The Lymphatic System
The Immune System
Dr. Gary Mumaugh
Lymphatic System: Overview

- Consists of two semi-independent parts
  - A meandering network of lymphatic vessels
  - Lymphoid tissues and organs scattered throughout the body
- Returns interstitial fluid and leaked plasma proteins back to the blood
- Lymph – interstitial fluid once it has entered lymphatic vessels
Regional lymph nodes:

- Cervical nodes
- Axillary nodes
- Inguinal nodes

Entrance of right lymphatic duct into right subclavian vein

Internal jugular vein

Entrance of thoracic duct into left subclavian vein

Thoracic duct
Aorta
Cisterna chyli
Lymphatic collecting vessels
Lymphangiogram. A dye that is radiopaque (blocks x-rays) is injected into the interstitial fluid that eventually drains into nearby lymphatic pathways. There the dye is seen as bright areas outlining the location of pelvic (iliac) and inguinal lymphatic vessels and lymph nodes.
Afferent lymphatic vessel are located between the cells & blood capillary tissues.

Once tissue fluid enters the lymphatic capillary, it is called lymph.
Lymphatic System: Overview

Venous system
- Heart
- Lymph duct
- Lymph trunk
- Lymph node

Arterial system

Lymphatic system
- Lymphatic collecting vessels, with valves
- Lymphatic capillary

Tissue cell
- Blood capillaries
- Lymphatic capillary

Tissue fluid

Loose connective tissue around capillaries

Venule

Arteriole
Where is the lymph going?

- As blood circulates through the body, nutrients, wastes and gases are exchanged between the blood and interstitial fluid
  - Interstitial fluid – extracellular fluid derived from blood
- The pressure of the capillary beds force fluid out of the blood
- The fluid that remains behind in the tissue spaces becomes part of the interstitial fluid
  - Up to 3 liters per day
- Once interstitial fluid enters the lymphatic's, it is called lymph
Lymphatic Vessels

- A one-way system in which lymph flows toward the heart
- Lymph vessels include:
  - Microscopic, permeable, blind-ended capillaries
  - Lymphatic collecting vessels
  - Trunks and ducts
Lymphatic Capillaries

- Similar to blood capillaries, with modifications
  - Remarkably permeable
  - Loosely joined endothelial minivalves
  - The minivalves function as one-way gates
Lymphatic Capillaries

- Filaments anchored to connective tissue
- Endothelial cell
- Flaplike minivalve
- Fibroblast in loose connective tissue
Lymphatic Capillaries

• During inflammation, lymph capillaries can absorb:
  • Cell debris
  • Pathogens
  • Cancer cells

• Cells in the lymph nodes:
  • Cleanse and “examine” this debris

• Lacteals – specialized lymph capillaries present in intestinal mucosa
  • Absorb digested fat and deliver chyle to the blood
Bacteria cannot be absorbed through blood capillary walls.

- Tissue cells
- Bacteria in tissues
- Blood capillary cells
- Endothelial cells of lymphatic capillary
Lymphatic Trunks

- Lymphatic trunks are formed by the union of the largest collecting ducts
- Lymph is delivered into one of two large trunks
  - Right lymphatic duct – drains the right upper arm and the right side of the head and thorax
  - Thoracic duct – arises from the cisterna chyli and drains the rest of the body
Lymphatic Trunks

Figure 20.2b

Right jugular trunk
Right lymphatic duct
Right subclavian trunk
Right subclavian vein
Right bronchomediastinal trunk
Brachiocephalic veins
Superior vena cava
Azygos vein
Cisterna chyli
Right lumbar trunk

Left jugular trunk
Internal jugular veins
Left subclavian trunk
Left subclavian vein
Left bronchomediastinal trunk
Entrance of thoracic duct into left subclavian vein
Esophagus
Trachea
Ribs
Thoracic duct
Hemiazygos vein

Left lumbar trunk
Inferior vena cava
Intestinal trunk
Lymph Transport

- The lymphatic system lacks an organ that acts as a pump
- Vessels are low-pressure conduits
- Uses the same methods as veins to propel lymph
  - Pulsations of nearby arteries
  - Contractions of smooth muscle in the walls of the lymphatics
Fig. 20-7. Lymphatic pump. The diagram shows a “muscle pump” in a lymphatic vessel similar to that which moves blood through the veins. Increased external pressure from muscle contraction also increases lymphatic pressure, pushing it past one-way lymphatic valves. Because the valves prevent backflow, the system becomes a pump that keeps lymph moving in one direction (toward a subclavian vein).
72-year-old insulin dependent diabetic female with bilateral lower extremity lymphedema and multiple cellulitic lesions requiring multiple hospitalizations over a 5 year period.

