

IMMUNE SYSTEM

The **body's defense** against:

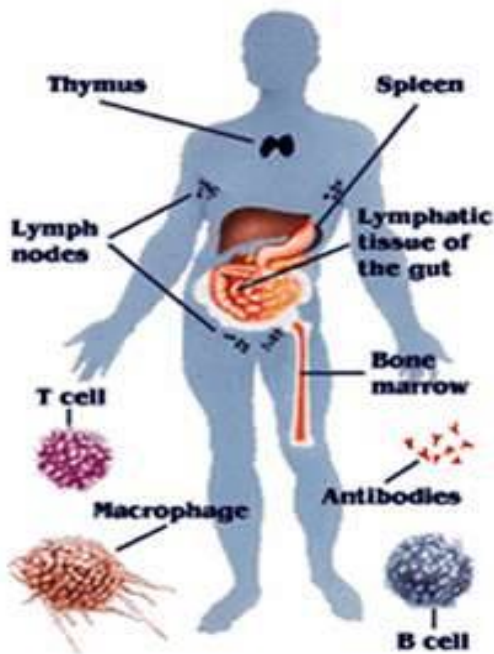
- disease causing organisms or infectious agents
- malfunctioning cells or abnormal body cells as cancer
- foreign cells or particles

Basic Immunity

- Depends on the ability of the immune system to distinguish between **self** and **non-self** molecules
- **Self** molecules are those components of an organism's body that can be distinguished from foreign substances by the immune system
 - **Autoimmunity** is an immune reaction against self molecules (causes various diseases)
- **Non-self** molecules are those recognized as foreign molecules
 - One class of non-self molecules are called **antigens** (short for *antibody generators*) and are defined as substances that bind to specific immune receptors and elicit an immune response

Immune System Components:

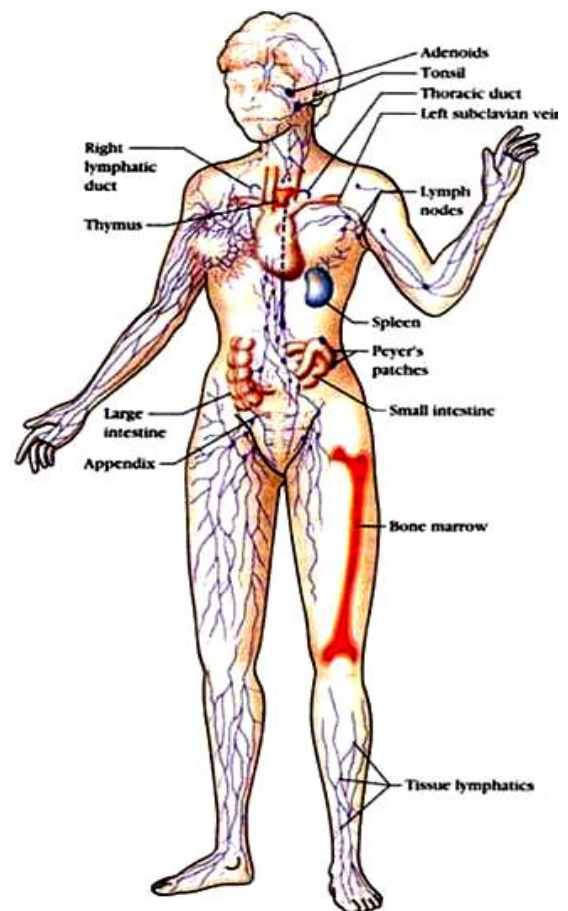
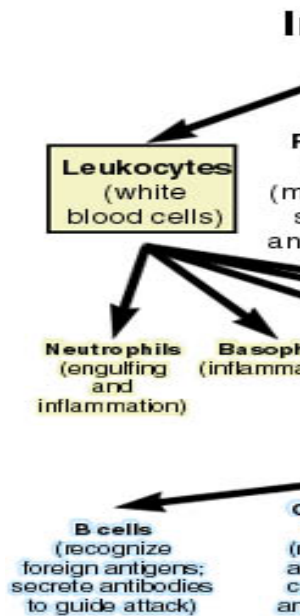
- **specific cells** - lymphocytes, macrophages, etc., originate from precursor cells in the bone marrow and patrol tissues by circulating in either the blood or lymphatics, migrating into connective tissue or collecting in immune organs
- **lymphatic organs**- thymus, spleen, tonsils, lymph nodes
- **diffuse lymphatic tissue** -collections of lymphocytes and other immune cells dispersed in the lining of the digestive and respiratory tracts and in the skin



Organs of the Lymphatic System Aid Immunity

Lymph Nodes

- Small (1- 25 mm) round structures found at points along lymphatic vessels that have fibrous connective tissue capsule with incoming and outgoing lymphatic vessels
- Each nodule contains sinus filled with lymphocytes and macrophages
- They occur in regions: auxiliary nodes in armpits and inguinal nodes in groin
- Occur singly or in groups of nodules:
 - **Tonsils** are located in back of mouth on either side
 - **Adenoids** on posterior wall above border of soft palate
 - **Peyer's patches** found within intestinal wall



Spleen

- Located in upper left abdominal cavity just beneath diaphragm.
- Structure similar to lymph node; outer connective tissue divides organ into lobules with sinuses filled with blood
- Blood vessels of spleen can expand so spleen functions as blood reservoir making blood available in times of low pressure or oxygen need
- **Red pulp** containing RBCs, lymphocytes, and macrophages; functions to remove bacteria and worn-out red blood cells
- **White pulp** contains mostly lymphocytes
- Both help to purify the blood

Thymus

- Located along trachea behind sternum in upper thorax
- Larger in children; disappears in old age
- Divided into lobules where T lymphocytes mature
- Interior (medulla) of lobule secretes *thymosin* thought to aid T cells to mature

Red Bone Marrow

- Site of origin of all types of blood cells
- Five types of white blood cells (WBCs) function in immunity
- Stem cells continuously divide to produce cells that differentiate into various blood cells
- Most bones of children have red blood marrow
- In adult, red marrow is found in the skull, sternum, ribs, clavicle, spinal column, femur, and humerus
- Red blood marrow has network of connective tissue where reticular cells produce reticular fibers; these plus stem cells fill sinuses; differentiated blood cells enter bloodstream at these sinuses

Immune tissue associated with various organs:

GALT—*gut-associated* lymphatic tissue; comprised of lymphoid tissue (lymph nodules) in the intestinal wall containing lymphocytes, plasma cells and macrophages.

