

See topic and resource outline for required reading etc.

In addition to the text, material from this unit comes from the unpublished work of Jean Dickey (Clemson University) and fact sheets from the Centers for Disease Control & Prevention (<http://www.cdc.gov>) and the National Institutes of Health (<http://www.nih.gov>). Historical material on the Black Death in Europe comes from the website Mosaic: Perspectives on Western Civilization, produced by Houghton Mifflin (<http://college.hmco.com/history/west/mosaic/chapter6/module22.html>).

- I. Overview of the unit: In this unit we'll look at infectious disease from several perspectives:
 - A. General introduction: the significance and consequences of infectious disease from individual to global levels
 - B. Microbes: the organisms that cause infectious diseases & how they do so
 - C. The body's defenses against disease: from the simplest and most general to the most elaborate and specific
 - D. Treatment and prevention, including some highlights from the history of medicine
 - E. Sexually transmitted infections: applying the general principles from the earlier units to particularly critical types of infections

Introduction: significance of infectious disease; microbes; defenses

- II. Introduction - the significance of infectious disease
 - A. Personal – Each of us comes into contact with many potential disease agents over the course of a day – and we've all experienced the consequences when one or more of these get the best of us:
 1. cold and flu viruses from the people around us
 2. harmful bacteria on/in the food we eat
 3. fungi causing skin diseases (ringworm, athlete's foot, etc.)
 - B. Even diseases as common and "harmless" as the common cold can have significant consequences on many levels. E.g., according to a University of Michigan Health System study, in the U.S.:

Unit 4: Infectious Disease

1. A total of 500 million colds will be contracted in a year
 2. People will spend \$2.9 billion on OTC medications; \$400 million on prescriptions – both to treat symptoms
 3. Colds will result in 100 million physician visits:
 - a. conservative cost = \$7.7 billion
 - b. more than 1/3 will result in a prescription for antibiotics – cost = \$1.1 billion – which don't affect the virus and contribute to growing antibiotic resistance
 4. Kids will miss a total of 189 million school days, which also results in parents missing 129 million workdays
 5. Total cost to U.S. economy of work loss = \$20 billion
- C. The global effects of infectious disease are numerous – and, rather than “winning the war” against major diseases, emerging infectious diseases are taking a huge toll. E.g. - HIV/AIDS – according to UNAIDS, in 2003
1. 40 million people were living with HIV/AIDS (37 million adults, 2.5 million children); Sub-Saharan Africa hardest-hit
 2. 5 million new infections occurred
 3. 3 million deaths occurred
 4. In some parts of Africa, AIDS is the leading cause of adult mortality and is leaving an entire generation of kids orphaned – what will be the long-term personal, social, cultural, political, economic cost?
- D. Some basic vocabulary:
1. **Microbe** = microscopic organism
 2. **Host** = organism inhabited by microbe
 3. **Pathogen** = microbe that causes disease
 4. **Infection** = microbe enters host and starts to reproduce
 5. **Disease** = cells/molecules in the body stop working properly, causing symptoms of illness

6. **Infectious disease** = disease caused by microbes (vs. diseases such as cancer, heart disease, arthritis, etc.)

E. *Summary:*

1. *Infectious disease is a significant issue on personal, national, and global scales.*
2. *Infectious diseases are caused by pathogens; infection occurs when a host is colonized by a microbe, and disease occurs when the host's cells and/or molecules stop working properly, causing symptoms of illness.*

III. Microbes - the causes of infectious disease

- A. The human body provides a wide range of excellent habitats for microbes. After all, both inside and outside, we provide:
 1. stable and moderate chemical, physical environment
 2. lots of fluid-filled spaces (tissues)
 3. nutritious body fluids
- B. We shouldn't be surprised, then, to discover that we have hundreds of species of microbes living in/on our bodies – mostly bacteria
 1. Many are commensals (remember from last semester – that's a +/- relationship) – they feed on dead tissues or cellular secretions, cause no harm, provide no benefit
 2. Some are mutualists, providing a range of services.
 - a. E.g., *Lactobacillus acidophilus* found in gut, vagina, and other places
 - (1) helps digest food
 - (2) creates low pH in vagina, preventing harmful microbes from colonizing
 - b. Simplest service is just potential competition against other microbes that might cause disease
 3. Under normal circumstances, our microbes act as a relatively stable ecological community – each species has its own niche, and populations

kept in check. But several conditions can cause the balance to be upset – and then the normal microbes can cause disease. E.g.

- a. Decrease in population of one may allow another to increase. E.g., when women take antibiotics, populations of some microbes in vagina decrease, allowing populations of fungi to increase, resulting in opportunistic yeast infection.
- b. Microbe that normally lives in one region is transferred to another, where it lacks competitors (sound familiar from last semester??) – e.g., *E. coli* from the gut can cause opportunistic urinary tract infection if transferred to the urethra
- c. Immune suppression – due to illness, malnutrition, stress, cancer treatment, HIV, immunosuppressive drugs for organ transplants – can let microbes get out of control; this is what HIV does.

C. Who's who: 3 major categories of pathogens

1. **Viruses**

- a. Not considered by many to be truly living things because they lack cellular organization, metabolism, homeostasis, etc. – all they do is reproduce!
- b. Structure relatively simple:
 - (1) genes in the form of RNA or DNA
 - (2) protein coat
 - (3) may or may not have a membranous outer envelope
- c. Life cycle can get complex; in essence, takes one of two forms:
 - (1) virus attaches to host cell
 - (2) “injects” genetic material (DNA or RNA)
 - (3) viral genetic material “forces” host cell to synthesize new viral genetic material and protein coats
 - (4) host cell builds, assembles new viruses

- (5) new viruses “explode” out of host cell, killing it in the process
- d. Among the complicating factors of this basic process is that viral genes may stay inactive – so host is infected, but not experiencing disease because viruses aren’t replicating and causing damage
- e. Examples of viral diseases: common cold, flu, Norwalk (“stomach flu”), herpes, genital warts, chicken pox, smallpox, mononucleosis

2. **Bacteria**

- a. Single-celled prokaryotic organisms (remember this means they lack membrane-bound organelles and are much smaller and simpler than eukaryotic cells)
- b. Much more complex than viruses
- c. Examples of bacterial diseases: strep and staph infections (including strep throat), meningitis, bubonic plague, many types of food poisoning (botulism, salmonella, shigellosis), Legionnaire’s disease, syphilis, gonorrhoea

3. **Eukaryotes**

- a. Eukaryotes are all organisms other than prokaryotes – characterized by large, complex cells
- b. Here we make a somewhat artificial distinction
 - (1) to qualify as causing infectious disease, eukaryotes must be microscopic – so only single-celled protists, small fungi and small worms qualify
 - (2) Diseases caused by larger eukaryotic organisms are classified as parasitic diseases, even though the small eukaryotes also qualify as parasites
- c. Examples of infectious eukaryotic pathogens include
 - (1) *Candida albicans*, the fungus that causes yeast infections. Other fungal infections would include ringworm and athlete’s foot

- (2) *Plasmodium* and *Trypanosoma*, the protozoans (single-celled animals) causing malaria and sleeping sickness, respectively
- (3) *Schistosoma* and *Wuchereria* are microscopic worms causing schistosomiasis and elephantiasis, respectively

D. Microbes can cause 3 kinds of infections:

1. Acute infections are short
 - a. Pathogen invades and body begins to fight it
 - b. Once the fight is won, the pathogen is gone
 - c. e.g., common cold: one viral infection = 1 cold lasting ~ 7 days; if you get another cold later, it's usually because you were infected by a different virus
2. Chronic infections develop from acute infections – but instead of getting rid of the pathogen quickly, the pathogen persists in the body for months to years (even a lifetime)
 - a. Carrier of a chronic infection may or may not experience obvious symptoms – but is often infectious anyway
 - b. E.g., hepatitis C is a chronic viral infection of the liver – and most don't even know they have it (but are still infectious). Serious symptoms (liver damage) may take 20 years to develop.
 - c. Latent infections are “hidden” or “silent” after the initial acute stage
 - (1) Some viruses can go through active and inactive stages
 - (2) When active, host experiences symptoms of the disease (like an acute infection) and is infectious
 - (3) When inactive, host has no symptoms and isn't infectious
 - (4) Examples are herpes simplex (causing genital herpes and cold sores) and chicken pox (causing chicken pox in children and shingles in adults)

E. Pathogens cause disease symptoms in three general ways:

1. Direct damage to cells and tissues (e.g., the HIV virus destroys cells of the immune system)
 2. Production of toxins that affect host cells in various ways (e.g., the bacterium that causes whooping cough secretes a variety of toxins that affect cells lining the lungs, causing them to produce too much mucus and inhibiting immune responses)
 3. Provoking immune responses – often, the symptoms we experience are our own body's way of fighting the disease (e.g., the runny nose and cough associated with a cold)
- F. To be evolutionarily successful, pathogens must have mechanisms allowing them to disperse to new hosts
1. Think from the pathogen's point of view: like all organisms, they are adapted for survival and reproduction
 - a. They cause disease because their particular modes of surviving and reproducing harm their hosts – but that's not their "goal"
 - b. Because all hosts die from some cause or another (even if it's not from the pathogen itself), a pathogen that can't move from host to host will not leave offspring – it won't be evolutionarily successful.
 - c. Obviously, the pathogens that are with us now are very successful!
 2. Pathogens usually disperse from the site where they reproduce (i.e., where they "live" in the host) – in fact, the symptoms they cause are often specific dispersal mechanisms. E.g.:
 - a. Cold and flu viruses reside in the respiratory tract; coughing and sneezing disperse them to new hosts.
 - b. Stomach and Intestinal bacteria cause vomiting and diarrhea – and bacteria are transmitted via those fluids
 - c. Some pathogens are transmitted by a carrier – blood-feeding insects, for example – and may actually change the behavior of their hosts or carriers to make transmission more likely (e.g., malarial parasite blocks

mosquito's gut, making it more hungry and likely to bite a prospective host)