After 6 weeks of daily treatments consisting of sequential lymphatic pumping, manual lymphatic drainage and compression wraps.
Lymphoid Cells

- Lymphocytes are the main cells involved in the immune response
- Infectious microorganisms manage to penetrate the body are encountered by a fight from the phagocytes and the lymphocytes
- The phagocytic macrophages are crucial in protection
Lymphoid Tissue

• Lymphoid (lymphatic tissue) is an important component of the immune system, mainly because it
  • Houses and provides a proliferation site for phagocytes
  • Furnishes a great surveillance point for lymphocytes and macrophages
Lymph Nodes

• Lymph nodes are the principal lymphoid organs of the body
• Nodes are imbedded in connective tissue and clustered along lymphatic vessels
• Aggregations of these nodes occur near the body surface in inguinal, axillary, and cervical regions of the body
Lymph Nodes

• Their two basic functions are:
  • Filtration – macrophages destroy microorganisms and debris
  • Immune system activation – monitor for antigens and mount an attack against them
Nodes are bean shaped and surrounded by a fibrous capsule. Most are less than 1 inch in size.
Circulation in the Lymph Nodes

- There are fewer efferent vessels draining the node than afferent vessels feeding it.
- Because there are fewer efferent vessels, lymph stagnates and pools somewhat in the node.
- This allows lymphocytes and macrophages time to carry out their protective functions.
- Nodes often become secondary cancer sites in metastasizing cancers.
Obstruction of Lymph Movement

Lymphatic vessels
Lymph node
Blood vessels
Muscle

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Fig. 20-16. Lymphatic drainage of the breast. Note the extensive network of lymphatic vessels and nodes that receive lymph from the breast.
Other Lymphoid Organs

- The spleen, thymus gland, and tonsils
- Peyer’s patches in the small intestine
- Appendix in the large intestine
- Lymphoid tissue in the walls of the bronchi
- Lymphatic tissue scattered in connective tissue
Spleen

- Largest lymphoid organ, located on the left side of the abdominal cavity beneath the diaphragm
- It extends to curl around the anterior aspect of the stomach
- Functions
  - Site of lymphocyte proliferation
  - Immune surveillance and response
  - Contains macrophages
  - Cleanses the blood
  - Produces antibodies
  - Stores platelets
    - Destroys them when they are no longer useful
Fig. 20-20. **Location of the spleen.** The spleen is located in the left hypochondrium of the abdominopelvic cavity, just inferior to the diaphragm and just deep to the lower portion of the rib cage.
Structure of the Spleen

- Capsule
- Trabecula
- Splenic cords
- Venous sinuses
- Red pulp
- White pulp
- Central artery
- Splenic artery
- Splenic vein

Diaphragm
Spleen
Adrenal gland
Left kidney
Splenic artery
Pancreas

Central artery
White pulp
Red pulp
Spleen Trauma

- Because the spleen capsule is very thin, a direct blow or infection may cause it to rupture
- This rupture spills blood into the peritoneal cavity
- In the past, a splenectomy was performed
- Now, the tendency is to let the spleen regenerate
- If the spleen is removed, the liver and bone marrow will attempt to take over most of its functions
Thymus

- A organ that secrets hormones that cause T lymphocytes to become immunocompetent
- The size of the thymus varies with age
  - In infants, it is found in the inferior neck and extends into the mediastinum where it partially overlies the heart
  - It increases in size and is most active during childhood
  - It stops growing during adolescence and then gradually atrophies
Thymus gland in adult
Tonsils

- Simplest lymphoid organs; form a ring of lymphatic tissue around the pharynx
- Location of the tonsils
  - Palatine tonsils – either side of the posterior end of the oral cavity
  - Lingual tonsils – lie at the base of the tongue
  - Pharyngeal tonsil – posterior wall of the nasopharynx
  - Tubal tonsils – surround the openings of the auditory tubes into the pharynx
Fig. 20-17. **Location of the tonsils.** **A,** Small segments of the roof and floor of the mouth have been removed to show the protective ring of tonsils (pharyngeal lymphoid ring) around the internal openings of the nose and throat. Tubal tonsils are not visible in this view. **B,** Tonsillitis. Note the swelling and presence of a white coating (exudate) indicating an infection.
Peyers’s Patches

