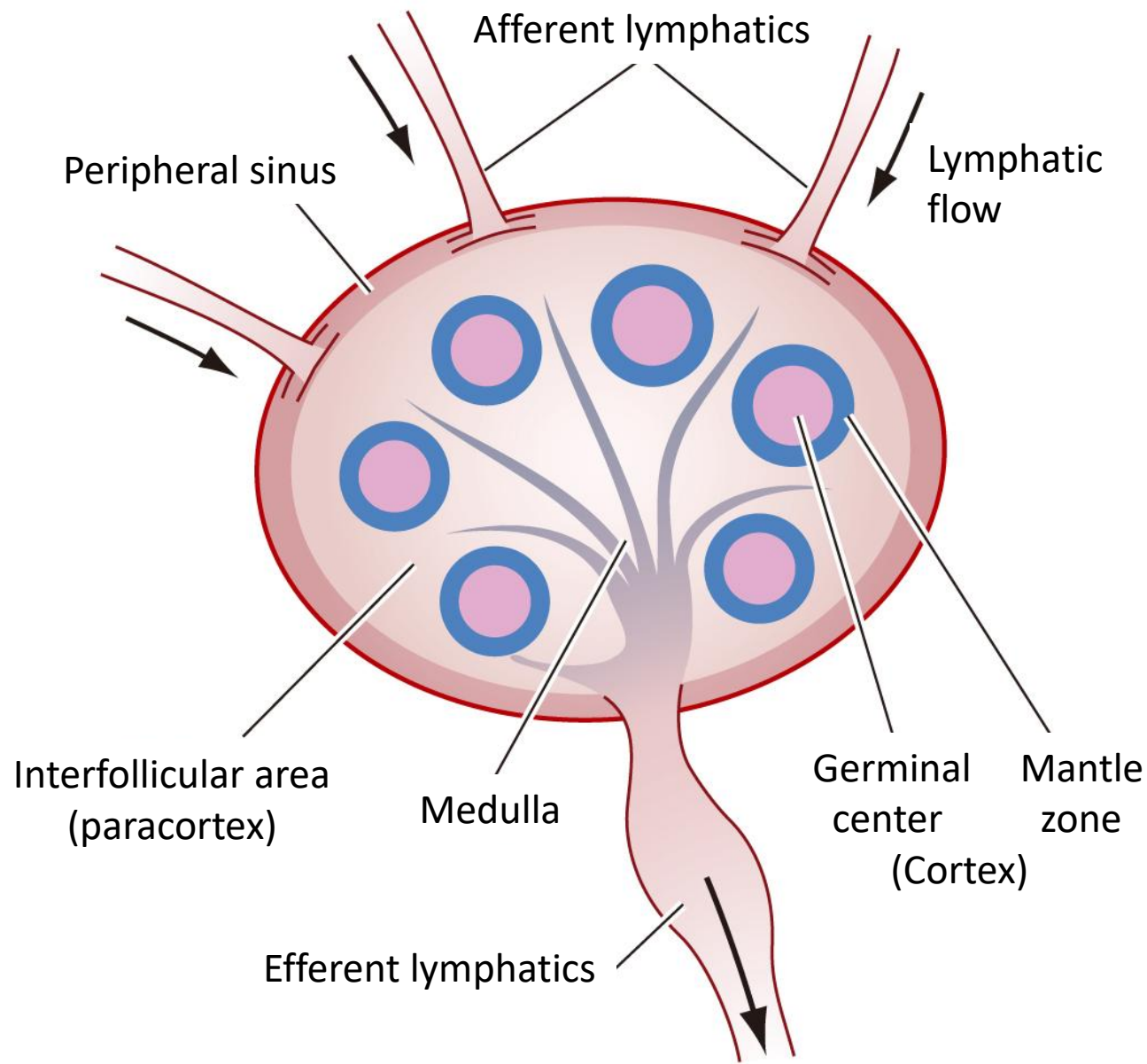


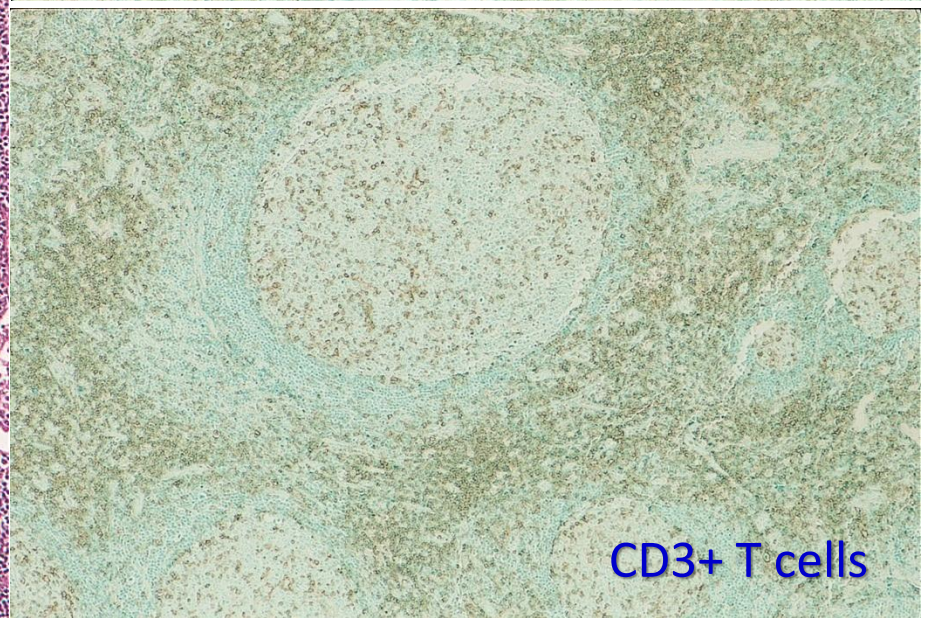
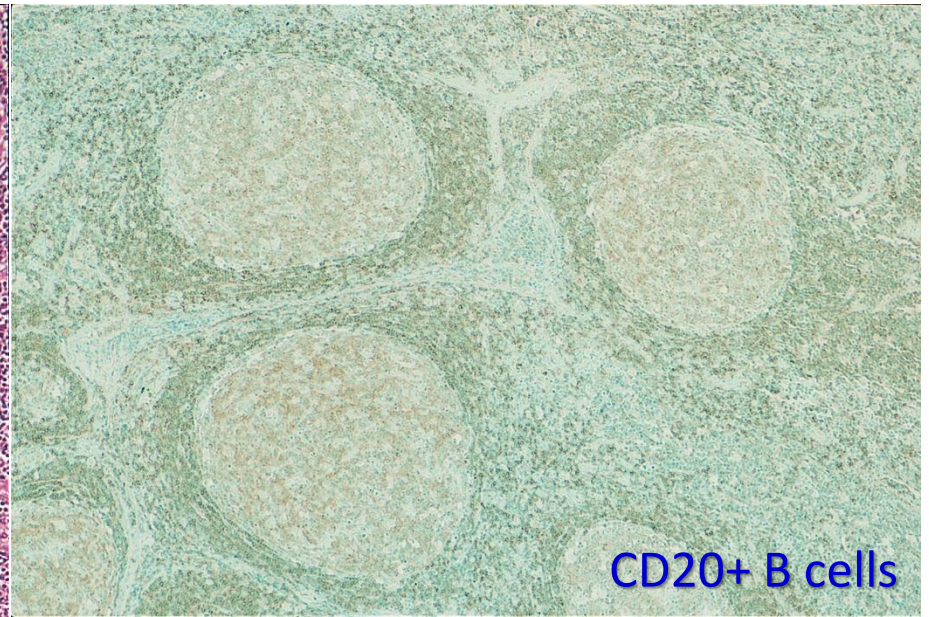
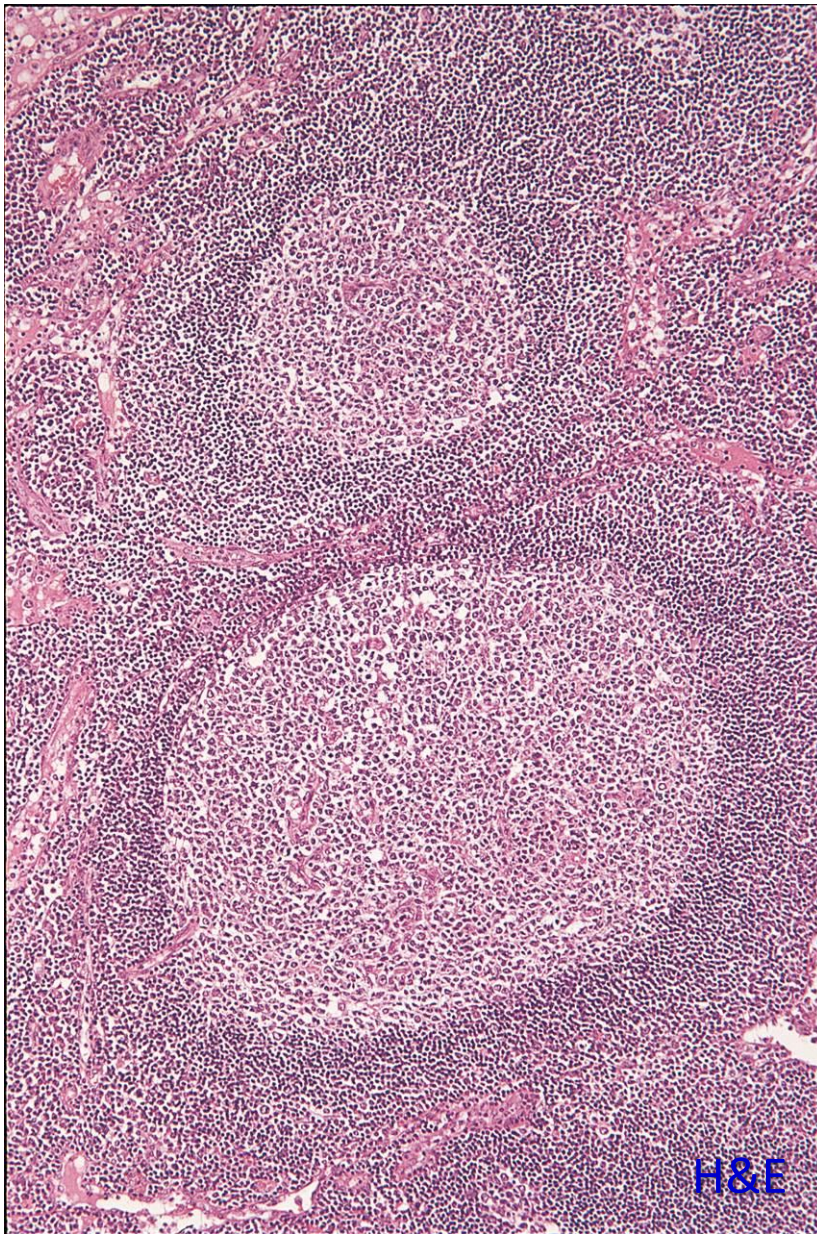
Immune systems and immune cells

