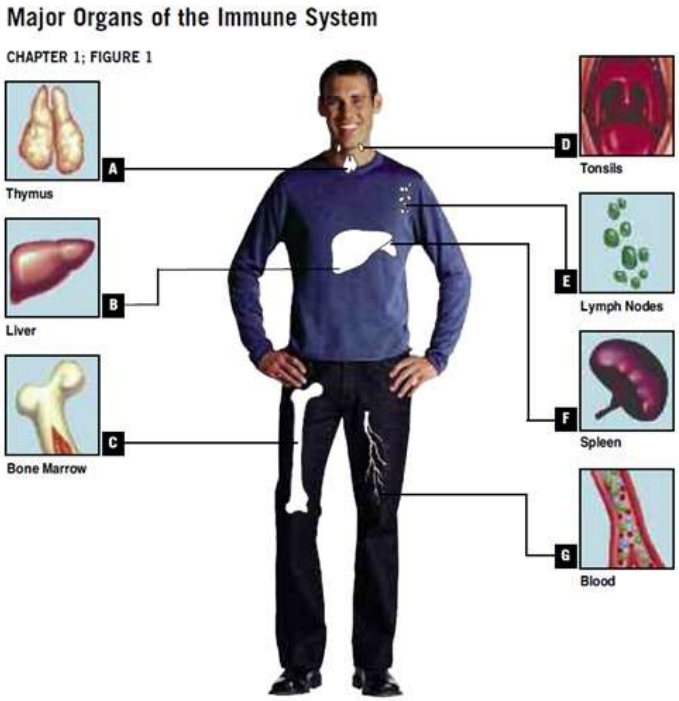
Corso di Laurea in
BIOTECNOLOGIE
Piano di studi Farmaceutico

Insegnamento di
Immunologia Farmaceutica



- ORGANI DEL SISTEMA IMMUNITARIO

12-03-2025

Organs of the Immune system

Primary lymphoid organs-

-where maturation takes place

-where lymphocytes become immunocompetent

-Thymus and bone marrow

-thymus= T-cells
-bone marrow= B-cells

Secondary lymphoid organs-

-where lymphoid cells encounter antigen

-where lymphoid cells are activated

-Lymph nodes, spleen, mucosal associated lymphoid tissue

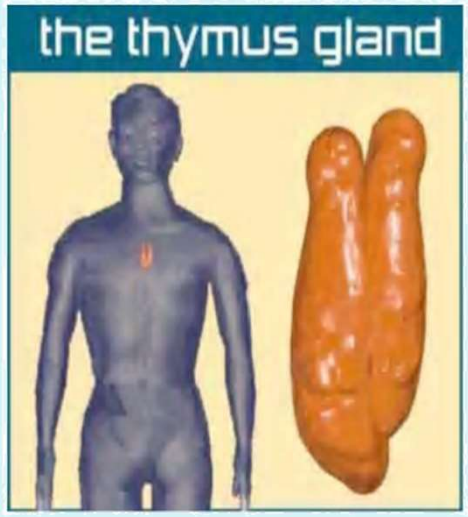
Lymphatic System- vascular network that collects fluid, cells and material from tissue and returns it to blood

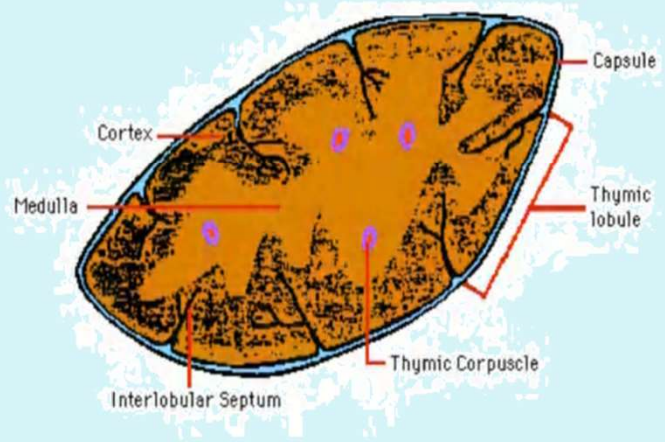
Thymus

Site of T-cell maturation

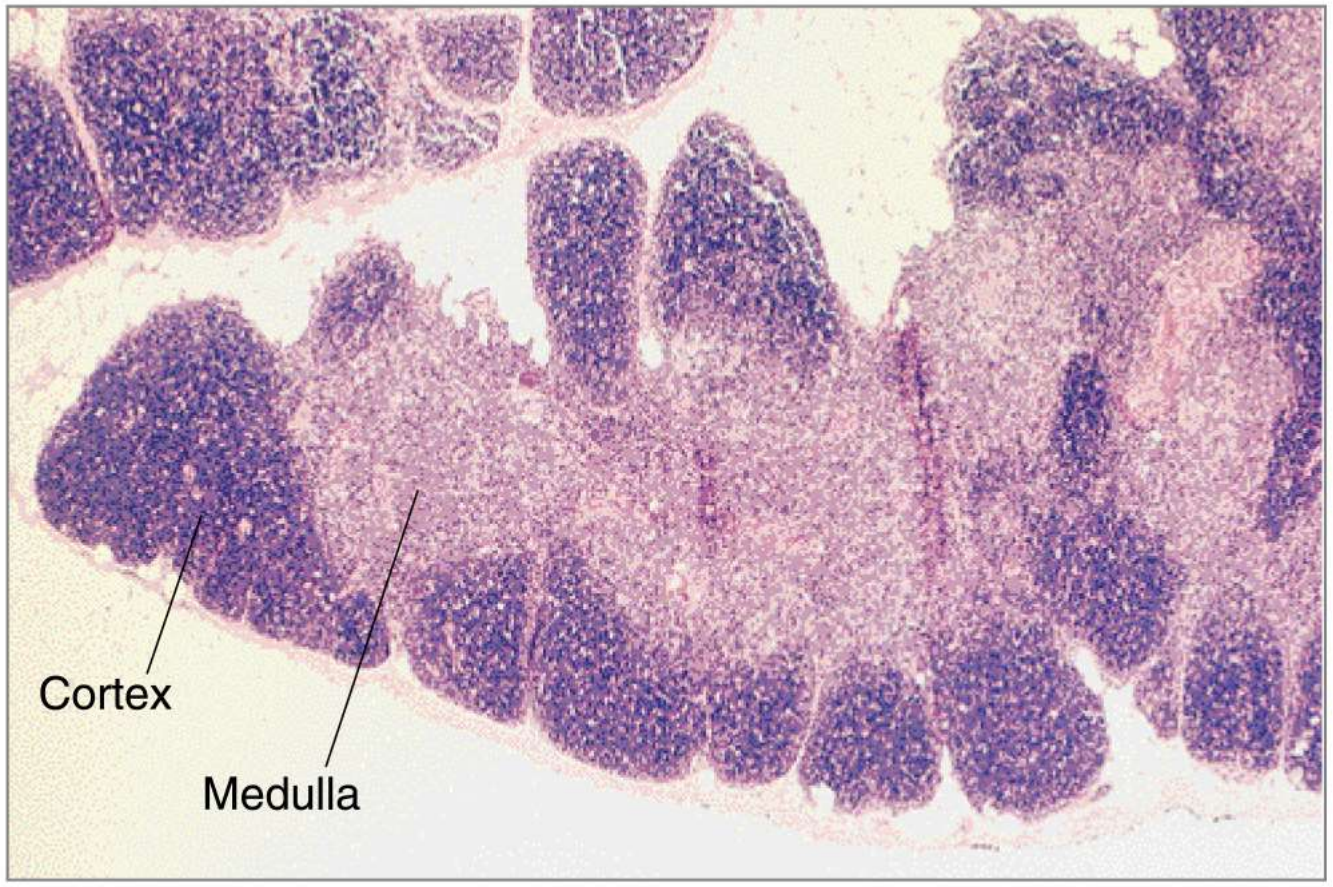
Bilobed organ, each lobe divided into lobules

Lobules organized into cortex (outer) and medulla (inner) region





Thymus



Fotografia al microscopio ottico di un lobo timico, che mostra il compartimento corticale, ricco di cellule T immature (timociti) e la zona midollare, meno popolata da timociti. Le cellule colorate in blu sono i timociti.

Thymus

The role of the thymus has been determined using several experimental systems and disease states.

Thymectomized mice- surgically remove thymus.

Nude Mice- genetic defect, results in mice lacking thymus.

DiGeorge's syndrome- microdeletion of chromosome 22 results in lack of thymus.

All conditions result in an organism without circulating T-cells that is very susceptible to infectious disease.

