Lymphoid and Immune System

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Immunity

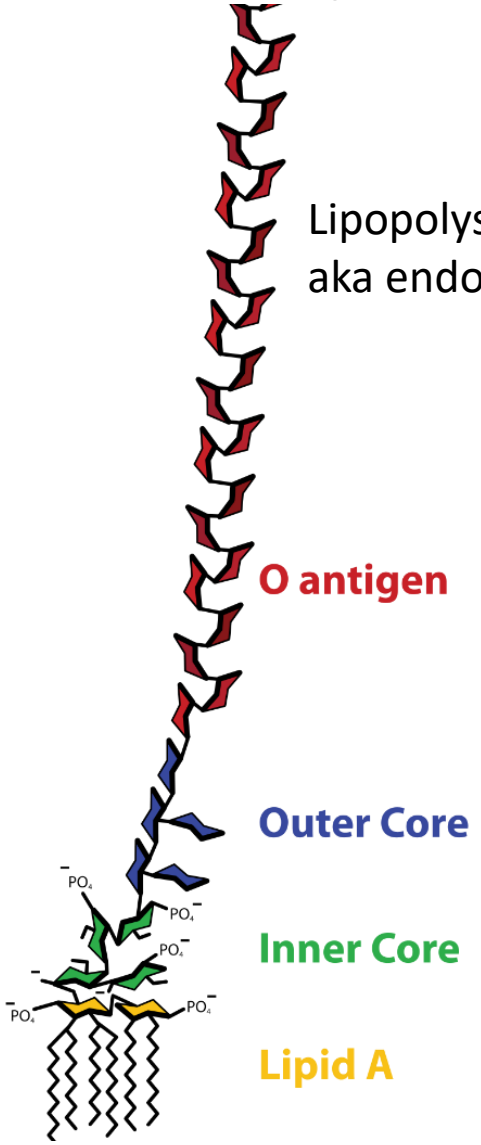
- The state of being insusceptible or resistant to a noxious agent or process, esp. a pathogen or infectious disease (oed.com)
- Defence against foreign substances, but also against components of the body's own organism
- Many mechanisms are involved

How does the immune system recognize harmful processes and agents?

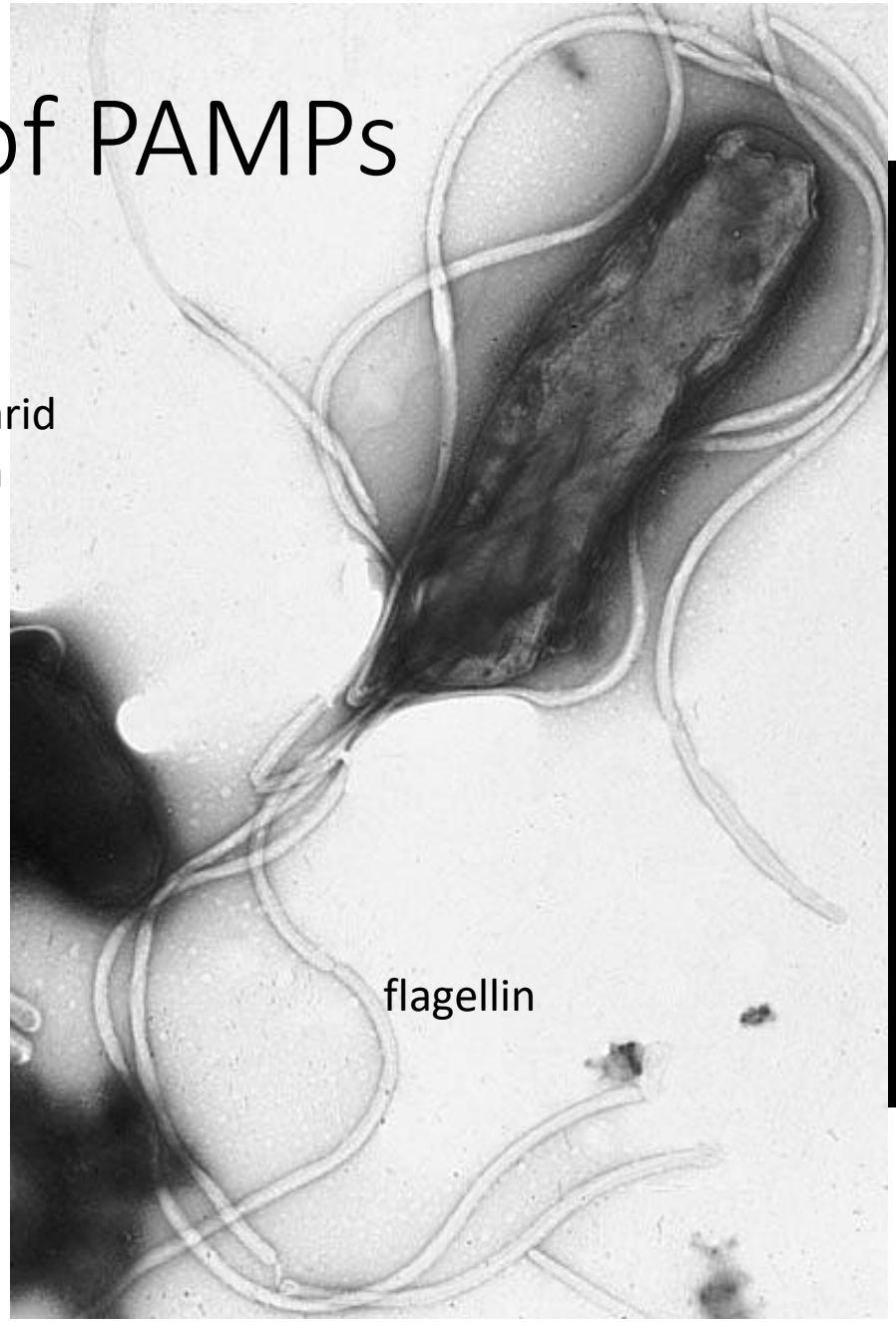
Pathogen recognition I.

- Using receptors - proteins that bind to a specific molecule
- Some molecules are typical of pathogens - pathogen associated molecular patterns (PAMPs)
- Receptors that recognise PAMPs are encoded by the corresponding genes - **innate immunity**
- Examples: lectins, Toll-like receptor, RIG-I-like receptor

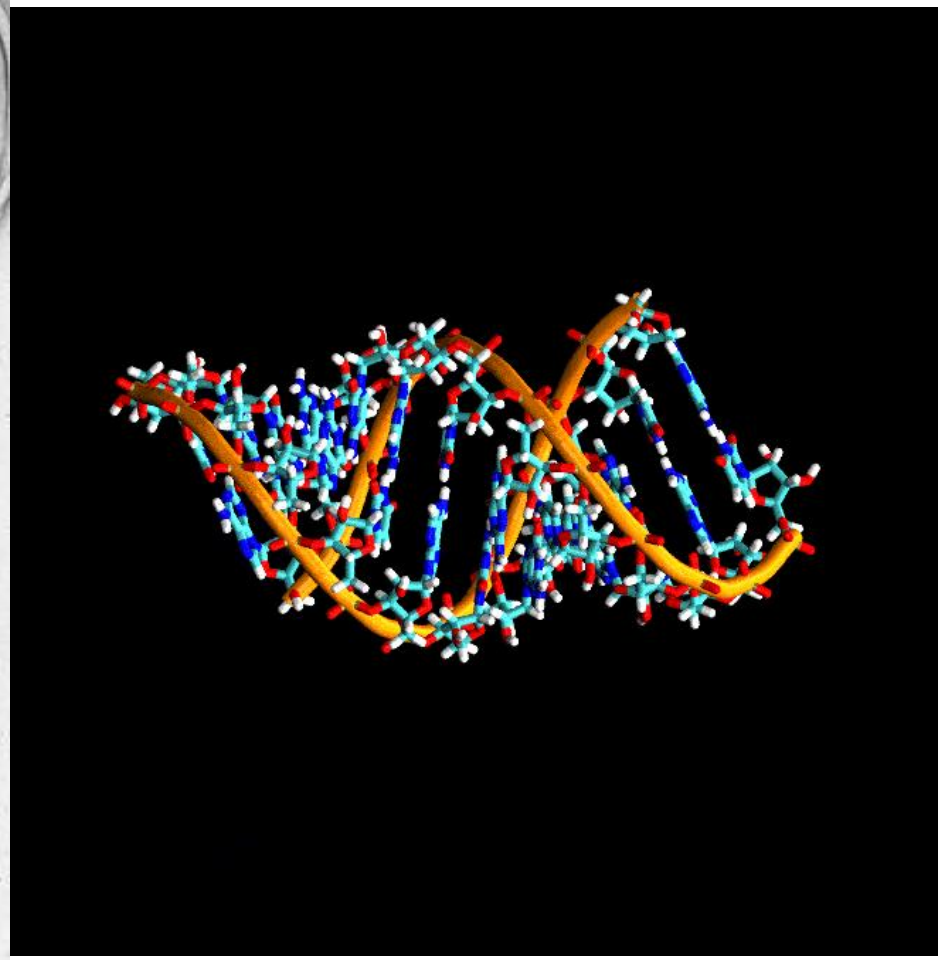
Examples of PAMPs



Lipopolysacharid
aka endotoxin



flagellin

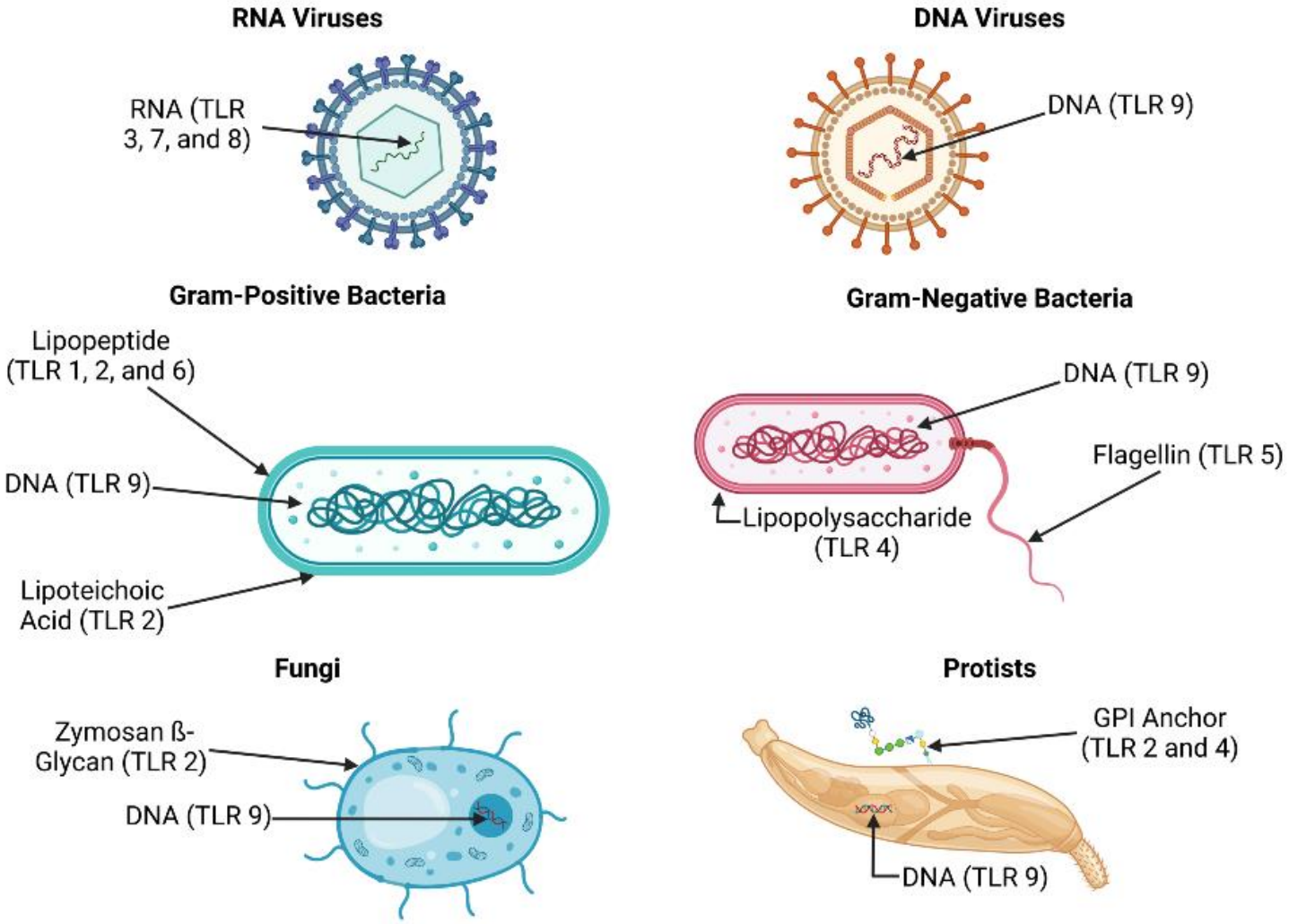


dsRNA

Advantages and disadvantages

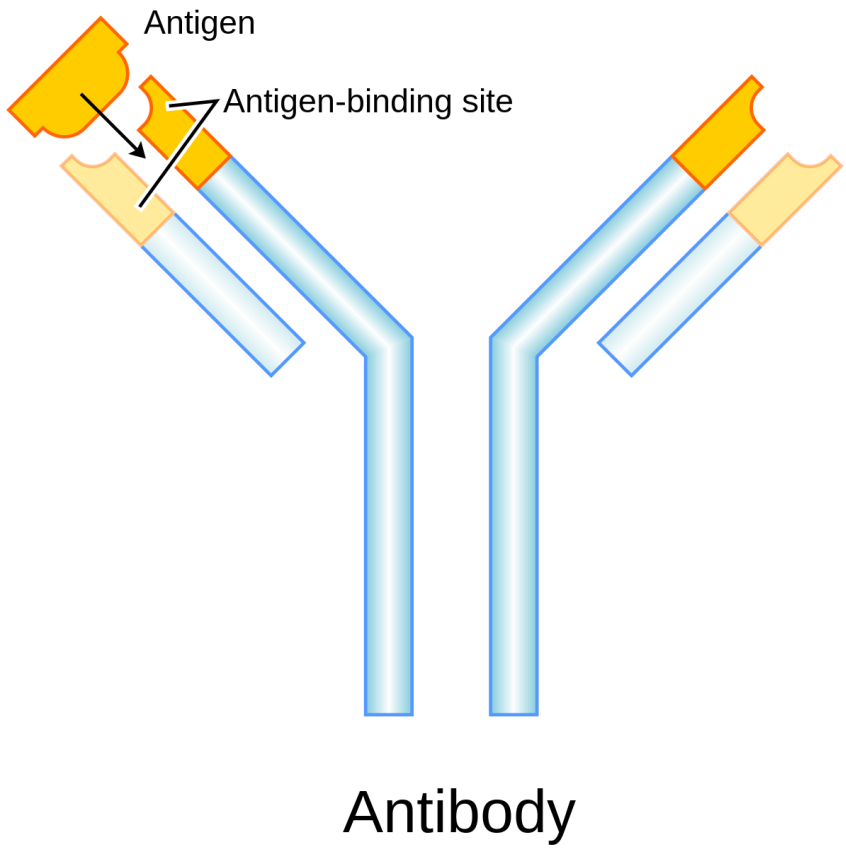
+ Fast reaction

- Limited number of targets



Pathogen recognition II.

- Specific immunity – later in evolution
- Receptors are created by somatic mutations of certain genes
- Immune cells with appropriate receptors are activated when they encounter a pathogen
- They bind to antigens - a broad group of molecules that trigger an immune response



Case 1

- A woman (60 years old) learns from her oncologist that a somatic mutation in the KRAS gene has been detected in her colorectal cancer
- She asks whether it is possible to arrange genetic testing of this gene for her family
- She has heard of genetic testing for the BRCA gene
- What do you recommend?

Case 1

- The somatic mutation is not in the germ cells and is therefore not transmitted to the offspring
- We probably wouldn't find it in the patient's genetic testing either, because most cells don't contain it

Advantages and disadvantages

+ Specific reaction
+ Broad range of targets

- Possible autoimmunity
- Demanding proces (a lot of dysfunctional receptors)

Immunity

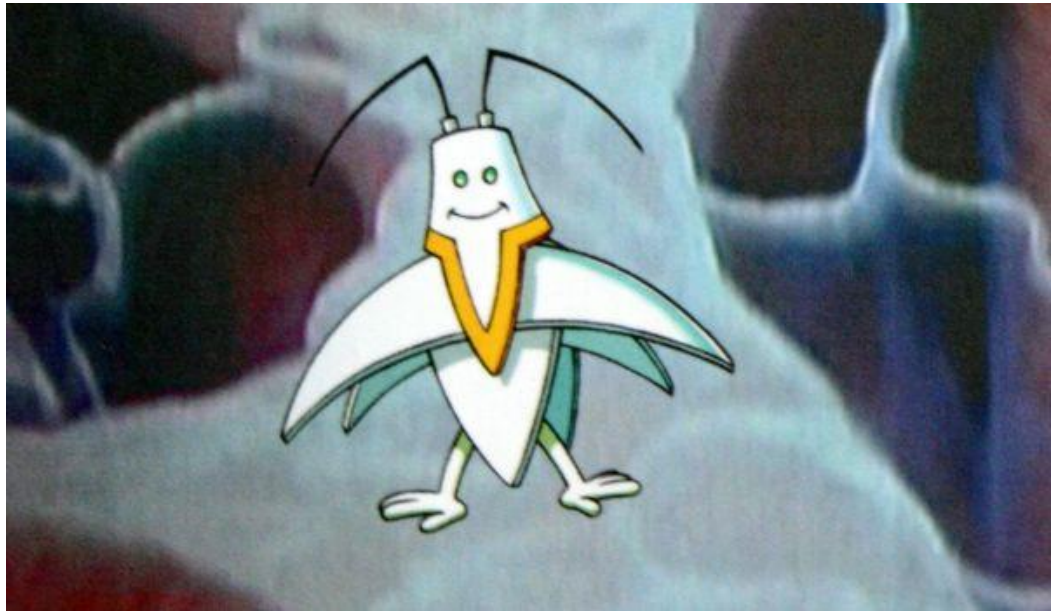
- Detection and elimination of foreign or abnormal substances
  1. Recognise danger using receptors
  2. Inform others - using cytokines (interferons, lymphokines, interleukins...)
  3. Countermeasures - increase in temperature, destruction of the pathogen by phagocytic cells, neutralization by antibodies, granuloma formation...
- Antigen is a particle capable of eliciting an immune response
- We distinguish between **innate** immunity and **acquired** immunity
- The second axis of division is **humoral** immunity and **cellular** immunity

Innate and acquired immunity

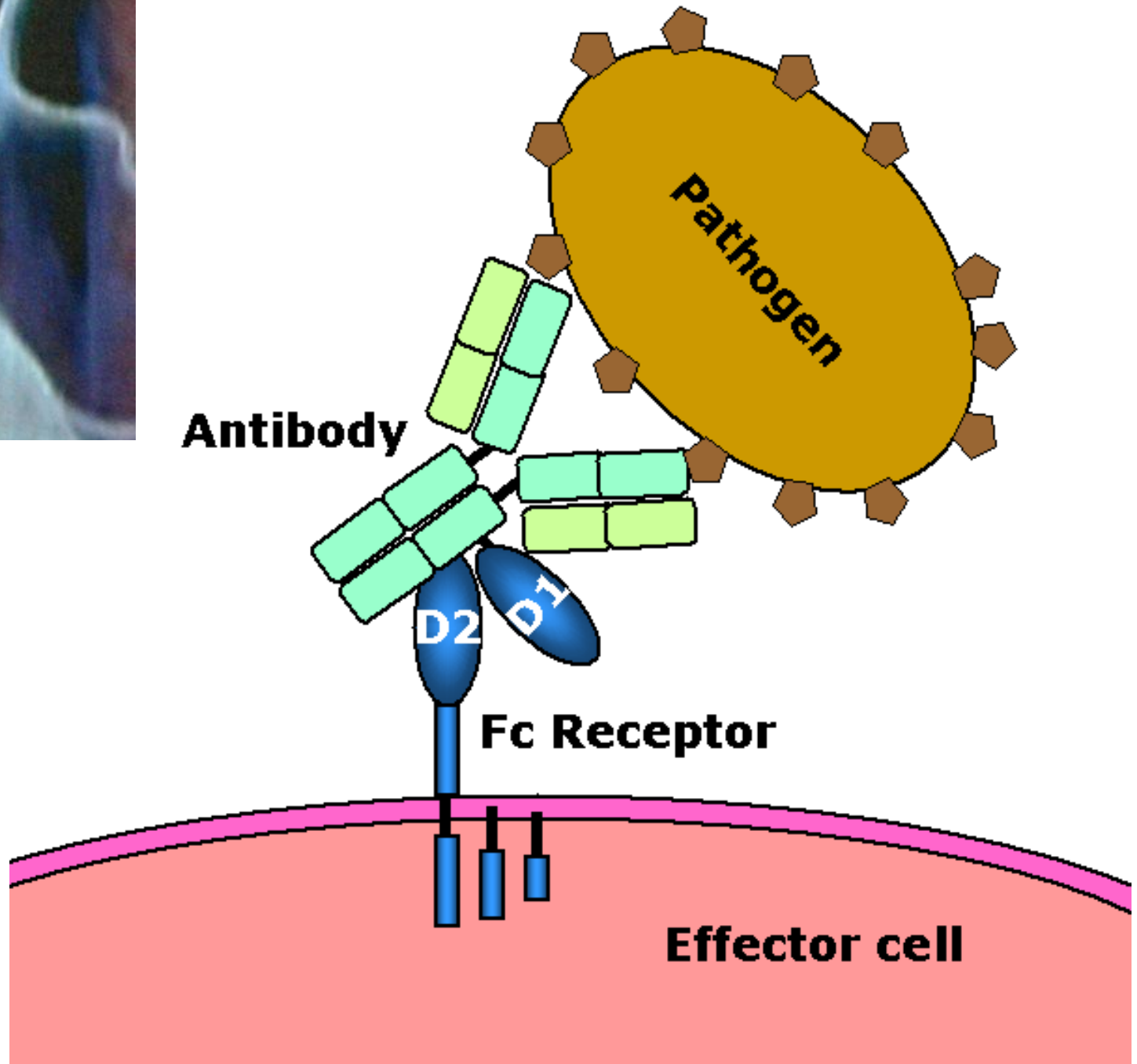
	Innate immunity	Acquired
How does it recognize its target?	PAMP, MHC absence, common features of many pathological processes, uses given receptors (e.g. TLR)	They select a receptor from a large number of randomly created receptors on the basis of interaction specificity
How fast is the response?	Immediate	There is a gap (selection of the right receptor), fast with immunological memory
How effective is the response?	Only limited range of targets	Specific binding to a molecule
Synonyms	Non-specific, non-adaptive	Specific, adaptive

Humoral and cellular immunity

	Humoral immunity	Cellular immunity
What executes it?	Circulating substances that are released by cells to the ECF, reaching their site of action by circulation and diffusion	Cells that make direct contact with the pathogens
How does it dispose of pathogens?	They neutralize toxins and other important parts of the pathogen, mark it as an enemy	They release enzymes (e.g. perforins, granzymes), that destroy the diseased cell, phagocytosis



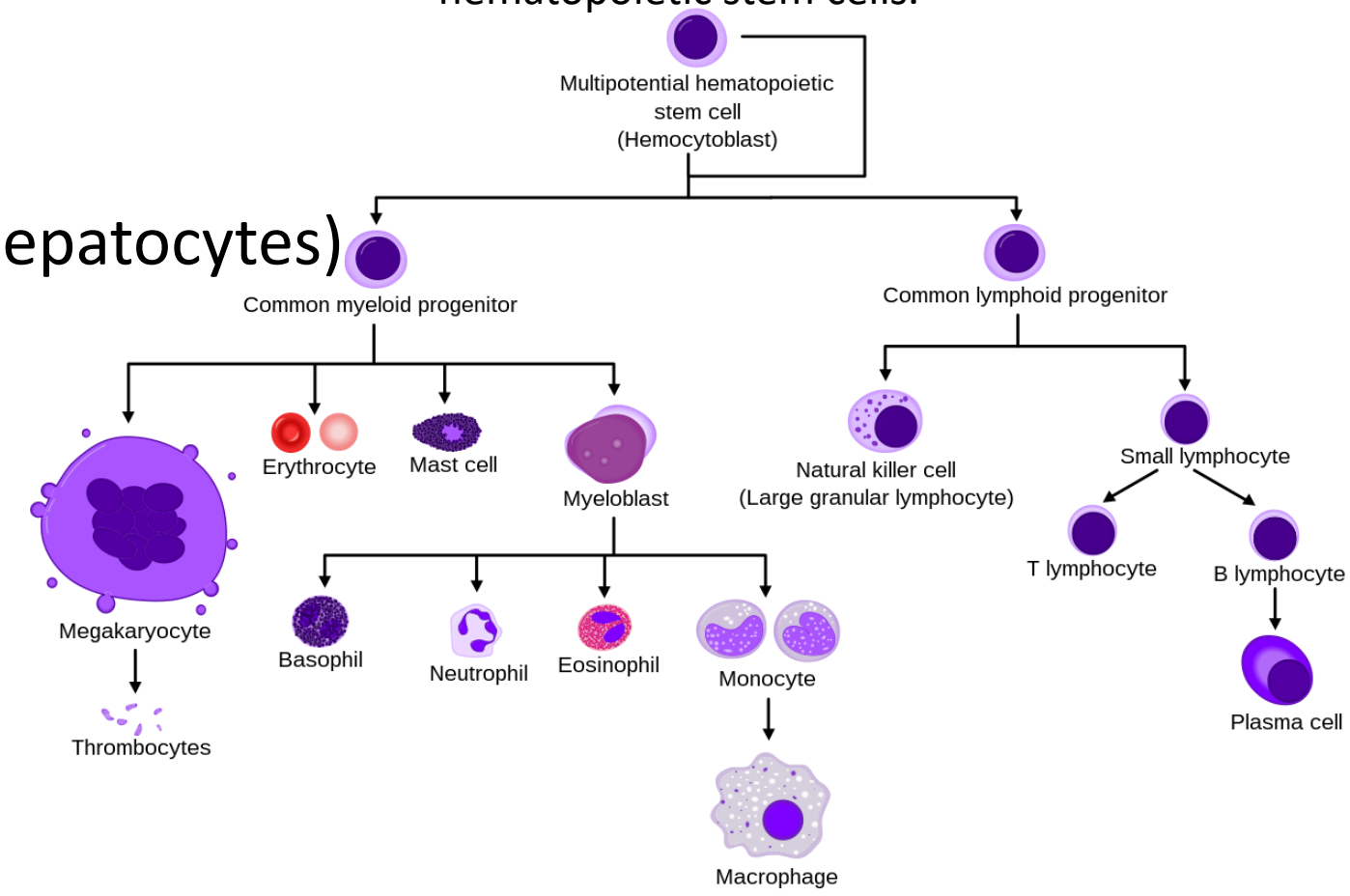
The antibody marks the particle for phagocytosis.