• There are about 30 clusters of lymphoid tissue in the small intestine
• They are similar to tonsils
• They destroy bacteria before they are absorbed
• They generate “memory” lymphocytes for long term immunity
MALT

- Mucosa Associated Lymphatic Tissue
- Protects digestive tract
  - Tonsils, Peyer’s Patches, Appendix
- Protects respiratory tract
  - Lymphoid nodules in walls of bronchi
Developmental Aspects

- Start of lymphatic vessels and clusters of nodes are seen by the 5th week of embryonic development.
- The spleen, tonsils and lymphoid organs are poorly developed at birth.
THE IMMUNE SYSTEM
INNATE AND ADAPTIVE BODY DEFENSES
Immunity
Two Intrinsic Defense Systems

• Nonspecific system responds quickly and consists of:
  o **First line of defense** – intact skin and mucosae prevent entry of microorganisms
  o **Second line of defense** – antimicrobial proteins, phagocytes, and other cells
    o Inhibit spread of invaders throughout the body
    o Inflammation is its hallmark and most important mechanism
• Specific defense system
  o **Third line of defense** – mounts attack against particular foreign substances
    o Takes longer to react than the innate system
    o Works in conjunction with the innate system
Surface Barriers

• Skin, mucous membranes, and their secretions make up the first line of defense
• Keratin in the skin:
  o Presents a formidable physical barrier to most microorganisms
  o Is resistant to weak acids and bases, bacterial enzymes, and toxins
• Mucosa provide similar mechanical barriers
Epithelial Chemical Barriers

• Epithelial membranes produce protective chemicals that destroy microorganisms
  o Skin acidity (pH of 3 to 5) inhibits bacterial growth
  o Sebum contains chemicals toxic to bacteria
  o Stomach mucosae secrete concentrated HCl and protein-digesting enzymes
  o Saliva and lacrimal fluid contain lysozyme
  o Mucus traps microorganisms that enter the digestive and respiratory systems
Respiratory Tract Mucosae

• Mucus-coated hairs in the nose trap inhaled particles
• Mucosa of the upper respiratory tract is ciliated
  o Cilia sweep dust- and bacteria-laden mucus away from lower respiratory passages
Internal Defenses: Cells and Chemicals

• The body uses nonspecific cellular and chemical devices to protect itself
  o Phagocytes and natural killer (NK) cells
  o Antimicrobial proteins in blood and tissue fluid
  o Inflammatory response enlists macrophages, mast cells, WBCs, and chemicals

• Harmful substances are identified by surface carbohydrates unique to infectious organisms
Phagocytes

• Macrophages are the chief phagocytic cells
• Free macrophages wander throughout a region in search of cellular debris
• Neutrophils become phagocytic when encountering infectious material
• Eosinophils are weakly phagocytic against parasitic worms
• Microbes adhere to the phagocyte
Mechanism of Phagocytosis

1. Microbe adheres to phagocyte
2. Phagocyte forms pseudopods that eventually engulf the particle
3. Phagocytic vesicle is fused with a lysosome (phagolysosome)
4. Microbe in fused vesicle is killed and digested by lysosomal enzymes within the phagolysosome, leaving a residual body
5. Indigestible and residual material is removed by exocytosis
In phagocytosis, phagocytes are attracted to the area of invasion by chemical products of the microorganism, phospholipids released by injured mammalian cells, or by components of the complement system.
Natural Killer (NK) Cells

• Cells that can lyse and kill cancer cells and virus-infected cells
• Natural killer cells:
  o Are a small, distinct group of large granular lymphocytes
  o React nonspecifically and eliminate cancerous and virus-infected cells
  o Kill their target cells by releasing perforins and other cytolytic chemicals
  o They “police” the blood and lymph and are the “pits bulls” of the defense system
Inflammation
Tissue Response to Injury

• The inflammatory response is triggered whenever body tissues are injured
  o Prevents the spread of damaging agents to nearby tissues
  o Disposes of cell debris and pathogens
  o Sets the stage for repair processes

• The four cardinal signs of acute inflammation are redness, heat, swelling, and pain
Neutrophils enter blood from bone marrow.

1. Margination
2. Diapedesis
3. Positive chemotaxis

Inflammatory chemicals diffusing from the inflamed site act as chemotactic agents.

