The Lymphatic System
Nonspecific Resistance and Immunity

Lymph System
• Functions include: draining interstitial fluid, return of leaked plasma proteins, transport of dietary fats, protection or resistance (both specific and non-specific)
• Body cells susceptible to a variety of damaging agents, chemical and biological

Lymph Circulation
• Vessels begin as blind-ended capillaries in all but avascular, nervous, splenic, and bone marrow tissue
• Capillaries drain interstitial fluid between endothelial cells held in place by anchoring filaments
  – Based on relative pressure in and outside
  – Lacteals are specialized lymph capillaries found in villi in small intestine
• Lymph vessels, lymph nodes, then trunks
• Thoracic duct or right lymphatic to subclavian veins
  – Thoracic collects from left side of head, neck, chest, left upper limb & everything below ribs; begins at cisterna chyli
  – Right collects from upper right side of body
  – Trunks are major inflow
• About 3 liters per day
• Lymph flows similarly to veins

Primary Lymphatic Tissue
• Bone marrow - site of B lymphocyte proliferation and pre-T cell production from pluripotent stem cells
• Thymus - located below the sternum, site of T cell proliferation & maturation
  – Two thymic lobes that consist of lobules
    • Each divided into a cortex and medulla
    • Cortex primarily packed, developing T lymphocytes and some reticular epithelial cells
    • Medulla primarily reticular epithelia cells that produce thymic hormones (probably important in managing T cell maturation) and some lymphocytes

Lymph Nodes (Secondary Lymphatic Tissue)
• Grouped in various regions particularly in mammary glands, and around axilla, and groin
• Outer structure or cortex surrounded by connective tissue capsule with trabeculae extensions inward
  – Inter-trabeculae spaces at perimeter - cortex
    • Outer cortex - B-cells (antibody forming plasma cells), dendritic cells
(APCs), and macrophages
- Inner cortex - T-cells (cytotoxic)
  - Inner structure or medulla - lymphocytes (B-cells and plasma cells) are arranged in cords
- One way flow through nodes (many afferent and few efferent vessels)
- Filtering effect - foreign substances trapped by reticular fibers, and then either physically attacked by macrophages or destroyed by immune response from lymphocytes
- T cells and plasma cells leave to provide immune response elsewhere

**Spleen (Secondary Lymphatic Tissue)**
- Spleen - located below diaphragm
- Similar capsule, trabeculae, reticular fiber structure
- Internal structure consists of white & red pulp
  - white - largely B & T lymphocytes for immune response around central arteries
  - red - venous sinuses with projection of splenic cords (concentrations of macrophages, lymphocytes, plasma cells, & granulocytes)
  - Important for phagocytosis of pathogens and removal of aged RBCs and platelets

**Diffuse Lymphatic Tissue**
- Lymph nodules or mucosa-associated lymphoid tissue (MALT)
  - Clusters of lymphocytes associated with connective tissue within mucous membranes in the GI, urinary and reproductive tracts, and respiratory passages
  - e.g. tonsils at back of oral cavity which include pharyngeal (adenoid), palatine, and lingual tonsils (the latter two commonly removed); portions of appendix
  - Their location provides protection against foreign substances inhaled or ingested
- Not encapsulated

**Nonspecific Resistance**
- General defense against a broad range of damaging agents
- Typically the first line of defense
- A variety of defense tactics
  - Mechanical barriers of skin and mucous membranes
  - Chemical & anti-microbial agents
  - Phagocytosis
  - Inflammation
  - Fever

**Skin and Mucous Membranes**
- Most exposure of all cells
  - Use mechanical & chemical protection
Mucous membranes line all cavities connected to exterior

### Mechanical protection
- Skin - tightly packed keratinized epithelial cells of epidermis that are continually shed
- Nasal passage mucous (plus hair) entraps pathogens, dust, other particulates and drains product into acidity of stomach
- Cilia & mucous in respiratory tract move particulates out and into stomach
- Tears, saliva, urine, vaginal secretions, vomiting carry on similar processes