- The digestive tract is a very important part of the immune system and the intestine possesses the largest mass of lymphoid tissue in the body.

Lymphoid tissue in the gut comprises the following:

- **Tonsils** (Waldeyer's ring)
- **Adenoids** (Pharyngeal tonsils)
- **Peyer's patches** – lymphoid follicles in wall of small intestine
- Lymphoid aggregates in the appendix and large intestine
- Lymphoid tissue accumulating with age in the stomach
- Small lymphoid aggregates in the esophagus
- Diffusely distributed lymphoid cells and plasma cells in lining of the gut

MALT—*mucosa-associated* lymphatic tissue; lymphoid tissue associated with the mucosa of the female reproductive tract, respiratory tract, etc.

SALT—*skin-associated* lymphatic tissue; lymphatic tissue associated with the dermis of the skin.

Plan of Protection – Immunity is the ability to defend against infectious agents, foreign cells and abnormal cells eg. cancerous cells

- **1st Line of defense** – Block entry
- **2nd Line of Defense** – Fight Local Infections
- **3rd Line of Defense** – Combat Major Infections

Nonspecific and Specific Defense Systems - work together to coordinate their responses

Nonspecific (Innate) Response - responds quickly, fights all invaders and consists of:

- **First line of defense** – intact skin and mucosae and secretions of skin and mucous membranes prevent entry of microorganisms
- **Second line of defense** – phagocytic white blood cells, antimicrobial proteins, and other cells
- Inflammatory response process is key
- Inhibit invaders from spreading throughout the body

Specific Response (Adaptive) Response - takes longer to react, works on specific types of invaders which it identifies and targets for destruction

- **Third line of defense** – mounts attack against particular foreign substances
- Lymphocytes and Antibodies
- Works in conjunction with the nonspecific or innate system

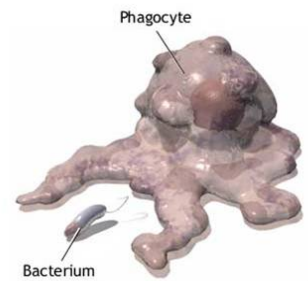
Nonspecific (Innate) Response – fight all invaders

First line of defense – Non specific barriers to block entry

- Skin provides an impervious barrier – physical or mechanical barrier
- Mucous membranes line the entrances of the body and produce mucus which traps foreign particles and directs them out of the body – physical or mechanical barrier
- Nasal hairs trap dirt and dust while microscopic cilia line some mucous membranes helping to trap foreign particles
- Gastric juice, vaginal secretions and urine are acidic fluids which provide protection
- Natural flora (harmless bacteria) in the intestine and vagina prevent pathogens from growing
- Tears, saliva and sweat possess some anti-bacterial properties
- Cerumen or ear wax protects the ear canal by trapping dirt and dust particles

Second line of defense – Fight local infection with Inflammation Process

- Begins as soon as the first line of defense is violated
- The response is a non-specific, immediate, maximal response to the presence of any foreign organism or substance and involves no immunological memory
- **Phagocytosis** is an important feature of cellular innate immunity performed by cells called 'phagocytes' that engulf, or eat, pathogens or particles
- **Phagocytes** – types of immune cells involved in phagocytosis - Produced throughout life by the bone marrow
- **Scavengers** – remove dead cells and microorganisms
- **Complement proteins** activate other proteins in a domino fashion resulting in a cascade of reactions which attract phagocytes to the site of the invasion, bind to the surface of microbes to insure WBC's can phagocytize the microbe and produce holes in the bacterial cell walls and membranes
- The **Inflammation Process** releases *histamines* causing redness, pain, swelling, and heat



Phagocytes and Their Relatives

The diagram illustrates seven types of phagocytes and their relatives, each with a distinct color and shape:

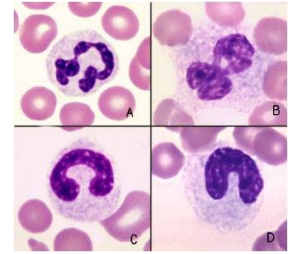
- Monocyte**: A green circle containing a white, kidney-shaped nucleus.
- Eosinophil**: A green circle containing a bilobed nucleus and several red granules.
- Mast cell**: A green, irregularly shaped cell containing a kidney-shaped nucleus and several red granules.
- Macrophage**: A green, irregularly shaped cell with a kidney-shaped nucleus and several red granules.
- Dendritic cell**: A blue, star-shaped cell with a central nucleus and several long, thin processes extending outwards.
- Neutrophil**: A green circle containing a multi-lobed nucleus and several red granules.
- Basophil**: A green circle containing a multi-lobed nucleus and several red granules.

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Phagocytes and their Relatives

Neutrophils - kill bacteria

- 60% of WBCs
- 'Patrol tissues' as they squeeze out of the capillaries
- Large numbers are released during infections
- Short lived – die after digesting bacteria
- Dead neutrophils make up a large proportion of puss



Monocytes – are chief phagocytes found in the blood

- Made in bone marrow as **monocytes** and circulate in the blood for 1-2 days before being called **macrophages** once they reach organs.

Macrophages - Found in the organs, not the blood

- Larger than neutrophils and long lived - involved in phagocytosis, release interferon and interleukin (which stimulates production of cells of the Specific Defense System)
- Macrophages also act as scavengers, ridding the body of worn-out cells and other debris by ingesting cellular debris, foreign material, bacteria and fungi
- Versatile cells that reside within tissues and produce a wide array of chemicals including enzymes, complement proteins, and regulatory factors such as interleukin 1
- **Antigen-presenting cells** that activate the adaptive immune system they display antigens from the pathogens to the lymphocytes.



Basophils – are capable of ingesting foreign particles and produce heparin and histamine and which induce inflammation, are often associated with asthma and allergies

Mast cells reside in connective tissues and mucous membranes, and regulate the inflammatory response.

