Section Three: Chapter 17: Lymphatics in Circulation and Immunity

Lymphatic System in the Circulatory System

The lymphatic system has an entire set of vessels, called lymphatic vessels that continually drain excess interstitial fluid from the interstitial fluid of the tissues and return it to the cardiovascular system. It also contains lymphoid organs and structures (see **Figure 17.1** below) that function to continually maintain and cleanse the body.

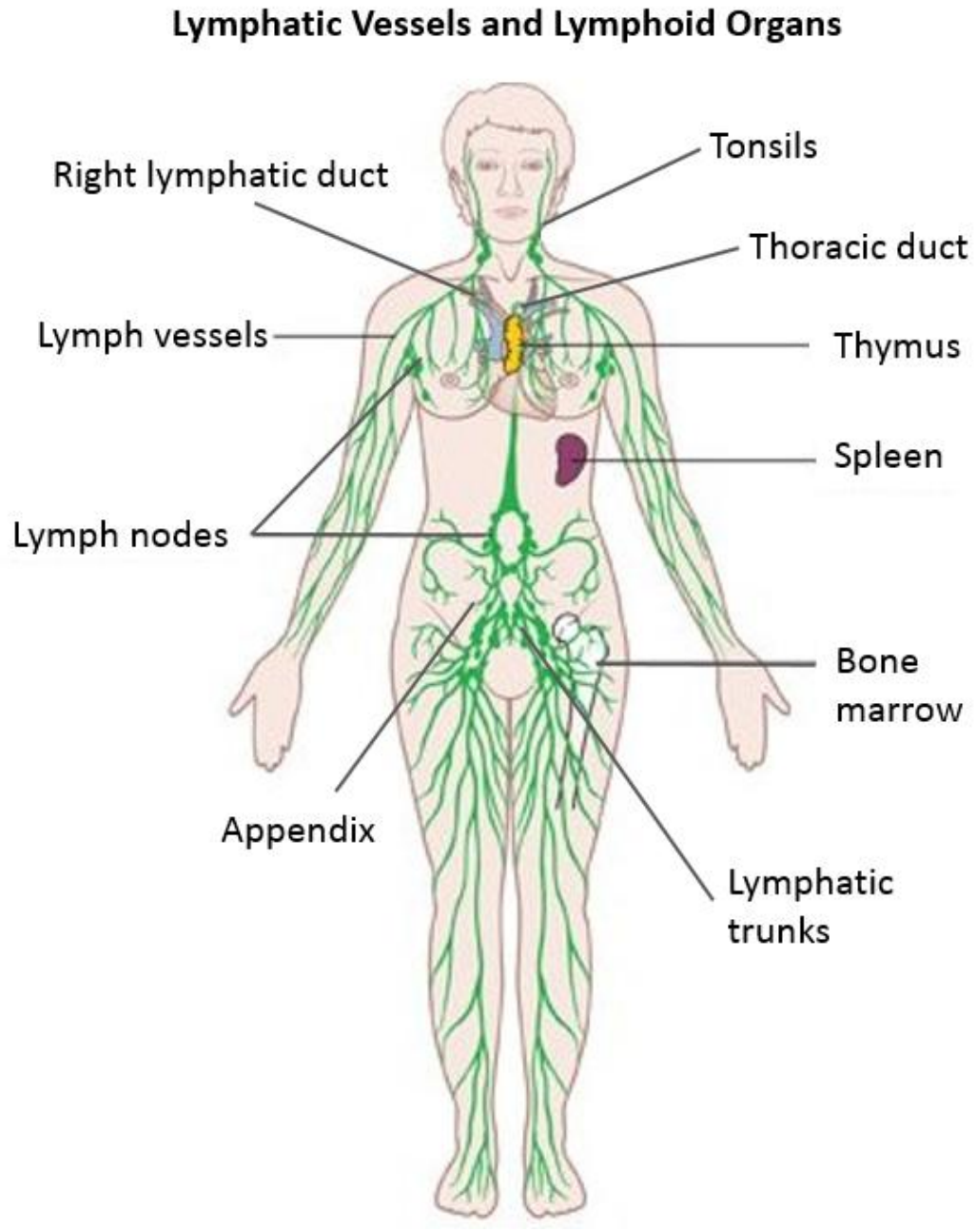


Figure 17.1 Shown here are the lymphatic vessels and lymphoid tissues and organs of the body. The lymphatic vasculature of the body is almost as extensive as blood vessels, however the lymphatic vessels only bring lymph in one direction, from the periphery back to the heart. The lymphoid organs include the lymph nodes, tonsils, red bone marrow, the thymus and the spleen.

Lymphatic Vessels

Lymphatic vessels, like blood vessels, are a network of various micro-vessels that merge into larger and larger conduits throughout the body as they transport lymph from the tissues spaces and bring that fluid back to the left and right subclavian veins in order to return it to the blood just prior to entering the heart (see **Fig. 17.2** below). The Lymphatic vessels collect and filter lymph through the lymph nodes as it makes it way toward larger vessels called collecting vessels, trunks and ducts.

Listed below are the major categories of the lymphatic vasculature. The innermost lining of any lymphatic vessel is composed of endothelium, just like all of the blood vessels.

1. **Initial lymphatics** – sometimes called ***lymphatic capillaries***, are thin walled, single celled vessels that are highly permeable. Once the **interstitial fluid,** also called **tissue fluid**, is inside a lymphatic vessel, it is called ***lymph*** (a Latin word meaning 'water'). Thus, lymph is very similar to interstitial fluid, as it comes directly from it. The role of all lymphatic vessels is to continuously return the excess interstitial fluid to the cardiovascular system. Initial lymphatic merge and become larger collecting lymphatics.

2. **Collecting lymphatics** – as initial lymphatics merge they become collecting lymphatics which are larger, thicker vessels, with ***smooth muscle*** lining their walls (to contract and pump lymph along the lymphatic vessels). These vessels have ***lymphatic valves*** (like veins) to ensure the flow of lymph is always in one direction - back toward the heart. Lymph does not contain RBC's and so is clear or opaque in color.

3. **Lymph nodes** are encapsulated lymphoid tissue; their main role is to ***filter the lymph*** of microbes, bacteria, debris, etc., on its way back to the blood and to the heart. Vessels that enter lymph nodes are called **afferent lymphatic vessels** (incoming). Lymph nodes have resident T-cells, B-cells and macrophages. For example, if a bacterial cell comes through a node, the lymphocytes will proliferate in order to defend the body – hence the swelling of lymph nodes during an infection. Vessels that exit lymph nodes are called **efferent lymphatic vessels** (outgoing).

4. As more and more lymphatic vessels converge, they get larger (again like veins) and are then referred to as **lymphatic trunks**. These continue to transport lymph toward the subclavian veins that will then lead to the heart. These trunks are still filtered by lymph nodes. These vessels converge and become **lymphatic ducts**. The lymphatic trunks of the lower body merge into the **cisterna chyli**.

There are 5 major Lymph Trunks, from superior to inferior:

1. Jugular trunks
2. Subclavian trunks
3. Bronchomediastinal trunks
4. Intestinal trunks
5. Lumbar trunks

5. The **cisterna chyli** is a hub for the lymph drainage of the lower body and represents the base of the **thoracic duct**. It is a large, dilated sac located just inferior to the aortic hiatus (opening) of the diaphragm. It collects lymph from the intestinal trunk and two lumbar lymphatic trunks.