Normal immune cells in human lymphoid tissues and intestinal mucosa are presented, including:

- 1) Normal lymph node
- 2) Normal thymus, palatine tonsil and splenic white pulp
- 3) Normal gut-associated lymphoid tissue
- 4) Secretory IgA, plasma cells and intestinal mucosa
- 5) Conventional and old-type of B-cells and T-cells
- 6) Extrathymic T-cells and graft-versus-host disease
- 7) Extrathymic T-cells and apoptosis in the intestinal mucosa



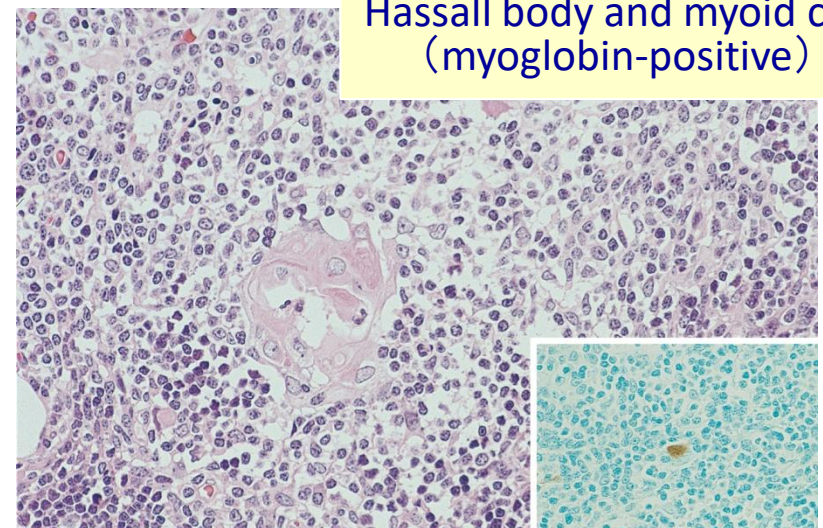
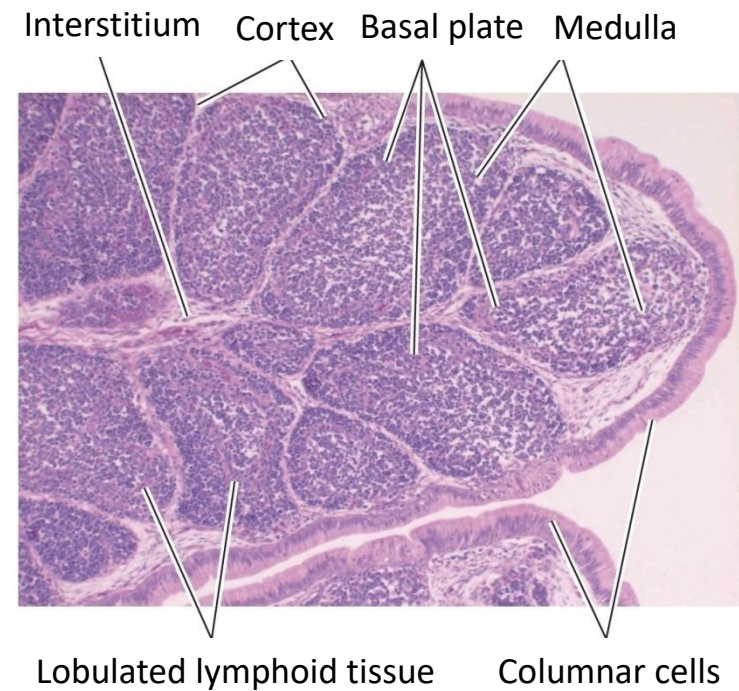
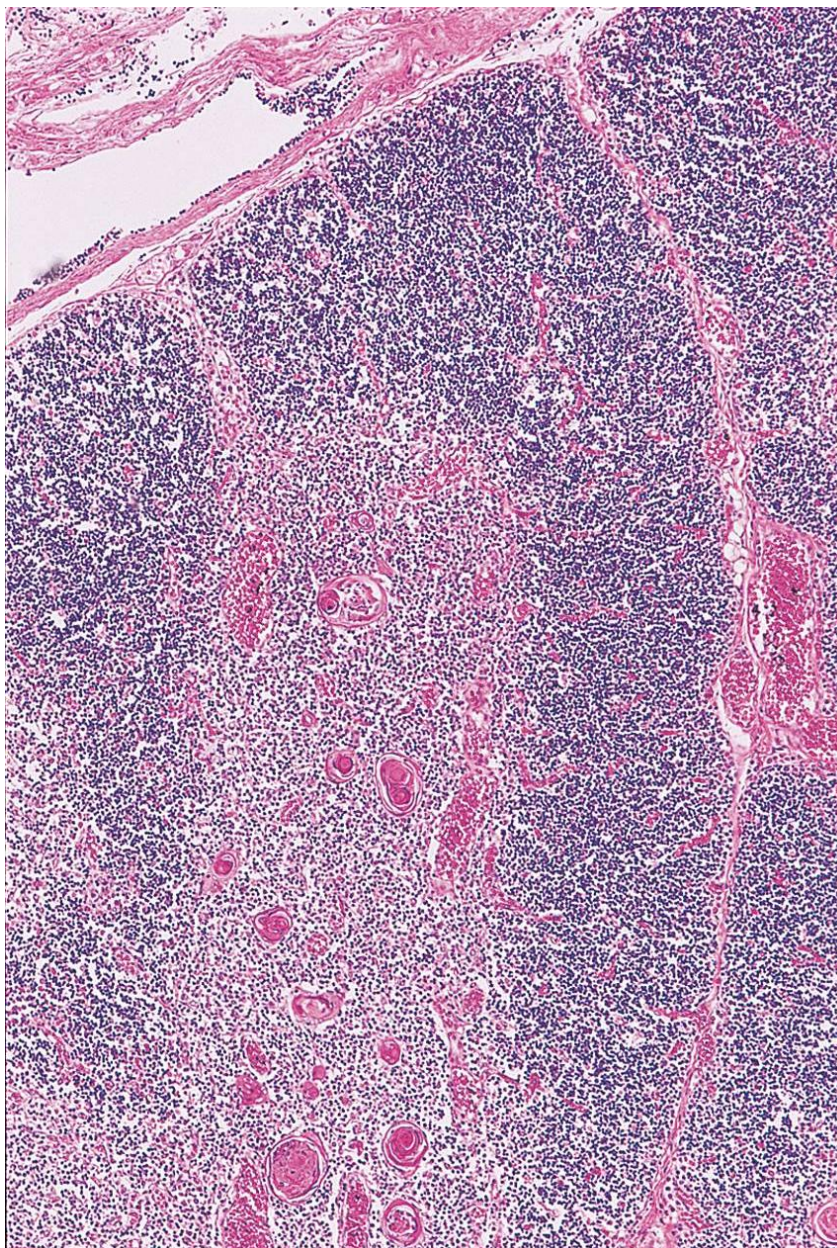
Normal structure of the lymph node (scheme)



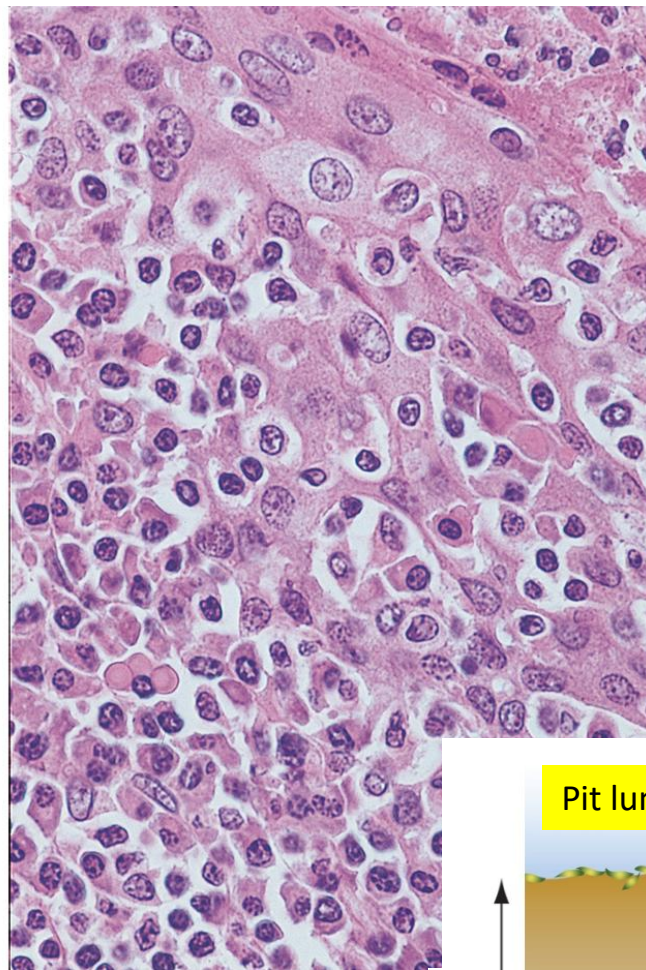
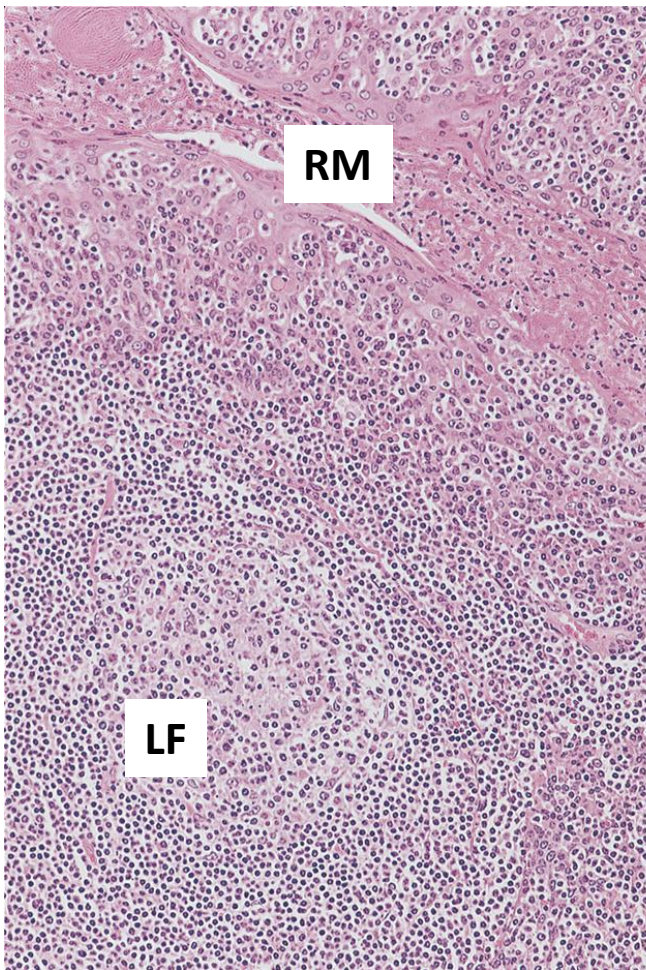
Germinal centers and interfollicular zone (paracortex) of the lymph node

