Lymphatic and Immune System
• The **immune system** is the complex collection of cells and organs that destroys or neutralizes pathogens that would otherwise cause disease or death.

• The **lymphatic system** is the system of vessels, cells, and organs that carries excess fluids to the bloodstream and filters pathogens from the blood.

• The swelling of lymph nodes during an infection and the transport of lymphocytes via the lymphatic vessels are but two examples of the many connections between these critical organ systems.
Functions of the Lymphatic System

• The lymphatic system drains body fluids and return them to the bloodstream. It drains the excess fluid and empties it back into the bloodstream via a series of vessels, trunks, and ducts. **Lymph** is the term used to describe interstitial fluid once it has entered the lymphatic system. When the lymphatic system is damaged in some way, such as by being blocked by cancer cells or destroyed by injury, protein-rich interstitial fluid accumulates (sometimes “backs up” from the lymph vessels) in the tissue spaces. This inappropriate accumulation of fluid referred to as lymphedema may lead to serious medical consequences.
Functions of the Lymphatic System

• Cells of the immune system not only use lymphatic vessels to make their way from interstitial spaces back into the circulation, but they also use lymph nodes as major staging areas for the development of critical immune responses. A lymph node is one of the small, bean-shaped organs located throughout the lymphatic system.
(a) Relationship of lymphatic capillaries to tissue cells and blood capillaries

(b) Details of a lymphatic capillary
Structure of the Lymphatic System

- The lymphatic vessels begin as open-ended capillaries, which feed into larger and larger lymphatic vessels, and eventually empty into the bloodstream by a series of ducts.
- 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
• A major distinction between the lymphatic and cardiovascular systems in humans is that lymph is not actively pumped by the heart, but is forced through the vessels by the movements of the body, the contraction of skeletal muscles during body movements, and breathing.

• One-way valves (semi-lunar valves) in lymphatic vessels keep the lymph moving toward the heart. Lymph flows from the lymphatic capillaries, through lymphatic vessels, and then is dumped into the circulatory system via the lymphatic ducts located at the junction of the jugular and subclavian veins in the neck.
Two Semi-independent Parts of the Lymphatic System

A. Lymphatic vessels (also lymphatics)

   it forms an elaborate drainage system that picks up excess interstitial fluid (lymph) and returns it to the blood.

   lymph → lymphatic capillaries → lymphatic collecting vessels → right lymphatic duct (lymph from the right arm, right side of the head and thorax / thoracic duct (lymph from the rest of the body) → subclavian vein (l and r)

B. Lymphoid tissues and organs
B. Lymphoid Tissues and Organs

1. Lymph nodes: removes foreign material and produces lymphocytes that functions in the immune response.

2. Spleen: remove microbes and other materials from the blood, including dying red blood cells.

3. Thymus Gland: (thymosin)

4. Tonsils: trap and remove any bacteria or other foreign pathogens entering the throat.

5. Peyer’s patches: captures and destroy bacteria.
BODY DEFENSES
The Organization of Immune Function

• The immune system is a collection of barriers, cells, and soluble proteins that interact and communicate with each other in extraordinarily complex ways. The modern model of immune function is organized into three phases based on the timing of their effects.
• The three temporal phases consist of the following:
  • **Barrier defenses** such as the skin and mucous membranes, which act instantaneously to prevent pathogenic invasion into the body tissues
    • The rapid but nonspecific **innate immune response**, which consists of a variety of specialized cells and soluble factors
    • The slower but more specific and effective **adaptive immune response**, which involves many cell types and soluble factors, but is primarily controlled by white blood cells (leukocytes) known as **lymphocytes**, which help control immune responses.
• The cells of the blood, including all those involved in the immune response, arise in the bone marrow via various differentiation pathways from hematopoietic stem cells.
• In contrast with embryonic stem cells, hematopoietic stem cells are present throughout adulthood and allow for the continuous differentiation of blood cells to replace those lost to age or function.
• These cells can be divided into three classes based on function:
  • Phagocytic cells, which ingest pathogens to destroy them
  • Lymphocytes, which specifically coordinate the activities of adaptive immunity
  • Cells containing cytoplasmic granules, which help mediate immune responses against parasites and intracellular pathogens such as viruses
After division some cells remain stem cells.

Multipotent hematopoietic stem cell (hemocytoblast)

The remaining cell goes down one of two paths depending on the chemical signals received.

