Basic Immunology
(Dentistry)

Lecture 1.

Introduction, phylogenesis of the immune system (innate-, adaptive- and natural immunity).

University of Pécs, Medical School, Department of Immunology and Biotechnology

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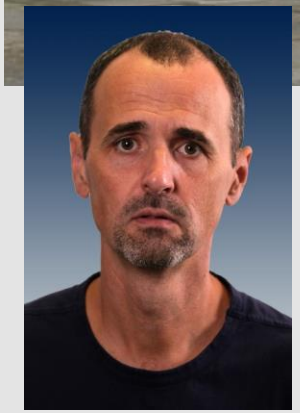


Dr. Ferenc Boldizsár

Dr. Péter Engelmann

Dr. Zoltán Kellermayer

Dr. Katalin Olasz

Introduction 1.

- Please follow our website www.immbio.hu through the whole semester for up-to-date informations about our education. Please pay attention that the published lecture slides alone are not suitable for learning the subject Basic Immunology because they are incomplete without the live explanations and additions given on the lectures by our teachers. For the complete understanding of our topics we expect that students take part on the lectures and make their own notes as well as the use of the Textbook: Abul K. Abbas et al.: Molecular and Cellular Immunology 10th Edition 2021.

- Student preparation and learning will be controlled with the help of the "**moodle.pte.hu**" website. At the beginning of the semester all students will be registered automatically with their specific neptun codes. After activation you will use this platform for completing the semester tests as well as the exam test.

Introduction 2.

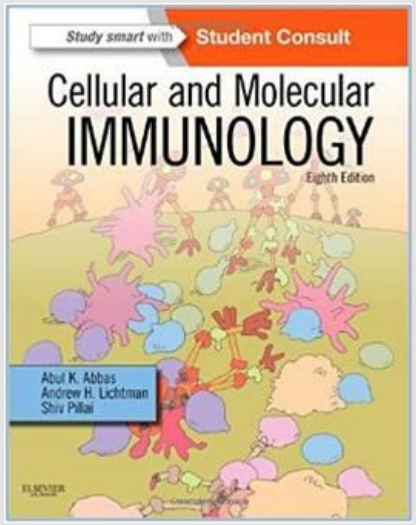
- **2 lectures / week** (preparation of own lecture notes!) Name list will be led every week. **Maximum 3 absences allowed!**

- **Semester tests:** We will check the progress of learning during the semester on 2 occasions (8. and 13. weeks). These tests (30 questions, 45min) will be written using **"moodle.pte.hu"** in the Computer Rooms of the University. For the acknowledgement of the semester 50% is required on both tests. When a student gets more than 25 points in both tests, we will offer a 5 (excellent) for the exam. There will be make up tests on the 9. and 14. weeks for those who miss one test or do not reach the 50% in one of the tests.
- **Exam:** online test exam in **"moodle.pte.hu"** from the lectures in the Computer Rooms of the University. Evaluation: minimum level: 60%; satisfactory 60-71%, average 72- 77%, good 78-83%, excellent 84%

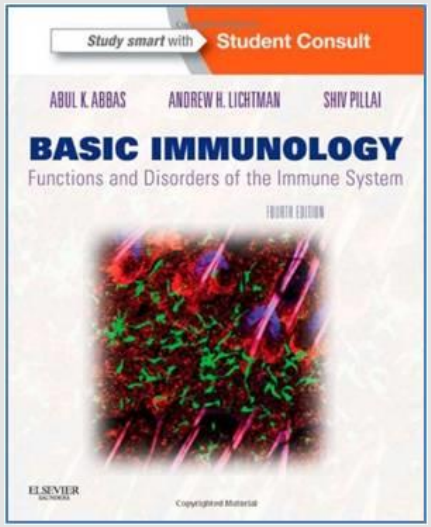
- **Website:** www.immbio.hu

Introducing the subject 3.

- Our official books you can learn from:



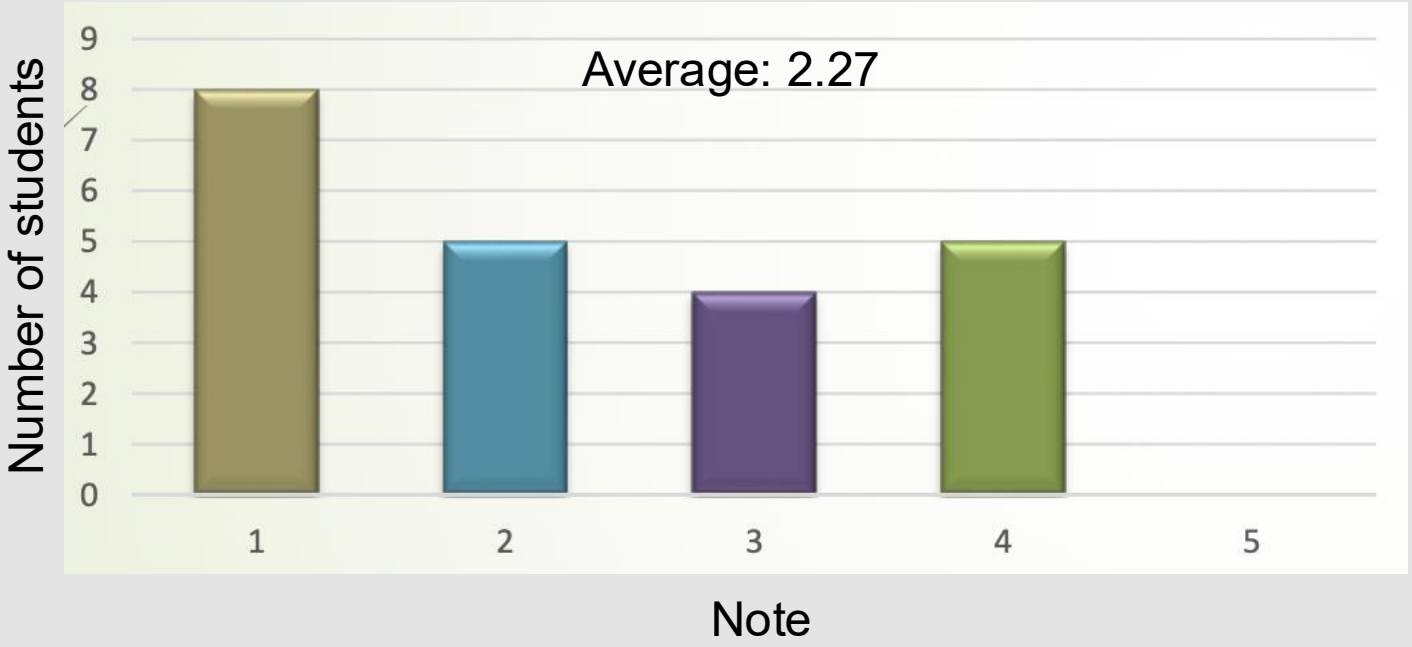
Abul K. Abbas, Andrew H.H. Lichtman, Shiv Pillai: **Cellular and Molecular Immunology**, 8th edition, 2015.



Abul K. Abbas, Andrew H.H. Lichtman, Shiv Pillai: **Basic Immunology**, 4th edition, 2012.

- **Attention!** Our department has never published or lectored any notes for students, therefore we recommend you to be cautious in case you decide to study from them.

Exam statistics 2024.



Total of 24 students:

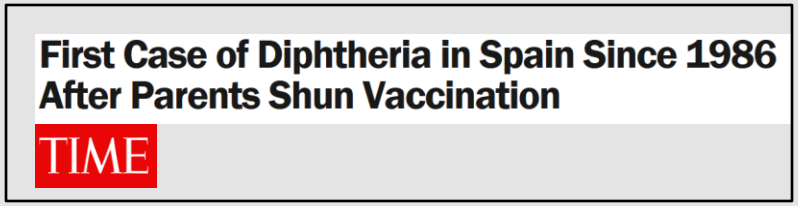
5 studets (21%) got exemption from the exam based on the midterm tests

3 students did not try the exam at all (12%)

5 students repeated the exam, 4 passed on “B”-, 1 passed on “C” chance

Introducing the subject 3.

- What makes immunology worth studying?
  - The immune system is involved one way or another in almost all human pathological conditions.
  - Many of the laboratory diagnostics are based on immunological methods. (see later)
  - More and more diseases get treatable by manipulating the immune system. (see later)
  - Autoimmune diseases affect 7-8% of the population, they are chronic and generally incurable, yet many can be treated effectively. (see later)
  - The number of immunocompromised patients increased recently. (Due to therapeutic immunosuppression and HIV, see later)
  - Laypeople also seem to have strong opinions regarding immunology. → Media tends to mix medical facts with quackery and pseudoscience.



A news report from June of 2015

Our approach

- Molecules
- Cells
- Organs
- Functions

Special emphasis on topics related to dentistry.

Basic terms

- **Immunis,- e** (*Julius Caesar*) = exempt, free of burden (E.g. tax, law, or diseases)
- **IMMUNE:** individuals who do not capitulate to a disease when infected;
- **IMMUNITY:** status of **specific** resistance to a disease;
- **IMMUNOLOGY:** branch of theoretical biology focuses on mechanisms responsible for **both self and non-self recognition, elimination of the invaders and protection of the basic structural elements.**

Definition of the antigen

Detre (Deutsch) László (1874-1939):

ANTIBODY **GEN**ERATOR: foreign substance induces antibody production (1899)

Modern definition: substance, which is recognized by T cell and/or B cell receptors, and it is able to induce ***active immune response or tolerance*** according to the host immunogenetic background (MHC haplotype).

Main tasks of the immune system

The immune system is a structural and functional network.

