 Viruses and Disease - 1

Special Section
Viruses and Human Disease

The ways in which viruses cause the symptoms of disease are as varied as the viruses themselves.

• Some viruses cause lysosomes to release their hydrolytic enzymes, which then destroy the host cell.
• Some induce the host cell to synthesize toxins that cause a disease
• Some have toxic proteins in their envelope

The intensity of a viral infection is related to the host's ability to regenerate and replace the damaged and infected cells as well as the host's immune system to be able to detect the virus and destroy it.

• **Human cold viruses** invade the upper respiratory cells. They are lytic viruses. The symptoms are caused by our immune system's response to the detected foreign substance. Symptoms include fever, inflammation and histamine reactions (the congestion, for example) -- Colds are "cured" because our epithelial tissues replace themselves about every 10 days or so, which coincides with the response time of our immune system to the invading viruses.

• **Chicken pox virus** is the equivalent of a temperate phage. It can invade nerve cells as a lysogenic virus and reside for years. It's original lytic stage concentrates in skin cells where it causes acne-like symptoms. The immune system response takes about 10 days. Chicken pox has few lasting effects. However, if activated in the nerve cells, it causes shingles, rumored to be excruciatingly painful.

• **Polio viruses** invade nerve cells that can not be repaired or replaced, so the damage caused prior to our immune system's means of destroying the foreign invader is permanent.

• **HIV** invades critical Helper T-cells of the immune system, which are essential for the body to mobilize the assorted armies needed to ward off any number of foreign invaders. HIV does not kill, per se, but weakens our immune system's ability to do its job so that we succumb eventually to any number of infectious diseases. Some diseases are more common in HIV-compromised individuals.

• There are also **cancer-causing viruses**. Liver cancer is related to the Hepatitis B virus, and Burkitt's lymphoma is related to the Epstein-Barr virus. One form of leukemia is linked to a virus, as is cervical cancer.

There is good evidence that some viruses activate cancer-causing genes (oncogenes). Oncogenes code for proteins that are involved with mitosis and the cell cycle as growth factors and growth factor receptor molecules. Similar genes, called proto-oncogenes, exist in non-cancer cells but are not active. Some viruses activate proto-oncogenes. Oncogenes work collaboratively with other carcinogens. They, by themselves, cannot produce cancers.
## Virus Pathogens and Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen</th>
<th>Genome</th>
<th>Vector/Epidemiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B (viral)</td>
<td>Hepadnavirus</td>
<td>Double-stranded DNA</td>
<td>Highly infectious through contact with infected body fluids. Approximately 1% of U.S. population infected. Vaccine available. No cure. Can be fatal.</td>
</tr>
<tr>
<td>Herpes</td>
<td>Herpes simplex virus</td>
<td>Double-stranded DNA</td>
<td>Fever blisters; spread primarily through contact with infected saliva. Very prevalent worldwide. No cure. Exhibits latency—the disease can be dormant for several years.</td>
</tr>
<tr>
<td>Mononucleosis</td>
<td>Epstein-Barr virus</td>
<td>Double-stranded DNA</td>
<td>Spread through contact with infected saliva. May last several weeks; common in young adults. No cure. Rarely fatal.</td>
</tr>
<tr>
<td>Smallpox</td>
<td>Variola virus</td>
<td>Double-stranded DNA</td>
<td>Historically a major killer; the last recorded case of smallpox was in 1977. A worldwide vaccination campaign wiped out the disease completely.</td>
</tr>
<tr>
<td>AIDS</td>
<td>HIV</td>
<td>(+) Single-stranded RNA (two segments)</td>
<td>Destroys immune defenses, resulting in death by infection or cancer. Over 42 million cases worldwide by 2002.</td>
</tr>
<tr>
<td>Polio</td>
<td>Enterovirus</td>
<td>(+) Single-stranded RNA</td>
<td>Acute viral infection of the CNS that can lead to paralysis and is often fatal. Prior to the development of Salk's vaccine in 1954, 60,000 people a year contracted the disease in the U.S. alone.</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Flavivirus</td>
<td>(+) Single-stranded RNA</td>
<td>Spread from individual to individual by mosquito bites; a notable cause of death during the construction of the Panama Canal. If untreated, this disease has a peak mortality rate of 60%.</td>
</tr>
<tr>
<td>Ebola</td>
<td>Filoviruses</td>
<td>(−) Single-stranded RNA</td>
<td>Acute hemorrhagic fever; virus attacks connective tissue, leading to massive hemorrhaging and death. Peak mortality is 50–90% if untreated. Outbreaks confined to local regions of central Africa.</td>
</tr>
<tr>
<td>Influenza</td>
<td>Influenza viruses</td>
<td>(−) Single-stranded RNA</td>
<td>Historically a major killer (22 million died in 18 months in 1918–19); wild Asian ducks, chickens, and pigs are major reservoirs. The ducks are not affected by the flu virus, which shuffles its antigen genes while multiplying within them, leading to new flu strains.</td>
</tr>
<tr>
<td>Measles</td>
<td>Paramyxoviruses</td>
<td>(−) Single-stranded RNA</td>
<td>Extremely contagious through contact with infected individuals. Vaccine available. Usually contracted in childhood, when it is not serious; more dangerous to adults.</td>
</tr>
<tr>
<td>SARS</td>
<td>Coronavirus</td>
<td>(−) Single-stranded RNA</td>
<td>Acute respiratory infection; an emerging disease, can be fatal, especially in the elderly.</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Influenza virus</td>
<td>(−) Single-stranded RNA</td>
<td>Acute infection of the lungs; often fatal without treatment.</td>
</tr>
<tr>
<td>Rabies</td>
<td>Rhabdovirus</td>
<td>(−) Single-stranded RNA</td>
<td>An acute viral encephalomyelitis transmitted by the bite of an infected animal. Fatal if untreated.</td>
</tr>
</tbody>
</table>
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Treating and Preventing Viral Infections - Vaccines
Viral infections cannot be treated with antibiotics or medications used for infections by bacteria or eukaryotic pathogens. In fact, the only "treatment" for most viral infections is the action of our immune system. We can however, augment the response of our immune system with vaccines. A vaccine triggers the immune system to develop memory cells so that exposure to that virus activates the immune system faster.

