# Immunology

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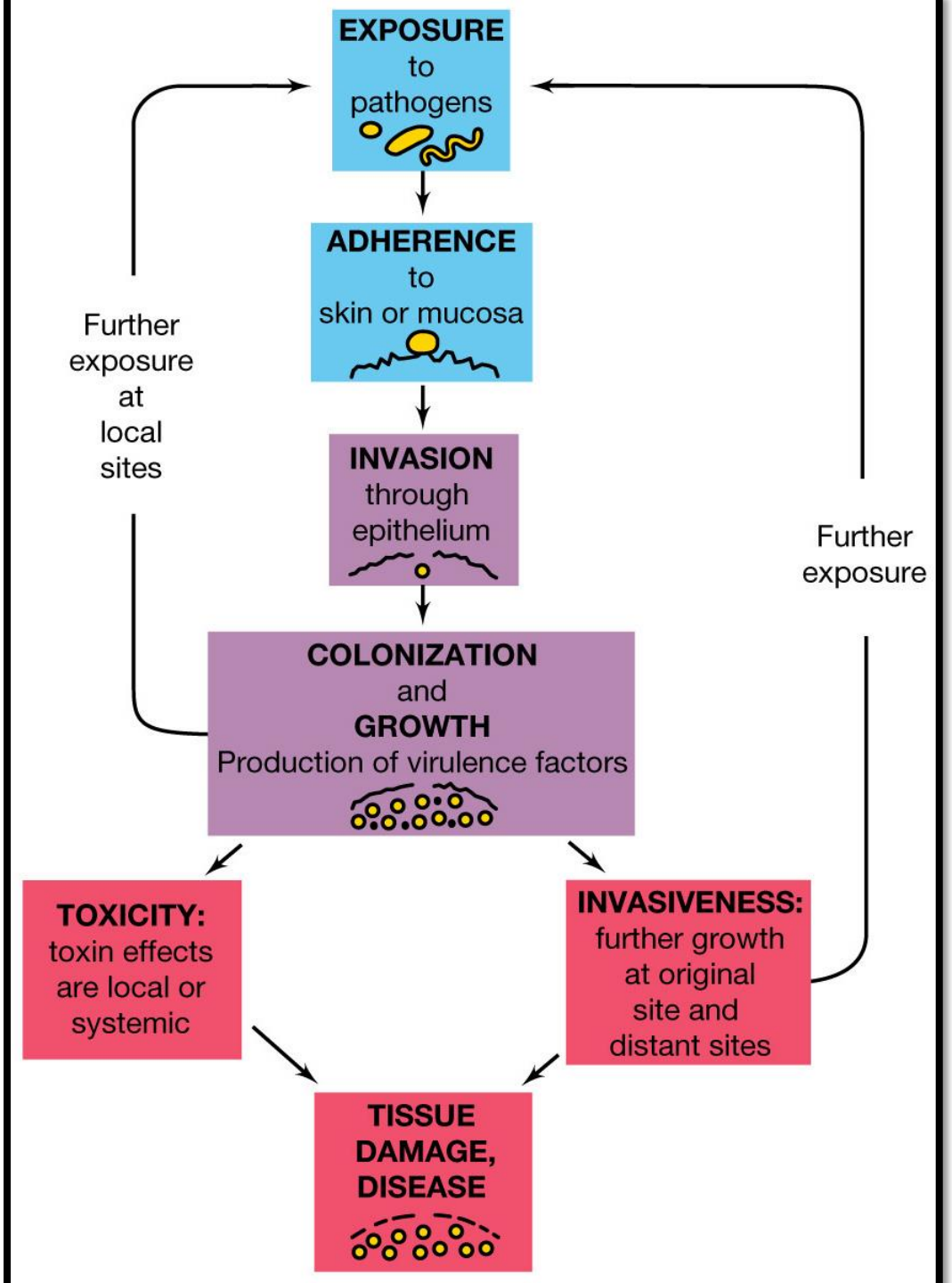
# Immunology

- Introduction and types
- Specific and non specific immunity
- Antigen-antibody reaction and their clinical applications
- Hypersensitivity and allergy
- Drug allergy mechanism

# Immunology

Cells and organs of the Immune System
Nonspecific Immunity
The Specific Immune Response




# Mechanisms for Disease

# Overview of Host Resistance

- To establish an **infection**, the pathogenic microorganism must first overcome many **surface barriers**, such as enzymes and mucus, that are either **directly antimicrobial** or **inhibit attachment** of the microorganism to the host.
- Because neither the **surface of the skin** nor the **mucus-lined body** cavities are ideal environments for many microorganisms, some pathogens must breach these barriers and get to underlying tissues.

- Any microorganism that penetrates these barriers encounters the **two levels of resistance**:
  - **1-Nonspecific resistance mechanisms**
  - **2- Specific immune response**.
- Vertebrates (including humans) are **continuously exposed** to microorganisms and their metabolic products that can cause disease.
- Fortunately these animals are equipped with an **immune system** that protects them against adverse consequences of this exposure.

- The **immune system** is composed of **widely distributed cells**, **tissues**, and **organs** that ***recognize foreign substances*** and ***microorganisms*** and **act to neutralize** or **destroy** them.
- **Immunity** [Latin *immunis*, free of burden] refers to the general ability of a host to resist a particular infection or disease.
- **Immunology** is the science that is concerned with **immune responses to the foreign challenge** and how these responses are used to resist infection.
- It includes the distinction between "**self**" and "**non-self**" and all the biological, chemical, and physical aspects of the immune response.

- There are two fundamentally different types of immune responses to invading microorganisms and foreign material.
- **1-Nonspecific/Innate resistance mechanisms**

  **2-Specific immune response/natural**.
- It offers resistance to any microorganism or foreign material encountered by the vertebrate host.
- It includes general mechanisms inherited as part of the innate structure and function of each animal, and acts as a **first line of defense**.

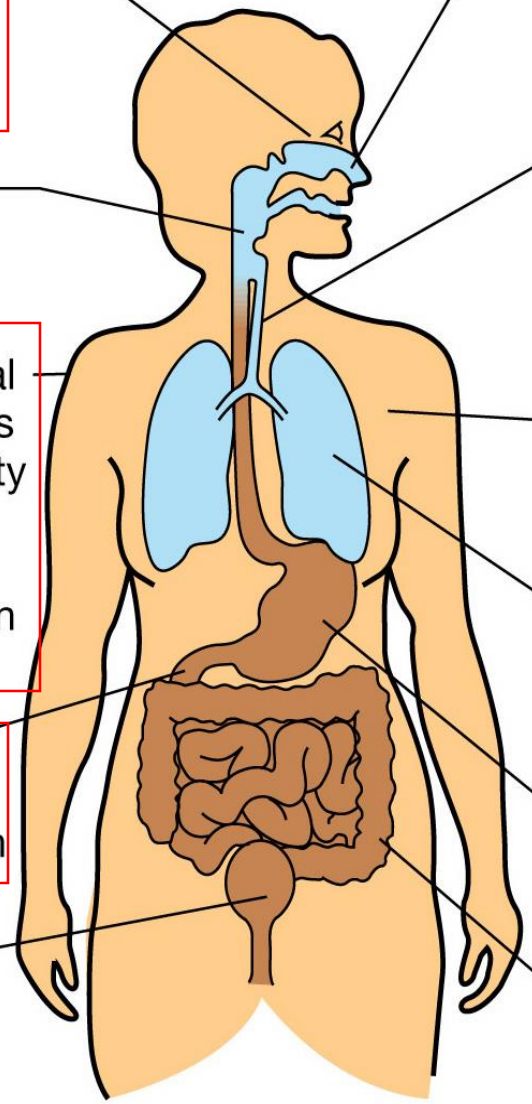
# Nonspecific Innate Resistance to Infection

**First line of host defense** against pathogens

Physical or chemical barriers present in most animals that act NONSPECIFICALLY to inhibit invasion by pathogens.

Prevents almost ALL pathogens we encounter from causing Disease.

# Physical and Chemical Defenses



Lysozyme in tears and other secretions dissolves cell walls

Normal flora compete with pathogens

Skin is a physical barrier, produces antimicrobial fatty acids, and its normal flora inhibits pathogen colonization

Rapid pH change inhibits microbial growth

Flushing of urinary tract prevents colonization

Removal of particles including microorganisms by rapid passage of air over cilia in nasopharynx