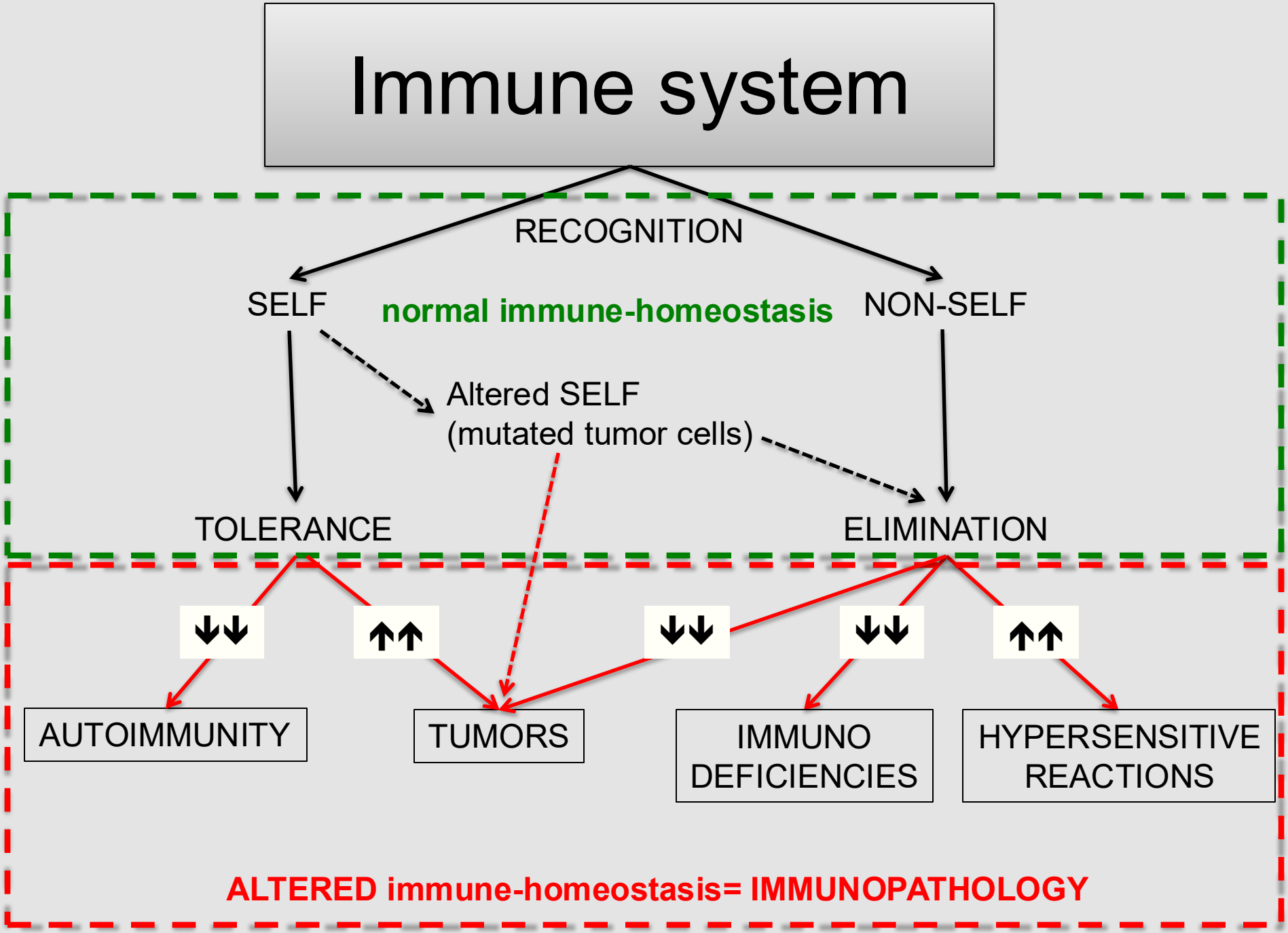
Preserving the integrity of an organism

Defense against **external pathogens** (e.g. viruses, bacteria, parasites)

Elimination of one's **pathologically altered cells** (e.g. virally infected cells, cancer cells)

Altered self- and foreign structures must be **recognized** and **distinguished** from the organism's own healthy cells.

IMMUNE RESPONSE (either an aggressive response or immunological tolerance)


Immune system
RECOGNITION
SELF
normal immune-homeostasis
NON-SELF
Altered SELF
(mutated tumor cells)
TOLERANCE
ELIMINATION
AUTOIMMUNITY
TUMORS
IMMUNO DEFICIENCIES
HYPERSENSITIVE REACTIONS
ALTERED immune-homeostasis= IMMUNOPATHOLOGY

Composition of the immune system

Innate

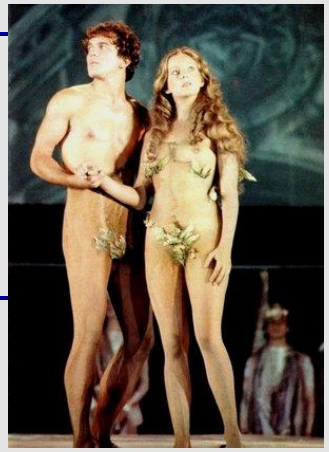
- None antigen specific
- No immunological memory
- Rapid reactivity
- Linear amplification of the reaction

Adaptive

- Antigen specific
- Immunological memory
- Activated after a latency
- Exponential amplification of the reaction

Natural

Innate-like immunity with adaptive features



Innate immune system

- **Pattern recognition receptors** (PRR)
- **Pathogen associated molecular patterns** (PAMP)
- **First line defence**
- **Low number of molecularly distinct receptors and high number of recognized patterns**
- **Main molecular components:** Antibacterial peptides, Complement factors and their receptors, Heat shock proteins, Fc receptors, Inflammatory cytokines, Growth factors, Histamine
- **Main cellular components:** Macrophages, Monocytes, NK cells, Granulocytes, Mast cells

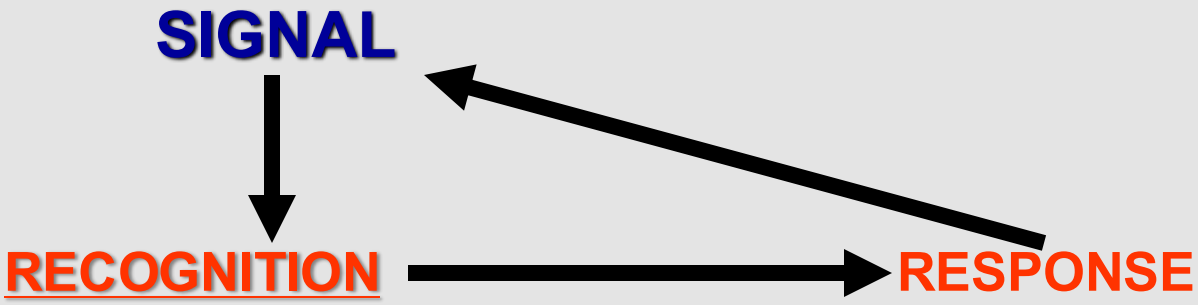
Adaptive immune system

- Antigen receptor (BCR,TCR)
- Epitope specific in a given antigen
- Adaptive immune response
- High number of distinct antigen receptors and high number of recognized antigens
- Main molcelar components: Antibodies, MHC, T and B cell receptors, Lymphatic citokines
- Main cellular components: T cells (both αβ and γδ), B cells, Antigen presenting cells

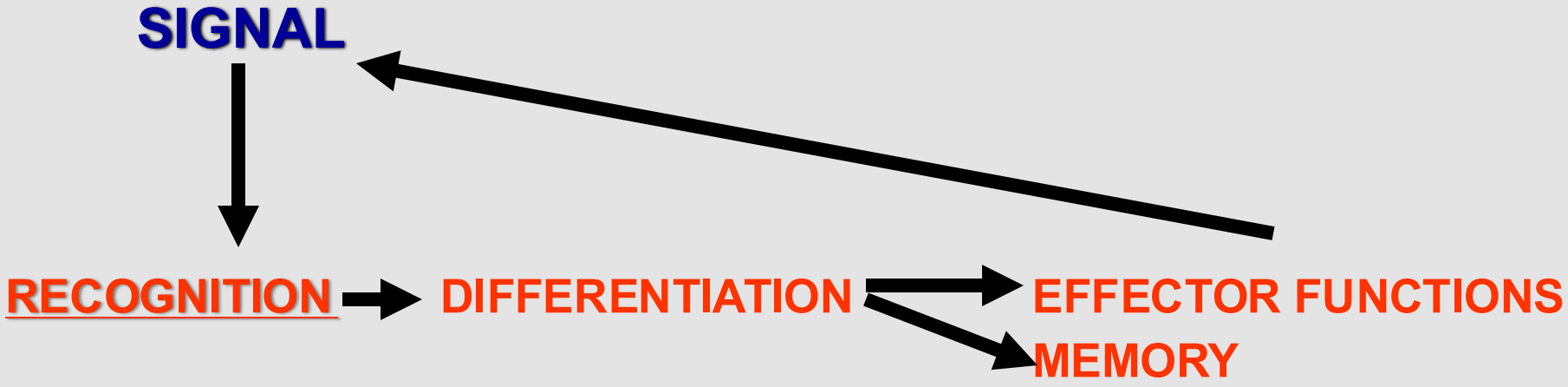
Natural immune system

- Antigen recognition receptors (BCR,TCR) with limited specificity
- Patern recognition profile
- Innate-like immune response
- Limited number of distinct antigen receptors and high number of recognized antigens
- Main cellular components: iNKT cells, iγδT cells, MAIT cells, IEL cells, CD5+ B1 cells
- Main molcelar components: natural (auto)antibodies

