MINISTRY OF EDUCATION AND SCIENCE
OF THE KYRGYZ REPUBLIC
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ADAM UNIVERSITY SCHOOL OF MEDICINE
DEPARTMENT OF MORPHOLOGICAL DISCIPLINES
AND PUBLIC HEALTH

PHYSIOLOGY OF LYMPHATIC SYSTEM AND IMMUNITY

(Study-methodical guidance)

Bishkek, 2024

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Study-methodical guidance for normal physiology practice classes on

“PHYSIOLOGY OF LYMPHATIC SYSTEM AND IMMUNITY”

Bishkek, 2024

УДК 612

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Ф50

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The given educational-methodical guidance provides better understanding of current curriculum in related topics. Material of the guidance is prepared according to the working program on normal physiology for students of the higher medical educational schools. The guidance contains information including data on achievements of a modern physiological science and consists of introduction, the basic part which contains the questions for self-control, illustrations, diagrams, tables, test tasks that contribute to the understanding of the topic.

The given materials will allow to facilitate studding of normal physiology by medical students, will provide more effective studying and can be used for self-checking during preparation both for separate practical classes and for the state end-of-year examination.

Authors realize that in the given guidance because of its small volume it was not possible to illuminate in detail all aspects of above-mentioned section of normal physiology. More expanded information can be received from the list of the literature located at the end of the guidance.

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CONTENTS

INTRODUCTION

The lymphatic system is an important and often underappreciated component of the circulatory, immune, and metabolic systems. The lymphatic system represents an accessory route through which fluid can flow from the interstitial spaces into the blood. Most important, the lymphatics can carry proteins and large particulate matter away from the tissue spaces, neither of which can be removed by absorption directly into the blood capillaries. This return of proteins to the blood from the interstitial spaces is an essential function without which we would die within about 24 hours.[1] Most of the fluid filtering from the arterial ends of blood capillaries flows among the cells and finally is reabsorbed back into the venous ends of the blood capillaries; but on the average, about one tenth of the fluid instead enters the lymphatic capillaries and returns to the blood through the lymphatic system rather than through the venous capillaries. The total quantity of all this lymph is normally only 2 to 3 liters each day.

[1] Guyton and Hall Textbook of Medical Physiology, 12 Ed. 2011, p-186.

Methodical guidance for students

The goal of the classes: to form a basic concept of the structural and functional organization of the Lymphatic system, lymph transport, types and mechanisms of Immunity.

The student must know:

- the structure of lymph outflow tracts - capillaries, vessels, trunks, ducts;
- the structure and functions of the lymphatic organs, their classification;
- location of regional lymph nodes that receive lymph from various organs and areas of the body;
- the organization of immunity, types of immunity, the functions of cells responsible for immunity;
- the main mechanisms of the immune response, defense lines of the immunity.

The student must acquire skills in solving situational tasks on the related topics.

Requirements for the initial level of knowledge: in order to figure out these topics, students should repeat the functions of blood cells, the general organization of cardiovascular system , structure and functions of the arterial and venous systems, microcirculation, and know the blood supply of organs, i. e. mechanisms of local blood flow.

Leaning objectives:

1. Functional organization of Lymphatic system.
2. Formation of lymph and its composition.
3. Circulation of lymph. Types of lymphatic vessels. Mechanisms of lymph flow.
4. Lymphatic tissue and lymphatic organs.
5. Nonspecific Resistance.
6. Process of inflammation and its cardinal signs.
7. Functions of each kind of leukocytes.
8. Role of the complement system in resistance and immunity.
9. Chemical properties of antigens.
10. Basic types of Immunity.

LECTURE MATERIALS

Contents

Functional organization of Lymphatic system

The Lymphatic system is the system of vessels, cells, and organs that carries excess fluids from interstitial compartment, and third spaces of the body back to the bloodstream and filters pathogens from the ECF (extra-cellular fluid). It consists of a complex network of:

1) lymph vessels (lymph capillaries, small, middle, large lymph vessels, lymph trunks, lymph ducts);

2) lymph (lymphatic fluid within lymph vessels);

3) lymphoid organs (primary lymphoid organs are: bone marrow and thymus gland, secondary lymphoid organs are: lymph nodes, spleen, and lymphoid nodules, like tonsils, appendix, MALT, BALT.).

Main functions of Lymphatic system are:

1. Maintains fluid levels in your body: Drains excess interstitial fluid, (containing proteins, glucose, electrolytes, toxins, foreign agents, cancer cells etc.) and excess fluid from third spaces (pleural cavity, pericardial cavity, peritoneal cavity, joints etc.) into the circulatory system.
2. Filtering the ECF. Transports and removes waste products and abnormal cells from the lymph. Before lymph is being drained back to the circulatory system, it passes though lymph nodes, where are found large number of macrophages, lymphocytes phagocyting and killing the foreign agents, abnormal cells…) Spleen, liver, tonsils provide the same function with the blood passing through them.
3. Absorbs fats from the digestive tract: In the small intestine, lymphatic capillaries called lacteals are critical for the transport of dietary lipids and lipid-soluble vitamins to the bloodstream, because In the small intestine, dietary triglycerides combine with other lipids and proteins, form large molecules called chylomicrons (which can’t be absorbed into capillary blood due to the large size) and enter the lacteals to form a milky fluid called chyle.
4. Protects your body against foreign invaders: production and maturation of lymphocytes takes place in lymphoid organs. The B cell undergoes nearly all of its development in the red bone marrow, whereas the immature T cell after they have been produced, leave the bone marrow and matures largely in the thymus gland. Without maturation they cannot provide immune response, monitor and then destroy the foreign invaders - such as bacteria, viruses, parasites and fungi - that may enter your body.

Formation of lymph

The supply of oxygen and nutrients to tissues is performed by the blood system, and involves a net leakage of fluid outward at the capillary level. Blood pressure causes leakage of fluid from the capillaries, resulting in the accumulation of fluid in the interstitial space. One of the principal functions of the lymphatic system is to gather this fluid and return it to the blood system to maintain overall fluid balance. In humans, 20 liters of plasma is released into the interstitial space of the tissues each day due to capillary filtration. Of this, 17 liters is reabsorbed directly by the blood vessels and 3 liters obtained by lymph capillaries and become a lymph. The lymphatic vessels begin as open-ended capillaries. Located in almost every tissue in the body, these vessels are interlaced among the arterioles and venules of the circulatory system in the soft connective tissues of the body as shown on the Figure 1.

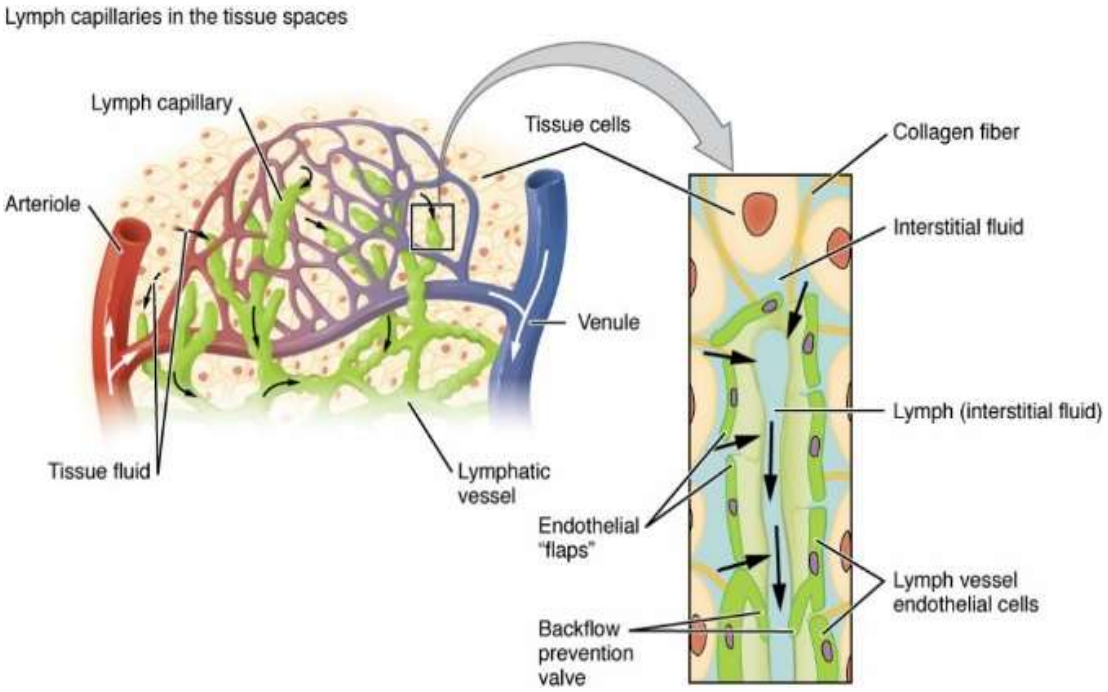


Figure 1. Structure of lymph capillary and formation of lymph

Only a few regions, including the epidermis of the skin, the mucous membranes, the bone marrow, bones, teeth, and the cornea of the eye and the central nervous system, are free of lymphatic capillaries, whereas regions such as the lungs, gut, genitourinary system, and dermis of the skin are densely packed with

these vessels. Composition of lymph and differences of other extracellular fluid is shown in the Figure 2 and Figure 3.

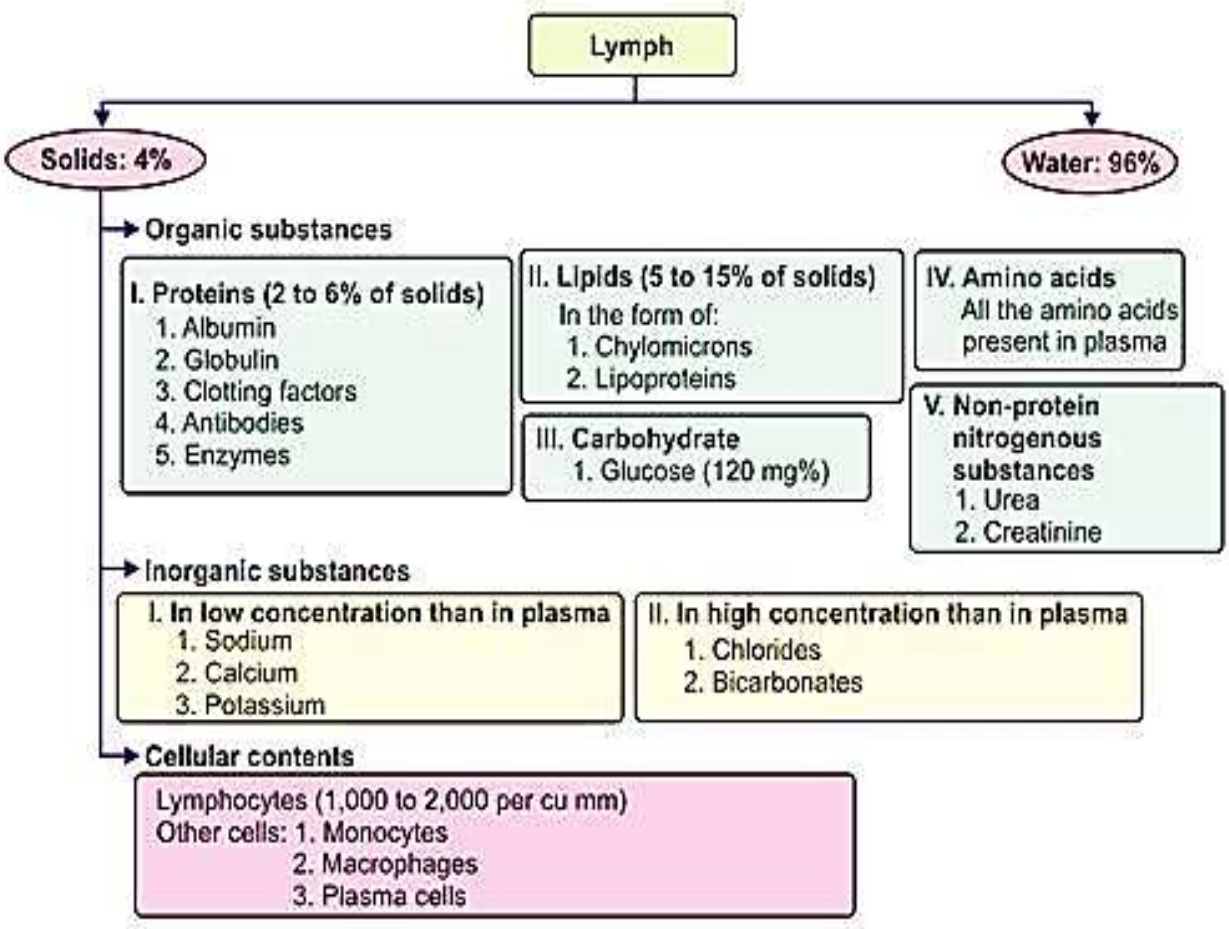


Figure 2. Composition of lymph

FEATURE	BLOOD	TISSUE	LYMPH
Cells	Erythrocytes Leucocytes and platelets	Some phagocytic white blood cells	Lymphocytes
Proteins	Hormones and plasma protein	Some hormones, protein secreted by bode cell	Some proteins
Fats	Some transported as lipoproteins	None	More than in blood (absorbed from lacteals in interesteni-villi)
Clouse	80-120 mg per 100 ml	Less (absorbed by body cells)	Less
Amino Acids	More	Less (absorbed by body cells)	Less
Oxygen	More	Less (absorbed by body cells)	Less
Carbon dioxide	Little	More (absorbed by body cells)	More

Figure 3. Differences between bool, interstitial fluid and lymph

Circulation of lymph

Lymphatic capillaries are formed by a one cell-thick layer of endothelial cells and represent the open end of the system, allowing interstitial fluid to flow into them via overlapping cells. When interstitial pressure is low, the endothelial flaps close to prevent "backflow." As interstitial pressure increases, the spaces between the cells open up, allowing the fluid to enter. Entry of fluid into lymphatic capillaries is also enabled by the collagen filaments that anchor the capillaries to surrounding structures. As interstitial pressure increases, the filaments pull on the endothelial cell flaps, opening up them even further to allow easy entry of fluid.

Normal lymph flow is very little at interstitial fluid pressures more negative than the normal value of −6mm Hg. Then, as the pressure rises to 0mm Hg (atmospheric pressure), flow increases more than 20-fold. Therefore, any factor that increases interstitial fluid pressure also increases lymph flow if the lymph vessels are functioning normally. Such factors include the following:

- Elevated capillary hydrostatic pressure.
- Decreased plasma colloid osmotic pressure.
- Increased interstitial fluid colloid osmotic pressure.
- Increased permeability of the capillaries.

But when the interstitial fluid pressure becomes 1- or 2-mm Hg greater than atmospheric pressure (>0 mm Hg), lymph flow fails to rise any further at still higher pressures. This results from the fact that the increasing tissue pressure not only increases entry of fluid into the lymphatic capillaries but also compresses the outside surfaces of the larger lymphatics, thus impeding lymph flow[2] [2].

The lymphatic capillaries empty into larger lymphatic vessels, which are similar to veins in terms of their three-tunic structure and the presence of valves. The superficial and deep lymphatics eventually merge to form larger lymphatic vessels known as **lymphatic trunks**. One of these trunks, the **right lymphatic duct**, drains the upper right portion of the body, returning lymph to the bloodstream via the right

[2] Guyton and Hall Textbook of Medical Physiology, 12 Ed. 2011, p-188.

subclavian vein. The other trunk, the **thoracic duct**, drains the rest of the body into the left subclavian vein. The thoracic duct itself begins just beneath the diaphragm in the **cisterna chyli**, a sac-like chamber that receives lymph from the lower abdomen, pelvis, and lower limbs by way of the left and right lumbar trunks and the intestinal trunk, as shown on the Figure 4.

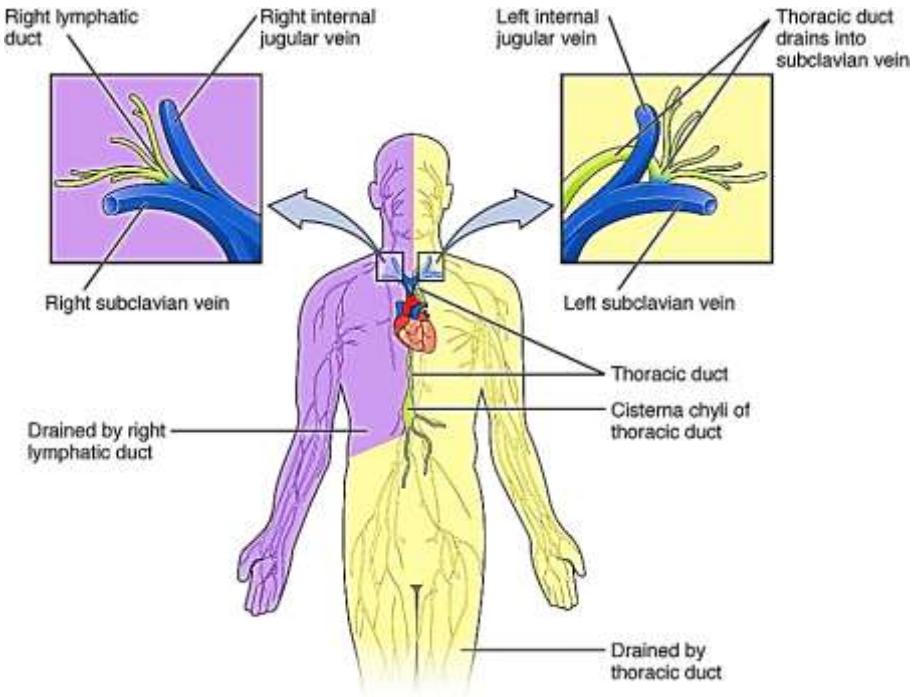


Figure 4a. Path of Lymphatic circulation

Functionally, the lymphatic vascular system runs in parallel to the blood venous system, in that both return fluids centrally.