Group by type of immunity

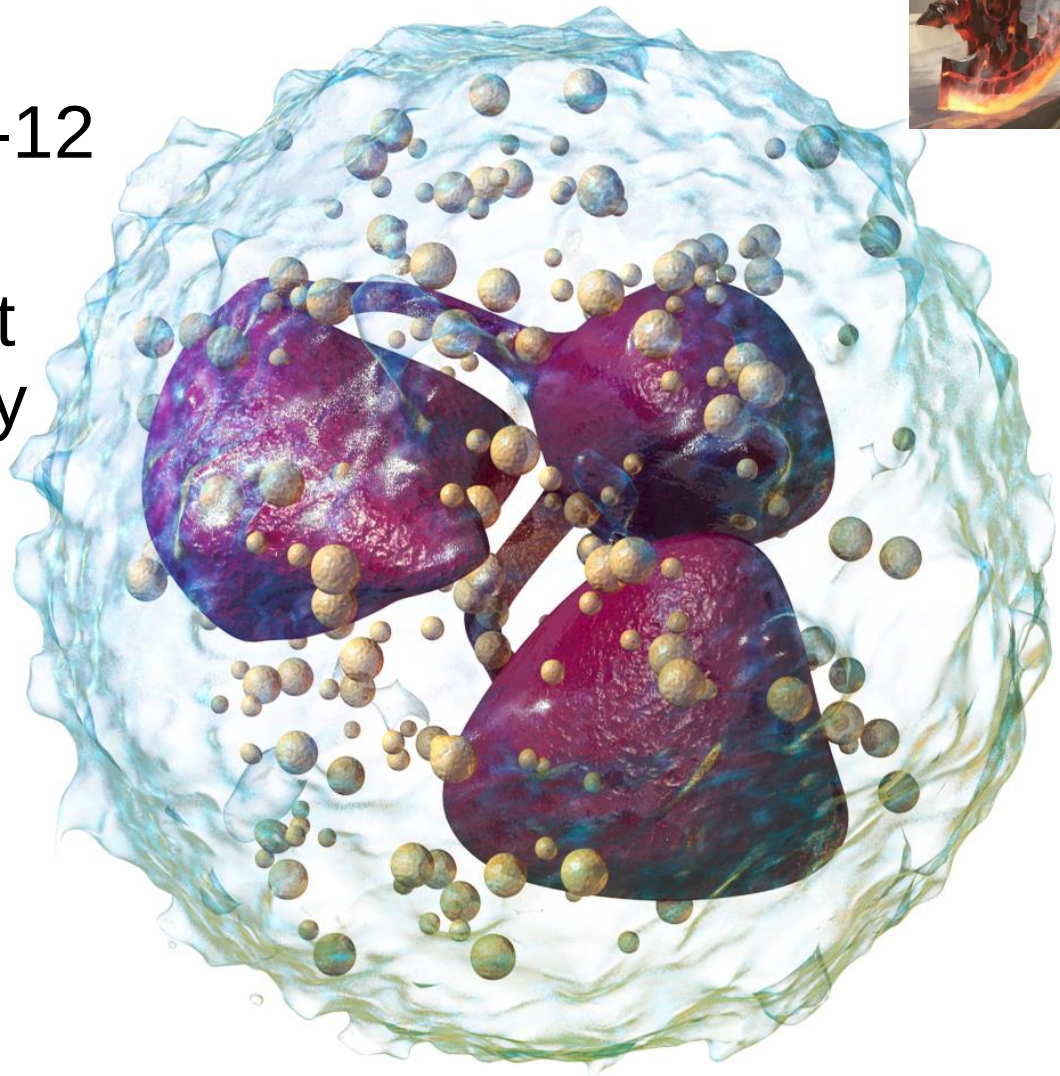
- T-lymfocyte
- B-lymfocyte
- Complement (produced by hepatocytes)
- Macrophage
- Plasma cell
- Neutrophil
- NK-cell

Cells of the immune system arise from hematopoietic stem cells.



Neutrophilic granulocyte

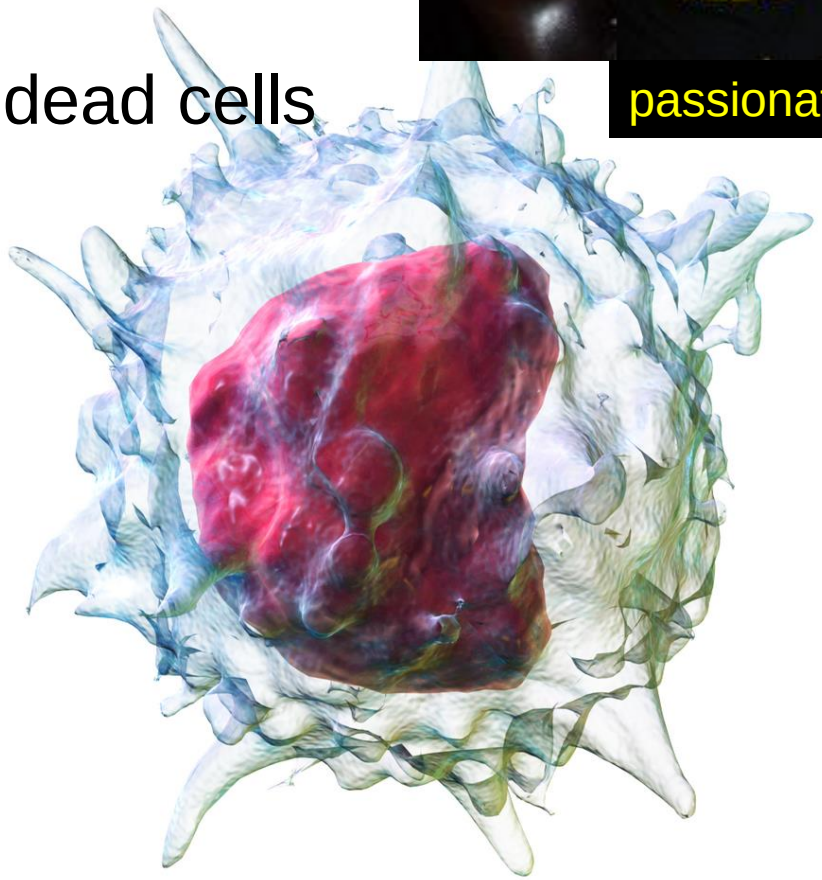
- In the blood circulation 6-12 hours
- They persist for 5 days at most, after activation they completely disintegrate (pus)
- Chemotaxis-guided diapedesis
- Myeloperoxidase



Monocyty a makrofágy

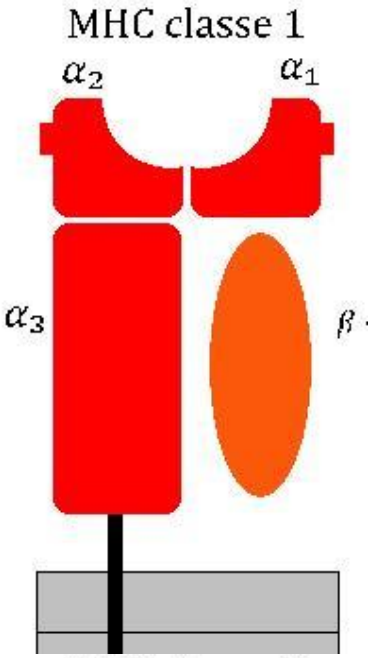
- In the blood for 3 days, followed by diapedesis into the connective tissue
- In tissue macrophages (histiocytes)
- Phagocytize pathogens and their own dead cells
- Present antigens, produce cytokines
- Involved in reparation
- Specific names in certain tissues
  - Liver - Kupffer cells
  - Lung - coniophages (dust cells)
  - Placenta - Hofbauer cells
  - Brain – microglia
  - Spleen – siderophages

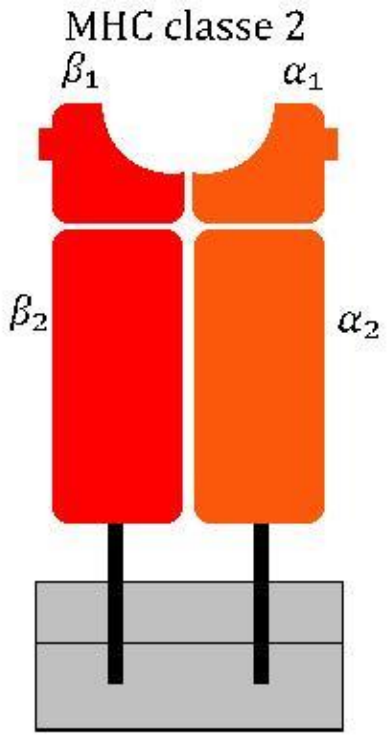
passionate eater

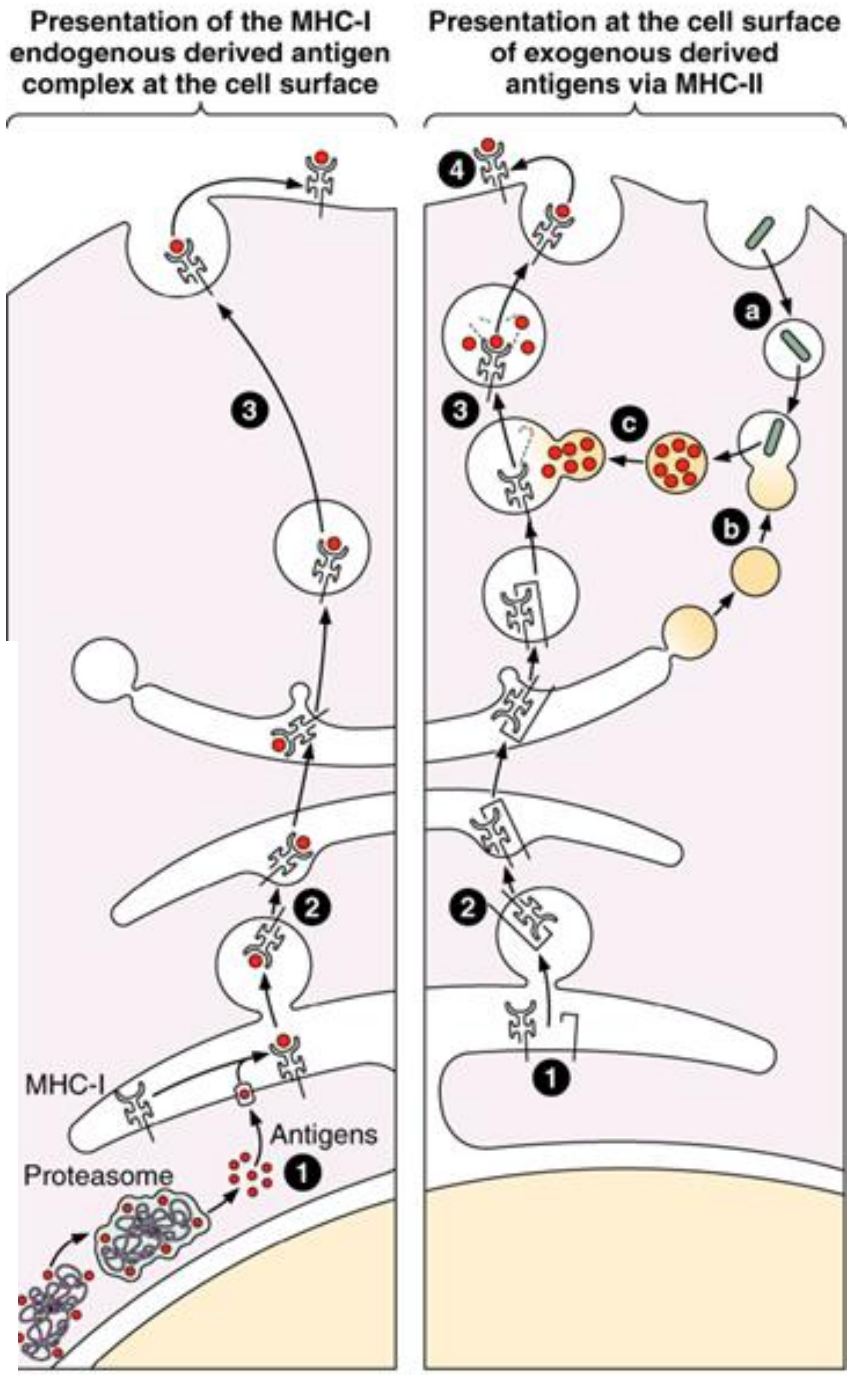


MHC komplex

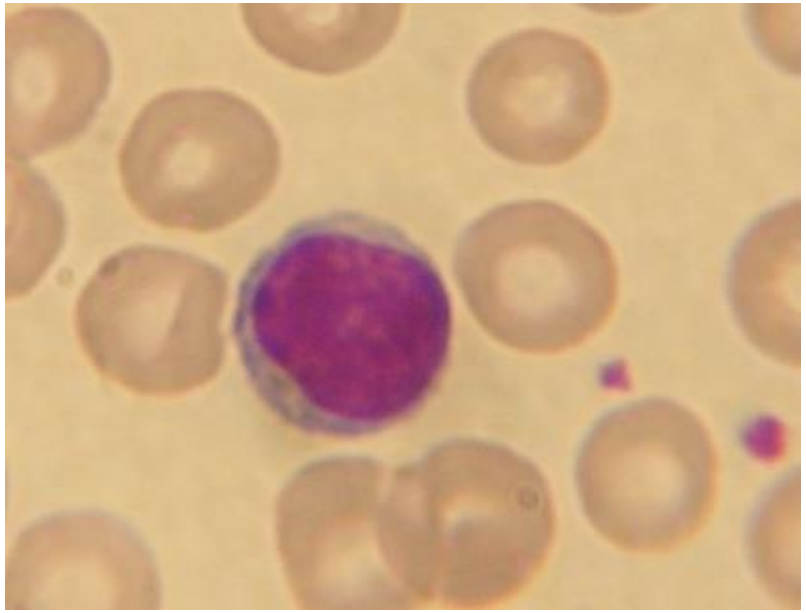
- Almost all cells have MHC class I, mainly for self antigens
- MHC class II have antigen presenting cells (APC), mainly for phagocytosed particles
- T-lymphocytes and NK cells have the ability to check them







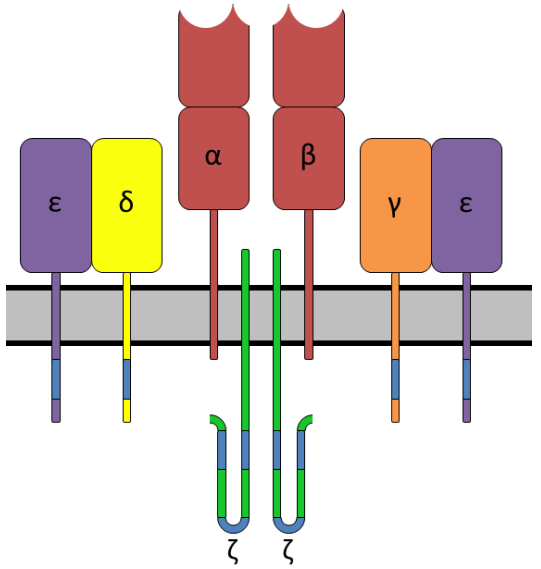
Lymfocytes



- 3 groups of the same morphology
- Born in the bone marrow, then migration
- T-lymfocytes
  - Migrate to thymus, where they are selected
- B-lymfocytes
  - Migrate to secondary lymphoid organs where they turn into plasma and memory cells
- NK-cells
  - A subset of lymphocytes responding to the absence of the MHC molecule, may also respond to antibody labeled cells and PAMP

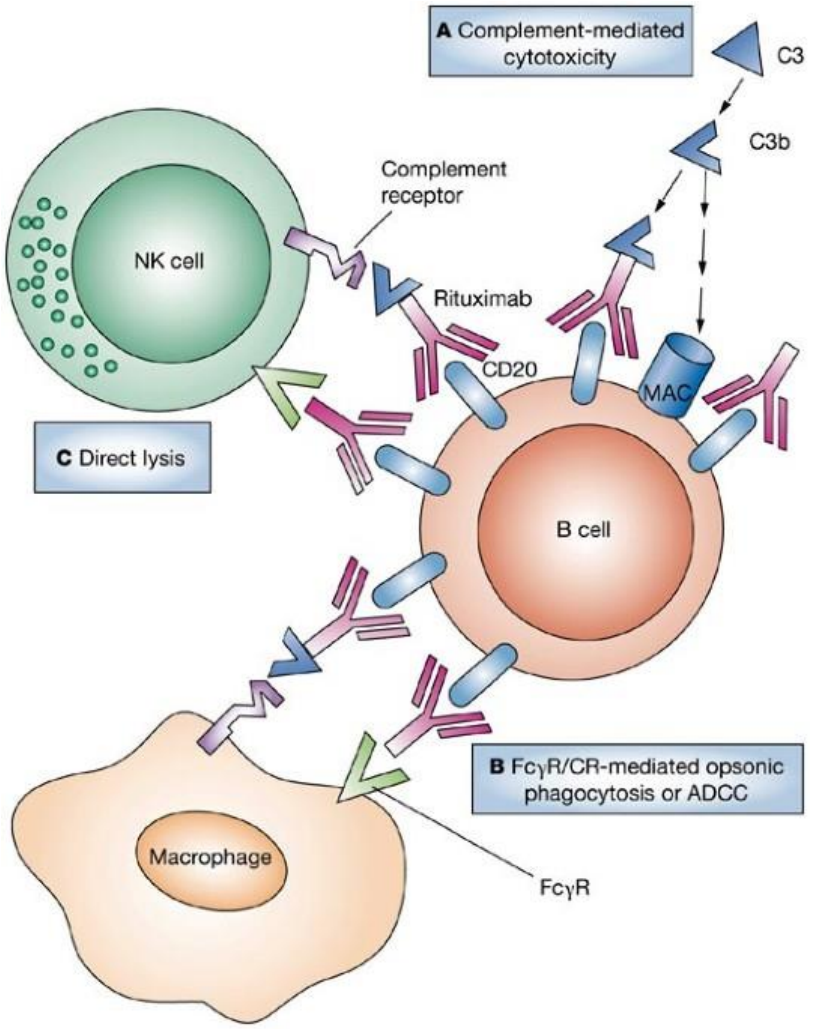
T-lymfocyte

- Their TCR is specific for an antigen
- T-lymphocytes undergo double selection in the thymus - ineffective or autoreactive ones die by apoptosis
- Groups:
  - CD4+ (helper T-cell) - MHC II, send chemical signals to other cells
  - CD8+ (killer T-cell) - MHC I, kills infected or tumor cells,secrete perforins and granzymes (destruction of affected cells)
  - Tregs are an autoreactive subset that increase autotolerance
  - Natural killer T-cell - combines properties of both NK cells and T-cells

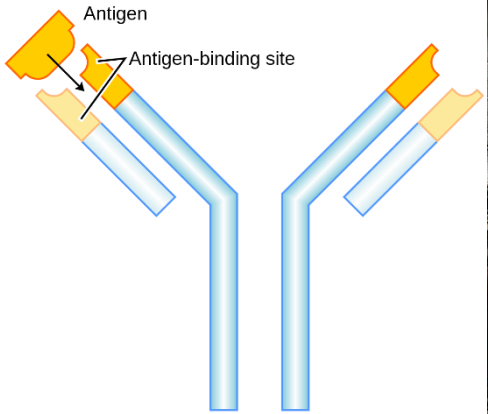


Surface antigens - CD

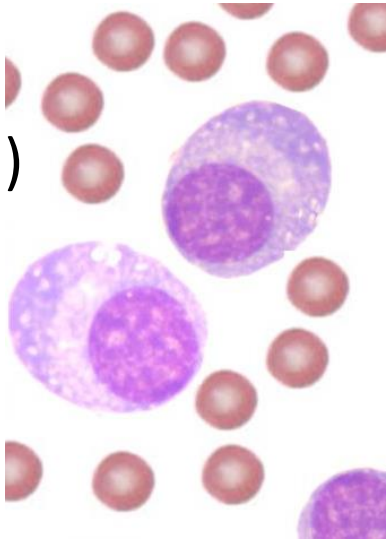
- Cluster of differentiation – naming of surface antigens for immunotyping purposes (e.g. for use in the treatment of haematological malignancies)
- Used also for cells outside the immune system
- Specific markers of lymphocytes
  - T-lymfocytes – TCR (**CD3**), subgroups **CD4** a **CD8**
    - Treg – FOXP3, CD25, NKTL – CD1d
  - B-lymfocytes – **BCR, CD19, CD20**
  - NK-cells – CD16

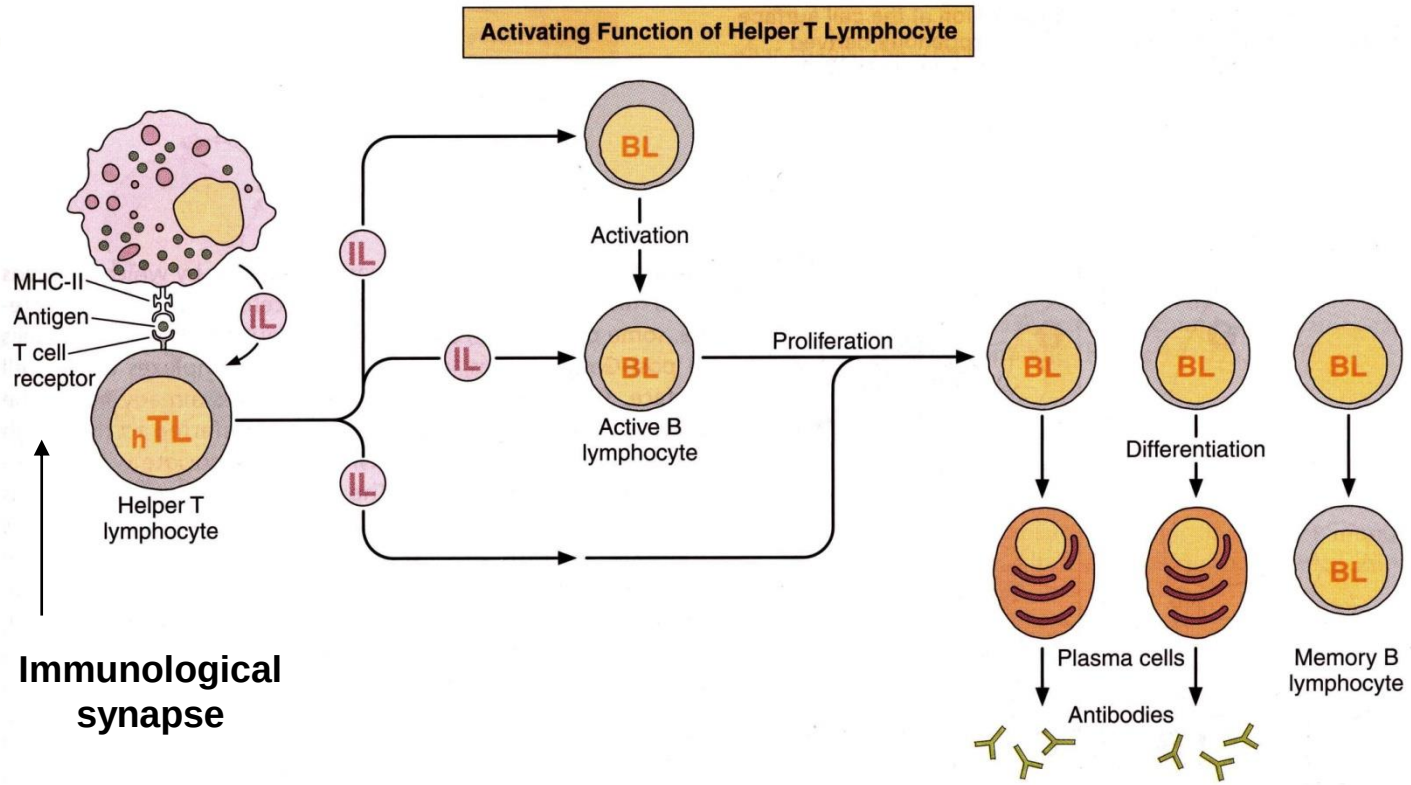


B-lymfocyte



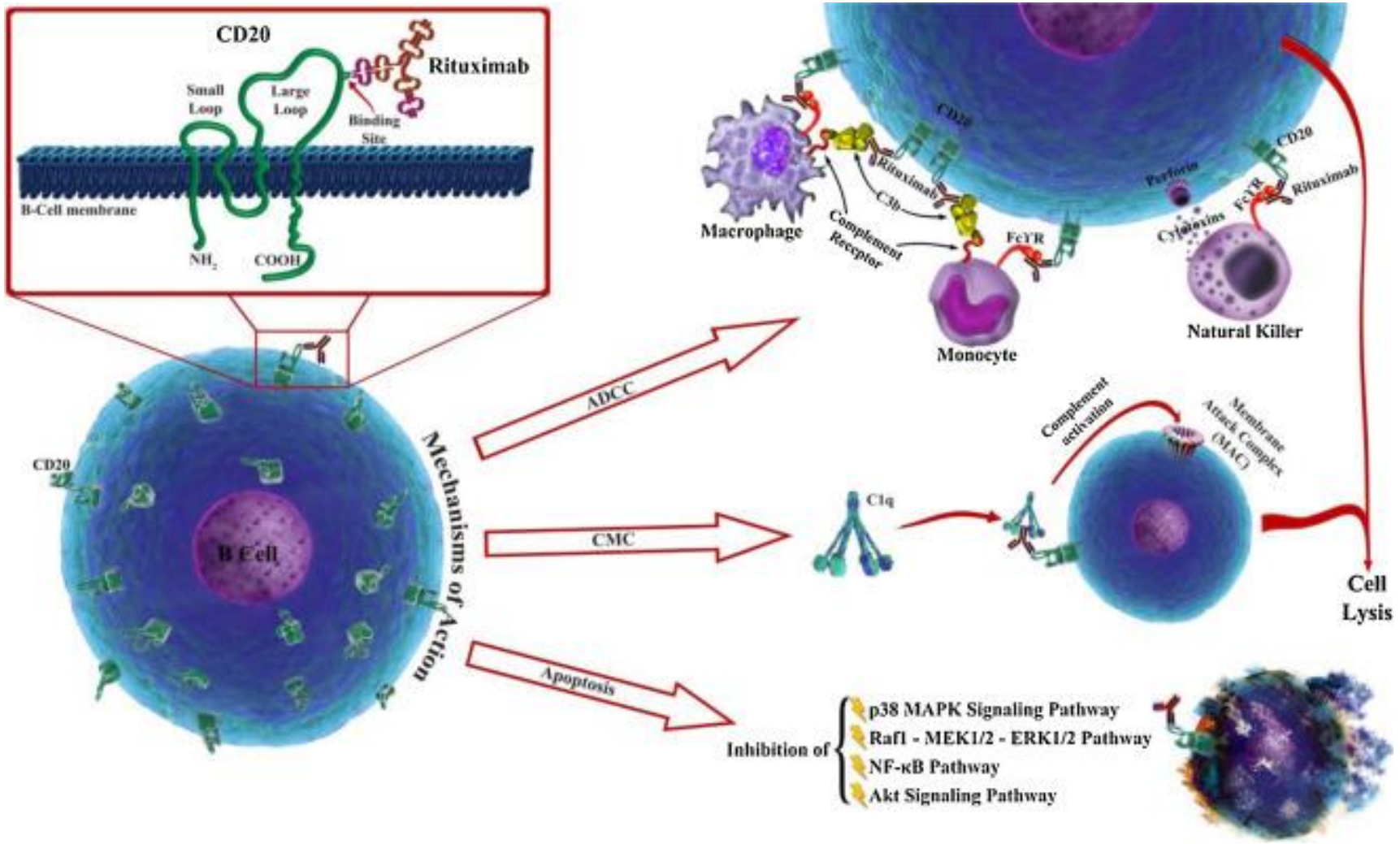
- Their task is to produce antibodies
  1. B-cell receptor (BCR) formation
  2. The lymphocyte travels to lymph nodes and encounters antigen-presenting cells (APCs) - macrophages, dendritic cells...
  3. Somatic hypermutation - another BCR change
  4. Helper T-cell sends a proliferation-promoting signal
  5. Selection of the clone with the highest affinity (affinity maturation)
  6. Class switching (e.g. IgM to IgG)
  7. Plasma and memory cells



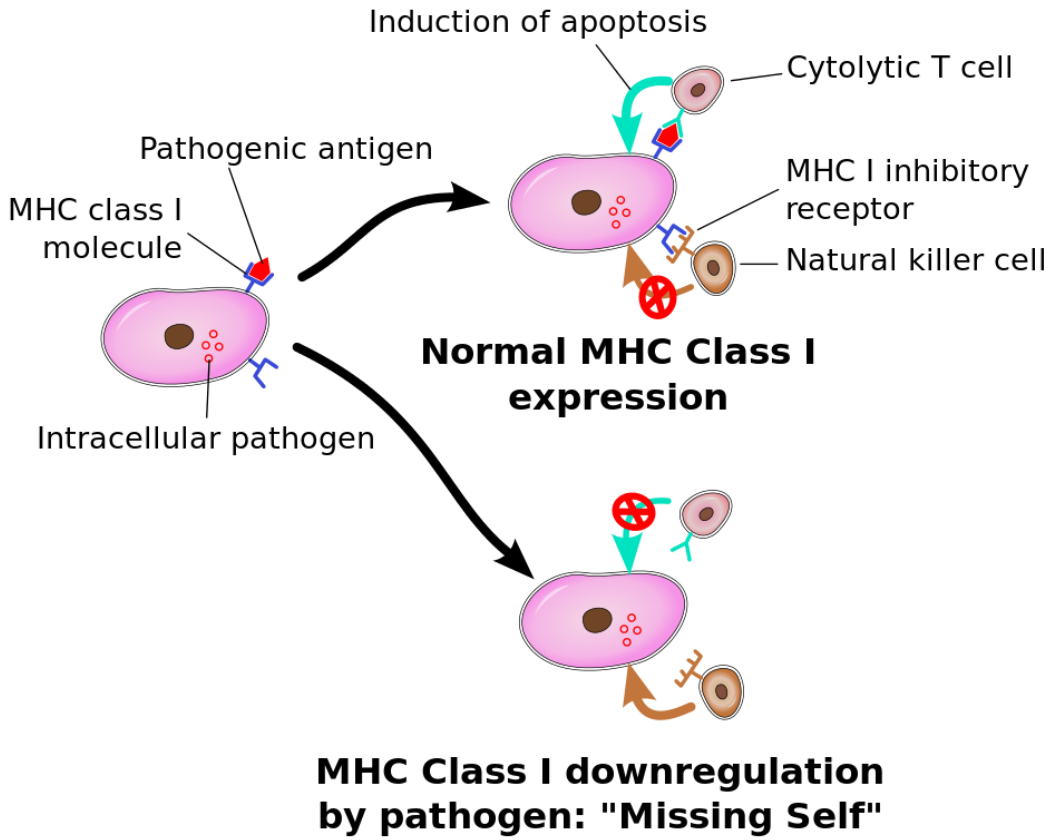


T_h1 activate macrophages by interferon-γ → phagocytosis (intracellular parasites)
T_h2 activate eosinophils, basophils and mast cells via IL-4 and IL-13 → extracellular parasites
T_h17 activate neutrophils with IL-17
T_hf activate B-cells with IL-21 a IL-4 → plasma cell
These pathways compete with each other

The anti-CD20 antibody (rituximab) is used in malignant diseases from B-lymphocytes or in some autoimmune diseases. Thus, we attack B-lymphocytes with their own weapons.