### Chemical protection
- Sebum (from sebaceous gland) has a pH of 3.5, poor environment bacterial and fungal growth
- Perspiration (from sudoriferous glands) floods skin washing skin surfaces
- Enzyme (lysozyme) in saliva, sweat, tears, etc. attack membranes of some bacteria
- Gastric juice in stomach (pH of 1.5-3) kills bacteria and their toxins
- Vaginal secretions are slightly acidic as well

### Antimicrobial Substances
- Act as second line of defense by inhibiting proliferation of bacteria and viruses
- Interferons
  - Produced by virus infected cells that diffuse to surrounding cells, activating the synthesis of anti-viral proteins that inhibit viral replication
  - Also enhance activity of phagocytes, and natural killer cells, inhibit general cell growth, suppress some tumor formation
- Complement System
  - A group of about 20 proteins, that when “activated”, complement or enhance portions of the immune, allergic, and inflammatory responses
  - Activation by either binding of antibodies and antigens (classical pathway) or microbial surface polysaccharides (alternate pathway)
  - Three general effects (overhead)
    - Reinforced activation of inflammation (arteriole dilation, histamine release, phagocyte chemotaxis)
    - Attachment to microbial surface (opsonization) to attract phagocytes
    - Formation of membrane attack complex (MAC) which cause cytolysis

### Natural Killer Cells
- Specialized lymphocytes that kill a variety of pathogens
- 5-10% of lymphocytes in blood are NK cells, also found in lymph nodes, spleen and red bone marrow
- Attack either by release of perforins (causing cytolysis) or binding

### Phagocytosis
- Third line of defense by identifying foreign substances or pathogens and consuming them
- Phagocytes include granulocytes (neutrophils & eosinophils) and
macrophages (wandering or fixed)

- **Mechanisms**
  - **Chemotaxis** - phagocytes attracted to a region of infection or damage by chemical agents released by WBCs, damaged cells, or activated complement proteins
  - **Adherence** - phagocyte adheres to foreign material, enhanced by opsonization
  - **Ingestion** - by phagocytosis resulting in a phagocytic vesicle
  - **Digestion** - lysosomes merge with vesicle to deliver a variety of substances
    - digestive enzymes
    - oxidative chemicals - hydrogen peroxide, hypochlorite, & super oxide \((O_2^-)\)
    - bactericidal substance - defensins
    - undigested parts removed by exocytosis
  - Some pathogens survive, proliferate and ultimately kill phagocyte

**Inflammation**

- Series of activities of blood & tissue cells in response to damage by pathogens, physical breakage or toxins
- Signs include redness, pain, heat, swelling, and possible loss of function
- Three basic stages - vasodilation and increased permeability of blood vessels, phagocyte migration, and tissue repair

**Vasodilation & Permeability**

- This stage primarily responsible for the signs of inflammation
- Vasodilation causes the reddening and increased heat
- Increased permeability enables movement of antibodies, phagocytes and clot forming chemicals to leave capillaries and general edema
  - Fibrinogen forms fibrin network around site and limits pathogen movement
- Several chemical causes for Stage I
  - Histamines released by mast cells, basophils and platelets
  - Kinins formed from precursor in blood (kininogens) - also enhance chemotaxis of phagocytes
    - Kinins, along with foreign substances, may stimulate pain
  - Prostaglandins released by damaged cells enhance histamine & kinin effects; and increased emigration of phagocytes
  - Leukotrienes released by basophils & mast cells
  - Complement components

**Phagocyte Migration**

- Neutrophils are first to arrive at site due to chemotaxis along with the nearby fixed macrophages - phagocytosis begins
- Wandering macrophages are hours later to clean up dying neutrophils, damaged tissue and pathogens
- Dying cells accumulate (pus)
• If pus cannot drain out, an abscess forms
• Prolonged inflammation may cause ulcers

