Chapter 21
Lecture Outline

See separate PowerPoint slides for all figures and tables pre-inserted into PowerPoint without notes.
Introduction

• The body harbors at least 10 times as many bacterial cells as human cells
  – Some beneficial
  – Some potentially disease-causing

• **Immune system**—not an organ system, but a cell population that inhabits all organs and defends the body from agents of disease
  – Especially concentrated in the true organ system: **lymphatic system**
    • Network of organs and vein-like vessels that recover fluid
    • Inspect it for disease agents
    • Activate immune responses
    • Return fluid to the bloodstream
The Lymphatic System

- **Expected Learning Outcomes**
  - List the functions of the lymphatic system.
  - Explain how lymph forms and returns to the bloodstream.
  - Name the major cells of the lymphatic system and state their functions.
  - Name and describe the types of lymphatic tissue.
  - Describe the structure and function of the red bone marrow, thymus, lymph nodes, tonsils, and spleen.
The Lymphatic System

• Fluid recovery
  – Fluid continually filters from the blood capillaries into the tissue spaces
    • Blood capillaries reabsorb 85%
    • 15% (2 to 4 L/day) of the water and about half of the plasma proteins enter the lymphatic system and then are returned to the blood
The Lymphatic System

• **Immunity**
  – Excess filtered fluid picks up foreign cells and chemicals from the tissues
    • Passes through lymph nodes where immune cells stand guard against foreign matter
    • Activates a protective immune response

• **Lipid absorption**
  – **Lacteals** in small intestine absorb dietary lipids that are not absorbed by the blood capillaries
The Lymphatic System

- Maintain fluid balance
- Protect body from infection and disease

Figure 21.3a
The Lymphatic System

• **Lymph**
  – The recovered fluid

• **Lymphatic vessels**
  – Transport the lymph

• **Lymphatic tissues**
  – Composed of aggregates of lymphocytes and macrophages that populate many organs in the body

• **Lymphatic organs**
  – Defense cells are especially concentrated in these organs
  – Separated from surrounding organs by connective tissue capsules
Lymph and the Lymphatic Vessels

• **Lymph**
  – Clear, colorless fluid, similar to plasma, but much less protein
  – Originates as extracellular fluid drawn into lymphatic capillaries
  – Chemical composition varies in different places (in intestines, after lymph nodes)
Lymph and the Lymphatic Vessels

• Lymphatic capillaries (terminal lymphatics)
  – Penetrate nearly every tissue of the body
    • Absent from central nervous system, cartilage, cornea, bone, and bone marrow
  – Capillary wall is endothelial cells overlapping each other like roof shingles
  – Closed at one end
  – Cells tethered to surrounding tissue by protein filaments
    • Gaps between cells are large enough to allow bacteria and cells to enter lymphatic capillary
  – Endothelium creates valve-like flaps that open when interstitial fluid pressure is high, and close when it is low
Lymphatic Capillaries

Figure 21.3b

- Lymph
- Opening
- Tissue fluid
- Endothelium of lymphatic capillary
- Anchoring filaments
Lymphatic Vessels

• Larger ones composed of three layers
  – *Tunica interna*: endothelium and valves
  – *Tunica media*: elastic fibers, smooth muscle
  – *Tunica externa*: thin outer layer

• Converge into larger and larger vessels

• Collecting vessels course through many lymph nodes
Valves in a Lymphatic Vessel

Figure 21.4a

Valve

Figure 21.4b

Lymph
Lymph flows forward through open valves
Closed valves prevent backflow
Lymphatic Vessels

- **Six lymphatic trunks** drain major portions of body
  - Jugular, subclavian, bronchomediastinal, intercostal, intestinal (unpaired), and lumbar trunks

- **Two collecting ducts**
  - **Right lymphatic duct**: receives lymph from right arm, right side of head and thorax; empties into right subclavian vein
  - **Thoracic duct**: larger and longer, begins as a prominent sac in abdomen called the cisterna chyli; receives lymph from below diaphragm, left arm, left side of head, neck, and thorax; empties into left subclavian vein

- **Subclavian veins**—collect from thoracic duct
Fluid Exchange

Lymphatic system
- Lymphatic capillaries
- Lymph nodes
- Lymphatic trunks
- Collecting duct
- Collecting vessels
- Lymph flow
- Lymphatic capillaries

Cardiovascular system
- Pulmonary circuit
- Subclavian vein
- Superior vena cava
- Blood flow
- Systemic circuit

Figure 21.5

Figure 21.1
Lymphatics of the Thoracic Region

Figure 21.6b

- Right lymphatic duct
- Right subclavian vein
- Axillary lymph nodes
- Lymphatics of breast
Drainage of Thorax