A vaccine is a deliberate introduction of the antigen to promote development of memory lymphocytes. A vaccine can be a weakened (non-lethal) form of the virus or a weakened toxic by-product of the virus. In either case it will trigger an immune system response without activating symptoms of the viral disease. It usually works. A tiny proportion of the time, individuals will have mild symptoms of the viral infection and with polio, a very few will have more serious symptoms. Boosters are often required to reactivate and ensure a faster response of the memory cells. How often one needs a booster depends on the particular vaccine and virus.

Since HIV, humans have been producing more classes of drugs that inhibit the virus from successfully invading its target cells by enhancing the immune system's methods of locating, targeting and de-activating the virus. There are a few drugs that attack viral genetic function, such as AZT for AIDS.

New Viruses
It seems as if new, lethal viruses have emerged in the world at an unprecedented rate during the past few decades. Whether this is true or not, viruses can evolve just like living organisms.

- RNA viruses in particular can mutate frequently because RNA polymerase lacks proofreading capabilities. Viral mutations can lead to more deadly forms of a virus, or mean the virus can increase its host range to spread to new species.
- In some cases loss of territory means that organisms that might carry a virus can now be in more frequent contact with humans than previously when they were not forced share their habitat with humans.
- Population growth patterns (exponential growth) also apply to viruses. A disease that was very, very rare slowly increases in occurrence and then goes around the proverbial J curve and "explodes".
- Changing environments can also affect the rate of virus spread.
The Immune System and Health
Our immune system is our first defense against foreign substances: spores, bacteria, viruses, particulates, etc. The immune system is a multiple defense system, comprised of specific and non-specific, external and internal components.

External Defenses of the Immune System
- The outer layer of our skin protects from water loss and penetration by unwanted substances
- Mucus membrane linings of digestive, respiratory and urinary systems prevent unwanted substances from penetrating into the body; mucus also traps bacteria and other substances
- A variety of secretions in saliva, tears and the gastric juices also protect.
Internal Defenses of the Immune System

Non-specific Inflammatory Response

- Responds to
  - Foreign substances
  - Damaged tissues
- Localized chemical signals are produced which include
  - Localized chemical signals (kinins and histamines), produced by "most cells", promote vasodilatation in response
  - Pyrogens affect the temperature regulators of the brain resulting in increased temperature, which may inhibit some pathogens
- Inflammation: Swelling and redness in area from increased blood flow and fluid accumulation results

Inflammation Response

- Capillaries become leaky to plasma proteins, including a special set or proteins called complement.
  - Complement enhances dilation and permeability of cell membranes. Natural "Killer" WBCs migrate from blood to the region of "damage" to destroy damaged cells.
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- Complement releases phagocytic-attracting chemicals. Phagocytic WBCs migrate from blood to region of "damage" to consume foreigners by phagocytosis.

Symptoms of non-specific inflammatory response in action
- Increased temperature, inflammation and pain in injured area
- Swelling stimulates pain receptors and pain-causing chemicals, such as prostaglandins so we are aware of the problem
- Fluids causing swelling may help to cushion injured area

Specific Immunity)
The specific immune response is responsible for maintaining tissue environment and for destroying specific invaders as well as damaged tissues.