**Fever**
• Not a bad thing, unless too high
• Found to enhance some of the non-specific responses including: effect of interferons and tissue repair

**Immunity**
• Also known as specific resistance
• Involves production of specific lymphocyte or antibody that acts on antigens from strains of bacteria, viruses, cancer cells or toxins
• Prolonged “memory” of antigens from previous exposure enhances a rapid second response
• Dependent on B & T cells, during maturation, cells acquire distinctive surface proteins (antigen receptors and self-receptors)
  – T cells with different proteins on membrane (CD4+ or CD8+)

**Types of Immunity**
• Cell-mediated immunity (CMI) - destruction of antigen by T cells or their derivatives (killer T cells)
  – Effective against intracellular pathogens
• Antibody-mediated immunity (AMI) - destruction of antigens by antibodies produced by plasma cells (activated B cells)
  – Effective against extracellular pathogens
• CD4+ T cells (helper) aid in both

**Antigens**
• Two characteristics
  – Immunogenic - stimulates proliferation of specific T and/or B cells or antibodies
  – Reactive - interacts with receptors on T and/or B cells or antibodies
  – An antigen with both characteristics - complete antigen or immunogen
• Microbial vs. non-microbial (pollen, egg white, incompatible blood or tissue)
• Antigens find their way to several lymphatic tissues - blood/spleen, skin/lymph nodes, mucus membranes/MALT)
• Major histocompatibility complex antigens - recognition of self
  – Class I MHC found on all cells except RBCs
  – Class II MHC found on antigen-presenting cells, thymus cells and activated T cells

**Structural Nature of Antigens**
• On your own

**Antigen Processing**
• Antigen-presenting cells - typically macrophages, B cells and dendritic cells (in epithelial tissue or lymph nodes)
• Exogenous (antigen outside cell) - ingestion, digestion, binding with MHC-II, display
• Endogenous (antigen inside cell - viral) - binding with MHC-I, display

**Cell-Mediated Immunity**
• Antigen is recognized (T cell receptors)
• Small group of specific T cells are activated and proliferate
  – Activation requires costimulator (20 currently known including some cytokines)
• Differentiate into a clone of effector cells (each derived from single activated T cell)
• Antigen is eliminated

**Types of T Cells**
• Helper T cells (T\textsubscript{H} or T4) - respond to MHC II and release interleukin-2 (a cytokine) which helps stimulate activation and/or proliferation of T\textsubscript{C}, B and more T\textsubscript{H} cells)
• Cytotoxic T cells (T\textsubscript{C}, T8 or killer T cells) - respond to MHC I or locate foreign cells and secrete substance to kill them (perforin, lymphotoxin)
• Memory T cells (T\textsubscript{M}) - recognize the original antigen

**Antibody-Mediated Immunity**
• Cells strictly limited to lymphoid tissue (unlike CMI)
• In presence of foreign antigens, specific B cells process and display MHC II, activate and differentiate into plasma cells (helper T cells are involved)
• Plasma cells produce the antibodies which circulate in lymph and blood

**Structure of Antibodies**
• A glycoprotein with four polypeptide chains, 2 identical heavy, and 2 identical light chains
• Disulfide bonds hold all chains together in constant portions
• Variable portions are presented at tips of Y or T shape and form the antigen binding sites
• The two receptor cites enable two antigen attachments
• Five classes of antibodies dependent on complexity

**Antibody Action**
• Neutralization - blanketing antigens
• Immobilization - binding on or near cilia or flagella
• Agglutination - two binding sites can assemble groups of antigens
• Activation of complement
• Enhancement of phagocytosis

**Immunological Memory**
• Presence of long-lived antibodies or lymphocytes (memory B and T cells)
• Fundamental concept to immunization
– Memory B and/or T cells formed during first exposure (primary response)
• See Exhibit 22.4

**Disorders**
• Pay particular attention to AIDS