Immunity in Animals

- An animal must defend itself against unwelcome intruders - the many potentially dangerous viruses, bacteria, and other pathogens it encounters in the air, in food, and in water.
- It must also deal with abnormal body cells, which, in some cases, may develop into cancer.
- Three cooperative lines of defense have evolved to counter these threats.
- Two of these are nonspecific – that is, they do not distinguish one infectious agent from another.

The skin and mucous membrane provide ***first-line*** barriers to infection

- Intact skin is a barrier that cannot normally be penetrated by bacteria or viruses, although even minute abrasions may allow their passage.
- Likewise, the mucous membranes that line the digestive, respiratory, and genitourinary tracts prevent the entry of potentially harmful microbes.
- The skin and mucous membranes also attack pathogens with chemical defenses.
  - In humans, for example, secretions from sweat glands give the skin a pH ranging from 3 to 5, which is acidic enough to prevent colonization by many microbes.
  - Microbial colonization is also inhibited by the washing action of saliva, tears, and mucous secretions that continually bathe the exposed epithelium.
  - All these secretions contain antimicrobial proteins.
    - One of these, the enzyme **lysozyme**, digests the cell walls of many bacteria, destroying them.
- *Mucus*, the viscous fluid secreted by cells of mucous membranes, also traps microbes and other particles that contact it.
- Microbes present in food or water, or those in swallowed mucus, must contend with the highly acidic environment of the stomach.
  - The acid destroys many microbes before they can enter the intestinal tract.

Phagocytic cells, inflammation, and antimicrobial proteins, all ***second line defenses***, function early in infection

- Microbes that penetrate the first line of defense face the second line of defense, which depends mainly on **phagocytosis**, the ingestion of invading organisms by certain types of ***white cells***.
- The phagocytic cells called **neutrophils** constitute about 60%-70% of all white blood cells (leukocytes).
  - Cells damaged by invading microbes release chemical signals that attract neutrophils from the blood.
  - The neutrophils enter the infected tissue, engulfing and destroying microbes there.
  - Neutrophils tend to self-destruct as they destroy foreign invaders, and their average life span is only a few days.
- **Monocytes**, about 5% of leukocytes, provide an even more effective phagocytic defense.
  - After a few hours in the blood, they migrate into tissues and develop into **macrophages**: large, long-lived phagocytes.
  - These cells extend long pseudopodia that can attach to polysaccharides on a microbe's surface, engulfing the microbe by phagocytosis, and fusing the resulting vacuole with a lysosome.
- Some macrophages migrate throughout the body, while others reside permanently in certain tissues, including the lung, liver, kidney, connective tissue, brain, and especially in lymph nodes and the spleen.

- **Eosinophils**, about 1.5% of all leukocytes, contribute to defense against large parasitic invaders, such as the blood fluke, *Schistosoma mansoni*.
  - Eosinophils position themselves against the external wall of a parasite and discharge destructive enzymes from cytoplasmic granules.
- **Natural killer** (**NK**) **cells** do not attack microorganisms directly but destroy virus-infected body cells.
  - They also attack abnormal body cells that could become cancerous.
  - NK cells mount an attack on the cell's membrane, causing the cell to lyse.
- Damage to tissue by a physical injury or by the entry of microorganisms triggers a localized **inflammatory response**.
  - Damaged cells or bacteria release chemical signals that attract phagocytic cells and cause nearby capillaries to dilate and become more permeable, leading to clot formation at the injury.
  - Increased local blood supply leads to the characteristic swelling, redness, and heat of inflammation.
- One of the chemical signals of the inflammatory response is **histamine**.
  - Histamine triggers both dilation and increased permeability of nearby capillaries.
- Enhanced blood flow and vessel permeability have several effects.
  - First, they aid in delivering clotting elements to the injured area, beginning the repair process
  - Second, this also enhances the migration of phagocytic cells from the blood into the injured tissues, usually within 1 hour after injury.
- A variety of proteins function in nonspecific defense either by attacking microbes directly or by impeding their reproduction.
  - In addition to lysozyme, other antimicrobial agents include about 20 serum proteins, known collectively as the **complement system**.
    - These carry out a cascade of steps, such as attracting phagocytes, that eventually lead to lysis of microbes.
- Another set of proteins that provide nonspecific defenses are the **interferons**, which are secreted by virus-infected cells.
- To summarize the nonspecific defense systems, the first line of defense, the skin and mucous membranes, prevents most microbes from entering the body.
- The second line of defense uses phagocytes, natural killer cells, inflammation, and antimicrobial proteins to defend against microbes that have managed to enter the body.
- These two lines of defense are ***<u>nonspecific</u>*** in that they ***<u>do not distinguish among pathogens.</u>***

Specific Defenses

- ***<u>Antigens</u>*** are foreign molecules that stimulate antibody production.

- ***<u>Antibodies</u>*** inactivate antigens by binding to them.

- ***<u>Lymphocytes</u>*** produce antibodies.

- Lymphocytes, the key cells of the immune system – are the body's third line of defense.