Mucus, cilia lining trachea suspend and move microorganisms out of the body

Blood proteins inhibit microbial growth

Mucus and phagocytes in lungs prevent colonization

Stomach acidity (pH 2) inhibits microbial growth

Normal flora compete with pathogens

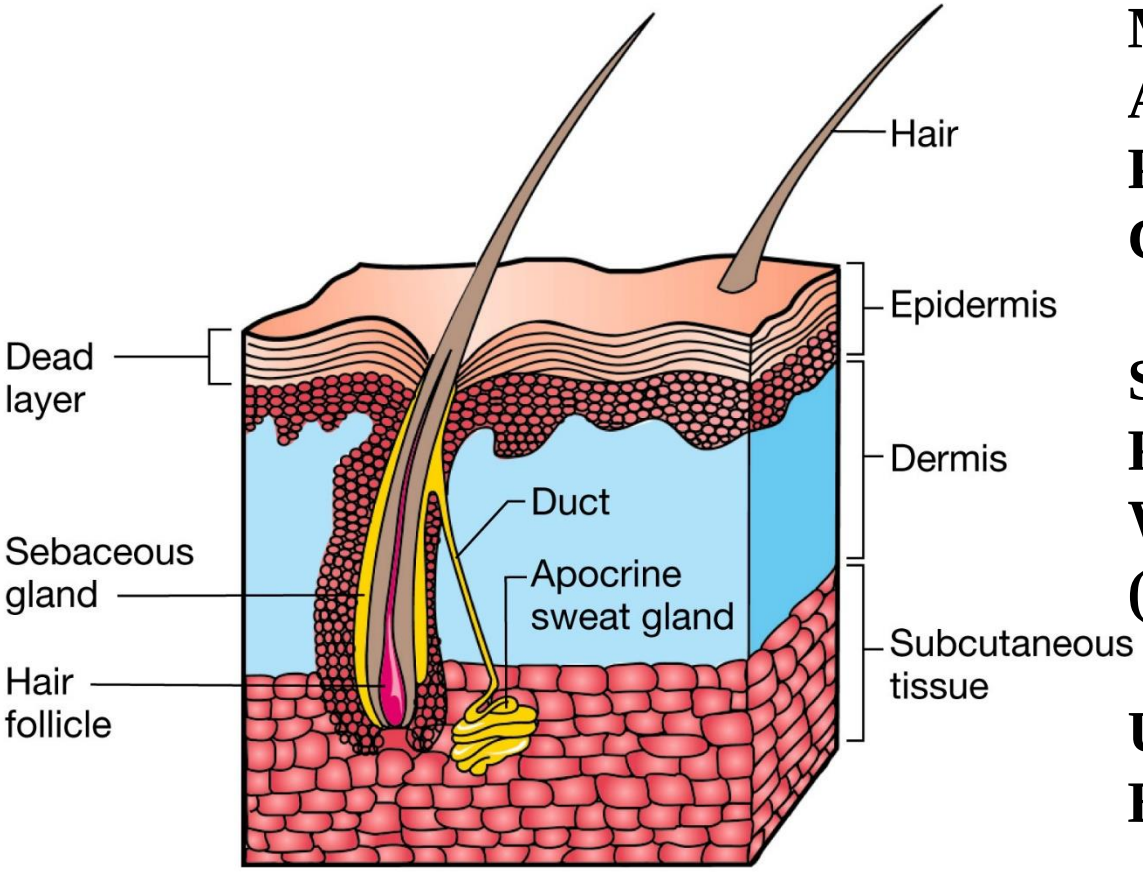
# Physical and Chemical Defenses—The Skin and Mucosal Tissues

**The structural integrity of tissue surfaces—barrier to penetration by microbes.**

**Intact surfaces prevent potential pathogens from adhering to surfaces Growing at these sites such that they do not travel elsewhere in the Body—COLONIZATION.**

**Damaged surfaces—abraded skin are often readily colonized promoting invasion of this and other tissues**

# The Skin




**Microorganisms normally Associated with skin prevent Potential pathogens from Colonizing**

**Sebaceous glands secrete Fatty acids and lactic acid Which lower the skin pH (pH 4-6)**

**Unbroken skin is a contiguous Barrier**

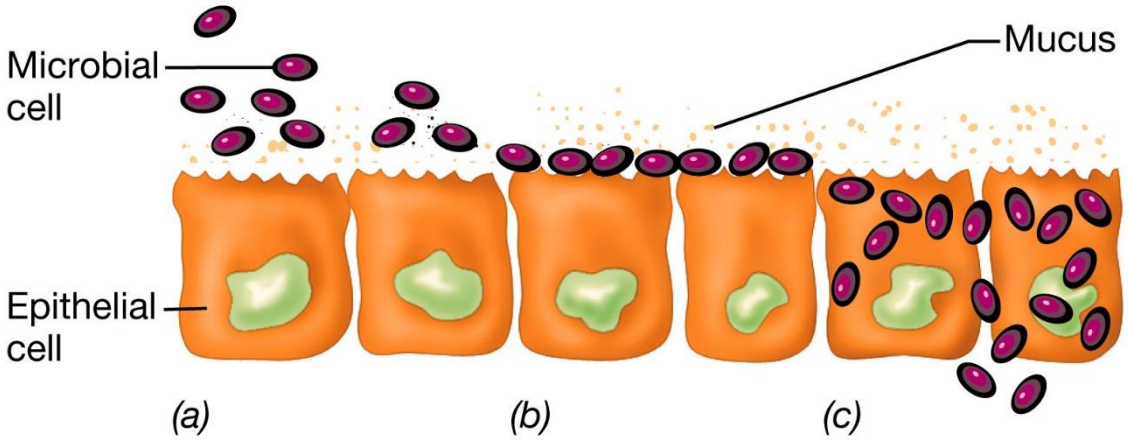
**The skin has a low moisture content**

# Mucosal membranes

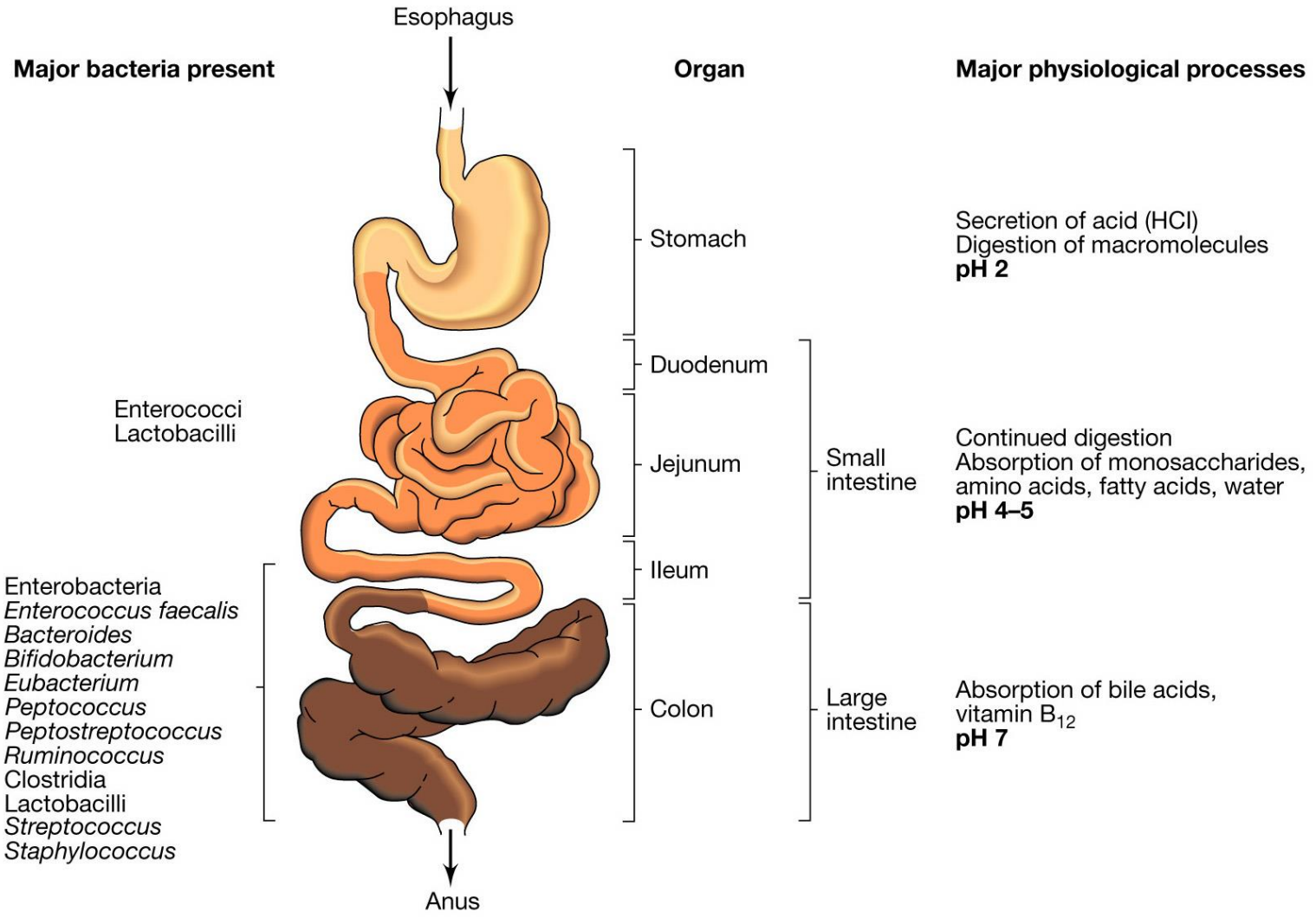
**Ciliated epithelial cells lining the trachea remove microbes inhaled through the nose and mouth.**

**Mucus secreted by these cells prevent the microbes from associating too closely with the cells**

**Cilia push microbes upwards until they are caught in oral secretions and expectorated or swallowed.**



# Normal Flora of the Gastrointestinal Tract



# Potential pathogens in the gastro-intestinal tract

The pH of the stomach is 2.0 which is too low for most pathogens.

Pathogens must compete with the normal flora associated with the small and large intestines. (pH 5 and 7, respectively)

The large intestines normally contain **approx $10^{10}$ bacteria per gram of content**—establishment of pathogens difficult

Microbes have **difficult time adapting to abrupt changes in pH** as they might encounter as they pass through the GIT.

# Lysozyme of the eye and kidney

Lysozyme constantly baths the kidney and the surface of the eye (tears).

(also found with egg whites and the female urogenital tract, and saliva)

Lysozyme breaks the glycosidic bonds between the NAG (N-acetylglucosamine) and NAM (N-acetylmuramic acid) that make up the backbone of peptidoglycan—causing bacteria to lyse**.**

# Extracellular Fluids

**Blood plasma contains bactericidal substances**

**Blood proteins called *beta-lysins* bind to and disrupt the bacterial cytoplasmic membrane-leads to leakage of the cytoplasmic constituents and bacterial cell death**

# Tissue Specificity

**Organisms first adhere and colonize at the FIRST site of exposure**

**If this site is not compatible with their environmental or nutritional needs they die.**

**EXAMPLE: *Clostidium tetani*—tetanus.**

**Ingestion: The organism does not survive the low pH of the stomach**

**Introduced into a deep wound: organism can grow in this anoxic environment that has been created by localized tissue death.**

# Inflammation

**Nonspecific reaction to stimuli such as toxins or pathogens.**

**Mediated by a subgroup of leukocytes (white blood cells) that produce cytokines that lead to fibrin clots at the site of inflammation.**

**The inflammatory response results in redness, swelling, heat and pain at the site of the infection**

**Most important outcome is the immobilization of the pathogen at the site of inflammation**

**Physical manifestations: Abscess—localized collection of pus surrounded By a wall of inflammatory tissue (surface localized)**
**Boils—abscesses located in the deeper layers of the skin**
**Ulcers—localized area of necrosis of the epithelial cells**

# When inflammation goes bad

Inflammation can aid in host pathogenesis since the inflammatory response can lead to damage of the host cells and tissues—creating a favorable environment for the invasion of a potential pathogen
(making nutrients available providing access to host tissues) some bacteria elicit an inflammatory response for that purpose!

