Cancer And Lymphatics: 
Part I

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ABSTRACT

In the human body, cells receive nutrition and oxygen from lymph, a fluid that is recirculated through the body via an extensive network of vessels. Upon arriving at one of many nodes found within the body, the lymph is filtered to discern healthy cells from those carrying disease or infection. However, cancer can either develop in the lymph nodes around the body, or it can travel there via the lymphatic vessel network. Understanding the role that the lymphatic system plays in the development, treatment, and prevention of cancer is vital for medical professionals who want to provide their patients with cutting-edge care. This is the first of a two-part series on Cancer and Lymphatics that discusses normal and disease states.
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This educational activity is credited for 5 hours. Nurses may only claim credit commensurate with the credit awarded for completion of this course activity.

**Statement of Learning Need**

Understanding the role of the lymphatic system is vital for all health professionals, especially nurses who deliver care to patients with a disorder involving the lymph system. There exist many misconceptions of the role of the lymphatic system; including prevention and the treatment of disease.

**Course Purpose**

To provide nurses with knowledge of the lymphatic system, and corresponding diseases, prevention and treatment.
Target Audience

Advanced Practice Registered Nurses and Registered Nurses

(Interdisciplinary Health Team Members, including Vocational Nurses and Medical Assistants may obtain a Certificate of Completion)

Course Author & Planning Team Conflict of Interest Disclosures

Jassin M. Jouria, MD, William S. Cook, PhD, Douglas Lawrence, MA, Susan DePasquale, CGRN, MSN, FPMHNP-BC – all have no disclosures

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There is no commercial support for this course.

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Please take time to complete a self-assessment of knowledge, on page 4, sample questions before reading the article.

Opportunity to complete a self-assessment of knowledge learned will be provided at the end of the course.
1. **The initial lymph vessels are the preliminary lymph vessels that**
   a. are located at the junction between the epidermis and the dermis.
   b. consist of a multiple layer of squamous epithelial cells.
   c. originate in the basal layer of the epidermis.
   d. fit tightly together to contain fluid.

2. **True or False: Although the lymph system and the circulatory system are similar in structure and function, they are separate and unconnected.**
   a. True
   b. False

3. **The precollector lymph vessels**
   a. are located at the junction between the epidermis and the dermis.
   b. that originate in the basal layer of the epidermis.
   c. whose epithelial cells fit tightly together.
   d. are less permeable than blood capillaries.

4. ________________ are semi-permeable in that fluid can move into and out of the vessel structures but not as readily as with initial vessels.
   a. Vessel structure walls
   b. Precollector vessel walls
   c. Initial vessel walls
   d. Squamous epithelial cells

5. **Fluid is then kept inside the lymph vessel because**
   a. of a decreased pressure inside the interstitial space.
   b. of an increase in the force inside the interstitial space.
   c. lymph vessels are impermeable.
   d. the anchor filaments pull the epithelial cells.
Introduction

The varied roles of the lymphatic system are crucial to sustaining and supporting the body’s immune system functions. While not as familiar as the cardiovascular circulatory system of the bloodstream, the lymphatic system actually works in tandem with many of the functions of the cardiovascular system to control interstitial fluid levels, to return some substances to blood circulation, and to remove potentially harmful substances that have made their way into the body.

The lymphatic system consists of certain organs, vessels, and fluids that provide protection and immunity. It is sometimes classified as being part of the blood circulatory system in that it has a similar structure of fluid transport: the lymph fluid that travels through the lymphatic vessels runs through a similar network of vessels as that of the cardiovascular circulatory system. The lymph system also empties lymph fluid into the veins of the circulatory system, which actually works as a means of connecting the two systems together as being similar in both structure and function.

The lymphatic system has an intricate design that performs multiple functions to support an individual’s immunity and to maintain a routine set of activities that sustain normal fluid levels. The lymph system has three major functions: it returns interstitial fluid to the blood, it is involved with absorption of fat and fat-soluble vitamins and their transport into the bloodstream, and it acts as a method of defense against foreign pathogens in the body.¹

The lymphatic system can help to prevent excess edema formation in the tissues when fluid accumulates in the interstitial spaces around the cells. As blood flows through the circulatory system, oxygen and nutrients are
transferred when the blood enters the capillary networks that serve various organs and peripheral tissues. The blood then leaves the capillaries and returns to the capillary network as it prepares to travel back to the heart and to the lungs to receive more oxygen. Most of the fluid in the blood re-enters circulation at the capillary level, but a small amount of fluid remains in the interstitial space surrounding the cells. When protein molecules leak through the capillary wall, less fluid is returned back into circulation and more is retained in the interstitial space, resulting in edema.

The entire lymphatic system is very complex and its components are found throughout the body. The process of maintaining fluid homeostasis and providing body defense occurs so routinely that most people are completely unaware of it. However, without the functions of the lymphatic system, life would be shortened due to fluid imbalances, lack of fat absorption, and little to no defense against harmful pathogens.

**Lymph Vessels**

Lymph vessels are designed as a network of circulatory pathways that wind through the body and that contain lymph fluid as it circulates to various areas of the body. The lymph vessels are similar in structure to blood vessels in that they have thin walls and they carry fluid to circulate it around the body. Lymph vessels vary in size from small vessels that circulate near the blood vessels to those that are much larger and that carry lymph fluid back into blood circulation. The work of the lymph vessels is similar to that of the veins however, unlike veins, most lymph vessels do not contain valves within their smaller capillaries; they instead propel lymph fluid when the vessels contract with pressure from nearby structures and external sources.
Lymph capillaries are divided into two different types: initial lymph vessels and collecting capillaries. The initial lymph vessels are the preliminary lymph vessels that originate in the basal layer of the epidermis. Initial vessels consist of a single layer of squamous epithelial cells, called endothelium, that overlap each other but that have gaps in between. Compared to the blood capillaries, whose epithelial cells fit tightly together to contain blood in circulation, the epithelial cells of the initial lymph vessels are much more porous. These gaps make these vessels much more permeable and able to absorb fluid and cells into the lymph system. Fluid is absorbed through these vessels through specific pathways within the interstitium. Fibers known as anchor filaments extend outward from the external layer of the lymph vessel and into the interstitial space. When the lymph vessel is stretched, the anchor filaments pull the epithelial cells so that gaps are created to allow fluid to enter the lymph vessel from the interstitial space. Fluid is then kept inside the lymph vessel because of the change in pressure that decreases the force inside the interstitial space and increases pressure within the lymph vessel, keeping the layers of the vessel wall closed and the fluid contained within its boundaries.

The initial lymph vessels drain fluid into the collecting lymph capillaries; the small, initial lymph vessels eventually come together to form the larger capillaries. Precollector lymph vessels collect lymph fluid from the initial vessels and drain it into the collecting lymph vessels. The precollector lymph vessels move deeper into the skin tissue and are
located at the junction between the epidermis and the dermis. As the vessels progress, small valves and smooth muscle tissue start to appear along the way; there is typically a one-way valve at the junction between the initial vessel and the precollecting lymph vessel. As the precollector vessels move closer to the collector vessels, more and more valves develop within their walls. At the other end of the precollector vessel, there is another one-way valve as it connects to the collector lymph vessels.

Precollector vessel walls are semi-permeable in that fluid can move into and out of the vessel structures, although not as readily as with initial vessels. They are still considered superficial vessels because of their location in the skin and they are not as large as the collector lymph vessels. Because of their location, precollector vessels can move lymph fluid through their walls even when the surrounding skeletal muscles and tissues are moved or manipulated. Fluid that flows through the precollecting lymph vessels eventually drains into the collector lymph vessels.

Despite the burgeoning vessel network of precollector vessels with their growing valve structure and movement of fluid, there are some areas where precollector vessels gather into groups where fluid flows in both directions. This arrangement of lymphatic precollector vessels is known as anastomoses and their grouping is similar in appearance to the capillaries of the bloodstream. The anastomoses do not contain valves within their vessel walls; instead, lymph fluid is allowed to flow back and forth in both directions. This backward and forward flow of fluid allows the lymphatic system to drain excess interstitial fluid that collects in nearby tissues and that causes edema.
The collector lymph vessels are most like the blood vessels in their structure. Similar to blood vessels, collector vessels consist of three tissue layers that make up the vessel walls: the intima, the media, and the adventitia. The intimal layer is composed of endothelial cells that are surrounded by a basement membrane; the medial layer contains nerve fibers and smooth muscle, and the adventitia is made up of collagen and elastin. The collector vessels are divided into two further types, depending on the direction that they carry lymph fluid. Afferent collector vessels are those that transport lymph toward the lymph node, while efferent collector vessels transport lymph away from the lymph node.³

Collector vessels differ from precollector vessels in that they contain bicuspid valves that assist with movement of fluid within their walls and prevent it from flowing backward; these valves are known as intralymphatic valves. The collector vessels are made up of units known as angions, each of which is contained in the spaces between the vessel valves. Each collector vessel is basically a chain of angions that segment fluid from one section to the next; because of this structure, the collector vessels may sometimes be referred to as lymphangia.²

As the collector vessels stretch with movement, such as when they are filled with fluid or due to such external factors as skeletal muscle contractions, peristalsis, massage, or breathing, the lymph fluid is propelled forward. For example, contraction of skeletal muscles applies pressure to the lymph vessels, which stimulates the contraction of the lymph vessels to move lymph fluid through their walls. Internal factors or those in the surrounding environment stimulate a stretch reflex in the wall of the lymph vessel; this reflex triggers the angions to shift the lymph fluid from one section to the next, in a manner similar to the peristaltic waves noted in the
gastrointestinal tract. The smooth muscles in the wall of the collector vessel contract, which propel the lymph fluid forward toward the valves. Because the lymph vessels are stimulated to propel fluid by external factors such as skeletal muscle contractions, an increase in exercise or activity that uses the skeletal muscles can then impact the flow of lymph fluid through the body and can reduce fluid accumulation and edema formation.

