I. Introduction
   A. Importance of disease
      1. historical
         a. cholera pandemic after each hajj (Moslem pilgrimage)
         b. crusaders brought back cholera and leprosy (1100 - 1300)
         c. plague (20% of European population died) (1300)
         d. syphilis brought back by Columbus
            (1) spread around world by other explorers
            (2) Charles VII of France died of syphilis, all heirs born dead of syphilis, end of dynasty
            (3) almost 80,000 Union soldiers during Civil War, 3 million during WWI, 1 million during WWII
      2. economic
      3. cultural/social
   B. Brief history of disease in the U.S.
      1. top 10 causes of death
         a. shift from infectious to chronic disease
         b. public health guidelines, including better sanitation and personal hygiene, are responsible for the increased life spans and overall better health we have today
         c. lifestyle
      2. less harmful diseases
      3. most common diseases (severity vs. frequency)
      4. emerging diseases/problems
      5. Darwinian medicine

II. Principles of Disease Occurrence
   A. Theories of disease causation
      1. germ theory
         a. infectious disease is caused by the transfer of infectious agents
         b. didn’t explain why some people got sick but others didn’t
      2. multiple-causation
         a. several factors contribute to development of disease
            (1) disease agents
            (2) host factors
            (3) environment
         b. accounts for noninfectious diseases, too
   B. Terminology
      1. morbidity rate = number of ill people per susceptible population during a specific time
      2. mortality rate = number of deaths per total number of disease cases
      3. incidence rate
         a. number of new cases occurring during a specific time
         b. number of new cases divided by population at risk (x 1000)
   C. Levels of prevention
      1. primary prevention = measures taken before disease occurs to reduce susceptibility
2. *secondary prevention* = diagnosis of disease already present
3. *tertiary prevention* = treatment of disease (return host to normal health)

D. Disease agents for infectious disease
   1. viruses
      a. acellular (protein coat around genetic material)
         (1) DNA or RNA as genetic material
         (2) single or double stranded
      b. obligate parasites
   2. bacteria (Table 2-2)
      a. prokaryotic (no membrane-bound organelles)
      b. normal flora helps protect against infection
   3. fungi
      a. eukaryotic
      b. secrete hydrolytic enzymes (breaks down tissues)
      c. diseases can arise if antibiotics alter bacterial normal flora
   4. protozoa
      a. animal-like eukaryotes
      b. release toxins and enzymes
   5. metazoa
      a. tapeworms, roundworms, flukes
      b. can migrate throughout the body

III. Principles of microbial disease
   A. most important technological application of microbiology is medical
      1. impetus for development of microbiology
      2. microbes cause disease in man, animals, plants, and each other
      3. not the only cause of disease
         a. schistosomiasis
         b. lung cancer
         c. hemophilia or sickle cell anemia
      4. disease is a form of parasitism (host supplies food)
      5. disease occurs when a microbe infects a host to which it is imperfectly adapted but can grow and flourish
         a. biological defense processes brought into play
         b. if defenses overstrained or unsuccessful, host sickens and may die
            (1) if host dies, parasite dies
            (2) well-adapted parasites cause little or no damage
            (3) poorly-adapted or inadvertent parasites are dangerous and sometimes lethal
      6. humans (and other higher organisms) have developed a balanced microbial flora, as bacteria are passed around between community members
         a. new-borns are almost sterile, carrying (inside and out) bacteria derived from the mother's vagina
            (1) soon pick up lactobacilli
            (2) gradually develops the adult population of mixed microbes
      7. normal equilibrium can be upset by travel to another area (country) and exposure to
new strains of bacteria

