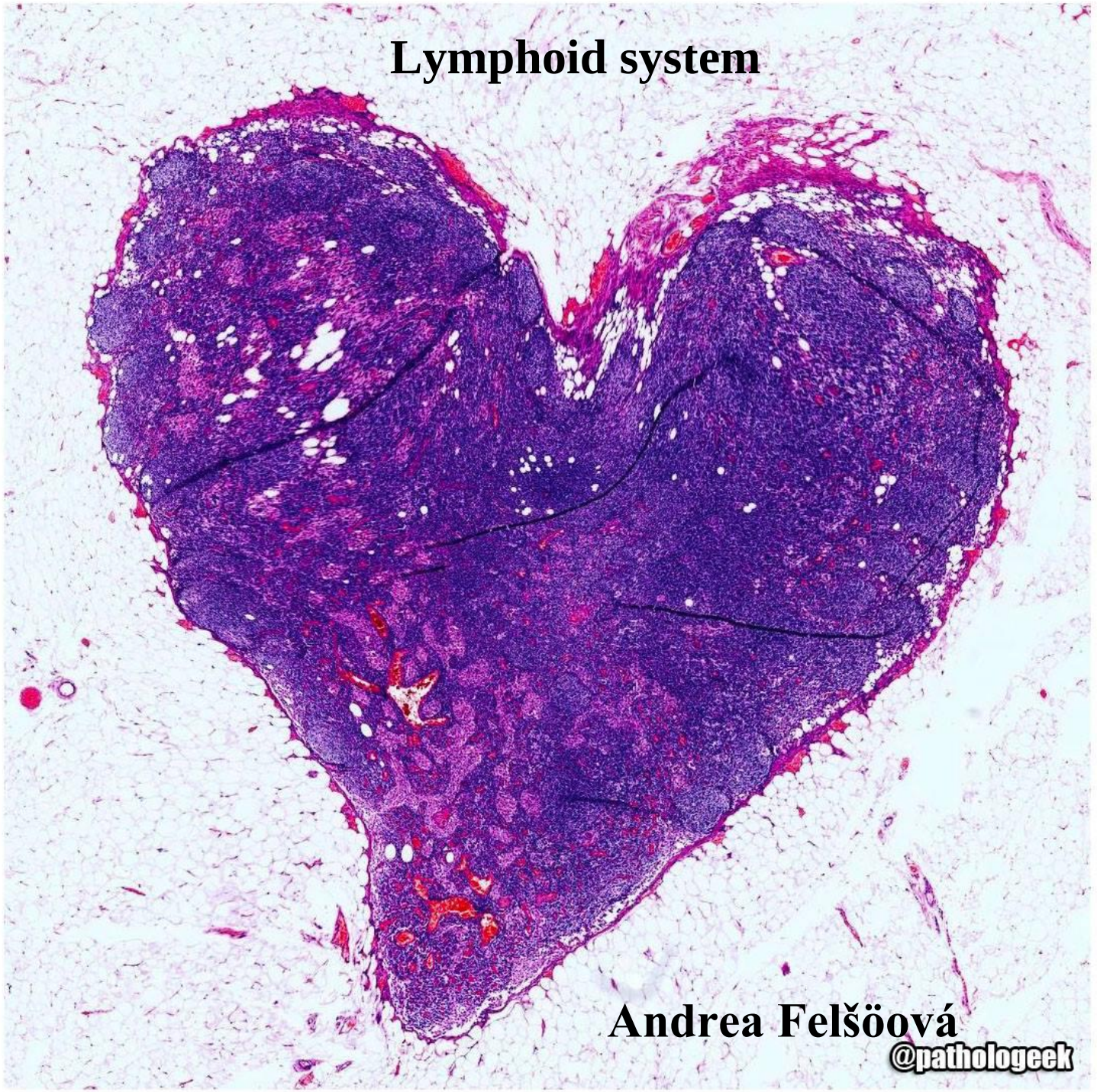
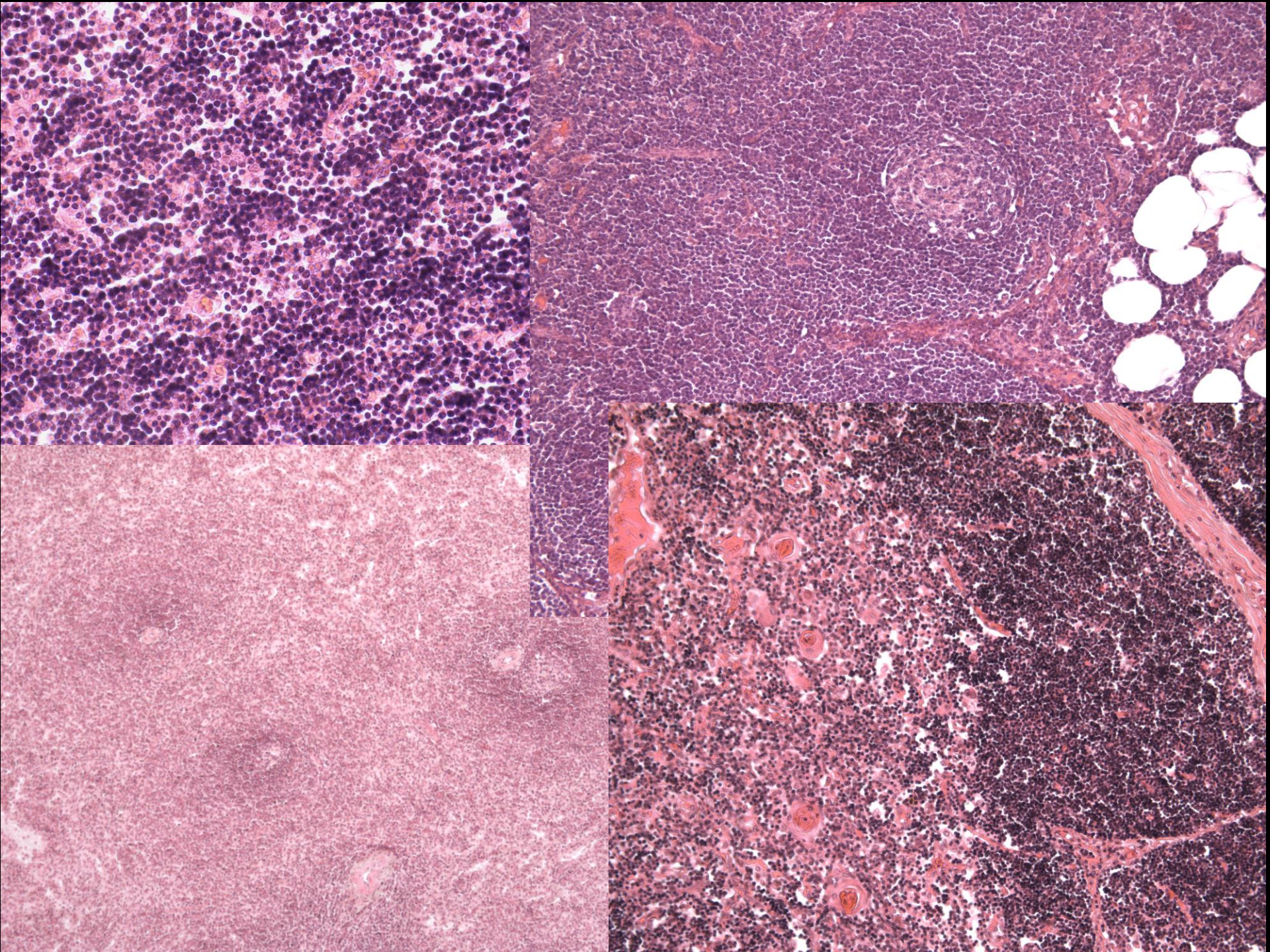
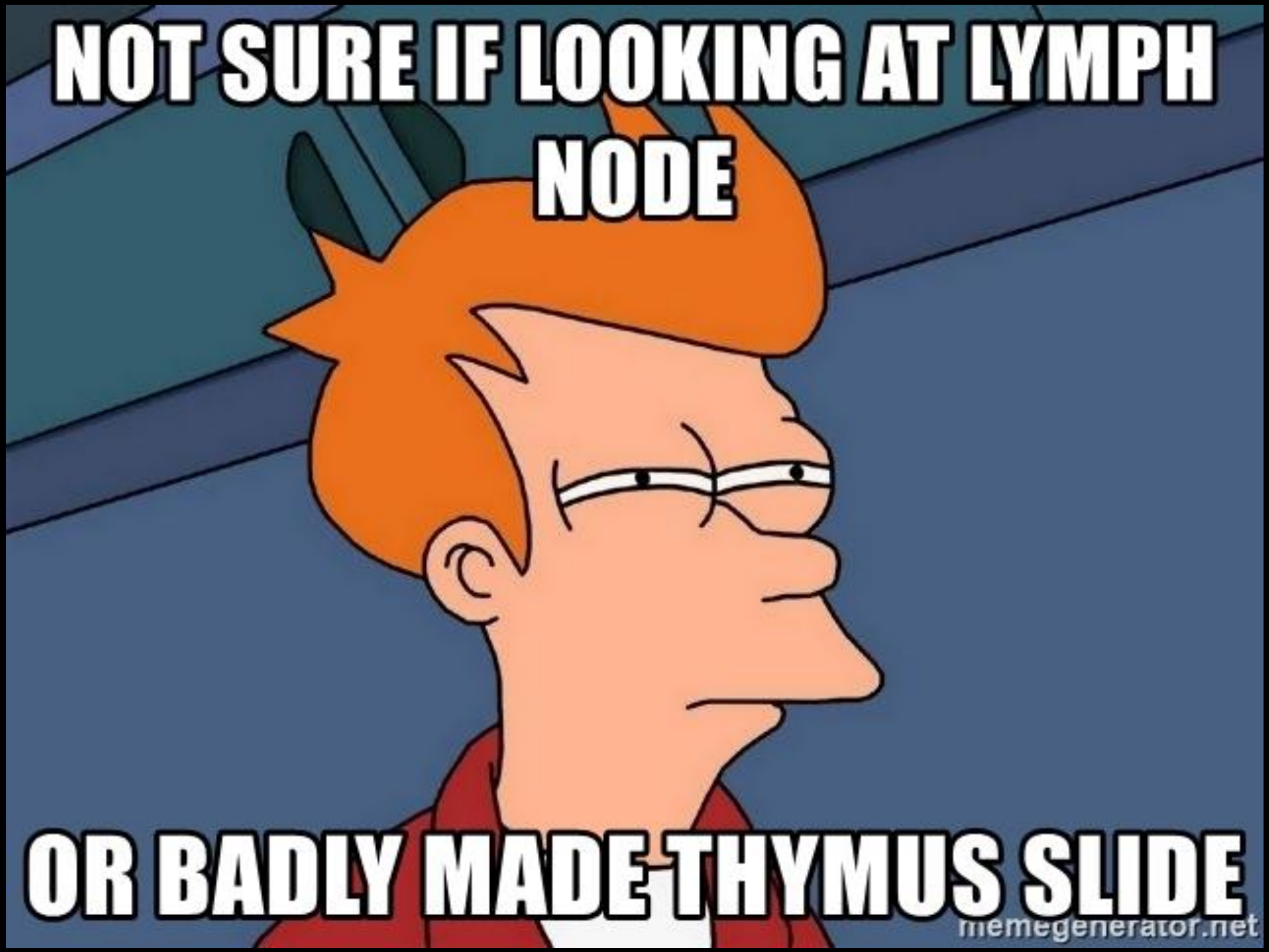
Lymphoid system



Andrea Felšöová

@pathologeek




NOT SURE IF LOOKING AT LYMPH NODE
OR BADLY MADE THYMUS SLIDE
memegenerator.net

Lymph

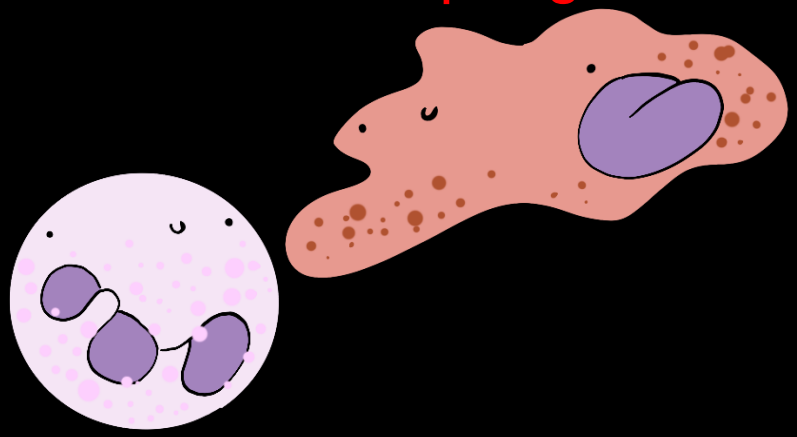
- colorless transparent fluid
- return of extravascular fluid into blood circulation
- daily production = about 60 ml/kg
- similar composition as plasma
  - fats (cholesterol, fatty acids), vitamins ADEK, steroid hormones, minerals, proteins
  - cells (lymphocytes, macrophages)
- chylus – intestinal lymph, milky fluid, chylomicrons
- filtration in lymph nodes
- dissemination of tumor cells = lymphogenic metastasis

Immunity

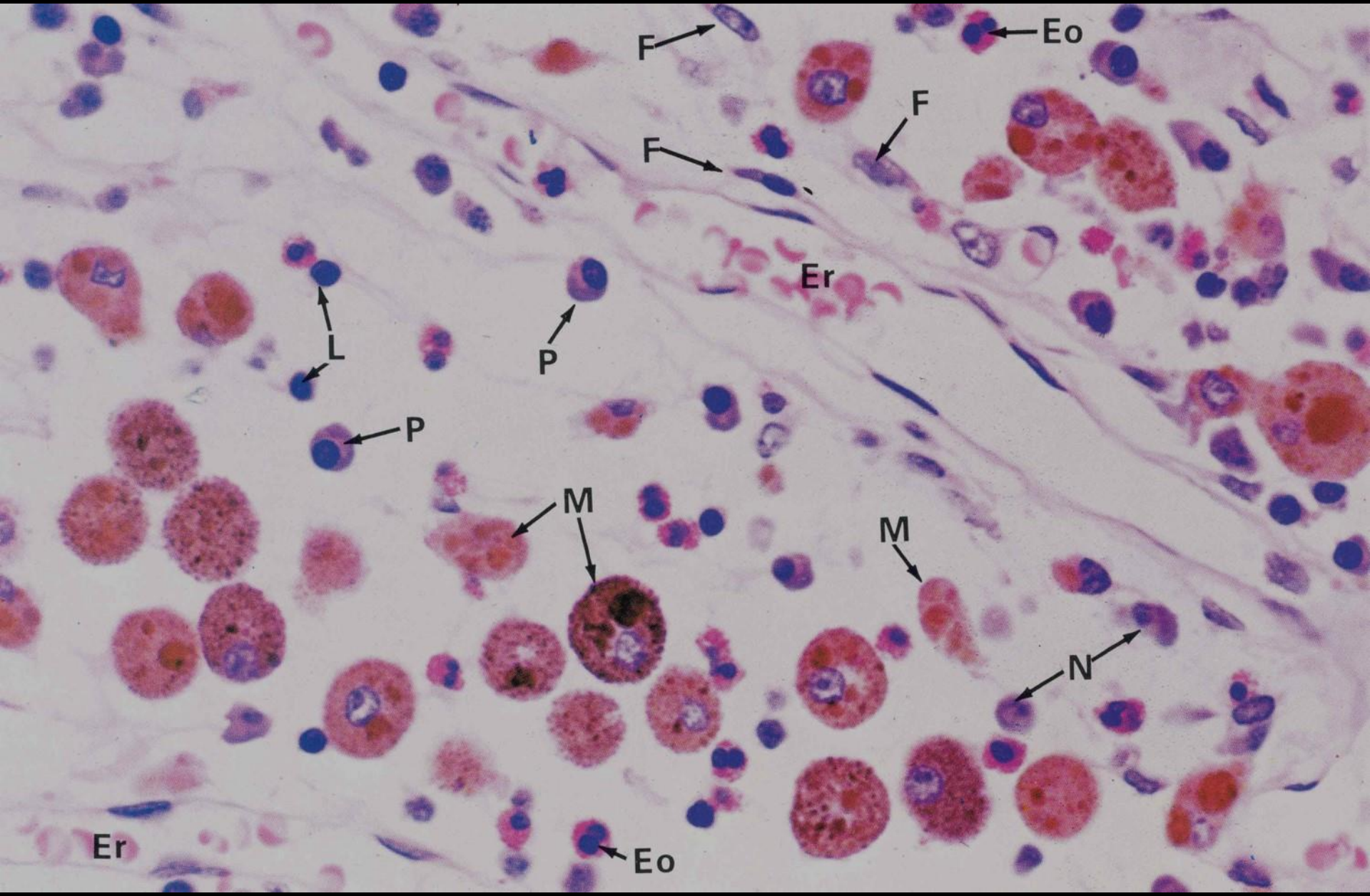
- **Antigen – any substance that can induce an immune response of an organism**
  - **foreign molecule, foreign cell, pathogenic organism – bacterion, virus, parasite, but also intrinsic cell damaged by tumor or intracellular infection**
- **The immune response is targeted to recognize the antigen and to react in 2 basic steps:**
  - **non-specific (innate) immunity**
    - **fast**
    - **neutrophilic granulocytes, monocytes/macrophages, NK cells, complement**
  - **specific (adaptive) immunity**
    - **4 to 7 days later**
    - **B and T lymphocytes, antigen presenting cells, antibodies**

Non-specific (innate) immune response

- **Monocytes**
  - in blood 68 – 72 hours
  - diapedesis into the connective tissue → macrophages (histiocytes), about 100 days
  - liver – Kupfer cells
  - lungs – coniophages (dust cells)
  - placenta – Hofbauer cells

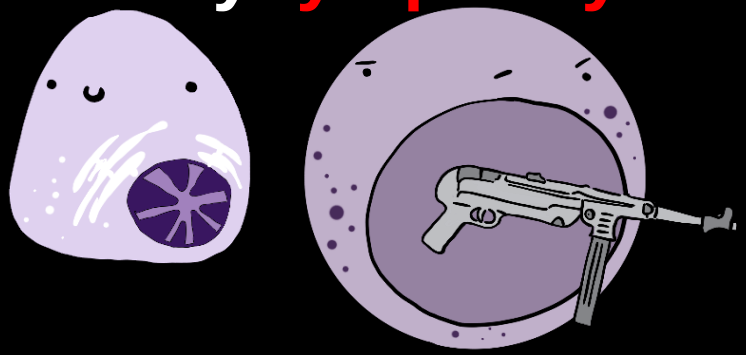


- **Neutrophilic granulocytes**
  - in blood 6 – 12 hours
  - diapedesis into the connective tissue → microphages, up to 4 days
- Both cells are the „**first army**“ in **phagocytosis** of the antigen
- Cells migrate actively to the place of the infection (chemotaxis)


F
Eo
F
F
Er
L
P
P
M
M
N
Er
Eo

Specific (adaptive) immune response

- **Phagocytic cells with the exposed fragments of the antigens now represent a new type of cells – antigen presenting cells (APC)**
  - **MHC (major histocompatibility complex) – integral membrane** glycoproteins binding the antigen fragments
    - MHC I – on all cells
    - MHC II – only on APC
- **Free antigens or complexes of antigens and MHC are recognized by lymphocytes**

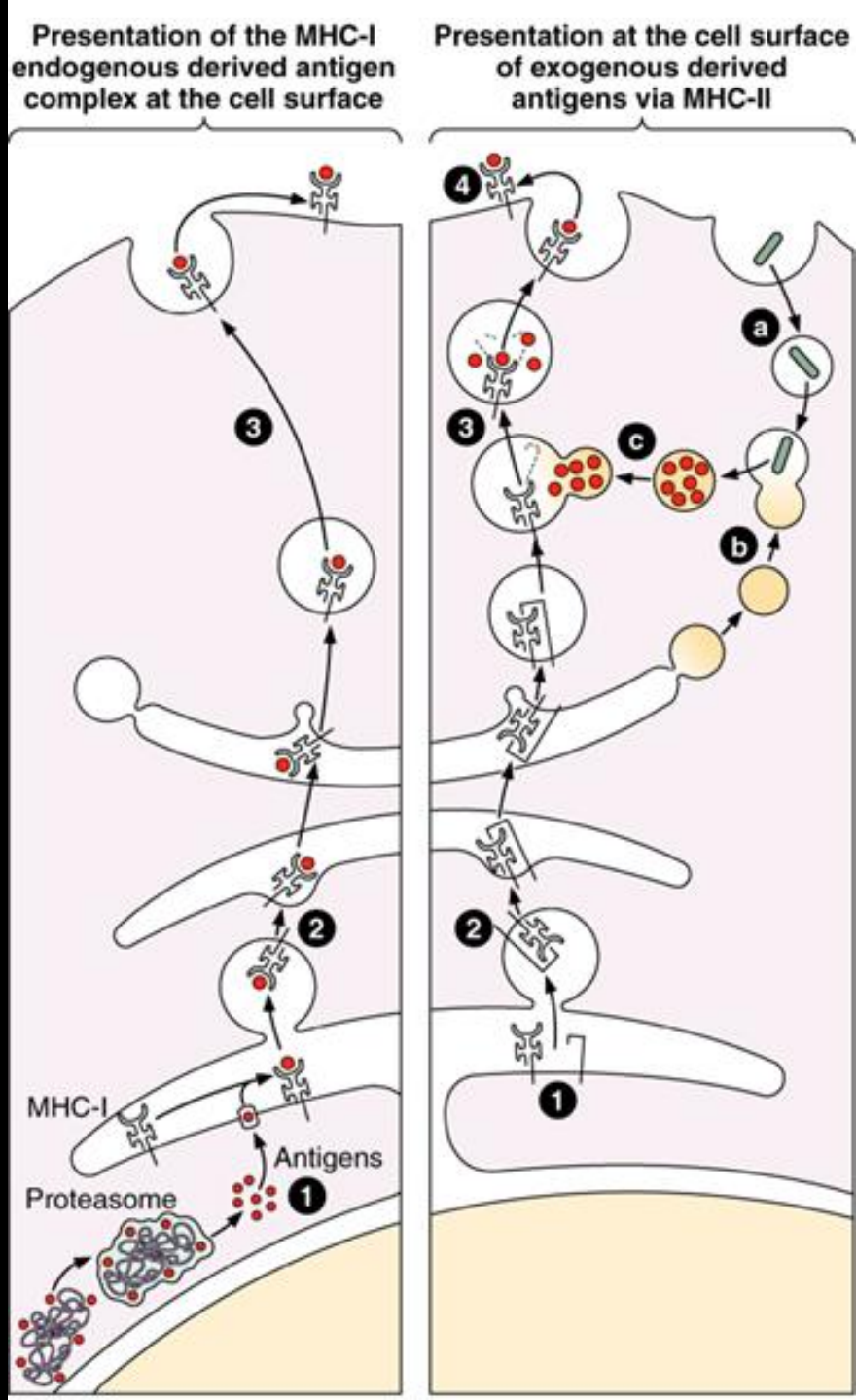


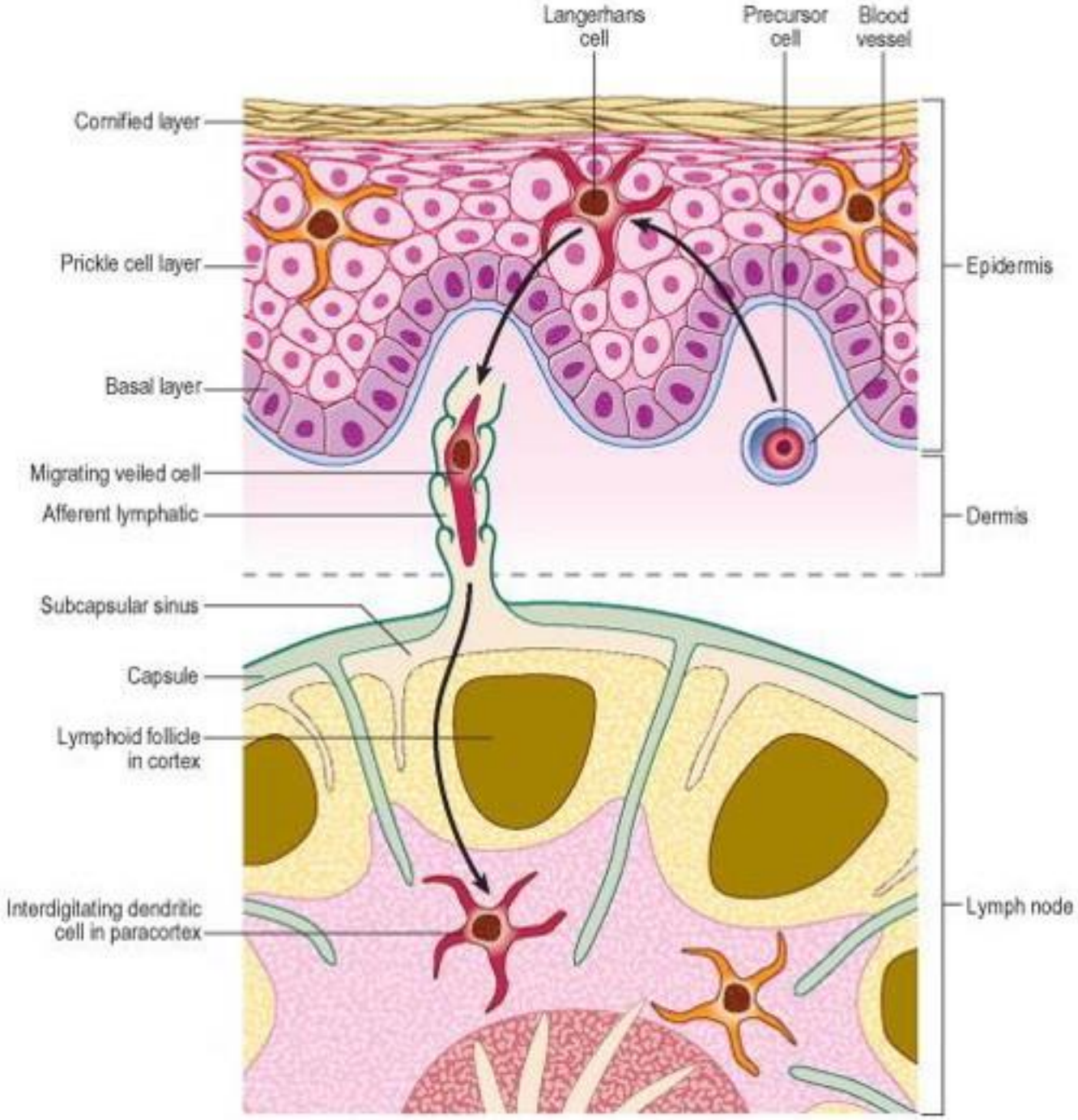
Antigen-presenting cells (APC)

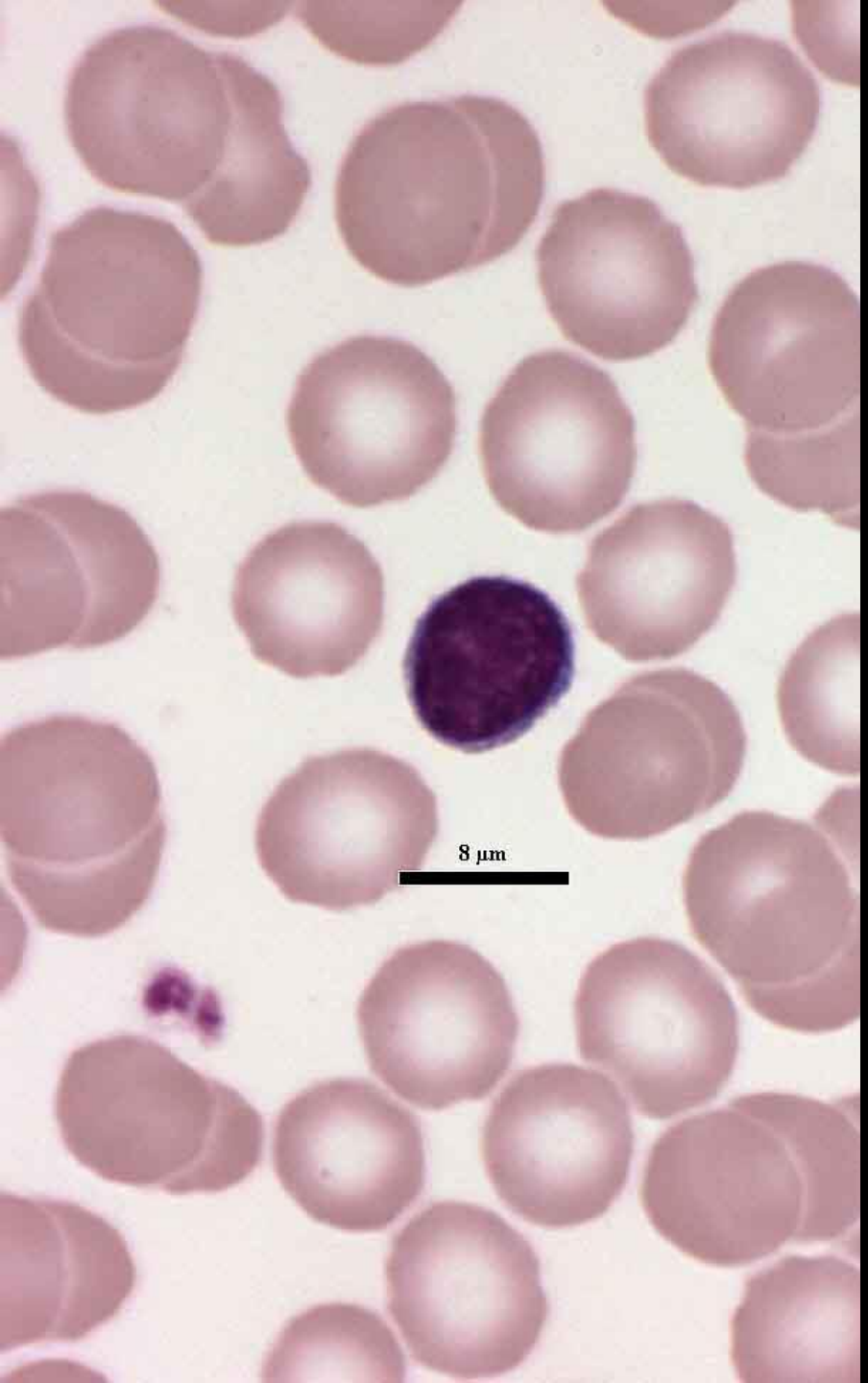
dendritic cells
Langerhans cells
follicular dendritic cells
M-cells
macrophages
some clones of B-lymphocytes

