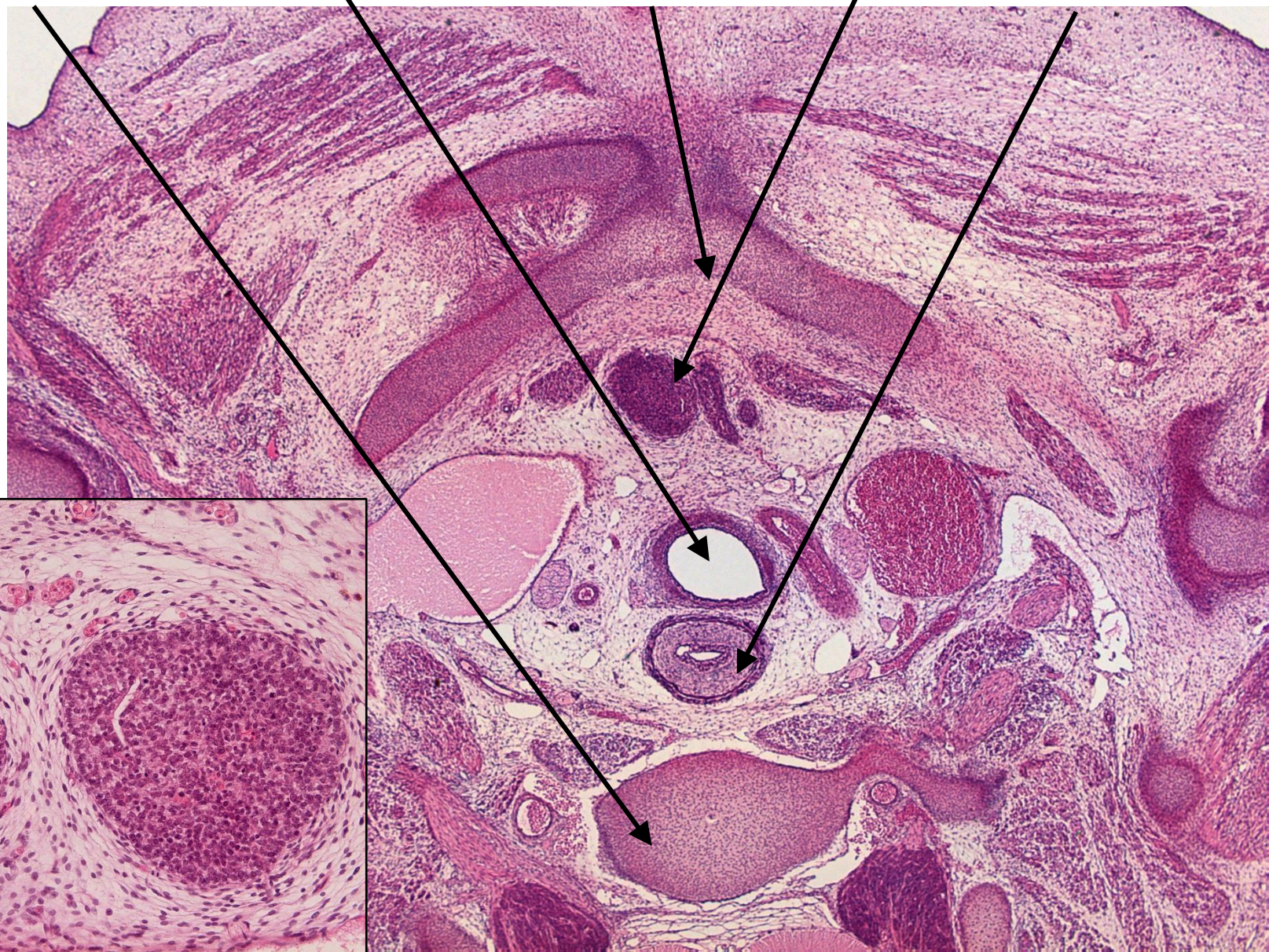




DEVELOPMENT OF THYMUS

