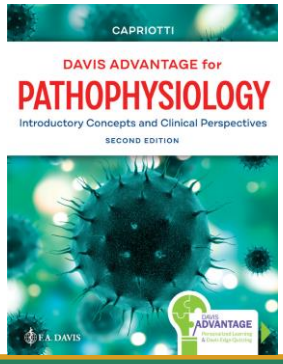


Chapter 11

Disorders of the Immune System

1

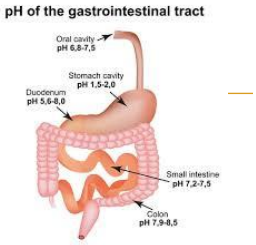
Overview of Immune System

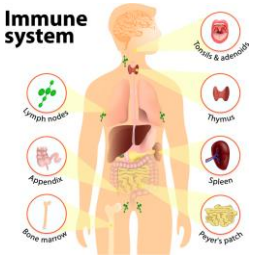
- Two parts
  - Innate
  - Adaptive
- Recognize "self" vs "non-self"
  - Antigens: "non-self" substances, target of immune response
- Immunodeficiency
  - Weakened immune system
- Autoimmunity
  - Attack "self" cells
- Hypersensitivity
  - Overreactive immune system

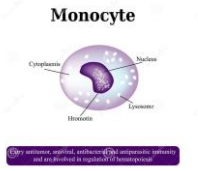
2

Innate Immunity

- Nonspecific
- Physical and chemical barriers
  - Skin, pH of GI tract, enzymes in tears, etc.
- Monocyte: macrophage
  - Macrophages arise from WBCs known as monocytes
    - » Migrate to tissues
    - » Phagocytize, release cytokines, present antigens
    - » Secretory products such as hydrolytic enzymes, TNF-alpha, interleukins







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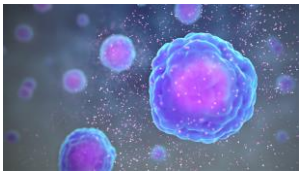
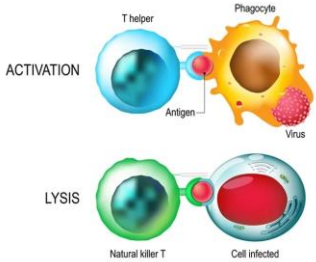
Innate Immunity (continued)

- Cytokines
  - Chemical signals produced by WBCs
  - Regulate/coordinate immune system
  - Inflammation regulation



- Natural killer cells (NK cells)
  - Granular lymphocytes, destroy tumor cells and virus-infected cells



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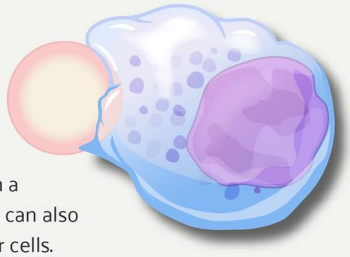
Natural Killer Cell

White Blood Cell



Function: These immune cells can recognize and kill the cells of someone's body that have been infected with a pathogen. Natural killer cells can also recognize and destroy tumor cells.

Disease: People who have deficient natural killer cells, usually because of an inherited immune disorder, may be more prone to certain viruses.

Location: Natural killer cells, or NK cells, are present in the blood and can move into other tissues to find targets.

NIH National Institute of Allergy and Infectious Diseases

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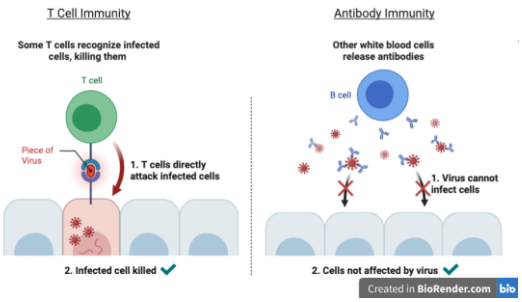
Adaptive Immunity