6. The **Thoracic Duct** is the ***largest lymphatic vessel*** in the human body. It receives lymph from 75% of the body (namely the lower limbs, trunk, left chest, left arm and left side of head). The lymph from the thoracic duct is returned to the blood by way of the **left subclavian vein**, this is where lymph is reunited with blood just prior to returning to the heart.

7. The **Right Lymphatic Duct** collects lymph from about 25% of the body (namely the right chest, right arm and right side of head). The lymph from the right duct is returned to the blood by way of the **right subclavian vein**. As seen in the diagram above, the L&R subclavian veins drain into L&R brachiocephalic veins and into the superior vena cava and finally into the R atrium.

The flow of Lymph through the Lymphatic System to the Cardiovascular System.

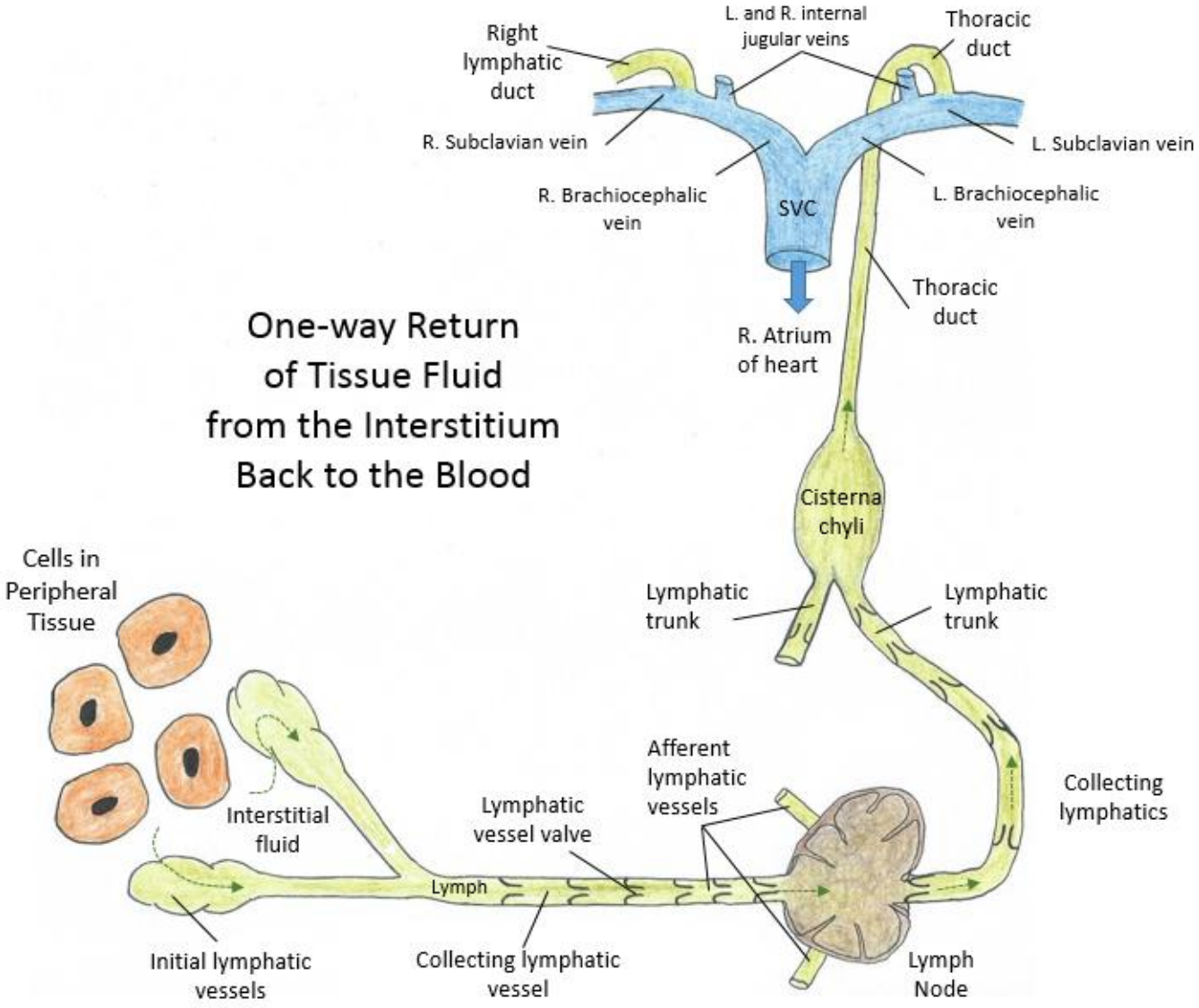


Figure 17.2 This drawing shows the flow of interstitial fluid at the peripheral tissues into highly permeable initial lymphatic vessels where it becomes lymph. These vessels merge to create larger collecting lymphatic vessels that enter lymph nodes where the lymph is filtered on its way back to the cardiovascular system. Collecting lymphatics merge to form larger lymphatic trunks that create the cisterna chyli which represents the base of the thoracic duct. This is the largest lymphatic vessel and it returns about 75% of all the lymph to the left subclavian vein. The right lymphatic duct returns about 25% of the lymph from the head right arm and chest to the right subclavian vein.

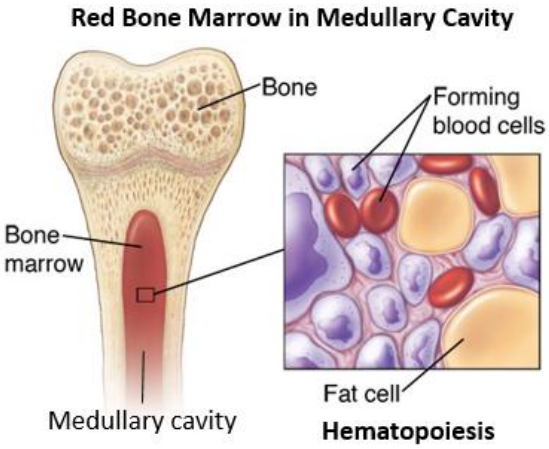
Lymphoid Organs and Structures

The organs of the lymphatic system carry out various immune functions. The lymphatic system is comprised of lymphatic vessels, and lymphoid organs, the primary structures are **red bone marrow**, **tonsils**, **lymph nodes**, the **thymus** and the **spleen**. There are also many other regions with lymphoid tissue, such as gut associated lymphoid tissue (**GALT**), bronchus associated lymphoid tissue (**BALT**), and mucosa associated lymphoid tissue (**MALT**) that are associated with most every mucous membrane in the body, as these areas are exposed to the external environment and are protected in this way.

When functioning properly, the process of the lymphoid organs act and learn to destroy only deleterious elements and pathogens, and should not attack the body's own cells. The lymphoid organs are where lymphocytes mature, proliferate, and are selected, which enables them to attack pathogens without harming the cells of the body.

Red Bone Marrow

Within the inner cavity of hardened bone, sits bone marrow. There is red bone marrow which is a sponge-like tissue that contains **hematopoietic stem cells** which form the cells of the blood. As we grow and develop, most of the red marrow is converted into yellow bone marrow, which is adipose tissue or fat. And this serves as a site of energy storage. Accordingly, in adults, the red bone marrow is limited mostly to flat bones, such as the os coxae bones of the pelvis, the sternum (breast), flat roofing bones of skull, the ribs, and the body of vertebrae.