They are most often associated with allergy and anaphylaxis: for example, they release histamine – this is why anti-histamines help allergic reactions

Dendritic cells are phagocytes in tissues that are in contact with the external environment

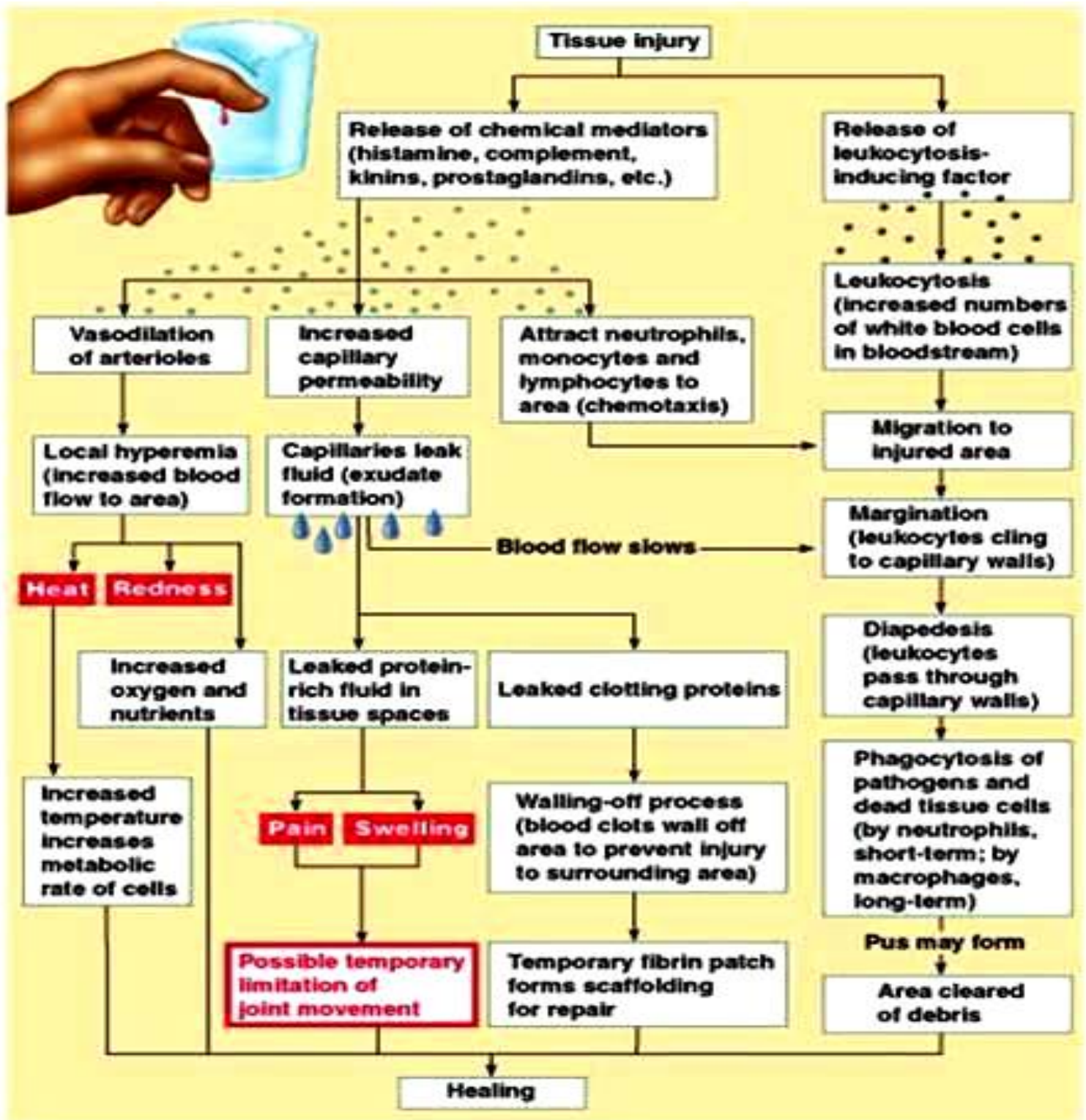
- Located mainly in the skin, nose, lungs, stomach, and intestines (are in no way connected to the nervous system)
- Dendritic cells serve as a link between the innate and adaptive immune systems, as they present antigens to T cells, one of the key cell types of the adaptive immune system

Eosinophils – weakly phagocytic of pathogens kill parasitic worms

NK cells (natural killer) - used to combat tumor cells or virus-infected cells

- A class of lymphocytes which attack and induce cells to kill themselves (self-induced apoptosis)
They complement both specific and nonspecific defenses
- May also attack some tumor cells
- Also secrete interferons, proteins produced by virus infected cells which binds to receptors of non-infected cells, causing these cells to produce a substance that will interfere with viral reproduction and activate macrophages and other immune cells