- Right jugular trunk
- Right lymphatic duct
- Right subclavian trunk
- Right bronchio-mediastinal trunk
- Azygos vein
- Diaphragm
- Cisterna chyli
- Right lumbar trunk
- Hemiazygos vein
- Thoracic duct
- Left jugular trunk
- Left subclavian trunk
- Left bronchiomediastinal trunk
- Thoracic duct
- Thoracic lymph nodes
- Intestinal trunk
- Left lumbar trunk
- Cisterna chyli

Figure 21.6a
Flow of Lymph

• 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

• Moved along by rhythmic contractions of lymphatic vessels
  – Stretching of vessels stimulates contraction
Flow of Lymph

- Flow aided by skeletal muscle pump
- 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
- Exercise significantly increases lymphatic return
Lymphatic Cells

• **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
Lymphatic Cells

- **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)
Figure 21.7

Macrophages

Macrophage
Bacteria
Pseudopods

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Lymphatic Cells

• **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
Lymphatic Tissues

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

• **Diffuse lymphatic tissue**—simplest form
  – Lymphocytes are scattered (not clustered)
  – Prevalent in body passages open to the exterior
    • Respiratory, digestive, urinary, and reproductive tracts
    • **Mucosa-associated lymphatic tissue (MALT)**
Lymphatic Tissues

• **Lymphatic nodules (follicles)**
  – Dense masses of lymphocytes and macrophages that congregate in response to pathogens
  – Constant feature of the lymph nodes, tonsils, and appendix
  – **Peyer patches**: dense clusters in the ileum, the distal portion of the small intestine
Figure 21.8

Lymphatic Nodule

Intestinal villus

Lymphatic nodule

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Lymphatic Organs

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

- Primary lymphatic organs
  - Red bone marrow and thymus
  - Site where T and B cells become immunocompetent: able to recognize and respond to antigens

- Secondary lymphatic organs
  - Lymph nodes, tonsils, and spleen
  - Immunocompetent cells populate these tissues
Red Bone Marrow

• Red bone marrow is involved in hemopoiesis (blood formation) and immunity
  – Soft, loosely organized, highly vascular material
  – Separated from osseous tissue by endosteum of bone
  – As blood cells mature, they push their way through the reticular and endothelial cells to enter the sinus and flow away in the bloodstream
Thymus

- **Thymus**—member of the endocrine, lymphatic, and immune systems
  - Houses developing lymphocytes
  - Secretes hormones regulating their activity
  - Bilobed organ located in superior mediastinum between sternum and aortic arch
  - Degeneration (involution) with age
Thymus

• Fibrous capsule gives off trabeculae (septa) that divide the gland into several lobes
  – Lobes have cortex and medulla populated by T lymphocytes

• Reticular epithelial cells seal off cortex from medulla forming blood–thymus barrier
  – Produce signaling molecules thymosin, thymopoietin, thymulin, interleukins, and interferon
Figure 21.10a,c
Histology of the Thymus

Figure 21.10b

Trabecula

Lobule

Cortex

Medulla

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(b)
Lymph Nodes

- **Lymph nodes**—most numerous lymphatic organs
  - About 450 in typical young adult
  - Serve two functions
    - Cleanse the lymph
    - Act as a site of T and B cell activation

- Elongated, bean-shaped structure with **hilum**

- Enclosed with **fibrous capsule** with **trabeculae** that divide interior into compartments
  - Stroma of reticular fibers and reticular cells
Lymph Nodes

• **Parenchyma** divided into **cortex** and **medulla**
  – **Germinal centers** where B cells multiply and differentiate into plasma cells

• Several **afferent lymphatic vessels** lead into the node along its convex surface

• Lymph leaves the node through one to three **efferent lymphatic vessels** that leave the hilum
Lymph Nodes

• **Cervical lymph nodes**
  - Deep and superficial group in the neck
  - Monitor lymph coming from head and neck

• **Axillary lymph nodes**
  - Concentrated in armpit
  - Receive lymph from upper limb and female breast

• **Thoracic lymph nodes**
  - In thoracic cavity, especially embedded in mediastinum
  - Receive lymph from mediastinum, lungs, and airway
Lymph Nodes

• **Abdominal lymph nodes**
  – Occur in posterior abdominopelvic wall
  – Monitor lymph from the urinary and reproductive systems

• **Intestinal and mesenteric lymph nodes**
  – Found in the mesenteries, adjacent to the appendix and intestines
  – Monitor lymph from the digestive tract

• **Inguinal lymph nodes**
  – In the groin and receive lymph from the entire lower limb

• **Popliteal lymph nodes**
  – Occur on the back of the knee
  – Receive lymph from the leg proper
Areas of Lymph Node Concentration

Colon
Appendix

Transverse mesocolic lymph nodes
Superior mesenteric artery
Inferior mesenteric artery
Inferior mesenteric lymph nodes

Superior mesenteric lymph nodes
Ileocolic lymph nodes
Small intestine
Appendicular lymph nodes
Appendix