The hematopoietic stem cells can turn into three lineages of blood cells, all of which have important functions that help keep a person alive and healthy. In the embryo, blood cells are made in the yolk sac. As development proceeds, this function is taken over by the **spleen**, **lymph nodes**, and **liver**, until after the fifth month of gestation, when the **red bone marrow** takes over most hematopoietic functions, although the final stages of the differentiation of some cells takes place in other organs, such as T-cell differentiation in the thymus. In addition, the spleen acts as a reservoir for platelets.

The **red bone marrow** (see **Fig. 17.3**) is a loose collection of cells where hematopoiesis occurs, and the B-cell undergoes almost all of its development in the red bone marrow, whereas the immature T cells called **thymocytes**, migrate from the bone marrow to the thymus gland where they complete their maturation process. The erythrocytes or red blood cells (RBCs) are constantly produced in the body's red bone marrow as typically they need to be replaced at about 2.5 million RBCs per second.

Figure 17.3 Shows the red bone marrow that fills the head of the femur in the bone of a developing skeleton, as the location of red bone marrow diminishes significantly after the onset of puberty. There is a spot of yellow bone marrow which is visible in the center of the cut bone in the image above.

The Tonsils

The tonsils are found on the tongue, near the palate, and in the pharynx (throat). Tonsils are **un-encapsulated** lymphoid tissues that form one part of the body's immune system. Unlike many other lymphoid tissues, this tonsils do not have a fibrous capsule encompassing them. What this means is that anything that makes contact with a tonsil can solicit a response from it, in contrast to encapsulated lymphoid tissue like the spleen, where there is a regulated entrance and exit into the structure.

Without a complete capsule, the surface invagination go deep into the interior of the tonsil, creating **tonsillar crypts**. All sorts of material taken into the body can accumulate into the tonsillar tissues where they are acted upon by numerous lymphoid follicles with many white blood cells responsible for defense and detoxification and elimination. This is especially important in forming a child's immunity, helping to recognize and remove common environmental elements that enable protection later in life.

The strategic location of the tonsils (see **Fig. 17.4** below) enable them to patrol for any toxic debris or germs as they enter the body through the mouth or the nose. In terms of prominence and size, there are **four groups of tonsils** in the body.

1) Pharyngeal tonsil is the largest and is a single tonsil cluster (also called the adenoids). As its name tells us, it is located high up in the pharynx, to be specific, in the **nasopharynx** which is the respiratory passageway leading from the nasal cavity to the back of the throat. It is positioned to capture any errant particles that are inspirited from the air and catch them before they can go any further into the body.

2) Palatine tonsils are the paired tonsils on either side of the dangly **uvula** that hangs like a punching bag when the mouth is open. These reside in the **oropharynx**, at the boarder of the oral cavity and soft palate. Each tonsil comprises similar tissue to that of lymph nodes, except for the absence of a capsule. Running through the pink mucosa of each tonsil are those crypts to trap and engulf any suspect substances that passes over it.

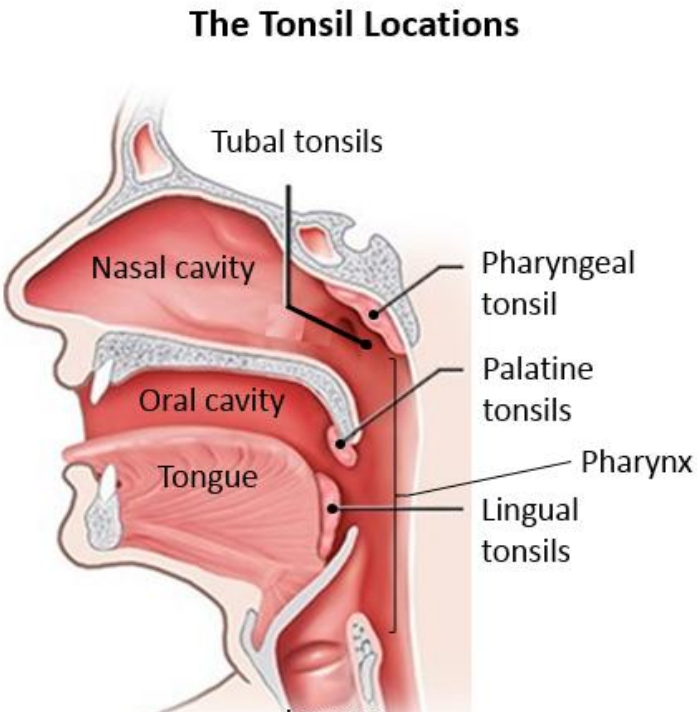


Figure 17.4 This mid-sagittal section of the head shows the locations of the four groups of tonsils in relation to the nasal cavity, oral cavity and the pharynx.

3) Lingual tonsils, are a collection of lymphatic tissue on the surface tissue of the base or root of the tongue, which is at the back, in the **oropharynx**. The tonsils are in the lamina propria of the tongue, and the lymphocytes and macrophages there provide protection against any potentially harmful substances the may enter through the mouth (which is also called the 'cake hole' in Australia)'.

4) Tubal tonsils are paired tonsils located just posterior to the opening of the auditory (Eustachian) tube that connects the **nasopharynx** to the middle ear. These are also called the tonsilla tubaria. It is thought that the tubal tonsils may have abilities to actively transportation foreign antigens in a way to act as inductive and effector sites in the mucosal immune system.

A swelling of a tonsil indicates an active immune response to infection. The condition of **tonsillitis** is when any of the tonsils become repeatedly or chronically inflamed. This is often accompanied by discomfort and difficulty swallowing, tender lymph nodes on the sides of the neck and a sore throat. Some suggest that a tonsillectomy is a good idea, but in the vast majority of cases, there is never any need to remove any tonsil, ever. If a person suffers from chronic tonsillitis, there are many preventative measures, such as stop eating refined sugar and many other substances that make the tonsil super-sensitive.

The **mouth** or **oral cavity** is the portal for ingestion of food and liquids; however, it is also an effective barrier to anything that does not belong in the body. It is layered with stratified squamous epithelium to provide protection. It has extrinsic salivary glands (the parotids, submandibular and sublingual) and intrinsic salivary glands within the cheeks and lips deliver saliva into the mouth. **Saliva** is rich in **lysozyme**, which is an enzyme that has a defensive role because it can destroy bacteria by digesting their cell walls.

Lymph Nodes

The fairly small bean-shaped lymph nodes is a structure that acts as a **filter** of the lymph as it flows through the lymphatic vasculature from the periphery to the heart.

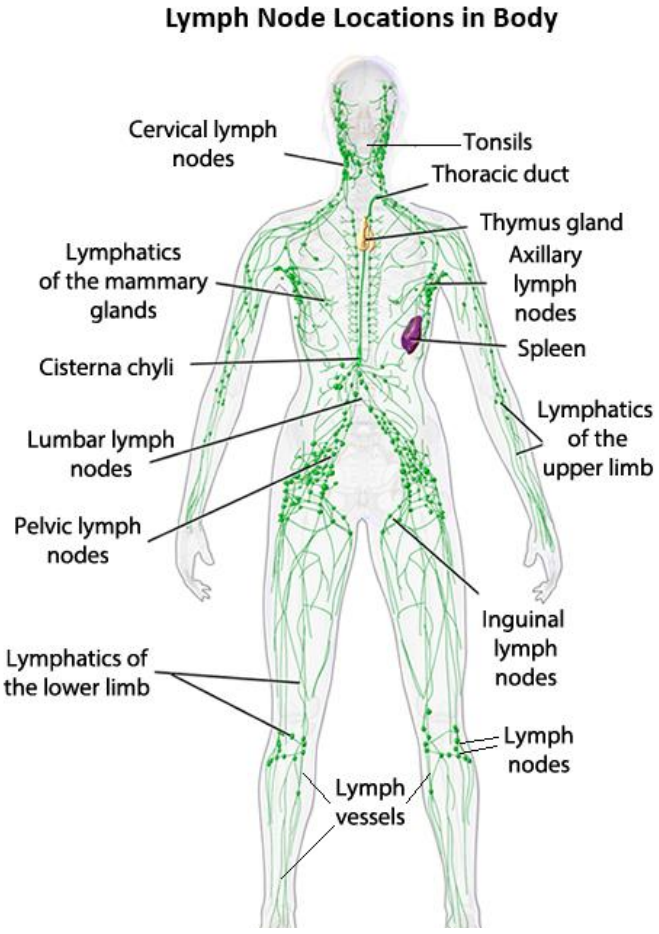


Figure 17.5 Shows the array of lymph nodes, lymphatic vessels and other lymphoid organs in almost every area of the body.