- G. Remember the “evolutionary arms race” from last semester: pathogens and hosts are locked into an evolutionary struggle:
1. Hosts are under strong selection favoring better ways to avoid/fight infection
 2. Pathogens are under strong selection favoring ways to “beat” the host’s defenses
 3. Our immune system and other defenses are the result of a long evolutionary process – but for every successful defense we have, some pathogen has a way to get around it!
- H. Overview of lines of defense
1. General (non-specific) defenses don’t distinguish among microbes. They include
 - a. Physical and chemical barriers to invasion
 - b. Specialized cells and proteins that attack a range of microbes
 - c. Inflammation, a localized response to cell/tissue damage
 - d. Fever, a rise in body temperature in response to infection
 2. Specific defenses, as the name implies, are responses targeted at specific pathogens and are a function of the immune system. Two major components are
 - a. Antibodies = specialized proteins that bind and neutralize specific pathogens
 - b. T-cells = specialized white blood cells that attack specific pathogens
 3. As we discuss each type of defense, we’ll also discuss how some pathogens manage to evade them.
- I. *Summary:*
1. *Because it creates many hospitable environments, the human body is host to hundreds of different microbes. Most are commensal or mutualistic; the mutualists provide a range of services including protecting us against*

potentially harmful microbes. Although most of our normal microbes are harmless, they can cause disease if the ecological balance among them is disturbed.

- 2. The major classes of disease-causing microbes are viruses, bacteria, and eukaryotes (protists, fungi, and worms). The distinction between the microbes that cause infectious disease and the larger organisms that cause parasitic disease is arbitrary and based only on size.*
 - 3. Microbes can cause three kinds of infections. Acute infections have a limited span and end when the pathogen is gone. Chronic infections last much longer (sometimes a lifetime); infected individuals may not even be aware that they are infected and infectious. Latent infections “hide” once the acute phase is over; some viral infections can cycle back and forth between active (symptomatic and infectious) stages and inactive (symptomless and non-infectious) stages.*
 - 4. Disease symptoms result from direct damage to cells and tissues, the action of toxins, and/or from our own defensive responses.*
 - 5. To be successful, pathogens must have mechanisms for dispersing to new hosts. Many of our disease symptoms (coughing, sneezing, vomiting, etc.) are dispersal mechanisms. Some pathogens use “carriers”, such as insects, to transmit their offspring to new hosts.*
 - 6. As hosts, we are locked into an evolutionary arms race with our pathogens. Selection constantly favors improved defenses against infection, but also improved “invasion mechanisms” in the pathogens.*
 - 7. In general, we can divide our defense mechanisms into two broad categories. General, non-specific defenses target all microbes, while specific defenses target individual microbes.*
- IV. General (non-specific) defenses – Think of this as the “border defenses”
- A. The first line of defense is physical and chemical barriers that prevent microbes

from reaching internal body tissues. Remember that only 3 organ systems are open to the external environment (respiratory, digestive, and urogenital)

1. Skin is an excellent barrier:
 - a. The outer layers of skin are tough because they consist of dead cells packed with tough protein
 - b. Secretions such as sweat, saliva, and tears have a special enzyme that breaks down bacterial cell walls
 - c. Many bacteria and fungi are adapted to live on the surface of the skin (estimates are that we have as many as 3 million bacteria per square centimeter of skin surface!)
 - d. Microbes can, of course, enter the body through cuts and sores that penetrate the skin.
2. The respiratory system is protected by a combination of filters and mucus
 - a. Hairs in the nose trap microbes, dirt, etc. and prevent them from entering the lungs.
 - b. The whole respiratory tract is lined with cells that produce a layer of mucus, which traps microbes and particles missed by the hairs.
 - c. Respiratory tissues are also lined with specialized ciliated cells – these have microscopic projections that wave back and forth, collectively moving mucus and trapped particles up and out of the system (usually into the oral cavity, where we either spit or swallow them)
 - d. Rhinoviruses (which cause the common cold) have spiky projections that allow them to cling to respiratory epithelia without being trapped and removed.
3. The urogenital system is protected by periodic “flushing”
 - a. Urine rinses the urethra, preventing microbes at its opening from moving up into the urinary tract
 - b. The vagina produces secretions that flush it out, protecting it (and the

uterus) from pathogens

4. The digestive system has both chemical and physical defenses:
 - a. Weak acids in the saliva and strong acids in the stomach kill many microbes (but not all – some, like *Shigella* bacteria and Norwalk virus, are adapted to withstand acid)
 - b. Movement of feces provides scouring/flushing of the large intestine (again keeping microbes from moving up the colon)
- B. Specialized cells and proteins attack microbes that make it past the barriers into the body tissues
 1. White blood cells = cells of the immune system
 - a. All immune system cells are “white blood cells” because they lack hemoglobin (so they aren’t red)
 - b. We have many different kinds of white blood cells – 2 are involved in non-specific defense
 - (1) **Phagocytes** (“cell eaters”) are a group of WBC’s that literally eat microbes (they also consume dead and damaged body cells)
 - (2) Natural Killer cells (**NK cells**) release chemicals that destroy the membranes of cancerous cells and cells that are infected with viruses.
 - c. These cells aren’t restricted to blood vessels. They are found
 - (1) wandering around the interstitial fluid that surrounds all cells of the body
 - (2) packed into lymph nodes (more on this later)
 2. Two kinds of specialized proteins also help repel microbes
 - a. Cells that have been invaded by viruses produce **interferon**, a protein that signals adjacent cells to produce anti-viral chemicals
 - b. **Complement proteins** have several functions, all of which “complement” (assist) other defensive mechanisms. General mode of

action =

- (1) circulate through body fluids in an inactive state
 - (2) become activated when an infection occurs
 - (3) when one becomes activated, it starts a chain-reaction – each one activates many others
 - (4) activated proteins attack microbes in a variety of ways – one, e.g., is to punch holes in bacterial cell membranes, causing the cells to burst
3. Not surprisingly, many microbes are adapted to avoid these defenses. E.g.:
- a. bacteria causing bacterial meningitis have a slimy outer coat that makes them hard for phagocytes to hang on to
 - b. *Shigella* (bacteria causing one form of food poisoning) spreads directly from cell to cell – it avoids the interstitial fluid where the phagocytes and complement proteins are
 - c. Some strep and staph bacteria produce chemicals that actively kill phagocytes
- C. Inflammation occurs when a combination of non-specific defenses are mobilized in response to local tissue damage
1. The basic process (see text fig. 24.2):
 - a. Damaged cells release signaling chemicals such as histamine
 - b. Signaling chemicals cause changes in surrounding tissues:
 - (1) neighboring blood vessels (capillaries) dilate (open wider) and become “leakier”
 - (2) more blood flows to the damaged area and plasma moves out of the blood vessels to the damaged tissues
 - (3) phagocytes and other white blood cells travel via the blood vessels into the area, then squeeze out into the damaged tissues
 - (4) note that redness, heat, and swelling caused by increased blood

flow, fluid, and cells in the damaged area

(5) WBC's engulf bacteria and damaged cells

(6) Clotting proteins move into surrounding tissue, sealing off the area and preventing any infection from spreading

2. Inflammatory response is usually local, but can be widespread, in which case it may lead to septic shock – a condition in which blood pressure drops dramatically and causes damage to body organs.