Structure of the lymph node and cell distribution

Site	Main cells	Associated cells
Cortex		
Germinal center	B-blasts	CD4 ⁺ T-cells, FDC cells
Mantle zone	Memory B-cells	
Primary follicle	Virgin B-cells	
(Marginal zone)	Monocytoid B-cells	
Paracortex		
Interfollicular area	T-cells (CD8 ⁺ >CD4 ⁺)	Langerhans cells
Medulla	Plasma cells	T-cells
Sinus	Macrophages	sinus endothelial cells

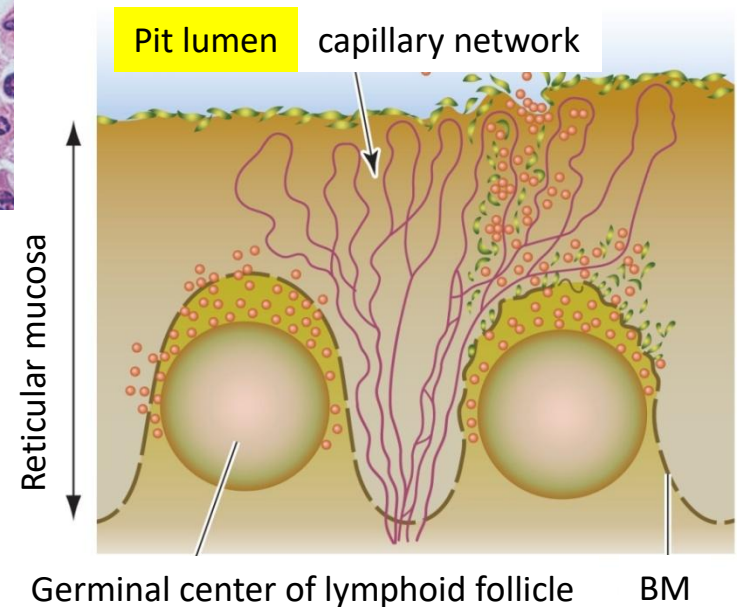


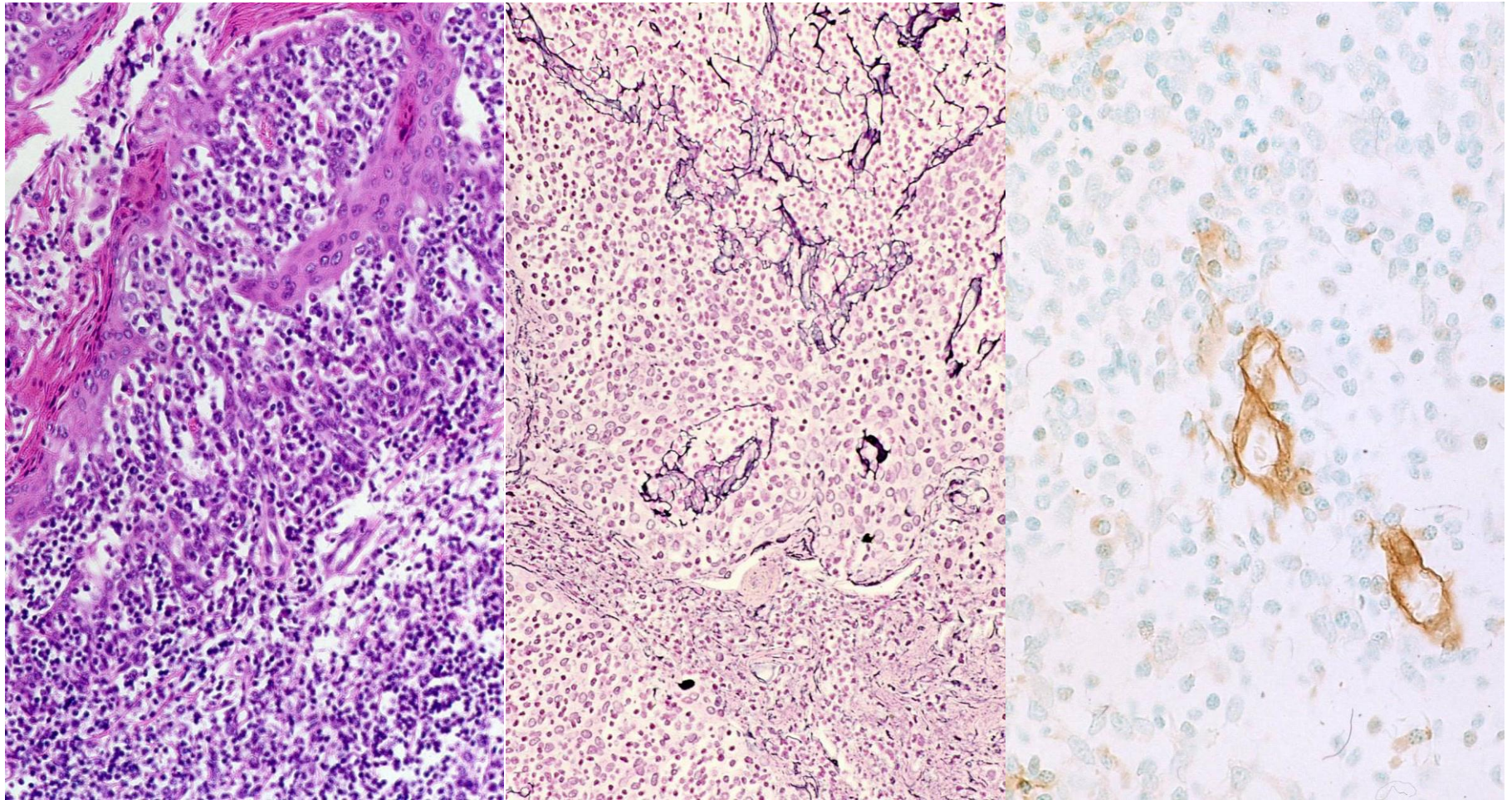
Resemblance of human thymus (left) and Fabricius' sinus (chicken, right top)



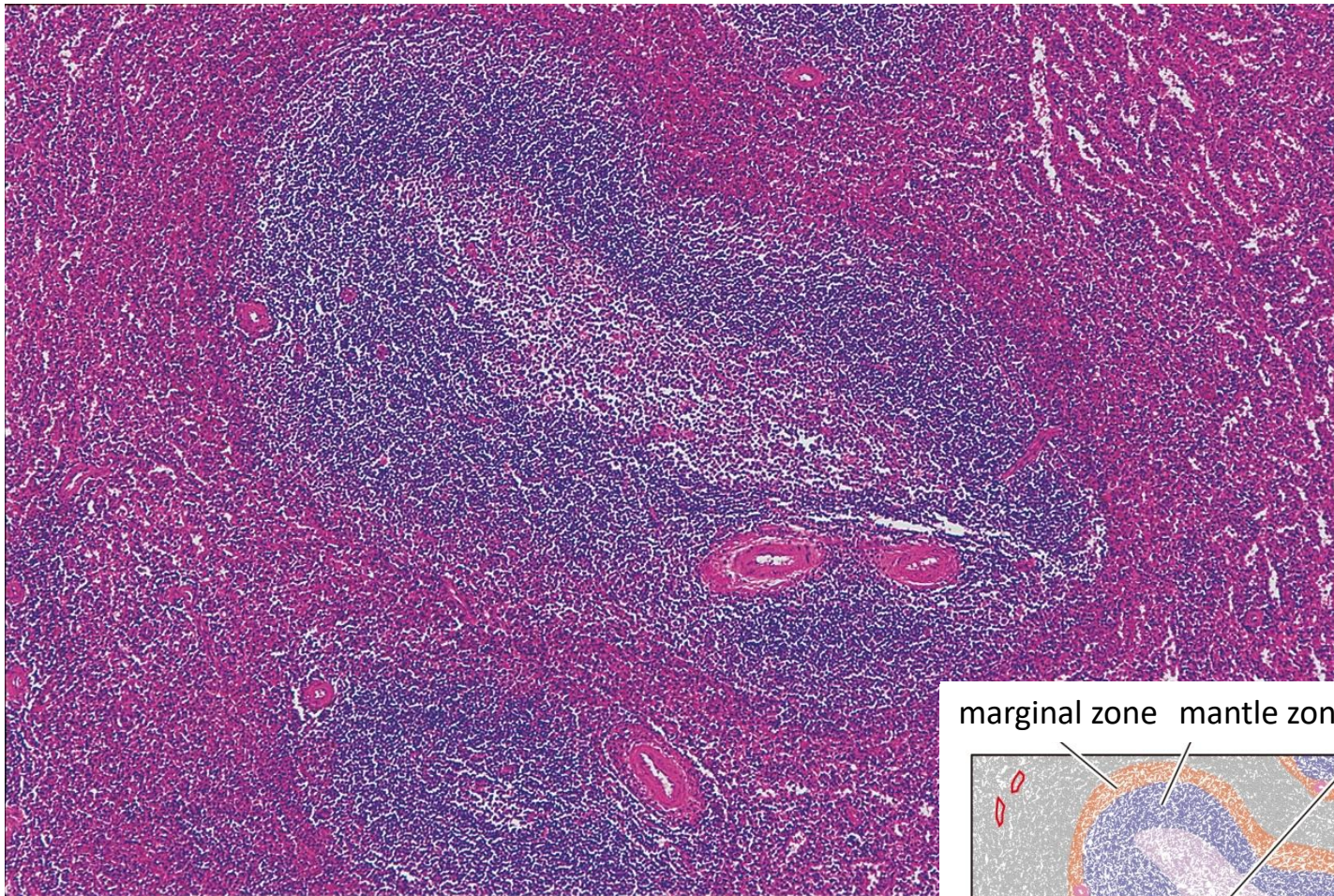
Reticular mucosa and lymphoid follicle (LF) of the palatine tonsil (H&E)

The reticular mucosa (RM) contains capillary networks and numbers of plasma cells.