The overall drainage system of the body is asymmetrical. The right lymphatic duct receives lymph from only the upper right side of the body (right side of the head, neck, upper chest, and right arm) and empties into the right subclavian vein beneath the right clavicle. The lymph from the rest entire (left side of the body and from the right side of the body below the chest of the body) enters the bloodstream through the thoracic duct via all the remaining lymphatic trunks. The thoracic duct itself begins just beneath the diaphragm in the cisterna chyli, a sac-like chamber that receives lymph from the lower abdomen, pelvis, and lower limbs by way of the left and right lumbar trunks and the intestinal trunk. In general, lymphatic vessels of the

subcutaneous tissues of the skin, that is, the superficial lymphatics, follow the same routes as veins, whereas the deep lymphatic vessels of the viscera generally follow the paths of arteries.

About 100 milliliters per hour of lymph flows through the thoracic duct of a resting human, and approximately another 20 milliliters flow into the circulation each hour through other channels, making a total estimated lymph flow of about 120ml/hr or 2 to 3 liters per day[3][3]. Along the way, the lymph travels through the lymph nodes, which are commonly found near the groin, armpits, neck, chest, and abdomen. Humans have about 500–600 lymph nodes throughout the body. that remove foreign materials such as infectious microorganisms from the lymph filtering through them.

Lymph circulation is a two-step process:

1. Interstitial fluid flows into the lymphatic capillaries. Plasma is forced out of blood capillaries into the spaces around the cell walls (interstitial fluid). As fluid pressure increases between the cells, the cells move apart, pulling on the microfilaments that connect the endothelial cells of the lymph capillaries to tissue cells. The pull on the microfilaments causes the lymph capillaries to open like flaps, allowing tissue fluid to enter the lymph capillaries.
2. Lymph moves through the network of contractile lymphatic vessels. The lymphatic system does not have a central pump like the heart. Various factors mentioned above assist the transport of lymph through the lymph vessels.

The lymphatic capillaries empty into larger lymphatic vessels, which are similar to veins in terms of their three-tunic structure and the presence of valves. These one-way valves are located fairly close to one another, and each one causes a bulge in the lymphatic vessel, giving the vessels a beaded appearance.

Mechanisms of lymph circulation

- Lymph flows under forces similar to those that govern venous return, except no pump (heart)
- Lymph flows at low pressure and slower speed than venous blood

[3] Guyton and Hall Textbook of Medical Physiology, 12 Ed. 2011, p-186

- Moved along by rhythmic contractions of lymphatic vessels– Stretching of vessels stimulates contraction.
- Flow aided by skeletal muscle pump - exercise significantly increases lymphatic return. The lymphatic pump becomes very active during exercise, often increasing lymph flow 10- to 30-fold. Conversely, during periods of rest, lymph flow is sluggish, almost zero[4][4].
- Arterial pulsation rhythmically squeezes lymphatic vessels.
- Thoracic pump aids flow from abdominal to thoracic cavity.
- Valves prevent backward flow.
- Rapidly flowing blood in subclavian veins, draws lymph into it.

Fluid in the interstitial spaces is often at subatmospheric pressure, and the return points into the venous system are at pressures of approximately 20 cm H_2O. This adverse pressure difference is overcome by the active pumping of collecting lymphatic vessels, which feature closely spaced one-way valves and contractile muscle cells in their walls. The movement of lymph occurs along a pressure gradient from areas of high pressure to areas of low pressure. Fluid moves from the interstitial space into the lymph capillaries by means of a pressure mechanism exerted by respiration, peristalsis of the large intestine, the compression of muscles, and during contraction, arterial pulse, the pull of the skin and fascia during movement. This action is especially prominent on the soles of the feet and the palms of the hands, which have major lymph plexuses. The rhythmic pumping of walking and grasping probably facilitates lymphatic flow.

The spontaneous contraction of lymphatic vessels in response to increased lymphatic fluid pressure constitutes the lymphatic pump. These contractions usually start in the lymphangions adjacent to the terminal end of the lymph capillaries and spread progressively from one lymphangion to the next, toward the thoracic duct or the right lymphatic duct. The contractions are similar to abdominal peristalsis and are

[4] Guyton and Hall Textbook of Medical Physiology, 12 Ed. 2011, p-188.

stimulated by increases in pressure inside lymphatic vessels. Contractions of the lymphatic vessels are not coordinated with the heart or breathing rate. If the pressure inside the lymphatic vessels exceeds or falls below certain levels, lymphatic contractions cease.

During inhalation, the thoracic duct is squeezed and fluid is pushed forward, creating a vacuum in the duct. During exhalation, fluid is pulled from the lymphatics into the thoracic duct to fill the partial vacuum.

Cells of Lymphatic system Natural killer (NK) cells. Large lymphocytes that attack and destroy bacteria, transplanted tissue, host cells infected with viruses or that have turned cancerous.

- T lymphocytes (T cells) – Mature in thymus.
- B lymphocytes (B cells)– Activation causes proliferation and differentiation into plasma cells that produce antibodies.
- Macrophages – Large, avidly phagocytic cells of connective tissue– Develop from monocytes– Phagocytize tissue debris, dead neutrophils, bacteria, and other foreign matter– Process foreign matter and display antigenic fragments to certain T cells alerting immune system to the presence of the enemy– Antigen-presenting cells (APCs).
- Dendritic cells – Branched, mobile APCs found in epidermis, mucous membranes, and lymphatic organs – Alert immune system to pathogens that have breached the body surface.
- Reticular cells – Branched stationary cells that contribute to the stroma of a lymphatic organ.

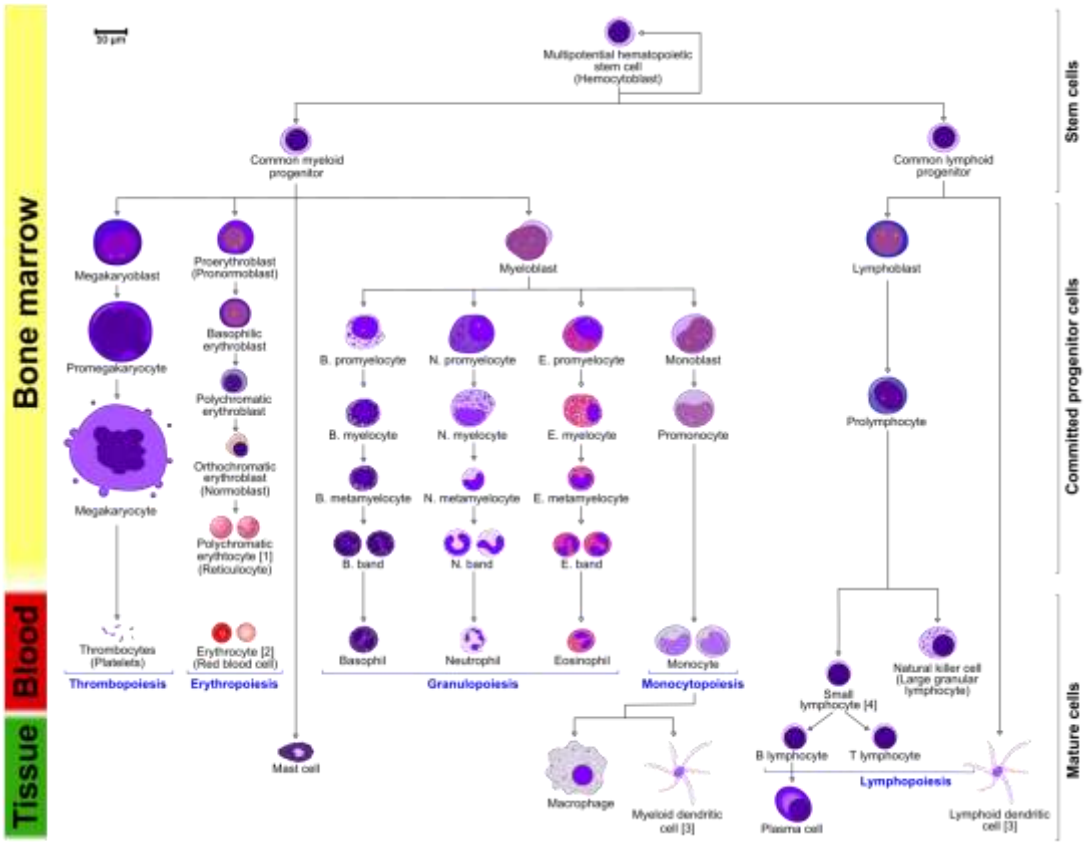


Figure 4b. Origin of cells of lymphatic system.

Lymphoid organs

Lymphatic (lymphoid) tissue - aggregations of lymphocytes in the connective tissues of mucous membranes and various organs

Lymphatic organs are anatomically well defined – Have connective tissue capsule that separates lymphatic tissue from neighboring tissues

Lymphatic cells are organized into tissues and organs based on how tightly the lymphatic cells are arranged and whether the tissue is encapsulated by a layer of connective tissue.

Three general categories exist:

- Diffuse, unencapsulated bundles of lymphatic cells. This kind of lymphatic tissue consists of lymphocytes and macrophages associated with a reticular fiber network. It occurs in the lamina propria (middle layer) of the mucus membranes (mucosae) that line the respiratory and gastrointestinal tracts.
- Discrete, unencapsulated bundles of lymphatic cells, called lymphatic nodules (follicles). These bundles have clear boundaries that separate them from

neighboring cells. Nodules occur within the lamina propria of the mucus membranes that line the gastrointestinal, respiratory, reproductive, and urinary tracts. They are referred to as **mucosa-associated lymphoid tissue (MALT).** The nodules contain lymphocytes and macrophages that protect against bacteria and other pathogens that may enter these passages with food, air, or urine. Nodules occur as solitary nodules, or they cluster as patches or aggregates. Here are the major clusters of nodules:

- **Peyer's patches** are clusters of lymphatic nodules that occur in the mucosa that lines the ileum of the small intestine.
- The tonsils are aggregates of lymphatic nodules that occur in the mucosa that lines the pharynx (throat). Each of the seven tonsils that form a ring around the pharynx are named for their specific region: a single pharyngeal tonsil **(adenoid)** in the rear wall of the nasopharynx, two palatine tonsils on each side wall of the oral cavity at its entrance in the throat, two lingual tonsils at the base of the tongue, and two small tubal tonsils in the pharynx at the entrance to the auditory tubes.
- The appendix, a small fingerlike attachment to the beginning of the large intestine, is lined with aggregates of lymph nodules.
- Encapsulated organs contain lymphatic nodules and diffuse lymphatic cells surrounded by a capsule of dense connective tissue: spleen, thymus gland.

The **primary lymphoid organs** are the bone marrow, and thymus gland. In these organs' lymphocytes mature, proliferate, and are selected, which enables them to attack pathogens without harming the cells of the body. Site where T and B cells become immunocompetent: able to recognize and respond to antigens.

The **secondary lymphoid organs** are lymph nodes, spleen, tonsils, MALT, BALT, appendix etc. Lymphocytes after development and maturation in the primary lymphoid organs, they migrate into secondary lymphoid organs to mount immune responses. Only maturated lymphocytes able to fight invading agents, to recognize and destroy them.

Lymph nodes

Lymph nodes are small, oval, or bean-shaped bodies that occur along lymphatic vessels. They function to remove debris and pathogens from the lymph, and are thus sometimes referred to as the “filters of the lymph”. Any bacteria that infect the interstitial fluid are taken up by the lymphatic capillaries and transported to a regional lymph node. Dendritic cells and macrophages within this organ internalize and kill many of the pathogens that pass through, thereby removing them from the body. Lymph nodes are surrounded by a tough capsule of connective tissue and are separated into compartments by trabeculae, the extensions of the capsule. In addition to the structure provided by the capsule and trabeculae, the structural support of the lymph node is provided by a series of reticular fibers laid down by fibroblasts. They are abundant where lymphatic vessels merge to form trunks, especially in the inguinal (groin), axillary (armpit), and mammary gland areas. Lymph flows into a node through afferent lymphatic vessels that enter the convex side of a node. It exits the node at the hilus, the indented region on the opposite, concave side of the node, through efferent lymphatic vessels. Efferent vessels contain valves that restrict lymph to movement in one direction out of the lymph node. The number of efferent vessels leaving the lymph node is fewer than the number of afferent vessels entering, slowing the flow of lymph through the node (Figure 5, 6).

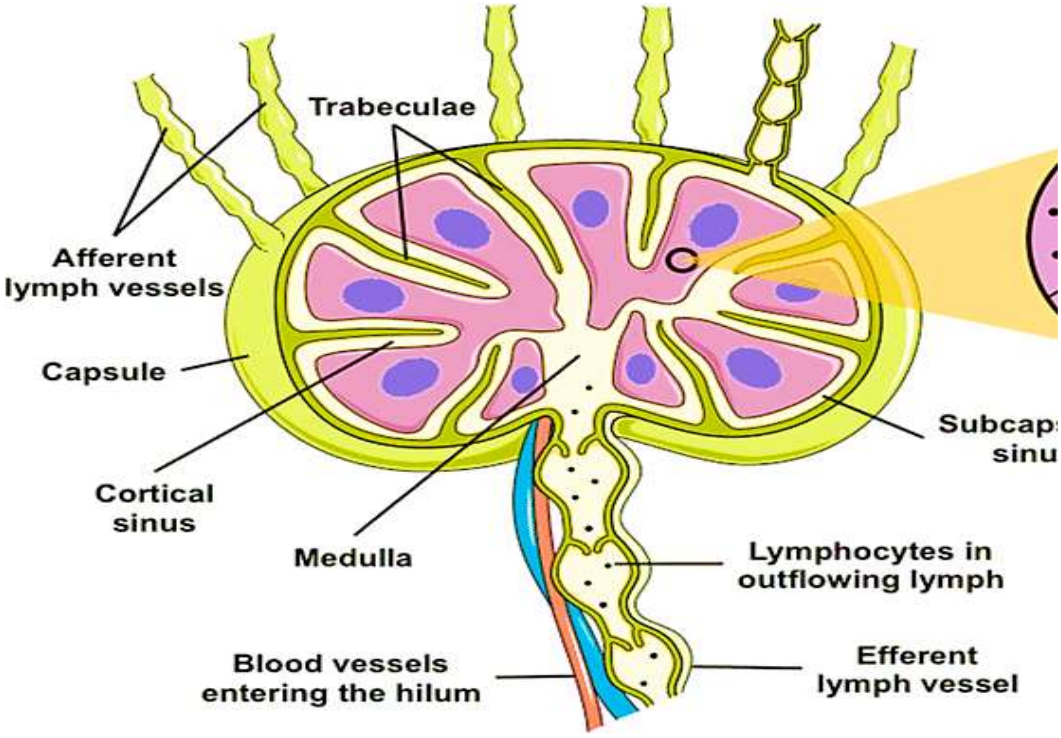


Figure 5. Structure of lymph node

Lymph nodes perform three functions:

- They filter the lymph, preventing the spread of microorganisms and toxins that enter interstitial fluids.
- They destroy bacteria, toxins, and particulate matter through the phagocytic action of macrophages.
- They produce antibodies through the activity of B cells.

The structure of a lymph node is characterized by the following features: lymph nodes are small, bean-shaped structures, usually measuring between 0.2 and 2 cm, and are surrounded by a fibrous capsule.

There is a capsule of dense connective tissue that surrounds the lymph node. Trabeculae are projections of the capsule that extend into the node, forming three cellular compartments:

- the cortex: contains lymphoid follicles composed mostly of B cells;
- paracortex: T cells predominate;
- medulla: it consists of the medullary sinuses, the medullary cords, which contain lymphocytes, plasma cells, and macrophages.