(a)

Figure 21.11a
Lymph Nodes

- When a lymph node is under challenge by an antigen
  - **Lymphadenitis**: swollen, painful node responding to foreign antigen
  - **Lymphadenopathy**: collective term for all lymph node diseases
Lymph Nodes and Metastatic Cancer

- **Metastasis**—cancerous cells break free from original tumor, travel to other sites in the body, and establish new tumors
  - Metastasizing cells easily enter lymphatic vessels
  - Tend to lodge in the first lymph node they encounter
  - Multiply there and eventually destroy the node
    - Swollen, firm, and usually painless
  - Tend to spread to the next node downstream
  - Treatment of breast cancer is lumpectomy, mastectomy, along with removal of nearby axillary nodes
Tonsils

- **Tonsils**—patches of lymphatic tissue located at the entrance to the pharynx
  - Guard against ingested or inhaled pathogens
  - Covered with epithelium
  - Have deep pits: *tonsillar crypts* lined with lymphatic nodules
- **Tonsillitis** and **tonsillectomy**
Tonsils

• Three main sets of tonsils
  – Palatine tonsils
    • Pair at posterior margin of oral cavity
    • Most often infected
  – Lingual tonsils
    • Pair at root of tongue
  – Pharyngeal tonsil (adenoids)
    • Single tonsil on wall of nasopharynx
The Tonsils

Figure 21.13a

Pharyngeal tonsil
Palate
Palatine tonsil
Lingual tonsil
Tonsils

- Covered by epithelium
- Pathogens get into tonsillar crypts and encounter lymphocytes
Spleen

- **Spleen**—the body’s largest lymphatic organ
- **Parenchyma** exhibits two types of tissue
  - **Red pulp**: sinuses filled with erythrocytes
  - **White pulp**: lymphocytes, macrophages surrounding small branches of splenic artery
Spleen

• Spleen functions
  – Healthy red blood cells (RBCs) come and go
  – For old, fragile RBCs, spleen is “erythrocyte graveyard”
  – Blood cell production in fetus (and very anemic adults)
  – White pulp monitors blood for foreign antigens and keeps an army of monocytes for release when needed
  – Stabilizes blood volume through plasma transfers to lymphatic system

• Spleen is highly vascular and vulnerable to trauma and infection
  – Ruptured spleen requires splenectomy, but this leaves person susceptible to future infections, premature death
Figure 21.14a

Diaphragm
Spleen
Splenic artery
Splenic vein
Pancreas
Kidney
Inferior vena cava
Aorta
Common iliac arteries

Figure 21.14b

Gastric area
Hilum
Renal area
Splenic vein
Splenic artery
Inferior

Figure 21.14c

Red pulp
Central artery (branching)
White pulp
Nonspecific Resistance

• **Expected Learning Outcomes**
  – Identify the body’s three lines of defense against pathogens.
  – Contrast nonspecific resistance with immunity.
  – Describe the defensive functions of each kind of leukocyte.
  – Describe the role of the complement system in resistance and immunity.
  – Describe the process of inflammation and explain what accounts for its cardinal signs.
  – Describe the body’s other nonspecific defenses.
Nonspecific Resistance

• **Pathogens**—agents capable of producing disease
  – Include viruses, bacteria, and fungi

• **Three lines of defenses** against pathogens
  – **First line of defense:** skin and mucous membranes
  – **Second line of defense:** several nonspecific defense mechanisms
    • Leukocytes and macrophages, antimicrobial proteins, natural killer cells, inflammation, and fever
  – **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

• **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
External Barriers

• Skin
  – Makes it mechanically difficult for microorganisms to enter the body
  – Toughness of keratin
  – Too dry and nutrient-poor for microbial growth
  – **Acid mantle:** thin film of lactic and fatty acids from sweat and sebum that inhibits bacterial growth
  – **Dermcidin, defensins, and cathelicidins:** peptides in the skin that kill microbes
External Barriers

• Mucous membranes
  – Digestive, respiratory, urinary, and reproductive tracts are open to the exterior and protected by mucous membranes
  – Mucus physically traps microbes
  – **Lysozyme**: enzyme destroys bacterial cell walls

• Subepithelial areolar tissue
  – Viscous barrier of **hyaluronic acid**
    • **Hyaluronidase**—enzyme used by pathogens to make hyaluronic acid less viscous
Leukocytes and Macrophages

- **Phagocytes**—cells that engulf foreign matter

- **Five types of leukocytes**
  - Neutrophils
  - Eosinophils
  - Basophils
  - Monocytes
  - Lymphocytes
Leukocytes and Macrophages

• 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
Leukocytes and Macrophages

• 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
Leukocytes and Macrophages

• **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
Leukocytes and Macrophages