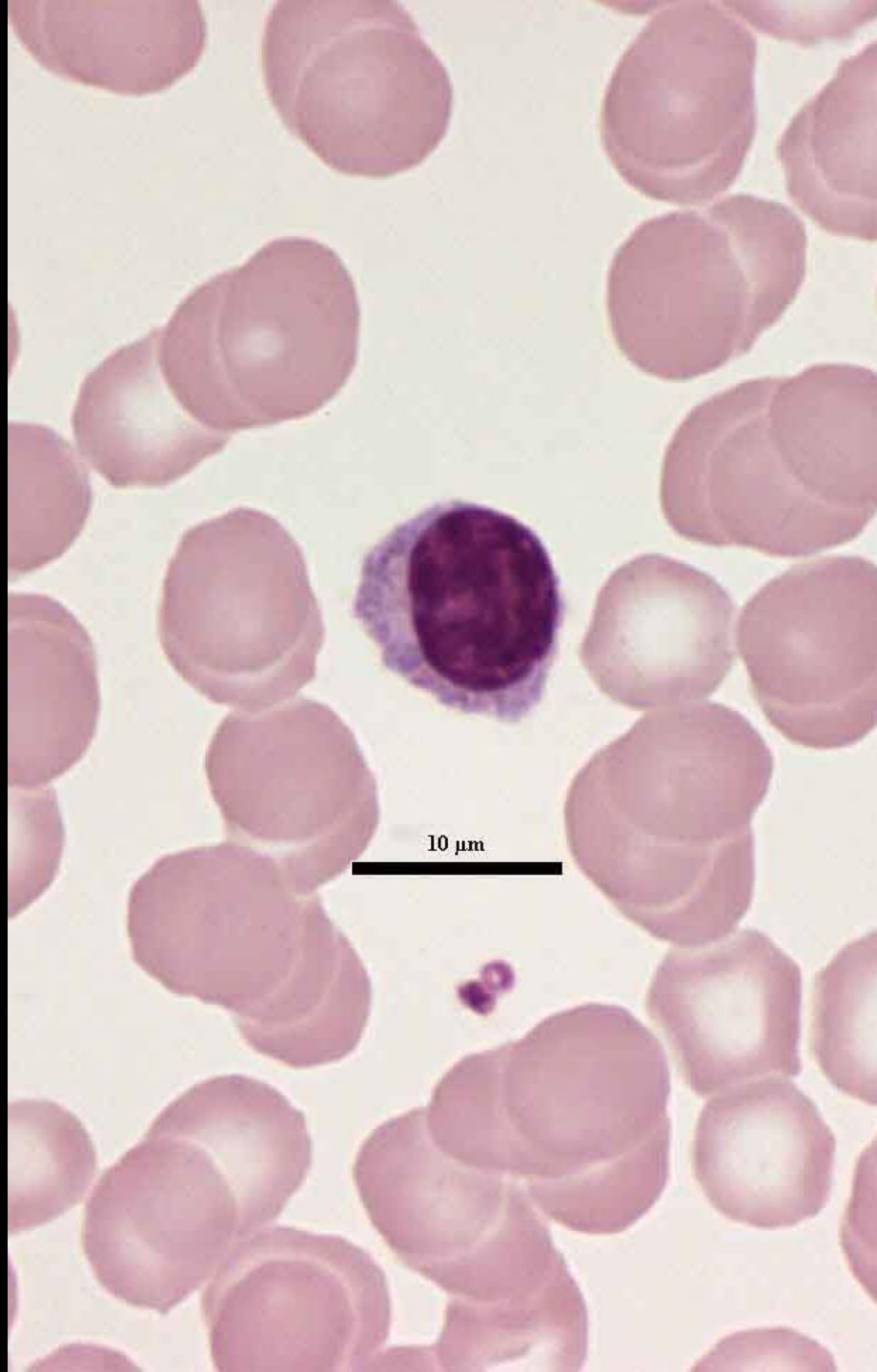
carry both MHC I and II

present antigen-MHC complexes to T lymphocytes (both T_cL and T_hL)




Langerhans cell
Precursor cell
Blood vessel
Cornified layer
Prickle cell layer
Basal layer
Migrating veiled cell
Afferent lymphatic
Epidermis
Dermis
Subcapsular sinus
Capsule
Lymphoid follicle in cortex
Interdigitating dendritic cell in paracortex
Lymph node

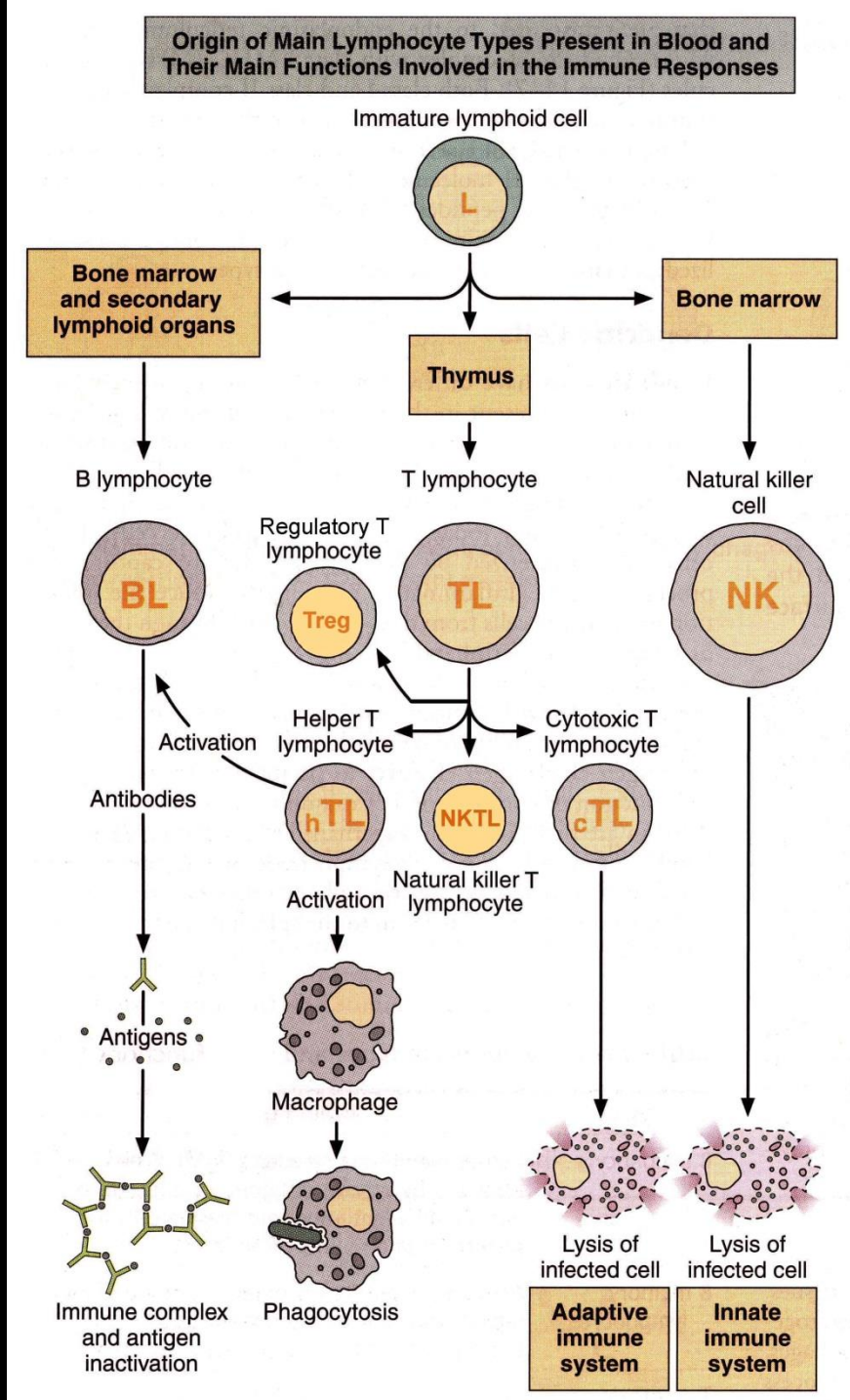

8 µm


10 µm

Lymphocytes

Places of maturation (immunocompetency acquirement)

Types of lymphocytes



SURFACE ANTIGENS

all T-lymphocytes
CD3 TCR

T_hL CD4
subpopulations
T_h1 T_h2 T_h17 T_hf

T_cL CD8

$T_{reg}L$ CD4 or CD8
CD25 and FOXP3

NKTL and other unconventional TL
CD1d CD16

---

all B- lymphocytes
CD19 (20,23) BCR
$B_{reg}L$

NK-cells
CD16 CD56

B lymphocytes

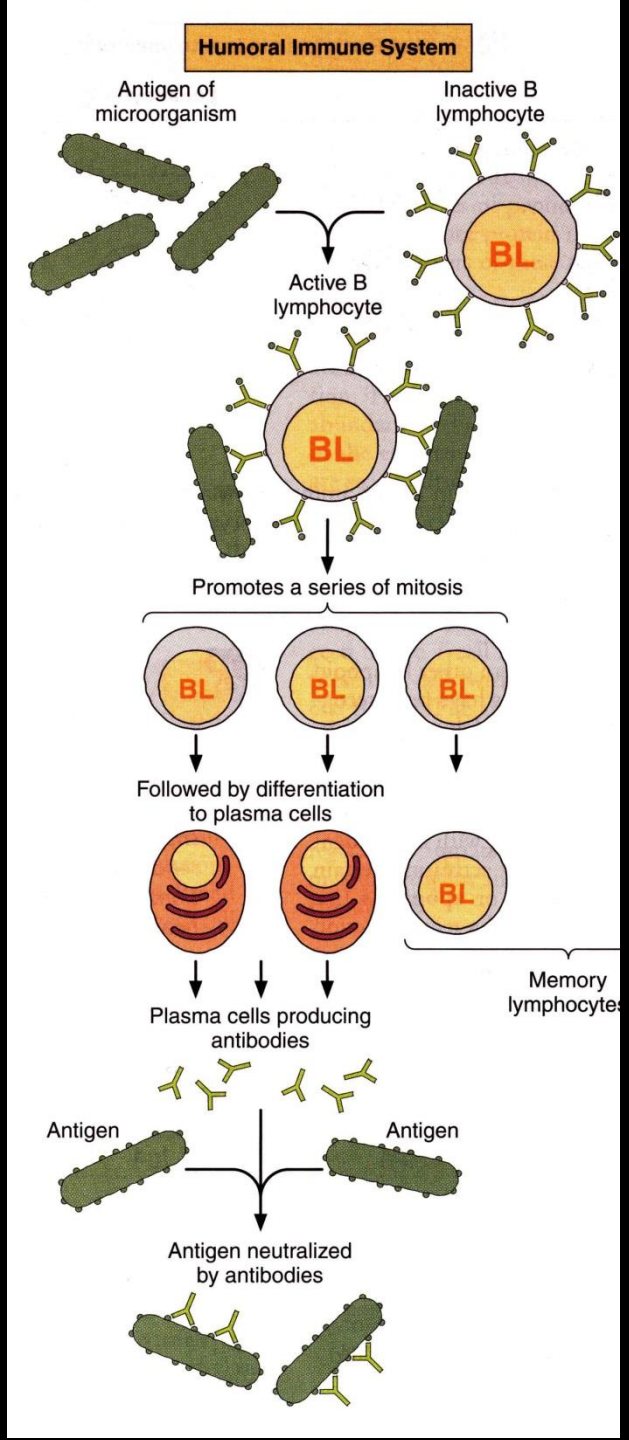
free antigens

BCR

somatic hypermutations

effector cells (plasma cells)

free antibodies (immunoglobulins) IgM, IgG, IgA, IgD, IgE



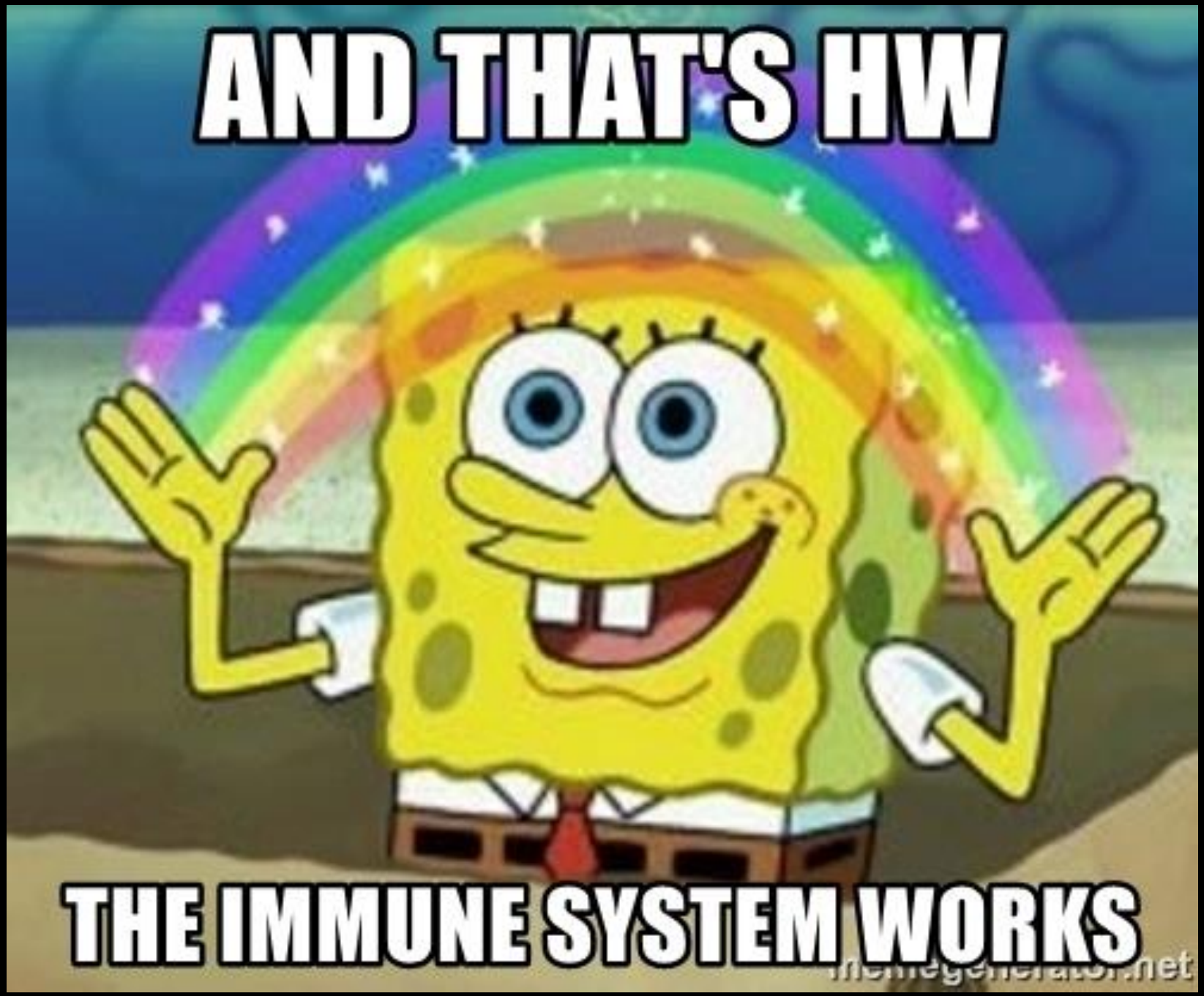
Humoral adaptive immunity

immunocompetent naive B lymphocyte

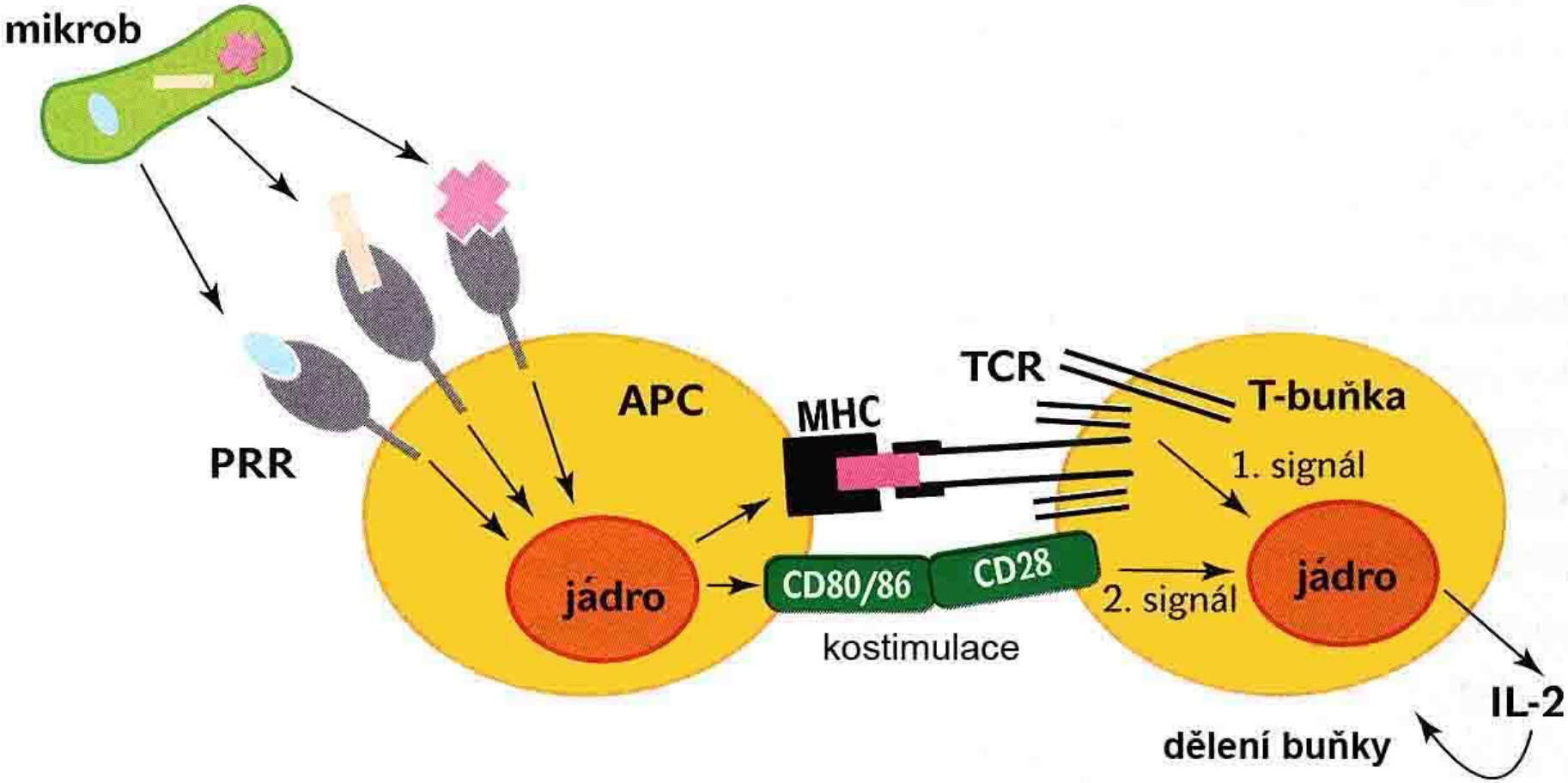
affinite maturation

clonal expansion

memory cell


AND THAT'S HW
THE IMMUNE SYSTEM WORKS


Fin



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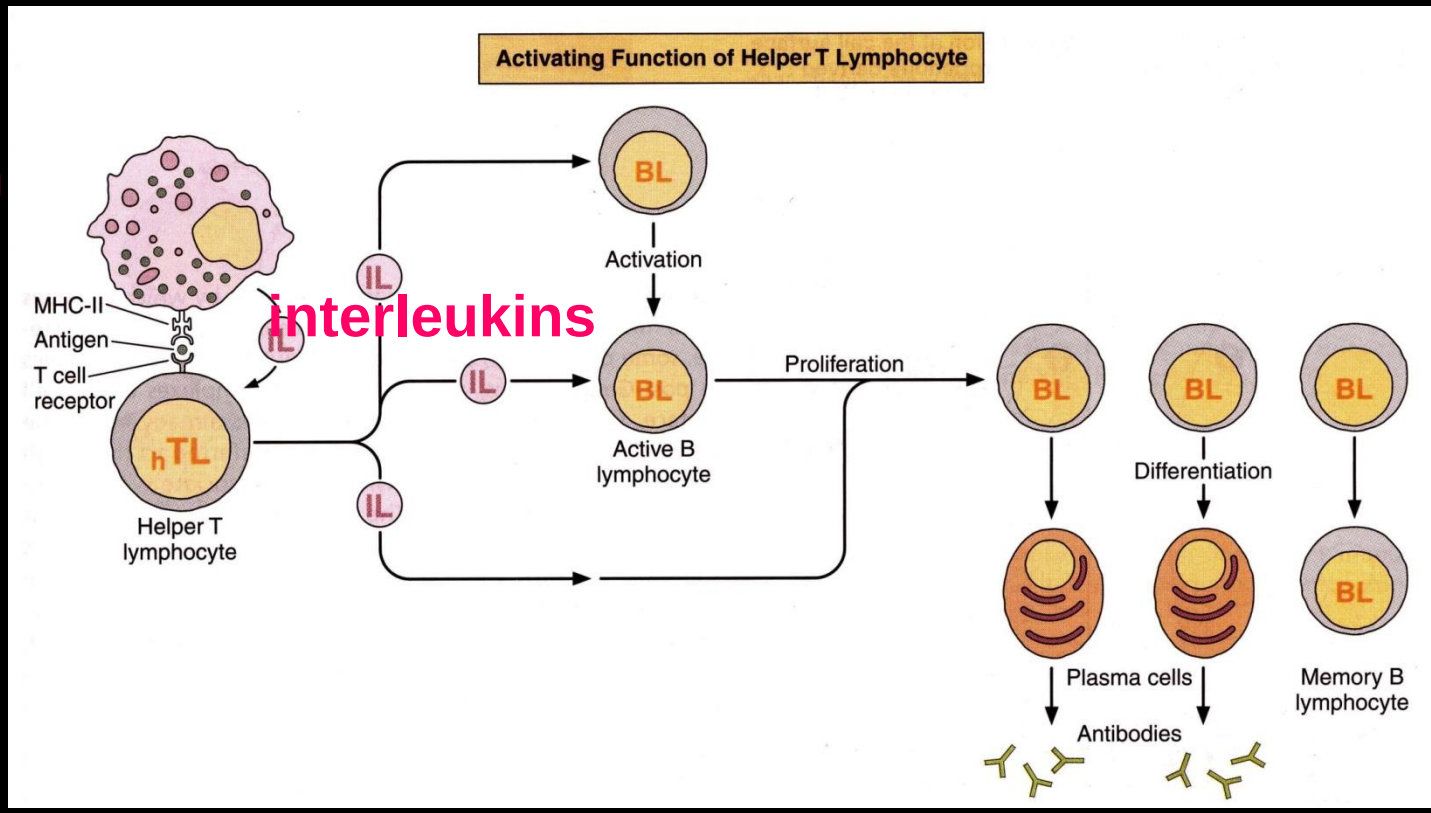
Th lymphocytes

MHC II - antigen complexes

ThL



T_h1 activate macrophages with interferon-γ → phagocytosis (intracellular parasites)

T_h2 activate eosinophilic and basophilic granulocytes and mast cells with IL-4 and IL-13 → extracellular parasites

T_h17 activate neutrophilic granulocytes with IL-17

T_hf co-activate BL with IL-21 and IL-4 → proliferation and differentiation into plasma cells; decision of the isotype

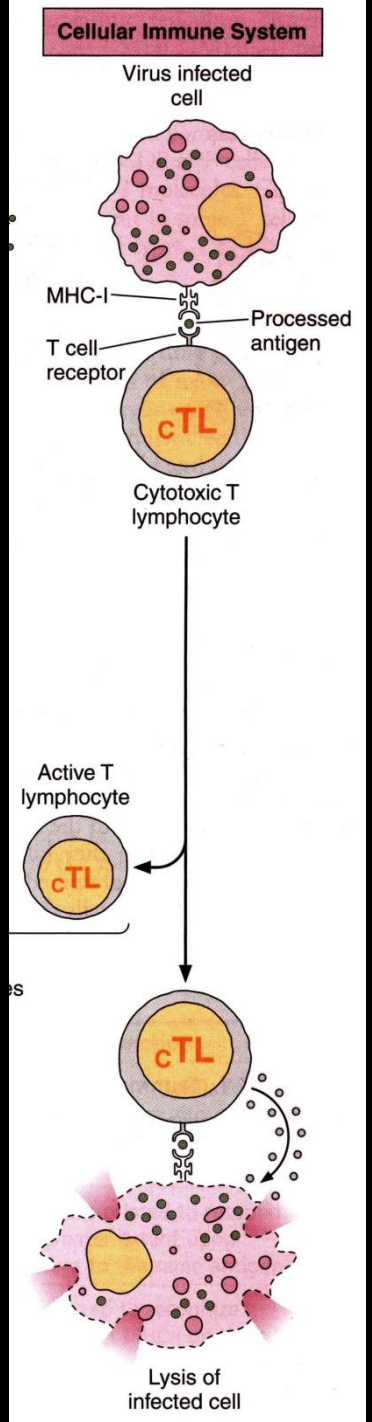
Tc lymphocytes

MHC I - antigen complexes

naive TcL

memory cell

effector cell



Cellular adaptive immunity

T_cL – recognize and bind cells with complexes MHC I and antigen

antigen is processed by proteasome digestion

immunological synapse

perforin
granzymes

General structure of lymphoid organs

Supporting tissue (stroma)

reticular epithelium

or

reticular connective tissue

Free cells

lymphocytes, their precursors and stimulated forms

macrophages

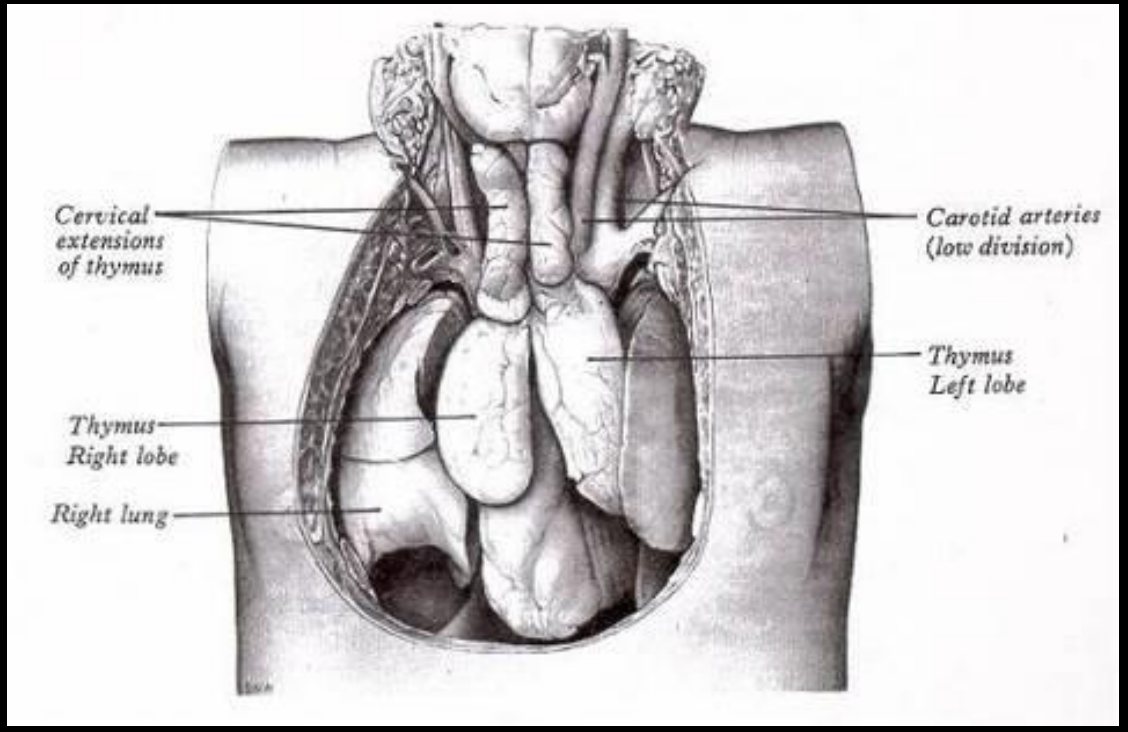
antigen presenting cells (APC)

(other blood elements)

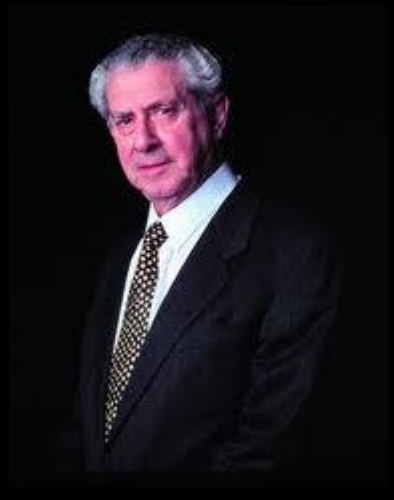
Lymphoid organs - classification

- central (primary)
  thymus, bone marrow, GALT, Fabricius bursa (in birds)
- peripheral (secondary)
  a) encapsulated
  lymph nodes, spleen
  b) incompletely encapsulated
  tonsils
  c) unencapsulated
  free lymphoid follicles and their aggregates

Thymus

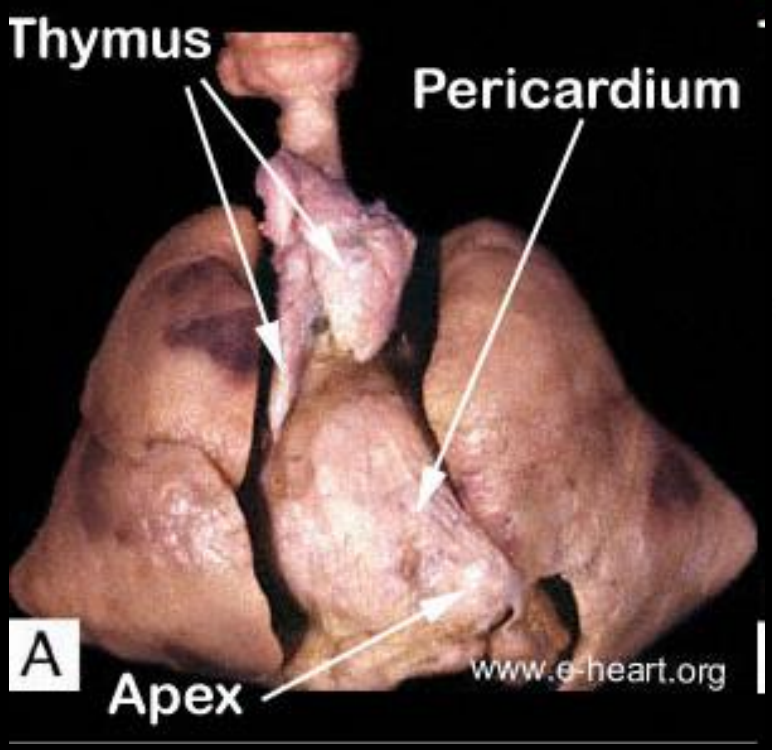


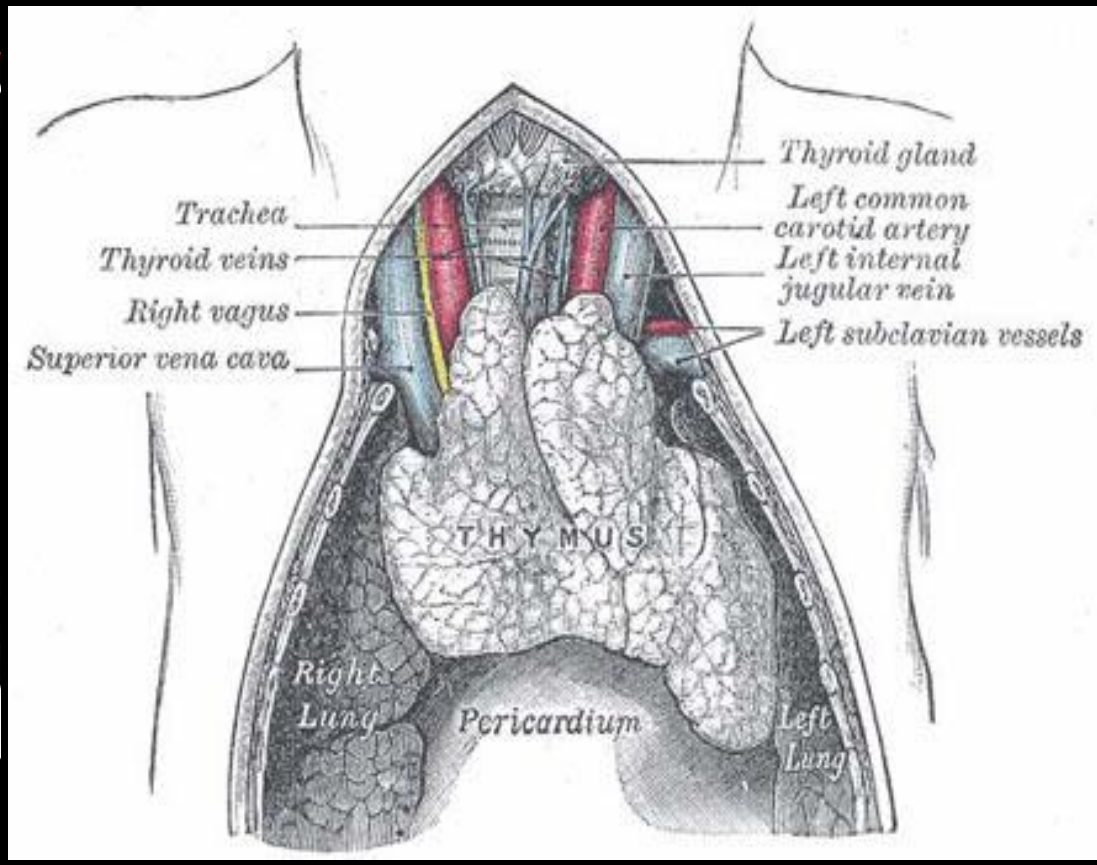
- lymphoepithelial organ
- primary lymphoid organ
- lobus dx. et sin.
- 2nd cent. – Galen: „organ of mystery“
- 1961 – discovery of the function by Jacques Miller