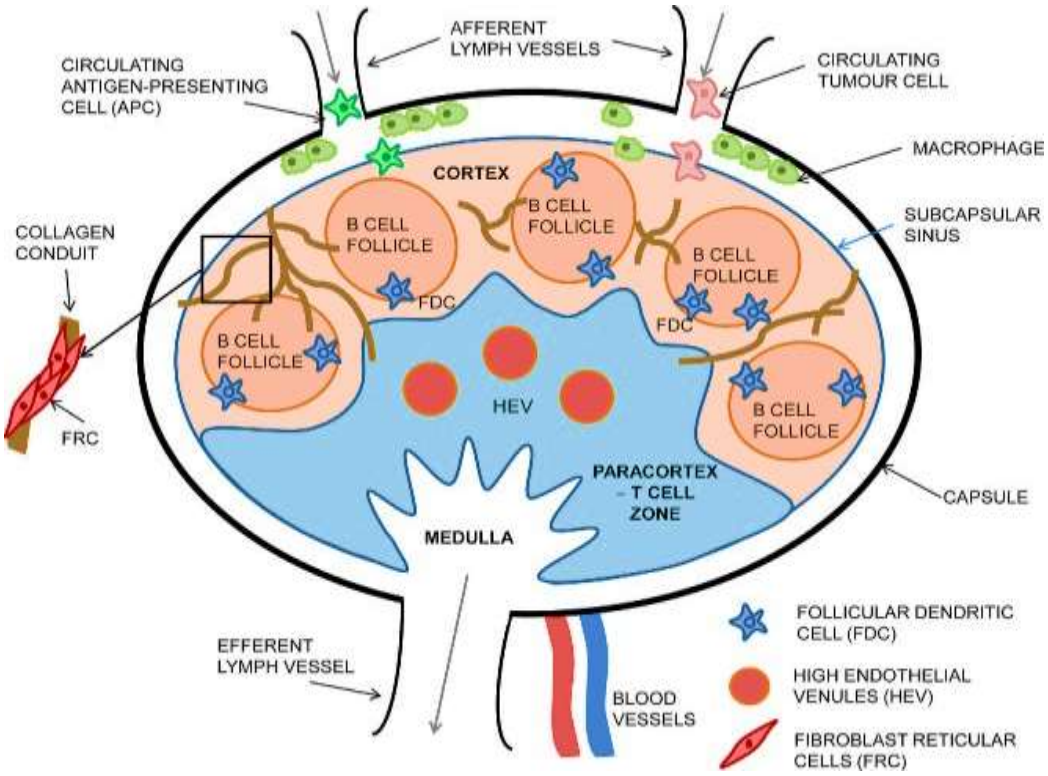


Figure 6. Compartments of lymph node

Lymphatic fluid containing antigens from tissues enters the lymph node via the afferent lymphatics, and flows into subcapsular, intermediate, and medullary sinuses, before exiting through the efferent lymphatics. The blood supply to the lymph node is derived from arteries that enter through the hilum of the node and branch into capillary loops that drain into postcapillary high endothelial venules in the paracortex. High endothelial venules are specialized vessels lined by cuboidal endothelial cells, and express lymphocyte adhesion molecules that facilitate extravasation of circulating lymphocytes through the vessel wall into the lymph node. The medulla is the center of the node. Less dense than the surrounding cortex, the medulla primarily contains T cells. Medullary cords are strands of reticular fibers with lymphocytes and macrophages that extend from the cortex toward the hilus. Sinuses are passageways through the cortex and medulla through which lymph moves toward the hilus. The cortex of an unstimulated lymph node consists of primary follicles composed of naïve B cells, with an underlying meshwork of follicular dendritic cells. The naïve B cells in primary follicles are small, mature lymphocytes with condensed chromatin and scant cytoplasm. After exposure to antigen, there is a rapid proliferation of B cells.

Germinal centers form in the center of B cell follicles; during this process, primary follicle cells are pushed to the periphery, where they form a mantle zone around the germinal center. The mantle zone also contains some memory B cells. A secondary follicle is made up of a germinal center and surrounding mantle zone.

Thymus

The thymus is a bi-lobed organ located in the upper chest region between the lungs, posterior to the sternum (Figure 7). It grows during childhood and reaches its maximum size of 40 g at puberty and begins to atrophy at puberty due to hormonal changes. After puberty, the thymus shrinks rapidly with age, is replaced by adipose and areolar connective tissue, eventually becoming almost indistinguishable from the surrounding fatty tissue. By age 65, it weighs about 6 g.

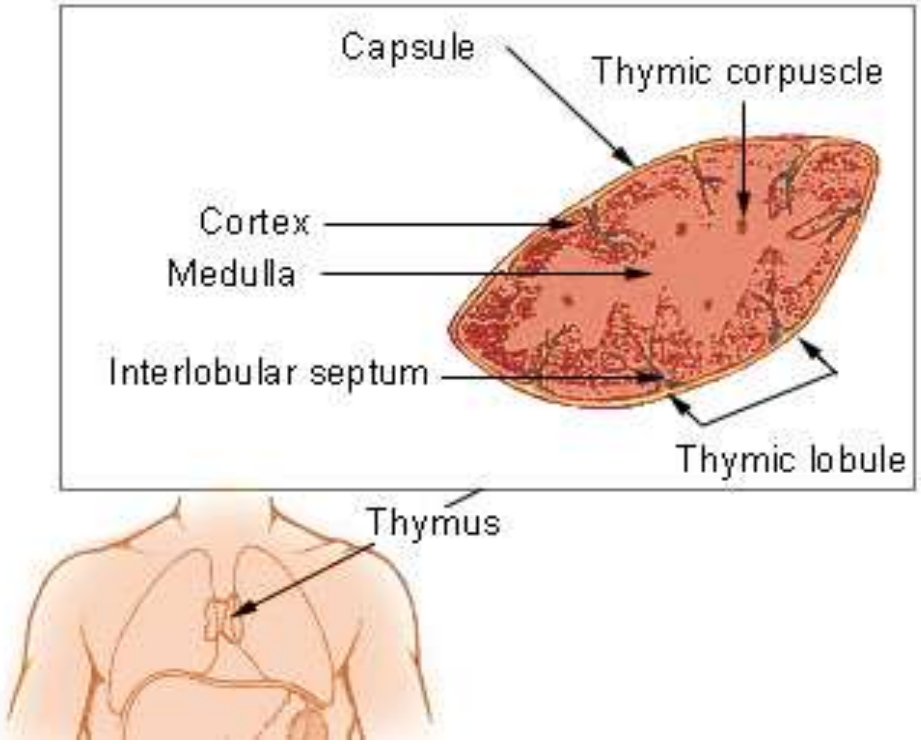


Figure 7. Structure of Thymus.

The Thymus consists of two lateral lobes placed in close contact along the middle line situated partly in the thorax, resting in the chest beneath the neck. The two lobes differ slightly in size, may be united or separated, and may be broken down into smaller lobules. Each lobe of the thymus is surrounded by a capsule of connective tissue. Lobules produced by trabeculae (inward extensions of the capsule) are

characterized by an outer cortex and inner medulla. Histologically, the thymus contains mature lymphocytes, immature lymphocytes, and stroma, while lobule tissues consist of an inner medulla and an outer cortex. The cortex and medulla play different roles in the development of T cells. The cortex is the site of T cell generation and proliferation, while the medulla connects to the venous bloodstream and allows for transport of mature inactive T cells to the lymph nodes and transport of immature T cells from bone marrow tissue into the thymus cortex for proliferation and maturation.

The following cells are present:

- Lymphocytes consist almost entirely of T cells.
- Epithelial-reticular cells resemble reticular cells, but do not form reticular fibers. Instead, these star-shaped cells form a reticular network by interlocking their slender cellular processes (extensions). These processes are held together by desmosomes, cell junctions formed by protein fibers. These cells establish a protective blood-thymus barrier that prevents the entrance of antigens from the blood and into the thymus where T cells are maturing. Thus, an antigen-free environment is maintained for the development of T cells.

Functions of the Thymus

The Thymus is the site of T-cell generation and maturation. Epithelial-reticular cells produce thymosin and other hormones believed to promote the maturation of T cells. First, immature T cells generated in bone marrow travel to the cortex tissues of the thymus through the bloodstream. Then the immature T cells undergo proliferative expansion, in which they are exposed to growth factors and antigen receptors are formed. Then the T cells are sorted by the thymus so that only T cells that express T-cell receptors (TcRs) and can bind to foreign MHC molecules will survive. The surviving cells will not mistake self-molecules for antigens. Only 2-4% of T cells survive this sorting process. The thymus is most active early in life for building a large reservoir of T cells. Each T cell is specialized to attack a different antigen, but those that attack self-antigens are destroyed by the thymus during selection processes in lymphocyte proliferation and maturation. Though removal of the thymus in

childhood causes severe immunodeficiency, later in life this is not an issue because of the proliferation of thymus activity early in life. The thymus does not provide a filtering function similar to lymph nodes (there are no afferent lymphatic vessels leading into the thymus), and unlike all other centers of lymphatic tissues, the thymus does not play a direct role in immune responses.

Central tolerance is another function of the thymus. Autoimmune diseases occur when central tolerance is lost, which causes lymphocytes to recognize host molecules as antigens and attack them, even if those tissues otherwise function normally. The thymus sorts T cells so that they will be inactive towards host molecules, though sometimes a few T cells evade this sorting process and may initiate an autoimmune disease. Though the thymus is mostly effective at preventing this occurrence, those with certain genetic characteristics (such as altered MHC complexes) may be more likely to develop autoimmune diseases with the few T-cells that aren't properly selected by the Thymus.

Spleen

Measuring about 12 cm in length, the Spleen is the largest lymphatic organ. It is located on the left side of the body, inferior to the diaphragm and at the left edge of the stomach. Like other lymphatic organs, the spleen is surrounded by a capsule whose extensions into the spleen form trabeculae. The splenic artery, splenic vein, nerves, and efferent lymphatic vessels pass through the hilus of the spleen located on its slightly concave, upper surface.

The functions of the spleen include the following:

- The Spleen filters the blood. Macrophages in the spleen remove bacteria and other pathogens, cellular debris, and aged blood cells, particularly those that cause pneumonia. There are no afferent lymphatic vessels, and unlike lymph nodes, the spleen does not filter lymph.
- The Spleen destroys old red blood cells and recycles their parts. It removes the iron from heme groups and binds the iron to the storage protein.
- The Spleen provides a reservoir of blood. The spleen holds extra blood that can help during hypovolemic shock. The diffuse nature of the red pulp retains large

quantities of blood, which can be directed to the circulation when necessary. One third of the blood platelets are stored in the spleen. During hypovolemic shock, the spleen can release up to a cup of extra blood.

- The Spleen is active in immune responses. T cells proliferate in the white pulp before returning to the blood to attack non-self-cells when necessary. B cells proliferate in the white pulp, producing plasma cells and antibodies that return to the blood to inactivate antigens. The Spleen produces blood cells. Red and white blood cells are produced in the spleen during fetal development, it is hematopoietic until about the fifth month of gestation when bone marrow becomes the main site for hematopoiesis.
- Survival is possible with removal of the spleen because the lymph nodes and liver can perform most of the same functions. (The spleen is often removed surgically if it becomes damaged or infected. This causes modest increases in circulating white blood cells and platelets, diminished responsiveness to some vaccines, and increased susceptibility to infection by bacteria and protozoa. In particular, there is an increased risk to infection from gram negative bacteria that cause pneumonia.)

Structure of the Spleen

There are two distinct areas within the spleen:

1. Red pulp consists of venous sinuses filled with blood. It mechanically filters old blood using macrophage activity. It is made of connective tissue called the cord of Billroth that can fill with blood and contains many macrophages. The red pulp makes up roughly 80% of the spleen parenchyma. It is separated from the white pulp by the marginal zone. The red pulp is primarily made up of tissue known as the cords, which is rich in macrophages, and the venous sinus, which have gaps in the endothelial lining which allows normal cells to pass through, abnormal cells remain in the cords and are phagocytosed by macrophages. The macrophages also remove pathogens, denatured hemoglobin, and other cellular debris.

2. White pulp consists of reticular fibers and lymphocytes in nodules that resemble the nodules of lymph nodes. White pulp is responsible for active immune response by synthesizing antibodies.

   The white pulp comprises lymph-related nodules called malpighian corpuscles which contain:

- Periarteriolar lymphoid sheaths rich in T-lymphocytes and macrophages.
- A marginal zone, rich in macrophages
- Lymphoid follicles, rich in naive B-lymphocytes.

Because of this, the white pulp of the spleen has a very important role in the normal immune response to infection. Antigen presenting cells may enter the white pulp, resulting in activation of the T-lymphocytes stored there. These in turn, activate the B-lymphocytes in the follicles, converting them to plasma cells which then produce of IgM antibodies initially and eventually IgG antibodies.

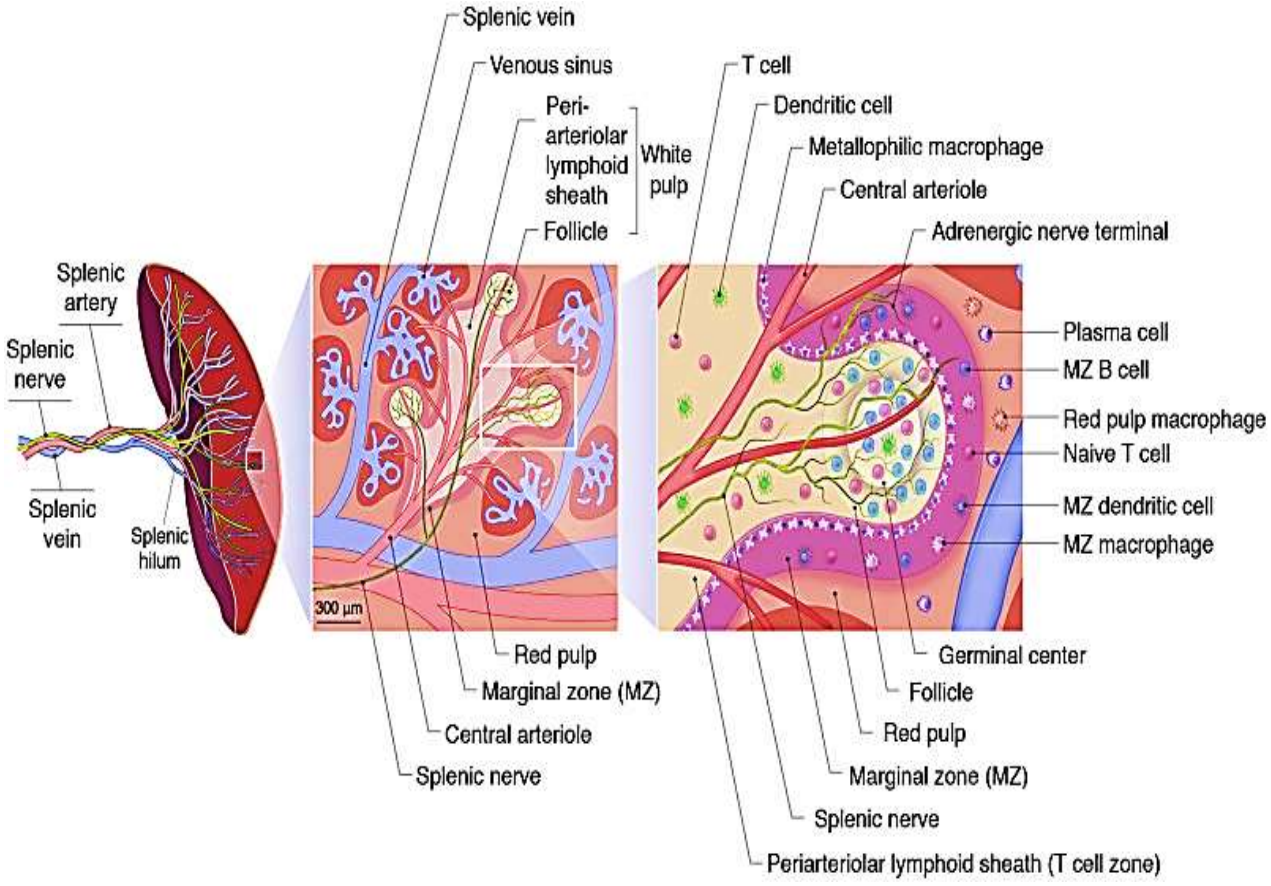


Figure 8. Structure of Spleen, red and white pulp

Pathogens may also enter the follicles directly. B-lymphocytes detect this and can then present the antigen to the T-lymphocytes. This leads to a process known as co-stimulation, in which the two cell types activate each other – so the B-lymphocyte is then able to become a plasma cell and produce antibodies against the pathogen. The white pulp is also important in how the body deals with encapsulated bacteria e. g. Neisseria meningitidis, Haemophiles influenzae and Streptococcus pneumoniae. Encapsulated bacteria tend to have a very smooth surface with a negative charge which therefore reduces the ability of phagocytes to attach and engulf the bacteria. The B-lymphocytes in the white pulp help opsonise these bacteria.

Tonsils

Tonsils are lymphoid nodules located along the inner surface of the pharynx and are important in developing immunity to oral pathogens. The tonsil located at the back of the throat, the pharyngeal tonsil, is sometimes referred to as the adenoid when swollen. Such swelling is an indication of an active immune response to infection. Histologically, tonsils do not contain a complete capsule, and the epithelial layer invaginates deeply into the interior of the tonsil to form tonsillar crypts. These structures, which accumulate all sorts of materials taken into the body through eating and breathing, actually “encourage” pathogens to penetrate deep into the tonsillar tissues where they are acted upon by numerous lymphoid follicles and eliminated. This seems to be the major function of tonsils - to help children’s bodies recognize, destroy, and develop immunity to common environmental pathogens so that they will be protected in their later lives. Tonsils are often removed in those children who have recurring throat infections, especially those involving the palatine tonsils on either side of the throat, whose swelling may interfere with their breathing and/or swallowing.