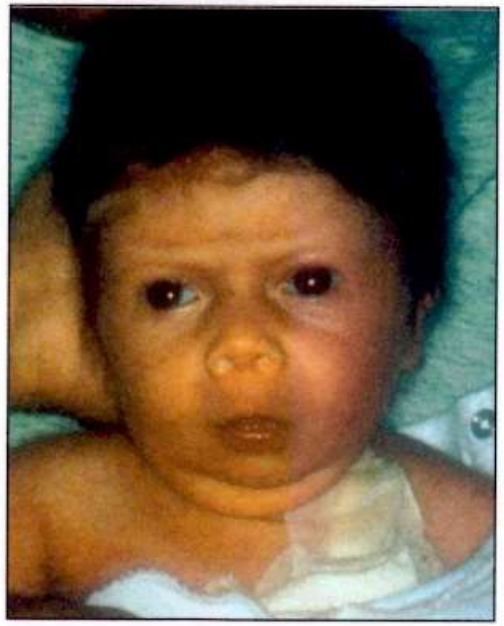


Fig. 9.3 Typical features of DiGeorge syndrome. These include low-set ears, hypertelorism (an increased distance between the eyes), and a small mouth and an underdeveloped jaw (micrognathia).

The case of Elizabeth Bennet: severe immunodeficiency as a result of disrupted development of the thymus.

Elizabeth Bennet was born at term after an uncomplicated pregnancy. She had a low birth weight of 2.1 kg, and dysmorphic facial features were noted at birth, including low-set ears as well as a relatively small mouth with an undersized lower jaw (micrognathia) (Fig. 9.3). At 2 days of life, Elizabeth developed feeding difficulties, rapid breathing, increased fatigue, and a bluish discoloration of the skin. She was diagnosed with truncus arteriosus, a severe congenital heart defect, characterized by a single common outflow tract leaving the heart instead of the normal two separate blood vessels—the aorta and the pulmonary artery. At 4 days of age, Elizabeth developed seizures. She was found to have very low blood levels of calcium (6.2 mg dl^{-1}, normal 8.5–10.2 mg dl^{-1}) and was treated with calcium and vitamin D.

Her hypocalcemia resulted from very low levels of parathormone in her blood, a hormone that is made by the parathyroid glands and is critical for regulating calcium and phosphorus homeostasis in the body.

Elizabeth underwent cardiac surgery for repair of her heart defect. No thymic tissue was identified intraoperatively. After successful surgery, genetic studies were done; these revealed a normal karyotype, which excluded major chromosomal rearrangements. However, with the help of fluorescence *in situ* hybridization (FISH), she was

found to have a deletion of the chromosomal region 22q11.2 on one of her two copies of chromosome 22, consistent with a diagnosis of DiGeorge syndrome (Fig. 9.4).

At an immune evaluation at 2 weeks old, Elizabeth's absolute lymphocyte count was low for her age, with 560 cells μl^{-1} (normal >2500 lymphocytes μl^{-1}). She had almost no $CD3^+$ T cells, with a count of 11 cells μl^{-1}, which was less than 1% of her total lymphocyte count, while $CD19^+$ B-cell numbers and $CD16^+/CD56^+$ NK cells were in the normal range for her age. Her peripheral blood mononuclear cells (PBMCs) responded poorly to the mitogens phytohemagglutinin (PHA) and concanavalin A (ConA), which is indicative of poor T-cell function (see Case 5 and Fig. 5.7). Her significant T-cell defect led to the diagnosis of complete DiGeorge syndrome, a rare variant of DiGeorge syndrome (less than 1% of all cases of DiGeorge syndrome) that is associated with severe immunodeficiency and death if not treated early in life.

Elizabeth was started on prophylactic antibiotics to prevent infection with the opportunistic pathogen *Pneumocystis jirovecii*. At 6 months of age she received a thymic transplant into her right leg quadriceps muscle. A biopsy of the thymic graft, performed a few months after transplantation, showed significant presence of thymocytes within the transplanted thymic tissue. One year after transplantation, Elizabeth had developed a significant number of T cells (860 $CD3^+$ cells μl^{-1}), although she did not reach normal T-cell counts. Her T cells responded normally to mitogens and antigens *in vitro*. After immunization, Elizabeth mounted protective antibody responses to tetanus toxoid, *Haemophilus influenzae* type b, and *Streptococcus pneumoniae* (pneumococcus). She required calcium supplementation for several months and needed repeat cardiac surgery at the age of 3 years, which she tolerated well.

At 6 years old Elizabeth developed purple bruises (purpura) and pinpoint red lesions (petechiae) on her skin. She was found to have a low platelet count of 15,000 μl^{-1} (normal 150,000–300,000 μl^{-1}). This was due to destruction of her platelets by autoantibodies, resulting in insufficient blood clotting and therefore bleeding into the skin, a condition called immune thrombocytopenia. She was successfully treated with high-dose intravenous gamma globulin (1 g per kg body weight), which resulted in a rapid increase in the platelet count to 115,000 μl^{-1}.

Newborn with heart defect, seizures, and hypocalcemia.

Severe T-cell lymphopenia.

Thymic transplantation, leading to improved T-cell count.

SECONDARY LYMPHOID ORGANS

- Organs with capsule
  - **Spleen**
  - **Lymph nodes**

- MALT: mucosal associated lymphoid tissue

  localized in the respiratory, gastrointestinae and urogenital trait.