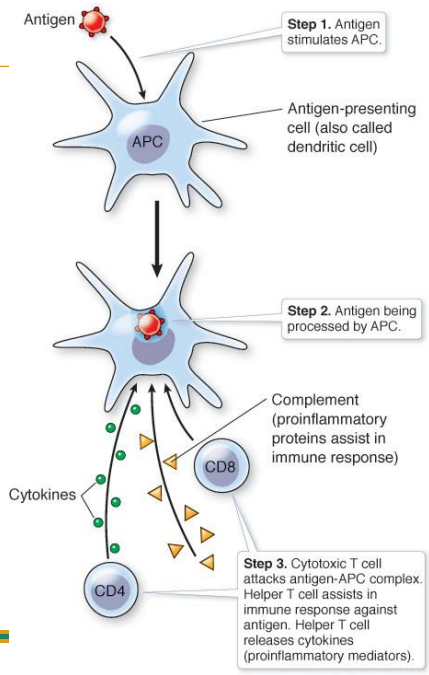


- Acquired
  - Specific response
  - Memory response
- Comprising lymphocytes:
  - T and B cells
  - T cells: cell-mediated immunity
  - B cells: antibody-mediated immunity (humoral immunity)
- Recognize self vs non-self
  - MHC: major histocompatibility complex
  - Also known as HLA: human leukocyte antigen

6

Cell Types

- Antigen-presenting cells (APCs)
  - Macrophages and dendritic cells
  - Present antigen to activate T cells
- CD4 and CD8 cells
  - CD4: helper T cell
  - CD8: cytotoxic T cell
  - HIV damages CD4 cells



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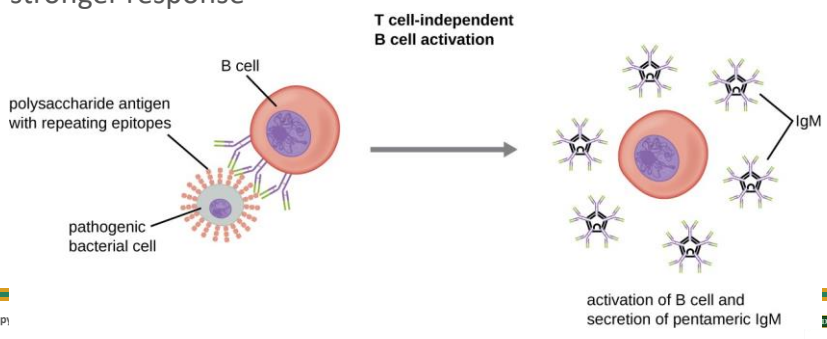
Plasma Cells

- Antigens activate a specific B cell
- Activated B cell becomes plasma cell that produces antibodies (immunoglobulins, Igs)
  - Known as antibody-mediated or humoral immunity
- First antibody-mediated response takes time
- Activated B cell also forms memory cell, which have quicker and stronger response



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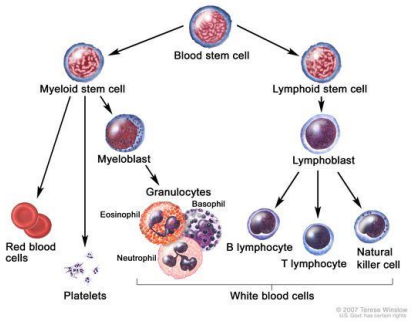
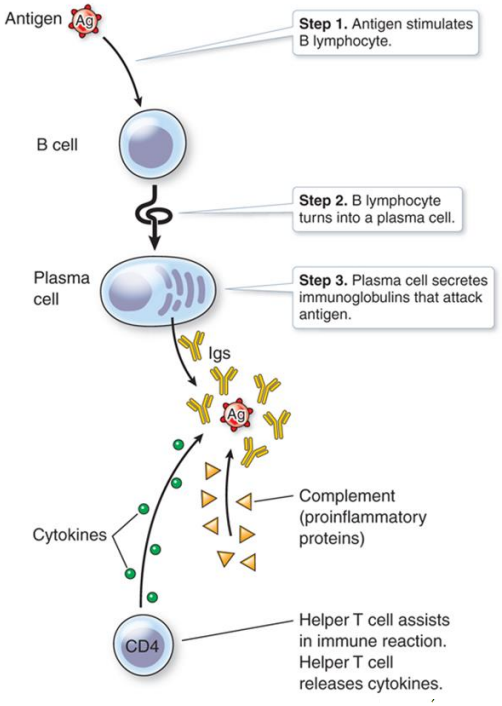
B Cell Activation





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Immunoglobulins (Igs)

- Produced by B cells
- 5 subtypes: *IgM, IgG, IgA, IgD, IgE*
- Bind to specific antigens
- Primary response
  - First exposure to antigen
  - Lag time before Ig levels increase
  - IgM first antibody
- Secondary response
  - Any exposure after the first
  - IgG levels increase rapidly (memory cell response)
  - Antigen neutralized before disease signs and symptoms

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Immunoglobulins (Igs) (continued)

