

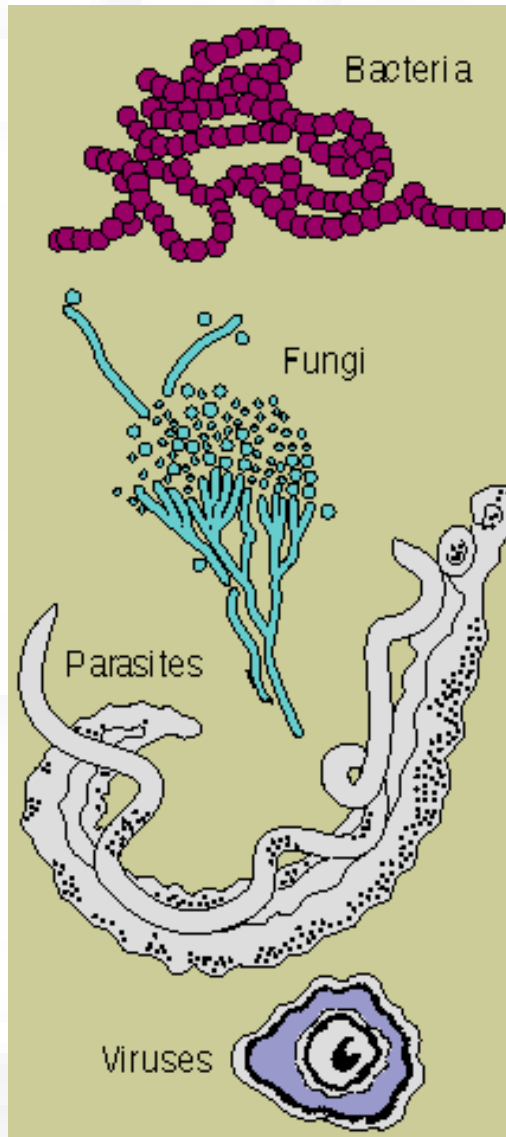
Immune Response and Extracorporeal Circulation ©

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The Immune Response and CPBP

- Infection post-OHS followed by death or severe morbidity
 - Sternal wound infection MOST costly consistent complication
 - Susceptibility increased due to CPBP
- Immunoglobulins most important part of immune system
 - Play a central role in allergic reactions, autoimmune responses
 - Neutralize toxins
 - Central role in infection defense
- Product of marrow B lymphocyte plasma cells

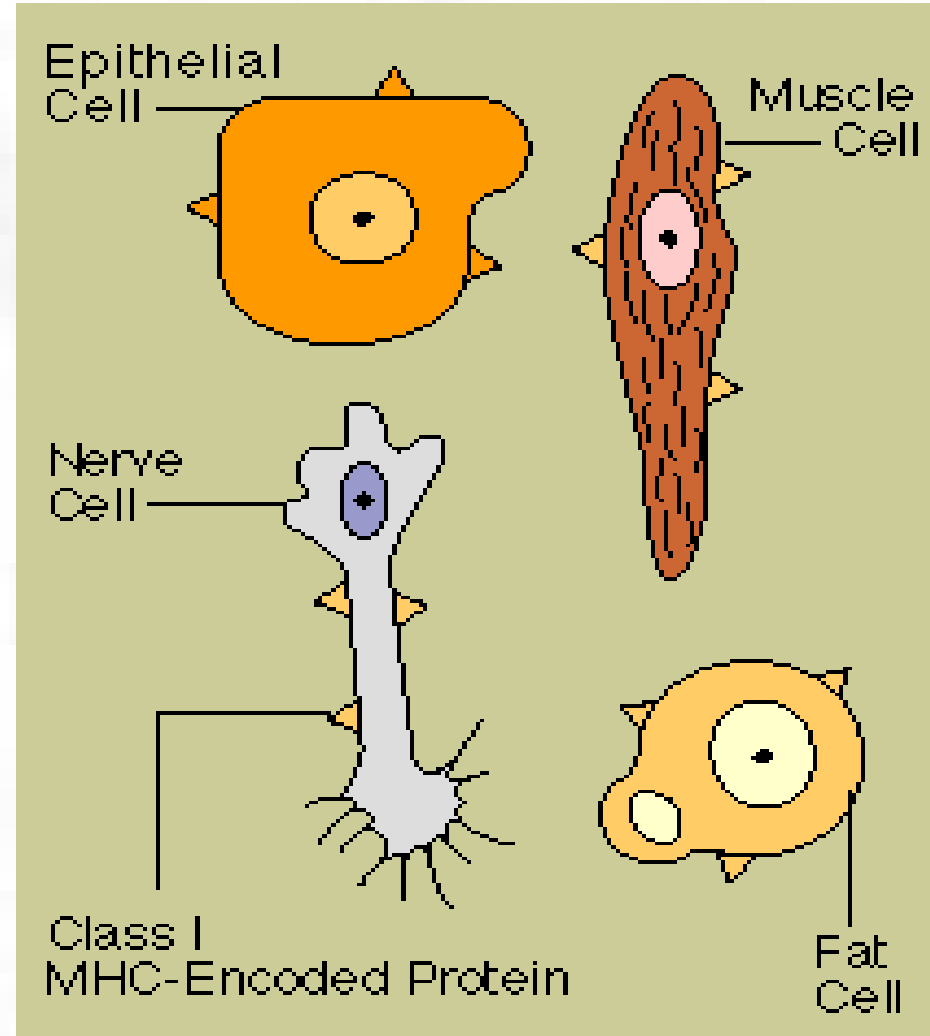
The Immune System



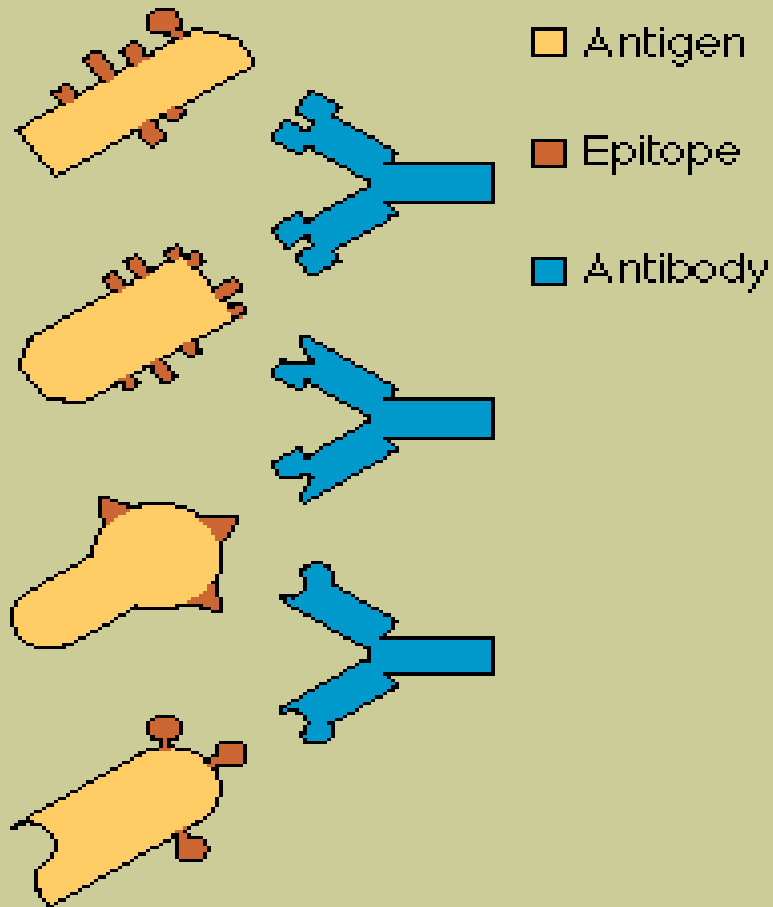
- body-wide network of cells and organs that has evolved to defend the body against attacks by "foreign" invaders.
 - “proper” targets of the immune defenses are infectious organisms
 - bacteria such as these streptococci;
 - Fungi (mold from which penicillin is made);
 - Parasites, including worm-like microbes that cause schistosomiasis
 - Viruses such as herpes virus.

Markers of Self

- ability to distinguish between self and non-self.
 - All cells carry distinctive molecules that distinguish it as "self."
 - Normally the body's defenses do not attack tissues that carry a self marker
 - immune cells coexist peaceably with other body cells in a state known as self-tolerance.



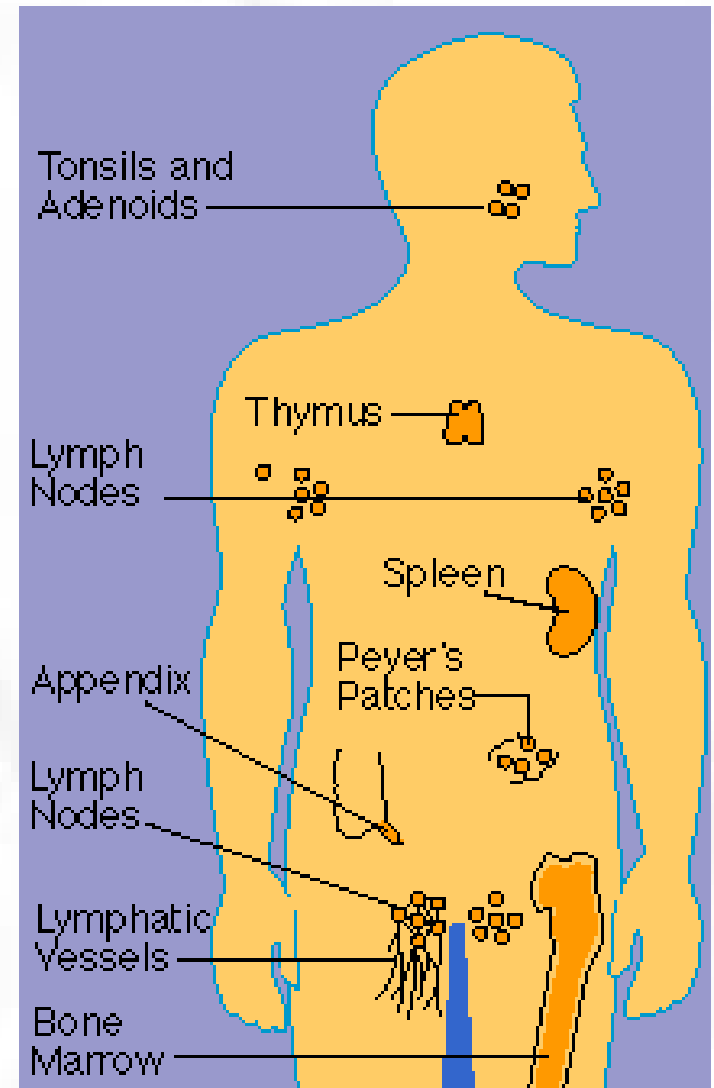
Markers of Non-Self



- Foreign molecules carry distinctive markers,
 - characteristic shapes called epitopes that protrude from their surfaces.
 - immune system has ability to recognize many millions of distinctive non-self molecules
 - respond by producing molecules such as antibodies that can match and counteract each non-self molecules.
 - Any substance capable of triggering an immune response is known as an antigen.
 - bacterium
 - virus
 - tissues or cells from another people also act as antigens