Theoretical scheme of the innate immunity

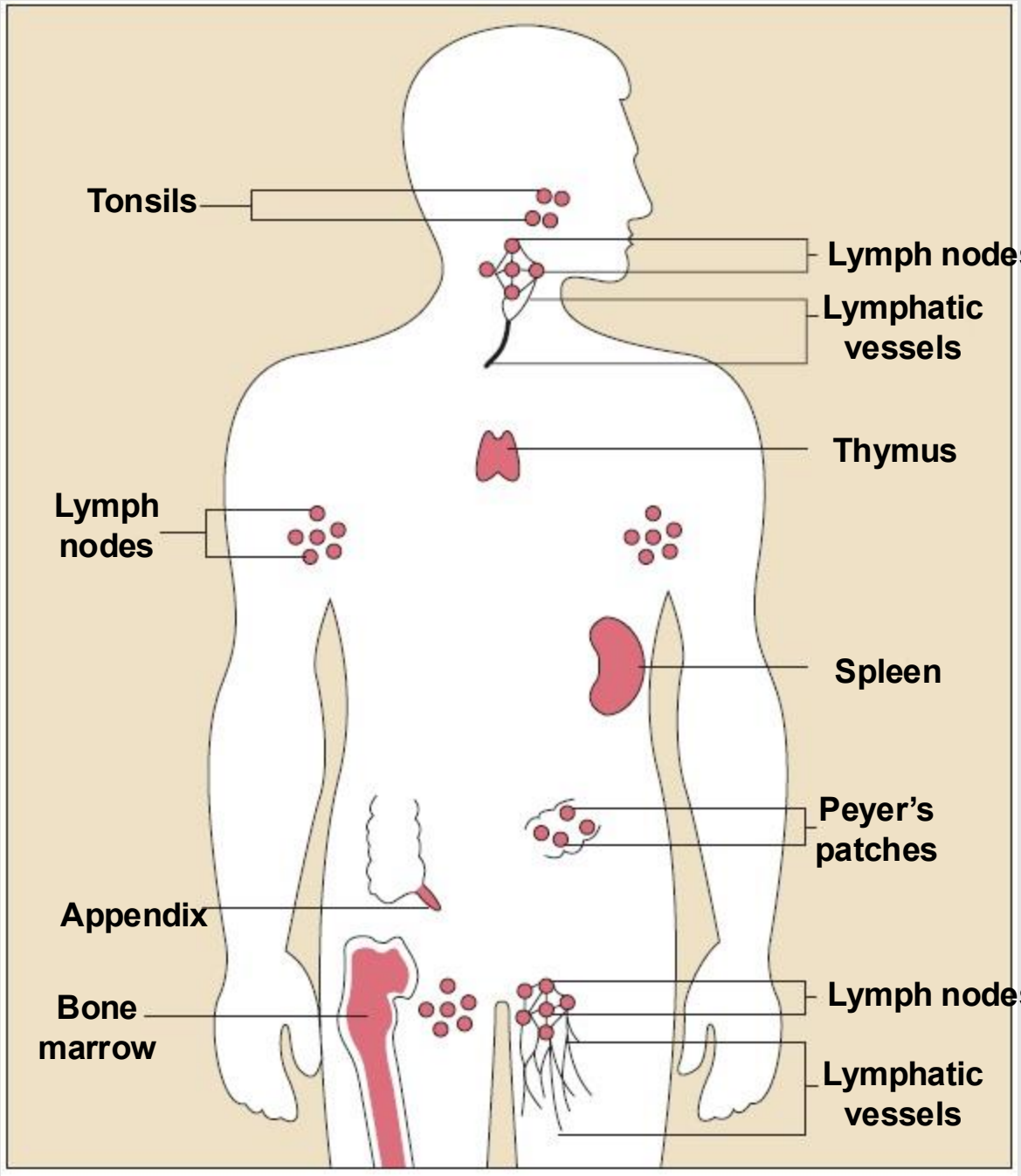


Theoretical scheme of the adaptive immunity



Organs of the immune system

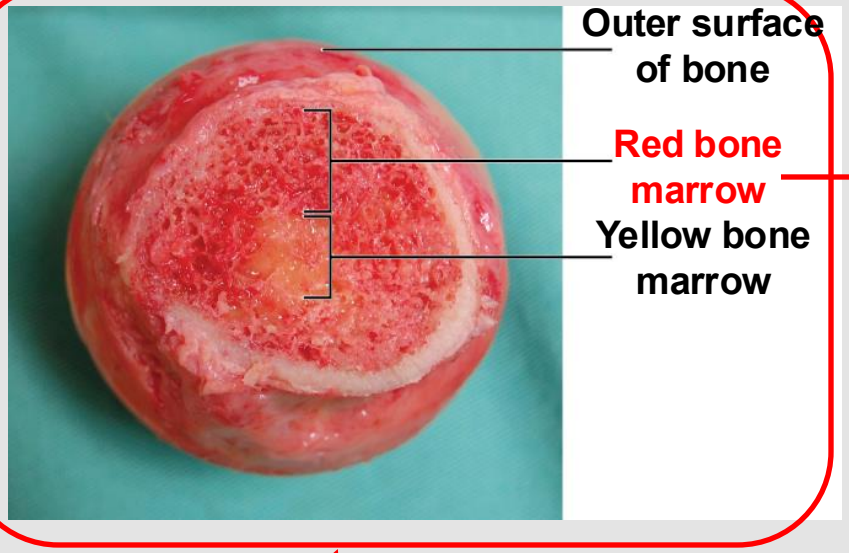
- The immune system is organized into a **network** of cells and organs. (the entire body must be protected from pathogens)
- Lymphoid organs:
  - **Primary** (production of immune cells)
    - **Bone marrow, thymus**, embryonic liver (+bursa of Fabricius in birds [nomenclature: „B" lymphocytes originating from the bursa and „T" cells from the thymus[1.]])
  - **Secondary** (site of antigen recognition, immune response)
    - **Lymph nodes, spleen, MALT** (mucosa-associated lymphatic tissue), **SALT** (skin-associated lymphatic tissue)
  - **Tertiary** (pathological, usually due to chronic inflammation)
    - E.g. ectopic (=at an abnormal site) lymphoid follicles

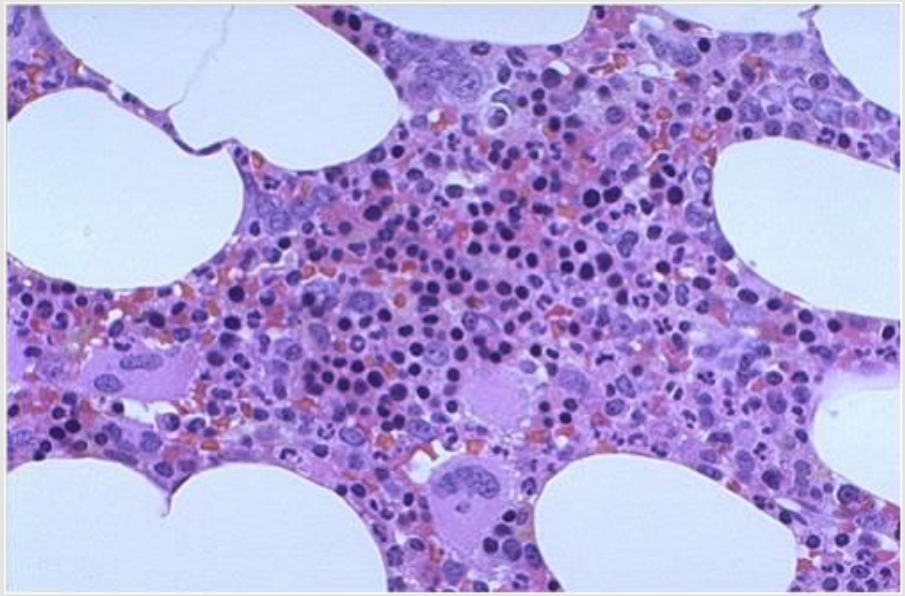

Tonsils
Lymph nodes
Lymphatic vessels
Thymus
Lymph nodes
Spleen
Peyer's patches
Appendix
Bone marrow
Lymph nodes
Lymphatic vessels

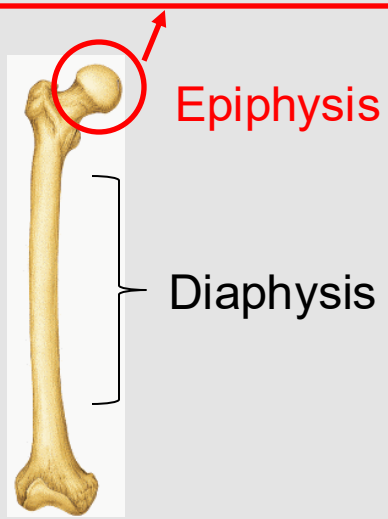
Bone marrow (medulla ossium)

- Spongiform tissue found within bones which constitutes 4-5% of the total body weight in adults. (≈2,6 kg)[2.]
- Red bone marrow (medulla ossium rubra):
  - Found **in short and flat bones** (sternum, ribs, clavicle, scapula, pelvis, vertebrae, skull) and the **epiphysis of long bones** (e.g. femur)
  - Role: **Producing blood cells** (hematopoiesis) → 10^{11} new cells daily of neutrophils alone[3.] (the human body is made of approx. $3{,}7 \times 10^{13}$ cells)[4.]
- Yellow bone marrow (medulla ossium flava):
  - Found in the diaphysis of long bones
  - Mainly composed of adipocytes, can turn into red bone marrow when needed (e.g. after blood loss)

Structure of the red bone marrow



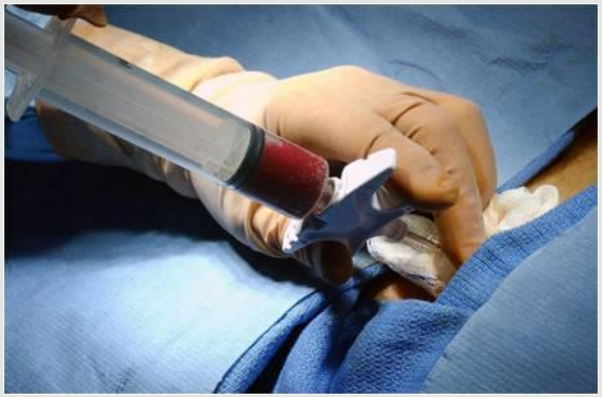




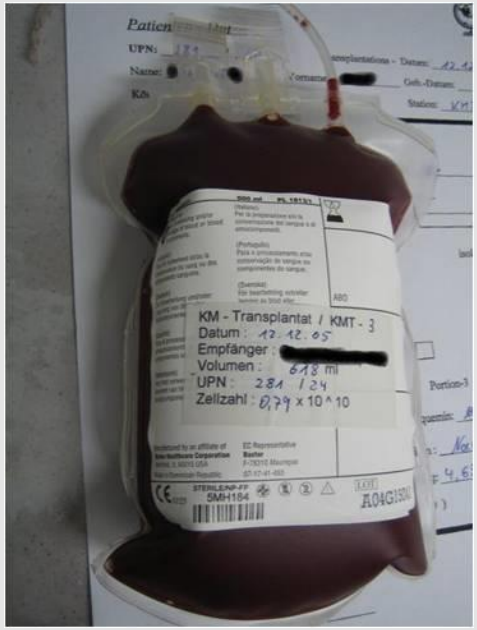
- Spongy bone tissue with sinusoids, spaces are filled with cells of various lineages undergoing hematopoiesis (see later), stromal cells and adipocytes.[2.]
- Mature and naive B cells leave the bone marrow, whereas T cells produced by the bone marrow are still immature and must undergo further maturation in the thymus.
- **Mature**: capable of recognizing an antigen
- **Naive:** haven't yet encountered an antigen

Clinical significance of the bone marrow

- Bone marrow biopsy or aspiration for histological or cytological assessment in case of hematological diseases (e.g. leukemias, aplastic anemia, etc.)
  - Performed from: **iliac crest** or **sternum**[5.]

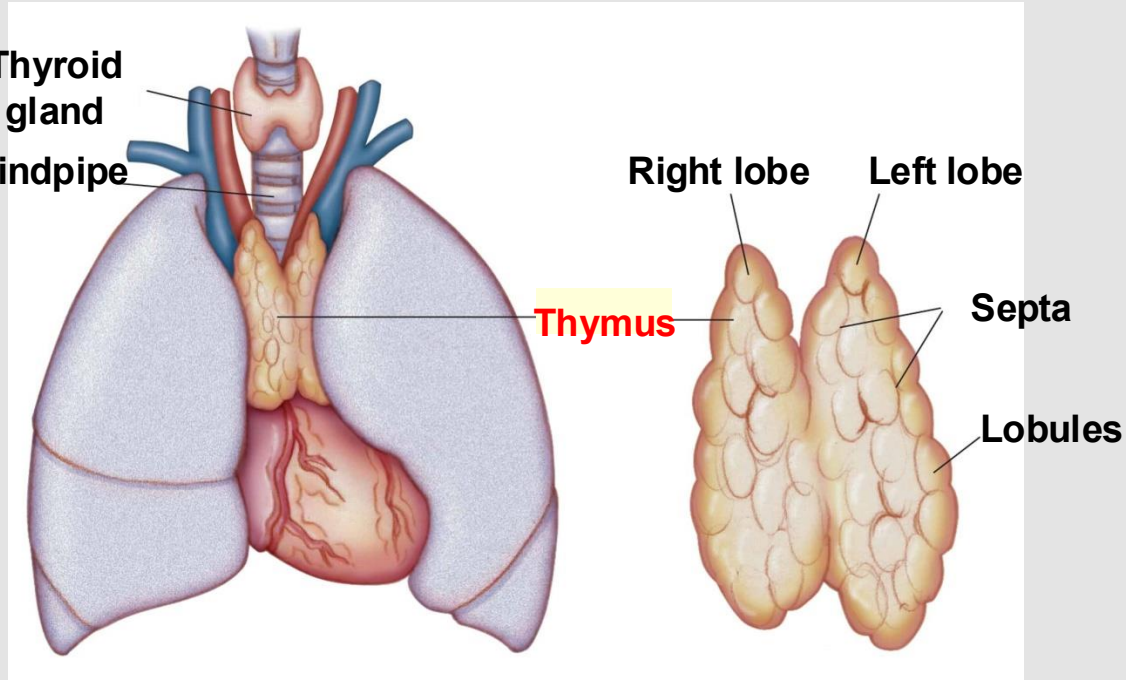


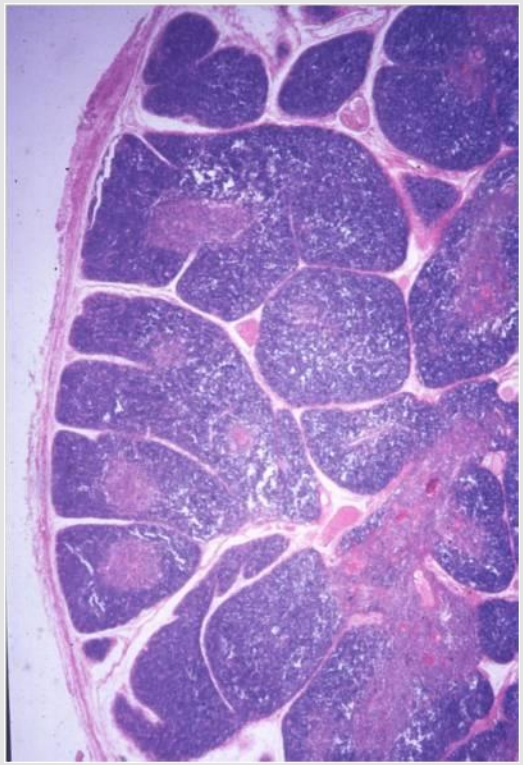
- Collecting hematopoietic stem cells (HSC) to perform bone marrow transplantation
  - Usually gathered from the peripheral blood after cell mobilization[6.]