- IgA
  - Mainly found within secretions
    - Tears, saliva, respiratory secretions, GI fluid, and breast milk
- IgE
  - Usually present in very low concentrations in the blood
  - Elevates during allergic reactions
- IgD
  - Hypersensitivity reactions
  - Comprises only 1% of immunoglobulins

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Active Acquired vs Passive Acquired Immunity

Active Acquired

- Exposure to antigen through illness or vaccination (provides immunity)
- Immune system activated and memory cells produced

Passive Acquired

- Individual receives premade antibodies
- Immediate immunity, but short-term
- *Examples:* hepatitis B immunoglobulin (HBIg) or antibodies transferred in breast milk

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Vaccines

- Specific formulation that contains a weakened, *nondisease-producing* pathogen
- Expose the body to the antigen
- Stimulate an immune response and produce memory cells WITHOUT disease contraction

Vaccines (continued)

- "Booster"
  - Additional dose of vaccine to stimulate the immune system's antigenic memory
- Toxoid
  - Vaccine produced against toxin-producing bacteria
  - *Example:* tetanus toxoid

Anergy Panel

- Test of immunocompetence
  - Inject common antigens (mumps, candida) intradermally
  - Patient should have positive skin reaction
  - Lacking response may indicate immunodeficiency

Antibody Screening and Titer

- Antibody titers
  - Antibody screening tests indicating presence and level of antibodies
- Antibody presence can indicate exposure to disease
- Titer can be used to indicate immunity
  - *Example:* antibodies to rubella following vaccination for rubella

Allergy Testing

- Skin test to measure reaction to allergen by scratching or injecting small amount of antigen into the skin

- Serology testing measures IgE levels in response to antigens

Basic Immune Disorders

Overreaction

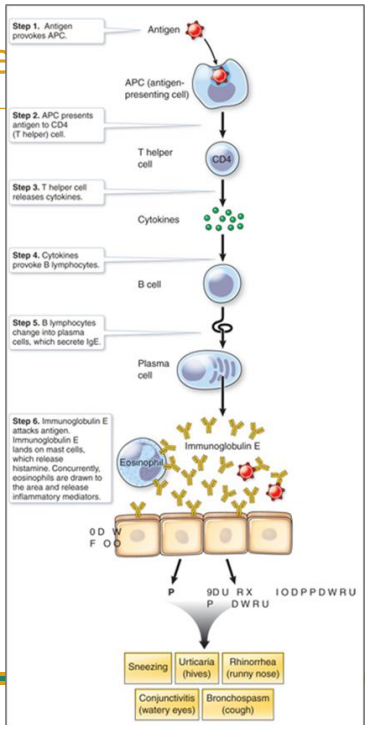
- Hypersensitivity: 4 types
  - Type I: Immediate (allergies)
  - Type II: Cytotoxic
  - Type III: Immune Complex
  - Type IV: Delayed
- Autoimmune disorders

Underreaction

- Immunodeficiency
- Primary (congenital)
  - Present at birth
- Secondary (acquired)
  - Develops due to infection, chemotherapy, immunosuppressive drugs, etc.

Type I: Immediate Hyperse

- Known as allergy or atopic disorder
- Process
  - Antigen (allergen) interacts with APC (antigen-presenting cell)
  - B cells are activated and produce IgEs
  - IgEs bind to mast cells
  - Cause degranulation (release of chemicals from mast cells)
  - Chemicals induce allergy symptoms



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Type I: Hypersensitivity

- Local or systemic response
- Hives (urticaria); nasal discharge; bronchial asthma; allergic gastroenteritis
- Allergic rhinitis
  - 50% of U.S. population test positively
  - Allergen causes release of histamines, prostaglandins, leukotrienes
  - Mucus hypersecretion, bronchiole constriction, pale nasal mucosa, watery eyes, sneezing

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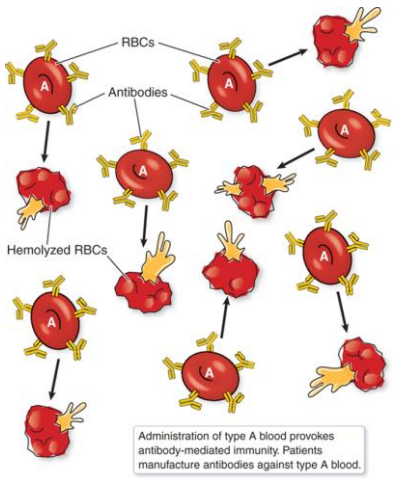
Anaphylaxis