• **Lymphocytes**
  – Three basic categories: T, B, and NK cells
  – Circulating blood contains
    • 80% **T cells**
    • 15% **B cells**
    • 5% **NK cells**
  – Many diverse functions
Leukocytes and Macrophages

- **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.
Antimicrobial Proteins

- Proteins that inhibit microbial reproduction and provide short-term, nonspecific resistance to pathogenic bacteria and viruses

- Two families of antimicrobial proteins
  - Interferons
  - Complement system
Interferons

- **Interferons**—secreted by certain cells infected by viruses
  - Of no benefit to the cell that secretes them
  - Alert neighboring cells and protect them from becoming infected
  - Bind to surface receptors on neighboring cells
    - Activate second-messenger systems within
Interferons

Interferons (Continued)

– 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

- **Complement system**—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
Complement System

– 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
Complement System

• **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
Complement System

• **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
Complement System

• **Mechanisms of action of complement proteins**
  
  – **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
  
  – **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
Complement System

• Mechanisms of action of complement proteins (Continued)

  – 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
  
  – 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 rapidly, cell ruptures
Complement Activation

Figure 21.15

Classical pathway (antibody-dependent)
- Antigen–antibody complexes form on pathogen surface
- Reaction cascade (complement fixation)

Alternative pathway (antibody-independent)
- C3 dissociates into fragments C3a and C3b
- C3b binds to pathogen surface
- Reaction cascade and autocatalytic effect

Lectin pathway (antibody-independent)
- Lectin binds to carbohydrates on pathogen surface
- Reaction cascade

Classical pathway

Antigen–antibody complexes form on pathogen surface

Reaction cascade (complement fixation)

Alternative pathway
- C3 dissociates into fragments C3a and C3b
- C3b binds to pathogen surface
- Reaction cascade and autocatalytic effect

Lectin pathway
- Lectin binds to carbohydrates on pathogen surface
- Reaction cascade

Four mechanisms of pathogen destruction

- Inflammation
- Immune clearance
- Phagocytosis
- Cytolysis

C3a
- Binds to basophils and mast cells
- Stimulates neutrophil and macrophage activity
- Release of histamine and other inflammatory chemicals

C3b
- Binds Ag–Ab complexes to RBCs
- Coats bacteria, viruses, and other pathogens
- Splits C5 into C5a and C5b
- C5b binds C6, C7, and C8
- C5b678 complex binds ring of C9 molecules
- Membrane attack complex

RBCs transport Ag–Ab complexes to liver and spleen

Opsonization

Phagocytes remove and degrade Ag–Ab complexes

C5b binds C6, C7, and C8

C5b678 complex binds ring of C9 molecules

Membrane attack complex

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The Membrane Attack Complex

- Complement proteins form ring in plasma membrane of target cell causing cytolysis
Natural Killer Cells

- **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)**
The Action of a Natural Killer Cell

1. NK cell releases perforins, which polymerize and form a hole in the enemy cell membrane.
2. Granzymes from NK cell enter perforin hole and degrade enemy cell enzymes.
3. Enemy cell dies by apoptosis.
4. Macrophage engulfs and digests dying cell.

Figure 21.17
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 more good than harm**
  – Promotes interferon activity
  – Elevates metabolic rate and accelerates tissue repair
  – Inhibits reproduction of bacteria and viruses
Fever

- **Antipyretics**—fever-reducing medications
  - Include aspirin and ibuprofen that inhibit Prostaglandin E$_2$ synthesis
- Fever usually triggered by **exogenous pyrogens**—fever-producing agents
  - 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 E$_2$** which also raises set point
- **Stages of fever**
  - Onset, stadium, defervescence
The Course of a Fever

Temperature (°C)

1. Infection and pyrogen secretion
2. Hypothalamic thermostat is reset to higher set point
3. Onset (body temperature rises)
4. Stadium (body temperature oscillates around new set point)
5. Infection ends, set point returns to normal
6. Defervescence (body temperature returns to normal)

Figure 21.18
Reye Syndrome

- **Reye syndrome**—serious disorder in children younger than 15 following an acute viral infection such as chickenpox or influenza
  - Swelling of brain neurons
  - Fatty infiltration of liver and other viscera
  - Pressure of swelling brain
    - Nausea, vomiting, disorientation, seizures, and coma
    - 30% die, survivors sometimes suffer mental retardation
- Can be triggered by the use of aspirin to control fever
- **Never give aspirin to children with chickenpox or flu-like symptoms**
Inflammation

• **Inflammation**—local defensive response to tissue injury, including trauma and infection

• **General purposes** of inflammation
  – Limits spread of pathogens, then destroys them
  – Removes debris from damaged tissue
  – Initiates tissue repair

• **Four cardinal signs of inflammation**
  – Redness, swelling, heat, pain
Inflammation

• **Suffix -itis denotes inflammation of specific organs:** *arthritis, pancreatitis, dermatitis*