- Neutrophils enter blood from bone marrow
- Diapedesis
- Margination
Flowchart of Events in Inflammation

1. Tissue injury
2. Release of chemical mediators (histamine, complement, kinins, prostaglandins, etc.)
   - Vasodilation of arterioles
   - Increased capillary permeability
   - Local hyperemia (increased blood flow to area)
   - Increased oxygen and nutrients
   - Increased temperature increases metabolic rate of cells
   - Heat
   - Redness

3. Release of leukocytosis-inducing factor
   - Leukocytosis (increased numbers of white blood cells in bloodstream)
   - Migration to injured area
   - Margination (leukocytes cling to capillary walls)
   - Diapedesis (leukocytes pass through capillary walls)

4. Attract neutrophils, monocytes and lymphocytes to area (chemotaxis)
   - Walling-off process (blood clots wall off area to prevent injury to surrounding area)
   - Temporary fibrin patch forms scaffolding for repair
   - Pus may form
   - Area cleared of debris

5. Blood flow slows

6. Increased capillary permeability
   - Capillaries leak fluid (exudate formation)
   - Leaked protein-rich fluid in tissue spaces
   - Leaked clotting proteins

7. Attract neutrophils, monocytes and lymphocytes to area (chemotaxis)
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10. Increased temperature increases metabolic rate of cells
    - Heat
    - Redness

11. Pain
    - Swelling

12. Possible temporary limitation of joint movement

13. Healing
Antimicrobial Proteins

• Enhance the innate defenses by:
  o Attacking microorganisms directly
  o Hindering microorganisms’ ability to reproduce

• The most important antimicrobial proteins are:
  o Interferon
    o blocks viral reproduction
  o Complement proteins
    o Amplifies all aspects of the inflammatory response
    o Kills bacteria and certain other cell types
C-reactive Protein (CRP)

• CRP is produced by the liver in response to inflammatory molecules
• CRP is a clinical marker used to assess for:
  o The presence of an acute infection
  o An inflammatory condition and its response to treatment
• Plays a surveillance role in targeting damaged cells for disposal
Fever

• Abnormally high body temperature in response to invading microorganisms
• The body’s thermostat is reset upwards in response to pyrogens, chemicals secreted by leukocytes and macrophages exposed to bacteria and other foreign substances
Fever

• High fevers are dangerous as they can denature enzymes

• Moderate fever can be beneficial, as it causes:
  o The liver and spleen to sequester iron and zinc (needed by microorganisms)
  o An increase in the metabolic rate, which speeds up tissue repair
Specific Defenses

• The adaptive immune system is a functional system that:
  o Recognizes specific foreign substances
  o Acts to immobilize, neutralize, or destroy foreign substances
  o Amplifies inflammatory response and activates complement
Adaptive Immune Defenses

• This is the third line of defense called immune response
• It is based on the ability to distinguish molecules that are part of the body ("self" from "non-self")
• Antigens are molecules that can elicit an immune response
• The adaptive immune system is:
  o Specific
  o Systemic
  o Has memory
Immunological Memory

- Primary immune response – cellular differentiation and proliferation, which occurs on the first exposure to a specific antigen
  - Lag period: 3 to 6 days after antigen challenge
  - Peak levels of plasma antibody are achieved in 10 days
  - Antibody levels then decline
Immunological Memory

- Secondary immune response – re-exposure to the same antigen
  - Sensitized memory cells respond within hours
  - Antibody levels peak in 2 to 3 days at much higher levels than in the primary response
  - Antibodies bind with greater affinity, and their levels in the blood can remain high for weeks to months
Cells of the Adaptive Immune System

- Two types of lymphocytes
  - B lymphocytes – oversee humoral immunity
  - T lymphocytes – non-antibody-producing cells that constitute the cell-mediated arm of immunity
Lymphocytes

- Whether a lymphocyte matures into a B cell or a T cell depends on where in the body it becomes immunocompetent
  - B cells mature in the bone marrow
  - T cells mature in the thymus
Lymphocyte Origins

Stem cells in red bone marrow give rise to lymphocyte precursors. Some lymphocyte precursors are processed within the bone marrow to become B cells. Both T cells and B cells are transported through the blood to lymphatic organs, such as the lymph nodes, lymphatic ducts, and spleen. Some lymphocyte precursors are processed in the thymus to become T cells. Red bone marrow

Some lymphocyte precursors are processed within the bone marrow to become B cells. T cells and B cells are transported through the blood to lymphatic organs, such as the lymph nodes, lymphatic ducts, and spleen.
Active Humoral Immunity

