Human Defense Mechanisms

• First line of defense
  – Innate resistance (or natural immunity)
  – Includes natural barriers
• Second line of defense
  – Inflammation
• Third line of defense
  – Adaptive (acquired or specific) immunity
  – Involves “memory”

First Line of Defense

• Physical and mechanical barriers
  – Skin
  – Mucous Membranes – linings of the GI, genitourinary, and respiratory tracts
    Mechanical removal:
    • Sloughing off of cells
    • Coughing and sneezing
    • Flushing from urinary system
    • Vomiting
    • Mucus and cilia

• Biochemical barriers
  – Enzymes synthesized and secreted in saliva, tears, ear wax, sweat, and mucus
  – Antimicrobial peptides
  – Normal bacterial flora on the skin and in gut

Second Line of Defense

• Inflammatory response
  – Caused by a variety of materials
    • Infection, mechanical damage, ischemia, nutrient deprivation, temperature extremes, radiation, etc.
  – Local manifestations
    • ___________ ___________ _______
  – Vascular response
    • Vasodilation (VD), blood vessels become leaky, WBCs adhere to inner walls of vessels & migrate through the vessels
Inflammation

- **Goals (Benefits of Inflammation)**
  - Limit tissue damage and control the inflammatory process
  - Prevent and limit infection and further damage
  - Initiate adaptive immune response
  - Initiate healing

Plasma Protein Systems

- **Protein systems**
  - __________ system
    - Circulating proteins that can destroy pathogens directly
  - __________ system
    - Forms a clot that stops bleeding
  - __________ system
    - Bradykinin - causes VD, pain, SMC contraction, vascular permeability, and leukocyte chemotaxis

Cellular Mediators of Inflammation

- **Cellular components**
  - Granulocytes, monocytes, platelets, lymphocytes
  - Neutrophils & macrophages (mature monocytes) → phagocytic
  - Eosinophils → kill parasites
  - Platelets → clotting sequence & release mediators
  - Lymphocytes (NK cells) → attack virus and cancer infected cells

Mast Cells

- Important activator of inflammatory response
- Contain granules, located in loose CT
- Skin, digestive lining, and respiratory tract
- **Release:**
  - Histamine → VC of large blood vessels & VD of venules
  - Leukotrienes → SMC contraction, incr. vascular permeability
  - Prostaglandins
    - Similar to leukotrienes; they also induce pain (affect nerves)
  - Platelet-activating factor (PAF)
    - Similar effect to leukotrienes and platelet activation

Mast Cell Degranulation
Phagocytes

- Neutrophils (PMNs)
  - Predominate in early inflammatory responses
    - Arrive 6-12 hr after injury
  - Ingest bacteria, dead cells, and cellular debris
  - Cells are short lived and become component of purulent exudate

Phagocytosis

Monocytes and Macrophages

- Monocytes and macrophages
  - Monocytes - produced in bone marrow → blood → inflammatory site, where they develop into macrophages
  - Macrophages typically arrive at the inflammatory site 24 hours or later after neutrophils

Phagocytes

- Eosinophils
  - Mildly phagocytic
  - Duties
    - Main defense against parasites and regulation of vascular mediators from mast cells

Phagocytes

- Natural killer (NK) cells
  - Function against cells infected with viruses and cancer
- Platelets
  - Activation results in degranulation (release of serotonin) and to stop bleeding
Cytokines

Most cytokines are classified as:

- **Interleukins (IL)**
  - Produced by macrophages and lymphocytes in response to a pathogen or stimulation by other products of inflammation

- **Interferon (INF)**
  - Protects against viral infections
  - Produced and released by virally infected host cells in response to viral double-stranded RNA

Local Manifestations of Acute Inflammation

- Due to vascular changes & leakage of circulating components into the tissue
  - Heat
  - Redness
  - Swelling
  - Pain

Exudative Fluids

- **Serous exudate**
  - __________ exudate: indicates early inflammation
- **Fibrinous exudate**
  - Thick, __________ exudate: indicates more advanced inflammation
- **Purulent exudate**
  - __________: indicates a bacterial infection
- **Hemorrhagic exudate**
  - Exudate contains __________: indicates bleeding

Systemic Changes due to Acute Inflammation

- **Fever**
  - Caused by exogenous and endogenous pyrogens → act on hypothalamus

- **Leukocytosis**
  - Increased numbers of circulating leukocytes

- **Increased plasma protein synthesis**
  - Produced in liver

Chronic Inflammation

- Inflammation lasting 2 weeks or longer
- Often related to an unsuccessful acute inflammatory response
Wound Healing: Resolution and Repair