Specific immunity is the function of two groups of WBC (lymphocytes) that "patrol" the body and reside in lymph tissues.
- T-cells (T-lymphocytes)
  T-cells are made in bone marrow and mature in the thymus (with specific antigen recognition). T-cells target body cells and tissues that are infected or damaged.
- B-cells (B-lymphocytes)
  B-cells are made and mature in bone marrow (with specific antigen recognition). B-cells target pathogens in the extracellular environment.
How Specific Immune Cells Work

Primary Immunity

Circulating macrophages of the non-specific defense system trigger the specific immune system. These macrophages are responsible for programming specific lymphocytes in the body.

- As circulating macrophages "digest" invaders, the antigen (the substance recognized as foreign, or the "trigger") of the invading substance is transferred to the macrophage surface as a unique antigen marker.

- Virgin B-cells may also contact the antigen while in circulation, and process the antigen. Once a B-cell processes an antigen it becomes a specific B-cell.

- As antigen-marked macrophages circulate, they come into contact with Helper T-cells. This contact stimulates the macrophage to secrete interleukin-1, which, in turn, stimulates helper T-cells to activate a series of specific immune system responses.
  - Helper T-cells bind to antigen-possessing B-cells to promote rapid division of specific B-cells with the antigen marker.
  - Helper T-cell secrete interleukin-2 to promote rapid division of Cytotoxic (Killer) T-cells

B-cell Antibody Sequence  Cytotoxic T-Cell Sequence
Anti-body (Humoral) Mediated Response for Extracellular Targets
Sensitized B-cells (with the antigen marker) divide rapidly and differentiate into plasma cells that secrete antibodies. Interleukin-2, secreted by Helper-T cells, promotes the differentiation. Antibodies act in the following ways:
- Antibodies neutralize toxins by coating the molecules so they become inactive.
- Antibodies cause agglutination of foreign cells, so macrophages can consume the clump.
- Antibodies can cause antigens to precipitate so macrophages can consume them.
- Antibodies can also activate the protein complement system.

Some B-cells divide and form memory cells for subsequent attacks. These memory cells reside in lymph nodes until needed. A first exposure (primary immunity) requires about 6 – 10 (or more) days to be effective. After the first exposure memory cells can activate responses in 1 – 2 days.

Cell-Mediated Immune Response (T-cell activity)
A few sensitized (marked) T-cells can be stimulated by the interleukin-2 secreted by helper T-cells to divide rapidly and form an army of Cytotoxic T-cells. Cytotoxic T-cells work by "punching holes" into target cells (those infected with a virus, damaged, diseased, or a foreign substance) causing the cells to lyse and be destroyed.

Other T-cells become suppressor T-cells that secrete chemicals to diminish the division of B and T cells as the amount of antigen diminishes (when the job is done).

The majority (60 – 70%) of T-cells in circulation, however, are the Helper T-cells that enhance the immune response when activated by antigens, as discussed.
HIV (the virus responsible for AIDS) attacks helper T-cells, specifically the CD4+ T-cells, seriously impacting the specific immune system response, as the T-cells are damaged and destroyed.

Ultimately, with the immune system undermined in this way, the body weakens and cannot fight off infectious diseases and other foreign substances. Once HIV infection progresses to AIDS, those infected too often exhibit wasting symptoms, related to starvation and the body's immune system's inability to respond to infection and disease. Inadequate food consumption, malabsorption, the drug therapies and other intestinal distress along with increased metabolic rate all contribute to the wasting symptoms. Nutritional adequacy and food safety is critical for those with HIV. People with weakened immune systems are more susceptible to food-borne illnesses.
Some current treatments for AIDS are shown in the summary below.
Secondary immunity - Immunization
The immune system can be activated by the deliberate introduction of an antigen to promote development of memory lymphocytes. **Active immunity** can be accomplished through vaccination. A vaccine can be a weakened (non-lethal) form of invader or a toxic by-product of an invader. A **booster** provides subsequent exposure that ensures more rapid future immune response.
Passive immunity can be obtained from a mother who passes antibodies through the placenta or when nursing to an infant. Passive immunity is sometimes distributed by injection of specific antibodies using an animal serum (such as horse serum). Passive immunity is not permanent since no memory cells are induced. The recipient is receiving pre-made antibodies only.

Monoclonal antibodies are used in medical diagnoses such as pregnancy detection. A host organism is exposed to a specific antigen and then "sacrificed". B-lymphocytes are removed from the spleen and incubated with cancer cells in culture. The cells formed produce large amounts of monoclonal antibodies with the specific antigen marker. Monoclonal antibodies can also be injected back into the antigen donor for passive immunity from the specific antigen. Genetically engineered monoclonal antibodies are used for some cancer treatments. They target growth factor signal proteins that promote cell division in cancer cells and signal the immune system to destroy them.

