

Unit 3 Lecture 8

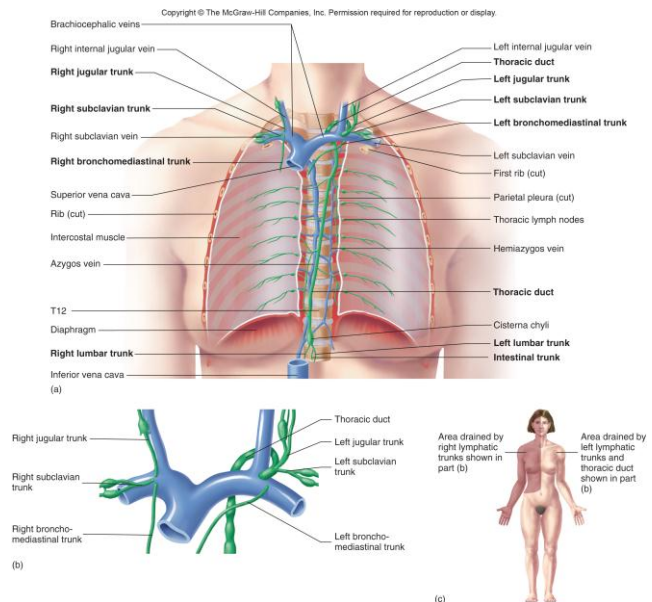
THE LYMPHATIC SYSTEM

The Lymphatic System is comprised of lymph (same as interstitial fluid but is found in lymphatic vessels), lymphatic vessels, lymphoid tissue, thymus gland, spleen, and bone marrow (site of lymphocytic production). The functions of the lymphatic system are to:

- Drain excess interstitial fluid,
- Transports dietary fats which are absorbed by the GI tract,
- Protect against microbe infection - the immune response. T-cells (lymphs) release cytotoxic substances that kill invaders and B-cells differentiate into plasma cells that make antibodies.
- Remove dead or damaged tissue.

Lymphatic system anatomy:

Lymphatic capillaries begin as closed-ended vessels in interstitial spaces and are found throughout the body. The capillaries unite to form larger lymph vessels and can usually be found near veins in subcutaneous tissue and near arteries in the viscera. The interstitial fluid flows into lymph capillaries but not out because the vessels are structurally adapted to ensure the return of proteins to the venous system. Anchoring filaments attach endothelial cells to surrounding tissue. Backflow is prevented by valves in lymph capillaries and lymph is forced to return towards the subclavian veins by milking action of skeletal muscles.



Lymph vessels unite to form trunks (larger lymph vessels). The major trunks are the lumbar, intestinal, subclavian, bronchomediastinal, and jugular which drain lymph from lymph capillaries and pass it into two main channels. The Thoracic duct (Left lymphatic duct) is the main collecting duct in the body. It starts at a structure called the cisterna chyli (lumbar region) and receives lymph from the entire left side of the body and from beneath the ribs on the right side of the body. It returns lymph to the blood by emptying into the left subclavian vein. The Right lymphatic duct receives lymph from the right side of the body above the ribs and returns lymph into the right subclavian vein.

Formation of Lymph

Fluid leaks from blood capillaries to form interstitial fluid. Some fluid returns to the capillaries, but not all. This excess fluid is devoid of cells and large proteins (they were too large to and remained in the blood capillaries). This fluid must be returned to the circulatory system. Excess fluid flows into the lymphatic system and becomes lymph. The entire route of fluid flow can be listed as follows: Starts as plasma in the blood (Arteries) → blood capillaries (still plasma) → interstitial spaces (interstitial fluid) → lymphatic ducts (lymph) → subclavian veins (blood).

Edema allows for greater fluid to flow into lymphatic capillaries.

Lymphatic Tissue

Not all lymphatic tissue is enclosed in a capsule. That not encapsulated is known as diffuse lymphatic tissue and is found throughout the body. Examples include the lamina propria of the GI tract, respiratory airways, urinary tract and reproductive tract. Lymphatic nodules are oval shaped concentrations of lymphatic tissue. Tonsils are an example of lymphatic nodules.