When compared to the initial vessels, the collecting vessels are much less absorbent and they take in less surrounding fluid. On average, collector lymph vessels contract 6 to 8 times per minute, but this amount can increase to up to 20 times per minute, depending on activity and the amount of fluid within the vessels. The collector vessels may be located in the junction between the dermis and the epidermis, but deeper vessels are in the dermal layer of the skin and in the underlying fascia.

The complete pathway from the initial lymph vessel through the precollector vessels and into the collecting vessels follows a specific pattern within particular areas. Each pathway is known as a lymphatome. Several lymphatomes may carry lymph fluid through their specified pathways until they gather together and reach a collection of lymph nodes. Once the lymph fluid has passed through the lymph nodes, it is then transported further into the larger collecting ducts where it will eventually be deposited into venous circulation.

The lymphatic vessels continue to become larger as they progressively move toward venous circulation. The vessels join together as they become larger, eventually becoming lymphatic trunks, which drain lymph fluid into the lymphatic ducts. The largest lymph vessel in the body is the thoracic duct in the chest. It is joined with the right lymphatic duct, which is also a large
lymph vessel. Together, these two vessels collect lymph fluid that has flowed through the initial, precollector, and collector ducts throughout the body. The thoracic duct and the right lymphatic duct join the large left subclavian and internal jugular veins that enter the heart, bringing the lymph fluid back into venous circulation. Between 2 and 4 liters of lymph fluid is emptied into the venous system at the venous arch near the heart every 24 hours.\(^3\)

The right lymphatic duct collects lymph fluid from smaller collecting vessels in the right upper quadrant of the body, including the right jugular trunk from the side of the head and the neck; the right subclavian trunk, which collects fluid from the right arm and axilla, and the bronchomediastinal trunk, which collects fluid from the organs in the chest. Once fluid from these areas is drained into the right lymphatic duct, it then empties into the right subclavian vein. It should be noted that not everyone has a right lymphatic duct and it is only present in a percentage of the general population.\(^8\) Of those who do not have this structure, the lymph vessels of the right upper quadrant of the body eventually merge to connect with the larger veins near the heart instead of forming a right lymphatic duct.

The cisterna chyli is a central sac in the lymphatic vessel network that acts as a collection chamber within the abdominal cavity and the lower part of the thoracic duct. Fluid enters the cisterna chyli from the lymph vessels near the intestines and the abdomen. After being held in the cisterna chyli, the fluid is then transferred to the thoracic duct. The thoracic duct also collects fluid from the left arm, and the left side of the head and neck. Eventually, fluid that has been transported to the thoracic duct is emptied into venous circulation when the thoracic duct deposits fluid into the left venous angle, which eventually connects to the subclavian vein or the jugular vein.
The act of respiration stimulates lymph circulation as lymph fluid enters the thoracic duct and as the duct empties lymph fluid into the venous system. The movement and displacement of abdominal organs when the diaphragm moves up and down during exhalation and inhalation stimulates and stretches the lymphatic vessels to propel lymph fluid forward through its channels. During inhalation, the lungs expand, which compresses the thoracic duct where it empties lymphatic fluid into the subclavian or the jugular veins. The thoracic duct is filled with lymph fluid again upon exhalation as the fluid moves forward into the vessels to start the cycle again.⁸

**Lymphedema**

The body can regulate edema formation when lymph fluid reaches the end point at the thoracic duct or the right lymphatic duct and lymph fluid is emptied into venous circulation. A larger rate or volume of fluid emptied into the venous system creates negative pressure within the lymph vessel that continues to pull more fluid into the lymphatic system. Because fluid can be pulled into the lymph vessel network from the interstitial spaces, a cyclical effect occurs. Increased amounts of fluid that are pulled into the lymph vessels from the interstitial spaces results in increased amounts of fluid being added to venous circulation, which creates a greater amount of negative pressure in the lymphatic system, which in turn pulls in more fluid from the interstitial spaces, and so on.

It should be noted that edema could still develop in many areas of the body, even with a fully functioning lymphatic system. Edema formation occurs when there is excess fluid accumulation in the interstitial space. It may develop as a result of another disease process, such as heart failure, which is not necessarily associated with lymph fluid collection, or electrolyte
imbalance; both conditions are more commonly associated with fluid levels within blood circulation.

Lymphedema is a condition that also can develop as swelling and fluid accumulation. If the lymph vessels become obstructed, such as through surgical excision of lymph nodes, lymphedema develops when fluid builds up in the soft tissues. Lymphedema causes swelling and pain; the affected area often becomes stiff and difficult to move. Unfortunately, the condition is often self-perpetuating, as the increased stiffness near the lymphatic channels only causes further constriction of the lymph vessels, causing fluid to slow and to back up even more. Lymphedema occurs in some locations more often than in others. It is more often seen in the arms, the hands, and the chest, although it can develop in the lower extremities as well.

Lymphedema is often associated with mastectomies, as there is an increased risk of lymphedema and swelling developing after this particular procedure. Lymphedema may also be more likely to develop with some other procedures, such as with removal of lymph nodes for biopsy or as part of cancer surgery, or due to damage to the lymph system because of some types of treatment, including radiation treatment for cancer. When breast cancer develops, the cancerous cells can spread quickly through the lymphatic tissue in and around the breast tissue. If this occurs, many lymph nodes and some surrounding tissue are also removed in addition to the breast tissue during a mastectomy. This procedure disrupts the normal flow of lymph in the nearby arm and the patient can develop lymphedema in the upper extremity. Although researchers understand the causes of lymphedema, it is not always clear which patients will develop the condition and which ones will not. Some people will develop lymphedema following
certain medical procedures, even though others who have undergone the same procedure do not necessarily develop lymphedema.

Lymphedema may be classified as primary or secondary categories of the condition. Primarily lymphedema develops when lymph vessels are damaged or missing completely because of a hereditary condition, such as with congenital lymphedema. Secondary lymphedema develops as a result of another condition, often because of traumatic injury to the lymphatic vessels through a disease process that causes obstruction of the lymphatic vessels, or due to iatrogenic causes such as with surgery or radiation treatments. In some rare cases, lymphedema develops because of filariasis, an infestation of parasitic worms that enter the lymphatic system and that block the flow of lymph fluid. Filariasis is caused by parasitic nematode infection. Different types of worms infect different areas of the body; for example, there are worms that are more likely to infect the skin and subcutaneous tissue, while different types of parasites infect the body cavities. Within the lymphatic system, the most common worms that cause infection are Wuchereria bancrofti, Brugia malayi, and Brugia timori.

Initially, an individual with lymphatic filariasis may be asymptomatic, although the worms can be detected in a peripheral blood smear. Unfortunately, while the condition may be asymptomatic, it can still cause enough damage within the lymphatic system such that changes are irreversible. When symptoms do develop, they often manifest as fever and painful, red, and swollen tissue in areas where there are clusters of lymph nodes, such as in the groin or the axilla. It eventually leads to lymphedema that can cause such large amounts of lymph fluid collection as to cause elephantiasis of the peripheral tissues. Lymphatic filariasis is more common among developing countries, particularly in the subtropical or tropical areas.
of the world. According to the World Health Organization (WHO), approximately 120 million people throughout the world are affected by lymphatic filariasis.\textsuperscript{22}

When lymphedema develops, the extent of its spread can vary and it may range in severity between very mild edema formation that is not clinically evident to massive swelling and pitting edema. Often, avoiding certain activities that exacerbate the condition, such as with immobility or exposure to increased temperatures is helpful in reducing the severity of lymphedema. For some people, use of compression devices is also helpful in controlling swelling. Compression devices, such as with a compression stocking or by wrapping the area with a tight bandage, help the muscles to support the flow of lymph fluid within the vessels, they facilitate better lymph drainage from the affected site, and prevent excess lymph fluid from building up in the affected area.\textsuperscript{48} Unfortunately, there is no cure for lymphedema and those who develop the condition must typically submit to lifelong management through physical therapy and lifestyle changes that improve circulation and that support movement of the affected area.