NK-cell kills cells not expressing MHC I molecules. In addition, it uses a number of other receptors of non-specific immunity.



Questions

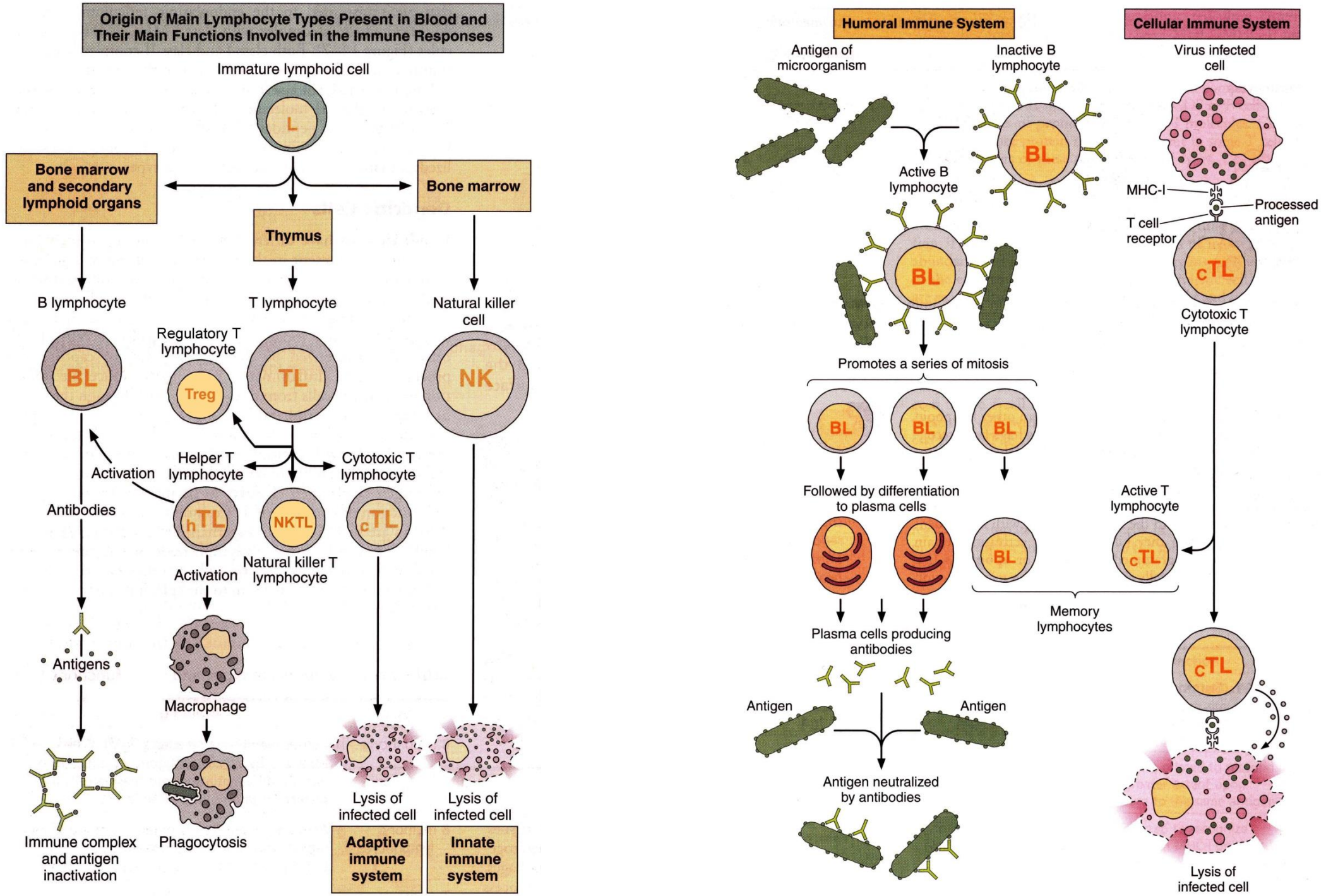
1. How do we use antibodies in histology?

2. How can antibodies be used to diagnose disease?

Answers

1. We can specifically monitor the presence of a particular molecule in the tissue, e.g. immunofluorescence and immunohistochemistry.

2. Antibody levels can be measured e.g. in infectious and autoimmune diseases (serology). A number of biotechnologies also use specific antibody binding, e.g. immunochromatography (pregnancy test, covid antigen test) or ELISA (analytical biochemistry) in addition to the histological methods mentioned above.

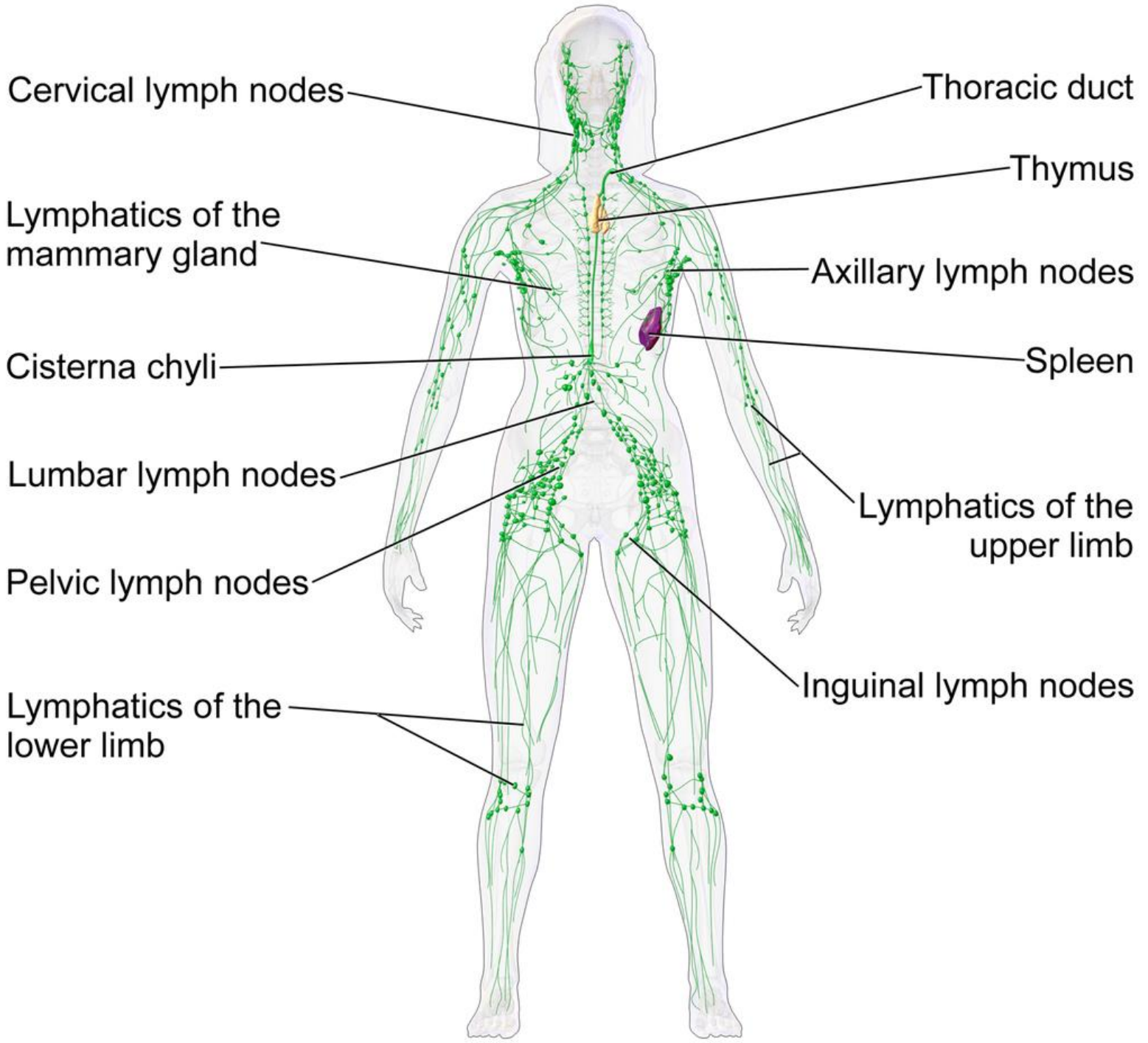

Origin of Main Lymphocyte Types Present in Blood and Their Main Functions Involved in the Immune Responses
Immature lymphoid cell
L
Bone marrow and secondary lymphoid organs
Thymus
Bone marrow
B lymphocyte
T lymphocyte
Natural killer cell
BL
Regulatory T lymphocyte
Treg
TL
NK
Activation
Helper T lymphocyte
Cytotoxic T lymphocyte
Antibodies
hTL
NKTL
cTL
Natural killer T lymphocyte
Activation
Antigens
Macrophage
Immune complex and antigen inactivation
Phagocytosis
Lysis of infected cell
Lysis of infected cell
Adaptive immune system
Innate immune system
Humoral Immune System
Antigen of microorganism
Inactive B lymphocyte
Active B lymphocyte
BL
Promotes a series of mitosis
BL
BL
BL
Followed by differentiation to plasma cells
Plasma cells producing antibodies
Antigen
Antigen
Antigen neutralized by antibodies
Memory lymphocytes
Cellular Immune System
Virus infected cell
MHC-I
Processed antigen
T cell receptor
cTL
Cytotoxic T lymphocyte
Active T lymphocyte
cTL
cTL
Lysis of infected cell

Lymphatic system

- Its function is to defend the body against the spread of infection and allow the flow of lymph
- It includes organs important for the formation of immune cells and for their maturation and function
- Lymphoid tissue - reticular connective tissue (or epithelium) with many lymphocytes and other IS cells
- Lymph is a colourless fluid that drains some of the fluid from the tissues
  - Composition similar to plasma but contains less protein
  - Lymph from the intestines (chylus) contains extra fat, so it is milky white
  - Contains various leukocytes (lymphocytes, macrophages)
  - Pathway of spread of both infectious and cancerous processes (lymphogenous metastasis)

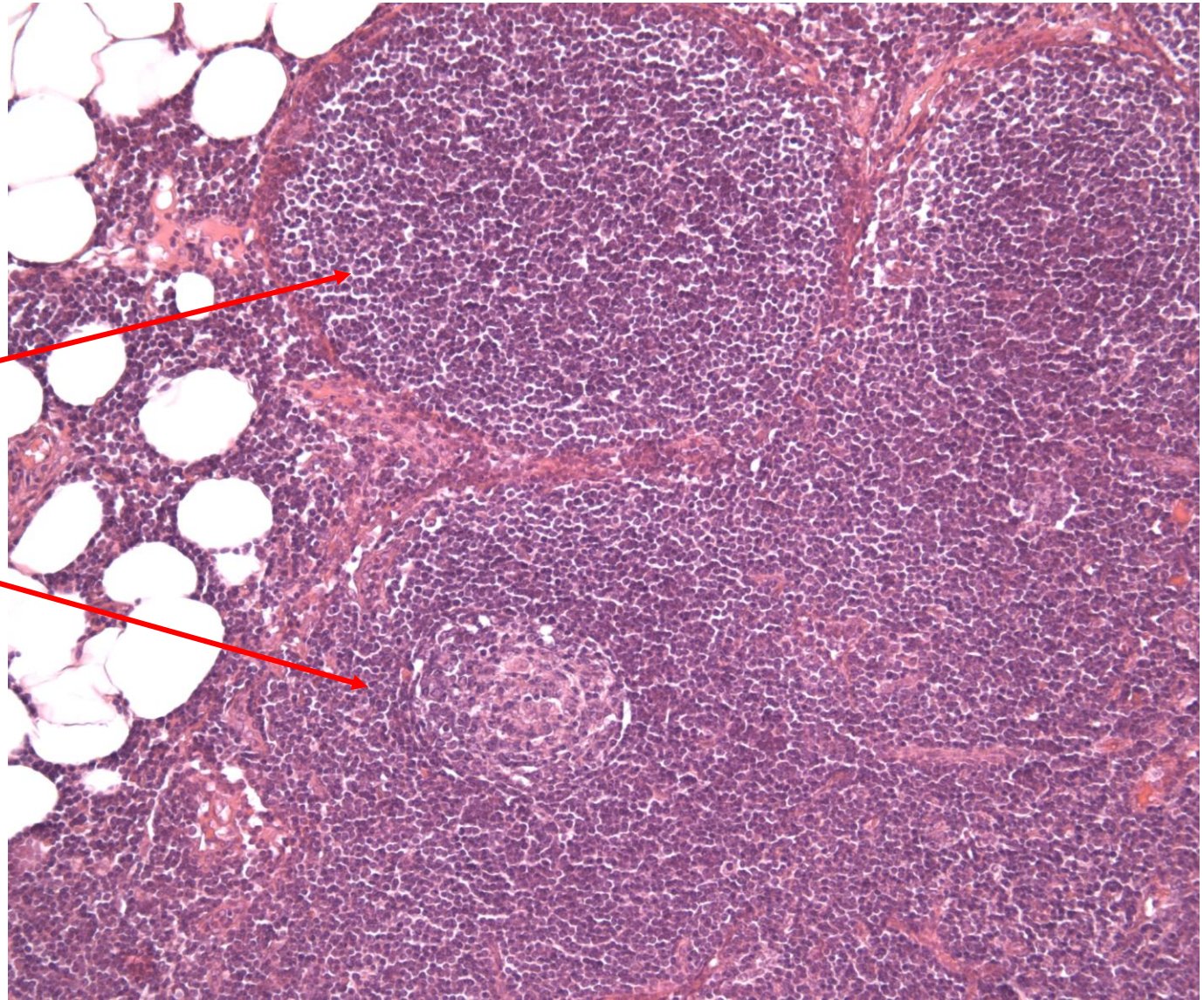
Lymphoid organs

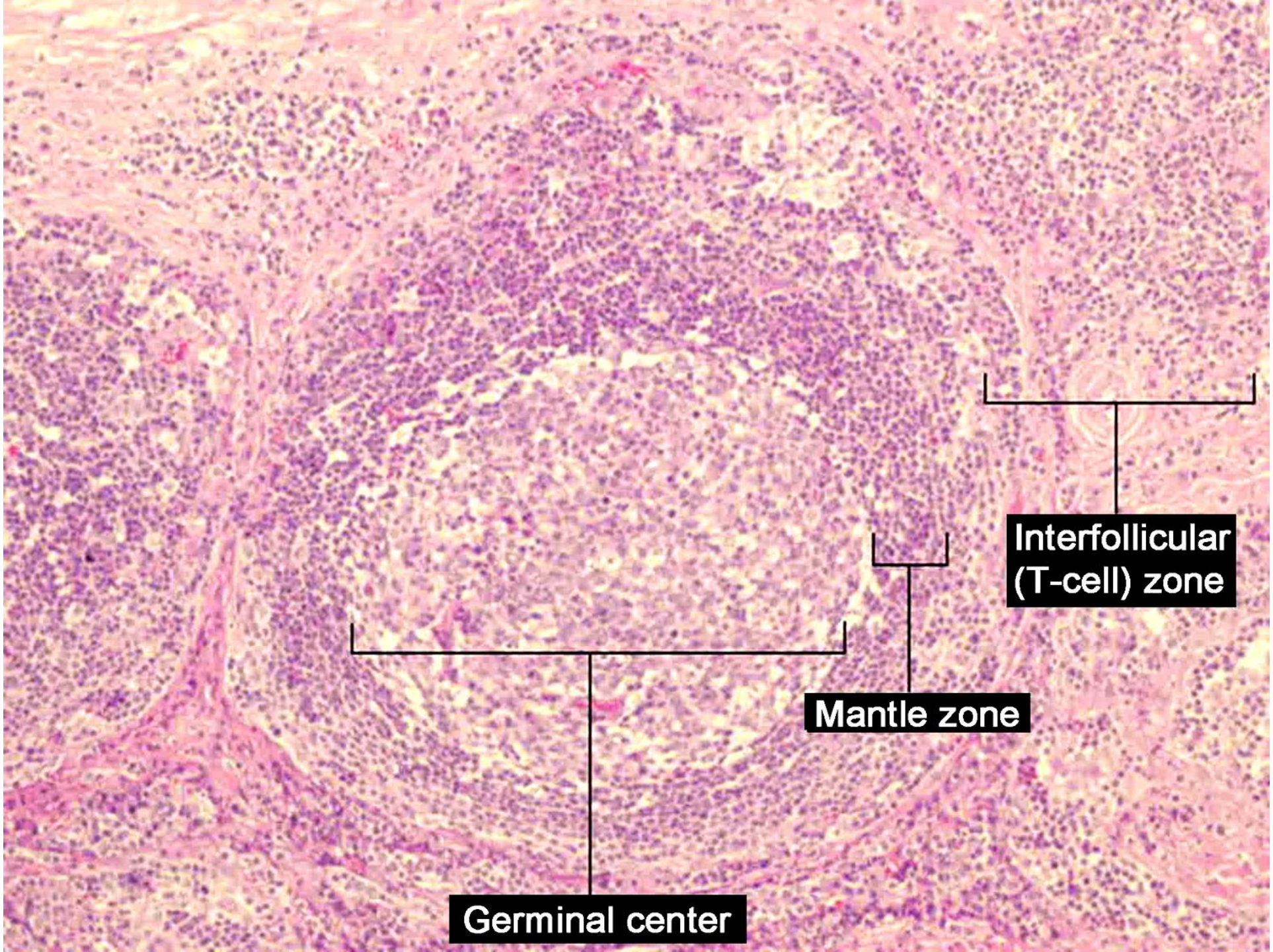
- Primary
  - Immune system cells arise here
  - Thymus, bone marrow (Bursa Fabricii in birds)
- Secondary
  - Combat infection
  - Encapsulated (spleen, lymph nodes)
  - Partially encapsulated (tonsils)
  - Non-encapsulated (MALT)

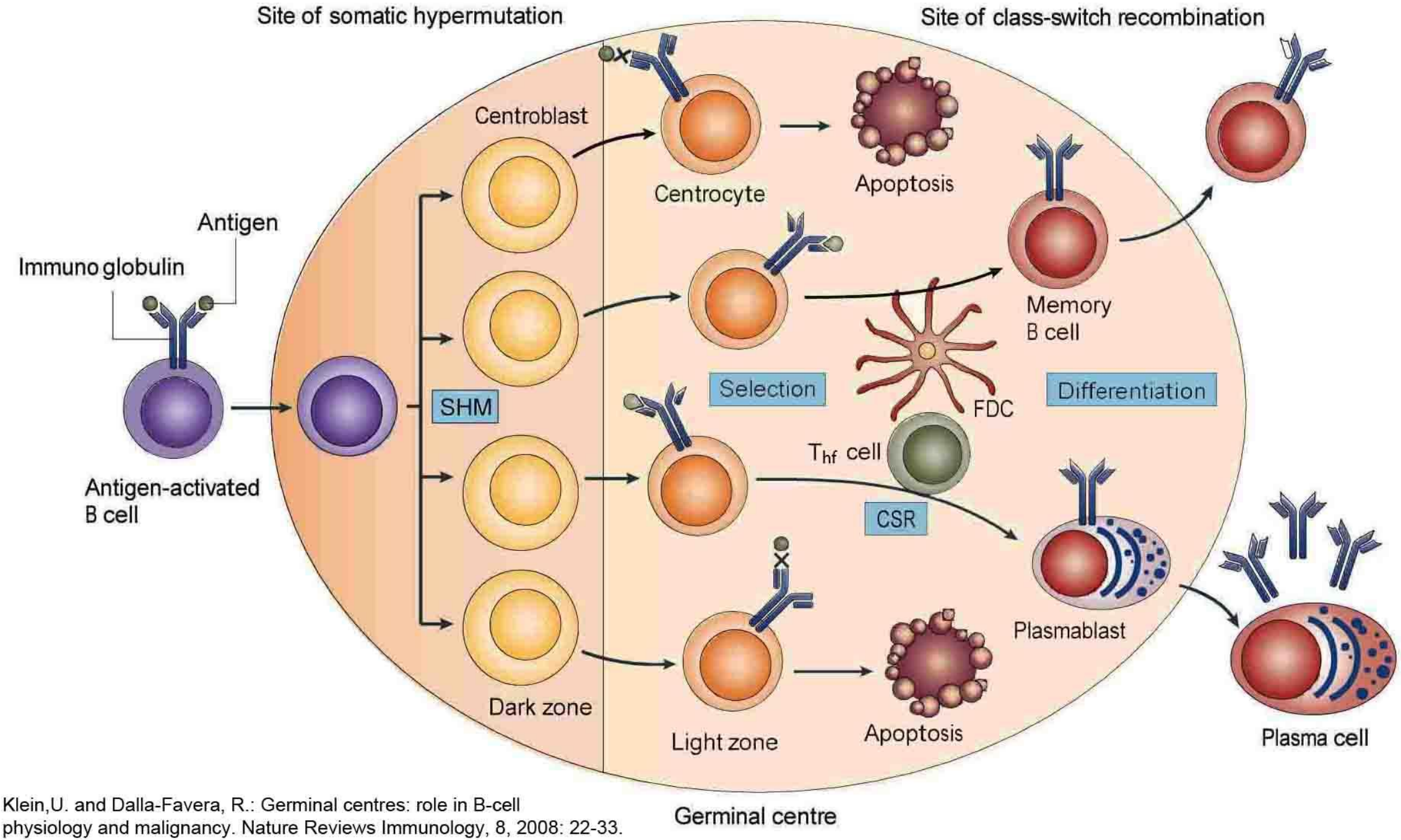


Noduli lymphoidei – lymphoid nodules

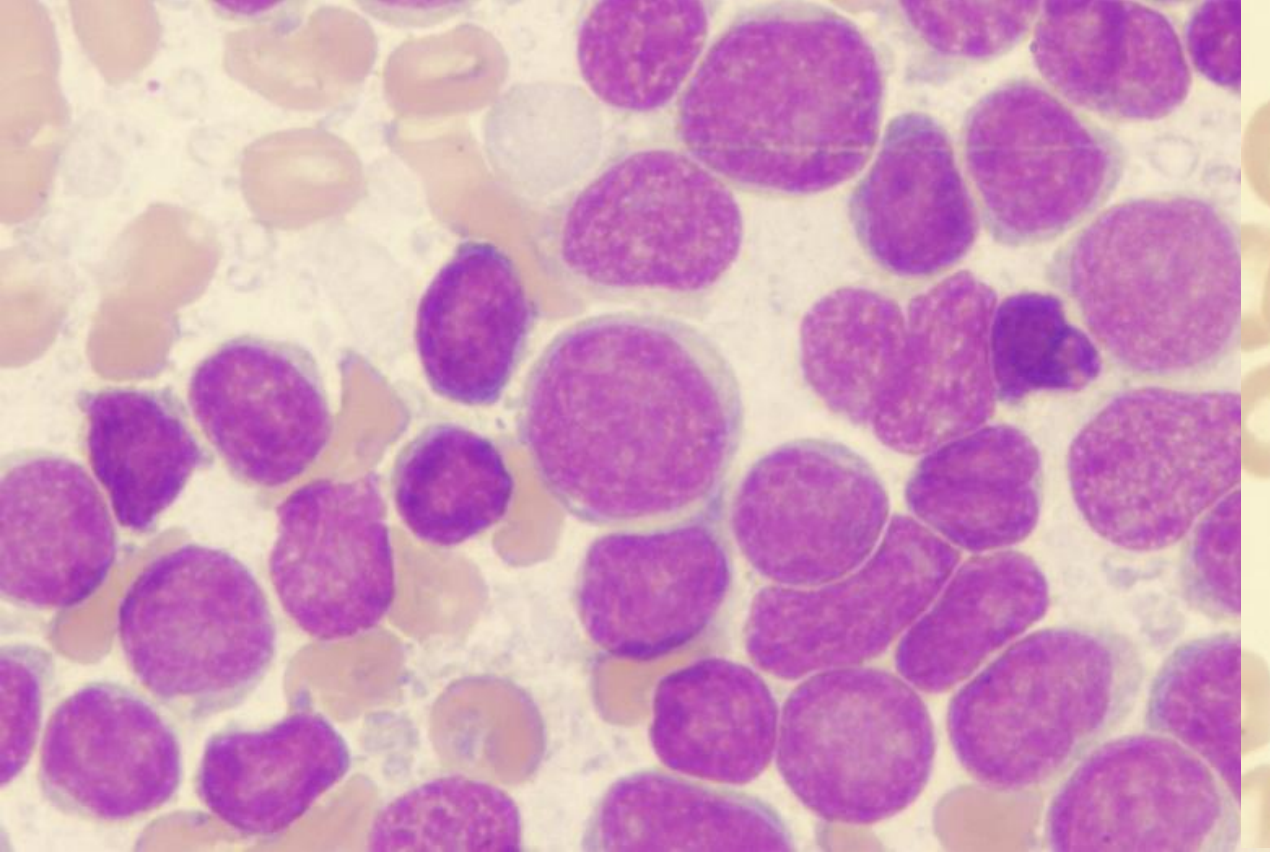
- Part of many lymphoid organs (lymph nodes, spleen, MALT, tonsils)
- Maturation of B-lymphocytes
- Primary x secondary
  - Difference is the germinal centre

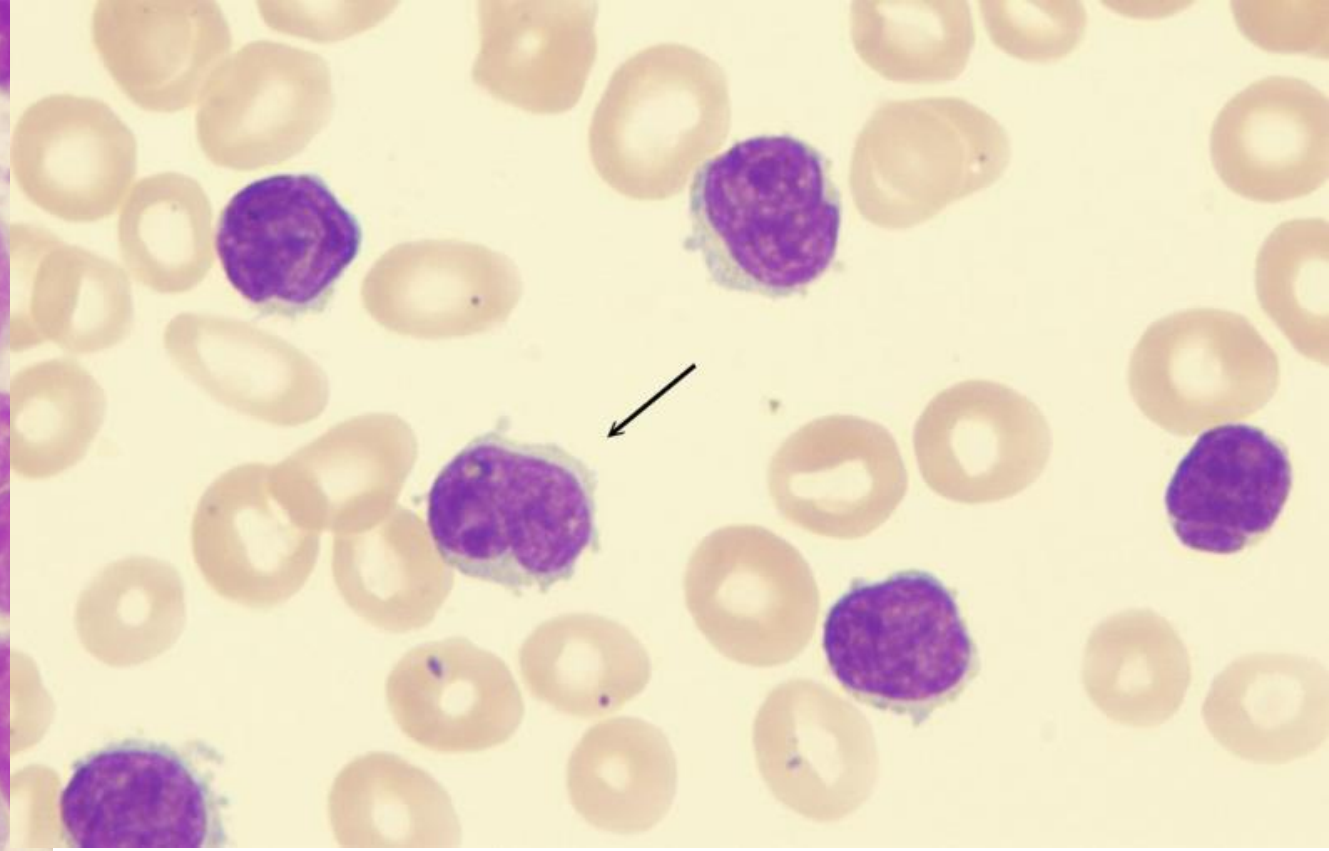



Interfollicular
(T-cell) zone
Mantle zone
Germinal center

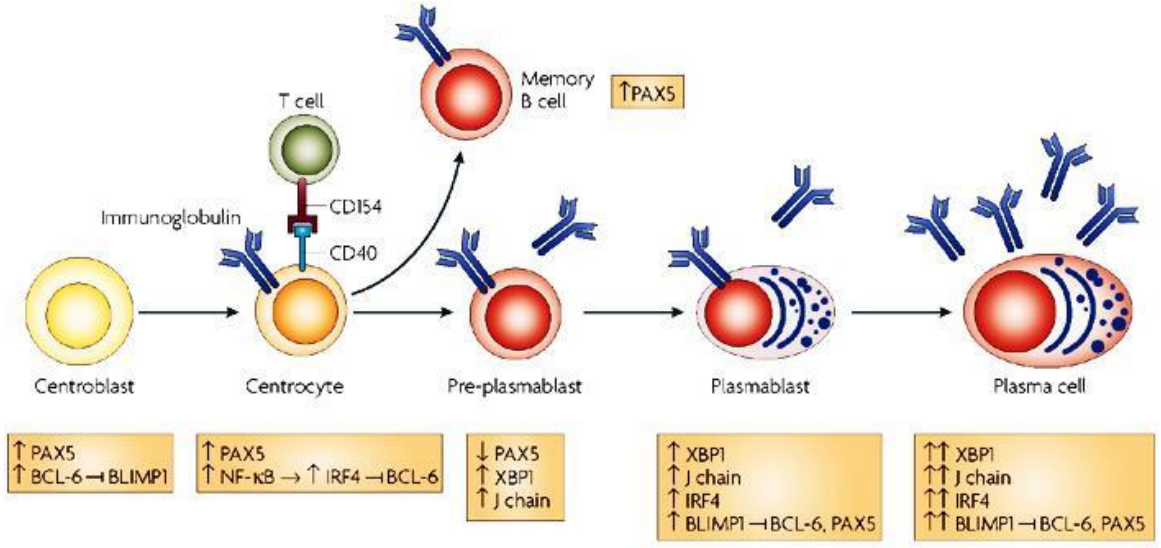


Klein,U. and Dalla-Favera, R.: Germinal centres: role in B-cell physiology and malignancy. Nature Reviews Immunology, 8, 2008: 22-33.