- Cutaneous immune system

Lymphatic system

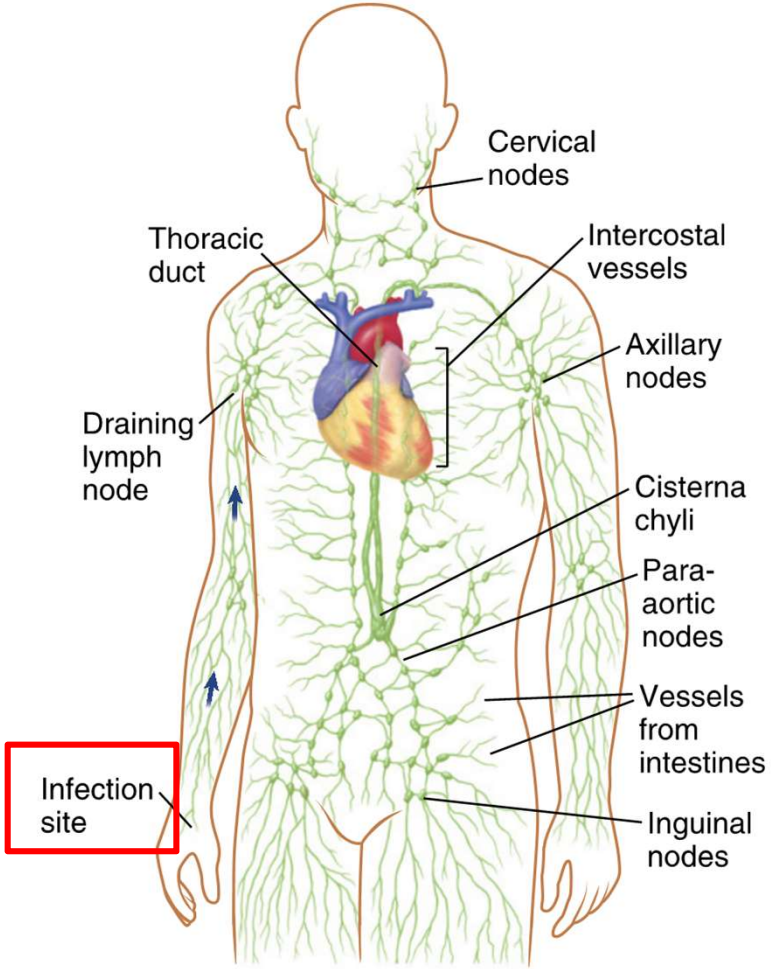
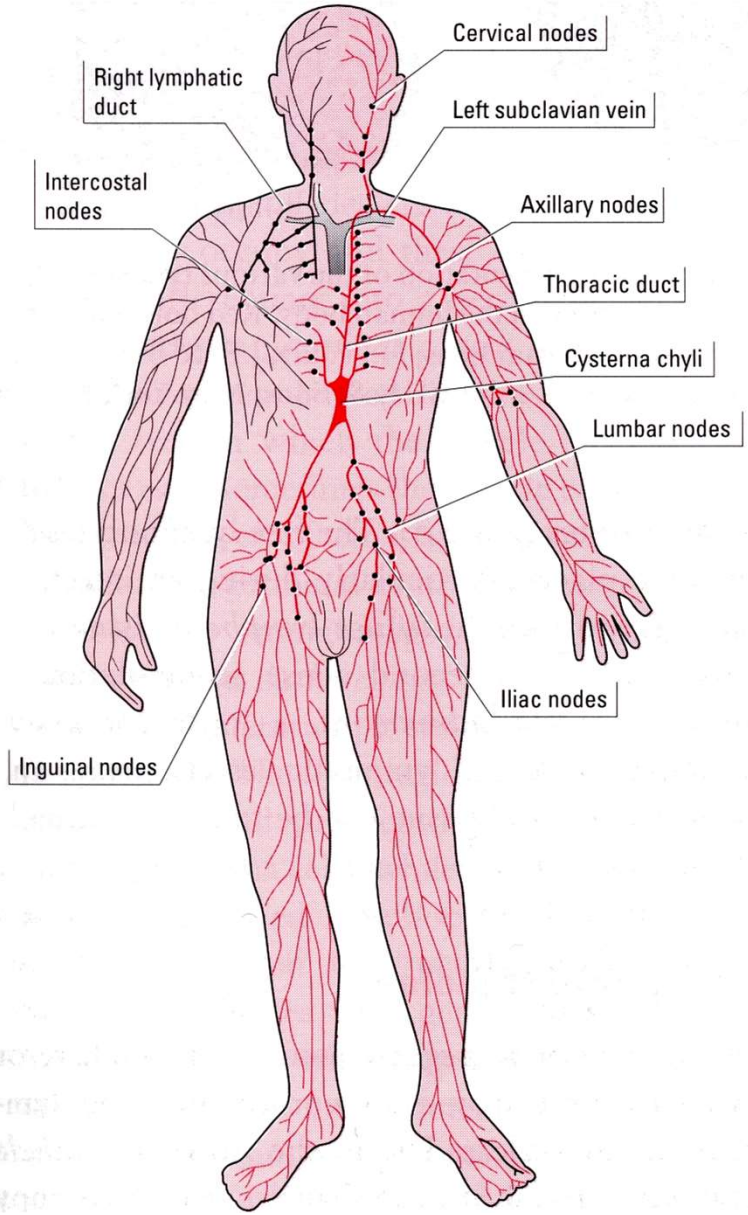
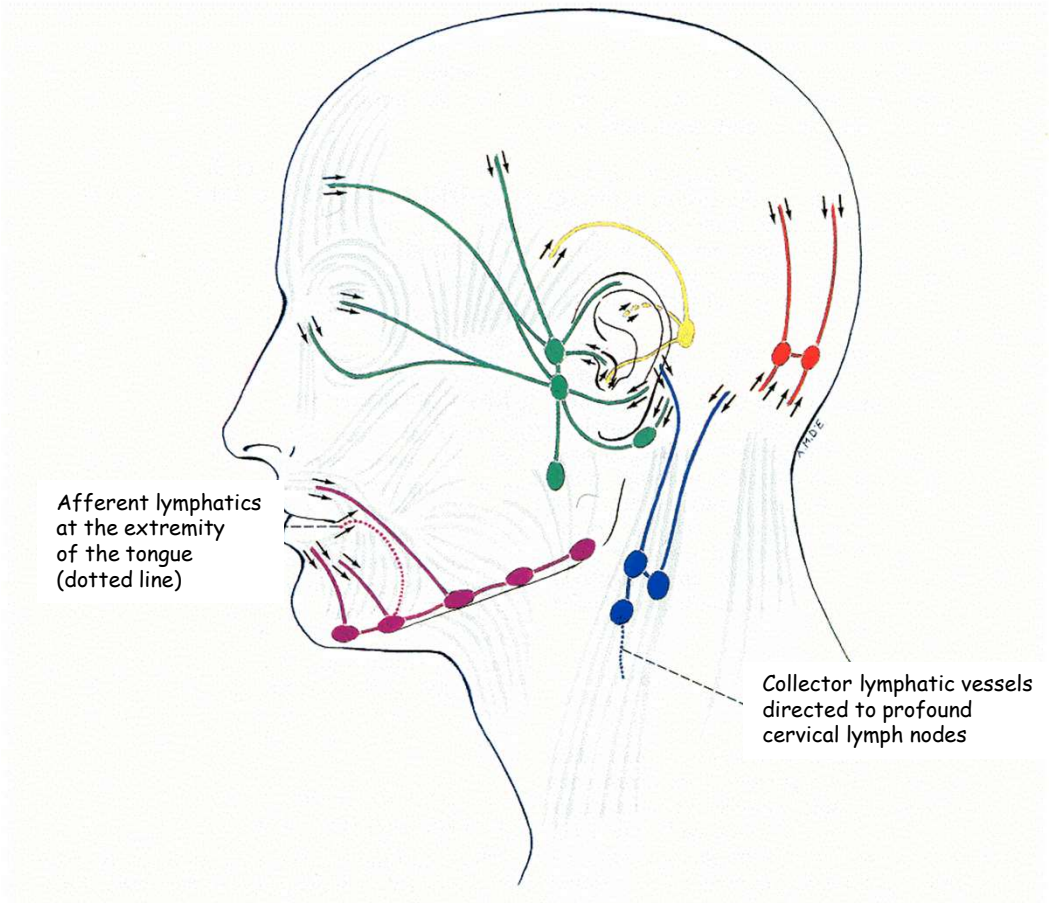


FIGURE 2.13 The lymphatic system. The major lymphatic vessels, which drain into the inferior vena cava (and superior vena cava, not shown), and collections of lymph nodes are illustrated. Antigens are captured from a site of infection and the draining lymph node to which these antigens are transported and where the immune response is initiated.

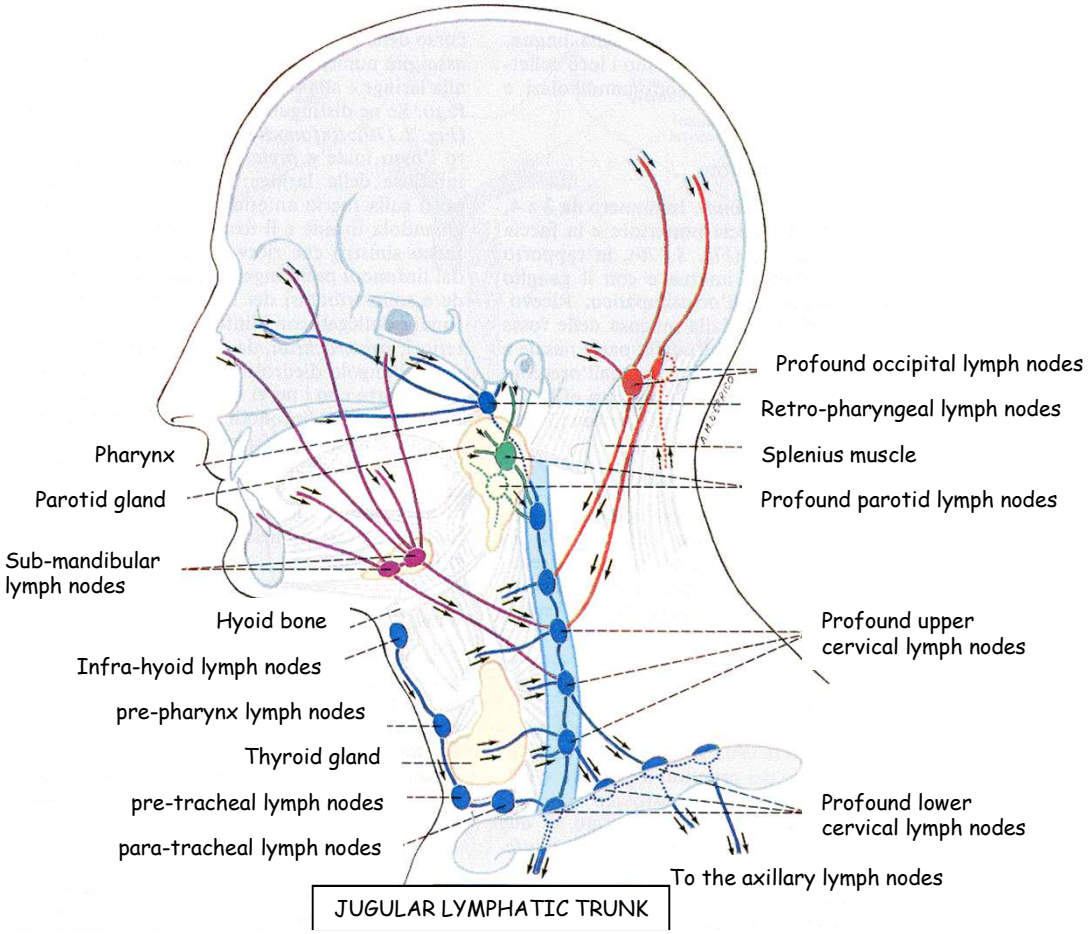


Superficial lymph nodes of head and neck



Orange: occipital lymph nodes
Blue: surface superior lymph nodes
Yellow: mastoid lymph nodes
Purple: under-chin lymph nodes