Lymph nodes are located throughout the body, and there are certain locations where major clusters are superficial and palpable, meaning you are able to feel them with your hands. For example, there areas are the **cervical nodes** in the neck, the **axillary nodes** in the armpit, the **mammary nodes** breast region of the chest, the **inguinal nodes** in the groin, and the **popliteal nodes** in the region behind the knee (see **Fig. 17.5**). There are many more lymph nodes, for example there are epi-trochlear lymph nodes that are located on the posterior aspect of the elbow.

The nodes contain **lymphocytes** that help protect the body and function to remove debris and toxins from the lymph. This is why they are often referred to as the "filters of the lymph". Any toxin or foreign cell may find itself in the interstitial fluid will be taken up by the lymphatic vessels and transported to a nearby lymph node. There are **dendritic cells** and **macrophages** within the node, these are two types of phagocytic cells derived from monocytes. These cells internalize and destroy many pathogens that pass through, removing them from the body. The lymph node is also the site of adaptive immune responses mediated by **T-cells**, **B-cells**, and accessory cells of the adaptive immune system.

Lymph nodes are **encapsulated** by a fibrous connective tissue capsule, which also intrudes and creates **trabeculae** which segment the node internally and together with reticular fibers made by fibroblasts, create support for blood vessels entering into the nodes.

The incoming lymph from **afferent lymphatic vessels** travels through cortical (outer) sinuses and then into the medullary (inner) sinuses, where cells and lymph fluid can exit by the **efferent lymphatic vessel** at the hilus (indentation) of the node. Lymph travels via the sub-capsular sinus, which is has macrophages, dendritic cells and reticular fibers.

The outer cortex has secondary **lymphatic nodules** which have **germinal centers** where the **B-cells** rapidly divide and proliferate into antibody secreting **plasma cells,** surrounded by a layer of T-cells with small lymphocytes in between the reticular fibers in the cortex. The primary follicle cells (with no germinal center) are pushed to the periphery, to form a **mantle zone**, which is an outer ring of small lymphocytes that now surround a germinal center. The mantle also has memory B cells. There are also **T-cells,** with **macrophages** and **dendritic cells** that trap antigens and present them on their surfaces to B-cells.

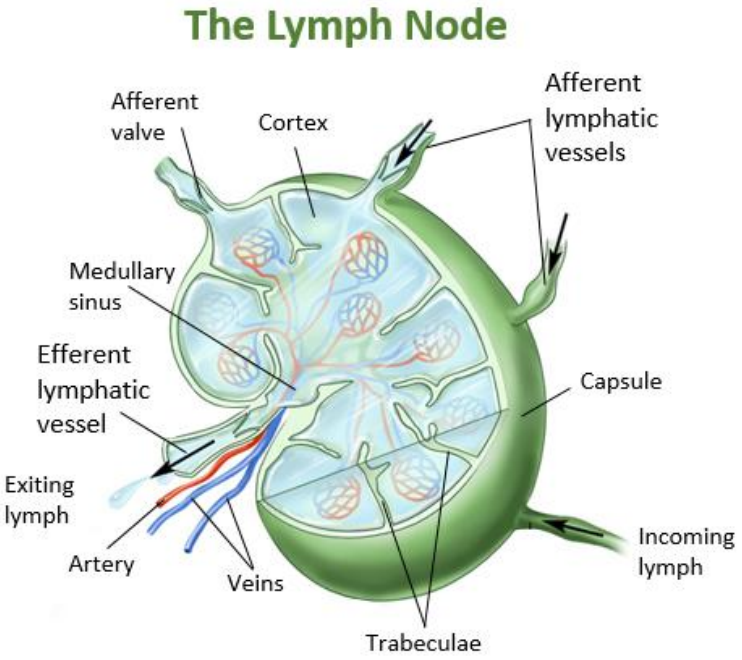


Figure 17.6 A lymph node section showing the many afferent (incoming) lymphatic vessels and how lymph is filtered through the node and exits in a single efferent (outgoing) lymphatic vessel.

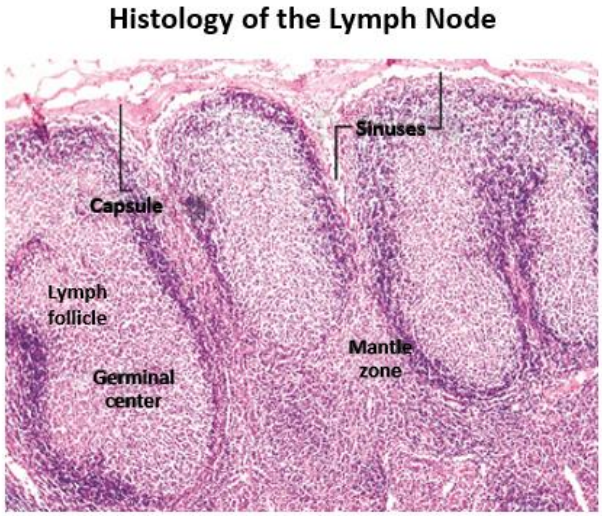


Figure 17.7 This shows the histology of a lymph node focusing primarily on the cortex to show the lymph follicle with the germinal center where B-cell proliferation occurs.

The **inner cortex** contains mostly T-cells. With the **deep cortical**, and **medullary cords** containing B-cells and plasma cells, which make IgG type antibodies and only live for a few days. As the lymph continues to flow through the node, it enters the **medulla**, which consists of **medullary cords** of B cells and plasma cells, and the **medullary sinuses** where the lymph and cells collect before exiting the node via the efferent lymphatic vessels.

Lymph nodes can also be called **lymph glands**, and they can become **enlarged** or **sensitive** to the touch indicating that the body is **detoxing** or fighting an **infection**. There are from 500 to 800 lymph nodes in the body that are constantly monitoring and filtering the lymph to remove toxins, debris, waste and pathogens.

The lymph nodes are central to the entire lymphatic system which more resembles a processing and filtering network, as the defense and detoxification aspects of the immune system works seamlessly with other immune structures and structures of other systems to protect the body.

The Thymus

The thymus gland is a bi-lobed lymphoid organ found behind the sternum and in front of the aorta. It can be described as having one of the best seats in the house, as it sits comfortably atop the heart. There is a fibro-connective tissue capsule that wraps around it and it also has fibers that hold the lobes together.