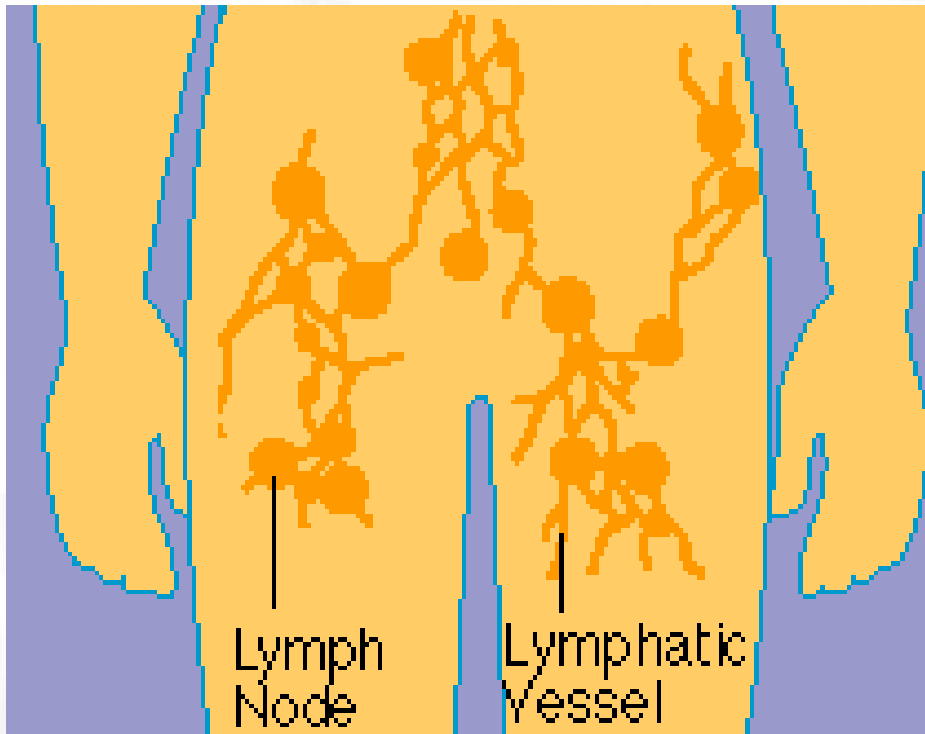
Organs of the Immune System

- The organs of the immune system are stationed throughout the body.
 - known as lymphoid organs
 - concerned with the growth, development, and deployment of lymphocytes
 - white blood cells that are key operatives of the immune system.



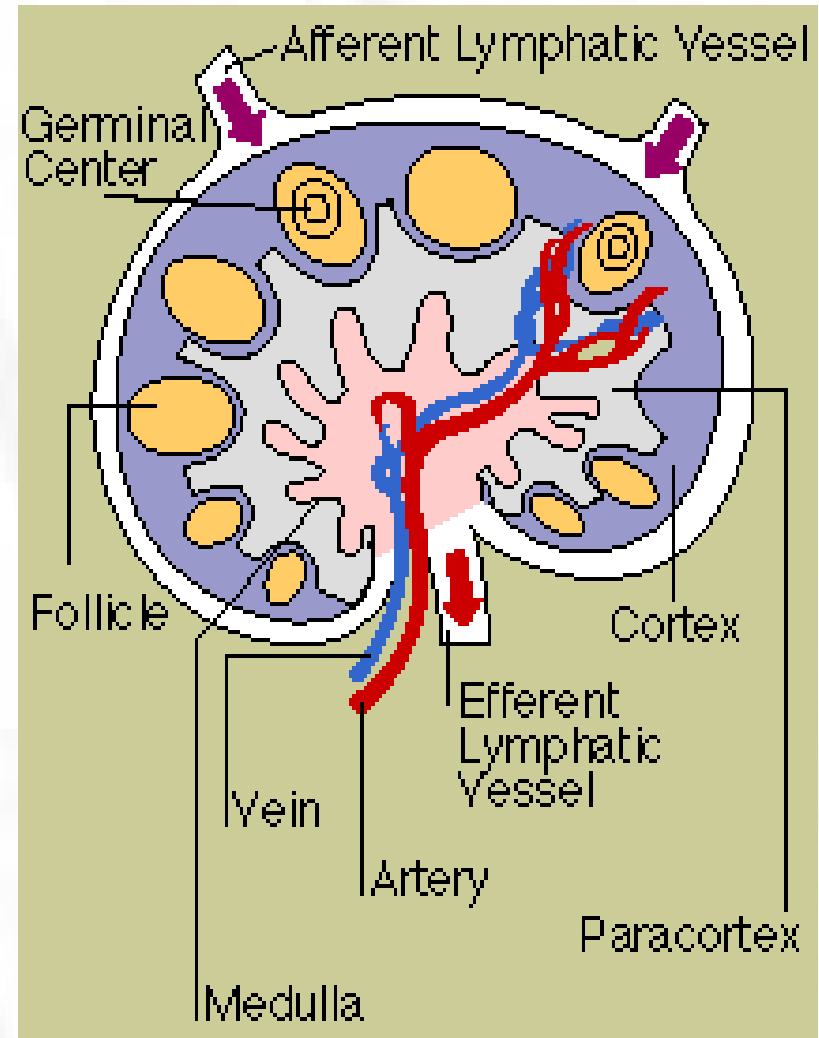
Lymphatic System

- The organs of the immune system are connected with one another and with other organs of the body
 - network of lymphatic vessels similar to blood vessels.
 - Immune cells and foreign particles are conveyed through the lymphatics
 - lymph, a clear fluid that bathes the body's tissues.

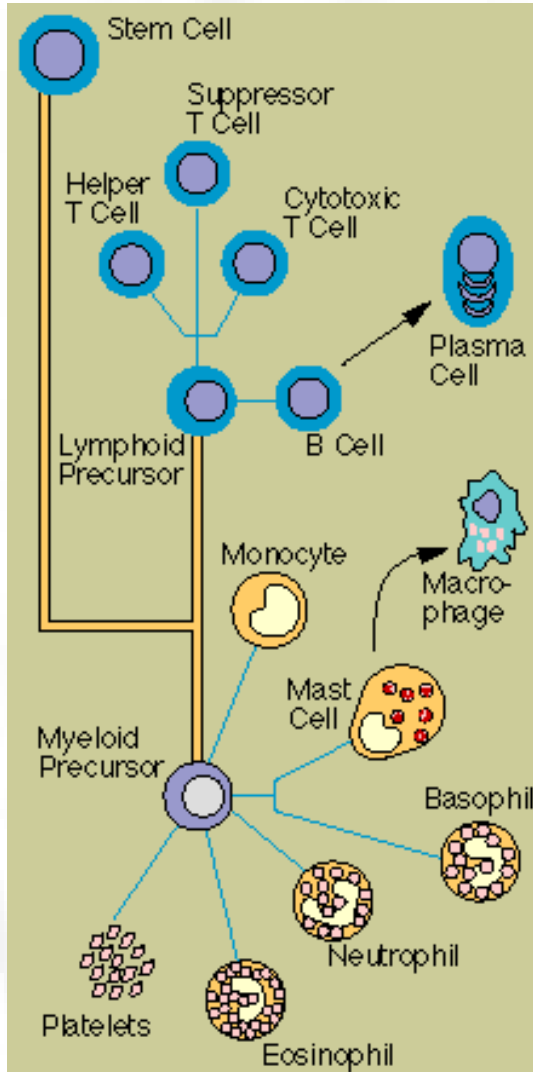


Lymph Node

- Lymph nodes
 - small, bean-shaped structures
 - laced throughout the body along the lymphatic routes.
 - contain specialized compartments where immune cells congregate and where they encounter antigens.



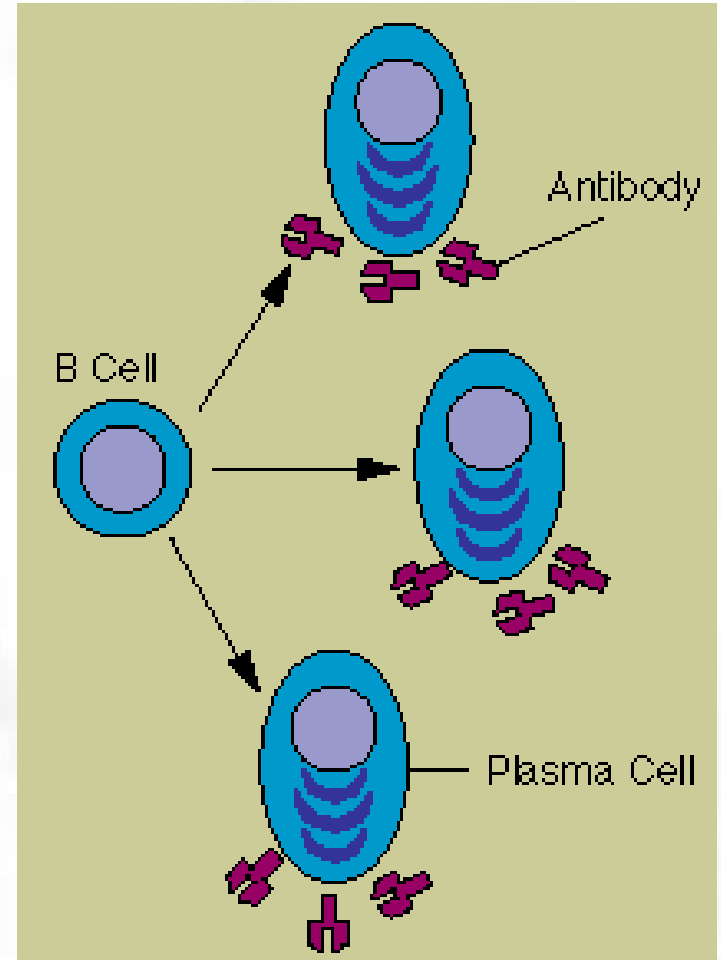
Cells of the Immune System



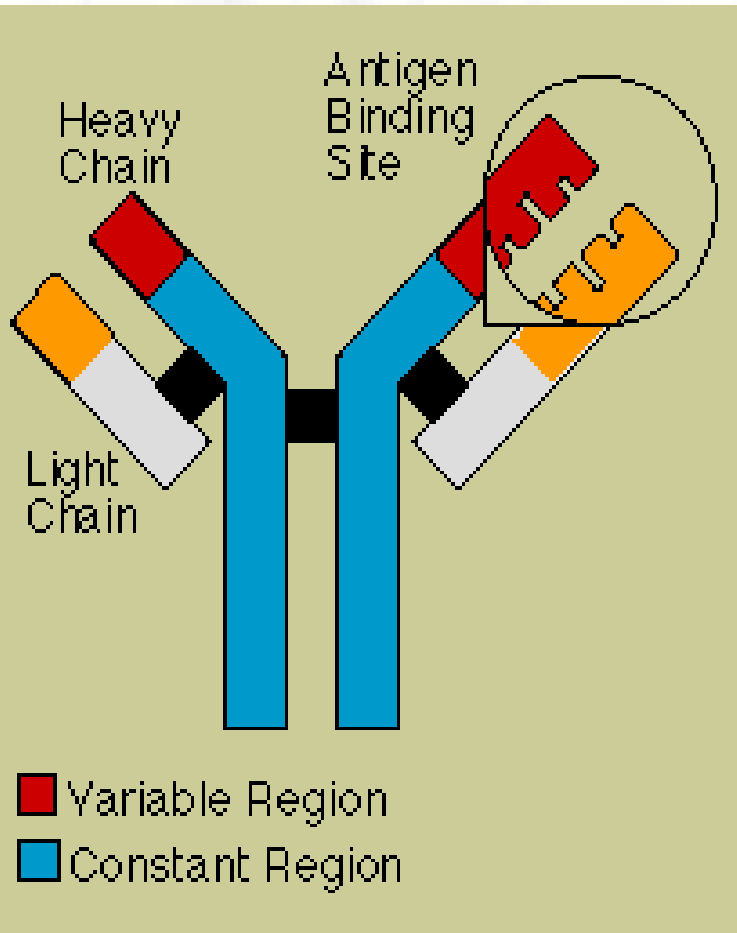
- Cells destined to become immune cells, like all blood cells, arise in the bone marrow from so-called stem cells.
 - Some develop into myeloid cells
 - group typified by the large, cell- and particle-devouring white blood cells known as phagocytes
 - include monocytes, macrophages, and neutrophils.
 - Other myeloid descendants become granule-containing inflammatory cells such as eosinophils and basophils.
 - Lymphoid precursors develop into the small white blood cells called lymphocytes.
 - The two major classes of lymphocytes are B cells and T cells.