**Myeloid stem cell**
- Megakaryoblast
  - Megakaryocyte
    - Platelets
  - Reticulocyte
    - Erythrocyte
  - Basophil
  - Neutrophil
  - Eosinophil
  - Monocyte
    - Macrophage

**Lymphoid stem cell**
- Lymphoblast
  - Natural killer cell (Large granular lymphocyte)
  - Small lymphocyte
    - T lymphocyte
    - B lymphocyte
  - Plasma cell
**Innate Immunity**

- Pathogens
- Palatine tonsil

**Surface Defenses:**
1. Skin
2. Hair
3. Mucus

**Internal Defenses:**
1. Mast cells and basophils (Inflammatory response)
2. Natural killer cells
3. Complement system
4. Phagocytes:
   - Monocytes
   - Neutrophils
   - Macrophages

**Adaptive Immunity**

- T memory cells
- T effector cells
- Antibodies
- B memory cells
- B effector cells

**Germinal center of palatine tonsil**
Innate Body Defenses

- Also called as nonspecific body defense, refers to the mechanical barriers that cover body surfaces and to the cells and chemicals that act on the initial battlefronts to protect the body from invading pathogens.
## Summary of Nonspecific Body Defenses

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact skin (epidermis)</td>
<td>Phagocytes</td>
</tr>
<tr>
<td>• Acid mantle</td>
<td></td>
</tr>
<tr>
<td>• Keratin</td>
<td></td>
</tr>
<tr>
<td>Intact Mucous membrane</td>
<td>Natural Killer Cells</td>
</tr>
<tr>
<td>• Mucus</td>
<td></td>
</tr>
<tr>
<td>• Nasal hairs</td>
<td></td>
</tr>
<tr>
<td>• Cilia</td>
<td></td>
</tr>
<tr>
<td>• Gastric juice</td>
<td></td>
</tr>
<tr>
<td>• Acid mantle of vagina</td>
<td></td>
</tr>
<tr>
<td>• Lacrimal secretions and saliva</td>
<td></td>
</tr>
<tr>
<td>Inflamatory response</td>
<td></td>
</tr>
<tr>
<td>Antimicrobial chemicals</td>
<td></td>
</tr>
<tr>
<td>• Complement</td>
<td></td>
</tr>
<tr>
<td>• Interferons</td>
<td></td>
</tr>
<tr>
<td>• Urine</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td></td>
</tr>
</tbody>
</table>
Cells of the Innate Immune System

• Phagocytes
• Monocytes
• Neutrophils
• Natural Killer Cells (NK Cells)
(a) Phases of phagocytosis

1. Chemotaxis and adherence of microbe to phagocyte.
2. Ingestion of microbe by phagocyte.
3. Formation of a phagosome.
4. Fusion of the phagosome with a lysosome to form a phagolysosome.
5. Digestion of ingested microbe by enzymes.
6. Formation of residual body containing indigestible material.
# Phagocytic Cells of the Innate Immune System

<table>
<thead>
<tr>
<th>Cell</th>
<th>Cell type</th>
<th>Primary location</th>
<th>Function in the innate immune response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrophage</td>
<td>Agranulocyte</td>
<td>Body cavities/organs</td>
<td>Phagocytosis</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>Granulocyte</td>
<td>Blood</td>
<td>Phagocytosis</td>
</tr>
<tr>
<td>Monocyte</td>
<td>Agranulocyte</td>
<td>Blood</td>
<td>Precursor of macrophage/dendritic cell</td>
</tr>
</tbody>
</table>

Table 21.3
Natural Killer Cell

• NK cells are a type of lymphocyte that have the ability to induce **apoptosis**, that is, programmed cell death, in cells infected with intracellular pathogens such as obligate intracellular bacteria and viruses.

• If apoptosis is induced before the virus has the ability to synthesize and assemble all its components, no infectious virus will be released from the cell, thus preventing further infection.
Natural Killer (NK) Cells

Why Are NK Cells so important?

They target:
- TUMOR CELLS
- CANCER CELLS
- INFECTED CELLS

The protect against a wide variety of

INFECTIONOUS MICROBES
(viruses, bacteria, parasites & fungi)
Soluble Mediators of the Innate Immune Response

- **CYTOKINES**: is a signaling molecule that allows cells to communicate with each other over short distances. Cytokines are secreted into the intercellular space, and the action of the cytokine induces the receiving cell to change its physiology.

- **CHEMOKINE**: a soluble chemical mediator similar to cytokines except that its function is to attract cells (chemotaxis) from longer distances.

- **INTERFERON**: Cells infected with viruses secrete interferons that travel to adjacent cells and induce them to make antiviral proteins.
  - *Opsonization is the tagging of a pathogen for phagocytosis by the binding of an antibody or an antimicrobial protein.*
**Host Cell 1**
Infected by virus; makes interferon; is killed by virus

**Host Cell 2**
Entered by interferon from cell 1; interferon induces changes that protect it
Extracellular bacteria

Macrophage

Opsonization

Ingestion by macrophage

Digestion in lysosome
Complementary System

• The complement system is a series of proteins constitutively found in the blood plasma.