D. Fever is another non-specific defense

1. *Triggered when infection causes the brain to reset its internal thermostat*
2. *Moderate fever helps fight infection in two ways*
 - a. *it creates an internal environment more hostile to pathogens (especially bacteria)*
 - b. *it speeds up host cells' metabolism, which increases the speed of repair and defense mechanisms*
3. *High fever, of course, is dangerous – it denatures proteins!*

E. Summary

1. *The skin is a strong physical barrier to infection, but microbes can enter through cuts and sores.*
2. *The respiratory, digestive, and urogenital systems are open to the external environment, so are potentially good ways for microbes to invade. Each is protected by a combination of chemical and physical defenses, which include flushing/scouring mechanisms that prevent microbes from moving deep into the system.*
3. *Phagocytes, NK cells, interferon, and complement proteins are specialized cells and molecules that target and destroy a range of microbes.*
4. *The inflammatory response is a coordinated general defense against localized damage or infection. If inflammation becomes widespread, it can lead to septic shock, a life-threatening condition.*

5. *Fever happens when the brain resets the body's "thermostat" in response to infection. Mild fever helps fight infection; a very high fever is dangerous.*
 6. *Although non-specific defenses work well, we can always find some pathogen adapted to avoid it.*
- V. The lymphatic system is part of both general and specific defenses
- A. The lymphatic system is part of both the circulatory and immune systems.
 - B. Anatomically, it consists of
 1. a branching network of vessels (lymphatic vessels) that run throughout the body in tandem with the blood vessels of the circulatory system
 - a. lymphatic vessels carry body fluid = **lymph** (more on this later)
 2. a large number of **lymph nodes** = sac-like organs packed with WBC's scattered throughout the system; these remove microbes from the lymph
 3. Accessory organs that remove microbes from blood and/or interstitial fluid (adenoids, tonsils, spleen, appendix)
 4. Bone marrow and thymus gland, where WBC's develop and mature
 - C. The role of the lymphatic system in the body's defenses is related to its role in circulation – so look at that first
 1. When blood flows through capillary beds, some of the **plasma** (fluid part of the blood) "leaks" out of the capillary beds to become **interstitial fluid** = fluid bathing cells and tissues. Some of it re-enters the capillaries, but some doesn't.
 2. Interstitial fluid that doesn't re-enter the capillaries still needs to return to circulation (what would happen if it didn't?). It enters the lymphatic vessels (becoming **lymph**), which merge (just like veins) and enter the circulatory system via large veins near the shoulders.
 3. Important point here is that much of the body's fluids circulate through the lymphatic system.
 - D. How does the lymphatic system help in defense (beyond the production and

maturation of WBC's)? Several mechanisms are important:

1. The smallest lymphatic vessels are much "leakier" than regular capillaries – microbes and larger cells can pass in and out .
 - a. This is good news when it means that microbes are washed into the lymphatic vessels with interstitial fluid.
 - b. This is bad news when cancer cells use the lymphatic system to travel around the body.
2. Lymphatic vessels carry WBC's – which can then attack microbes that are washed into the vessels.
3. Lymph vessels pass through lymph nodes, which are packed with defensive WBC's. This means that all the interstitial fluid returning to circulation gets carefully screened and filtered.
4. Note - when an infection occurs, WBC's in the lymph nodes start reproducing, causing the nodes to swell. These are the "swollen glands" that accompany a variety of illnesses.
5. The lymphatic system is part of both general and specific defense because it is the source and residence of both the phagocytes involved in general defense and the more specialized WBC's involved in specific defense (coming up next).

E. Summary:

1. *The lymphatic system is part of both general and specific defense; it is also part of both the circulatory and immune systems.*
2. *The lymphatic system consists of branching lymphatic vessels that carry the body fluid called lymph; a large number of lymph nodes that screen the lymph and remove microbes from it; organs that screen other body fluids; and bone marrow and the thymus gland, where WBC's develop and mature.*
3. *As part of the circulatory system, the lymphatic system returns interstitial fluid to circulation. Interstitial fluid begins as blood plasma that "leaks" out*

of capillaries and becomes lymph when it enters lymph vessels.

4. *As part of the immune system, the lymphatic system receives microbes washed in from the interstitial fluid, transports WBC's, and screens lymph and destroys microbes before the lymph is returned to circulation.*
5. *The lymphatic system contributes to both general and specific defense because it is the source and primary residence of both the general-defense phagocytes and the more specialized WBC's involved in specific defense.*

VI. Specific defenses against microbes: the immune system and immune responses

- A. The specific defenses of the immune system are the most powerful “weapons” we have against microbes.
 1. As we'll see, they take some time to mobilize – so our general defenses are very important for “buying time” for the specific defenses to get to work.
 2. In contrast to general defenses, the specific defenses of the immune system target one type of pathogen at a time (e.g., one strain of cold or flu virus).
 3. Importantly, the immune system retains a “memory” of all the pathogens it has fought in the past – so when the same pathogen invades again, the immune system can respond very rapidly (this is where immunity comes from).
- B. For the immune system to work, its cells must be able to recognize the difference between “self” and “non-self” cells and molecules
 1. Among the proteins on our cell membranes are a class of markers that identify cells as belonging to “self”
 - a. all cells in a person's body have the same “self” proteins (except for some cancer cells - more on that later)
 - b. “self proteins” are determined by our genes
 - c. every individual – except for identical twins – has unique “self” proteins

2. The cells of the immune system “cruise” body fluids (they travel from plasma → interstitial fluid → lymph → plasma) checking out cells and molecules
 - a. cells with “self” proteins are OK
 - b. cells with other proteins = “non-self” – these evoke an immune response
3. “Non-self” proteins are called **antigens** (short for “**antibody generating**”) – these include proteins on the surfaces of
 - a. virus coats
 - b. bacterial cell membranes and capsules
 - c. mold spores
 - d. pollen
 - e. transplanted organs
4. Why do microbes have “non-self” markers? From the microbe’s perspective, these are simply normal proteins essential to the microbe’s function. E.g.:
 - a. what our bodies recognize as viral antigens are the proteins on virus coats that allow viruses to bind to host cells
 - b. bacterial antigens may be
 - (1) toxins that stimulate host symptoms enhancing bacterial dispersal
 - (2) proteins that allow bacteria to “recognize” each other for sexual reproduction
 - c. antigens on transplanted organs are just the donor’s “self” proteins – different from the host’s
5. The immune system “finds” antigens three ways:
 - a. on microbes “swimming around” in body fluids (blood plasma, interstitial fluids, lymph)
 - b. on the cell membranes of phagocytes that have attacked and “eaten” microbes

- (1) These phagocytes are called **macrophages**; they link the general defenses with the specific defenses of the immune system
 - (2) once eaten, the microbe is broken down
 - (3) some of the microbe's proteins are transported to the phagocyte's cell membrane and displayed there as a signal to the rest of the immune system
- c. on the cell membranes of host cells that viruses/bacteria have invaded
- (1) as microbes replicate, host cells grab some of their proteins
 - (2) like phagocytes, invaded host cells transport proteins to cell surfaces and display them to the immune system.

C. Summary:

1. *The specific defenses immune system targets specific microbes.*
2. *Specific defenses depend on the ability of the immune system to tell "self" from "non-self"*
 - a. *Special molecules on cell membranes identify "self".*
 - b. *Proteins on the surfaces of bacteria, viruses, molds, etc. are recognized as "non-self"; they are called antigens.*
3. *Antigens can be detected on microbes present in body fluids, on the surfaces of macrophages that have ingested microbes, and on the surfaces of cells that have been invaded by microbes.*

D. Specialized white blood cells mount the immune response

1. Lymphocytes ("white cells") = small WBC's that look for & respond to antigens
2. All lymphocytes develop in bone marrow, then travel to one of two places to mature
 - a. B cells remain in the bone marrow
 - (1) defend primarily against bacteria & viruses in body fluids
 - (2) produce antibodies (more on this below)

- b. T cells migrate to the thymus gland in the throat (not the same as the thyroid!) to mature
 - (1) one type of T cell triggers/coordinates the immune response to a new pathogen
 - (2) the other type defends against pathogens that have already invaded host cells
- 3. Both B and T cells have a common structure: specialized molecules on the cell membrane = **antigen receptors**
 - a. each B and T cell carries many copies of one type of receptor
 - b. each type of receptor has a specific shape that lets it bind only one kind of antigen
 - c. the genes controlling antigen receptors allow us to produce 100 million - 100 billion different kinds of antigen receptors – enough to recognize virtually any antigen we're likely to encounter
- 4. B and T cells differ in the nature of their antigen receptors: B cells use **antibodies** as antigen receptors
 - a. Antibodies are specialized proteins with two functions:
 - (1) recognize and bind antigens
 - (2) help inactivate the antigens and destroy the microbes that carry them
 - b. Each antibody has the right shape to recognize, bind one kind of antigen
 - c. Each B cell uses one kind of antibody as its antigen receptor. When a B cell's antibody "finds" an antigen it can bind to, the B cell will make tens of thousands of antibodies to fight the antigen (more below)
- E. B and T cells mount rapid and long-lasting immune responses through a special process called **clonal selection**
 - 1. The process begins when an antigen from a microbe binds to a B or T cell's antigen receptor. Because each antigen will bind to only 1 B or T cell, we

can say that the antigen actually *selects* the cell that can fight it! (That's the "selection" part of clonal selection)

2. Binding induces that one B or T cell to start reproducing itself exactly – it makes clones of itself (that's the "clonal" part).
3. The replicates (or clones) of the B or T cell divide themselves into two groups
 - a. One group immediately starts to fight the invading pathogen
 - b. The other group becomes "memory cells" that just hang out in the lymph nodes for years – up to a lifetime. We'll come back to the "memory cells" in a bit.