Lymphedema may also develop as a result of lymphangitis, which describes lymph vessel inflammation. Lymphangitis is demonstrated as red streaks that extend from the area of infection. It most often develops from streptococcal infection of the skin that enters the body through a break in the skin’s barrier. For example, streptococcus species may be present on the surface of the skin and may then enter the body if an individual sustains a skin laceration. The affected individual often suffers from symptoms of infection, including fever, chills, anorexia, and headache. The affected lymph nodes become swollen and tender. The condition requires antibiotic treatment to control the streptococcal infection and to prevent it from...
worsening and spreading through the lymphatic vessels. Untreated, lymphangitis may lead to abscess, cellulitis, or septicemia if the initial infection is disseminated through the lymphatic system and enters the bloodstream.21

**Gastrointestinal Lymphatics**

The lymphatic vasculature that serves the gastrointestinal system appears to consist of two different networks of vessels that drain into a common collecting network. As noted, lacteals are lymph ducts found within the villous projections in the intestinal tract. Each lacteal within a villus connects with other lacteals from other villi to form a lymphatic network connected together at the base of the villi in the submucosal layer of the intestine. This submucosal network contains few valves and fluid may flow freely throughout the system. A second lymphatic network is found in the mucosal muscle layer of the intestinal tract. The two systems of the villi and submucosal lymphatics and the lymphatics in the intestinal muscle layer do not actually connect. Instead, they each drain into the same larger collector vessels outside of the gastrointestinal tract and near the mesenteric border.5

The gastrointestinal lymphatic system, while responsible for the transport of nutrients, has also been shown to play a role in certain disease processes. A study by Bäckhed, *et al.*, in the *Proceedings of the National Academy of Sciences* discussed fasting-induced adipose factor (Fiaf), a protein produced in the intestine that plays a
role in the formation of new lymphatic channels. The study showed that when deleting Fiaf, the blood and lymph vessels in the gastrointestinal system were not partitioned in the small intestine.

The effects of Fiaf deletion were actually only seen in the small intestine, but not in other areas where lymphatic vessels were located, such as within the skin. This suggests that Fiaf is selective only for gastrointestinal lymphatic vessels and its requirement for the development of new lymphatic vessels in the gastrointestinal tract. Fasting-induced adipose factor has been associated with regulation of adipose tissue and fat storage and it plays a role in lipid metabolism. The presence of Fiaf and its effects on lymphatic vessels supports not only the distinctive role of lymphatic channels for nutrient absorption, but it also may guide further work in the development of treatments and management strategies for certain gastrointestinal disorders, dyslipidemia, or other nutrient deficiencies.

The lymph nodes in the digestive system also play a role in protecting the body from pathogens that enter the body after being swallowed. All of the organs of the digestive tract have surrounding lymph nodes that carry away excess fluid for it to eventually be deposited into venous circulation. The digestive system also contains lymph nodes that manage many pathogens that enter the gastrointestinal tract through eating or drinking. Normally, when pathogens enter the body through food they are destroyed after reaching the stomach and its gastric acid. If any pathogens are able to move past the stomach acid and enter the small intestine, they may be captured and carried away by the lymphatic system. Because lymph vessels and lymph nodes are found near various portions of the digestive tract, the lymph fluid can carry away toxins that have reached the intestinal tract and
transport them to the lymph nodes where they will be filtered and destroyed.

**Lymph Fluid**

Lymph fluid begins at the level of the blood capillaries when fluid is forced from the interstitial spaces and enters the initial lymph vessels. There are lymph vessels in almost all of the tissues, except within some portions of the central nervous system and in bone. When it is still in the interstitial space, the fluid surrounds the cells where it fills in the gaps and bathes and nourishes the cells. The interstitial fluid also takes up foreign particles, enzymes, and certain microorganisms during this time, which are also often transferred into the lymphatic system when the fluid becomes lymph.

Lymph fluid is similar in composition to plasma, in that it contains water, plasma proteins and lipoproteins, although it does not contain some other components of blood, including platelets or red blood cells. Lymph fluid contains a large supply of white blood cells — lymphocytes — that are pertinent for supporting the body’s immune system. Because lymph fluid takes on the “overflow” of interstitial fluid that has moved out of the capillaries, it also contains cellular debris, some foreign substances, and long-chain fatty acids that have been absorbed through the villi in the large intestine. Lymph also contains some of the same electrolytes, lymphocytes, and organic particles that are found in plasma.

As it moves through the lymphatic system and passes through the lymph vessels, lymph becomes more concentrated. In particular, lymph fluid near the gastrointestinal tract may take on a milky appearance because of the accumulation of fat that has been absorbed through the lacteals in the digestive tract. It contains chylomicrons, which are types of triglycerides
that contain long chains of fatty acids. This specific type of lymph fluid from the intestinal tract with its high fat content is known as chyle.\textsuperscript{12} Often, when people think of lymph fluid, they may imagine it as a milky white appearance that is often seen in and around the lymph nodes of the digestive tract.

Unlike the heart, there is no central pump that pushes lymph fluid along through its channels. Instead, the lymph vessels are able to move the lymph through a series of segments based on changes in the pressure gradient between the inside and the outside of the vessel. As lymph fluid moves from its start in the initial vessels through the precollector vessels and into the collector vessels, water filters out through the vessels and the lymph nodes, making the remaining lymph more concentrated with the larger molecules, such as protein. The lymph fluid is eventually deposited into venous circulation after it passes through the lymph channels in the lymphatic vascular network. Once it reaches the thoracic duct, approximately 90 percent of lymph fluid is transferred back into the venous circulation, while the remaining 10 percent is added back into the interstitial fluid.\textsuperscript{1} Once the levels of lymph fluid increase in the interstitial space, fluid is absorbed once more into the lymphatic vessels and the cycle begins again.

Lymph is extremely important as part of the lymphatic system because it carries foreign particles and potentially harmful microorganisms through the lymphatic vessels to the lymph nodes where they can be destroyed. When cancer cells metastasize and move to areas away from the primary tumor, lymph fluid may also carry the tumor cells so that they do not settle in another area and proliferate there. After lymph fluid leaves the lymph node, it contains many lymphocytes, which are essential components of the immune system and that protect the body from infection and disease.
**Lymph Nodes**

A lymph node is a structure about the size of a pea that is found along the lymphatic vessel pathways. There are over 600 lymph nodes located throughout the body and most are less than 1 cm in size; each node is the approximate shape of a bean. The exterior portion of a lymph node is made up of a thin layer that forms a capsule around the node. Afferent collector vessels transport lymph fluid toward the lymph nodes where some of it is then reabsorbed into the venous system. When the afferent vessels bring lymph fluid to the nodes, approximately half of the fluid, as well as some of the dissolved substances within the fluid, is absorbed to be returned to venous circulation. The other half is transported away from the lymph node via the efferent collector lymph vessels.

Each lymph node has afferent and efferent vessels that carry lymph fluid toward or away from the node, respectively. Most lymph nodes have more afferent vessels than efferent vessels, which means that lymph circulation is slowed when the fluid reaches the nodes. Lymph fluid leaves the lymph node through the efferent vessels at a point called the hilum, which is a small depression on the side of the node. Alternatively, afferent vessels bring lymph fluid toward the node and are attached at various points on the surface of the node.

Lymph nodes are responsible for filtering lymph fluid through biological filtration as it passes through the nodes. Because they contain both T lymphocytes and B lymphocytes, by filtering, the lymph nodes catch and destroy potentially harmful pathogens in the body. Once the fluid has passed through the filter of the lymph node, it continues on to rejoin the bloodstream. Each lymph node is composed of two sections: the cortex and the medulla. The cortex of the lymph node contains collections of
lymphocytes known as follicles, and the centers of these follicles consist mostly of B lymphocytes while the rest of the surrounding cells are T lymphocytes.

Within the lymph node, connective tissue partitions divide the interior portions into its compartments. Within the medullary portion of the node, the partitions continue to divide until they become a connective tissue framework that connects to the hilum, the area on the side of the lymph
node where efferent vessels leave the structure. Within the total structure of
the lymph node are lymph sinuses; it is in these areas that lymph fluid
cIRCulates.\textsuperscript{12} The lymph fluid enters the node and passes through these
sinuses. These are the areas where damaged tissue cells, cancer cells,
bacteria, and other microorganisms are removed so that they do not
continue to circulate through the lymphatic system and enter the
bloodstream.

A catchment refers to a bed of lymph nodes. There are various catchments
located in certain areas throughout the body. For example, cervical lymph
nodes are a catchment to drain lymph fluid from the head and face, and,
femoral lymph nodes are the catchment for the thigh, the groin, and the
lower part of the abdomen. Lymph vessels carry fluid to a catchment, where
the lymph nodes clean and filter the fluid. Catchments often appear as
clusters of lymph nodes, which are often seen on physical examination and
are associated with certain areas of the body. For example, these clusters of
lymph nodes are often seen and felt around the neck and chin, in the axillae,
and in the groin.

Some deep catchment areas receive fluid that has first passed through
superficial lymph nodes before entering the deeper tissues. When this
occurs, the lymph fluid passes through more lymph nodes on its route to the
deeper tissues; it often passes through at a much faster rate because the
fluid does not have to be filtered with every lymph node that it passes. This
may help with some areas of the body that develop edema, such as in the
lower extremities.\textsuperscript{3} As an example, the popliteal catchment of lymph nodes
typically receives fluid from the feet and lower legs; however, lymph fluid
may also flow from the popliteal catchment to the deep inguinal catchment
of lymph nodes found in the hip. The fluid from the popliteal catchment has
already flowed through some of the superficial lymph nodes behind the knee before it travels to the deep inguinal lymph nodes. This system can better protect against edema formation in the lower legs and feet, which are common areas of swelling and fluid accumulation.

Lymph nodes may be superficial or they may be deep. Many people are familiar with superficial lymph nodes, as many nodes can be palpated during the physical exam and they are often more prominent when illness is present. Superficial lymph nodes are served by superficial lymphangia in the upper layers of the skin and they are found in the subcutaneous and fatty layers under the skin’s surface. They can be palpated and moved slightly and the flow of lymph fluid can be somewhat manipulated by pressing on adjacent areas of tissue. Deep lymph nodes receive fluid from the deep collecting afferent vessels located in the deeper layers of tissue and within the fascia under the skin. Deep lymph nodes are often located in groups and are found alongside major arteries, including such vessels as the aorta, the carotid arteries, and the mesenteric arteries.

