- Bio217 Pathophysiology Class Notes
- Professor Linda Falkow

- **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

1

Innate Immunity: Inflammation & Wound Healing

Chapter 5

2

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"

3

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

4

First Line of Defense

- 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

5

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

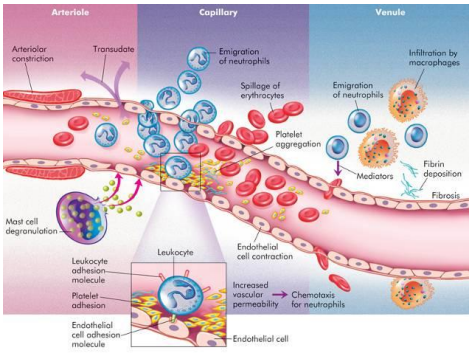
6

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

7

Inflammation



8

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

9

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

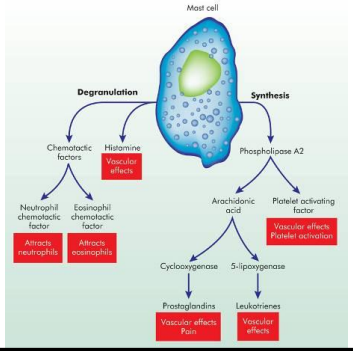
10

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

11

Mast Cell Degranulation



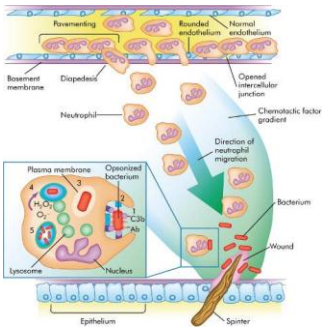
12

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

13

Phagocytosis



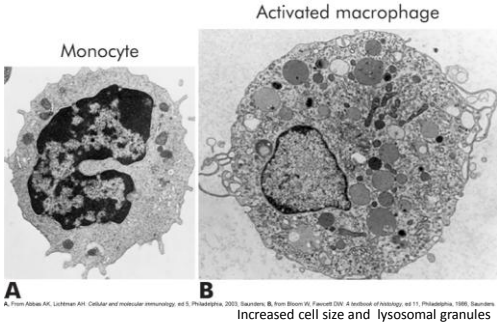
14

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

15

Monocytes and Macrophages



Increased cell size and lysosomal granules

16

Phagocytes

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

17

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

18

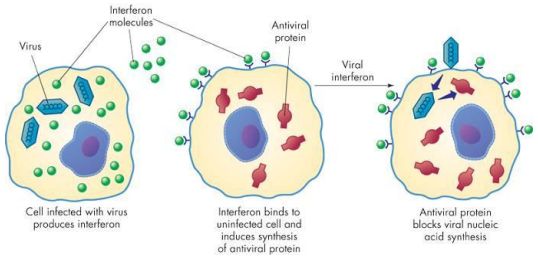
Cytokines

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

19

Cytokines



20

Local Manifestations of Acute Inflammation

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

21

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

22

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

23

Chronic Inflammation

- Inflammation lasting 2 weeks or longer
- Often related to an unsuccessful acute inflammatory response

24

Wound Healing : Resolution and Repair

- Resolution:
  - Restoration of damaged tissue
- Repair:
  - Replacing destroyed tissue with scar tissue

