Immunology

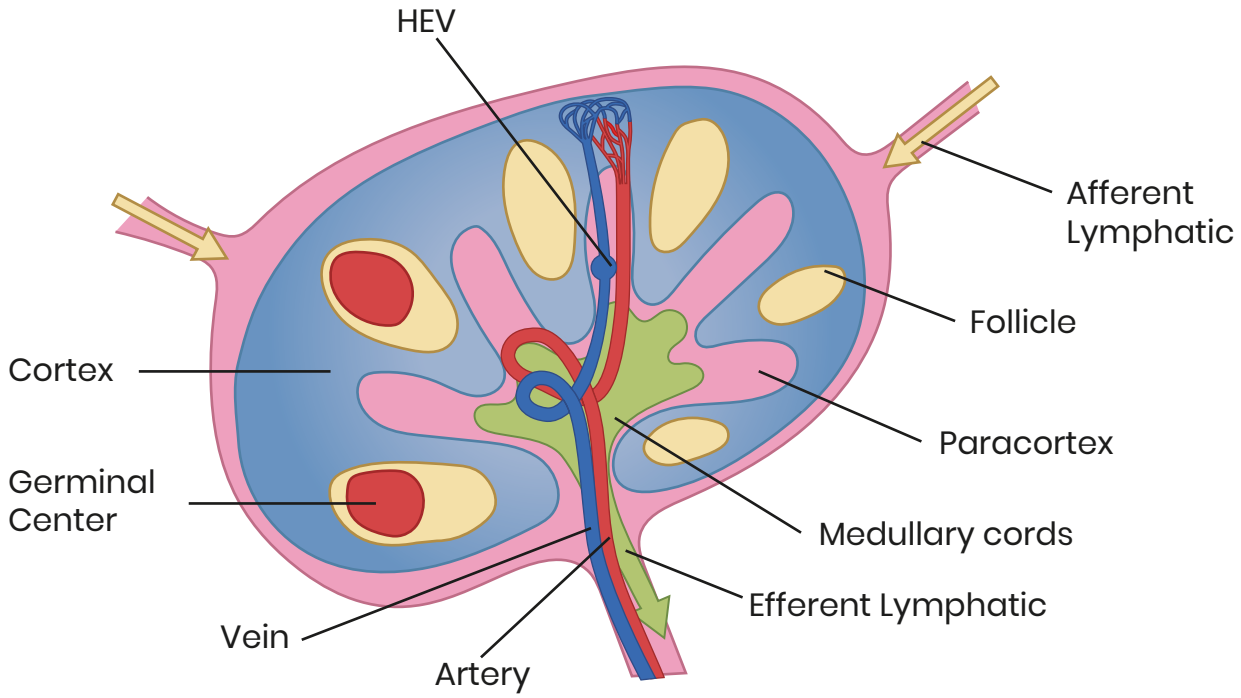
Lymphocyte Trafficking

Chapter three

The adaptive lymphocytes which have finished their development in the primary lymphoid organs (bone marrow and thymus) have not yet "seen" the foreign molecule (antigen) that will bind to their BCR or TCR and are said to be "naïve" or "virgin". The anatomical locations in which these cells can now be exposed to their cognate antigen and "trained in battle" are the **secondary lymphoid organs**; the **lymph nodes**, **spleen** and **mucosal associated lymphoid tissues (MALT).** These organs have evolved to sample the fluids at key points of entry for microbial pathogens. The lymph nodes filter lymph and therefore sample entry from any cutaneous or mucosal surface. The spleen filters the blood and therefore catches pathogens that have become blood borne. The MALT (specifically the Peyer's patches) sample the intestinal contents to evaluate the difference between potentially harmful invaders and harmless commensals and useful calories.