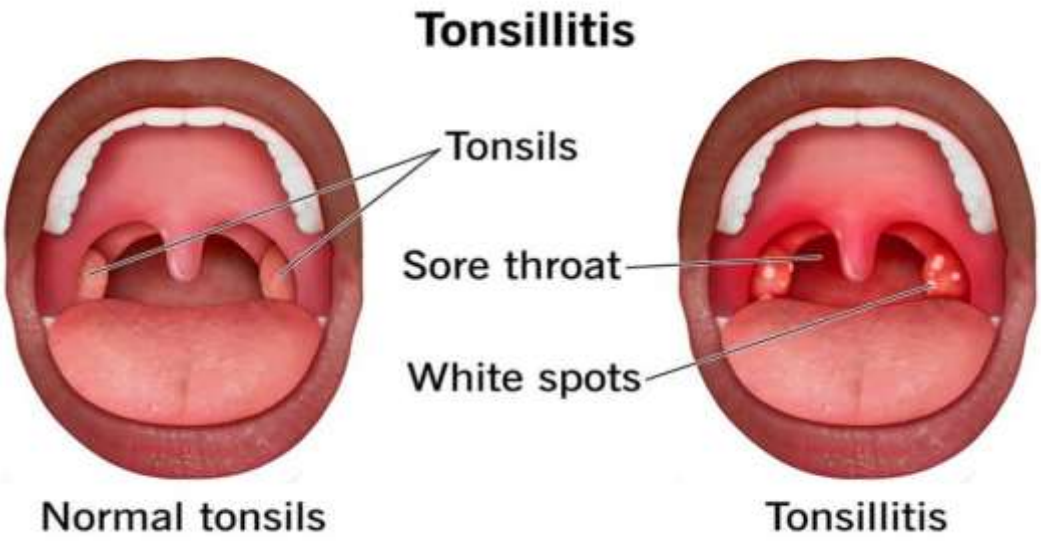


Figure 9. Tonsils

Production and maturation of B cells

Like T cells, B cells are formed from multipotent hematopoietic stem cells (HSCs) in the bone marrow and follow a pathway through lymphoid stem cell and lymphoblast (see Figure 1 in Cellular Defenses). Unlike T cells, however, lymphoblasts destined to become B cells do not leave the bone marrow and travel to the thymus for maturation. Rather, eventual B cells continue to mature in the bone marrow. The first step of B cell maturation is an assessment of the functionality of their antigen-binding receptors. This occurs through positive selection for B cells with normal functional receptors. A mechanism of negative selection is then used to eliminate self-reacting B cells and minimize the risk of autoimmunity. B cells that pass the selection in the bone marrow then travel to the spleen for their final stages of maturation. There they become naïve mature B cells, i.e., mature B cells that have not yet been activated. B cells can be activated without help from T cells. B-cell receptors (BCRs) for naïve mature B cells are membrane-bound monomeric forms of IgD and IgM. They have two identical heavy chains and two identical light chains connected by disulfide bonds into a basic “Y” shape (Figure 10). The trunk of the Y-shaped molecule, the constant region of the two heavy chains, spans the B cell membrane. The two antigen-binding sites exposed to the exterior of the B cell are involved in the

binding of specific pathogen epitopes to initiate the activation process. It is estimated that each naïve mature B cell has upwards of 100,000 BCRs on its membrane, and each of these BCRs has an identical epitope-binding specificity.

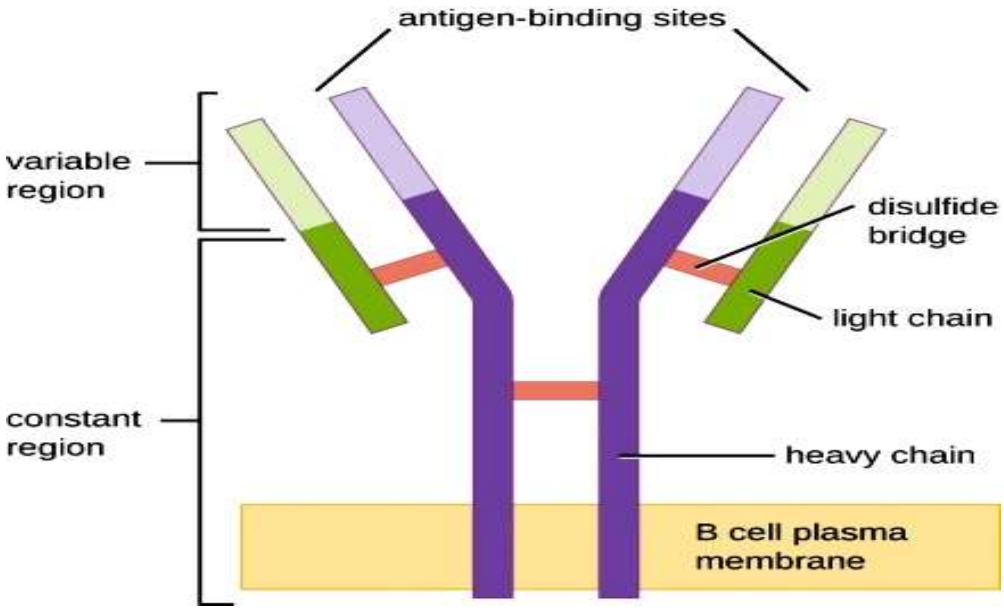


Figure 10. Structure of immunoglobulin

TCRs can only interact with antigenic epitopes that are presented within the antigen-binding cleft of MHC I or MHC II, BCRs do not require antigen presentation with MHC; they can interact with epitopes on free antigens or with epitopes displayed on the surface of intact pathogens. Another important difference is that TCRs only recognize protein epitopes, whereas BCRs can recognize epitopes associated with different molecular classes (e.g., proteins, polysaccharides, lipopolysaccharides). Activation of a B cell by a protein antigen requires the B cell to function as an APC, presenting the protein epitopes with MHC II to helper T cells. Because of their dependence on T cells for activation of B cells, protein antigens are classified as T-dependent antigens. In contrast, polysaccharides, lipopolysaccharides, and other nonprotein antigens are considered T-independent antigens because they can activate B cells without antigen processing and presentation to T cells. The T cell-independent response is short-lived and does not result in the production of memory B cells. Thus, it will not result in a secondary response to subsequent exposures to T-independent

antigens. Once a B cell is activated, it undergoes clonal proliferation and daughter cells differentiate into plasma cells. Plasma cells are antibody factories that secrete large quantities of antibodies. After differentiation, the surface BCRs disappear and the plasma cell secretes pentameric IgM molecules that have the same antigen specificity as the BCRs (Figure 11).

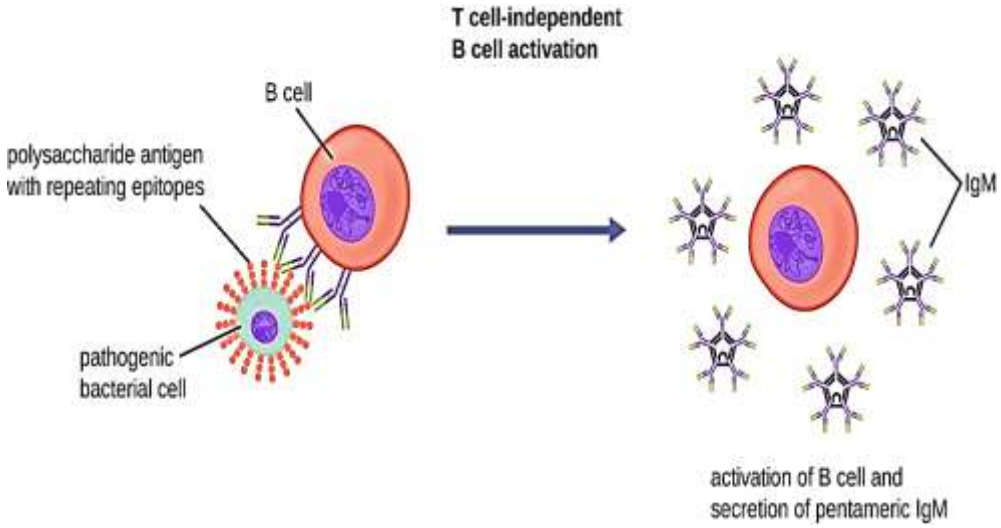


Figure 11. T cell dependent B cell activation

Interaction between the BCRs on a naïve mature B cell and a free protein antigen stimulate internalization of the antigen, Once internalized inside the B cell, the protein antigen is processed and presented with MHC II. The presented antigen is then recognized by helper T cells specific to the same antigen. The TCR of the helper T cell recognizes the foreign antigen, and the T cell's CD4 molecule interacts with MHC II on the B cell. The coordination between B cells and helper T cells that are specific to the same antigen is referred to as linked recognition.

Once activated by linked recognition, T helper 2 (TH2) cells produce and secrete cytokines that activate the B cell and cause proliferation into clonal daughter cells. After several rounds of proliferation, additional cytokines provided by the TH2 cells stimulate the differentiation of activated B cell clones into memory B cells, which will quickly respond to subsequent exposures to the same protein epitope, and plasma cells that lose their membrane BCRs and initially secrete pentameric IgM.

After initial secretion of IgM, cytokines secreted by TH2 cells stimulate the plasma cells to switch from IgM production to production of IgG, IgA, or IgE. This process, called class switching or isotype switching, allows plasma cells cloned from the same activated B cell to produce a variety of antibody classes with the same epitope specificity.

The major histocompatibility complex (MHC) (also called human leukocyte antigens, HLAs) is the mechanism by which the immune system is able to differentiate between self and non-self-cells. The MHC is a collection of glycoproteins (proteins with a carbohydrate) that exist on the plasma membranes of nearly all body cells. The proteins of a single individual are unique, originating from 20 genes, with more than 50 variations per gene between individuals. Thus, it is extremely unlikely that two people, except for identical twins, will possess cells with the same set of MHC molecules. The immune system is able to identify non-self-cells by aberrations in the MHC displayed on the plasma membrane. There are two groups of MHC molecules, and each group generates different markings on the plasma membrane:

- MHC-I glycoproteins are produced by all body cells (except red blood cells). When a cell becomes cancerous or is invaded by a virus, unfamiliar proteins are synthesized in the cell. These proteins are endogenous antigens—that is, antigens produced inside the cell. Portions of these antigens are combined with MHC-I glycoproteins and, when displayed on the plasma membrane, indicate a nonself cell.
- MHC-II glycoproteins are produced only by antigen-presenting cells (APCs)—mostly macrophages and B cells. APCs actively ingest exogenous antigens—antigens that originate outside the cell. Exogenous antigens include viruses, toxins, pollen, or bacteria that are circulating in the blood, lymph, or body fluids. APCs break down the antigens and incorporate pieces of them with MHC-II glycoproteins. This aberrant display of MHC markers is recognized as nonself.

Production and maturation of T cells

T lymphocytes originate from bone marrow progenitors that migrate to the thymus for maturation, selection, and subsequent export to the periphery. The

developing progenitors within the thymus, also known as thymocytes, undergo a series of maturation steps that can be identified based on the expression of different cell surface markers. The majority of cells in the thymus give rise to αβ T cells, however approximately 5% bear the γδ T cell receptor (TCR). Developing thymocytes interact with the thymus stromal (non-haematopoietic) cells, and undergo the process described below in distinct regions of the thymus. The thymus is made up of an outer **cortex** and an inner **medulla** region.

The earliest developing thymocytes lack the expression of the co-receptors CD4 and CD8 and are termed **double negative** (DN) cells. The DN population can be further sub-divided by the expression of CD44 (an adhesion molecule) and CD25 (Interleukin-2 receptor α chain), Figure 1 shows the ordered expression of these markers. Cells that lack expression of CD44, but express CD25 (DN3) undergo a process termed **beta-selection**. This process selects for cells that have successfully rearranged their TCR-β chain locus. The β chain then pairs with the surrogate chain, pre-Tα, and produces a pre-TCR, which forms a complex with CD3 molecules. This complex leads to the survival, proliferation, arrest in further β chain loci rearrangement, and further differentiation by up-regulation and expression of CD4 and CD8, these cells are termed **double positive** (DP) cells. Cells that do not undergo beta-selection die by apoptosis. DP cells rearrange their TCR-α chain loci, to produce an αβ-TCR. These cells then undergo positive selection, in the cortex. DP cells interact with self-antigens in the context of major histocompatibility complex (MHC) class I or class II molecules. Those cells that engage antigen/MHC with an appropriate affinity survive, whereas those cells that interact with a weaker affinity die by apoptosis. Thymocytes then migrate into the medulla to undergo negative selection. They are presented self-antigens on antigen presenting cells (APCs), such as dendritic cells and macrophages. Thymocytes that interact too strongly with antigen undergo apoptosis. The majority of developing thymocytes die during this process. Following selection, down-regulation of either co-receptor produces either naïve CD4 or CD8 single positive cells that exit the thymus and circulate the periphery. Peripheral T cells comprise different subsets including naïve T cells, which

have the capacity to respond to new antigens, memory T cells that derive from previous antigen activation and maintain long-term immunity, and regulatory T (Treg) cells which keep immune responses in check. Negative selection leaves the body in a state of self-tolerance—the surviving T cells respond only to suspicious antigens (ignoring the body's own proteins). Only 2% of T cells pass the test.

• In thymus medulla, surviving T cells undergo positive selection: they multiply and form clones of identical cells programmed to respond to a specific antigen.

• Naive lymphocyte pool: immunocompetent T cells that have not yet encountered foreign antigens.

• Naive T cells leave thymus and colonize lymphatic tissues and organs everywhere in the body.

Innate immunity (non-specific immunity)

Immunity which is present after birth. is also known as the first defense barrier exists in order to prevent infection. For example, our skin is the anatomy blockade which needs to be penetrated by infectious germs before entering into the body. Germs may infect through bruises or fire burns. In addition, acid in the stomach helps inhibit growth or kill bacteria contaminated in food or drinks. Tears also contain enzymes which can prevent infection.

Pathogens - agents capable of producing disease. Include viruses, bacteria, and fungi.

Three lines of defenses against pathogens:

1. First line of defense: skin and mucous membranes.
2. Second line of defense: several nonspecific defense mechanisms. Leukocytes and macrophages, antimicrobial proteins, natural killer cells, inflammation, and fever.
3. Third line of defense: the immune system. Defeats a pathogen, and leaves the body with a "memory" of it so it can defeat it faster in the future.

Nonspecific Resistance or Innate immunity

Nonspecific defenses - guard equally against a broad range of pathogens. They lack capacity to remember pathogens.

Three kinds of nonspecific defenses:

• Protective proteins

• Protective cells

• Protective processes

Specific or adaptive immunity - body must develop separate immunity to each pathogen. Body adapts to a pathogen and wards it off more easily upon future exposure.

First line of innate immunity

External barriers to infection. The skin and the mucous membrane linings of the respiratory, gastrointestinal, and genitourinary tracts provide the first line of defense against invasion by microbes or parasites. Human skin has a tough outer layer of cells that produce keratin. This layer of cells, which is constantly renewed from below, serves as a mechanical barrier to infection. In addition, glands in the skin secrete oily substances that include fatty acids, such as oleic acid, that can kill some bacteria; skin glands also secrete lysozyme, an enzyme (also present in tears and saliva) that can break down the outer wall of certain bacteria. Victims of severe burns often fall prey to infections from normally harmless bacteria, illustrating the importance of intact, healthy skin to a healthy immune system.

Mucous membranes. Like the outer layer of the skin but much softer, the mucous membrane linings of the respiratory, gastrointestinal, and genitourinary tracts provide a mechanical barrier of cells that are constantly being renewed. The lining of the respiratory tract has cells that secrete mucus (phlegm), which traps small particles. Other cells in the wall of the respiratory tract have small hairlike projections called cilia, which steadily beat in a sweeping movement that propels the mucus and any trapped particles up and out of the throat and nose. Also present in the mucus are protective antibodies, which are products of specific immunity. Cells in the lining of the gastrointestinal tract secrete mucus that, in addition to aiding the passage of food, can trap potentially harmful particles or prevent them from attaching to cells that make up the lining of the gut. Protective antibodies are secreted by cells underlying the gastrointestinal lining. Furthermore, the stomach lining secretes hydrochloric acid that is strong enough to kill many microbes.

Second line of innate immunity

Chemical barriers to infection. Some microbes penetrate the body's protective barriers and enter the internal tissues. There they encounter a variety of chemical substances that may prevent their growth. These substances include chemicals whose protective effects are incidental to their primary function in the body, chemicals whose principal function is to harm or destroy invaders, and chemicals produced by naturally occurring bacteria.

Chemicals with incidental protective effects

Some of the chemicals involved in normal body processes are not directly involved in defending the body against disease. Nevertheless, they do help repel invaders. For example, chemicals that inhibit the potentially damaging digestive enzymes released from body cells which have died in the natural course of events also can inhibit similar enzymes produced by bacteria, thereby limiting bacterial growth. Another substance that provides protection against microbes incidentally to its primary cellular role is the blood protein transferrin. The normal function of transferrin is to bind molecules of iron that are absorbed into the bloodstream through the gut and to deliver the iron to cells, which require the mineral to grow. The protective benefit transferrin confers results from the fact that bacteria, like cells, need free iron to grow. When bound to transferrin, however, iron is unavailable to the invading microbes, and their growth is stemmed.

Antimicrobial proteins

Complement. A number of proteins contribute directly to the body's nonspecific defense system by helping to destroy invading microorganisms. One group of such proteins is called complement because it works with other defense mechanisms of the body, complementing their efforts to eradicate invaders. Many microorganisms can activate complement in ways that do not involve specific immunity. Once activated, complement proteins work together to lyse, or break apart, harmful infectious organisms that do not have protective coats. Other microorganisms can evade these mechanisms but fall prey to scavenger cells, which engulf and destroy

infectious agents, and to the mechanisms of the specific immune response. Complement cooperates with both nonspecific and specific defense systems.

Interferons. Another group of proteins that provide protection are the interferons, which inhibit the replication of many—but not all—viruses. Cells that have been infected with a virus produce interferon, which sends a signal to other cells of the body to resist viral growth. When first discovered in 1957, interferon was thought to be a single substance, but since then several types have been discovered, each produced by a different type of cell. Alpha interferon is produced by white blood cells other than lymphocytes, beta interferon by fibroblasts, and gamma interferon by natural killer cells and cytotoxic T lymphocytes (killer T cells). All interferons inhibit viral replication by interfering with the transcription of viral nucleic acid. Interferons exert additional inhibitory effects by regulating the extent to which lymphocytes and other cells express certain important molecules on their surface membranes.