• Resolution:
  – Restoration of damaged tissue

• Repair:
  – Replacing destroyed tissue with scar tissue

Healing

• Primary intention
  – Wounds that heal under conditions of minimal tissue loss

• Secondary intention
  – Wounds that require a great deal more tissue replacement
    • Open wound

Healing by Primary Intention

Healing by Secondary Intention

Dysfunctional Wound Healing

• Dysfunction during inflammatory response due to:
  – Hemorrhage
  – Fibrous adhesion
  – Infection
  – Excess scar formation

Dysfunctional Wound Healing - Keloid (scar) formation
Dysfunctional Wound Healing

- Wound disruption
  - Dehiscence
    - Wound pulls apart at the suture line
      - Excessive strain and obesity are causes
    - Increases risk of wound sepsis

Concept Check

1. Inflammation:
   - A. Confines and destroys injurious agents
   - B. Stimulates and enhances immunity
   - C. Promotes healing
   - D. All of the above

2. Which of the following is not a local manifestation of inflammation?
   - A. Swelling
   - B. Pain
   - C. Heat and redness
   - D. Leukocytosis

3. The inflammatory response:
   - A. Prevents blood from entering injured tissue
   - B. Elevates body temp. to prevent spread of infection
   - C. Prevents formation of abscesses
   - D. Minimizes injury and promotes healing

4. Scar tissue is:
   - A. Nonfunctional collagen and fibrous tissue
   - B. Functional tissue that follows wound healing
   - C. Regenerated tissue formed in area of injury
   - D. Fibrinogen with entrapped phagocytes and neurons

Adaptive Immunity

Chapter 6

Adaptive (specific) Immunity
- state of protection against infectious agents mainly
  - 3rd line of defense
- Antigens – found on infectious agents, environmental substances, cancers
- Specificity – of antigens for antibodies
- Memory – long lived response
- Antibodies – protect individual from infection
- Lymphocytes – mediate immune response
  - B and T cells
**Humoral & Cellular Immunity**

- Adaptive immunity has 2 components:
  - _______________ _______________

- **Humoral Immunity**
  - Interaction of antibodies with antigens to destroy microbe directly or indirectly via inflammatory mediators

- **Cellular (cell-mediated) immunity**
  - T cells that kill target directly

**Active & Passive Immunity**

- **Active acquired immunity** (active immunity)
  - Produced individual as result of natural exposure or immunization
  - Long lived

- **Passive acquired immunity** (passive immunity)
  - Antibodies or T cells are transferred from donor to recipient (i.e. during pregnancy, immunoglobulin shots)
  - Donor antibodies or T cells destroyed

**Antigens**

- Antigen – proteins or CHO that bind to antibodies or receptors on B and T cells

- Immunogen – will solicit an immune response

**Antibodies**

- Also called immunoglobulins (Ig)

- Produced by plasma cells (mature B cells) in response to exposure to antigen

- Classes of antibody
  - IgG - most abundant class (80-85%), major antibody found in fetus & newborn
  - IgA – found in blood and secretions
  - IgM – largest, produced 1st in initial response to antigen
  - IgE - lowest blood conc., allergic rxn.
  - IgD – low conc. in blood, receptor on B cells.

**Antibodies**

- Structure of Different Immunoglobulins
Primary and Secondary Responses

• Primary response
  – Initial exposure
  – Latent period or lag phase
  • B cell differentiation is occurring
  – After 5 to 7 days, an IgM antibody for a specific antigen is detected
  – An IgG response equal or slightly less follows the IgM response

• Secondary response
  – More rapid
  – Larger amounts of antibody are produced
  – Rapidity is caused by the presence of memory cells that do not have to differentiate
  – IgM is produced in similar quantities to the primary response, but IgG is produced in considerably greater numbers

Concept Check

• 1. An antigen is
  A. A foreign protein capable of stimulating immune response in healthy person
  B. A foreign protein capable of stimulating immune response in susceptible person
  C. A protein that binds with an antibody
  D. A protein that is released by the immune system

• 2. Antibodies are produced by
  A. B cells
  B. T cells
  C. Plasma cells
  D. Memory cells

• 3. The antibody with the highest concentration in blood is:
  – A. IgA
  – B. IgD
  – C. IgE
  – D. IgG

• 4. If a child develops measles and acquires immunity to subsequent infections, the immunity is:
  – A. Acquired
  – B. Active
  – C. Natural
  – D. A and B are correct

