**NONSPECIFIC DEFENSE RESPONSES - 1st & 2nd LINES OF DEFENSE**

[Nonspecific defenses are general attack responses; the response is the same, no matter who the "invader" is.]

**I.                The Body's First Line of Defense:  Structural, Mechanical, & Chemical Defense Responses on Internal & External Body Surfaces:**

**A.   Skin & mucous membranes (epithelial surface tissues)**

1.       Cells are tightly joined together, preventing bacteria from invading deeper tissues.

2.      Sloughing of dead cells prevents microbial population from continually increasing.

3.      The protein, keratin, fills the cells in the outer layers of the epidermis.  These cells then contain little water, making the skin dry & inhospitable to many microbes.

4.      Ciliated, mucous membranes  (ex. in the respiratory tract) trap microbes, dust etc. in mucous & cilia move mucous toward mouth, where it is coughed up and swallowed.

**B.    Normal flora** - Normal bacterial inhabitants of the skin, gut, & vagina - the "natives" outcompete the "foreigners" for resources.  Also, some normal bacteria produce acid from sugar fermentation, creating an acidic environment that keeps other populations in check (ex. lactic acid produced by bacteria in the vagina keep the yeast *Candida albicans* under control).

In the vagina, low estrogen concentrations in prepubertal and postmenopausal women result in a decrease in bacterial numbers in the vagina; this can lead to vaginal yeast infections.  Yeast infections can also result from antibiotic treatments (broad spectrum antibiotics kill the pathogen and the normal flora) & douching.

**C.**Movement of body fluids dislodges microbes. Ex. urine, tears, saliva.  Peristalsis in digestive tract causes food & digestive juices to sweep microbes away.   (Urine itself is not microbiocidal!)

**D.**Secretions:

1.       Tears, perspiration, & saliva contain lysozyme, an enzyme that destroy the bacterial cell wall.  Lysozyme is especially destructive to G(+) bacteria because they lack an outer membrane.

2.      Perspiration also contains high concentrations of salt, creating a hypertonic environment.

3.      Bile, produced by the liver, also disrupts the bacterial cell wall.  Bile is secreted into the small intestine to aid in the digestion of lipids.  It passes from the small intestine into the colon in feces; the bacterium *E. coli* *,*which is part of the normal flora of the colon, is resistant bile.  Remember that bile salts are an important ingredient in some selective media that select for G(-) bacteria and against G(+) bacteria.

4.      Hydrochloric acid produced in the stomach (pH of the stomach is 2!).

5.      Fatty acids are contained in the oil secreted from oil glands in the skin.  It makes the skin slightly acidic.

**II.            The Body’s Second Line of Defense – What Happens Once the Microbes Get Past the Surface Defenses:**

**First a little about the types of white blood cells (called leukocytes):**

**a. macrophages** - phagocytic

**b. eosinophils -**phagocytic

**c.     neutrophils** - phagocytic

**d.    basophils**- release histamine; involved in the inflammatory response.

**e.     lymphocytes -**3 types:  B cells, T cells, Natural Killer cells.

(Be careful not to get the terms leukocyte and lymphocyte confused!)

**A.   Natural Killer Cells** - Type of lymphocyte (type of wbc); most lymphocytes are involved in specific defense responses (ex. B & T lymphocytes).  NK cells are unlike other lymphocytes in that they lack antibodies & antigen receptors (we’ll talk about these under the specific defenses); they are like a specific type of T lymphocyte called a killer T cell in that they release **perforins** [chemicals that cause lysis of the bacterium - they perforate or punch holes in the cell envelope of bacterium].

**B.   Phagocytic White Blood Cells (Phagocytes) -**[Phagocytosis](http://www.cellsalive.com/mac.htm) occurs in 3 phases:

                  (remember CAI)

**1.    Chemotaxis** - the chemical attraction of phagocytes to a particular location; chemotactic chemicals that attract phagocytes include bacterial toxins components of damaged tissue cells, complement proteins, & antibodies.

**2.    Adherence** or Attachment - Because of certain microbial defenses, adherence of the phagocyte cell membrane to the surface of the microbe may be difficult (for example some bacteria produce a slimy outer capsule that makes them slippery).  Opsonization of microbes by complement proteins and antibody facilitates phagocytosis.