The primary lymphatic organs (where cells are formed) are the bone marrow and thymus gland. The bone marrow produces immunocompetent T & B cells. The thymus gland is where T-cells mature. Secondary lymphatic sites (where most immune reactions occur) are lymph nodes and spleen. **Lymph nodes** are oval or bean shaped and scattered throughout the body. They are usually found in clusters and covered by a capsule. Capsular extensions into the node are called trabeculae. The cortex or outer region of the node is packed with lymphocytes that are arranged in masses called follicles. The medulla or inner region of the node contains lymphocytes, macrophages and plasma cells. Flow into nodes via afferent lymphatic vessels and out via efferent lymphatic vessels. Efferent vessels emerge from the node at the hilum. The function of the node is to filter foreign materials from lymph (immune surveillance) and destroy filtered material by phagocytosis.

The thymus gland is located in the superior mediastinum behind the sternum and between the lungs. It serves as a site for lymphocyte maturation into T-cells. In infants, the thymus is large. After puberty it is composed mostly of fat and connective tissue.

The tonsils are large aggregation of nodules in a mucous membrane. A single pharyngeal tonsil (also called adenoid) is found in posterior wall of nasopharynx. Paired palatine tonsils are the ones removed during a tonsillectomy. Paired lingual tonsils found at base of tongue. Lingual tonsils are also sometimes removed during a tonsillectomy. The function of the tonsils is to protect against foreign substances that are inhaled or ingested.

The spleen is the largest mass of lymphatic tissue in the body. Vessels enter and leave through a hilum. The spleen contains two types of tissue white pulp (mostly lymphocytes located around central arteries) and red pulp (venous sinuses filled with blood and cords of splenic tissue). The spleen does not filter lymph. Rather it functions as the site of B-cell proliferation into plasma cells, site of phagocytosis of bacteria and worn out RBC and platelets, and as a blood storage area.

Nonspecific Resistance to Disease

General resistance is the ability to fight off disease. Nonspecific resistance uses defense mechanisms that fight off a wide range of pathogens whereas specific resistance involves antibody formation against specific pathogen. A non-specific body defense is any defense that protects against a variety of invaders. Nonspecific defenses are innate and present at birth. A specific body defense is defense directed against a single kind of invader of the body. Specific body defense involves the formation of antibodies and will be covered later.

The **first line of defense** involves both mechanical factors and chemical factors. Skin and mucous membranes provide a mechanical barrier that prevents microorganisms from penetrating sterile body compartments. Mechanisms such as filtering by hairs, blinking, coughing and sneezing, ciliary and washing action are all mechanical actions the body performs to protect against invasion by microbes. Chemical factors in the first line of defense include the production of mucus/mucin, an acidic pH, bile salts, and nutritional factors. Those that are primarily antimicrobial are lysozyme (found in tears and perspiration breaks apart bacterial cells (esp. Gram-pos)).

The **second line of defense**, also nonspecific, comes into play if organisms breach the first line, that is, penetrate into the body. Components of the second line include complement (opsonin and MAC complex), interferon (protects against viral infections), the inflammatory response, fever, natural killer cells (special type of lymphocyte), and phagocytes.

Complement is a series of twenty plasma proteins that interact in sequence. The complement cascade is normally initiated by reaction of antigen with antibody. C3b is called "opsonin". Opsonin coats invading antigens enabling phagocytosis. The C5-C9 (membrane attack complex) is called "cytolysin". Cytolysin coats invading cells and pokes holes through the cell wall which destroys cell. Two complements are called "anaphylotoxins" (C3a, C4a, and C5a). Anaphylotoxins bring about histamine release from platelets, basophils and mast cells. Histamine then causes vasodilation and increased capillary permeability. This is manifested by inflammation. Chemotaxis summons WBC's to the site of infection. Properdin, a plasma protein, stimulates the "alternate pathway" of complement cascade. It is initiated by cell wall polysaccharides or endotoxins. The alternate pathway has same results as normal pathway of cascade.

Prostaglandins are localized tissue hormones that have many functions. They increase capillary permeability for inflammation and cause the pain of inflammation. Interleukins (cytokines, leukotrienes) are produced by WBC's for communication. There are over one hundred kinds.

