What causes disease?

- **Microbes**, microscopic organisms (including viruses, bacteria, fungi, and protists), are often harmless but can sometimes be parasitic.
  - Parasites are living organisms on or within a host organism that causes harm in the process.
  - Disease-causing microbes are called pathogens.

Mechanisms of Defense

- Vertebrates have three lines of defense against pathogens:
  - Nonspecific external barriers.
    - Skin, hair, cilia, and secretions (tears, saliva, and mucus).
  - Nonspecific internal defenses.
    - White blood cells that engulf or destroy all foreign particles.
  - Specific internal defenses, the Immune Response.
    - Special white blood cells, or immune cells selectively destroy invaders and remember them for future attacks.

Mechanisms of Defense

- First the pathogen must cross nonspecific external barriers (skin, hair, tears, saliva).
- If successful, it faces nonspecific internal barriers that make us feel sick (fever, coughing, sore, inflammation).
- The final line of defense is the adaptive immune response in which special immune cells kill and remember pathogens for future infections.
Nonspecific External Defense

• Animals have two surfaces which are exposed to pathogens: skin and mucus membranes.
  – **Skin** is composed of several layers of thick cells, the exterior of which is covered with a layer of dead cells.
  – Few pathogens penetrate the layer of dead skin before it is sloughed off.

http://www.eyeofscience.com/eos2/index2.html

Nonspecific External Defense

• Animals have two surfaces which are exposed to pathogens: skin and mucus membranes.
  – Within the layers of **skin** are **pores** which secrete fluids (sweat on the skin, wax in the ear) containing natural antibiotics that inhibit pathogens.

http://www.eyeofscience.com/eos2/index2.html

Nonspecific External Defense

• Animals have two surfaces which are exposed to pathogens: skin and mucus membranes.
  – **Mucus membranes** surround the eyes, and line the digestive and respiratory tracts of all mammals.
  – These are much more hospitable to pathogens.
  – However, tears and mucus contain antibacterial enzymes called **lysozymes** that destroy bacterial cell walls.

Bacteria trapped by mucus and cilia

Nonspecific External Defense

• Animals have two surfaces which are exposed to pathogens: skin and mucus membranes.
  – **Mucus membranes** also physically trap microbes and foreign objects entering the body in the mucus and **cilia** (protein filament-like hairs) that line the membranes.
  – If microbes are swallowed, they are met with extreme acidity and digestive enzymes in the digestive tract.

Bacteria trapped by mucus and cilia
Nonspecific Internal Defenses

- Once past external barriers (skin and mucus membranes), pathogens encounter internal defenses:
  - An **inflammatory response** is triggered, bringing white blood cells to the scene.
  - **Phagocytes**, a type of white blood cell (a leukocyte), attack and destroy all foreign particles.
  - If an infection occurs, a **fever** brings elevated temperatures which slow microbial reproduction.

http://www.eyeofscience.com/eos2/index2.html

Nonspecific Internal Defenses

- The inflammatory response sends specialized **phagocytes**.
  - Phagocytes consume infecting particles that penetrate external defenses.
  - Phagocytes make up 50-70% of white blood cells in the body.
  - **Macrophages**, specialized phagocytes, consume dead or dying cells to prevent the cytosol from leaking and possibly infecting nearby cells.
  - Macrophages also act in the specific immune response.

Macrophage consuming infecting bacteria.

Nonspecific Internal Defenses

The **inflammatory response** causes injured tissues to become warm, red, swollen, and painful.

Tearing of the epidermal (skin) tissue (1) causes wounded cells to release chemicals that stimulate mast cells (2).

Nonspecific Internal Defenses

The **inflammatory response** causes injured tissues to become warm, red, swollen, and painful.

**Mast cells** release histamine and respond to allergic reactions (3).
**Histamine** makes capillary walls leaky and relaxes the smooth muscles lining blood vessels (4).
Nonspecific Internal Defenses

The **inflammatory response** causes injured tissues to become warm, red, swollen, and painful.

With capillary walls relaxed and leaky, phagocytes can easily squeeze through walls and reach the site of infection (5).

**Nonspecific Internal Defenses**

- At the site of infection, an inflammatory response is felt:
  - Painful, swollen tissues as phagocytes rush to the scene.
  - Increased fluid production to remove any remaining external pathogens.
  - Pain caused by swelling and chemicals released by injured tissues to warn the injured organisms.

**Nonspecific Internal Defenses**

- At the site of infection an inflammatory response is felt.
- If this does not kill the pathogen and a full scale attack is launched, the body elevates its body temperatures causing a **fever**.
  - Increased fat metabolism.
  - Constriction of the blood vessels.
  - Conservation of heat through shivering.
- This enhances **leukocyte** (white blood cell) reproduction and slows down microbial cell division.