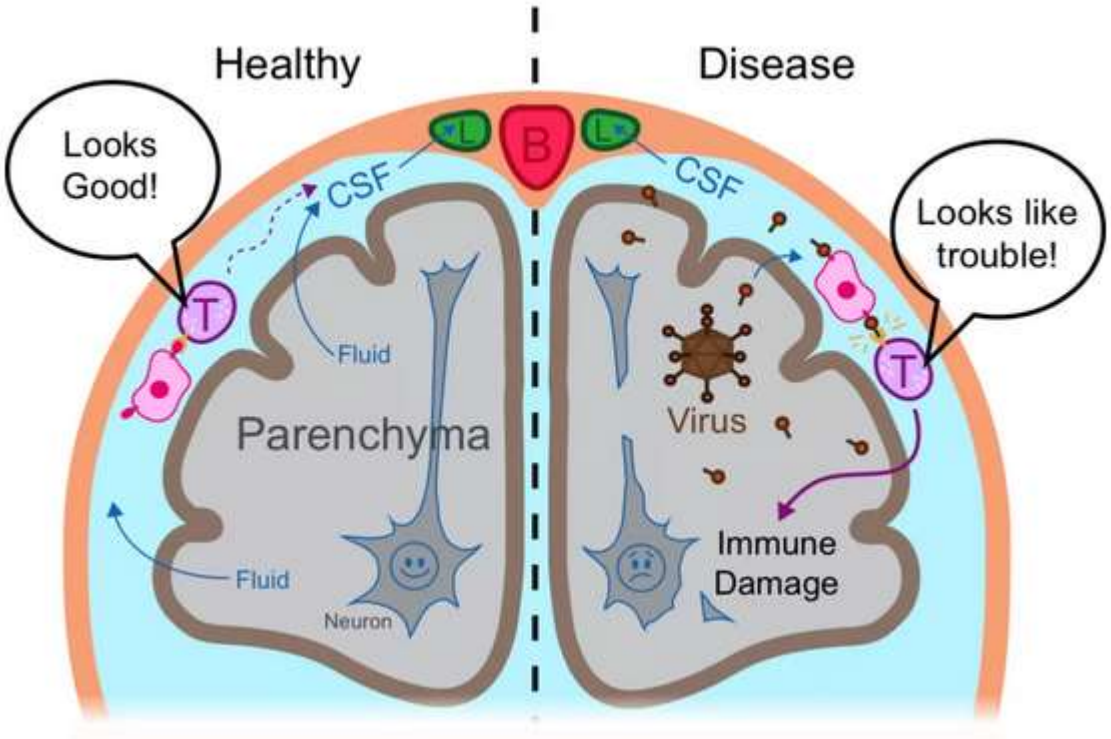
Profound lymph nodes of head and neck



Immunology of the CNS: still a matter of privilege?

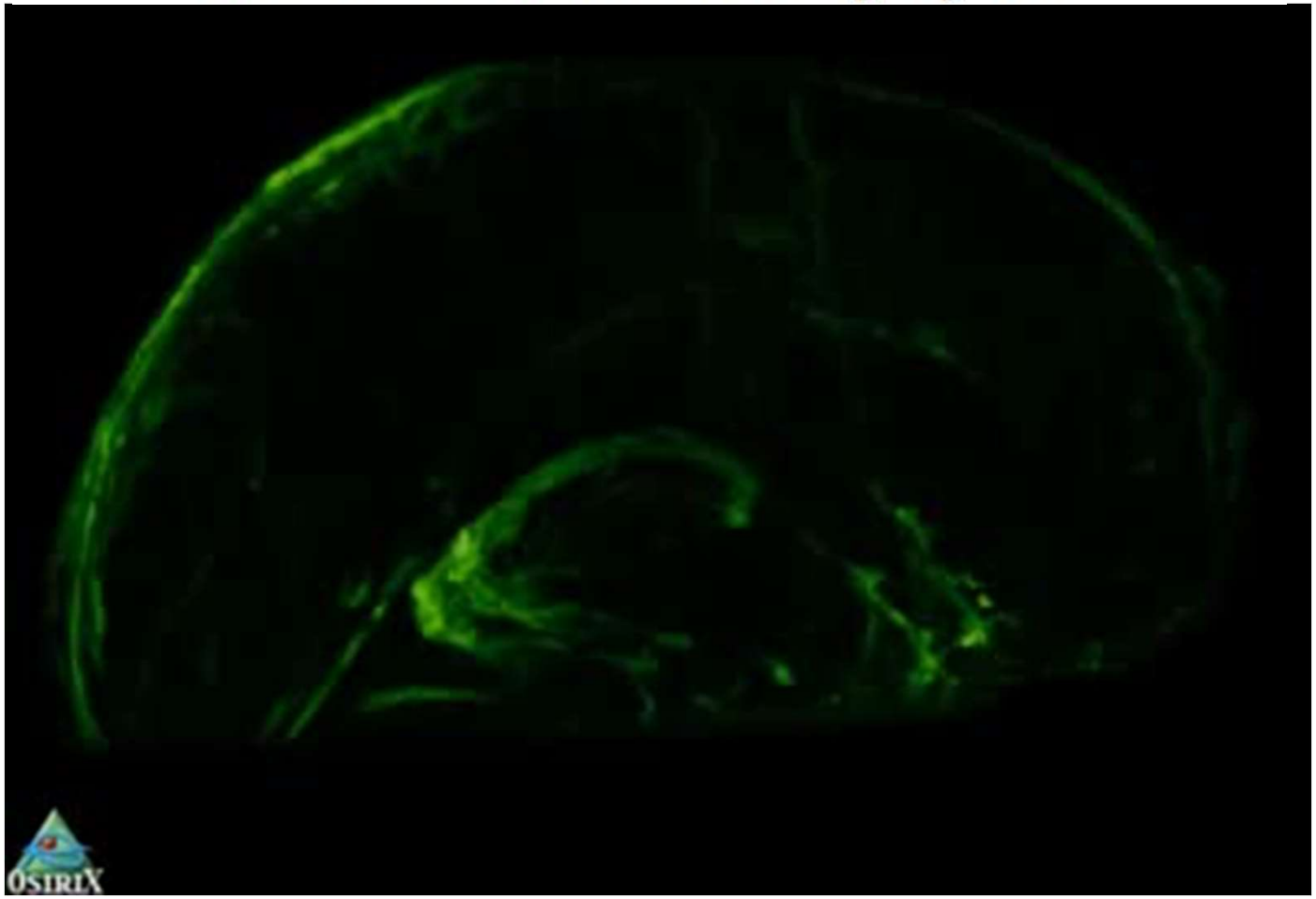
Is the brain: an immunological no-fly zone?

The brain was considered an immune-privileged site, meaning it doesn't play by typical immune system rules