The pulse impacts the flow of lymph fluid through the lymph vessels when blood flows through the nearby blood vessel. The blood flow with each heartbeat presses against the adjacent lymph vessels, which stimulates the stretching of the smooth muscle fibers in the lymph vessels. This stimulation is what propels the lymph fluid along its vessel; changes in heart rate thereby have an effect on the body’s ability to transport lymph fluid when stimulation of contractions of the deep collecting vessels is dependent on stimulation from the pulse. If the heart rate quickens, lymph flow may move at a faster rate because of an increase in stretch fiber stimulation; alternatively, a decrease in heart rate slows down the rate at which lymph fluid flows through the deep collecting vessels. Deep lymph nodes usually
cannot be felt with palpation during the physical exam, however, they may be seen during imaging studies.

**Lymphadenitis**

A potential complication associated with lymph nodes is lymphadenitis, which is technically described as inflammation or enlargement of the lymph node. Lymph node enlargement is associated with various illness states; for example, it may develop following a bacterial infection at some point in the body when the bacteria travel through the lymph vessels and infect the lymph nodes. The infection can also develop after viral or fungal infections as well. Lymphadenitis may also occur when cells from outside of the lymph node, such as cancer cells, infiltrate the lymph node and cause it to enlarge. For instance, an individual with lymphoma, which is a type of cancer of the lymphatic system, may develop enlarged, painless lymph nodes when the cancerous cells enter the lymph nodes and proliferate in a condition known as lymphadenopathy.

The signs and symptoms of lymphadenitis are based on the underlying cause of the enlargement. When infection has prompted lymphadenitis, the affected individual typically has pain, redness, and swelling in the skin over the site of the lymph node. Other causes of enlargement, such as with certain types of cancer, cause the lymph node to grow but may not cause
pain or tenderness in the node. These causes may, however, lead to other symptoms of fever, cough, anorexia, or weight loss, particularly if there is systemic infection. The affected lymph node may be enlarged and it may feel firm or rubbery; there may be red streaks on the skin surface and the skin may be warm. The condition is managed by treating the underlying cause of the lymphadenitis when bacterial infection has caused lymph node swelling and antibiotics are required. Likewise, treatment with antiviral medications and cancer treatment therapies are applied accordingly.

Because enlarged lymph nodes could develop for any number of reasons, it is important to examine the lymph node at the cellular level in order to differentiate the exact cause of the enlargement and the swelling. Lymphadenitis treatment regimens are also varied because of the numerous physiological causes of the condition. A study by Safont, et al., in the *Journal of Clinical Microbiology* used molecular techniques and bacterial cultures to analyze a large number of lymph node samples in patients with lymph node enlargement over a period of four years. In the study, cancerous cells were associated with 7 percent of the samples of infected lymph nodes, while the most common cause of infectious lymphadenitis was from infection with *Bartonella henselae*.

Other infectious agents noted to cause lymphadenitis among the selected lymph nodes were *Mycobacterium* species, including associated tuberculosis, as well as organisms such as staphylococcus and streptococcus species. One of the main points of the study was not only to identify causative organisms that lead to lymphadenitis, but also to call attention to the need for histologic analysis when lymphadenitis is present through biopsy or some other method of specimen retrieval and microscopic examination. It is only through this type of examination that the particular cause of the
lymphadenitis can be identified, as cancerous cells could be present as part of infectious causes as well. With the use of this form of examination, the clinician would be better able to identify causative agents, which is essential for guiding treatment of lymphadenitis.

**Immune System**

The immune system is the body’s defense mechanism against foreign substances that can enter the body and develop disease or infection. The body uses the immune system to protect itself when foreign particles, known as antigens, enter the body; antigens consist of microorganisms such as bacteria, viruses, fungi, toxic substances, allergens, cancer cells, or tumors. Antigens enter the body and stimulate immune defenses in various ways, depending on their background and type of cells. Antigens such as cancer cells develop within the body as abnormalities of certain cells. Other antigens enter the body from the outside. They may enter the bloodstream through an injury in a blood vessel; some antigens are able to penetrate the skin, where they then enter the lymphatic system and travel to lymph nodes. When foreign pathogens infect mucous membranes, they then settle in the mucosa-associated lymphoid tissue.

Alternatively, the cells that the body releases to fight invading antigens are known as antibodies. These are protein-based elements that are normally present in the body; they are made up of gamma globulins but are typically referred to as immunoglobulins because of their role in the immune system. They are categorized according to differences in the heavy chains of their amino acid sequences; for example, IgG immunoglobulins have gamma heavy chains, while IgA immunoglobulins have alpha heavy chains. Each antibody has the ability to combine with an antigen based on its shape, which fits with a specific antigen that it is designed to protect against. The
The foundation of the immune system process is the antigen-antibody reaction, which is a complex system that describes the body’s reaction to foreign antigens by releasing its own cells that provide a defense mechanism.

The body knows which cells and tissues belong and which are considered to be foreign. It is in this way that it knows to release antibodies to provide protection. Every organism has certain proteins that are recognized as self; those that do not contain the same combination of proteins are considered non-self in that they do not belong or are foreign. A biological cell marker known as human leukocyte antigen (HLA) is found on the cells in the body, which marks them as the body’s own. The body then knows that cells with HLA belong, whereas those that do not contain HLA do not belong and they are considered non-self. Human leukocyte antigen is also referred to as major histocompatibility complex (MHC); it is a glycoprotein structure that makes up part of the cell membrane in all cells in the body that contain a nucleus. It is so named because it refers to how the body detects compatibility between itself and other foreign cells.

There are also different classes of MHC present on cell surfaces, depending on the type of cell. Class I MHC is found on the surface of all body cells, with the exception of red blood cells. The Class II MHC glycoproteins are typically only expressed on certain cells of the immune system, such as with macrophages and B lymphocytes. Class I MHC (MHC-I) consists of two major protein chains; a long chain of amino acids, known as a heavy chain, and a shorter chain of amino acids. The main purpose of MHC-I glycoproteins is to display antigens found on the surface of the cell so that T cell lymphocytes will recognize them as self. When they display abnormal antigens, the body recognizes them as non-self and will know that the cell does not belong. As an example, MHC-I glycoproteins would display appropriate antigens when
the cell is healthy and the body should recognize it as such. Alternatively, if cancer cells are present, the MHC-I signals that there are abnormal antigens present and the lymphocytes can try to attack and destroy the cells.

Class II MHC glycoproteins (MHC-II) consist of two polypeptides that are located on immune cells. The MHC-II cells still present antigens on the surface of the cell, but in a manner that differs from MHC-I. The antigens displayed on the cell that have been acquired from MHC-I glycoproteins have come from molecules inside the cell. Alternatively, the antigens displayed in MHC-II molecules have been acquired from outside the cell and from another location.11

Histocompatibility complex is also involved when an individual receives an organ transplant. Because most people have unique MHC markers on their cells, when the body receives a new organ as a transplant, it often recognizes the MHC markers on the new tissue as being foreign antigens and will try to attack them. This is why transplant recipients must take anti-rejection drugs after transplant surgery. Adding new tissue from another person, even if it is an organ and is not considered harmful tissue, such as a virus or bacteria, still provokes an immune response from the body. An autoimmune reaction is one in which the mechanisms of the body’s defense against foreign pathogens are distorted and the body attempts to attack some of its own tissues. Conditions such as type 1 diabetes or rheumatoid arthritis have been shown to develop because of flaws in the immune system process and the body attacks its own cells, causing pain, inflammation, and possibly fever or fatigue for the affected person. At other times, the immune system works properly, but it is overtaken by too many foreign pathogens and it cannot adequately protect itself. For example, when a person is exposed to influenza, his or her body may not be able to defend
against the virus. When this happens, the individual suffers from illness and develops symptoms associated with the infection.

Some elements of the immune system serve to provide protection through filtration of substances, rather than actively attacking them. Instead of striking foreign pathogens that have already invaded the body, certain elements of the immune system prevent these substances from getting past the initial barriers to enter the body. They filter particles and destroy those that do not belong. For example, the tonsils, located in the back of the throat, are organs of the immune system that act as a barrier to prevent some substances from entering the body through eating or breathing. The skin, while technically not an organ of the immune system, still provides a physical barrier that supports the immune system in that it prevents certain pathogens and other particles from entering the body. It is when microorganisms are able to get past these barriers that the immune system steps in to respond and to prevent potentially harmful substances from causing infection and disease.

The immune system is also responsible for initiating the inflammatory process; with localized inflammation on surface structures, such as in the skin or the subcutaneous tissue, inflammation is often manifested as redness, warmth, pain, and swelling. Inflammation also occurs in the deeper tissues to cause systemic inflammation and can affect areas such as the fascia, the blood vessels, and the visceral membranes. Inflammation serves as part of the body’s defense against antigens. It involves the cells of the immune system, as well as other types of clotting proteins and signaling molecules. The process develops when there is an injury or foreign pathogen that enters the body; the B cells release antibodies, which helps the immune system to recognize the cells that do not belong. This initiates the
inflammatory response and the immune system cells travel to the site. Vasodilation occurs as a method of getting the immune system cells to the site of injury much more quickly. This vasodilation is what causes the typical symptoms of inflammation.