Phagocytic cells are found in the second line of defense. Fixed phagocytes or fixed macrophages comprise the basic cells of the reticuloendothelial system (RES). They sit in prominent locations such as the spleen, liver (Kupffer cells), lymph nodes, bone marrow, lung (Dust cells), nervous tissue (Microglia), and connective tissue (Histiocytes). Circulating phagocytes or wandering macrophages are also known as Monocytes. Microphages include the neutrophils (PMN's) and eosinophils. The main function of phagocytes is to ingest foreign substances and destroy them.

Fever or pyrexia is a most common mechanism associated with invasion of microbes. It is stimulated by presence of foreign or abnormal protein. This protein affects the thermoregulator of the hypothalamus. The source of unrecognized proteins is exogenous pyrogens, viral infections, pyogenic bacterial infections, endotoxins from Gram-negative bacteria, eukaryotic infections, allergies, endogenous pyrogens, destroyed phagocytes, and tumor cells. Other organic causes include neural disorders and endocrine disorders. Lastly, fevers may be of an unknown origin (FUO).

Specific Resistance to Disease (Immunity)

As stated earlier, a non-specific body defense is any defense that protects against a variety of invaders. A specific body defense is defense directed against a single kind of invader of the body. Specific body defense involves the formation of antibodies in response to the presence of a single antigen. The specific body defense is the **third line of defense**. Lymphocytes are exclusively responsible for production of antibodies.

An antigen is defined as a chemical with the potential to stimulate lymphocytes to produce antibodies. Antigens are characterized by usually being foreign or "non-self" molecules, except alloantigens and isoantigens. Antigens are macromolecules with formula weights of 10,000 or more. Smaller molecules are haptens, which become antigens when combined with proper proteins. They may be single molecules (simple antigens). Antigens are usually a protein or protein and a polysaccharide or lipid. Rarely are they a nucleic acid. Cell membrane components form the ABO or blood typing antigens.

Antibodies are proteins that are produced by lymphocytes in response to the presence of an antigen. Antibodies are macromolecules with formula weights in excess of 150,000. They are found as gamma globulins (immunoglobulins that circulate in the body) or on cell membranes of basophils & T-lymphocytes. Their basic structure is that of two light chains and two heavy chains. Variation in light chains accounts for "specificity" of antibodies.

For an immune response to occur, T and B-cells must recognize that a foreign antigen is present. The exogenous antigens are processed by antigen presenting cells (APC) that either ingest or bring the antigen into itself by endocytosis. There is a partial digestion the antigen, fusion of molecules within the APC, and finally the complex is released from the APC to combine with a B-cell. The B-cell is transformed into plasma cells that secrete antibodies into tissue or memory cells that can react with the antigen at later contact.

Antibodies combine with specific antigenic determinant that triggered its production. Antibodies consist of 2 heavy chains and two light chains. Within the chains are a variable portion (antigen binding site) and a constant portion (determines which class the antibody belongs too). The classes are IgA, IgG, IgM, IgE, and IgD. IgG is the only antibody that can cross the placenta (because it's small), indicates a previous infection or immunization has occurred, and comprises about 75% of all the antibodies in the body. IgM is the largest antibody, makes up 5-10% of antibodies in body, is the first antibody secreted after the initial exposure to any antigen, and indicates a current or recent infection. IgA antibodies are the second most abundant immunoglobulin. They are found associated with mucous membranes and are secreted onto membranes when antigens are present. IgE antibodies are found attached to basophils and mast cells after production by lymphocytes. They cause histamine release when reacted with antigen and are present in allergic or helminth infections. IgD immunoglobulins are the least abundant immunoglobulin class and are found on the surface of competent B-cells to possibly trigger IgG release.

Formation of T & B cells

Lymphocytes carry out the immune responses. T and B-cells develop in the bone marrow. B-cells mature in the bone marrow. T-cells migrate to the thymus gland where they mature and become immunocompetent (the ability to carry out immune responses). Both cell types acquire antigen receptors (proteins that recognize antigens). T-cells develop into CD4 or CD8 cells by acquiring different proteins which allow for different functions. In a cell-mediated immune response, CD8 cells proliferate into Killer T-cells which directly attack cells (invading antigen). Examples of invading antigens include intracellular pathogens, fungi, parasites, viruses, some cancer cells and tissue transplants. In antibody-mediated immune response, B-cells transform into plasma cells and make antibodies (immunoglobulins). These antibodies bind to and inactivate specific antigens. Antibodies work against antigens found in body fluids, viruses, and extracellular pathogens such as bacteria. Most CD4 T-cells become helper cells that aid both CMI and AMI responses.