- Severe, life-threatening response
- Overwhelming allergic response
  - Urticaria, bronchoconstriction, laryngeal edema, angioedema (swelling of facial area)
- Death can happen within minutes
- Medical emergency
- EpiPen (epinephrine)
  - Used to counteract response until medical help can be obtained

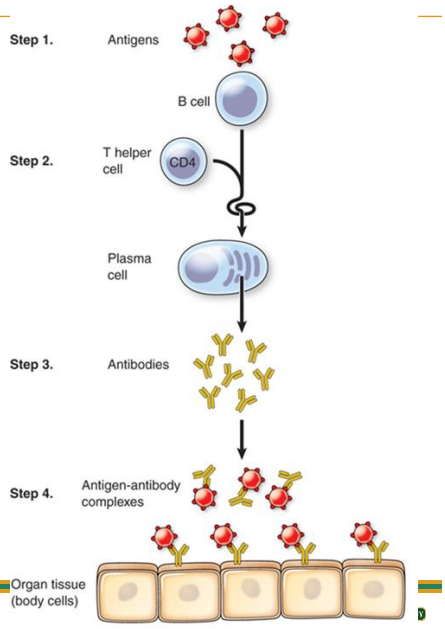
Type II: Cytotoxic Hypersensitivity

- Igs attack antigens on cell surface
- Antibody-mediated cell lysis results
- Blood transfusion reaction is an example of a Type II hypersensitivity



Type III: Immune Complex Hypersensitivity

- Antigen-antibody complex deposited in tissues
- Also known as "immune complex"
- Tissue damage results
- May be systemic (lupus) or localized (rheumatoid arthritis)



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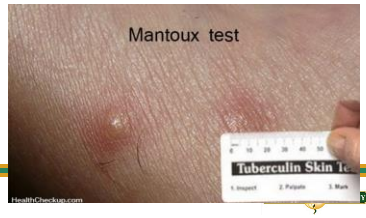
Type IV: Delayed Hypersensitivity

- T cell mediated
- Previous exposure to antigen primes the T cells
- T cell attack does not occur until days after initial exposure (delayed)
- *Example:* poison ivy, transplant rejection
- Mantoux test for tuberculosis demonstrates a Type IV hypersensitivity



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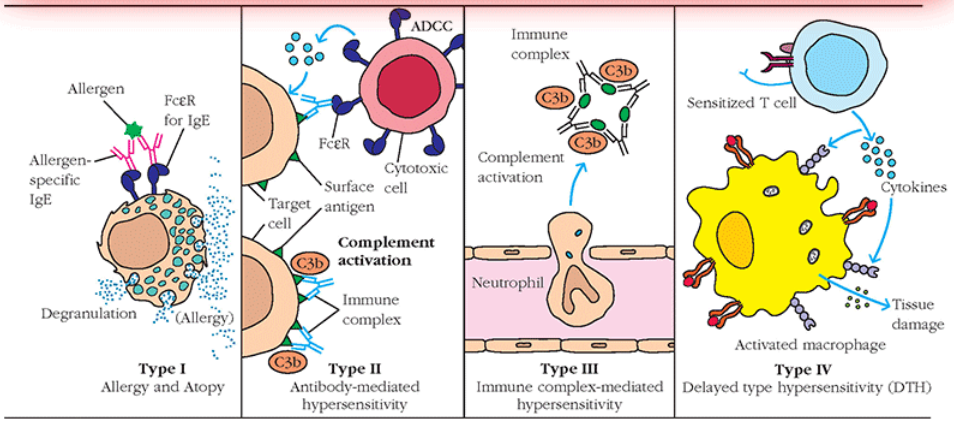
Type I vs Type II vs Type III vs Type IV



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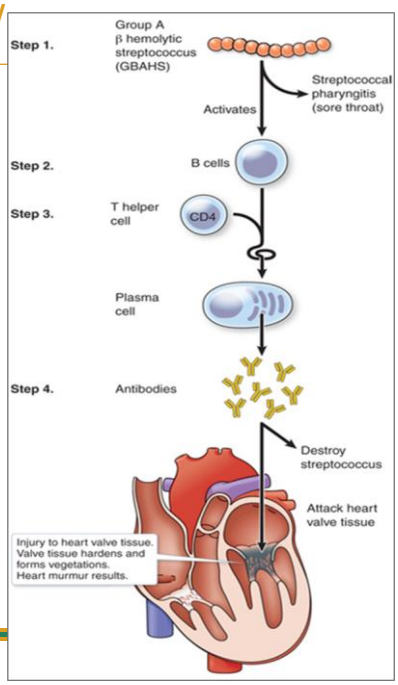
Autoimmune Disorder Overview