Thymus

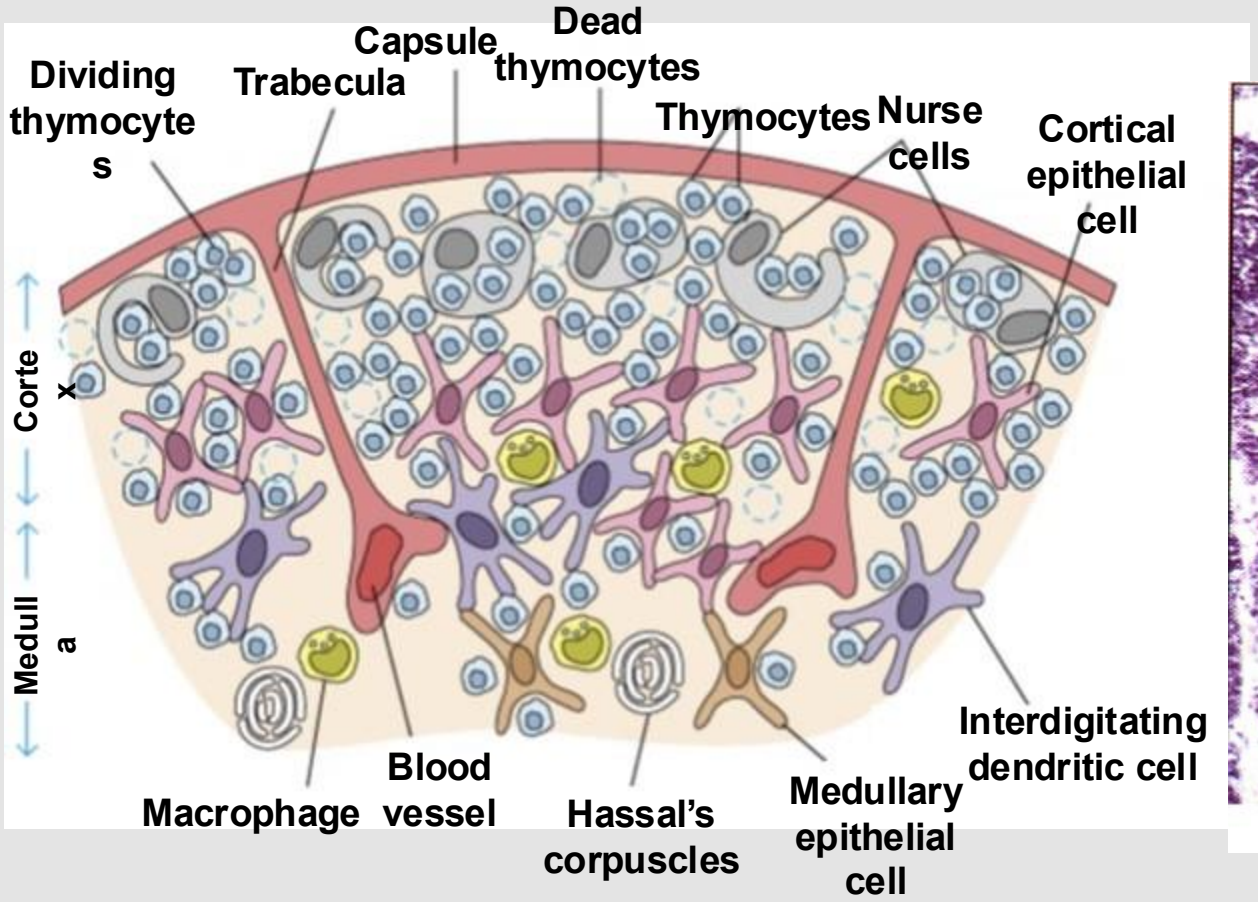
- A lobulated organ located in the superior mediastinum, it is the **primary site of T cell maturation**.
- Consists of **2 lobes** further divided into **lobules** separated by connective tissue septa. The inner layer of the lobules is called **medulla**, the

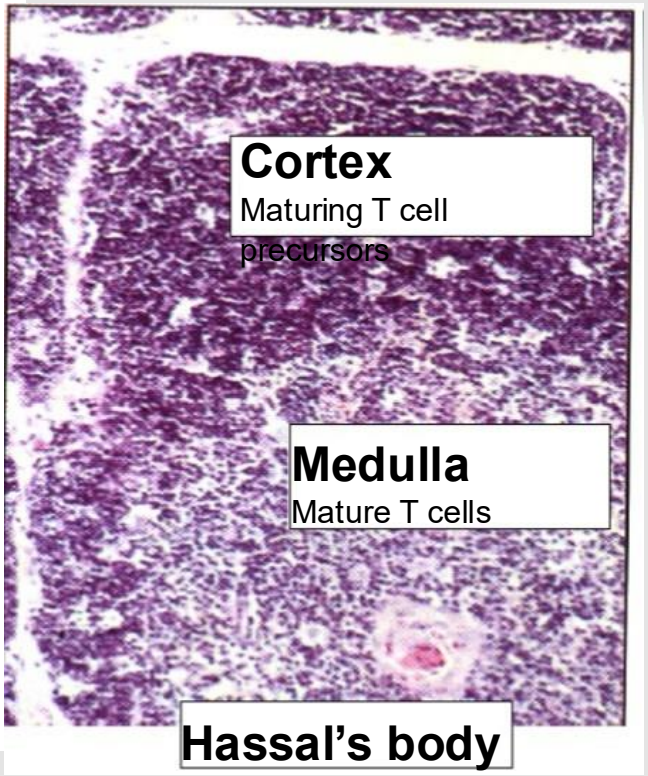




Thymus (H&E staining): the peripheral, basophilic layer is the cortex. The inner medulla seems more eosinophilic because it contains less cell nuclei.

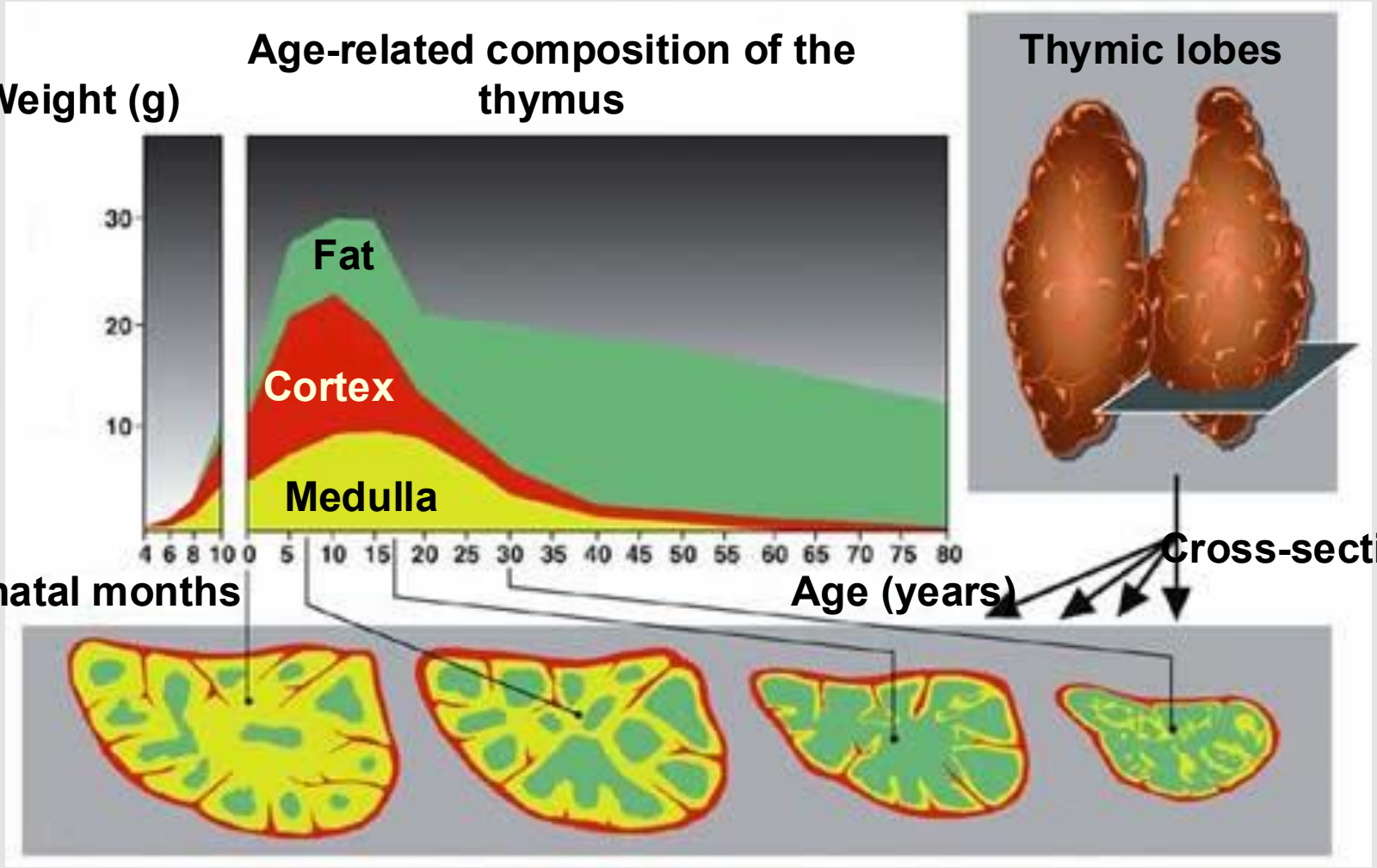
Histology of the thymus





- T cell precursors (=immature cells) produced by the bone marrow enter the thymus through blood vessels → **MATURATION** (see later) → Mature and naive T cells leave the thymus and enter circulation
- **Main cellular components of the thymus: T cells (thymocytes), thymus epithelial cells, dendritic cells, macrophages, epithelioreticular cells**[7.]