• **Cytokines**—small proteins that regulate inflammation and immunity
  – Secreted mainly by leukocytes
  – Alter physiology of receiving cell
  – Act at short range, neighboring cells *(paracrines)* or the same cell that secretes them *(autocrines)*
  – Include interferon, interleukins, tumor necrosis factor, chemotactic factors, and others
Inflammation

• Three major processes of inflammation
  – Mobilization of body defenses
  – Containment and destruction of pathogens
  – Tissue cleanup and repair
Mobilization of Defenses

• 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
Mobilization of Defenses

- **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
Mobilization of Defenses

• 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**
Mobilization of Defenses

• Neutrophil behavior
  – Margination
    • Selectins cause leukocytes to adhere to blood vessel walls
  – Diapedesis (emigration)
    • Leukocytes squeeze between endothelial cells into tissue space

Figure 21.19
Containment and Destruction of Pathogens

• Priority of inflammation is to **prevent pathogens from spreading** throughout body
  – **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
    • Attacked by antibodies, phagocytes, and other defenses
Containment and Destruction of Pathogens

- **Neutrophils**, the chief enemy of bacteria, accumulate at the injury site within an hour
  - After leaving the bloodstream, they exhibit chemotaxis

- **Chemotaxis**—attraction to chemicals such as bradykinin and leukotrienes that guide them to the injury site
Containment and Destruction of Pathogens

• **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
Tissue Cleanup and Repair

- **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
Tissue Cleanup and Repair

- **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
Tissue Cleanup and Repair

- **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
Tissue Cleanup and Repair

• 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
General Aspects of Adaptive Immunity

• Expected Learning Outcomes
  – Define adaptive immunity.
  – Contrast cellular and humoral immunity, active and passive immunity, and natural and artificial immunity.
  – Describe the chemical properties of antigens.
  – Describe and contrast the development of T and B lymphocytes.
  – Describe the general roles played by lymphocytes, antigen-presenting cells, and interleukins in the immune response.
General Aspects of Adaptive Immunity

- **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.
Forms of Immunity

• **Two types of immunity:** cellular and humoral

  – **Cellular (cell-mediated) immunity:**
    • Lymphocytes directly attack and destroy foreign cells or diseased host cells
    • Rids the body of pathogens that reside inside human cells, where they are inaccessible to antibodies
    • Kills cells that harbor them
Forms of Immunity

(Continued)

- **Humoral (antibody-mediated) immunity:**
  - Mediated by antibodies that do not directly destroy a pathogen but tag it for destruction
  - Many antibodies are dissolved in body fluids ("humors")
  - Can only work against the extracellular stages of infections by microorganisms
Forms of Immunity

• **Natural active immunity**
  – Production of one’s own antibodies or T cells as a result of infection or natural exposure to antigen

• **Artificial active immunity**
  – Production of one’s own antibodies or T cells as a result of vaccination against disease
  – **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
Forms of Immunity

• **Natural passive immunity**
  - Temporary immunity that results from antibodies produced by another person
    • Fetus acquires antibodies from mother through placenta, milk

• **Artificial passive immunity**
  - 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
Antigens

- **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
Antigens

• **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
Lymphocytes

- Major cells of the immune system
  - Lymphocytes
  - Macrophages
  - Dendritic cells

- Especially concentrated in strategic places such as lymphatic organs, skin, and mucous membranes

- Three categories of lymphocytes
  - Natural killer (NK) cells: immune surveillance
  - T lymphocytes (T cells)
  - B lymphocytes (B cells)
Lymphocytes

Figure 21.20
Lymphocytes

- **Lymphocytes**, macrophages, and dendritic cells are the major cells of the immune system.

- There are 3 classes of lymphocytes:
  - T cells
  - B cells
  - NK cells
T Lymphocytes (T Cells)

• Three stages in life of T Cell:
  – Born in bone barrow
  – Educated in thymus
  – Deployed to carry out immune function

• Within the thymus
  – Reticular epithelial (RE) cells release chemicals that stimulate maturing T cells to develop surface antigen receptors
  – With receptors, the T cells are now immunocompetent: capable of recognizing antigens presented to them
T Lymphocytes (T Cells)

Within the thymus (Continued)

– RE cells test T cells by presenting *self-antigens* to them; T cells can fail by:
  • Being unable to recognize the RE cells at all
    – Would be incapable of recognizing foreign attack
  • Reacting to the self-antigen
    – Would attack one’s own tissues
– T cells that fail are eliminated by negative selection
  • **Clonal deletion**—self-reactive T cells die and macrophages phagocytize them
  • **Anergy**—self-reactive T cells remain alive but unresponsive
T Lymphocytes (T Cells)

• 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

• Deployment
  – Naive T cells leave thymus and colonize lymphatic tissues and organs everywhere in the body
B Lymphocytes (B Cells)