- Attack "self" cells
- T cell or Ig-mediated (autoantibodies)
- Organ-specific or systemic
- Underlying etiology is unknown
- Molecular mimicry
  - Body's antigens resemble infectious agent, immune system mistakenly attacks body's cells
  - *Example:* rheumatic fever
    - Antistreptococcal antibodies attack heart valves



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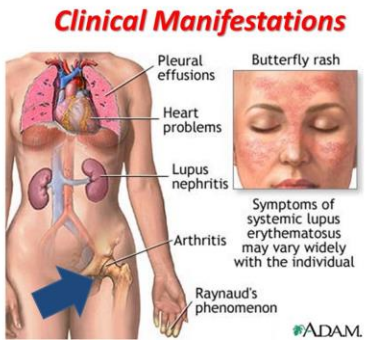
Systemic Lupus Erythematosus (SLE)

- Multisystem disease
- Pathophysiology:
  - Formation of antibodies, particularly antibodies (ANAs)
  - Antibody complexes deposited in tissues lungs, joints, kidney) → triggers inflammation reaction that damages small blood vessels and organ
- Chronic disease with remission and



- Etiology:
  - Genetic predisposition, environmental factors (EBV infection), and hormonal component

- Clinical Presentation (SIGNS AND SYMPTOMS):
- Skin rash (butterfly rash across cheeks), joint inflammation, kidney damage, vasculitis, Raynaud's phenomenon

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Raynaud's Phenomenon

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Systemic Lupus Erythematosus (SLE) (continued)

- Diagnosis:
  - based on history, physical exam, and lab results
- 11 criteria for accurate lupus diagnosis
  - No single lab test is diagnostic for lupus (BOX 11-2)
- ANA elevated in 95% of lupus cases
  - ANA elevation not specific to lupus
- Treatment
  - NSAIDs, corticosteroids, methotrexate

Rheumatoid Arthritis (RA)

- Chronic joint inflammation
  - May affect other tissues
- Etiology (Causes):
  - Genetic factors, environmental factors (infections), hormonal influence (females more likely to develop RA)
- Clinical manifestation (Signs and Symptoms):
  - Symmetrical, tender, swollen joints
    - Joints in fingers, wrists, knees, and hips most common
  - Painful, stiff joints for 30 minutes or more in morning

Rheumatoid Arthritis (RA) (continued_3)

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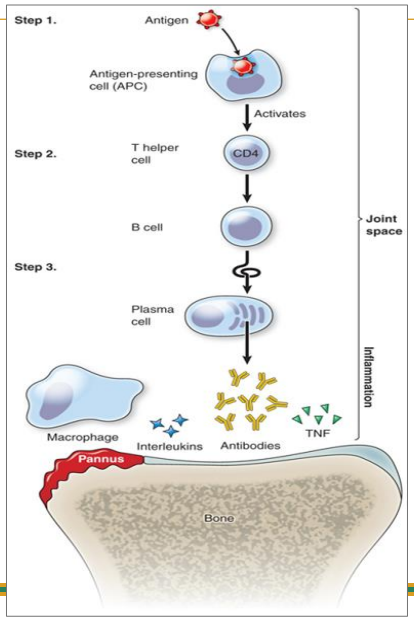
Rheumatoid Arthritis (RA) (continued_1)



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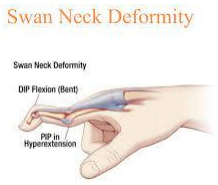
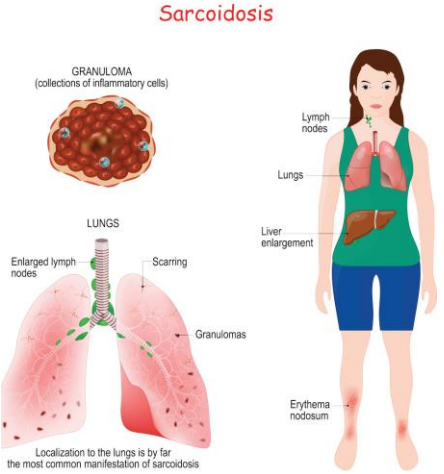
Rheumatoid Arthritis (RA) (continued_2)