Septic Shock Syndrome:: Uncontrolled systemic inflammatory responses causes severe swelling and fever—occurs when the infections and Inflammatory responses are not localized to one site

# Fever

**Normal body temperature is 37 degrees Celsius**

**Abnormal increase in the body temperature—usually caused by infectious agents**

**Certain products of pathogenic bacteria can be pyrogenic—**
**EXAMPLE:**
**Endotoxin (LPS) from gram-negative bacteria.**
**Some bacteria cause the release of endogenous pyrogens from the WBCs that kill them.**

**Slight temperature increases, boost the immune system by increasing The activity of phagocytic cells and antibody responses to pathogens.**

**Strong fevers (40 degrees Celsius) harm the host by damaging host tissues**

# The Compromised Host—hosts in which one or more resistance mechanisms are inactive increasing the probability of infections

**Hospital patients with noninfectious diseases acquire infections through invasive procedures—catheterization, biopsy, surgery, hypodermic injection etc. Nosocomial infections—hospital acquired**

**Stress and prolonged exertion—production of hormones like cortisone that is an effective anti-inflammatory agent**

**Diets low in protein alter the composition of the normal flora thus allowing opportunistic pathogens a chance to colonize**

**Smoking—destroys or immobilizes cilia associated with the nasopharyngeal and tracheal regions.**

# Overview of the Immune Response

**IMMUNITY—The ability of a host to resist infection**

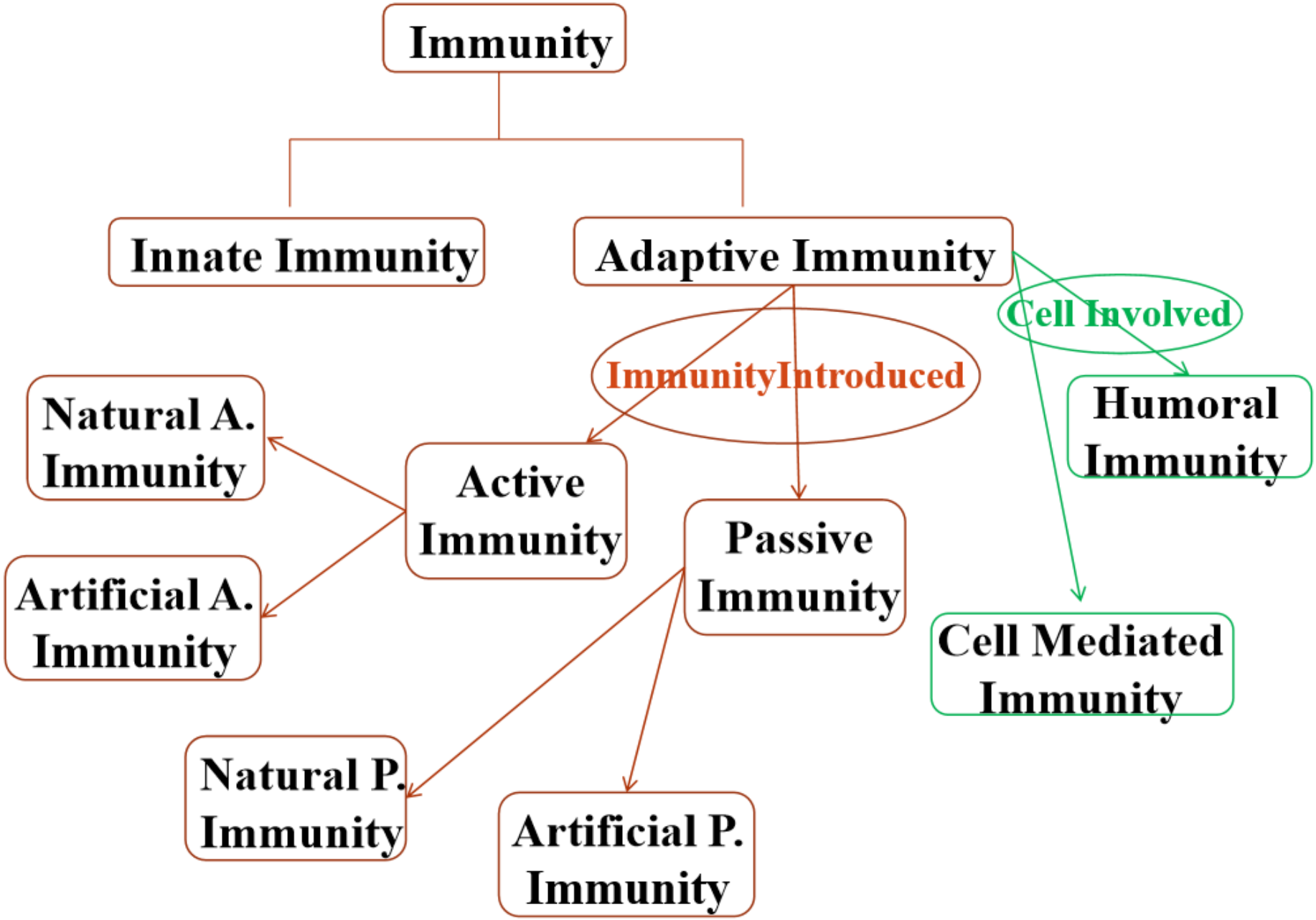
**Nonspecific immunity**

- **Body's INNATE ability to resist infections**
- **Phagocytes—cells that engulf, digest and destroy pathogens**

**THIS IS SOMETIMES NOT ENOUGH!!!**

**Specific Immunity—ACQUIRED ability to recognize and destroy an individual pathogen and its products**

# Types of Immunity



# Specific/Adaptive Immunity

- It is an **acquired resistance of the body** against infections.
- Immunity acquired or **adapted during life time** of an individual is termed as acquired immunity.
- It involves the formation of antibodies (Protein based substances produced from the body in response to specific foreign particles / antigens) as a result of stimulation by foreign particles; called antigens (Substances when introduced (artificially or naturally) inside body result in the production of antibodies).
- In acquired immunity, specific antibodies produced against specific antigens and thus provides specific resistance hence termed as specific immunity.

# Comparison of Innate and Adaptive Immunity

| Innate Immunity | Adaptive Immunity |
| --- | --- |
| • Antigen independent | • Antigen dependent |
| • No time lag | • A lag period |
| • Not specificity | • Antigen specific |
| • No Immunological memory | • Development of memory |
| • Various secretions | • Only antibodies |
| • Various types of cells | • B and T lymphocytes |

# Collaboration between innate and adaptive immune system

- Two systems do not work independently
- Function in a highly interactive way
- Combined responses are more effective
- Molecular events are common

- Example
  - 1. Encounter between macrophages and microbes
  - 2. Cytokines are released
  - 3. Cytokines react with receptors on cells
  - 4. Signaling for synthesis of new factors or to undergo differentiation

- Specially the adaptive immune system is dependent on innate immunity for knowing when to respond how to respond and for how long should respond.

- Innate Immune system call (informs) adaptive system and also tells them the nature of the antigen (antigen presentation).

# The Specific Immune Response

# Overview of the immune response

**Pathogens and their disease causing by-products are eradicated by three mechanisms.**

**Nonspecific Immunity—physical and chemical barriers including the action of phagocytic cells**

**Antibody Mediated Immunity (Humoral Immunity)—free circulating antibodies found in the blood and lymph fluids that are effective against viruses, bacteria and toxins**

**Cell Mediated Immunity—leads to killing by cells through the recognition of antigens that are present on pathogen infected cells**

# Specific Immunity (as well as non-specific immunity) results from the actions of cells present in the blood and lymph

Of the blood –most cells present are the non-nucleated red blood cells ---Lymph is distinguished from blood in that it does NOT contain red blood cells.

0.1% of the cells found in blood are the nucleated leukocytes (WBCs).
Lymph is composed entirely of leukocytes.

Stem cells are the precursors to all of these cells (an undifferentiated cell of a multicellular organism which is capable of giving rise to indefinitely more cells of the same type, and from which certain other kinds of cell arise by differentiation.)