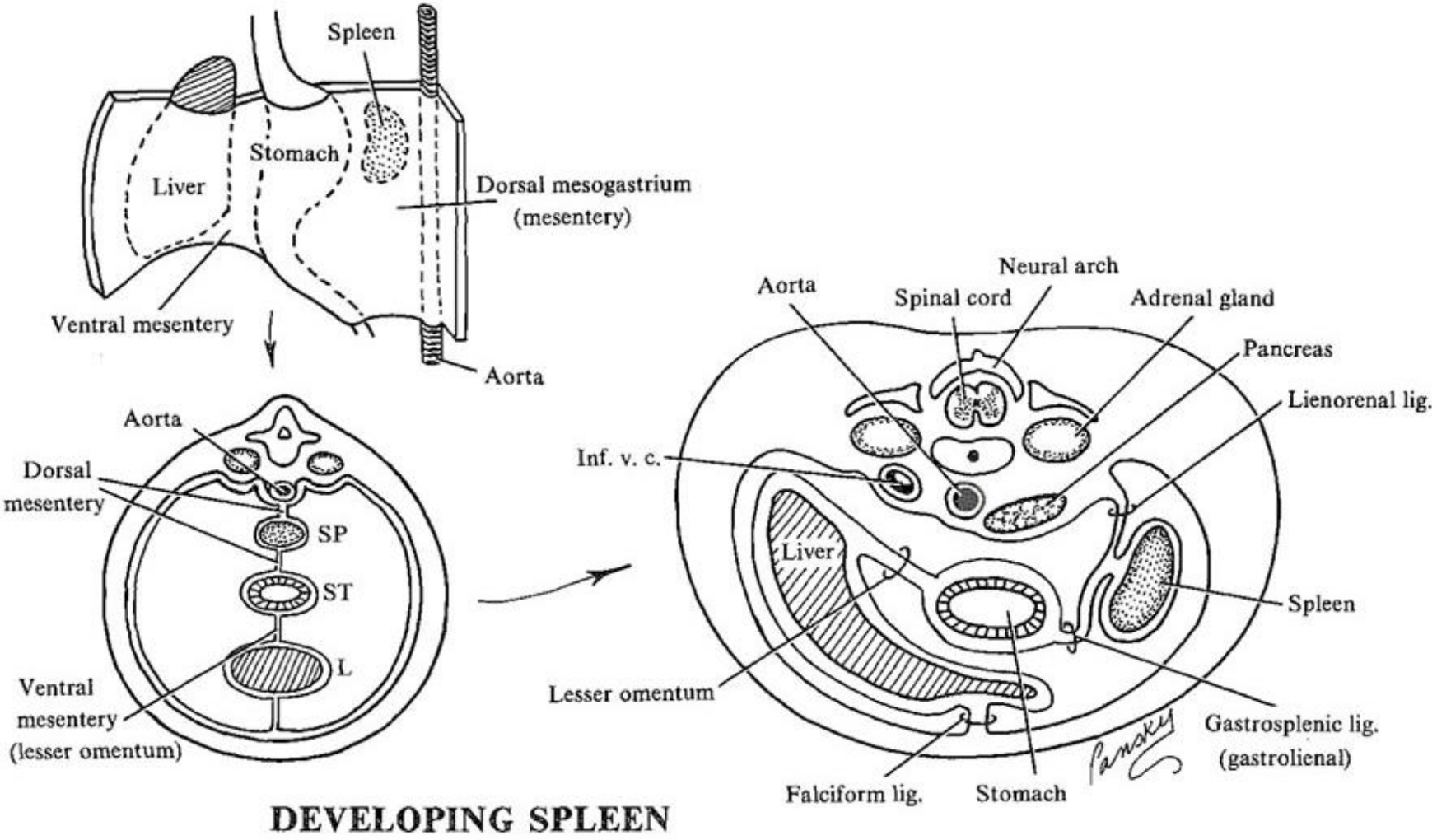
Week 8





DEVELOPMENT OF SPLEEN