FLOW CHART OF INFLAMMATION PROCESS

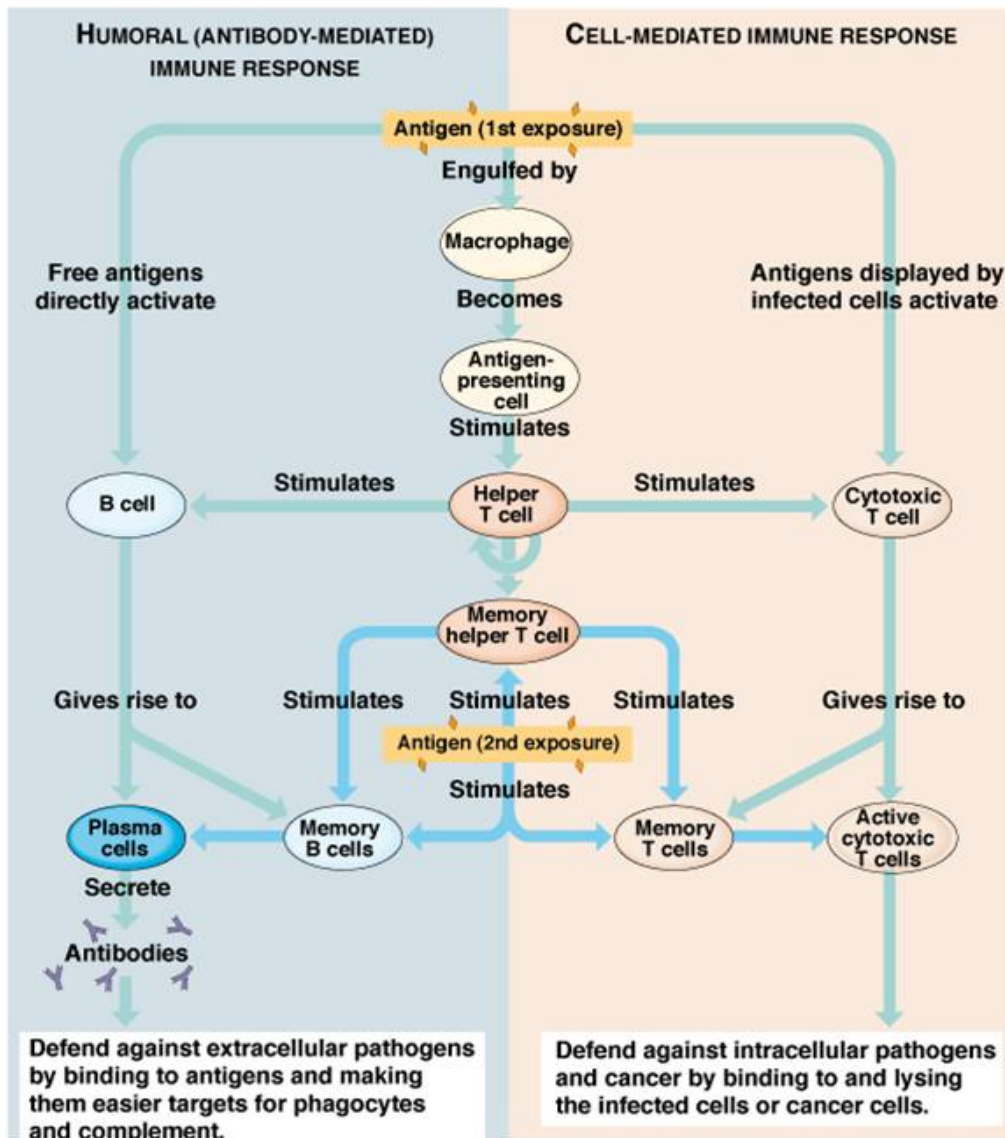


Most infections never make it past the first and second level of defense.

Specific (Adaptive) Response – work on specific types of invaders which it identifies and targets for destruction - takes longer to react

- The response is directed at specific targets and is not restricted to initial site of invasion/infection
- Lag time occurs between exposure and maximal response
- The adaptive immune system allows for a stronger immune response as well as immunological memory, where each pathogen is "remembered" by its signature antigen
- **Antigens** are proteins or carbohydrate chain of a glycoprotein within a plasma membrane which the body recognizes as “nonself”
- The specific immune response is antigen-specific and requires the recognition of specific “non-self” antigens during a process called **antigen presentation**
- Antigen specificity allows for the generation of responses that are tailored to specific pathogens or pathogen-infected cells
- The ability to mount these tailored responses is maintained in the body by "**memory cells**"
- Should a pathogen infect the body more than once, these specific memory cells are used to **quickly** eliminate

Third line of defense – mounts attack against particular foreign substances antigens throughout the body

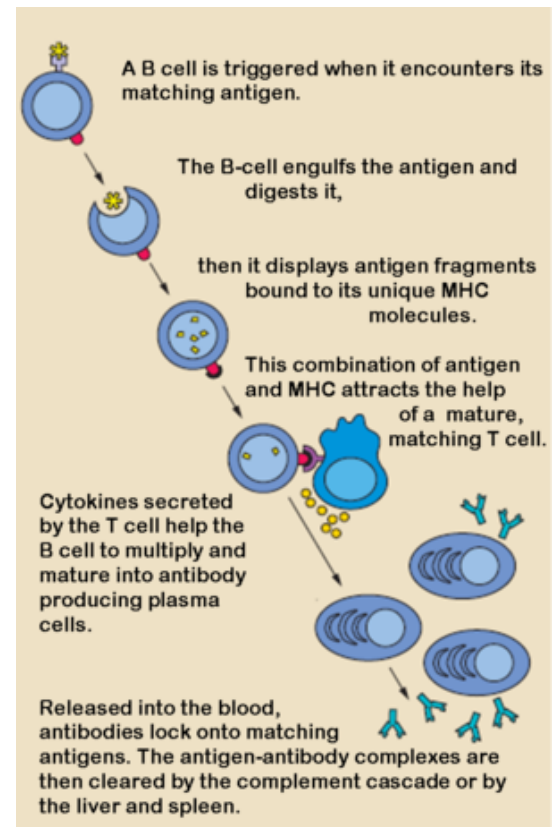


Components of the Specific Defense System

- Identify, destroy, remember
- **Cellular components** – B cells and T cells - lymphocytes which are white blood cells
- **Humoral (antibody-mediated response)** defends against extracellular pathogens by binding to antigens and making them easier targets for phagocytes and complement proteins
- **Cell mediated immune response** – defends against intracellular pathogens and cancer by binding to and lysing the infected cells or cancer cells

Humoral or antibody-mediated response – termed anti-body mediated because B cells produce antibodies and Humoral because antibodies are released into the bloodstream

