LEARNING OBJECTIVES:

The student should be able to:

- Define the term "lymph", lymphoreticular system.
- Identify the primary and secondary lymphoid organs.
- Explain the primary and secondary lymphoid follicles (Germinal center).
- Compare between the follicular dendritic cells (FDC) "star fish", and the professional dendritic cells.
- Explain the light and dark zone.
- Explain the importance of, lymph node, high endothelial venules, spleen, thymus, bone marrow, and Peyer's patches.
- Define the M cells.
- Explain the systemic lymphoid system, such as:
  A. Spleen
  B. Lymph node
  C. Mucosal system includes all the lymphoid tissues associated with mucosal surfaces.

- Explain the importance of the presence of the phagocytic cells in the peripheral (secondary) lymphoid tissues.
- Define the lymphocytes circulation within the mucosal lymphoid system.
- Define the mucosal associated lymphoid tissues (MALT).
- Define the mucosal lymphocytes, such as those found in the connective tissues and are called Lamina propria lymphocytes (LPLs), and Intra-epithelial lymphocytes (IELs).

LECTURE REFERENCE:

THE LYMPHOID SYSTEM

Overview

The lymphoid cell line traces its origin to a pluripotential stem cell that in the fetus is found within the yolk sac, bone marrow, and liver and in the adult in the bone marrow. The differentiation of the stem cell to lymphoid or myeloid pathways is dependent upon the microenvironments in which these stem cells develop. These environments are provided in what is called the lymphoid system.

The lymphoid system involves the organs and tissues in which lymphocytic cells originate as lymphocyte precursors and then mature and differentiate; the cells finally lodge in the lymphoid organs or move throughout the body.

The Lymphoid Organs

The lymphoid tissues are divided functionally into primary and secondary organs.

a. The central (primary) lymphoid organs are the thymus and the bursa or bone marrow.

b. The peripheral (secondary) lymphoid tissues are the lymph nodes, spleen, diffuse lymphoid tissues, and lymphoid follicles.

Stem cells from bone marrow or embryonic tissues are deposited in the primary lymphoid organs, where the cells mature into lymphocytes. It is here where the precursors acquire the ability to recognize antigens through the development of specific surface receptors.

Lymphocytes are precursor cells of immunologic function as well as regulators and effectors of immunity. T cells have a long life span of months or years, where most B cells have a shorter life span of 5 to 7 days.

The immunocompetent cells produced in the thymus are called T lymphocytes (T cells), and those produced and mature in the bone marrow are the B lymphocyte (B cells). The site in the lymph node where the plasma cell produces the antibodies is called germinal centers or follicles. The primary follicles contain small B lymphocytes, following antigenic stimulation; secondary follicles develop which contain many large dividing lymphocytes and plasma cells.

In order to carry out the functions of the immunity, a ubiquitous immunologic cell system has appeared with in the vertebrates; the lymphoreticular system. This collection of cellular elements is distributed strategically throughout the tissues as well as lining lymphatic and vascular channels. Its cells are housed within the blood, tissues, thymus, lymph nodes, and spleen (internal secretory system), and in those body tracts exposed to the external environment – the respiratory, gastrointestinal, and genitourinary systems (external secretory system), Figure-1.
Figure-1 The collection of cellular elements is distributed strategically throughout the tissues as well as lining lymphatic and vascular channels. Its cells are housed within the blood, tissues, thymus, lymph nodes, and spleen (internal secretory system), and in those body tracts exposed to the external environment – the respiratory, gastrointestinal, and genitourinary systems (external secretory system).
A. PRIMARY (CENTRAL) LYMPHOID ORGANS