F. *Summary:*

1. *Lymphocytes mount the immune response. All lymphocytes develop in the bone marrow; B lymphocytes mature there, while T lymphocytes mature in the thymus gland.*
2. *Both B and T cells carry antigen receptors on their cell membranes. Each antigen receptor is specific for only one antigen.*
3. *The genes controlling antigen receptors allow our bodies to produce a huge diversity of receptors – enough to recognize virtually any antigen we might encounter.*
4. *B cells use specialized proteins called antibodies as their antigen receptors. Antibodies recognize, bind, and inactivate antigens; they also help destroy the microbes that carry them.*
5. *B and T cells respond to the presence of antigens by undergoing clonal selection. The B and T cells that "match" an antigen reproduce themselves exactly. One group of replicated cells begins to fight the pathogen; a second group becomes "memory cells."*

- G. B and T cells work together to fight infection, often with the help of macrophages. To illustrate, begin with a group of microbes

1. The process begins when a macrophage consumes one of the microbes and displays its antigens on its own cell membrane. This alerts the rest of the immune system that invaders are present.
2. Special T cells called **helper T cells** are constantly patrolling body fluids. Eventually, a helper T cell with a matching antigen receptor will meet the macrophage and its displayed antigen.
3. The helper T cell begins to undergo clonal selection – starts dividing rapidly. Each helper T cell starts to send out chemical signals to other B and T lymphocytes, activating them to start fighting the infection.
4. The B lymphocytes whose antibodies match the antigen will respond by producing antibodies.
 - a. Like helper T cells, only one kind of B lymphocyte will be selected to fight the pathogen – the one whose antigen receptors = antibodies match the antigen.
 - b. Once selected, the B lymphocytes also undergo clonal selection, reproducing rapidly.
 - c. Cloned B lymphocytes produce many antibodies – up to 10,000 per minutes, which they release into the body's fluids.
 - d. The antibodies circulate in the plasma, interstitial fluid, and lymph, attaching to any microbes with the matching antibodies. This has several possible outcomes:
 - (1) 3 mechanisms make microbes easier for macrophages to engulf:
 - (a) Neutralization: antibodies may block important microbial activities – e.g., binding to viral proteins may prevent viruses from attaching to host cells
 - (b) Agglutination: antibodies grab two microbes at a time, causing them to clump together
 - (c) Precipitation: antibodies cause dissolved antigens to form solids

- (2) The fourth mechanism is activation of complement proteins – bound antibodies can make it easier for complement proteins to attack the microbe’s cell membrane and rupture it.
5. While the B lymphocytes are cloning and producing antibodies, another group of T cells is also being activated.
 - a. Killer T cells (cytotoxic T cells) are also activated by helper T’s
 - b. Like helper T’s and B’s, Killer T’s have specific antigen receptors and are “selected” by specific antigens.
 - c. Once a Killer T has been activated, it undergoes clonal selection and starts dividing rapidly.
 - d. Killer T’s then hunt out host cells that have already been invaded by the microbes
 - (1) Remember that invaded host cells display their pathogen’s antigens on their own cell membranes
 - (2) Killer T’s attach to these cells and destroy them.
 - (3) Although this means that host cells get destroyed, it also means that pathogens are destroyed before they can infect additional host cells.
 - e. Note: Killer T’s are also involved in fighting cancer. Cancer cells often display different “self” proteins than normal cells; killer T’s recognize the difference and help destroy cancer cells before they can spread.
6. Combined, then, B and T cells produce a rapid, dual defense:
 - a. Clonal selection, with its rapid reproduction of the appropriate B and T cells is an adaptation to the premise that, if one macrophage is displaying antigens, there must be a lot of invading pathogens to fight.
 - b. By working together, B and T cells give us good protection against
 - (1) “mobile” pathogens moving through body fluids
 - (2) “entrenched” pathogens that have already taken over host cells and started reproducing in them

- H. Long-term immunity is a function of the immune system's "memory"
1. When the immune system first encounters a specific antigen, clonal selection produces an immediate "army" of B and T cells to fight it – but the process takes ~ 2 weeks to reach its strongest point.
 2. Because clonal selection also produces a "reserve" of memory B and T cells specific for that antigen, a second exposure to the same antigen will produce a faster and stronger response – much of the preliminary work has already been done.
 3. Because the second response is so rapid and strong, we may not even experience symptoms – our first exposure made us immune to the disease.
 4. This is the principle we use when we get vaccinated:
 - a. A vaccine contains weakened or killed pathogens that still have intact antigens.
 - b. When we get the shot, our bodies mount an initial immune response, and also produce memory cells.
 - c. When we are exposed to the live pathogen, we are able to respond very rapidly.
 5. Why can't we develop vaccines to everything?
 - a. Remember that immune responses are very specific – a vaccination protects us against only one specific antigen (and the microbe that carries it).
 - b. Some microbes mutate very rapidly – their antigens change rapidly (HIV, common cold, and influenza viruses are all like this). So, although we can potentially develop a vaccine to one antigen, we're not protected against the many other strains that exist.
- I. *Summary:*
1. *Macrophages, B cells and T cells work together to fight infections. Macrophages ingest pathogens and display the antigens on their own*

surfaces.

- 2. Helper T cells patrol body fluids. When they find macrophages displaying antigens that match their antigen receptors, they undergo clonal selection.*
- 3. Helper T cells stimulate B cells. As B cells undergo clonal selection, they secrete antibodies that circulate in the body fluids. The circulating antibodies help destroy pathogens in the body fluids.*
- 4. Helper T cells also stimulate Killer T cells to undergo clonal selection. Killer T's find host cells that have already been invaded by pathogens, destroying them before the pathogens can spread.*
- 5. Helper T, B, and Killer T cells all produce memory cells through clonal selection. Memory cells remain in the body, sometimes for life, providing immunity against a second attack by the same pathogen.*
- 6. Vaccines work by producing a primary immune response and a body of memory cells. The memory cells provide long-term immunity against the pathogen we're vaccinated against.*
- 7. Our ability to develop vaccinations is limited by the ability of many microbes to mutate very rapidly.*

VII. Problems of the immune system

- A. Autoimmune diseases occur when the immune system targets "self" instead of "non-self"
 1. The causes of autoimmune diseases aren't clearly understood.
Autoimmune diseases affect millions of Americans and, for reasons that we don't understand, affect more women of reproductive age than men.
 2. Autoimmune diseases can affect most body systems. Some are very specific, while others are less so. E.g.:
 - a. Rheumatoid arthritis results from "attacks" on the synovial membranes of joints.
 - b. Multiple sclerosis results when the immune system destroys nervous

tissue

- c. Inflammatory bowel diseases (Crohn's disease, ulcerative colitis) are conditions of the large and small intestines
 - d. Type I diabetes results from destruction of insulin-producing cells in the pancreas
 - e. Lupus is more non-specific: it affects connective tissue generally, but different individuals may experience symptoms in different kinds of connective tissues.
3. The symptoms of autoimmune diseases generally stem from inflammation, triggered by the destruction of tissues by the immune system.
 4. Treatment is usually for control of inflammation and its side effects; we don't have cures for any of the autoimmune diseases.
- B. Allergies occur when the immune system overreacts to environmental antigens
1. Antigens that cause allergies are called allergens; examples include proteins associated with pollen, mold spores, dust and dust mites, pet dander, and pet saliva.
 2. Allergic responses are usually fairly rapid in response to small amounts of allergens.
 3. Reactions may occur in many parts of the body, typically the nasal passages, bronchi, digestive tract, and skin.
 4. Allergic reactions occur in two stages:
 - a. Sensitization = first exposure to allergen
 - (1) In response to allergen, B cells make a special class of antibodies.
 - (2) Instead of binding directly to the allergen, these antibodies bind to specialized body cells called mast cells. Mast cells contain histamine and are important components of the inflammatory response.
 - b. The second exposure to the allergen causes the problem

- (1) The allergen binds to the antibodies on the mast cells
 - (2) This triggers the mast cells to release histamine – which triggers the inflammation that causes the allergy symptoms.
5. Allergic responses can be annoying, but they can also be deadly. The most dangerous type of allergic reaction is **anaphylactic shock**
- a. This occurs when people are extremely sensitive to very tiny amounts of allergens (e.g., peanuts, bee stings)
 - b. Any contact with the allergen causes many mast cells to release lots of histamines very rapidly
 - c. This produces a wide-spread inflammatory response – so what happens?
 - (1) blood vessels dilate rapidly
 - (2) blood pressure drops rapidly (shock)
 - d. Anaphylactic shock can be reversed by epinephrine, which is why people with severe allergies often carry “epi sticks” – pre-loaded hypodermics of epinephrine.
6. Mild allergies are treated with antihistamines – drugs that interfere with the action of histamine.
7. For more severe allergies, allergy shots can be effective.
- a. Allergy shots consist of increasing doses of the allergen that causes the allergy – how does this help?
 - b. Shots cause the body to produce a special type of antibody that binds the antibodies on the mast cells – so exposure to allergens doesn't trigger a reaction.
 - c. Usually takes ~ 3-5 years for sensitivity to allergen to drop; more in some cases.

C. *Summary:*

1. *Autoimmune diseases arise when the immune system mistakes “self” for*

“non-self”.

- a. *Symptoms of autoimmune diseases are usually caused by inflammation triggered by the destruction of tissues by the immune system.*
 - b. *We have no cures for autoimmune diseases; treatment generally involves controlling inflammation.*
2. *Allergies occur when the immune system overreacts to environmental antigens.*
- a. *Allergies usually involve rapid responses to small amounts of antigen; the responses can occur in many parts of the body.*
 - b. *Allergic reactions develop in two stages. In the first, special antibodies are made and bind to mast cells, which produce histamine. In the second, a second response to the antigen stimulates the mast cells to release large quantities of histamine. Histamine triggers an inflammatory response, which produces the symptoms.*
 - c. *Anaphylactic shock is a potentially deadly type of allergic response in which exposure causes a rapid and widespread inflammatory response, leading to rapid drop in blood pressure.*
 - d. *Allergy symptoms are treated with antihistamines; allergy shots help the body produce a “blocking” antibody that prevents mast cells from responding to allergens.*

Treatment & prevention, with historical perspective

VIII. Treatment and prevention of infectious disease

A. Historical perspective: bubonic plague (“Black Death”) in Europe

1. Basic timeline:

- a. *Plague originated in Asia, probably China, in the 1340's*
- b. *It reached Europe via trade routes – Italy in 1347 and England in 1348*
- c. *Within a few years, it killed 20-30 million people.*

(1) *In terms of total numbers, that’s roughly equivalent to the influenza*

pandemic of 1918-1919 and the total deaths from AIDS from 1982-present

- (2) In terms of the total population, though, it was much more devastating – killed ~ 30% of the population of Europe.

