Chapter 14 – Pathology

A. Overview of terms
   a. Pathology – study of disease
   b. Etiology – cause of disease
   c. Pathogenicity – how a pathogen overcomes host defenses to produce disease
   d. Pathogenesis – development and progression of disease
   e. Epidemiology – occurrence and spread of disease

B. Microbial - Host relationships
   a. Normal Flora
      i. Resident flora – permanent microbes in the body.
         1. Most are commensals, some mutualistic.
         2. Located on skin, mucous membranes of urinary and respiratory systems, intestines
      ii. Transient flora – temporary microbes
   b. Symbiosis – relationship between two organisms
      i. Mutualism – both benefit. E.g. *E. coli* break down food and release vitamin K.
         Also may outcompete pathogens: *microbial antagonism*.
      ii. Commensalism – one benefits, other unharmed. E.g. organisms that live on our skin.
      iii. Parasitism – one benefits, other is harmed. Diseases caused by these. Some are *opportunistic* – causes disease in different environment. E.g. *E. coli* outside of intestine can be harmful, or breakage in skin lets in *Staph*, or weakened immune system lets in *Pneumocytis*.

C. Etiology - Koch’s Postulates
   a. Postulates (Fig. 14.3)
      i. Same pathogen must be present in every case of disease.
      ii. Pathogen must be able to be isolated and cultured in pure media.
      iii. Cultured pathogen must be able to cause disease again.
      iv. Same pathogen must be able to be isolated from the organism given disease.
   b. Exceptions
      i. Pathogen may not be able to be cultured in pure media (e.g. viruses, *Rickettsia*).
      ii. Diseases with multiple causes (e.g. nephritis, UTI)
      iii. Pathogen causes multiple diseases/symptoms (e.g. *Mycobacterium tuberculosis*)

D. Pathogenesis
   a. Types of infections
      i. Duration and severity
         1. Subclinical – no symptoms (e.g. Hepatitis A)
         2. Acute – quick and severe (e.g. flu)
         3. Chronic – slow but continuous (e.g. tuberculosis)
         4. Latent – has an inactive phase (e.g. HIV)
      ii. Placement
         1. Local – confined to one area
         2. Focal – localized to one area but toxins/pathogens can affect other areas
         3. Systemic – affects entire body
      iii. Sequence
         1. Primary infection – the first infection of a healthy person
         2. Secondary infection – the second pathogen. Usually opportunistic
b. Disease progression – general stages (Fig. 14.5)
   i. Incubation – initial infection but no symptoms yet
   ii. Prodromal – early/mild symptoms
   iii. Illness – most acute symptoms, immune system over-run. Acme is the peak.
   iv. Decline – begin recovery. Symptoms subside, immunity recovers

E. Epidemiology
   a. Spread of infection
      i. Occurrence (Fig. 14.4)
         1. Incidence - # of people who got the disease during a period of time
         2. Prevalence - # of people who have the disease at a given point in time
      ii. Degree of spreading
         1. Endemic – localized to a certain geographic region and considered “normal”. Sometimes seasonal (e.g. chickenpox)
         2. Epidemic – an outbreak at higher than normal rates (e.g. Diphtheria in former USSR 1990s)
         3. Pandemic – world wide. E.g. 1918 flu or current AIDS
      iii. Reservoirs – sources of infection
         1. Human – e.g. HIV
         2. Animal – usually vectors such as arthropods
         3. Non-living – soil and water are main ones
      iv. Transmission (Fig. 14.6-8)
         1. Contact
            a. Direct – requires touching of individuals
            b. Indirect - use nonliving intermediate called a fomite
            c. Droplet – in a liquid droplet (e.g. sneezing)
         2. Vehicle – uses medium (e.g. water, air, food)
         3. Vector – uses a living organisms
            a. Mechanical – passive transfer
            b. Biological – transfer is necessary for lifecycle of pathogen
   b. Nosocomial infections – spread through hospitals (Fig. 14.9)
      i. Common microbes and infections (Tab. 14.5)
      ii. Compromised host – wounds, lowered immunity
      iii. Chain of transmission – hospital practices may spread disease
         1. Multiple modes of transmission
         2. Equipment and procedures contribute to transmission
   c. Methods of investigation
      i. Descriptive – describes occurrence of disease to trace back to origin. E.g. John Snow (1850) solved cholera outbreak by mapping individuals and finding common water source.
      ii. Analytical – cause and effect relationship of disease. E.g. Florence Nightingale found factors contributing to epidemic typhus (poor sanitation and food)
         1. Handout on hot tub rash
      iii. Experimental – potential causative agents are tested to see if they cause disease. Not ethical in humans.