1. Thymus

The thymus is responsible for the development of lymphocytes involved in cell mediated immune responses (thymus-derived or T-lymphocytes). The gland appears to be a master organ important in immunogenesis in the young and in orchestrating the total lymphoid system throughout life. This central lymphoid organ differs in a number of respects from other lymphoid tissues. All the lymphoid tissues described thus far are advantageously and strategically positioned for contact with foreign configurations that may enter or arise within the host. The thymus, on the other hand, is protected from rather than exposed to antigen. In addition, the rate of mitotic activity in the thymus is greater than in any other lymphatic tissue, yet the number of cells leaving it is fewer than the number accounted for by this high rate of mitosis. The assumption made from these findings is that a large number of lymphocytes produced within the thymus die within its substance. Although originally considered to be a mechanism for removal of "forbidden" autoreactive lymphocyte clones, this function of the thymus probably represents homeostatic activity involved in the production of T-lymphocytes.

The thymus consists of two lobes (Figure-2) surrounded by a thin capsule of connective tissues (Figure-3). The capsule extends into the substance of the gland, forming septa that partially divide the lobes into lobules. Peripheral portions of the lobule (cortex) are heavily infiltrated with lymphocytes. More central portions (medulla) contain fewer lymphocytes but more epithelial elements. Within the substance of the thymus are cystic structures containing keratin (Hassall's corpuscles). The thymus is believed to perform two main functions; the production of lymphocytes within the cortex and the production of a humoral substance (s) by epithelial elements of the gland. These humoral substances (or hormones) may induce differentiation of lymphocytes directly within the thymus or may control their differentiation in the periphery. Although the thymus gland has a cortex and a medulla, neither contains germinal centers or plasma cells in the normal situation. These may appear when the gland is abnormal, e.g., in thymoma or in certain autoimmune diseases. Unlike other lymphoid organs, the thymus is composed of two tissue types: lymphoid and epithelial. The lymphoid cells are of mesenchymal origin, and the epithelial cells are of endodermal origin. The thymus initially develops as a continuous epithelium of cells from the third and fourth pharyngeal pouches. Then the mesenchyme derived lymphoid cells seed this epithelial thymus and convert this structure into a lymphoepithelial organ. The process of differentiation in the human begins as a ventral out pocketing from these pouches about the sixth week of fetal life (Figure-4).

Figure-2 diagrammatic representation of right and left lobes of the thymus gland
Figure- 3 Schematic representation of thymus gland, showing division into cortex and medulla

Figure-4 Embryology of the thymus gland from III to IV pharyngeal pouches. Note close proximity of site of differentiation of thyroid gland (II-III) and parathyroid glands (III-IV)
It is noteworthy that the parathyroids begin their development about the same time from the same pouches. A caudal migration of epithelium occurs with further differentiation. Failure of this migration is seen in one of the immunologic deficiency disorders—thymic dysplasia. By the tenth week, the thymic epithelium is differentiated into a compact epithelial structure interlaced with a fibrous reticular network. The epithelial cells are secretory cells with a well-developed Golgi apparatus, a rough endoplasmic reticulum, and a large nucleus with multiple nucleoli. With further development, the thymus is infiltrated with precursor cells migrating from the liver and yolk sac during fetal life and bone marrow during adult life. Large lymphoblastoid cells first enter the subcapsular cortex and subsequently undergo further differentiation as they migrate through the different areas of the thymus. The clinical importance of the simultaneous embryogenesis of parathyroid glands and the thymus is seen in another of the immunologic deficiency disorders of man, the DiGeorge syndrome. Infants with this disorder are born not only lacking in thymic function but also without parathyroid glands. Thus they present with hypocalcaemia tetani in the newborn period and with subsequent failure of the development of cell mediated immunity.

After birth the role of the thymus continues to change. The changes in the size of the gland with age are shown in Figure-5. Relative to body size it is largest during fetal life and at birth weighs from 10 to 15 gm. The gland continues to increase in size, reaching a maximum of 30 to 40 gm at puberty. This follows the same pattern of change that occurs in all lymphoid tissue during childhood. It is of interest that this pattern of growth parallels the sequential appearance of T and B cell function during maturation. Following adolescence, the gland begins to involutes. The parallel continues in that lymphoid tissues and immunoglobulins also diminish with increasing age. In addition, the development of autoimmune phenomena and malignant disease increase with advancing age with a loss of T cell (e.g., suppressor) function. Thus the thymus and its associated lymphoid tissues and their products play a dynamic role from early embryogenesis throughout the life span of the individual.