**Phagocytes attacking invading particles.**

*E. coli* cells being consumed and destroyed.  
A nematode under attack.

http://www.eyeofscience.com/eos2/index2.html

**Nonspecific Internal Defenses**

Normal lung cells  
Lung cells infected with *Streptococcus pneumoniae*
Influenza Virus Activates the Non-Specific Immune Response

• Influenza is an RNA virus that enters the body through the nasal cavity.
• Causes "flu-like symptoms":
  – Chills, fever, sore throat, muscle aches, coughing, weakness.
  – Transmitted from person to person through the air.

How the Influenza Virus Attacks

The virus particle binds to receptor proteins on the surface of the cell (1) and enters the cell by endocytosis forming a vacuole (2).
The viral membrane fuses with the vacuole membrane (3), releasing viral components into the cytoplasm (4).

Summary of Nonspecific Defenses

• External Barriers:
  – Layers of dead skin cells present an almost impregnable barrier.
  – Mucus membranes trap and destroy foreign particles.
• Internal Barriers:
  – Special leukocytes (white blood cells) called phagocytes engulf and break down foreign particles that get inside.
  – An inflammatory response calls phagocytes to the scene of infection, triggered by mast cells releasing histamine.
    • Histamine relaxes capillary blood vessel walls to allow access to phagocytes traveling with blood.
  – If all this fails, a fever is induced with elevated body temperatures to retard pathogen growth.
Adaptive Immune Response

• When the nonspecific response (exterior barriers, phagocytes, inflammatory response, and fever) fail, the body mounts a highly specific and coordinated Adaptive Immune Response.
  – A host of specialized white blood cells excrete a variety of chemicals and communicate in complex ways.

Specific Immune Response

• Two types of leukocytes are important:
  – B cells are white blood cells that produce antibodies.
    • Plasma cells are B cells which secrete antibodies.
    • Memory B cells provide immunity against future infections.
  – T cells are white blood cells that regulate the immune response.
    • Cytotoxic T cells destroy foreign eukaryotic and cancerous cells.
    • Helper T cells stimulate the immune response.
    • Memory T cells which provide future immunity.

Adaptive Immune Response

White blood cells (leukocytes) are formed in bone marrow and reside in the lymph nodes, waiting for invaders. The spleen allows leukocytes to enter the blood.

Specific Immune Response

• Both B cells and T cells follow the same fundamental steps in the immune system:
  – They respond to the immune system alarm, recognizing the invaders.
  – They launch an attack (Plasma cells and Cytotoxic T cells).
  – They remember the invader for future infections (Memory B cells and Memory T cells).

http://www.eyeofscience.com/eos2/index2.html
Recognizing the Invader

- Immune cells recognize molecules specific to the invading microbe called **antigens**.
  - Antigens generally are large complex molecules like proteins, polysaccharides, and glycoproteins located on the surface of the cell.
  - Antibody proteins are produced by B cells to recognize pathogens.

- **Antibodies** are Y-shaped proteins with a variable region at one end.
  - The variable region is altered between different antibodies to recognize and bind to different antigens.
  - Binding of an antibody to a pathogen’s antigen initiates the adaptive immune response.

- Influenza virus has two main antigens:
  - Hemagglutinin (the H protein)
  - Neuraminidase (the N protein)

- Influenza virus strains are named by their H and N proteins. (H1N1, H5N1, etc.)

- Antibodies are made from a patchwork of genes, creating the variable region from a pool of shorter gene sequences.
- This allows the body to produce an “army” of B cells, each with its own unique antibody, without coding for each one individually.
Recognizing the Invader

- Plasma cells secrete additional antibodies that bind and can modify antigens.
  - Some antibodies make antigens more appealing to phagocytes.
  - Some prevent the microbes from adhering to host cells.
  - Some block viral entry into the cell.
  - Some deactivate toxins.

The B cell Attack

- When an invader is recognized, B cells containing different antibodies appear on the scene of infection.
- Only the B cell carrying the antibody that recognizes the antigen will reproduce a clonal population.

The B cell Attack

- This cloned population of daughter cells differentiate into two types of B cells:
  - Memory B cells and Plasma cells.
- Memory B cells preserve the antibody specific to this invading microbe for future infections.

The B cell Attack

- This cloned population of daughter cells differentiate into two types of B cells:
  - Memory B cells and Plasma cells.
- Plasma cells are packed with rough endoplasmic reticulum to synthesize large quantities of antibody to deactivate the microbe.
The Plasma Cell

- The B cell before infection.
- The B cell differentiated into a Plasma cell after infection.

Endoplasmic Reticulum

B Cells Fighting an Infection by Clonal Selection

Recognizing the Invader

- T cells produce T cell receptor proteins that also recognize and help destroy pathogens.
- T cell receptor proteins remain attached to the surface of T cells.
- They alter the activity of the attached T cell rather than alter the antigen directly.

The T cell Attack

- Helper T cells respond to antigens on the surface of macrophages (from deactivated pathogens), causing T cell differentiation into Cytotoxic T cells and Memory T cells.
- Cytotoxic T cells are covered with T cell receptors that recognize infected cells.
- They bind to the infected cell and release proteins to inside the cell causing it to break down.
- Memory T cells develop when the infection is over to remember the type of attack that worked on this particular infection.
**Medical Care Assists the Immune Response**

- **Vaccines** introduce the body to pathogens to make memory B cells and memory T cells before an infection.