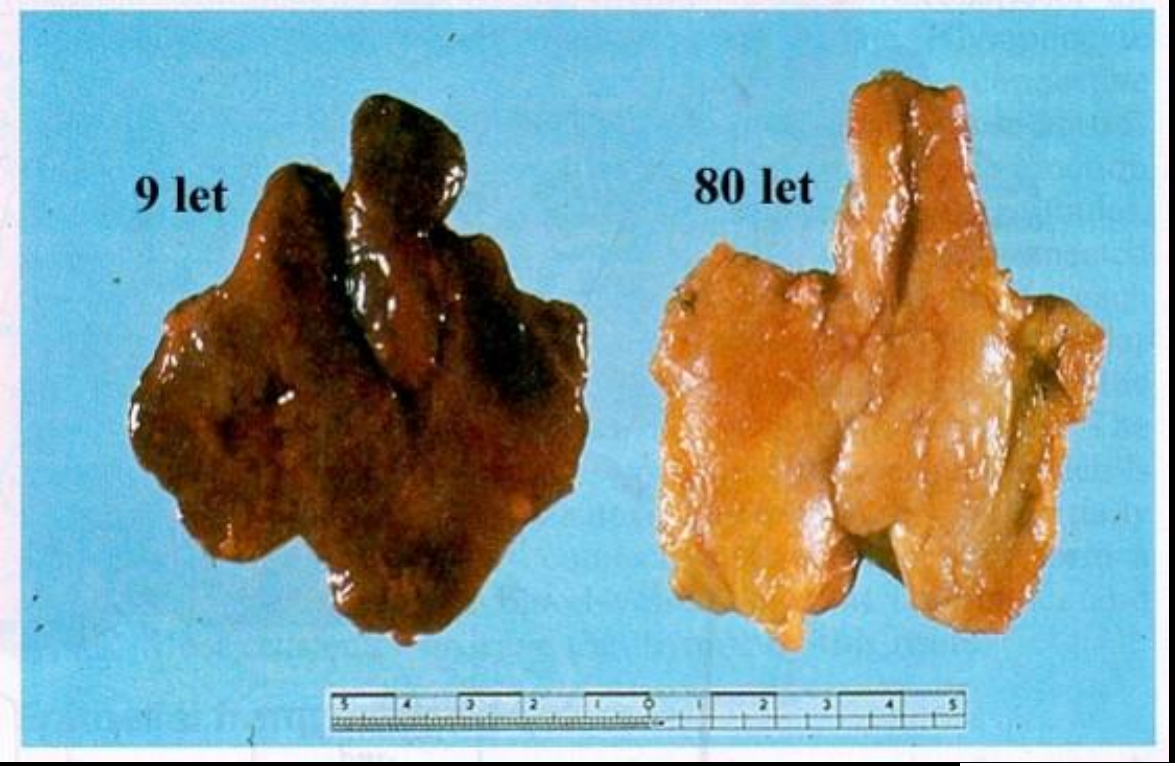


Thymus - location

- mediastinum superius (1st layer) behind sternum
- covered with mediastinal connective tissue



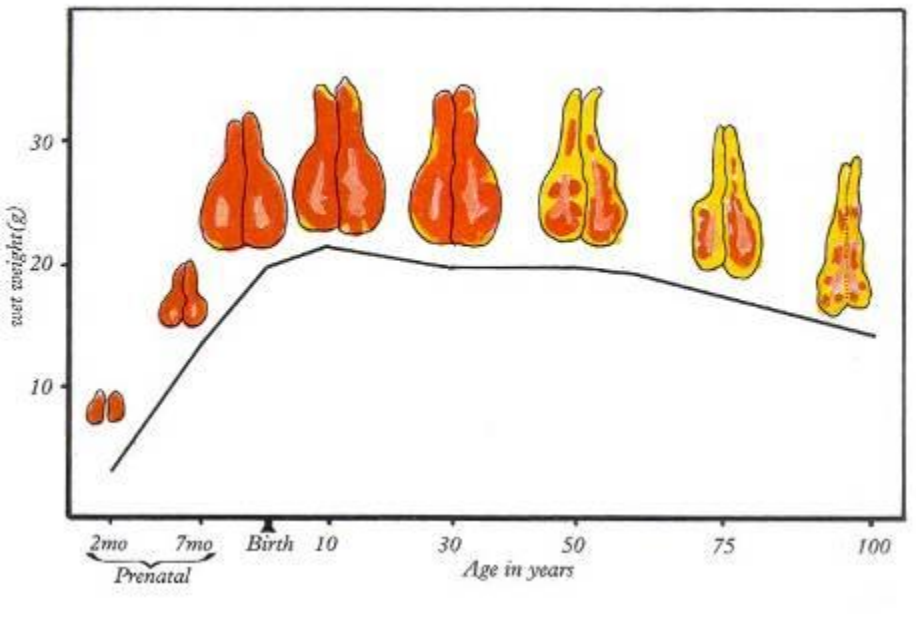




adult 20-50 g

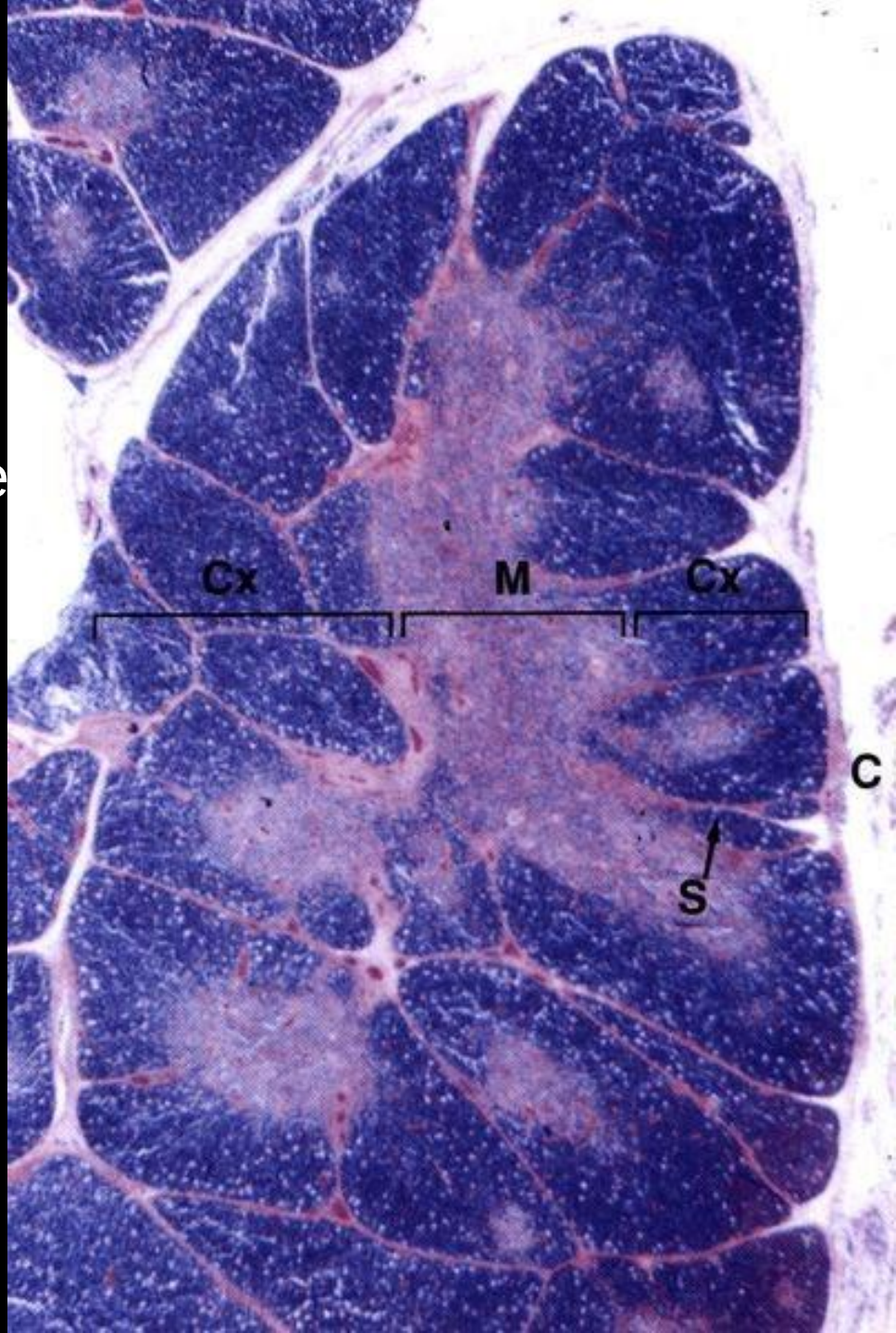
newborn 16 g (10-35 g) from below thyroid gland down to pericardium

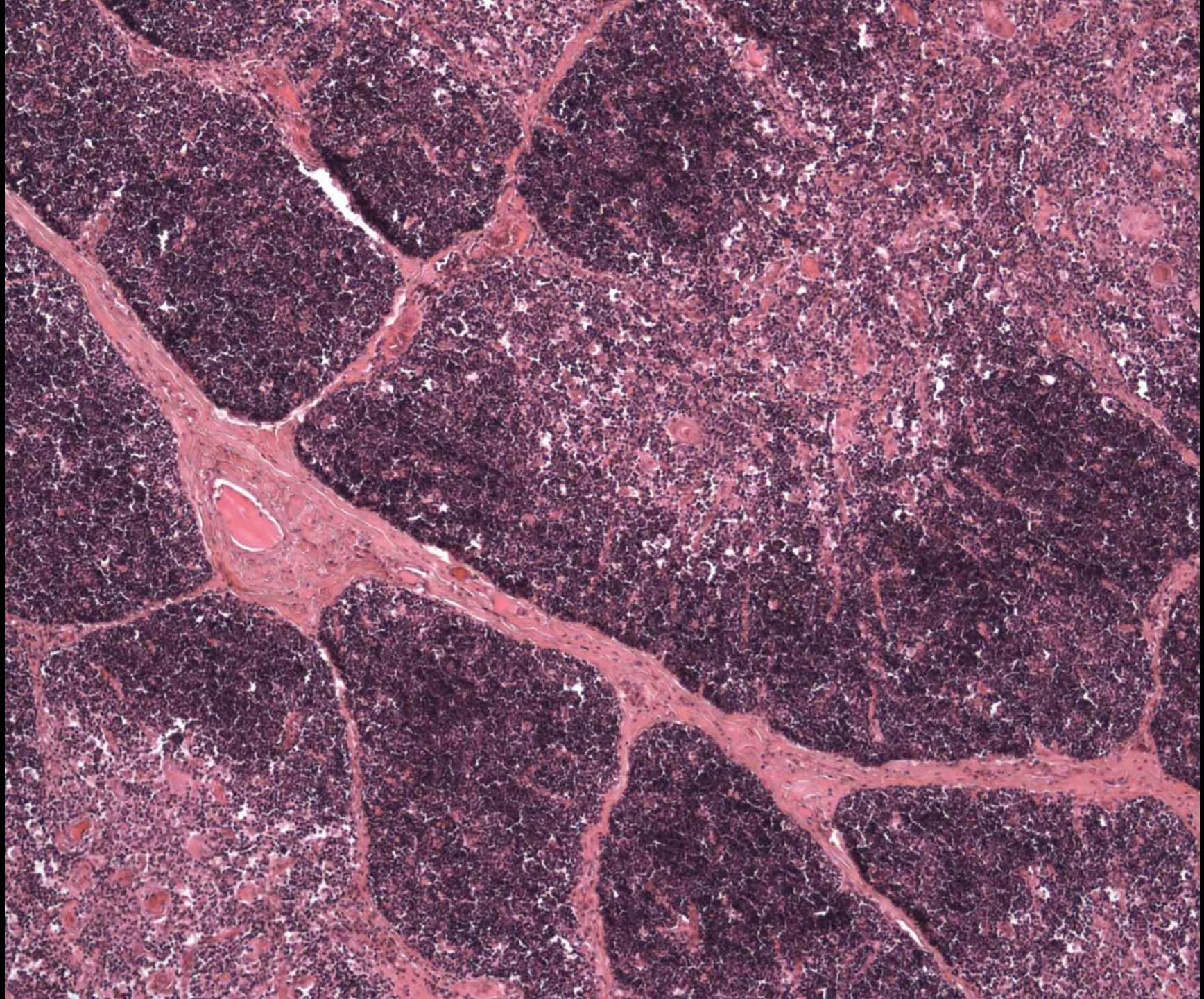
- successive atrophy from puberty
- replaced with adipose tissue after 50th year of age (5-15 g)



Thymus – structure

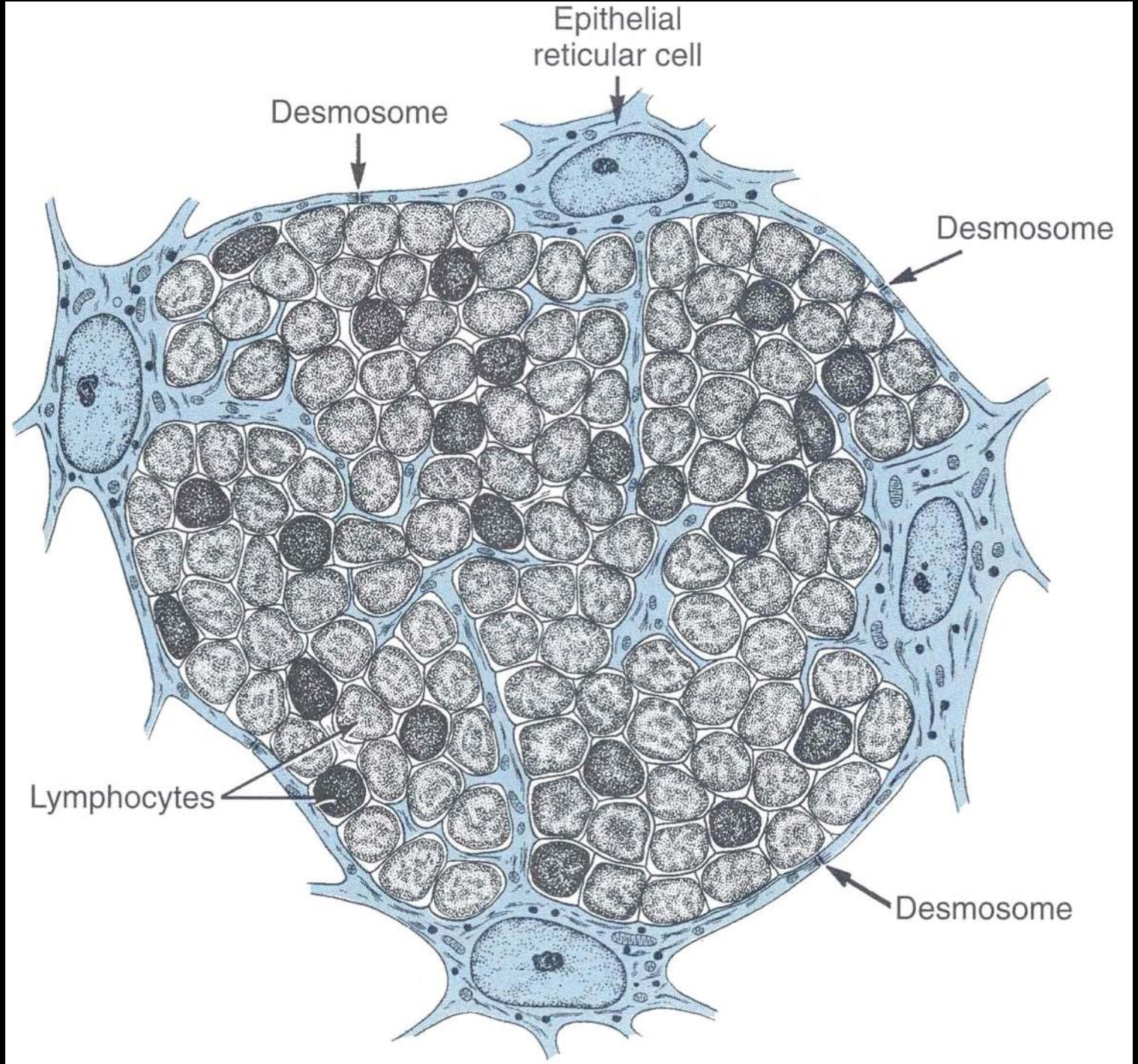
- covered with CT capsule
  - contains vessels
  - forms septa → false lobule (pseudolobules)
- *Cortex thymi*
  - darker appearance
- *medulla thymi*
  - lighter appearance

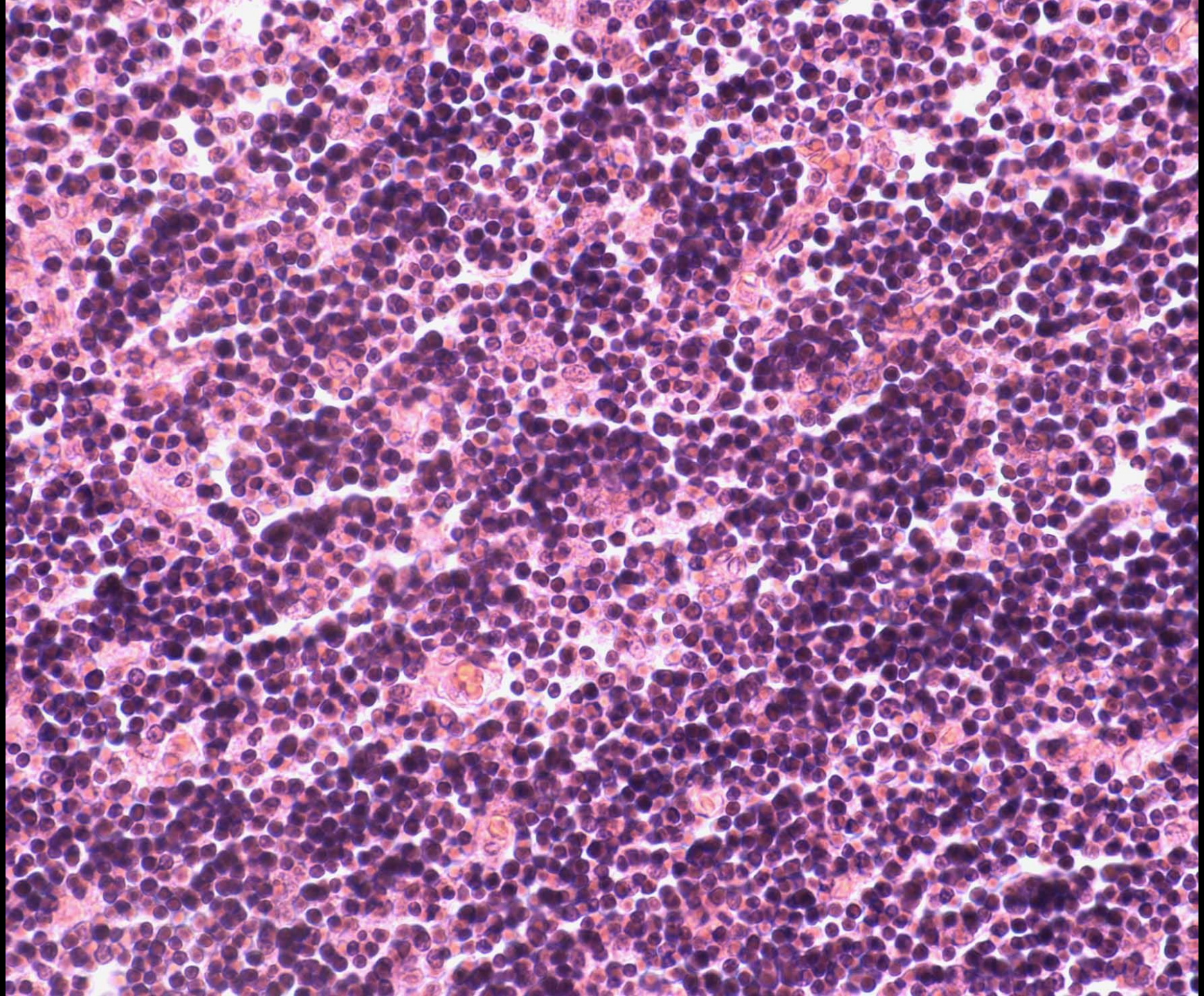


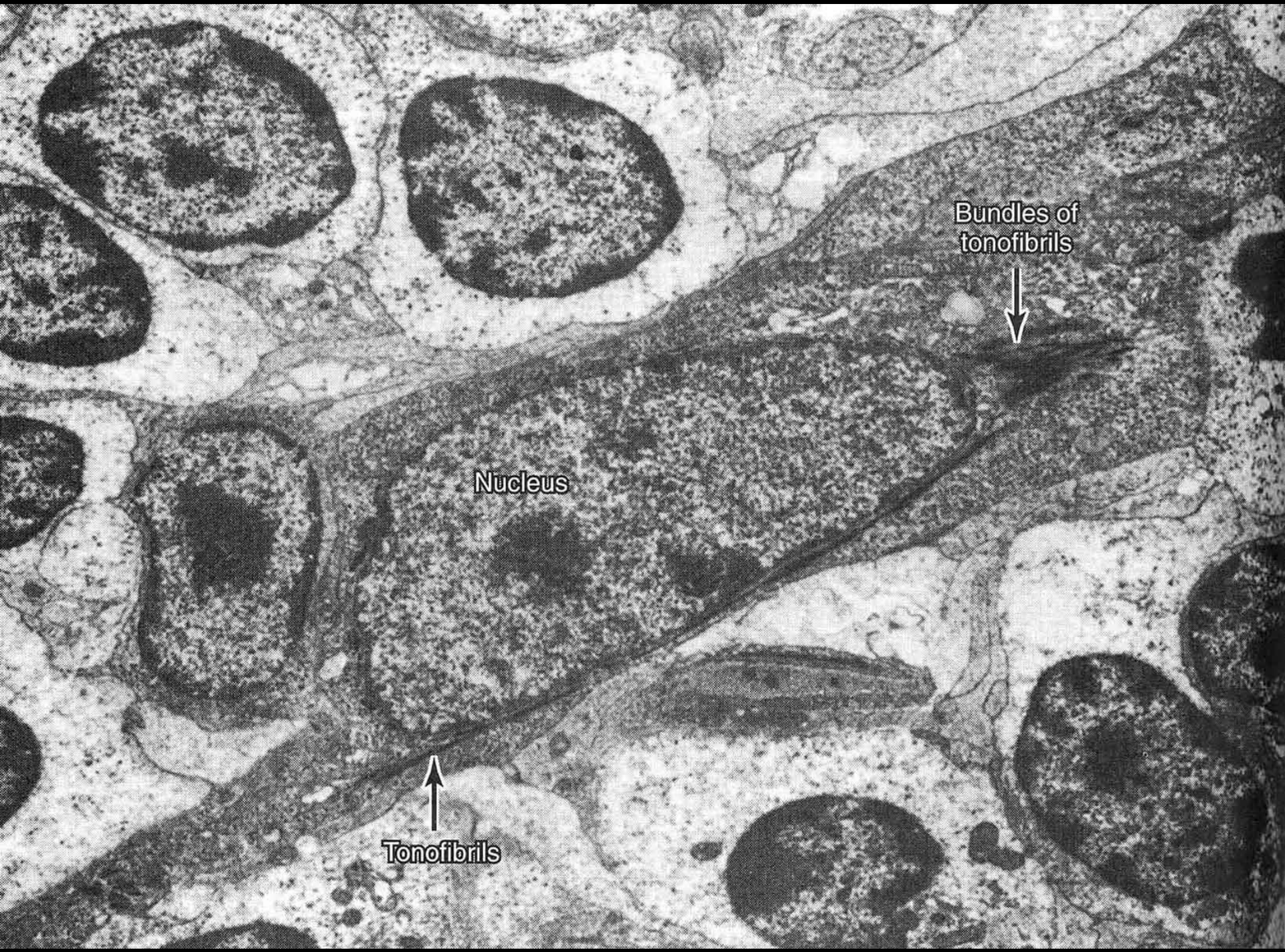


Thymus – cortex

- **Stroma - reticular epithelium**
  - stellate cells connected with desmosomes
    - types I-III (cTEC)
    - form a spatial network
    - present MHC I and II
- **Free cells**
  - mainly **T**-lymphocytes (thymocytes)
    - rapidly multiply during development
    - their TCR bind empty MHC
    - if not → apoptosis (99%) = positive selection
  - macrophages

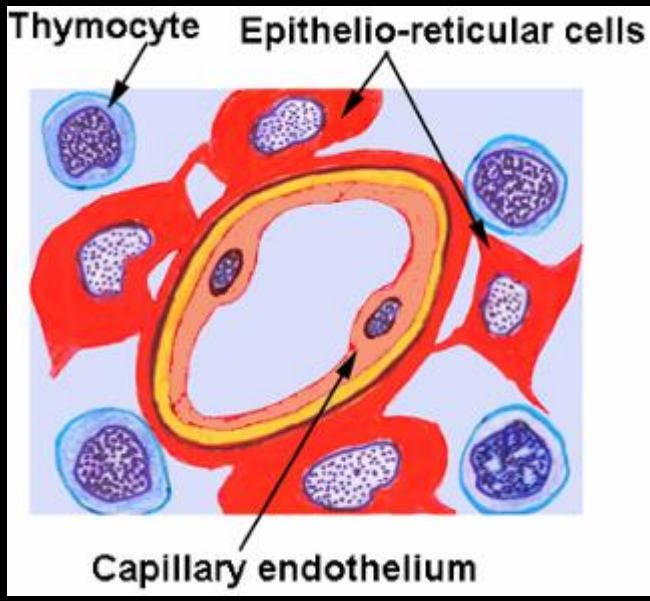

Epithelial
reticular cell
Desmosome
Desmosome
Lymphocytes
Desmosome

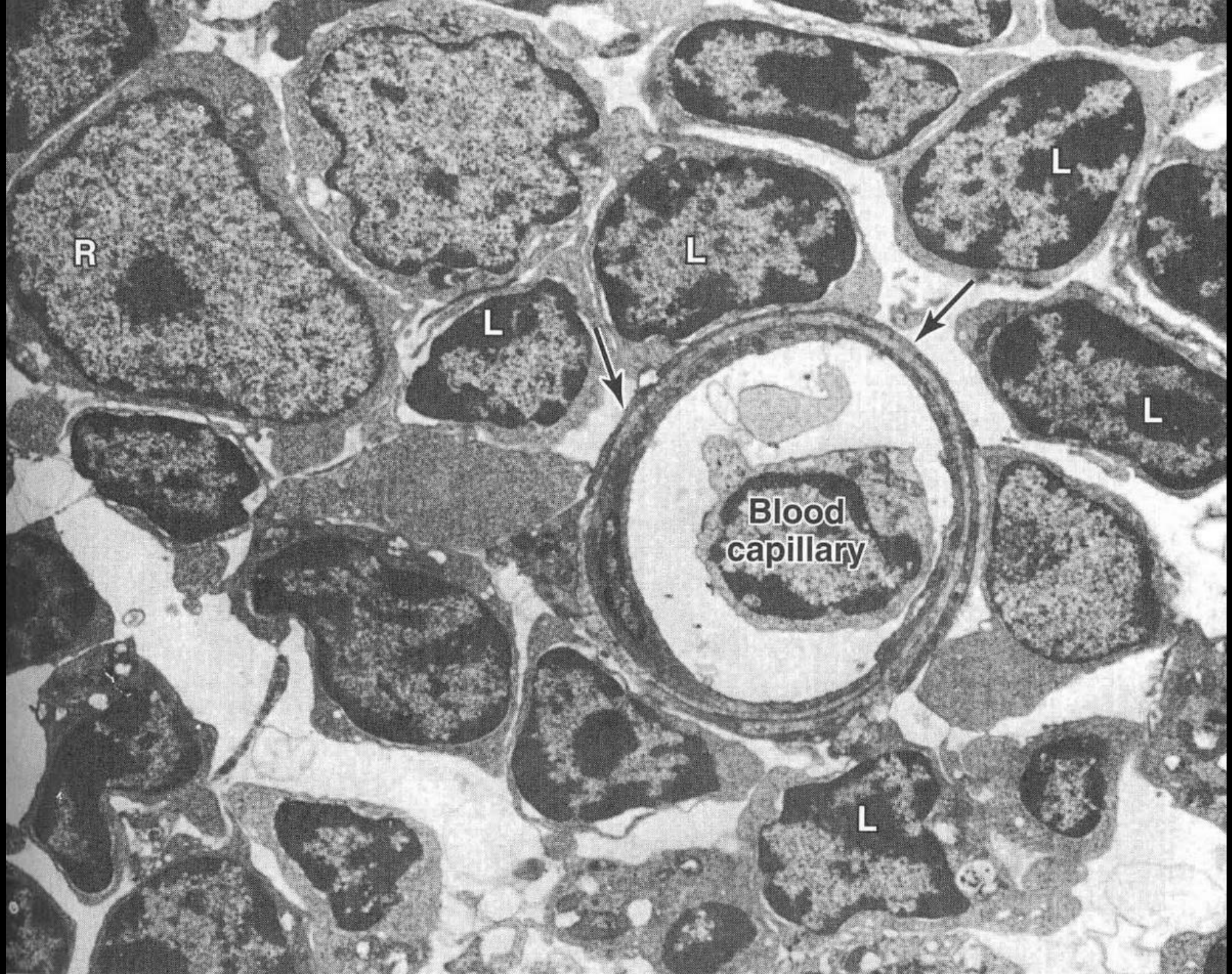



Bundles of
tonofibrils
Nucleus
Tonofibrils

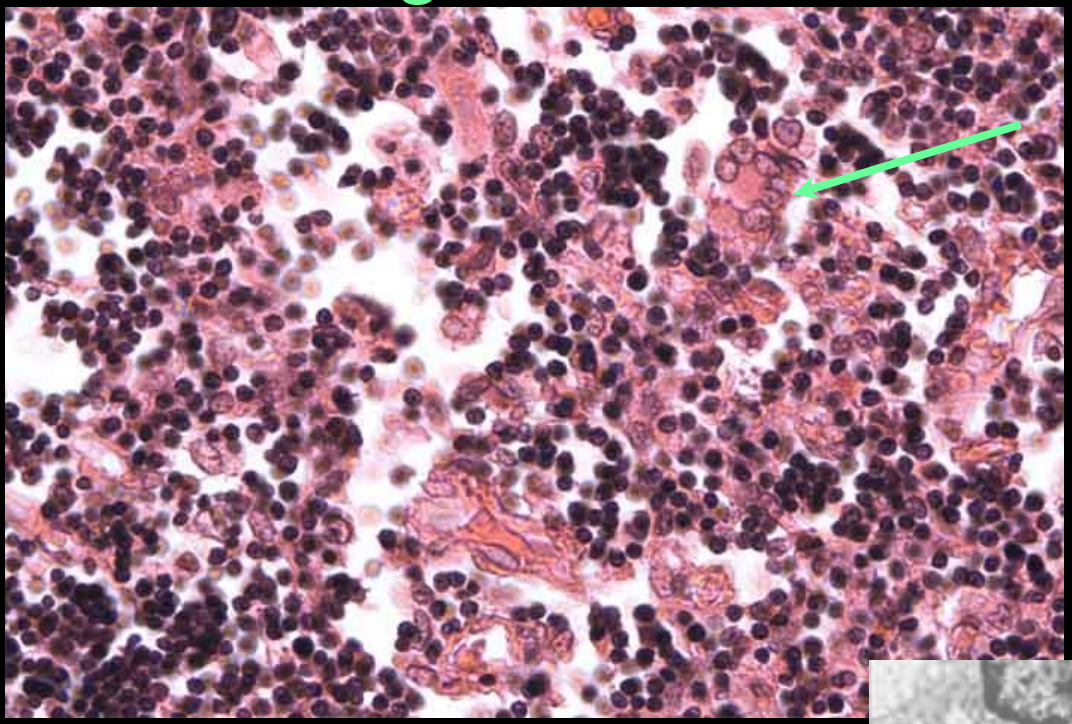
Thymus – blood vessels

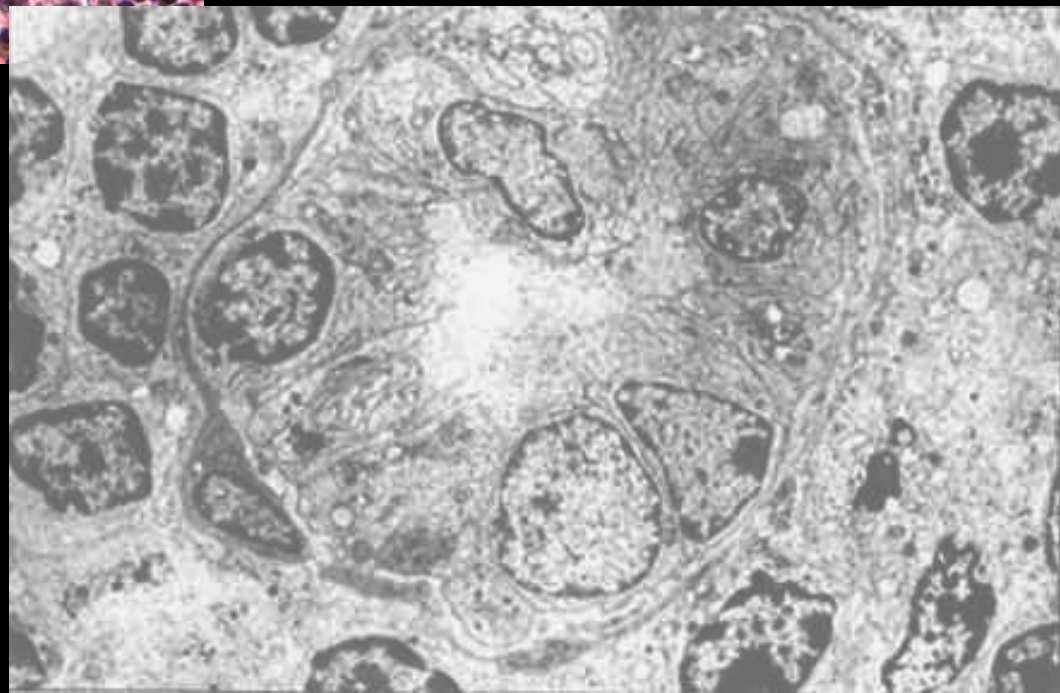
- branches from:
  - a. thyroidea inf.
  - thoracica int. (a. pericardiacophrenica)
  - arcus aortae
- non-fenestrated capillaries
- haemato-thymic barrier
  - **cortex**
  - endothelium of capillaries
  - basal lamina of capillaries (+ pericytes, resp.)
  - connective tissue layer (+ macrophages)
  - basal lamina of epithelial reticular cells
  - epithelial reticular cells
- high-endothelium venules – cortico-medullary junction