- The vertebrate body is populated by two main types of lymphocytes: **B lymphocytes** (**B cells**) and **T lymphocytes** (**T cells**).

  - Both types of lymphocytes circulate throughout the blood and lymph and are concentrated in the spleen, lymph nodes, and other lymphatic tissue.

- Because lymphocytes recognize and respond to particular microbes and foreign molecules, they are said to display *specificity*.
  - A foreign molecule that elicits a specific response by lymphocytes is called an **antigen**.
    - Antigens include molecules belonging to viruses, bacteria, fungi, protozoa, parasitic worms, and non- pathogens like pollen and transplanted tissue.
  - B cells and T cells specialize in different types of antigens, and they carry out different, but complementary, defensive actions.
- One way that an antigen elicits an immune response is by activating B cells to secrete *proteins* called **antibodies**.
  - Each antigen has a ***particular molecular shape*** and stimulates certain B cells to secrete antibodies that interact specifically with it.

  - In fact, B and T cells can distinguish among antigens with molecular shapes that are only slightly different, leading the immune system to target specific invaders.

- B and T cells recognize specific antigens through their plasma membrane-bound **antigen receptors.**

  - A single T or B lymphocyte has about 100,000 receptors for antigen, all with exactly the same specificity.

Antigens interact with specific lymphocytes, inducing immune responses and immunological memory

- A microorganism interacts ***only with lymphocytes bearing receptors specific for its various antigenic molecules.***
- The "selection" of a lymphocyte by one of the microbe's antigens activates the lymphocyte, stimulating it to divide and differentiate, and eventually, producing two clones of cells.
  - One clone consists of a large number of ***effector cells***, short-lived cells that combat the same antigen.
  - The other clone consists of ***memory cells***, long-lived cells bearing receptors for the same antigen.
- The selective proliferation and differentiation of lymphocytes that occur the *first time* the body is exposed to an antigen is the **primary immune response**.
  - About 10 to 17 days are required from the initial exposure for the maximum effector cell response.
  - During this period, selected B cells and T cells generate antibody-producing effector B cells, called **plasma cells**, and effector T cells, respectively.
- A second exposure to the same antigen at some later time elicits the **secondary immune response**.
  - This response is faster (only 2 to 7 days), of greater magnitude, and more prolonged due to ***immunological memory***.
  - In addition, the antibodies produced in the secondary response tend to have greater affinity for the antigen than those secreted in the primary response.

Lymphocyte Development and Reactivity

- Lymphocytes, like all blood cells, originate from pluripotent stem cells in the bone marrow or liver of a developing fetus.
- Early lymphocytes are all alike, but they later develop into T cells or B cells, depending on where they continue their maturation.
- Lymphocytes that migrate from the bone marrow to thymus develop into T cells.
- Lymphocytes that remain in the bone marrow and continue their maturation there become B cells.
- While B cells and T cells are maturing in the bone marrow and thymus, their antigen receptors are tested for potential self-reactivity.
- Lymphocytes do not react to most self antigens, but T cells do have a crucial interaction with one important group of native molecules (molecules belonging to us).
  - These are a collection of cell surface glycoproteins encoded by a family of genes called the **major histocompatibility complex** (**MHC**).
  - Two main classes of MHC molecules mark body cells as self.
    - **Class I MHC molecules** are found on almost all nucleated cells - that is, on almost every cell.
    - **Class II MHC molecules** are restricted to a few specialized cell types, including macrophages, B cells, activated T cells, and those inside the thymus.
- MHC molecules vary from person to person because of their central role in the immune system.
  - Through **antigen presentation**, an MHC molecule cradles a fragment of an intracellular protein antigen in its hammock-like groove, carries it to the cell surface, and "presents" it to an antigen receptor on a T cell.
  - Thus T cells are alerted to an infectious agent after it has been internalized by a cell (through phagocytosis or receptor-mediated endocytosis), or after it has entered and replicated within a cell (through viral infection).
- There are two main types of T cells, and each responds to one class of MHC molecule.
  - **Cytotoxic T cells** (**T_C**) have antigen receptors that bind to protein fragments displayed by the body's class I MHC molecules.
  - **Helper T cells (T_H**) have receptors that bind to peptides displayed by the body's class II MCH molecules.
- Class I MHC molecules, found in almost all cells, are ready to present fragments of proteins made by infecting microbes, usually viruses, to cytotoxic T cells.
  - Cytotoxic T cells respond by killing the infected cells.
  - Because all of our cells are vulnerable to infection by one or another virus, the wide distribution of class I MHC molecules is critical to our health.
- Class II MHC molecules are made by only a few cell types, chiefly macrophages and B cells.
  - These cells, called **antigen-presenting cells** (**APCs**) in this context, ingest bacteria and viruses and then destroy them.
  - Class II MHC molecules in these cells collect peptide remnants of this degradation and present them to helper T cells.
  - In response, the helper T cells send out chemical signals that incite other cell types to fight the pathogen.