Proteins from naturally occurring bacteria. In the small and large intestines the growth of invading bacteria can be inhibited by naturally gut-dwelling bacteria that do not cause disease. These gut-dwelling microorganisms secrete a variety of proteins that enhance their own survival by inhibiting the growth of the invading bacterial species.

Third line of innate immunity

Nonspecific responses to infection. Phagocytosis and inflammation. Phagocytes - cells that engulf foreign matter.

Five types of leukocytes:

- Neutrophils
- Eosinophils
- Basophils
- Monocytes
- Lymphocytes

However, there are infectious germs that can overcome the first defense barrier and try attacking our bodies If an infectious agent is not successfully repelled by the chemical and physical barriers described above, it will encounter cells whose function

is to eliminate foreign substances that enter the body. These cells are the nonspecific effector cells of the innate immune response. They include scavenger cells - i.e., various cells that attack infectious agents directly - and natural killer cells, which attack cells of the body that harbour infectious organisms. Some of these cells destroy infectious agents by engulfing and destroying them through the process of phagocytosis, while other cells resort to alternative means. As is true of other components of innate immunity, these cells interact with components of acquired immunity to fight infection.

The body has a number of nonspecific methods of fighting infection that are called early induced responses. They include the acute-phase response and the inflammation response, which can eliminate infection or hold it in check until specific, acquired immune responses have time to develop. Nonspecific immune responses occur more rapidly than acquired immune responses do, but they do not provide lasting immunity to specific pathogens. Nonadaptive immune responses rely on a number of chemical signals, collectively called cytokines, to carry out their effects. These cytokines include members of the family of proteins called interleukins, which induce fever and the acute-phase response, and tumor necrosis factor-alpha, which initiates the inflammatory response.

Scavenger cells

Neutrophils are the most common type of granulocyte, making up about 60 to 70 percent of all white blood cells. These granulocytes ingest and destroy microorganisms, especially bacteria. Less common are the eosinophils, which are particularly effective at damaging the cells that make up the cuticle (body wall) of larger parasites. Fewer still are the basophils, which release heparin (a substance that inhibits blood coagulation), histamine, and other substances that play a role in some allergic reactions (*see* immune system disorder: Allergies). Very similar in structure and function to basophils are the tissue cells called mast cells, which also contribute to immune responses. Granulocytes, which have a life span of only a few days, are continuously produced from stem (i.e., precursor) cells in the bone marrow. They enter the bloodstream and circulate for a few hours, after which they leave the

circulation and die. Granulocytes are mobile and are attracted to foreign materials by chemical signals, some of which are produced by the invading microorganisms themselves, others by damaged tissues, and still others by the interaction between microbes and proteins in the blood plasma. Some microorganisms produce toxins that poison granulocytes and thus escape phagocytosis; other microbes are indigestible and are not killed when ingested. By themselves, then, granulocytes are of limited effectiveness and require reinforcement by the mechanisms of specific immunity. Within the body the neutrophils migrate to areas of infection or tissue injury. The force of attraction that determines the direction in which neutrophils will move is known as chemotaxis and is attributed to substances liberated at sites of tissue damage. Of the many neutrophils circulating outside the bone marrow, half are in the tissues and half are in the blood vessels; of those in the blood vessels, half are within the mainstream of rapidly circulating blood and the other half move slowly along the inner walls of the blood vessels (marginal pool), ready to enter tissues on receiving a chemotactic signal from them. Neutrophils are actively phagocytic; they engulf bacteria and other microorganisms and microscopic particles. The granules of the neutrophil are microscopic packets of potent enzymes capable of digesting many types of cellular materials. When a bacterium is engulfed by a neutrophil, it is encased in a vacuole lined by the invaginated membrane. The granules discharge their contents into the vacuole containing the organism. As this occurs, the granules of the neutrophil are depleted (degranulation). A metabolic process within the granules produces hydrogen peroxide and a highly active form of oxygen (superoxide), which destroy the ingested bacteria. Final digestion of the invading organism is accomplished by enzymes. Monocytes, which constitute between 4 and 8 percent of the total number of white blood cells in the blood, move from the blood to sites of infection, where they differentiate further into macrophages. These cells are scavengers that phagocytose whole or killed microorganisms and are therefore effective at direct destruction of pathogens and cleanup of cellular debris from sites of infection. Neutrophils and macrophages are the main phagocytic cells of the body, but macrophages are much larger and longer-lived than neutrophils. Some

macrophages are important as antigen-presenting cells, cells that phagocytose and degrade microbes and present portions of these organisms to T lymphocytes, thereby activating the specific acquired immune response. Compared with granulocytes, macrophages move relatively sluggishly. They are attracted by different stimuli and usually arrive at sites of invasion later than granulocytes.

Natural killer cells do not attack invading organisms directly but instead destroy the body's own cells that have either become cancerous or been infected with a virus. NK cells are the third most abundant type of lymphocyte in the body (B and T lymphocytes being present in the greatest numbers). They develop from hematopoietic stem cells and mature in the bone marrow and the liver.

Neutrophils

- Wander in connective tissue killing bacteria
- Can kill using phagocytosis and digestion
- Can kill by producing a cloud of bactericidal chemicals

• Lysosomes degranulate - discharge enzymes into tissue fluid causing a respiratory burst

• Creates a killing zone around neutrophil, destroying several bacteria

Eosinophils

- Found especially in mucous membranes
- Guard against parasites, allergens (allergy-causing agents), and other pathogens
- Kill tapeworms and roundworms by producing superoxide, hydrogen peroxide, and toxic proteins
- Promote action of basophils and mast cells
- Phagocytize antigen–antibody complexes
- Limit action of histamine and other inflammatory chemicals

Basophils

- Secrete chemicals that aid mobility and action of other leukocytes
- Leukotrienes: activate and attract neutrophils and eosinophils
- Histamine: a vasodilator, which increases blood flow
- Speeds delivery of leukocytes to the area

- Heparin: inhibits clot formation
- Clots would impede leukocyte mobility
- Mast cells also secrete these substances
- Type of connective tissue cell very similar to basophils

Lymphocytes

- Three basic categories: T, B, and NK cells
- Circulating blood contains
• 80% T cells
• 15% B cells
• 5% Natural killer (NK) cells continually patrol body looking for pathogens and diseased host cells. NK cells attack and destroy bacteria, transplanted cells, cells infected with viruses, and cancer cells. Recognize enemy cell and bind to it. Release proteins called perforins. Polymerize a ring and create a hole in its plasma membrane. Secrete a group of protein-degrading enzymes - granzymes. Enter through pore and degrade cellular enzymes and induce apoptosis (programmed cell death).

Monocytes - emigrate from the blood into connective tissues and transform into macrophages **Macrophage system -** all the body's avidly phagocytic cells, except leukocytes.

- Wandering macrophages: actively seek pathogens
- Widely distributed in loose connective tissue
- Fixed macrophages: phagocytize only pathogens that come to them
• Microglia - in central nervous system
• Alveolar macrophages - in lungs
• Hepatic macrophages - in liver

Acute-phase response when the body is invaded by a pathogen, macrophages release the protein signals interleukin-1 (IL-1) and interleukin-6 (IL-6) to help fight the infection. One of their effects is to raise the temperature of the body, causing the fever that often accompanies infection. (The interleukins increase body temperature by acting on the temperature-regulating hypothalamus in the brain and by affecting energy mobilization by fat and muscle cells.) Fever is believed to be

helpful in eliminating infections because most bacteria grow optimally at temperatures lower than normal body temperature. But fever is only part of the more general innate defense mechanism called the acute - phase response. In addition to raising body temperature, the interleukins stimulate liver cells to secrete increased amounts of several different proteins into the bloodstream. These proteins, collectively called acute-phase proteins, bind to bacteria and, by doing so, activate complement proteins that destroy the pathogen. The acute-phase proteins act similarly to antibodies but are more democratic - that is, they do not distinguish between pathogens as antibodies do but instead attack a wide range of microorganisms equally. Another effect the interleukins have is to increase the number of circulating neutrophils and eosinophils, which help fight infection.

Inflammatory response

Inflammation - local defensive response to tissue injury, including trauma and infection. General purposes of inflammation. Infection often results in tissue damage, which may trigger an inflammatory response. The signs of inflammation include pain, swelling, redness, and fever, which are induced by chemicals released by macrophages. These substances promote blood flow to the area, increase the permeability of capillaries, and induce coagulation. The increased blood flow is responsible for redness, and the leakiness of the capillaries allows cells and fluids to enter tissues, causing pain and swelling. These effects bring more phagocytic cells to the area to help eliminate the pathogens.

There are three main purposes of inflammation:

1. Limits spread of pathogens: Fibrinogen that filters into tissue fluid clots. Forms a sticky mesh that walls off microbes. Heparin prevents clotting at site of injury. Pathogens are in a fluid pocket surrounded by clot and attacked by antibodies, phagocytes, and other defenses)

2. Destroys pathogens. Neutrophils, the chief enemy of bacteria, accumulate at the injury site within an hour. After leaving the bloodstream, they exhibit (Chemotaxis - attraction to chemicals such as bradykinin and leukotrienes that guide them to the injury site)

• Most immediate requirement after tissue injury is to get defensive leukocytes to the site quickly. Achieved by local hyperemia - increasing blood flow. Local vasodilation due to vasoactive chemicals (Histamine, leukotrienes, and other cytokines, secreted by basophils, mast cells, cells damaged by trauma, toxins, or organisms triggering inflammation) Hyperemia also washes toxins and metabolic waste from the site more rapidly

• Vasoactive chemicals also stimulate endothelial cells to contract, thereby widening gaps between them

- This increases capillary permeability

- Fluid, leukocytes, and plasma proteins leave bloodstream (Including complement, antibodies, and clotting proteins)

• Selectins: cell-adhesion molecules made by endothelial cells that aid in the recruitment of leukocytes.

- Make membranes sticky, so leukocytes adhere to vessel wall (margination).

- Diapedesis or emigration: leukocytes crawl through gaps in the endothelial cells and enter tissue fluid.

• Extravasated: cells and chemicals that have left the bloodstream

• Basis for the four cardinal signs of inflammation.

- Heat: results from hyperemia.

- Redness: due to hyperemia, and extravasated RBCs in the tissue.

- Swelling (edema): due to increased fluid filtration from the capillaries.

- Pain: from direct injury to the nerves, pressure on the nerves from edema, stimulation of pain receptors by prostaglandins, bacterial toxins, and bradykinin.

• Neutrophils quickly respond to and kill bacteria

- Phagocytosis

- Respiratory burst

- Secrete cytokines for recruitment of macrophages and additional neutrophils

- Macrophages and T cells secrete colony-stimulating factor to stimulate leukopoiesis (production of more leukocytes) thereby raising WBC counts in blood

• Neutrophilia - 5,000 cells/μL to 25,000 cells/μL in bacterial infection

• Eosinophilia - elevated eosinophil count in allergy or parasitic infection.

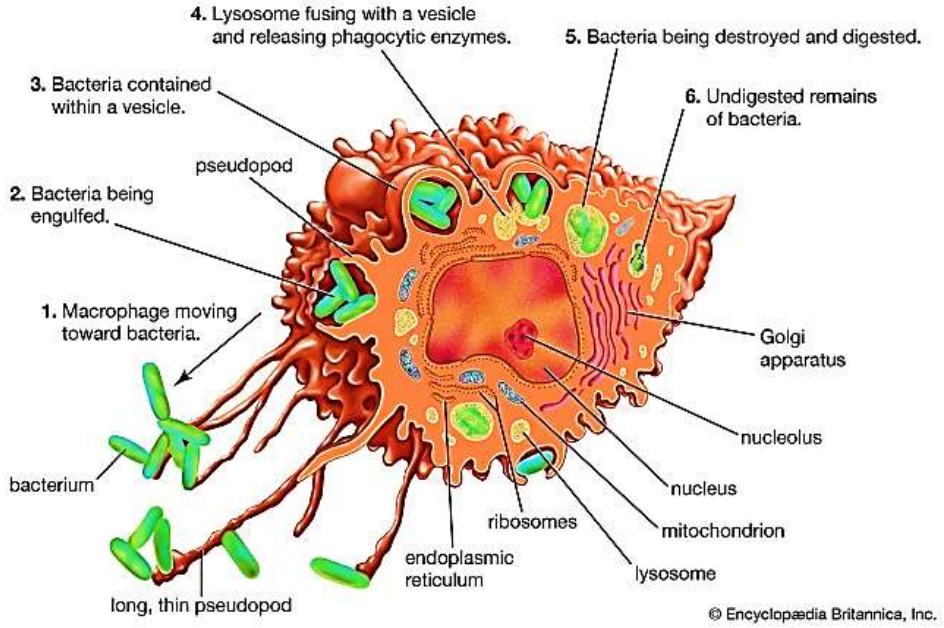


Figure 12. Phagocytosis by macrophage

Removes debris from damaged tissue. Tissue Cleanup and Repair

Cytokines - small proteins that regulate inflammation and immunity. Secreted mainly by leukocytes. Alter physiology of receiving cell. Act at short range, neighboring cells (paracrine) or the same cell that secretes them (autocrine). Include interferon, interleukins, tumor necrosis factor, chemotactic factors, and others.

• Monocytes - the primary agents of tissue cleanup and repair. Arrive in 8 to 12 hours and become macrophages. Engulf and destroy bacteria, damaged host cells, and dead and dying neutrophils

•Edema contributes to tissue cleanup. Swelling compresses veins and reduces venous drainage. Forces open valves of lymphatic capillaries, promoting lymphatic drainage. Lymphatics collect and remove bacteria, dead cells, proteins, and tissue debris better than blood capillaries

Pus - yellow accumulation of dead neutrophils, bacteria, cellular debris, and tissue fluid.

Abscess: accumulation of pus in a tissue cavity

• Platelet-derived growth factor is secreted by blood platelets and endothelial cells in injured area

- Stimulates fibroblasts to multiply
- Synthesizes collagen

• Hyperemia delivers oxygen, amino acids, and other necessities for protein synthesis

• Increased heat increases metabolic rate, speeds mitosis, and tissue repair

• Fibrin clot forms a scaffold for tissue reconstruction

• Pain makes us limit the use of a body part so it has a chance to rest and heal**.**

Antimicrobial Proteins

Proteins that inhibit microbial reproduction and provide short-term, nonspecific resistance to pathogenic bacteria and viruses. Two families of antimicrobial proteins.

Interferons: secreted by certain cells infected by viruses. There is no benefit to the cell that secretes them. They alert neighboring cells and protect them from becoming infected. Bind to surface receptors on neighboring cells and activate second-messenger systems, then the alerted cell synthesizes various proteins that defend it from infection. Breaks down viral genes or prevents replication Also activates NK cells and macrophages. Destroy infected cell before they can liberate a swarm of newly replicated viruses. Activated NK cells destroy malignant cells.

Complement system is a group of 30 or more globular proteins that make powerful contributions to both nonspecific resistance and adaptive immunity**.** Synthesized mainly by liver**.** Circulate in the blood in inactive form**.** Activated by presence of a pathogen.

Activated complement brings about four methods of pathogen destruction:

• Inflammation

• Immune clearance

• Phagocytosis

• Cytolysis

Three routes of complement activation:

• Classical pathway

• Alternative pathway

• Lectin pathway

Classical pathway

Requires antibody molecule. Thus, part of adaptive immunity. Antibody binds to antigen on surface of the pathogenic organism. Forms antigen–antibody (Ag–Ab) complex. Changes the antibody's shape. Exposing a pair of complement-binding sites/ Binding of the first complement (C1) sets off a reaction cascade called complement fixation. Results in a chain of complement proteins attaching to the antibody

Alternative pathway

Nonspecific, does not require antibody. C3 breaks down in the blood to C3a and C3b. C3b binds directly to targets such as human tumor cells, viruses, bacteria, and yeasts. Triggers cascade reaction with autocatalytic effect where more C3 is formed

Lectin pathway

Lectins: plasma proteins that bind to carbohydrates. Bind to certain sugars of a microbial cell surface. Sets off another cascade of C3 production.