**Figure-5** Schematic representation of changes in weight and composition of thymus gland with maturation, showing involution of the gland with age
The thymus thus appears to be equipped to maintain lymphopoiesis while segregated from antigen. This curious finding may be explained in part by the barrier that is made up of a continuous epithelium surrounding blood vessels in the cortex (Figure-6). This epithelial membrane forms a perivascular space between the capillary endothelium and the epithelial sheath. The barrier might prevent macromolecules in the blood stream from entering the substance of the thymus gland. Although macromolecules may be prevented from entering the epithelial barrier, lymphocytes produced within the cortex are capable of passing freely through this epithelium into the blood system, as in other anatomic sites (e.g., postcapillary venule of the lymph nodes) Figure-6. Thus the thymus may be viewed as a lymphoid organ, anatomically distinct, upon which all other peripheral lymphoid organs are dependent. It is an organ actively engaged in lymphopoiesis but indecent of antigenic stimulation. It appears important as a central lymphoid tissue essential for the development and maturation of peripheral lymphoid tissues. Two major functions have been attributed to the thymus: (1) that it acts by the elaboration of a hormone that expand peripheral lymphocyte populations in much the same way as erythropoietin expands erythrocyte populations, and (2) that it acts by direct seeding of peripheral lymphoid tissues with lymphocytes.

Figure-6 Schematic presentation of the perivascular epithelium surrounding blood vessels in the cortex, note the barrier provides by this sheath and the pathways of lymphocytes formed in the cortex into the blood vessels.
B. SECONDARY LYMPHOID ORGANS

All immune cells including the lymphocytes are generated in the bone marrow and then migrated into the secondary lymphoid organs. The immune system's defense against an invader has three phases: recognition of danger, production of weapons specific for the invader, and transport of these weapons to the site of attack. Today we'll discuss when and where these three phases take place. The recognition phase of the adaptive immune response takes place in the so called "secondary lymphoid organs". These include the lymph node, spleen, Peyer's patches, and (MALT) mucosal associated lymphoid tissues (Figure-7).

Figure-7 Schematic diagram showing the primary and secondary lymphoid organs
LYMPHOID FOLLICLE

All secondary lymphoid organs have one anatomical feature in common: they all contain lymphoid follicles. These follicles are critical for the functioning of the adaptive immune system, so we need to spend a little time getting familiar with them. Lymphoid follicles start life as "primary" lymphoid follicles: loose networks of follicular dendritic cells (FDCs) that are embedded in regions of the secondary lymphoid organs that are rich in B cells. Thus lymphoid follicles are really islands of follicular dendritic cells within a sea of B cells Figure-8.

