Bio217 Pathophysiology Class Notes

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Fall 2012

- **Unit 2: Mechanisms of Defense**
  - Chapter 5: Innate Immunity: Inflammation & Wound Healing
  - Chapter 6: Adaptive Immunity
  - Chapter 7: Infection & Defects in Mechanisms of Defense
  - Chapter 8: Stress and Disease

Innate Immunity: Inflammation & Wound Healing

Chapter 5

Immunity

- First line of defense
  - Innate resistance (or natural immunity)
  - Includes natural barriers
- Second line of defense
  - Innate resistance (or natural immunity)
  - Inflammation
- Third line of defense
  - Adaptive (acquired) 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 (dead skin cells)
    - Coughing and sneezing
    - Flushing from urinary system
    - Vomiting
    - Mucus and cilia (mucus escalator)

First Line of Defense

- Biochemical barriers
  - Enzymes synthesized and secreted in saliva, tears, ear wax, sweat, and mucus (lysozymes)
  - Antimicrobial peptides (acidic)
  - Normal bacterial flora on the skin and in gut

Second Line of Defense

- Inflammatory response
  - Response to cellular injury
  - Local manifestations
    - Heat, swelling, pain, loss of function
  - Vascular response
    - Vasodilation (VD), blood vessels become leaky, WBCs adhere to inner walls of vessels & migrate through vessels

Inflammation

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

Inflammation

Microscopic level
- characterized by fluid accumulation and cells at site of injury

Plasma Protein Systems

- - used in mediation of inflammation
  - Complement system
    - Circulating proteins that can destroy pathogens directly
  - Coagulation system
    - Forms a clot that stops bleeding
  - Kinin system
    - Bradykinin - causes VD, pain, SMC contraction, vascular permeability, and leukocyte chemotaxis

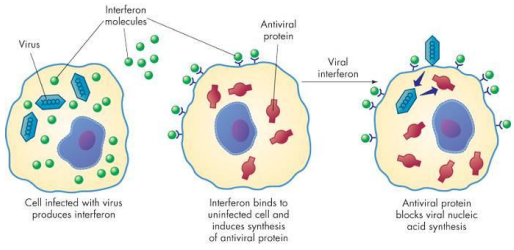
Cellular Mediators of Inflammation

- Cellular components
  - found in blood and surrounding tissues
  - Cytokines (ILs and IFNs)
  - Mast cells
  - Endothelial cells & platelets
  - Phagocytes (neutrophils, macrophages, eosinophils)
  - Lymphocytes (NK cells) → attack virus and cancer infected cells

Cytokines

- 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 RNA

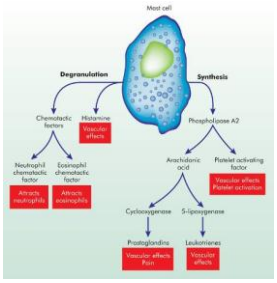
Cytokines



Mast Cells

- Most important activator of inflammatory response
- Skin, digestive lining, and respiratory tract
- Releases:
  - Histamine (vasoactive substance)
    → VD of blood vessels
  - 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

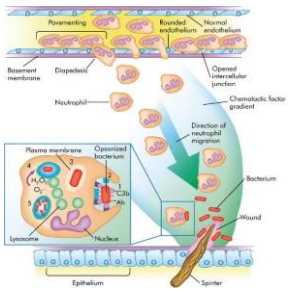
Mast Cell Degranulation



Endothelial Cells & Platelets

- Endothelial cell lining (of blood vessels)
  – prevents blood clotting normally
  - during inflammation allows leukocyte migration
- Platelets
  - activation results in degranulation (release of serotonin) and to stop bleeding

Phagocytosis



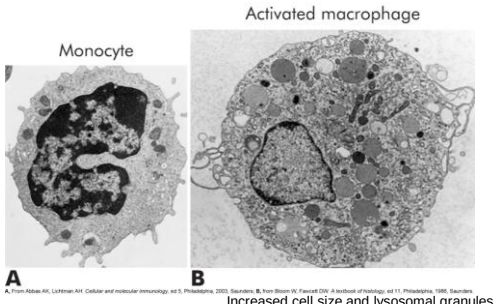
Phagocytes

- 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 a component of the purulent exudate

Phagocytes

- 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

Monocytes and Macrophages



Increased cell size and lysosomal granules

Phagocytes

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

Lymphocytes

- Natural killer (NK) cells
  - Lymphoid tissue derived
  - Function against cells infected with viruses and cancer

Local Manifestations of Acute Inflammation

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

Exudative Fluids

- Serous exudate
  - Watery exudate: indicates early inflammation
- Fibrinous exudate
  - Thick, clotted exudate: indicates more advanced inflammation
- Purulent exudate
  - Pus: indicates a bacterial infection
- Hemorrhagic exudate
  - Exudate contains blood: indicates bleeding