Mechanisms of action of complement proteins:

1. Inflammation. C3a stimulates mast cells and basophils to secrete histamine and other inflammatory chemicals. Activates and attracts neutrophils and macrophages. Speeds pathogen destruction in inflammation
2. Immune clearance. C3b binds with antigen–antibody (Ag-Ab) complexes to red blood cells. These RBCs circulate through liver and spleen. Macrophages of those organs strip off and destroy the Ag–Ab complexes leaving RBCs unharmed. Principal means of clearing foreign antigens from the bloodstream.
3. Phagocytosis. Neutrophils and macrophages cannot phagocytize "naked" bacteria, viruses, or other pathogens. C3b assists them by opsonization. Coats microbial cells and serves as binding sites for phagocyte attachment. Makes the foreign cell more appetizing.
4. Cytolysis. C3b splits complement protein C5 into C5a and C5b. C5b binds to enemy cell. Attracts more complement proteins - membrane attack complex

forms. Forms a hole in the target cell. Electrolytes leak out, water flows in

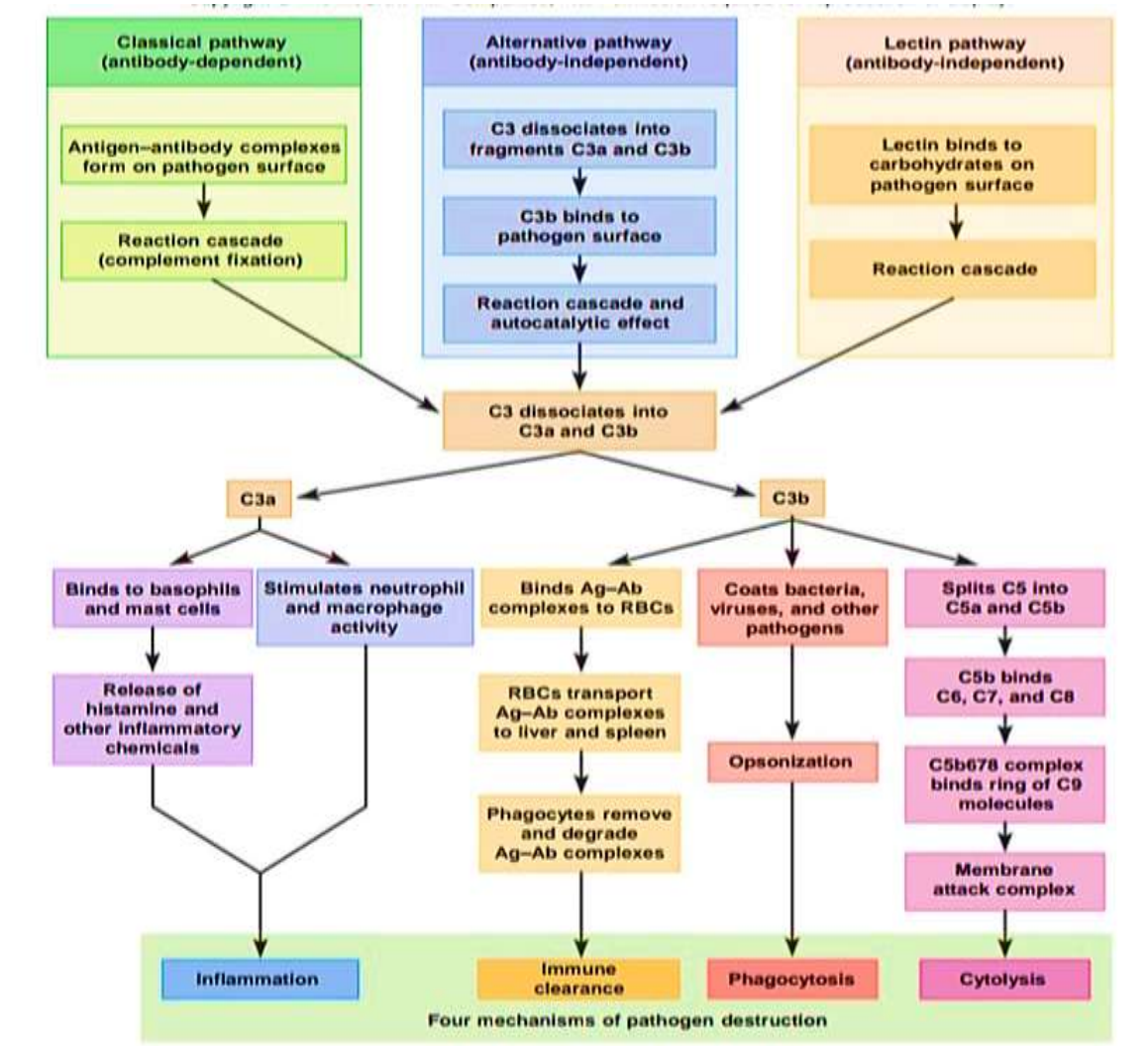


Figure 13. Activation of complement system

Fever

Fever - an abnormal elevation of body temperature. Synonym: pyrexia; febrile - pertaining to fever. Results from trauma, infections, drug reactions, brain tumors, and other causes. Fever is an adaptive defense mechanism that, in moderation, does better than harm. Promotes interferon activity. Elevates metabolic rate and accelerates tissue repair. Inhibits reproduction of bacteria and viruses.

The Action of a Natural Killer Cell

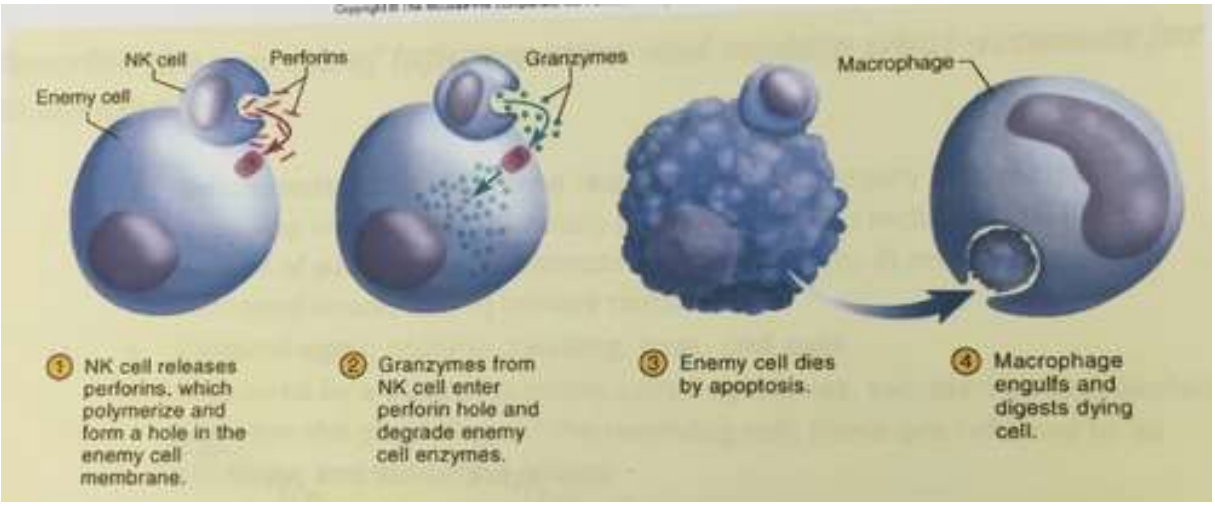


Figure 14. Activation of Natural Killer (NK) ctll

Antipyretics - fever-reducing medications. Include aspirin and ibuprofen that inhibit Prostaglandin E2 synthesis. Fever usually triggered by exogenous pyrogens - fever-producing agents, like Glycolipids on bacterial and viral surfaces. Endogenous pyrogens include polypeptides secreted by neutrophils and macrophages. These raise hypothalamic set point for body temperature. Neurons in the anterior hypothalamus secrete prostaglandin E2 which also raises set point

Stages of fever:

- **Onset** (body temperature rises).
- **Stadium**, (body temperature oscillates around new set point).
- **Defervescence** (body temperature returns to normal) Infection ends, set point returns to normal.

Feedback Control of the Macrophage and Neutrophil Responses. Although more than two dozen factors have been implicated in control of the macrophage response to inflammation, five of these are believed to play dominant roles. It is consisted of tumor necrosis factor (TNF), interleukin-1 (IL-1), granulocyte-monocyte colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), and monocyte colony stimulating factor (M-CSF). These factors are formed by activated macrophage cells in the inflamed tissues and in smaller quantities by other inflamed tissue cells. The cause of the increased production of granulocytes and monocytes by the bone marrow is mainly the three colony-stimulating factors, one of

which, GM-CSF, stimulates both granulocyte and monocyte production; the other two, G-CSF and M-CSF, stimulate granulocyte and monocyte production, respectively. This combination of TNF, IL-1, and colony-stimulating factors provides a powerful feedback mechanism that begins with tissue inflammation and proceeds to formation of large numbers of defensive white blood cells that help remove the cause of the inflammation[5][5].

Adaptive immunity

The germs that enter our bodies will stimulate the lymphocytes in the spleen and lymph nodes. This is an immune reaction which produces immunity with the production of antibodies and cytotoxic T cell against specific foreign agent, or antigen. Immune system - a large population of widely distributed cells that recognize foreign substances and act to neutralize or destroy them. Two characteristics distinguish immunity from nonspecific resistance.

- Specificity: immunity directed against a particular pathogen
- Memory: when reexposed to the same pathogen, the body reacts so quickly that there is no noticeable illness

• T cells cannot recognize antigens on their own. There special Antigen-presenting cells (APCs) probiding this function: Dendritic cells, macrophages, reticular cells, and B cells function as APCs.

• Function of APCs depends on major histocompatibility (MHC) complex proteins

- Act as cell "identification tags" that label every cell of your body as belonging to you
- Structurally unique for each individual, except for identical twins
- APCs alert the immune system to presence of foreign antigen
- Key to successful defense is to quickly mobilize immune cells against the antigen

• **Antigen processing**: APC encounters antigen Internalizes is by endocytosis Digests in into molecular fragments (epitopes) in the grooves of the MHC protein Wandering T cell inspect APCs for displayed antigens:

[5] Guyton and Hall Textbook of Medical Physiology, 12 Ed. 2011, p-430.

a) If APS only displays a self-antigen, the T cell disregards it

b) If APS displays a no self-antigen, the T cell initiated an immune attack

Antigen processing occurs the following steps**:**

1. Phagocytosis of antigen
2. Lysosome fuses with phagosome
3. Antigen and enzyme mix in phagolysosome
4. Antigen is degraded
5. Antigen residue is voided by exocytosis
6. Processed antigen fragments (epitopes) displayed on macrophage surface

• **Antigen -** any molecule that triggers an immune response

- Large molecular weights of over 10,000 amu
- Complex molecules with structures unique to the individual
- Proteins, polysaccharides, glycoproteins, glycolipids
- Characteristics enable body to distinguish "self" molecules from foreign ones

• **Epitopes** (antigenic determinants) - certain regions of an antigen molecule that stimulate immune responses.

• **Haptens -** too small to be antigenic in themselves. Can trigger an immune response by combining with a host macromolecule and creating a complex that the body recognizes as foreign. Subsequently, haptens alone may trigger response. Cosmetics, detergents, industrial chemicals, poison ivy, and animal dander. Penicillin binds to host proteins in allergic individuals

The immune system distinguishes two groups of foreign substances. One group consists of antigens that are freely circulating in the body. These include molecules, viruses, and foreign cells. A second group consists of self-cells that display aberrant MHC proteins. Aberrant MHC proteins can originate from antigens that have been engulfed and broken down (exogenous antigens) or from virus-infected and tumor cells that are actively synthesizing foreign proteins (endogenous antigens). Depending on the kind of foreign invasion, two different immune responses occur: humoral and cell mediated.

The humoral response (or antibody-mediated response) involves B cells that recognize antigens or pathogens that are circulating in the lymph or blood ("humor" is a medieval term for body fluid). The response follows this chain of events:

1. Antigens bind to B cells.

2. Interleukins or helper T cells costimulate B cells. In most cases, both an antigen and a costimulatory are required to activate a B cell and initiate B cell proliferation.

3. B cells proliferate and produce plasma cells. The plasma cells bear antibodies with the identical antigen specificity as the antigen receptors of the activated B cells. The antibodies are released and circulate through the body, binding to antigens.

4. B cells produce memory cells. Memory cells provide future immunity.

The cell-mediated response involves mostly T cells and responds to any cell that displays aberrant MHC markers, including cells invaded by pathogens, tumor cells, or transplanted cells. The following chain of events describes this immune response:

1. Self-cells or APCs displaying foreign antigens bind to T cells.

2. Interleukins (secreted by APCs or helper T cells) costimulate activation of T cells.

3. If MHC-I and endogenous antigens are displayed on the plasma membrane, T cells proliferate, producing cytotoxic T cells. Cytotoxic T cells destroy cells displaying the antigens.

4. If MHC-II and exogenous antigens are displayed on the plasma membrane, T cells proliferate, producing helper T cells. Helper T cells release interleukins (and other cytokines), which stimulate B cells to produce antibodies that bind to the antigens and stimulate nonspecific agents (NK and macrophages) to destroy the antigens. There are two groups of MHC molecules, and each group generates different markings on the plasma membrane:

1. MHC-I glycoproteins are produced by all body cells (except red blood cells). When a cell becomes cancerous or is invaded by a virus, unfamiliar proteins are synthesized in the cell. These proteins are endogenous antigens - that is, antigens produced inside the cell. Portions of these antigens are combined with MHC-I glycoproteins and, when displayed on the plasma membrane, indicate a nonself cell. 2. MHC-II glycoproteins

are produced only by antigen-presenting cells (APCs) - mostly macrophages and B cells. APCs actively ingest exogenous antigens - antigens that originate outside the cell. Exogenous antigens include viruses, toxins, pollen, or bacteria that are circulating in the blood, lymph, or body fluids. APCs break down the antigens and incorporate pieces of them with MHC-II glycoproteins. This aberrant display of MHC markers is recognized as nonself.

Cellular (cell-mediated) immunity

A form of specific defense in which the T lymphocytes directly attack and destroy diseased or foreign cells. The immune system remembers the antigens and prevents them from causing disease in the future. Uses 4 classes of T-cells: cytotoxic, helper, regulatory, and memory.

1. Cytotoxic T (TC) cells: killer T cells (T8, CD8, or CD8+) “Effectors” of cellular immunity; carry out attack on enemy cells
2. Helper T (TH) cells. Help promote TC cell and B cell action and nonspecific resistance
3. Regulatory T (TR) cells: T-regs. Inhibit multiplication and cytokine secretion by other Tcells; limit immune response. Like TH cells, TR cells can be called T4, CD4, CD4+
4. Memory T (TM) cells. Descend from the cytotoxic T cells. Responsible for memory in cellular immunity

• Both cellular and humoral immunity occur in three stages

1. **Recognition**- Recognize- antigen presentation and T cell activation
   APC encounters and processes an antigen

- Migrates to nearest lymph node
- Displays it to the T cells
- When T cells encounter a displayed antigen on the MHC protein, they initiate the immune response

2. **Attack** -React

• Helper and cytotoxic T cells play different roles in the attack phase of cellular immunity

- Helper T cells play central role in coordinating both cellular and humoral immunity
- When helper T cell recognizes the Ag-MHCP complex secretes interleukins that exert three effects
- Attract neutrophils and NK cells
- Attract macrophages, stimulate their phagocytic activity, and inhibit them from leaving the area
- Stimulate T and B cell mitosis and maturation
- Attack
- Cytotoxic T (TC) cells are the only T cells that directly attack other cells
- When TC cell recognizes a complex of antigen and MHC-I protein on a diseased or foreign cell, its “docks” on that cell
- After docking TC cells deliver a lethal hit of chemicals:
- Perforin and granzymes - kill cells in the same manner as NK cells
- Interferons - inhibit viral replication and recruit and activate macrophages
- Tumor necrosis factor (TNF) - aids in macrophage activation and kills cancer cells
- After releasing chemicals, TC cell goes off in search of another enemy cell while chemical do their work

Memory - Remember Immune memory follows primary response in cellular immunity.

- Following clonal selection, some TC and TH cells become memory cells
- Long-lived
- More numerous than naive T cells
- Fewer steps to be activated, so they respond more rapidly
- T cell recall response

- Upon re-exposure to same pathogen later in life, memory cells launch a quick attack so that no noticeable illness occurs
- The person is immune to the disease

Suppressor T Cells Much less is known about the suppressor T cells than about the others, but they are capable of suppressing the functions of both cytotoxic and helper T cells. It is believed that these suppressor functions serve the purpose of preventing the cytotoxic cells from causing excessive immune reactions that might be damaging to the body's own tissues. For this reason, the suppressor cells are classified, along with the helper T cells, as regulatory T cells. It is probable that the suppressor T-cell system plays an important role in limiting the ability of the immune system to attack a person's own body tissues, called immune tolerance, as we discuss in the next section [6][6].

Humoral Immunity

• Humoral immunity is a more indirect method of defense than cellular immunity

• B lymphocytes of humoral immunity produce antibodies that bind to antigens and tag them for destruction by other means, while the cellular immunity attacks the enemy cells directly

• Works in three stages like cellular immunity

1. Recognition. Immunocompetent B cell has thousands of surface receptors for one antigen. Activation begins when an antigen binds to several of these receptors, links them together and is taken into the cell by receptor-mediated endocytosis. Small molecules are not antigenic because they cannot link multiple receptors together. B cell processes (digests) the antigen. Links some of the epitopes to its MHC-II proteins. Displays these on the cell surface

2. Attack. Usually, B cell response goes no further unless a helper T cell binds to this Ag - MHCP complex. Bound TH cell secretes interleukins that activate B cell, Triggers clonal selection. B cell mitosis gives rise to a battalion of identical B cells programmed against the same antigen. Most differentiate into plasma cells- Larger

[6] Guyton and Hall Textbook of Medical Physiology, 12 Ed. 2011, p-442.

than B cells and contain an abundance of rough ER. Plasma cells secrete antibodies at a rate of 2,000 molecules per second during their life span of 4 to 5 days. First exposure to antigen triggers production of IgM antibodies, later exposures to the same antigen, IgG - Antibodies travel through body in blood, other body fluids. Antibodies bind to antigen, render it harmless, "tag it" for destruction

3. Memory. Some B cells differentiate into memory cells.

Immunoglobulin (Ig) - an antibody - a defensive gamma globulin found in blood plasma, tissue fluids, body secretions, and some leukocyte membranes

Antibody monomer - the basic structural unit of an antibody

- Composed of four polypeptide chains linked by disulfide (–S–S–) bonds
- Two larger heavy chains about 400 amino acids long

• Heavy chains have a hinge region where antibody is bent

- Two light chains about half as long
- Variable (V) region in all four chains

• Gives the antibody its uniqueness

- Antigen-binding site: formed from the V regions of the heavy and light chain on each arm

• Attaches to the epitope of an antigen molecule

- Constant (C) region has the same amino acid sequence within one person and determines mechanism of antibody action

The 5 main immunoglobulins:

TYPE	WHERE FOUND	STRUCTURE	FUNCTION
IgM	attached to the B cell; free in Plasma	Cluster of many Y shapes bound together	bond to B cell membrane serves as antigen receptor; 1st Ig class released to plasma-by-plasma cells during response, potent agglutinating agent, **fixes complement**

IgA	in plasma	Two Y shapes	protects **mucosal** surfaces
IgD	attached to B cell	Simple Y shape	**activation of B cell**
IgG	in plasma	Simple Y shape	**main antibody** of both primary and secondary responses, crosses placenta and provides passive immunity to fetus; fixes complement
IgE	in skin; mucosa of gastro-intestinal and respiratory tracts, and tonsils	Simple Y shape	binds to mast cells and basophils and triggers **release of histamine** and other chemicals that mediate **inflammation** and certain **allergic reactions**

• Antibody classes are named for the structure of their C region

IgA: monomer in plasma; dimer in mucus, saliva, tears, milk, and intestinal secretions. Prevents pathogen adherence to epithelia and penetrating underlying tissues. Provides passive immunity to newborns.