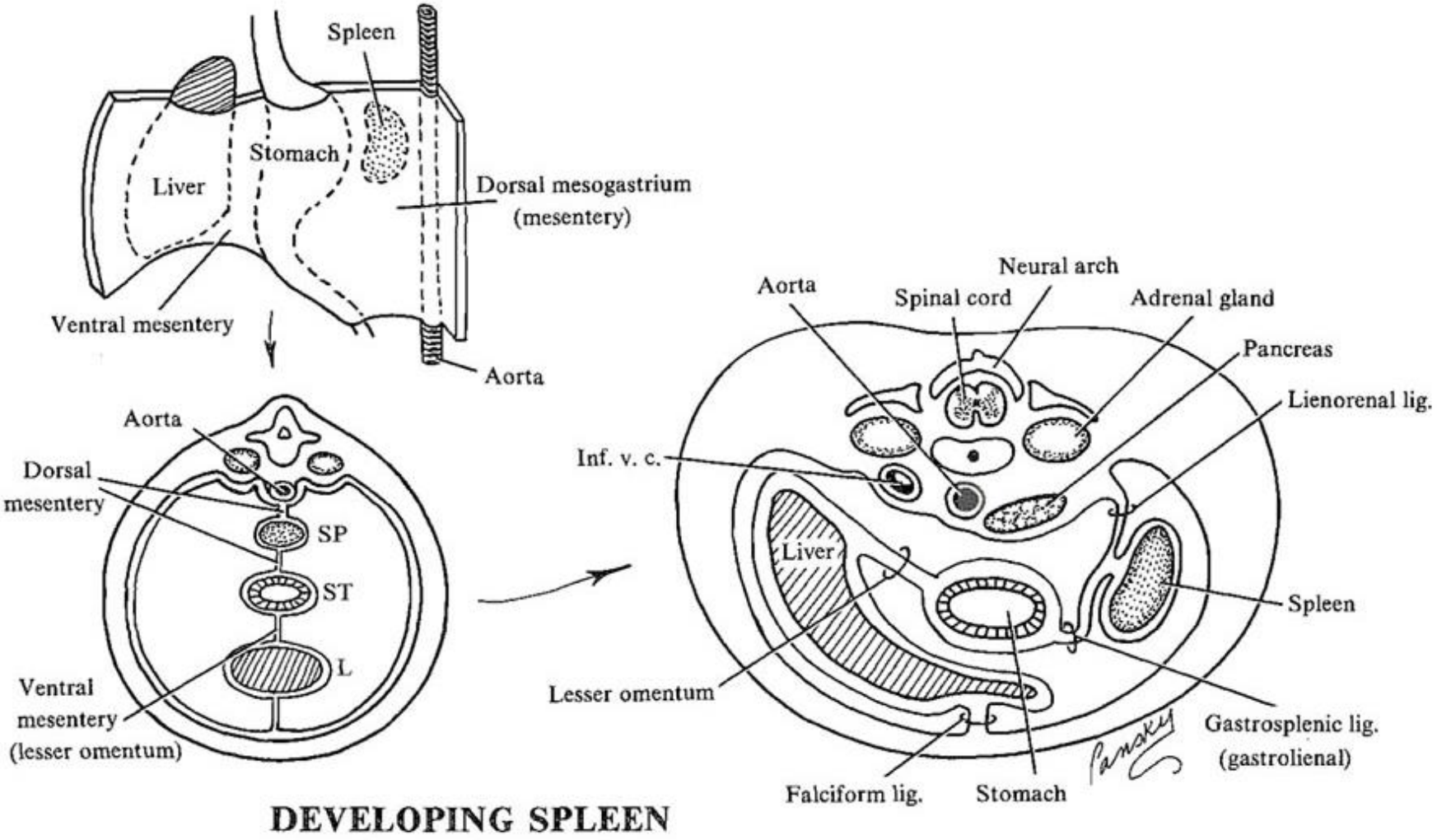
- Dorsal mesentery of stomach
- Mesenchymal origin