- Diagnosis
  - Set of specific criteria (ACR)
  - Rheumatoid factor (RF)
  - ESR, C-RP elevation
  - Swan neck and Boutonniere deformities
  - Elevated anti-citrullinated protein antibodies (ACPAs)
- Treatment
  - NSAIDs, methotrexate
  - DMARDs (disease-modifying antirheumatic drugs)
  - Immunosuppressants



Sarcoidosis

- Chronic, multi-system disorder
- Pathophysiology
  - Accumulation of T cells, macrophages and inflamamatory mediators in organs
    - Chronic inflammation → causes granulomas → cause structural distortions → cause organ disfunction
    - Lungs most frequent place of involvement; skin and eyes also
  - Clinical Manifestation:
    - Erythema nodosum
      - Tender, erythematous nodules on anterior legs
    - Fever, fatigue, malaise, anorexia, weight loss



Sarcoidosis (continued)

- Diagnosis
  - Chest x-ray revealing bilateral hilar lymphadenopathy
  - No diagnostic blood tests
  - Biopsy of sarcoid lesion is mandatory
- Treatment
  - Good prognosis
  - Glucocorticoids, immunosuppressive agents
  - Disease clears spontaneously in 50% of patients

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Sjögren's Syndrome

- Clinical manifestation:
  - Dry eyes (keratoconjunctivitis sicca)
  - Dry mouth (xerostomia)
- Etiology:
- Infiltrate of lymphocytes in exocrine glands → causes hyperplasia of Ductal epithelial cells → lumen of ducts are obstructed
- Immunological destruction of lacrimal and salivary glands
- Women more commonly affected, may also suffer from RA
- Diagnosis
  - ANAs
  - anti-Ro/SSA and anti-La/SSB
- Treatment
  - Symptom relief and limit damage due to dry eye and mouth

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Scleroderma (systemic sclerosis)

- Abnormal accumulation of fibrous tissue in skin and organs
- Etiology: Associated with several gene mutations
- Pathophysiology:
  - Injury to endothelial lining of blood vessels → inflammation → cells infiltrate vasculature, skin, organs
- Clinical manifestation:
  - Most noticeable change is "tightening" of skin; skin appears smooth, shiny, and stretched
  - Contractures of fingers may occur

Scleroderma (continued)

- CREST
  - A type of scleroderma with the Signs/symptoms:
    - Calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia syndrome
- Diagnosis
  - Elevated ANAs
  - "Ground glass" appearance in lungs
- Treatment
  - NSAIDs, corticosteroids, immunosuppressants

Polyarteritis Nodosa

- Necrotizing inflammation of blood vessel walls
- Clinical manifestation:
  - Lesions resemble Type III hypersensitivity damage
- most commonly affected:
  - Renal and visceral blood supplies
- Diagnosis
  - Anti-cytoplasmic antibodies
- Renal involvement is often severe, may lead to death

Immunodeficiency Disorders

- Severe Combined Immunodeficiency Disorder (SCID)
  - Both B and T cells malfunction
  - Live vaccines can not be administered
  - Treatment
    - Bone marrow transplant
  - Death within 2 years from infection without treatment

Immunodeficiency Disorders (continued_1)

- Selective IgA Deficiency (sIgAD)
  - One of most common primary immune deficiencies
  - May be asymptomatic with normal IgG and Ig
  - Increased risk for atopic and autoimmune diseases
  - Some medications can cause IgA deficiency
  - Some infections increase susceptibility for sIgAD
  - Treatment: Monthly injections of Igs can be used, if needed

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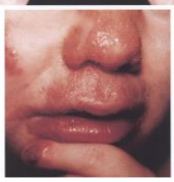
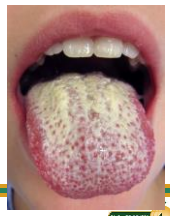
Immunodeficiency Disorders (continued_2)

- Chronic Mucocutaneous Candidiasis
  - Cause:
    - Inability of T cells to respond to *Candida* infection
    - Autoimmune regulator (AIRE) deficiency
  - 80% of cases in children less than 3 years of age
  - S/S: Oral candidiasis and candida dermatitis present
  - Treatment: Systemic antifungal treatment is necessary





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Immunodeficiency Disorders (continued_3)

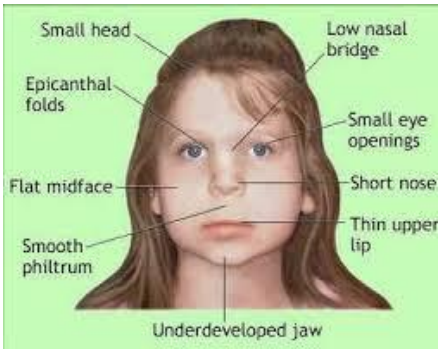
- Hypogammaglobulinemia
  - Igs decreased
  - Defect in B cell development
  - Primary or secondary causes
  - Diagnosis after age of 2 (due to delayed Ig production in some until age of 2)
  - Poor Ig response to vaccination