B Cells

- Secreting soluble substances known as antibodies.
- Each B cell is programmed to make one specific antibody.
- When a B cell encounters its triggering antigen (along with various accessory cells), it gives rise to many large plasma cells.
- Each plasma cell is essentially a factory for producing that one specific antibody.



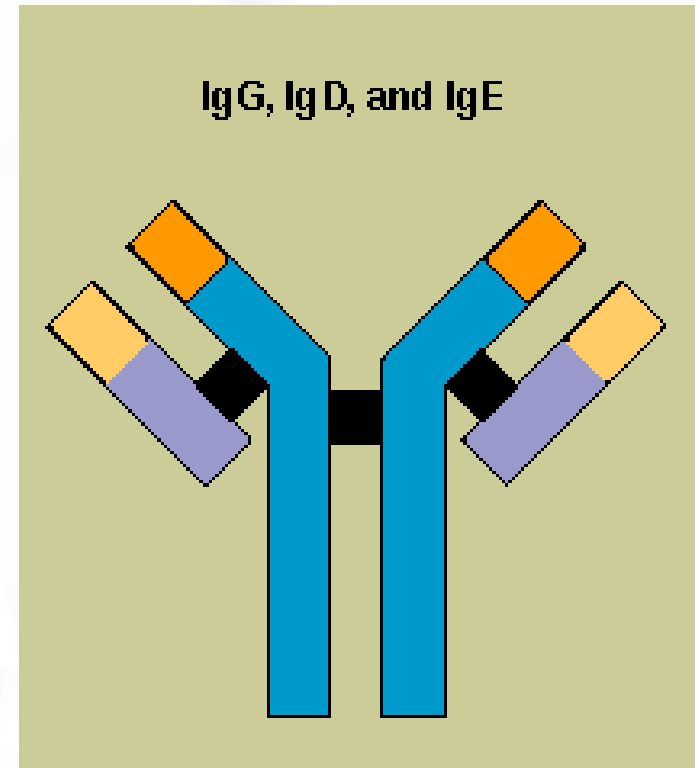
Antibody



- made up of two identical heavy chains and two identical light chains, shaped to form a Y.
 - the tips of the Y's arms vary greatly from one antibody to another
 - this is called the variable region.
 - these unique contours in the antigen-binding site allow the antibody to recognize a matching antigen, much as a lock matches a key.
 - stem of the Y links the antibody to other participants in the immune defenses.
 - This area is identical in all antibodies of the same class—for instance, all IgEs—and it's called the constant region.

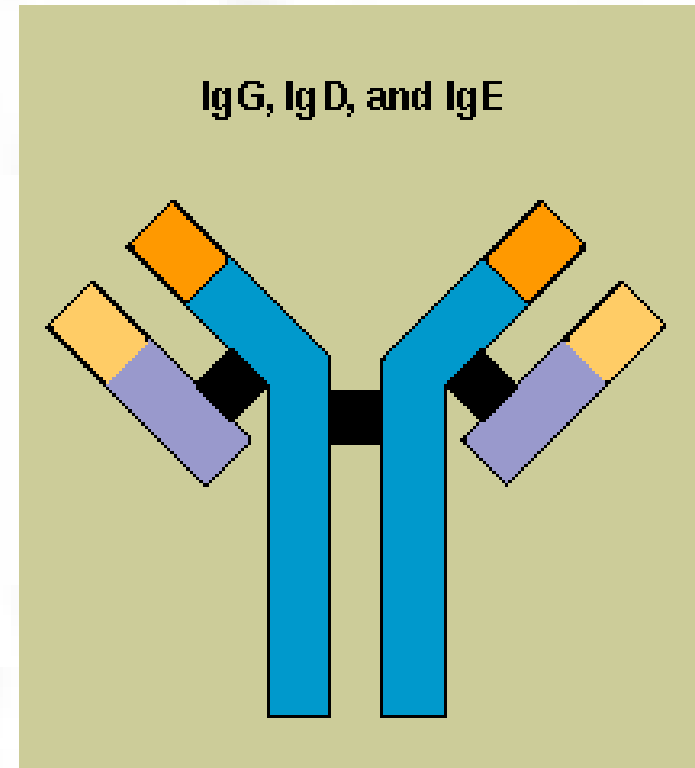
IgG, IgD, and IgE

- Antibodies belong to a family of large protein molecules known as immunoglobulins.
- nine chemically distinct classes of human immunoglobulins
 - four kinds of IgG
 - two kinds of IgA
 - plus IgM, IgE, and IgD.
- Immunoglobulins G, D, and E are similar in appearance

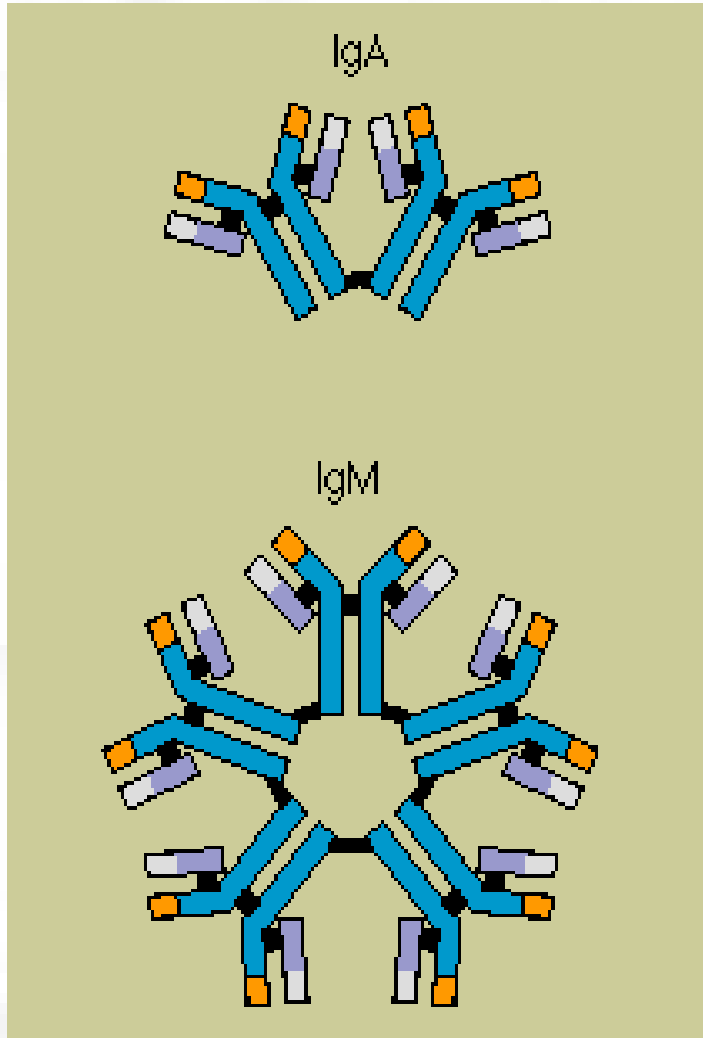


IgG, IgD, and IgE

- IgG, the major immunoglobulin in blood
 - able to enter tissue spaces
 - it works efficiently to coat microorganisms, speeding their uptake by other cells in the immune system.
- IgD is almost exclusively found inserted into the membrane of B cells
 - somehow regulates B cell's activation.
- IgE is normally present in only trace amounts
 - responsible for the symptoms of allergy.



IgA and IgM



- IgA
 - Doublet
 - concentrates in body fluids such as tears, saliva, and the secretions of the vagina, respiratory and gastrointestinal tracts.
 - guards the entrances to the body!
- IgM usually combines in star-shaped clusters.
 - It tends to remain in the bloodstream, where it is very effective in killing bacteria.

Bypass' effects on Immunity

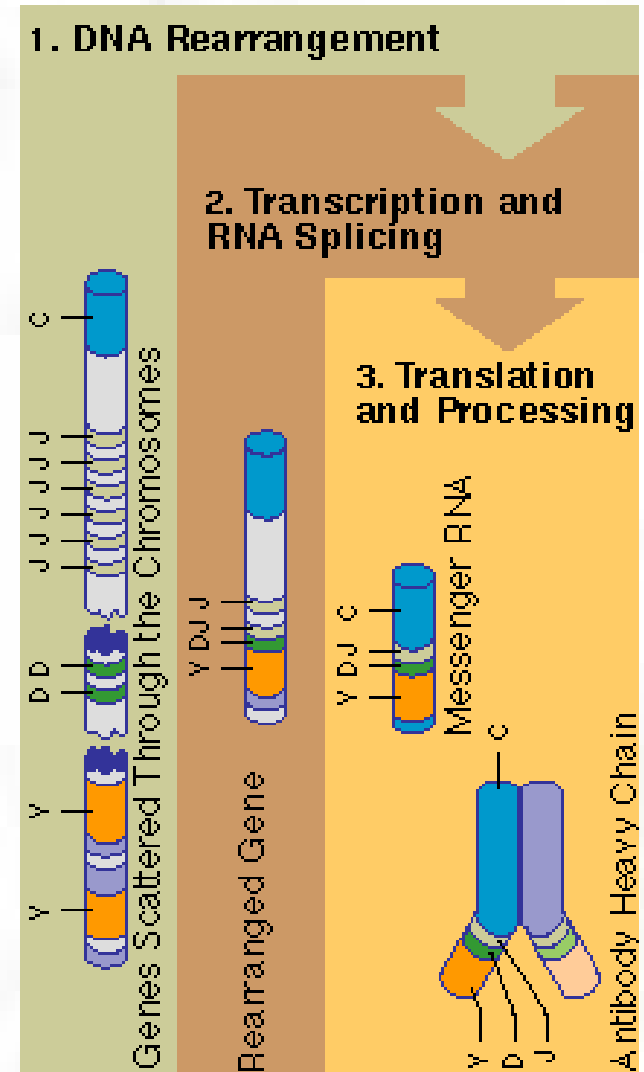
- CPBP known to reduce bactericidal activity
 - Decrease in total complement
 - Decrease in IgA, IgM, IgG

Hemodilution reduces protein concentration proportional to HCT

- Albumin / globulin concentration fall during CPBP
- Lowers complement, IgM, IgA, IgG, opsonic capacity
- Proteins are denatured and macroaggregated by ECC
 - At air-fluid interfaces
 - Electrostatic forces cause molecular asymmetry and reactivity enhanced by ECC components and albumin and aggravated by hypothermia
 - Leads to macromolecular formation
 - Lipid transport proteins release lipids causing microvascular emboli
 - Macroaggregates uptaken by reticuloendothelial system, causing partial blockade

Antibody Genes

- How can all the genetic information needed to make millions of different antibodies could fit in a limited number of genes?
 - antibody genes are pieced together from widely scattered bits of DNA,
 - the possible combinations are nearly endless.
 - As this gene forms, it assembles segments that will determine
 - the variable-V,
 - diversity-D,
 - joining-J,
 - constant-C segments of this antibody molecule,
 - a typical IgM heavy chain.