Although FDCs have the classic starfish dendritic shape, they are very different from the dendritic cells (DC) of the skin and mucosa that we have talked about before. Those dendritic cells, which function as professional antigen presenting cells, are white blood cells that are produced in the bone marrow, and which then migrate to their sentinel positions in tissues. In contrast, follicular dendritic cells are regular old cells (like skin cells or liver cells) that take up their final positions in the body as the embryo develops. In fact, follicular dendritic cells are already in place during the second trimester of gestation. Not only are the origins of follicular dendritic cells and antigen presenting dendritic cells quite different, these two types of starfish shaped cells have very different functions. Whereas the role of dendritic APCs is to present antigen to T cells via MHC molecules, the function of follicular dendritic cells is to display antigen to B cells. Here's how this works: Early in an infection, complement proteins bind to invader, and some of this complement opsonized antigen will be delivered by the lymph or blood to the secondary lymphoid organs. Follicular dendritic cells that reside in these organs have receptors on their surfaces that bind complement fragments, and as a result, follicular dendritic cells pick up and retain the opsonized antigen. In this way, follicular dendritic cells become "decorated" with antigens that are characteristic of the battle that is being waged out in the tissues. Later in infection, when antibodies have been produced, invaders opsonized by antibodies can also be captured by FDCs, because these cells have receptors that can bind to the constant regions of antibody molecules. So the function of follicular dendritic cells is to capture opsonized antigen and to "advertise" this antigen to B cells. Those B cells that recognize their cognate antigens hanging from these follicular dendritic "trees" are retained for a while in the lymphoid follicle where they proliferate.
Once this happens, the "follicle" begins to grow and to become the center of B cell development. Such an active lymphoid follicle is called a "secondary" lymphoid follicle or a "germinal center". The role of complement opsonized antigen in triggering the development of a germinal center cannot be over emphasized: lymphoid follicles in humans who have a defective complement system never progress past the primary stage. This is another example of an important concept in immunology: For the adaptive immune system to respond, the innate system must first react to impending danger.

Once B cells have proliferated in germinal centers they become very "fragile". Unless they receive the proper "rescue" signals, they will commit suicide (die by apoptosis). Fortunately, helper T cells that have been activated in the T cell areas of the secondary lymphoid organs migrate to the lymphoid follicle. These activated Th cells express high levels of the CD40L protein that can plug into the CD40 protein on the surface of the B cell. When B cells whose receptors are cross linked receive this co-stimulatory signal, it is temporarily rescued from apoptotic death, and continues to proliferate. The rate at which these B cells multiply is truly amazing ---the number of B cells can double every six hours. These proliferating B cells push aside other B cells that have not been activated, and establish a region of the germinal center that is called the dark zone because it contains so many proliferating B cells that is looks dark under the microscope **Figure-9**.

**Figure-9** Schematic diagram showing the secondary lymphoid follicle or a "germinal center", the dark and light zone are illustrated as well as follicular dendric cells.
After a period of proliferation, some of the B cells will "decide" to become plasma B cells, while others will undergo somatic hypermutation to "fine tune" their receptors. After each round of mutation, the affinity of the mutated BCR is tested. Those B cells that have mutated BCRs do not have a high enough affinity for antigen to be efficiently crosslinked will die by apoptosis, and be eaten by macrophages in the germinal center. In contrast, B cells will be rescued from apoptosis if their receptors have high enough affinity to be efficiently crosslinked by antigen on FDCs, and if they receive co-stimulation from activated Th cells that are present in the light zone of the germinal center. The current picture is that B cells "cycle" between periods of proliferation in the dark zone and periods of testing in the light zone. Sometime during all this action, B cells can also switch the class of antibody they produce. This process is believed to take place in the light zone of the germinal center with the aid of activated Th cells. In summary, lymphoid follicles are specialized regions of secondary lymphoid organs in which B cells percolate through a lattice of follicular dendritic cells that have captured opsonized antigen on their surfaces. B cells that encounter their cognate antigen and receive T cell help are rescued from death. These "saved" B cells proliferate and can undergo somatic hypermutation and isotype switching. Clearly lymphoid follicles are extremely important for B cell development. That's why all the secondary lymphoid organs have them.

**HIGH ENDOTHELIAL VENULES**

A second anatomical feature common to all secondary lymphoid organs except the spleen is the "high endothelial venule" (HEV). The reason the HEV is so important is that it is the "doorway" through which B and T cells enter these secondary lymphoid organs from the blood. Most endothelial cells that line the inside of blood vessels resemble overlapping shingles that are tightly "glued" to the cells adjacent to them to prevent the loss of blood cells into the tissues. In contrast, the blood vessels that collect blood from the capillary beds (the post-capillary venules) in most secondary lymphoid organs have endothelial cells that are shaped more like a column than like a shingle: These tall cells are the high endothelial cells – so a high endothelial venule is a special region in a blood vessel (venule) where there are high endothelial cells. Instead of being glued together, the high endothelial cells are "spot welded". As a result, there is space between the cells of the HEV for lymphocytes to wriggle through. Actually, lymphocytes exit the blood very efficiently at these high endothelial venules: about 10,000 lymphocytes enter an average lymph node each second by passing between high endothelial cells Figure-10.