2. Presumed causes

- a. At the time, diseases were thought to be caused by **miasma** = poisonous elements from decaying organic matter mixed with air
 - (1) To an extent, this was a good start, as it led to general sanitation (removal of garbage, excrement, and cadavers).
 - (2) Because physical filth was thought to be related to moral corruption, though, “cleansing” also included ridding areas of prostitutes, Gypsies, Jews, and other “unclean” people
- b. People also assumed that whatever the physical mechanism, the ultimate cause of the plague was God, who brought down the plague as punishment
 - (1) To appease God, some authorities tried to ban cursing, gambling, drinking, and other behaviors they thought would displease God.
 - (2) Others went to extremes, including public displays of penitence (including self-flagellation)

3. No treatment existed. Those who attempted to take care of patients used a variety of spices and herbs, but nothing worked. Physical isolation was the most effective preventative measure, but even that wasn't very effective.

B. What we know now . . .

1. A brief timeline of medical advances:
 - a. Microbes (primarily single-celled eukaryotes and some bacteria) were discovered in the 1600's with the invention of microscopes.
 - b. By the 1850's, the “miasma theory” of disease was replaced with the “germ theory”. Although people didn't really know or understand

- microbes, they inferred that diseases were caused by germs – “seeds” – that developed into specific illnesses.
- c. In 1877, Robert Koch developed the “one microbe - one disease” hypothesis and developed a series of steps still used to demonstrate a cause-effect relationship between specific microbes and specific diseases. At this time, bacteria were the microbes primarily identified with disease.
 - d. Later, scientists inferred the presence of viruses when body fluids from diseased organisms were filtered of their bacteria – and found to be still capable of causing disease. The cause must have been some kind of microbe too small to be filtered.
 - e. During the 1940's, we developed tools to see viruses.
2. What about bubonic plague?
- a. The microbiologist Alexandre Yersin identified the bacterium that causes the disease; it's named *Yersinia pestis* after him.
 - b. A few years later, scientists worked out the rest of the story:
 - (1) Bacteria live and reproduce in the guts of fleas. Eventually the population is so large it blocks the digestive tract. This makes the fleas hungry and induces them to bite harder and more frequently – injecting more bacteria into their hosts.
 - (2) Rats are the normal hosts, but hungry fleas will feed off any available mammal, including humans.
 - (3) Rats are responsible for carrying the plague around the world – wherever humans go, rats go with them
 - c. Our current understanding of the immune system also helps explain the disease symptoms:
 - (1) Bacteria are injected into interstitial fluids by flea bites; from there, they enter lymphatic vessels and are transported to lymph nodes.

- (2) Inside the lymph nodes, bacteria are attacked by macrophages. But instead of being destroyed, they either kill the macrophages or reproduce inside of them.
- (3) Damaged macrophages inside the lymph nodes induce an inflammatory response – the lymph nodes swell with fluids, creating the big lumps, or buboes, characteristic of the plague.
- (4) Black splotches appear when bacteria proliferate in clots under the skin (hence “Black Death”)
- (5) Note: plague takes two forms:
 - (a) the description above is the bubonic form – about 25% of untreated victims survive
 - (b) The more deadly form is pneumonic plague: the bacteria travel to the lungs and reside inside macrophages there.
 - i) As they proliferate, they cause the lungs to deteriorate.
 - ii) This causes the host to cough, which transmits the bacteria into the air and into the respiratory systems of other hosts.
 - iii) This form of the disease is 100% fatal if left untreated!

C. Vaccination is a way to prevent specific diseases from occurring.

1. Vaccination as a procedure was developed by Edward Jenner in 1795 as a way to prevent smallpox, the most devastating disease of the 17th and 18th centuries.
 - a. Jenner knew that milkmaids who contracted cowpox – a milder variant of smallpox – were immune to smallpox.
 - b. He took scrapings from cowpox blisters and scratched them into the skin of his subjects. They got cowpox, but were immune to smallpox.
 - c. How did this work?
 - (1) Cowpox and smallpox viruses are closely related - so they must

- have similar antigens.
- (2) When subjects got cowpox, their immune systems developed memory B and T cells for those antigens.
 - (3) When the individuals were later exposed to smallpox, the memory cells mounted a strong secondary immune response.
2. Vaccines now are much more specific and precise. They all work the same way – by stimulating a primary immune response and generating memory cells that provide a strong secondary immune response. To do this, vaccines may contain:
- a. killed microbes
 - b. weakened microbes
 - c. just the antigens from the microbes (this is becoming more common as genetic engineering techniques allow us to replicate antigens precisely and efficiently)
3. Compulsory vaccination is an important public health issue. Specifically, controversy exists over whether or not childhood vaccination should be required of all children.
- a. Childhood vaccines protect against a range of potentially deadly childhood diseases, including measles, mumps, diphtheria, tetanus, and whooping cough.
 - b. All 50 states in the US require that schoolchildren be vaccinated against various childhood diseases (the exact ones differ from state to state).
 - (1) All 50 states allow medical exemptions – this is important for children who are immunocompromised (have weakened immune systems) due to AIDS, cancer treatment, or other illnesses.
 - (2) 48 states allow religious exemptions
 - (3) 15 states permit exemptions for personal or philosophical reasons.
 - c. On one side of the debate: why not vaccinate?

- (1) Some people simply object to government interference in what they perceive as an individual choice.
 - (2) Some have religious objections.
 - (3) Some are afraid of side effects because they've read or heard about alleged links between vaccinations and a variety of problems, including autism, seizures, and SIDS.
 - (4) Some simply can't face the prospect of subjecting their kids to so many shots.
- d. On the other side of the debate: why is vaccination important? This is a little more complex:
- (1) First, we have to remember that a portion of the population can't be vaccinated
 - (a) This includes infants, immunocompromised children, and some adults.
 - (b) Because they can't be vaccinated, these individuals are at risk of contracting potentially deadly diseases.
 - (2) Large-scale vaccination protects these individuals (as well as the ones who are vaccinated) through "herd immunity."
 - (a) When 90-95% of a population is vaccinated against a pathogen, the pathogen is effectively "walled out" of the population.
 - (b) That's because an introduced pathogen is extremely unlikely to find a susceptible host.
 - (c) Without a susceptible host, the pathogen can't reproduce and spread.
 - (3) So vaccination protects not just the individuals who are vaccinated, but also individuals who can't be vaccinated.
 - (4) Parents who "opt out" of vaccination for religious, personal, or philosophical reasons are essentially relying on herd immunity to

protect their kids.

- e. Is “opting out” a real problem in the US?
 - (1) Overall, the vaccination rate in the US is about 90%, so we have good herd immunity for the most part.
 - (2) However, vaccine-preventable disease outbreaks still occur in subpopulations with lower rates of immunization.
 - (3) E.g.: in 1989-1990, a measles outbreak in CA resulted in 43,000 cases and 101 deaths – primarily among immigrants who hadn’t been vaccinated.
 - (4) Periodic smaller outbreaks clearly support the fact that vaccination compliance is critical to keeping the incidence of these diseases low.
- f. What’s the controversy? Ultimately, it’s the conflict between our desire for personal autonomy and the needs of the community
 - (1) As a public policy issue: is compulsory immunization an acceptable means of protecting public health, or should parents have full autonomy to make decisions about their children’s health care?
 - (2) As a matter of personal ethics: is it right for a parent whose child could safely be vaccinated to refuse to do so, relying on herd immunity? In essence, that parent is reaping the benefit of someone else’s risk-taking.

D. Although vaccination is a powerful preventative measure, vaccinations can’t be developed for all the microbes that cause disease. Prevention, therefore, is critical. Two important forms of prevention are key:

- 1. Personal hygiene:
 - a. To keep from getting sick, keep the microbes away from points of entry into the body (eyes, nose, mouth).
 - b. Single most effective method is **frequent, careful handwashing**

(preferably with hot water and soap, but even cold water is better than nothing).

- c. To be most effective, you should wash your hands for 20 seconds (long enough to sing “Happy Birthday” twice).

2. Food safety:

- a. In spite of improvements in sanitation etc., food-borne illnesses are increasingly common.

- (1) The CDC estimates that food-borne illnesses affect 76 million people annually, causing > 300,000 hospitalizations and 5,000 deaths

- (2) Culprits are a variety of bacteria and viruses. Some of the more common ones are

- (a) *E. coli*, *Salmonella*, and *Staphylococcus* bacteria

- (b) Norwalk virus probably causes most cases of “stomach flu”, including outbreaks on cruise ships, in schools and in day-care centers

- b. Four simple steps can go a long way toward preventing food-borne illnesses:

- (1) **Clean**: get rid of microbes by

- (a) frequent handwashing before and during food preparation

- (b) thoroughly washing all fruits and vegetables and discarding outer layers of leaves in leafy greens

- (c) washing all cooking implements and surfaces with hot, soapy water

- (d) frequently washing kitchen towels, sponges, etc.