Systemic Changes due to 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

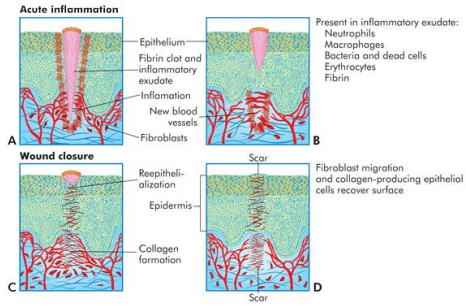
Resolution and Repair

- Resolution
  - Regeneration of tissue to normal structure & fcn
- Repair
  - Extensive damage → scar tissue forms

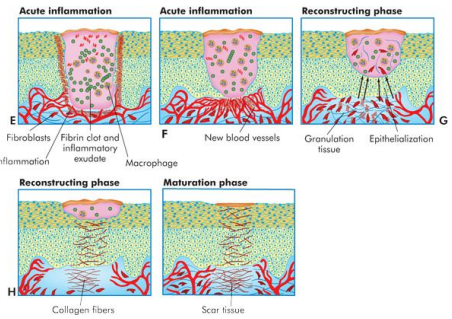
Healing

- 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



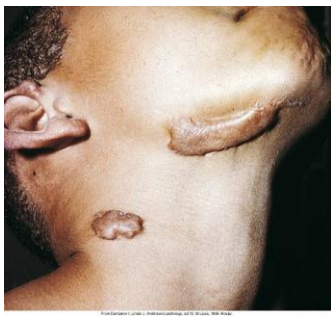
Healing



Dysfunctional Wound Healing

- Dysfunction during inflammatory response
  - 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

Antigen Presentation

- Located on :
  - infectious agents (viruses, bacteria, parasites)
  - noninfectious env. substances (pollen, food, bee venom)
  - drugs, vaccines, transplanted tissues

- Foreign or "nonself"
  - recognized by immune system

Humoral vs Cell Mediated Response

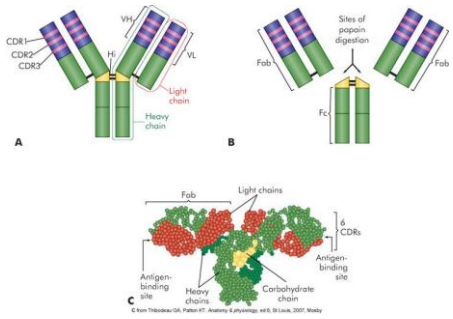
- Humoral immunity
  - mediated by memory B cells and plasma cells
  - B cells dev. into plasma cells that produce antibodies that attack antigen

- Cell-Mediated immunity
  - T cells remove invading antigens by destruction of infected or damaged cell

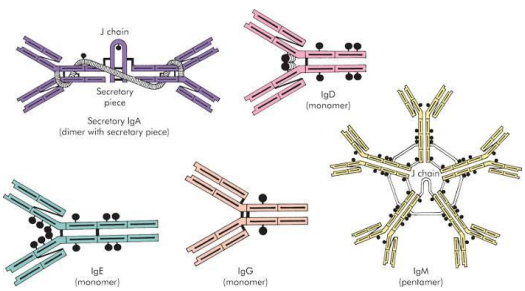
Antibodies

- aka immunoglobulins (Ig)
- Produced by plasma cells (mature B cells) in response to exposure to antigen
- Classes of antibodies
  - 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 - low blood conc., allergic rxn.
  - IgD – low conc. in blood, receptor on B cells

Antibodies



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 IgM response

Primary & Secondary Immune Responses

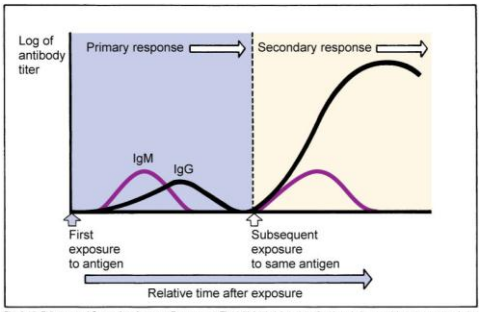


Fig. 6-12. **Primary and Secondary Immune Responses.** The initial administration of antigen induces a primary response during which IgM is initially produced, followed by IgG. Another administration of the antigen induces the secondary response in which IgM is transiently produced and larger amounts of IgG are produced over a longer period of time.