![Figure-10](image)

**Figure-10** Schematic diagram showing the high endothelial venule (HEV), includes the have endothelial cells that are shaped more like a column than like a shingle, these tall cells are the high endothelial cells.
LYMPH NODES

The lymph node is a plumber's dream. This organ has incoming lymphatics which bring lymph into the node, and outgoing lymphatics through which lymph exit the node. In addition, there are arterioles that bring blood into the lymph node, and veins through which blood exits. Figure-11 exhibits the high endothelial venules. With this plumbing in mind, can you see how B and T cells enter the lymph node? That's right, they can enter between the high endothelial cells.

**Figure-11** Schematic structure of the lymph node, lymphocytes and antigens from surrounding tissue spaces or adjacent nodes, pass into the sinus via the incoming lymph (afferent). The cortex contains aggregates of B cells (primary follicles) most of which are stimulated (secondary follicles) and have a site of active proliferation, or germinal centre. The paracortex contains mainly T cells, many of which are associated with the interdigitating cells (antigen presenting cells). Each lymph node has its own arterial and venous supply. Lymphocytes enter the node from the circulation through the specialized high endothelial venules (HEVs) in the paracortex. The medulla contains both T and B cells, as well as most of the lymph node plasma cells organized into cords of lymphoid tissue. Lymphocytes can only leave the node through the efferent (out going lymph) lymphatic vessels.

There is also another way lymphocytes can enter the lymph node through the lymph node. All lymph nodes are class rooms, positioned along the route the lymph takes on its way to be reunited with the blood. Lymphocytes actively engage in class hopping, and are carried from node to node by the lymph. Although lymphocytes have two ways to gain entry to a lymph node, they only exit via the lymph—those high endothelial venules don't let lymphocytes back into the blood. Since lymph nodes are places where antigen and lymphocytes meet, we need to discuss how antigen enters a node. Dendritic cells stationed out in the tissues can be stimulated by battle cytokines to enter the lymph and carry antigens they have acquired at the battle scene into the secondary lymphoid organs for presentation to T cells. So this is one way that antigen can enter the lymph node: as "cargo" aboard APCs. In addition, antigen that has been opsonized by complement or antibodies can be carried by the lymph into the lymph node where it can be phagocytosed by macrophages for presentation to Th cells, or captured by follicular dendritic cells for presentation to B cells. From these plumbing considerations, you probably have guessed that one function of a lymph node, it percolates through holes in the marginal sinus (sinus is a fancy word for cavity), through the cortex and paracortex, and finally into the medullary sinus where it is collected and leaves the node.
The walls of the marginal sinus are lined with macrophages that are tasked with cleaning up the lymph by phagocytosis. Other macrophages are found in the part of the lymph node called the paracortex. The high endothelial venules are also located in the paracortex, so lymphocytes pass through this region of the node when they arrive from the blood. In fact, T cells tend to accumulate in the paracortex, being retained there by adhesion molecules. This accumulation of T cells makes good sense, because macrophages and dendritic cells are also found in the paracortex, and of course, one object of this game is to get T cells together with these APCs. If a helper T cell encounter its cognate antigen presented by an APC; it will be activated and will begin to proliferate in the paracortex. This proliferation phase lasts a few days. Most of these newly activated Th cells will then exit the node via the lymph, recirculate through the blood, and reenter lymph nodes via high endothelial venules. This process of recirculation is fast, it generally takes less than a day, and it is extremely important. Four major ingredients are required in order for the adaptive immune system to make antibodies: APCs to present antigen to Th cells, Th cells with receptors that recognize the presented antigen, opsonized antigen displayed by follicular dendritic cells, and B cells with receptors that recognize the antigen.