**3.    Ingestion** - The phagocyte engulfs the microbe with its cell membrane.  The engulfed microbe moves into the cytoplasm of the phagocyte inside a vesicle (sac); these vesicles fuse with lysosomes containing digestive enzymes; phagocytes include the wbc’s such as neutrophils, eosinophils, & macrophages; phagocytes circulate within blood vessels, & are also located in the lymph nodes, spleen, liver, kidneys, lungs, joints, skin, red bone marrow, & brain.

**Fever -**When phagocytes ingest certain bacteria, the phagocytes secrete a type of interleukin, which circulates to the hypothalamus & causes it to secrete prostaglandins; these chemicals "reset" the hypothalamic thermostat at a higher temperature; temperature-regulating mechanisms (vasoconstriction, increased metabolism, shivering) act to bring the core body temperature to this new setting. [Aspirin, ibuprofen, & acetaminophen inhibit the synthesis of prostaglandins.]  A low grade fever has a beneficial effect on the body:

**1.)**It inhibits the growth of some microbes.

**2.)**It increases the heart rate so that white blood cells, etc. are delivered to infection sites more rapidly.

**3.)**   B cell & T cell proliferation (division) increases.

**4.)**   Heat speeds up chemical reaction rates.

High grade fevers are dangerous - they can denature the body's own enzymes & other proteins.

**What’s low grade?**  What is considered low grade in infants is much lower in adults.  This is due to a baby’s higher surface area to volume ratio.  Basically, a baby has more surface area compared to her volume than an adult does.  So, it’s easier for heat to reach the skin and dissipate into the air.  Heat does not dissipate as easily from an adult’s body (too much volume for it to move through) and so it does more damage to internal organs.

**D.   Interferon (IFN)**- Interferons are proteins that are produced by certain viral-infected cells (particularly macrophages).  Once interferons are released from viral-infected cells, they diffuse to neighboring uninfected cells & bind to their surface protein receptors.  This binding induces the uninfected cells to synthesize antiviral proteins that interfere with or inhibit viral replication.  In other words, interferons serve as a red flag to warn uninfected cells that there's a "stranger among us" & the uninfected cells take action to protect themselves.

Certain interferons also enhance the activity of phagocytes & natural killer cells.

Certain interferons also inhibit cell growth & suppress tumor formation.  Ex.  Alpha-IFN is approved in the U.S. for treating Kaposi's sarcoma, a cancer that often occurs in patients infected with HIV; it is also used for treating genital herpes & hepatitis B & C.

**E.**[**Complement System**](http://www.clevelandclinic.org/health/health-info/docs/1000/1021.HTM)- When certain microorganisms invade the body, about 20 complement proteins in blood plasma & on cell membranes interact as a system.  When activated, these proteins "complement" or enhance certain immune, allergic, & inflammatory reactions; therefore, the complement system enhances the effectiveness of both nonspecific & specific defense responses.  Complement proteins respond to the binding of antibodies to the cell membrane of the invading microbe; the complement proteins are activated one after another in a "cascade" of reactions [one reaction catalyzes the next.]  These reactions have the following results:  (use the acronym COLA to remember them!)

**1.**Chemotaxis - They act as chemotactic chemicals to attract phagocytes to the scene.

**2.**Opsonization - Complement proteins bind to the surface of the microbe & then interact with receptors on phagocytes to promote phagocytosis.  In this way complement proteins give macrophages a "foot hold."

**3.**Lysis - Other complement proteins kill the microbe by causing lysis.

**4.**Activation of Inflammatory response (See below).

**F.    Inflammatory Response**- Many cells, the complement system, & other substances take part in this response.  This response is a series of events that destroys invaders & restores damaged tissues to normal.  The 4 major symptoms of inflammation are redness, heat, swelling, & pain (think about what happens when a bee stings you or a cut gets infected).  Inflammation is a nonspecific defense - the response of a tissue to a cut is similar to the response that results from a burn, radiation, or microbial invasion.  The inflammatory response involves the following events:

             **1.** **Vasodilation & Increased Permeability of Blood Vessels -**

¨       Vasodilation is an increase in diameter of the arterioles.  Arteriole dilation enables white blood cells & other substances to more easily penetrate the tissues.  Increased permeability means that an increased amount of material is allowed to pass out of the blood vessels.