The first exposure to the killed antigen causes a small immune response allowing the immune response to the second exposure to come on much faster and stronger than without the vaccine.

**The First Vaccine**

- Smallpox was once one of the deadliest killers of the human race.
  - The virus killed 30% of infected persons.
- The first vaccines against the disease were developed in 1796 when an English surgeon recognized the similarities between smallpox and cowpox (a severe but not as deadly disease).
  - He inoculated an 8 year old boy with bacteria possessing the cowpox virus.
  - Months later, he inoculated the boy with the smallpox virus and he survived the infection.
  - Soon people all over Europe were being vaccinated against smallpox using the cowpox virus.

**Medical Care Assists the Immune Response**

- Vaccines, a “short-cut” to immunity, can be made in several different ways:
  - Disease-causing organisms are killed or weakened so they cannot cause disease but still retain surface antigens.
  - Specific antigenic molecules are purified from the disease-causing organism.
  - Harmless organisms are genetically modified to encode for a specific antigen without causing disease.
  - A related pathogen that causes no (or very mild) symptoms is used to stimulate an immune response to a common antigen.
Medical Care Assists the Immune Response

Exposure to the antigen of a disease-causing microbe causes memory cells to remember the antibodies specific for that pathogen.

- Now many diseases are controlled with vaccinations: polio, typhoid fever, mumps, measles.
- Smallpox has been completely eradicated since 1980 due to vaccinations by the World Health Organization.
  - Only two laboratories in the world legally keep stocks of smallpox, in case “bioterrorists” have a store and use it as an attack and more vaccines are needed.

Immune System Malfunctions

Allergies are an immune response to harmless substances.

- B cells recognize an antigen on the surface of the allergen, launching an immune response.
- Antibodies produced bind to nearby mast cells which release histamine whenever the allergen antigen binds its antibodies.

Medical Care Assists the Immune Response

- Just like a fever, antibiotics slow down microbial reproduction.
  - An antibiotic is a chemical drug that targets specific cellular functions in invading Prokaryotes and Eukaryotic pathogens (fungi and protists).
  - Antibiotics are not capable of destroying the microbe.
  - They slow down its progress so that the body’s immune response can launch its attack.
  - Mutants can spontaneously arise that are immune to a specific antibiotic and spread that mutation to future populations.

Immune System Malfunctions

- Autoimmune Disease occurs when the body initiates an immune response against a particular type of normal body cell.
  - After a pathogen infection, B cells mistake body cells for pathogens and create antibodies against them.
    - Multiple sclerosis occurs when immune cells attack the insulating fatty coating neurons of the brain and spinal cord.
    - Rheumatoid arthritis occurs when the immune system attacks cartilage of the joints.
Immune System Malfunctions

**Immune Deficiency Diseases** disable the immune system.

- AIDS (acquired immune deficiency syndrome) is caused by HIV, the human immunodeficiency virus, which infects and destroys Helper T cells.
  - Without Helper T cells, B cells and Cytotoxic T cells are not activated to combat diseases.
  - AIDS patients often die from common diseases (like pneumonia) that healthy people fight off every day.

**HIV is a Retrovirus**

- HIV is a **retrovirus**, an RNA virus that reverse transcribes (RNA → DNA) its genome into DNA to incorporate it into its host genome.
  - Retroviruses are the only type of RNA virus that can incorporate its genome into a host genome.
  - Once incorporated, the host cell becomes a viral manufacturing plant, producing thousands of viral particles in an average Eukaryotic cell’s lifespan.

---

Cancer results when cells fail to recognize signals to stop dividing and avoid apoptosis (programmed cell death).

Since most cancers are not caused by an external pathogen, cancer is hard to target by the immune system.

Cancerous cells grow, unchecked, and form **malignant tumors** that eventually spread throughout the body.

**Benign tumors** do not spread.

---

**Immune System Malfunctions**

- We are exposed to carcinogens (cancer-causing agents) every day.
- The most common carcinogens are gamma rays from the sun and naturally produced carcinogens in our food.

Skin cancer, one of the most common forms of cancer, begins with a melanoma.
Immune System Malfunctions

- Cancer, unlike other forms of immune system malfunctions, can be treated and cured.
  - **Surgery** is the first step to remove the cancerous tumors.
  - **Radiation** bombards the tumor cells with high energy electrons to disrupt their DNA.
  - **Chemotherapy** drugs attack the machinery of cell division, but unfortunately also kills some healthy cells too (in particular hair follicles and the lining of the intestines).

- The best medicine is **preventative**: refrain from engaging in activities that expose you to carcinogens (quit smoking, stop sunbathing, eat lots of vegetables and less fat, exercise, etc.)

---

**Homework**

Describe the non-specific immune response that results after getting a splinter, starting from the puncture site.