• 5. Which cells are phagocytic?
  – A. B cells
  – B. T cells
  – C. T killers
  – D. Macrophages

• 6. When and antigen binds to its appropriate antibody:
  – A. Agglutination may occur
  – B. Phagocytosis may occur
  – C. Antigen neutralization may occur
  – D. All of the above

Infection & Defects in Mechanisms of Defense

Chapter 7
Microorganisms & Humans

- **Mutual relationship**
  - Normal flora (supplied with nutrients, temp. & humidity)
  - Relationship can be breached by injury

- **Pathogens circumvent host defenses**
  - Factors for infection include:
    - Communicability – ability to spread from one individual to another and cause disease
    - Immunogenicity – ability to induce immune response
    - Infectivity – ability to invade and multiply in host

Factors for Infection

- **Pathogenicity** – ability to produce disease
- **Mechanism of action** – how organism damages tissue
- **Portal of entry** – route of infection
- **Toxigenicity** – ability to produce toxins
- **Virulence** – ability of pathogen to cause severe disease

Classes of Infectious Microorganisms

- **Bacteria** – produce toxins, septicemia
- **Viruses** – use host metabolism to proliferate, disrupt host activities; transform
- **Fungi** – mycoses (yeast or mold)
  - Dermatophytes – affect integ. system
- **Parasites**
  - Protozoa – cause of global infections
  - Helminths – flukes and worms

Countermeasures

- **Vaccines**
- **Antimicrobials**
  - Antimicrobial resistance
  - Can destroy normal flora
    - C. difficile
    - Genetic mutations
    - Inactivation
    - Multiple antibiotic-resistance bacteria
    - Methicillin-resistant Staph. aureus (MSSA)

Immune Deficiencies

- **Failure of immune mechanisms of self-defense**
- **Primary (congenital) immunodeficiency**
  - Genetic anomaly
- **Secondary (acquired) immunodeficiency**
  - Caused by another illness
  - More common

Immune Deficiencies

- **Clinical presentation**
  - Development of unusual or recurrent severe infections
    - T cell deficiencies
    - B cell and phagocyte deficiencies
    - Complement deficiencies
Acquired Immunodeficiency Syndrome (AIDS)

- Syndrome caused by a viral disease
  - Human immunodeficiency virus (HIV)
  - Depletes body’s Th cells
- Incidence:
  - Worldwide - 34 million live with AIDS (2011)
  - 1.4 million deaths
  - US newly infected 51,000

Acquired Immunodeficiency Syndrome (AIDS)

- Effective antiviral therapies have made AIDS a chronic disease
- Epidemiology
  - Blood-borne pathogen
  - Heterosexual activity is most common route worldwide
  - Increasing faster in women than men, esp. adolescents
- Pathogenesis
  - Retrovirus
    - Genetic information is in form of RNA
    - Contains reverse transcriptase to convert RNA to DNA

Acquired Immunodeficiency Syndrome (AIDS)

Clinical manifestations

Serologically neg. (no Antibodies); serologically positive but asymptomatic; early stages HIV; or AIDS

Window period
Th cells < 200 cells/mm³ diagnostic for AIDS

Diagnosis of AIDS made in assoc. with various clinical conditions and lab tests
  - Atypical or opportunistic infections and cancer
  - Presence of antibodies against HIV (4 to 7 weeks after blood transmission; 6-14 months after sexual intercourse)
  - Western blot analysis

Acquired Immunodeficiency Syndrome (AIDS)

- Treatment and prevention
  - Highly active antiretroviral therapy (HAART)
    - Reverse transcriptase inhibitors
    - Protease inhibitors
  - New Drugs
    - Entrance inhibitors
    - Integrase inhibitors
  - Vaccine development

Hypersensitivity

- Altered immunologic response to an antigen that results in disease or damage to the host

Hypersensitivity

- Allergy
  - Deleterious effects of hypersensitivity to environmental (exogenous) antigens
- Autoimmunity
  - Disturbance in the immunologic tolerance of self-antigens
- Alloimmunity
  - Immune reaction to tissues of another individual
    - transient neonatal diseases (HDN)
    - transplant rejection and transfusion reaction
Hypersensitivity
- Characterized by the immune mechanism
  - Type I
    - IgE mediated
  - Type II
    - Tissue-specific reactions
  - Type III
    - Immune complex mediated
  - Type IV
    - Cell mediated

Type I Hypersensitivity
- IgE mediated
- Against environmental antigens (allergens)
- IgE binds to Fc receptors on surface of mast cells (cytotropic antibody)
- Histamine release
  - H₁ and H₂ receptors
  - Antihistamines