R
L
L
L
L
L
Blood
capillary

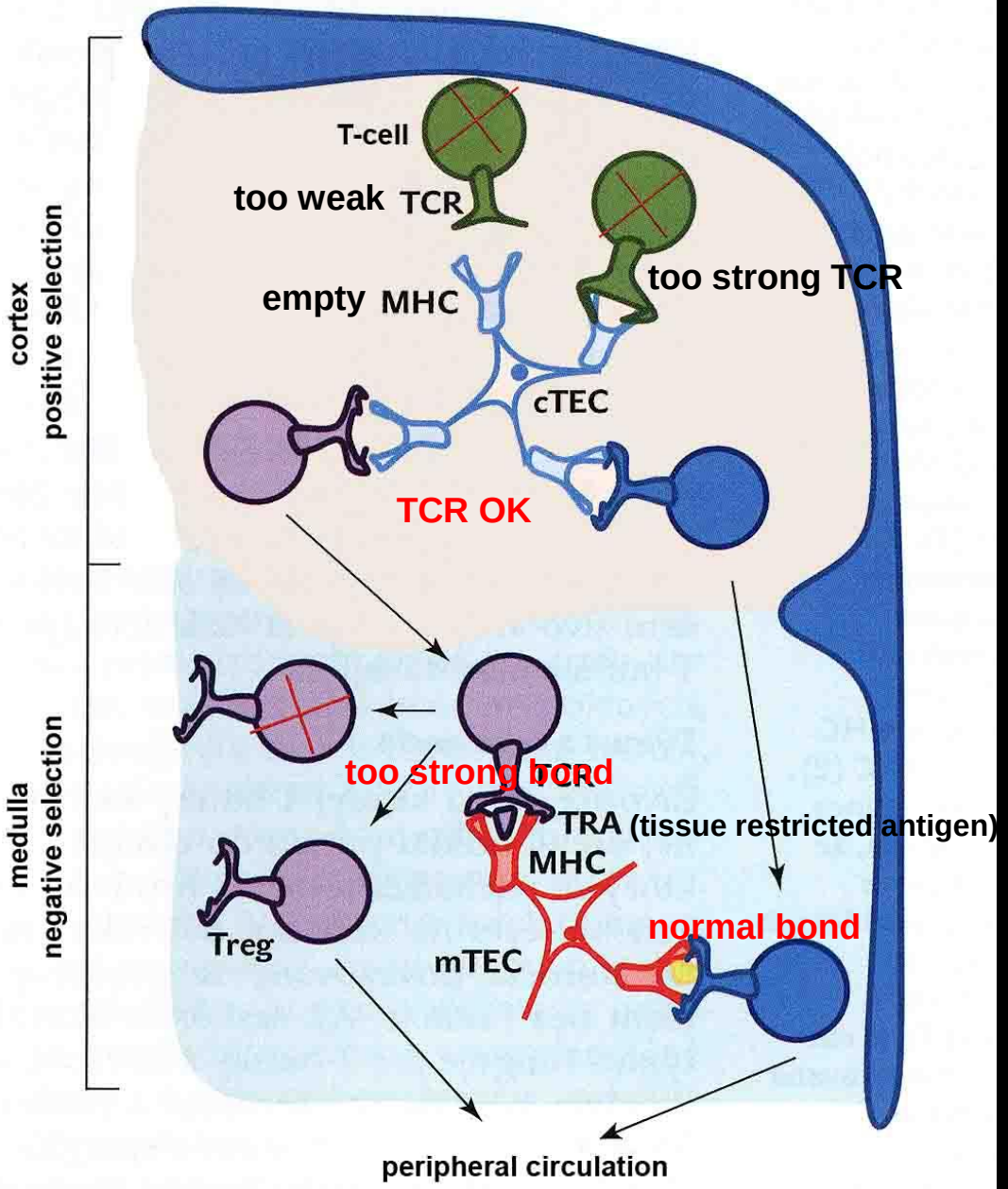
high-endothelium venule (HEV)





Thymus – medulla

- **Stroma - reticular epithelium**
  - stellate cells connected with desmosomes
    - types IV-VI (mTEC)
    - present complexes of MHC and TRA (tissue restricted antigens) – their production directed by AIRE genes
    - form Hassall's bodies
- Free cells
  - T lymphocytes (thymocytes)
    - not so densely
    - their TCR bind complexes of MHC and TRA
    - if yes → apoptosis = negative selection
    - exception – TregL bind the complexes, but preserved
  - macrophages



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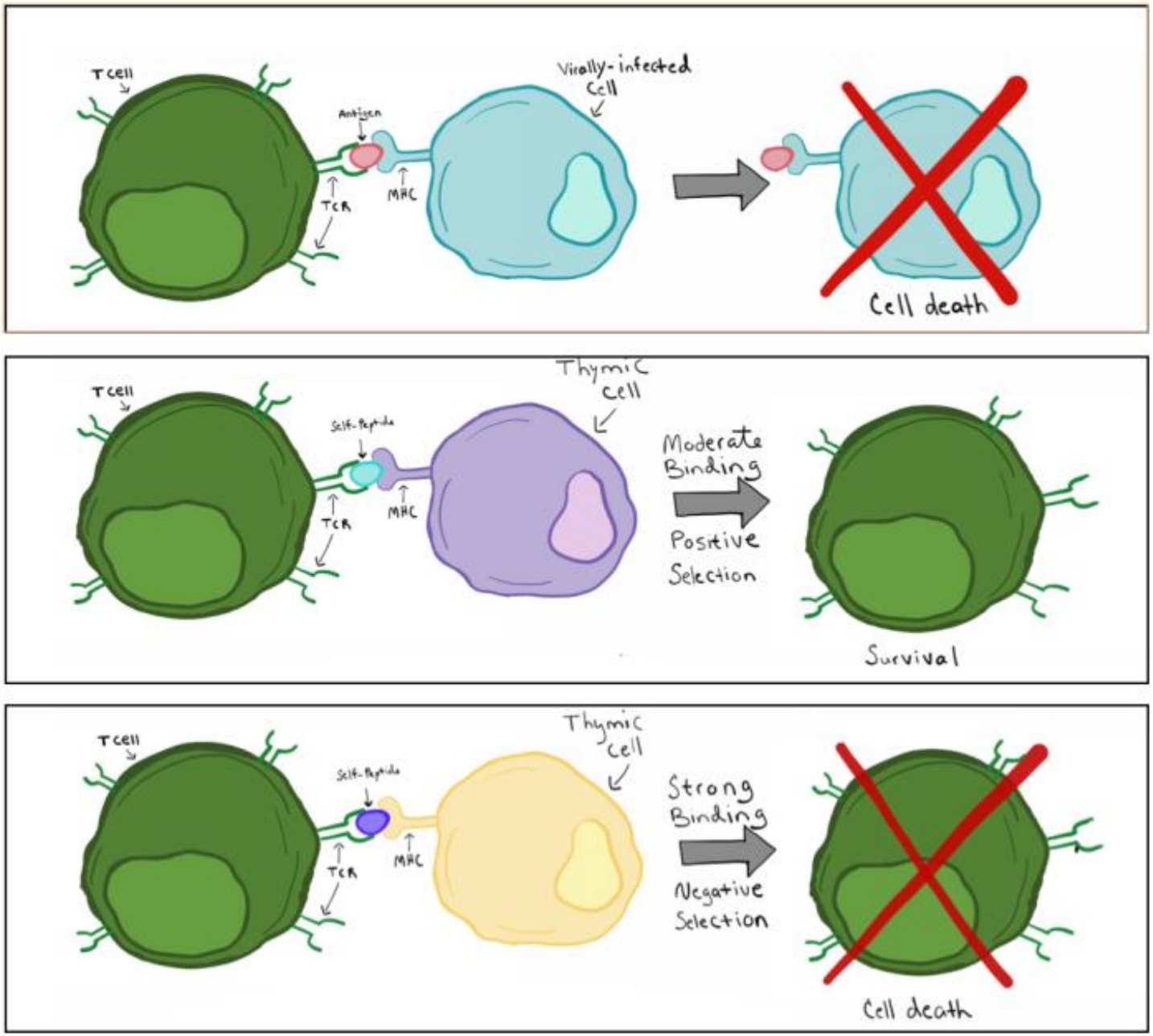
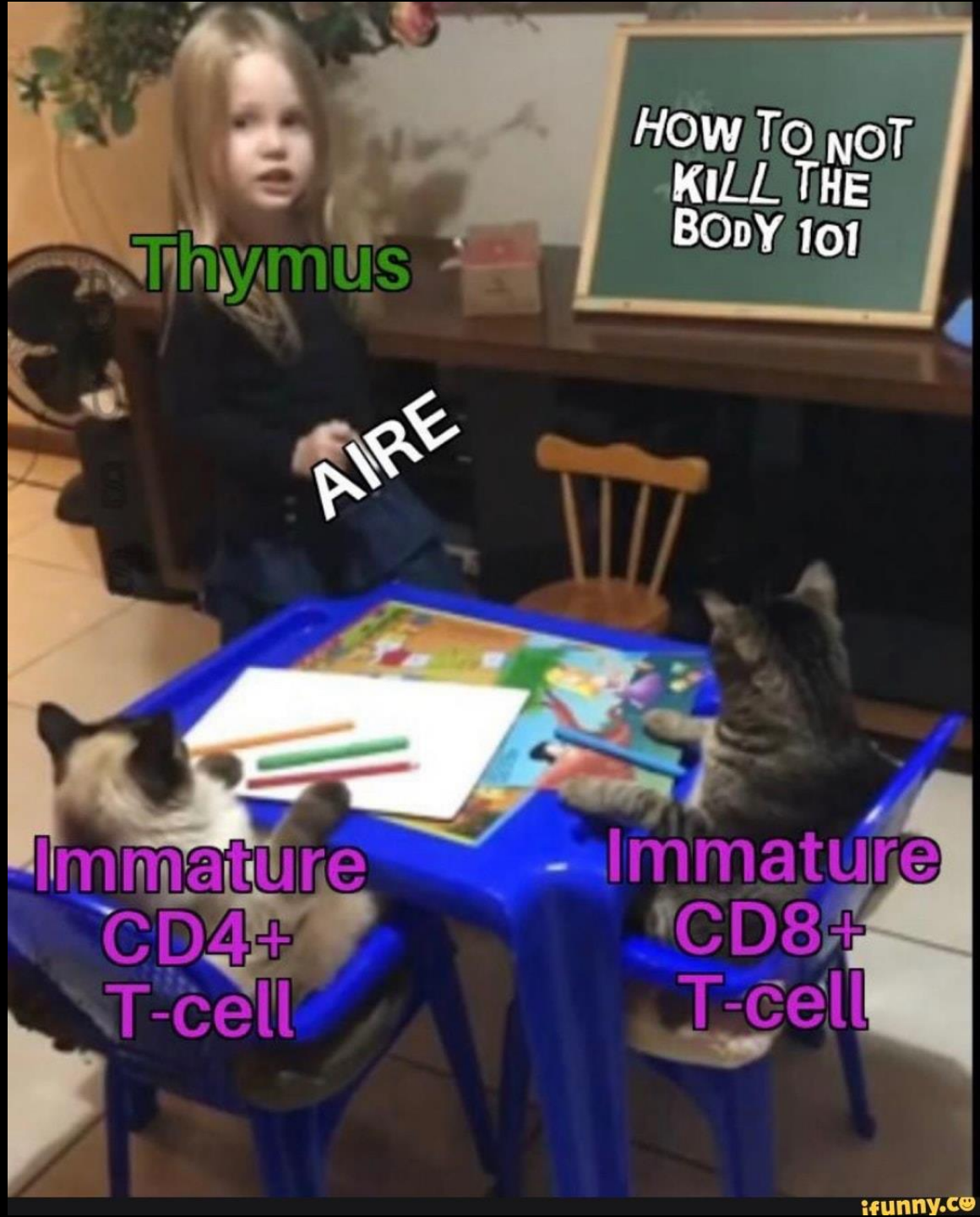
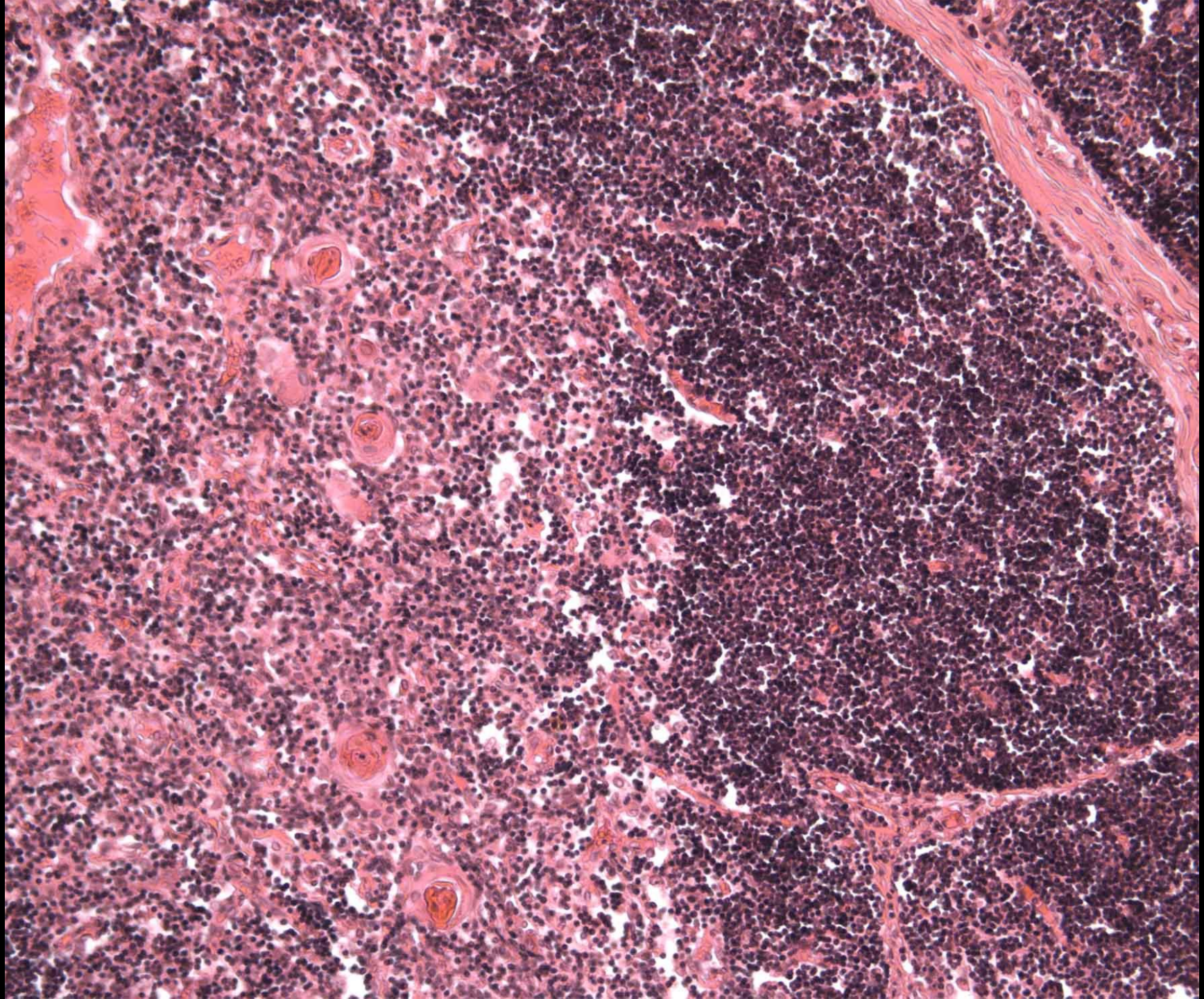
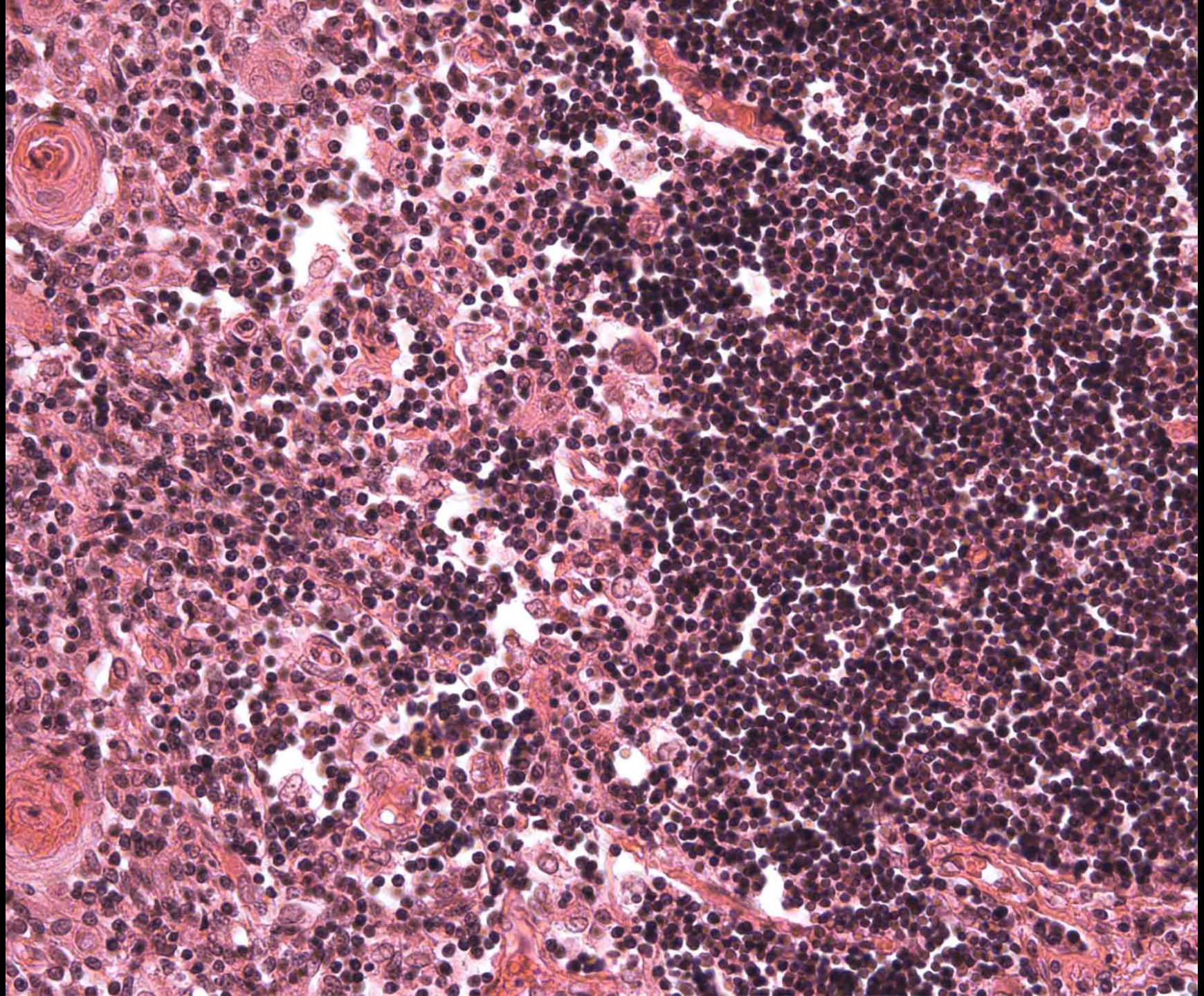
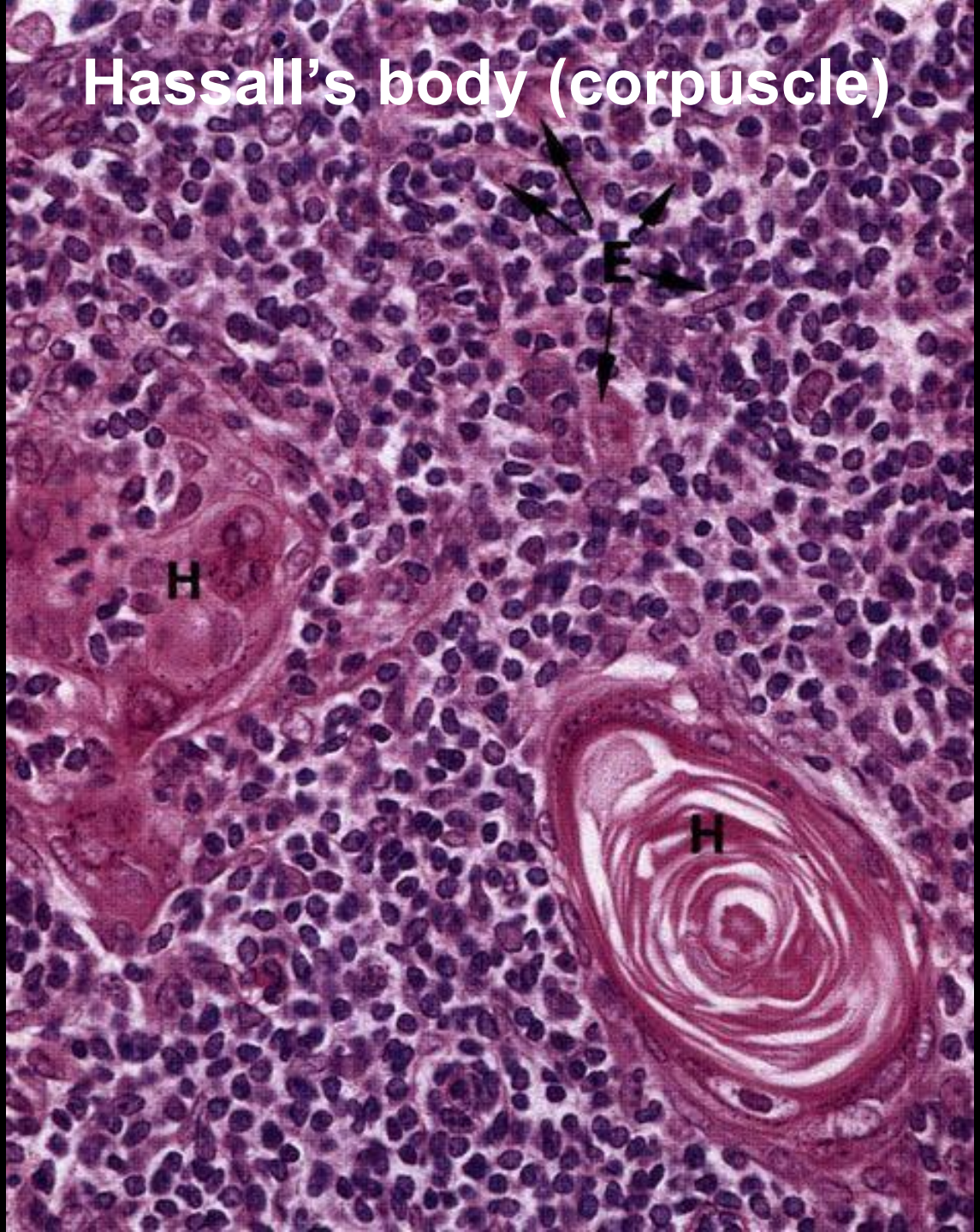

T cell
Antigen
TCR
MHC
Virally-infected Cell
Cell death
T cell
Self-Peptide
TCR
MHC
Thymic Cell
Moderate Binding
Positive Selection
Survival
T cell
Self-Peptide
TCR
MHC
Thymic Cell
Strong Binding
Negative Selection
Cell death

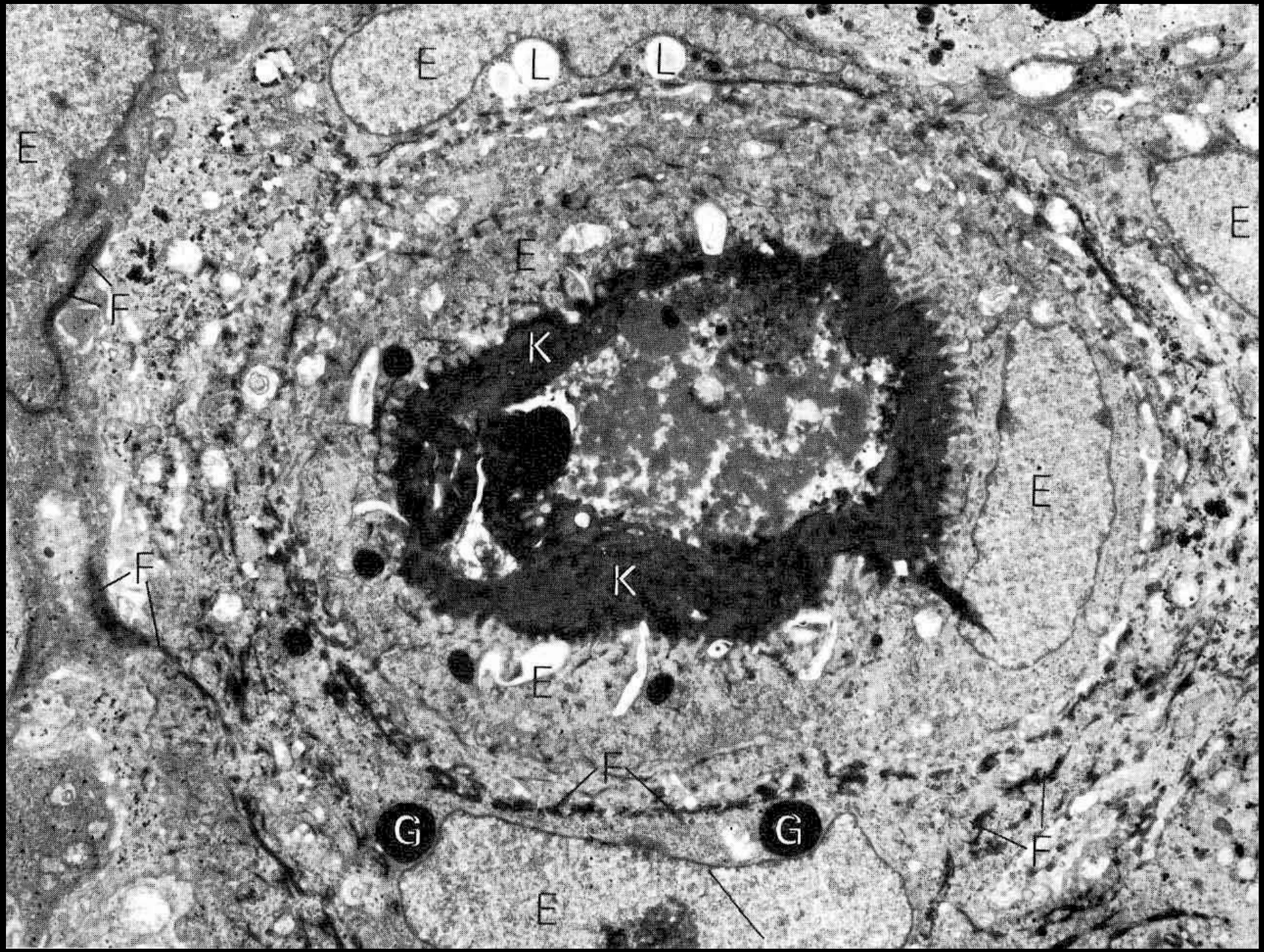

HOW TO NOT KILL THE BODY 101
Thymus
AIRE
Immature CD4+ T-cell
Immature CD8+ T-cell





Hassall's body (corpuscle)