B. **pathology** = scientific study of disease
   1. **etiology** = the cause of disease
   2. **pathogenesis** = manner in which a disease develops
   3. structure and functional changes brought about by disease and its final effects on the body
   4. **infection** = invasion or colonization of the body by pathogens
      a. normal flora can be present in abnormal area (e.g., *E. coli* OK in intestine, pathogenic in urinary tract)
      b. most microbes are non-pathogenic
   5. **disease** = result of an infection that changes the state of health
      a. = abnormal state in which part or all of the body is not properly adjusted or carrying out normal functions
      b. infections can exist without disease (e.g., HIV)
   6. **normal flora**
      a. animals are germ-free in utero
      b. microbial populations begin to establish themselves at birth
      c. estimated $10^{13}$ body cells and $10^{14}$ bacterial cells
      d. normal flora = microorganisms that colonize the body but do not produce disease under normal conditions
      e. **transient flora** = microorganisms that are present for brief periods (days - months) and then disappear
   7. **symbiosis** = living together
      a. **commensalism** = one organism benefits, the other is unaffected
         (1) many, if not most, of normal flora
         (2) especially common relationship on external skin
      b. **mutualism** = both organisms benefit
         (1) common with intestinal bacteria
         (2) *E. coli* gets nutrients in large intestine, produces vitamin K and B vitamins
      c. **parasitism** = one benefits, the other is harmed (typical pathogenic relationship)
   8. **opportunists** = potentially pathogenic organisms that do not ordinarily cause disease in their normal habitat in a healthy person
      a. organisms that gain entrance to the bloodstream through broken skin
      b. compromised hosts are subject to diseases caused by normal flora
      c. often, normal flora includes pathogens kept in check
   9. for determination of the etiological agent, recall Koch's postulates
      a. The organism should be present in every case of the disease, but absent in healthy individuals
      b. The suspected microorganism must be isolated and grown in pure culture
      c. The disease must result when the isolated microorganism is inoculated into a healthy host
      d. The same microorganism must be isolated again from the diseased host
   10. some exceptions, where causative agent cannot be identified using Koch's
postulates
a. *Treponema pallidum*, the causative agent of syphilis, has never been cultured on artificial medium
b. *Mycobacterium leprae*, the causative agent of leprosy, has never been cultured on artificial medium
c. alternative steps can be used to modify Koch's postulates, for example inoculating test organisms with infected tissue instead of isolated microorganisms

C. classification of infectious diseases

1. **symptoms** = changes in body function
   a. e.g., pain and malaise
   b. often subjective (not apparent to an observer)
2. **signs** = objective changes that can be observed and measured by a physician
   a. lesions (changes in tissue caused by disease), swelling, fever, paralysis
   b. **syndrome** = specific group of symptoms that always accompany a particular disease
3. **communicable** = able to spread (directly or indirectly) from one host to another (chicken pox, measles, herpes, tuberculosis)
   a. **contagious** = easily communicable (chicken pox, measles)
   b. **noncommunicable** = not spread from one host to another (tetanus)
4. infection can be **localized** (invading MO limited to relatively small body area) or **systemic (generalized)** (spread throughout the body)
   a. localized = boils or abscesses
   b. systemic = measles
5. **reservoir of infection** = source of disease organisms
   a. human body is primary reservoir
      (1) **carriers** = harbor and transmit pathogens without exhibiting illness themselves
      (2) latent diseases can be spread during incubation period (before symptoms appear) or during the convalescent period (during recovery)
   b. animal reservoirs
      (1) **zoonoses** = diseases that occur primarily in animals but can be transmitted to humans
      (2) rabies (mammals), Rocky Mountain spotted fever (ticks)
   c. non-living reservoirs
      (1) soil and water
      (2) soil has low levels of pathogens (under normal conditions)
      (3) pathogens often introduced to water (or soil) by humans (e.g., fecal contamination)
6. disease transmission has three principle routes
   a. **contact transmission** = spread of agent by direct contact (person to person transmission)
      (1) respiratory diseases, measles, smallpox, STDs
      (2) can also be by indirect contact
         (a) **indirect contact transmission** relies on inanimate objects
(handkerchiefs, eating utensils)

(b) **droplet transmission** = discharged mucous droplets that only travel short distances (sneezing, coughing, laughing)

b. **vehicle transmission** = agents like water, food, air
c. **vectors** = animals that carry pathogens from host to host
   (1) insects (arthropods) most common
   (2) transmission can be passive (surface transfer) or active (transmitted through bites)

7. **nosocomial infections** = acquired as a result of a hospital stay
   a. MO in hospital environments and compromised hosts
      (1) gram positive cocci (*Staphylococcus aureus*) used to be most common
      (2) major causes today are gram negatives (*E. coli* and *Pseudomonas aeruginosa*), especially antibiotic-resistant strains
   b. **compromised host** = resistance to infection impaired by disease, therapy or burns
      (1) broken skin or mucous membranes remove protective barrier
      (2) suppressed immune system
c. controlled by scrupulous cleaning and disinfection

8. **pathogenicity** = ability of a pathogen to produce a disease by overcoming host defenses