¨       Blood vessels dilate & become more "leaky" due to the release of histamine by basophils, which are activated by the complement system.  Prostaglandins, released by damaged cells, intensify the effects of histamine.

¨       Within minutes after injury, dilation & increased permeability of blood vessels produces heat, redness, & swelling.

¨       Warmth & redness occurs from the large amount of warm blood flowing through the area.  Temperatures will continue to rise due to the release of heat energy from chemical reactions (increased metabolic activity).

¨       Fluid seeping from "leaky" capillaries causes swelling.

¨       Pain can result from injury of nerve fibers, from irritation by toxins produced by microbes, from increased pressure due to swelling, or from prostaglandin release.

**2.  Phagocytosis**

¨       Fluid seeping from "leaky" arterioles causes local swelling & delivers more complement proteins to the tissues (remember, proteins are large molecules - they would normally stay in the blood vessels & couldn't get into the interstitial spaces between cells).

¨       Phagocytes, following increased concentrations of complement proteins to affected tissues, engulf foreign invaders & damaged cells.

¨       Eventually phagocytes die.  Within a few days a pocket of dead phagocytes & damaged tissue forms (called pus).

**3.** **Tissue Repair**

¨       Platelets initiate clotting mechanisms, help wall off the pathogen, & help repair tissues.

**III. THIRD LINE OF DEFENSE - SPECIFIC DEFENSE RESPONSES:**

**THE IMMUNE SYSTEM**

When general attack responses are not enough to stop the spread of an invader & illness follows, three types of white blood cells (macrophages, T cells, & B cells) will counterattack.  Their interactions are the basis of the immune system.  Two important characteristics of the immune system are its specificity & its memory.

**Summary Table:  White Blood Cells Involved in Specific Defense Responses:**

**1.    Macrophages**- phagocytic; involved in inflammatory, antibody-mediated, & cell-mediated responses (nonspecific responses); important not only for phagocytosis, but also for **antigen presentation.**

**2.    Lymphocytes  (these are not all of the lymphocytes, but some of the important ones)**

**a.     B cells** - produce [**antibodies (Ab)**](http://www.path.cam.ac.uk/~mrc7/igs/mikeimages.html) [Y-shaped protein molecules which bind to specific targets (antigens) & tag them for destruction by phagocytes or the complement system].

**b.    Cytotoxic T cells**- involved in the cell-mediated response; directly destroy body cells already infected by certain viruses or parasitic fungi.

**c.     Helper T cells** - involved in the antibody-mediated & cell-mediated responses; they stimulate the rapid division of B cells & cytotoxic T cells by producing compounds called interleukins.

**d.    Memory cells** - certain B cell & T cells, which are produced during a first encounter with a specific invader (primary immune response), but are not directly involved in this first attack; they circulate freely & respond rapidly to any subsequent attacks (secondary immune response) by the same type of invader.

**Recognition of Self & Nonself**

Among the surface proteins on your own body cells are **MHC markers** ("self" markers), which are normally ignored by your own white blood cells; MHC markers are unique to each individual (no one has the same kinds, except in the case of identical twins); microbes, etc. also have markers [called **antigens** (Ag) because they are foreign to your cells] on their surfaces which are not ignored by white blood cells; **antigens** are usually surface proteins with distinct configurations that trigger immune responses.

**I.  PRIMARY IMMUNE RESPONSE:**

A first-time encounter with an antigen elicits a primary immune response from the lymphocytes & their products.  We will consider an antibody-mediated immune response & a cell-mediated immune response to such an encounter:

**A.   Antibody-Mediated (Humoral) Immune Response**- The main targets of this type of response are extracellular organisms: bacteria, extracellular phases of viruses, some fungal parasites, & some protozoans.  Antibodies can't bind to antigen if the invader has already entered the cytoplasm of a host cell!!  The following events involve a bacterial infection:

**1.**[**Macrophages**](http://wsrv.clas.virginia.edu/~rjh9u/macro.html)- When bacteria enter the body, their invasion triggers a general inflammatory response, & macrophages engulf some of the bacterial cells by phagocytosis.  The engulfed bacteria move into the cytoplasm of the macrophages inside vesicles.  These vesicles fuse with lysosomes (vesicles containing digestive enzymes) & enzymes digest the bacterial cells, but do not destroy their surface antigens.  At the same, the cell synthesizes MHC markers & is packaging them into vesicles in its golgi apparatus.  The vesicles containing the antigen & the vesicles containing the MHC markers fuse.  Inside the vesicle, the antigen binds to the MHC markers (now called antigen-MHC marker complexes).  The vesicle containing the complexes undergoes exocytosis & the complexes are inserted in the cell membrane of the macrophage.  Macrophages can now present the antigen to other white blood cells (ex. helper T cells).