T Cells

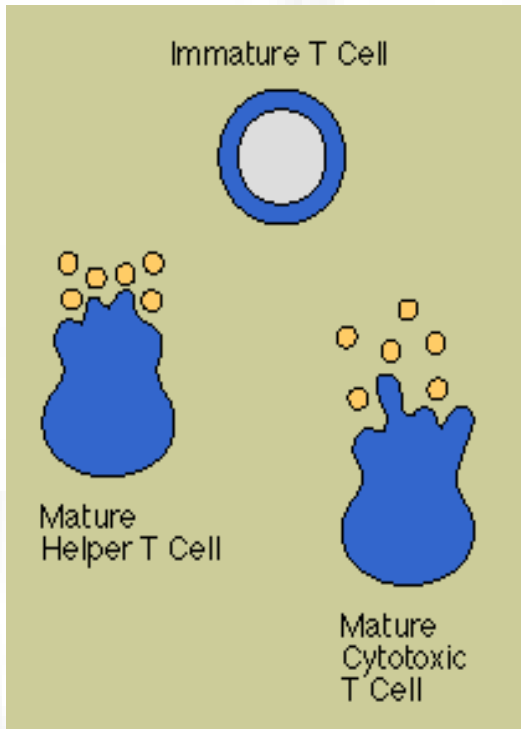
- contribute to the immune defense 2 ways

- Chief among the regulatory T cells are "helper/inducer" T cells.

- They are needed to activate many immune cells, including B cells and other T cells.
- Another subset of regulatory T cells acts to turn off or suppress immune cells.

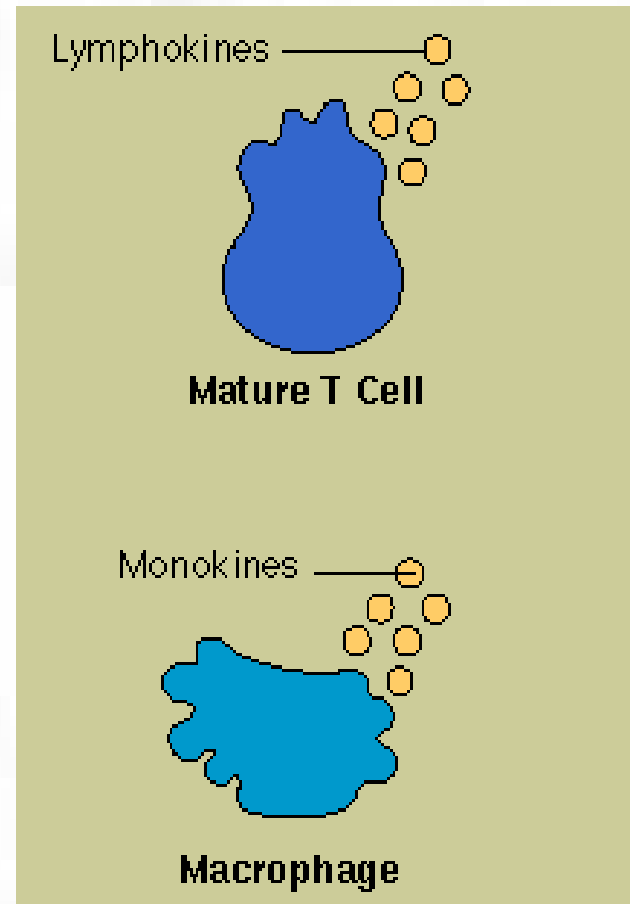
- Cytotoxic T cells help rid the body of toxic cells

- Cells infected by viruses
- Cells transformed by cancer.
- They are also responsible for the rejection of tissue and organ grafts.

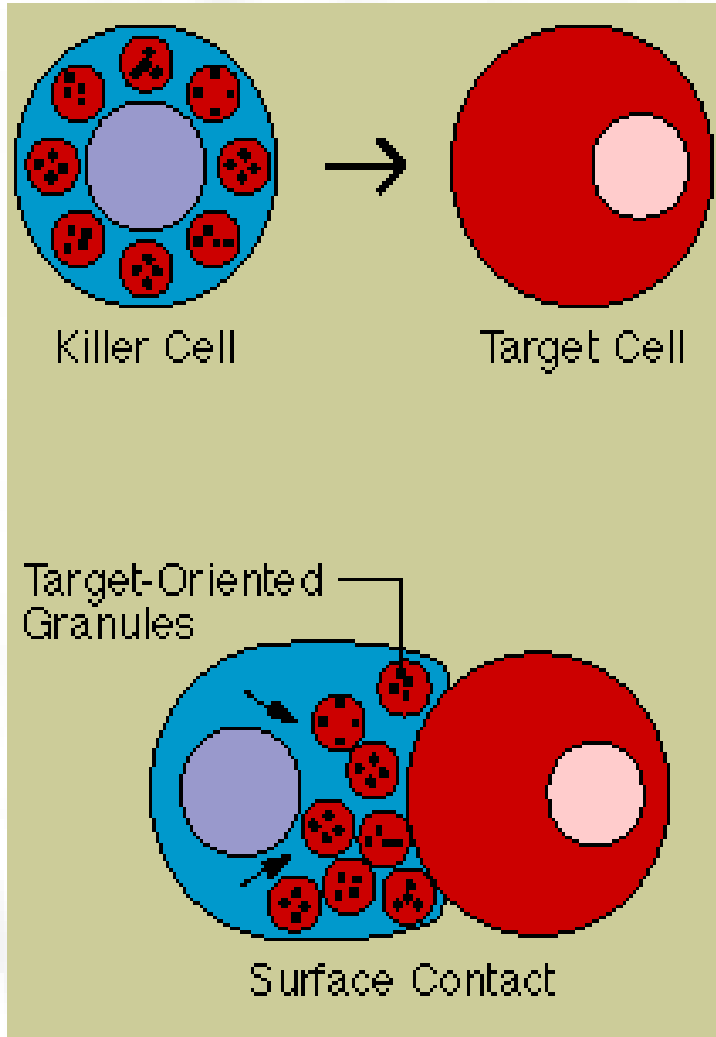


Cytokines

- diverse and potent chemical messengers secreted by the cells of the immune system
 - Primary tool of T cells.
 - Lymphocytes, including both T cells and B cells, secrete lymphokines, while monocytes and macrophages secrete monokines.
- recruit other cells and substances
- encourage cell growth
- direct cellular traffic
 - destroy target cells—including cancer cells.
- Since they serve as a messenger between white cells, or leukocytes, many cytokines are also known as interleukins.



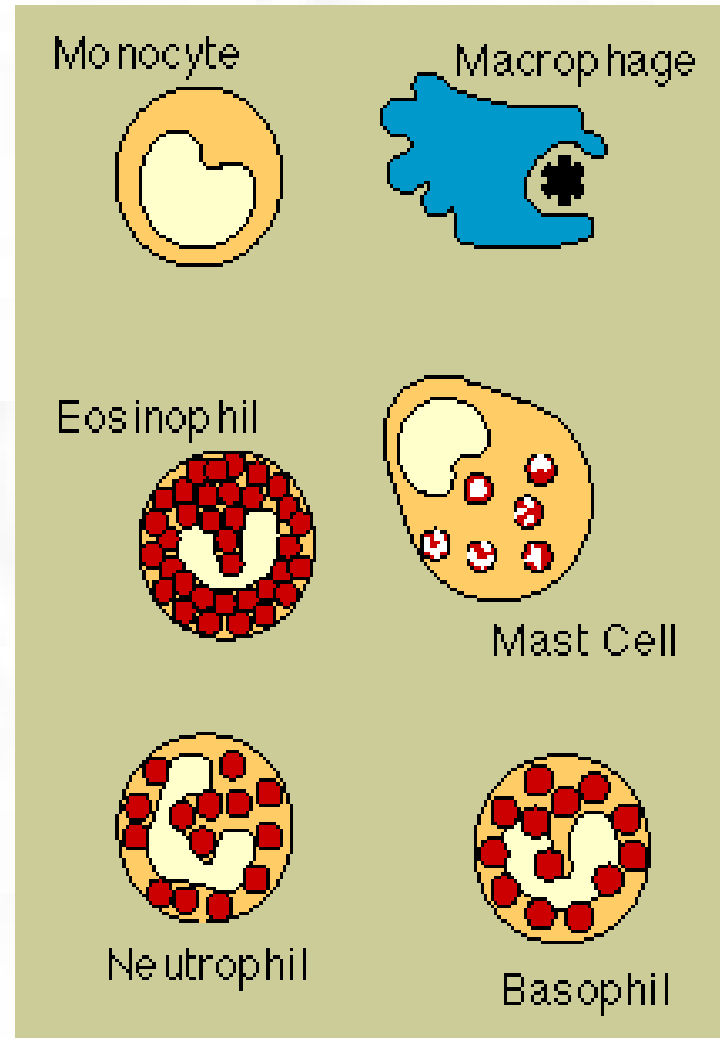
Natural Killer Cells



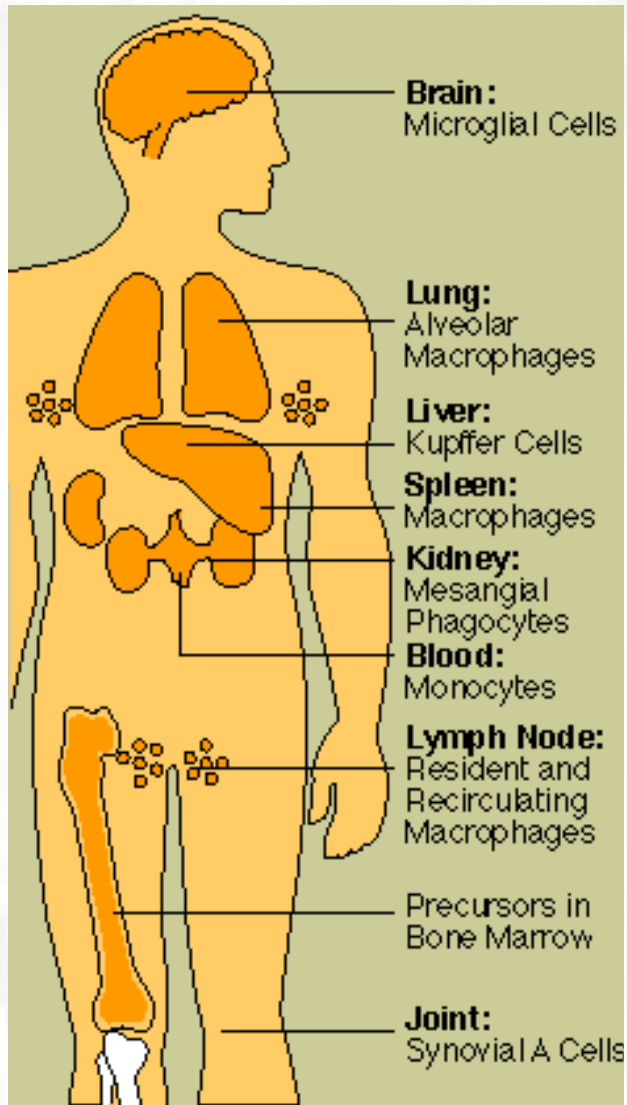
- At least two types of lymphocytes are killer cells
 - cytotoxic T cells
 - need to recognize a specific antigen
 - natural killer cells.
 - natural killer or NK cells do not need antigen recognition.
 - Both types contain granules filled with potent chemicals
 - Both types kill on contact.
 - The killer binds to its target, aims its weapons, and delivers a burst of lethal chemicals.

Phagocytes and Granulocytes

- large white cells that can engulf and digest foreign invaders.
 - monocytes
 - which circulate in blood
 - Macrophages
 - which are found throughout the body
 - are versatile cells
 - act as scavengers
 - secrete a wide variety of powerful chemicals
 - play an essential role in activating T cells.
 - Neutrophils
 - cells that circulate in the blood but move into tissues where they are needed.