Immunodeficiency Disorders (continued_4)

- Wiskott-Aldrich Syndrome
  - X-linked recessive disease
  - Eczema, thrombocytopenia, and increased infectious disease risk
  - Genetic defect impairs development of T cells, platelets, and Igs
  - Bleeding is usually first presentation
  - Test for antibody-mediated response to vaccines
  - Treatment
    - Bone marrow transplant, prophylactic antibiotics, Igs

Immunodeficiency Disorders (continued_5)

- DiGeorge Syndrome
  - T cell deficiency due to lack of thymus development
  - Genetic deletion at 22q11.2
  - Other tissues are affected
    - Heart, parathyroid gland, facial structure, cognitive development disorder
  - Multidisciplinary coordinated health care needed



Human Immunodeficiency Virus (HIV)

- Virus that infects CD4 cells (T helper cells)
- Infection has 3 stages
  1. Acute
  2. Chronic
  3. AIDS
     - Acquired Immune Deficiency Syndrome
  - CDC and WHO declare AIDS most rapidly spreading epidemic in world

Human Immunodeficiency Virus (HIV) (continued_1)

- Routes of transmission
  - Sexual activity; semen and vaginal secretions
  - Blood
  - Transplacental
  - Breast milk
  - Organ transplants
  - Saliva (into open mouth wounds)
- High-risk individuals
  - Participate in unsafe sex
  - MSM (men who have sex with men)
  - IV drug abusers

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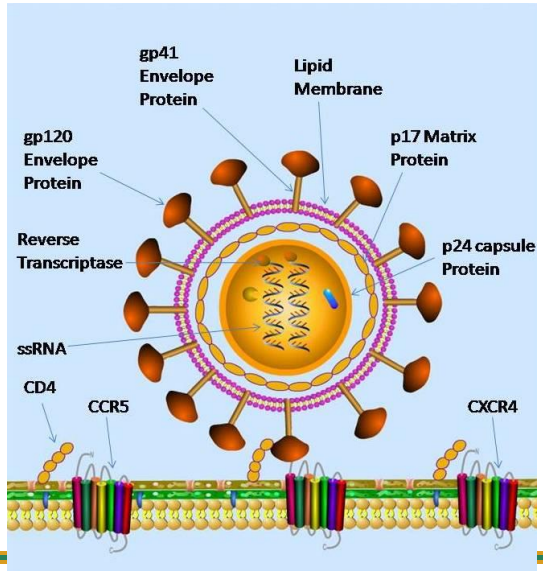
Human Immunodeficiency Virus (HIV) (continued_2)

- HIV-1: More common in US
- HIV-2: More common in West Africa
- Etiology:
  - Retrovirus - RNA virus
    - Reverse transcriptase: enzyme converts HIV RNA into DNA
- Targets cells that express CD4 receptors and chemokine receptors CCR5 or CXCR4



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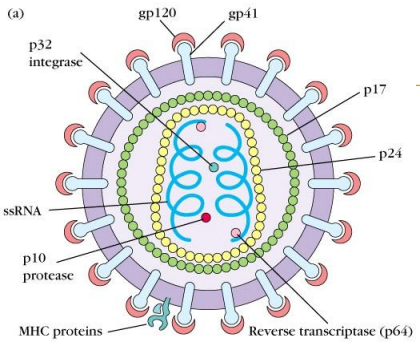
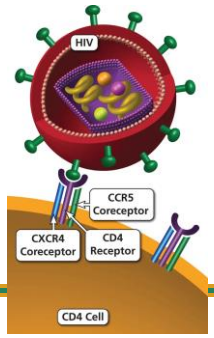
Human Immunodeficiency Virus (HIV) (continued_3)



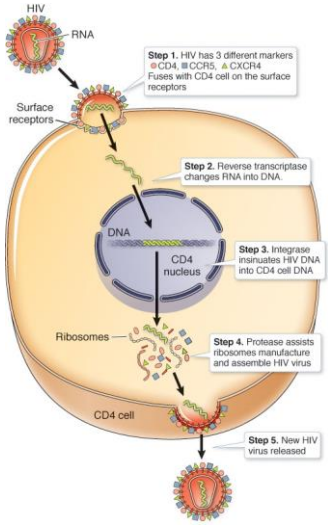
- CCR5 receptor (on surface of T cells)
  - Needed for HIV attachment to T cell
  - Segment of population has genetic mutation
    - HIV resistors
- HIV infection
  - Initial infection leads to flulike symptoms, which resolve, and patient becomes asymptomatic
  - Severe immunodeficiency eventually develops