- **B cells develop in bone**
  - Some fetal stem cells remain in **bone marrow** and differentiate into B cells

- **B cells that react to self-antigens** undergo either **anergy** or **clonal deletion**, same as T cell selection

- **Self-tolerant B cells** synthesize antigen surface receptors, divide rapidly, produce immunocompetent clones

- Leave bone marrow and colonize same lymphatic tissues and organs as T cells
Antigen-Presenting Cells

• T cells cannot recognize antigens on their own. **Antigen-presenting cells (APCs)** are required
  – 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
Antigen-Presenting Cells

• **Antigen processing**
  – APC encounters antigen
  – Internalizes it by endocytosis
  – Digests it into molecular fragments
  – Displays relevant fragments *(epitopes)* in the grooves of the MHC protein
Antigen-Presenting Cells

• Antigen presenting
  – Wandering T cells inspect APCs for displayed antigens
  – If APC only displays a self-antigen, the T cell disregards it
  – If APC displays a nonself-antigen, the T cell initiates an immune attack
  – APCs alert the immune system to presence of foreign antigen
  – Key to successful defense is to quickly mobilize immune cells against the antigen
  – With so many cell types involved in immunity, they require chemical messengers to coordinate their activities—interleukins
Antigen-Presenting Cells

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

Figure 21.21a
Cellular Immunity

• **Expected Learning Outcomes**
  – List the types of lymphocytes involved in cellular immunity and describe the roles they play.
  – Describe the process of antigen presentation and T cell activation.
  – Describe how T cells destroy enemy cells.
  – Explain the role of memory cells in cellular immunity.
Cellular Immunity

- **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
Cellular Immunity

- **Cytotoxic T (T\(_C\)) cells**: killer T cells (T8, CD8, or CD8+)
  - “Effectors” of cellular immunity; carry out attack on enemy cells

- **Helper T (T\(_H\)) cells**
  - Help promote T\(_C\) cell and B cell action and nonspecific resistance

- **Regulatory T (T\(_R\)) cells: T-reg**
  - Inhibit multiplication and cytokine secretion by other T cells; limit immune response
  - Like T\(_H\) cells, T\(_R\) cells can be called T4, CD4, CD4+

- **Memory T (T\(_M\)) cells**
  - Descend from the cytotoxic T cells
  - Responsible for memory in cellular immunity
Cellular Immunity

- Both cellular and humoral immunity occur in three stages
  - Recognition
  - Attack
  - Memory

- Thought of as “the three Rs of immunity”
  - Recognize
  - React
  - Remember
Recognition

• Aspects of recognition in cellular immunity: antigen presentation and T cell activation

• Antigen presentation
  – 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
Antigen Presentation

• T cells respond to **two classes of MHC proteins:** MHC-1 and MHC-II

  – **MHC-I proteins**
    • Constantly produced by nucleated cells, transported to, and inserted on plasma membrane
    • If they are normal self-antigens, they do not elicit a T cell response
    • If they are viral proteins or abnormal cancer antigens, they do elicit a T cell response
      – Infected or malignant cells are then destroyed before they can do further harm to the body
Antigen Presentation
(Continued)

– **MHC-II proteins (human leukocyte antigens, HLAs)**
  • Occur only on APCs and display only foreign antigens

• **T<sub>C</sub> cells respond only to MHC-I proteins**
• **T<sub>H</sub> cells respond only to MHC-II proteins**

<table>
<thead>
<tr>
<th>TABLE 21.2</th>
<th>Comparison of the Responses of Cytotoxic and Helper T Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristic</strong></td>
<td><strong>T&lt;sub&gt;C&lt;/sub&gt; Cells</strong></td>
</tr>
<tr>
<td>Cells capable of stimulating a response</td>
<td>Any nucleated cell</td>
</tr>
<tr>
<td>MHC protein</td>
<td>MHC-I</td>
</tr>
</tbody>
</table>

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T Cell Activation

• T cell activation
  – Begins when $T_C$ or $T_H$ cell binds to a MHCP displaying an epitope that the T cell is programmed to recognize
  – T cell must then bind to another APC protein related to the interleukins
  – T cell must check twice to see if it is really bound to a foreign antigen—costimulation
    • Helps ensure the immune system does not launch an attack in the absence of an enemy
    • Would turn against one’s own body and injure our tissues
T Cell Activation

• Successful **costimulation** will trigger **clonal selection**
  – Activated T cell undergoes repeated mitosis
  – Gives rise to a clone of identical T cells programmed against the same epitope
  – Some cells of the clone become **effector cells** and carry out the attack
  – Other cells become **memory T cells**
T Cell Activation

1. Antigen recognition
   T cell binds to an APC displaying an antigen fragment (epitope).

2. Costimulation
   T cell binds to a second protein on the APC.

3. Clonal selection
   T cell undergoes repeated mitosis and produces a large number of effector cells and memory T cells.