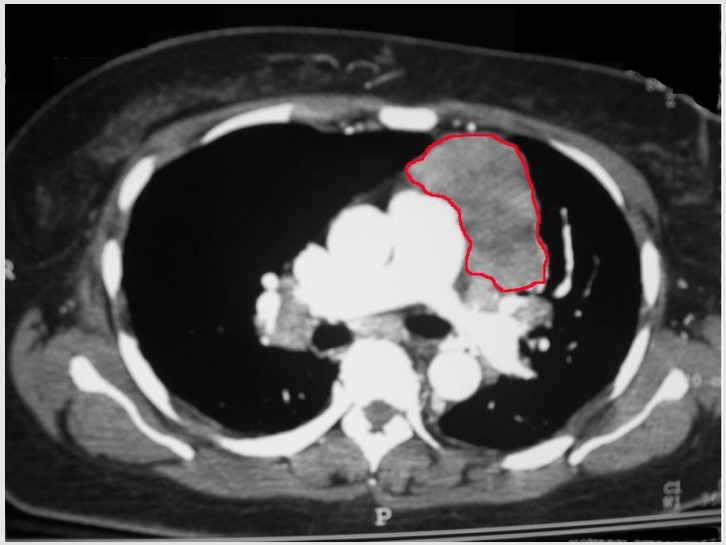
Involution of the thymus



Clinical significance of the thymus

- Congenital abnormalities (e.g. ectopic thymus or thymic aplasia [=absence of thymus] for instance in DiGeorge syndrome → **immunodeficiency**)

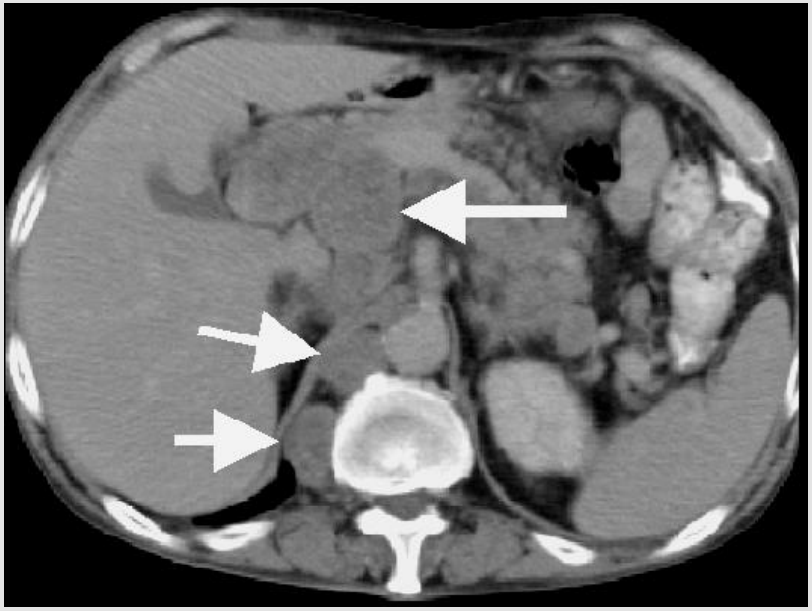
- Tumors (thymoma, thymus carcinoma)[8.]
  - May be associated with autoimmune disorders such as myasthenia gravis (see later)
  - Might compress nearby structures (e.g. superior vena cava syndrome, dysphagia, see later in the clinical phase of your studies)



Thoracic CT angiography (dye seen in blood vessels): The red line marks a thoracic mass later confirmed to be a thymoma by histological evaluation.

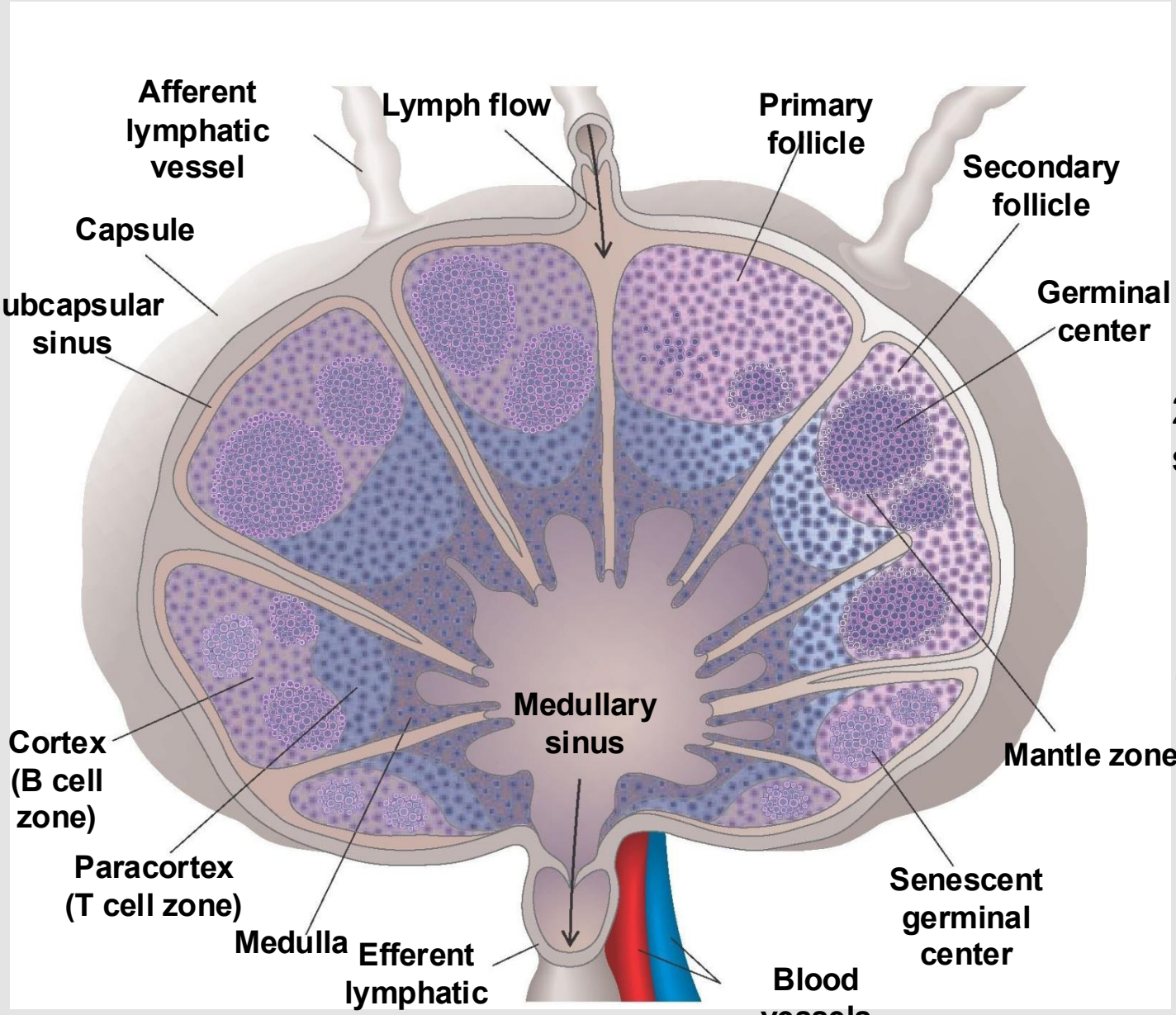
Lymph node (nodus lymphaticus)

- They act as **filters of the lymph:** lymph reaching the node through the afferent lymphatic vessels is filtered for **pathogens** and **cancer cells**. (one of the organs where the adaptive immune cells can meet with antigens the first time)
- This is the place where the antigens that entered the lymphatic system will be **recognized** by the adaptive immune cells followed by cell **proliferation** and **differentiation**.
- **Tremendous clinical significance**: Infectious agents and cancer cells may



Retroperitoneal lymphadenomegaly (=enlarged lymph nodes) seen on a CT scan image. Arrows mark enlarged lymph nodes.

Structure of lymph nodes



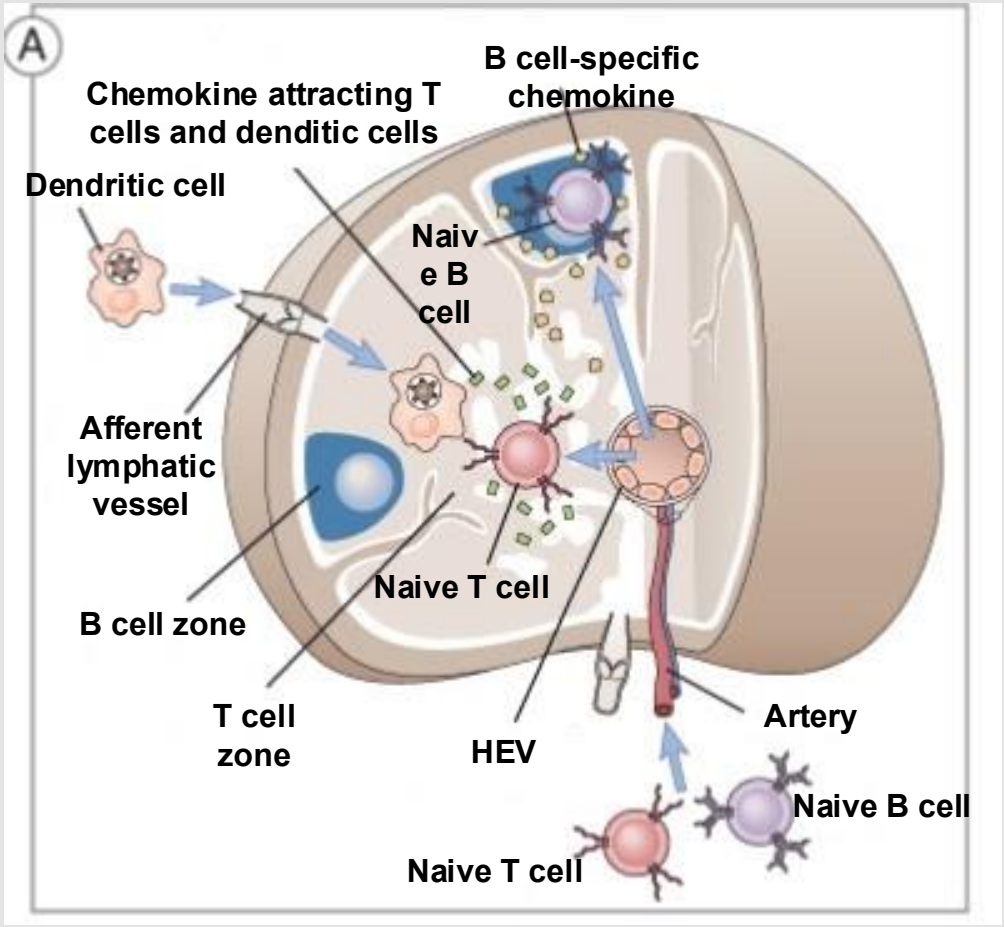
Route of lymph (covered with endothelial cells):

1. Afferent lymphatic vessel
2. Subcapsular sinus
3. Cortical sinus
4. Paracortical sinus
5. Medullary sinus
6. Efferent lympahtic vessel

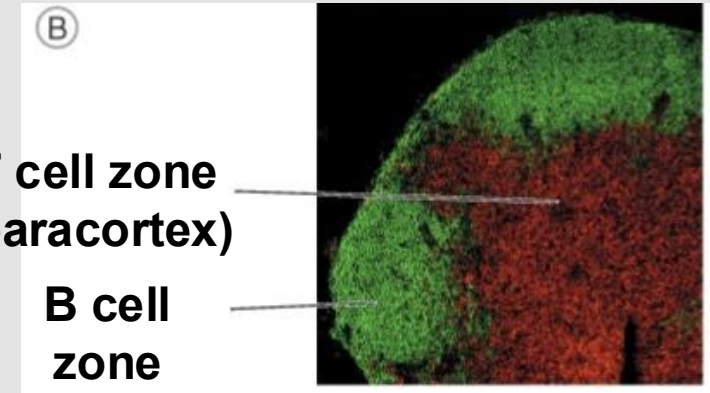
Structure of lymph nodes

- Have outer fibrous capsule from which trabeculae radiate towards the inner part of the organ.
- Layers from outermost to innermost: **cortex**, **paracortex** and the **medulla**.
- Afferent lymphatic vessels enter through the convex surface; the efferent lymphatic vessels and blood vessels (artery and venule) are located at the hilum.
- Reticular connective tissue forms the frameworks of the lymph nodes.
- Sites where immune cells enter:
  - From the bloodstream: **high endothelial venules** (HEV)
  - From the lymphatic system: afferent lymphatic vessels
- Cellular zones:[9.]
  - Cortex: **B cells** organized into **follicles**, cells that recognized an antigen proliferate and form germinal centers
  - Paracortex: **T cells** and **dendritic cells** diffusely
  - Medulla: mainly antibody-producing **plasma cells**

Structure of lymph nodes 3.