9. **virulence** = the degree of pathogenicity

D. Mechanisms of pathogenicity

1. **portal of entry** = how pathogen gains access to the body
   a. mucous membranes
      (1) respiratory, gastrointestinal, genitourinary tracts; conjunctiva (membrane around eyeball)
      (2) gastrointestinal and respiratory tracts most common
   b. skin
      (1) usually a defense against disease
      (2) microbes gain entrance through openings
         (a) sweat gland ducts
         (b) hair follicles
   c. parenteral route = direct deposition into tissues beneath skin or mucous membranes
      (1) wounds
      (2) bites
d. use of preferred portal of entry often prerequisite to ability to cause disease
   (1) ingested *Salmonella typhi* (preferred portal) produce typhoid fever, but no reaction when rubbed on skin
   (2) inhaled streptococci can cause pneumonia, but if swallowed, usually no signs or symptoms

2. dose (number of invading cells) important, as defense mechanisms will eliminate many

3. **adherence** = attachment to host tissues
   a. essential for most pathogens (to result in pathogenicity)
b. surface molecules (ligands or adhesins), often located on glycocalyx or fimbrae, bind to host receptors
   (1) most adhesins are glycoproteins or lipoproteins
   (2) most receptors are sugars (mannose)

4. Penetration of host defenses
   a. capsules
      (1) protects cells against phagocytosis
      (a) **phagocytosis** = process where certain body cells engulf and destroy microbes
      (b) in second line of defense, human body produces antibodies against the capsule which, when on the capsule surface, allow phagocytosis to occur
      (2) common with pneumonia-causing organisms (**Streptococcus pneumoniae**, **Klebsiella pneumoniae**, **Hemophilus influenzae**)
   b. cell wall components
      (1) **Mycobacterium tuberculosis** has a waxy cell wall that resists digestion by phagocytes
      (2) **Streptococcus pyogenes** has a heat- and acid-resistant M protein
         (a) aids attachment
         (b) resists phagocytosis

5. enzymes
   a. extracellular enzymes that break cells open, dissolve materials between cells, form or dissolve blood clots, and other functions
   b. leukocins destroy neutrophils (white blood cells) and macrophages
   c. hemolysins lyse red blood cells
   d. coagulases clot blood (may protect bacteria)
   e. several enzymes that enhance spread from a focal infection
      (1) kinases dissolve blood clots formed to isolate infection
      (2) hyaluronidase breaks down connective tissue, allowing cells to spread
      (3) collagenase hydrolyzes connective tissue
   f. necrotizing factors kill cells
   g. hypothermic factors lower body temperature
   h. proteases break down tissues

6. damage mechanisms
   a. three basic ways for successful invaders to damage host cells
      (1) direct damage in immediate vicinity of invasion
      (2) toxin production, transported by fluids to damage distant sites
      (3) induction of hypersensitivity reactions
   b. host cells destroyed when pathogens metabolize and multiply inside the host cells
   c. toxins = poisonous substances produced by specific MO
      (1) usually the primary mechanism of host damage (pathogenicity)
      (2) **toxigenicity** = ability to produce toxins
      (3) **toxemia** = symptoms caused by toxins in blood
   d. **exotoxins** = secreted proteins, usually enzymes
(1) exotoxin, not bacterium, produces disease symptoms  
   (a) usually produced by gram positives  
   (b) genes often plasmid encoded  
   (c) tend to be very toxic (1 mg botulinum toxin enough to kill 1 million guinea pigs)  

(2) **antitoxins** = antibodies produced against exotoxins  

(3) cytotoxins kill host cells or affect functions  
   (a) diphtherotoxin (inhibits protein synthesis)  
   (b) erythrogenic toxins (damage capillaries)  

(4) neurotoxins interfere with nerve impulses  
   (a) botulinum toxin (prevents nerve transmission)  
   (b) tetanus toxin (prevents inhibitory nerve transmission)  

(5) enterotoxins affect cells lining the GI tract, inducing fluid and electrolyte loss from host cells  
   (a) **Vibrio** choleragen  
   (b) staphylococcal enterotoxin  

**e. endotoxins** = part of outer wall of cell wall of gram negative bacteria (lipid portion of lipopolysaccharide layer = lipid A)  
(1) endotoxins = lipopolysaccharides, exotoxins = proteins  
(2) endotoxin released when cells are lysed  
   (a) cell death  
   (b) antibiotics  
   (c) antibodies  

(3) all produce fever (pyrogenic response), weakness, aches, sometimes shock  
(4) do not promote formation of effective antitoxins  
   (a) **antitoxin** = specific antibody produced in response to an exotoxin or its toxoid  
   (b) antibodies are produced, but they do not counter the effect of the toxin and can often enhance its effect  

7. **hypersensitivity** = allergy = exaggerated or heightened immune reaction that is injurious  
   a. contact with heterophile antigens on bacteria can cause a host to produce antibodies against any A or B antigens they are lacking  
   b. these antibodies can react with these antigens if the wrong blood type is transfused without regard to compatibility  