In cell-mediated immunity (CMI), there again is antigen recognition by T cells, proliferation of specific T-cells and differentiation into effector cells. The antigen is attacked and eliminated.

T-cells can differentiate into helper T-cells (have the CD4 protein, assist in CMI and AMI responses), killer T-cells (display the CD8 protein, kill foreign cells), suppressor T-cells, and memory T-cells (long lasting lymphocyte programmed to recognize the initial invader).

In antibody-mediated immunity B-cells differentiate into plasma cells which make antibody to specific antigen. This antibody is released into the circulation to reach the site of invasion. B-cells that don't differentiate into plasma cells remain as memory cells ready to respond to future invasions. B-cells can respond to unprocessed antigens, but their response is more intense when dendritic cells present antigen to them.

Comparisons/contrasts of forms of immune response.

| Humoral immunity (antibodies) | Cell-mediated immunity |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Afferent phase <ul style="list-style-type: none"> • Entry of antigen • Entrapment by macrophage • Antigen to T_H cell | Afferent phase <ul style="list-style-type: none"> • Entry of antigen • Entrapment by macrophage • Antigen to T_H cell |
| Central phase <ul style="list-style-type: none"> • B cells sensitized • Clones of B cells form • B cells convert to plasma cells • Retention of B "memory" cells in lymph tissue | Central phase <ul style="list-style-type: none"> • T cells sensitized • Clones of T cells form • T cells differentiate to T_C, T_S, & T_D • Retention of T "memory" cells in lymph tissue |
| Effector phase <ul style="list-style-type: none"> • Plasma cells secrete immunoglobulins • Immunoglobulins react with antigens anywhere blood or tissue fluid is found • Elicit all responses of the classes of immunoglobulins | Effector phase <ul style="list-style-type: none"> • T cells carrying receptors go via blood to site of antigen • Receptors on T cells react with antigens only where activated T-cells are found • Elicit all responses of T_C & T_D cells |

Types of Immunity

Innate or native immunity means that there is a natural resistance to the microbe. It is genetic in nature and can be species or individual specific. [Acquired immunity](#) comes from contact with a microbe or virus either through an infection or by artificial means. The types of acquired immunity

are active or passive, natural or artificial. Combining two of the terms demonstrates the different types that can exist. **Natural active** immunity is acquired by contracting the disease. In most cases it gives lifelong protection. **Artificial active** immunity is the basis of vaccination. It is acquired through injection of antigen and tries to create lifelong protection. Because of the variation in degree of response boosters are usually required at some point (anamnestic response). Immunological memory is the basis for immunization. Immunization against certain microbes is possible because of memory B and T-cells that remain after the primary response to an antigen. The secondary response provides protection much more rapidly should the same microbe enter the body again.

Natural passive immunity is acquired by the fetus or newborn from mother. IgG antibodies cross the placenta and IgA in mother's milk protect the infant for up to six months. **Artificial passive** immunity is acquired through injection of antiserum. It is short term protection for up to six weeks. Examples include gamma globulins from humans and lab animals, convalescent serum, or hyperimmune serum. Immune serum globulin is derived from pool of donors. Specific immune globulins (SIG) are derived from a more defined group of donors and limited in availability and can be quite costly. Examples of SIG are antitoxins to botulism, diphtheria, and tetanus, antivenom, Rhogam, and pooled globulins to a specific agent. Drawbacks to the use of antiserum involve its specificity, side reactions, the accidental acquisition of viral diseases, and the limited time of protection - short term.

Immunological Disease

As good for us as the immune system is, it is not without problems; specifically the development of hypersensitivities or deficiencies in the development of a response at all. The host must have capacity to be sensitized. Therefore, genetic make-up, age, and emotional state are all important in the development of hypersensitivity reactions. The sequence of sensitization requires an initial exposure (first exposure to antigen causing immune response, but symptoms usually not present or mild at most). The sensitizing dose sets up the individual for the shocking or provocative dose (a later exposure to antigen that causes serious tissue reaction).