# Stem Cells-Progenitors of cells involved in the immune response

**Stem cells are found in the bone marrow of the host**

**Cytokines (**a number of substances, such as interferon, interleukin, and growth factors, which are secreted by certain cells of the immune system and have an effect on other cells.**)** cause stem cells to develop into immune cells, stem cells develop into two classes of leukocytes**:**

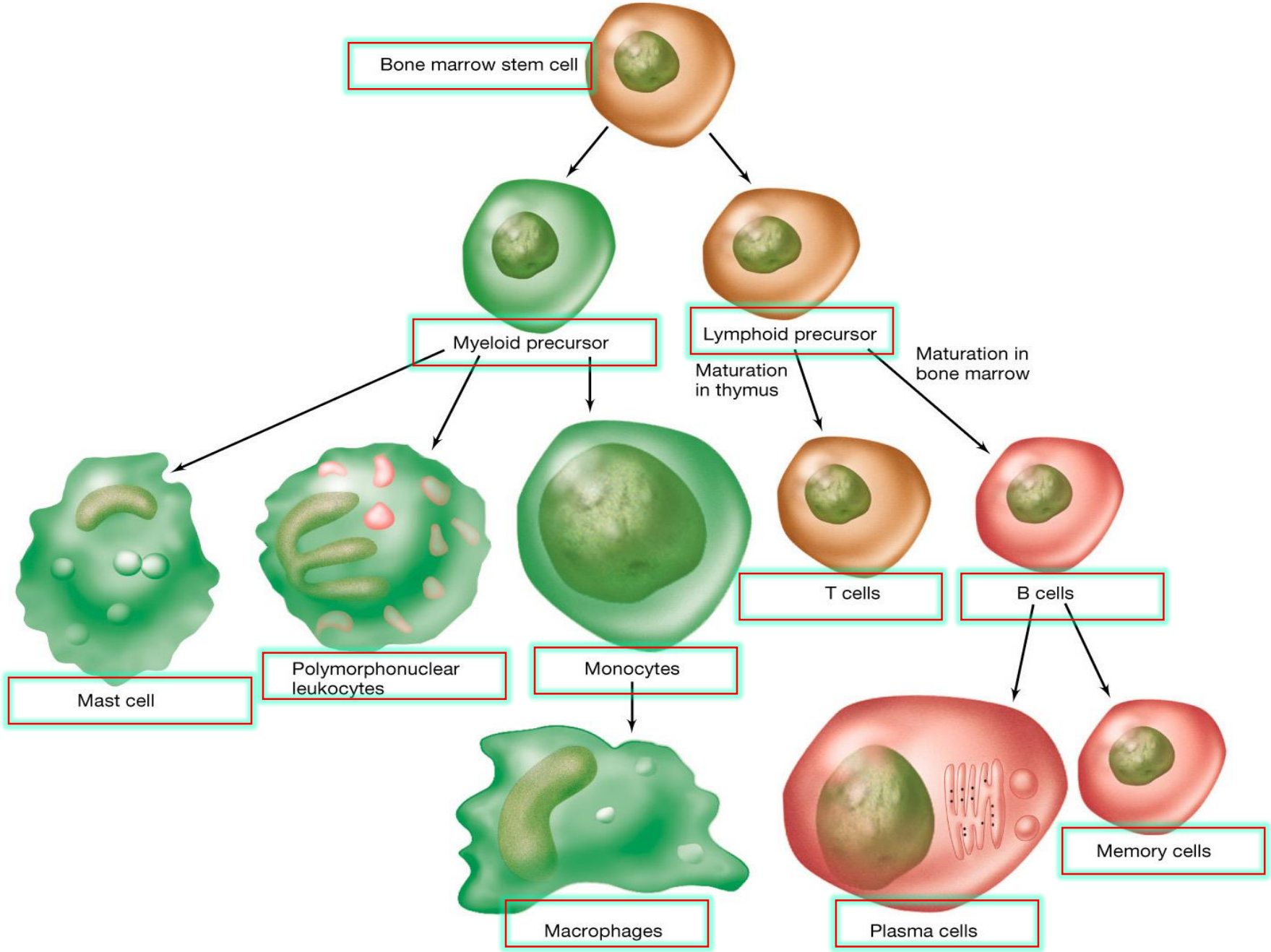
1. **monocytes**→ phagocytic cells which develop from **a myeloid precursor**

2. **specialized lymphocytes** that are involved in antibody production and cell mediated killing of pathogens these develop from a **lymphoid precursor**

**B-cells**- produce antibodies & continue to differentiate and mature in the **bone marrow (B cells**, also known as **B** lymphocytes, are a type of white blood **cell** of the lymphocyte subtype. They function in the humoral immunity component of the adaptive immune system by secreting antibodies**).**

**T-cells**- mediate killing and differentiate and mature in the **thymus. (**A **T cell**, or **T** lymphocyte, is a type of lymphocyte (a subtype of white blood **cell**) that plays a central role in **cell**-mediated immunity. **T cells** can be distinguished from other lymphocytes, such as B **cells** and natural killer **cells**, by the presence of a **T-cell** receptor on the **cell** surface.)

# Development of cells involved in the immune response



# Myeloid Precursor

- The term ***myeloid*** is an adjective that in its broadest sense means either "resembling bone marrow" or "pertaining to bone marrow", and the related adjective ***myelogenous*** means "arising from bone marrow". In hematopoiesis, both terms refer to blood cells that arise from a progenitor cell for granulocytes, monocytes, erythrocytes, or platelets although all blood cells, even lymphocytes, are born in the bone marrow, *myeloid* cells in the narrowest sense of the term can be distinguished from lymphoid cells, that is, lymphocytes, which come from common lymphoid progenitor cells (CLPs) that give rise to B cells and T cells.

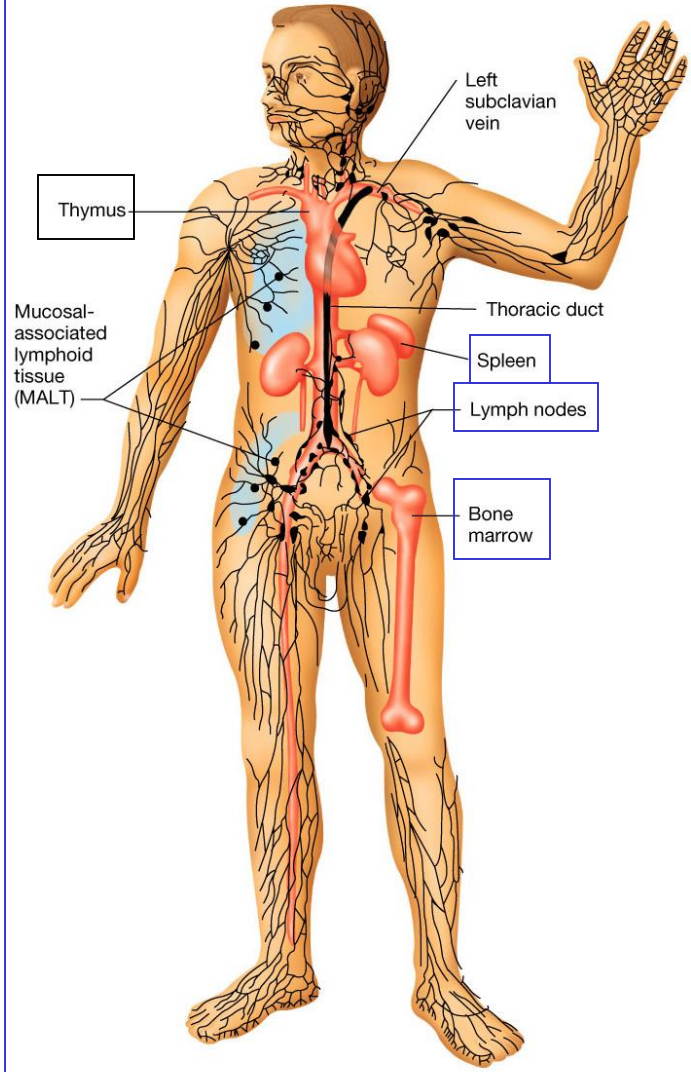
- Those cells' differentiation (that is, lymphopoiesis) is not complete until they migrate to lymphatic organs such as the spleen and thymus for programming by antigen challenge. Thus, among leukocytes, the term *myeloid* is associated with the innate immune system, in contrast to *lymphoid*, which is associated with the adaptive immune system. Similarly, *myelogenous* usually refers to nonlymphocytic white blood cells, and *erythroid* can often be used to distinguish "erythrocyte-related" from that sense of *myeloid* and from *lymphoid*. The word *myelopoiesis* has several senses in a way that parallels those of *myeloid*, and myelopoiesis in the narrower sense is the regulated formation specifically of myeloid leukocytes (myelocytes), allowing that sense of *myelopoiesis* to be contradistinguished from erythropoiesis and lymphopoiesis (even though all blood cells are produced in the marrow).

- Myeloid neoplasms always concern bone marrow and are related to hematopoietic cells.

# Lymphoid Precursor

- **Lymphopoiesis** (or **lymphocytopoiesis**) is the generation of lymphocytes, one of the five types of white blood cell (WBC). It is more formally known as lymphoid hematopoiesis.
- Pathosis in lymphopoiesis leads to any of various lymphoproliferative disorders, such as the lymphomas and lymphoid leukemias.

# The blood and lymph systems




**Overall view of the lymph system, showing the locations of major organs**

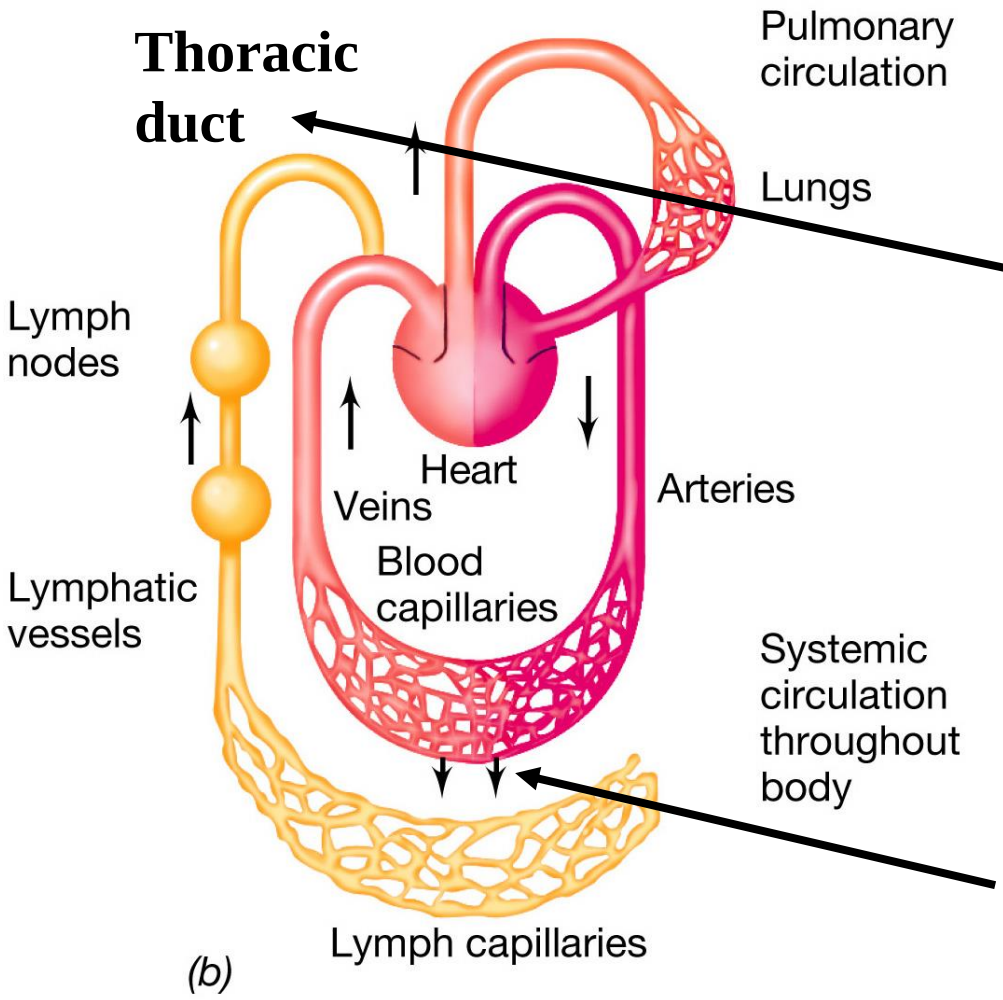
**The circulatory system is the means by which cells of the immune system directly or indirectly interact with all of the cells of the body**