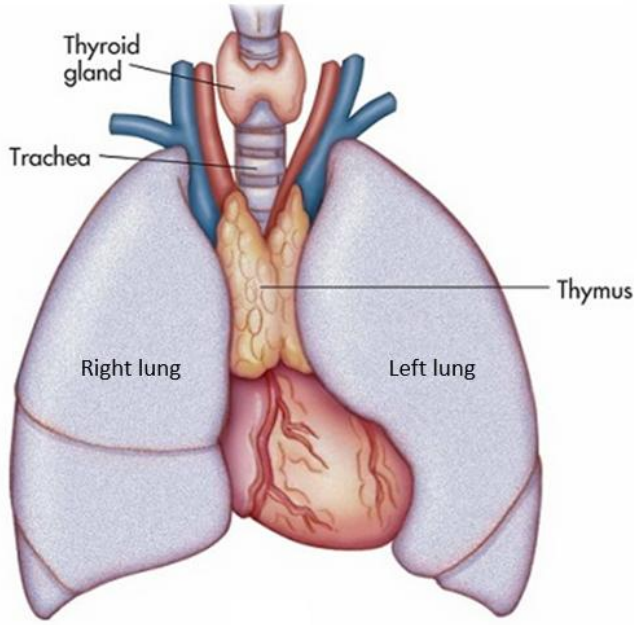


Figure 17.8 The thymus gland is located in the chest between the lungs directly behind the

It makes white blood cells (T lymphocytes) which are part of the immune system and help fight infection. The thymus gland is in the chest, between the lungs and behind the breastbone (sternum). The thymus produces all our T cells before we become teenagers.

Internally, the thymus is divided into lobules (see **Fig. 17.9** below) by trabeculae (little struts). The outer cortex contains large numbers of **thymocytes** with some epithelial cells, **macrophages**, and **dendritic cells** (just as in the lymph nodes and spleen). The cortex is densely packed (histologically it stains more heavily than the rest of the thymus), and the inner medulla, is much less dense and where thymocytes migrate before leaving the thymus.

As discussed in the endocrine section, the thymus produces and secretes the hormone **thymosin**, which is necessary for T cell development and production. The thymus is an organs that at its largest in children, and that makes sense since it is playing a significant role in the developing immune system

The "**Thymus Thump"** is a technique, also known as the happiness point. It can be easily practiced to assist in exuding **calmness**. It is known as a way to neutralize negative energy, and to revamp good energy levels, in order to support healing and vibrant health, and give a boost to the immune system. A simple but very effective energy technique involves tapping, thumping or scratching on the thymus point on your chest.

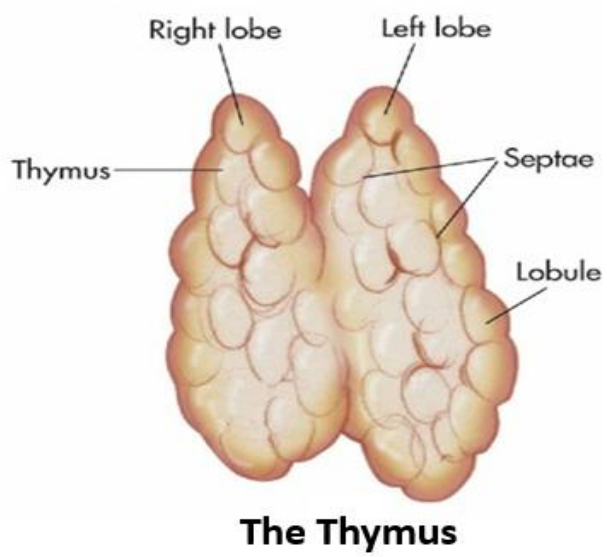


Figure 17.9 The two lobes of the thymus both contain lobules that are divided by septae.

The thymus gets its name from its resemblance to the bud of the leaf for cooking herb thyme (pronounced time), and also because of its 'warty' appearance. Often people ask, "Can a person live without a thymus?" Or a Spleen? Or tonsils? Or lymph nodes? The answer is **why** would you want to live without them? You can live without hands, should you get them removed if they have problems? No! Fix the issue rather than remove a body part - that goes for everything on your body. There are important reasons for every cell in your amazing body that even 'Brainiac scientist' don't know about. So, if an answer is to remove something in your body, get another opinion.

The Spleen

The spleen is the largest lymphoid organ in the body, usually measuring at about 5 in (12 cm) in length and is tethered to the lateral border of the stomach. The spleen has a deep dark red color, due to its extensive vascularization, and although it is an encapsulated organ, it does not have a very tough outer capsule. This is why it's sometimes considered a fragile organ, and because it also lacks any bony protection from ribs or the pelvis, in addition to residing in the abdominal cavity, which is the least protected region of the body.

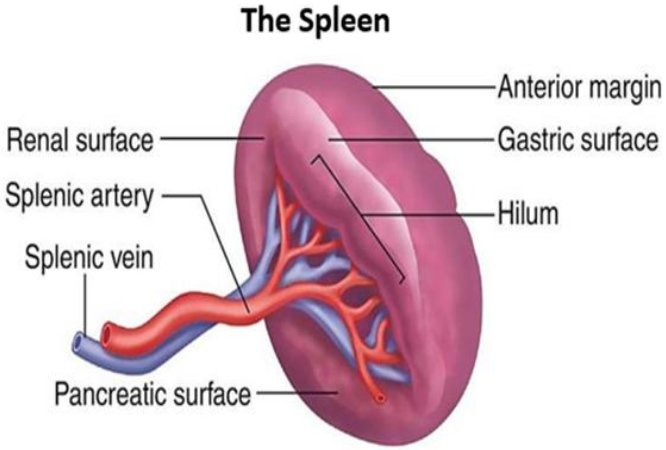


Figure 17.10 The red spleen with its significant vascular supply as it filters the blood.

The spleen is somewhat like a "filter of the blood", and like the lymph nodes and the thymus, it has the same **macrophages** and **dendritic cells** that remove any microbes and other materials from the blood as it flows through. As it filters the blood it is a key site for the removal of old or damaged red blood cells. It is often called the erythrocyte graveyard, recycling the iron from the heme group. The liver also culls RBCs from circulation and recycles the material.

The splenic artery splits into several arterioles filing the venous sinuses and into the highly permeable sinusoidal capillaries that departs via the splenic vein (see **Fig. 17.10**). Our spleen is a **reservoir** for **red blood cells** (RBCs) and can contain up to about 8 ounces (250 ml) of RBCs that can be released in times of hypovolemia and hypoxia. The spleen also **stores platelets** in case additional sources are needed and clears old platelets from the circulation. The spleen provides extramedullary hematopoiesis, in that is a place outside of the medullary cavity of bone that makes white blood cells lymphocytes and antibodies to defend the body. The spleen in the developing fetus makes red blood cells, but after the fifth month of gestation, it stops. The spleen produces compounds called **opsonins** (such as *properdin* and *tuftsin)* which are substances that bind to foreign microorganisms or cells making them more susceptible to phagocytosis.

At the histological level, the spleen has two main types of tissue, **white pulp** and **red pulp**, and is segmented by trabeculae of connective tissue.

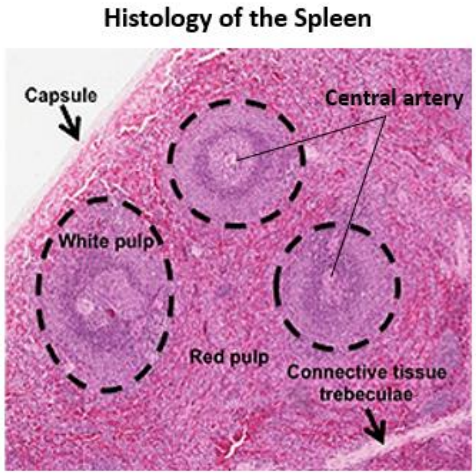


Figure 17.11 The histology showing the white and red pulp of the spleen.