4. Attack
   Effector T cells attack and destroy abnormal cells with a lethal hit; Th cells secrete interleukins that stimulate multiple forms of attack.

Figure 21.22
Attack

- **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
Figure 21.23

Attack

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Macrophage, B cell, or other antigen-presenting cell

Helper T (T4) cell

Macrophage-activating factor
Other cytokines

Macrophage activity
Leukocyte chemotaxis
Inflammation

Interleukin Other cytokines

Clonal selection of B cells

Interleukin Other cytokines

Clonal selection of cytotoxic T cells

Nonspecific defense
Humoral immunity
Cellular immunity
Attack

- **Cytotoxic T (T\(^c\)) cells** are the only T cells that directly attack other cells.

- When T\(^c\) cell recognizes a complex of antigen and MHC-I protein on a diseased or foreign cell, it “docks” on that cell.
• Cytotoxic T cell binding to cancer cell
Attack

• After docking $T_C$ cells deliver a **lethal hit** of chemicals:
  – **Perforin** and **granzymes**—kill cells in the same manner as NK cells
  – **Interferons**—inhibit viral replication
    • Recruit and activate macrophages
  – **Tumor necrosis factor (TNF)**—aids in macrophage activation and kills cancer cells

• After releasing chemicals, $T_C$ cell goes off in search of another enemy cell while chemical do their work
Memory

- **Immune memory** follows primary response in cellular immunity

- Following clonal selection, some $T_C$ and $T_H$ cells become **memory cells**
  - Long-lived
  - More numerous than naive T cells
  - Fewer steps to be activated, so they respond more rapidly
Memory

• 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
Humoral Immunity

• Expected Learning Outcomes
  – Explain how B cells recognize and respond to an antigen.
  – Describe the structure, types, and actions of antibodies.
  – Explain the mechanism of memory in humoral immunity.
  – Compare and contrast cellular and humoral immunity.
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
  - Cellular immunity attacks the enemy cells directly

- **Works in three stages like cellular immunity**
  - Recognition
  - Attack
  - Memory
Recognition

- **Recognition** in humoral immunity
  - *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
Recognition
(Continued)

– Usually B cell response goes no further unless a helper T cell binds to this Ag–MHCP complex
  • Bound $T_H$ 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 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
Attack and Memory

• **Attack** in humoral immunity
  – Antibodies bind to antigen, render it harmless, “tag it” for destruction

• **Memory** in humoral immunity
  – Some B cells differentiate into memory cells
Humoral Immune Response

Figure 21.25

1. **Antigen recognition**
   - Immunocompetent B cells exposed to antigen. Antigen binds only to B cells with complementary receptors.

2. **Antigen presentation**
   - B cell internalizes antigen and displays processed epitope. Helper T cell binds to B cell and secretes interleukin.

3. **Clonal selection**
   - Interleukin stimulates B cell to divide repeatedly and form a clone.

4. **Differentiation**
   - Some cells of the clone become memory B cells. Most differentiate into plasma cells.

5. **Attack**
   - Plasma cells synthesize and secrete antibody. Antibody employs various means to render antigen harmless.
B Cell and Plasma Cell

Figure 21.26a,b
Attack

- **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
(Continued)

- 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
Antibody Structure

Figure 21.27
Attack

• 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
Attack

(Continued)

– **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
Attack

(Continued)

- **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
Attack

• 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, so the variety of proteins must be accomplished by:
  – Somatic recombination
    • DNA segments shuffled and form new combinations of base sequences to produce antibody genes
  – Somatic hypermutation
    • B cells in lymph nodules rapidly mutate creating new sequences
Attack

• **Antibodies** have four **mechanisms** of attack against antigens: neutralization, complement fixation, agglutination, and precipitation

• **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
Attack

• **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
Agglutination by Antibodies

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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
Memory

• Primary response leaves one with an immune memory of the antigen
  – During clonal selection, some of the cells becomes memory B cells
  – Found mainly in germinal centers of the lymph nodes
  – Mount a very quick secondary response
Memory

- **Secondary (anamnestic) response**—if reexposed 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
Humoral Immunity Responses

Figure 21.29

Primary response

Secondary response

Serum antibody titer

Days from first exposure to antigen

Days from reexposure to same antigen

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# Comparison of Cellular and Humoral Immunity