Type I Hypersensitivity
- Manifestations
  - Itching
  - Urticaria
  - Conjunctivitis
  - Rhinitis
  - Hypotension
  - Bronchospasm
  - Dysrhythmias
  - GI cramps and malabsorption

Type I Hypersensitivity
- Genetic predisposition
- Tests
  - Food challenges
  - Skin tests
  - Laboratory tests
- Desensitization
  - cautiously
Type II Hypersensitivity

- Tissue specific
  - Specific cell or tissue (tissue-specific antigens) is the target of an immune response

- Five mechanisms
  - Cell is destroyed by antibodies & complement
  - Cell destruction through phagocytosis
  - Soluble antigen may enter the circulation and deposit on tissues
  - Antibody-dependent cell-mediated cytotoxicity
  - Causes target cell malfunction

Type III Hypersensitivity

- Immune complex mediated
  - Antigen-antibody complexes are formed in the circulation and are later deposited in vessel walls or extravascular tissues
- Not organ specific
- Serum sickness
- Raynaud phenomena
- Arthus

Immune complex disease

- Serum sickness
  - Caused by formation of immune complexes that lodge in tissues (vessels, kidneys, joints)
- Raynauds
  - Temperature dependent deposits of immune complexes in peripheral capillaries
- Arthus reaction
  - Observed after injection, ingestion, or inhalation
  - Skin reactions after repeated exposure

Type IV Hypersensitivity

- Does not involve antibody
- Cytotoxic T-lymphocytes or lymphokine producing Th1 cells
  - Direct killing by Tc or recruitment of phagocytic cells by Th1 cells
- Examples
  - Acute graft rejection, skin test for TB, contact allergic reactions, and some autoimmune diseases

Allergy

- Most common hypersensitivity and usually Type I
- Environmental antigens that cause atypical immunologic responses in genetically predisposed individuals
  - Pollens, molds and fungi, foods, animals, etc.
- Allergen is contained within a particle too large to be phagocytosed or is protected by a nonallergenic coat
- Bee stings
Autoimmunity

- Breakdown of tolerance
  - Body recognizes self-antigens as foreign
- Sequestered antigen
  - Self-antigens not normally seen by the immune system
- Infectious disease (rheumatic fever, glomerulonephritis)
  - Molecular mimicry
- Neoantigen
  - Haptens become immunogenic when they bind to host proteins

Autoimmune Examples

- Systemic lupus erythematosus (SLE)
  - Chronic multisystem inflammatory disease
  - Autoantibodies against:
    - Nucleic acids, erythrocytes, coagulation proteins, phospholipids, lymphocytes, platelets, etc.

Autoimmune Examples

- Systemic lupus erythematosus (SLE)
  - Deposition of circulating immune complexes containing antibody against host DNA
  - More common in females

Autoimmune Examples

- Eleven common findings:
  - Facial rash (malar rash)
  - Discoid rash
  - Photosensitivity
  - Oral or nasopharyngeal ulcers
  - Nonerosive arthritis
  - Serositis
  - Renal disorder
  - Neurologic disorder
  - Hematologic disorders
  - Immunologic disorders
  - Presence of antinuclear antibodies (ANA)

  - Serial or simultaneous presence of at least four indicates SLE

Alloimmunity

- Immune system reacts with antigens on the tissue of other genetically dissimilar members of the same species
  - Transient neonatal alloimmunity
    - Rh incompatibility
  - Transplant rejection (MHC and HLC) and transfusion reactions (ABO blood groups)
Concept Check

1. What is not characteristic of hypersensitivity?
   A. Specificity
   B. Immunologic mechanisms
   C. Inappropriate or injurious response
   D. Prior contact not needed to elicit a response

2. Which hypersensitivity is caused by poison ivy?
   A. Type I
   B. Type II
   C. Type III
   D. Type IV

3. Which is not an autoimmune disease?
   A. MS
   B. Pernicious anemia
   C. Transfusion reaction
   D. Ulcerative colitis
   E. Goodpasture disease

4. An alloimmune disorder is:
   A. Erythroblastosis fetalis
   B. IDDM
   C. Myxedema
   D. All of the above

5. A positive HIV antibody test signifies that the:
   A. Individual is infected with HIV and likely so for life
   B. Asymptomatic individual will progress to AIDS
   C. Individual is not viremic
   D. Sexually active individual was infected last weekend

Stress and Disease

Chapter 8

Stress

A person experiences stress when a demand exceeds a person’s coping abilities, resulting in reactions such as disturbances of cognition, emotion, and behavior that can adversely affect well-being.