- (2) **Separate**: avoid transferring microbes from one food source to another

- (a) keep raw meats away from everything else

- i) separate them in shopping carts
 - ii) wrap carefully and place on bottom shelf in refrigerator
 - iii) always transfer cooked meats to fresh plates/trays, rather than back on the same plate the uncooked meat was on
 - (b) thoroughly wash cutting boards, counters, hands, implements after using them on raw meat before using them on something else
 - (3) **Cook:** use appropriate levels of heat to kill microbes
 - (a) follow cooking directions carefully to – different kinds of foods are susceptible to infection with different kinds of microbes, which have different heat tolerances
 - (b) don't eat raw eggs (even in cookie dough), seafood, etc.
 - (c) drink pasteurized milk and juices (these have been heat-treated to kill microbes)
 - (4) **Chill:** keep microbes from reproducing by refrigerating foods promptly after cooking
- E. When prevention doesn't work, treatment is the next step.
- 1. Antibiotics treat the cause of bacterial illnesses
 - a. Antibiotics are chemicals that kill bacteria in a variety of ways. Originally, they were derived from soil bacteria and fungi – think about why
 - (1) Most pathogenic bacteria can also live in the soil.
 - (2) Soil microbes compete against each other for resources.
 - (3) Antibiotics are simply the chemical weapons soil microbes have evolved to compete with one another.
 - b. Antibiotics work by reducing the size of the pathogen population so the immune system can more easily eliminate the pathogens.
 - c. Taking the full course of antibiotics is very important:

- (1) The initial doses will kill off the weakest bacteria, reducing their population and providing relatively quick symptomatic relief.
 - (2) But many, often stronger bacteria are still present. Taking the antibiotics continues to work against these individuals.
 - (3) If you stop taking the antibiotics early, these stronger individuals may simply start reproducing again, making you sicker than before.
 - d. Antibiotic resistance is a major public health issue (more on this later).
To help reduce the problem:
 - (1) Take antibiotics only when necessary (don't push your physician for antibiotics when you have a virus!).
 - (2) Complete the full course of whatever antibiotics you are prescribed.
2. Anti-viral drugs are in their infancy. Currently, very few drugs are effective at preventing viruses from reproducing once they've caused a disease.
- a. One problem is that free-living viruses are hard to destroy – so it's hard to develop drugs that attack them while they're in the body fluids (this is what antibiotics do with bacteria).
 - b. Once they're inside host cells, they reproduce by taking over normal host cell metabolism.
 - (1) To stop the virus from reproducing you have to stop the cell from carrying out its normal functions.
 - (2) Obvious problem: how do you target only the cells that have been invaded by viruses and leave the rest alone?
3. Other medicines treat symptoms, keeping the pathogens from doing too much damage while the immune system gets rid of them.
- a. Historically, medicines were derived primarily from plants – and plants are still the source of ~ 25% of prescription drugs.
 - b. Currently, we are increasingly able to chemically engineer drugs directly – essentially by analyzing the “target” and “building” a chemical whose

effects we can predict based on our understanding of biochemistry.

c. How are new drugs developed? Use an organism-based drug to follow the process:

- (1) We begin with a candidate organism – usually a plant (but increasingly other kinds of organisms, including deep-sea bacteria) suspected to have medicinal value
 - (a) Note: good candidates are often “nominated” by native peoples practicing traditional medicine – as these cultures are lost, so is a lot of good information about potentially valuable medicines!
 - (b) The other problem, of course, is loss of species due to habitat loss . . .
- (2) Extracts of the plant are tested to see if they have desirable medicinal properties – anti-bacterial and anti-tumor properties are especially valuable
- (3) If the preliminary results are positive, the extracts must be screened to find out exactly which of the many different chemicals is producing the effect.
- (4) Once the specific chemical has been identified, it must be carefully researched to determine its properties and potential effects using a variety of laboratory techniques (including testing on lab animals).
- (5) If these results are promising AND the chemical appears to be safe, it may be approved for human clinical trials. These are carefully designed, controlled, and regulated. In the US, the FDA (Food and Drug Administration) is the monitoring body.
- (6) If the clinical trials go well, the drug will be approved for use – this can take a decade!
- (7) Even once it’s approved, the FDA will continue to monitor the drug for side effects and interactions – it can and does remove drugs

- from the market if unanticipated dangerous side-effects appear.
- d. What about herbal remedies like echinacea, ginkgo, etc.?
- (1) These are also regulated by the FDA, but as nutritional supplements rather than medicines.
 - (2) Because they're not considered medicines, manufacturers only need to demonstrate that they're safe – not that they actually have the effects the manufacturers claim.
 - (3) If they prove to be unsafe (like ephedra, e.g.), the FDA can remove them from the market.

F. Summary:

1. *Until the 1850's, the cause of infectious disease was unknown and treatments were often limited. Key advances in medicine included the discovery of microbes, the development of the germ theory of diseases, and the ability to demonstrate a cause-effect relationship between individual microbes and specific diseases.*
2. *Vaccines prevent the occurrence of specific diseases by promoting a secondary immune response.*
 - a. *Beyond individual protection, community-wide protection is conferred by "herd immunity" when 90-95% of the population is vaccinated.*
 - b. *A major current public health issue is whether or not individuals should be free to "opt out" of compulsory vaccination requirements due to personal or philosophical concerns, as this reduces herd immunity and increases the risk for individuals who can't be vaccinated for medical reasons.*
3. *Personal hygiene and basic food safety are simple and effective preventative measures.*
 - a. *Frequent, careful handwashing is the single most effective preventative measure.*

- b. Food-borne illnesses can be prevented by following the four basic steps of cleaning, separating, cooking, and chilling.*
- 4. Antibiotics treat bacterial disease by reducing bacterial populations so that the immune system can eliminate them more effectively. Antibiotic resistance is a major public health concern; important precautions are to use antibiotics only when necessary and to complete the full course of treatment when they are prescribed.*
 - 5. Antiviral drugs are in their infancy; because of their biology, viruses are extremely difficult to target without also targeting uninfected host cells.*
 - 6. Other medicines treat disease symptoms, not causes. The process of bringing a drug to market is complex, time-consuming, and carefully regulated.*
 - 7. Herbal supplements are also regulated, but much more loosely. Manufacturers need only show that supplements are safe, not that they are effective.*

Sexually Transmitted Infections

IX. Introduction to STI's

A. The name:

1. First modern “comprehensive” name for infectious diseases transmitted through sexual intercourse was “venereal disease” from Venus, the goddess of love.
2. Later, the common term was “sexually transmitted diseases”, or STD's.
3. Currently, the term “sexually transmitted infections” (STI's) is becoming more common – because the term “disease” implies that enough damage has occurred to interfere with normal body function. That isn't always the case with all sexual infections.

B. The scope of the problem: more than just HIV/AIDS

1. 15 million people contract one or more new infections annually; half of

those with life-long infections (65 million may be currently infected)

2. The incidence of many STI's is rising, especially among young people (ages 10-25)
 - a. for some diseases, young women are the most physiologically susceptible
 - b. people are beginning sexual activity at younger ages, and
 - (1) deferring marriage until later in life, and
 - (2) divorce is becoming more common
 - (3) Result = more people have more sexual partners, increasing the spread of STI's
 - c. younger people may also be at higher risk because of multiple barriers to quality prevention
 - (1) lack of insurance/ability to pay for screening, treatment
 - (2) lack of comfort discussing STI's with health care providers
 - d. 2/3 of all new STI's occur in people under the age of 25 (NIH); 1/4 in teenagers (CDC)
3. As we'll see later, many STI carriers, especially women, are asymptomatic – they don't know they're infected
4. Some numbers for common STI's (primarily CDC, 1999 data)
 - a. note that total annual cost was over \$10 billion EXCLUSIVE of Trichomoniasis, the most common new STI!

Disease	# new infections annually	annual cost in millions
Chlamydia	3 million	\$2,013
Gonorrhea	650,000	\$1,051
Syphilis	70,000	\$106
Genital herpes	1 million	\$237
HPV/genital warts	5.5 million	\$3,827

Hepatitis B	120,000	\$156
Trichomoniasis	5 million	?
HIV/AIDS	40,000	\$6,683

- C. Over 20 infectious agents for STI's have been identified. Here we'll briefly introduce each one in (we'll discuss them all in more detail later):
- D. The "top 3": chlamydia, human papillomavirus (HPV) and trichomoniasis account for ~88% new infections
1. **Chlamydia**
 - a. agent = bacterium *Chlamydia trachomatis*
 - b. can have serious long-term consequences, but women are often asymptomatic
 2. **Genital warts**
 - a. agent = human papillomavirus (HPV)
 - b. warts vary in shape, size
 - c. many different strains present; some implicated in cervical cancer
 - d. more than 20 million currently infected! (note that this number just goes up because it's a lifelong disease)
 3. **Trichomoniasis** = "trich"
 - a. agent = protozoan (eukaryotic) parasite = *Trichomonas vaginalis*.
 - b. unusual in that infection more noticeable in women than in men, but can affect both (as we'll see, more normal for women to be asymptomatic and men to have noticeable symptoms)
- E. The other major STI's
1. **HIV/AIDS**
 - a. agent = human immunodeficiency virus
 - b. attacks the immune system; death is by opportunistic infection

c. we'll discuss this separately

2. **Hepatitis B**

a. agent = hepatitis B virus

b. Although it's sexually transmitted (among other things), it doesn't actually affect the reproductive system – as name implies, it's a (serious) disease of the liver

(1) causes liver damage

(2) can predispose people to cirrhosis, liver cancer

c. highly contagious – can also be transmitted via shared toothbrushes, razors!