E
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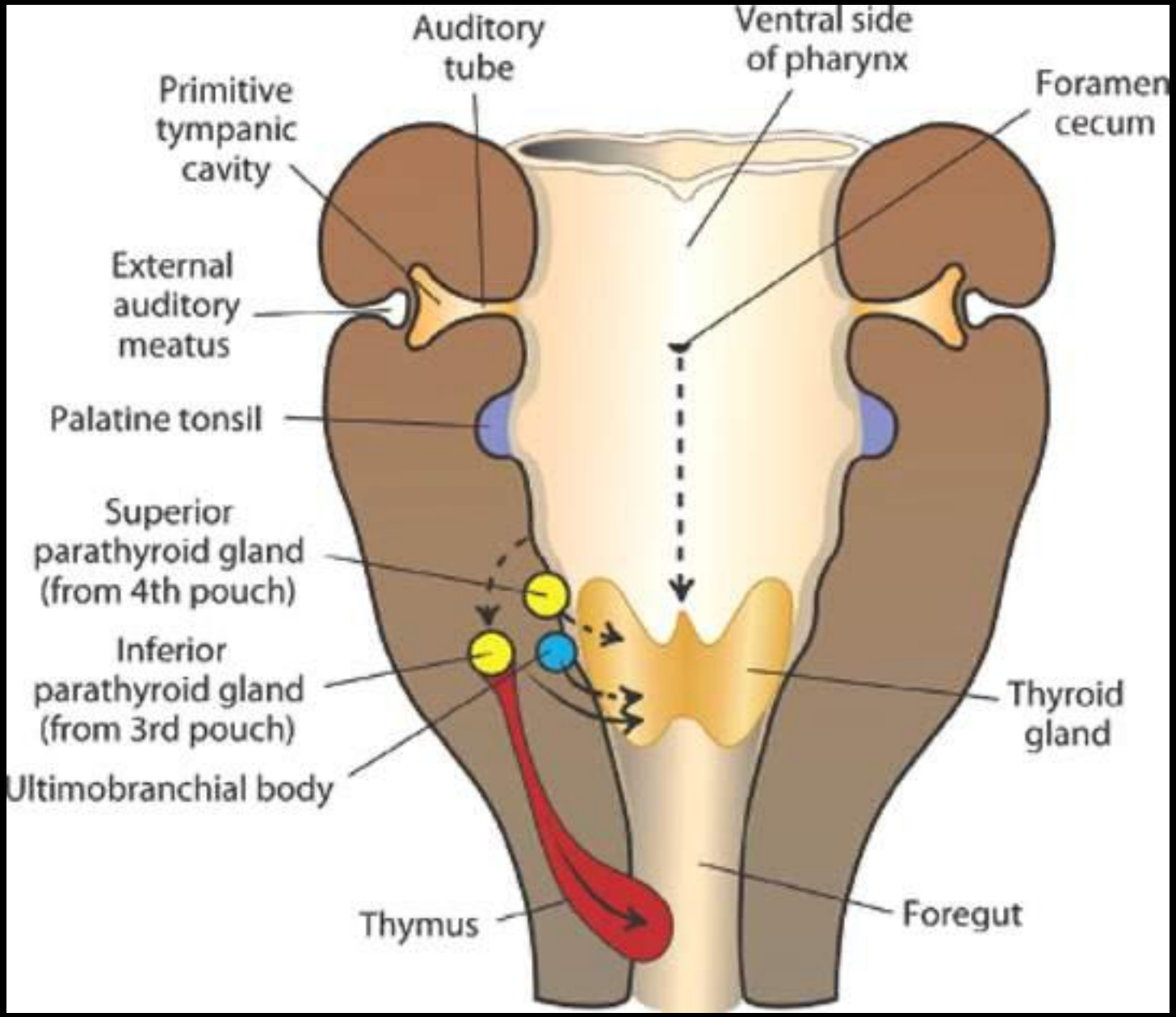
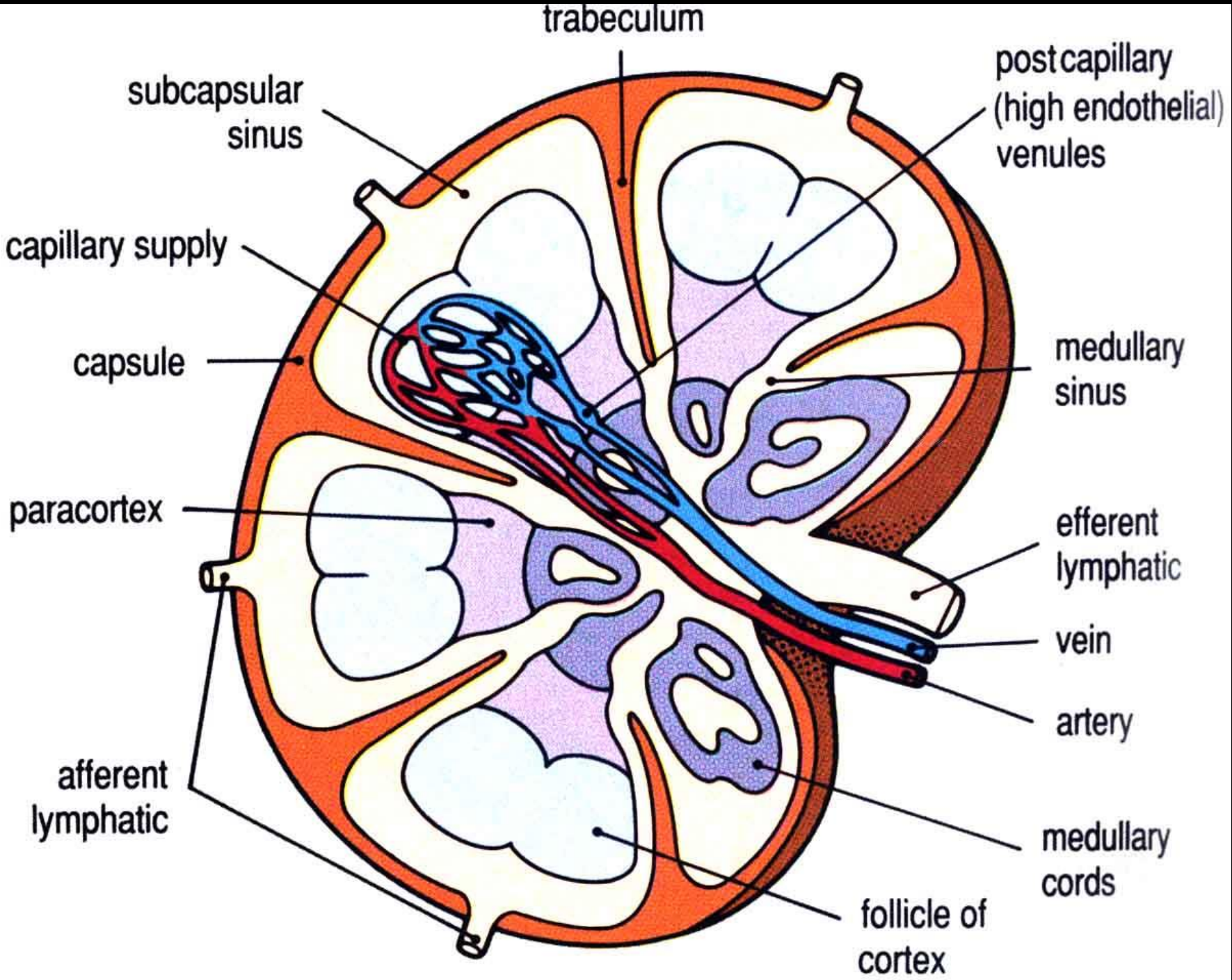
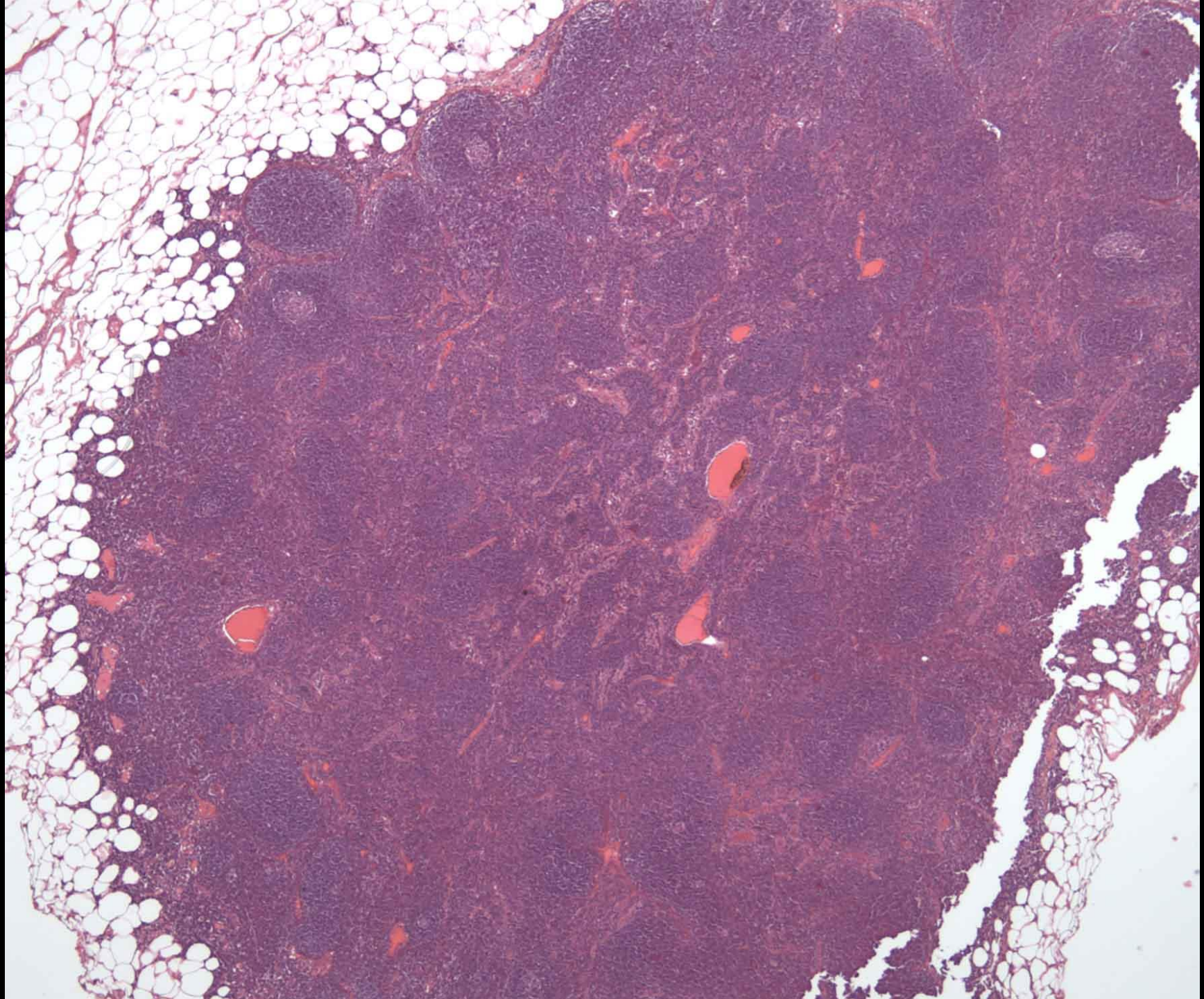
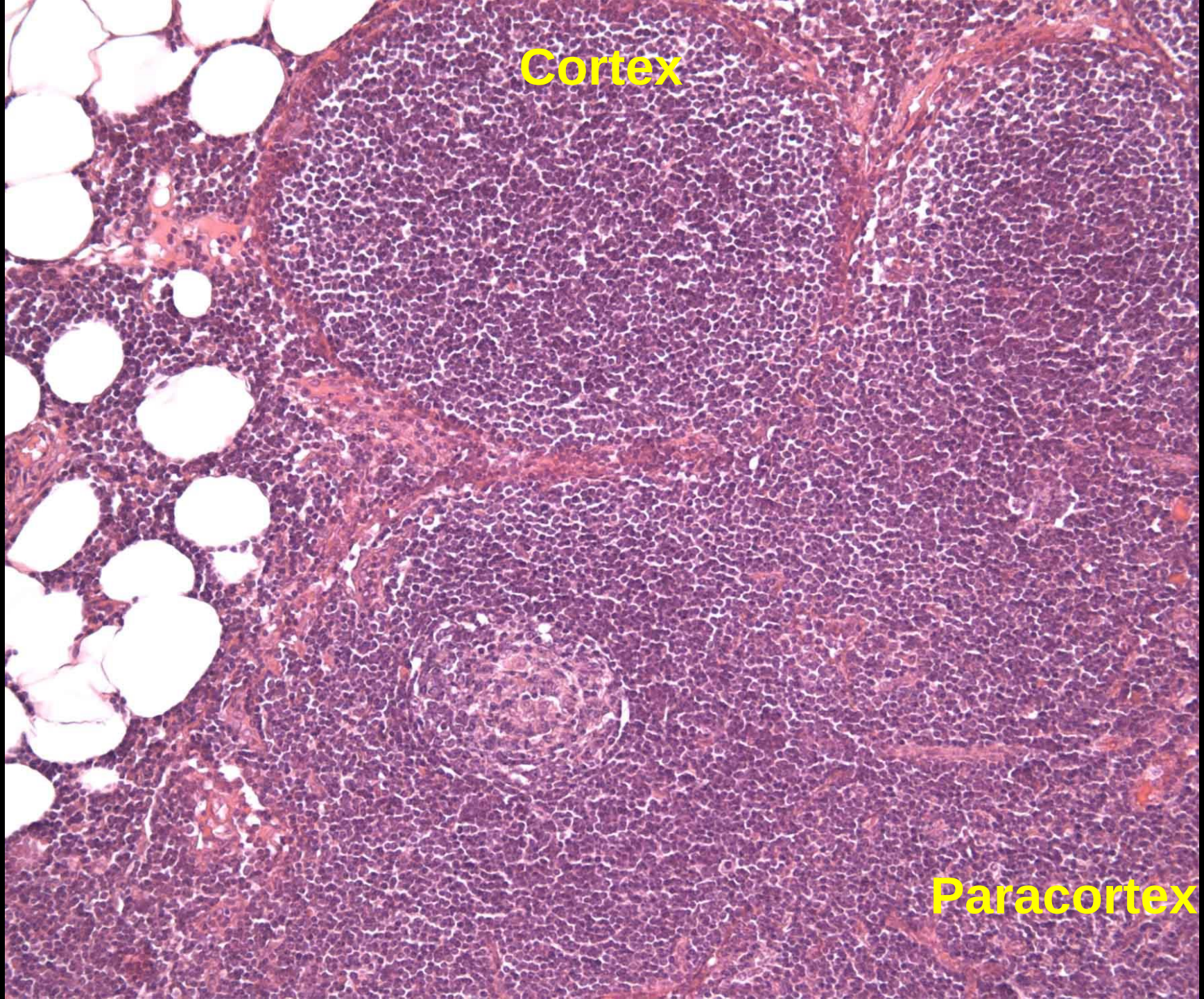

Auditory tube
Ventral side of pharynx
Primitive tympanic cavity
Foramen cecum
External auditory meatus
Palatine tonsil
Superior parathyroid gland (from 4th pouch)
Inferior parathyroid gland (from 3rd pouch)
Ultimobranchial body
Thyroid gland
Thymus
Foregut

Lymph nodes

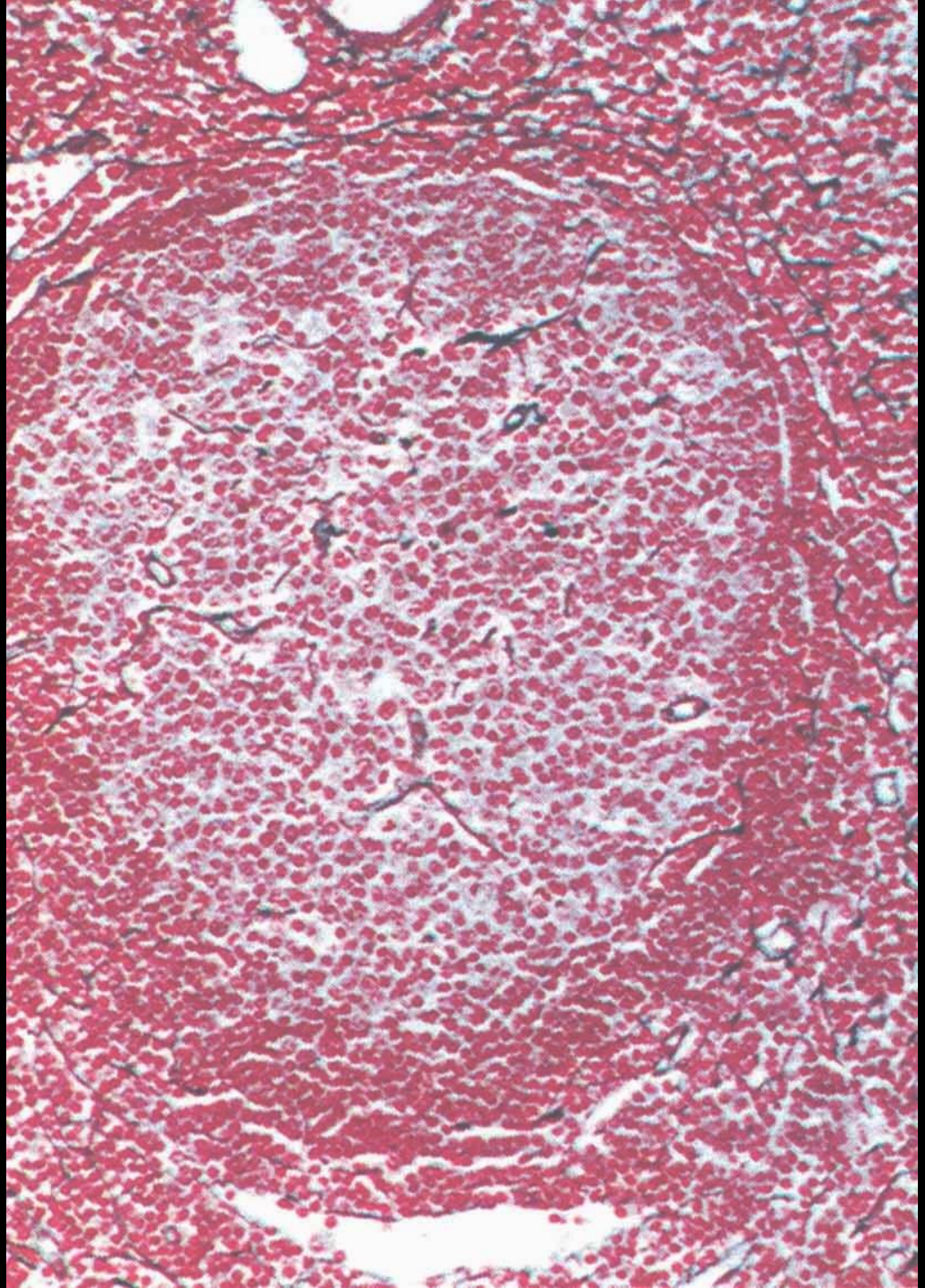
- secondary lymphoid organs
- cca 500 in the body
- ø 1-25 mm
- filtration of lymph → afferent and efferent lymphatic vessels
- stroma – reticular connective tissue
- free cells – B and T lymphocytes, plasma cells, macrophages, dendritic cells

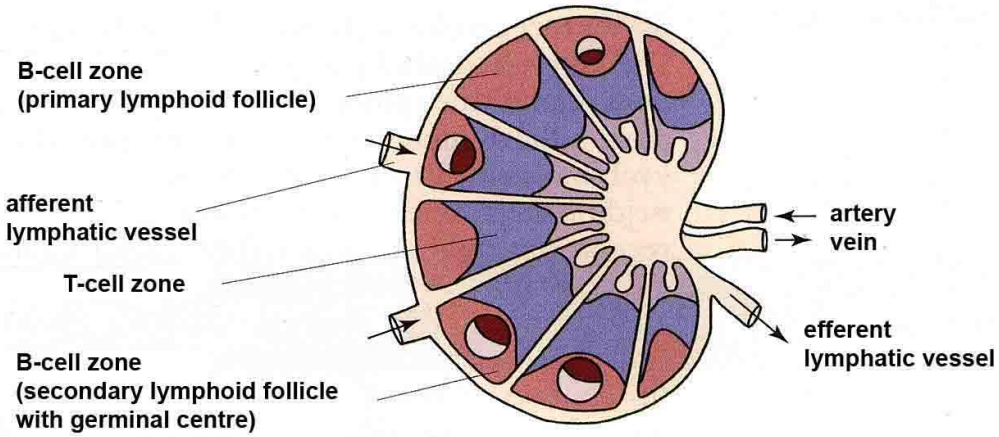

trabeculum
subcapsular sinus
post capillary (high endothelial) venules
capillary supply
capsule
medullary sinus
paracortex
efferent lymphatic
vein
artery
afferent lymphatic
medullary cords
follicle of cortex

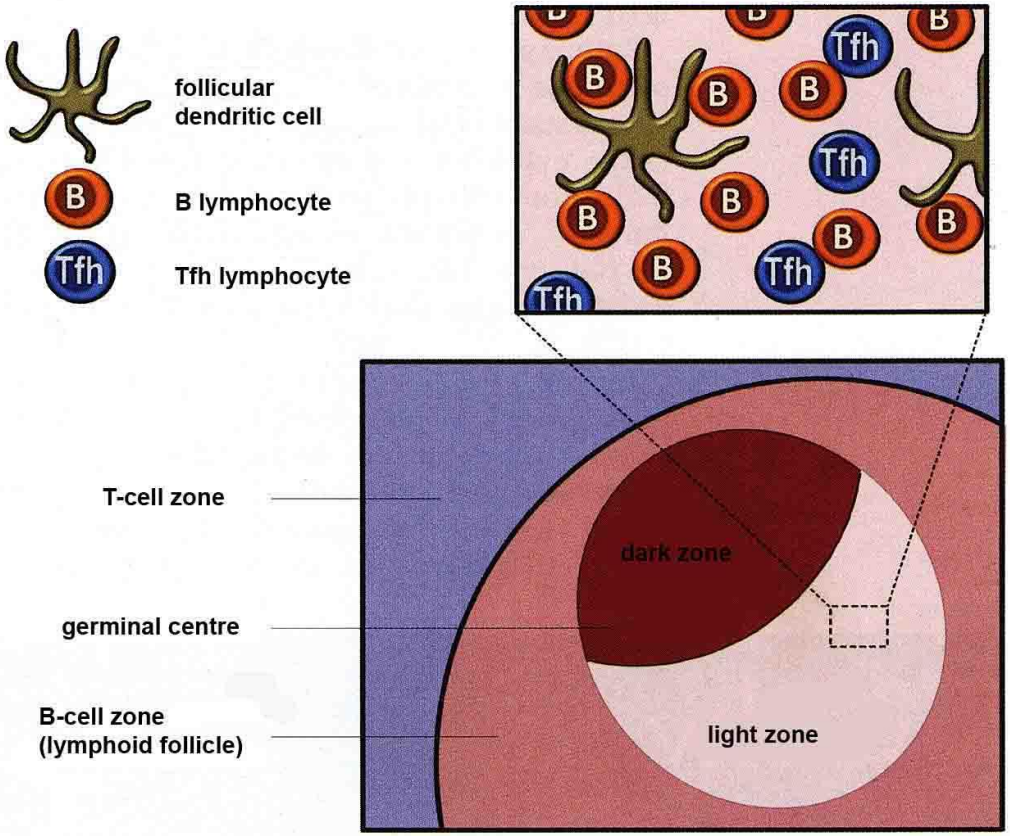



Cortex
Paracortex

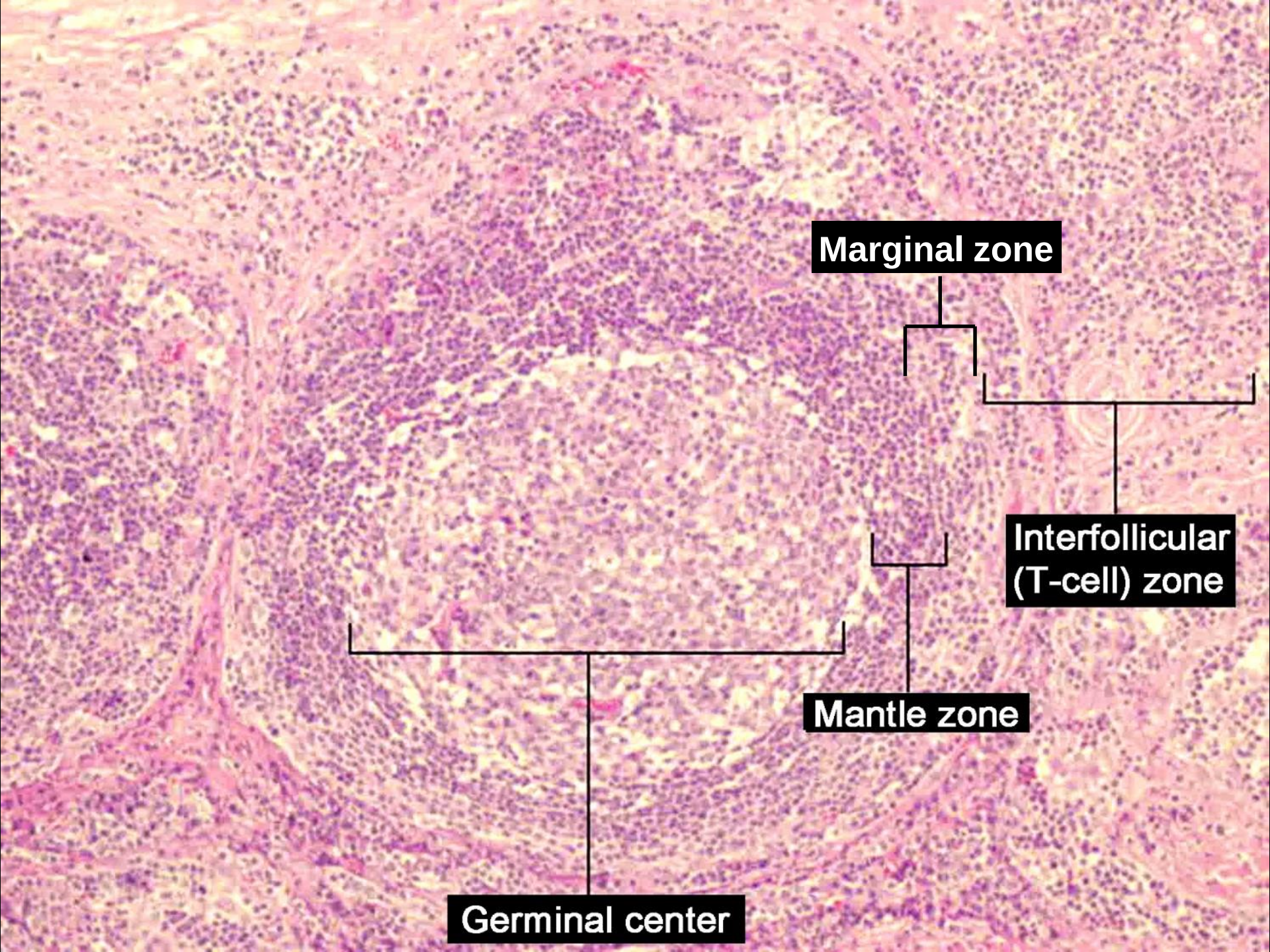
impregnation of reticular fibers

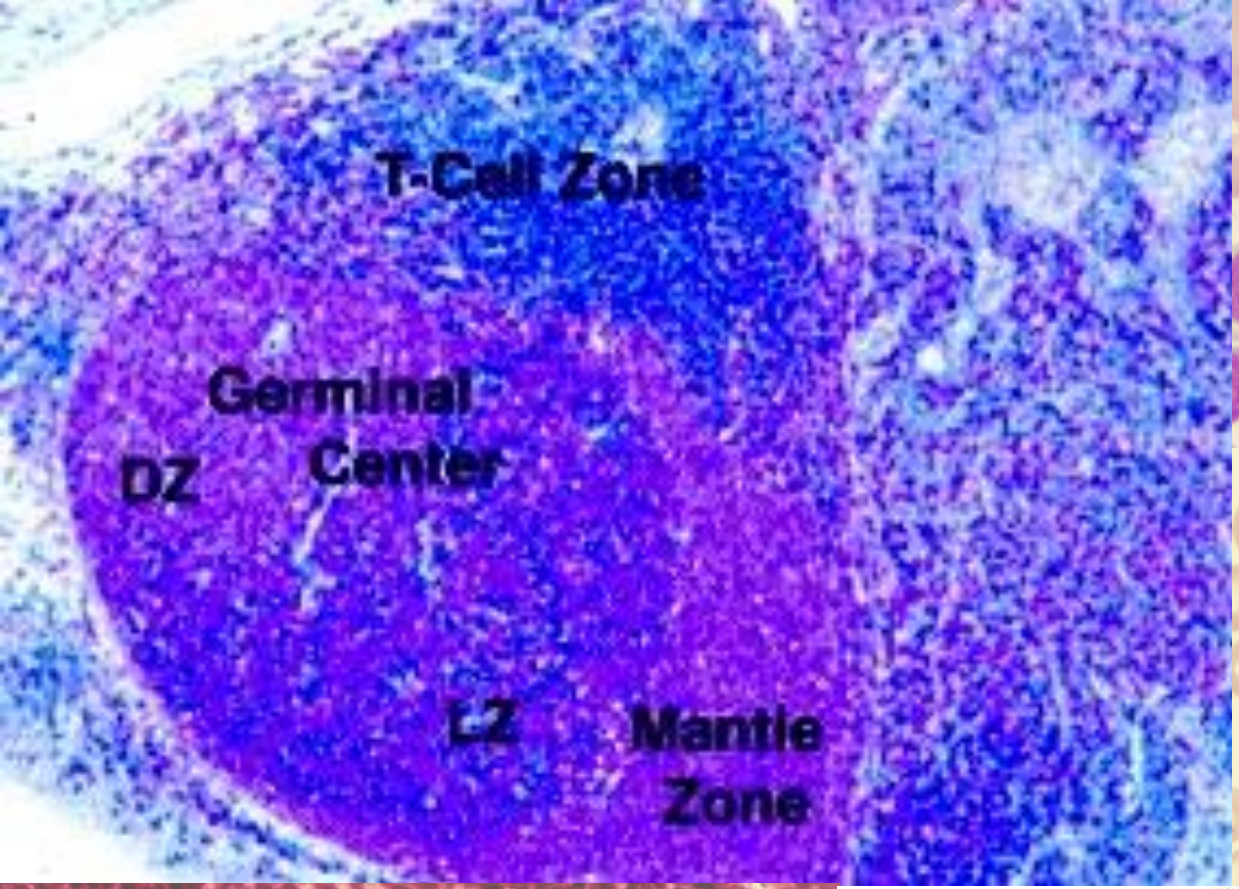


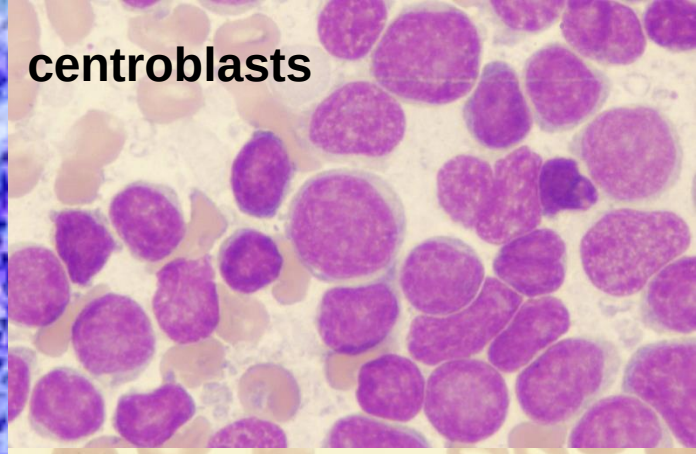




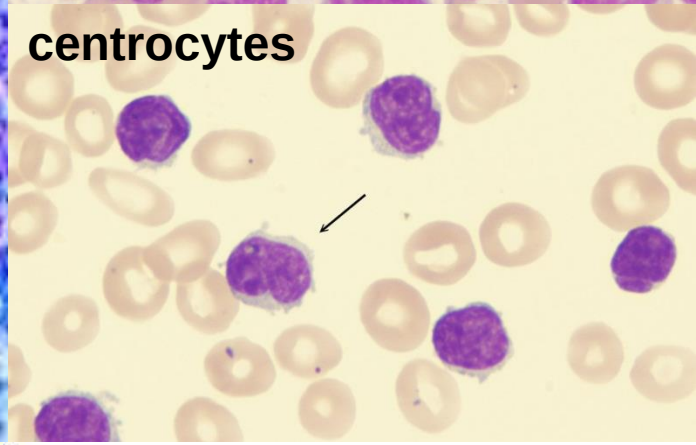
Hořejší,V., Brdička,T.: Kdo pomáhá B-lymfocytům produkovat protilátky?
Vesmír 92(10), 2013: 542-544.