F. Public Health Organizations
   a. Center for Disease Control and Prevention (CDC) – US organization
      i. Charge
         1. Provide safety guidelines
2. Recommendations on drugs and vaccines
3. Storing drugs and vaccines in cases of emergency

b. World Health Organization (WHO) – International
   i. Similar charge as CDC but on a global scale. Have many direct activities as well
   ii. Publishes *Weekly Epidemiological Record*.

**Chapter 15 – Pathogenicity**

A. Host Entry
   a. Portals
      i. Mucous membranes – on most inner linings (e.g. respiratory, gastrointestinal, entourinary, conjunctiva)
      ii. Skin – outer lining.
      iii. Parenteral – directly deposited on target tissue. Usually due to wounds, surgery, animal bites.
   b. Dosage
      i. ID$_{50}$ – pathogen dose necessary to infect half of population.
      ii. LD$_{50}$ – toxin dose necessary to kill half of population.
   c. Adherence
      i. Use pili, fimbriae, capsule, cell wall etc. for binding.
      ii. May use adhesins to specifically bind receptors in tissue specific adherence. (Fig. 15.1)
      iii. Biofilms – mass of pathogens in cooperative adherence. First organisms attached secrete materials that assist others to help form the biolayer. E.g. dental plaques on teeth.

B. Tissue Penetration – most pathogens must enter a cell to thrive.
   a. Entry
      i. Endocytosis – adherence can trigger endocytosis in host cell. Invasins may be involved that help rearrange cytoskeleton to facilitate entry and intracellular movements. (Fig. 15.2)
      ii. Tissue degradation – enzymes secreted that dissolve barriers.
         1. E.g. hyaluronidase – produced by *strep* breaks down hyaluronic acid, a sugar that holds cells together. This is the cause of gangrene.
         2. E.g. collagenase - produced by *Clostridium* breaks down protein collagen which holds together connective tissue.
   b. Evasion
      i. Structures
         1. Capsules – resists phagocytosis by white blood cells.
         2. Cell wall – proteins and waxes in cell wall also resist phagocytosis.
      ii. Enzymes
         1. Induce clots – coagulases produced by *staph* allow clots to form and shield the pathogen from host defenses.
      iii. Antigenic variation – surface proteins are changed to avoid immune detection. Due to built-in variation and high mutation rate.

C. Tissue Damage
   a. Use up resources – nutrients are taken from host. E.g. mechanism of siderophores that scavenge iron.
   b. Direct damage – physical destruction by movements, digestion.
   c. Toxins
i. Exotoxins – secreted proteins
   1. A-B toxins (Fig. 15.5)
      a. B binds host cell receptor, A inhibits protein synthesis.
      b. E.g. diphtheria toxin – nerve, heart, kidney cells.
   2. Membrane-disrupting – may lyse cell by forming protein channels in membrane, or direct interference of phospholipids bilayer.

ii. Endotoxins – lipopolysaccharides (LPS) of cell wall
   1. In Gram- bacteria only. Released upon death of bacterium.
   2. Effects
      a. Stimulate macrophages to release cytokines. This may result in fever, chills, shock etc. (Fig. 15.6)
      b. Activates blood clotting.

Chapter 16 – Innate Immunity (Non-specific Defenses)

A. Barriers - physical and chemical protection
   a. Skin – protective layer + oil glands (Fig. 16.2)
   b. Mucous membranes – acids, mucous, saliva, tears (Fig. 16.3)
   c. Competition with normal flora.

B. Cellular
   a. Cell types (Tab. 16.1)
      i. Granulocytes – have granules. Some release chemicals, others are phagocytic
      ii. Agranulocytes – no granules. Some release chemicals, others are phagocytic, lymphocytes are used in specific defense.
   b. Phagocytosis
      i. Steps: chemotaxis, adherence, ingestion, digestion, excretion (Fig. 16.7).
      ii. Some will hold on to antigens to activate specific defenses.

C. Inflammatory Response
   a. Caused by direct damage to tissue. Symptoms include swelling, redness, pain.
   b. Mechanism (Fig. 16.8)
      i. Damaged tissue releases chemicals that lead to vasodilation and leaky vessels. E.g. histamine released by mast cells in connective tissue.
      ii. White blood cells migrate to site of damage by squeezing through leaky walls by diapedesis (includes margination and emigration). Some cells fight infection, platelets help clot broken vessels.
      iii. Abscess forms with pus from concentration of cells and debris.
   c. Chronic inflammation
      i. Continuous inflammation response due to persistent damaging agent.
      ii. Granulomas can form – a pocket containing the walled-off agent. E.g. tubercles in tuberculosis.