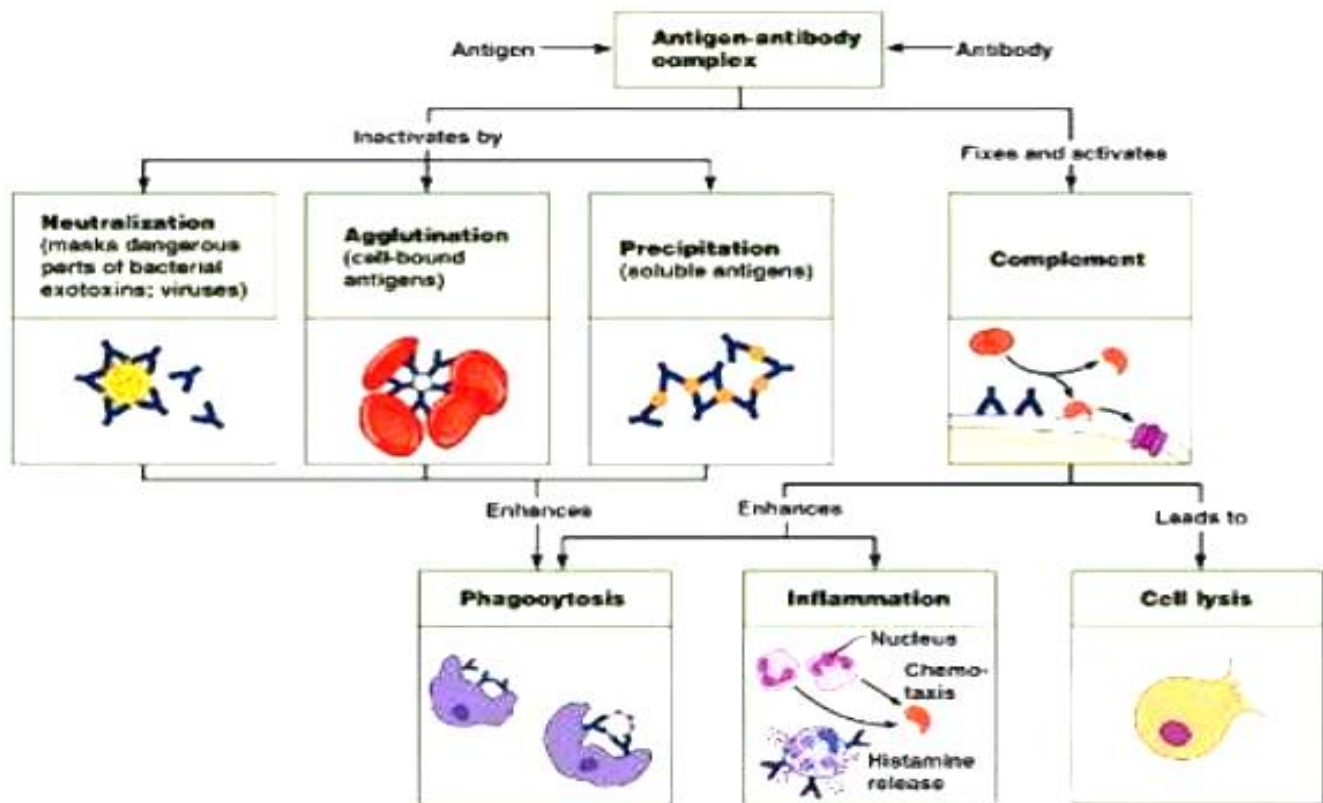
- **B cells** - are produced and mature in the bone marrow – they possess a protein on the B cells outer surface known as the B cell receptor (BCR) which allows them to bind to a specific antigen
- **Plasma B cells** also known as plasma cells, plasmocytes, and effector B cells– they produce antibodies
- **Memory B cells** – ready for the next invasion
- B cell comes into contact with antigen on microbe
- it attaches to the antigen and becomes an antigen-presenting B cell with antigen-MHC complex
- Helper T cell that binds to the complex
- Helper T secretes interleukin that stimulates mitosis in B cells so they multiply
- Some B cells mature into **plasma cells** and other become **memory cells**
- The **plasma cells** produce **antibodies** also called **immunoglobins** – proteins which attach to the antigens
- Antibodies can clump microbes for destruction, mark microbes for destruction by phagocytes, activate complement proteins that rupture/lyse microbe cell membranes or infected host cells



Antibody Targets and Functions

- **Complement fixation:** Foreign cells are tagged for destruction by phagocytes and complement fixation. Immune complex formation exposes a complement binding site on the C region of the Ig and Complement fixation results in cell lysis.
- **Neutralization:** immune complex formation blocks specific sites on virus or toxin & prohibit binding to tissues (antibodies block active sites on viruses and bacterial toxins so they can no longer bind to receptor sites on tissue cells and cause injury)
- **Agglutination:** cells are cross-linked by immune complexes & clump together
- **Precipitation:** soluble molecules (such as toxins) are cross-linked, become insoluble, & precipitate out of the solution
- **Inflammation & phagocytosis** prompted by debris

Antigen-Antibody Complex – Functions



Human Antibody Classes (Isotopes) & Their Functions

IgA	Antibodies are dimers – contain two Y shaped structures. Found in mucosal areas, such as the gut, respiratory tract and urogenital tract. Also found in saliva, tears, and breast milk. They attack microbes and prevents colonization by pathogens before they reach the blood stream so it is most important antibody in local immunity
IgD	Functions mainly as an antigen receptor on B cells that have not been exposed to antigens. It has been shown to activate basophils and mast cells to produce antimicrobial factors.
IgG	In its four forms, provides the majority of antibody-based immunity against invading pathogens. It makes up about 75 % of all human antibodies and is the body's major defense against bacteria. The only antibody capable of crossing the placenta to give passive immunity to fetus. It is the most versatile of antibodies because it carries out functions of the other antibodies as well.
IgE	Binds to allergens and triggers histamine release from mast cells and basophils, and is involved in allergy. Also protects against parasitic worms.
IgM	Expressed on the surface of B cells and in a secreted form with very high avidity. Eliminates pathogens in the early stages of B cell mediated (humoral) immunity before there is sufficient IgG.

- **Memory B cells** are stimulated to multiply but do not differentiate into plasma cells; they provide the immune system with long-lasting memory.

Cell-mediated immune response (within the cell) - does not involve antibodies but rather involves the activation of phagocytes, antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen

- **T cells** – are produced in bone marrow but mature in the thymus gland T cells contribute to immune defenses in two major ways: some direct and regulate immune responses; others directly attack infected or cancerous cells.