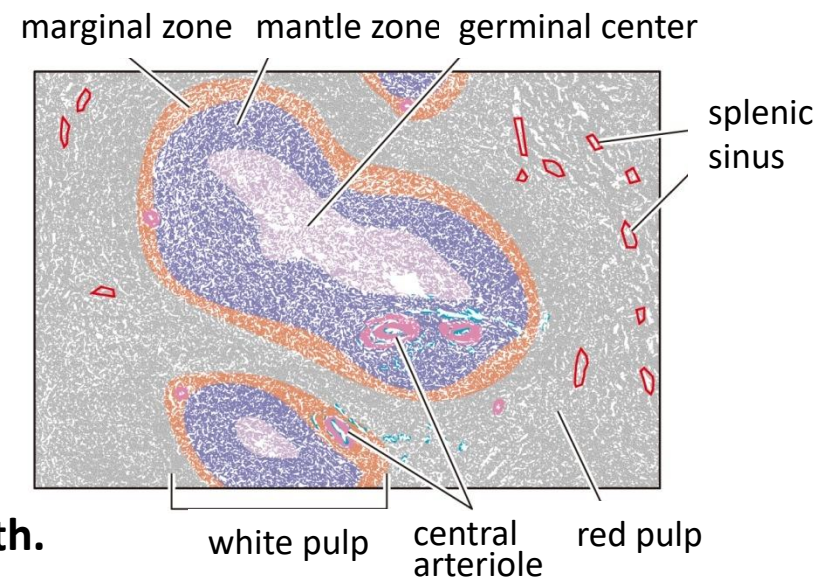


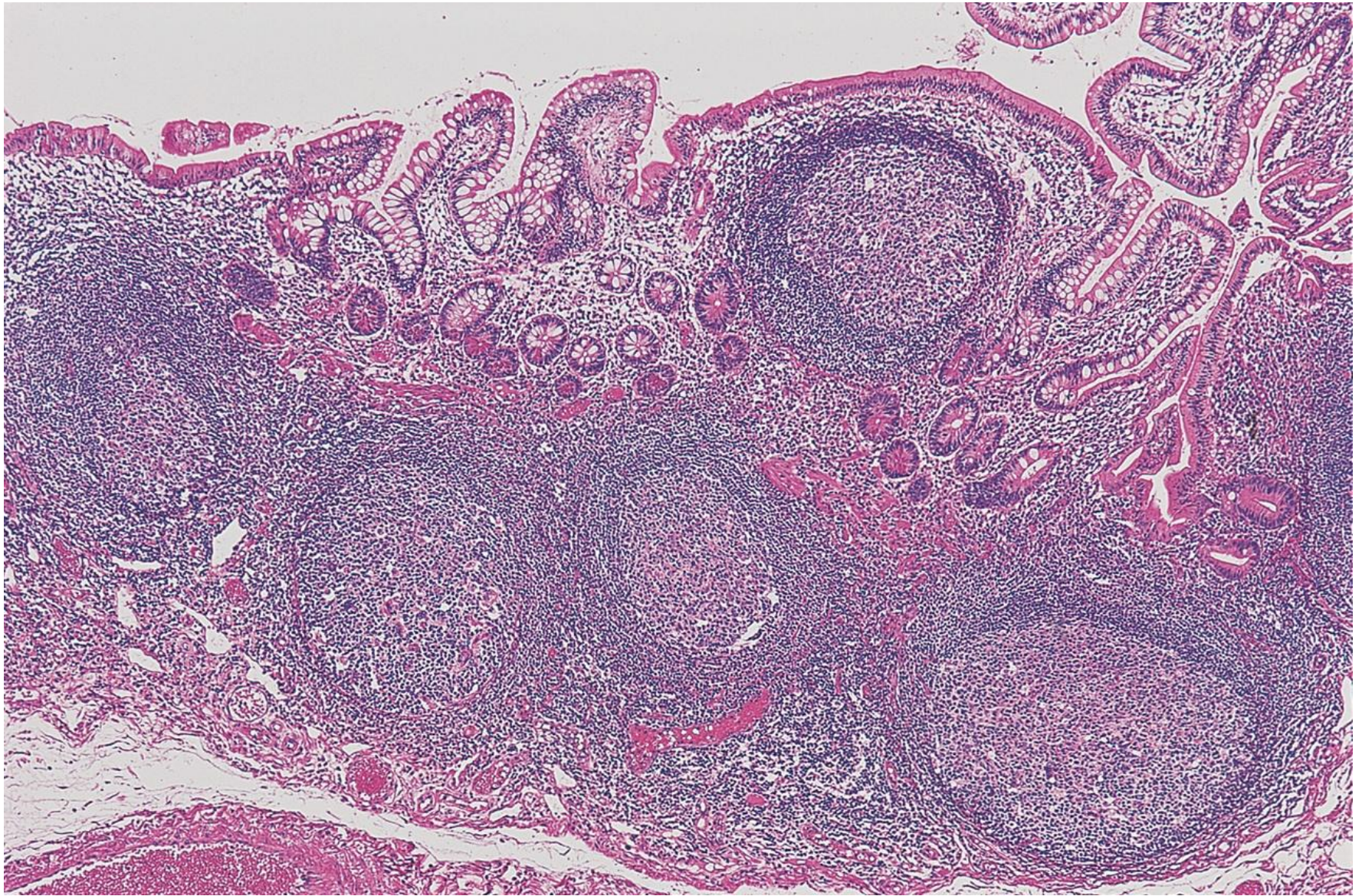
Reticular mucosa of the palatine tonsil. Numbers of plasma cells are distributed within the mucosa (left: H&E). It is of note that capillary vessels are seen in the mucosa (center: silver impregnation, right: immunostaining for type 4 collagen).



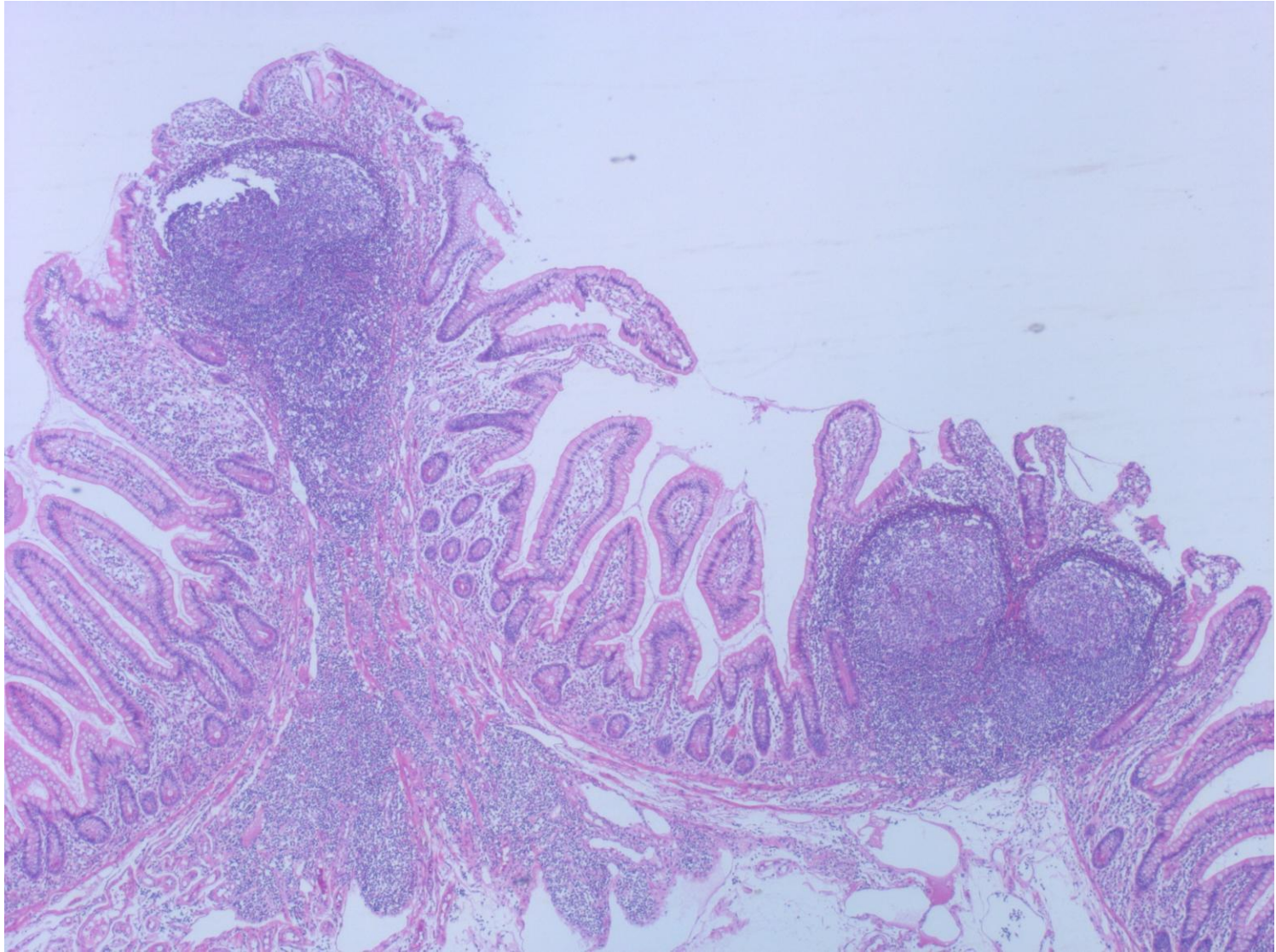
Splenic white pulp and red pulp (H&E)
 The white pulp contains the marginal zone

Splenic T-cells accumulate the periarteriolar sheath.