Marginal zone
Interfollicular
(T-cell) zone
Mantle zone
Germinal center

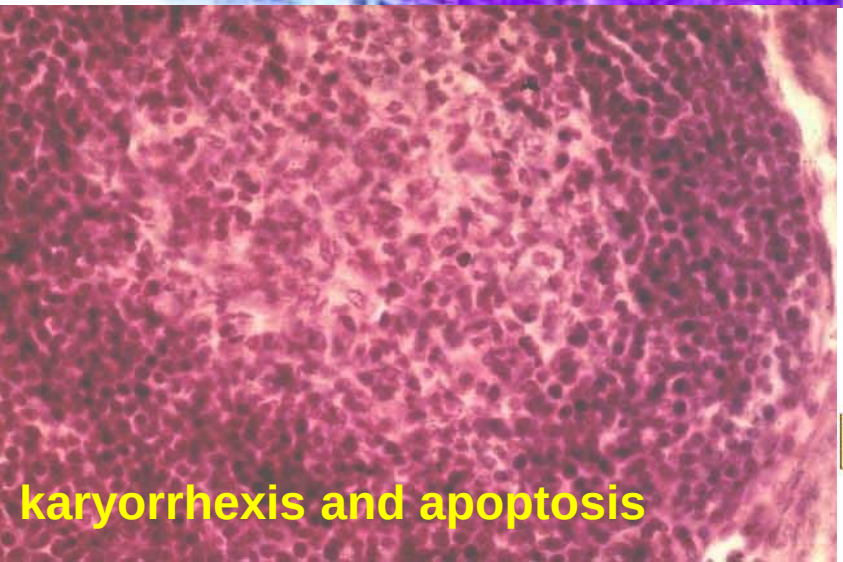




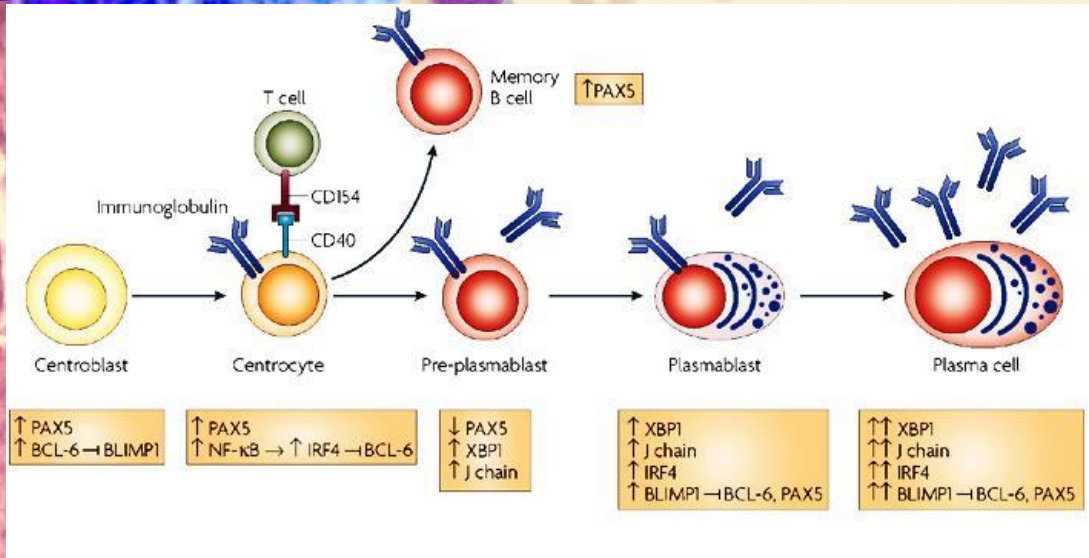
centroblasts

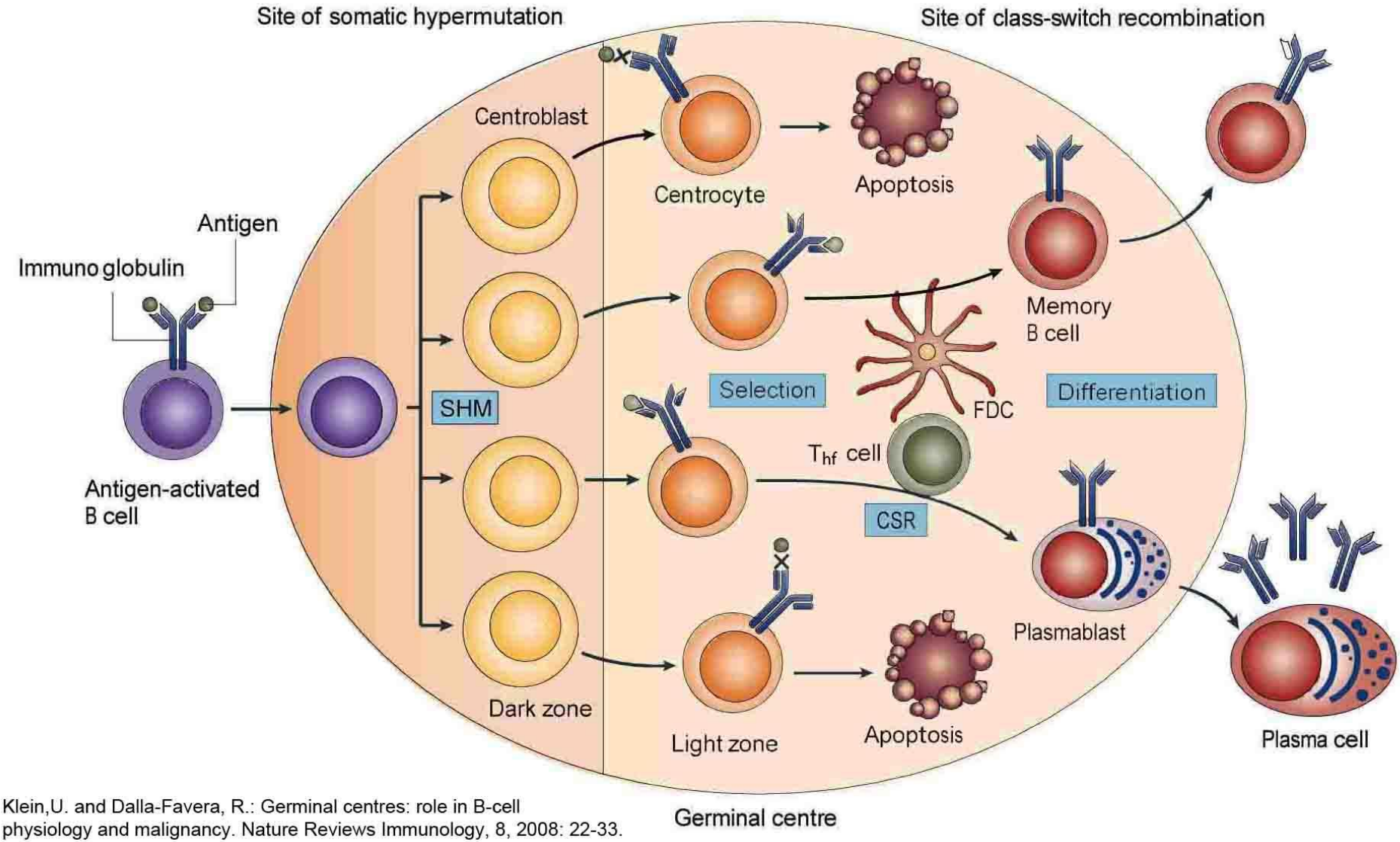


centrocytes



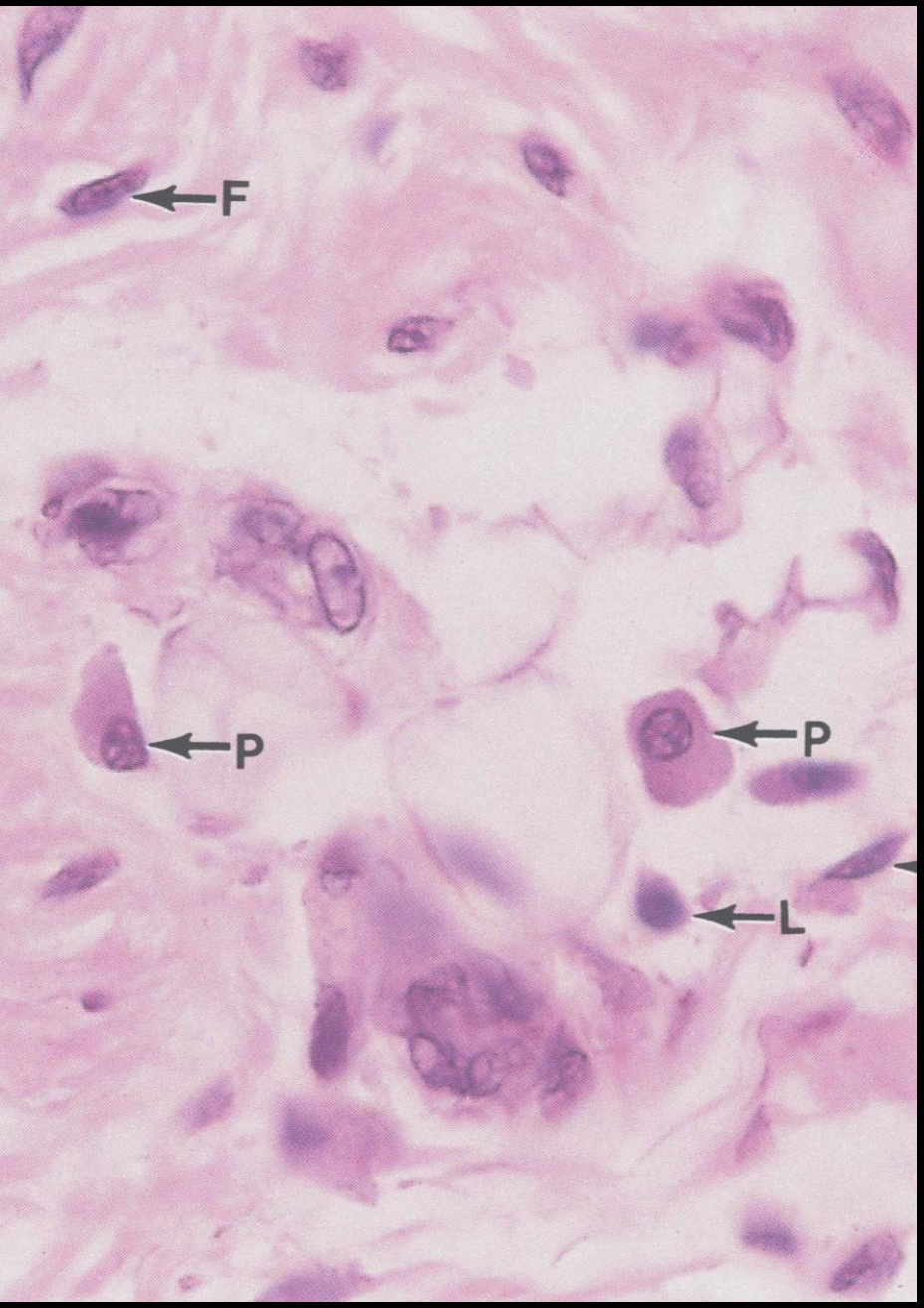
karyorrhexis and apoptosis

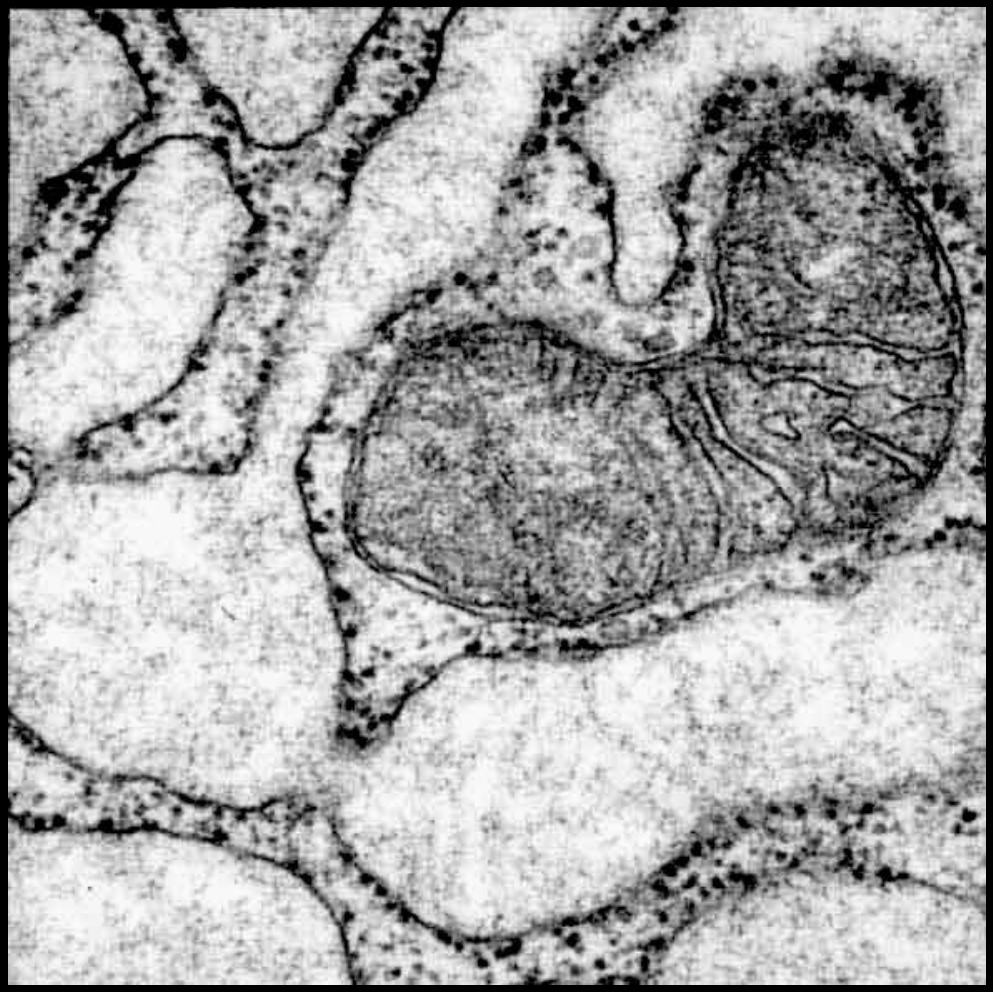


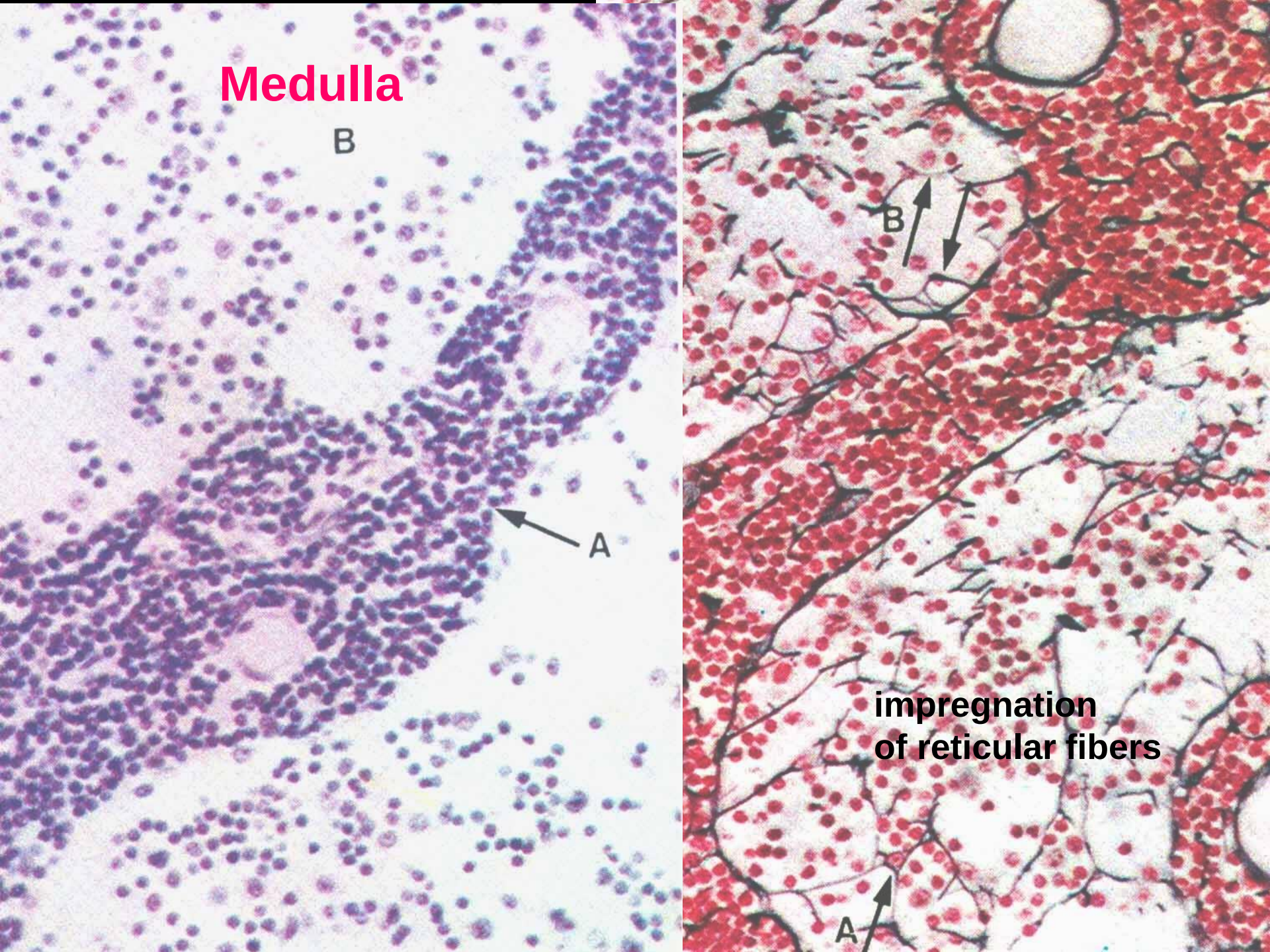


Klein,U. and Dalla-Favera, R.: Germinal centres: role in B-cell physiology and malignancy. Nature Reviews Immunology, 8, 2008: 22-33.

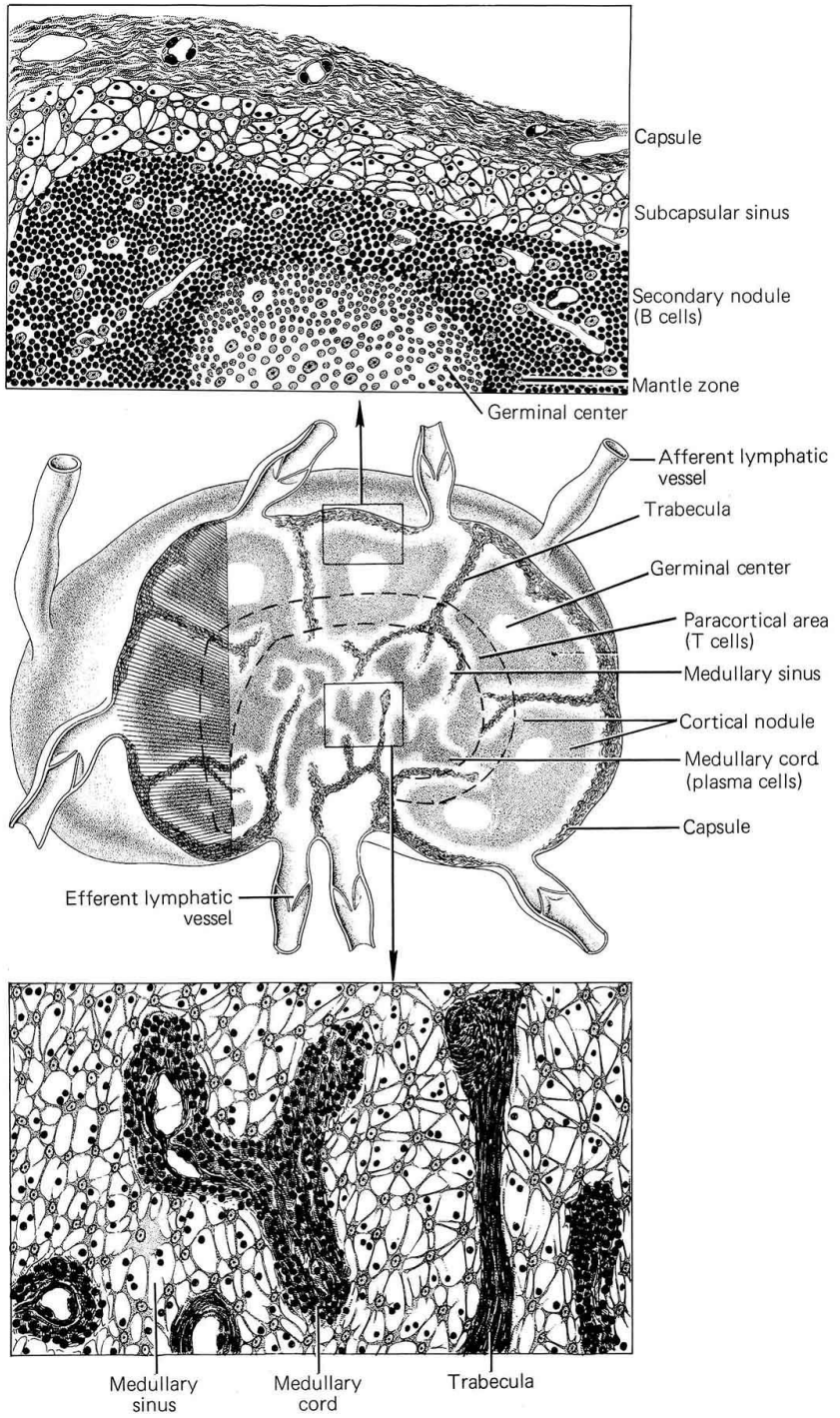
Plasma cells






Medulla
B
A
B
impregnation
of reticular fibers
A

Lymphatic sinuses



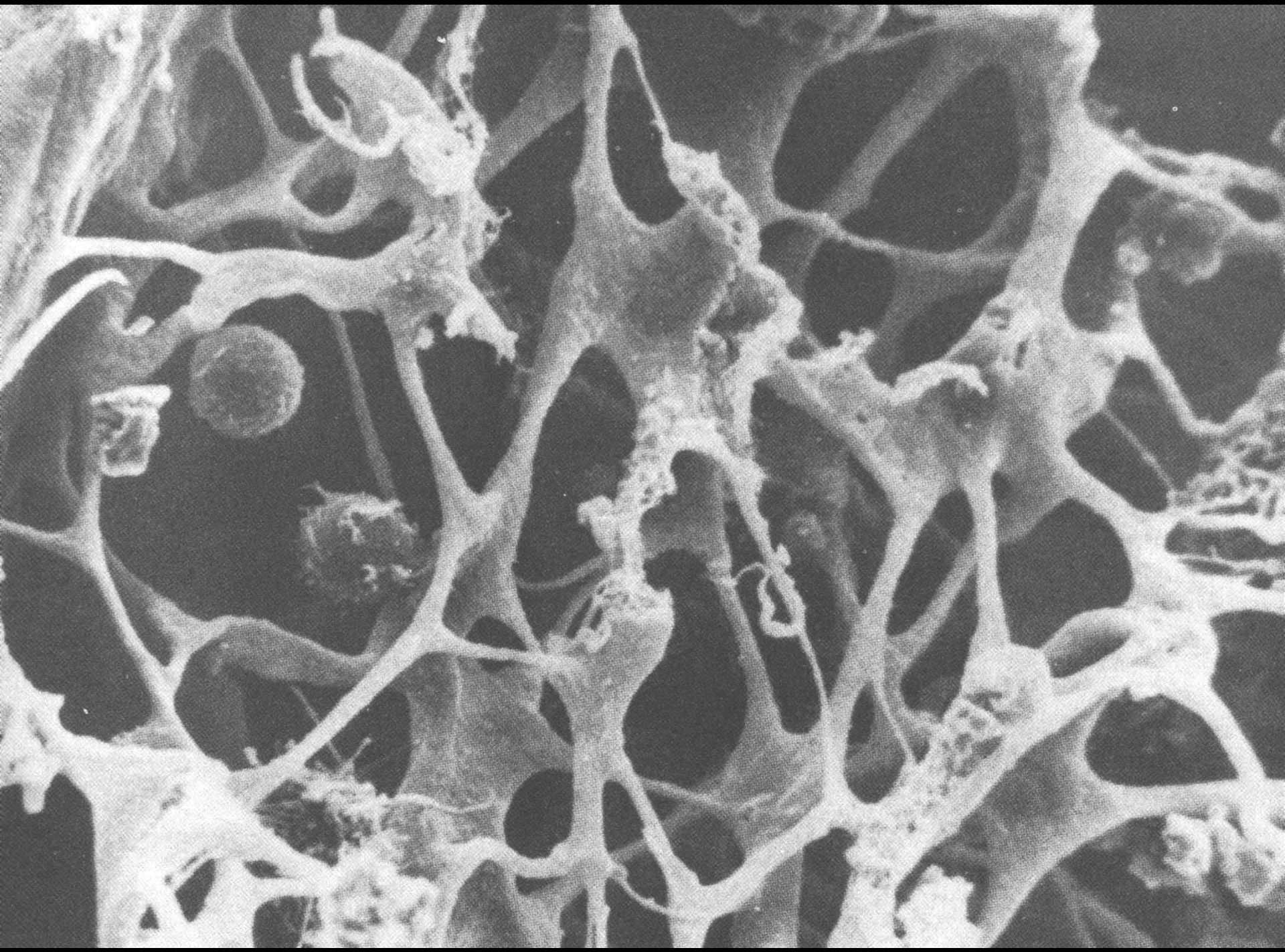
subcapsular (marginal)

↓

perifollicular (internodular, cortical)

↓

medullary

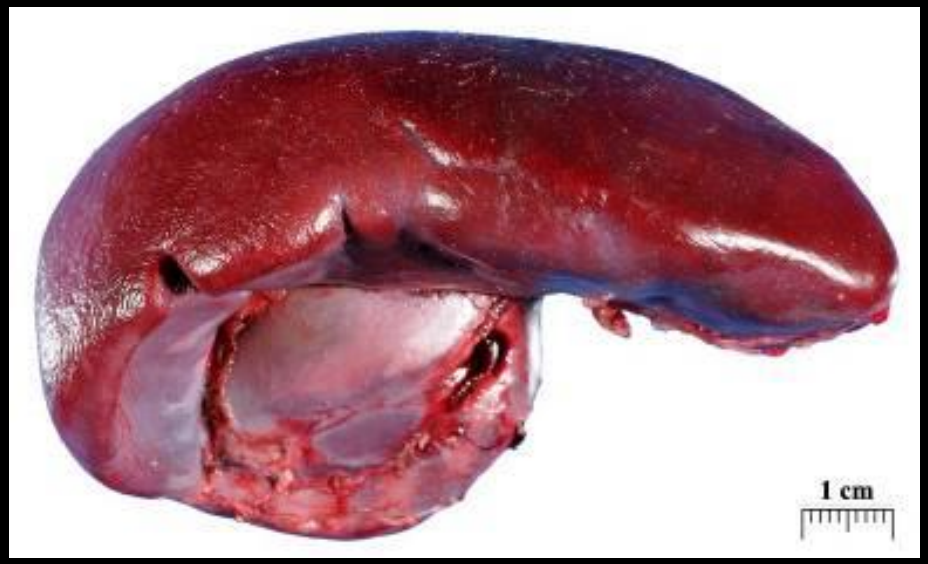


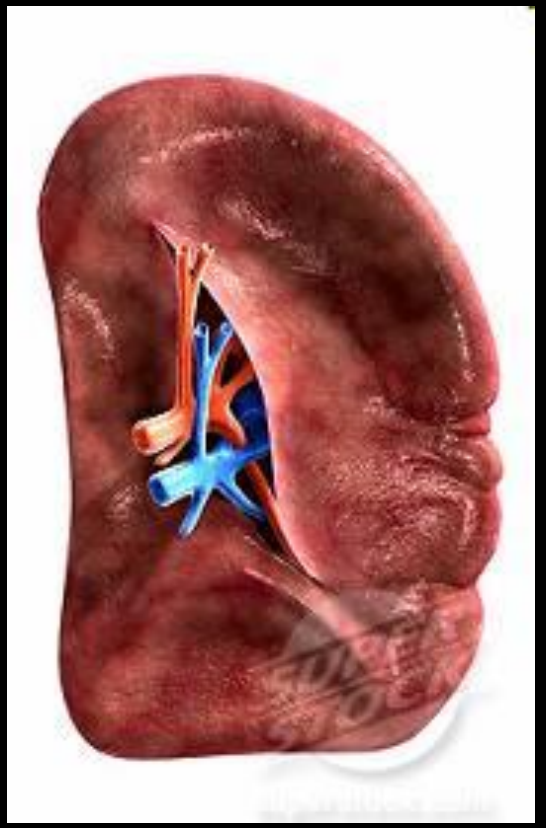
Spleen (splen, „lien“)

- secondary lymphoid organ
- largest lymphoid organ
- immunologic blood filter
  - removal of microorganisms
- „cemetery“ of erythrocytes
- storage of blood
- hematopoiesis during development

Spleen

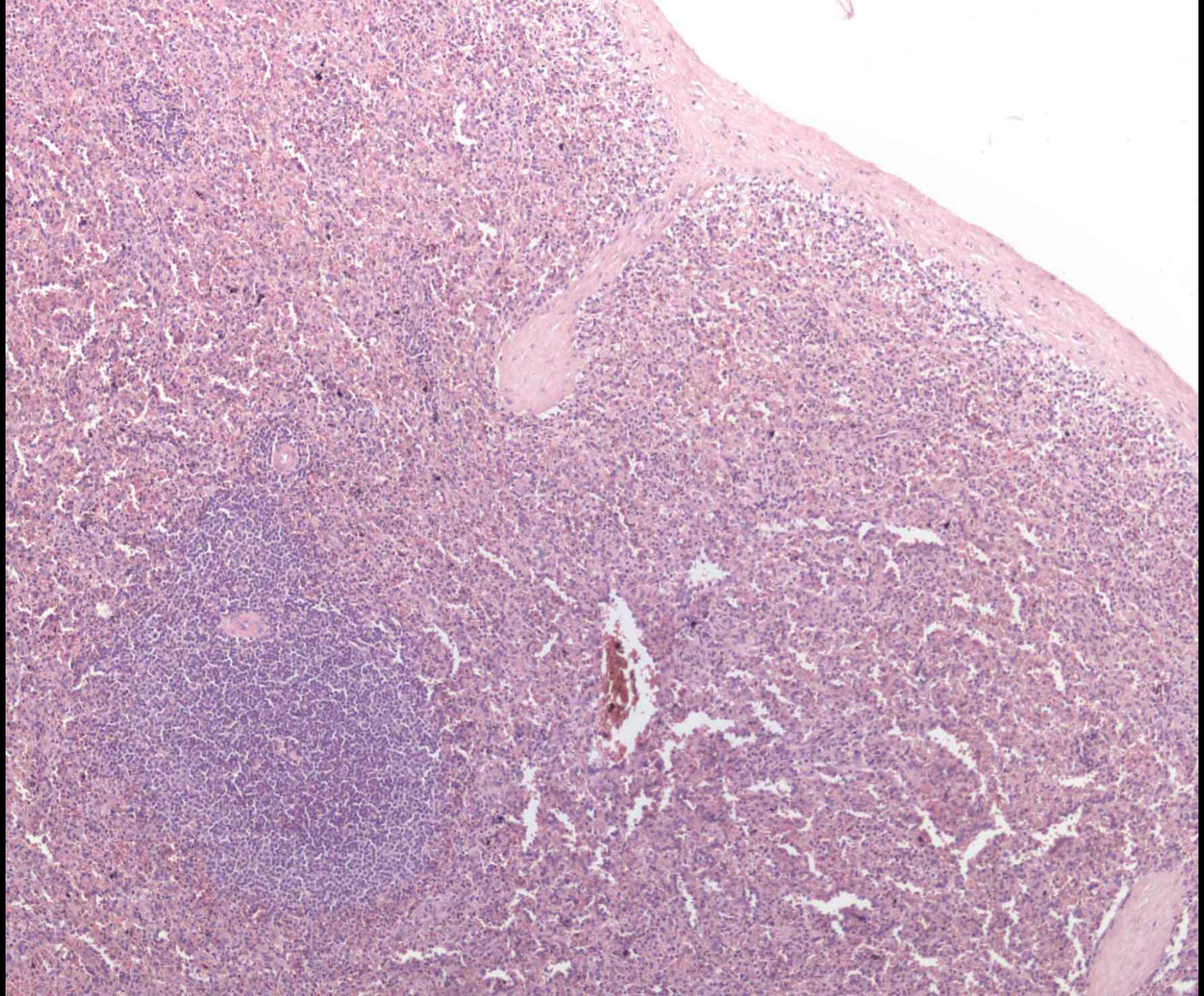
- length 10-13 cm; width 6-8 cm; thickness 4 cm
- weight depends on the blood fillling
- ♂ 140-160 g / ♀ 120-150 g
- weight 200 g is not pathological