Inflammation, while painful and seemingly detrimental, is actually a positive response to tissue damage that has occurred because of trauma or infection. The process of inflammation is designed to respond and to stop the damage before it spreads. The process of inflammation that occurs at the cellular level stimulates the body to respond to better protect itself; for instance, in response to inflammation, the bone marrow produces more white blood cells as a defense mechanism. The immune cells associated with inflammation are responsible for destroying the microorganisms that are causing harm. Although inflammation often feels uncomfortable, it should be noted that it is often a protective function and is not designed to instill further tissue damage.¹

The immune system is classified as having two components: innate immunity and adaptive immunity. Innate immunity is a nonspecific response of the body as a line of defense. Innate immunity provides different mechanisms that protect the body from disease when antigens are present. As stated, the skin is an actual barrier that protects the internal organs from contact with various organisms outside of the body. In this manner, the skin provides a form of innate immunity that is a physical obstacle for foreign pathogens to pass through if they want to enter the body. The inflammatory response is another form of innate immunity. Inflammation occurs when extra blood cells are sent to an area of infection or injury in order to prevent bacteria from spreading or to prevent further damage from developing at the site.
Adaptive immunity involves the work of T and B lymphocytes and their response when the body has been exposed to a previous antigen. Adaptive immunity is also called specific or acquired immunity. Its role as a defense mechanism is one that provides protection against specific types of foreign substances that can be harmful. When microorganisms invade the body and the cells recognize the antigen, adaptive immunity initiates its mechanisms of action to ensure that the foreign particles are destroyed before they can cause harm. The affected individual often develops some signs or symptoms of the disease as the body attacks the pathogens. However, after the person has been exposed to the pathogen one time, the body recognizes it with exposure the next time. When exposure happens again, the affected individual will typically not develop any symptoms of illness because the body has already attacked and destroyed the infectious organism. Although the process of adaptive immunity is slower when compared to innate immunity, adaptive immunity still has the benefit of memory to specific antigens and it can respond much more quickly each time with repeated exposures. This is what is described as immunity, which is when an individual is protected against certain organisms because the body has recognized the threat and has attacked.

Adaptive immunity is further classified into cell-mediated immunity and humoral immunity. Cell-mediated immunity involves the work of T lymphocytes and occurs when certain cells — the phagocytes and killer T cells — are called to respond to a potential threat from an antigen. Cell-mediated immunity provides a form of defense when these cells destroy the foreign particles, either by directly ingesting them or by secreting chemicals that kill them. Alternatively, humoral immunity describes the process of how antigens are changed to prevent them from harming the body. Humoral immunity involves B lymphocytes; the antibody binds to its specific antigen
to form an antigen-antibody complex and to alter the antigen so that it will not cause damage.

Adaptive immunity is also categorized as natural or artificial immunity. Natural immunity occurs as part of everyday living with exposure to potentially harmful agents. For example, a child who plays in the mud may develop natural immunity from exposure to some of the microorganisms found in the soil. Artificial immunity describes the deliberate application of factors that will foster immunity. A common example is the administration of vaccines as protection against certain diseases; the vaccines contain small amounts of harmful organisms and the body defends itself against these pathogens so that if it is later exposed to the actual microorganism, it will already have established immunity to these specific antigens.

All immune system cells stem from white blood cells, which are also known as leukocytes. The main types of leukocytes are the granulocytes, which consist of basophils, eosinophils, and neutrophils, as well as the lymphocytes and the monocytes. Monocytes, along with neutrophils, are types of cells called phagocytes; these are also important cells of the immune system, and they are created in the bone marrow and are responsible for ingesting foreign particles as a method of defense. When an infection develops somewhere in the body, the phagocytes travel to the affected area of tissue. At this point, monocytes change to become macrophages, which are the cells that engulf other microorganisms.

Once they arrive at the location of the infection, the monocytes-turned-macrophages search out foreign particles to engulf and destroy. Additionally, the neutrophils also kill foreign particles; they have much shorter lives than monocytes and often die more quickly at the site of the infection. As an
example, when pus develops in an infected area, its white appearance is largely due to the collection of dead neutrophils.

In addition to destroying foreign particles, macrophages also secrete substances that promote healing when infection is present; these chemicals include certain types of growth factors, complement, and prostaglandins. Removal of debris and of certain microbes after infection requires phagocytosis, which is the first line of defense against invasion of foreign pathogens.

Phagocytosis actually consists of a six-step process in which a foreign cell is literally killed, engulfed, and digested. The six stages include:

1. **Chemotaxis**
   This refers to the movement of the cells to the site of the injury, based on a chemical released to stimulate their arrival. The chemical released is known as a chemoattractant, which literally attracts the immune system cells to the site to begin the process of destroying foreign cells.

   There are a number of different chemicals that may act as attractants to draw phagocytic cells to the site. Antigens are examples of chemoattractants in that their presence stimulates certain cells to move in to begin phagocytosis.

2. **Adherence**
   Adherence describes the process of the particle sticking to the surface of the phagocytic cell. There are several receptors on the surface of the phagocytic cell; once the particle binds to the phagocytic cell, the next step of ingestion can begin.
3. *Engulfment*
   This portion of the process begins when the membrane enclosing the particle is folded in on itself and it is then released into a cytoplasmic membrane. Engulfment basically describes the process of moving the particle into an enclosed area, which is known as the phagosome.

4. *Phagosome formation*
   The phagosome describes the enclosed vacuole that contains the particle being destroyed as it is enclosed within a cell membrane.

5. *Fusion*
   The next step describes how the phagosome is fused with lysosomes, which are portions of the cell that enzymatically break down the microorganism. Following fusion, the cell becomes a phagolysosome.

6. *Digestion and destruction*
   During this last stage of the process, the cells demonstrate increased metabolic activity and they release digestive enzymes into the enclosed vacuole, which breaks down the particle so that it can be absorbed.

   The destruction of particles through phagocytosis is an important component of the immune system and is a primary activity of the phagocytic cells; namely, the macrophages and the neutrophils. While these cells are essential for the breakdown of debris and other microorganisms, other white blood cells also play key roles in immune system functions as part of the body’s defense mechanisms.

   As with other types of white blood cells, granulocytes begin as stem cells in the bone marrow. Each type of granulocyte plays a role in defense as part of
the immune system. The neutrophils, as discussed, travel to the site of infection and work with monocytes to destroy foreign particles. Neutrophils typically provide defense against bacterial or viral infections. The neutrophils also play other important roles in this process; they are responsible for transporting some of the pathogens to surrounding lymph nodes where they can then be filtered and destroyed by the lymphocytes within the node. Neutrophils also act as antigen-presenting cells that, similar to dendritic cells, present antigens to lymphocytes so that appropriate antibodies can be formed in response. Finally, neutrophils play a key role in phagocytosis by releasing enzymes that damage the foreign cells so that they are rendered incapable of harm.

Eosinophils and basophils are other types of granulocytes that also participate in phagocytosis of foreign particles, but on a smaller scale because of their comparatively smaller numbers in circulation. Eosinophils can suppress inflammation and can prevent it from spreading too far when it does develop. The eosinophils also play a role in attacking the cells of certain parasites when they enter the body; the eosinophils have the ability to damage some types of parasitic organisms through oxidation when they are present. Basophils are more commonly associated with an allergic response to an antigen, as these cells contain heparin and histamine, two components of the body’s reactive response to allergens. Basophils play a role in increasing blood flow to specific sites and their contents increase vascular permeability and promote vasodilation, which may account for the signs and symptoms that occur with an allergic response to a foreign substance in the body.

Another element important to the immune process is the dendritic cells. These cells are a type of accessory cell to the immune system; they are a
form of antigen-presenting cell (APC), in which they introduce antigens to lymphocytes. Dendritic cells play a role in initially trapping an antigen to prevent it from spreading further; they then notify the lymphocytes of the antigen’s presence so that the lymphocytes can take over the immune defense. Dendritic cells are a very important part of the immune system. They are consequently located throughout the body at various points so that they can quickly respond to wherever an antigen may try to settle in the body. They remain in close contact with the lymphoid tissues to maintain communication whenever there is a possible infection or illness from an antigen.

The main component that allows lymph nodes to filter and destroy foreign particles are the lymphocytes found within their borders. These cells are also circulating within lymph fluid to destroy harmful products and to prevent some microorganisms from reproducing. Lymphocytes are some of the most important types of cells involved in the immune system. These white blood cells promote antibody production. Lymphocytes circulate through body fluids to look for foreign cells; their large numbers pass through the lymphatic system and the lymph nodes, as well as in the organs of the immune system, such as the thymus and the spleen.

All lymphocytes begin in the bone marrow as stem cells and then go through two stages of development. Their life spans are typically much longer than other types of blood cells, because of their roles in defense and memory for certain antigens. Approximately 80 percent of lymphocytes in the body live for 4 years with some lymphocytes living up to 20 years. While there are several types of lymphocytes, the two main types are the B lymphocytes, often referred to as B cells, and T lymphocytes, or T cells.
**B Cells**

The B cells are one of the primary types of lymphocytes that provide immune defense for the body. The B cells are so named because they were first discovered in the Bursa of Fabricus, a small organ found only in birds. The “B” actually comes from the word “bursa,” rather than from the words “bone marrow,” which is a common assumption based on where they are formed. The main function of B cells is to regulate the production of antibodies. They are responsible for producing IgG, IgM, IgA, IgD, and IgE immunoglobulins. B cells begin in the bone marrow as stem cells, and they then develop into immature B cells in the bone marrow. This change occurs only in the bone marrow in adults, but it also occurs in the bone marrow and in the liver before birth. When the cells are immature, they undergo immunoglobulin change rearrangement and certain antibody molecules are added to their cytoplasmic membranes. These antibody receptors on the surface of the cell match certain antigens.