IgD: monomer; B cell transmembrane antigen receptor. Thought to function in B cell activation by antigens.

IgE: monomer; transmembrane protein on basophils and mast cells.

• Stimulates release of histamine and other chemical mediators of inflammation and allergy

• Attracts eosinophils to parasitic infections

• Produces immediate hypersensitivity reactions.

IgG: monomer; constitutes 80% of circulating antibodies

• Crosses placenta to fetus, secreted in secondary immune response, complement fixation

IgM: pentamer in plasma and lymph.

• Secreted in primary immune response, agglutination, complement fixation

• Human immune system capable of as many as 1 trillion different antibodies

• But there are as few as 20,000 genes in the human genome.

Antibodies have four mechanisms of attack against antigens:

• **Neutralization:** Antibodies mask pathogenic region of antigen

• **Complement fixation**: IgM or IgG bind to antigen, change shape and initiate complement binding which leads to inflammation, phagocytosis, immune clearance, or cytolysis. Primary defense against foreign cells, bacteria, and mismatched RBCs.

• **Agglutination**: Antibody has 2 to 10 binding sites; binds to multiple enemy cells, immobilizing them from spreading

• **Precipitation**: Antibody binds antigen molecules (not cells); creates antigen–antibody complex that precipitates, allowing them to be removed by immune clearance or phagocytized by eosinophils. These direct actions of antibodies attacking the antigenic invaders often are not strong enough to play a major role in protecting the body against the invader. Most of the protection comes through the amplifying effects of the complement system.[7]

Memory

• Primary immune response - immune reaction brought about by the first exposure to an antigen

- Appearance of protective antibodies delayed for 3 to 6 days while naive B cells multiply and

differentiate into plasma cells

- As plasma cells produce antibodies, the antibody titer (level in the blood plasma) rises

• IgM appears first, peaks in about 10 days, soon declines

• IgG levels rise as IgM declines, but IgG titer drops to a low level within a month

• Primary response leaves one with an immune memory of the antigen

- During clonal selection, some of the cells becomes memory B cells

[7] Guyton and Hall Textbook of Medical Physiology, 12 Ed. 2011, p-432.

- Found mainly in germinal centers of the lymph nodes
- Mount a very quick secondary response

• Secondary (anamnestic) response - if re-exposed to the same antigen

- Plasma cells form within hours
- IgG titer rises sharply and peaks in a few days
- Response is so rapid that the antigen has little chance to exert a noticeable effect on the body
- No illness results
- Low levels of IgM also secreted (then quickly decline)
- IgG remain elevated for weeks to years

• Conferring long-lasting protection

• Memory does not last as long in humoral immunity as in cellular immunity

Forms of Immunity

All forms of adaptive immunity can be described as either active or passive. Active immunity refers to the activation of an individual's own adaptive immune defenses, whereas passive immunity refers to the transfer of adaptive immune defenses from another individual or animal. Active and passive immunity can be further subdivided based on whether the protection is acquired naturally or artificially.

Natural active immunity Production of one's own antibodies or T cells as a result of infection or natural exposure to antigen. It is adaptive immunity that develops after natural exposure to a pathogen. Examples would include the lifelong immunity that develops after recovery from a chickenpox or measles infection (although an acute infection is not always necessary to activate adaptive immunity). The length of time that an individual is protected can vary substantially depending upon the pathogen and antigens involved. For example, activation of adaptive immunity by protein spike structures during an intracellular viral infection can activate lifelong immunity, whereas activation by carbohydrate capsule antigens during an extracellular bacterial infection may activate shorter-term immunity.

Natural passive immunity Temporary immunity that results from antibodies produced by another person. Fetus acquires antibodies from mother through placenta,

milk. It involves the natural passage of antibodies from a mother to her child before and after birth. IgG is the only antibody class that can cross the placenta from mother's blood to the fetal blood supply. Placental transfer of IgG is an important passive immune defense for the infant, lasting up to six months after birth. Secretory IgA can also be transferred from mother to infant through breast milk.

Artificial passive immunity. refers to the transfer of antibodies produced by a donor (human or animal) to another individual. Temporary immunity that results from the injection of immune serum (antibodies) from another person or animal. Treatment for snakebite, botulism, rabies, tetanus, and other diseases. This transfer of antibodies may be done as a prophylactic measure (i.e., to prevent disease after exposure to a pathogen) or as a strategy for treating an active infection. For example, artificial passive immunity is commonly used for post-exposure prophylaxis against rabies, hepatitis A, hepatitis B, and chickenpox (in high-risk individuals). Active infections treated by artificial passive immunity include cytomegalovirus infections in immunocompromised patients and Ebola virus infections. In 1995, eight patients in the Democratic Republic of the Congo with active Ebola infections were treated with blood transfusions from patients who were recovering from Ebola. Only one of the eight patients died (a 12.5% mortality rate), which was much lower than the expected 80% mortality rate for Ebola in untreated patients. Artificial passive immunity is also used for the treatment of diseases caused by bacterial toxins, including tetanus, botulism, and diphtheria.

Artificial active immunity - Production of one's own antibodies or T cells as a result of vaccination against disease. It is the foundation for vaccination. It involves the activation of adaptive immunity through the deliberate exposure of an individual to weakened or inactivated pathogens, or preparations consisting of key pathogen antigens.

- Vaccine: consists of dead or attenuated (weakened) pathogens that stimulate the immune response without causing the disease.
- Booster shots: periodic immunizations to stimulate immune memory to maintain a high level of protection.

HYPERSENSITIVITY REACTIONS

Immune response may be:

- Hyperreactive -Too vigorous
- Hyporeactive - Too weak
- Distractive Misdirected against wrong targets.

Hypersensitivity - an excessive immune reaction against antigens that most people tolerate.

Includes:

- Alloimmunity: reaction to transplanted tissue from another person
- Autoimmunity: abnormal reactions to one's own tissues
- Allergies: reactions to environmental antigens (allergens) - dust, mold, pollen, vaccines, bee and wasp venom, poison ivy and other plants; foods such as nuts, milk, eggs, and shellfish; drugs such as penicillin, tetracycline, and insulin etc.

Four kinds of hypersensitivity based on the type of immune agents involved (antibodies or T cells) and their method of attack on the antigen

- Type I acute (immediate) hypersensitivity: very rapid response
- Type II and Type III subacute hypersensitivity: slower onset (1 to 3 hours after exposure) Last longer (10 to 15 hours)

• Types I, II, and III are quicker **antibody-mediated** responses

- Type IV: delayed **cell-mediated** response

Hypersensitivity reaction Type I

- Includes most common allergies
- IgE-mediated reaction that begins within seconds of exposure to allergen
- Usually subsides within 30 minutes, although it can be severe to fatal
- Allergens bind to IgE on the membranes of basophils and mast cells and stimulate them to secrete histamine and other inflammatory and vasoactive chemicals, which then trigger glandular secretion, vasodilation, increased capillary permeability, smooth muscle spasms, and other effects
- Clinical signs include: Local edema, mucus hypersecretion and congestion, watery eyes, runny nose, hives, and sometimes cramps, diarrhea, and vomiting

Hypersensitivity includes the production of antibodies (IgE) towards environmental substances such as pollens, home dust, food, and others which are known as allergens. The pathology effect which takes place is as a result of mast cell activities that secretes enzymes and therefore, causes muscle contraction, overproduction of mucus and finally causing clinical symptoms such as allergic diseases. An example of an allergic disease is asthma, allergic rhinitis (runny nose), and others.

• **Anaphylaxis**

- Immediate, severe type I reaction
- Local anaphylaxis can be relieved with antihistamines

• Anaphylactic shock

- Severe, widespread acute hypersensitivity that occurs when an allergen is introduced into the bloodstream or when certain foods are ingested by an allergic individual
- Characterized by bronchoconstriction, dyspnea (labored breathing), widespread vasodilation, circulatory shock, and sometimes death
- Antihistamines are inadequate by themselves
- Epinephrine relieves the symptoms by dilating bronchioles, increasing cardiac output, and restoring blood pressure
- Fluid therapy and respiratory support are sometimes required

• **Asthma**

- Most common chronic illness in children
- Allergic (extrinsic) asthma is most common form

• Respiratory crisis triggered by inhaled allergens
• Stimulate plasma cells to secrete IgE
• Binds to most cells in respiratory mucosa
• Mast cells release a mixture of inflammatory chemicals
• Triggers intense airway inflammation

- Nonallergic (intrinsic) asthma

• Triggered by infections, drugs, air pollutants, cold dry air, exercise, or emotions
• More common in adults, but effects are the same:

- Bronchospasms within minutes

- Severe coughing, wheezing, and sometimes fatal suffocation
- Second respiratory crisis often occurs 6 to 8 hours later
- Interleukins attract eosinophils to bronchial tissue
- Secrete proteins that paralyze respiratory cilia
- Severely damage epithelium leading to scarring and long-term damage to lungs
- Bronchioles become edematous and plugged with thick, sticky mucus

• Treatment: Epinephrine and other β-adrenergic stimulants to dilate airway and restore breathing, and with inhaled corticosteroids to minimize inflammation and long-term damage.

Hypersensitivity reaction Type II

Type II (antibody-dependent cytotoxic)

- Occurs when IgG or IgM attacks antigens bound to cell surfaces
- Reaction leads to complement activation
- Lysis or opsonization of the target cell
- Macrophages phagocytize and destroy opsonized platelets, erythrocytes, or other cells involves antibodies (IgG & IgM) towards surface-bound proteins, or cell membranes, or our body tissue.

The pathology effects which happen include lysis and cell destruction. Example diseases are such as autoimmune haemolytic anemia (AIHA), myasthenia gravis (MG), autoimmune diabetes (Type 1) and others. In AIHA, red blood cells lysis due to autoantibodies against the red blood cells takes place causing anemia. In MG, there are autoantibodies which destroys/blocks acetylcholine receptors and therefore causing muscle-nerve weakening. Meanwhile in autoimmune diabetes, there are autoantibodies that destroys insulin hormone production cells and therefore, causing symptoms of diabetes. Blood transfusion reaction, causing hemolysis, pemphigus vulgaris, and some drug reactions.

Hypersensitivity reaction Type III (immune complex)

Involves antibody production towards soluble protein in the body. IgG or IgM form antigen-antibody complexes, and these circulating immune complexes (CIC) circulate in our blood system and precipitate beneath endothelium of blood vessels and other

tissues. CIC may precipitate in certain organs such as kidney, joints, and others. At the base of this precipitation, at site activate complement and trigger intense inflammation and a demolishing or tissue lysis may occur. For example, glomerulonephritis in the glomerulus of the kidney or arthritis of the joints. Erythematosus Lupus Systemic (SLE).

SLE is an autoimmune disease, with prolonged chronic inflammation which involves numerous organs. Among the main symptoms of SLE include rashes known as butterfly rashes in the face (rashes which resembles butterflies). Rashes may also present in body parts exposed to sunlight such as the neck and arms as patients develop sensitive skin towards sunlight. SLE's main symptoms are serious with joint arthritis and renal disruption (glomerulonephritis). Apart from that, it may also damage the brain, heart, lungs, and the blood circulatory system. The autoantibody profile which includes anti-nuclear antibody (ANA), anti-ds DNA antibody have been shown to have an association with clinical manifestations in Malay SLE patients.

Hypersensitivity reaction Type IV (delayed)

- Cell-mediated reaction in which the signs appear 12 to 72 hours after exposure
- Begins when APCs in lymph nodes display antigens to helper T cells
- T cells secrete interferon and cytokines that activate cytotoxic T cells and macrophages
- Result is a mixture of nonspecific and immune responses
- Examples: haptens in cosmetics and poison ivy, graft rejection, TB skin test, dermato-myositis disease.

It does not involve antibody but on the contrary involves the activities of cytotoxic T cells and activated macrophages which destroy our own cell and body tissue. For example, in the dermato-myositis disease, lysis happens to the muscle by specific cytotoxic T cells towards muscle cells which weaken the function of the muscle.

Autoimmune Diseases

Failure of the Tolerance Mechanism Causes **Autoimmune Diseases.** Sometimes people lose their immune tolerance of their own tissues. This occurs to a greater extent the older a person becomes. It usually occurs after destruction of some of the body's

own tissues, which releases considerable quantities of "self-antigens" that circulate in the body and presumably cause acquired immunity in the form of either activated T cells or antibodies. Several specific diseases that result from autoimmunity include rheumatic fever, in which the body becomes immunized against tissues in the joints and heart, especially the heart valves, after exposure to a specific type of streptococcal toxin that has an epitope in its molecular structure similar to the structure of some of the body's own self-antigens; one type of glomerulonephritis, in which the person becomes immunized against the basement membranes of glomeruli; myasthenia gravis, in which immunity develops against the acetylcholine receptor proteins of the neuromuscular junction, causing paralysis; and lupus erythematosus, in which the person becomes immunized against many different body tissues at the same time, a disease that causes extensive damage and often rapid death[8][8]. **Autoimmune diseases** - failures of self-tolerance

• Immune system does not correctly distinguish self-antigens from foreign ones. Produces autoantibodies that attack body's own tissues

• Three reasons for failure of self-tolerance:

1) Cross-reactivity

• Some antibodies against foreign antigens react to similar self-antigens

• Rheumatic fever - streptococcus antibodies also react with heart valves

2) Abnormal exposure of self-antigens in the blood

• Some of our native antigens are not normally exposed to blood

• Blood - testes barrier isolates sperm from blood

3) Changes in structure of self-antigens

• Viruses and drugs may change the structure of self-antigens or cause the immune system to perceive them as foreign

• Self-reactive T cells

Not all are eliminated in thymus and are normally kept in check by regulatory T (TR) cells.

[8] Guyton and Hall Textbook of Medical Physiology, 12 Ed. 2011, p-442.

Immunodeficiency Diseases

• Immune system fails to react vigorously enough

• Severe combined immunodeficiency disease (SCID)

- Hereditary lack of T and B cells

- Vulnerability to opportunistic infection and must live in protective enclosures

• Acquired immunodeficiency syndrome (AIDS)

- Nonhereditary diseases contracted after birth

- Group of conditions that severely depress the immune response

- AIDS is caused by infection with the human immunodeficiency virus (HIV)

- Invades helper T cells, macrophages, and dendritic cells by "tricking" them to internalize viruses by receptor - mediated endocytosis.

- Reverse transcriptase (retrovirus) uses viral RNA as template to synthesize DNA.

- New DNA inserted into host cell DNA (may be dormant for months to years).

- When activated, it induces the host cell to produce new viral RNA, capsid proteins, and matrix proteins.

- They are coated with bits of the host cell's plasma membrane.

- Adhere to new host cells and repeat the process

- By destroying TH cells, HIV strikes at the central coordinating agent of nonspecific defense, humoral immunity, and cellular immunity

- Incubation period ranges from several months to 12 years

- Early symptoms: flu-like symptoms of chills and fever

- Progresses to night sweats, fatigue, headache, extreme weight loss, lymphadenitis

- Normal TH count is 600 to 1,200 cells/mL of blood, but in AIDS it is less than 200 cells/mL

- Person susceptible to opportunistic infections (Toxoplasma, Pneumocystis, herpes simplex virus, cytomegalovirus, or tuberculosis)

- Candida (thrush): white patches on mucous membranes

- Kaposi sarcoma: cancer originates in endothelial cells of blood vessels; causes purple lesions in skin

- HIV is transmitted through blood, semen, vaginal secretions, breast milk, or across the placenta
- Most common means of transmission
- Sexual intercourse (vaginal, anal, oral)
- Contaminated blood products
- Contaminated needles

• Not transmitted by casual contact.

• Undamaged latex condom is an effective barrier to HIV.

Self-control questions

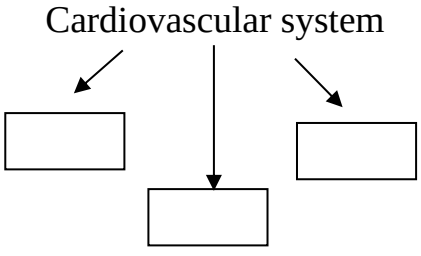
1. Define adaptive immunity.
2. Contrast cellular and humoral immunity, active and passive immunity, and natural and artificial immunity.
3. Describe the chemical properties of antigens.
4. Describe and contrast the development of T and B lymphocytes.
5. Describe the general roles played by lymphocytes, antigen-presenting cells, and interleukins in the immune response.
6. Immune System Disorders
7. Distinguish between the four classes of immune hypersensitivity and give an example of each.
8. Explain the cause of anaphylaxis and distinguish local anaphylaxis from anaphylactic shock.
9. State some reasons immune self-tolerance may fail, and give examples of the resulting disease.
10. Describe the pathology of immunodeficiency diseases, especially AIDS.
11. Cellular Immunity
12. List the types of lymphocytes involved in cellular immunity and describe the roles they play.
13. Describe the process of antigen presentation and T cell activation.
14. Describe how T cells destroy enemy cells.
15. Explain the role of memory cells in cellular immunity.