Spleen – structure

- fibrous capsule – dense irregular CT
  - sparse smooth muscle cells
  - covered with serosa (except hilum)
  - fibrous trabecules into pulp (*trabeculae splenicae*)
- stroma - reticular connective tissue
- free cells – B and T lymphocytes, macrophages, dendritic cells, all other blood elements
- pulpa splenica
  - white pulp (pulpa alba)
  - red pulp (pulpa rubra)



Spleen – blood supply

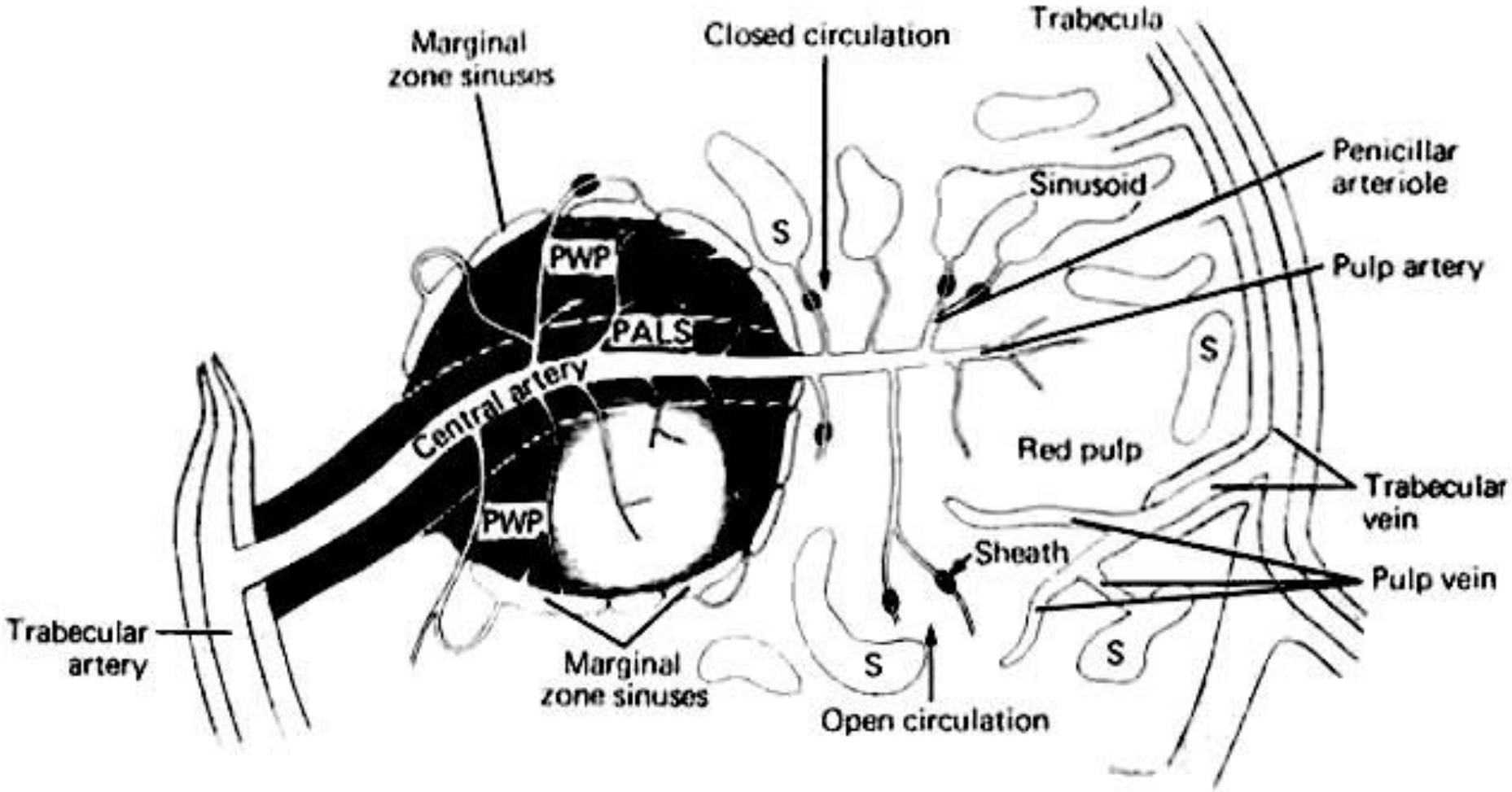
- truncus coeliacus → a. splenica → rr. splenici → aa. trabeculares → arteriolae vaginatae pulpae albae
  - within periarterial lymphatic sheath (PALS; vagina lymphoidea periarteriolaris)
  - arteriolae centrales (nodulares) within noduli lymphoidei splenici
  - sinuses of zona marginalis

→ aa. pulpae rubrae → aa. penicillares → arteriolae penicillares

→ vagina perioarteriolaris macrophagocytica (Schweigger-Seidel‘s caspule)

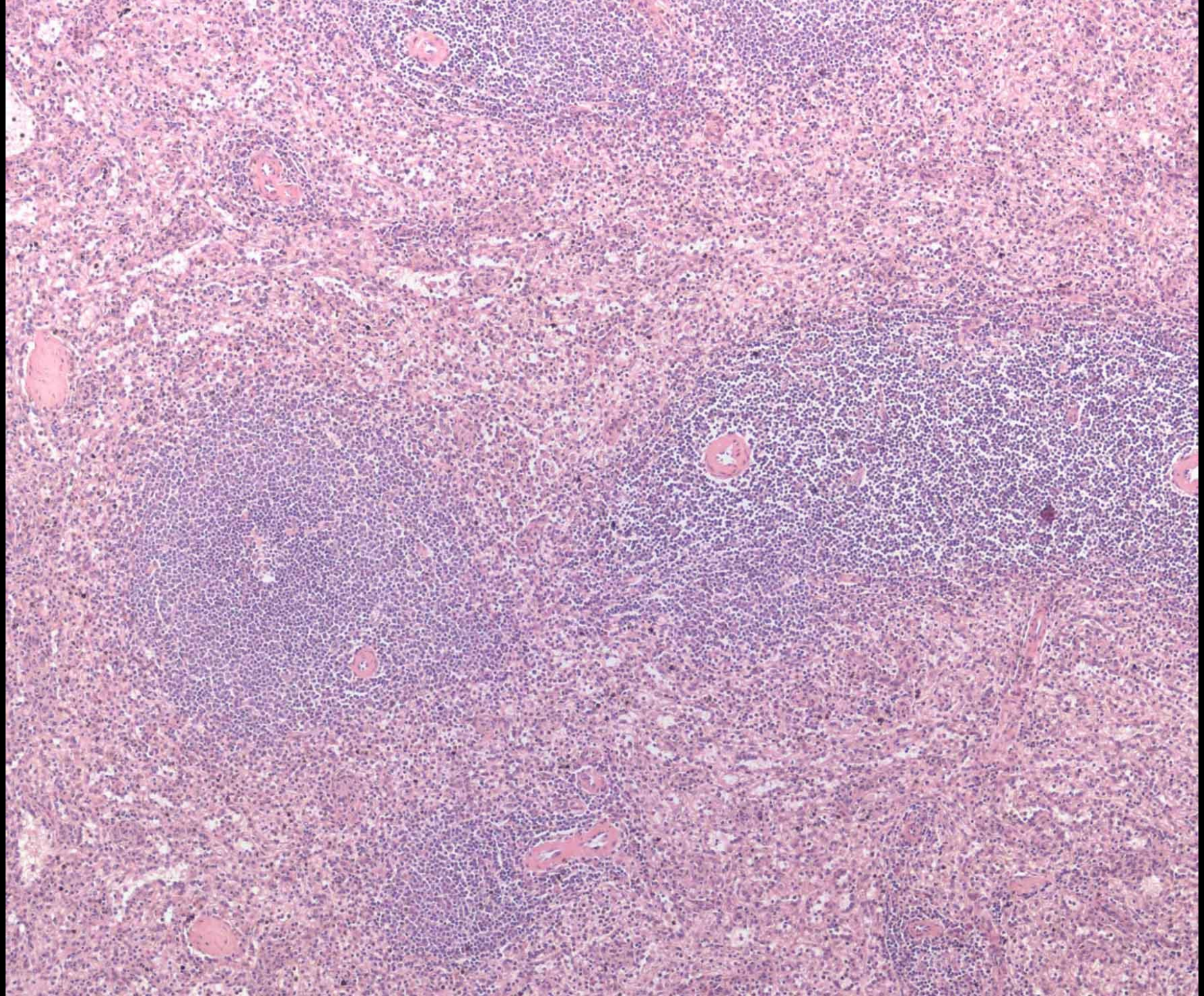
- vasa sinusoidea splenica (in pulpa rubra)
  - **open** x **closed** circulation
  - fusiform endothelial cells, clefts, interrupted basal lamina

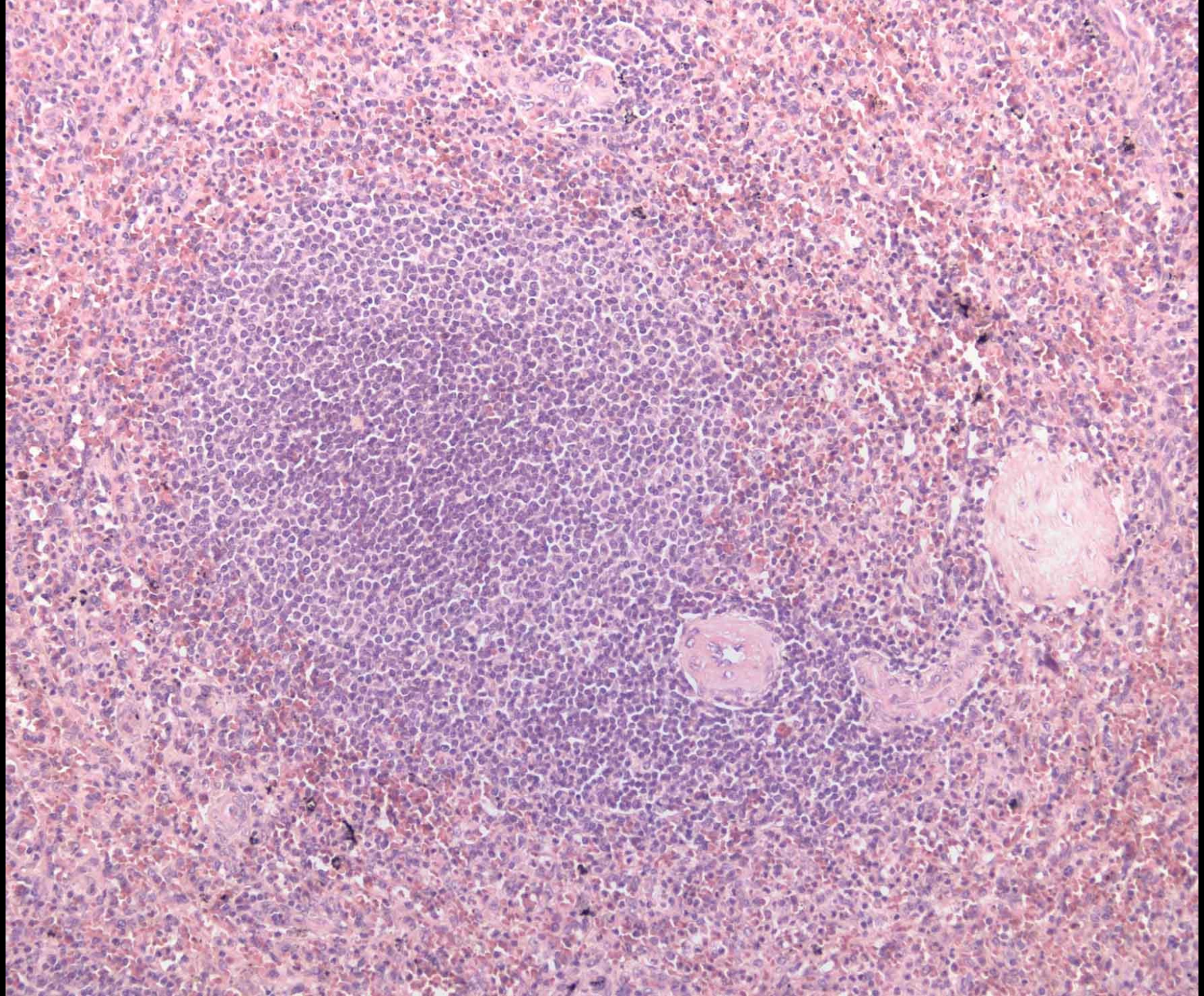
→ vv. pulpae rubrae → vv. trabeculares → v. splenica → v. portae


Marginal zone sinuses
Closed circulation
Trabecula
Penicillar arteriole
Sinusoid
Pulp artery
S
PWP
PALS
Central artery
S
Red pulp
Trabecular vein
PWP
Sheath
Pulp vein
Trabecular artery
Marginal zone sinuses
S
S
Open circulation

Spleen – white pulp

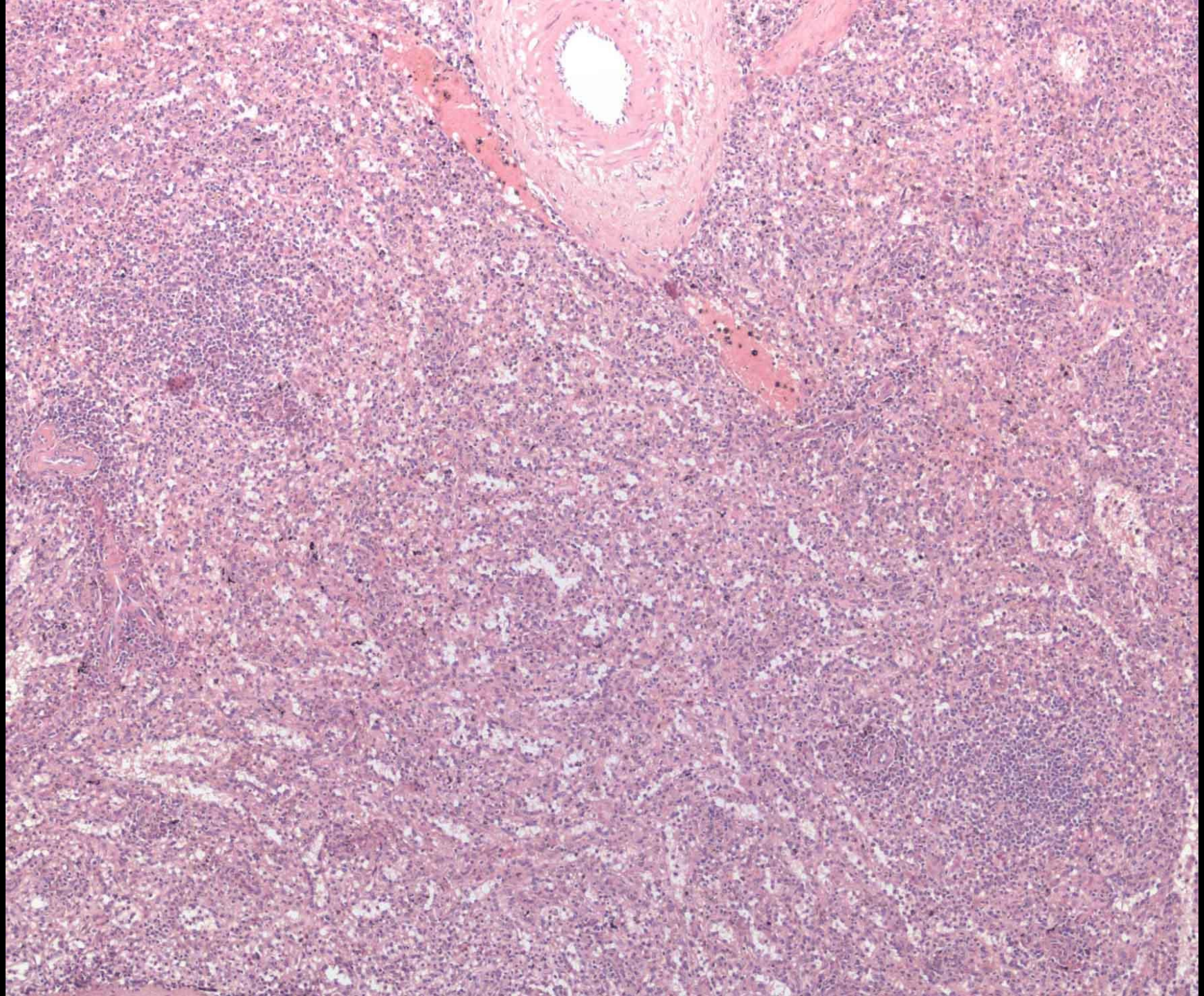
- reticular connective tissue with lymphocytes
- **PALS** (perioarteriolar lymphoid sheath)
    - *T-lymphocytes*
- **PWP** (peripheral white pulp)
  - lymphoid nodules (Malpighi‘s corpuscles)
    - *B-lymphocytes*
  - marginal zone – between white and red pulp
    - sinusoids and lymphoid tissue
    - macrophages (antigen presentation)

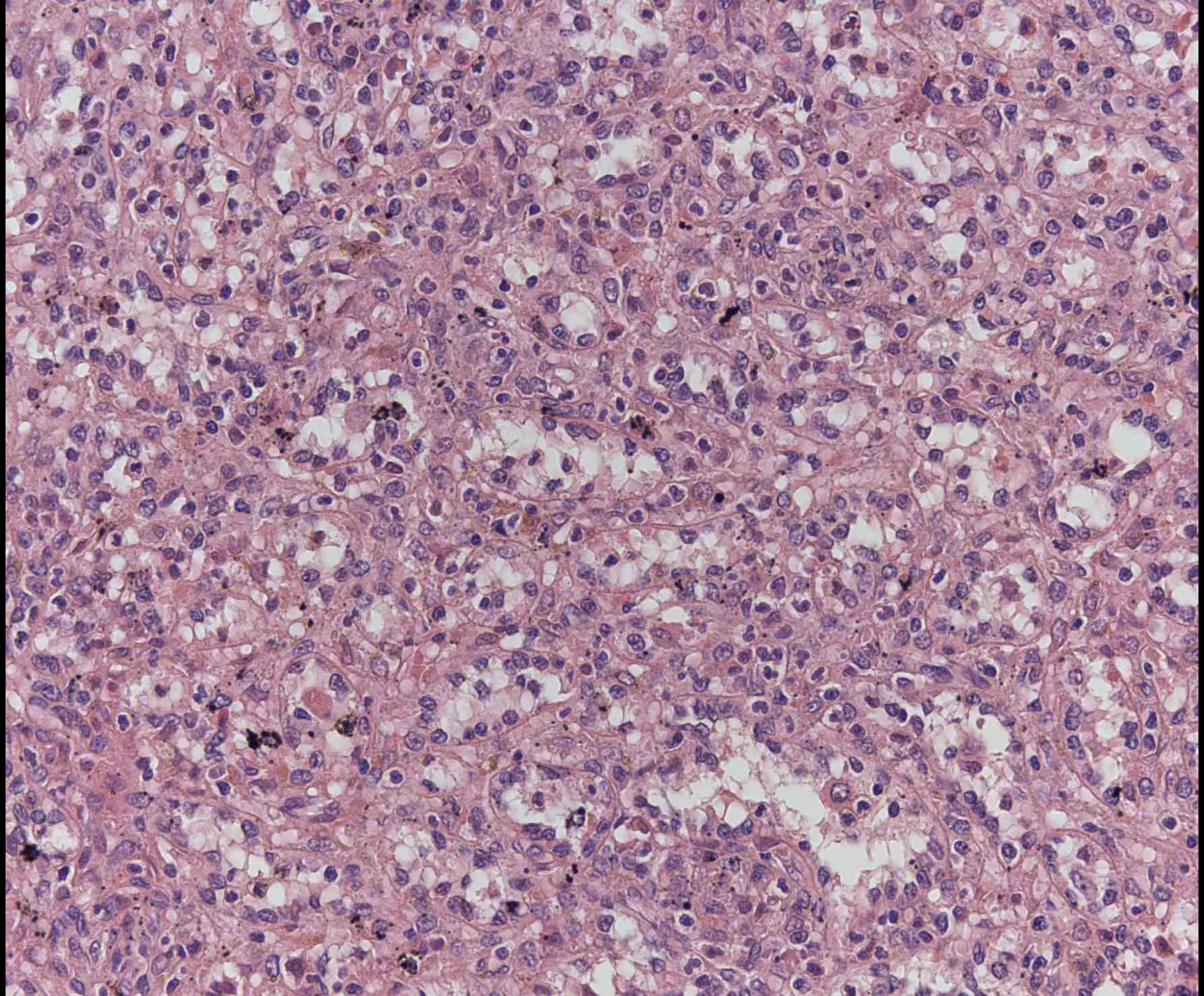


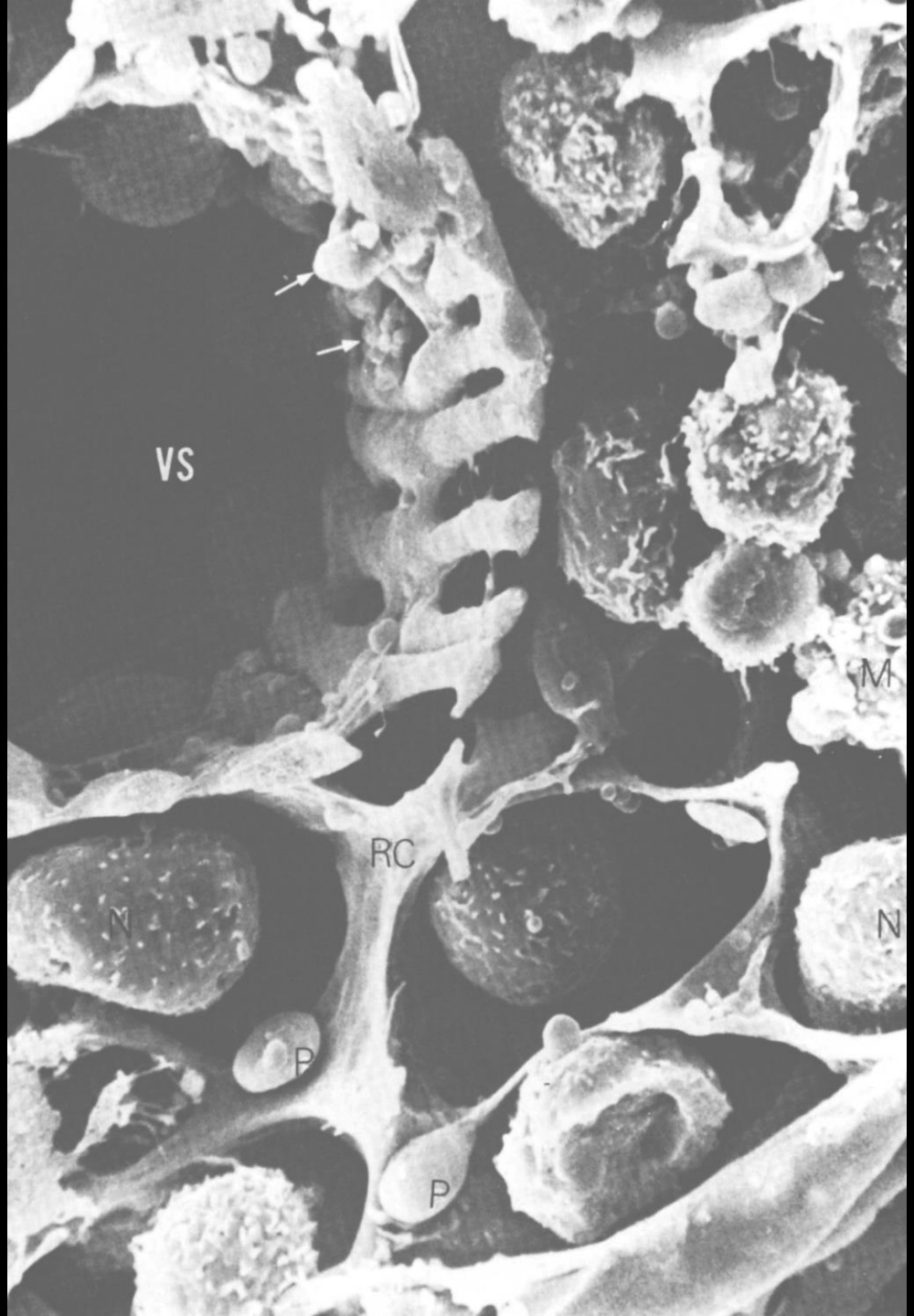


Spleen – red pulp

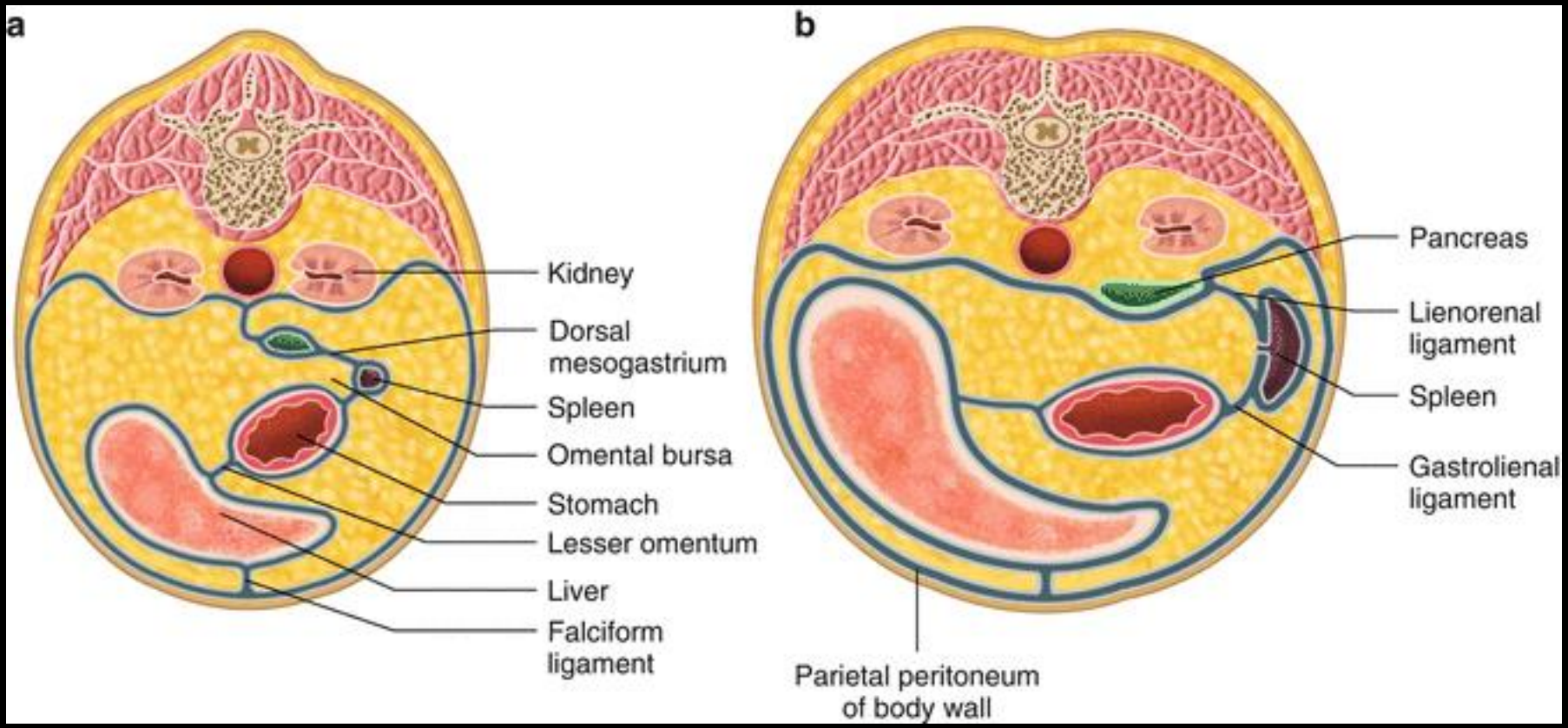
- **splenic (Billroth‘s) cords** (*chordae splenicae*)
  - cells between sinusoids
  - lymphocytes, macrophages, erythrocytes
  - reticular fibers (*fibrae reticulares anulares)* – hoop arrangement
- blood sinusoids
  - fusiform endothelial cells *(endotheliocyti fusiformes),* interrupted endothelium (*endothelium disjunctum*)
  - located close to reticular fibers
  - spatium intersinusoideum splenicum