**Lymph nodes: contain high concentrations of leukocytes that filter out microbes and toxins**

**Spleen of the blood circulatory system has the same function as the lymph nodes**

***lymph nodes and spleen can sometimes become infected by the organisms that have been collected during filtration***

# Overview of blood and lymph system and how leukocytes travel from one system to another

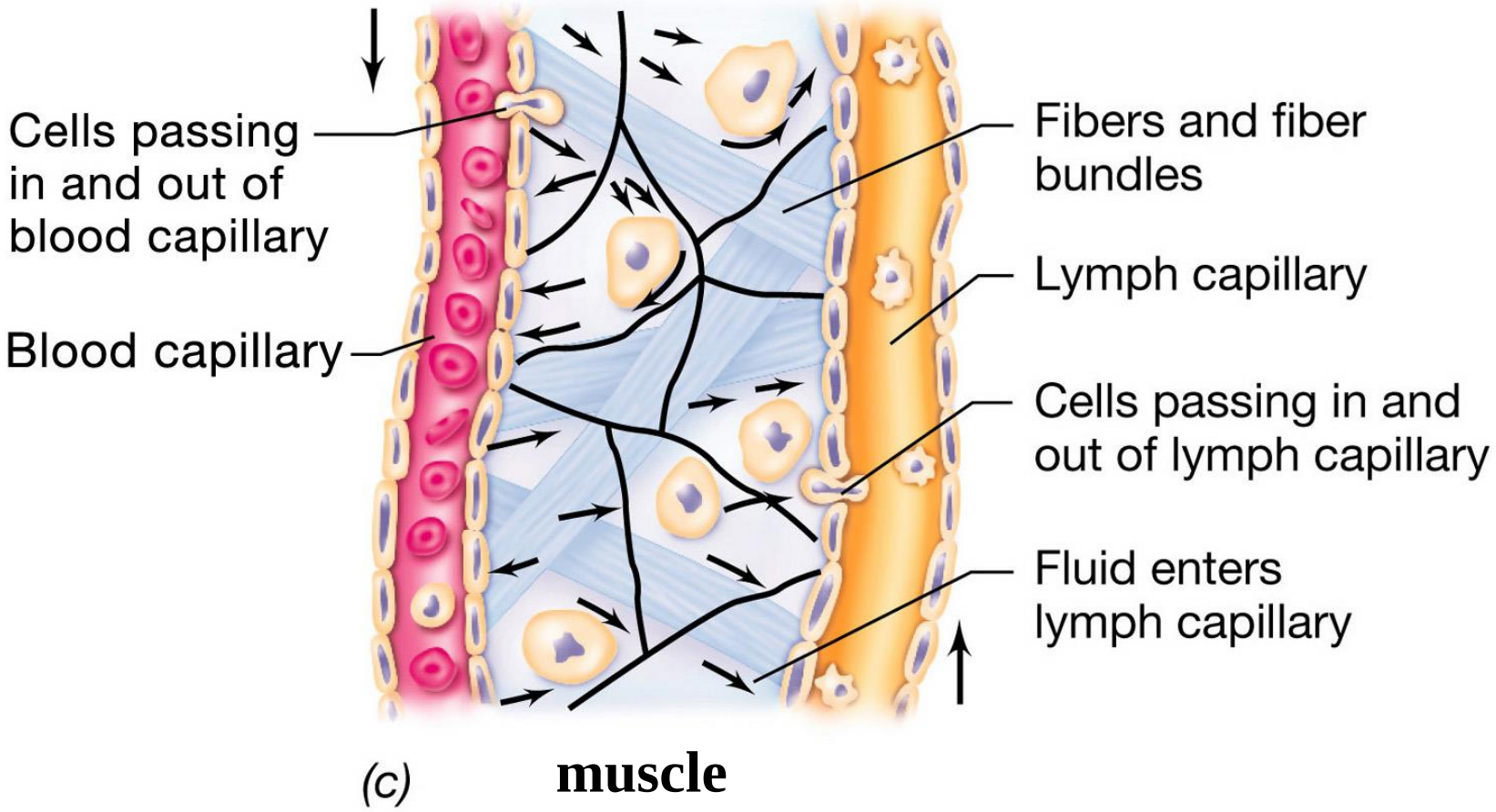



**Lymph carrying antibodies and immune cells collect in thoracic duct where the lymph empties back into the blood circulatory system**

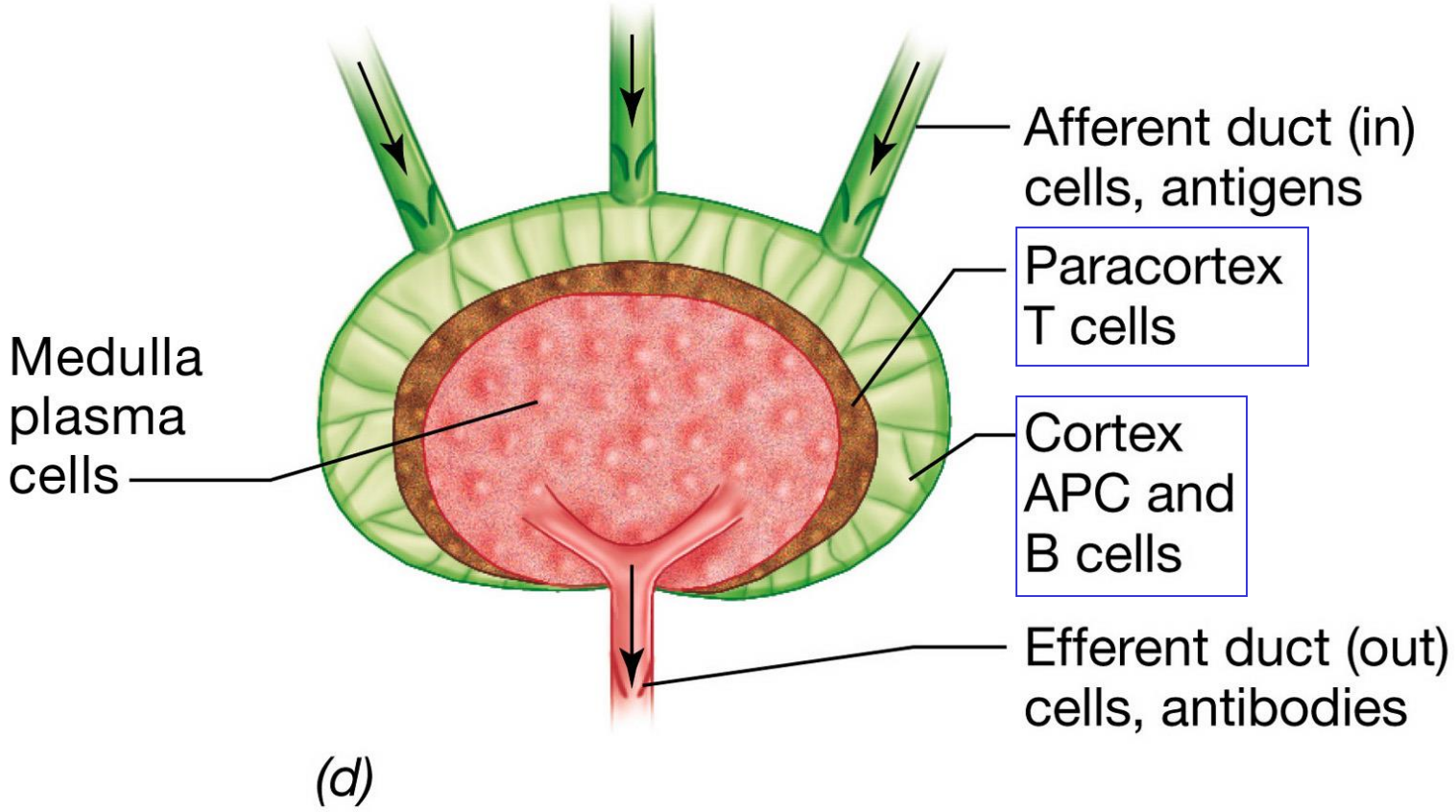
**Site of exchange between the blood and lymph systems**

**Immune cells travel back and forth from the blood and lymph circulatory systems and interact with extra-vascular tissues in the process--**

**extravasation**



**A lymph node:Antigens (proteins produced by pathogens and cells enter through the afferent duct and cells and antibodies to these antigens exit through the efferent duct**