IV. Host defense mechanisms  
A. Non-specific defenses  
   1. **resistance** = ability to ward off diseases through body defenses  
      a. **susceptibility** = lack of resistance  
      b. **nonspecific resistance** = all defenses that protect host from any kind of pathogen  
      c. **specific resistance** = antibodies against specific microorganisms  
   2. skin and mucous membranes protect through a combination of mechanical and chemical factors
a. mechanical factors include physical barrier to microbial invasion
   (1) intact skin difficult to penetrate
   (2) keratin (skin protein) is waterproof
   (3) some pathogens in large numbers can penetrate mucous membranes
b. bacteria can be washed from surfaces
   (1) lacrimal apparatus in eyes
   (2) saliva washes MO from teeth and gums
   (3) urine move MO out of urinary tract
   (4) vaginal secretions move MO out of vagina
   (5) perspiration washes MO off skin
c. mucus traps many MO that enter respiratory or GI tracts
d. sebum contains unsaturated fatty acids, which can inhibit pathogens
   (1) sebum = oily substance produced by sebaceous glands that coats some
       areas of skin and keeps hair from getting brittle
   (2) some skin bacteria metabolize sebum and cause the inflammatory
       response associated with acne
e. lysozyme in tears, saliva, nasal secretions, and perspiration lyse bacteria
f. high acidity (pH 1.2-3.0) of gastric juice prevents microbial growth in stomach
   and kills many ingested organisms
g. normal flora prevent the growth of many pathogens

3. phagocytosis is the ingestion of MO or particulate matter by phagocytes
   a. phagocytes = white blood cells (or derivatives) = leukocytes
      (1) infection stimulates WBC synthesis (leukocytosis)
   b. two types of phagocytotic WBC
      (a) neutrophils (a type of granulocyte), commonly called
          polymorphonuclear leukocytes (PMNs)
      (b) monocytes, which lack granules and mature into macrophages once
          they leave blood and enter tissues
   c. neutrophils are highly phagocytic and motile
      (a) able to leave the blood, enter tissues, and destroy microbes
      (b) active in initial stages of infection
   d. monocytes more active in later stages of infection

b. phagocytosis involves four major steps
   (1) phagocytes attracted to MO by chemotaxis
   (2) phagocyte adheres to the MO
   (3) phagocyte ingests MO
   (4) phagocyte digests MO