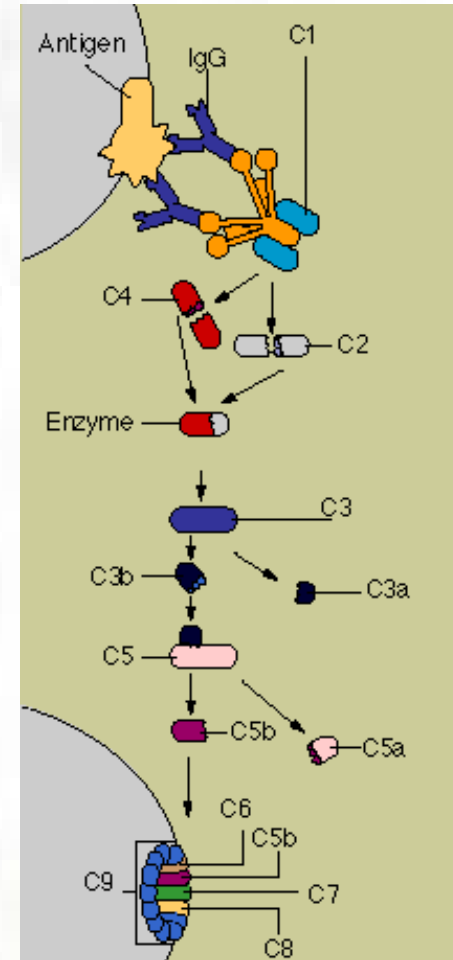
Phagocytes in the Body



- Specialized phagocytes are found in organs throughout the body.

Complement

- The complement system consists of a series of proteins that work to "complement" the work of antibodies in destroying bacteria.
 - Complement proteins circulate in the blood in an inactive form
 - "complement cascade" is set off when the first complement molecule, C1, encounters antibody bound to antigen in an antigen-antibody complex.
 - Each of the complement proteins performs its specialized job in turn, acting on the molecule next in line.
 - The end product is a cylinder that punctures the cell membrane and, by allowing fluids and molecules to flow in and out, dooms the target cell.



Bacterial / Fungal Infections after CPBP

- Greater M & M following OHS than other surgery
- Risks include:
 - Procedure duration
 - Sternotomy
 - Use of prosthetic and intravascular foreign bodies
 - Vascular grafts, Valve prostheses, Pledgets, Pacemakers
 - PostOp immunosuppression
 - Air contact (esp. high volume suction)
 - Indwelling vascular catheters, endotracheal tubes
 - Presence of hematoma / coagulated tissues

Bacterial / Fungal Infections after CPBP

- Risks include:
 - Lethal post-op infection factors include:
 - Preop bacterial endocarditis
 - CPBP greater than 3.5 hrs
 - Low CO
 - Post-op cerebral dysfunction
 - DIC
 - Most surgeons treat patients prophylactically with antibiotics

Immunological Goal

- Decrease number / pathogenicity of microorganisms accessing wound. Risk of infection following bacteremia greatest between post-CPBP to six weeks
 - attention to sterility of instruments and materials
 - management of bacterial SOURCES (infected patients)
 - Avoidance of infected patients by OR personnel
 - Rigid adherence to good surgical technique

Methods for improving antisepsis following open-heart surgery

- Prophylactic antibiotics
 - Local irrigation is effective
 - Prophylaxis as effective for 2 as 5 days
 - Most surgeons prefer broad spectrum cephalosporins
 - Significantly reduces overall cost by reducing hospital stays related to infection control.
- Preop infection screening
- Optimal housekeeping

Methods for improving antisepsis following open-heart surgery

- Air delivery filtration
 - High flow vertical unidirectional ventilation
- Minimizing coronary suction
- Heat exchanger leaks
- Oxygen line control
- Maximizing protective clothing, hats, masks, drapes, gloves
- Traffic control
- Exclusion of contaminated operations from Cardiac Suites
- Isolation of infected patients

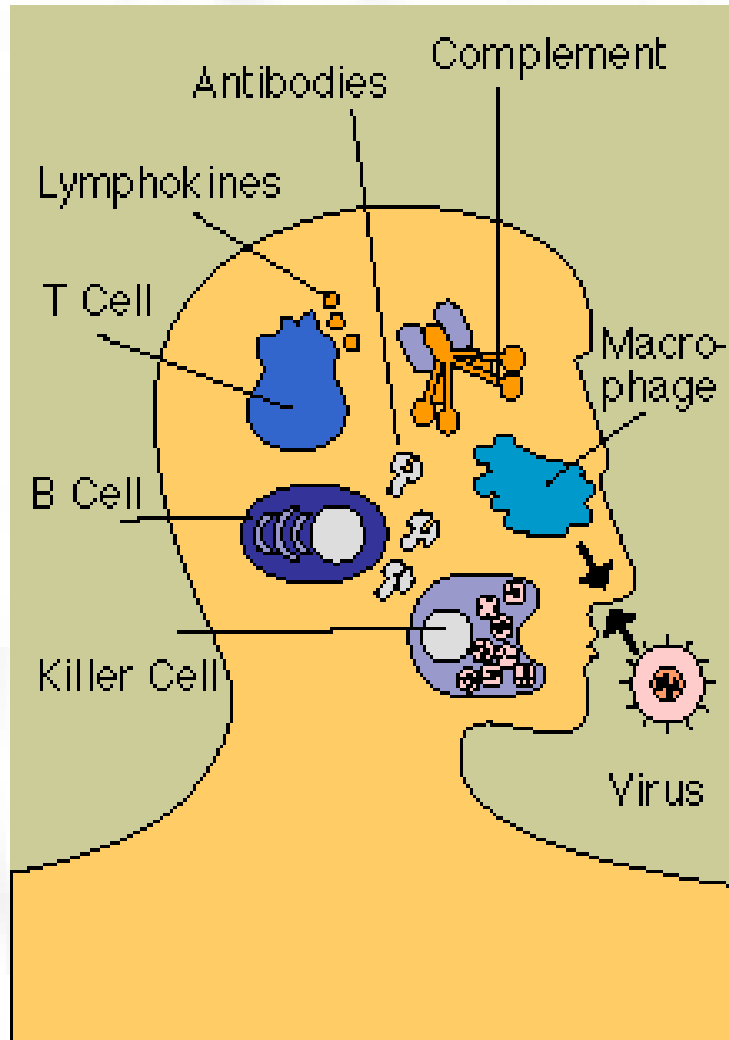
ECC Contribution to Sepsis

- Air drawn in at 1-2 ft² / min
 - OR may have 10 bacteria / ft²
 - Influenced by number of people in room
 - Ventilation system
 - Number of times doors open/close
 - Estimates are 1200 colony-forming particles are drawn into suction per hour
 - Add 1 colony-forming unit / 6cc blood / hour
- select membrane and minimizing use of suction

Bacterial Reality

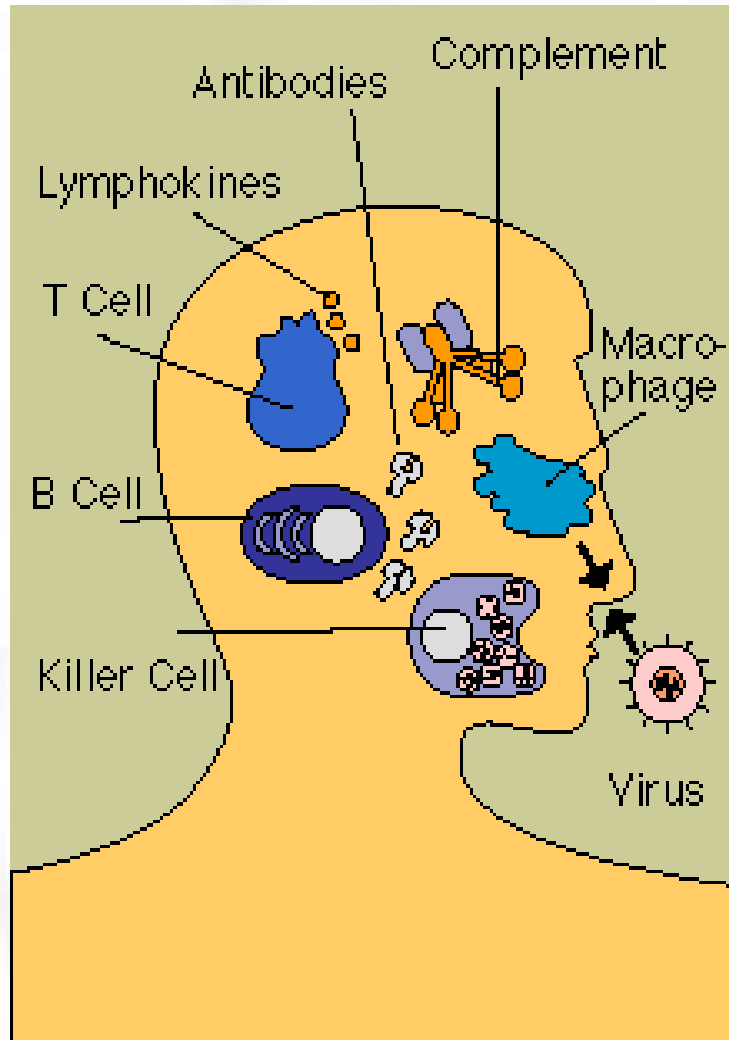
- Estimates of 1000 bacteria settle into sternotomy wound in course of 2-hour operation
- With Infection epidemic, eliminate source
- Change in immune system and inflammatory response ALTER relationship between fever, leukocytosis and infection
 - NO correlation for up to 6 days post-op
 - 15% correlation after 6 days to up to 6 week

Mounting an Immune Response



- Microbes attempting to get into the body
 - must first get past the skin and mucous membranes
 - pose a physical barrier
 - rich in scavenger cells and IgA antibodies.
- Next, they must elude a series of nonspecific defenses
 - cells and substances that attack all invaders regardless of the epitopes they carry including:
 - patrolling scavenger cells
 - complement,
 - various other enzymes and chemicals.

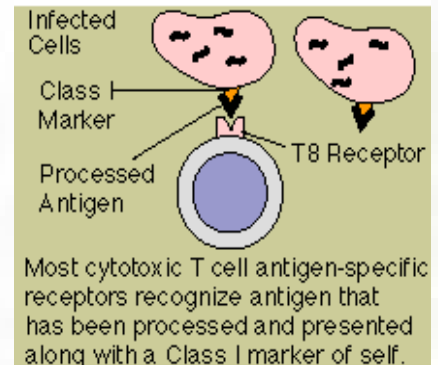
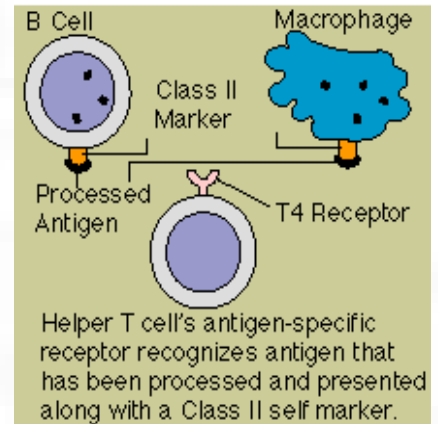
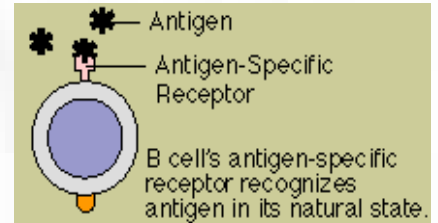
Mounting an Immune Response



- Infectious agents that get past the nonspecific barriers must confront specific weapons
 - tailored just for them!
 - include both antibodies and cells
 - almost all antigens trigger both nonspecific and specific responses.