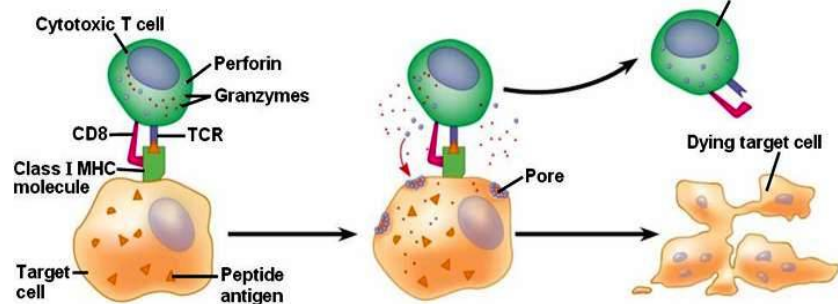
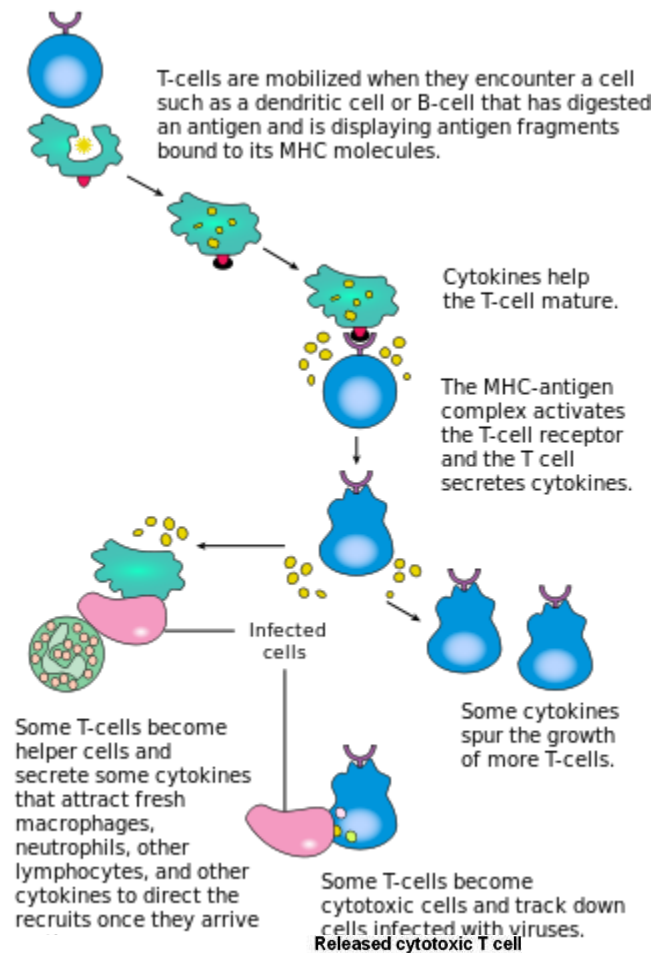
Helper T cells – assist other white blood cells in the immunologic process including maturation of B cells into plasma cells and memory B cells and activation of T cells and macophages

Cytotoxic T cells – sometimes called killer T cells destroy virally infected cells and tumor cells and play a role in transplant rejection

Memory T cells –antigen-specific T cells the persist long-term after an infection has been resolved that will provide memory of past infection and earlier defense for new infection

Regulatory T cells – formally called **suppressor T cells** maintain balance by shutting down T-cell mediated immunity toward the end of an immune reaction – they are a self check built into the immune system to prevent excessive reactions. They play a key role in prevent autoimmunity

- **Antigens** are proteins or carbohydrate chain of a glycolprotein within in plasma membrane that the body recognizes as *nonself*
- The antigens on the cell membrane of the target or invader cell are recognized
- MHC (a protein marker on body’s cell) binds to the antigen of the foreign cell forming an MHC complex
- The MHC complex alerts the T cells about an invasion, macrophage, virgin B cell or cell infected by a microbe that displays the antigen on its membrane
- The MHC complex activates the T cell receptor and the T cell secretes cytokines
- The cytokines spur the production of more T cells
- Some T cells mature into **Cytotoxic T cells** which attack and destroy cells infested with viruses or cancerous cells
- **Cytotoxic T cells** or **Killer T cells (NKT)** share the properties of both T cells and natural killer (NK) cells. They are T cells with some of the cell-surface molecules of NK cells. The kills cancer cells, cells that are infected (particularly with viruses), or cells that are damaged in other ways -They have storage granules containing porfirin and granzymes (proteins which perforates the cell membrane of the cell to be destroyed allowing water & salts to enter and rupture the cell). They and are implicated in disease progression of asthma and in protecting against some autoimmune diseases, graft rejection, and malignant tumors