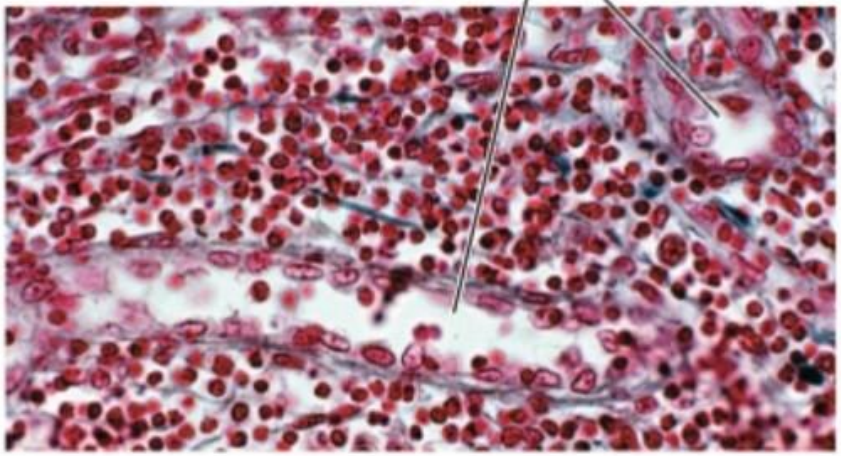
The cellular organization is controlled by **chemokines**. (see later in lectures)



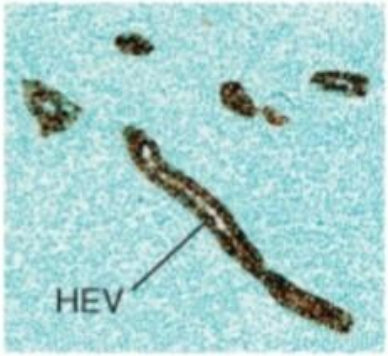
Immunofluorescence microscopy

High endothelial venules (HEV)

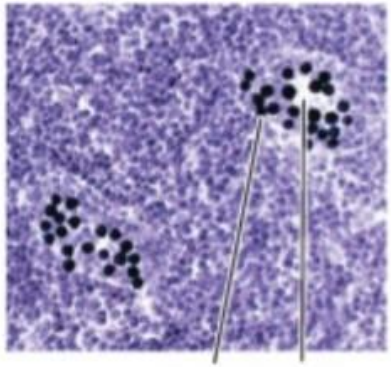
A HEVs in a lymph node



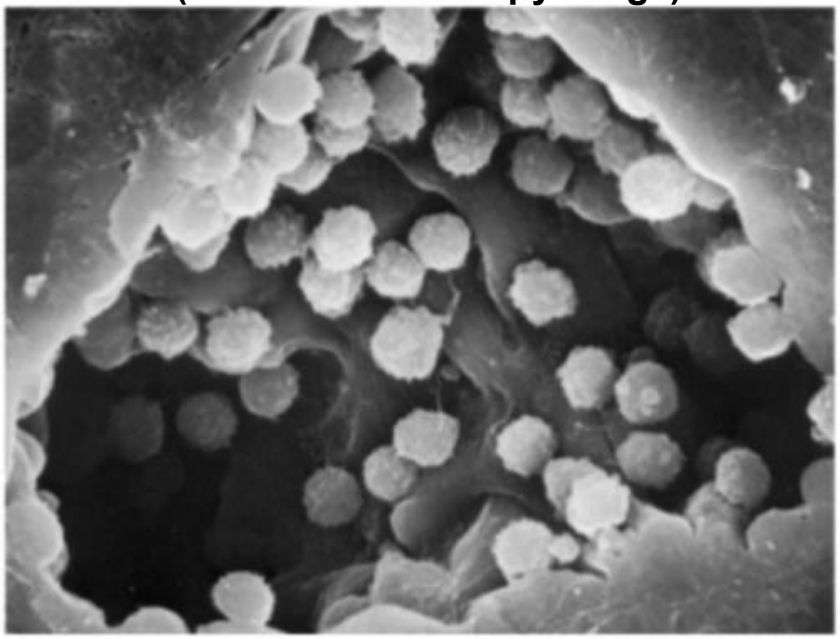
B L-selectin ligand on endothelial cells (IHC)



C T cells binding to HEV (frozen section assay)

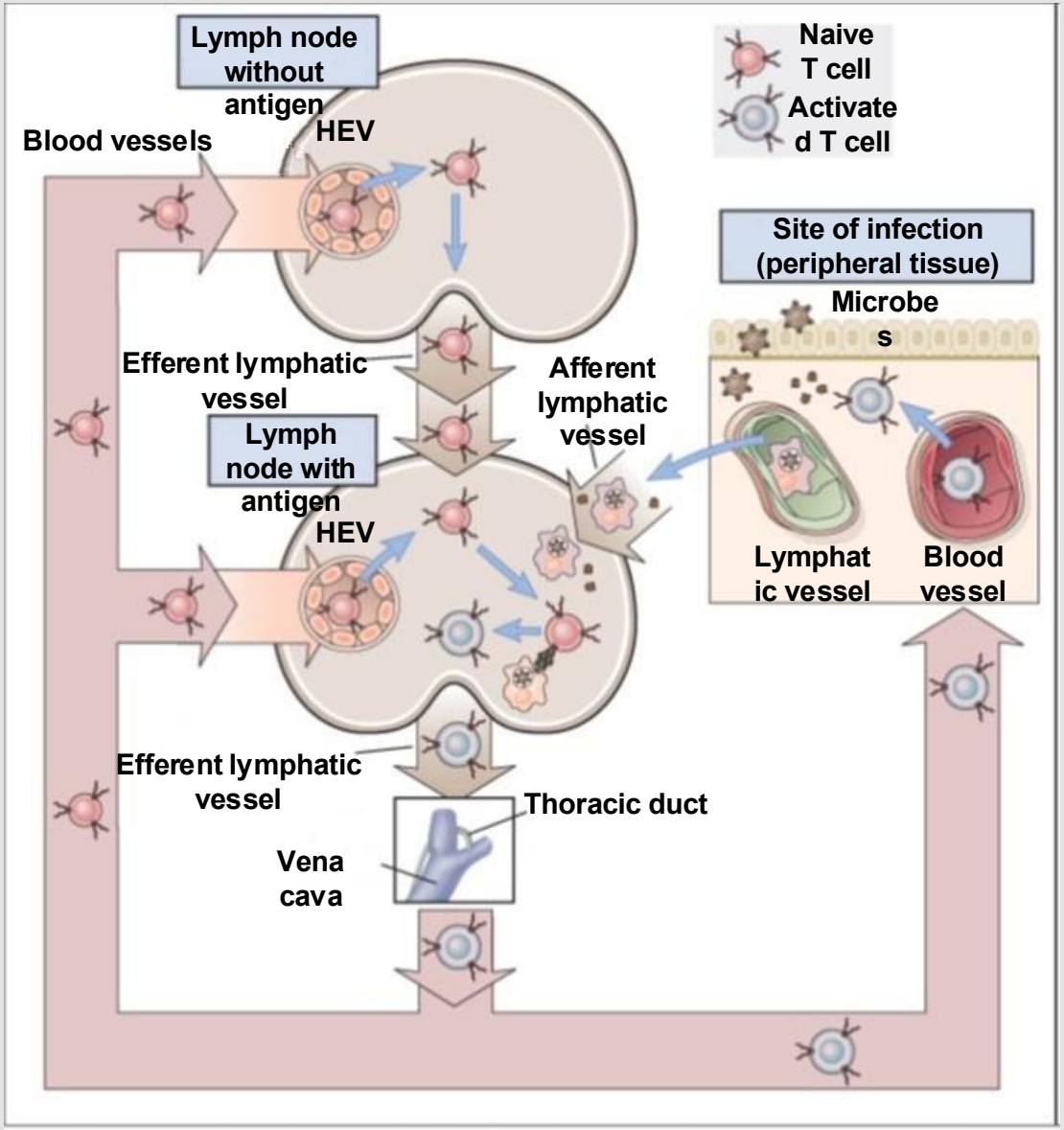


D T cells binding to the luminal surface of a HEV (electron microscopy image)



- Lymphocytes use HEVs to enter lymphoid organs. (through L-selectin, see later)
- Found in all secondary lymphoid organs (e.g. lymph nodes, tonsils, Peyer's patches), **EXCEPT THE SPLEEN**[10.]