**2.    Helper T cells**- When the appropriate helper T cells make contact with the macrophages, some of their membrane-bound **antigen-receptors** bind to the macrophage antigen-MHC complexes (these receptors are specific for these particular complexes - they won't bind to any other type!).  This binding causes macrophages to secrete a compound called **interleukin** that stimulates the helper T cells to secrete their own interleukins.  The helper T cell interleukins will cause activated B cells to start dividing  (see below).

**3.  B cells**

**a.**B cells "mature" in bone marrow.  While each B cell is maturing, it makes many copies of just one kind of antibody (each B cell is unique in that it will only make one kind of antibody that no other B cell makes - each kind of antibody will only react to one antigen).  While the B cell is maturing, some of the antibodies it is producing become positioned at the cell's surface, where they will later bind to a specific antigen.  The "tail" of each antibody is embedded in the cell membrane, & the "arms" stick out above the cell membrane's surface.  From the bone marrow, B cells migrate to the lymph nodes, the spleen, or lymphatic tissue in the g.i. tract.

**b.**When a B cell is released from the bone marrow into circulation, it is known as a **"virgin" B cell** because its antibodies have not yet made contact with antigen.

**c.**A virgin B cell with the right antibodies binds to a specific antigen.  Some of the antigen is then taken into the B cell, combined with MHC markers, & moved to the B cell surface (see how macrophages do this above).  The B cell is now said to be **activated**; it's no longer virgin - it's come into contact with a specific antigen.

**d.**If an activated B cell interacts with the appropriate interleukin-producing helper T cell (see above under helper T cell), the B cell will start dividing quickly, giving rise to a **clonal population** of identical B cells.

**e.**Part of the B cell clonal population differentiates into **plasma cells**, which secrete thousands of copies of the particular antibody that had been produced by the virgin B cell (the antibody actually leaves the plasma cells!).  Antibodies have different effects on antigen:

1.)     **Neutralizing** - the binding of Ab with AG blocks or neutralizes the damaging effect of some bacterial toxins and prevents attachment of some viruses to body cells.

2.)    **Immobilization** - If Ab forms against cilia or flagella of motile bacteria, the Ab-Ag complex may cause the bacteria to lose their motility, limiting their spread into nearby tissues.

3.)    **Agglutination** - Because antibodies have tow or more sites for binding to Ag, the Ab-Ag reaction may cross-link pathogens to one another, causing agglutination (clumping together); this enhances phagocytosis.

4.)    **Activation of complement system**- complement proteins cause lysis of microbe; complement also cause opsinization, which enhances phagocytosis.

5.)    **Opsinization** - Antibodies enhance phagocytosis by coating the microbe (remember that complement protein can also be opsonins).

**f.**Some of the B cell clones differentiate into **memory B cells**, which are involved in a secondary response (will be discussed later).

**How do B cells produce the millions of different antibodies required to detect all of the millions of possible antigens?**  Part of each arm of an antibody is a polypeptide chain made up of amino acids, folded into a groove or cavity, which "fits" with the antigen (there are poor fits & better fits - the better the fit the better the immune response).  All B cells have the same genes for coding the amino acids in the chain, but each maturing B cell shuffles the genetic code into one of millions of possible combinations, so that the sequence of amino acids then gets shuffled (this changes the shape of the protein, thus changing the shape of the antibody).  So B cells can give rise to virtually unlimited chain configurations.  Therefore, when an antibody comes into contact with an antigen for the very first time, the right antibody just happened to be there!  Your immune system did not produce the virgin B cell antibodies in response to a particular antigen!  It is our genes that determine what specific foreign substances our immune system will be able to recognize & resist!  (The same rule applies to T cell Ag receptors.)

**The 5 Classes of Antibodies (Ab):**

(Ab's are part of the immunoglobulin (Ig) family of proteins)

**1.)  IgG** - largest class, activates the complement system; effective opsonin (enhances phagocytosis); only Ab that can cross the placenta (protects the newborn for several months after birth); predominates in secondary immune responses; all antitoxins belong to this class (remember antitoxins are antibodies made against exotoxins made by G(+) & G(-) bacteria); found in blood & extracellular fluids.