The white pulp is made of **lymphoid nodules** and is contains mostly white blood cells with germinal centers of dividing B cells, surrounded by T-cells, macrophages, and dendritic cells around a small central artery. It is similar to lymphoid follicles of lymph nodes. The white pulp is where adaptive T-cell and B-cell responses occur.

The red pulp consists mostly of **red blood cells**, as mentioned that give the spleen its color. These blood-filled cavities (venous sinuses) have convoluted sinusoidal capillaries into which arteriolar blood empties for filtering. There are macrophage present here too. The red pulp primarily functions as a filtration system of the blood, utilizing cells of the non-specific immune response.

Other Lymphoid Tissue

Lymphoid nodules consist of a dense cluster of lymphocytes without a surrounding fibrous capsule. These nodules are located in the respiratory and digestive tracts, areas routinely exposed to environmental pathogens. All of these create barriers that afford protection to the body.

Mucosa-associated lymphoid tissue (MALT) consists of an aggregate of lymphoid follicles directly associated with the mucous membrane epithelia. MALT makes up dome-shaped structures found underlying the mucosa of the gastrointestinal tract, breast tissue, lungs, and eyes. Peyer's patches, a type of MALT in the small intestine, are especially important for immune responses against ingested substances. Peyer's patches contain specialized endothelial cells called M (or micro-fold) cells that sample material from the intestinal lumen and transport it to nearby follicles so that adaptive immune responses to potential pathogens can be mounted.

Gut-associated lymphoid tissue (GALT) is a component of the MALT (above) which works in the immune system to protect the body from invasion in the gut. GALT is the largest mass of lymphoid tissue in the body. It consists of immune cells such as B and T lymphocytes, macrophages, antigen-presenting cells, including dendritic cells, and specific epithelial and intra-epithelial lymphocytes.

Bronchus-associated lymphoid tissue (BALT) consists of lymphoid follicular structures with an overlying epithelial layer found along the bifurcations of the bronchi, and between bronchi and arteries. They also have the typically less-organized structure of other lymphoid nodules. These tissues, in addition to the tonsils, are effective against inhaled pathogens.

Barrier Defenses and the Innate Immune Response

The immune system can be divided into two overlapping mechanisms to destroy pathogens: the innate immune response, which is relatively rapid but nonspecific and thus not always effective, and the adaptive immune response, which is slower in its development during an initial infection with a pathogen, but is highly specific and effective at attacking a wide variety of pathogens (see Figure 1).

Any discussion of the innate immune response usually begins with the physical barriers that prevent pathogens from entering the body, destroy them after they enter, or flush them out before they can establish themselves in the hospitable environment of the body's soft tissues. Barrier defenses are part of the body's most basic defense mechanisms. The barrier defenses are not a response to infections, but they are continuously working to protect against a broad range of pathogens.

The Skin Barrier

There are several modes of barrier defenses that are associated with external surfaces of the body, which is a key site of possible entry of toxins, and the primary barrier to the entrance into the body is the **skin**.

Not only is the skin covered with a layer of dead, keratinized epithelium that is too dry for most organisms to grow on, but as these cells are continuously sloughed off (shed) from the skin, they carry off any creatures with them. Additionally, sweat, oil and other skin secretions act to lower pH, plus they contain repellant lipids that assist in constantly physically cleansing the body surfaces.

Cells of Lymphatics and Immunity

Cells of the Innate Immune Response

A phagocyte is a cell that is able to surround and engulf a particle or cell, a process called **phagocytosis**. The phagocytes of the immune system engulf other particles or cells, either to clean an area of debris, old cells, or to kill pathogenic organisms such as bacteria. The phagocytes are the body's fast acting, first line of immunological defense against organisms that have breached barrier defenses and have entered the vulnerable tissues of the body.

Phagocytes: Macrophages and Neutrophils

Many of the cells of the immune system have a **phagocytic** ability, at least at some point during their life cycles. Phagocytosis is the ingestion of bacteria or other material by phagocytes, form the Latin phage to eat! This is an effective mechanism of destroying pathogens during innate (immediate) immune responses. The phagocyte takes the organism inside itself as a phagosome, which subsequently fuses with a lysosome and its digestive enzymes, effectively killing many pathogens. On the other hand, some bacteria including *Mycobacteria tuberculosis*, connected to tuberculosis, may be resistant to these enzymes and are therefore much more difficult to clear from the body. **Macrophages**, **neutrophils**, and **dendritic cells** are the major phagocytes of the immune system. As seen in the discussions above of the lymph nodes, thymus and spleen, these cells are always present as resident phagocytes.

Recall form our discussions of the hematopoiesis in the blood sections, that the **macrophage** is derived from a leukocyte (white blood cell) called a **monocyte**. In general there are wandering macrophages that are on the move and fixed macrophages that remain in specific tissues. The macrophage is a large irregularly shaped phagocyte that is amoeboid in nature and is the most versatile of the phagocytes in the body.

When any leukocyte or macrophage needs to get to the site of an infection, they can exit the bloodstream via a process called **diapedesis**. The terms diapedesis describes how white blood cells (WBC's) can **change their shape** in order to squeeze between or through adjacent endothelial cells of the blood vessel. Macrophages move through tissues and squeeze through capillary walls using their **pseudopodia**, cell process extensions that are like feet. Not only do they participate in innate immune responses, but they cooperate effectively with lymphocytes as part of the **adaptive** (long-term memory) immune response.

Macrophages exist in many tissues of the body, either freely roaming through connective tissues or fixed to reticular fibers within specific tissues such as lymph nodes. When pathogens breach the body's barrier defenses, macrophages are the first line of defense. An important point is that macrophages are called different names, depending on the tissue where they are found. For example, in the liver the resident macrophage are called **Kupffer cells**. This is an eponym, named after a person, the German pathologist Karl Wilhelm von Kupffer. In 1876 he originally called them star cells (sternzellen) of the liver. These macrophages are located in the hepatic sinusoidal capillaries. In a wide range of connective tissue there are **histiocytes**, which are fixed macrophages. And 'alveolar macrophages' in the lungs are … macrophages.

A **neutrophil** is another example of a powerful and effective phagocytic cell that is attracted via chemotaxis (chemical signals) from the bloodstream to the site of the infected tissues. These spherical cells are granulocytes, meaning they contains cytoplasmic **granules**, which in turn contain a variety of powerful digestive enzymes such as **myeloperoxidase**, and vasoactive mediators. In contrast, macrophages are agranulocytes, meaning they have few or no cytoplasmic granules. Whereas

macrophages act like sentries, always on guard against infection, neutrophils can be thought of as military reinforcements that are called into a battle to hasten the destruction of the enemy. Although, usually thought of as the primary pathogen-killing cell of the inflammatory process of the innate immune response, new research has suggested that neutrophils play a role in the adaptive immune response as well, just as macrophages do.

A **monocyte** is a circulating precursor cell that differentiates into either a **macrophage** or **dendritic cell**, which can be rapidly attracted to areas of infection by signal molecules of inflammation.