• B cells encounter antigens and produce antibodies against them
  o Naturally acquired – response to a bacterial or viral infection
  o Artificially acquired – response to a vaccine of dead or attenuated pathogens
• Vaccines – spare us the symptoms of disease, and their weakened antigens provide antigenic determinants that are immunogenic and reactive
Passive Humoral Immunity

- Differs from active immunity in the antibody source and the degree of protection
- Naturally acquired – from the mother to her fetus via the placenta
- Artificially acquired – from the injection of serum, such as gamma globulin
Acquired immunity

Naturally acquired

Active
- Infection; contact with pathogen

Passive
- Antibodies pass from mother to fetus via placenta; or to infant in her milk

Artificially acquired

Active
- Vaccine; dead or attenuated pathogens

Passive
- Injection of immune serum (gamma globulin)
T Cell Summary

• Each T cell has unique roles to play in the immune response
• Each T cell is heavily involved in interactions with other immune cells and elements
• Without helper T cells, there would be no adaptive immune response
• The helper T cells direct and help complete the activation of other cells
• Their role is evident when they are destroyed in AIDS
Organ Transplants

• The four major types of grafts are:
  o Autografts – graft transplanted from one site on the body to another in the same person
  o Isografts – grafts between identical twins
  o Allografts – transplants between individuals that are not identical twins, but belong to same species
  o Xenografts – grafts taken from another animal species
Prevention of Rejection

• Prevention of tissue rejection is accomplished by using immunosuppressive drugs
• However, these drugs depress patient’s immune system so it cannot fight off foreign agents
Immunodeficiencies

• Congenital and acquired conditions in which the function or production of immune cells, phagocytes, or complement is abnormal
Acquired Immunodeficiencies

• Hodgkin’s disease – cancer of the lymph nodes leads to immunodeficiency by depressing lymph node cells
• Acquired immune deficiency syndrome (AIDS) – cripples the immune system by interfering with the activity of helper T (CD4) cells
  o Characterized by severe weight loss, night sweats, and swollen lymph nodes
  o Opportunistic infections occur
AIDS

• Caused by human immunodeficiency virus (HIV) transmitted via body fluids – blood, semen, and vaginal secretions

• HIV enters the body via:
  o Blood transfusions
  o Contaminated needles
  o Intimate sexual contact, including oral sex

• HIV:
  o Destroys $T_H$ cells
  o Depresses cell-mediated immunity
AIDS

- HIV multiplies in lymph nodes throughout the asymptomatic period
- Symptoms appear in a few months to 10 years
- Treatments include:
  - Reverse transcriptase inhibitors (AZT)
  - Protease inhibitors (saquinavir and ritonavir)
  - New drugs currently being developed that block HIV’s entry to helper T cells
Hypersensitivity

• Immune responses that cause tissue damage
• Different types of hypersensitivity reactions are distinguished by:
  o Their time course
  o Whether antibodies or T cells are the principle immune elements involved
• Antibody-mediated allergies are immediate and subacute hypersensitivities
• The most important cell-mediated allergic condition is delayed hypersensitivity
Anaphylaxis

- Reactions include runny nose, itching reddened skin, and watery eyes
- If allergen is inhaled, asthmatic symptoms appear – constriction of bronchioles and restricted airflow
- If allergen is ingested, cramping, vomiting, or diarrhea occur
- Antihistamines counteract these effects
Anaphylactic Shock

• Response to allergen that directly enters the blood (e.g., insect bite, injection)
• Basophils and mast cells are enlisted throughout the body
• Systemic histamine releases may result in:
  o Constriction of bronchioles
  o Sudden vasodilation and fluid loss from the bloodstream
  o Hypotensive shock and death
• Treatment – epinephrine is the drug of choice
Delayed Hypersensitivities

- Onset is slow (1–3 days)
- Antihistamines are ineffective and corticosteroid drugs are used to provide relief
- Example: allergic contact dermatitis (e.g., poison ivy)
- Involved in protective reactions against viruses, bacteria, fungi, protozoa, cancer, and rejection of foreign grafts or transplants
Lifestyle Changes

• The immune system declines early in life as the thymus gland shrinks
• There is a higher risk of infection
• Antibody response to antigens become slower
• Elderly may not be candidates for certain medical treatments that suppresses immunity
Developmental Aspects

• Immune system stem cells develop in the liver and spleen by the ninth week
• Later, bone marrow becomes the primary source of stem cells
• Lymphocyte development continues in the bone marrow and thymus system begins to wane
• The immune system is impaired by stress and depression
• With age, the immune system begins to wane