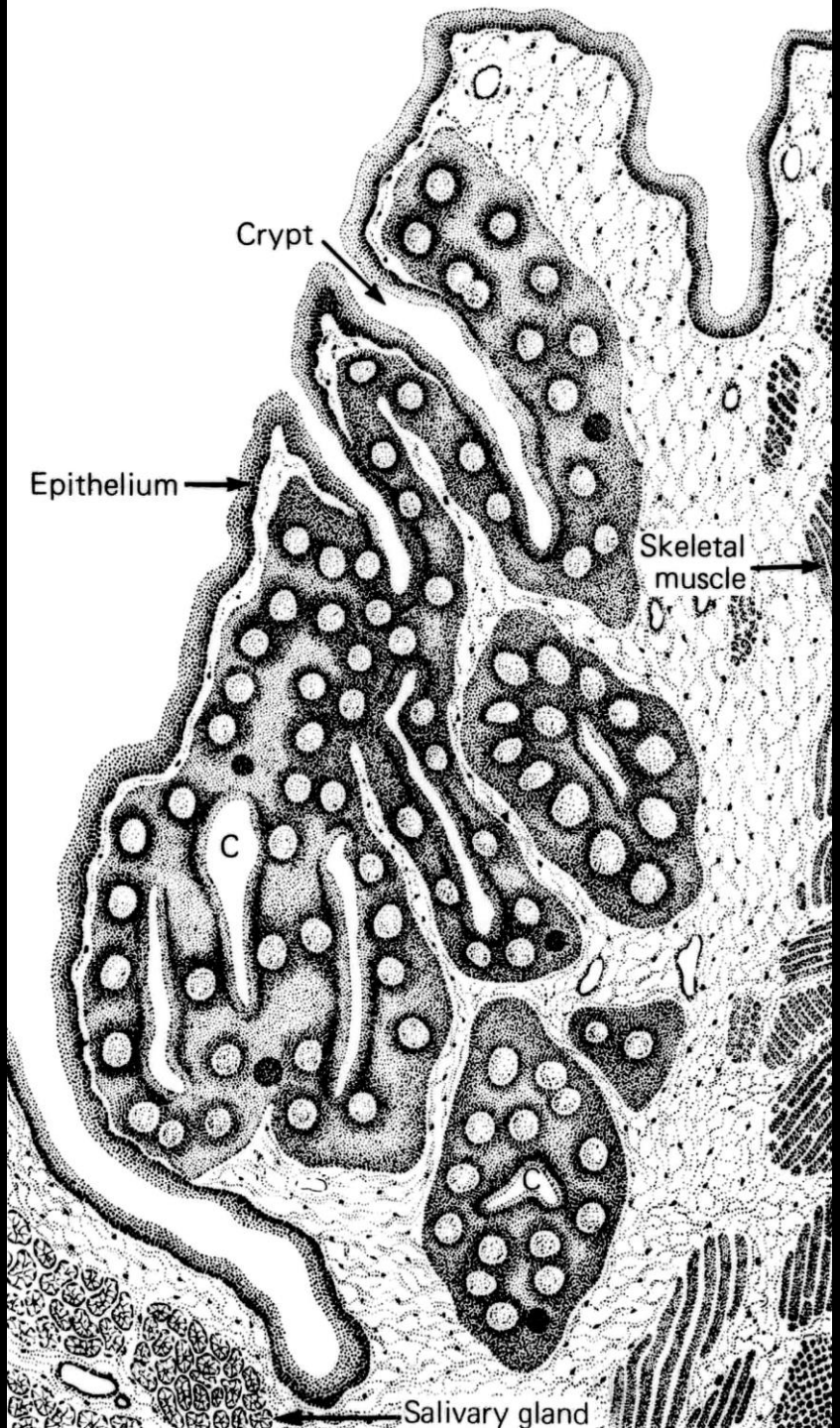

VS
M
RC
N
N
P
P


M
N
stave cells (specialized endothelia)

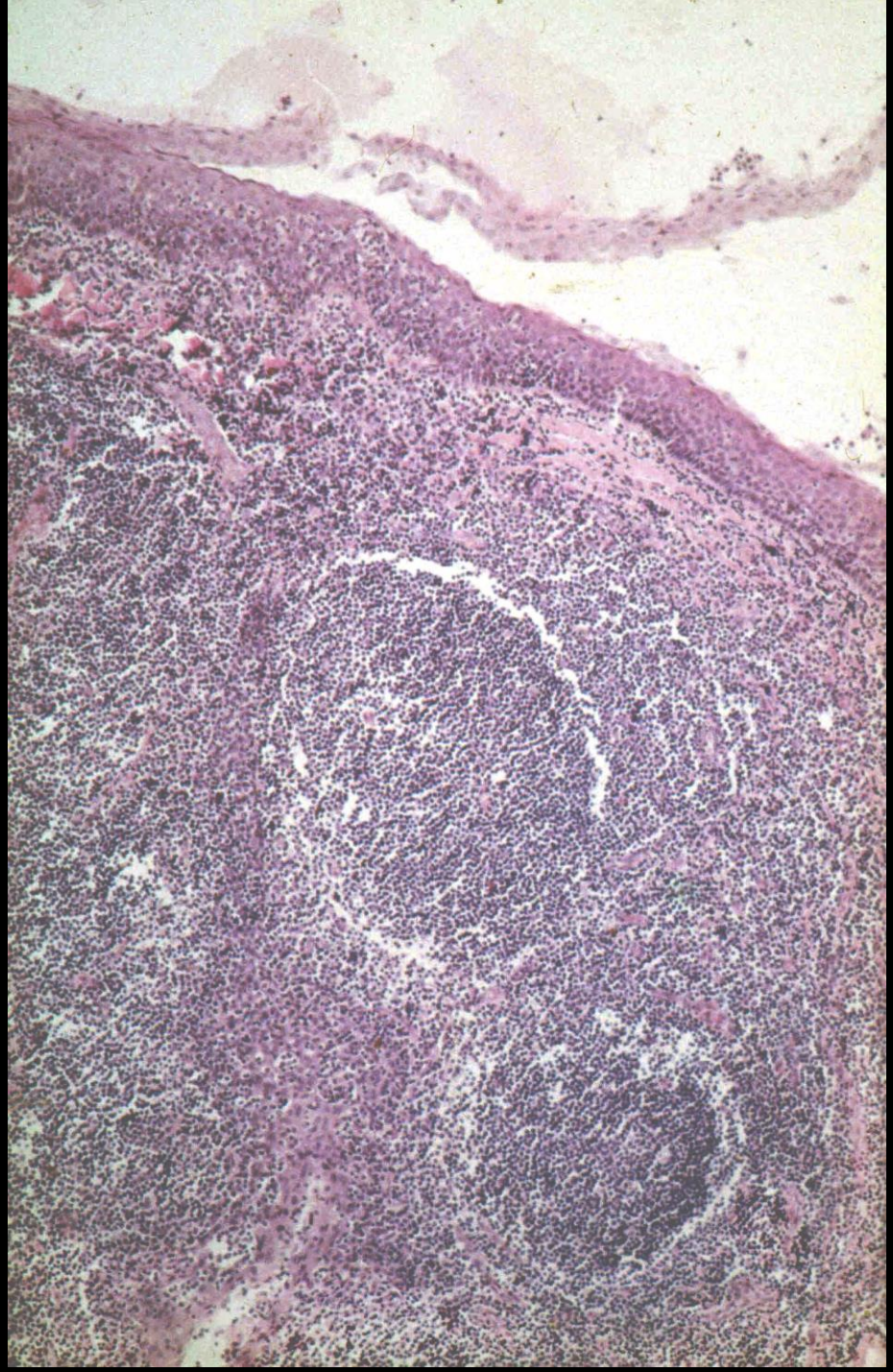

a
Kidney
Dorsal mesogastrium
Spleen
Omental bursa
Stomach
Lesser omentum
Liver
Falciform ligament
b
Pancreas
Lienorenal ligament
Spleen
Gastrolienal ligament
Parietal peritoneum of body wall

Lymphoid tissue incompletely encapsulated and unencapsulated

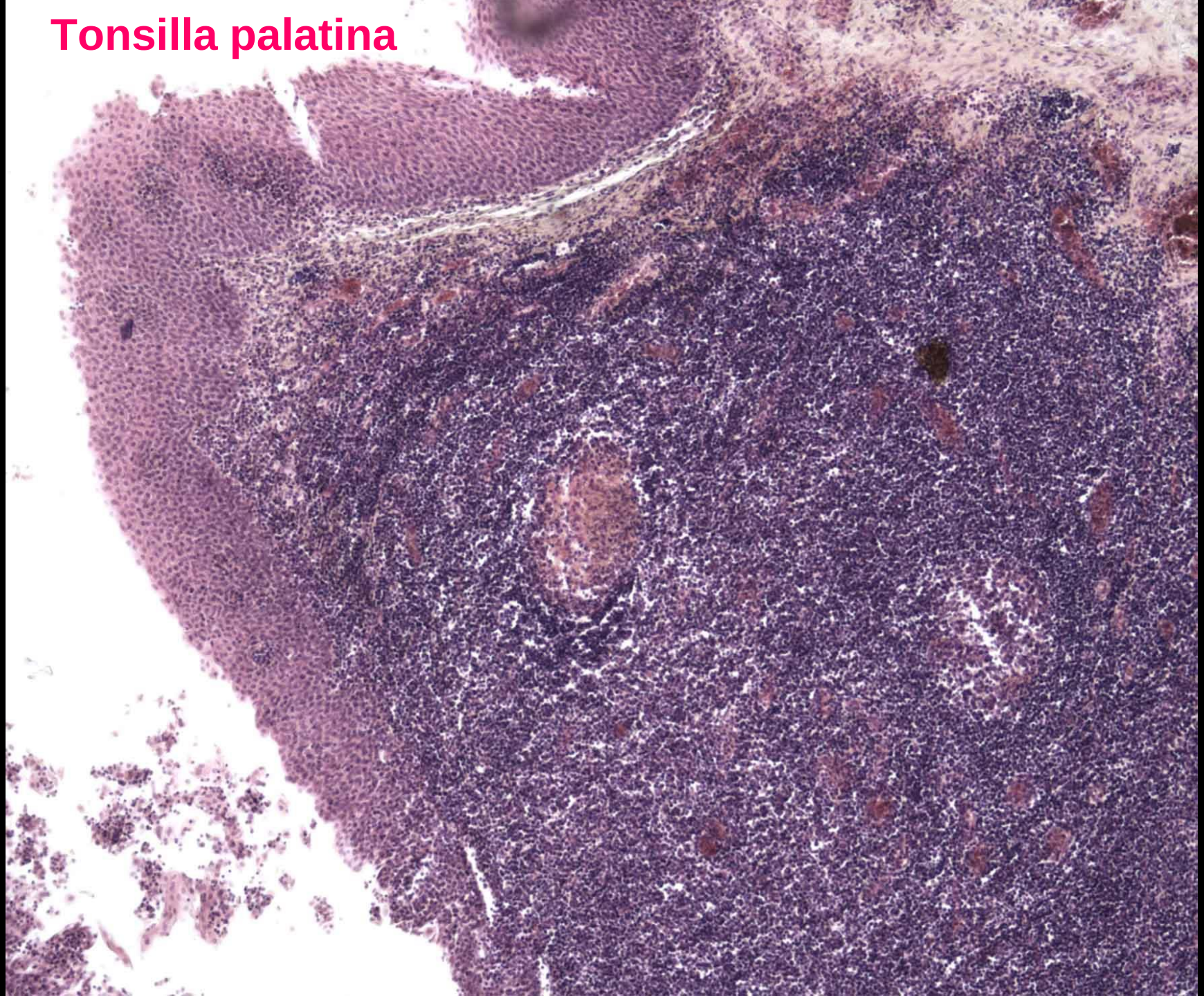
Tonsils

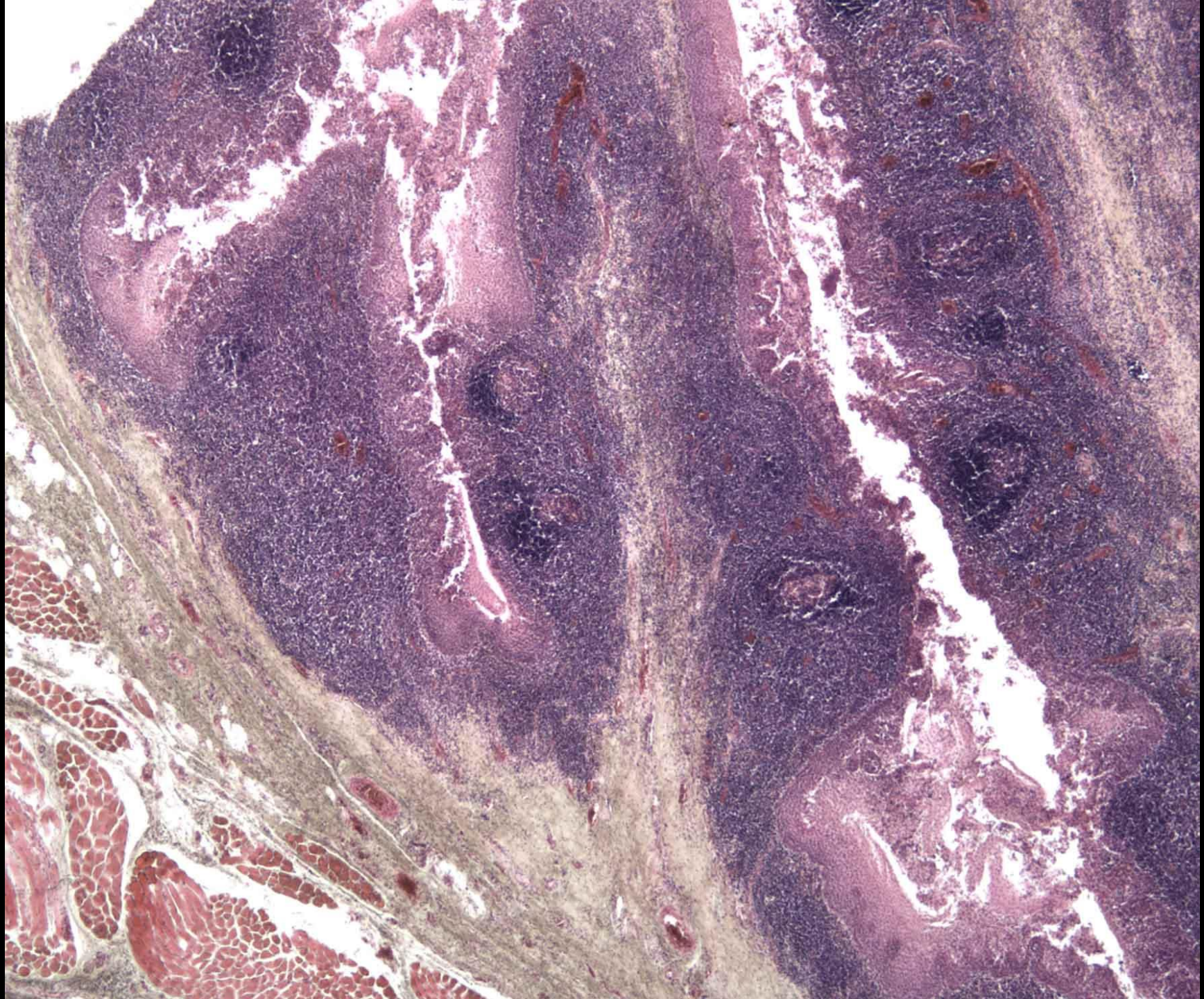


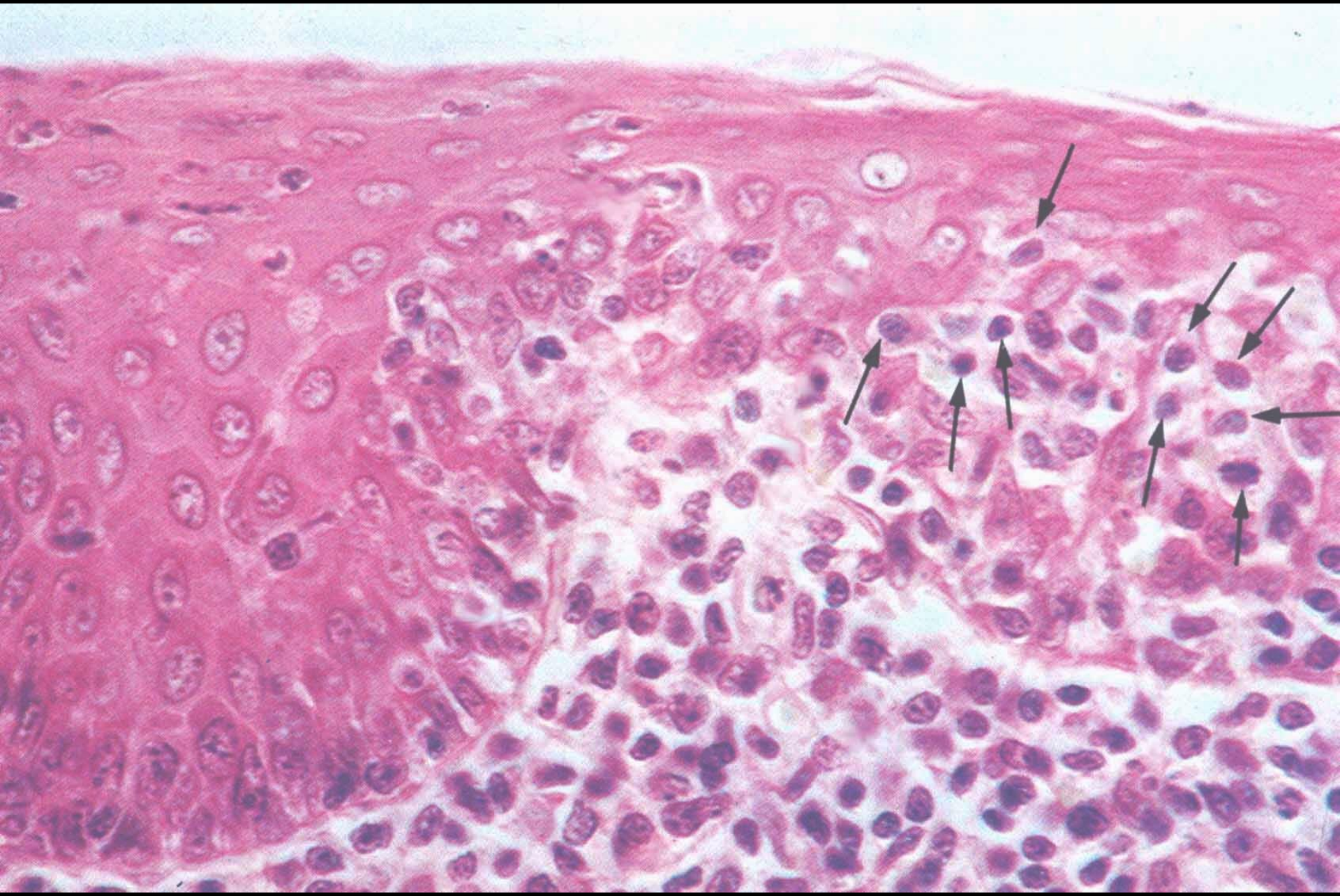
Tonsilla lingualis



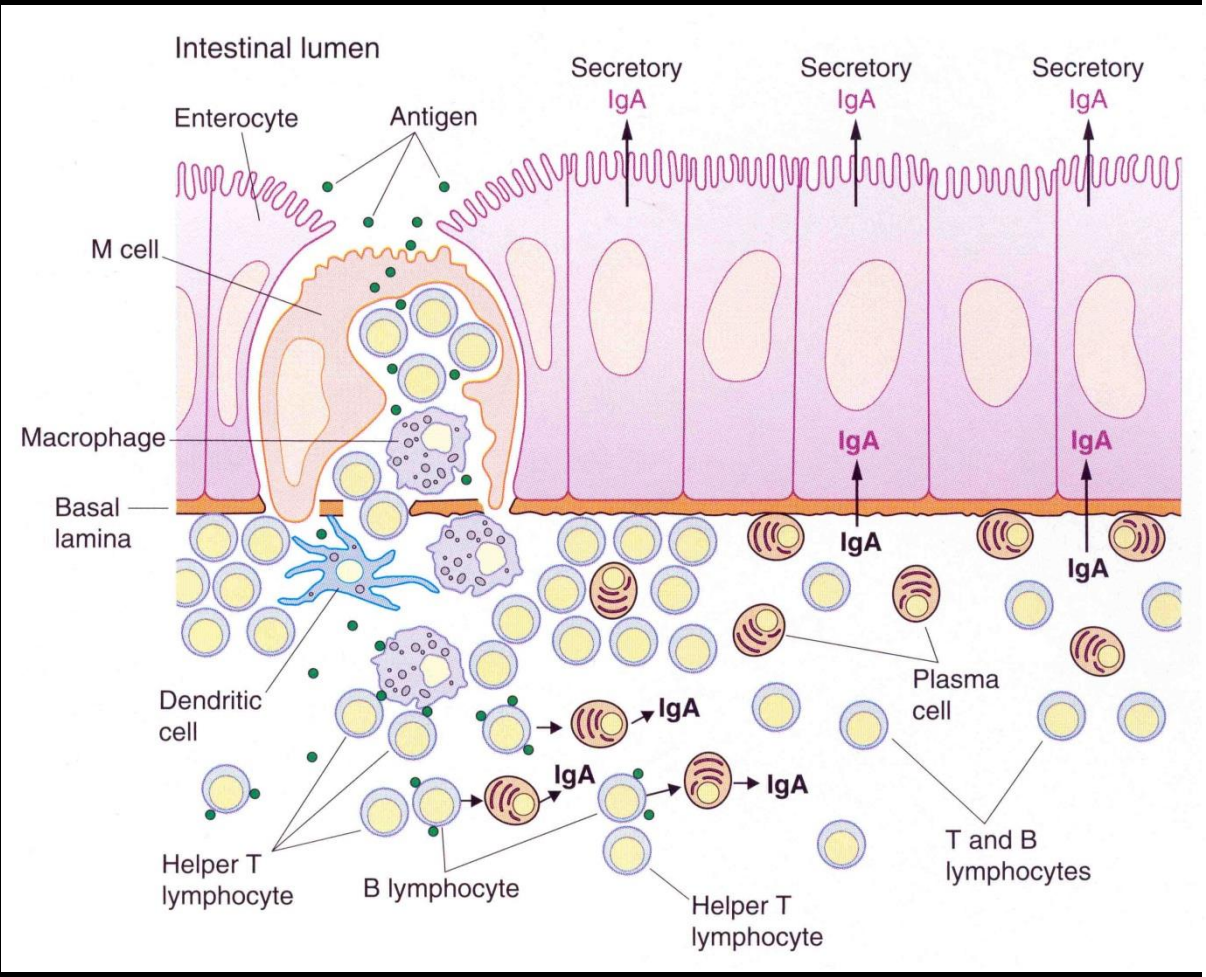
Tonsilla palatina

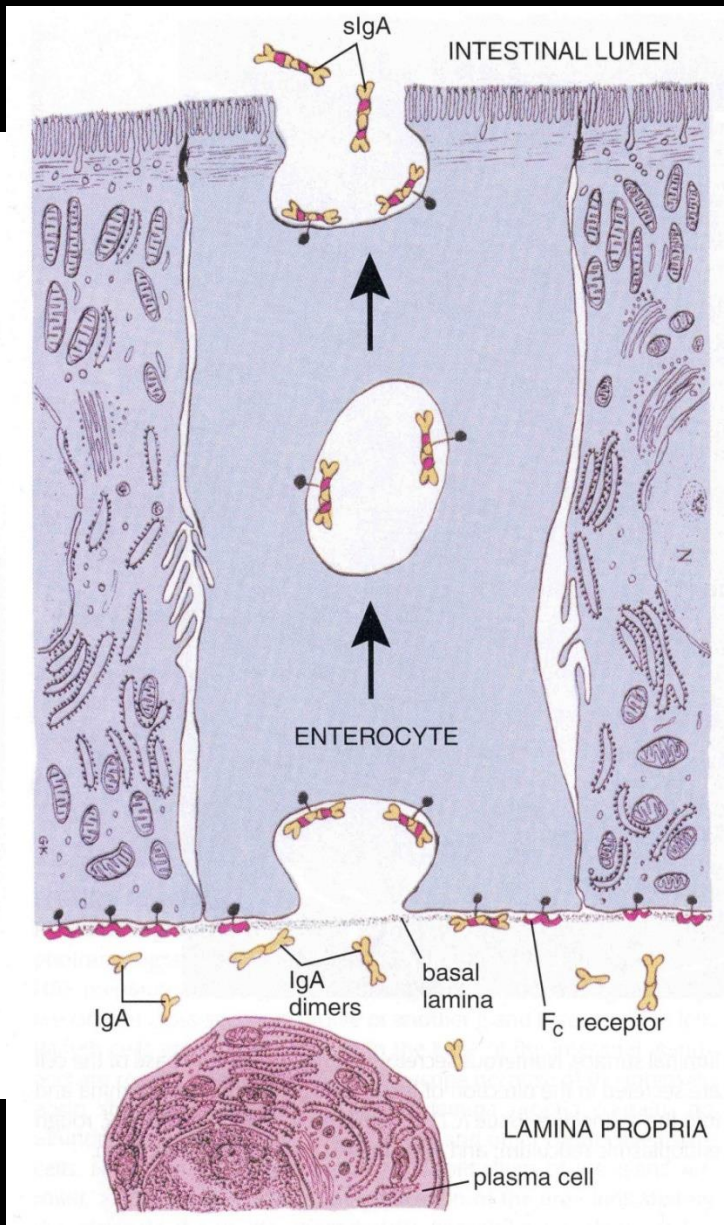


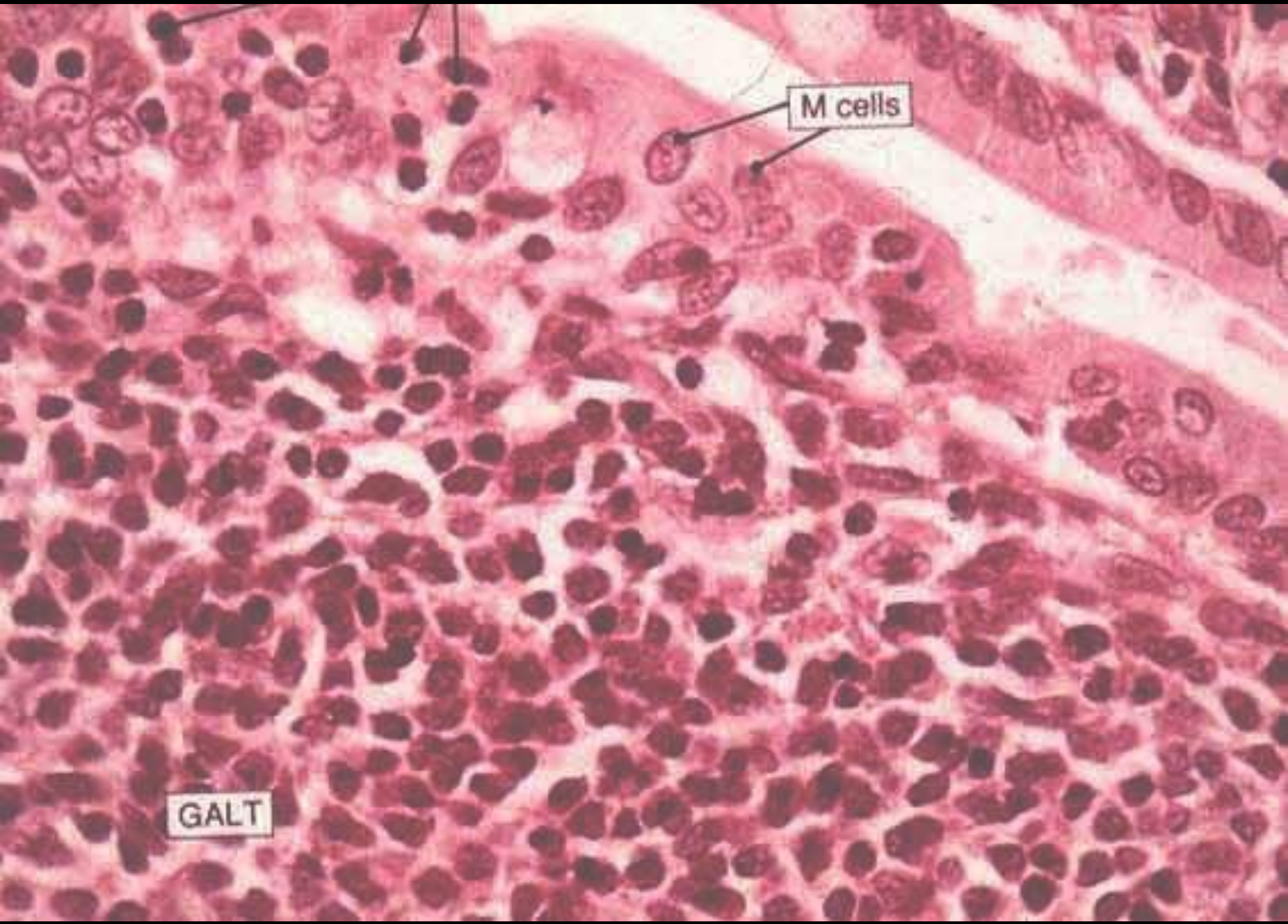


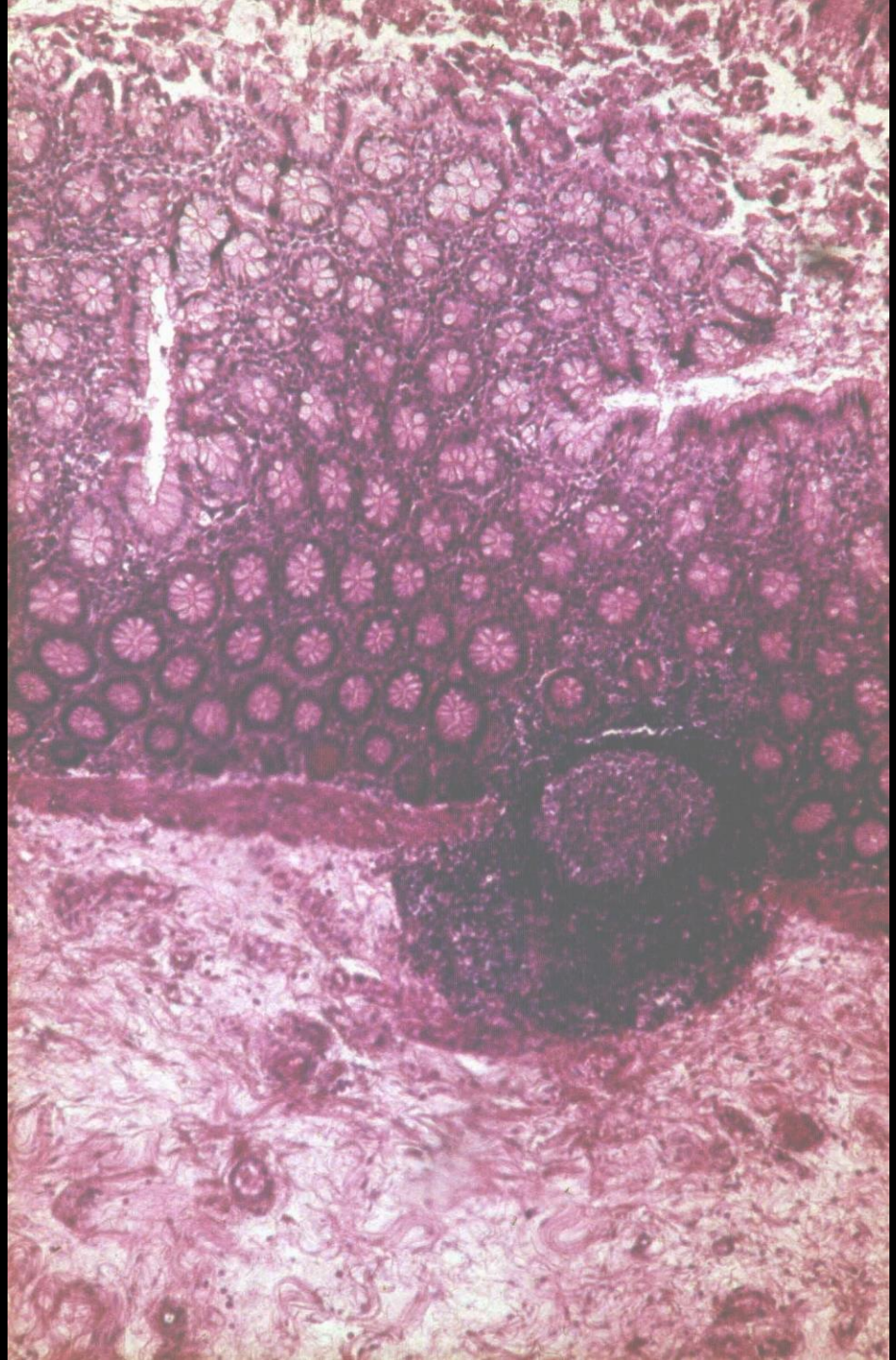


MALT


Intestinal lumen
Enterocyte
Antigen
Secretory IgA
Secretory IgA
Secretory IgA
M cell
Macrophage
Basal lamina
IgA
IgA
IgA
Dendritic cell
Plasma cell
IgA
IgA
IgA
Helper T lymphocyte
B lymphocyte
Helper T lymphocyte
T and B lymphocytes


sIgA
INTESTINAL LUMEN
ENTEROCYTE
IgA
IgA dimers
basal lamina
F_c receptor
LAMINA PROPRIA
plasma cell


M cells
GALT

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