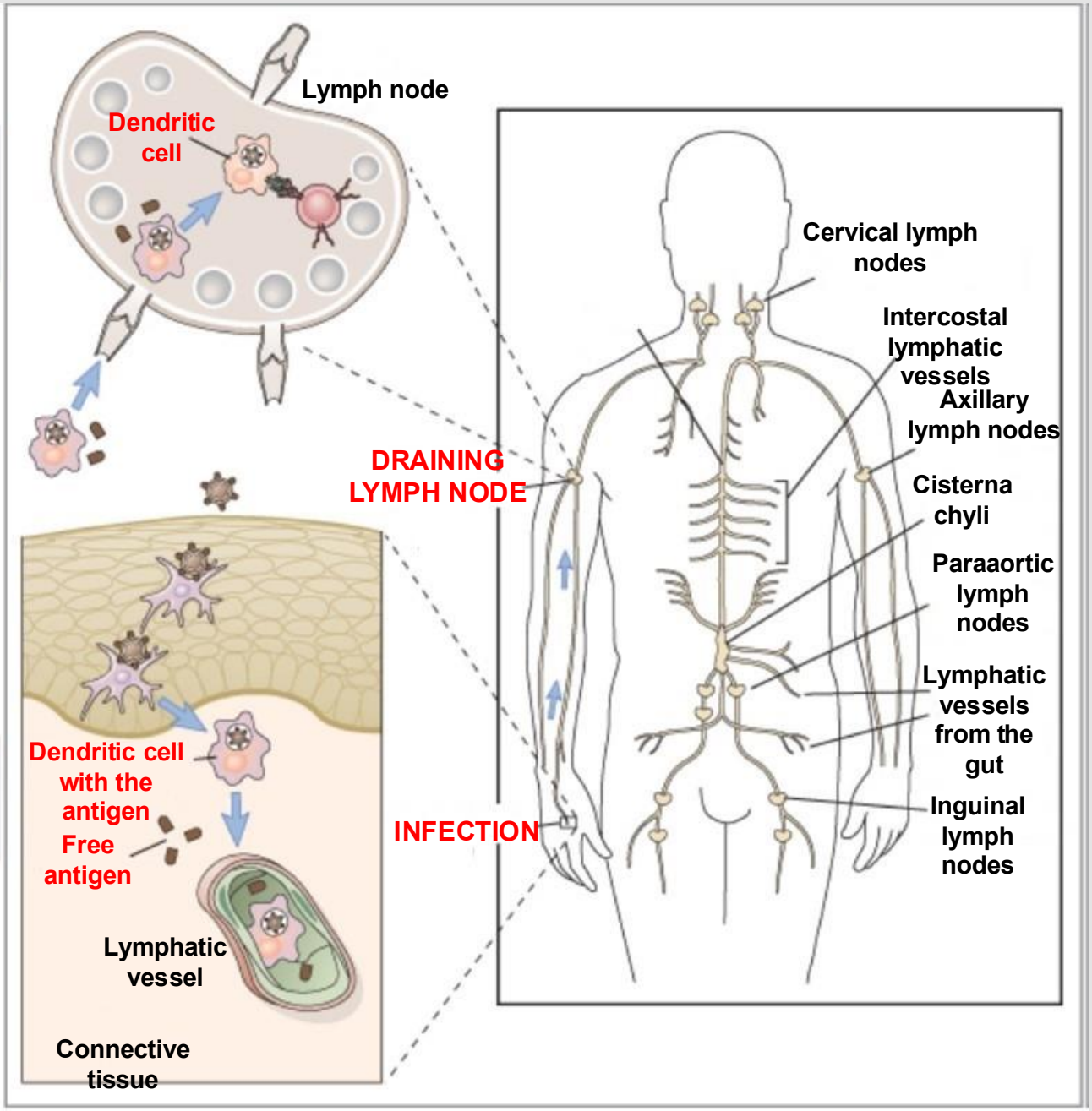
Filtration of lymph by nodes



1. Infection on the periphery
2. The same antigen may enter the **lymphatic vessels** in different forms:
   - **Native bound antigen** (e.g. living bacteria)
   - **Native soluble form** (e.g. proteins derived from dead bacteria)
   - **Processed form: dendritic cells** phagocytose the antigen and **present it** as a peptide to **helper T cells** (see later)
3. Lymphocytes enter lymph nodes either through **afferent lymph vessels** or **HEV**s and meet with the antigens.

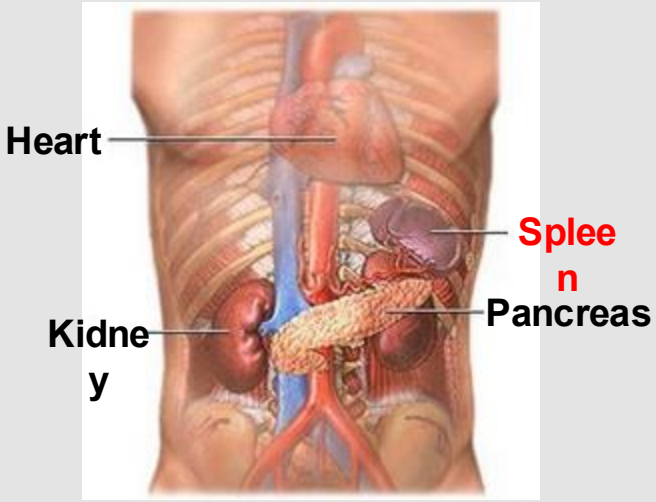
ANTIGEN PRESENTATION AND T CELL RESPONSE

ANTIGEN CAPTURE AND TRANSPORT



Spleen (lien or splen)

- Located in the left hypochondriac region of the abdomen, weighs approx. 150-200 grams.
- Functions:
  - Immunological: **filtering the blood** for pathogens
  - Hemoglobin metabolism: elimination of aged red blood cells by the reticuloendothelial cells→ formation of bilirubin
  - Site of hematopoiesis in the embryo as in the liver (can produce red blood cells in pathological conditions even in adults)
  - Acts as a storage of red blood cells and platelets (less significant in humans)

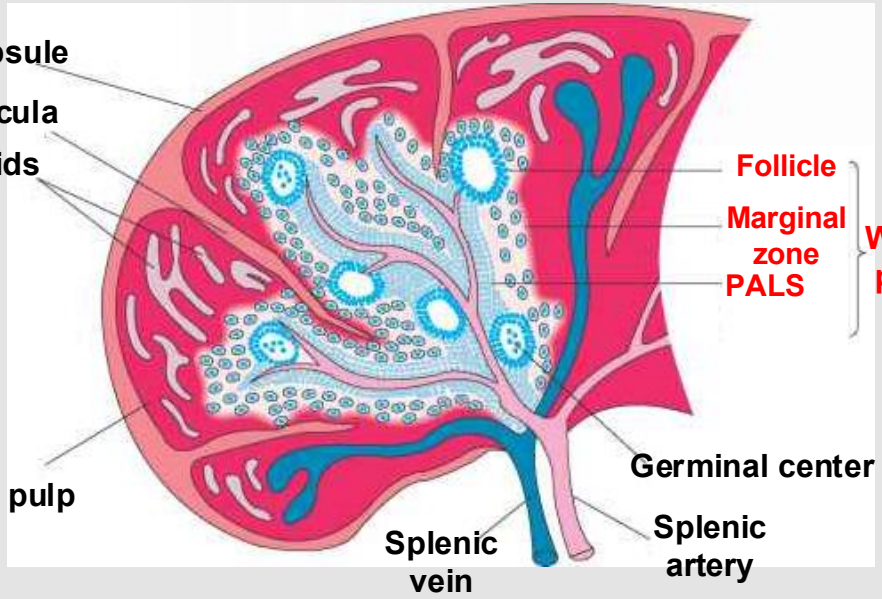


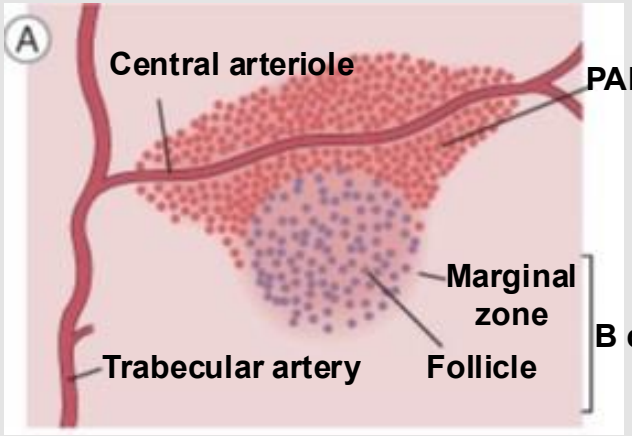
Structure of the spleen 1.

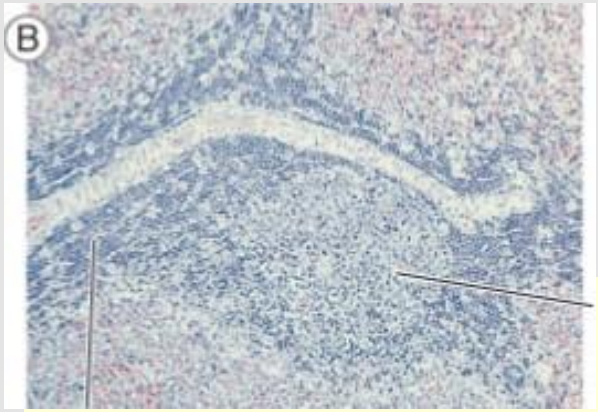
- Has a fibrous capsule and trabeculae.
- **THERE ARE NO** afferent lymphatic vessels and HEVs.
- Tissue architecture:[11.]
  - Red pulp: sinusoids with an open circulation filled with blood: has a reticular framework populated mainly by red blood cells, macrophages, plasma cells and reticular fibrocytes.
  - **White pulp: lymphoid tissue**
    - **PALS** (periarteriolar lymphatic sheath):

      T cells, dendritic cells
    - **Follicles** (Malpighian follicles)**: B cells and follicular dendritic cells (FDC)**
    - **Marginal zone:** special, **marginal zone B cells** (**MZB**, see later) and **MZ macrophages**

Structure of the spleen 2.

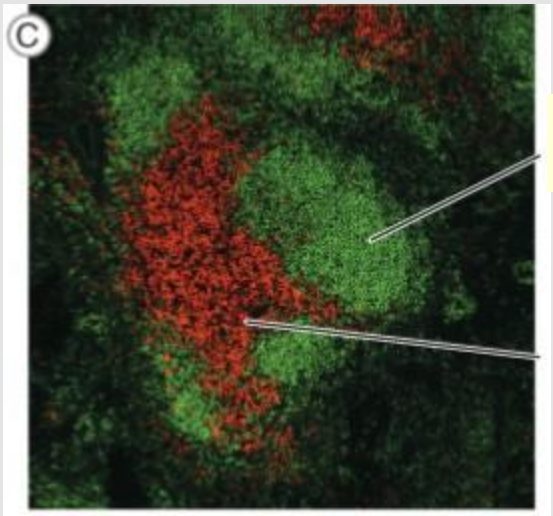






PALS (periarteriolar lymphatic sheath)

Germinal center (secondary follicle also called Malpighian follicle in the spleen)



B cell zone (follicle)

T cell zone (PALS)

Clinical significance of the spleen

- Splenomegaly (=enlarged spleen):

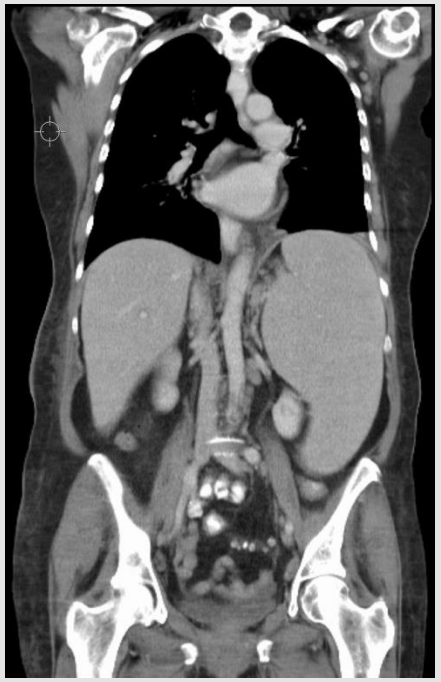
  Can have several causes such as hematological malignancies, hypersplenism (e.g. hemolytic anemia), increased pressure in the portal veins (cirrhosis), infections (mononucleosis, malaria), storage diseases[12.]

- Splenic rupture (ruptura lienis):

  Caused by trauma or an underlying pathological condition, high risk of intra-abdominal hemorrhage

- Splenectomy (=surgical removal of the spleen):

  Leads to increased vulnerability to polysaccharide encapsulated bacteria (see later)[13.]