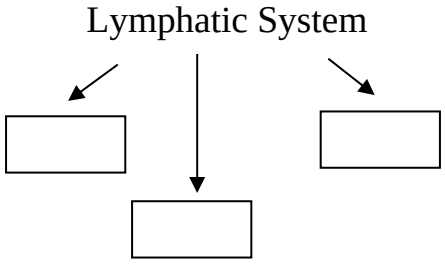
16. Humoral Immunity.
17. Explain how B cells recognize and respond to an antigen.
18. Describe the structure, types, and actions of antibodies.
19. Explain the mechanism of memory in humoral immunity.
20. Compare and contrast cellular and humoral immunity.
21. Nonspecific Resistance
22. Identify the body's three lines of defense against pathogens.
23. Contrast nonspecific resistance with immunity.
24. Describe the defensive functions of each kind of leukocyte.
25. Describe the role of the complement system in resistance and immunity.
26. Describe the process of inflammation and explain what accounts for its cardinal signs.
27. Describe the body's other nonspecific defenses.
28. Describe the compare the structure of B-cell receptors and T-cell receptors.
29. Compare T-dependent and T-independent activation of B cells.
30. Compare the primary and secondary antibody responses.
31. What types of molecules serve as the BCR?
32. What are the differences between TCRs and BCRs with respect to antigen recognition?
33. Which molecule classes are T-dependent antigens and which are T-independent antigens?

TEST

Task 1.

Complete the diagram by filling the missing components:





Task verification:

Cardiovascular system consists of heart, blood vessels and blood.

Lymphatic System consists of lymph organs, lymph vessels and lymph.

Task 2.

Follow the movement of lymph through the vessels:

Build a logical chain of lymph outflow by entering the numbers in brackets corresponding to the words.

Lymph nodes and filters1, tissue fluid and lymph 2, lymphatic capillaries 3, thoracic duct 4, lymphatic vessels 5, cell vital substances nutrients 6, jugular veins 7.

Task verification:

Tissue fluid and lymph (2) —> cell materials and nutrients (6) —> lymph capillaries (3) lymphatic vessels (5) —> lymph nodes and filters (1) —> thoracic duct (4) —> cervical veins (7).

Task 3. Describe the difference between Blood plasma, tissue fluid, and lymph.

Task verification:

- Blood Plasma turns into —> Tissue fluid when it leaves a blood capillary to deliver O2

- Tissue Fluid becomes —>Lymph when it enters the lymphatic capillary

(Tissue fluid = blood plasma - plasma proteins)

- Lymph is just Tissue fluid that had entered the lymphatic capillary, but they are chemically identical

Which of the following will increase lymph flow?

A. Elevated cardiovascular capillary pressure
B. Increased plasma colloid osmotic pressure
C. Decreased interstitial fluid colloid osmotic pressure
D. Decreased cardiovascular capillary permeability

Correct answer: A.

QUIZZES:

1. What is found in the spleen, red bone marrow, and lymph nodes that fight microbes?

a) Lymph
b) Natural killer cells
c) Inflammation
d) Red blood cells

2. What makes the lymph fluid move through the body?

a) Gravity and skeletal muscle contractions
b) Pressure changes caused by breathing and gravity
c) He beating of the heart and gravity
d) Muscle contractions and pressure changes caused by breathing

3. What happens in the lymph nodes as lymph flows through them

a) Reticular fibers filter out debris
b) Foreign substances are destroyed
c) Plasma and mature T cells are added
d) A, B, and C are correct

4. What is the role of mucus in the immune system?

a) To transport macrophages
b) To transport B and T cells
c) To trap microbes
d) To supply lymph

5. The role of the lacrimal glands is to ___

a) Produce mucous to protect the throat
b) Produce tears to protect the eyes
c) Produce mucous to protect the nose
d) Produce saliva to protect the mouth

6. What is the role of cilia in the mucous membrane?

a) To move mucous
b) To warm the throat

c) To absorb water

d) To store B and T cells

7. Which substance is secreted by glands, then deposited on the surface of the epidermal cells, where it makes a protective barrier against pathogens.

a) Gastric juice

b) Tears

c) Sebum

d) Urine

8. Which substance below uses pH to keep microbial invaders out of the cervical region?

a) Urine

b) Stomach

c) Mucous

d) Vaginal secretions

9. How does fever affect microbes?

a) It slows them down when moving

b) It makes them swell

c) It dehydrates them

d) It slows their growth

10. What passes through the urethra to clear it of microbes?

a) Lymph

b) Blood

c) Mucous

d) Urine

11. When tissue is inflamed, the tissue is warm. Why?

a) Blood clotting creates heat

b) The increased blood flow makes it warm

c) Muscle contractions cause heat to be released

d) The area around the wound cools, making the wound feel warmer

12. Not long after sticking yourself with a pin, you see pus draining from the wound. What is pus?

a) Dead immune cells
b) Interstitial fluid
c) Lymphatic fluid
d) Platelets

13. An antigen is...

a) A type of immune cell
b) A substance that the immune system recognizes as foreign
c) A cell that attacks microbes
d) A symptom of an allergic attack

14. Self tolerance is...

a) The ability to tolerate illness
b) The ability to withstand a fever
c) The ability to allow certain pathogens to exist in the body
d) The immune system's ability to recognize tissues as being self

15. An autoimmune disease is..

a) The loss of immunity
b) The loss of self tolerance
c) The loss of an antigen
d) The loss of lymph

16. Imagine that you are a pathogen in the human body. Suddenly, a large cell approaches you. The cell "reads" the antigens on your cell membrane, then it clamps on to you and prevents you from reproducing. In a few hours, you die. What kind of cell just killed you?

a) Macrophage
b) T-cell
c) Red blood cell
d) B-cell

17. Aids is ...

a) An opportunistic disease
b) The cause of HIV
c) The last stage in HIV infection
d) The source of the HIV infection

18. The HIV virus can be killed by which item?

a) The immune system
b) Opportunistic diseases
c) Detergents
d) All of the above

19. As the body ages, the T-cells and B-cells become less responsive to ___

a) Antigens
b) Self tolerance
c) Antibodies
d) Immunity

20. Which organ receives immature T cells, then raises them to maturity- then releases them?

a) Thymus
b) Liver
c) Spleen
d) Heart
e) Hypothalamus

21. Which of the following would be least likely to be found in lymph fluid?

a) Fatty acids
b) Bacteria
c) T cells
d) Red blood cells

22. Mature T-lymphocytes accumulate at which of the following organs, where they play a central role in the adaptive immune response?

a) Thymus
b) Appendix
c) Bone marrow
d) Lymph nodes

23. The lining of lymphatic vessels is composed of which of the following cell type?

a) simple squamous epithelium
b) simple cuboidal epithelium
c) stratified squamous epithelium
d) stratified cuboidal epithelium

24. Lymph from the right lymphatic duct enters the systemic circulation at what point?

a) The junction of the right subclavian vein and the jugular vein
b) The junction of the left subclavian vein and the jugular vein
c) At the proximal aorta
d) At the femoral artery

25. Scientists isolate the lymph fluid from the right thoracic duct of a fasted (~24 hours) experimental animal 20 minutes after a meal. After chemical analysis, they find a high concentration of fatty acid (~2% of total volume) and no detectable amounts a free carbohydrate: what does such data indicate about the composition of the meal?

a) The meal contained fats but no carbohydrates
b) The meal contained carbohydrates but not fats
c) The meal contained fats, but no conclusion about carbohydrates is warranted from the data
d) No conclusions can be drawn regarding the fat or carbohydrate content of the meal from this data

26. Which of the following is not a commonality shared by large lymph vessels and cardiovascular veins (veins of the cardiovascular system)?

a) Forms a closed system

b) Surrounded by smooth muscle

c) Valves to insure directionality of flow

d) Partly composed of individual epithelial cells

27. Which of the following will increase lymph flow?

a) Increased plasma colloid osmotic pressure

b) Elevated cardiovascular capillary pressure

c) Decreased cardiovascular capillary permeability

d) Decreased interstitial fluid colloid osmotic pressure

28. Which of the following is not a basic function of the lymphatic system?

a) Transport of immune cells

b) Transport of proteins, fats, and other macromolecules

c) Maintenance of blood pressure

d) Equalization of fluid distribution throughout the body

29. Lymph from which of the following parts of the body does not enter into the systemic circulation through the thoracic duct?

a) Lymph from the left arm

b) Lymph from the right arm

c) Lymph from the lower body

d) Lymph from the left side of the head

30. Which of the following best describes the immediate fate of high-molecular weights proteins that are removed from the interstitial spaces of the body and taken up by the lymphatic system?

a) Drainage into the colon for elimination.

b) Drainage into the urinary tract for elimination.

c) Emptying into the circulatory system at the jugular vein.

d) Emptying into the circulatory system at the aorta.

31. Of the approximately 20 liters of fluid that filters from the blood into tissue spaces each day, roughly how much enters the lymphatic system?

a) 3 liters

b) 17 liters

c) 20 liters

d) 22 liters

32. Which lymphatic duct returns lymph collected from the left side of the body and from below the thorax?

a) the right subclavian vein

b) the thoracic duct

c) the right lymphatic duct

33. Why are lipids and lipid-soluble vitamins transported by the lacteals of the lymphatic system, rather than in the blood?

a) they are too fragile

b) they are too large

c) they are too small

34. Skeletal muscle contractions, the pull of the skin and fascia on movement, and pressure changes during breathing move lymph along the lymphatic vessels. What are these forces called?

a) internal pressures

b) circulation pressures

c) external pressures

35. The internal pressure which helps move lymph within the lymphatic vessels comes from smooth muscle contraction in ...

a) the walls of the blood capillaries

b) the walls of the lymphatic vessels

c) the walls of the heart

36. The lymph vessels which drain lymph out of a lymph node are referred to as ...

a) afferent lymph vessels

b) subclavian vessels

c) efferent lymph vessels

37.Where in the body are lymphocytes formed?

a) in the spleen

b) in the red bone marrow

c) in the thymus

38. Which of the following are one of the main types of lymphocytes?

a) T cells

b) A cells

c) C cells

39. The primary site for the maturation of T cells is ...

a) the red bone marrow

b) the thymus

c) the spleen

40. In specific (or 'adaptive') immunity, which type of lymphocyte produces antibodies?

a) B cells

b) T cells

c) natural killer cells

41. Which type of cells produce cytokines to direct the immune response?

a) the cytotoxic T cells

b) the B cells

c) the T helper cells

42. What is synthesised in the white pulp of the spleen?

a) the B cells

b) the lymph

c) the antibodies

43. What is the name of the clear fluid carried within lymph vessels?

a) the cytoplasm

b) the lymph

c) the plasma

44. Lymph is initially formed from ...

a) the blood plasma

b) the cytoplasm

c) the interstitial fluid

45. The lymphatic vessels carry the lymph ...

a) towards the intestines

b) towards the heart

c) away from the heart

46. The lymph within the lymphatic vessels is eventually emptied into the blood stream via ..

a) the subclavian veins

b) the subclavian arteries

c) the hepatic veins

47. The movement of lymph through the lymphatic system depends on ...

a) muscle contraction

b) the heart

c) gravity

48. Lymph is prevented from moving backwards in the lymphatic system by which of the following?

a) muscular contraction

b) valves within the vessels

c) gravity

49. A second function of the lymphatic system is to absorb and transport which of the following from the digestive tract?

a) fats

b) water

c) sugars

50. The special lymphatic capillaries responsible for the absorption of fats, known as lacteals, can be found in ...

a) the esophagus

b) the stomach

c) the intestinal villi

Answers:

1	B	9	D	17	C	25	C	33	B	41	C	49	A
2	D	10	D	18	C	26	A	34	C	42	C	50	C
3	D	11	B	19	A	27	B	35	B	43	B		
4	C	12	A	20	A	28	C	36	A	44	A		
5	B	13	B	21	D	29	D	37	B	45	C		
6	A	14	D	22	D	30	D	38	A	46	A		
7	C	15	B	23	A	31	A	39	B	47	A		
8	D	16	B	24	A	32	B	40	A	48	B		

INDEPENDENT WORK OF STUDENT

Themes for reports:

1. Mechanism of adaptive immunity. Cellular Immunity. Humoral Immunity.
2. Contrast cellular and humoral immunity, active and passive immunity, and natural and artificial immunity.
3. Immune System Disorders. Distinguish between the four classes of immune hypersensitivity and give an example of each.
4. Immune System Disorders. Explain the cause of anaphylaxis and distinguish local anaphylaxis from anaphylactic shock.
5. State some reasons immune self-tolerance may fail, and give examples of the resulting disease.
6. Pathology of immunodeficiency diseases, especially AIDS.

REFERENCES

1. Guyton-and-Hall-Textbook-of-Medical-Physiology-14th-Ed.
2. K. Sembulingam - Essentials of Medical Physiology, 6th Edition
3. Kaplan medical-USMLE_STEP_1_Lecture_Notes_2016
4. K. Sembulingam, Prema Sembulingam Essentials of Medical Physiology, 6-th Edition, 2012.-1048p.
5. Starling E. H. (1968). Principles of Human Physiology, ed. Davson H. and Eggleton G., 14th end, 1668 pages. J & A Churchill, London.
6. Mountcastle V. B. (ed) (1968). Medical Physiology. 12th edn. CV Mosby Company, Saint Louis.
7. William F. Ganong, Review of Medical Physiology, 20th Edition. Text book, 2019.
8. Linda S. Costanzo Ph.D., BRS Physiology. 7th edition, 2017.
9. Suzanne Keller Elaine Marieb, Essentials of Human Anatomy & Physiology, Global Edition, 2017.
10. Walter F. Boron MD, PhD Emile L. Boulpaep MD Medical Physiology. Study smart with student consult. 3rd Edition. 2016.
11. Dejaco C., Duftner C., Grubeck-Loebenstein B., Schirmer M. Imbalance of regulatory T cells in human autoimmune diseases. *Immunology*. 2006; 117:289–300.
12. DeWitt WS, Emerson RO, Lindau P., Vignali M., Snyder TM, Desmarais C., Sanders C., Utsugi H., Warren EH, McElrath J, et al. Dynamics of the cytotoxic T cell response to a model of acute viral infection. *J Virol.* 2015; 89:4517–4526.
13. Stritesky GL, Jameson SC, Hogquist KA. Selection of self-reactive T cells in the thymus. *Annu Rev Immunol.* 2012; 30:95–114.
14. Bronte V, Pittet MJ. 2013. The spleen in local and systemic regulation of immunity. Immunity 39:806–18.
15. Negrini D., Moriondo A. 2011. Lymphatic anatomy and biomechanics. J. Physiol. 589:2927–34.

16. Lammermann T, Bader BL, Monkley SJ, Worbs T, Wedlich-Soldner R, et al. 2008. Rapid leukocyte migration by integrin-independent flowing and squeezing. Nature 453:51–55.
17. Johnson LA, Clasper S, Holt AP, Lalor PF, Baban D, Jackson DG. 2006. An inflammation-induced mechanism for leukocyte transmigration across lymphatic vessel endothelium. J. Exp. Med. 203:2763–77.
18. Schmid-Schonbein GW. 1990. Microlymphatics and lymph flow. Physiol. Rev. 70:987–1028
19. Scallan JP, Zawieja SD, Castorena-Gonzalez JA, Davis MJ. 2016. Lymphatic pumping: mechanics, mechanisms and malfunction. J. Physiol. 594:5749–68.
20. Scallan JP, Wolpers JH, Davis MJ. 2013. Constriction of isolated collecting lymphatic vessels in response to acute increases in downstream pressure. J. Physiol. 591:443–59.
21. Liao S, Cheng G, Conner DA, Huang Y, Kucherlapati RS, et al. 2011. Impaired lymphatic contraction associated with immunosuppression. PNAS 108:18784–89.
22. Park SM, Angel CE, McIntosh JD, Mansell C, Chen CJ, et al. 2014. Mapping the distinctive populations of lymphatic endothelial cells in different zones of human lymph nodes. PLOS ONE 9: 94781.
23. Rouhani SJ, Eccles JD, Tewalt EF, Engelhard VH. 2014. Regulation of T-cell tolerance by lymphatic endothelial cells. J. Clin. Cell Immunol. 5:1000242.
24. Dubrot J, Duraes FV, Potin L, Capotosti F, Brighouse D, et al. 2014. Lymph node stromal cells acquire peptide-MHCII complexes from dendritic cells and induce antigen-specific CD4+ T cell tolerance. J. Exp. Med. 211:1153–66 114a. Kedl R, Finlon J, Tamburini B. 2016.
25. Steinskog ES, Sagstad SJ, Wagner M, Karlsen TV, Yang N, et al. 2016. Impaired lymphatic function accelerates cancer growth. Oncotarget 7:45789–802.

26. Scallan JP, Huxley VH. 2010. In vivo determination of collecting lymphatic vessel permeability to albumin: a role for lymphatics in exchange. J. Physiol. 588:243–54