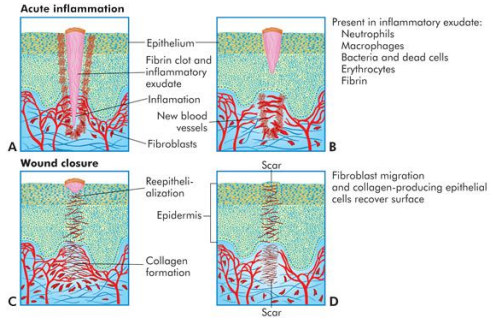
25

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

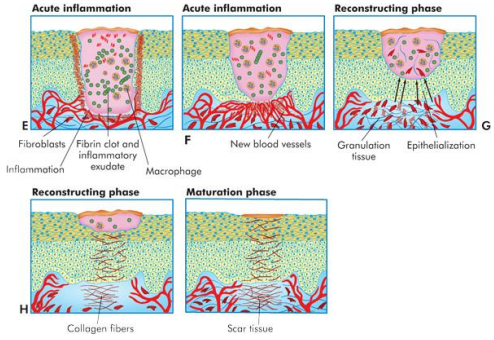
26

Healing by Primary Intention



27

Healing by Secondary Intention



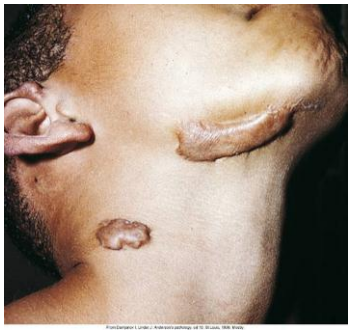
28

Dysfunctional Wound Healing

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

29

Dysfunctional Wound Healing - Keloid (scar) formation



30

Dysfunctional Wound Healing

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

31

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

32

- 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

33

34

Adaptive Immunity

Chapter 6

35

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

36

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

37

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

38

Antigens

- Antigen – proteins or CHO that bind to antibodies or receptors on B and T cells
- Immunogen – will solicit an immune response

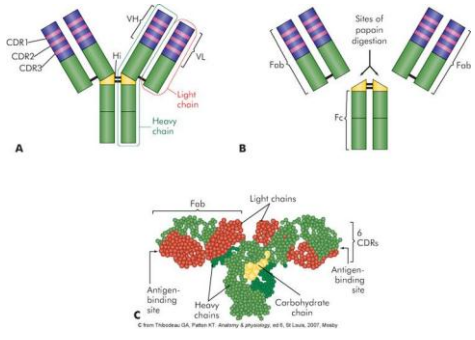
39

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

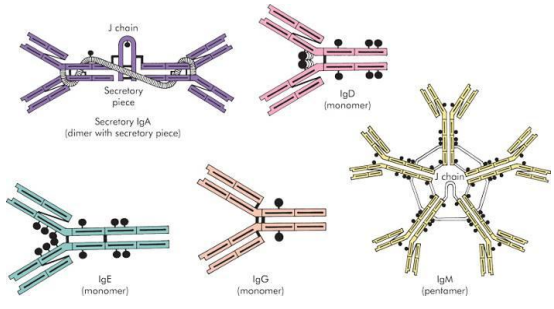
40

Antibodies



41

Antibodies



Structure of Different Immunoglobulins

42

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

43

Primary and Secondary Responses

- 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

44

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

45

- 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

46

- 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

47

Infection & Defects in Mechanisms of Defense

Chapter 7

48

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

49

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

50

Classes of Infectious Microorganisms

- Bacteria – produce toxins, septicemia
- Viruses – use host metabolism t proliferate, disrupt host activities; transform
- Fungi – mycoses (yeast or mold)

  Dermatophytes – affect integ. system
- Parasites

  Protozoa – cause of global infections

  Helminths – flukes and worms

51

Countermeasures

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

52

Immune Deficiencies

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

53

Immune deficiencies

- Clinical presentation
  - Development of unusual or recurrent severe infections
    - T cell deficiencies
    - B cell and phagocyte deficiencies
    - Complement deficiencies

54

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

55

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 iniformation is in form of RNA
    - Contains reverse transcriptase to convert RNA to DNA

56

Acquired Immunodeficiency Syndrome (AIDS)

Clinical manifestations

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

Window period

Th cells <200 cells/mm^3 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

57

Acquired Immunodeficiency Syndrome (AIDS)