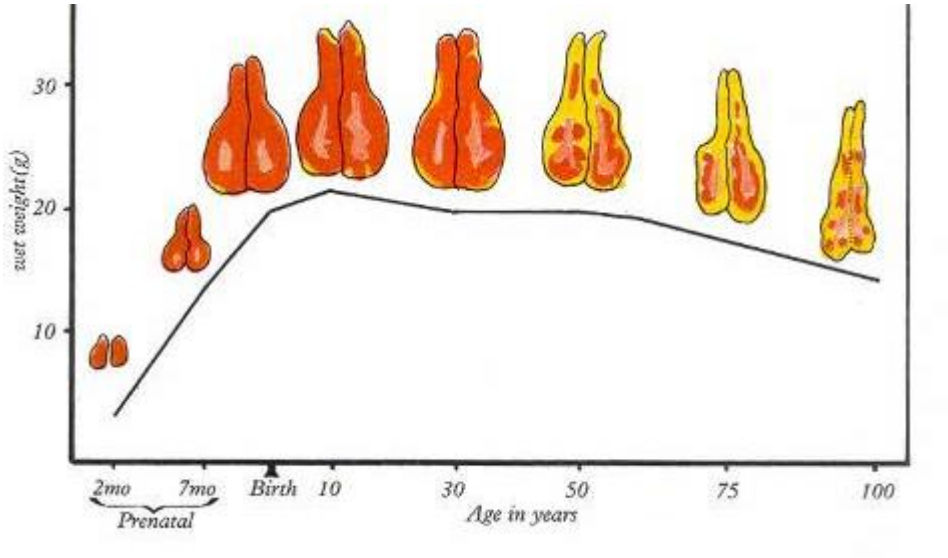
Centroblasts
Dark zone

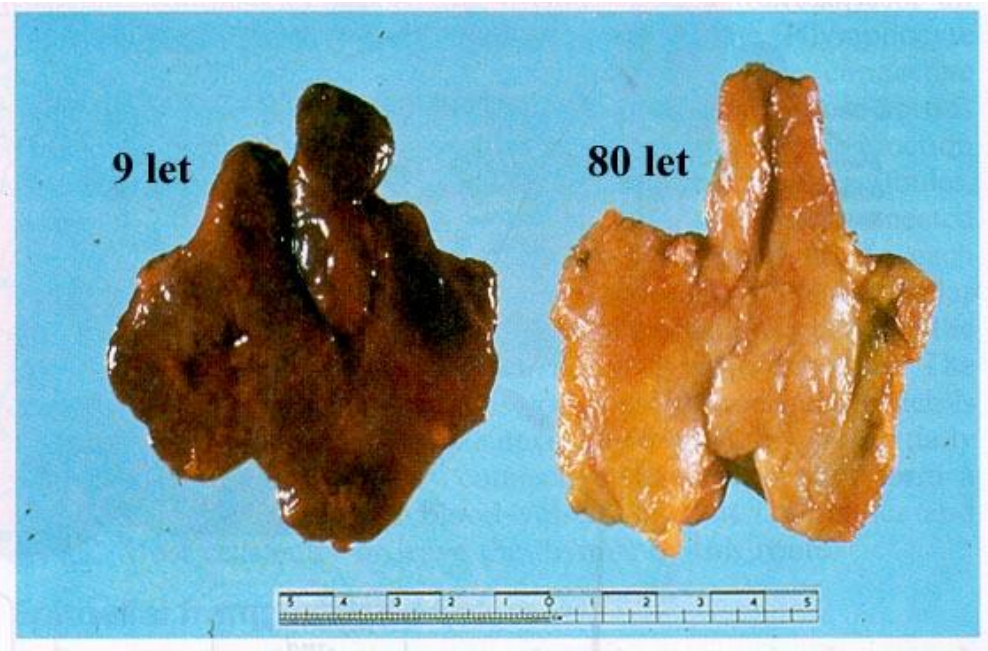


Centrocytes
Light zone

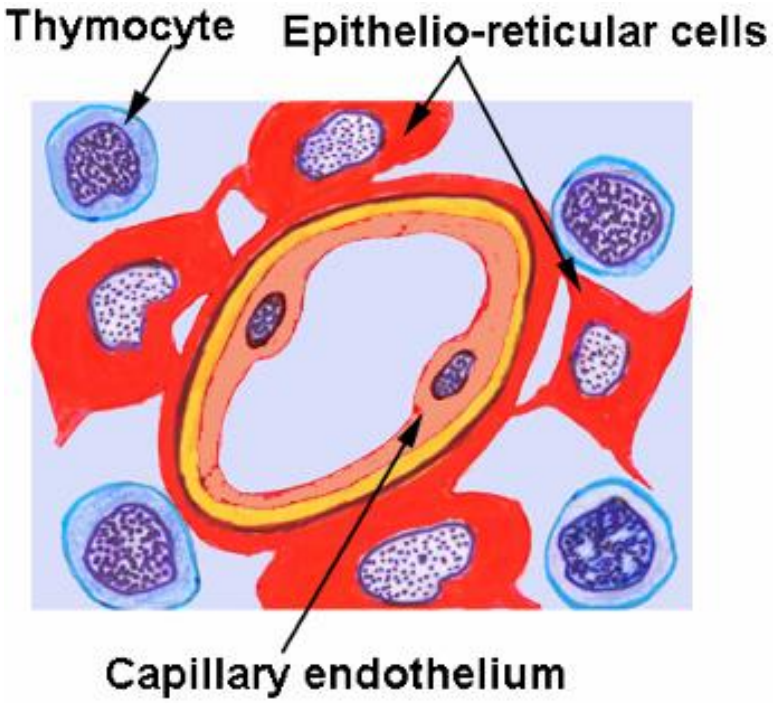
Thymus

- Primary lymphatic organ, lymphoepithelial organ
- Relatively largest in the newborn, gradual involution (replacement by fat) from puberty
- Lobus dx. et sin., lobuli, cortex, medulla

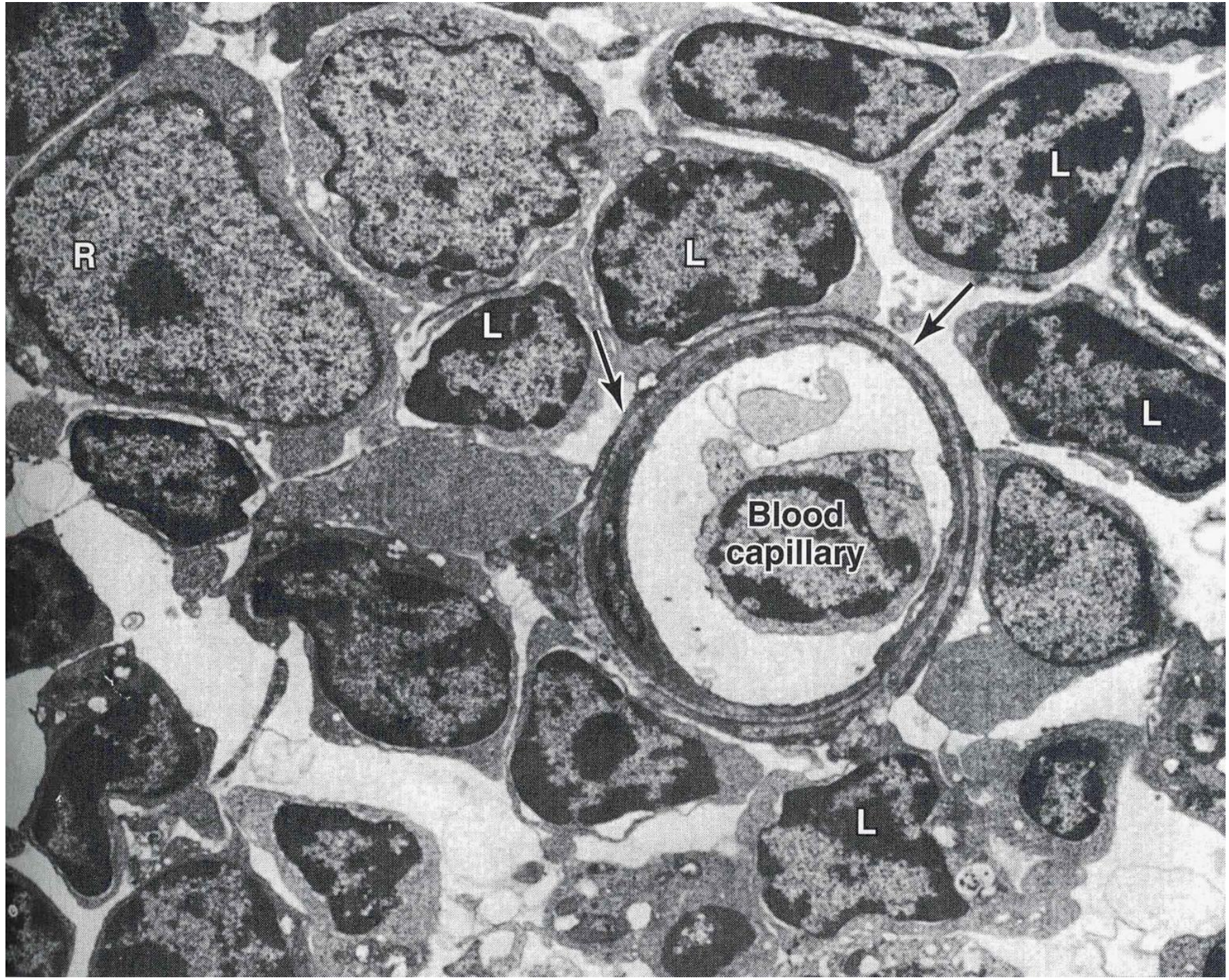




Vascular supply

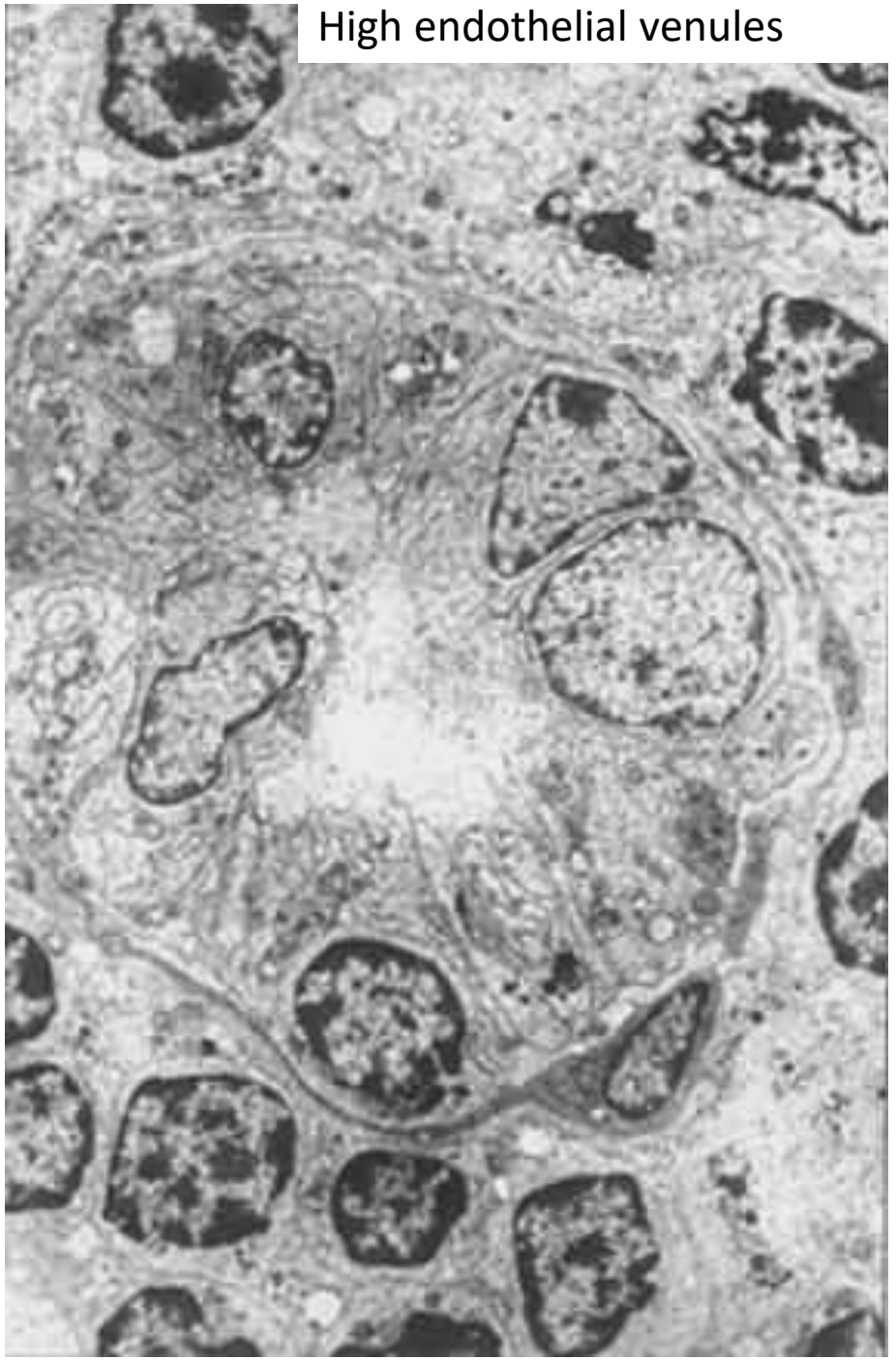


- Branches of the surrounding arteries
  - a. thyroidea inf.
  - thoracica int. (a. pericardiacophrenica)
  - arcus aortae
- Capillaries are continuous, together with epithelia they form a haematothymic barrier in the cortex
  - the endothelium of the capillaries
  - basal lamina of capillaries (+ possibly pericytes)
  - connective tissue layer (+ macrophages)
  - basal lamina of reticular epithelial cells
  - reticular epithelial cells


R
L
L
L
L
L
L
Blood
capillary

Vascular supply

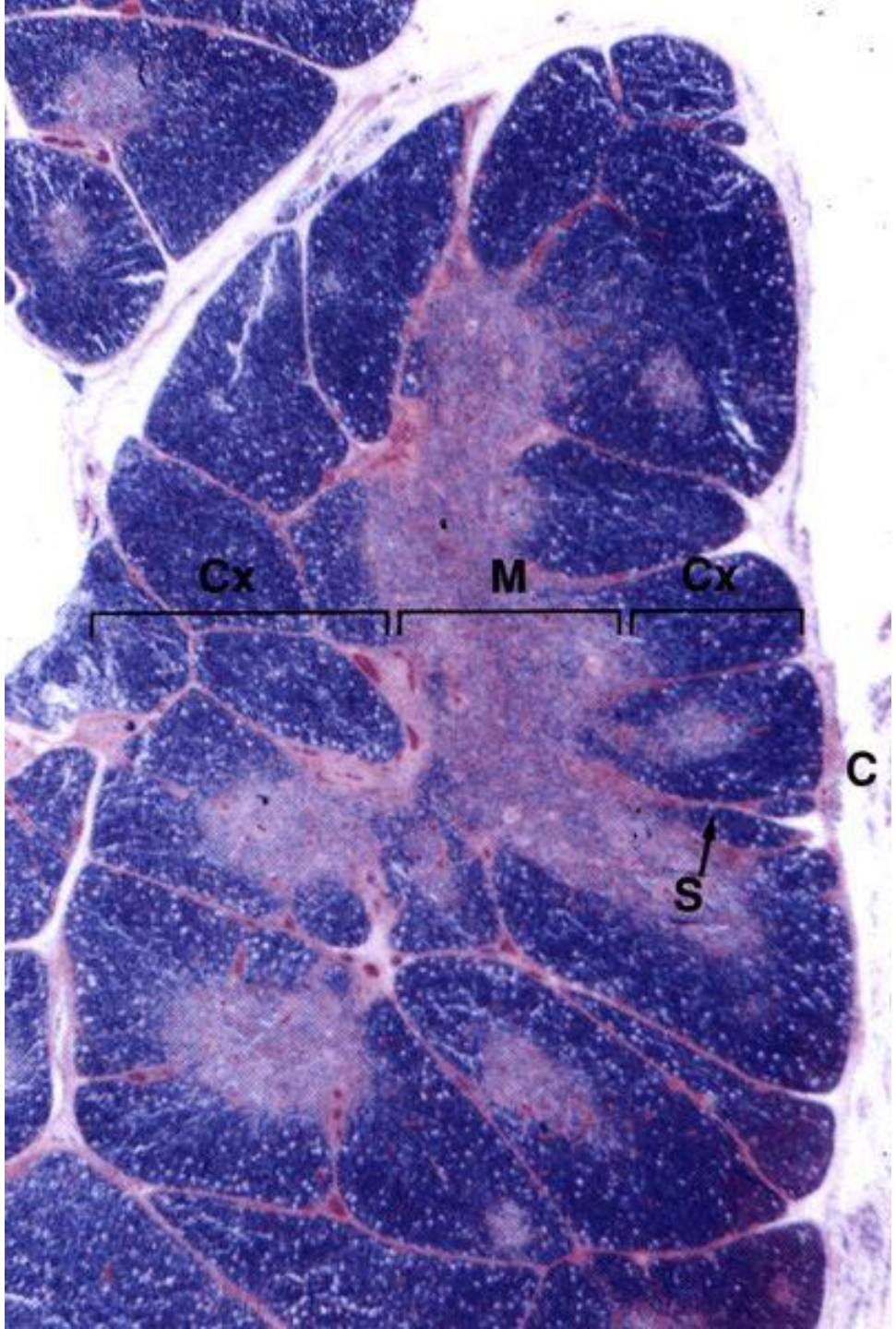
- Postcapillary high endothelial venules (located in the cortico-medullary junction) allow lymphocytes to enter the bloodstream more easily
- Venous drainage has a similar pathway to arteries, blood drains to v. brachiocephalica sinistra, v. thyroidea inf., v. thoracica interna
- We also find the efferent lymphatic vessels