3. **Genital herpes**

a. agent = herpes simplex virus - 2 (HSV-2)

b. has less serious effects on the body than many STI's, but incurable

c. causes latent infections with intermittent flare-ups

d. outbreaks cause painful sores on the genitals

e. 45 million or more currently infected (like HPV, number just goes up because it's incurable)

4. **Syphilis**

a. infectious agent = bacterium *Treponema pallidum*

b. bacterium is extremely fragile; doesn't live well/long outside host (even difficult for scientists to maintain in culture)

c. origin in Europe unclear and matter of scholarly debate; first epidemic in 1495 was widespread and devastating

d. symptoms may occur in stages over years/decades

e. incidence is declining rapidly in U.S.; may be eradicated within 10 years

5. **Gonorrhea**

a. agent = bacterium *Neisseria gonorrhoeae*

b. disease has been known since Roman times; named by Galen in 2nd

century A.D.

- c. incidence has been steadily declining since 1970's, but still significant health threat
- d. incidence of antibiotic resistance is rising

X. Reproductive organs are the site of most STI symptoms

A. Overview of female reproductive system, starting from the outside and working inward:

1. **Labia majora** and **minora**: folds of tissue protecting vaginal opening
 - a. Herpes, syphilis, HPV infect here (causing sores/warts)
2. **Vagina** = birth canal
 - a. thin-walled, muscular chamber
 - b. sperm deposited, stored
 - c. baby delivered through this passageway
 - d. lined with mucous membrane; produces secretions that acidify the internal environment and help protect against many microbes
 - e. *Trichomonas* feed on vaginal cells, causing inflammation that releases copious smelly discharge
3. **Cervix** = opening to uterus
 - a. Cells lining cervix are a different form of epithelial cells from those lining the vagina
 - b. Cervical cells more susceptible to microbial invasion – infections include
 - (1) *Chlamydia*
 - (2) *N. gonorrhoea*
 - (3) Syphilis
 - (4) Herpes
 - (5) HPV
 - c. Aside: younger women and women taking birth control pills have more of the “susceptible” cells on the outer part of the cervix, so are more

susceptible to these microbes.

- d. Chlamydia & gonorrhea are usually “silent” in women – they don’t experience symptoms (at least, not until late in the infection)

4. **Uterus** = womb

- a. site of pregnancy
- b. thick muscular wall with lining (endometrium) that becomes thick, highly vascularized prior to/during pregnancy (and before menstrual period)
- c. ~ 3 inches long and stretches to accommodate fetus

5. **Oviducts = fallopian tubes**

- a. very thin (~ thickness of a human hair) tubes
- b. egg travels down oviduct from ovary
- c. sperm travels up oviduct from vagina & uterus
- d. fertilization usually takes place here
- e. if fertilized egg implants in oviduct wall, = ectopic pregnancy; requires surgical removal
- f. *Chlamydia* & *N. gonorrhoeae* can “hitchhike” on sperm; if they infect the oviducts, they can cause pelvic inflammatory disease (PID) (more on this later)

6. **Ovary** = site of egg production

- a. ~ 1 inch long
- b. contains 40,000 - 400,000 immature eggs when female baby is born
- c. after puberty, ~ 1 egg released each month
- d. ovary also produces estrogen, progesterone
- e. ovaries also generate estrogen, progesterone

B. Overview of male reproductive system, starting with site of sperm production:

1. **Testes** = sites of sperm production

- a. housed outside body in **scrotum**
- b. in addition to sperm, testes also produce testosterone

2. **Epididymis** = stores developing sperm
3. **Vas deferens** = tubes carrying sperm to urethra (vasectomy = cutting the vas deferens)
4. **Ejaculatory ducts** join to form **urethra**
 - a. urethra = tube carrying urine and semen through the penis
 - b. so sperm flows from vas deferens into urethra via ejaculatory ducts
 - c. cells lining the urethra similar to those lining cervix in women; susceptible to similar infections
 - (1) chlamydia
 - (2) gonorrhea
 - (3) herpes
 - (4) HPV
 - d. Inflammation caused by these infections will cause
 - (1) discharge from penis
 - (2) possible itching/pain inside penis and/or burning with urination
5. Accessory glands add secretions to sperm to form semen:
 - a. **seminal vesicles** produce thick, clear fluid that nourishes and protects sperm
 - b. **prostate gland** secretes milky alkaline fluid to counteract acidity of vagina
 - c. **bulbourethral glands** secrete fluid into urethra during arousal, possibly lubricating inside to help sperm move through
6. **Penis**: delivers sperm (semen) into vagina
 - a. normal ejaculate = ~ 5 mL (1 tsp)
 - b. 95% secretions, 5% sperm (250-500 million)
 - c. This is the primary site of infection in men.
 - (1) Externally, ulcers, sores and warts may be caused by herpes, syphilis, HPV

(2) Although it's not a favorable environment as the vagina, penis & surrounding area may host *Trichomonas*

- C. Males and females share some risks:
1. Gonorrhea, *Chlamydia*, *Trichomonas*, HPV, and herpes can all affect the anus/rectum
 - a. pathogens can be transmitted during anal sex
 - b. vaginal secretions &/or semen can transmit pathogens to the anal region
 2. Chlamydia, gonorrhea, syphilis, and genital herpes can all be transmitted to the mouth & throat via oral sex
- D. Note that two sexually transmitted diseases don't actually affect the reproductive organs:
1. HIV affects the immune system
 2. Hepatitis B affects the liver
 3. Both viruses are carried in the blood & can be transmitted via blood or semen
- E. Differences in anatomy explain why STI's affect women more strongly than men (in general):
1. Tissues of the female reproductive tract more delicate, easier for microbes to invade than the skin of the penis and external organs of men
 2. Infections of the penis are visible, so can be recognized and treated earlier in the infectious process
- F. *Summary*
1. *STI's affect millions of Americans and cost billions of dollars annually*
 2. *3 microbes cause 88% of new infections: the bacterium *Chlamydia trachomatis*, the human papillomavirus (HPV), and the eukaryotic parasite *Trichomonas vaginalis**
 3. *Other major STI agents are the bacteria causing syphilis and gonorrhea and the viruses that cause genital herpes, hepatitis B and AIDS*

4. *The male and female reproductive organs are the site of most STI symptoms. Because of differences in their reproductive tracts, women are more susceptible to infection than are men.*
 5. *Two STI's, HIV and hepatitis B, do not affect the reproductive organs. HIV attacks the immune system while hepatitis B affects the liver.*
- XI. The microbes causing STI's have adaptations to initiate infections, evade defenses and spread their offspring
- A. Initiating infections
 1. The HIV, hepatitis B and HPV viruses lack specialized "attack" mechanisms – all invade through cracks/abrasions/cuts in the skin
 2. Chlamydia attacks mucous membranes by inducing host cells to engulf it, then completes its life cycle inside the host cell
 3. N. gonorrhoeae uses hair-like projections to latch onto cells
 - B. Evading/defeating defenses
 1. HPV viruses infect superficial skin layers & time life cycle to avoid defenses
 - a. Skin is several cell layers deep - activity dividing cells are the deepest layer
 - b. As new cells develop, they fill with tough protein and flatten out into tough, protective cells
 - c. As that happens, the production of new cells below them pushes the developing cells up to the skin's surface
 - d. HPV takes advantage of this process
 - (1) uses cut/abrasion to invade actively dividing cells deep in the skin
 - (2) DNA stays dormant until host cell begins to mature & migrate to skin surface
 - (3) As host matures & migrates, HPV replicates & invades surrounding cells
 - (4) Infected cells on the outer layer of skin = wart – this will allow

viruses to invade new host

(5) T lymphocytes eventually identify & destroy infected cells – but viral DNA is still dormant in the deep layers & can be reactivated

2. Herpes viruses also “hide” from the immune system
 - a. Reproduce in host cells near site of infection
 - b. Cause host cells to fuse with neighbors, so viruses can spread directly from cell to cell without ever entering body fluids
 - c. Viruses also travel, remain latent in nerve clusters
3. *Trichomonas*, a eukaryotic parasite, is big enough to resist phagocytosis, slowing down the mobilization of body defenses (why?)
4. *N. gonorrhoeae* has several defenses:
 - a. Resist phagocytosis – get engulfed by phagocytes, but reproduce & travel in them rather than being destroyed
 - b. Produce an enzyme that destroys key antibody
 - c. Can actively switch among up to 300 different antigens!