Early in an infection, there are not a lot of any of these ingredients around, and naïve B and B cells just circulate through the secondary lymphoid organs at random, checking for a match to their receptors. So the probability is pretty small that the rare Th cell that recognizes a particular antigen will arrive at the very same lymph node that is being visited by the rare B cell with specificity for that same antigen. However, if activated Th cells first proliferate to build up their numbers, and then recirculate to lots of lymph nodes and other secondary lymphoid organs, the Th cells with the right stuff get "spread around", so they have a much better chance of encountering those B cells for which they can provide help.

When the recalculating Th cells enter anode where their cognate antigen is being presented, they will be restimulate. Some of the restimulated Th cells will proliferate more and recirculate again to spread the help even further. Other restimulated Th cells will move to the lymphoid follicles of the lymph node to provide help to needy B cells, and still others will exit the blood to provide cytokine help to warriors doing battle in the tissues. Killer T cells are also activated in the paracortex of the lymph node if they find their cognate antigen presented by virus infected macrophages or dendritic cells, and if they receive cytokine help (e.g., IL-2) from activated Th cells. Once activated, CTLs proliferate and recirculate. Some of these CTLs reenter secondary lymphoid organs and begin this cycle again, whereas others exit the blood at sites of infection to kill virus infected cells. B cells also engage in cycles of activation, proliferation, circulation, and restimulati8on, but there are still some mysteries surrounding just where and how virgin B cells are first activated.

The most recent evidence indicates that B cells, which have encountered their cognate antigen displayed on follicular dendritic cells, migrate to the border of the lymphoid follicle where they meet activated T cells that have migrated there from the paracortex. It is during this "meeting" that B cells receive the co-stimulation they require for activation. Both B and T cells then enter the lymphoid follicles and the B cells begin to proliferate. Many of these newly made B cells exit the lymphoid follicle via the lymph. Some become plasma cells that take up residence in the spleen to bone marrow where they pump out tonnes of antibodies. Others recirculate through the lymph and blood, and reenter secondary lymphoid organs. As a result, activated B cells are spread around to many secondary lymphoid organs fwhere3e, it they are restimulated in lymphoid follicles, and they can undergo somatic hypermutation and class switching. The frantic activity in germinal centers is usually over in about three weeks. By this time, the invader has been repulsed, and most of the opsonized antigen has been "p8iched" from the dendritic cells by B cells, you remember that antigen is taken into the B cells after it has been bound by the BCR. At thi8s point most B cells will have left the follicles or will have died there, and the areas that once were germinal centers will look much more like primary lymphoid follicles. In summary, lymph nodes act as "lymph filters" in which antigen is picked up by APCs and follicular dendritic cells. These nodes also provide a concentrated environment of APCs, T cells, and B cells in which naïve B and T cells can be activated, and experienced B and T cells can be restimulated.
In lymph nodes, naïve B and T cells can mature into cells that produce antibodies (B cells), provide cytokine help (Th cells), and kill infected cells (CTLs). In short, the lymph node can do it all. As everyone knows, lymph nodes that drain sites of infection tend to swell. For example, if you have a viral infection of your upper respiratory tract (e.g., influenza), the cervical nodes in your neck may become swollen. You understand now that this swelling is due in part to the proliferation of lymphocytes in the node. In additional macrophages which tend to plug up the medullary sinus. As a result, fluid is retained in the node, causing further swelling. When the invader has been defeated, there is no longer sufficient antigen to maintain B and T cells in an activated state. At this point, most B and T cells die from exhaustion or from lack of stimulation, but some of them go back to a resting state to provide a reservoir of memory cells that can quickly be reactivated if the virus attacks again. And of course, the swelling in your lymph nodes goes away.