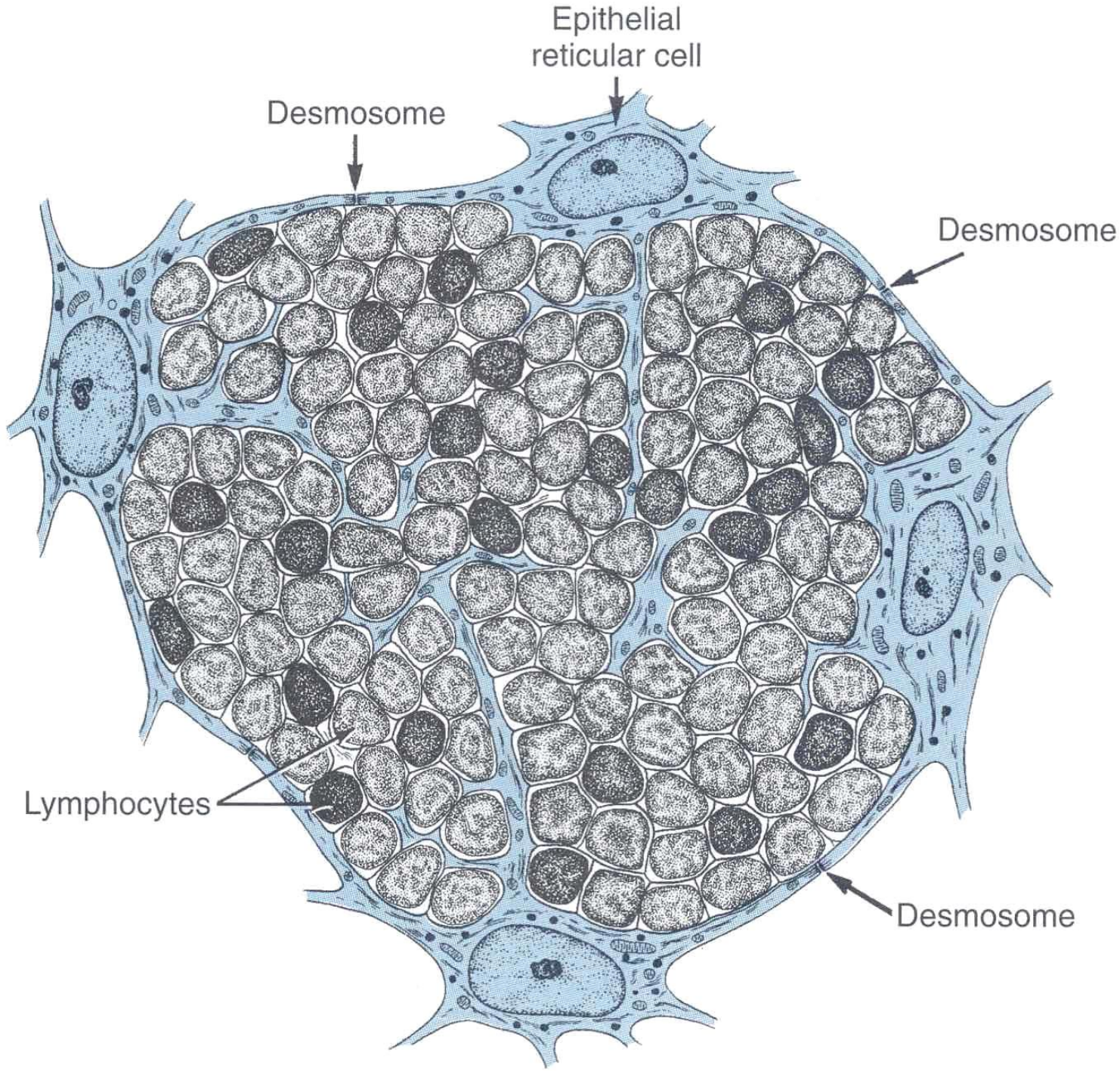


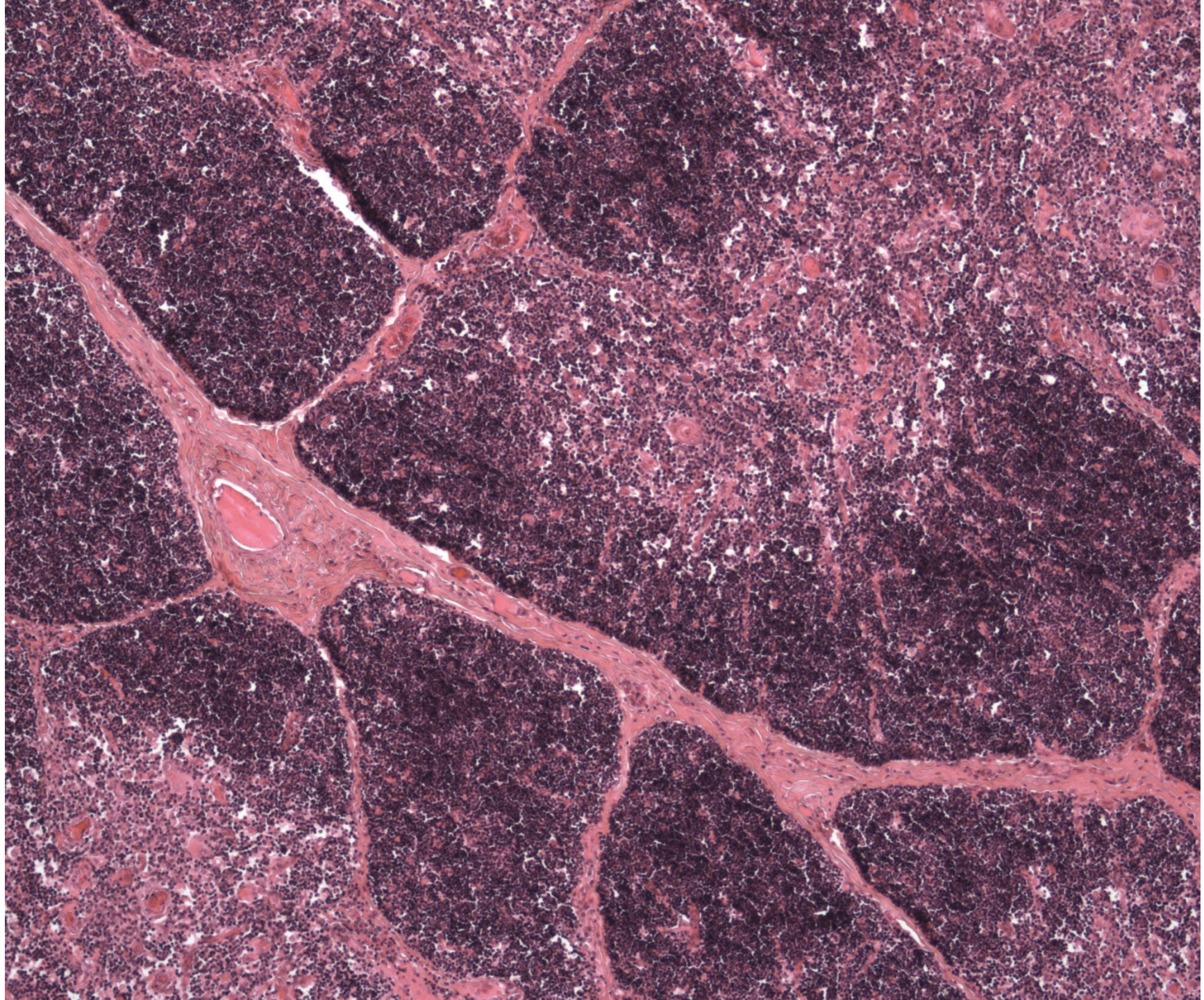
High endothelial venules

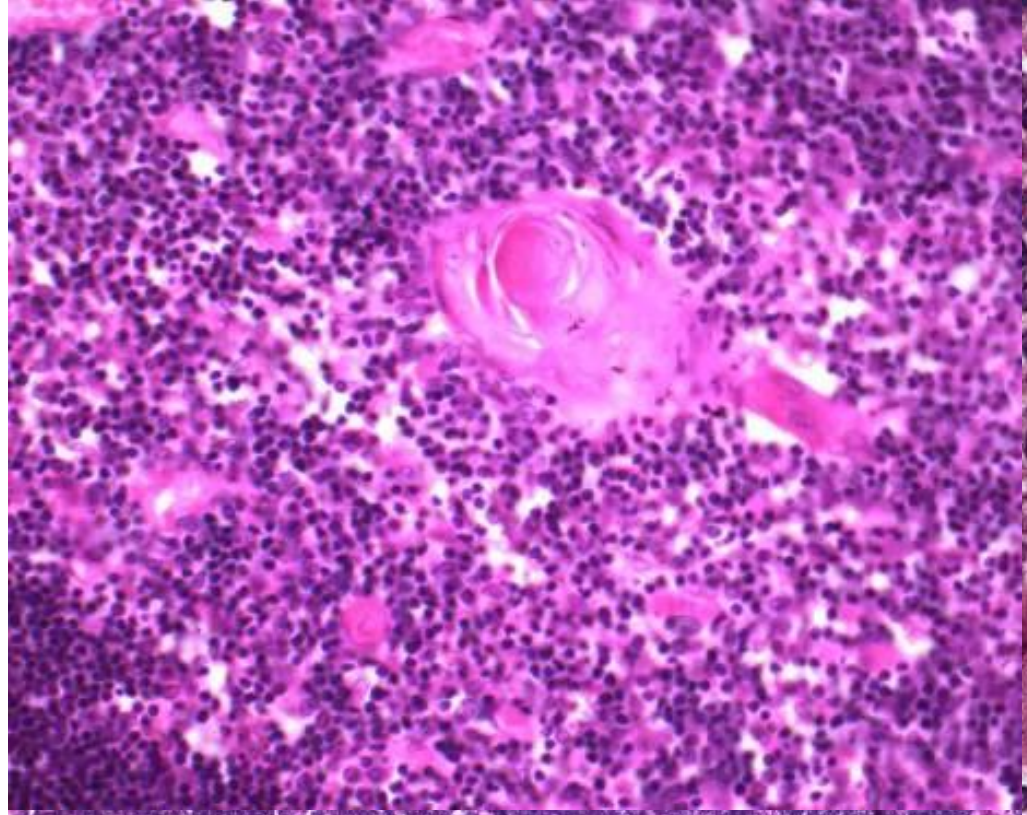
Thymus - structure

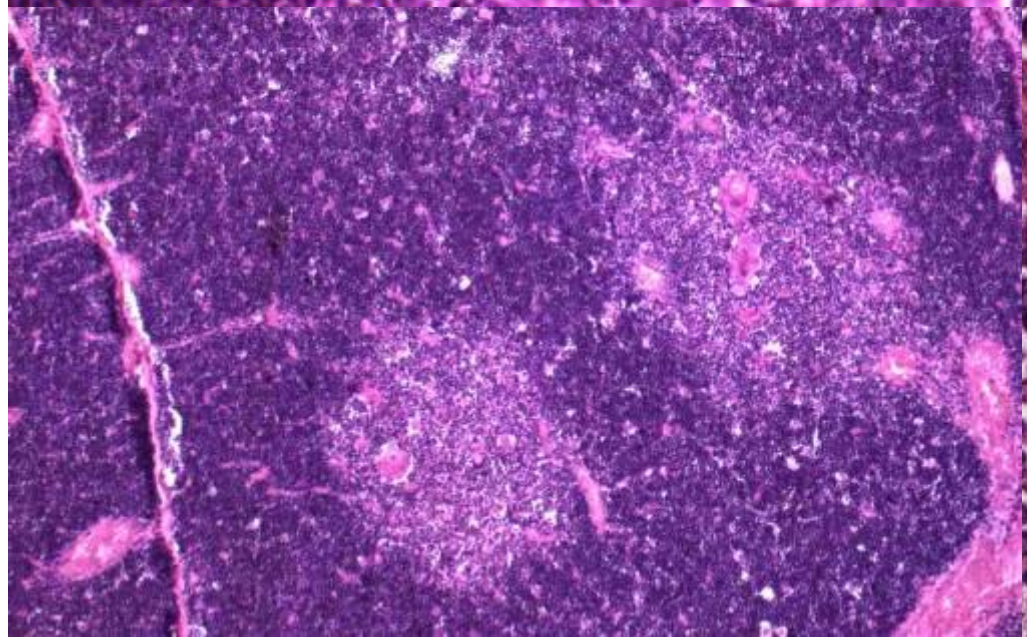
- Capsule and septa from CT
- Cortex (dark area)
  - Reticular epithelial cells types I - III, numerous lymphocytes, macrophages
- Medulla (light area)
  - Reticular epithelial cells types IV - VI, lymphocytes, dendritic cells, myoid cells
  - Hassall's corpuscles (eosinophilic round bodies formed by reticular epithelial cells)

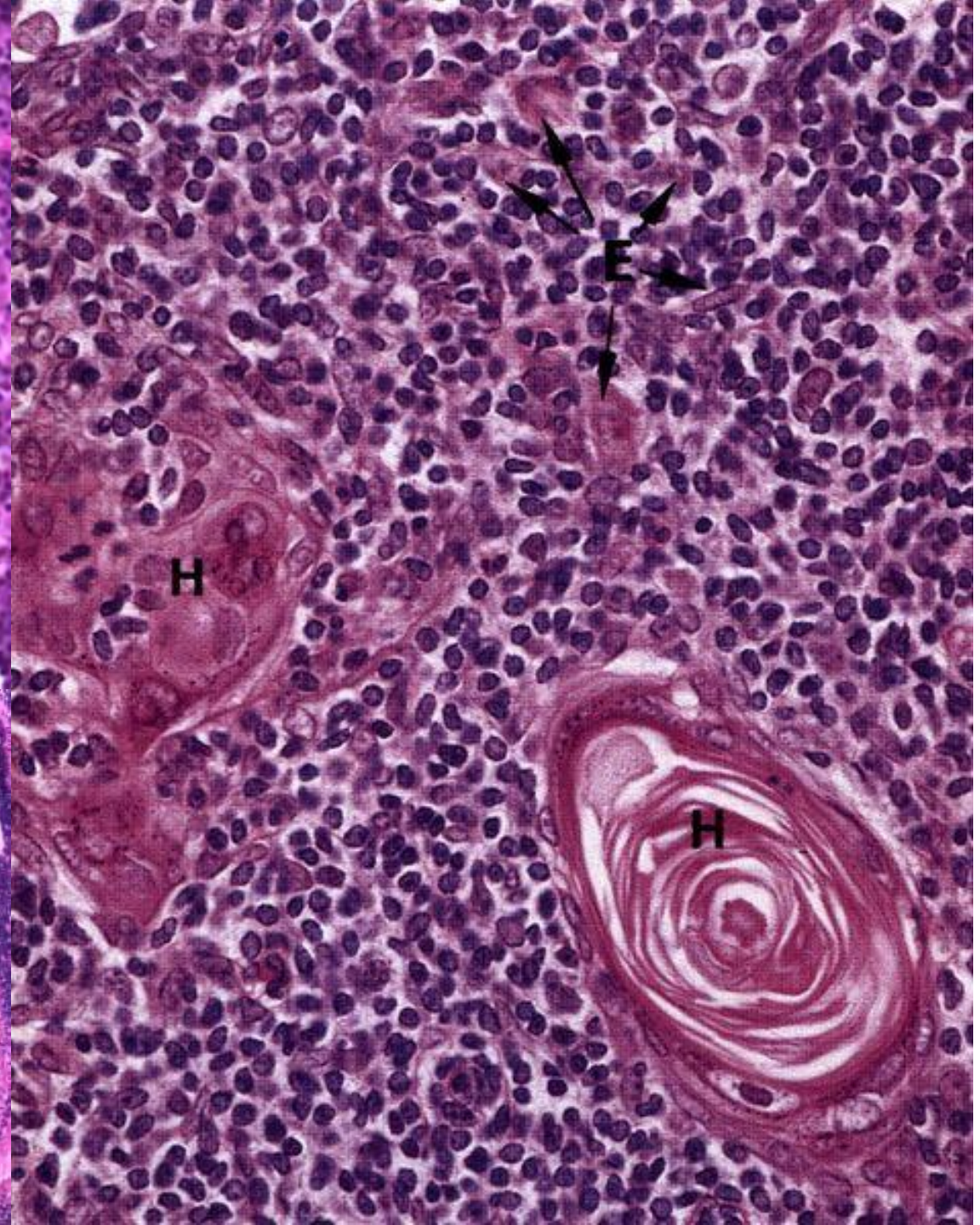



Epithelial
reticular cell
Desmosome
Desmosome
Lymphocytes
Desmosome



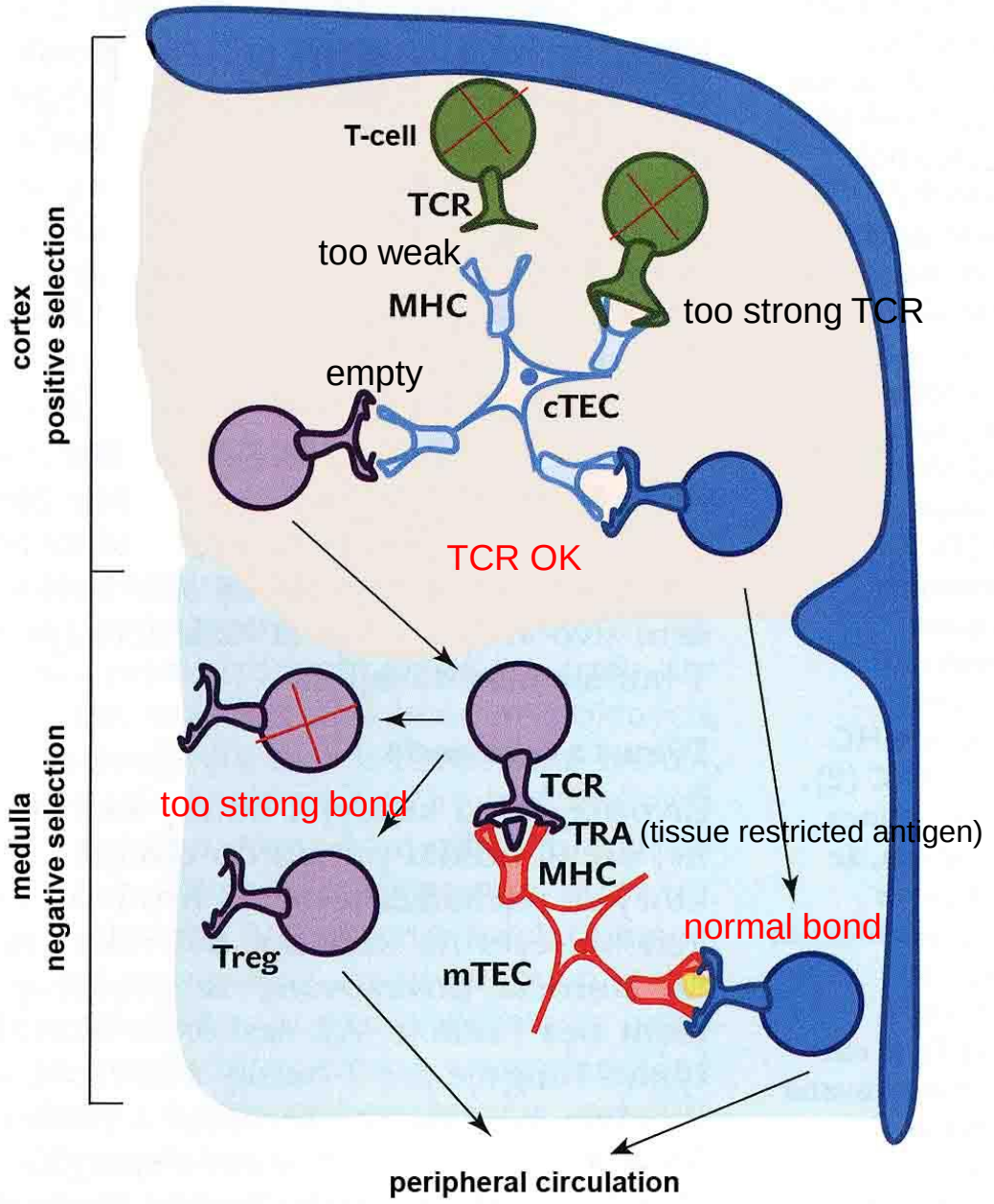





E
H
H

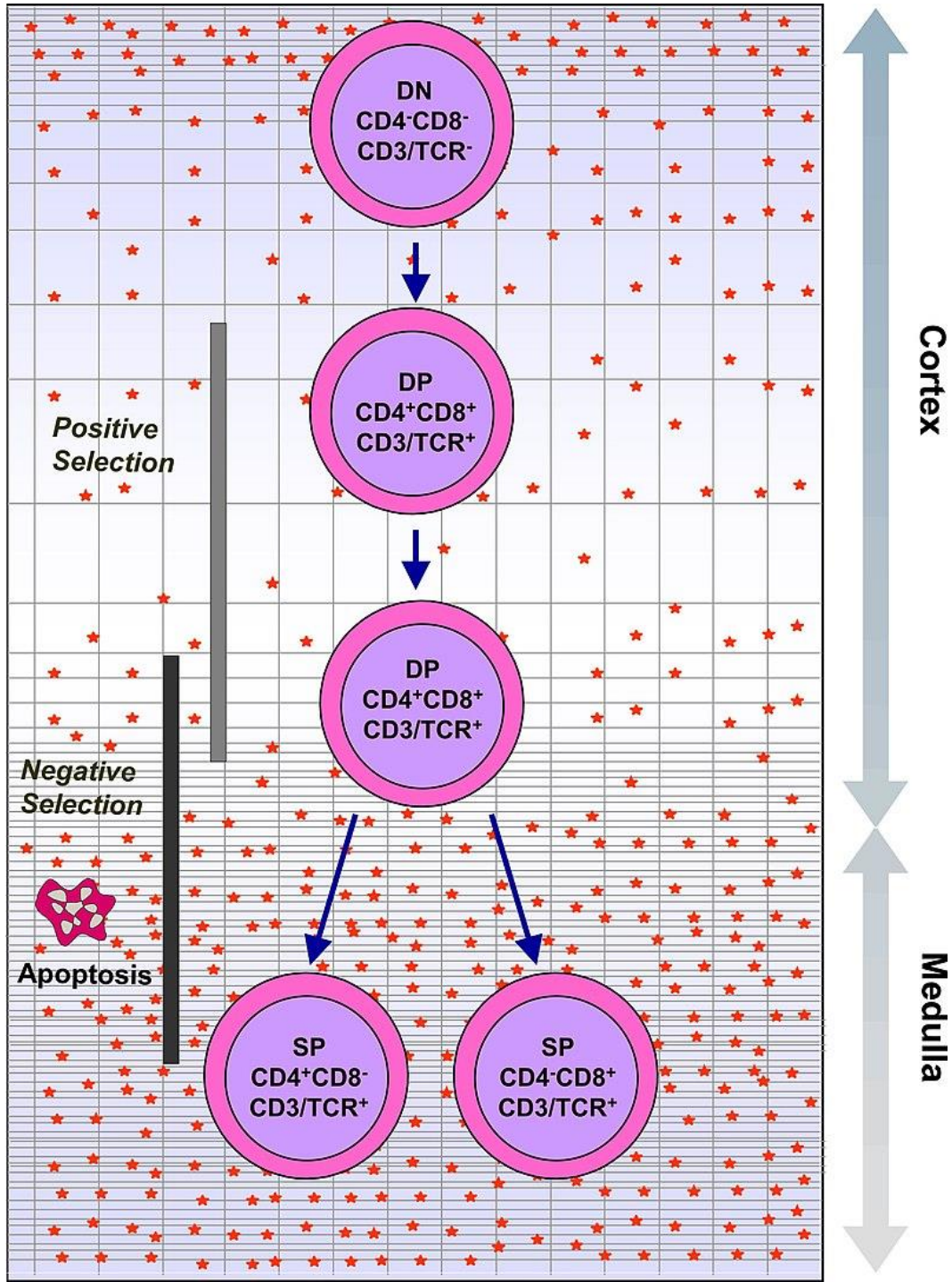
T-cells selection

- 99% die by apoptosis
- Positive selection in the cortex removes lymphocytes with dysfunctional TCR
  - Cells reacting with MHC receive a rescue signal
- Negative selection in the marrow removes autoreactive clones
  - Cells reacting strongly with MHC presenting self-antigens (tissue restricted antigen) die by apoptosis or become regulatory T-lymphocytes
  - AIRE is a gene that allows expression of self antigens in the thymus



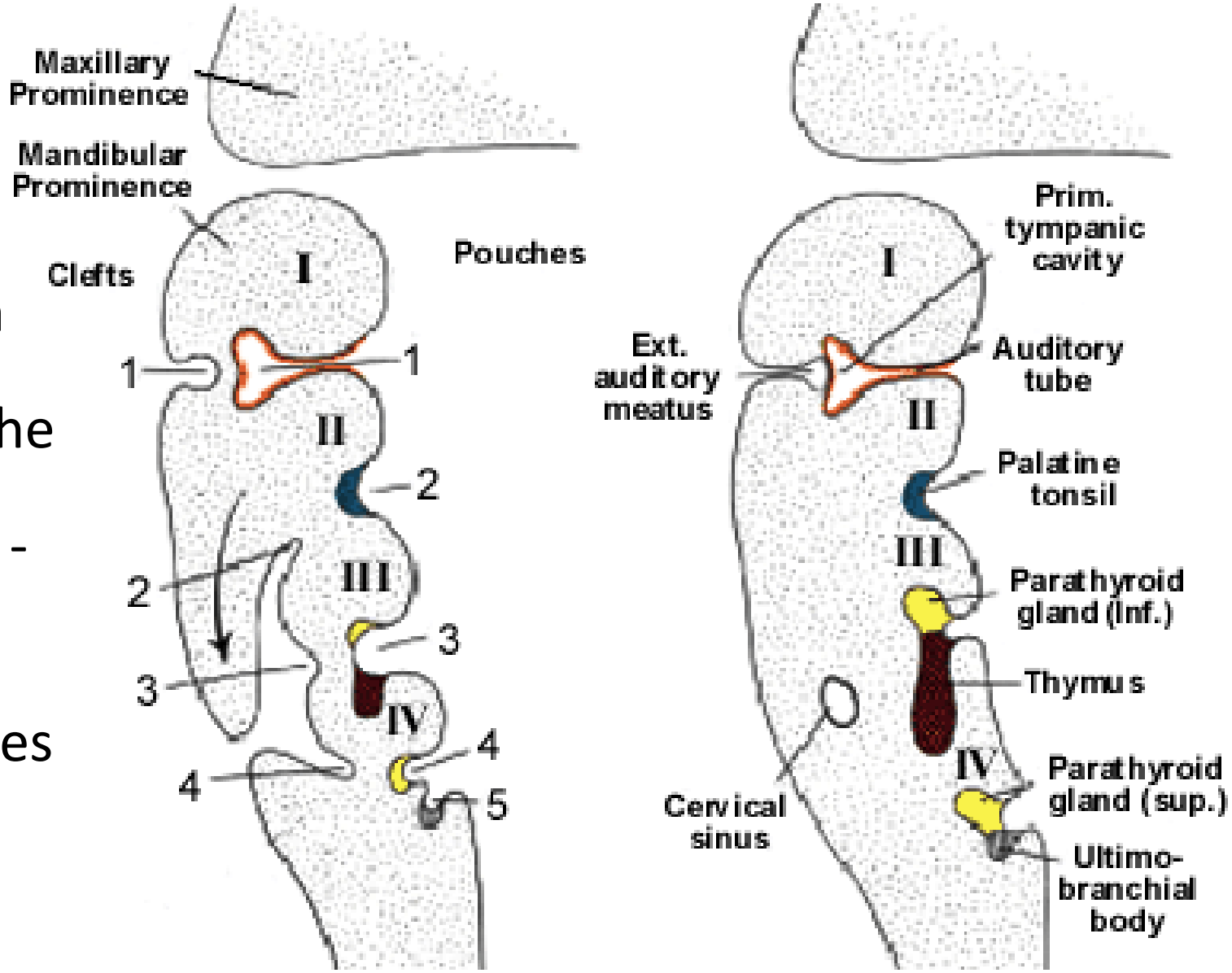
Filipp,D., Dobeš,J.: Imunita a tolerancia. Vesmír 92(4), 2013: 224-227

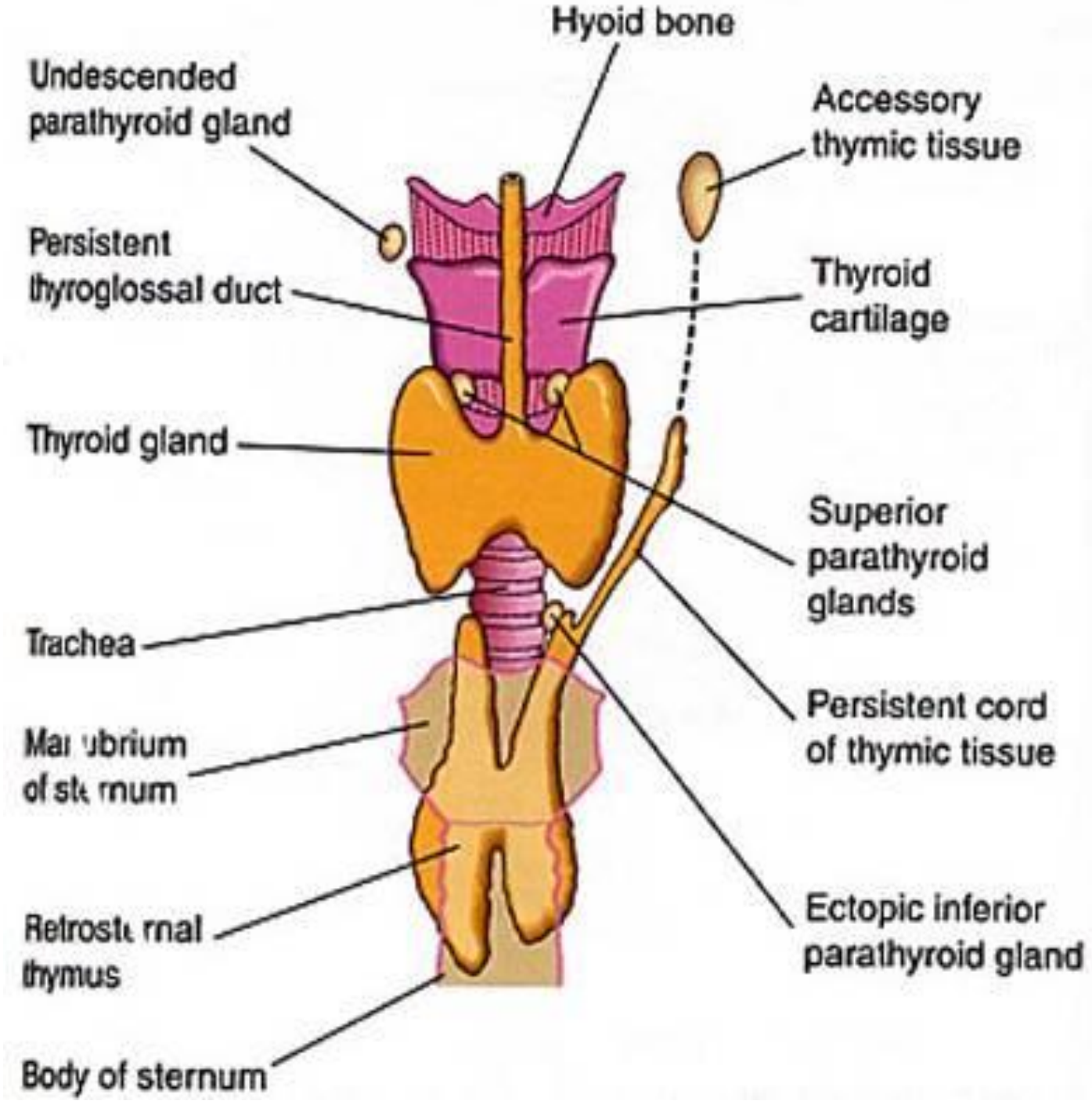
T-lymphocytes undergoing positive selection have both CD4 and CD8. Depending on the strength of binding with MHC I and MHC II, it loses one of them. Example: a CD4+CD8+ T-lymphocyte binds more strongly to MHC I and thus loses CD4 and becomes a CD8+ cytotoxic T-lymphocyte.