C. STI microbes have two major strategies for dispersing offspring:

1. In semen or vaginal fluids: *Chlamydia*, *N. gonorrhoeae*, HIV, hepatitis B, *Trichomonas*.
2. Via contact with surface lesions/warts packed with microbes: Herpes, syphilis, HPV
3. Note that transmission via body fluids not necessarily symmetrical:
 - a. 20-35% of men who have sex once with an infected woman will contract gonorrhea
 - b. 60-90% of women who have sex once with an infected man will be infected

XII. Long-term consequences, prevention, treatment & screening

A. Untreated STI's can have severe long-term consequences.

1. In women, bacterial infections can cause PID, which can affect uterus,

- oviducts, and/or ovaries.
 - a. Symptoms, if any, include pain in lower abdomen & sometimes vaginal discharge
 - b. long-term consequences = infertility and/or ectopic pregnancy if inflammation & scarring close oviducts
- 2. A few strains of HPV are associated with cervical cancer
 - a. All cervical cancer now thought to be caused by HPV, but not all strains of HPV cause cervical cancer
- 3. Because symptoms in men are more noticeable, they tend to get treatment early enough to prevent serious long-term consequences. But untreated infections can cause
 - a. infected testes
 - b. blockage of the vas deferens
 - c. blockage of urethra
- 4. In both males and females:
 - a. untreated hepatitis B can cause chronic liver disease and liver cancer
- B. Prevention requires care and vigilance
 - 1. Only sure method is sexual abstinence
 - 2. Next best is monogamous relationship with uninfected partner
 - 3. Third choice is consistent, proper use of condoms – but note that
 - a. condoms reduce risk of HIV infection, but don't eliminate it
 - b. sores that transmit herpes, syphilis may be in areas not covered by condom
 - c. condom use can be difficult to discuss with a sexual partner (see website)
 - 4. We can vaccinate against hepatitis B – and it is now a recommended infant vaccination
- C. STI screening is an important aspect of health maintenance

1. Women, in particular, are at risk of having STI's without knowing it, either because the infection is asymptomatic (e.g., *Chlamydia*) or because the symptoms occur where they can't be seen (e.g., syphilis sores on the cervix)
 2. STI risks & concerns should be discussed with your physician – risk factors include
 - a. multiple sex partners (especially if they have had multiple partners)
 - b. unprotected vaginal or anal intercourse
 3. Pregnant women should be tested for STI's as soon as pregnancy is confirmed because of the health risks to the infant:
 - a. HIV, syphilis, herpes (herpes rarely) can cross the placenta and infect the fetus in the womb with potentially deadly consequences to the infant
 - b. Chlamydia, gonorrhea, hepatitis B, HPV, and herpes can be transmitted to the fetus during vaginal delivery, with a variety of potential outcomes.
- D. Many STI's can be treated, but not all
1. Bacterial diseases are treated with antibiotics, but problems are beginning to arise with antibiotic-resistant gonorrhea
 2. The viral diseases such as hepatitis B, herpes, and HIV can't be cured, although they can be managed to varying degrees
- E. *Summary*
1. *Like other microbes, those causing STI's have a variety of adaptations for invading a new host, evading the host's defenses, and dispersing their offspring. The two common dispersal mechanisms are semen and vaginal fluids and contact with sores/lesions/warts packed with microbes. Transmission via sexual contact is not always symmetrical; men may transmit STI's more easily than do women.*
 2. *Both men and women can suffer long-term consequences from untreated STI's, but women are more commonly affected because STI's are more commonly cryptic or asymmetric in women than they are in men.*

- a. Long-term consequences in men include infections of the testes and blockages of the testes and urethra.*
 - b. Untreated bacterial infections may cause PID in women, leading to infertility and/or ectopic pregnancy.*
- 3. Except for sexual abstinence, no one method is 100% effective at preventing STI's. Care, vigilance, and willingness to discuss prevention with sexual partners are all extremely important. Anyone who feels he or she is at risk and may have an STI should consult a qualified health practitioner.*
- 4. Pregnant women should be screened for STI's as soon as pregnancy is confirmed. Many of the microbes causing STI's can be transmitted to fetuses across the placenta and others can be transmitted to infants during vaginal delivery.*

XIII. HIV/AIDS: pandemic here for good?

A. Overview of the history of HIV:

1. Evolutionary/DNA analysis of HIV viruses indicate that HIV originated from a relatively harmless virus (SIV) infecting African monkeys & chimps.
 - a. Monkeys & chimps are used for meat in many parts of Africa.
 - b. Consensus hypothesis is that mutant form of SIV was transferred to humans who were using monkeys/chimps for food
 - c. This probably happened ~ 1930.
2. Disease was probably initially confined to villages near the site of origin
 - a. HIV doesn't survive well outside human host and is best transmitted blood-to-blood or during unprotected anal intercourse
 - (1) blood carries far more virus than semen
 - (2) anal intercourse more dangerous than vaginal because of increased likelihood of microtears in the lining of the anus during intercourse
 - b. These were probably not very common in rural Africa

3. Political/economic upheaval, especially after WWII (and continuing very rapidly today) led to increased travel & urbanization
 - a. More rural men moved to big cities
 - b. More women in the cities involved in sex trade
 - c. Virus began to spread in these new urban areas, and from there to other parts of the world
 4. Earliest documented case was in the Democratic Republic of the Congo (Zaire) in 1959.
 5. Spread to U.S. in 1981 – by then it was well established in central Africa.
 6. As of the end of 2003, 34-46 million people were living with HIV/AIDS
 - a. Largest epidemic is in sub-Saharan Africa, where it affects men & women and is spread primarily through heterosexual intercourse
 - b. Rising numbers in India and China; India may see 30 million cases in 10 years and China 4 million by 2010
 - c. Currently ~ 5 million new infections each year, with devastating social, economic & potentially global political consequences
 7. In the U.S:
 - a. ~ 1 million infected and ½ million deaths by the end of 2002
 - b. ~ 40,000 new cases annually
 - (1) Men having sex with men are still the largest proportion of infected individuals
 - (2) New infections in gay men holding steady
 - (3) New infections growing in women – especially minorities – infected via heterosexual sex (often with sex partners who are also IV drug users)
 - (4) Minority men and women disproportionately likely to be infected and to die from AIDS
- B. HIV's adaptations for infection, evading defenses, & dispersing offspring

1. HIV doesn't have highly specialized mechanisms for infection or for offspring dispersal – it must be transmitted from body fluid to body fluid
 - a. It is extremely fragile outside the human host – it doesn't live long on surfaces and isn't airborne
 - b. Enters host either as body fluids contact open sores/cuts, or from direct blood-blood contact
 - c. That's how the virus is dispersed as well
2. HIV's first adaptation for evading defenses is to attack them
 - a. HIV specifically attacks helper T lymphocytes – those are its primary host cells
 - b. Initial infection prompts primary immune response, and antibodies reduce the number of viruses
 - c. Problem: as helper T cells undergo clonal selection as part of the body's defenses, they are also providing more and more host cells for the virus
 - d. ongoing "battle" continues between virus & immune system:
 - (1) immune system produces T cells that viruses demolish (reproducing themselves in the process)
 - (2) viruses reproduce like crazy, but antibodies destroy them
 - e. Eventually, the virus wins, starting a downward spiral:
 - (1) Helper T's can't keep up with viruses, so their numbers drop
 - (2) Over course of years, drop in T cells causes B cells to decline (think about why)
 - (3) When B cells decline, antibody production falls – immune system crashes
 - f. Remember that people with AIDS die from opportunistic infections – diseases that would normally not be serious, but that their weakened immune systems can't fight off.
3. HIV's second adaptation is also what has made it impossible to cure (much

less prevent via vaccination) – it has the highest mutation rate of any virus known. This has several consequences:

- a. Within an individual, the virus mutates throughout the course of the infection
 - (1) The viral strain a patient started with isn't necessarily the one s/he'll have 2, 5, 10 years later
 - (2) At any one time, patient may have up to 100 different strains!
 - (3) Each strain presents a different kind of antigen – so the immune system is effectively trying to fight many different infections at once.
- b. High mutation rate means that drug resistance is a big problem.
 - (1) This was discovered when AZT first began to be used – worked great at reducing HIV replication for a while, but eventually mutant strains arose that were resistant to it, so it stopped being effective.
 - (2) Current strategy is to use many different drugs because odds of any one virus being resistant to all of them is low
 - (3) Problem is that drugs have many side effects
- C. Developing a vaccine for HIV is problematic, for several reasons:
 1. Vaccines work by creating a bank of memory cells that can destroy the infectious agent – but HIV destroys memory cells, not vice-versa
 2. HIV's extremely high mutation rate means trying to figure out which antigen to target in the vaccine is difficult at best
 3. HIV is only pathogenic in humans – no other animals actually contract the disease. That means that, even when a vaccine is ready for trial, we can only test it in humans – which is a problem in itself.
- D. *Summary*
 1. *HIV originated as a harmless monkey/chimpanzee virus that mutated and "jumped" to humans, probably around 1930. Since then it has become a global pandemic, currently affecting 10's of millions of individuals.*

2. *HIV is a relatively “weak” infectious agent – it doesn’t live well outside its human host and can only be transmitted via direct contact between body fluids.*
3. *Once HIV infects a new host, it is extremely successful. It evades host defenses by attacking them. By selectively invading helper T lymphocytes, the virus eventually undermines the entire immune system; death is due to opportunistic infections. HIV is also extremely mutable, making it even more difficult for the immune system to fight; it also makes the infection difficult to treat.*
4. *Developing an effective vaccine for HIV is problematic because of its life history: it attacks the memory cells vaccines rely on, its high mutation rate makes determining an appropriate antigen difficult, and the lack of non-human animal models makes testing a problem.*