D. Fever – raised body temperature
   a. Mechanism
      i. Phagocyte stimulation releases IL-1 which stimulates hypothalamus to raise thermostat set point. Other cytokines (e.g. TNFs) may also stimulate hypothalamus. (Fig. 15.6)
      ii. Temperature raised by blood vessel constriction, increase metabolism, shivering.
   b. Purposes – slow pathogen growth, stimulate macrophages, speed tissue repair.
c. Complications – heart dysfunction, metabolic side effects (dehydration, acidosis, electrolyte imbalance)

E. Complement System
   a. Components – made of proteins that activate and work with one another. Activation through cascades.
   b. Pathways of action (Fig. 16.9)
      i. Opsonization – enhancement of phagocytosis by coating bacteria.
      ii. Inflammation – stimulates mast cell release of histamine and a chemoattractant for macrophages.
      iii. Cytolysis – membrane attack complex (MAC) forms and creates pores in membrane of pathogen. (Fig. 16.10)
   c. Pathways for activation – these allow for multiple ways to initiate cascade.
      i. Classical – uses antibodies to recognize antigens (Fig. 16.12)
      ii. Alternative – uses protein factors to recognize lipocarbohydrates. (Fig. 16.13)
      iii. Lectin – uses lectin to recognize carbohydrates. (Fig. 16.14)

F. Interferon
   a. Small proteins that induce transcription.
   b. \(\alpha\)-IFN and \(\beta\)-IFN produced by infected cells as a distress signal. (Fig. 16.15)
      i. Txn and tln of IFN triggered by infection.
      ii. IFN is released and sensed by uninfected cells. Usually by cell signaling (receptor, signal transduction, response)
      iii. Uninfected cell produces antiviral proteins (AVP) which inhibit viral replication.
   c. \(\gamma\)-IFN produced by lymphocytes. Stimulates neutrophils and macrophages.

**Chapter 17 – Adaptive (Specific) Immunity**

A. Main components
   a. Features of Adaptive Immunity
      i. Recognition of foreign particles. Antigens are foreign and recognized by antibodies or T-cell receptors (Fig. 17.1)
      ii. Specificity and diversity – we can make up to 100 million different antibodies/T-cell receptors. Each can recognize a specific shape.
      iii. Memory – we can be trained to respond more quickly to a second exposure of an antigen.
   b. Main Parts
      i. Humoral Immunity – fights small pathogens (viruses, bacteria, toxins)
         1. Uses B cells.
         2. Antibody is main weapon. Soluble factor.
      ii. Cell-Mediated Immunity – fights larger organisms (infected cells, eukaryotes)
         1. Uses T cells.
         2. T-cell receptor is main weapon. Fights “hand-to-hand.”
   c. Differentiation
      i. Both B cells and T cells are derived from stem cells (Fig. 17.8).
      ii. Lymphocytes that recognize self-antigens are destroyed in the fetus. This is clonal deletion
      iii. T cells mature in thymus gland which is mostly active in children.

B. Humoral Immunity
   a. Clonal Selection (Fig. 17.5)
      i. \(10^8\) antibodies. Each B cell makes one type of antibody. Binding of an antigen to the one cell that has the correct antibody. Makes it divide.
ii. Activated B cell will produce memory and plasma cells.
iii. Memory cells remain in body for a long time in case of subsequent exposure to antigen.
iv. Plasma cells produce antibodies (2000/sec)
b. Antibody Structure
   i. Y shaped (Fig. 17.3)
      1. Made of two heavy and two light chains. Each has a constant (C) and variable (V) region.
      2. V regions make up the antigen binding sites.
      3. Fc domain is stem formed from heavy C regions
   ii. 5 Classes – IgG, M, A, D, E (Table 17.1)
c. Antibody Action (Fig. 17.7)
   i. Agglutination – clumping of pathogen. Eases phagocytosis of small sized objects.
   ii. Opsonization – coats pathogen for better phagocytic recognition.
   iii. Neutralization – surrounds pathogen or toxin preventing it from attaching or entering cell.
   iv. Cytotoxicity – coated pathogen will be recognized by cytotoxic lymphocytes.
   v. Complement – classical system activated by antibodies.
   vi. Inflammation – complement will induce inflammation.
d. Immune Response (Fig. 17.16)
   i. Initial exposure triggers primary response. May not be protective.
   ii. Second exposure triggers stronger secondary response. Usually more protective.
C. Cell-Mediated Immunity
   a. Communication
      i. Cell-cell contact via receptors. E.g. CD4 and CD8 receptors.
      ii. Chemicals – uses cytokines
   b. Cell types and functions
      i. Antigen presenting cells (APC) (Fig. 17.13-14)
         1. Displays an antigen on MHC (major histocompatibility complex), a protein that marks cell as “self” and to display an antigen.
         2. Dendritic or macrophages
      ii. Clonal selection – a T cell will become activated by being bound by an antigen and differentiate into the cell types below.
         1. Helper – produce cytokines
            a. T_{H1} – these produce cytokines to activate cell-mediated immunity
            b. T_{H2} – cytokines that stimulate some B cells.
            c. Activation (Fig. 17.10)
               i. APC presents antigen and binds T_{H} receptor.
               ii. IL1-1 induces T_{H} to produce IL-2
               iii. This causes further clonal selection of T_{H}.
         2. Cytotoxic – destroys cells on contact (Fig. 17.11)
            a. Binds to cells with MHC presenting antigen.
            b. Perforin released. This, like complement, makes holes in membrane and lyses cell.
D. Humoral and Cell-mediated Immunity working together (Fig. 17.19)
   a. Antibody production
      i. T_{H} binds APC
      ii. T_{H} also binds B cell and acts as a bridge.
      iii. IL-2 stimulates B cell clonal selection
b. Antibody-dependent cell-mediated toxicity (ADCC) (Fig. 17.15)
   i. Pathogen is first coated with antibody
   ii. Macrophages, NK, etc. bind to Fc and release toxic compounds.