Natural Killer Cells

NK cells are a type of lymphocyte that have the ability to induce apoptosis, that is, programmed cell death, in cells infected with intracellular pathogens such as obligate intracellular bacteria and viruses. NK cells recognize these cells by mechanisms that are still not well understood, but that presumably involve their surface receptors. NK cells can induce apoptosis, in which a cascade of events inside the cell causes its own death by either of two mechanisms:

1. NK cells are able to respond to chemical signals and express the Fas ligand (Fas cell surface death receptor) The **Fas ligand** is a surface molecule that binds to the Fas molecule on the surface of the infected cell, sending it apoptotic signals, thus killing the cell and the pathogen within it
2. The granules of the NK cells release perforins and granzymes. A **perforin** is a protein that forms pores in the membranes of infected cells. A **granzyme** is a protein-digesting enzyme that enters the cell via the perforin pores and triggers apoptosis intracellularly.

Both mechanisms are especially effective against virally infected cells. If apoptosis is induced before the virus has the ability to synthesize and assemble all its components, no infectious virus will be released from the cell, thus preventing further infection.

Recognition of Pathogens

Cells of the innate immune response, the phagocytic cells, and the cytotoxic NK cells recognize patterns of pathogen-specific molecules, such as bacterial cell wall components or bacterial flagellar proteins, using pattern recognition receptors. A **pattern recognition receptor (PRR)** is a membrane-bound receptor that recognizes characteristic features of a pathogen and molecules released by stressed or damaged cells.

These receptors, which are thought to have evolved prior to the adaptive immune response, are present on the cell surface whether they are needed or not. Their variety, however, is limited by two factors. First, the fact that each receptor type must be encoded by a specific gene requires the cell to allocate most or all of its DNA to make receptors able to recognize all pathogens. Secondly, the variety of receptors is limited by the finite surface area of the cell membrane. Thus, the innate immune system must “get by” using only a limited number of receptors that are active against as wide a variety of pathogens as possible. This strategy is in stark contrast to the approach used by the adaptive immune system, which uses large numbers of different receptors, each highly specific to a particular pathogen.

Should the cells of the innate immune system come into contact with a species of pathogen they recognize, the cell will bind to the pathogen and initiate phagocytosis (or cellular apoptosis in the case of an intracellular pathogen) in an effort to destroy the offending microbe. Receptors vary somewhat according to cell type, but they usually include receptors for bacterial components and for complement, discussed below.

Soluble Mediators of the Innate Immune Response

The previous discussions have alluded to chemical signals that can induce cells to change various physiological characteristics, such as the expression of a particular receptor. These soluble factors are secreted during innate or early induced responses, and later during adaptive immune responses.

Cytokines and Chemokines

A **cytokine** is signaling molecule that allows cells to communicate with each other over short distances. Cytokines are secreted into the intercellular space, and the action of the cytokine induces the receiving cell to change its physiology. A **chemokine** is a soluble chemical mediator similar to cytokines except that its function is to attract cells (chemotaxis) from longer distances.

Early Induced Proteins

Early induced proteins are those that are not constitutively present in the body, but are made as they are needed early during the innate immune response. **Interferons** are an example of early induced proteins. Cells infected with viruses secrete interferons that travel to adjacent cells and induce them to make antiviral proteins. Thus, even though the initial cell is sacrificed, the surrounding cells are protected. Other early induced proteins specific for bacterial cell wall components are mannose-binding protein and C-reactive protein, made in the liver, which bind specifically to polysaccharide components of the bacterial cell wall.

Phagocytes such as macrophages have receptors for these proteins, and they are thus able to recognize them as they are bound to the bacteria. This brings the phagocyte and bacterium into close proximity and enhances the phagocytosis of the bacterium by the process known as opsonization. **Opsonization** is the tagging of a pathogen for phagocytosis by the binding of an antibody or an antimicrobial protein.

Complement System

The **complement** system is a series of proteins constitutively found in the blood plasma. As such, these proteins are not considered part of the **early induced immune response**, even though they share features with some of the antibacterial proteins of this class. Made in the liver, they have a variety of functions in the innate immune response, using what is known as the “alternate pathway” of complement activation.

Additionally, complement functions in the adaptive immune response as well, in what is called the classical pathway. The complement system consists of several proteins that enzymatically alter and fragment later proteins in a series, which is why it is termed cascade. Once activated, the series of reactions is irreversible, and releases fragments that have the following actions:

- Bind to the cell membrane of the pathogen that activates it, labeling it for phagocytosis, which is the process of **opsonization**.
- Diffuse away from the pathogen and act as chemotactic agents to attract phagocytic cells to the site of inflammation.
- Form damaging pores in the plasma membrane of the pathogen.

The classical pathway requires antibodies of the adaptive immune response. The alternate pathway does not require an antibody to become activated.

The splitting of the C3 protein is the common step to both pathways. In the alternate pathway, C3 is activated spontaneously and, after reacting with the molecules factor P, factor B, and factor D, splits apart.

The larger fragment, C3b, binds to the surface of the pathogen and C3a, the smaller fragment diffuses outward from the site of activation and attracts phagocytes to the site of infection. Surface-bound C3b then activates the rest of the cascade, with the last five proteins, C5–C9, forming the membrane-attack complex (MAC). The MAC can kill certain pathogens by disrupting their osmotic balance. The MAC is especially effective against a broad range of bacteria.

The classical pathway is similar, except the early stages of activation require the presence of antibody bound to antigen, and thus is dependent on the adaptive immune response. The earlier fragments of the cascade also have important functions. Phagocytic cells such as macrophages and neutrophils are attracted to an infection site by chemotactic attraction to smaller complement fragments. Additionally, once they arrive, their receptors for surface-bound C3b opsonize the pathogen for phagocytosis and destruction.

The Inflammatory Response

The central characteristic of the innate immune response (which means the immediate response) is **inflammation**. Inflammation is something everyone has experienced. If you have stubbed a toe, cut a finger, or engaged in any other activity that causes tissue damage, inflammation will result. It will include its four (or five) characteristics and they do not need to be in any specific order:

1) Pain; **2)** Heat; **3)** Redness; **4)** Swelling… and **5)** Some loss of function (may not always occur).