# AIDS and T-cells

**AIDS (Acquired Immuno-Deficiency Syndrome is caused by HIV (Human Immunodeficiency Virus)**

**AIDS victims suffer because HIV has destroyed their CD4 T lymphocytes**

**AIDS patients are unable to mount an effective immune response to pathogens**

**Death is usually due to an infectious agent**

# Indications for AIDS

**Patient have opportunistic infections: Infections that are rarely observed in individuals with normal immune systems**

**Patients**

**Test positive for HIV**
**Have a CD4 T-cell number of less than 200/mm3 (normal is 600/mm3)**
**Acquire infections that are not normally found in healthy individuals**

- ***Pneumocystis carinii*—pneumonia**
- **Kaposi's sarcoma –atypical cancer of the cells lining blood vessels (purple patches on skin) caused by herpesvirus 8**
- **A number of fungal diseases**
- **recurrent *Salmonella* mediated septicemia**

# The AIDS epidemic

**First cases diagnosed and reported in the US in 1981**

**2000: Approximately 800, 000 cases have been reported in the US with 450,000 deaths**

**1981-2000: 56 million individuals have been diagnosed with HIV worldwide—20 million have died from AIDS**

**North America has approx. 1 million infected individuals**

**Sub-Saharan Africa has 25 million infected individuals**

**In Botswana 36% of the adult population are infected**
**3 million individuals die annually—mostly in developing countries**

# Antigens, T Cells and Cellular Immunity

# B cells and Humoral Immunity

# Antigens, T Cells and Cellular Immunity

**Antigen specific T cells are the first cells to specifically recognize antigen.**

**Activated T-cells are involved in a number of antigen specific reactions**

- **cell mediated killing**
- **inflammatory responses**
- **T helper cells "help" B-cells produce antibodies**

***Without T cells there is NO EFFECTIVE ANTIGEN SPECIFIC IMMUNITY!!!***

# Presentation of Antigen to T lymphocytes

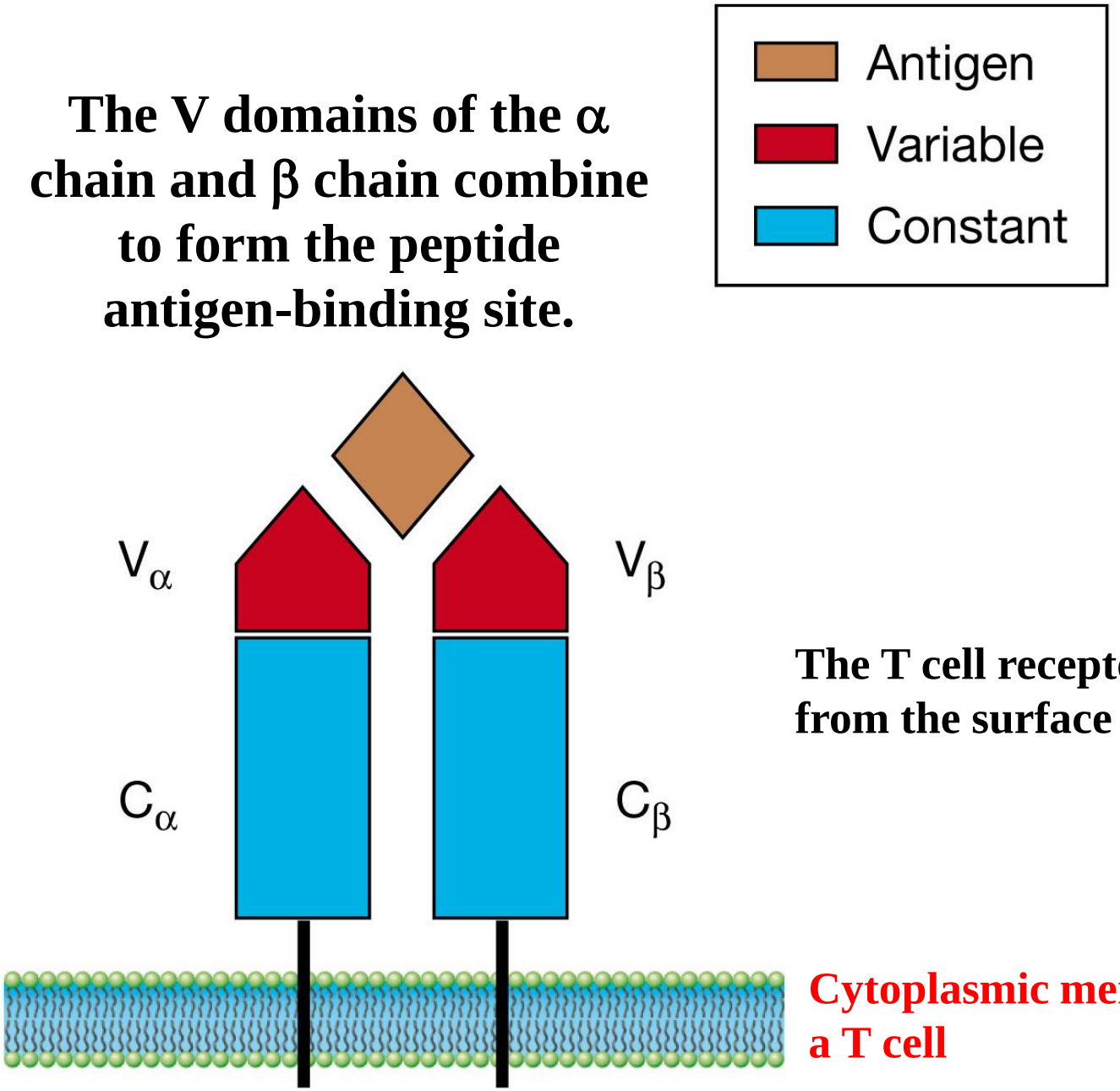
**T cells interact SPECIFICALLY with antigen through T cell receptors (TCR).**

**TCRs on T cells interact with antigens that are held in place on the surface of antigen presenting cells (APC) by major histocompatibility complex proteins (MHC).**

**The MHC complex proteins are encoded on chromosome 6 in humans and is more than 4 million base pairs in length.**

# Structure of the T-cell receptor (TCR)

**The V domains of the α chain and β chain combine to form the peptide antigen-binding site.**




**The T cell receptor extends from the surface of a T cell**

**Cytoplasmic membrane of a T cell**

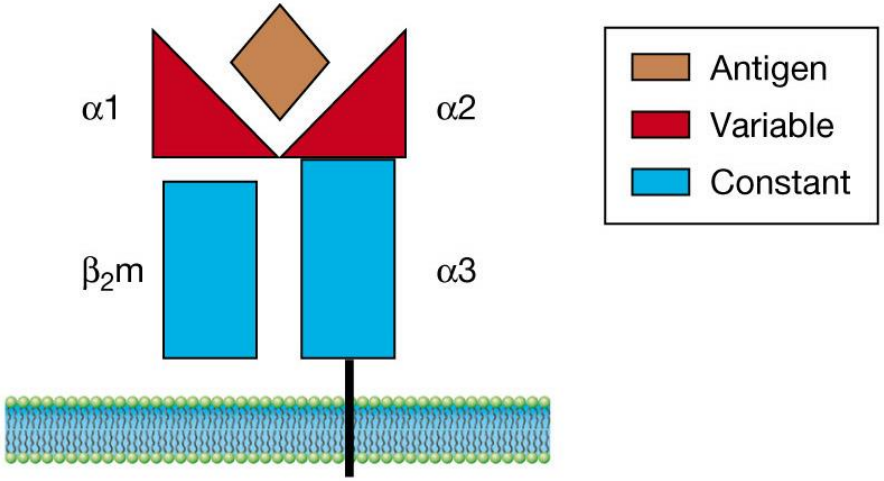
# The T cell receptor

**Each T cell has thousands of copies of the SAME TCR on its surface**

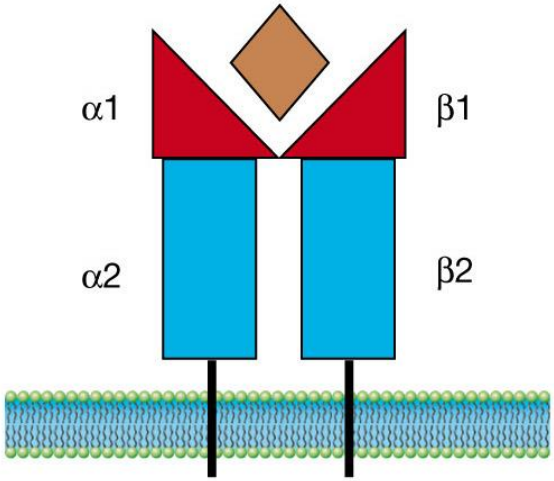
**The immune system can generate TCRs that will bind nearly every known peptide antigen**

**The TCR can only recognize and bind a peptide antigen if the antigen is bound first to "self" proteins known as MHC proteins**

# Major Histocompatibility complex proteins are found on the surface of cells: T cells cannot recognize foreign antigens unless they are associated with these MHC proteins




(a)