Human Immunodeficiency Virus (HIV) (continued_4)

- Can remain dormant in inactive CD4 cell
- Macrophages serve as reservoir for HIV
- Infected CD4 cells are unable to carry out normal functions (adaptive immunity compromised)
- HIV eventually destroys the CD4 cell
- Risk of opportunistic infection increases

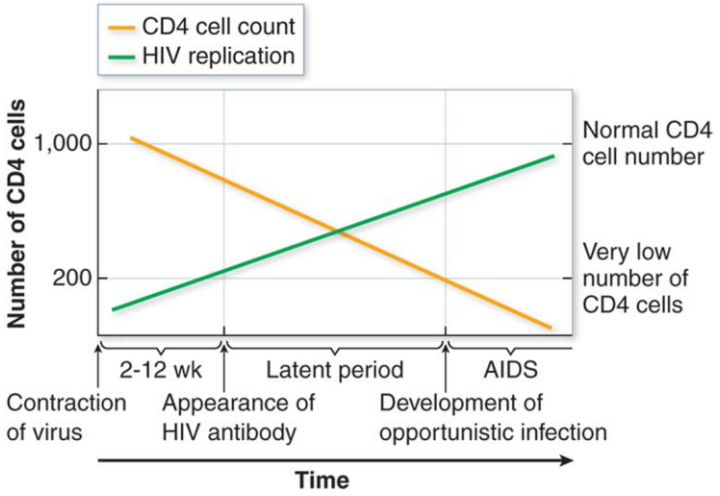
Human Immunodeficiency Virus (HIV) (continued_5)



Human Immunodeficiency Virus (HIV) (continued_6)

- Following initial infection, detectable antibody levels develop in 2 weeks to 6 months
- Early in disease, asymptomatic, but can infect others
  - "Latent period"
- Over time, CD4 levels fall, as HIV RNA levels increase
  - Less than 500 CD4 cells per microliter increase opportunistic infection risk
  - Less than 200 CD4 cells per microliter lead to AIDS classification

Human Immunodeficiency Virus (HIV) (continued_7)



Human Immunodeficiency Virus (HIV) (continued_8)

- Diagnosis
  - HIV RNA assay is earliest means of detection
    - Viral load greater than 100,000 copies/mL indicates high risk for AIDS development
  - Inversion of CD4: CD8 ratio
    - Normal: 2 to 1
    - HIV infection: 1 to 2

Human Immunodeficiency Virus (HIV) (continued_9)

- Seroconversion
  - Antibody negative to antibody positive
  - Detectable antibodies (2 weeks to 6 months after initial infection)
  - ELISA must be confirmed by Western blot
- CD4 levels are monitored
  - Fall below 200 cells, development of AIDS
- Continual viral load testing
  - Severity of disease
  - Effectiveness of treatment

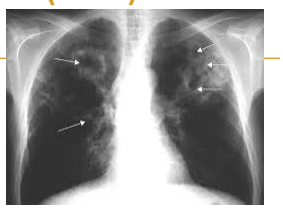
Human Immunodeficiency Virus (HIV) (continued_10)

- Treatment
  - High mutation rate makes vaccine development difficult
- Antiretroviral therapy (ART)
  - Different medications with different mechanisms
    - Fusion inhibitors
    - CCR5 antagonists (aka: early entry antagonists)
    - Nonnucleoside reverse transcriptase inhibitors
    - Nucleoside reverse transcriptase inhibitors
    - Protease inhibitors
    - Integrase strand transfer inhibitors

Human Immunodeficiency Virus (HIV) (continued_11)

- Preventive treatment
  - PrEP (pre-exposure prophylaxis)
    - Use of antiretroviral medications in highly susceptible individuals to prevent infection

Human Immunodeficiency Virus (HIV) (continued_12)



- Complications
  - Opportunistic infections
    - Pneumocystic pneumonia, tuberculosis
  - Malignancies
    - Kaposi sarcoma, non-Hodgkin's lymphoma
  - Paradoxical ART response
    - Inflammatory response to ART (Immune Reconstitution Inflammatory Syndrome: IRIS)
  - AIDS