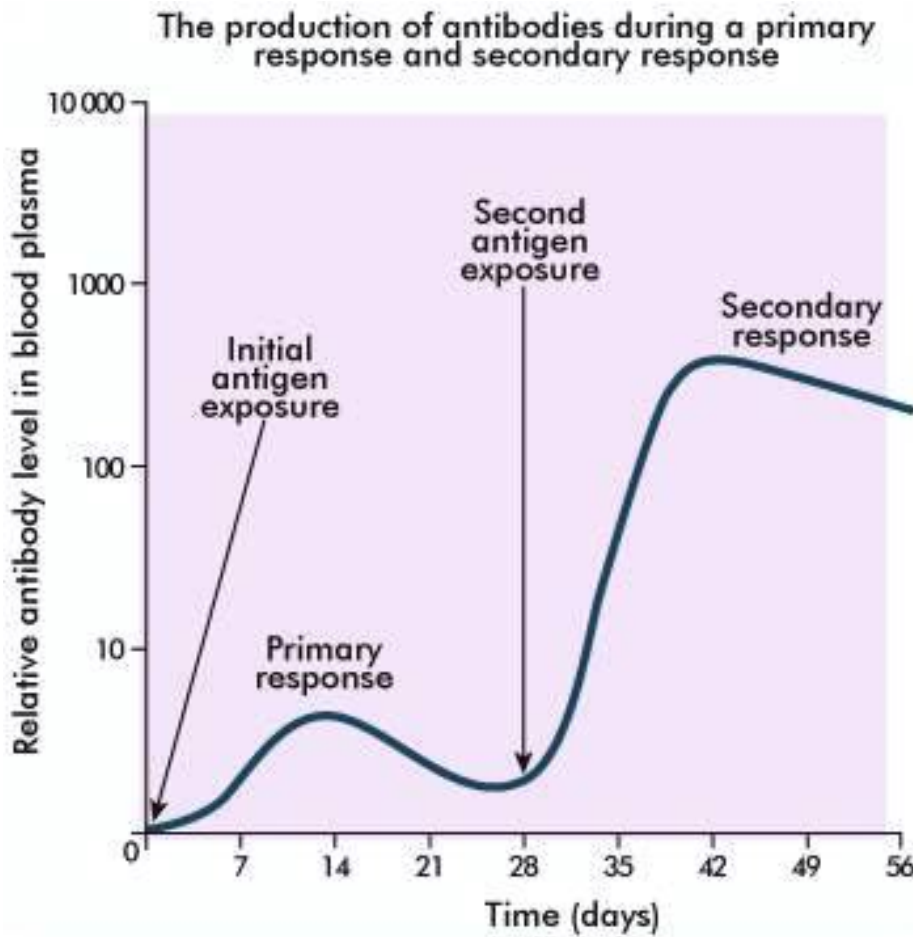


- Other T cells mature into **Helper T cells** which regulate immunity by increasing the response of other immune cells
- **Helper T cells** secrete **cytokines** (messenger molecules) when exposed to antigens that causes more Helper T cells to be cloned, B cells to make antibodies and macrophages to destroy cells by phagocytosis
- AID's virus attacks to Helper T cells so it inactivates the immune system
- **Regulatory T cells** will shut down T-cell mediated immunity when things are under control
- **Memory T** cells persist sometimes for life and protect in case of re-infection

Primary and Secondary Immunity

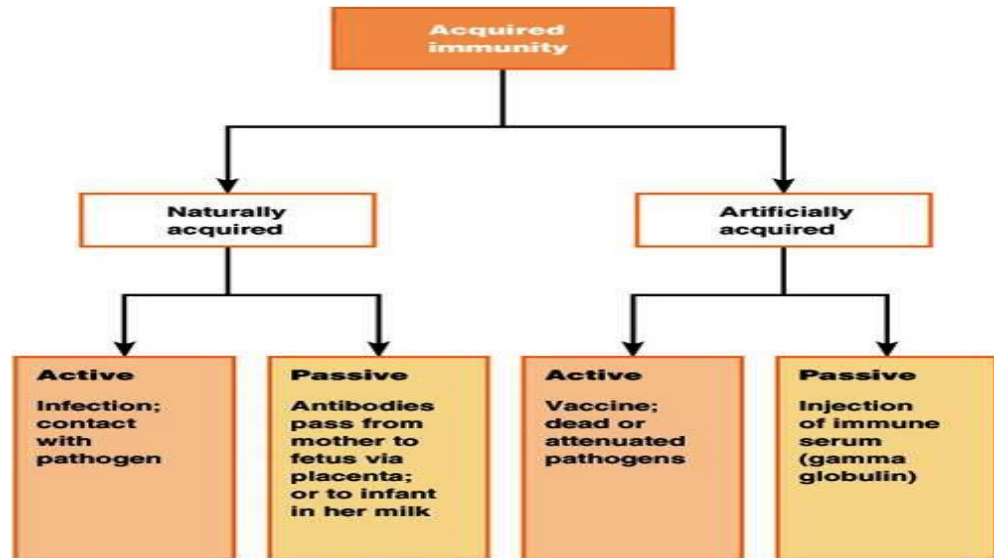
Primary Immunity – When first exposed to an antigen, the body usually takes several days to respond and build up a large supply of antibodies. The number of antibodies will peak and then begin to decline.

Secondary Immunity – The production of Memory B or T Cells allows the cell to recognize the antigen much quicker if it is introduced again so the body will often be able to destroy the invading antigen before its numbers become great enough to initiate symptoms. Memory B cells rapidly divide and develop into plasma cells and the antibody levels in the body rise quickly and reach greater numbers. Active immunity lasts as long as clones of memory B and memory T cells are present.



Sources of Specific Immunity – resistance to a disease causing organism or harmful substance

- **Inborn Immunity** – Immunity for certain diseases is inherited
- **Acquired Immunity** – immunity can be acquired through infection or artificially by medical intervention



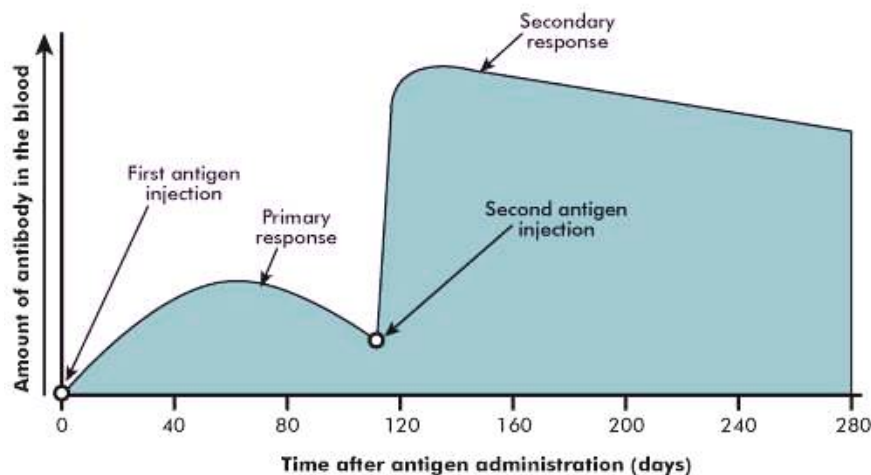
○ **Natural Immunity**

– exposure to causative agent or antigen is not deliberate and occurs in the course of everyday living as exposure to a disease causing pathogen or allergen

- **Active Exposure** – you develop your own antibodies – Immunity is long lived
- **Passive Exposure** – you receive antibodies from another source as infants receiving antibodies from mother’s milk. This immunity is short-lived

○ **Artificial Immunity or Immunization** – exposure to causative agent or antigen is deliberate

- **Active Exposure** – injection of causative agent that has been weakened or killed such as a **vaccine** and you develop your own antibodies - Immunity is long lived



Result of an immunization and a booster injection

- **Passive Exposure** - injection of protective **gamma globulin** serum containing antibodies that were developed by someone else’s immune system - This immunity is short-lived but immediate so it prevents full infection from developing in patients just exposed to serious agents when there is not time to develop active immunity from immunization

Role of Antibiotics and Antivirals

- **Antibiotics or antibacterials** – group of medications used to kill bacteria by preventing them from dividing
There is concern about the extensive use of antibiotics resulting in resistant forms of bacteria and “superbugs”
- **Antivirals** – group of medications used to treat viral infections but they cannot destroy the virus. Rather they inhibit the virus from reproducing and developing.