Antigen sources can be exogenous antigens (Allergens) from a non-living source or different species. Examples include food, drug, pollens, insect bites, poison ivy, and vaccine allergies. Homologous antigens (Isoantigens) come from another human. Sources include transfusion reactions (wrong blood type given), transplant rejections, Erythroblastosis fetalis or hemolytic disease of the newborn (HDN). An Rh- woman gives birth to an Rh+ infant. If measures are not taken to neutralize this reaction, antibodies are formed in the mother against Rh+ antigens. Subsequent Rh+ births are affected because IgG antibodies cross the placenta. The result is massive destruction of red blood cells in the fetus requiring immediate intervention.

Hypersensitivity Reactions - classified into four types

- Type I Classical immediate (anaphylaxis): hypersensitivity reaction to an antigen.
 - IgE's react with exogenous antigens only in 30 minutes or less.
 - Due to histamine release and subsequent reactions. Atopic allergies (localized) depend on portal of entry such as Asthma, Hay fever, GI distress, and the Wheal & flare.
 - Anaphylaxis (generalized) requires antigen in blood: Small arteries dilate, decrease BP, circulatory failure. Bronchioles constrict causing asphyxiation. Reversal by adrenalin and antihistamines.
- Type II = Cytotoxic (attack cells)
 - Circulating IgM and/or IgG from B-lymphocytes that react in variable time frame. Transfusion reactions (immediate). Autoimmune disease (longer). Erythroblastosis fetalis (longer).
 - Due to reaction of complement with antigens on specific cells. Destruction of cells leads to cell debris & kidney damage.
- Type III = Immune-complex mediated.
 - Circulating IgM and/or IgG from B-lymphocytes forming complexes and these complexes being deposited on basement membranes. As a result, circulating neutrophils release lysosomal granules that destroy tissue. React in 3-8 hours or longer.
 - Autologous antigens (Autoantigens) come from own body. Some examples include:
 - Systemic lupus erythematosus (SLE) - DNA of connective tissue
 - Rheumatoid arthritis - Hyaluronic acid
 - Pernicious anemia - Intrinsic factor
 - Hashimoto's thyroiditis - Follicular cells of thyroid
 - Rheumatic fever - Endocardium
 - Thrombocytopenic purpura - Platelets
 - Multiple sclerosis - Myelin sheath of nerve
 - Guillain-Barré syndrome - Myelin sheath of nerve
 - Myasthenia gravis - Neuromuscular junction
 - Diabetes (Type I) - Beta cells of pancreas
 - Acute Glomerulonephritis - kidneys.
- Type IV = Delayed hypersensitivity.
 - T-lymphocyte dependent. Reaction requires 24-72 hours. Direct destruction of cells by T-cells. Skin tests (TB), poison Ivy.

The immune system can also dysfunction by being depressed. This immunodeficiency can be the result of a congenital condition or the result of disease such as AIDS. Immunosuppression can be drug induced (cortisones inhibit both B- & T-cell reactions, Cyclosporin inhibits T helper cells) or radiation induced.

- Primary Immune Deficiencies
 - B-cell defects
 - Agammaglobulinemia
 - hypogammaglobulinemia
 - T-cell defects
 - Thymic aplasia (DeGeorge syndrome)
 - Combined B-cell and T-cell defects
 - SCID
 - Wiskott-Aldrich Syndrome
 - Phagocytic Defects
 - Chediak-Higashi Syndrome
- Secondary
 - From natural causes
 - AIDS, Cancer, nutritional deficiency, stress, pregnancy
 - From immunosuppressive agents such as irradiation, burns, steroids, drugs, spleen removal

A word on grafts. An autograft is obtained from one's own self. Examples include skin grafts for burn patients to donating your own blood to be transfused at a later date. An isograft is a graft between identical twins. Allografts (homograft) come from the same species. Most grafts are of this type. A xenograft is a graft between different species.

Self-Recognition and Immunological Tolerance

T-cells undergo \pm selection to ensure that they can recognize self and that they do not react to other self proteins (tolerance). Negative selection involves both deletion and anergy which ensures that T-cells will not respond to fragments of molecules that are present in the body. T-cells develop tolerance through deletion (cells die) and anergy (cells become unresponsive to antibody stimulation). The loss of immunological tolerance leads to autoimmune disease. B-cells also develop tolerance through deletion and anergy.