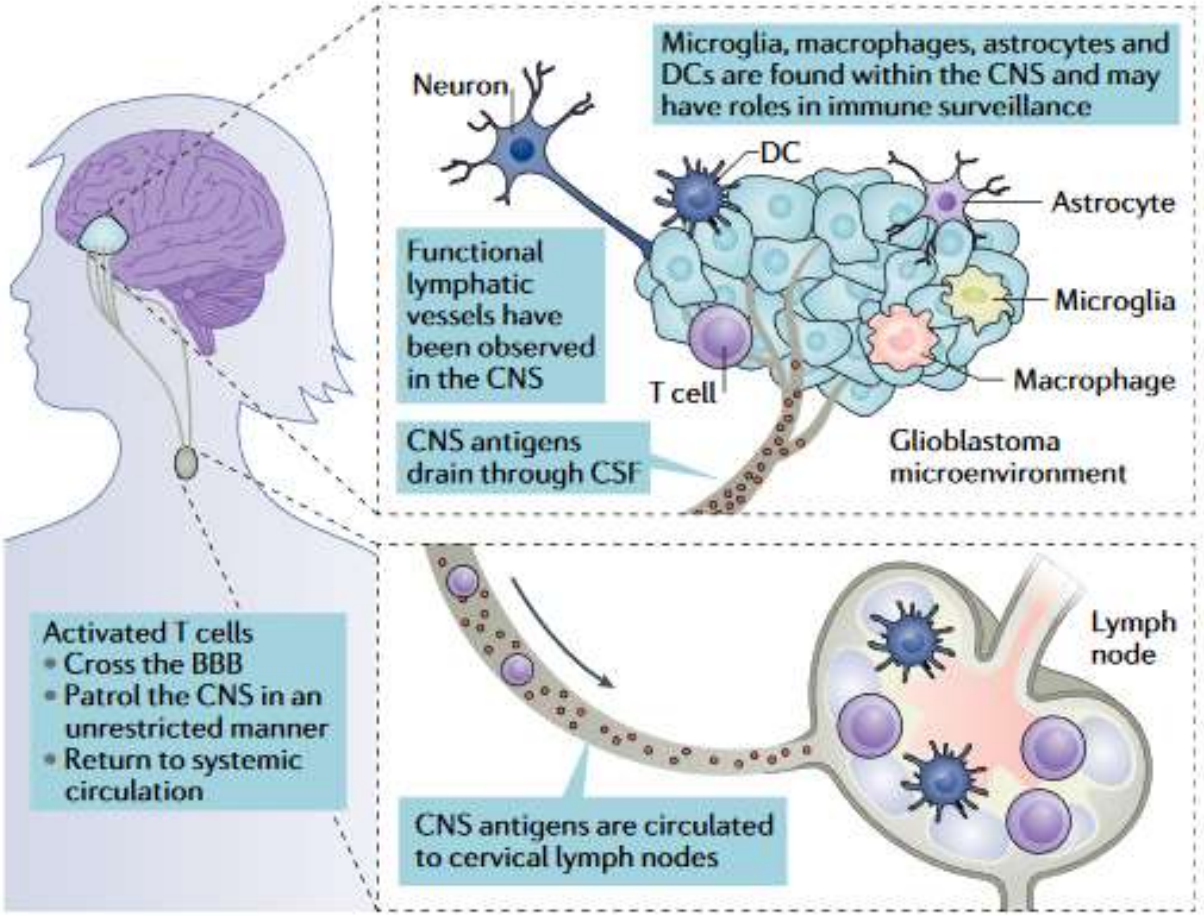
New Imaging Approach Reveals Lymph System in Brain

Human and nonhuman primate meninges harbor lymphatic vessels that can be visualized noninvasively by MRI



eLife 2017;6:e29738 DOI: 10.7554/eLife.29738

Novel insights in the immunology of the CNS



Sampson et al., Nat. Rev. Cancer, 2020

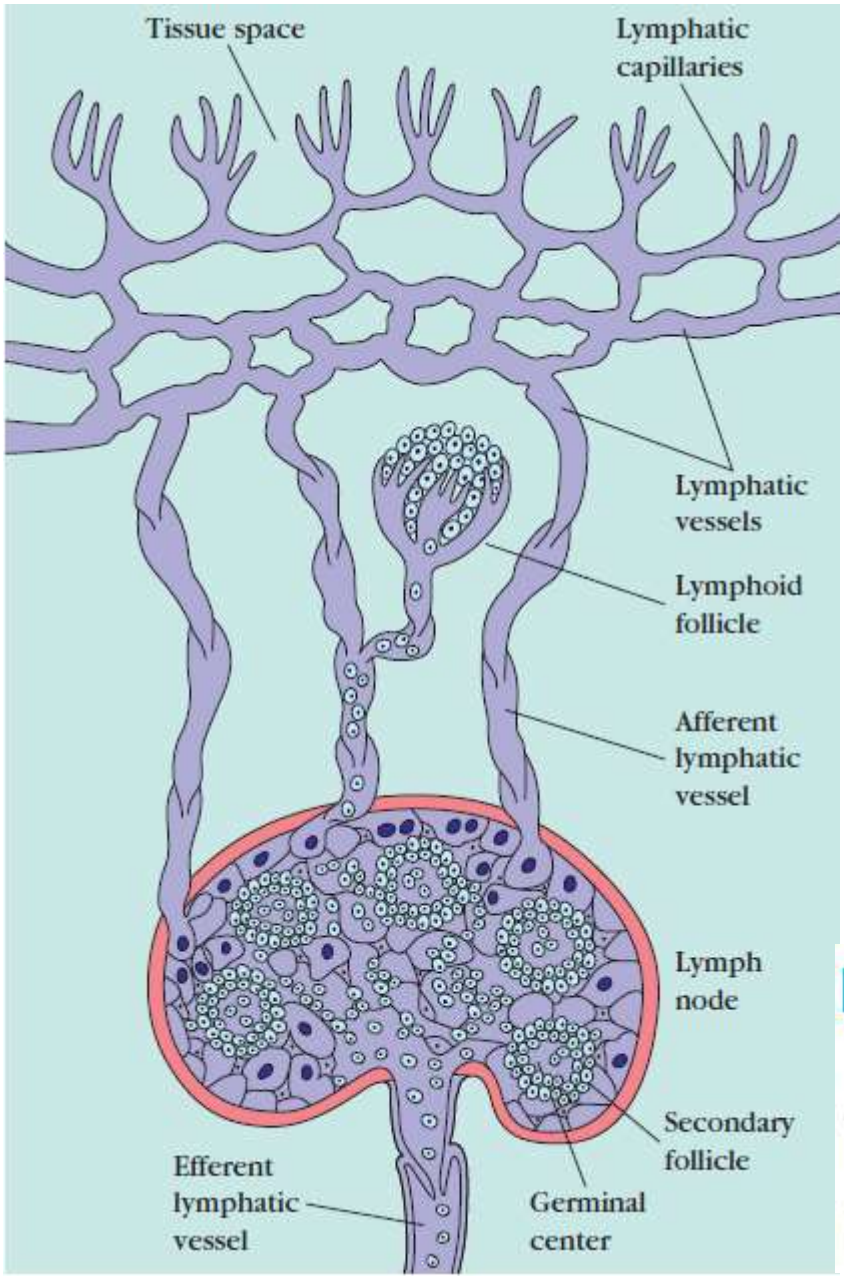
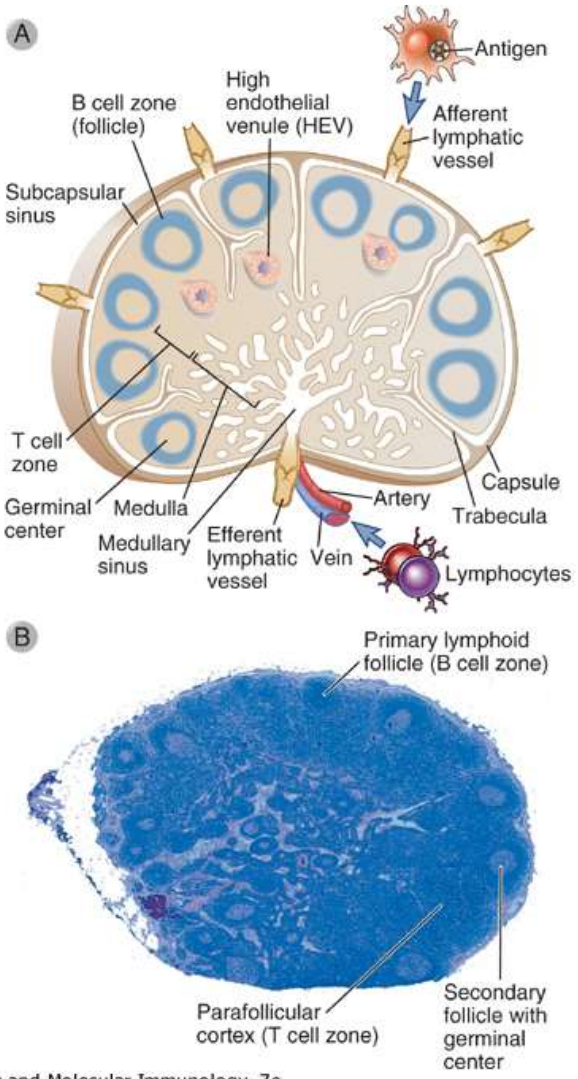


FIGURE 2-16 Lymphatic vessels. Small lymphatic capillaries opening into the tissue spaces pick up interstitial tissue fluid and carry it into progressively larger lymphatic vessels, which carry the fluid, now called lymph, into regional lymph nodes. As lymph leaves the nodes, it is carried through larger efferent lymphatic vessels, which eventually drain into the circulatory system at the thoracic duct or right lymph duct (see Figure 2-13).

Lymph node structure: T and B areas



Abbas et al: Cellular and Molecular Immunology, 7e.