After the B cells mature, they leave the bone marrow and travel to lymphoid tissues, primarily the lymph nodes, the spleen, or the Peyer’s patches in the gastrointestinal tract. B lymphocytes, in addition to T lymphocytes, are in a state of constant circulation through the lymph vessels and the lymph nodes. At this stage, the B cells are mature but they are not necessarily active; instead, they may be known as transitional B cells. Recall that B cells are involved in the humoral response, which involves production of antibodies that bind to specific antigens. Each inactive B cell carries an antibody on its cell surface that was programmed for the cell when it was formed in the bone marrow. When the antibody receptors on the surface of the cell detect matching antigens, they reproduce to form many more B cells with the same antibody so that they can protect the body against the antigen.
Each new cell that has been formed in response to an antigen has an identical antibody to the original cell, which matches the antigen and that provides immunity. Each new B cell that is formed in response to an antigen is a clone of the original B cell. Each of these clones then contains two main types of cells; effector cells and memory cells. Effector cells secrete large amounts of antibodies into the bloodstream to respond to the antigen. The memory cells also secrete antibodies, but at a slightly later time than the effector cells. Memory cells actually act as more a backup supply of cells within the lymph nodes and they move into action when they are needed. Once recruited, these memory cells are transformed into effector cells that then also secrete antibodies as an additional form of defense. The process of reproducing to form B cell clones to provide antibodies is what changes the inactivated B cell into an active B cell; however, it should be noted that not all mature B cells will actually undergo this process.

Alterations in B cells are commonly associated with cancerous processes, particularly with development of different types of leukemia, lymphoma, and sarcoma. When chromosomes are rearranged in B lymphocytes, the abnormal cells are more likely to proliferate and to become cancerous cells; alternatively, chromosome abnormalities among B lymphocytes may disrupt the work of tumor suppressor genes, which can further interrupt the process of protecting the body from tumor formation. When chromosome translocations develop on certain cells, double-strand breaks in DNA may occur, which means that there is a disruption in the double helix of the DNA strand. These types of breaks are more commonly associated with cancer development. While many different types of cells may be subject to chromosome abnormalities, B cells are particularly susceptible to developing into malignant cells as a result of chromosome translocations. Researchers
who work specifically with B cells developed a gene sequencing method that documented chromosome rearrangements in these specific types of cells.

Klein, *et al.*, in the journal *Cell*, found that among B cells, chromosome rearrangements tend to occur within certain genes and that the proximity of double-strand breaks in DNA are directly associated with chromosome rearrangements. With further work in observing DNA sequencing and chromosome analysis of many B lymphocytes, researchers may be able to more closely determine the route that B cells undergo with chromosome translocations that would eventually lead to cancer formation. The body contains almost 10 billion different types of B cells, which emphasizes the importance of this specific kind of lymphocyte. Because there are so many of these special cells, the body typically has a very strong defense against most types of foreign invaders, including bacteria, viruses, fungi, or other microorganisms that could potentially cause harm.

**T Cells**

The T cells are another important kind of lymphocyte that circulate through the body and look for foreign particles or cellular abnormalities. The T cells are specialized cells that are formed in the bone marrow but that mature in the thymus within the chest cavity. Once they have matured within the thymus gland, the T cells travel into circulation where most of them inhabit the lymph nodes so that they can provide protection through the immune system. Known for their role in cell-mediated immunity, T cells are responsible for destroying cells that have been infected with foreign pathogens as well as cells that have developed abnormally and that could increase an individual’s potential to develop cancer within those cells.
Each T cell has a specific type of protein molecule that is found on the cytoplasmic membrane of the cell; this protein molecule is designed to match a particular antigen. The T cell will only fully develop if it comes into contact with its matching antigen. If it does, the antigen binds to the protein on the surface of the T cell, which activates the T cell. If the T cell never comes into contact with its matching antigen, it is developed but not activated. Once the T cell is activated, it produces clones of itself that all contain the same protein molecule that matches the offending antigen, in a process that is similar to B cell cloning in the antigen-antibody complex. T cells also form effector cells and memory cells, which work in much the same method as those produced by B cells to actively protect the body by producing antibodies.

In contrast to B cells, which work through humoral immunity, T cells are involved with cell-mediated immunity as a method of protecting the body. This specific type of immunity means that the T cells are actively involved in destruction of foreign cells and those substances that could cause illness or disease. T cells participate in cell-mediated immunity in various methods. Sometimes, they directly attack foreign cells and kill them by releasing toxic substances into the area surrounding the abnormal cells.

The T cells are actually divided into two different forms - helper T cells and killer T cells. Helper T cells are activated forms of T cells that coordinate attacks on foreign antigens, and they work indirectly by releasing substances into the area around the antigens that attracts macrophages to the site, acting as sort of a stimulant to get the macrophages to assemble. Once the macrophages arrive in the area, they physically destroy the foreign cells through phagocytosis. Helper T cells also coordinate immune activity by releasing chemicals that attract B cells and killer T cells to the site. Once the
B cells arrive, they can reproduce to form clones that release antibodies against the antigen. When the killer T cells arrive, they also kill the foreign cells by destroying their structures. Helper T cells are also commonly known as CD4 cells because of the type of glycoprotein found on their cell membranes.

When a macrophage ingests an antigen, it displays some of the antigen’s proteins on its own surface. The helper T cell comes into contact with the macrophage and can identify what type of antigen it just ingested, based on the proteins found on the surface of the macrophage. If the helper T cell recognizes that the antigen is harmful, it becomes activated and sends messages for other cells to arrive to take up the defense against the antigen. The macrophage further replicates so that there are more of it to continue to destroy the antigen.

Killer T cells, also called cytotoxic T cells, kill foreign cells by injecting them with enzymes that destroy their structure through apoptosis. Killer T cells are sometimes referred to as CD8 cells because of glycoproteins on their cell surfaces. They often specifically work against cancer cells as well as those cells that have been infected with viruses or bacteria. When a cell is infected, it displays a specific antigen on its surface, which demonstrates that it is non-self. The killer T cell recognizes the antigen and binds to it; it also releases cytokines that act as messengers to signal other T cells and macrophages to the site of infection. Killer T cells destroy the infected cells once they become activated, while the macrophages clean up some of the debris from the cell. Following the infection, some killer T cells remain in the body as memory cells that remember the specific antigens associated with the virus or the bacteria that caused the infection, so that if it ever develops
again, the body will quickly recognize it and set off the immune response again.

Modification of T cells may be able to help some patients who have been diagnosed with certain types of leukemia. The field of genetics research has studied some of the effects of altered T cells and their antigen receptors to treat chronic lymphocytic leukemia and they may be able to treat acute lymphoblastic leukemia as well. T cells with modified antigen-receptors on their cell surfaces that have an affinity for CD19, a specific biomarker found on some cancer cells, have been shown to expand in the body after their administration and to target these cancerous cells. Research performed by Grupp, et al., in the *New England Journal of Medicine* showed that when these types of genetically modified T cells were administered to patients with acute lymphoblastic leukemia, the patients responded by either achieving complete remission from the cancer or by relapsing but producing other cells that did not contain the CD19 antigen.62

This research and other information that is known about T cells can help healthcare providers with the care of patients who are suffering from some forms of cancer. It further supports the facts that T cells are extremely important in providing protection against certain diseases and illnesses. With further study, these cells could be specifically applied to work against some of the most lethal forms of illnesses, thereby preventing severe illness and early death due to these conditions.

**Other Cells**

In addition to the important work of B lymphocytes and T lymphocytes, there are other types of cells that play essential roles in protecting the body through the immune system. Some of these cells are variations of B cells or
T cells and have lymphocytic activity similar to that of the B and T cells previously described. Other cells are part of the immune system but they have slightly different functions, yet still work to protect the body.

Suppressor cells are T lymphocytes that suppress the activities of both B cells and killer T cells. Although the work of T cells and B cells is very important in defending the body, suppressor cells moderate these responses and prevent them from getting out of control. These types of cells are also called regulatory cells. Once an infection has passed, suppressor T cells conclude the immune response when it is no longer necessary. Suppressor T cells are also important for regulating autoimmune reactions and preventing significant illness with allergic or autoimmune responses. During an autoimmune reaction, the body attacks its own cells and can cause damage and severe symptoms. Suppressor T cells help to protect the body from autoimmune reactions by dampening the immune response when it is overactive and controlling it so that the body does not consistently attack its own tissues.

One of the more selective cells that are critical to immune defenses against certain types of antigens are natural killer cells. These cells are able to identify specific targets, namely cancer cells and certain types of infections. Natural killer (NK) cells are similar to killer T cells in that their significant purpose is to identify harmful antigens and destroy them. However, NK cells do not contain the same form of antigen receptors as is included with T lymphocytes. Natural killer cells move throughout the body and mark infected cells or cancerous cells; they usually circulate in their resting phase, but become activated once they start marking these harmful cells. Once the cells are marked, the NK cells move in and attack through cell lysis when they release toxic granules that damage the target cell membrane. This
causes the foreign cell to rupture and it dies in the process. The NK cells also release cytokines, which stimulates other lymphocytes to also come to the site to participate in cell destruction.