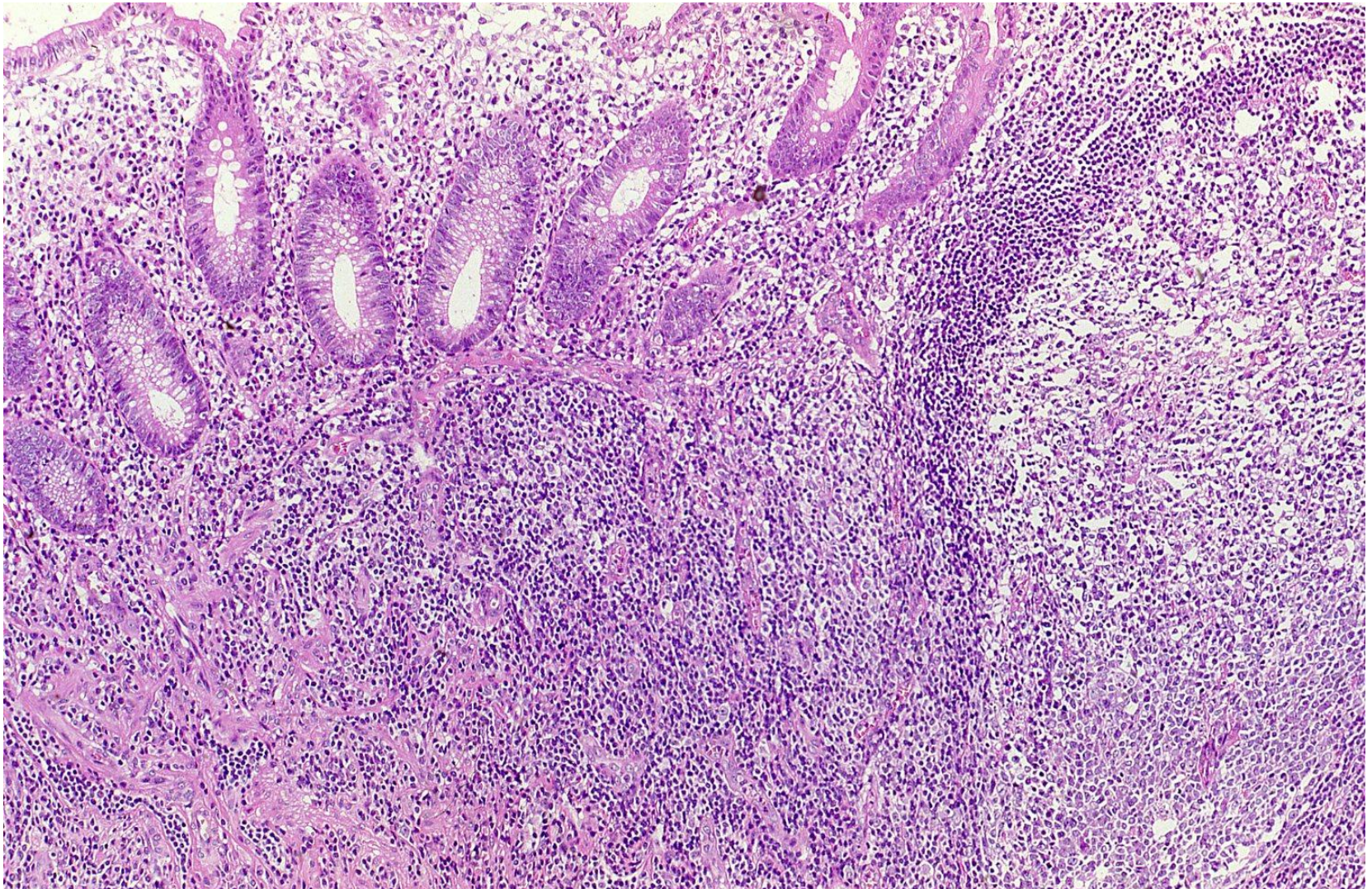




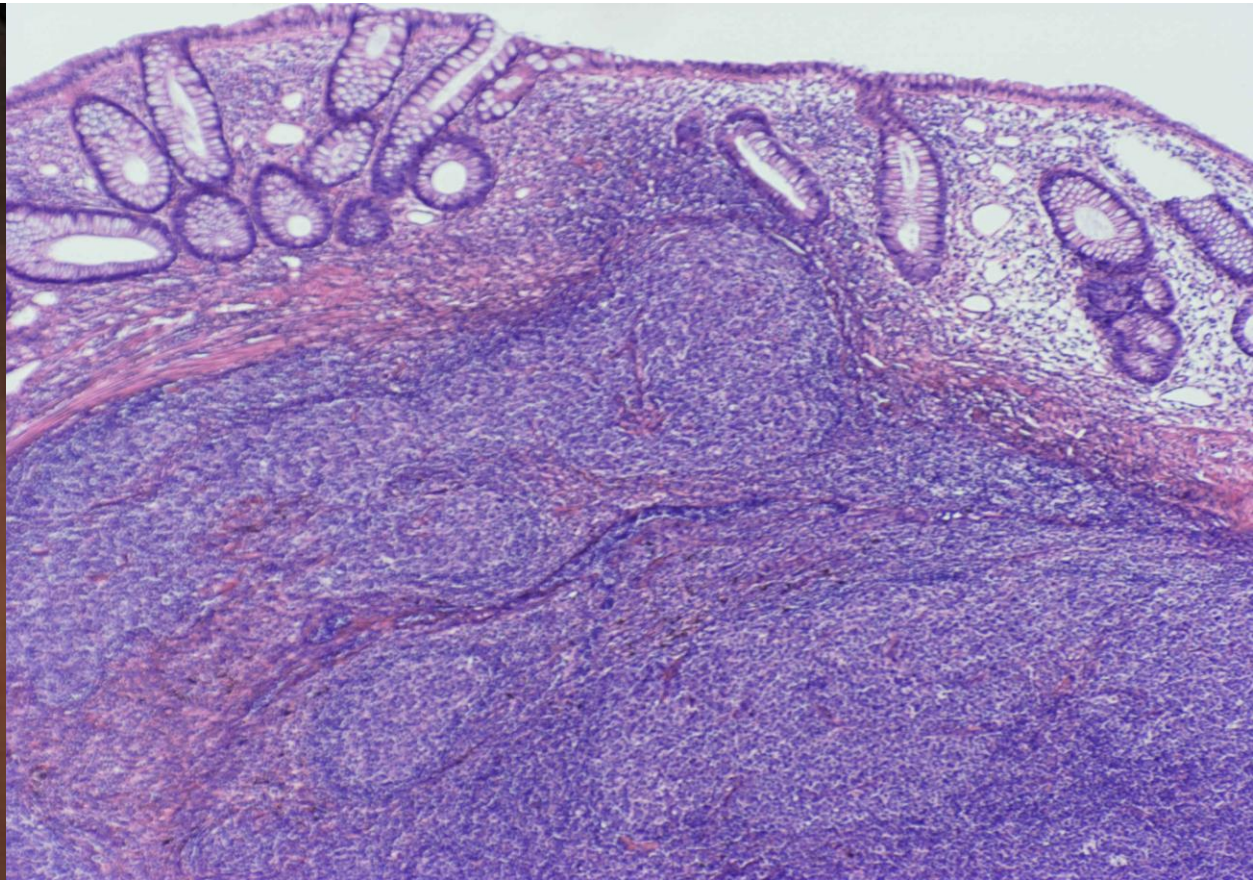
Peyer patch in the terminal ileum with well-developed lymphoid follicles (H&E)



Solitary lymphoid nodules of the gut mucosa. Normal ileal mucosa contains isolated lymphoid tissue with germinal center formation (H&E).



Normal vermiform appendix contains well developed lymphoid follicles with enlarged germinal centers (H&E).



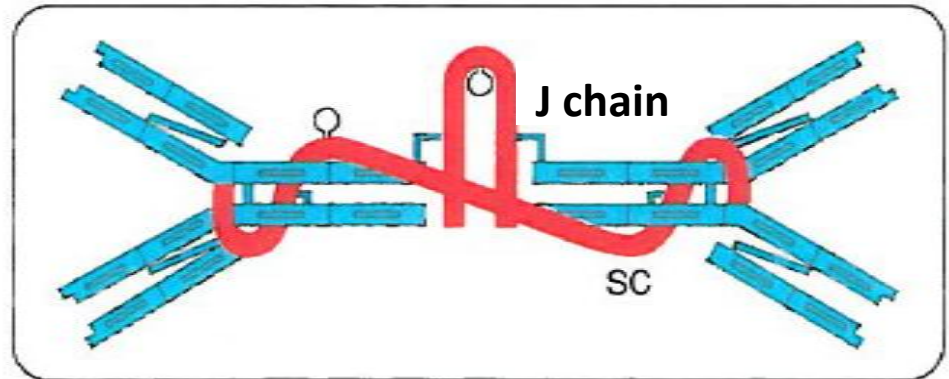
“Rectal tonsil” (left: endoscopic finding, right: H&E). Polypoid nodules in the rectal mucosa consist of clusters of lymphoid tissue, somewhat resembling Fabricius sinus of the bird’s cloaca

Mucosal immunity: protecting invasion of pathogens at the mucosal surface by secretory IgA

Secretory IgA = dimeric IgA + secretory component (produced by mucosal columnar cells)

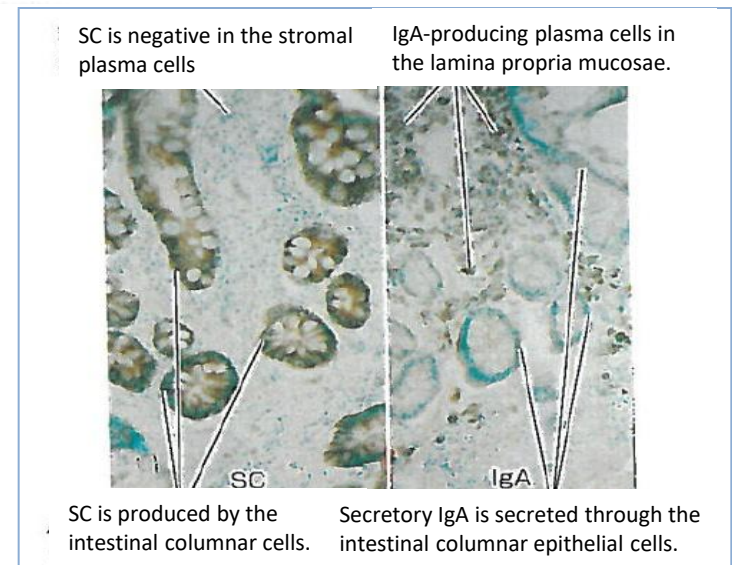
Enterohepatic circulation of IgA:

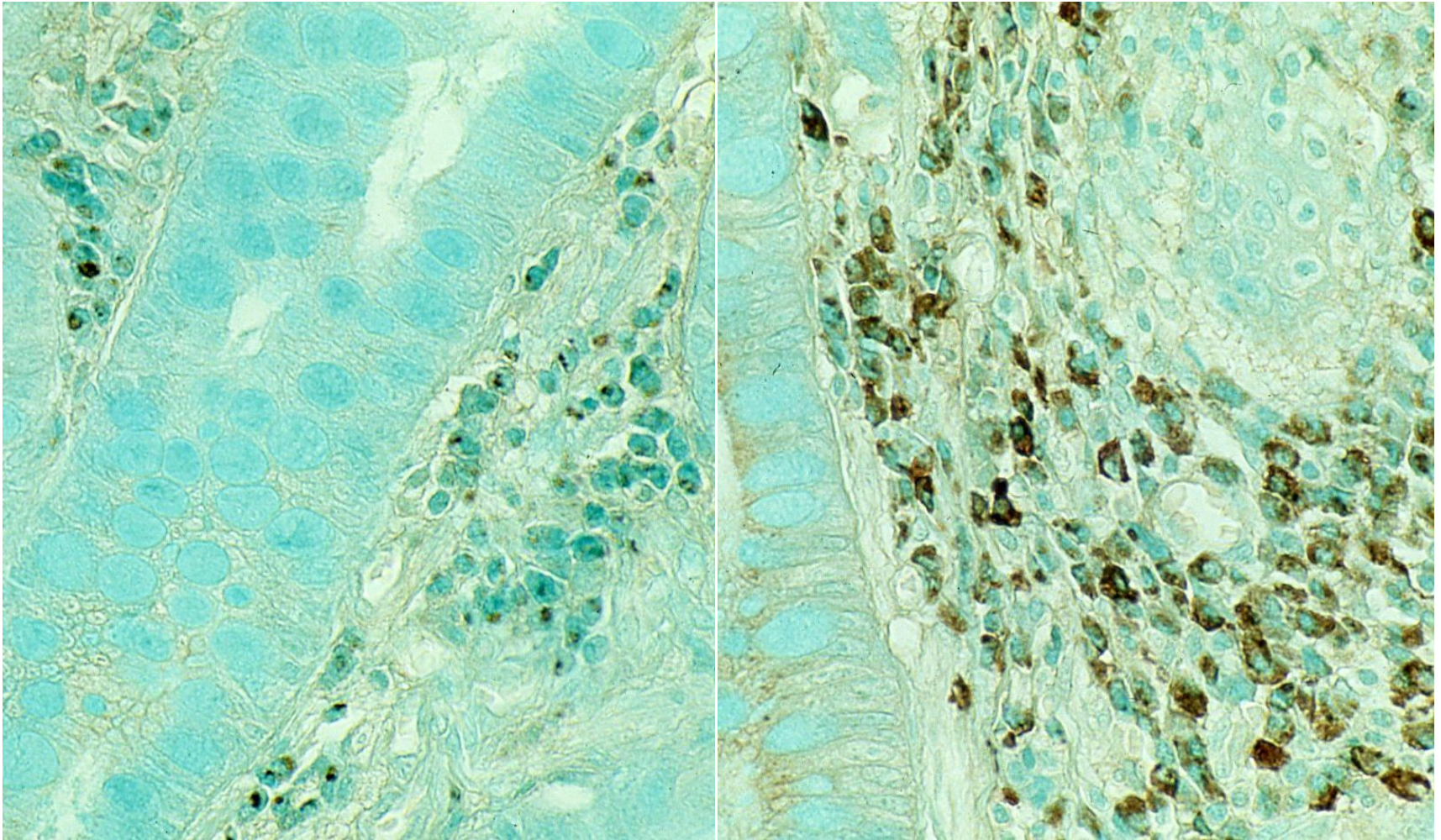
Dimeric IgA produced in the intestinal mucosa enters to the portal vein, and combines with secretory component produced by the bile duct epithelial cells to secrete into the bile.



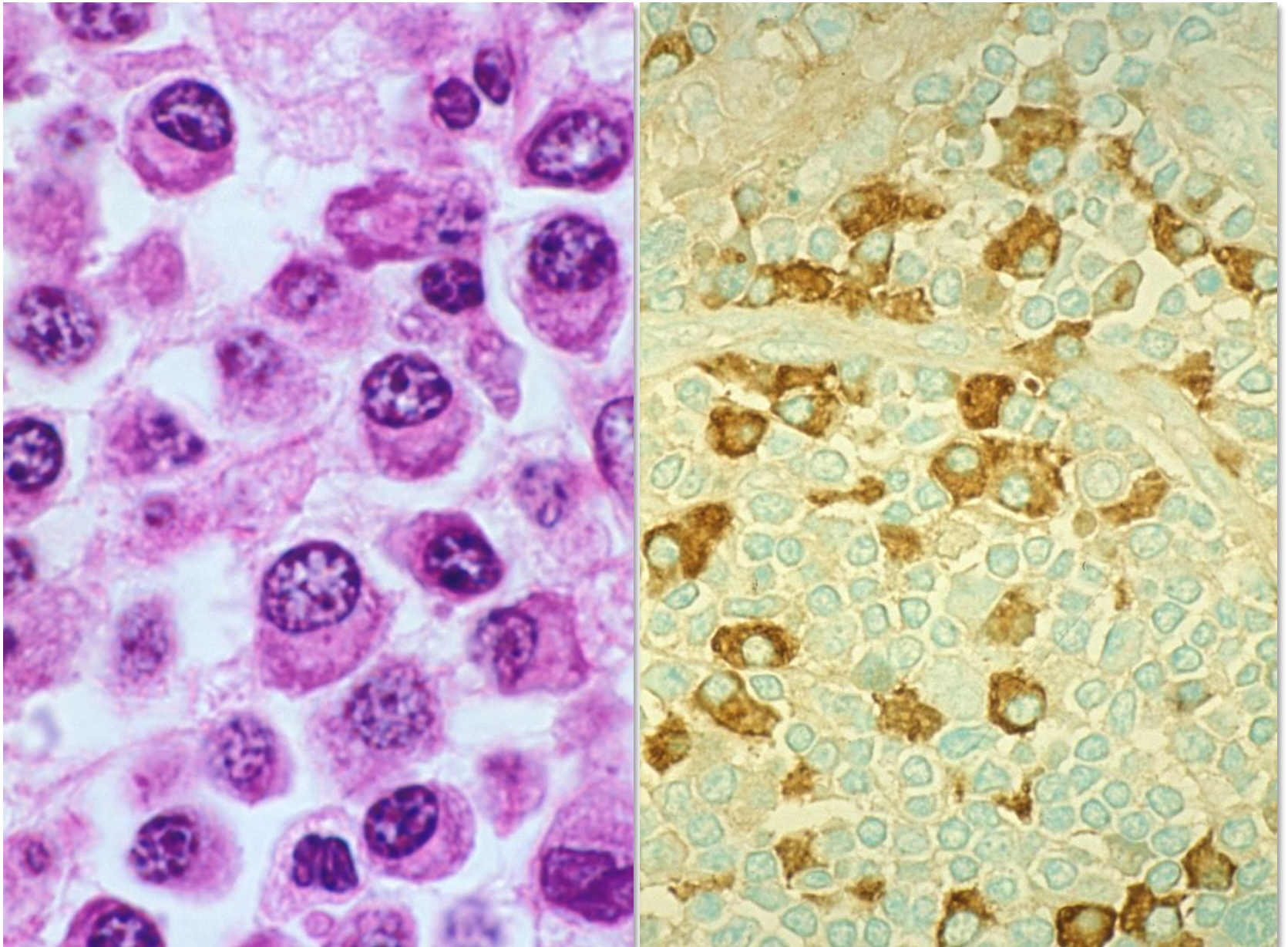
Features of IgA nephropathy

- 1) Intestinal symptoms (such as diarrhea) precede.
- 2) Dimeric IgA deposits to the glomeruli
- 3) The renal lesion in Henoch-Schoenlein purpura nephritis is identical to IgA nephropathy. IgA deposition is also seen in the skin purpura.
- 4) Hepatic glomerulosclerosis reveals deposition of dimeric IgA in the glomeruli.

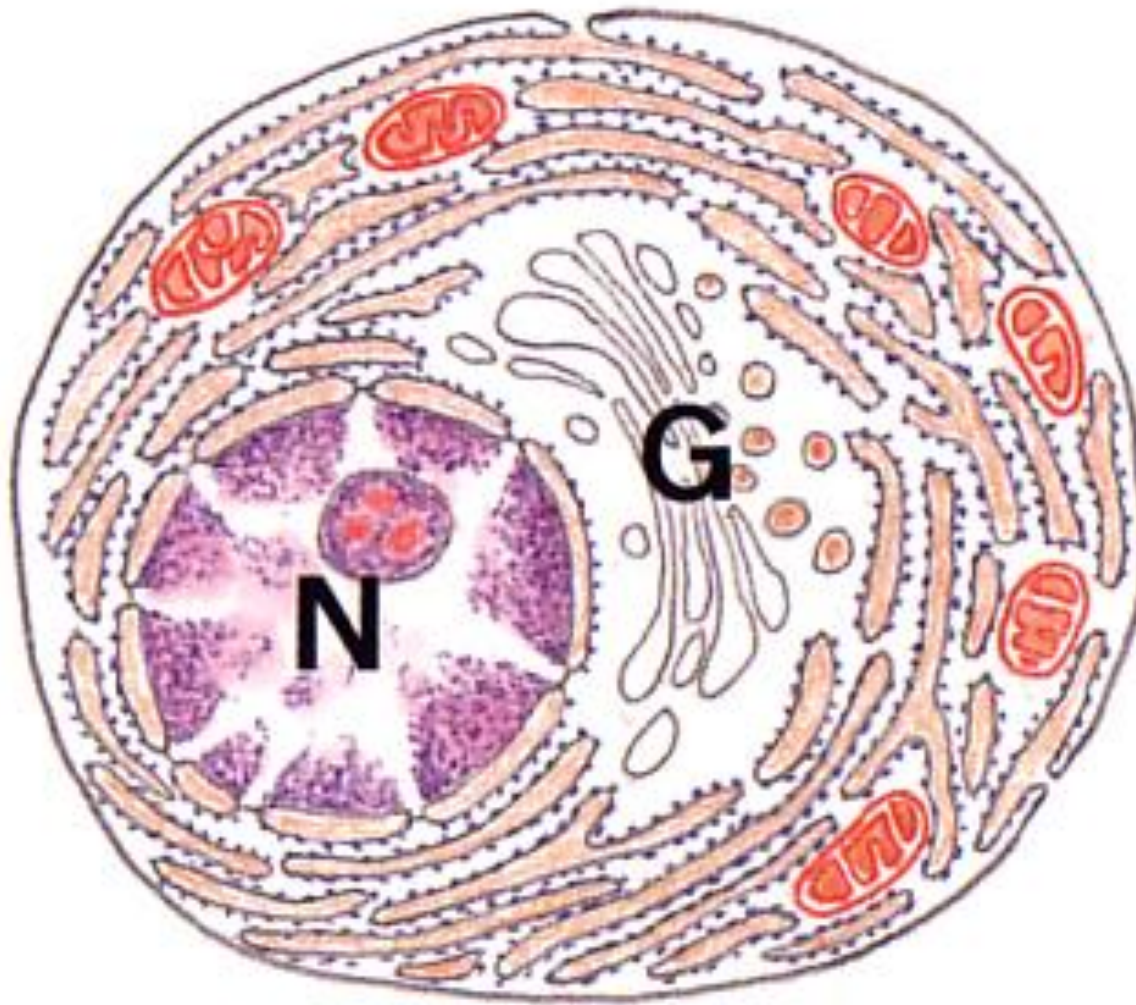




Production of dimeric IgA in the small intestinal mucosa. The plasma cells located in the lamina propria mucosae are immunoreactive for both IgA (left) and J-chain (right). The dimeric IgA contains J-chain within the molecules.



Plasma cells and IgG production in granulation tissue (H&E and IgG immunostaining)



Scheme of plasma cell (G: Golgi apparatus, N: nucleus)

Immunoglobulin is produced in the very well-developed rough endoplasmic reticula (rER).

“Immunity” started with the recognition of self!