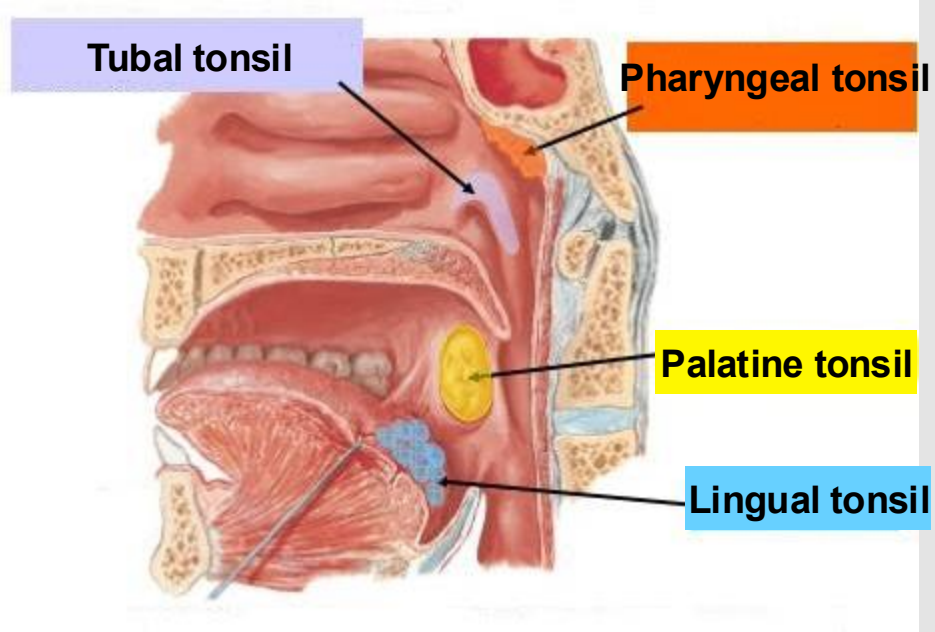
CT scan of a patient with chronic lymphocytic leukemia (CLL) showing massive splenomegaly.

MALT (mucosa-associated lymphoid tissue)

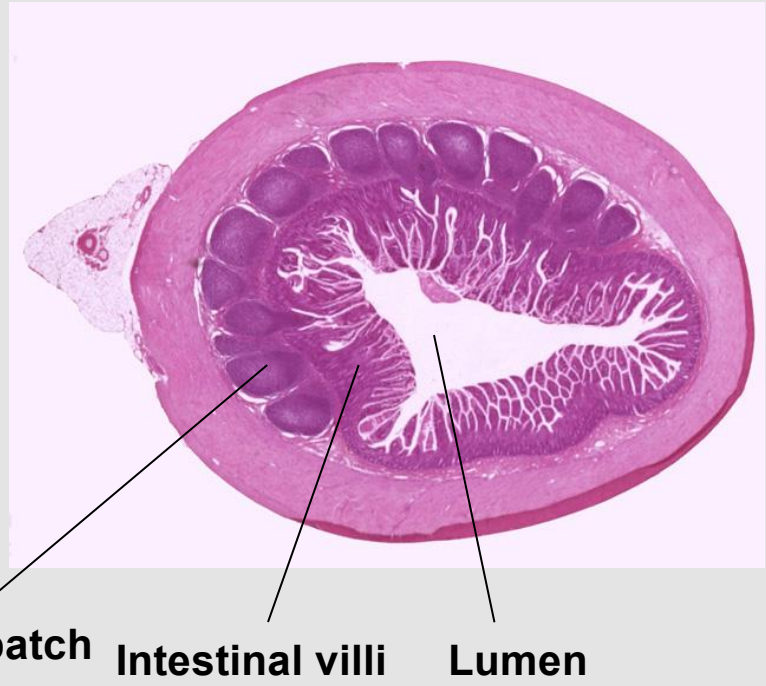
- Mucosa = **enormous surface** for the pathogens to enter the body!
- MALT = The **biggest lymphoid tissue**.
- MALT: can be further classified based on location:[14.]
  - GALT (gut-associated lymphoid tissue)
  - BALT (bronchus-associated lymphoid tissue)
  - NALT (nasopharynx-associated lymphoid tissue)
- Organized MALT (site of antigen recognition):
  - **Lymphoid cells form organized structures** such as follicles (e.g. tonsils of the Waldeyer-ring, Peyer's patches, cryptopatches, isolated follicles, see in the lectures)
- Diffuse MALT (has effector functions):
  - **Lymphocytes diffusely scattered** in the epithelial layer and lamina propria of mucosal surfaces (IEL=intraepithelial lymphocyte)

Organized MALT

Waldeyer-ring (tonsils):



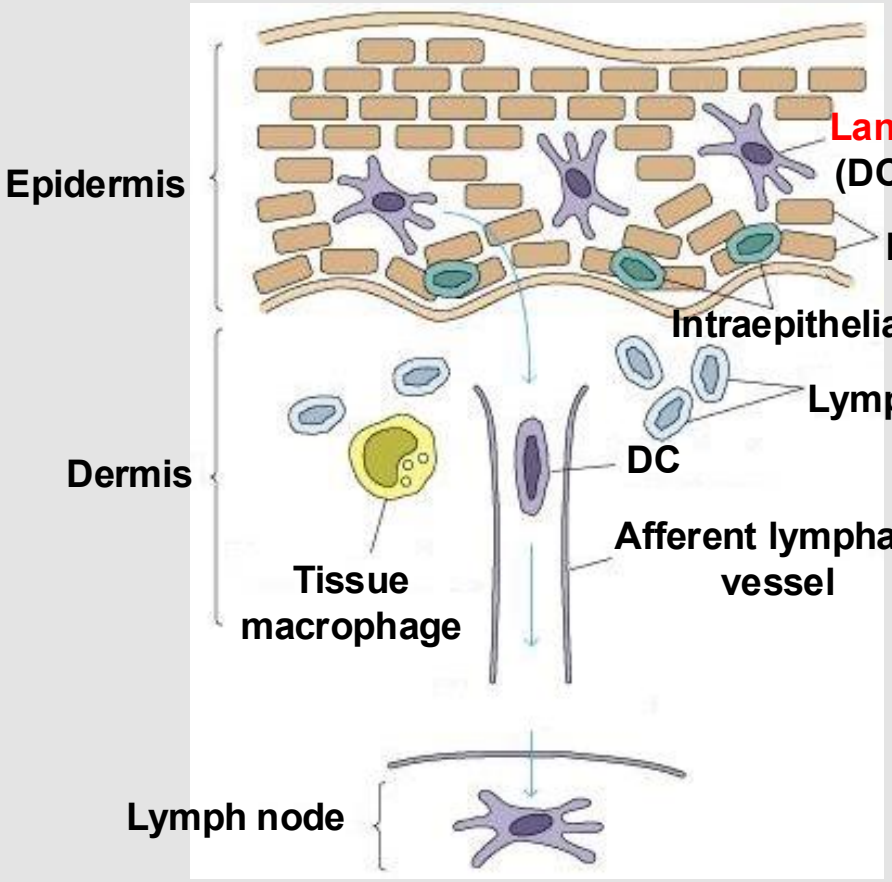
Peyer's patches in the ileum (H&E, cross-section):



Both tonsils and Peyer's patches have tissue architecture similar to that of lymph nodes (follicles with B cells, separated T cell zones, HEVs), but unlike lymph nodes **they do not have fibrous capsules**.

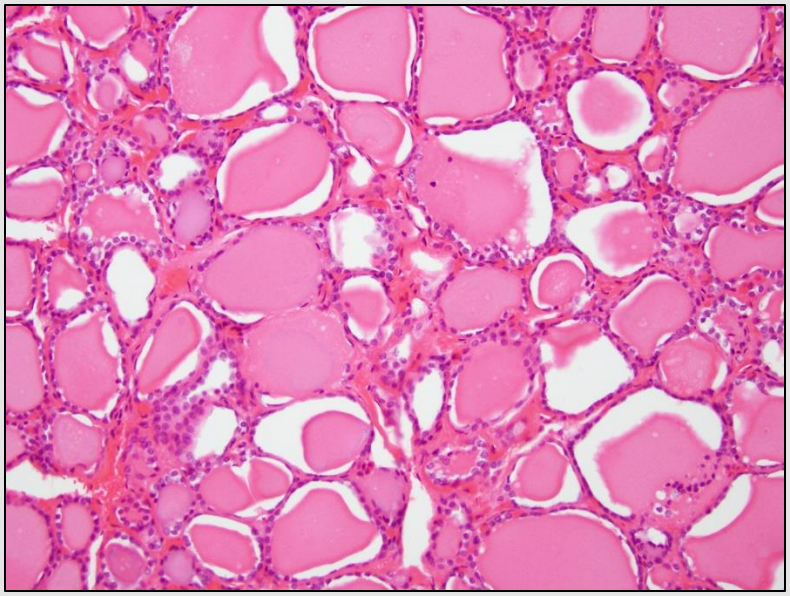
SALT (skin-associated lymphoid tissue)

Langerhans cells capture the antigen in the epidermis, then process it and move to the draining lymph node through lymphatic vessels. In the lymph node **they present the processed antigen** to helper T cells.[15.] Several cell types participate in the immunological defense of the skin. (e.g. keratinocytes, macrophages, γδ T cells, see later)

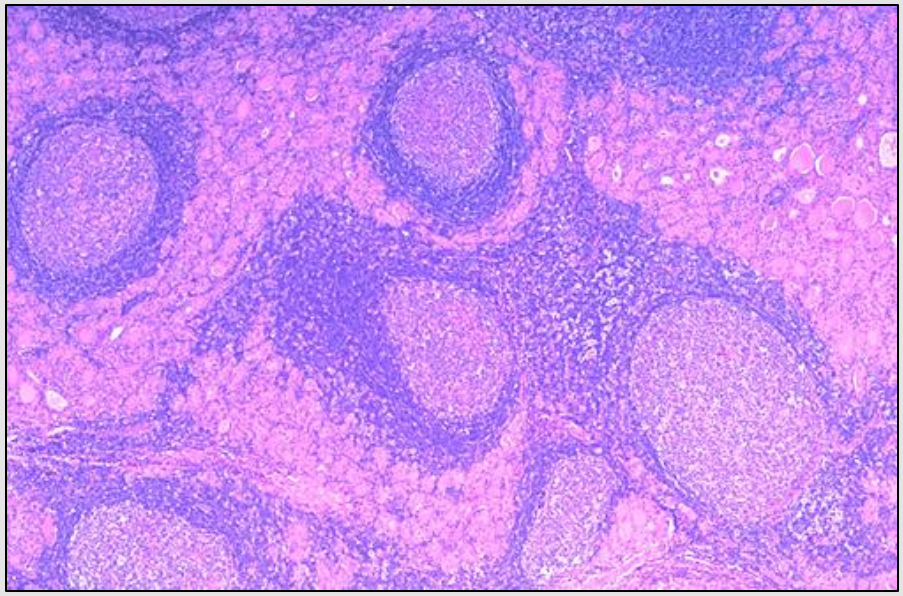


Example for tertiary lymphatic tissue

IT IS PATHOLOGICAL!



Healthy thyroid tissue
(medium magnification)



Ectopic lymphoid follicles in the thyroid gland in Hashimoto's thyroiditis
(small magnification)

Thank you for your attention!