Although the NK cells do not contain the same proteins on their cell surfaces that detect foreign antigens, they are still able to perceive which cells are harmful and which ones are not. The NK cells contain signaling pathways that send information to the cell nucleus so that it can determine if it needs to kill the other cell or not. Instead of the same proteins on their cell surface as the killer T cells, NK cells contain activating or inhibitory receptors on their cell surfaces.

Each cell expresses a combination of both inhibitory and activating receptors. Because NK cells display different combinations of receptors, there is more variety within the cell population, which allows the cells to recognize and respond to many different types of potential pathogens. Through these methods, they are able to detect whether a cell is self or non-self. They become activated when they come into contact with cells that do not contain MHC-1; if another cell does not contain the MHC-1, then the NK cell knows that it is non-self and it does not belong.

Natural killer cells are large lymphocytes that develop in the bone marrow, although research suggests that they may also develop in the lymph nodes and in the liver. They are the third most common lymphocyte in the body, after the B and T lymphocytes. Natural killer cells are found throughout the body, although they are activated in different ways, depending on their location. Those NK cells that are found in circulation are different from NK cells found in secondary lymph tissue, such as in the tonsils or the spleen. Natural killer cells within circulation are activated through dendritic cells and
they release more cytokines when compared to the NK cells in the secondary lymph tissue.

Natural killer cells are very important in protecting the body against cancer and against the growth of tumor cells. An article by Mandal and Viswanathan in the journal *Hematology/Oncology and Stem Cell Therapy* discussed the role of NK cells in protection against cancer and the research studies that have been conducted to identify the benefits of NK cells. Studies have demonstrated that NK cells perform tumor cell surveillance, in which they closely watch for the growth of cancerous cells, and their work has prevented the development of certain types of B-cell lymphomas in mice.47

As with other forms of lymphocytes, NK cells are also important for supporting immunity and for protecting the body against attacks. The NK cells can sense when other cells do not belong or when they appear abnormal and can prevent their further growth so that the body stays healthy and is less susceptible to disease.

**Summary**

The lymph system has three major functions. It returns interstitial fluid to the blood, is involved with absorption of fat and fat-soluble vitamins and their transport into the bloodstream, and acts as a method of defense against foreign pathogens in the body. The lymphatic system can also help to prevent excess edema formation in the tissues when fluid accumulates in the interstitial spaces around the cells. Most of the fluid in the blood re-enters circulation at the capillary level; and, when protein molecules leak through the capillary wall, less fluid returns into circulation and more is retained in the interstitial space, which leads to edema.
The lymph system prevents excess edema formation, which otherwise leads to swelling and imbalanced fluid collection when there is a shift out of the intravascular and interstitial spaces. If too much fluid remains out of blood circulation, the affected person may experience hypotension because of decreased intravascular volume; the individual may also experience decreased oxygenation of the peripheral tissues when less fluid in the blood leaves a lesser amount in circulation. The lymphatic system plays a key role in preventing fluid imbalances that can otherwise lead to complications.

The lymphatic system can help to prevent excess edema formation in the tissues when fluid accumulates in the interstitial spaces around the cells. The lymph system also protects against edema by gathering excess interstitial fluid and proteins into the lymph vessels. It also plays a key role to prevent fluid imbalances that can otherwise lead to complications.

A key role of the lymphatic system is immunity and to defend the body against invading pathogens and microorganisms. The lymph nodes and the lymphatic vessels each help to protect the body by filtering lymph fluid to remove foreign particles. The lymphatic organs, including such organs as the spleen, the thymus, and the tonsils and adenoids, work by filtering particles or actively attacking microorganisms when they enter the body.

When the mechanisms of the body’s defense against foreign pathogens are distorted and the body attempts to attack some of its own tissues, this is known as an autoimmune disease. Conditions such as type 1 diabetes or rheumatoid arthritis have been identified as flaws in the immune system process where the body attacks its own cells; causing pain, inflammation, and possibly fever or fatigue for the affected person. Alternatively, the
immune system may work properly but be overtaken by too many foreign pathogens and therefore not be able to adequately protect itself.

The entire lymphatic system is very complex and its components are found throughout the body. The process of maintaining fluid homeostasis and providing body defense occurs so routinely that most people are completely unaware of the role of their lymphatic system. However, without the functions of the lymphatic system, life would be shortened due to fluid imbalances, lack of fat absorption, and little to no defense against harmful pathogens.

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1. **The initial lymph vessels are the preliminary lymph vessels that**
   a. are located at the junction between the epidermis and the dermis.
   b. consist of a multiple layer of squamous epithelial cells.
   c. originate in the basal layer of the epidermis.
   d. fit tightly together to contain fluid.

2. **True or False: Although the lymph system and the circulatory system are similar in structure and function, they are separate and unconnected.**
   a. True
   b. False

3. **The precollector lymph vessels**
   a. are located at the junction between the epidermis and the dermis.
   b. that originate in the basal layer of the epidermis.
   c. whose epithelial cells fit tightly together.
   d. are less permeable than blood capillaries.

4. ______________ are semi-permeable in that fluid can move into and out of the vessel structures but not as readily as with initial vessels.
   a. Vessel structure walls
   b. Precollector vessel walls
   c. Initial vessel walls
   d. Squamous epithelial cells

5. **Fluid is then kept inside the lymph vessel because**
   a. of a decreased pressure inside the interstitial space.
   b. of an increase in the force inside the interstitial space.
   c. lymph vessels are impermeable.
   d. the anchor filaments pull the epithelial cells.
6. Precollector vessels arranged into groups where fluid flows in both directions is/are called
   a. semi-permeable.
   b. squamous epithelial cells.
   c. anchor filaments.
   d. anastomoses.

7. True or False: The anastomoses do not contain valves within their vessel walls.
   a. True
   b. False

8. ____________ occurs when excess interstitial fluid collects in nearby tissue.
   a. Anastomoses
   b. Absorption
   c. Circulation
   d. Edema

9. Collector vessel walls include the adventitia, which is composed of
   a. nerve fibers and smooth muscle.
   b. collagen and elastin.
   c. three layers of tissue.
   d. endothelial cells.

10. Collector vessels that transport lymph toward the lymph node are called
    a. efferent collector vessels.
    b. lymph transporters.
    c. afferent collector vessels.
    d. precollector vessels.
11. How do collector vessels differ from precollector vessels?
   a. Collector vessels are much more porous.
   b. Collector vessels are much more permeable.
   c. Unlike precollector vessels, collector vessels do not have valves.
   d. Collector vessels contain bicuspid valves that prevent backward flow.

12. True or False: Fibers known as anchor filaments extend outward from the external layer of the lymph vessel and into the interstitial space.
   a. True
   b. False

13. Lymph fluid in the collector vessels are propelled forward by
   a. skeletal muscle contractions.
   b. breathing.
   c. collector vessels being filled with fluid.
   d. all of the above.

14. Collector vessel walls include the adventitia, which is composed of
   a. nerve fibers and smooth muscle.
   b. collagen and elastin.
   c. three layers of tissue.
   d. endothelial cells.

15. Valves in the collector vessels are known as
   a. angions.
   b. two-way valve.
   c. intralymphatic valves.
   d. section valves.

16. The stretch reflex in the wall of the lymph vessel acts similar to
a. the circulation of the bloodstream.
b. the peristaltic waves in the gastrointestinal tract.
c. the contraction of skeletal muscles.
d. the backward flow of two-way valves.

17. **Exercise or activity that uses the skeletal muscles can**
   a. reduce the flow of lymph fluid through the body.
b. reduce the flow of fluid from one angion segment to the next.
c. reduce fluid accumulation and edema formation.
d. reduces pressure to the lymph vessels.

18. **The collecting vessels ________________ than the initial vessels.**
   a. take in more surrounding fluid
   b. are more superficial
   c. are more static
   d. are much less absorbent

19. **Each pathway (through the initial lymph vessel, precollector vessels, and collecting vessels) is known as**
   a. a lymphatome.
b. a peristaltic wave.
c. a reflex trigger.
d. a lymphangion.

20. **True or False: Once the lymph fluid passes through the lymph nodes and into the larger collecting ducts, it is eventually deposited into venous circulation.**
   a. True
   b. False

21. **On average, collector lymph vessels contract 6 to 8 times per minute, but this amount can increase to up to 20 times per minute**
a. depending on exercise and activity.
b. depending on the amount of fluid within the vessels.
c. when a person is at rest.
d. a and b.

22. The largest lymph vessel in the body is the _______________.
   a. right lymphatic duct
   b. thoracic duct
   c. large left subclavian
   d. right subclavian trunk

23. The lymphatic vessels continue to become ____________ as they progressively move toward venous circulation.
   a. smaller
   b. static
   c. larger
   d. sectioned

24. The right lymphatic duct collects lymph fluid from
   a. the thoracic duct.
   b. large left subclavian.
   c. internal jugular veins.
   d. the bronchomediastinal trunk.

25. The ___________ is a central sac in the lymphatic vessel network.
   a. axilla
   b. cisterna chilii
   c. lymphangion
   d. angion

26. The right subclavian trunk collects fluid from
   a. the right jugular trunk.
   b. the right arm and axilla.
c. organs in the chest.
d. The internal jugular veins.