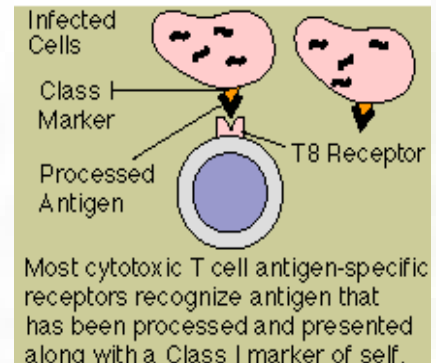
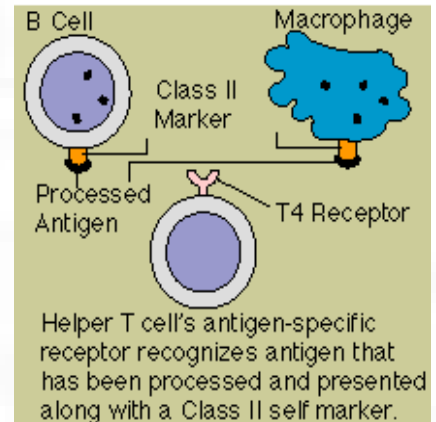
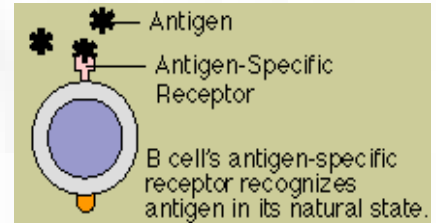
Antigen Receptors

- Both B cells and T cells carry customized receptor molecules that allow them to recognize and respond to their specific targets.
- The B cell's antigen-specific receptor is a sample of the antibody it is prepared to manufacture
 - it recognizes antigen in its natural state.

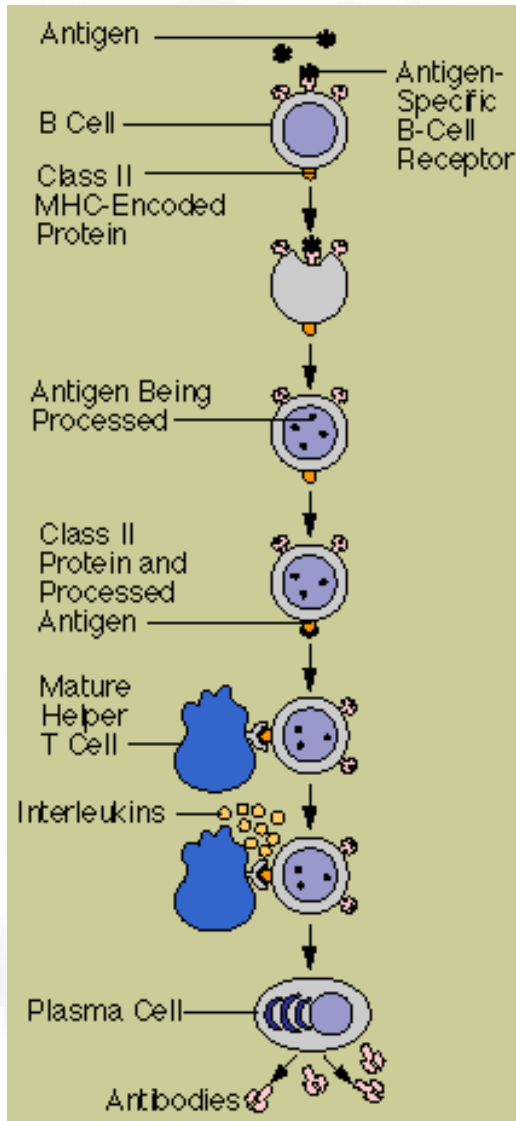


Antigen Receptors

- The T cell receptor system is more complex
 - A T cell can recognize an antigen only after the antigen is processed and presented to it by a so-called antigen-presenting cell in combination with a special type of cell marker.
 - The T4 T cell's receptor looks for an antigen that has been broken down by an immune system cell
 - such as a macrophage or a B cell and combined with a marker, known as a class II protein, carried by immune cells.
 - The T8 T cell's receptor recognizes an antigen fragment produced within the cell, combined with a class I protein
 - class I proteins are found on virtually all body cells.



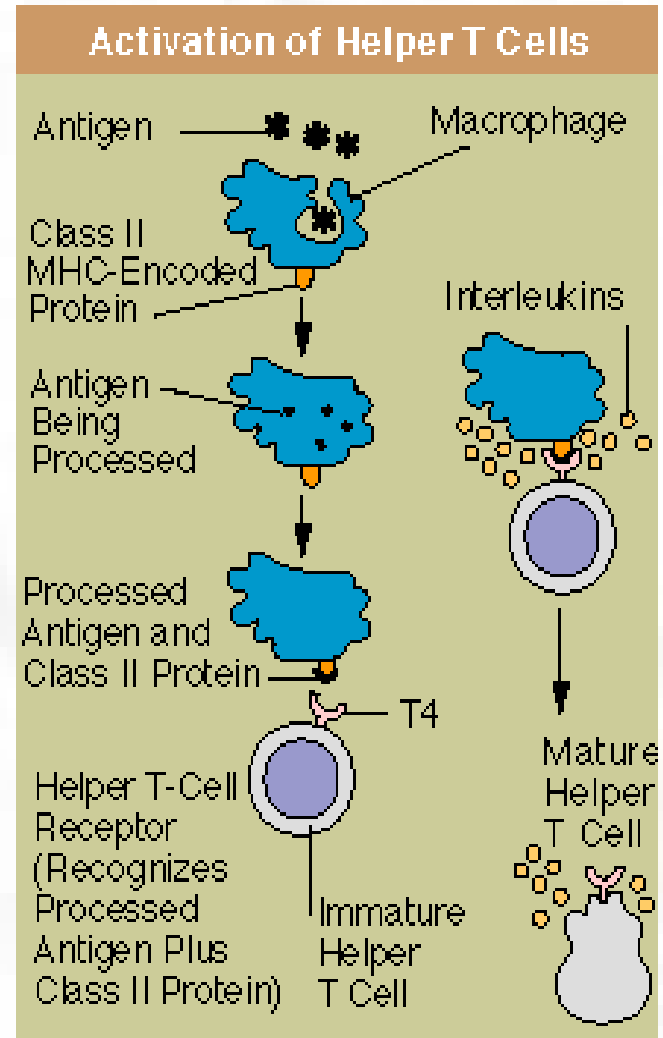
Activation of B Cells to Make Antibody



- The B cell uses its receptor to bind a matching antigen
 - Then proceeds to engulf and process.
 - Then it combines a fragment of antigen with its special marker,
 - the class II protein
 - This combination of antigen and marker is recognized and bound by a T cell carrying a matching receptor.
 - The binding activates the T cell, which then releases lymphokines (interleukins) that transform the B cell into an antibody-secreting plasma cell.

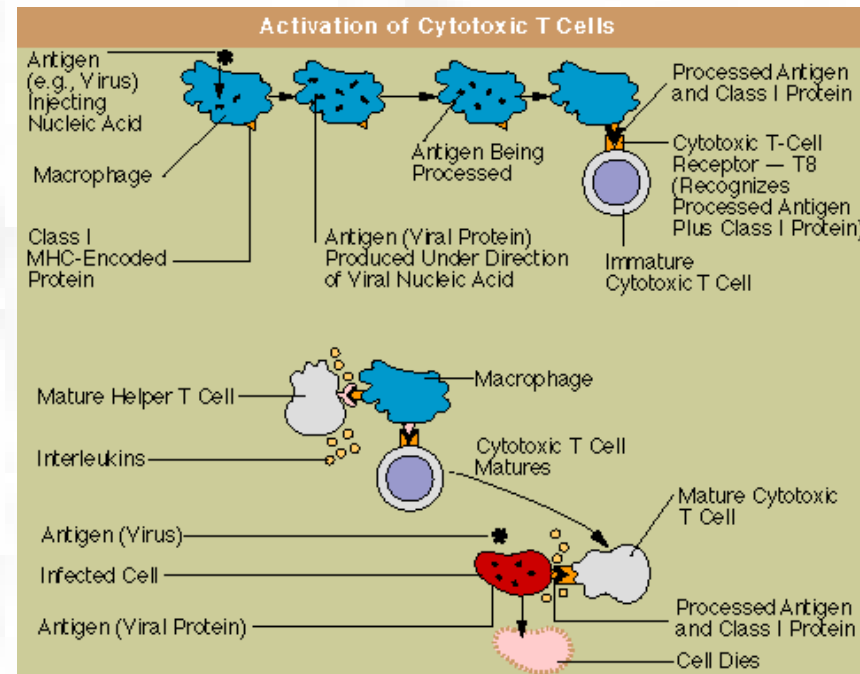
Activation of T Cells: Helper and Cytotoxic

- After an antigen-presenting cell such as a macrophage has ingested and processed an antigen, it presents the antigen fragment, along with a class II marker protein, to a matching helper T cell with a T4 receptor.
 - The binding prompts the macrophage to release interleukins that allow the T cell to mature.



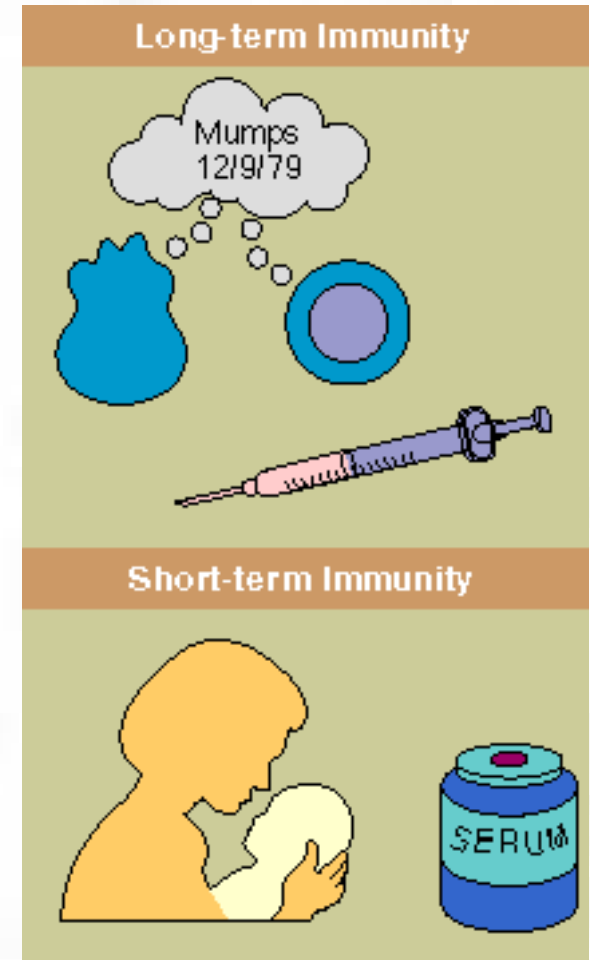
Activation of T Cells: Helper and Cytotoxic

- A cytotoxic T cell recognizes antigens such as virus proteins, which are produced within a cell, in combination with a class I self-marker protein.
 - With the cooperation of a helper T cell, the cytotoxic T cell matures.
 - When the mature cytotoxic T cell encounters its specific target antigen combined with a class I marker protein—for instance, on a body cell that has been infected with a virus—it is ready to attack and kill the target cell.