4. Inflammation is a response to bodily damage, characterized by redness, pain, heat,
   swelling, and sometimes loss of function
   a. vasodilation and increased permeability of blood vessels
      (1) vasodilation = increase in diameter of blood vessels
          (a) increases blood flow to damaged area
          (b) responsible for redness and heat
      (2) increased permeability allows defensive substances normally retained in
          blood to pass into injured area
(a) responsible for swelling
(3) vasodilation and increased permeability induced by histamines, kinins, prostaglandins, and leukotrienes
b. phagocytes squeeze through blood vessels into infected tissue
c. pus is the accumulation of damaged tissue and dead microbes, granulocytes, and macrophages
d. repair = final stage of inflammation
5. fever = abnormally high body temperature produced in response to bacterial or viral infection
   a. increased body temperature increased production of immune system components
   b. may inhibit growth of some bacteria
   c. may increase repair rate
6. the body produces certain antimicrobial substances in addition to chemical already mentioned
   a. interferons probably best known
   b. interferons are antiviral proteins
      (1) 3 types of human interferon
      (2) induce uninfected cells to produce antiviral proteins that prevent viral replication
         (a) good only on short-term basis
         (b) does not prevent viral multiplication in cells already infected
      (3) host-cell specific, but not virus specific
B. The immune system
1. an inducible system that acts as the last line of defense
   a. activation indicates that general resistance mechanisms have failed
   b. must have an extensive repertoire but focus on specific foreign substance
   c. must be shut down upon removal of foreign material
2. types of immunity
   a. innate (genetic)
      (1) genetically determined
      (2) species immunity
   b. acquired immunity
      (1) natural (by having a disease)
      (2) artificial (vaccination)
   c. active vs. passive
      (1) active = own system produces antibodies
         (a) naturally acquired active immunity = from disease
         (b) artificially acquired active immunity = from vaccine
      (2) passive
         (a) naturally acquired passive immunity = antibodies from mother passed to offspring
         (b) artificially acquired passive immunity = antibodies obtained from other hosts
3. antigen = immunogen = substance the body identifies as foreign and mounts a
defense against
a. most are large proteins (MW > 10,000)
   (1) polysaccharides or protein complexes (glycoproteins, nucleoproteins)
       work well
   (2) lipid work poorly
b. epitope = antigenic determinant
4. antibody = antiantigen protein produced by immune system against antigens
5. lymphocytes = cells that carry out specific immune responses
   a. develop from stem cells (like other wbc, rbc, and platelets)
   b. B cells or B lymphocytes mature in bursal cells of birds (or equivalent in
      humans)
      (1) most believe they develop in bone marrow or gut-associated lymphoid
          tissues
      (2) about one-fourth of lymphocytes circulating in blood
   c. T cells or T lymphocytes undergo differentiation in the thymus
      (1) as adults (thymus less active) differentiation occurs in blood marrow or
          tissues under the influence of hormones from the thymus
      (2) four different types
         (a) cytotoxic (killer) T cells
         (b) delayed-hypersensitivity T cells
         (c) helper T cells
         (d) suppressor T cells
6. humoral immunity is carried out by antibodies circulating in the blood
   a. B cells release antibodies
   b. most effective against bacterial toxins, bacteria, and viruses before they enter
      cells
   c. IgG makes up about 80% of plasma antibodies
      (1) appears in all body fluids
      (2) major antibacterial and antiviral antibody
   d. IgM is the first immunoglobulin produced during immune response
      (1) very large
      (2) usually found only in vascular system
   e. IgA is found mainly in bodily secretions
      (1) saliva, sweat, tears, mucus, bile, and colostrum
      (2) defends against surface pathogens especially those that enter the
          respiratory and GI tracts
   f. IgD is the predominant antibody on the surface of B cells and acts mainly as
      an antigen receptor
   g. IgE is involved in hypersensitivity reactions
      (1) develops within minutes of exposure to antigen
      (2) stimulates the release of mast cell granules, which contain histamine and
          heparin
   h. inflammatory response is part of humoral immunity
7. cell mediated immunity is carried about by T cells
   a. works against antigens in cell membranes or inside cells
b. defends primarily against virus-infected cells, but can also work with
eukaryotic parasites, cancers, and foreign tissues (transplants)

8. recognition of self
   a. major histocompatibility complex (MHC)
      (1) cell surface components
      (2) secondary interactions
   b. clonal selection theory
      (1) timing of exposure between lymphocytes and antigens determines if it is
          recognized as self or not
      (2) early exposure (embryonic development) leads to destruction of specific
          lymphocytes

9. specificity = different reactions of immune system to each foreign substance

10. heterogeneity = ability for immune system to respond to all the different antigens
     encountered

11. memory = recognition of antigens previously encountered
    a. memory cells produced
    b. memory cells have different lifetimes

12. immunoglobulins = antibodies
    a. Y-shaped molecules made up of two light chains and two heavy chains
    b. constant and variable regions responsible for different combinations

C. Immune Disorders
1. hypersensitivity (allergies)
   a. immune system over-reacts
   b. can harm the host
   c. usually treated with antihistimines
   d. several different manifestations
      (1) allergic rhinitis (hay fever)
      (2) urticaria (hives)
      (3) asthma

2. autoimmunity
   a. immune system attacks host
   b. several manifestations
      (1) rheumatoid arthritis
      (2) lupus erythematosus
... in fact, the body has at least four lines of defence. The first is an enzyme called lysozyme, which is found in saliva, tears and nose mucus and has the property of dissolving many bacteria. The second is a group of substances collectively called interferon, proteins produced by virus-infected cells which interfere with the further growth of viruses. The body's third line of defence is based on the fact that the blood contains certain white corpuscles (leucocytes) which are rather like domesticated protozoa and live in the blood stream. Some of them, known as phagocytes, actually eat up and digest any extraneous microbes that get in. If a slight wound occurs, the damaged tissue causes these phagocytes to congregate near the site of damage and thus be ready to forestall infection.

How does the body cope with a well-established infection involving billions of cells?

"Massive microbial growth only occurs if the body's initial defences have been broken down, and then one is very ill and, if the bacteria produce particularly nasty toxins, one may die. If one recovers, the reason is that the fourth defence mechanism has been successful: the body has made certain proteins called antibodies which, dissolved in the blood stream, react with the invading microbes and cause them to coagulate in lumps. In this condition they do less harm and are more easily ingested by the phagocytes. The serum of the blood is now immune to the particular microbe and this immunity can be retained, sometimes only for a few months, sometimes for many years, even a whole lifetime."