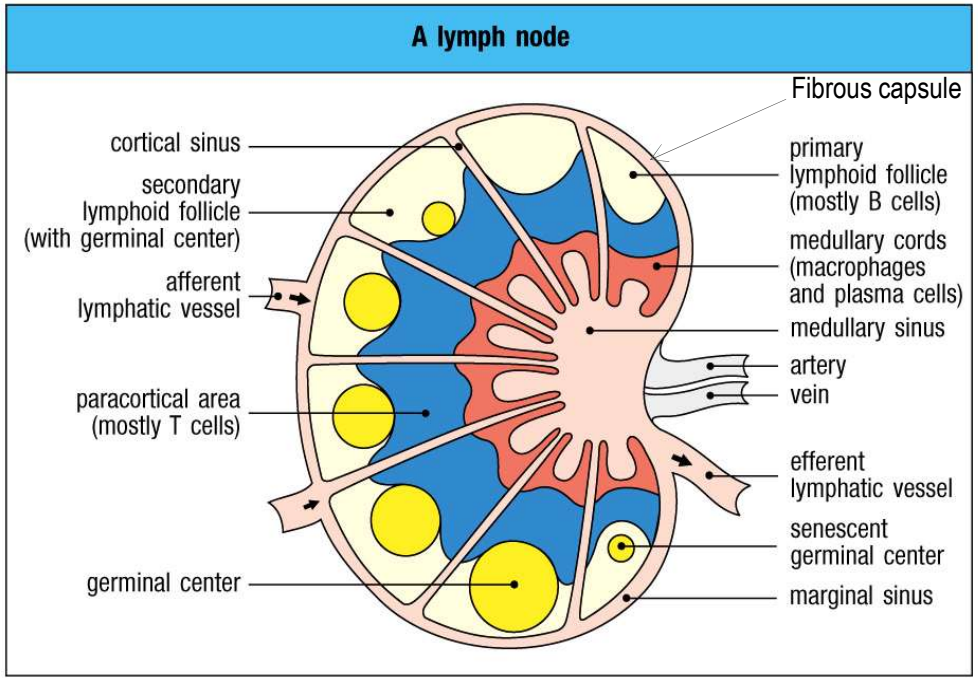
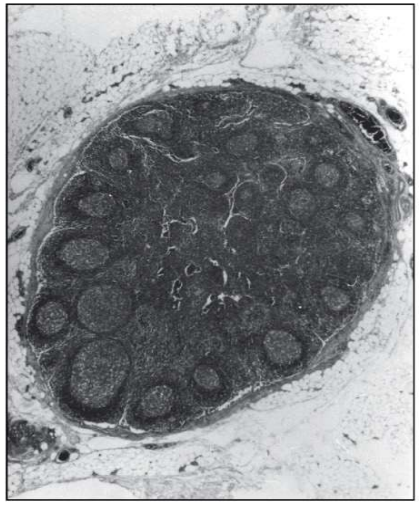
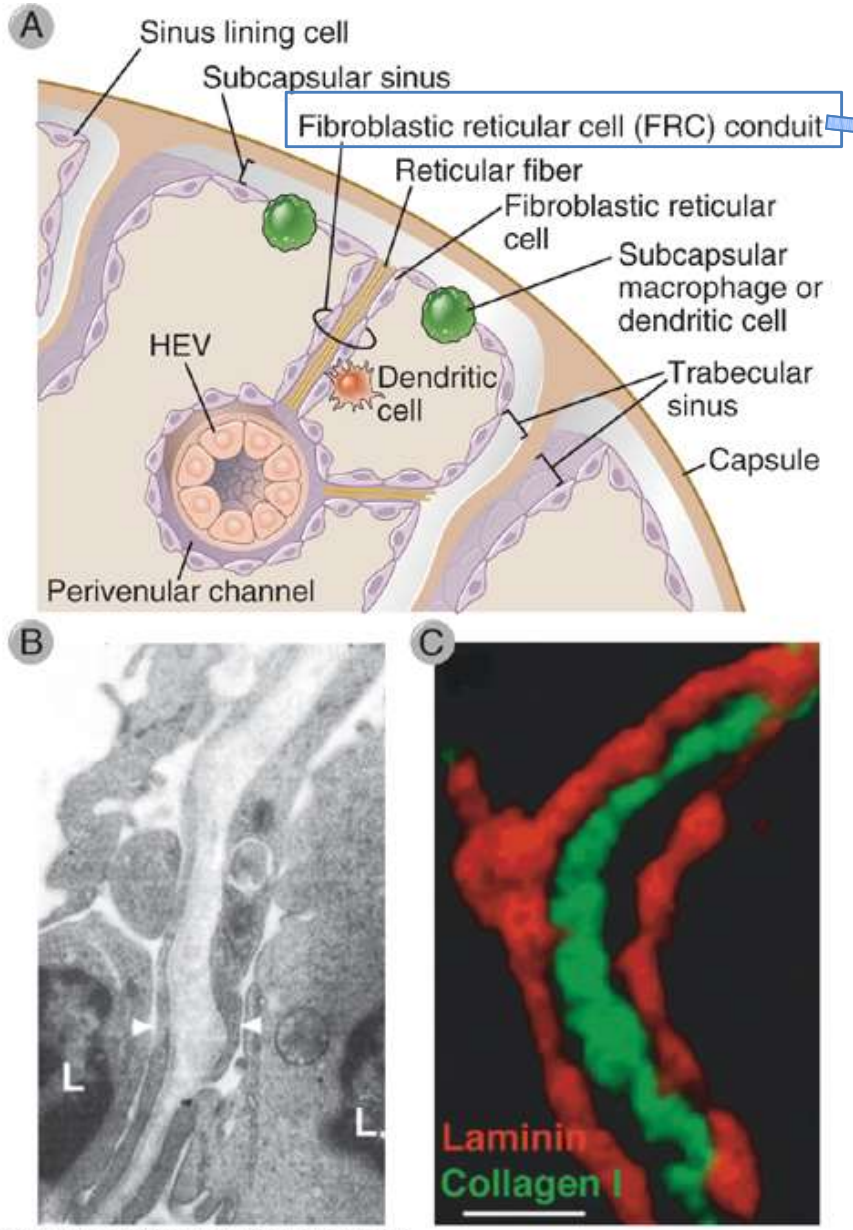


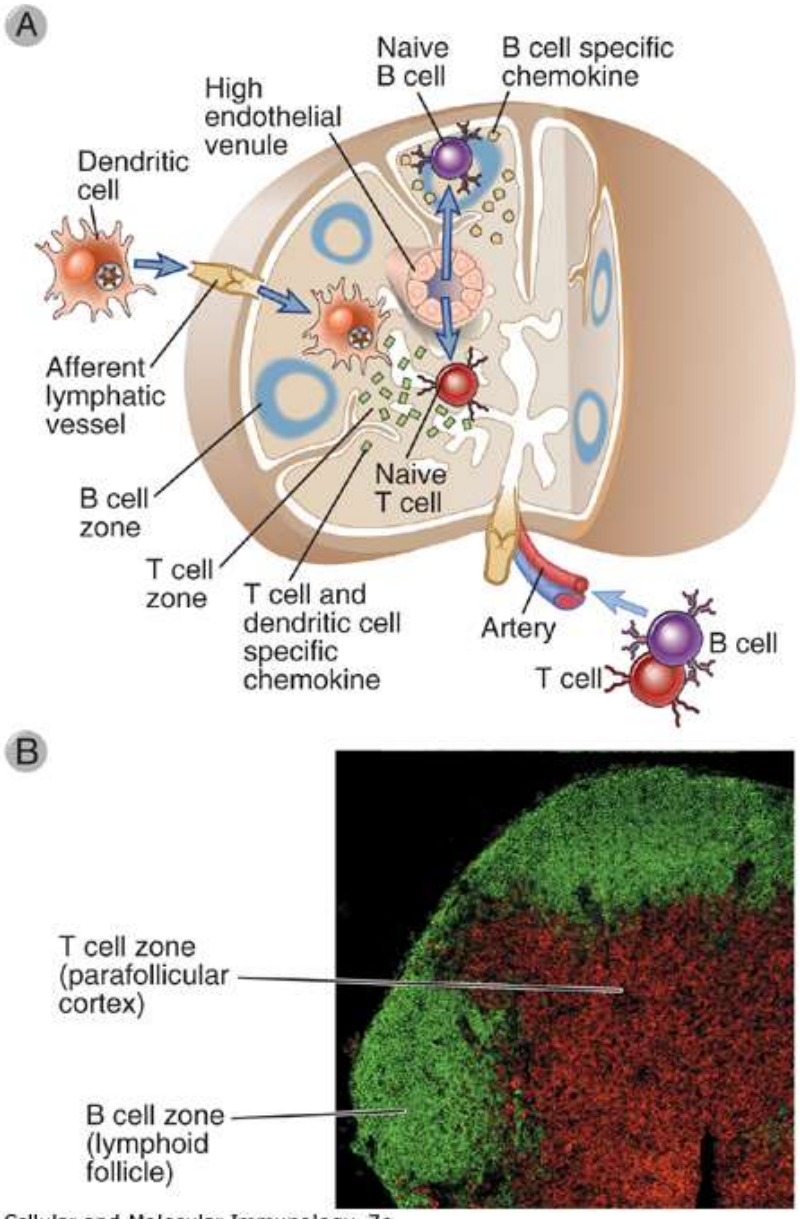
Figure 1.22 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)