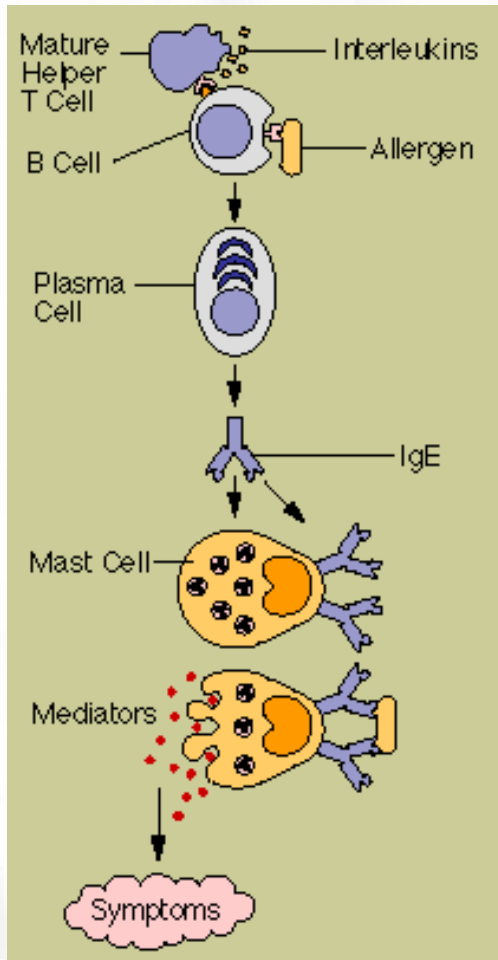


Immunity: Short- and Long-Term Cell Memory

- Whenever T cells and B cells are activated, some become "memory" cells.
 - next time that an individual encounters that same antigen, the immune system destroys it
 - Long-term immunity can be stimulated not only by infection but also by vaccines made from infectious agents that have been inactivated or, more commonly, from minute portions of the microbe.
 - Short-term immunity can be transferred passively from one individual to another via antibody-containing serum; similarly, infants are protected by antibodies they receive from their mothers (primarily before birth).



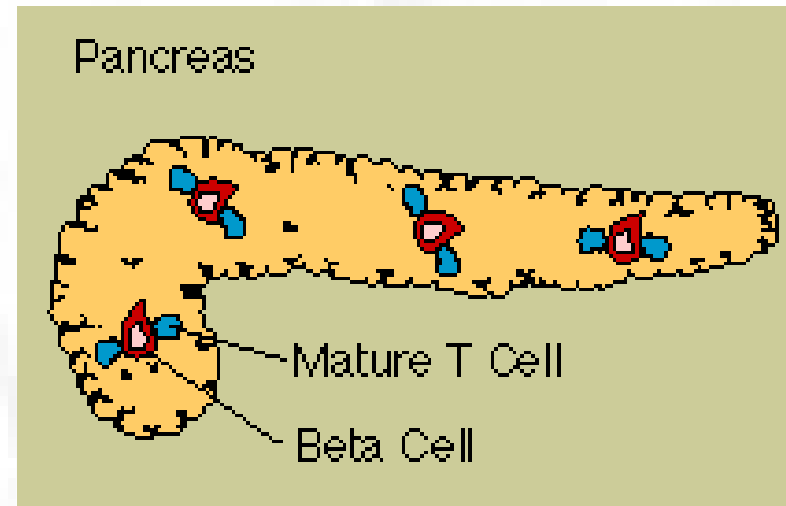
Disorders of the Immune System: Allergy



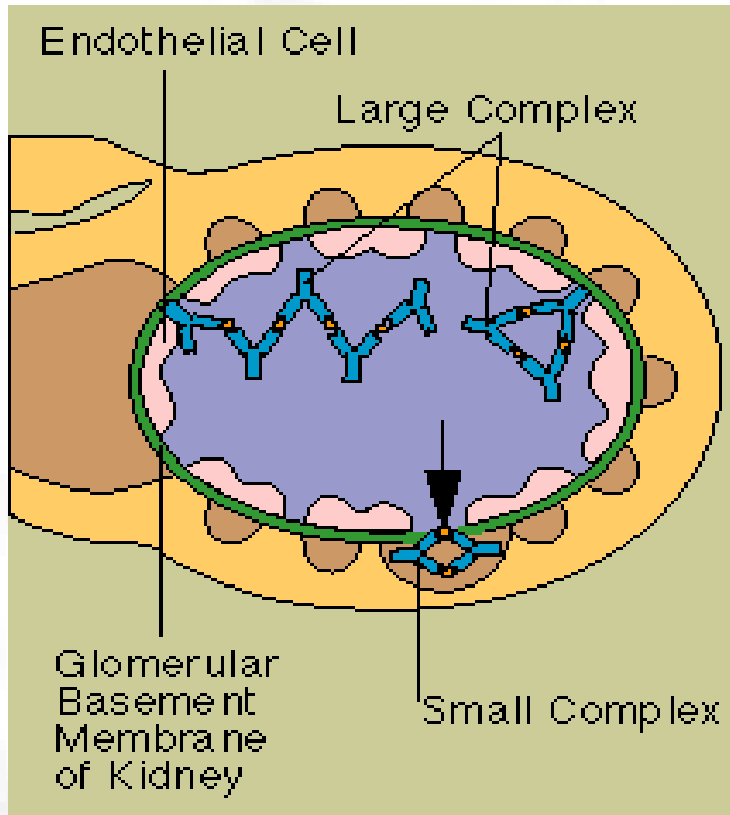
- When the immune system malfunctions, it can unleash a torrent of symptoms:
 - One of the most familiar is allergy.
 - Allergies such as hay fever and hives are related to the antibody known as IgE.
 - The first time an allergy-prone person is exposed to an allergen—for instance, grass pollen—the individual's B cells make large amounts of grass pollen IgE antibody.
 - These IgE molecules attach to granule-containing cells known as mast cells, which are plentiful in the lungs, skin, tongue, and linings of the nose and gastrointestinal tract.
 - The next time that person encounters grass pollen, the IgE-primed mast cell releases powerful chemicals that cause the wheezing, sneezing, and other symptoms of allergy.

Disorders of the Immune System: Autoimmune Disease

- Sometimes the immune system's recognition apparatus breaks down
 - body begins to manufacture antibodies and T cells directed against the body's own cells and organs.
 - Such cells and autoantibodies
 - contribute to many diseases
 - For instance, T cells that attack pancreas cells contribute to diabetes
 - an autoantibody known as rheumatoid factor is common in persons with rheumatoid arthritis.



Disorders of the Immune System: Immune Complex Disease

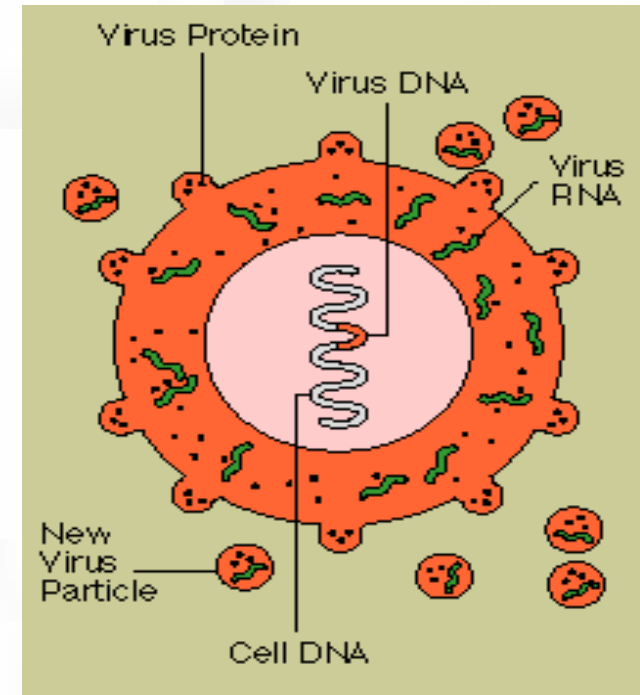


- Immune complexes are clusters of interlocking antigens and antibodies.
 - Normally they are rapidly removed from the bloodstream.
 - Sometimes, they continue to circulate, and eventually they become trapped in and damage the tissues of the kidneys, the lungs, skin, joints, or blood vessels.

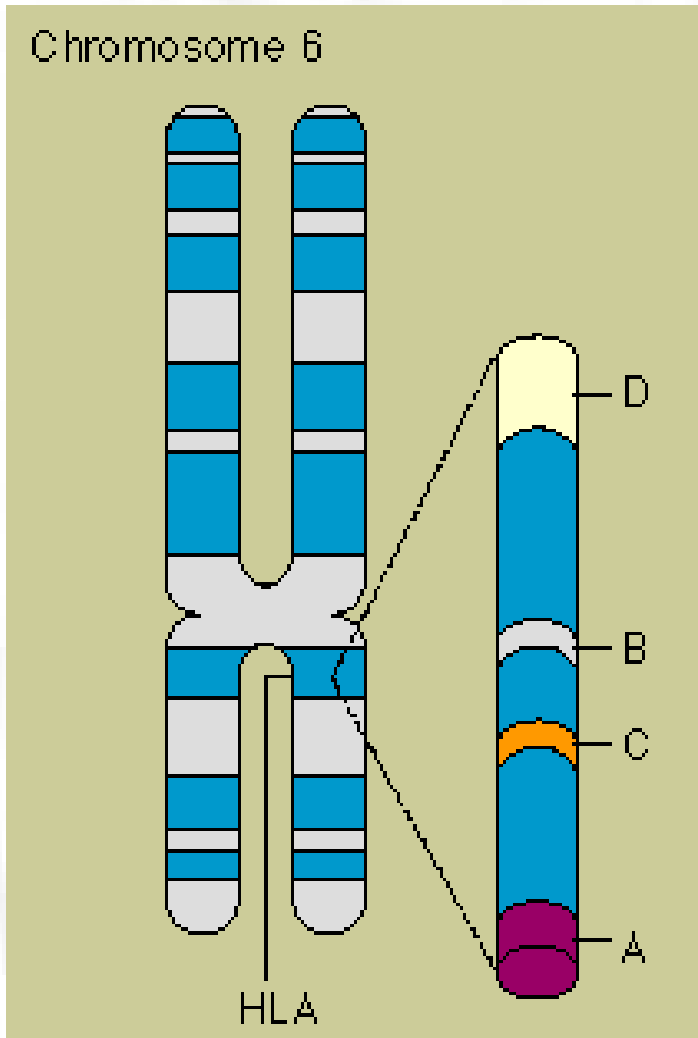
Disorders of the Immune System:

AIDS

- When the immune system is lacking one or more of its components, the result is an immunodeficiency disorder.
 - can be inherited
 - acquired through infection
 - produced as an inadvertent side effect of drugs such as those used to treat cancer or transplant patients.
- AIDS is an immunodeficiency disorder
 - caused by a virus that destroys helper T cells
 - is harbored in macrophages as well as helper (T4) T cells.
 - AIDS virus splices its DNA into the DNA of the cell it infects;
 - cell is then directed to churn out new viruses.