Problems with the Immune System
The immune system is not perfect. Allergies are caused by an immune system that is too reactive, particularly the non-specific histamine responses. Autoimmune diseases such as rheumatoid arthritis and lupus are debilitating. Those who require organ transplants face tissue rejection because the transplanted tissue is recognized as foreign. Some components of aging may be related to the failure to recognize non-self, opening our bodies up to foreign invasion.
## Bonus Section On Bacterial Pathogens and Disease – For the Curious

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen</th>
<th>Vector/Reservoir</th>
<th>Epidemiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthrax</td>
<td><em>Bacillus anthracis</em></td>
<td>Animals, including processed skins</td>
<td>Bacterial infection that can be transmitted through contact or ingestion. Rare except in sporadic outbreaks. May be fatal.</td>
</tr>
<tr>
<td>Botulism</td>
<td><em>Clostridium botulinum</em></td>
<td>Improperly prepared food</td>
<td>Contracted through ingestion or contact with wound. Produces acute toxic poison; can be fatal.</td>
</tr>
<tr>
<td>Chlamydia</td>
<td><em>Chlamydia trachomatis</em></td>
<td>Humans, STD</td>
<td>Urogenital infections with possible spread to eyes and respiratory tract. Occurs worldwide; increasingly common over past 20 years.</td>
</tr>
<tr>
<td>Cholera</td>
<td><em>Vibrio cholera</em></td>
<td>Human feces, plankton</td>
<td>Causes severe diarrhea that can lead to death by dehydration; 50% peak mortality if the disease goes untreated. A major killer in times of crowding and poor sanitation; over 100,000 died in Rwanda in 1994 during a cholera outbreak.</td>
</tr>
<tr>
<td>Dental caries</td>
<td><em>Streptococcus</em></td>
<td>Humans</td>
<td>A dense collection of this bacteria on the surface of teeth leads to secretion of acids that destroy minerals in tooth enamel; sugar alone will not cause caries.</td>
</tr>
<tr>
<td>Diphtheria</td>
<td><em>Corynebacterium diphtheriae</em></td>
<td>Humans</td>
<td>Acute inflammation and lesions of mucous membranes. Spread through contact with infected individual. Vaccine available.</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td><em>Neisseria gonorrhoeae</em></td>
<td>Humans only</td>
<td>STD, on the increase worldwide. Usually not fatal.</td>
</tr>
<tr>
<td>Hansen disease</td>
<td><em>Mycobacterium leprae</em></td>
<td>Humans, feral armadillos</td>
<td>Chronic infection of the skin; worldwide incidence about 10–12 million, especially in southeast Asia. Spread through contact with infected individuals.</td>
</tr>
<tr>
<td>Lyne disease</td>
<td><em>Borrelia burgdorferi</em></td>
<td>Ticks, deer, small rodents</td>
<td>Spread through bite of infected tick. Lesion followed by malaise, fever, fatigue, pain, stiff neck, and headache.</td>
</tr>
<tr>
<td>Peptic ulcers</td>
<td><em>Helicobacter pylori</em></td>
<td>Humans</td>
<td>Originally thought to be caused by stress or diet, most peptic ulcers now appear to be caused by this bacterium; good news for ulcer sufferers because it can be treated with antibiotics.</td>
</tr>
<tr>
<td>Plague</td>
<td><em>Yersinia pestis</em></td>
<td>Fleas of wild rodents: rats and squirrels</td>
<td>Killed ¾ of the population of Europe in the 14th century; endemic in wild rodent populations of the western U.S. today.</td>
</tr>
<tr>
<td>Pneumonia</td>
<td><em>Streptococcus</em>, <em>Mycoplasma</em>, <em>Chlamydia</em></td>
<td>Humans</td>
<td>Acute infection of the lungs; often fatal without treatment.</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Humans</td>
<td>An acute bacterial infection of the lungs, lymph, and meninges. Its incidence is on the rise, complicated by the development of new strains of the bacterium that are resistant to antibiotics.</td>
</tr>
<tr>
<td>Typhoid fever</td>
<td><em>Salmonella typhi</em></td>
<td>Humans</td>
<td>A systemic bacterial disease of worldwide incidence. Less than 500 cases a year are reported in the U.S. The disease is spread through contaminated water or foods (such as improperly washed fruits and vegetables). Vaccines are available for travelers.</td>
</tr>
<tr>
<td>Typhus</td>
<td><em>Rickettsia typhi</em></td>
<td>Lice, rat fleas, humans</td>
<td>Historically a major killer in times of crowding and poor sanitation; transmitted from human to human through the bite of infected lice and fleas. Typhus has a peak untreated mortality rate of 70%.</td>
</tr>
</tbody>
</table>