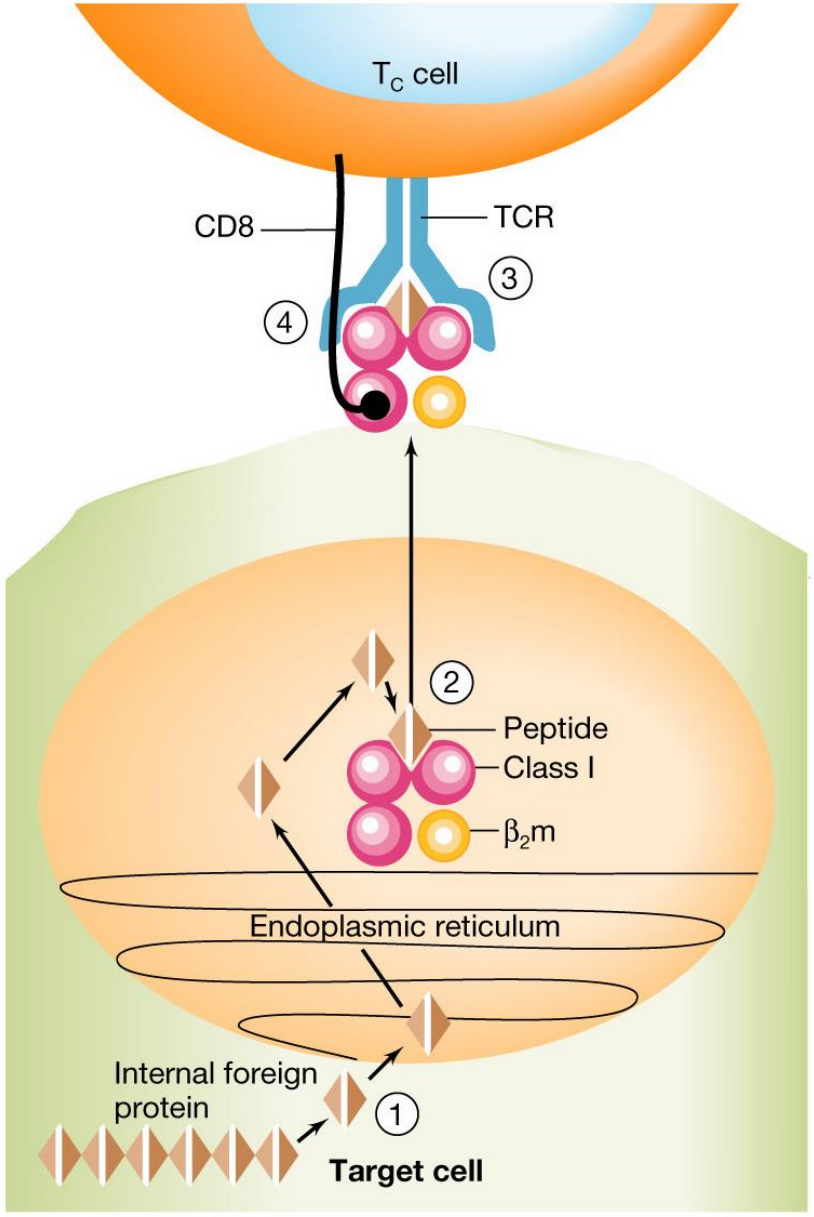

(b)

**Class I MHC proteins are found on the surface of ALL nucleated cells**

**Class II MHC proteins are only found on the surface of B lymphocytes, macrophages and other antigen presenting cells**

**ALL MHC proteins are imbedded in the cytoplasmic membrane of cells and project outward from the cell surface**

# Class I MHC proteins and cytotoxic T cells (Tc)

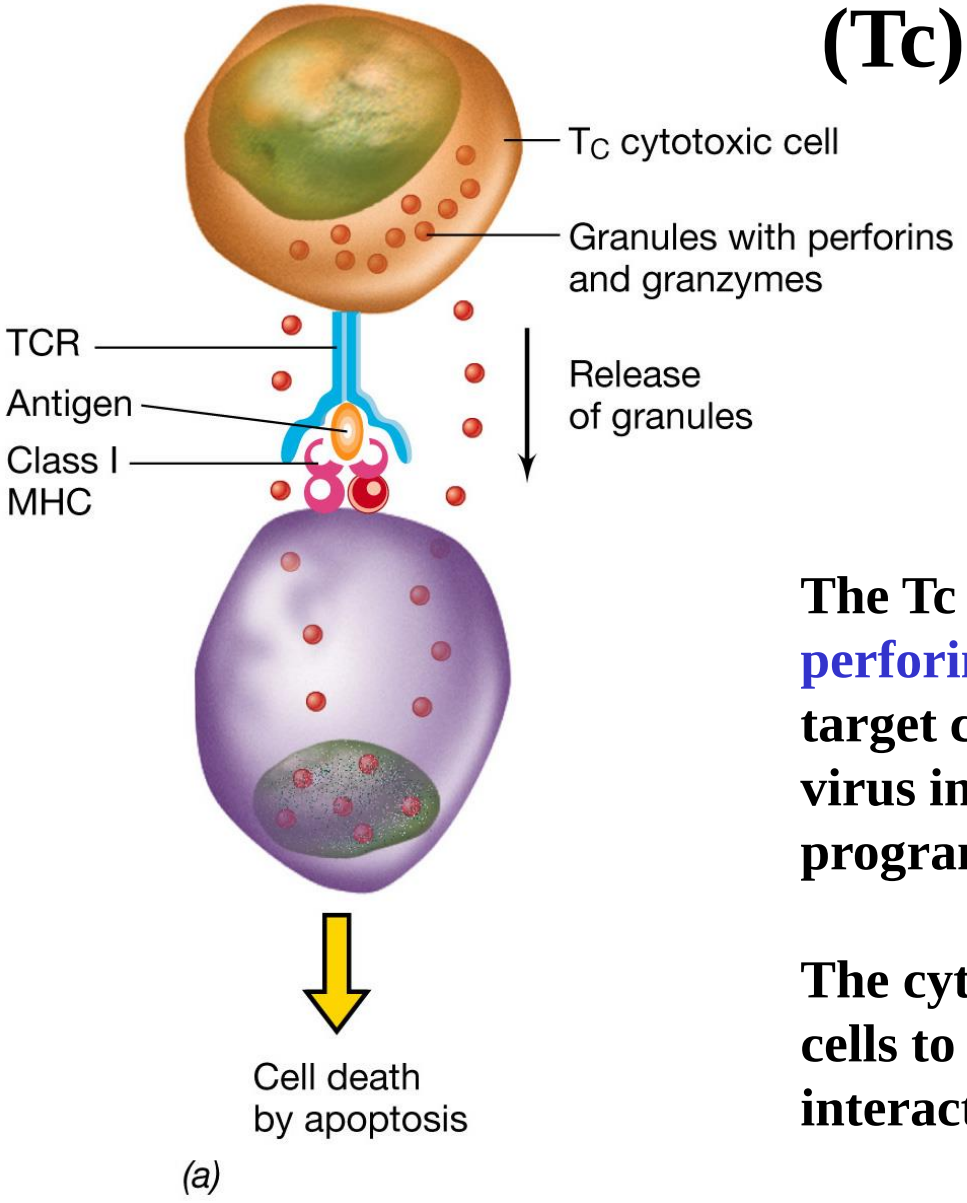



(a)

**Class I pathway is useful in destroying cells that have been infected by viruses or have been transformed by tumors**

1. **Protein antigens manufactured in the cell by viruses or tumors are degraded in the cytoplasm and transported to the endoplasmic reticulum**
2. **The processed antigens bind to Class I MHCs and are transported to the cell surface**
3. **Together this complex interacts with the TCR of a Tc cell, the binding of the complex with the TCR is strengthened by a CD8 co-receptor**

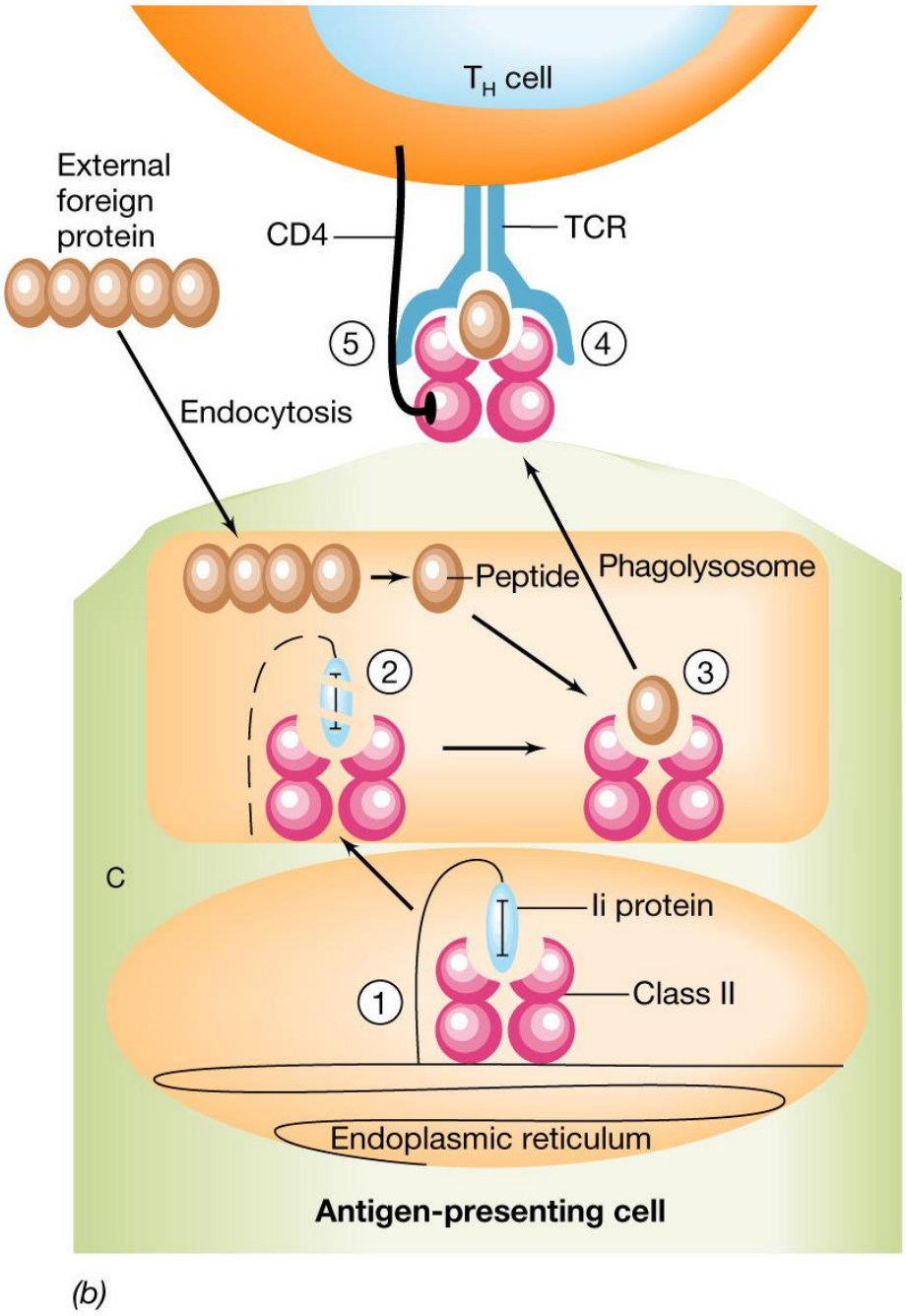
# Class I MHC proteins and cytotoxic T cells (Tc)