Primary and Secondary Responses

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

Monoclonal Antibody

- - produced in lab from single B cell that is cloned
- - produces known response to antigen
- - high conc. with optimum function

- Used for
  - testing (home and lab)
  - experimental cancer treatments

Active vs Passive immunity

- Active (acquired) immunity – produced by host in response to exposure to antigens or immunization (long lived)
- Passive (acquired) immunity – preformed antibodies are transferred from donor to recipient (mother to baby) or injection of antibodies to fight a particular infection (temporary)

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 an 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 and Defects in Mechanisms of Defense

Chapter 7

Microorganism and Human Relationship

- Mutual relationship
  - Normal flora (supplied nutrients, temp., humidity)
  - Relationship can be breached by injury
- Pathogens circumvent host defenses

Factors for infection include:

- Communicability - ability to spread from one individual another and cause disease
- Immunogenicity - ability to induce immune response
- Infectivity – ability to invade and multiply in the host

Factors for Infection (cont'd)

- Pathogenicity - ability of an agent to produce disease
- Mechanism of action - how organism damages tissue
- Portal of entry – route of infection
- Toxigenicity - ability to produce toxins
- Virulence - ability of a 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 (e.g., MRSA)

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 (cont'd)

- 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 the body's Th cells
  - Incidence:
    - Worldwide: 33.4 million (2008)
    - United States: about 56,000 (2008)

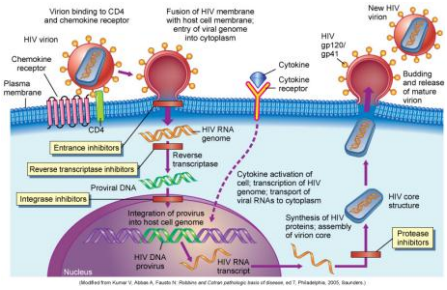
Acquired Immunodeficiency Syndrome (AIDS) (cont'd)

- 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 especially in adolescents

Acquired Immunodeficiency Syndrome (AIDS) (cont'd)

- Pathogenesis
  - Retrovirus
    - Genetic information is in the form of RNA
    - Contains reverse transcriptase to convert RNA into double-stranded DNA

Human Immunodeficiency Virus (HIV)



AIDS

- Clinical Manifestations
  - Depressed levels T helper cells
  - Opportunistic infections (fungal, bacterial, viral, parasitic)
  - Neoplasms (Karposi sarcoma)
- Treatment
  - reverse transcriptase inhibitors, protease inhibitors
  - HAART (highly active antiretroviral therapy)
- Vaccine ??

Hypersensitivity

- Excessive immunologic reaction to an antigen that results in disease or damage to the host after reexposure

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

Hypersensitivity

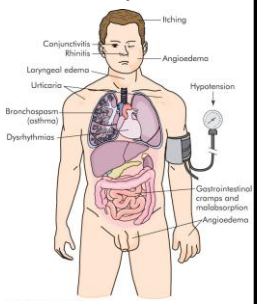
- Immediate hypersensitivity reactions
  - rxn. ccurs in minutes to hours
- Anaphylaxis – within minutes
- Delayed hypersensitivity reactions
  - hours to days

Type I Hypersensitivity

- IgE mediated
- Against environmental antigens (allergens)
- Histamine release (mast cells)

Type I Hypersensitivity

- Manifestations
  - Itching
  - Urticaria
  - Conjunctivitis
  - Rhinitis
  - Hypotension
  - Bronchospasm
  - Dysrhythmias
  - GI cramps & malabsorption



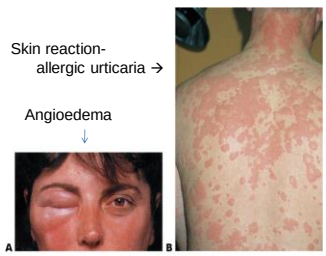
Type I Hypersensitivity

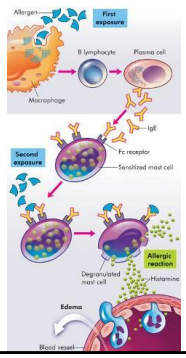
- Genetic predisposition
- Tests
  - Food challenges
  - Skin tests
  - Laboratory tests

Type I Hypersensitivity

Skin reaction-
allergic urticaria →

Angioedema





Type II Hypersensitivity

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

Type II Hypersensitivity

- Five mechanisms of how cells is affected:
  - Cell is destroyed by antibodies and 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 circulation and later deposited in vessel walls or extravascular tissues
- Not organ specific

Type III Hypersensitivity

Immune complex clearance

- Large—macrophages
- Small—renal clearance
- Intermediate—deposit in tissues

Type III Hypersensitivity

- Serum sickness (Raynaud's – rare form)
  - Caused by formation of immune complexes and lodge in tissues (vessels, kidneys, joints)

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
- Examples
  - Acute graft rejection, skin test for TB, contact allergic reactions (poison ivy), and some autoimmune diseases