Dr. Hans Selye (1946)

- Worked to discover a new sex hormone
- Injected ovarian extracts into rats
- Witnessed 3 structural changes:
  - Enlargement of the adrenal cortex
  - Atrophy of thymus and other lymphoid structures
  - Development of bleeding ulcers in the stomach and duodenum
Dr. Hans Selye

- Dr. Selye witnessed these changes with many agents (cold, surgery, restraint). He called these stimuli “stressors.”

- Many diverse agents caused same general response:
  - general adaptation syndrome (GAS)

General Adaptation Syndrome (GAS)

- Three stages
  - Alarm stage
    - Arousal of body defenses (fight or flight)
  - Stage of resistance or adaptation
    - Mobilization contributes to fight or flight
  - Stage of exhaustion
    - Progressive breakdown of compensatory mechanisms
    - Onset of disease

GAS Activation

- Alarm stage
  - Stressor triggers the hypothalamic-pituitary-adrenal (HPA) axis
    - Activates sympathetic nervous system (SNS)
- Resistance stage
  - Begins with the actions of adrenal hormones
- Exhaustion stage
  - Occurs if stress continues and adaptation is not successful

Stress Response

- Nervous system
- Endocrine system
- Immune system

Neuroendocrine Regulation

- Catecholamines
  - Released from chromaffin cells of the adrenal medulla
    - Epinephrine released
  - α-adrenergic receptors
    - α₁ and α₂
  - β-adrenergic receptors
    - β₁ and β₂
  - Mimic direct sympathetic stimulation
Neuroendocrine Regulation

• Cortisol (hydrocortisone)
  – Activated by adrenocorticotropic hormone (ACTH)
  – Stimulates gluconeogenesis
  – Elevates the blood glucose level
  – Powerful anti-inflammatory and immunosuppressive agent

Cortisol and Immune System

• Glucocorticoids and catecholamines
  – Decrease cellular immunity while increasing humoral immunity
  – Increase acute inflammation
  – Th2 shift

Stress Response

Stress-Induced Hormone Alterations

• β-Endorphins
  – Proteins found in the brain that have pain-relieving capabilities
  – Released in response to stressor
  – Inflamed tissue activates endorphin receptors
  – Hemorrhage increases levels, which inhibits blood pressure increases and delay compensatory changes

Stress-Induced Hormone Alterations

• Growth hormone (somatotropin)
  – Produced by the anterior pituitary and by lymphocytes and mononuclear phagocytic cells
  – Affects protein, lipid, and carbohydrate metabolism and counters the effects of insulin
  – Enhances immune function
  – Chronic stress decreases growth hormone

Stress-Induced Hormone Alterations

• Prolactin
  – Released from the anterior pituitary
  – Necessary for lactation and breast development
  – Prolactin levels in the plasma increase as a result of stressful stimuli
Stress-Induced Hormone Alterations

• **Oxytocin**
  – Produced by the hypothalamus during childbirth and lactation
  – Produced during orgasm in both sexes
  – May promote reduced anxiety

• **Testosterone**
  – Secreted by Leydig cells in testes
  – Regulates male secondary sex characteristics and libido
  – Testosterone levels decrease because of stressful stimuli
  – Exhibits immunosuppressive activity

Concept Check

1. Which is not characteristic of Selye’s stress syndrome?
   – A. Adrenal atrophy
   – B. Shrinkage of thymus
   – C. Bleeding GI ulcers
   – D. Shrinkage of lymphatic organs

2. Which characterizes the alarm stage?
   – A. Increased lymphocytes
   – B. Incr. SNS act.
   – C. Incr. PSN act.
   – D. Incr. eosinophils

3. CRF is released by the:
   – A. Adrenal medulla
   – B. Adrenal cortex
   – C. Anterior pituitary
   – D. Hypothalamus

4. Stress is defined as any factor that stimulates:
   – A. Posterior pituitary
   – B. Anterior pituitary
   – C. Hypothalamus to release CRF
   – D. Hypothalamus to release ADH

5. Which would not occur in response to stress?
   – A. Increased systolic BP
   – B. Increased Epi
   – C. Constriction of pupils
   – D. Increased adrenocorticoids

6. Which would not be useful to assess stress?
   – A. Total cholesterol
   – B. Esosinophil count
   – C. Lymphocyte count
   – D. Adrenocorticoid levels