DEVELOPING SPLEEN

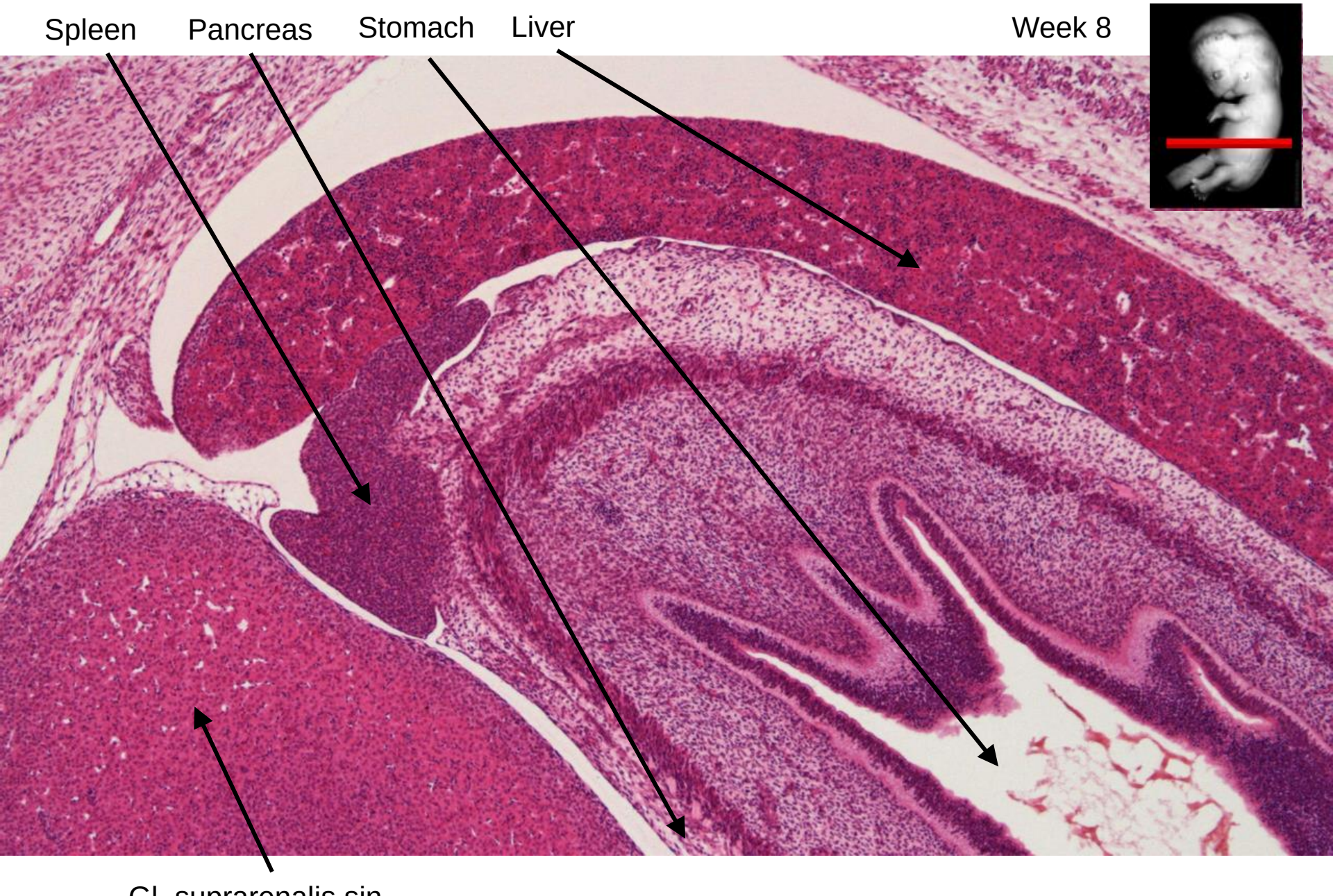
DEVELOPMENT OF SPLEEN

- Dorsal mesentery of stomach
- Mesenchymal origin



DEVELOPING SPLEEN

DEVELOPMENT OF SPLEEN



Thank you for attention

Questions? Comments?

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Special thanks to CellCartoons.net