Development

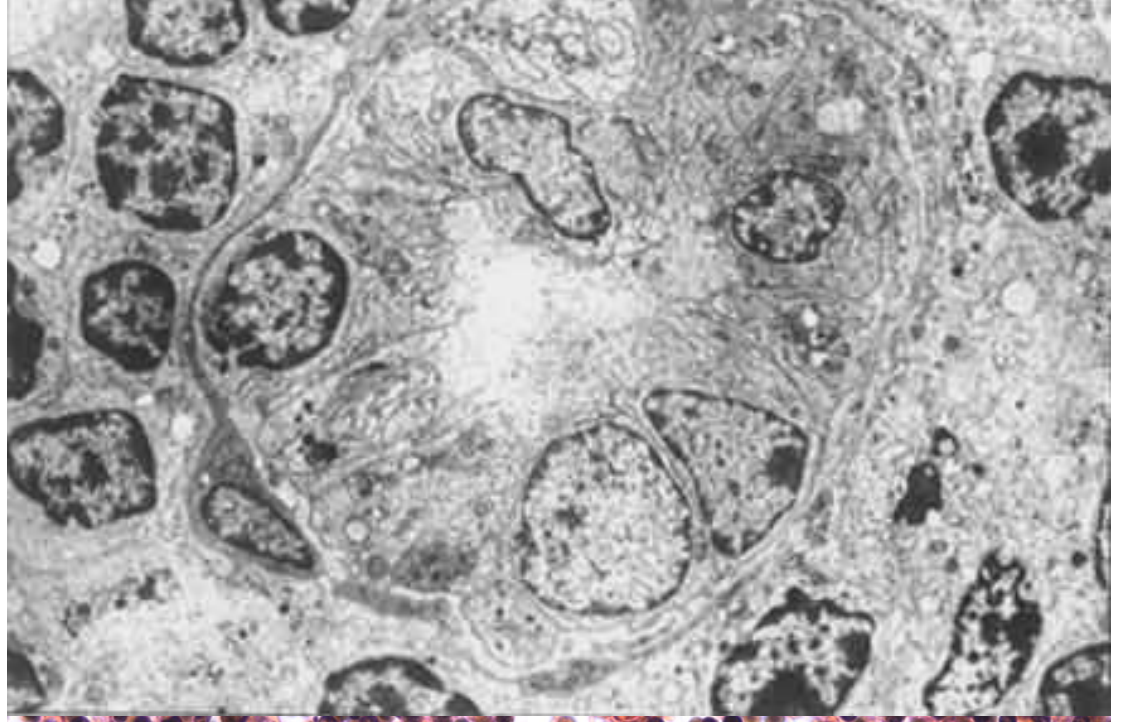
- Descends caudally from the third pharyngeal process together with the cells of the inferior parathyroid glands (4th - 7th week)
- Around week 10 colonized by lymphocytes
- Capsule and septa from the surrounding mesenchyme

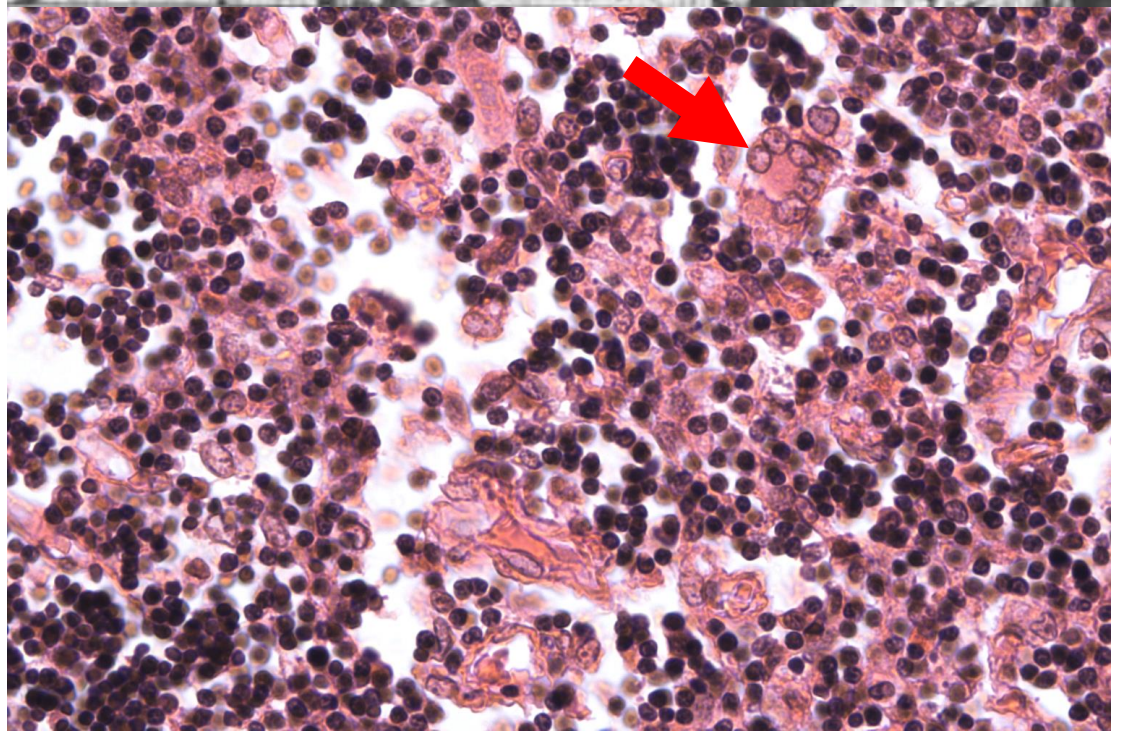



Hyoid bone
Undescended parathyroid gland
Accessory thymic tissue
Persistent thyroglossal duct
Thyroid cartilage
Thyroid gland
Superior parathyroid glands
Trachea
Persistent cord of thymic tissue
Manubrium of sternum
Retrosternal thymus
Ectopic inferior parathyroid gland
Body of sternum

T-cells after thymus

- They cross into the blood and meet the antigens in tissues
- Lymphatic capillaries
- Diapedesis (between endothelia) and emperipolesis (through endothelia)





DiGeorge syndrome

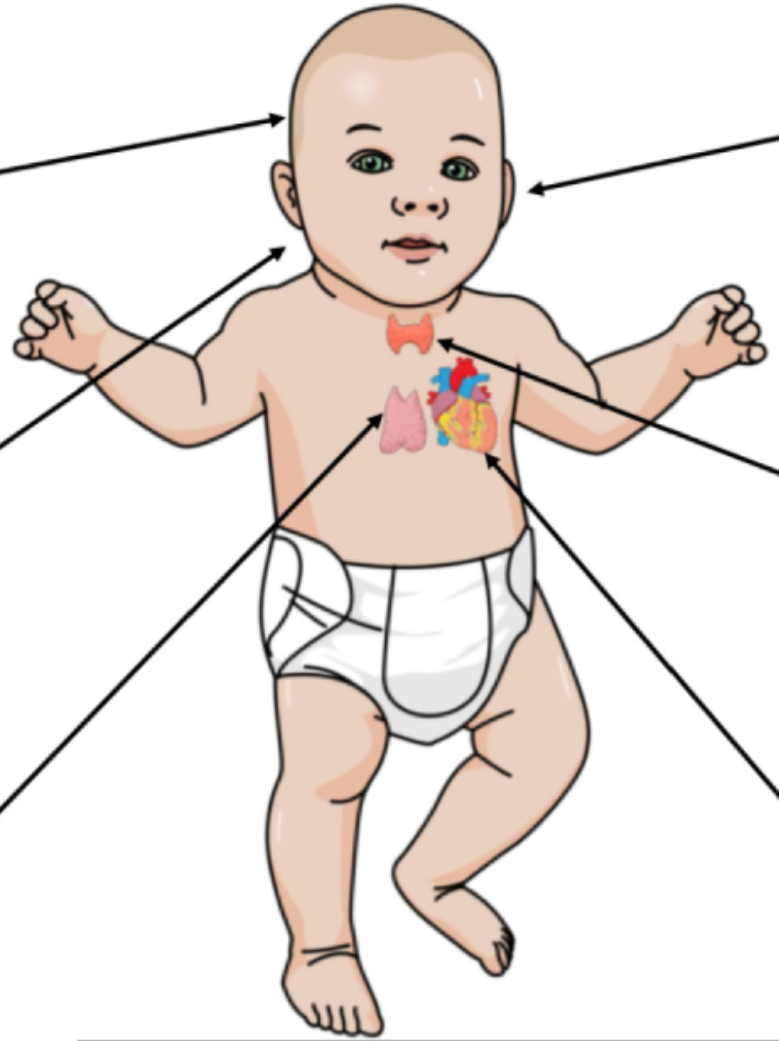
- **C**ardiac abnormality
- **A**bnormal facies
- **T**hymic aplasia or hypoplasia
- **C**left palate
- **H**ypocalcemia/hypoparathyroidism
- **22** chromosome
- Variable extent

Clinical features in DGS:

Neurodevelopmental and psychiatric disorders:
- Anxiety
- Attention disorders
- Autism spectrum disorders
- Schizophrenia
- Intellectual disability
- Language delay

Facies dysmorphisms:
- Hypertelorism
- Narrow palpebral rims
- Coloboma
- Small auricles implanted
- Ear helix folded
- Nose with broad root
- Root hypoplasia
- Small mouth
- Palatal anomalies

Immunological alterations:
- Thymic aplasia or hypoplasia
- Cellular and humoral abnormalities



Otorhinolaryngology alterations:
- Small auricles implanted
- Ear helix folded
- Palatal anomalies
- Velopharyngeal muscle insufficiency
- Hearing loss (sensorineural or conductive)

Endocrinological diseases:
- Hypoparathyroidism
- Hypocalcemia

Heart defects:
- Fallot's tetralogy
- Pulmonary atresia
- Arterial trunk
- Interruption of the aortic arch
- Septal defects

Non-typical manifestations:
- Ophthalmic anomalies
- Genito-urinary anomalies
- Vascular anomalies
- Musculoskeletal anomalies

Menghi M, Micangeli G, Tarani F, Putotto C, Pirro F, Mariani A, Petrella C, Pulvirenti F, Cinicola B, Colloridi F, et al. Neuroinflammation and Oxidative Stress in Individuals Affected by DiGeorge Syndrome. *International Journal of Molecular Sciences*. 2023; 24(4):4242. https://doi.org/10.3390/ijms24044242

Myth or fact?

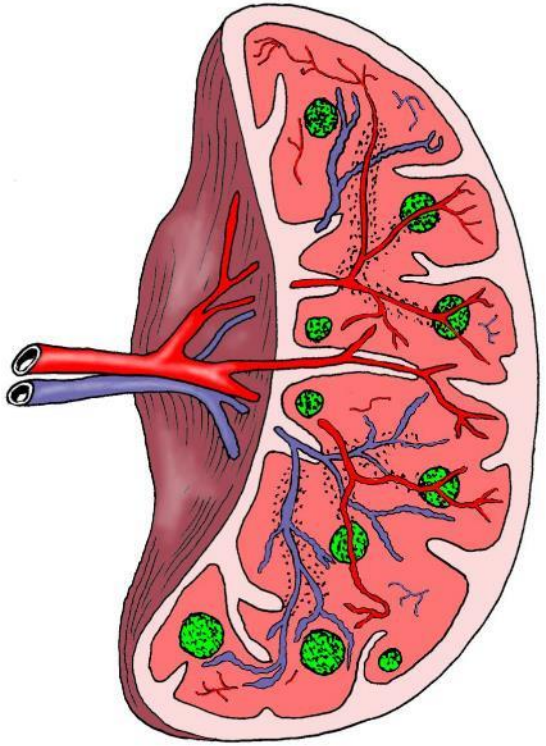
- Patients with DiGeorge syndrome can undergo thymic transplantation. The donor thymus tissue is specially processed and then transplanted into the patient's thigh. This procedure is only performed in a few centres worldwide (e.g. London).

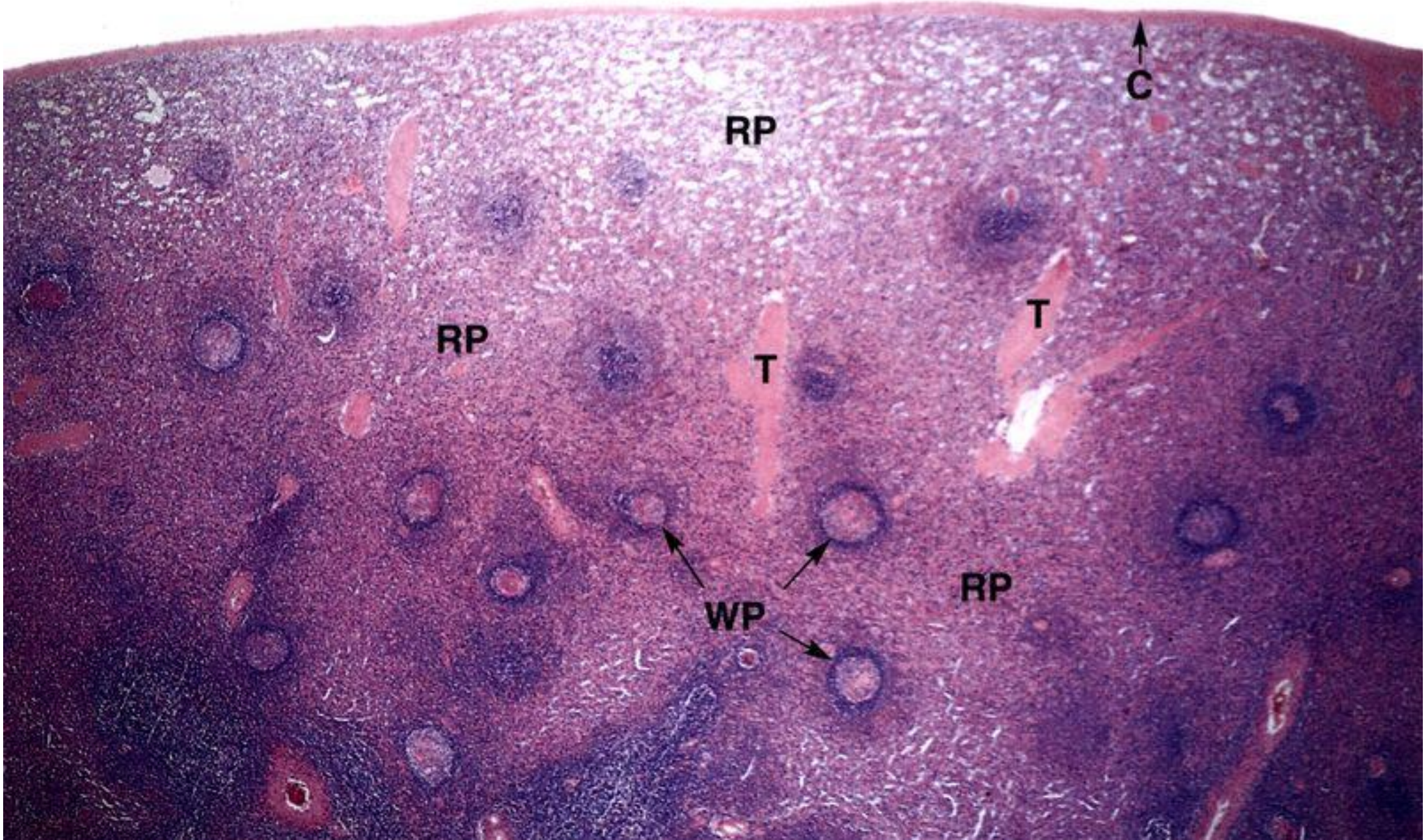
- Newborns with DiGeorge syndrome require special attention during breastfeeding.

- Athymic patients receive blood transfusions irradiated with X-rays or gamma radiation.

Spleen

- Serosa on the surface
- connective tissue sheath (dense collagen connective tissue)
  - smooth muscle cells
  - sends out trabeculae splenicae
- pulpa splenica (reticular connective tissue)
- pulpa alba
  - zona marginalis + noduli lymphoidei splenici
  - Immune reaction, B-lymphocyte maturation
- pulpa rubra
  - Anastomosing cords of Billroth (from reticular connective tissue) + sinusoids




C
RP
RP
T
T
WP
RP

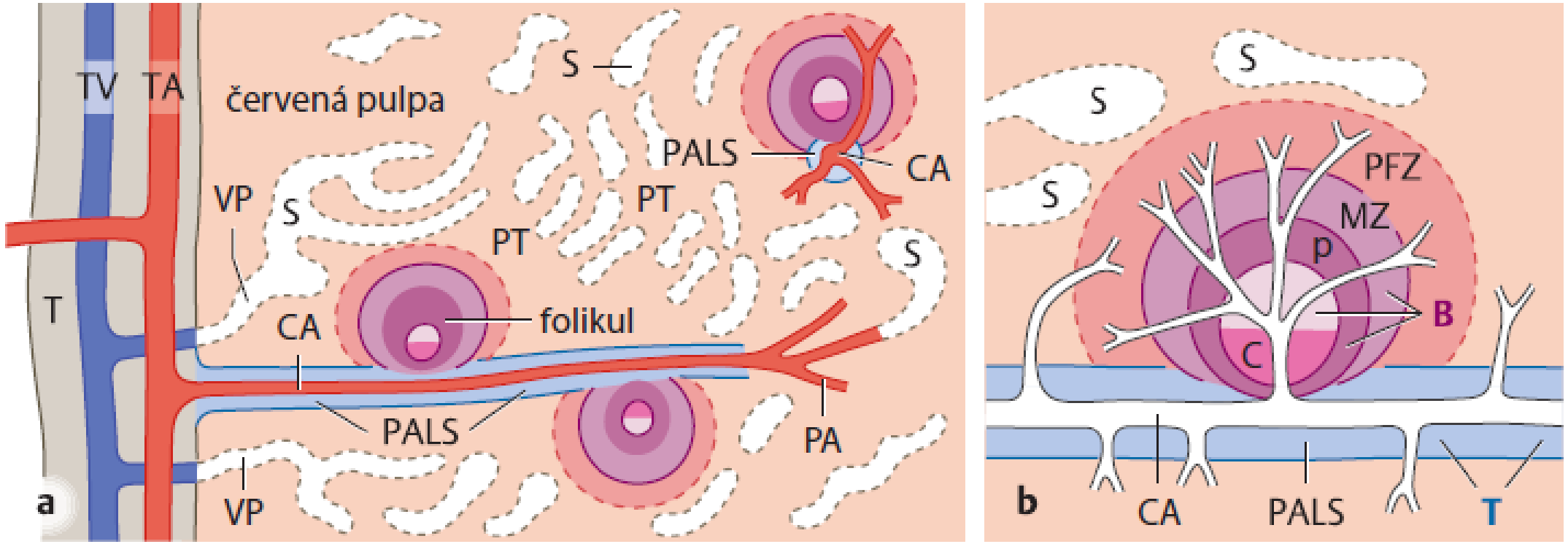
Vessels

- truncus coeliacus → a. splenica → rr. splenici →
  aa. trabeculares → arteriolae vaginatae pulpae
  albae (central artery)
  - in the periarterial lymphatic sheath (PALS; vagina lymphoidea periarteriolaris)
  - arteriolae centrales (nodulares) to noduli lymphoidei splenici
  - sinuses of the marginal zone

→ aa. pulpae rubrae → aa. penicillares → arteriolae penicillares
→ vagina perioarteriolaris macrophagocytica (Schweigger-Seidel sheath)

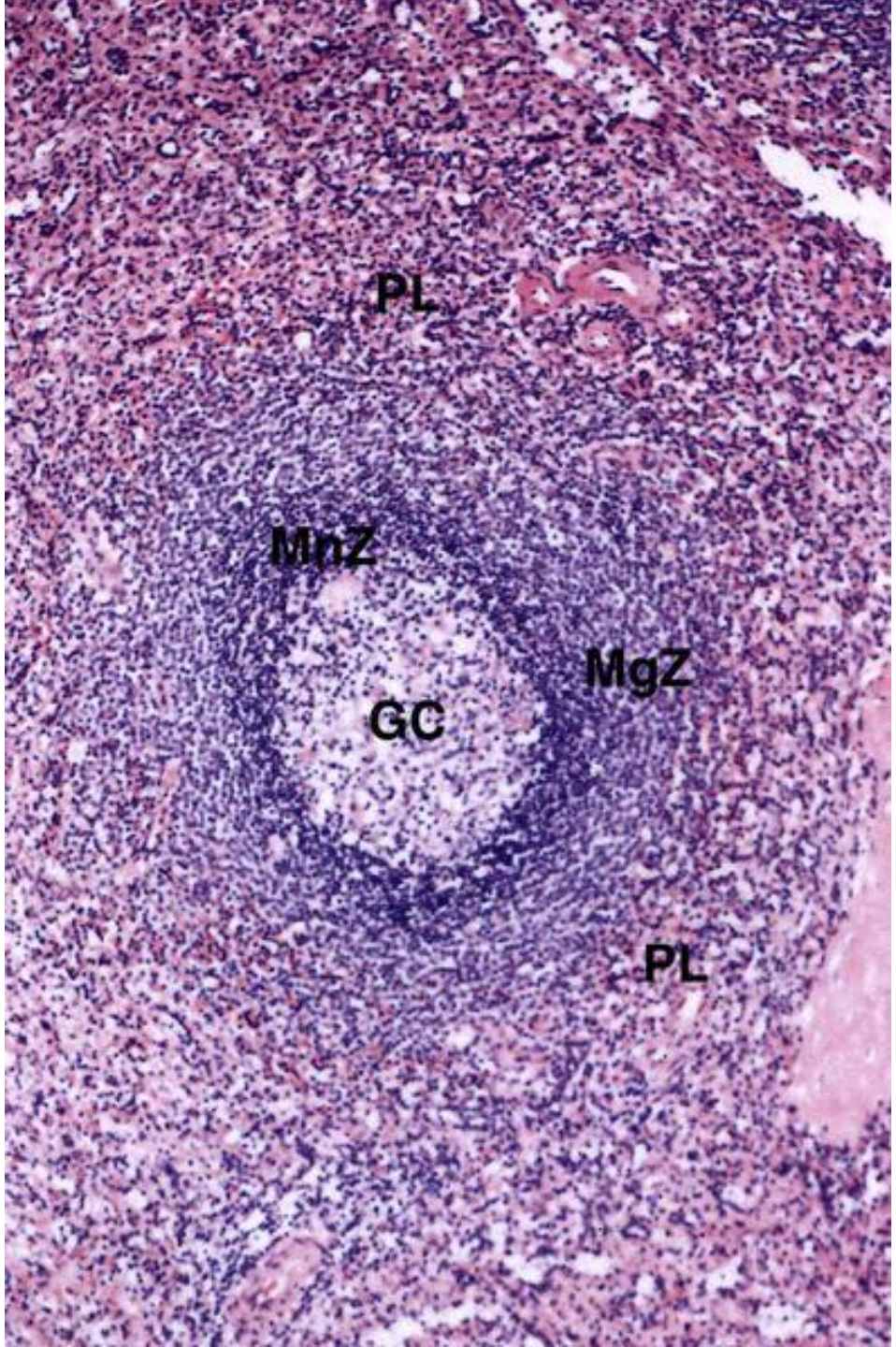
- vasa sinusoidea splenica (in red pulp)
  - open x closed circulation
  - Elongated discontinuous endothelial cells, discontinuous basal lamina

→ vv. pulpae rubrae → vv. trabeculares → v. splenica → v. portae

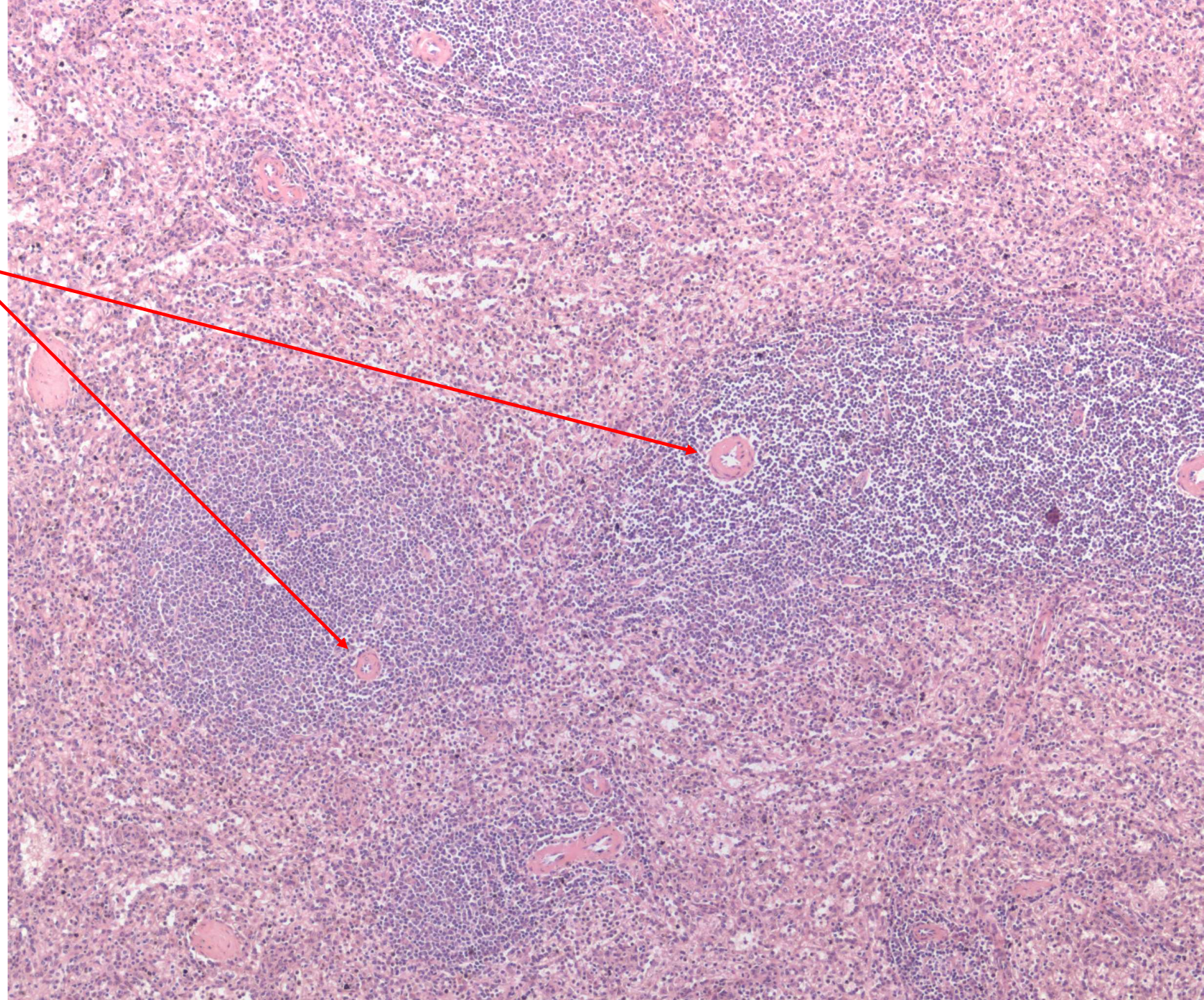


Obr. 13.17 **Schéma stavby sleziny člověka.** **a** Přehled. **b** Detail. **T**, vazivový trámec. **Cévy: TA, TV**, trabekulární arterie a véna. **CA**, centrální arteriola; ve schématu a jsou vynechány radiální větve podélně probíhající CA (dole) a zobrazeny jsou jen větve CA zachycené v příčném průřezu (nahoře). **PA**, arteriolae penicillatae. **S**, sinus. **VP**, véna pulpy. **Bílá pulpa: PALS** (periarteriolární lymfatická pochva, *modře* je T-zóna), dále lymfatický folikul a marginální zóna (**MZ**) (*nachově* = B-zóna). **C**, zárodečné centrum folikulu; **p**, lymfocytární plášť. **Červená pulpa:** perifolikulární zóna (**PFZ**), sinusoidy a trámce pulpy (**PT**, vyplňují prostor mezi sinusy). Bližší vysvětlení viz text.

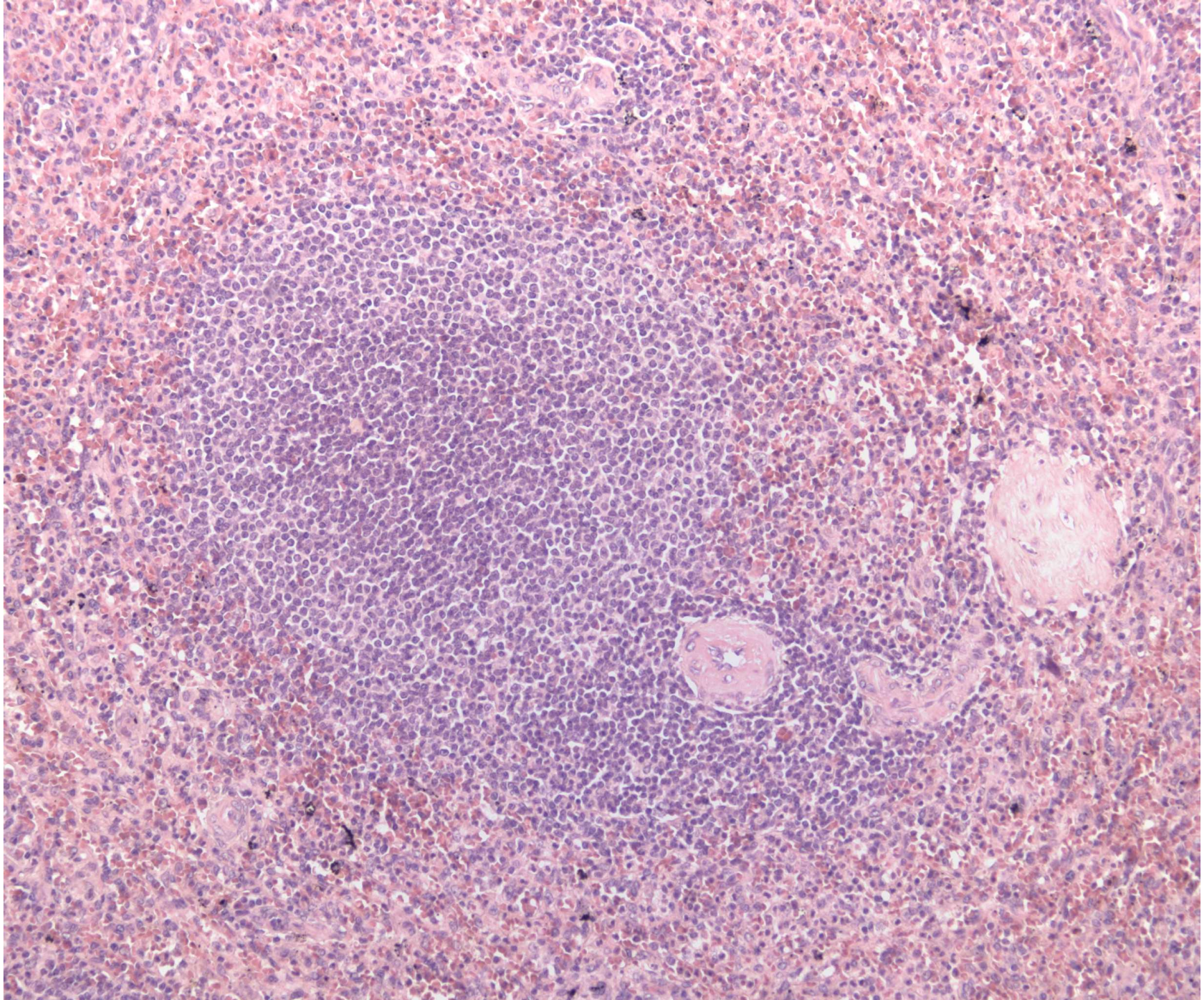
The lymph nodule is the most conspicuous part of the white pulp. The germinal center is surrounded by the mantle zone and then the marginal zone.