Chapter 18 – Applications of Immunology

A. Immunization
   a. Overview
      i. Active
         1. Give an antigen (vaccine), causing an immune response.
         2. Many require multiple challenges to produce stronger secondary/tertiary responses, gives long-term protection.
      ii. Passive
         2. No immune response, but gives temporary protection.
   b. Types of Vaccines
      i. Traditional
         1. Attenuated whole-agent. Live but weakened strain. Can reproduce. Most effective but dangerous if it mutates. (e.g. polio, MMR)
         2. Inactivated whole-agent – chemically killed. (e.g. flu)
         3. Toxoids – inactivated toxins (e.g. tetanus, diphtheria)
         4. Subunit – antigenic fragment (e.g. hep B viral coat)
         5. Conjugated – put two kinds of compounds together. (e.g. protein and carbohydrate in children’s H. influenza B)
      ii. Newer Vaccines
         1. DNA – a plasmid is injected. It contains a gene that when txn and tln will produce a protein that gives immune response.
         2. Gene therapy – can use viral infections to insert a gene.
      iii. Safety
         1. Rare cases of vaccine causing the disease itself (e.g. attenuated polio)
         2. Unlikely but potential link to autoimmune diseases. Some believe boosting immunity may overstimulate it. Very unlikely cause of autism.
   c. Types of Passive Immunizations
      i. Antisera – noncellular part of blood containing antibodies (e.g. snake venum treatments)
      ii. Breast milk – contains IgG – immunoglobulin G.
      iii. Purified antibodies – specific antibodies can be purified for maximum effect.

B. Diagnostics
   a. Natural Antibody Function
      i. Precipitation – when antibodies bind antigen, a large complex if formed and precipitates out of solution (Fig. 18.4)
      ii. Agglutination – used to clump larger particles that are already precipitates. E.g. red blood cells in blood typing. (Fig. 18.5)
      iii. Neutralization – a toxin is neutralized by antibodies (Fig. 18.9)
   b. Fluorescence
      i. Direct – fluorescent dye-labeled antibody binds to antigen and glows. (Fig. 18.11)
      ii. Indirect – primary antibody binds antigen. Secondary fluorescently labeled antibody binds primary. This gives greater sensitivity.
iii. FACS – fluorescence activated cell sorter. Sorts cells. (Fig. 18.12)
   1. Pool of cells is labeled with antibody.
   2. Dripped through a small opening allowing only one cell at a time.
   3. Laser detects fluorescence.
   4. Electrode charges droplet.
   5. As it falls it moves towards opposite charged plate and goes into correct collection tube.

c. ELISA – enzyme linked immunosorbent assay. (Fig. 18.14)
   i. Direct
      1. Antibody adsorbed to well.
      2. Sample added and antigen binds antibody.
      3. Antibody linked to an enzyme is added.
      4. Substrate added and when cleaved forms color.
   ii. Indirect
      1. Cell/antigen adsorbed to well.
      2. Test serum with potential primary antibody added.
      3. Secondary antibody with linked enzyme (e.g. peroxidase, phosphatase) that recognizes primary Fc binds if primary is present.
      4. Substrate added. If cleaved by enzyme, color forms.
   iii. Pregnancy test uses a direct method (video)
      1. Antibody to chorionic gonadotropin (hCG), a placental hormone, is adsorbed to test site.
      2. Antibody to a free antibody is adsorbed to control site.
      3. Labeled free antibody that can bind to hCG is deposited at end of stick.
      4. Urine deposited at end of stick and draws free antibody up stick.
      5. In control, free antibody always binds.
      6. In test site, only free antibody bound to hCG will bind.