Two types of antigens

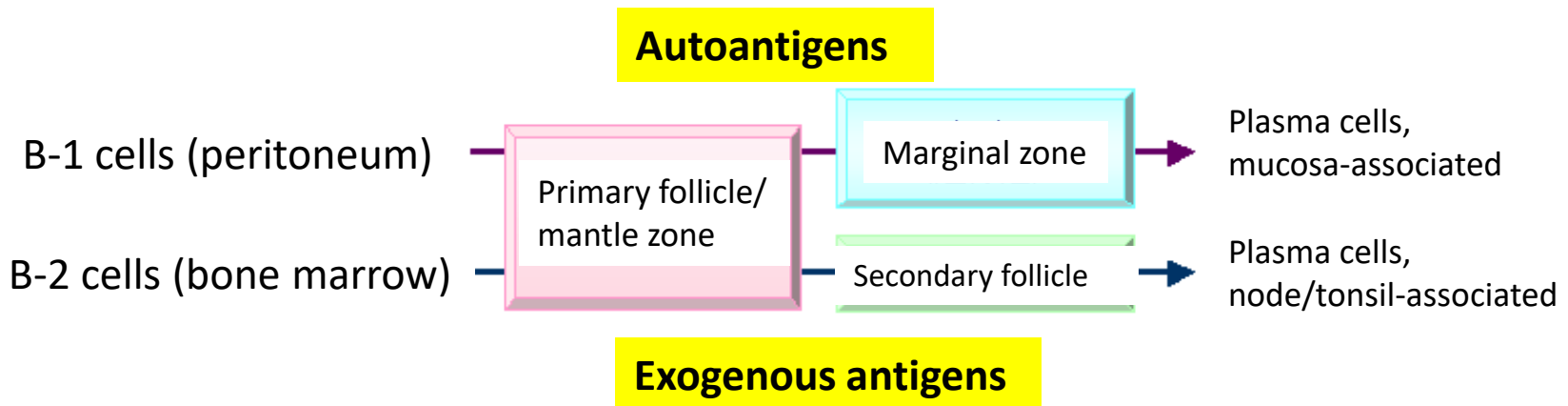
- ① Exogenous antigens: defense ② Endogenous (auto)antigens: homeostasis

Two types of T-cells

- ① Thymus-educated T-cells ② Extrathymic T-cells (old system T-cells)
(inducing apoptosis)

Two types of B-cells

- ① Germinal center-educated B-cells ② B-1 cells (old system B-cells)
(reactive with enterobacteria and blood groups)



Extrathymic T-cells and GVHD (graft versus host disease)

Distribution of extrathymic T-cells

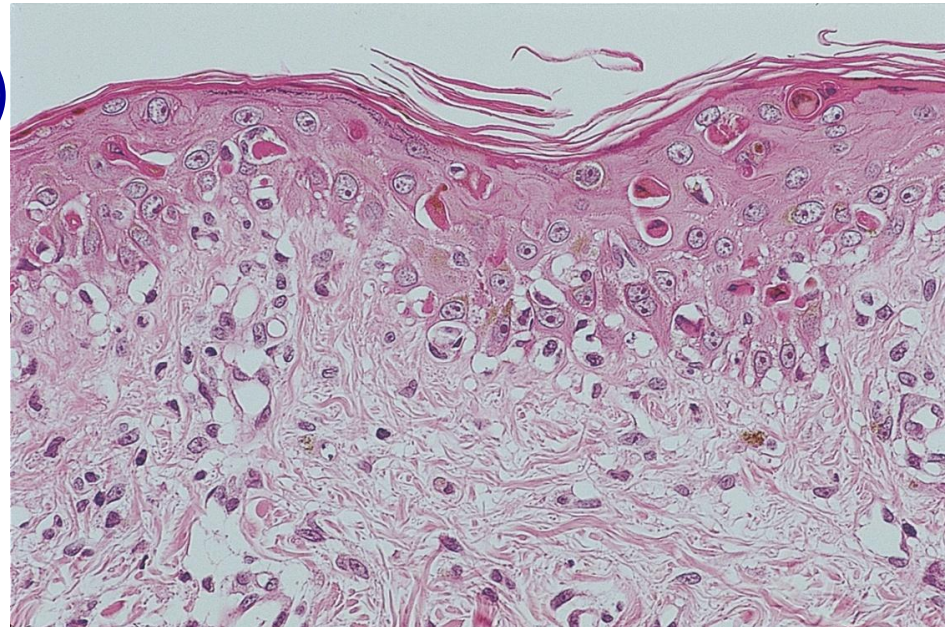
Intestinal mucosa
Epidermis
Liver (Disse's space)
Decidua
(absent from the bone marrow)

Features of extrathymic T-cells

CD8+
 $\gamma\delta$ -type T-cell receptors
perforin +
granzyme B +
TIA-1 +

Target organs of GVHD

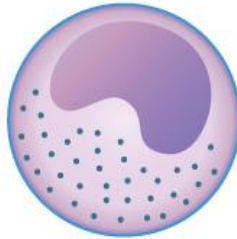
Intestinal mucosa (diarrhea/vomiting)
Skin (eruptions)
Liver (jaundice)



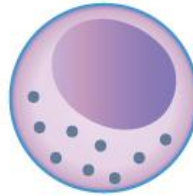
Skin lesion of GVHD (H&E, apoptosis of keratinocytes)

NK cells, extrathymic T-cells and killer T-cells

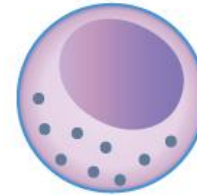
Macrophage



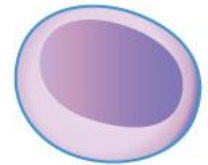
NK cell
LGL



Extrathymic T-cell
LGL



Killer T-cell
Small lymphocyte

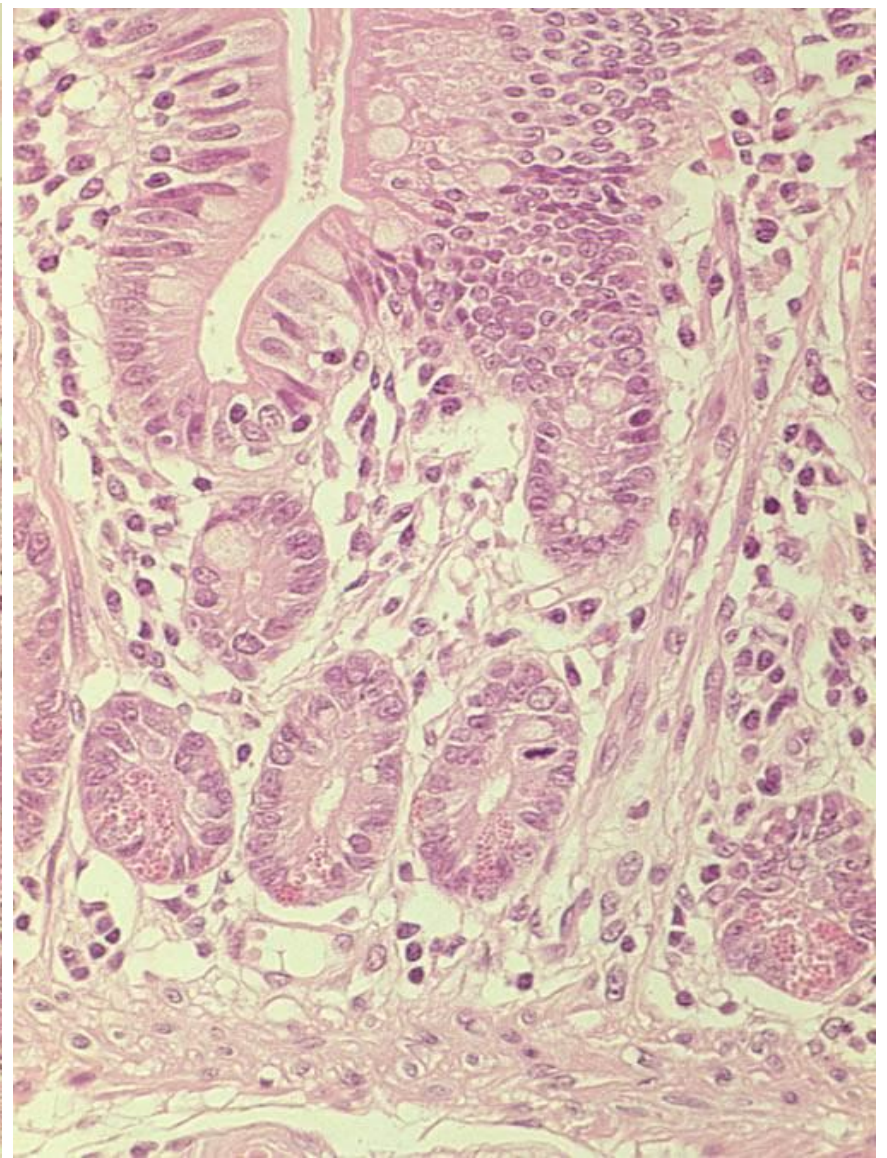


CD68	+	-	-	-
CD3	-	-	+	+
TCR $\alpha \beta$	-	-	+/-	+
TCR $\gamma \delta$	-	-	+	-
CD8	-	-	+	+
CD4	+	-	+/-	-
CD56	-	+	+	-
Perforin	-	+	+	-
CD57	-	+	-	-