Although they are usually located eccentrically in the white pulp, they are called **central arteries** (arteriae centrales). In the white pulp we distinguish a narrow sheath that surrounds the central artery. This area is called the **periarterial lymphatic sheath** (PALS). It is a thymodependent area containing T-lymphocytes. (Vajner a kol., Lékařská histologie II., originally in Czech)



White pulp



Question time

1. What are some reasons for splenectomy?

2. Does splenectomy have some implications for patients health?

Odpovědi

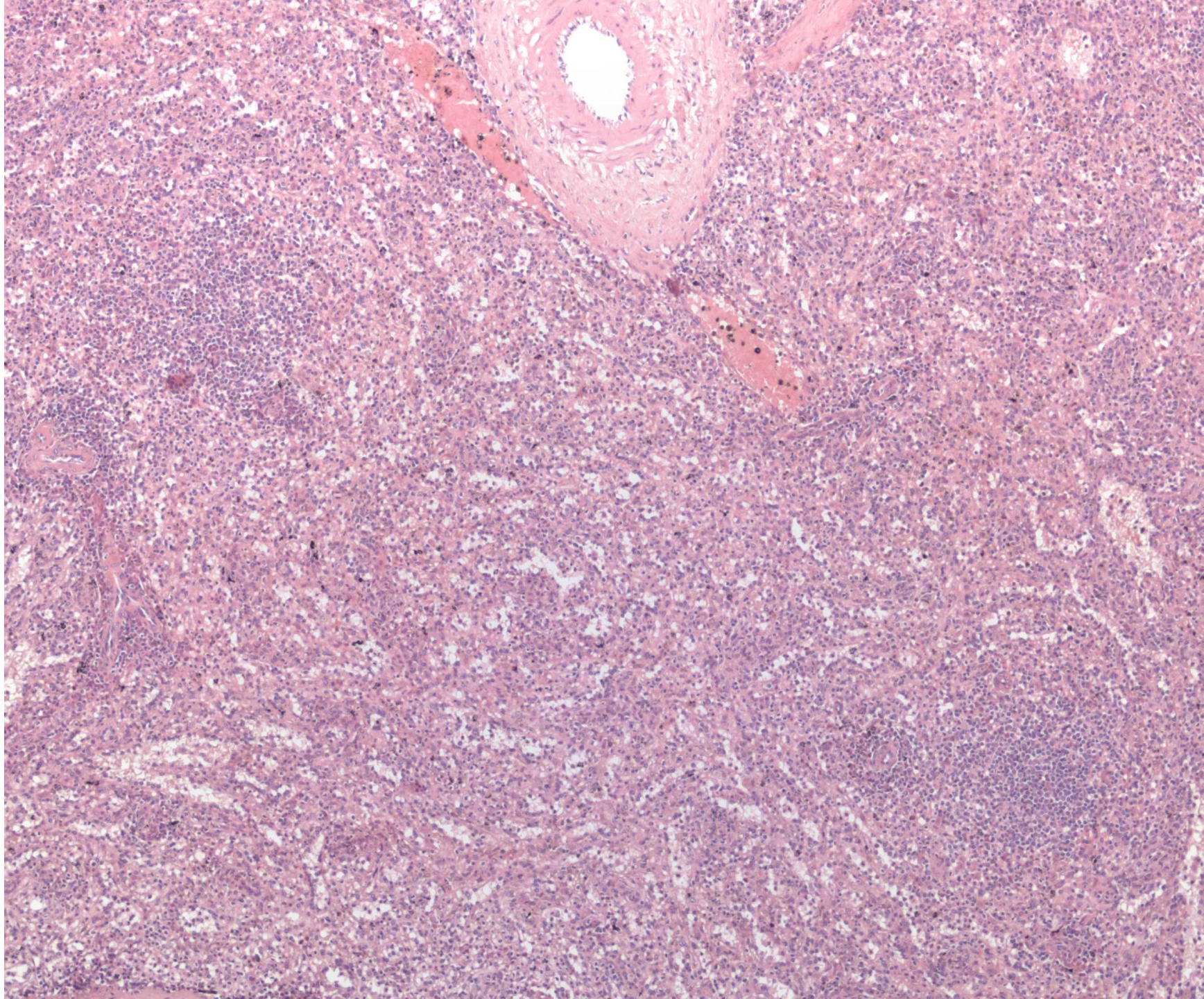
1. Hypersplenism, trauma (risk of rupture and life-threatening bleeding)

2. Impaired immunity, especially against encapsulated bacteria (e.g. pneumococcus, meningococcus, haemophilus). Vaccination is recommended.

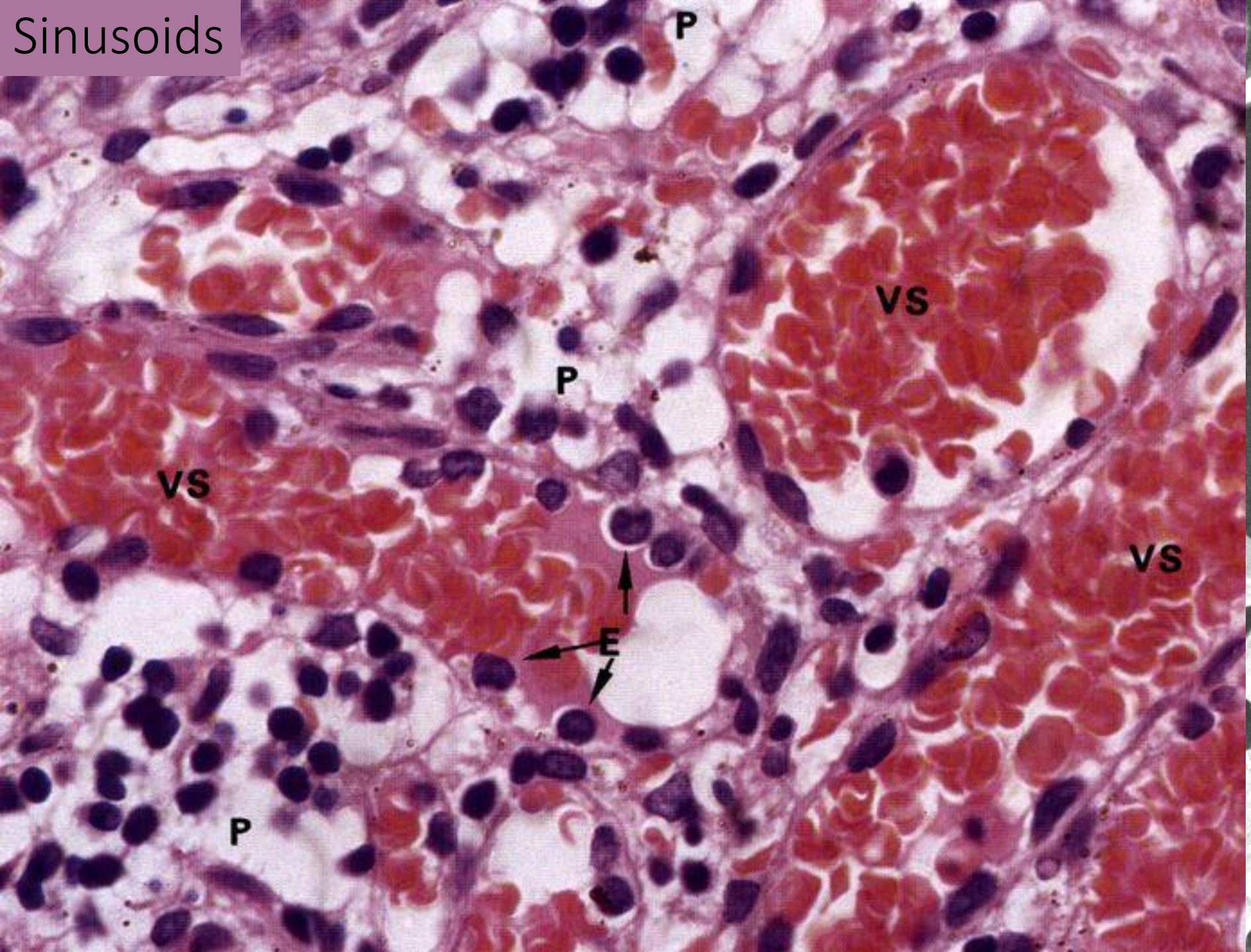
Red pulp optically

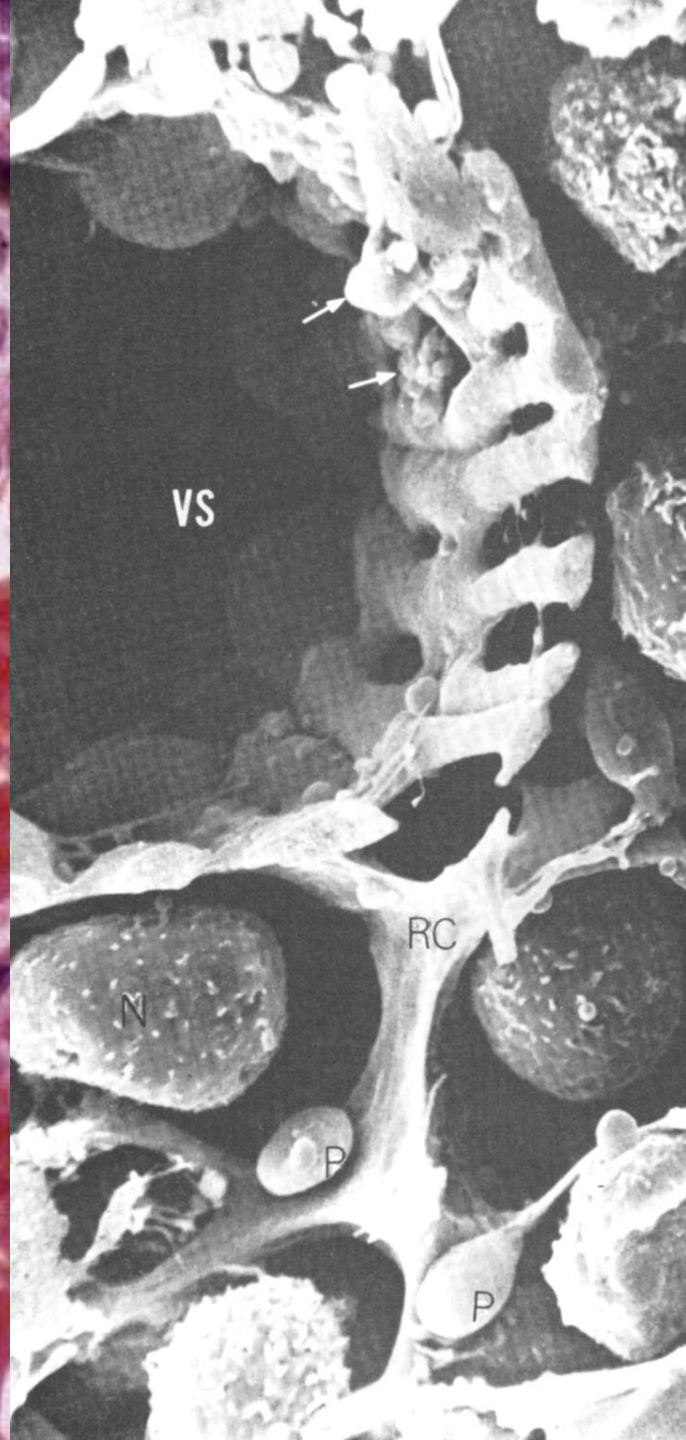
empty spaces - sinusoids

surrounding reticular connective tissue – cords of Billroth

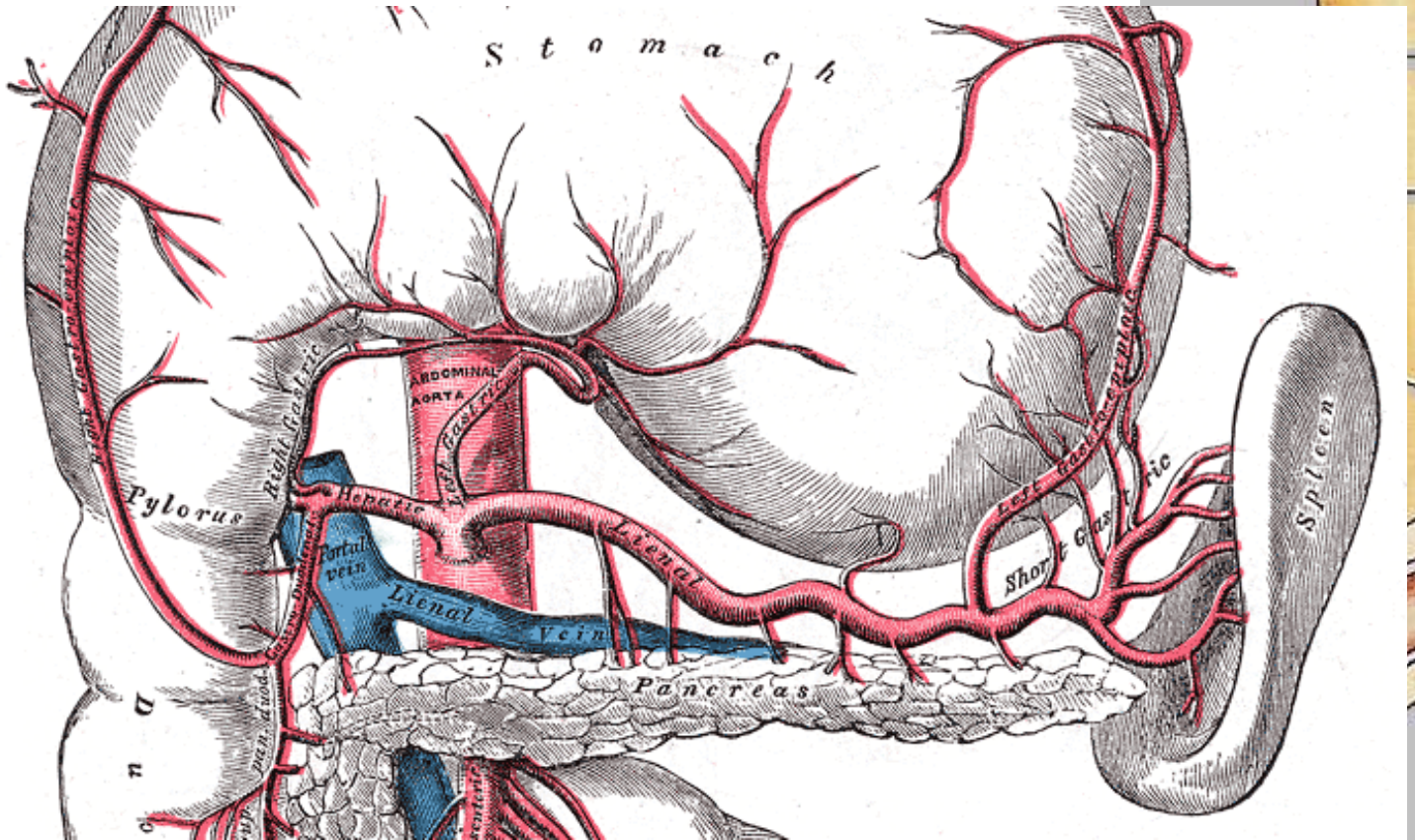


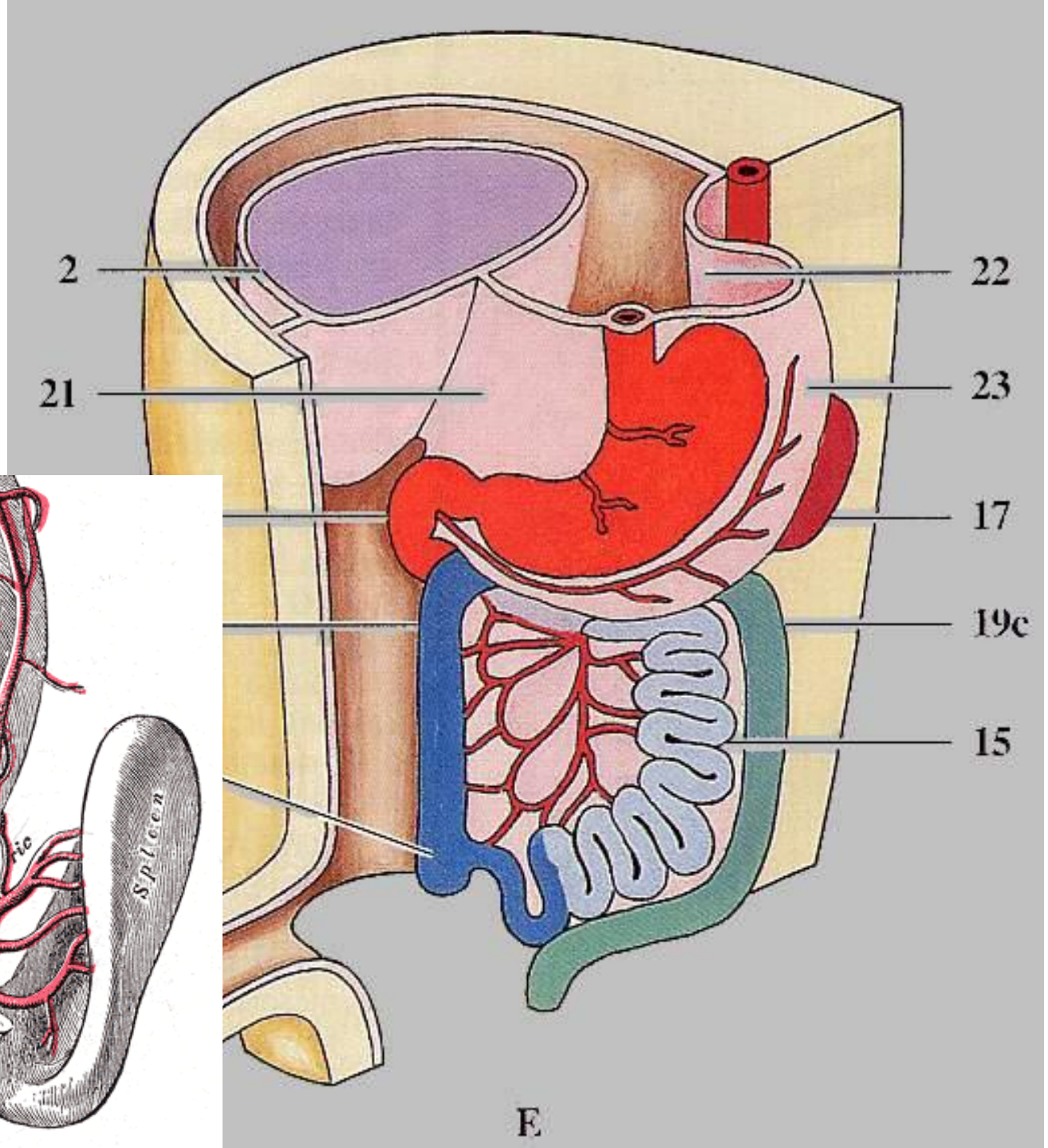
Sinusoids



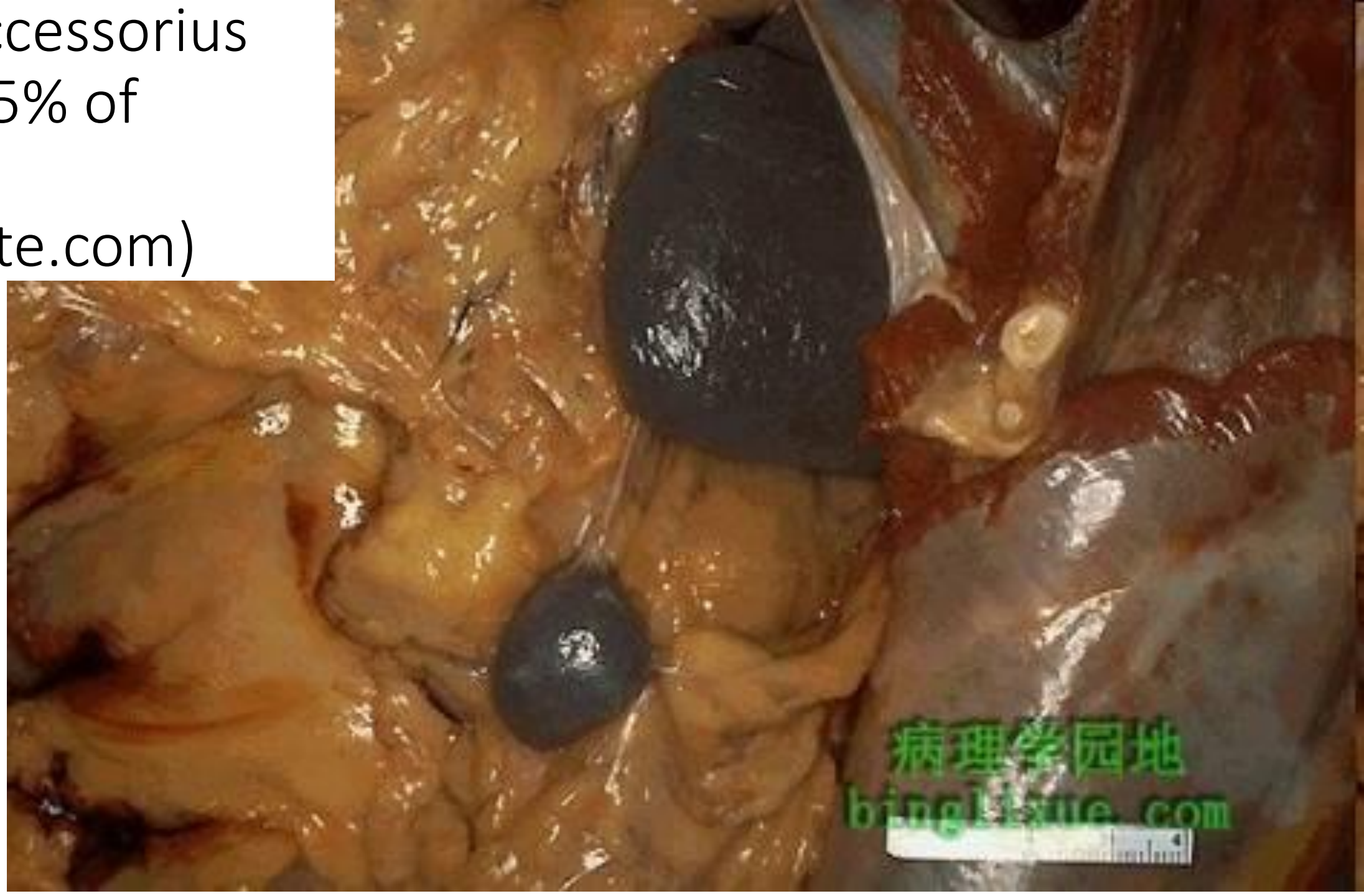


The spleen develops as a condensation of the mesenchyme in the posterior mesogastrium. It is therefore a derivative of the mesoderm. In accordance with the rotation of the stomach, it reaches the left side.



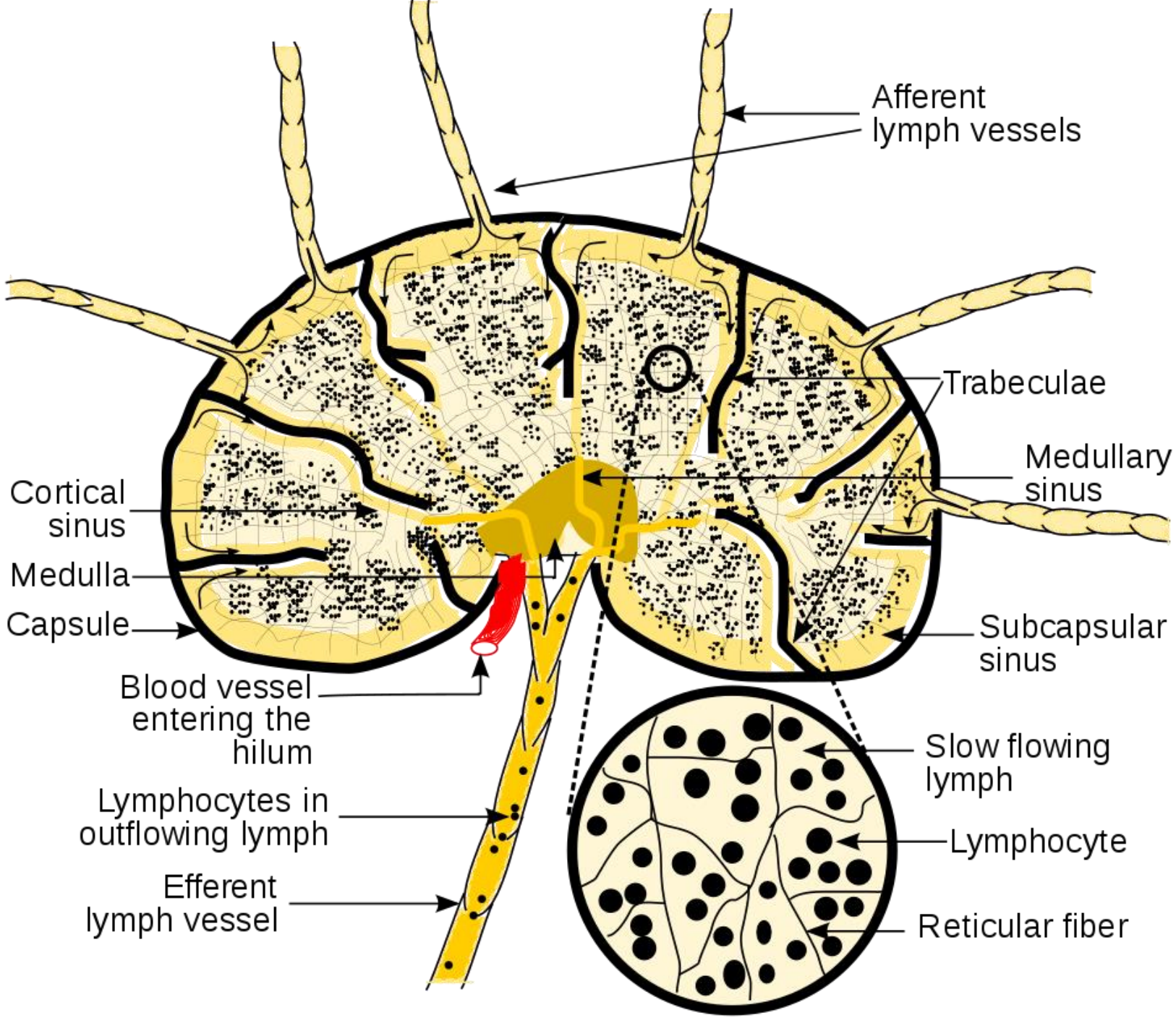


Splen accessorius about 15% of people (uptodate.com)



Lymph nodes

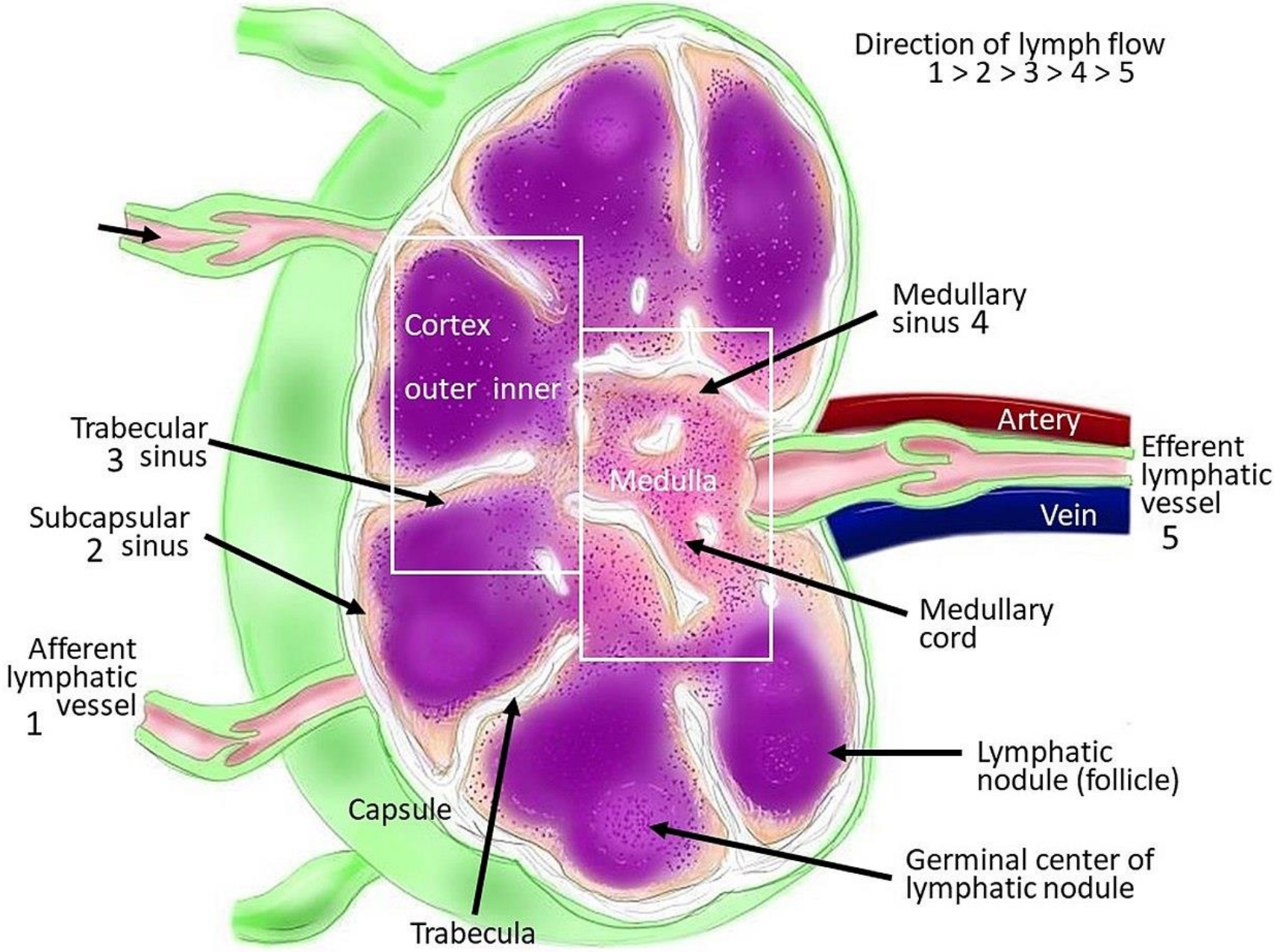
- Encapsulated secondary lymph organs located along lymphatic vessels
- Checkpoints where cells (e.g. lymphocytes) can react to passing antigens
- Afferent lymphatic vessels, efferent lymphatic vessels, blood vessels
- Trabeculae from the capsule to the interior of the node
- Stroma - reticular connective tissue
- Parenchyma - B-cells, T-cells, macrophages, dendritic cells
- Cortex, paracortex, medulla


Afferent
lymph vessels
Trabeculae
Medullary
sinus
Cortical
sinus
Medulla
Capsule
Subcapsular
sinus
Blood vessel
entering the
hilum
Slow flowing
lymph
Lymphocytes in
outflowing lymph
Lymphocyte
Efferent
lymph vessel
Reticular fiber

Superficial cortex contains lymphatic nodules. Deep corte (paracortex) contains a lot T-cells, it is not arranged in nodules. Medulla contains lymphatic sinuses and the medullary cords of reticular CT.