Microanatomy of the cortical to paracortical zone (paracortex)



Servono a trasportare antigeni che arrivano ai ln attraverso i linfatici afferenti verso le aree T



Chemokines and naïve limphocytes migration

B Lymphocytes

CXCR5 - CXCL13

- Espresso da B naive
- Prodotto da FDC presenti nei follicoli

T Lymphocytes and DC

CCR7 - CCL19, CCL21

- Espresso da T naive e da DC
- Prodotte da FRC e altre cellule delle aree T del ln

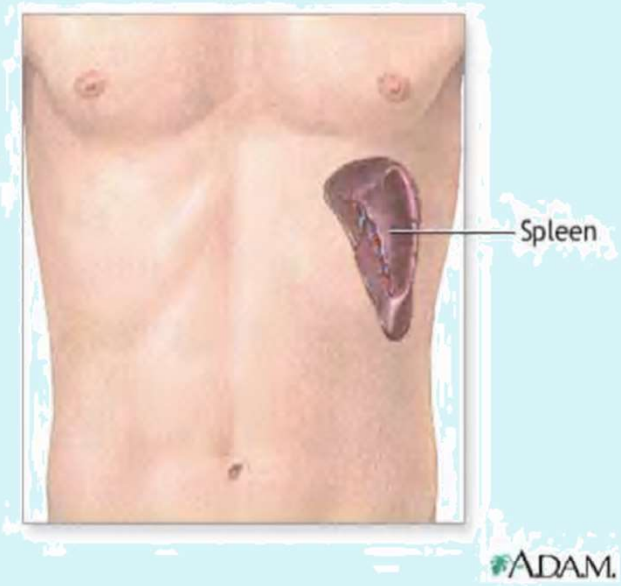
Antigen Presenting Cells (APC) and lymph node areas

Follicles (B lymphocytes)
Follicular Dendritic Cells

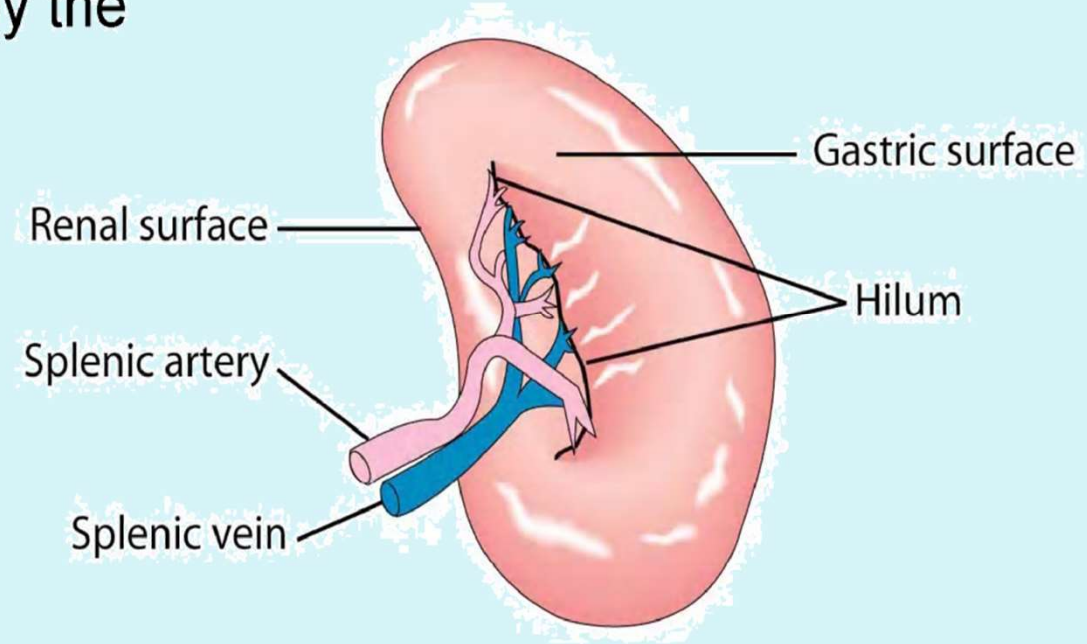
Paracortical (T lymphocytes)
(Interstitial) Dendritic Cells

MILZA

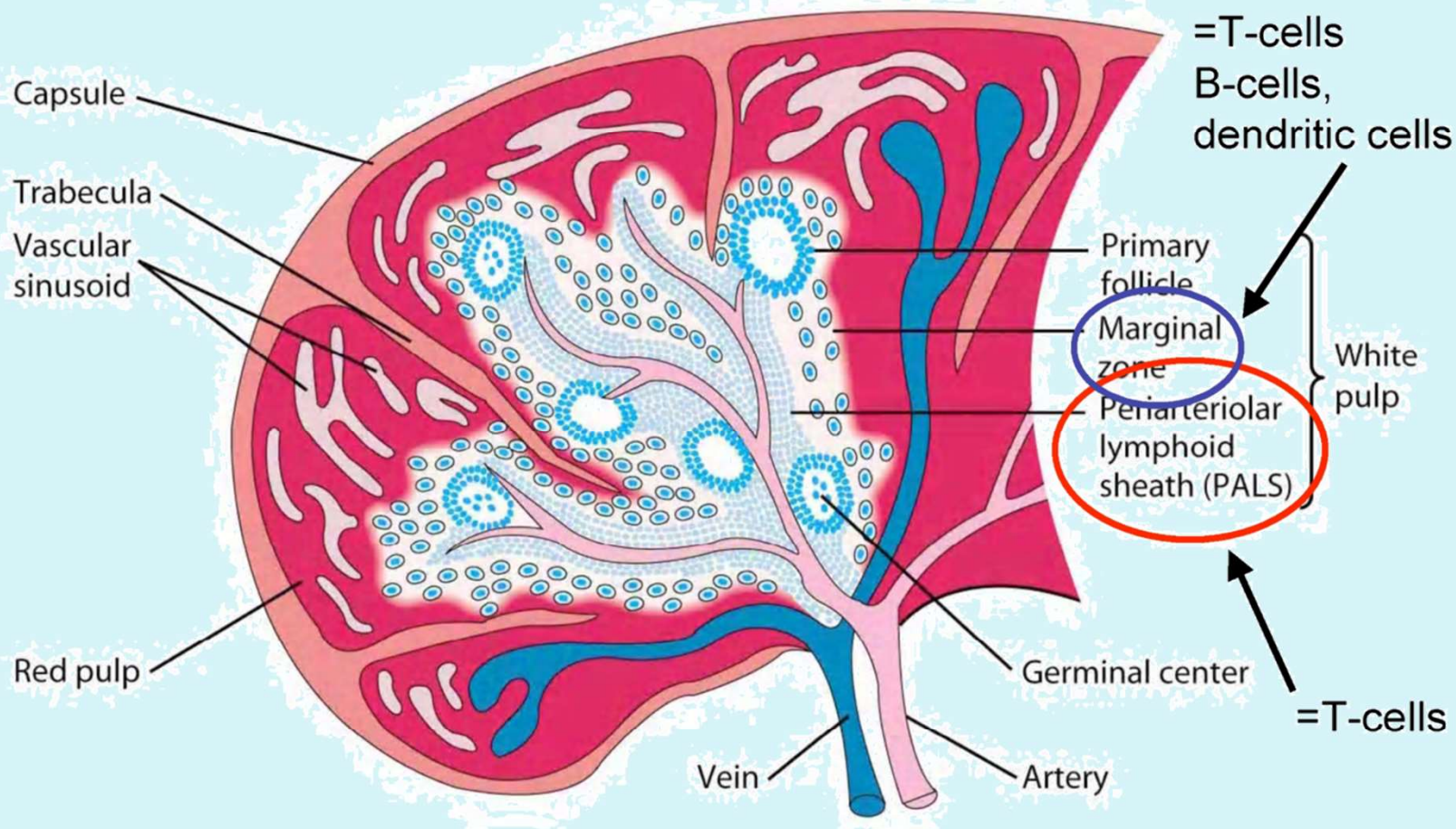
It carries out the function of filtering foreign substances present in the blood and of blood purification from dying or damaged cells



Lymphocytes and antigen are carried to the spleen by the splenic artery



The Spleen


Capsule
Trabecula
Vascular sinusoid
Red pulp
Vein
Artery
Germinal center
Primary follicle
Marginal zone
Periarteriolar lymphoid sheath (PALS)
White pulp
=T-cells
B-cells,
dendritic cells
=T-cells