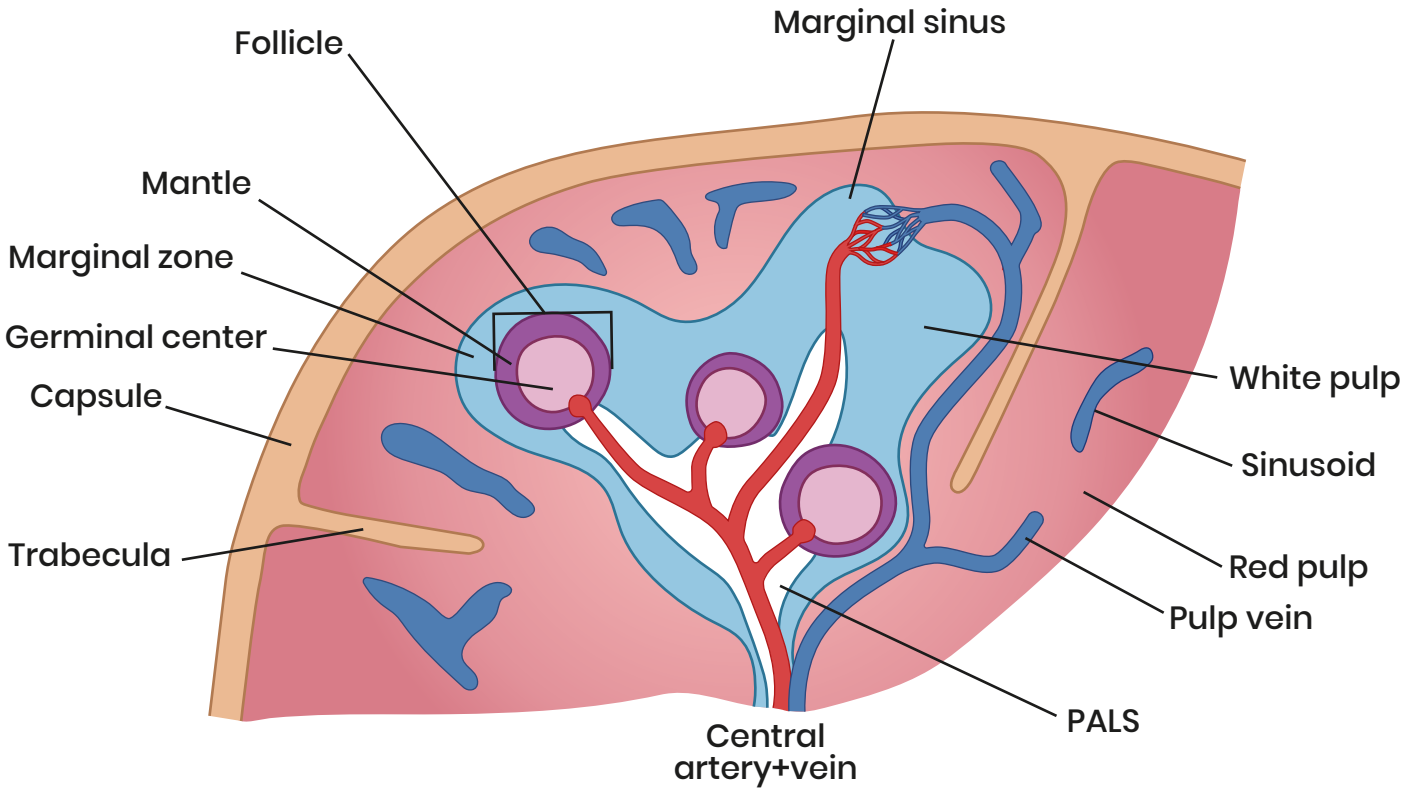
The trafficking or recirculation of lymphocytes is controlled by chemokines and adhesion molecules. Different categories of lymphocytes have receptors for different **chemokines**, which attract them, along a chemical gradient toward specific regions of the secondary lymphoid organs. The lymph nodes and Peyer's patches contain **high endothelial venules (HEV)** which allow the **L-selectins** on the lymphocytes to bind to their complementary **addressin molecules (Sialyl Lewis-X)** on HEVs, and "home" to particular locations in those organs. The spleen does not contain HEVs, but instead lymphocytes leave the blood sinusoids which make up the red pulp and travel by a process of diapedesis (discussed with inflammation in the next chapter) to establish residence in the white pulp. All of the secondary lymphoid organs are designed to be locations where lymphocytes can be exposed to their cognate antigen and collaborate with one another to make the most effective immune response possible. The rate of recirculation of mature, naïve lymphocytes through these areas is quite dramatic: it is estimated that on average, a given lymphocyte will check in to each lymph node in the body once a day, and the spleen every other day.

The Architecture of the Lymph Node Figure 9



Lymph and foreign antigen enter the lymph node through afferent lymphatics and the subcapsular sinus. The subcapsular sinus is lined with macrophages. Lymphocytes arrive through high endothelial venules and move to their respective regions; **B lymphocytes to the cortex** where they form **follicles** and **germinal centers**, and **T lymphocytes to the paracortex.** As antigen percolates over the layers of cells, it would first have the opportunity to be captured by macrophages, then B lymphocytes and follicular dendritic cells in the cortex. If it is not bound by any of these cells, the medullary cords are also lined with macrophages for a final chance at capture. If lymphocytes are activated, they will clone themselves and the node will swell in size. Immunologic products of their activation (antibodies, effector cells, memory cells) will leave through the hilum, and circulate in lymphatic vessels until they are combined into the **thoracic duct** which drains into the systemic circulation through the **left subclavian vein.**

The Architecture of the Lymph Node Figure 10



The spleen is the body's largest secondary lymphoid organ. The spleen red pulp serves the function of filtering the blood through sinusoids which are lined with macrophages. Aged red blood cells are removed here, and any foreign material that has gotten into the blood will also be phagocytized. The blood supply to the spleen is by the single splenic artery, and the arterioles which branch off become surrounded by **periarteriolar lymphoid sheaths** which are **T cell rich** areas. B lymphocytes create **follicles** outside of the T cell area. The lymphocyte rich areas comprise the **white pulp.**

Mucosal Associated Lymphoid Tissue

The Peyer's patches which form in the submucosa of the small intestine begin to develop before birth. They do not have incoming lymphatics, but instead sample antigen from the lumen of the small intestine through M cells to the tissues beneath. **M cells** are not covered with mucus, but instead trap antigens with ability to bind to the surface of the cell (an obvious determinant of pathogenicity).

These are endocytosed in vesicles and then released for recognition by the lymphocytes beneath. Over a lifetime, these areas become populated with memory B cells dedicated to the production of IgA and memory T cells necessary to provide help for them. The chemokine receptor and adhesion molecule patterns of naïve and memory adaptive lymphocytes are tailored to the location in which they first met their cognate antigen, so over a lifetime, this concentrates the "troops" where they are most likely to be quickly effective.

#MMC (Make Me Care!)

1. Virchow's node is a supraclavicular lymph node found near the junction of the thoracic duct and the left subclavian vein. Palpation of its enlargement is called Troisier's sign. Can you explain why this finding would be suggestive of an advanced malignancy?

2. Patients who have been surgically or naturally splenectomized (sickle cell anemia) require special vaccination protocols to protect them from encapsulated microbes which can invade the blood. Can you explain why this would be so?