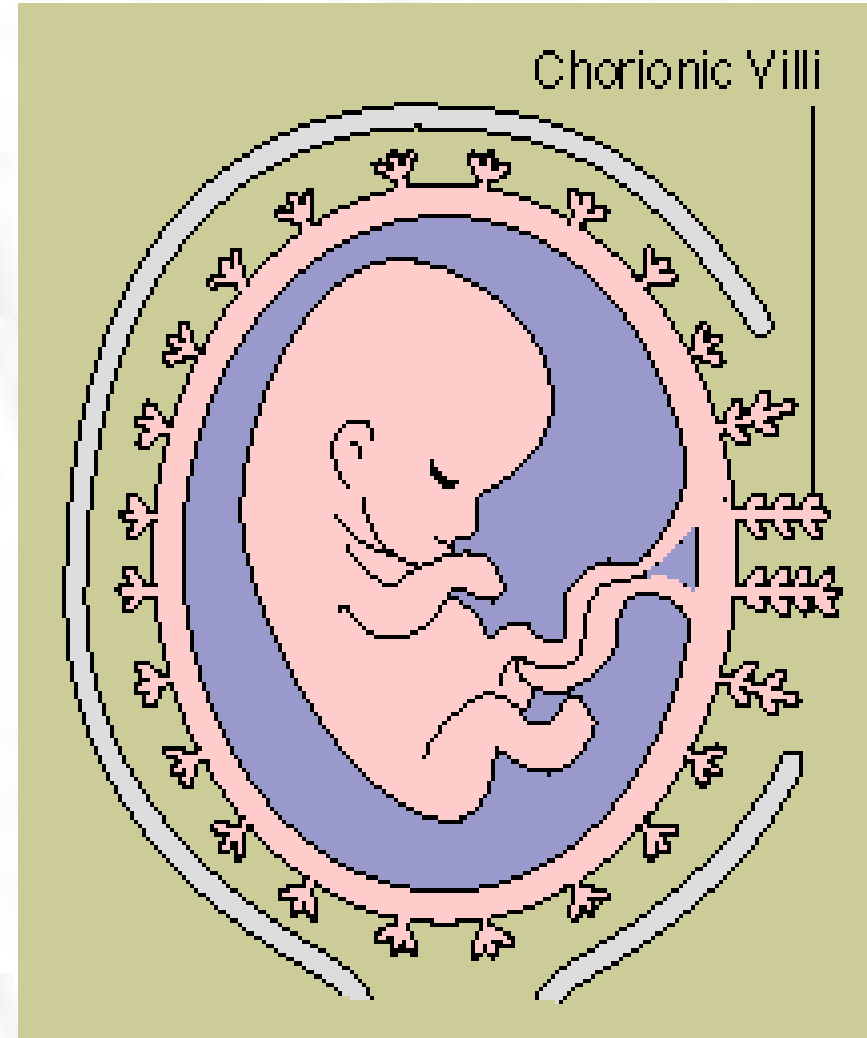
Human Tissue Typing for Organ Transplants



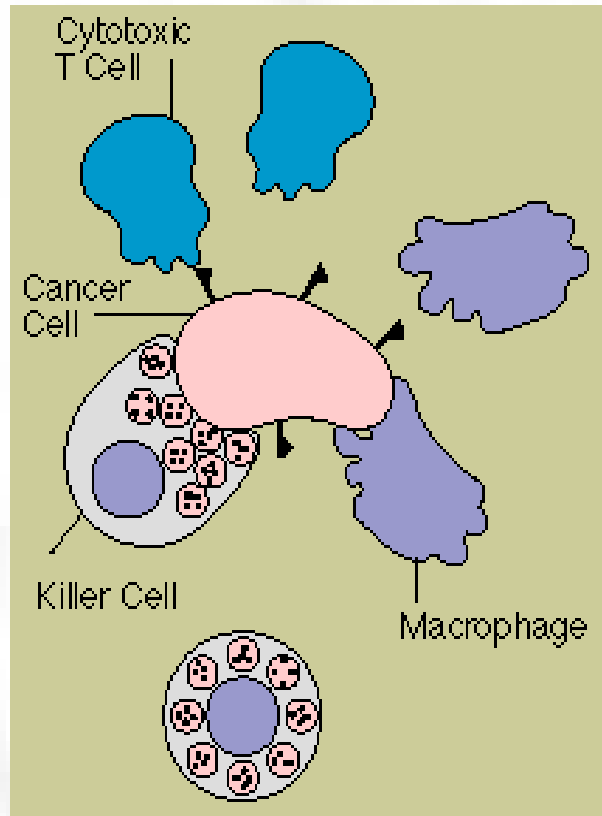
- For an organ transplant to "take," it is necessary to minimize the body's drive to rid itself of foreign tissue.
 - One way is to make sure that the markers of self on the donor's tissue are as similar as possible to those of the recipient.
 - Because tissue typing is usually done on white blood cells, or leukocytes, the markers are referred to as human leukocyte antigens, or HLA.
 - Each cell has a double set of six major antigens, HLA-A, B, and C, and three types of HLA-D.
 - Since each of the antigens exists, in different individuals, in as many as 20 varieties, the number of possible HLA types is about 10,000.

"Privileged" Immunity

- A child in the womb carries foreign antigens from the father as well as immunologically compatible self antigens from the mother.
 - One might expect this condition to trigger a graft rejection
 - does not because the uterus is an "immunologically privileged" site where immune responses are subdued.



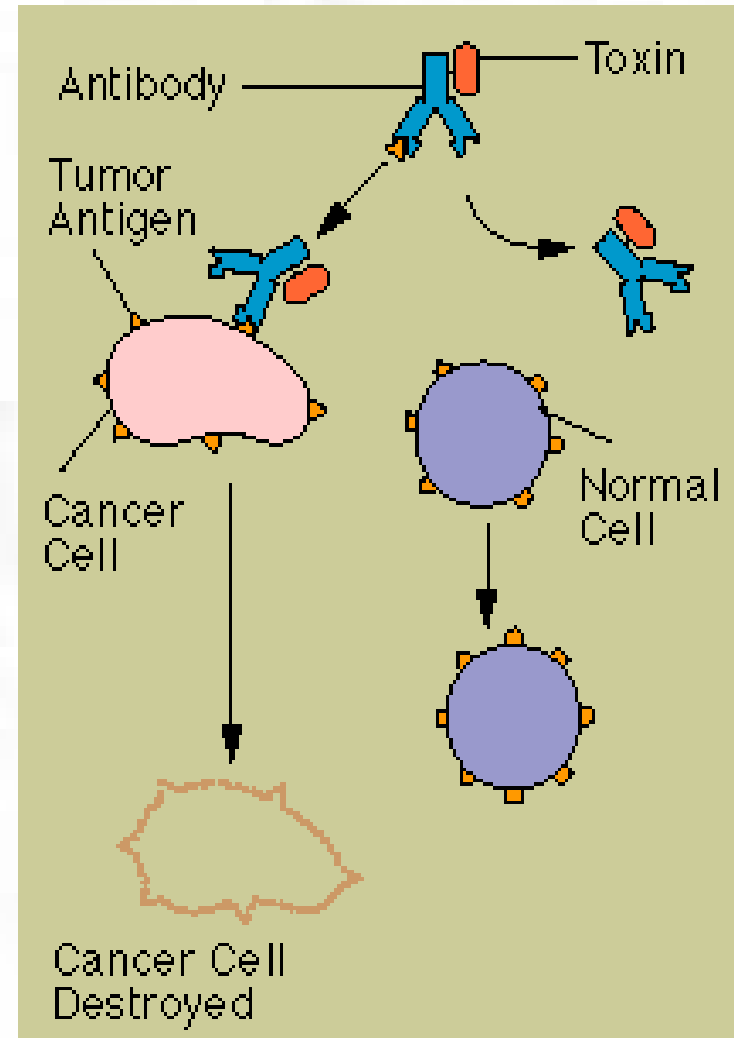
Immunity and Cancer



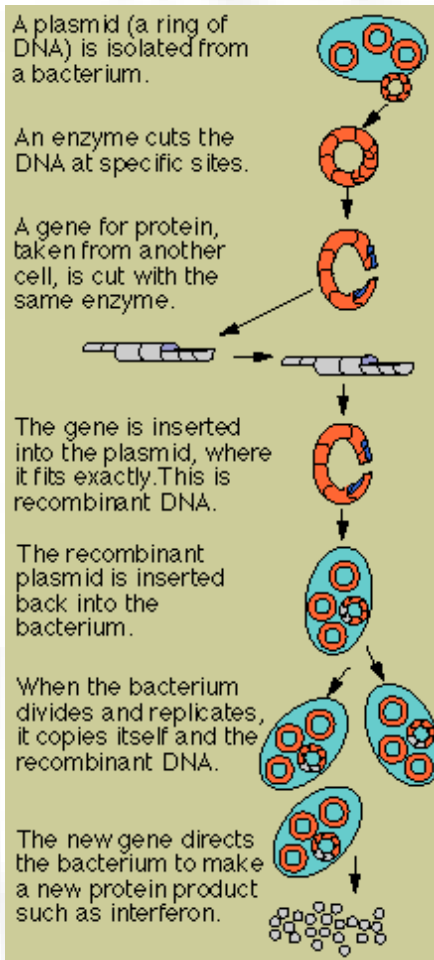
- When normal cells turn into cancer cells, some of the antigens on their surface change.
 - These new or altered antigens flag immune defenders, including cytotoxic T cells, natural killer cells, and macrophages.
 - patrolling cells of the immune system provide continuing bodywide surveillance, spying out and eliminating cells that undergo malignant transformation.
 - Tumors develop when the surveillance system breaks down or is overwhelmed.

Immunotherapy

- A new approach to cancer therapy uses antibodies that have been specially made to recognize specific cancer.
 - When coupled with natural toxins, drugs, or radioactive substances, the antibodies seek out their target cancer cells and deliver their lethal load.
 - Alternatively, toxins can be linked to a lymphokine and routed to cells equipped with receptors for the lymphokine.



Genetic Engineering



- Allows scientists to pluck genes—segments of DNA—from one type of organism and combine them with genes of a second organism.
 - simple organisms such as bacteria or yeast can be induced to make quantities of human proteins, including interferons and interleukins.
 - can also manufacture proteins from infectious agents such as the hepatitis virus or the AIDS virus, for use in vaccines.

Cellular Immunity

- Effects are direct and indirect
 - Leukocyte counts fall with onset of CPBP
 - Leukocyte tissue sequestration increases after anaphylatoxin (C3a and C5a) activation
 - RA leukocyte concentration > LA leukocyte concentration suggesting sequestration in pulmonary vascular bed
 - Leukocyte activation increases elastase and lactoferrin causing tissue injury

Cellular Immunity

- Blood Transfusions exacerbate lymphocyte changes
 - some lymphocyte count/function changed by bld transfusion alone
 - Similar changes in groups with autologous vs.. no transfusion
 - Homologous transfused patients had activated T-cells
 - Lymphopenia, reduced helper T-cells, reversal of helper/suppressor ratio, depressed local graft vs.. host reaction for 6 days post-CPBP
 - Contributes to transmission of human T-cell lymphotropic virus (HTLV) III and HIV post CPBP

Cellular Immunity

- Blood Transfusions exacerbate lymphocyte changes
 - Natural killer cells decrease in number/function after CPBP
 - Hypersensitivity to common antigens increases after CPBP

Cellular immunity with institution

- WBC counts decrease
 - Bubblers > membranes
 - Decrease followed by leukocytosis, appearance of immature WBC's and nucleated red cells
 - Bone marrow stimulation increased

Cellular immunity with termination

- WBC count increase
 - Immunoglobulin and complement remain decreased
 - Increase in mitosis of myelopoietic series
 - Phagocytic function diminished for 15 days post-CPBP

Reticuloendothelial Function

- CPBP produces a form of reticuloendothelial blockade
 - ECC stimulated phagocytic depression
 - Caused by exposure of BOTH plasma proteins and blood cells to ECC
 - Reticuloendothelial system clears circulating blood of bacteria, Hb (free), thrombin, fibrin, etc
 - May return to normal 3 days post ECC

Effects of Anesthesia, Operation, Trauma

- Depression of immune system will occur following surgery even without CPBP
 - Many Steroids / Antibiotics depress immunity
 - Tetracyclines, Chloramphenicol, Clindamycin
 - Streptomycin, Gentamicin, Kanamycin, Neomycin
 - Inhalation Agents are know to depress immunity
 - Halothane, Cyclopropane, Ether, Nitrous oxide
 - Illegitimate drug use, esp. Barbiturates
 - Shock
 - Other blood transfusion