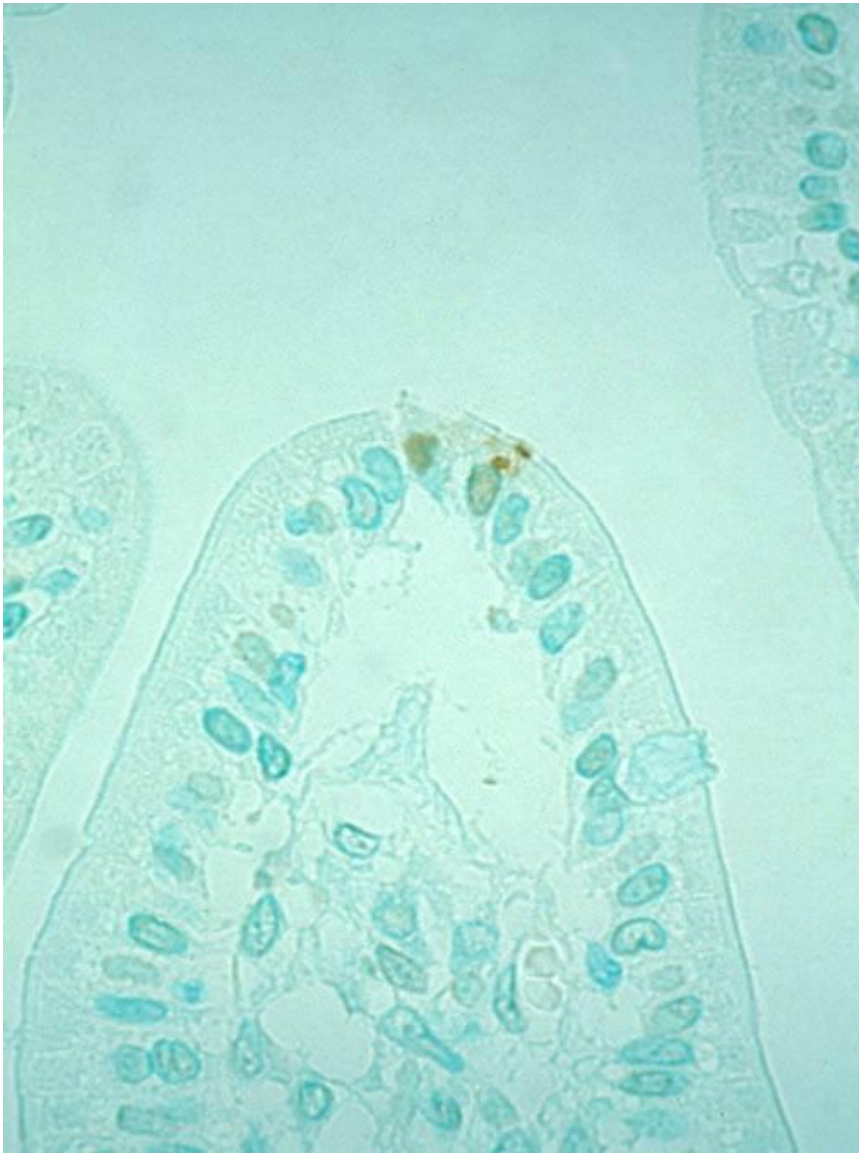
LGL: large granular lymphocyte



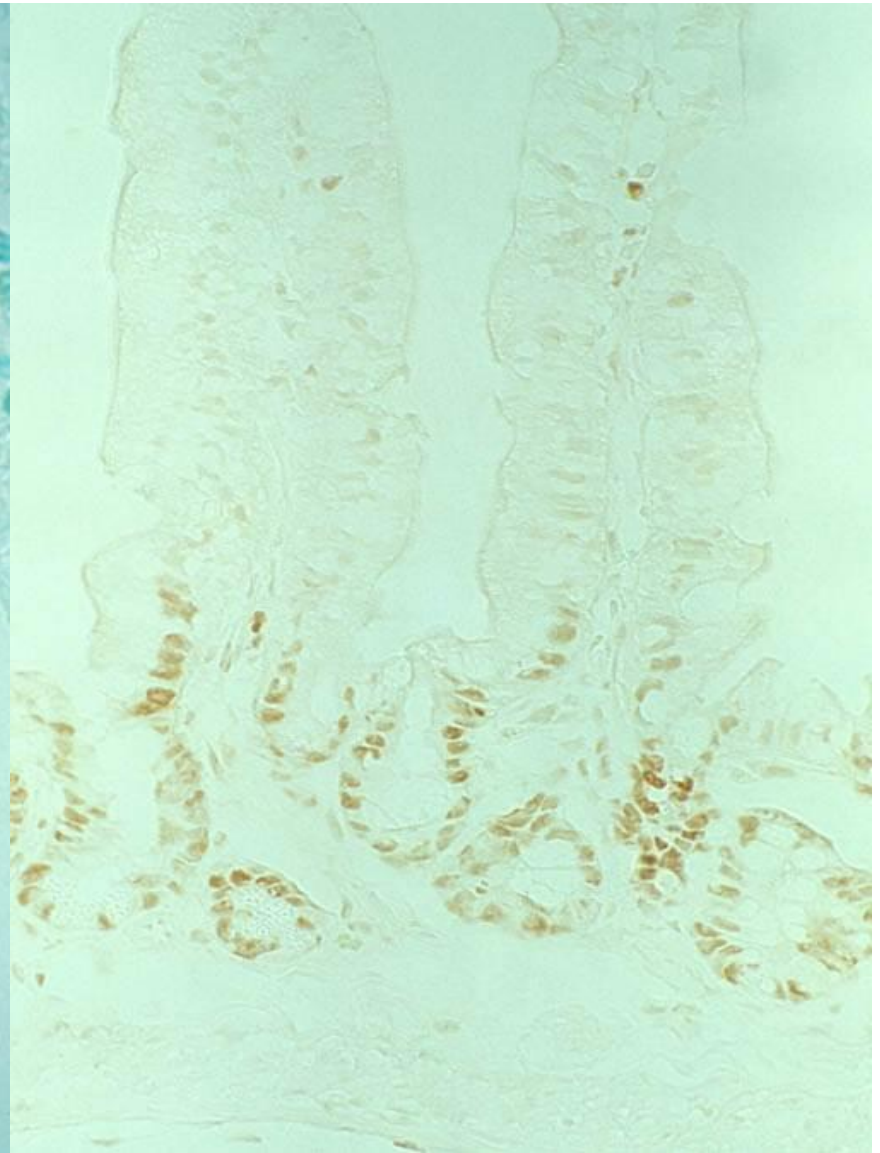
Normal small intestinal mucosa
(villi and crypts, H&E)



Normal small intestinal crypts
(mitotic figures, H&E)



The apical part of the villi of the small intestinal mucosa (apoptosis shown by TUNEL method)

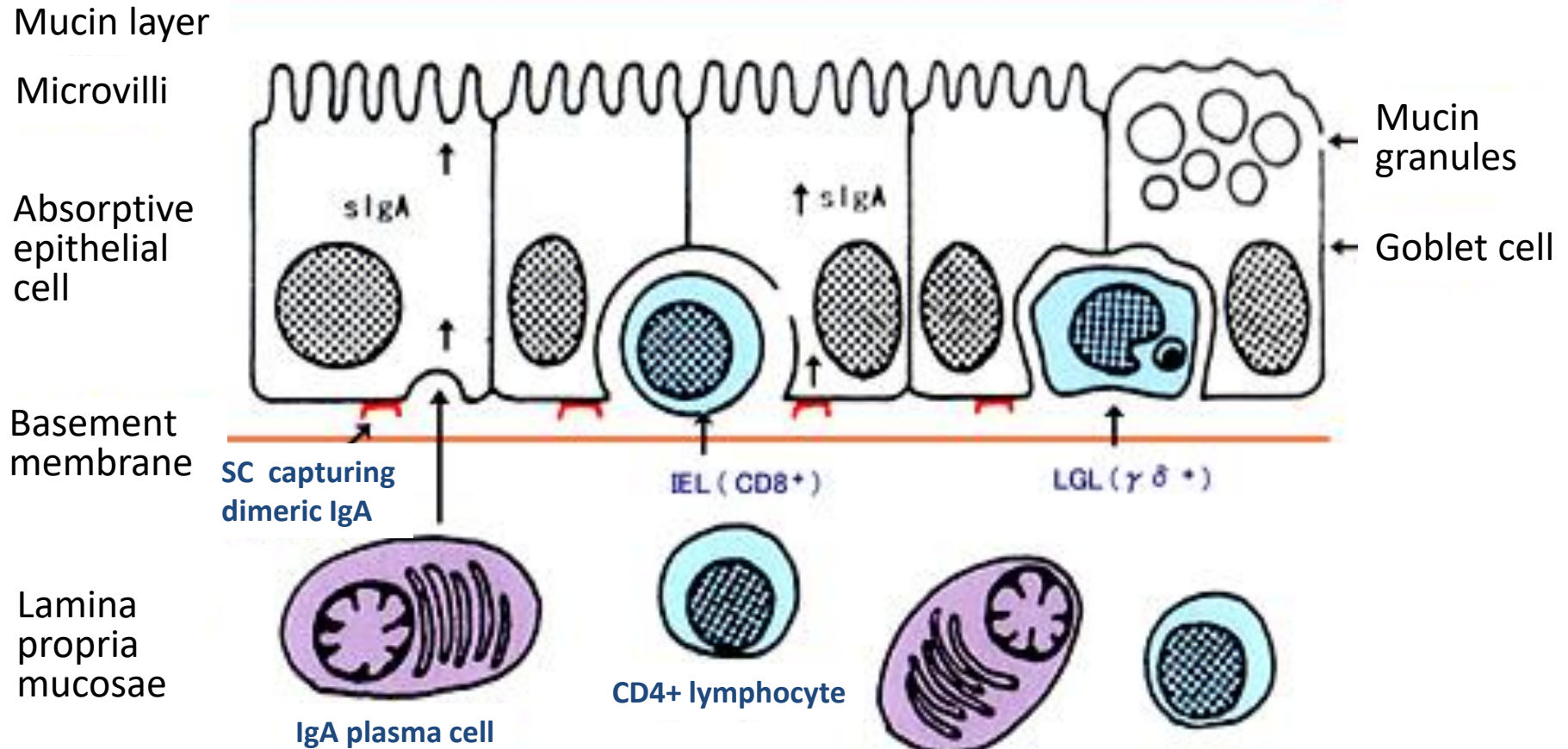


Proliferative cells in the small intestinal mucosa: proliferative cells accumulate in the crypts (PCNA immunostaining)



Intraepithelial lymphocytes in the villi of the normal small intestinal mucosa. Small lymphocytes are distributed among the columnar epithelial cells (arrows). The intraepithelial lymphocytes express CD8 and belong to the killer T-cells, and the possibility to induce apoptosis of the epithelial cells is considered (H&E).

Enterobacteria in the gut lumen



Schematic presentation of secretory IgA through the intestinal columnar epithelial cells and CD8-positive intraepithelial lymphocytes (IEL)

SC: secretory component, LGL: large granular lymphocyte

Mucosal immunity vs systemic immunity

B-cell system

	Site	Secretion	Serum	Roles	Specificity	Memorization
Mucosal	mucosa	sIgA	monomer IgA	defense on mucosal surface	low	difficult
Systemic	serum	Fcγbp	IgG	killing of invaded pathogens	high	easy

	Feature	Site of Ig production	Cell of production	Cell supply source
Mucosal	enterohepatic circulation	lamina propria mucosae	B-1 cells (GC-skipped)	milky spots (omentum)
Systemic	booster effect	lymph node	B-2 cells (GC-needed)	Peyer's patch, appendix

Fcγbp: IgG Fc-binding protein (Kobayashi K, et al: Mucosal Immunity 2021; 27(6): 423-436), GC: germinal center

T-cell system

	Site	Functioning cell	Morphology	Markers
Mucosal	mucosa	extrathymic T-cell	large granular lymphocyte	CD8 ⁺ , CD56 ⁺ , TCRγδ
Systemic	systemic	thymus-educated T-cell	small lymphocyte	CD4 ⁺ >CD8 ⁺ , TCRαβ

	Autoimmunity	Site of production	Distribution
Mucosal	present	lamina propria crypt patch	gut mucosa (IEL), epidermis, liver sinusoid, decidua
Systemic	absent	paracortex of lymph nodes	systemic

IEL: intraepithelial lymphocytes