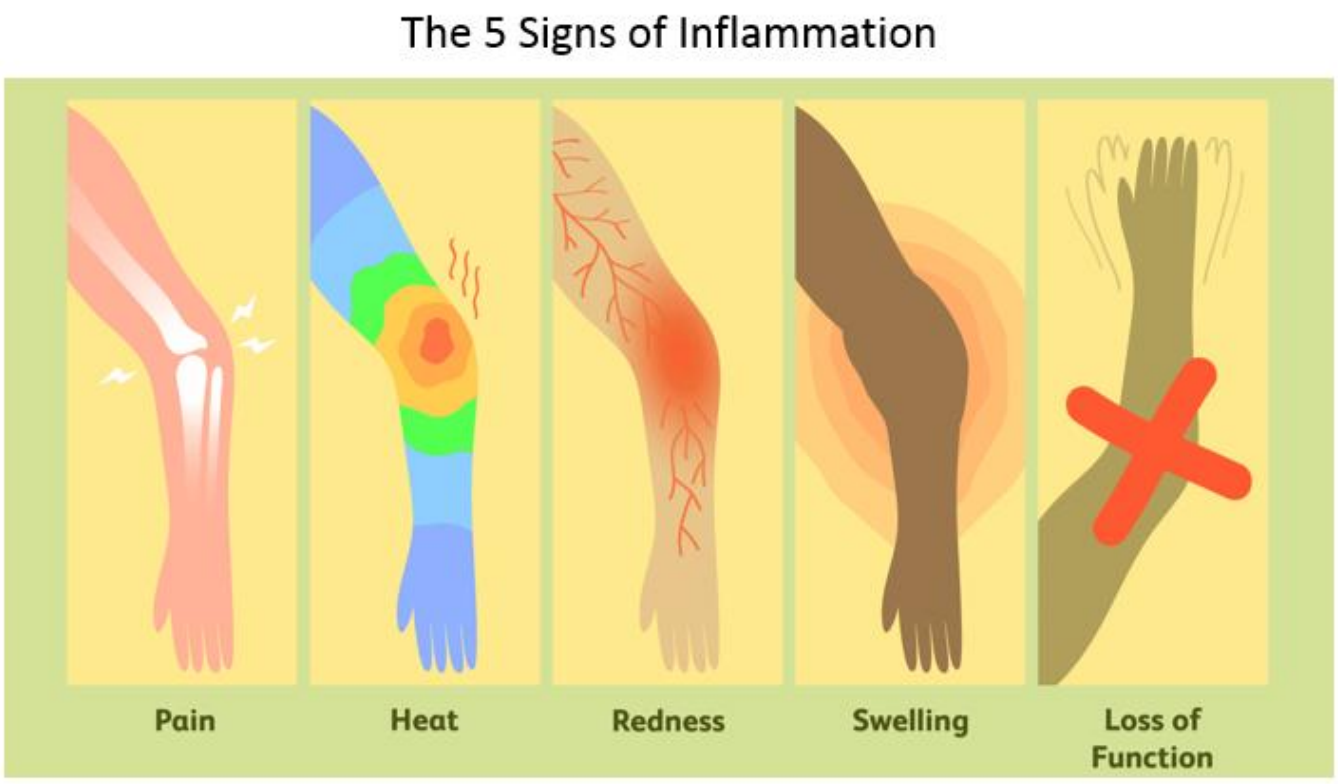


Figure 17.12 The panels above show the typical signs of inflammation that can start with the onset of pain from an injury. This is a signal for increasing blood flow to the area in order to start the repair process and this brings heat, redness and swelling with it. This often results in an immobilization of the affected area, which is protective in that it prevents any further injury from occurring.

It is important to note that inflammation does not have to be initiated by an infection, but can also be caused by tissue injuries. The release of damaged cellular contents into the site of injury is enough to stimulate the response, even in the absence of breaks in physical barriers that would allow pathogens to enter (by hitting your thumb with a hammer, for example). The inflammatory reaction brings in phagocytic cells to the damaged area to clear cellular debris and to set the stage for wound repair.

This reaction also brings in the cells of the innate the repair processes, allowing the body to get rid of the sources of a possible irritation. Inflammation is not bad. On the contrary it is the essence of the healing process in the body. The process not only brings needed fluid and cells into the site of injury to provide all the elements needed by the tissue, but it also allows the body to begin to resolve some of the debris from the site while keeping it isolated, to protect the region for any further harm.

Acute inflammation is a short-term inflammatory response to an insult to the body. If the cause of the inflammation is not resolved, however, it can lead to chronic inflammation, which is associated with major tissue destruction and fibrosis. **Chronic inflammation** is ongoing inflammation. It can be caused by foreign bodies, persistent toxicity of tissues and other disease states characterized by imbalance.

There are four important parts to the inflammatory response:

- ***Tissue Injury***. The released contents of injured cells stimulate the release of **mast cell** granules and their potent inflammatory mediators such as histamine, leukotrienes, and prostaglandins. **Histamine** increases the diameter of local blood vessels (vasodilation), causing an increase in blood flow. Histamine also increases the permeability of local capillaries, causing plasma to leak out and form interstitial fluid. This causes the swelling associated with inflammation. Additionally, injured cells, phagocytes, and basophils are sources of inflammatory mediators, including **prostaglandins** and **leukotrienes**. Leukotrienes attract neutrophils from the blood by chemotaxis and increase vascular permeability. Prostaglandins cause vasodilation by relaxing vascular smooth muscle and are a major cause of the pain associated with inflammation. The mode of action of drugs such as *aspirin* and ibuprofen is to inhibit *prostaglandin* production, thus those inhibit true repair.

- ***Vasodilation***. Many inflammatory mediators such as histamine are vasodilators that increase the diameters of local capillaries. This causes increased blood flow and is responsible for the heat and redness of inflamed tissue. It allows greater access of the blood to the site of inflammation.

- ***Increased Vascular Permeability***. At the same time, inflammatory mediators increase the permeability of the local vasculature, causing leakage of fluid into the interstitial space, resulting in the swelling, or edema, associated with inflammation.

- ***Recruitment of Phagocytes***. Leukotrienes are particularly good at attracting neutrophils from the blood to the site of infection by chemotaxis. Following an early neutrophil infiltrate stimulated by macrophage cytokines, more macrophages are recruited to clean up the debris left over at the site. When local infections are severe, neutrophils are attracted to the sites of infections in large numbers, and as they phagocytose the pathogens and subsequently die, their accumulated cellular remains are visible as pus at the infection site.

The Benefits of Inflammation

Inflammation is a necessary and beneficial process for a number of reasons. Firstly, it neutralizes or eliminates the pathogens and removes the cellular debris that is created. The **increased vascular permeability** facilitates the entry of clotting factors into the damaged regions and is the first step towards wound repair. Inflammation also promotes the transport of **antigens** to nearby **lymph nodes** by dendritic cells, in preparation for the adaptive immune response. This is carried out by the lymphocytes, via **antibody responses** (**B**-cells) and cell-mediated immune responses (**T**-cells).

Review Questions for Chapter 17: Lymphatics and Immunity

1. The largest lymphatic structure is the _____.

- **a)** thymus
- **b)** lymph node
- **c)** spleen
- **d)** tonsils

2. Which is not an organ of the Lymphatic system?

- **a)** Spleen
- **b)** Thymus
- **c)** Tonsils
- **d)** Liver

3. Which of the following is **not** a function of the lymphatic system?

- **a)** Circulates blood proteins
- **b)** Removes excess fluid from around organs
- **c)** Absorbs and transports fats
- **d)** Produces white blood cells
- **e)** Regulates tissue fluid volume

4. Two main organs of the lymph system:

- **a)** Thymus and Pancreas
- **b)** Pancreas and Thyroid
- **c)** Spleen and Thymus
- **d)** Tonsils and Thyroid
- **e)** Spleen and Liver

5. A soft lymphoid tissue that produces all blood cells

- **a)** Thymus immune cells
- **b)** Lymph nodes
- **c)** Spleen
- **d)** Red bone marrow
- **e)** Yellow bone marrow

6. What is the largest lymphatic vessel in the body?

- **a)** The aorta
- **b)** The right lymphatic duct
- **c)** The thoracic duct
- **d)** The cisterna chyli
- **e)** The lumbar duct

7. A lymphatic structure located in the upper left quadrant of the abdomen is called?

- **a)** Lymph
- **b)** Lymph fluid
- **c)** Spleen

8. The tiny oval shaped lymph structure located throughout the body are known as?

- **a)** Lymph nodes
- **b)** Spleen
- **c)** Lymph fluid

9. The structure of a lymphatic vessel is most similar to that of a(n)

- **a)** Artery
- **b)** Vein
- **c)** Arteriole
- **d)** Capillary
- **e)** Venule

10. The _____ lymph nodes are in your groin

- **a)** axillary
- **b)** femoral
- **c)** lumbar
- **d)** inguinal
- **e)** cervical

Answers in Appendix B