Types of Immune Responses

- The immune system can mount two types of responses to antigens: a humoral response and a cell-mediated response.
  - In **<u>cell-mediated immunity</u>**, T lymphocytes attack viruses and bacteria within infected cells and defend against fungi, protozoa, and parasitic worms.
    - They also attack "nonself" cancer and transplant cells.
  - **<u>Humoral immunity</u>** involves B cell activation and results from the production of antibodies that circulate in the blood plasma and lymph.
    - Circulating antibodies defend mainly against free bacteria, toxins, and viruses in the body fluids.
- The cell-mediated and humoral immune responses are linked by cell-signaling interactions, especially via helper T cells.

In the cell-mediated response, cytotoxic T cells counter intracellular pathogens: *a closer look*

- Antigen-activated cytotoxic T lymphocytes kill cancers cells and cells infected by viruses and other intracellular pathogens.
- This is mediated through class I MHC molecules.
  - Remember…***<u>all</u>*** nucleated cells continuously produce class I MHC molecules, which capture a small fragment of one of the other proteins synthesized by that cell and carries it to the surface.
- If the cell contains a replicating virus, class I MHC molecules expose these foreign proteins that are synthesized in infected or abnormal cells to cytotoxic T cells.
  - The activated cytotoxic T cell (TC) differentiates into an active killer, which kills its target cell - the antigen-presenting cell - primarily by releasing **perforin**.
    - This protein forms pores into the target cell, which swells and eventually lyses.
  - In the same way, TC cells defend against malignant tumors.

In the humoral response, B cells make antibodies against extracellular pathogens: *a closer look*

- The humoral immune response is initiated when B cells bearing antigen receptors are selected by binding with specific antigens.
  - These B cells proliferate and differentiate into a clone of antibody-secreting plasma cells and a clone of memory B cells.
- Any given humoral response stimulates a variety of different B cells, each giving rise to a clone of thousands of plasma cells.
  - Each plasma cell is estimated to secrete about 2,000 antibody molecules per second over the cell’s 4- to 5-day life span.
- Antigens that elicit a humoral immune response are typically the protein and polysaccharide surface components of microbes, incompatible transplanted tissues, or incompatible transfused cells.
- Antibodies make up a group of globular serum proteins called **immunoglobins (Igs**).
- There five major classes of immunoglobulins:
- IgM – first alert; indicates current infection
- IgG – most abundant; triggers action of complement system
- IgA – prevents viral and bacterial attachment
- IgD – mostly found on surface of B cells
- IgE – cause cells to release histamine/other chemicals that cause an allergic response

Immunity can be achieved naturally or artificially

- Immunity conferred by recovering from an infectious disease such as chicken pox is called **active immunity** because it depends on the response of the infected person’s own immune system.
  - Active immunity can be acquired naturally or artificially, by **immunization**, also known as **vaccination**.
  - Vaccines include inactivated toxins, killed microbes, parts of microbes, and viable but weakened microbes.
  - These no longer cause disease, but they can act as antigens, stimulating an immune response, and more important, ***<u>immunological memory</u>***.
  - A vaccinated person who encounters the actual pathogen will have the same quick secondary response based on memory cells as a person who has had the disease.
- Antibodies can be transferred from one individual to another, providing **passive immunity**.
  - This occurs naturally when IgG antibodies of a pregnant woman cross the placenta to her fetus.
  - In addition, IgA antibodies are passed from mother to nursing infant in breast milk, especially in early secretions called colostrum.
  - Passive immunity persists as long as these antibodies last, a few weeks to a few months.
    - This protects the infant from infections until the baby’s own immune system has matured.

- Passive immunity can be transferred artificially by injecting antibodies from an animal that is already immune to a disease into another animal.
  - This confers short-term, but immediate protection against that disease.
  - For example, a person bitten by a rabid animal may be injected with antibodies against rabies virus because rabies may progress rapidly, and the response to an active immunization could take too long to save the life of the victim.
    - Actually, most people infected with rabies virus are given both passive immunizations (the immediate fight) and active immunizations (longer term defense).

Invertebrates have a rudimentary immune system

- Invertebrate animals also exhibit highly effective mechanisms of host defense.

- The ability to make the distinction between self and non-self is seen in animals as ancient as sponges.

- Invertebrates depend on innate, nonspecific mechanisms of defense rather than acquired, antigen-specific mechanisms.

  - However, some invertebrates possess lymphocyte-like cells that produce antibody-like molecules.

  - For example, insects have a hemolymph protein, called *hemolin*, that binds to microbes and assists in their disposal.

    - Hemolin molecules, members of the immunoglobin superfamily and related to antibodies, do not exhibit diversity, but they are likely evolutionary precursors of vertebrate antibodies.

- By and large, invertebrates do not exhibit the hallmark of acquired immunity - immunological memory.

  - For example, sea star coelomocytes respond to a particular microbe with the same speed no matter how many times they have encountered that invader before (no primary/secondary response).

  - However, earthworms do appear to have a kind of immunological memory.

    - When a portion of body wall from one worm is grafted onto another, the recipient rejects the initial graft in about two weeks, but a second graft from the same donor is rejected in just a few days.