Allergy

- Most common hypersensitivity, 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

- Genetic predisposition
- Breakdown of tolerance
  - –Body recognizes self-antigens as foreign
- Infectious disease (rheumatic fever, glomerulonephritis)

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
- Clinical manifestations
  - – Arthralgias or arthritis (90% of individuals)
  - – Vasculitis and rash (70%-80%)
  - – Renal disease (40%-50%)
  - – Hematologic changes (50%)
  - – Cardiovascular disease (30%-50%)

Treatment

- No cure for most autoimmune disorders
- NSAIDS, corticosteroids, immunosuppressant drugs
- IV immune globulin, monoclonal antibodies

Alloimmunity

- Immune system reacts with antigens on tissue of other genetically dissimilar members of same species
  - – Transfusion reactions (ABO blood groups)
  - – Transplant rejection and transfusion reactions
    - Major histocompatibility complex (MHC)
    - Human leukocyte antigens (HLC)
    - Rh incompatibility (Hemolytic disease of newborn)

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 rxn.
  - D. Ulcerative colitis
  - E. Goodpasture disease
- 4. An alloimmune disorder is:
  - A. Erythroblastosis fetalis (HDN)
  - 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
- 6. The mechanism of hypersensitivity for drugs is:
  - A. Type I
  - B. Type II
  - C. Type III
  - D. Type IV

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)**

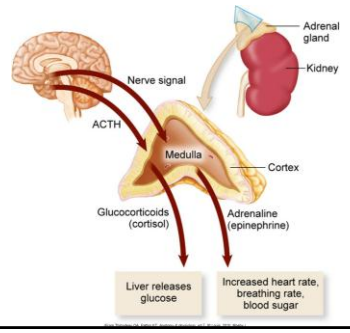
General Adaptation Syndrome (GAS)

- 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

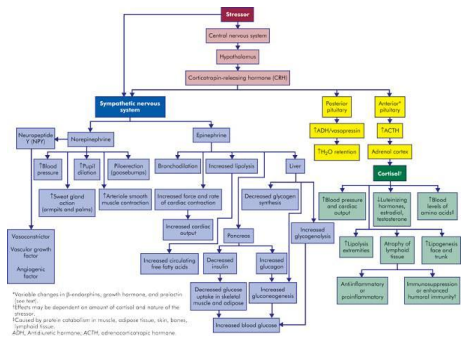
Alarm Stage



Stress Response

- Nervous system
- Endocrine system
- Immune system

Neuroendocrine Regulation



Neuroendocrine Regulation

- Catecholamines
  - Released from adrenal medulla
    - Epinephrine (80%), Norepinephrine (20%) released
  - Mimic direct sympathetic stimulation
    - Increased cardiac output
    - VD to heart, muscles, brain
    - Bronchodilation

Prepares body to act.

Neuroendocrine Regulation

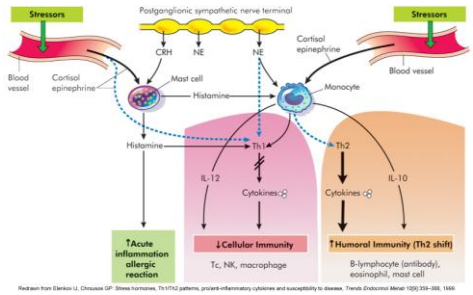
- Cortisol (hydrocortisone)
  - Adrenocorticotropic hormone (ACTH) stimulates release from adrenal cortex
  - Elevates the blood glucose levels
  - Powerful anti-inflammatory and immunosuppressive agent

Prepares body for action by supplying glucose (energy).

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 brain that have pain-relieving capabilities
  - Released in response to stressor
  - Inflamed tissue activates endorphin receptors
  - Hemorrhage increases levels, which inhibits BP increases and delays compensatory changes

Stress-Induced Hormone Alterations

- **Growth hormone** (somatotropin)
  - Produced by anterior pituitary and by lymphocytes and mononuclear phagocytic cells
  - Affects protein, lipid, and carbohydrate metabolism and counters 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 plasma increase as a result of stressful stimuli

Stress-Induced Hormone Alterations

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

Stress-Induced Hormone Alterations

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

Coping

- Manage stressful challenges
- Coping strategies
  - adaptive
  - maladaptive

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 (corticotropic RF) 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

7. A patient experiences a stressor that activates the stress response. What is a physiological effect seen related to the release of catecholamines (80% epinephrine and 20% norepinephrine) into the bloodstream?

A. Increased heart rate.
B. Bronchoconstriction.
C. Increased insulin release.
D. Decreased blood pressure.

8. An example of an adaptive coping response to stress is:

A. Sleeping less
B. Increased smoking
C. Seeking social support
D. Change in eating habits