**2.)  IgA** - second largest class; found in blood and body secretions (saliva, milk, mucus, tears); protects mucosal surfaces, especially preventing attachment of viruses; its presence in colostrum defends the g.i. tract of newborn humans against infection.

**3.)  IgM** - extremely effecting in fixing complement; sometimes called **early Ab**, because it is the first Ab to form during a primary immune response; its structure allows it to build complex Ag-Ab lattices that clump, forming a visible precipitate; it’s found in blood & extracellular fluids.

**4.)  IgD** - main type of Ab displayed on the surface of B cells.

**5.)  IgE**- fixed to the surface of basophils; stimulates the microbe to release histamine when the basophil binds to Ag; basophils then releases histamine; this can contribute to **allergies**

**B.    Cell-Mediated Immune Response (Cellular Immunity)**- This type of response deals with viruses & other pathogens that have already penetrated host cells (they are intracellular!), where they remain hidden from antibodies.  In the cell-mediated immune response, the host cells are killed by cytotoxic T cells (killer T cells) before the pathogens can replicate & spread to other cells.  The following events involve a viral infection:

**1.    Cytotoxic T cells** or **Killer T cells**- Cells in the bone marrow give rise to forerunners of killer T cells, which travel to the thymus gland, where they mature into killer T cells.  Each T cell produces antigen receptors that become positioned at its surface (these receptors are not antibodies, but are similar!!!).  Ag receptors recognize specific Ag-MHC marker complexes.  When an Ag enters the body, only a few T cells have receptors that can recognize & bind to the Ag.

**2.**Killer T cells are released into circulation by the thymus gland.  When a virus infects a cell, viral proteins become associated with MHC markers on the host cell's surface.

**3.**The antigen receptors of killer T cells, bind to the antigen-MHC complexes of macrophages, infected cells, etc.

**4.**Cytotoxic T cells secrete **perforins** (proteins that punch holes in the infected cell's cell membrane).

**5.**This kills the infected cell, but prevents the virus from replicating & spreading to other cells.

**Note:**As in antibody-mediated immune responses, macrophage-stimulated helper T cells stimulate killer T cells to divide by secreting interleukins.  This creates a clonal population of killer T cells, all with the same antigen receptor as the original killer T cell (these cells are not called plasma cells!!!!!).  As with B cells, some of the clones become memory T cells & will be involved in a secondary immune response.  (When the body rejects a tissue graft or an organ transplant, cytotoxic T cells are one of the reasons why.  They recognize MHC markers on the grafted cells as being foreign.  Organ recipients take drugs to destroy cytotoxic T cells, but this compromises their ability to mount immune responses against pathogens.)

**II.  TYPES OF IMMUNITY**

**1.      Active** - a product of a person's own immune system.

**a.       naturally acquired** - comes from infections encountered in daily life.

**b.      artificially acquired** - stimulated by vaccines.

**2.      Passive** - Ab's produced elsewhere are given to a person.

**a.     naturally acquired** - refers to Ab's transferred from mother to fetus across the placenta & to the newborn in colostrum & breast milk.

**b.    artificially acquired** - consists of Ab's formed by an animal or a human & administered to an individual to prevent or treat infection; ex. hepatitis A, diphtheria.

**III.  SECONDARY IMMUNE RESPONSES:**

A secondary immune response to a previously encountered antigen can occur in 2 or 3 days.  It is greater in magnitude than the primary response & of longer duration.  This is because some of the B & T cells of the clonal populations do not get involved in the primary response attack.  They circulate for years as **memory cells**.  When a memory cell encounters the same type of antigen that initiated the primary response, it divides at once (no helper T cells are needed to stimulate cell division!).  A large clonal population of active B or T cells can then be produced in just a matter of days.

**IV.           IMMUNIZATIONS:**

**Defined:**Immunization means deliberately introducing an antigen into the body that can provoke an immune response & the production of memory cells.  The first injection elicits a primary immune response.  A second injection (the "booster shot") elicits a secondary response, which provokes the production of even more antibodies and memory cells to provide long-lasting protection against the disease.   We will discuss the types of vaccines in chapter 15.