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

58

Hypersensitivity

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

59

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

60

Hypersensitivity

- Characterized by the immune mechanism
  - Type I
    - IgE mediated
  - Type II
    - Tissue-specific reactions
  - Type III
    - Immune complex mediated
  - Type IV
    - Cell mediated

61

Hypersensitivity

- Immediate hypersensitivity reactions
- Anaphylaxis
- Delayed hypersensitivity reactions

62

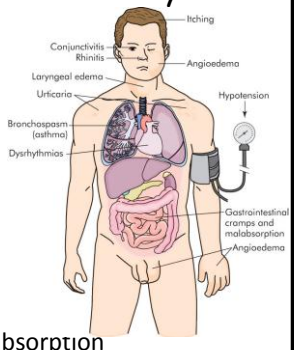
Type I Hypersensitivity

- IgE mediated
- Against environmental antigens (allergens)
- IgE binds to Fc receptors on surface of mast cells (cytotropic antibody)
- Histamine release
  - H_1 and H_2 receptors
  - Antihistamines

63

Type I Hypersensitivity

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



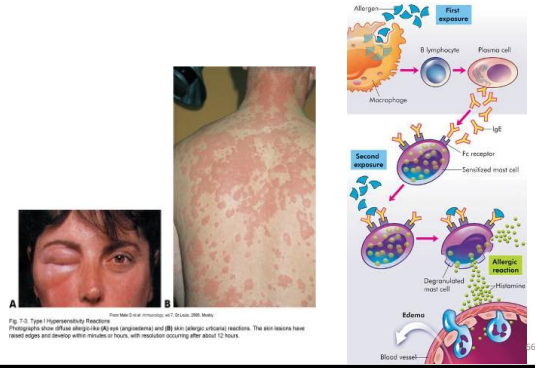
64

Type I Hypersensitivity

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

65

Type I Hypersensitivity



66

Type II Hypersensitivity

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

67

Type II Hypersensitivity

- 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

68

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

69

Type III Hypersensitivity

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

70

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

71

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

72

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

73

Autoimmune Examples

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

74

Autoimmune Examples

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

75

Autoimmune Examples

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

76

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

77

Alloimmunity

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

78

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

79

- 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
  - B. IDDM
  - C. Myxedema
  - D. All of the above

80

- 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

81

Stress and Disease

Chapter 8

82

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

83

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

84

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)**

85

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

86

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

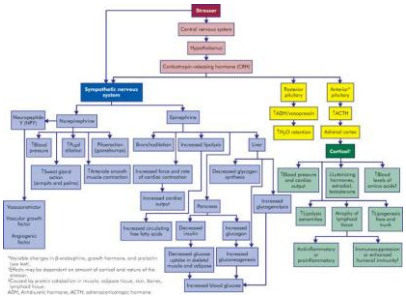
87

Stress Response

- Nervous system
- Endocrine system
- Immune system

88

Neuroendocrine Regulation



89

Neuroendocrine Regulation

- Catecholamines
  - Released from chromaffin cells of the adrenal medulla
    - Epinephrine released
  - α-adrenergic receptors
    - α_1 and α_2
  - β-adrenergic receptors
    - β_1 and β_2
  - Mimic direct sympathetic stimulation

90

Neuroendocrine Regulation

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

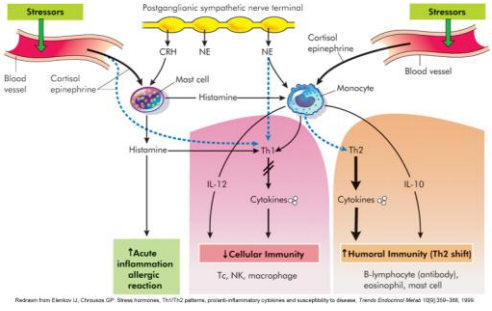
91

Cortisol and Immune System

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

92

Stress Response



93

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 c compensatory changes

94

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

95

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

96

Stress-Induced Hormone Alterations

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

97

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

98

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

99

- 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

100

- 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

101