• Functions:
  – Bind to the cell membrane of the pathogen that activates it, labeling it for phagocytosis (opsonization)
  – Diffuse away from the pathogen and act as chemotactic agents to attract phagocytic cells to the site of inflammation
  – Form damaging pores in the plasma membrane of the pathogen
Inflammatory Response

• The hallmark of the innate immune response is inflammation.
• Four characteristics: heat, redness, pain, and swelling.
• Inflammation does not have to be initiated by an infection, but can also be caused by tissue injuries. The release of damaged cellular contents into the site of injury is enough to stimulate the response, even in the absence of breaks in physical barriers that would allow pathogens to enter. The inflammatory reaction brings in phagocytic cells to the damaged area to clear cellular debris and to set the stage for wound repair.
Inflammatory Response

There are four important parts to the inflammatory response:

1. **Tissue Injury.** *Injured cells stimulate the release* inflammatory mediators such as histamine, leukotrienes, and prostaglandins. **Histamine increases the diameter of** local blood vessels (vasodilation), causing an increase in blood flow. Histamine also increases the permeability of local capillaries, causing plasma to leak out and form interstitial fluid. This causes the swelling.

Injured cells, phagocytes, and basophils are sources of inflammatory mediators, including prostaglandins and leukotrienes. Leukotrienes attract neutrophils from the blood by chemotaxis and increase vascular permeability. Prostaglandins cause vasodilation by relaxing vascular smooth muscle and are a major cause of the pain associated with inflammation. Nonsteroidal anti-inflammatory drugs such as aspirin and ibuprofen relieve pain by inhibiting prostaglandin production.

2. **Vasodilation.**

3. **Increased Vascular Permeability.** *Inflammatory mediators increase the permeability of the local* vasculature, causing leakage of fluid into the interstitial space, resulting in the swelling, or edema.

4. **Recruitment of Phagocytes**
ADAPTIVE BODY DEFENSE
Adaptive Body Defense

• Also called as Specific Defense System.
• Sometimes referred to as the third line of defense, it is a functional system that recognizes foreign molecules (antigens) and acts to inactivate or destroy them.
• Three important aspects;
  - it is antigen specific: it recognizes and acts against particular pathogens or foreign substances.
  - It is systemic: immunity is not restricted to the initial infection site.
  - It has memory: it recognizes and mounts even stronger attacks on previously encountered pathogens.
Two Types of Adaptive Defense System

1. Humoral Immunity or Antibody-Mediated Immunity
   - It is provided by antibodies present in the body’s “humors” or fluids.

2. Cellular Immunity or Cell-Mediated Immunity
   - Provided by the lymphocytes or living cells.
Antigens

• Any substance capable of mobilizing our immune system and provoking an immune response.
• They are large, complex molecules that are not normally present in our bodies.
• They are foreign intruders or nonself.
Cells of the Adaptive Defense System

I. Lymphocytes
   A. B lymphocytes or B cells
   B. T lymphocytes
The Adaptive Immune Response: T lymphocytes and Their Functional Types

• T cells recognize antigens with their antigen receptor, a complex of two protein chains on their surface.

• T cells develop in the thymus, where they learn to recognize only foreign antigens, thus making them tolerant to self-antigens.

• There are several functional types of T lymphocytes, the major ones being helper, regulatory, and cytotoxic T cells.
• Helper T Cell: T cells that secrete cytokines to enhance other immune responses, involved in activation of both B and T cell lymphocytes

Regulatory T Cell: (also, suppressor T cells) class of CD4 T cells that regulates other T cell responses

Cytotoxic T cells: T lymphocytes with the ability to induce apoptosis in target cells.
The Adaptive Immune Response: B-lymphocytes and Antibodies

• B cells, which develop within the bone marrow, are responsible for making five different classes of antibodies, each with its own functions.
# Antibody isotypes of mammals