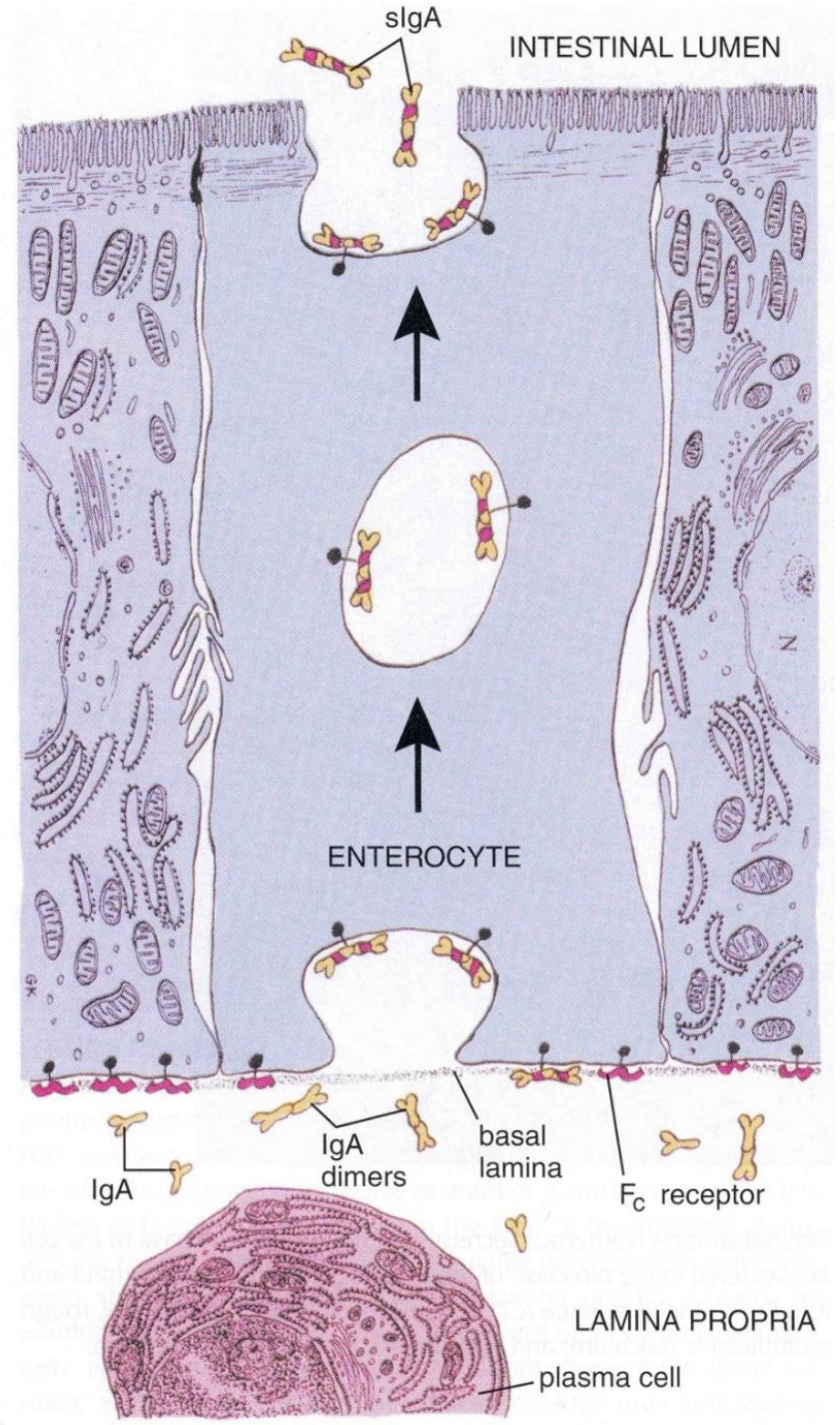
There are three types of channels allowing the passage of lymph – subcapsular, trabecular and medullary sinuses. Cells can send processes into the sinuses.

Lymph nodes contain high endothelial venules, through which the lymphocytes can easily pass.

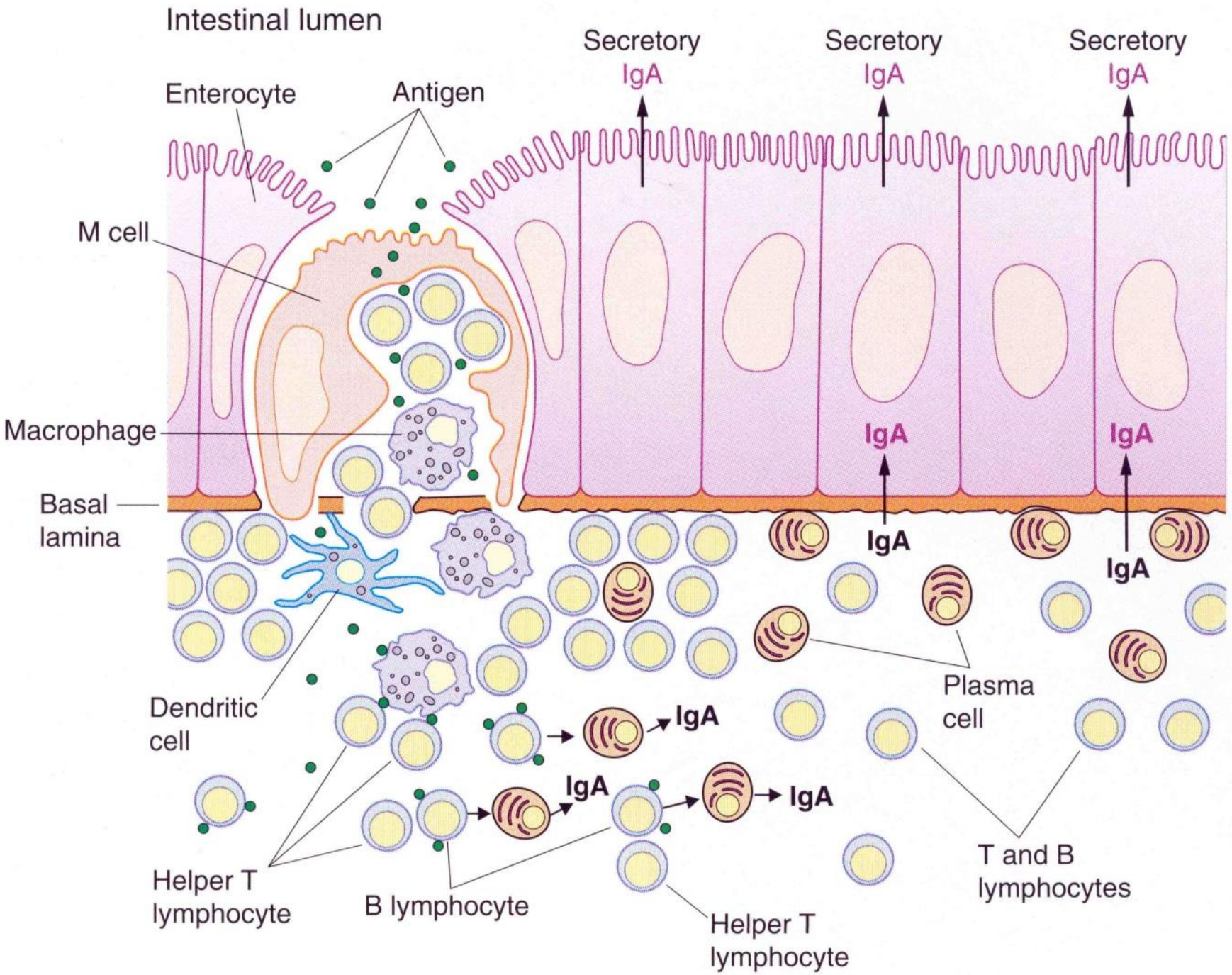


MALT

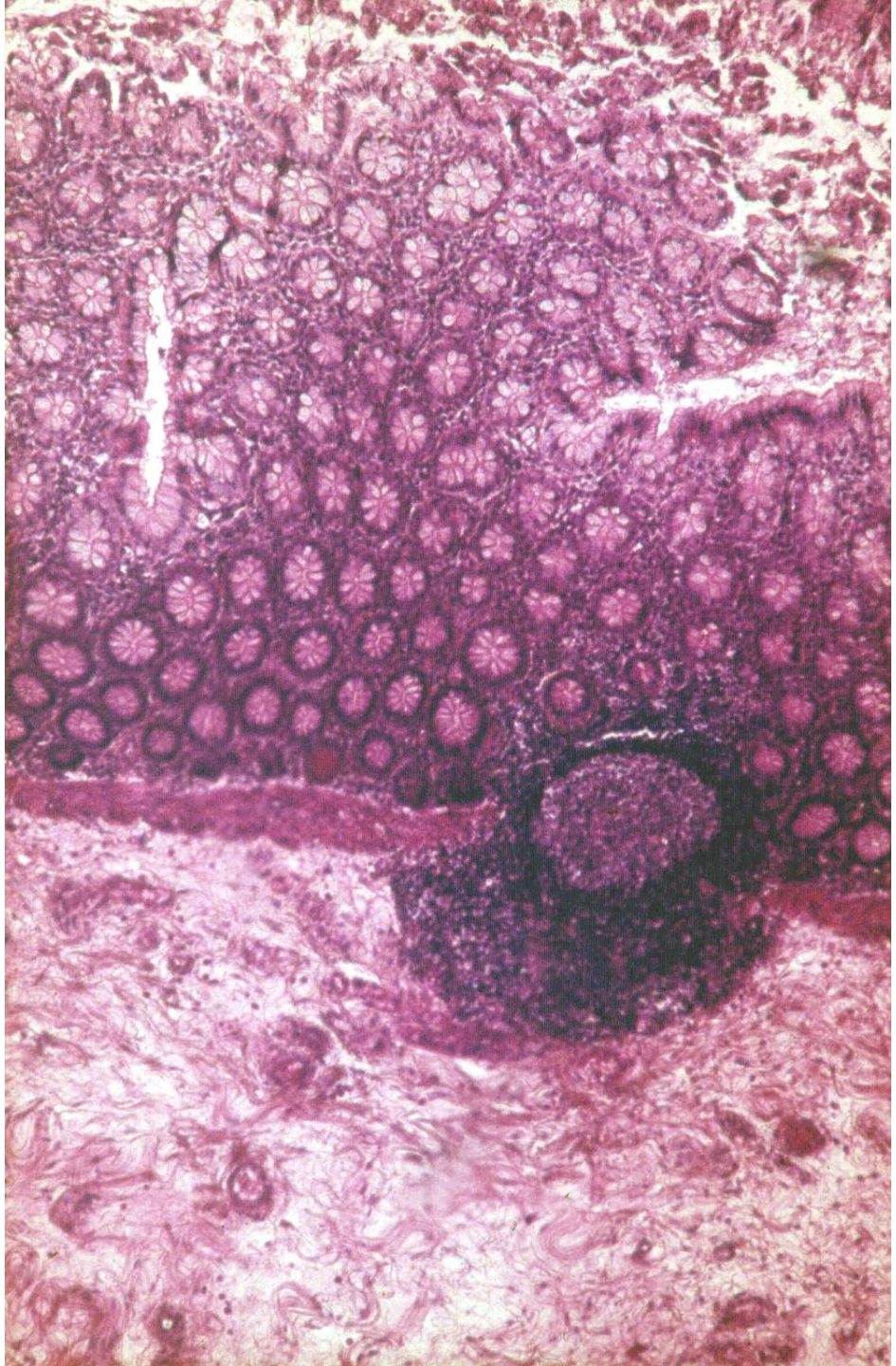
- Mucosa-associated lymphoid tissue
- Lymphoid nodules found diffusely in the mucosa of various organs
- BALT – bronchi, GALT – gut, NALT – nose…
- Peyer‘s patches (lymphonoduli aggregati) – larger aggregates of nodules found in ileum
- IgA secreted into the lumen



M-cells transport antigens to the cells of MALT.

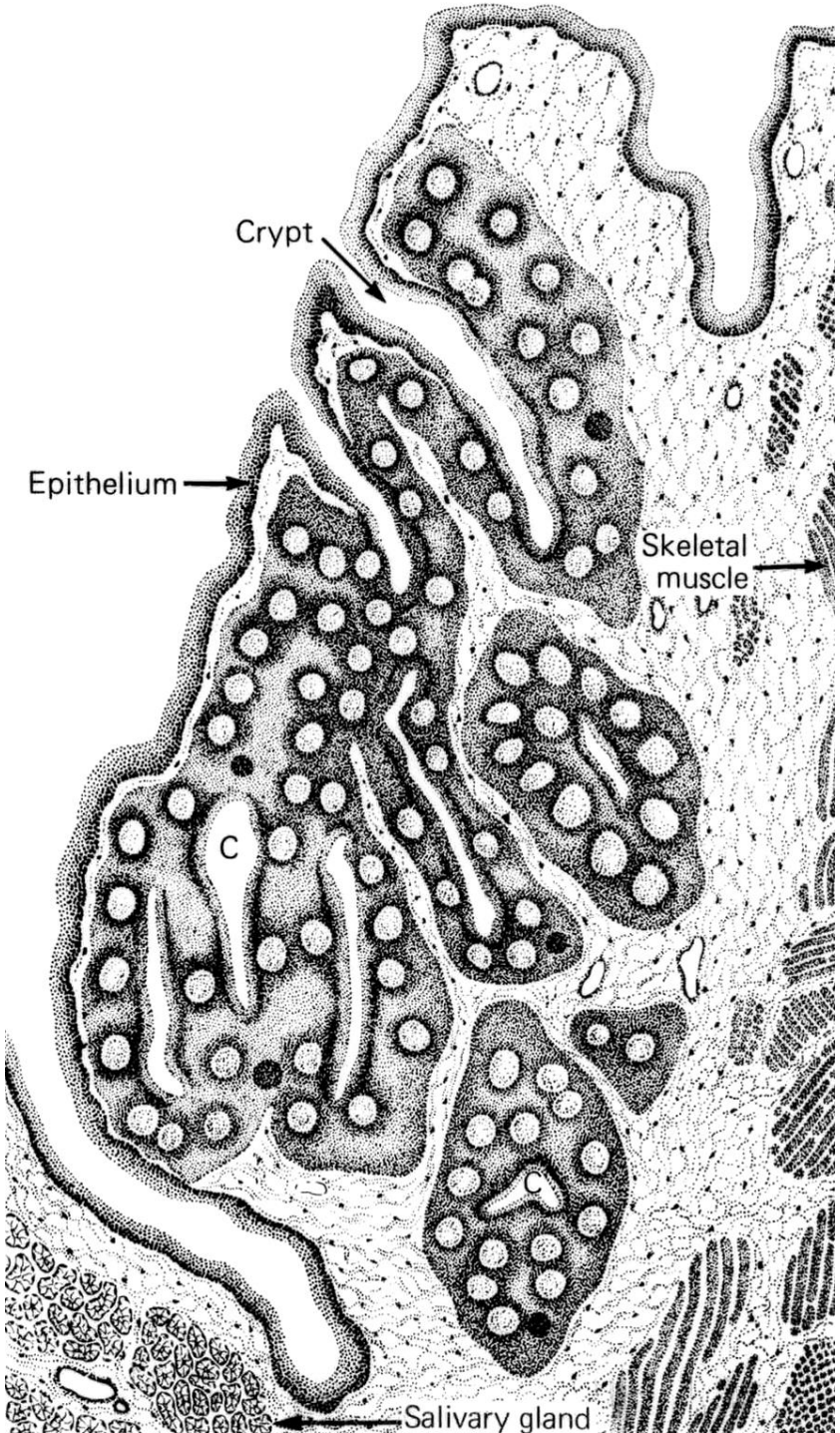


GALT – lymphoid nodule

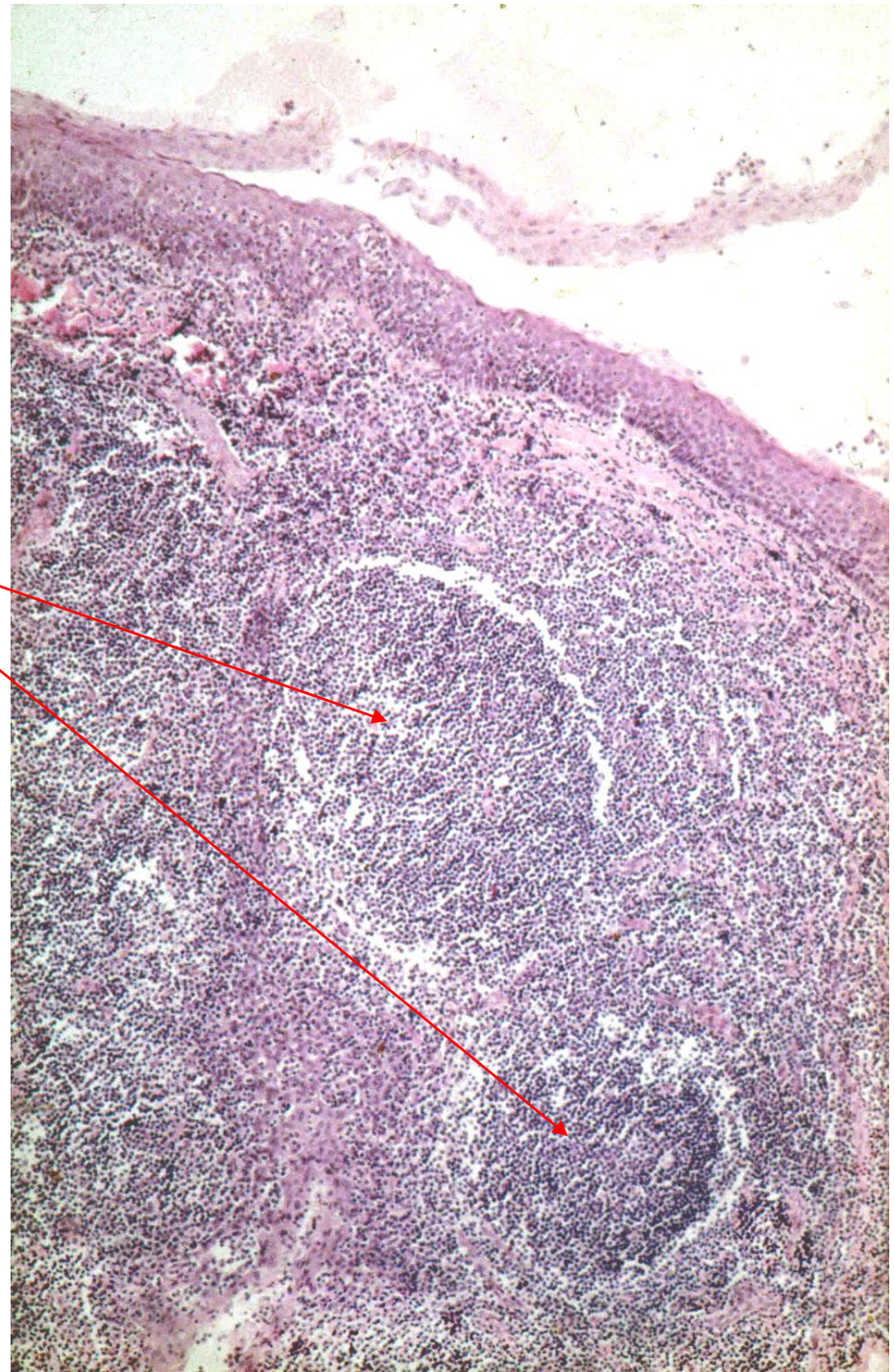


Tonsils

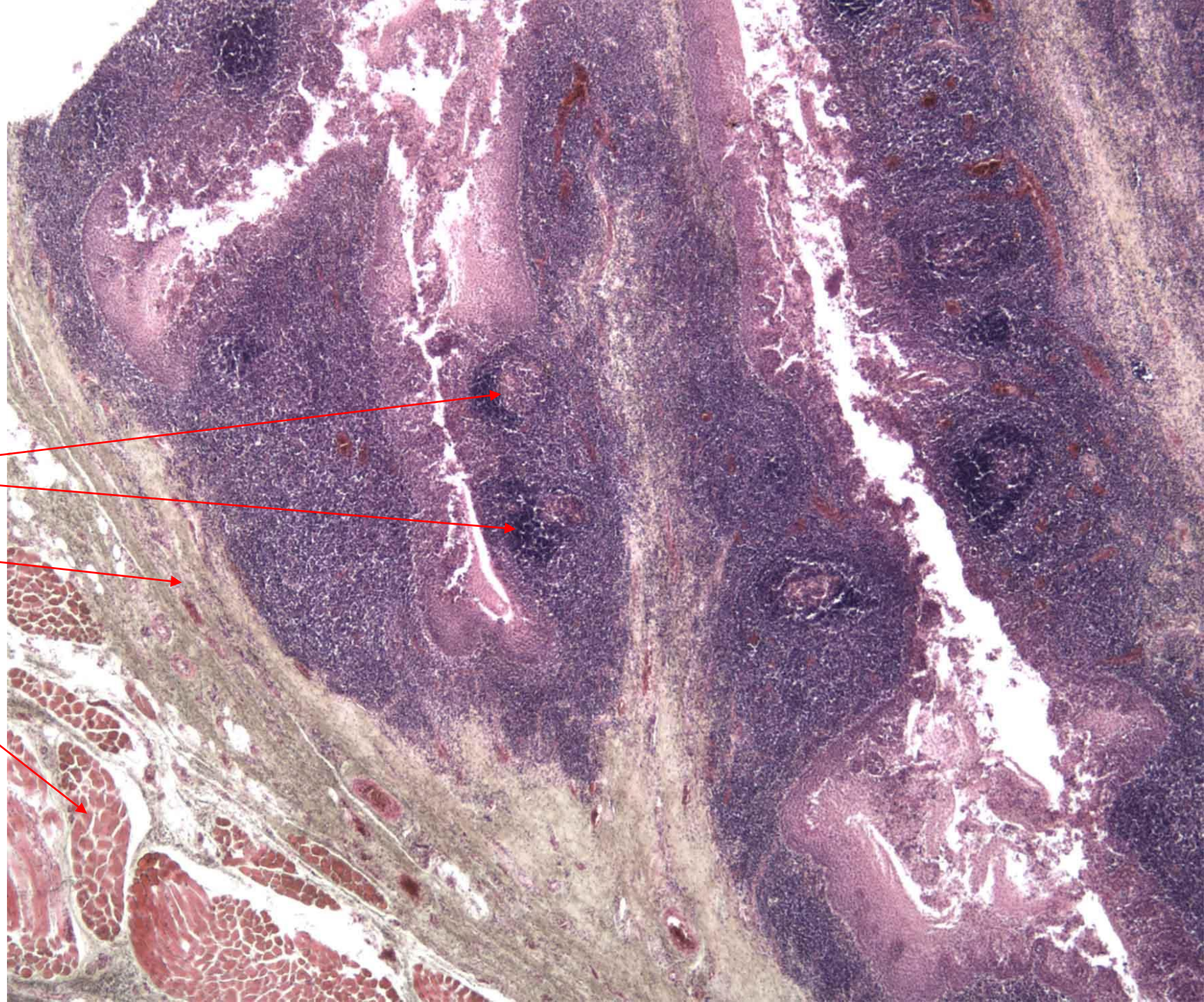
- Incompletely encapsulated lymphoid organs
- Lingualis, palatina, tubaria – Waldeyer‘s ring
- Epithelium on the surface, crypts
- Numerous lymphoid nodules
- Dense CT underneath

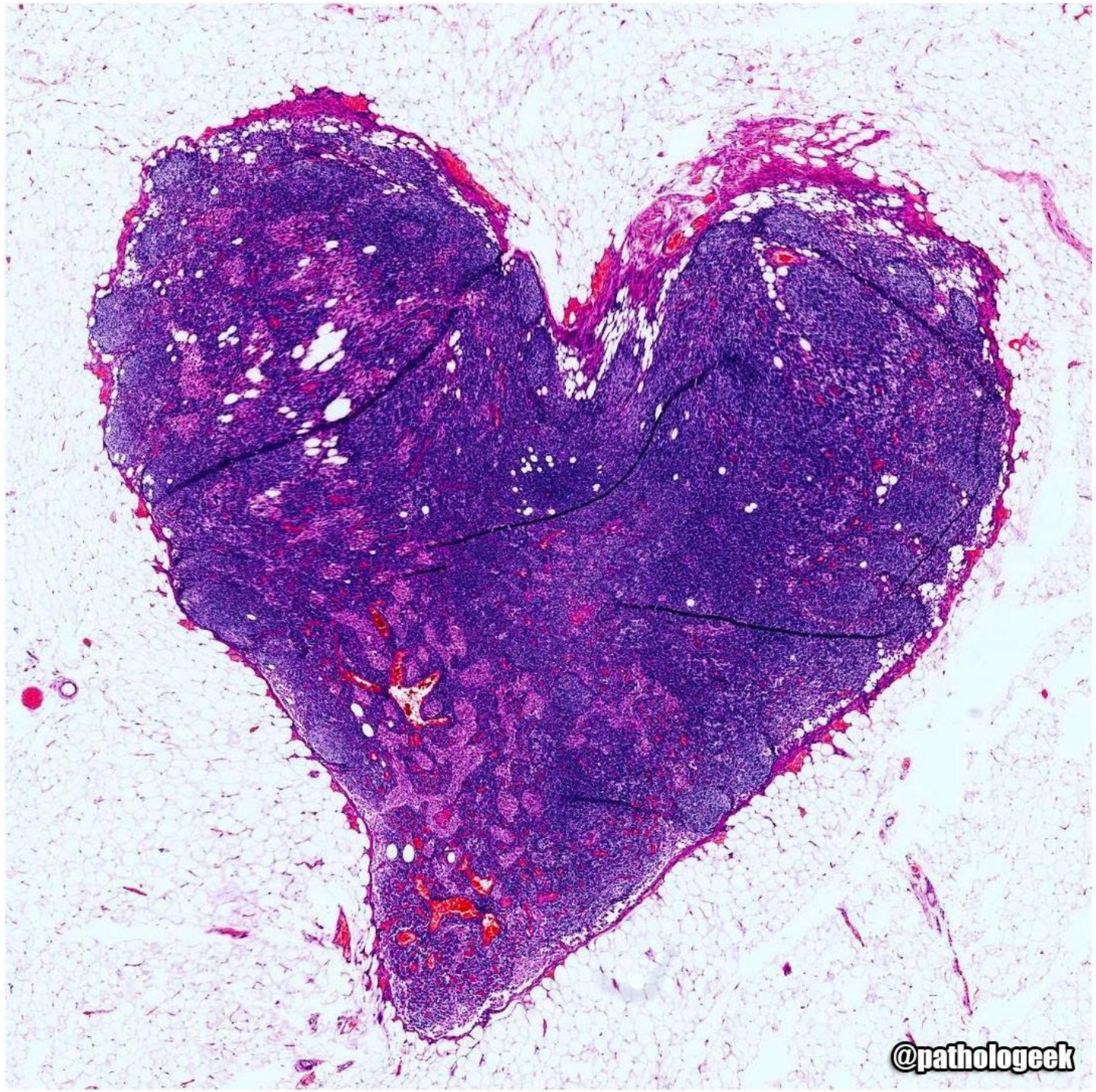


Tonsilla lingualis lymphoid nodules



Crypts of the palatine tonsil – stratified squamous epithelium.
Lymphoid nodules
capsule
skeletal muscle




@pathologeek