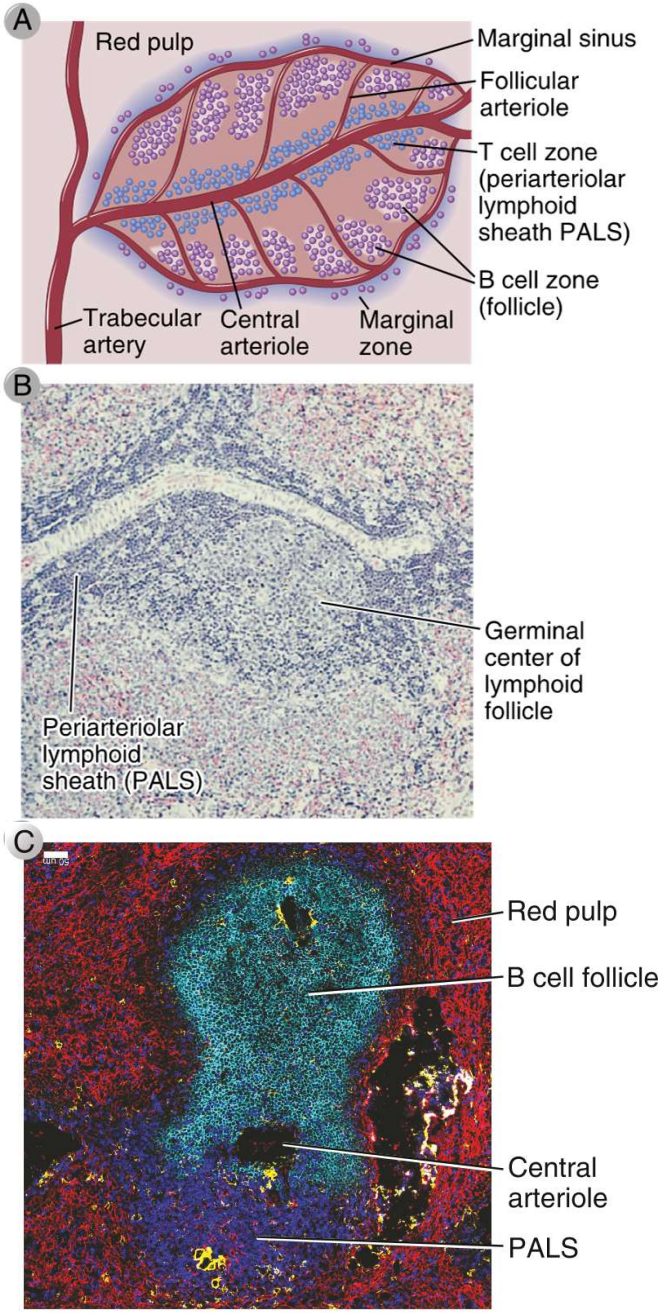
The red pulp is the place of the emo-cateresis functions of the organ

The white pulp is the place of the functions of the lymphoid organ

Gli individui splenectomizzati sono suscettibili a infezioni disseminate da parte di batteri capsulati come i pneumococchi e i meningococchi.

Questo perché probabilmente tali organismi sono normalmente eliminati tramite opsonizzazione e fagocitosi.

Inoltre la milza è un importante sito di produzione di anticorpi.



Mucosal Associated Lymphoid Tissue

Mucosal tissue- digestive, urogenital and respiratory tracts
-cumulatively about 400 m^2= a basketball court

-major site of pathogen entry

Consequently hosts defense are marshaled to these tissues in the form of mucosal associated lymphoid tissue (MALT).

Tonsils
Appendix
Intestinal Tract

Il MALT è presente in tutte le mucose al di sotto della membrana basale.
Alcune mucose hanno una organizzazione simile ai linfonodi, con zone distinte per i linfociti T e B e i tipici follicoli linfoidi, ad esempio nelle tonsille, nelle placche di Peyer dell'intestino tenue.

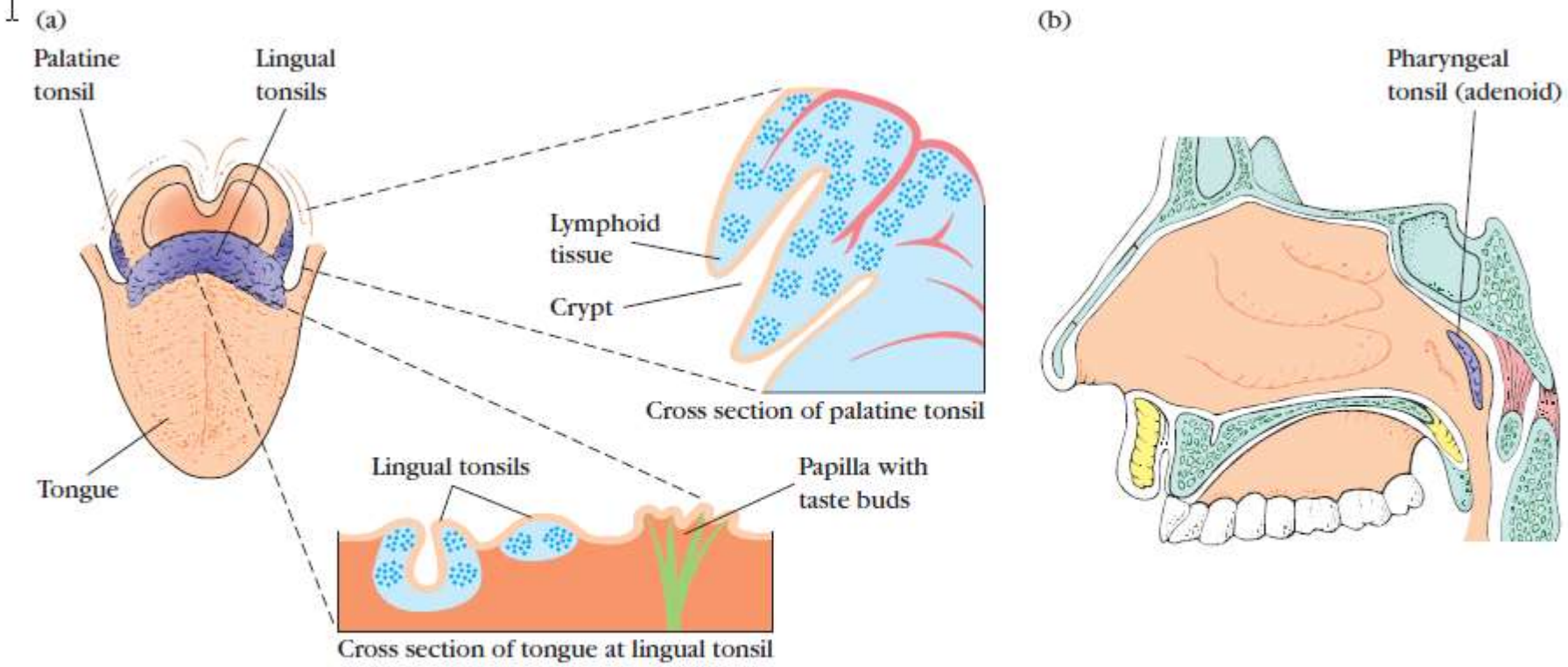


FIGURE 2-20 Three types of tonsils. (a) The position and internal features of the palatine and lingual tonsils; (b) a view of the position of the nasopharyngeal tonsils (adenoids). [*Part b adapted from J. Klein, 1982,* Immunology, The Science of Self-Nonself Discrimination, © *1982 by John Wiley and Sons, Inc.*]

Tutte e tre i tipi di tonsille (palatina, linguale e faringea) sono strutture nodulari che consistono di una rete di cellule reticolare e fibre disperse tra linfociti, macrofagi, granulociti e mastociti.
Le cellule B sono organizzate in follicoli e centri germinativi.
Le tonsille ci difendono contro antigeni che entrano attraverso gli epiteli del naso e della bocca.
MALT associato all'intestino= GALT
Quello associato all'albero bronchiale= BALT

Infiltrato linfocitario e tessuto linfoide terziario

In qualsiasi tessuto un processo infiammatorio cronico prolungato può portare allo sviluppo di un infiltrato linfocitario organizzato in modo simile a quello del tessuto linfoide secondario.

Questo accade, per esempio, nella ghiandola tiroide colpita da **tiroidite di Hashimoto** e nella sinovia articolare affetta da alcune forme di **artrite reumatoide.**

Questo tessuto linfoide neoformato è detto **tessuto linfoide terziario**.