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
<th>Antibody Complexes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IgA</strong></td>
<td>Found in mucosal areas, such as the gut, respiratory tract and urogenital tract, and prevents colonization by pathogens. Also found in saliva, tears, and breast milk.</td>
<td></td>
</tr>
<tr>
<td><strong>IgD</strong></td>
<td>Functions mainly as an antigen receptor on B cells that have not been exposed to antigens. It has been shown to activate <strong>basophils</strong> and <strong>mast cells</strong> to produce <strong>antimicrobial</strong> factors.</td>
<td><img src="image1" alt="Monomer IgD, IgE, IgG" /></td>
</tr>
<tr>
<td><strong>IgE</strong></td>
<td>Binds to allergens and triggers histamine release from mast cells and basophils, ad is involved in allergy. Also protects against parasitic worms.</td>
<td><img src="image2" alt="Dimer IgA" /></td>
</tr>
<tr>
<td><strong>IgG</strong></td>
<td>In its four forms, provides the majority of antibody-based immunity against invading pathogens. The only antibody capable of crossing the placenta to give passive immunity to the <strong>fetus</strong>.</td>
<td><img src="image3" alt="Pentamer IgM" /></td>
</tr>
<tr>
<td><strong>IgM</strong></td>
<td>Eliminates pathogens in the early stages of B cell-mediated (humoral) immunity before there is sufficient IgG.</td>
<td></td>
</tr>
</tbody>
</table>
The Immune Response against Pathogens

- Early childhood is a time when the body develops much of its immunological memory that protects it from diseases in adulthood.
- Bacteria and fungi are especially susceptible to damage by complement proteins, whereas viruses are taken care of by interferons and cytotoxic T cells.
- Worms are attacked by eosinophils.
- Pathogens have shown the ability, however, to evade the body’s immune responses, some leading to chronic infections or even death.
- The immune system and pathogens are in a slow, evolutionary race to see who stays on top. Modern medicine, hopefully, will keep the results skewed in humans’ favor.
Diseases Associated with Depressed or Overactive Immune Responses

• The immune response can be under-reactive or over-reactive.
• Suppressed immunity can result from inherited genetic defects or by acquiring viruses.
• The worst cases of overreactive immune responses are autoimmune diseases, where an individual’s immune system attacks his or her own body because of the breakdown of immunological tolerance.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Autoantigen</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celiac disease</td>
<td>Tissue transglutaminase</td>
<td>Damage to small intestine</td>
</tr>
<tr>
<td>Diabetes mellitus type I</td>
<td>Beta cells of pancreas</td>
<td>Low insulin production; inability to regulate serum glucose</td>
</tr>
<tr>
<td>Graves' disease</td>
<td>Thyroid-stimulating hormone receptor (antibody blocks receptor)</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Hashimoto's thyroiditis</td>
<td>Thyroid-stimulating hormone receptor (antibody mimics hormone and stimulates receptor)</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Lupus erythematosus</td>
<td>Nuclear DNA and proteins</td>
<td>Damage of many body systems</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Acetylcholine receptor in neuromuscular junctions</td>
<td>Debilitating muscle weakness</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Joint capsule antigens</td>
<td>Chronic inflammation of joints</td>
</tr>
</tbody>
</table>

Table 21.7
Active versus Passive Immunity

• Immunity to pathogens, and the ability to control pathogen growth so that damage to the tissues of the body is limited, can be acquired by
• (1) the active development of an immune response in the infected individual or
• (2) the passive transfer of immune components from an immune individual to a nonimmune one.
• Both active and passive immunity have examples in the natural world and as part of medicine.
Active Immunity

• The resistance to pathogens acquired during an adaptive immune response within an individual.
• Naturally acquired active immunity, is the response to a pathogen.
• Artificially acquired active immunity involves the use of vaccines.
• A vaccine is a killed or weakened pathogen or its components that, when administered to a healthy individual, leads to the development of immunological memory (a weakened primary immune response) without causing much in the way of symptoms. Thus, with the use of vaccines, one can avoid the damage from disease that results from the first exposure to the pathogen, yet reap the benefits of protection from immunological memory.
Passive Immunity

- arises from the transfer of antibodies to an individual without requiring them to mount their own active immune response.
- Naturally acquired passive immunity is seen during fetal development. IgG is transferred from the maternal circulation to the fetus via the placenta, protecting the fetus from infection and protecting the newborn for the first few months of its life.
- A newborn benefits from the IgA antibodies it obtains from milk during breastfeeding. The fetus and newborn thus benefit from the immunological memory of the mother to the pathogens to which she has been exposed.
- Artificially acquired passive immunity usually involves injections of immunoglobulins, taken from animals previously exposed to a specific pathogen. This treatment is a fast-acting method of temporarily protecting an individual who was possibly exposed to a pathogen.
- The downside to both types of passive immunity is the lack of the development of immunological memory. Once the antibodies are transferred, they are effective for only a limited time before they degrade.
<table>
<thead>
<tr>
<th></th>
<th>Natural</th>
<th>Artificial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active</strong></td>
<td>Adaptive immune response</td>
<td>Vaccine response</td>
</tr>
<tr>
<td><strong>Passive</strong></td>
<td>Trans-placental antibodies/breastfeeding</td>
<td>Immune globulin injections</td>
</tr>
</tbody>
</table>

Table 21.6