27. _____________ stimulates lymph circulation as lymph fluid enters the thoracic duct and as the duct empties lymph fluid into the venous system.
   a. Anastomosis
   b. Peristalsis
   c. Respiration
   d. Absorption

28. True or False: Not everyone has a right lymphatic duct.
   a. True
   b. False

29. During inhalation, the lungs expand, which compresses the thoracic duct, where it empties lymphatic fluid into
   a. the right subclavian vein.
   b. the jugular vein only.
   c. the subclavian vein only.
   d. the subclavian or the jugular veins.

30. Because fluid can be pulled into the lymph vessel network from the _____________, causing a cyclical effect.
   a. thoracic duct
   b. cisterna chyli
   c. interstitial spaces
   d. intralymphatic valves

31. Edema may develop in areas of the body, even with a fully functioning lymphatic system as a result of, by example,
   a. when there is negative pressure in the lymphatic system.
   b. when lymph fluid reaches the thoracic duct.
c. heart failure.
d. when lymph fluid is emptied into venous circulation.

32. **Lymphedema often results from** ____________________________
   a. a mastectomy.
b. cellulitis.
c. septicemia.
d. the absence in a person of a right lymphatic duct.

33. **Primarily lymphedema**
   a. results from a traumatic injury to the lymphatic vessels.
b. is due to iatrogenic causes, *i.e.*, surgery.
c. is an obstruction of the lymphatic vessels caused by a disease.
d. is a hereditary condition.

34. **Elephantiasis is a type of lymphedema caused by _______.**
   a. parasitic worms
   b. an electrolyte imbalance
   c. an inherited condition
   d. a traumatic injury

35. **Which of the following statements is true of lymphedema?**
   a. Exposure to increased temperatures exacerbates it.
b. It may be managed through physical therapy.
c. There is no cure for lymphedema.
d. All of the above.

36. **True or False:** A smaller rate or volume of fluid emptied into the venous system creates negative pressure within the lymph vessel.
   a. True
   b. False

37. **Lymphangitis most often develops from**
a. nematode infection.
b. a protein known as Fiaf (“fasting-induced adipose factor”).
c. streptococcal infection of the skin.
d. use of compression stockings.

38. **A study showed that when deleting Fiaf,**
   a. lymphatic vessels within the skin were affected.
   b. the blood and lymph vessels in the small intestine were not partitioned.
   c. a patient develops cellulitis.
   d. a patient develops septicemia

39. **Which of the following, found in plasma, is/are also found in lymph fluid?**
   a. Plasma proteins
   b. Platelets
   c. Red blood cells
   d. None of the above

40. **Fasting-induced adipose factor has been associated with**
   a. regulation of adipose tissue.
   b. fat storage.
   c. lipid metabolism.
   d. all of the above.

41. **Once it reaches the thoracic duct, approximately ____ percent of lymph fluid is transferred back into the venous circulation.**
   a. 35
   b. 50
   c. 90
   d. 10
42. After lymph fluid leaves the lymph node, it contains many __________, which are essential components of the immune system.
   a. triglycerides
   b. lymphocytes
   c. chylomicrons
   d. electrolytes

43. Most lymph nodes have more afferent vessels than efferent vessels, so lymph circulation is _______ when the fluid reaches the nodes.
   a. not affected
   b. sped up
   c. slowed
   d. blocked

44. True or False: Some people will develop lymphedema following certain medical procedures, while others who have undergone the same procedure do not.
   a. True
   b. False

45. The following is true of lymph nodes:
   a. It is found at the end of a lymphatic vessel pathway.
   b. It is a structure about the size of a walnut.
   c. 60 lymph nodes are located throughout the body.
   d. It is a structure about the size of a pea.
46. Approximately ____ of the fluid brought to the nodes via afferent vessels is absorbed to be returned to venous circulation.
   a. all
   b. 1/3
   c. 90%
   d. half

47. The lymph fluid leave the lymph node through the ______________ at a point called the hilum.
   a. afferent vessels
   b. efferent vessels
   c. lymphatic vessel pathway
   d. nodule

48. Each lymph node is composed of two sections:
   a. the cortex and medulla.
   b. the cisterna chilii and medulla.
   c. plasma and the capsule.
   d. the lymph channels and lymphatic vascular network.

49. Lymph nodes catch and destroy potentially harmful pathogens in the body because
   a. they contain T lymphocytes.
   b. they contain B lymphocytes.
   c. they contain both T lymphocytes and B lymphocytes.
   d. lymph fluid is passed to the bloodstream.

50. True or False: The villi and submucosal lymphatics, and the lymphatics in the intestinal muscle layer, are connected so that fluid may pass between them.
   a. True
   b. False
51. The cortex of the lymph node contains collections of lymphocytes, consisting of
   a. B lymphocytes only.
   b. an equal number of B and T lymphocytes.
   c. mostly B lymphocytes.
   d. T lymphocytes only.

52. In the lymph nodes, lymph fluid circulates within the
   a. cortex of the lymph nodes.
   b. medulla.
   c. efferent vessels.
   d. lymph sinuses.

53. True or False: Damaged tissue cells, cancer cells, bacteria, and other microorganisms are removed as they pass through the lymph sinuses.
   a. True
   b. False

54. A ____________ refers to a bed of lymph nodes.
   a. filament
   b. lymphatome
   c. catchment
   d. system

55. _______________ can protect against edema formation in the lower legs and feet.
   a. Cervical lymph nodes
   b. Popliteal catchment
   c. Femoral lymph nodes
   d. Axillae catchment
56. Antigens such as ______________ develop within the body due to certain cell abnormalities.
   a. bacteria
   b. cancer cells
   c. toxic substances
   d. allergens

57. An ______________ is when mechanisms of the body’s defense attack some of its own tissue.
   a. histocompatibility complex
   b. immune response
   c. allergen reaction
   d. autoimmune reaction

58. Which of the following is not part of the immune system?
   a. The inflammatory process
   b. The tonsils
   c. The skin
   d. Lymphocytes

59. True or False: Antibodies are protein-based elements that the body releases to fight invading antigens.
   a. True
   b. False

60. ____________ is a method of getting immune system cells to an injury sight more quickly.
   a. Vasodilation
   b. Autoimmune reaction
   c. The central pump of the lymphatic system
   d. The “cyclical effect”

61. The immune system is classified as having two components:
a. specific and acquired immunity.
b. nonspecific and specific response.
c. innate immunity and adaptive immunity.
d. nonspecific and innate immunity.

62. ______________ is/are part of adaptive immunity.
   a. Vasodilation
   b. The inflammatory process
   c. The skin
   d. B lymphocytes

63. **Humoral immunity is a further classification under**
   a. cell-mediated immunity.
   b. nonspecific immunity.
   c. innate immunity.
   d. adaptive immunity.

64. **Which of the following is an example of natural immunity?**
   a. The inflammation process.
   b. A child exposed to microorganisms while playing in the mud.
   c. Administration of vaccines as protection against certain diseases.
   d. An autoimmune reaction.

65. **True or False: Natural immunity involves vaccines that are made from nature, not synthetic.**
   a. True
   b. False

66. ______________ refers to the movement of cells to the site of the injury.
   a. Fusion
   b. Phagosome formation
c. Adherence
d. Chemotaxis

67. **Engulfment describes the process of**
   a. releasing digestive enzymes into an enclosed area.
   b. phagosome formation.
   c. moving a particle into an enclosed area.
   d. a phagocytic cell sticking to a particle.

68. **True or False: Eosinophils can suppress inflammation and can prevent it from spreading too far when it does develop.**
   a. True
   b. False

69. **Dendritic cells are a type of accessory cell for the immune system that**
   a. suppress inflammation to prevent it from spreading too far.
   b. release digestive enzymes into an enclosed area.
   c. trap an antigen to prevent it from spreading further.
   d. destroy harmful products or microorganisms.

70. **Killer T cells, also called cytotoxic T cells, kill foreign cells by**
    a. sticking to a particle.
    b. injecting them with enzymes that destroy their structure through apoptosis.
    c. reproducing to form clones that release antibodies.
    d. trap an antigen to prevent it from spreading further.

71. **Which of the following are true of the helper T cell?**
    a. Helper T cells attack harmful antigens.
b. Helper T cells replicate so that there are more to destroy antigens.
c. Helper T cells identify and attack macrophage.
d. Helper T cells release chemicals that attract other cells.

72. A "T cell" is said to be developed but not activated until
   a. it comes in contact with its matching antigen.
   b. it comes in contact with helper T cell chemicals.
   c. it is released from the bone marrow.
   d. it is released from the thymus within the chest cavity.

73. T cells travel into circulation and most of them inhabit
   a. the lymph nodes.
   b. the bloodstream.
   c. interstitial spaces.
   d. central sac in the lymphatic vessel network.

74. Basophils are more commonly associated with
   a. monocytes to destroy foreign particles.
   b. fighting type 1 diabetes.
   c. an allergic response to an antigen.
   d. attacking rheumatoid arthritis.

75. Suppressor cells suppress the activities of both B cells and killer T cells
   a. to enable the inflammation process.
   b. to coordinate immune activity.
   c. to allow vaccines to work against certain diseases.
   d. to prevent them from getting out of control.

Correct Answers:
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The reference section of in-text citations include published works intended as helpful material for further reading. Unpublished works and personal communications are not included in this section, although may appear within the study text.

*Cancer and Lymphatics Part I and Part II References*


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