**PEYER'S PATCHES**

Back in the late seventeenth century, a Swiss anatomist, Johann Peyer, noticed that embedded in the villi-covered cells that line the small intestine are patches of smooth cells. We now know that these "Peyer's patches" are examples of mucosal-associated lymphoid tissues (MALT) which function as secondary lymphoid organs. Peyer's patches have high endothelial venules through which lymphocytes can enter, and of course, there are outgoing lymphatics that drain lymph away from these tissues. However, unlike lymph nodes, there are no incoming lymphatics that bring lymph into Peyer's patches. Here's a diagram in the figure 12 shows one of the smooth cells that is part of a Peyer's patch:

![Figure 12 Schematic structure of the Peyer's patch, no incoming lymphatics.](image)
So if there are no incoming lymphatics, how does antigen enter this secondary lymphoid organ? That smooth cell that crowns the Peyer's patch the one that doesn't have "hairs" (villi) on it is called an "M" cell. It is a specialized cell that transports antigen from the interior (lumen) of the intestine into the Peyer's patch. To sample the contents of the intestine, M cells take in "sips" of antigen and enclose them in vesicles called endosome that are roughly similar to the phagosomes of macrophages. These endosomes are transported across the M cell, and their contents are then spit out the other side. So, whereas lymph nodes sample antigens from the lymph, Peyer's patches sample antigens from the intestine, and they do it by transporting the antigen through the M cell! Antigen has been collected by M cells can be carried by the lymph to the lymph nodes that drain the Peyer's patches. In addition, if the collected antigen is opsonized by complement or antibodies, it can be captured by follicular dendritic cells in the lymphoid follicles that are below the M cells. In fact, except for its unusual method of acquiring antigen, a Peyer's patch is quite similar to a lymph node, with high endothelial venules to bring in T and B cells and special areas where these cells congregate.

SPLEEN

The spleen is located between an artery and a vein, and it functions as a blood filter. As with Peyer's patches, there are no lymphatics that bring lymph into the spleen. However, in contrast to lymph nodes and Peyer's patches, where entry of B can T cells from the blood occurs only via high endothelial venules, the spleen is like an "open-house party" in which everything in the blood is invited to enter. The following diagram figure 13 shows one of the filter units that make up the spleen.

![Schematic structure of the spleen, no lymphatic that bring to lymph into the spleen.](image)

When blood enters from the splenic artery, it is diverted out to the marginal sinuses from which it percolates through the body of the spleen before it is collected into the splenic vein. The marginal sinuses are lined with macrophages that clean up the blood by phagocytosing cell debris and foreign invaders. As they ride along with the blood, B cells and T cells are temporarily retained in different areas, T cells in a region called the periarteriolar lymphocyte sheath (PALS) that surround the central arteriole, and B cells in the region between the PALS and the marginal sinuses. Once activated by APCs in the PALS, T cells move into the lymphoid follicles, and give help to B cells that have recognized their cognate antigen.
Each secondary lymphoid organ is strategically positioned to intercept invader that enter the body by different routes. If the skin is punctured and the tissues become infected, an immune response is generated in the Peyer's patches that line your intestine. If you are invaded by blood borne pathogens, your spleen is there to filter them out and to initiate an immune response. If you are attacked via your respiratory tract, another set of secondary lymphoid organs that includes your tonsil is there to defend you.

Not only are the secondary lymphoid organs strategically positioned, they react by mobilizing weapons that are appropriate to the kinds of invaders they are most likely to encounter. For example, Peyer's patches specialized in Th cells that secrete a Th2 profile of cytokines, and B cells that secrete IgA antibodies, weapons that are perfect to defend against intestinal invaders. In contrast, if you are attacked by bacteria from a splinter in your toe, lymph that contains bacteria and bacterial debris will find its way to the lymph node behind your knee. That node will produce Th1 cells and B cells that secrete IgG antibodies, weapons that are ideal for defending against bacteria.

DR. MUSTAFA LINJAWI