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cellular Immunity</th>
<th>Humoral Immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease agents</td>
<td>Intracellular viruses, bacteria, yeasts, and protozoans; parasitic worms; cancer cells; transplanted tissues and organs</td>
<td>Extracellular viruses, bacteria, yeasts, and protozoans; toxins, venoms, and allergens; mismatched RBCs</td>
</tr>
<tr>
<td>Effector cells</td>
<td>Cytotoxic T cells</td>
<td>Plasma cells (develop from B cells)</td>
</tr>
<tr>
<td>Other cells involved in attack</td>
<td>Helper T cells</td>
<td>Helper T cells</td>
</tr>
<tr>
<td>Antigen-presenting cells</td>
<td>B cells, macrophages, dendritic cells, nearly all cells</td>
<td>B cells</td>
</tr>
<tr>
<td>MHC proteins</td>
<td>MHC-I and MHC-II</td>
<td>MHC-II only</td>
</tr>
<tr>
<td>Chemical agents of attack</td>
<td>Perforins, granzymes, interferons, tumor necrosis factor</td>
<td>Antibodies, complement</td>
</tr>
<tr>
<td>Mechanisms of counteracting or destroying pathogens</td>
<td>Cytolysis, phagocytosis, apoptosis</td>
<td>Cytolysis, phagocytosis, immune clearance, inflammation, neutralization, agglutination, precipitation</td>
</tr>
<tr>
<td>Memory</td>
<td>T cell recall response</td>
<td>Secondary (anamnestic) response</td>
</tr>
</tbody>
</table>
Immune System Disorders

• **Expected Learning Outcomes**
  – Distinguish between the four classes of immune hypersensitivity and give an example of each.
  – Explain the cause of anaphylaxis and distinguish local anaphylaxis from anaphylactic shock.
  – State some reasons immune self-tolerance may fail, and give examples of the resulting disease.
  – Describe the pathology of immunodeficiency diseases, especially AIDS.
Immune System Disorders

• Immune response may be:
  – Too vigorous
  – Too weak
  – Misdirected against wrong targets
Hypersensitivity

- **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
Hypersensitivity

- **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

• Type I (acute)
  – Includes most common allergies
  – IgE-mediated reaction that begins within seconds of exposure
  – Usually subsides within 30 minutes, although it can be severe to fatal
  – Allergens bind to IgE on the membranes of basophils and mast cells
    • Stimulate them to secrete histamine and other inflammatory and vasoactive chemicals
    • Chemicals trigger glandular secretion, vasodilation, increased capillary permeability, smooth muscle spasms, and other effects
Hypersensitivity

(Continued)

– Clinical signs include:
  • Local edema, mucus hypersecretion and congestion, watery eyes, runny nose, hives, and sometimes cramps, diarrhea, and vomiting

– Examples: **food allergies** and **asthma**—local inflammatory reaction to inhaled allergens
Hypersensitivity

• **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
Hypersensitivity

• 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
Hypersensitivity

• Asthma
  – Effects
    • 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

• **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
  – Examples: blood transfusion reaction, pemphigus vulgaris, and some drug reactions
Hypersensitivity

- **Type III (immune complex)**
  - Occurs when IgG or IgM form antigen–antibody complexes
  - Precipitate beneath endothelium of blood vessels and other tissues
  - At site, activate complement and trigger intense inflammation
  - Examples: two autoimmune diseases—acute glomerulonephritis and systemic lupus erythematosus
Hypersensitivity

• 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, beta cell destruction that causes type 1 diabetes mellitus
Autoimmune Diseases

- **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:** cross-reactivity, abnormal exposure to self-antigens, changes in self-antigens
  - **Cross-reactivity**
    - Some antibodies against foreign antigens react to similar self-antigens
    - **Rheumatic fever**—streptococcus antibodies also react with heart valves
Autoimmune Diseases

(Continued)

– 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

– 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 (T\(_R\)) cells
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
Immunodeficiency Diseases

• 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
HIV Structure

Envelope:
- Glycoprotein
- Phospholipid

Matrix

Capsid

RNA

Reverse transcriptase

Figure 21.31a
Acquired Immunodeficiency Syndrome

• By destroying $T_H$ 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
Acquired Immunodeficiency Syndrome

• Signs and symptoms
  – Early symptoms: flu-like symptoms of chills and fever
  – Progresses to night sweats, fatigue, headache, extreme weight loss, lymphadenitis
  – Normal $T_H$ count is 600 to 1,200 cells/$\mu$L of blood, but in AIDS it is less than 200 cells/$\mu$L
  – 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
Kaposi Sarcoma

Figure 21.32
Acquired Immunodeficiency Syndrome

• 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
Acquired Immunodeficiency Syndrome

• Strategies to combat AIDS
  – Prevent binding to CD4 proteins of $T_H$ cells
  – Disrupt reverse transcriptase to inhibit assembly of new viruses or their release from host cells
  – Medications
    • None can eliminate HIV, all have serious side effects
    • HIV develops drug resistance
      – Medicines used in combination
    • Azidothymidine (AZT)
      – First anti-HIV drug: inhibits reverse transcriptase
    • Protease inhibitors
      – Inhibit enzymes HIV needs to replicate
    • Now more than 24 anti-HIV drugs on the market