Cultured Antibodies

- **Monoclonal antibodies** – cloning of many copies of the same antibody which can be useful in fighting diseases because they can be designed specifically to only target a certain antigen, such as one that is found on cancer cells.

Immunity Disorders - the Immune System can be under productive when it fails to recognize abnormal cells as cancerous cells or it can be over protective and cause other types of difficulties

- **Allergies** – hypersensitivity of the immune system to relatively harmless environmental antigens - the immune system reacts to an outside substance that it normally would ignore- **allergy** types (food, dust, mold, seasonal), symptoms and signs (skin rash, itching, red bumps, sneezing).



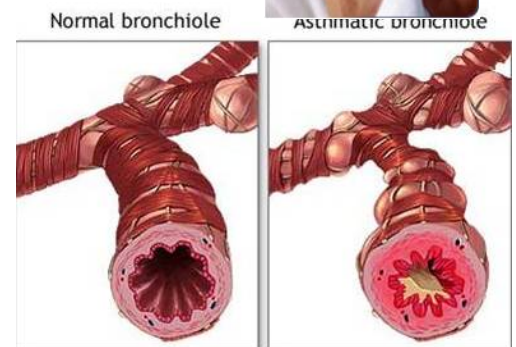
- **Asthma** - an obstructive pulmonary disorder characterized by recurring spasms of muscles in bronchial walls accompanied by edema and mucus production which make breathing difficult - it causes the airways of the lungs to swell and narrow, leading to wheezing, shortness of breath, chest tightness, and coughing

Extrinsic, or allergic asthma, is more common (90% of all cases) and typically develops in childhood

Intrinsic asthma represents about 10% of all cases. It

usually develops after the age of 30 and is not typically associated with allergies

Treatment – inhaler with medications as albuterol to open airways



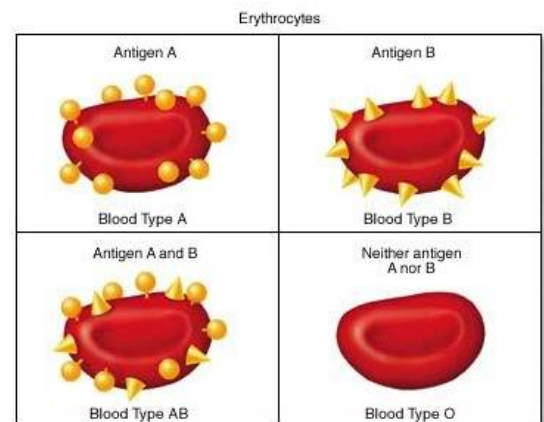
- **Autoimmune Disorder** - a condition that occurs when the **immune** system mistakenly attacks and destroys healthy body tissue- more than 80 different types - the immune system can't tell the difference between healthy body tissue and antigens. The result is an immune response that destroys normal body tissues. This response is a hypersensitivity reaction similar to the response in allergic conditions- Examples of autoimmune (or immune-related) disorders include Addison's disease , Celiac disease - (gluten-sensitive enteropathy), Graves disease, Hashimoto's thyroiditis, Multiple sclerosis, Myasthenia gravis, Pernicious anemia, Rheumatoid arthritis, Systemic lupus erythematosus, Type I diabetes

- **AIDS - (acquired immune deficiency syndrome)** is the final stage of HIV disease, which causes severe damage to the immune system-caused by infection with **human immunodeficiency virus (HIV)**.- HIV infects vital cells in the human immune system such as helper T cells, macrophages, and dendrite cells
- **Tissue Rejection – Foreign MHC Proteins** - human immune system is designed to attack anything it doesn't recognize –white blood cells recognize the body's tissues by looking for a set of antigens on the surface of each cell
 - The most important of these make up the **major histocompatibility complex (MHC)**.
 - Self-antigens - Major-histocompatibility complex (MHC) protein markers - Two groups
 - Class I MHC markers – displayed on all cells except RBCs
 - Class II MHC markers – displayed on mature B-cells, some T-cells, and antigen-presenting cell
 - When your immune system finds cells in your body that don't show the right MHC proteins (foreign MHC proteins), it tries to destroy them-Doctors test the MHC of potential organ donors to find the best match

- **Blood typing problems – ABO System**

The surface membranes of RBCs carry proteins that act as antigens in some recipients

- **Type A** blood has A antigens only.
- **Type B** blood has B antigens only.
- **Type AB** blood has both A and B antigens present
- **Type O** blood lacks both A and B antigens
- Blood plasma contains antibodies to the blood types not present.
- Exposure to foreign blood antigens results in agglutination or clumping of RBCs, prevents circulation of blood, and the RBCs burst



- **Rh System problems**

- Another important antigen used in matching blood types.
- Persons with Rh factor on RBC membrane are Rh positive; Rh negative lack the Rh factor protein.
- Rh negative individuals do not automatically have antibodies to Rh factor but develop immunity when exposed to it.
- **Hemolytic disease of the newborn (HDN)** can occur when mother is Rh negative and baby is Rh positive.
 - Mother is not exposed to infants blood unless baby's RBCs leak across placenta; otherwise mother is only "inoculated" with small amount of baby's blood (and Rh protein) at birth.
 - Mother builds up antibodies that are small enough to pass placenta and can destroy baby's RBC; mother receives a booster at each baby's birth; therefore danger to successive infants grows.
 - Problem is solved by giving the mother anti-Rh antibodies, usually after baby's birth, that attack any of baby's RBCs left in mother's blood before mother can produce antibodies.