**The cell-cell interaction between the infected cell and the Tc cell is mediated by the MHC/antigen complex and TCR**

**The Tc cell produces cytotoxic proteins perforins—produce holes or pores in the target cell and granzymes enter the virus infected cell causing apoptosis or programmed cell death**

**The cytotoxic proteins only affect those cells to which the Tc cell has specifically interacted**




(b)

# Class II MHC proteins and helper T cells ($T_H$)

**The Class II proteins and antigen are expressed on B cells, APCs and macrophages**

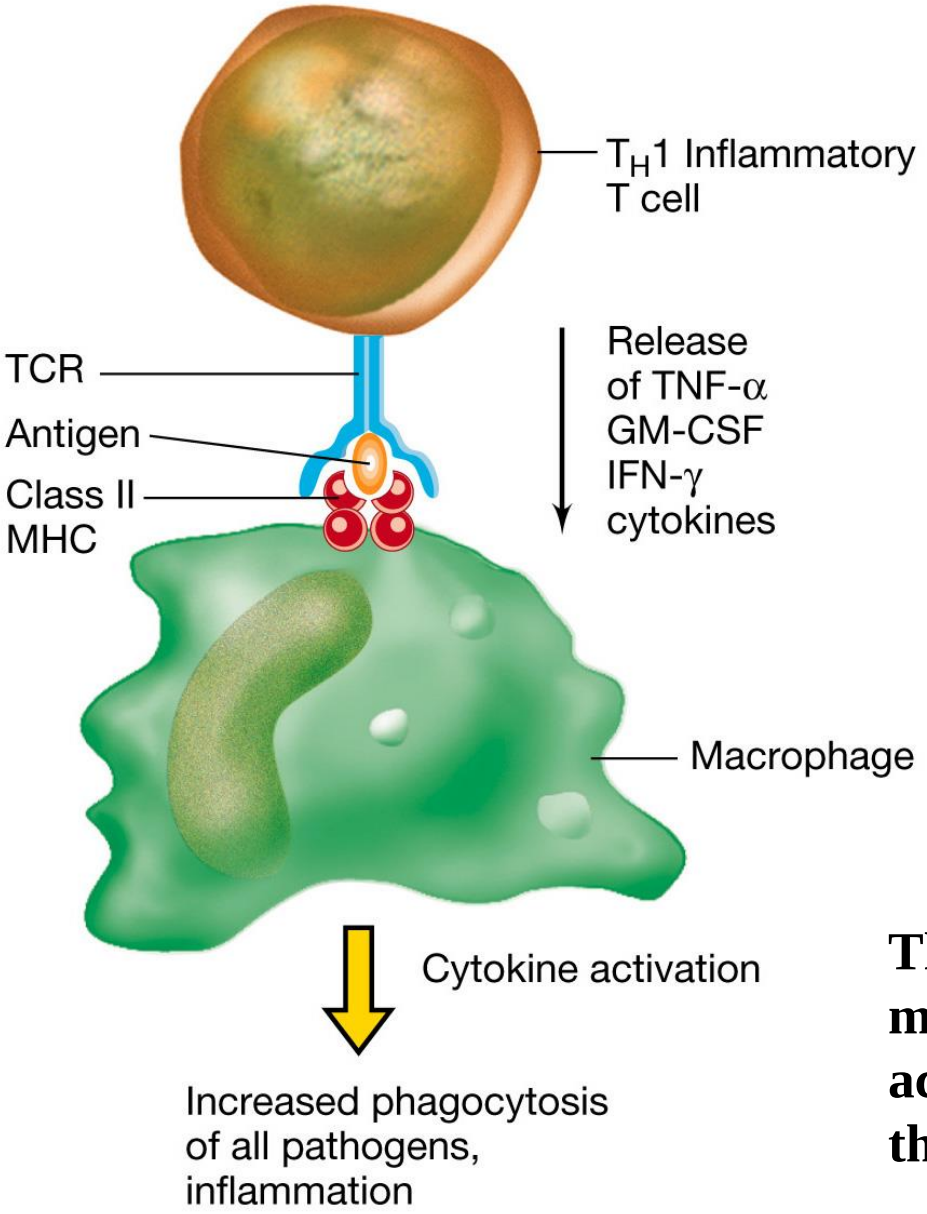
**1. The APC takes up an external foreign protein via phagocytosis or endocytosis**

**2. Class II proteins are produced in the endoplasmic reticulum and assembled with a blocking protein (Ii) or invarient chain**

**3. The Class II proteins enter the phagolysosome where the Ii is degraded and the partially processed antigen binds to the class II molecule**

**4. The complex is translocated to the surface of the APC where it interacts with the TCR of a T helper cell**

# Class II MHC proteins and helper T cells ($T_H$)




**Specialized $T_H$ cell involved in the inflammatory response**

**Cell-cell interaction mediated by the TCR and the class II MHC-antigen complex activates The $T_H$ cell which produces**

**cytokines**

**TNF-alpha (tumor necrosis factor)**

**IFN-gamma (interferon)**

**GM-CSF (granulocyte-monocyte colony stimulating factor)**

**These cytokines further stimulate macrophages to increase phagocytic activity and to in turn produce cytokines that promote inflammation**

# Class II MHC proteins, helper T cells ($T_H$ inflammatory T cells) and activated macrophages

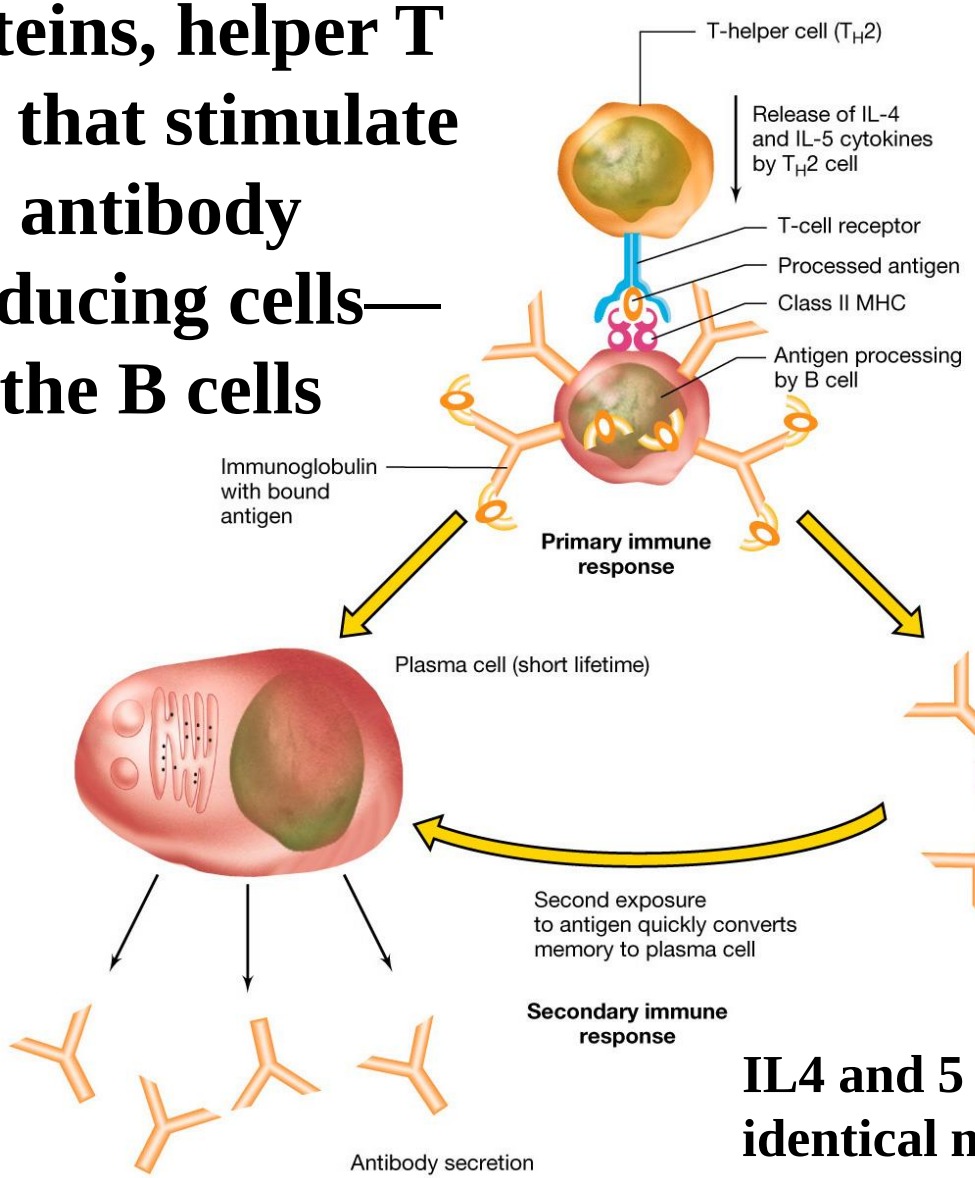
**Particularly useful in eradicating pathogenic bacteria**

**Activated macrophages can kill intracellular pathogens that would normally divide in a non-activated macrophage**

***Mycobacterium leprae, Mycobacterium tuberculosis* and *Listeria monocytogenes*.**

**Activated macrophages also kill foreign mammalian cells (tissue transplantation) and in some cases tumor cells (have specific antigens that are not found on normal cells)**

# Class II MHC proteins, helper T cells that stimulate antibody producing cells—the B cells




**B cells are coated with antibodies that react with specific antigens**

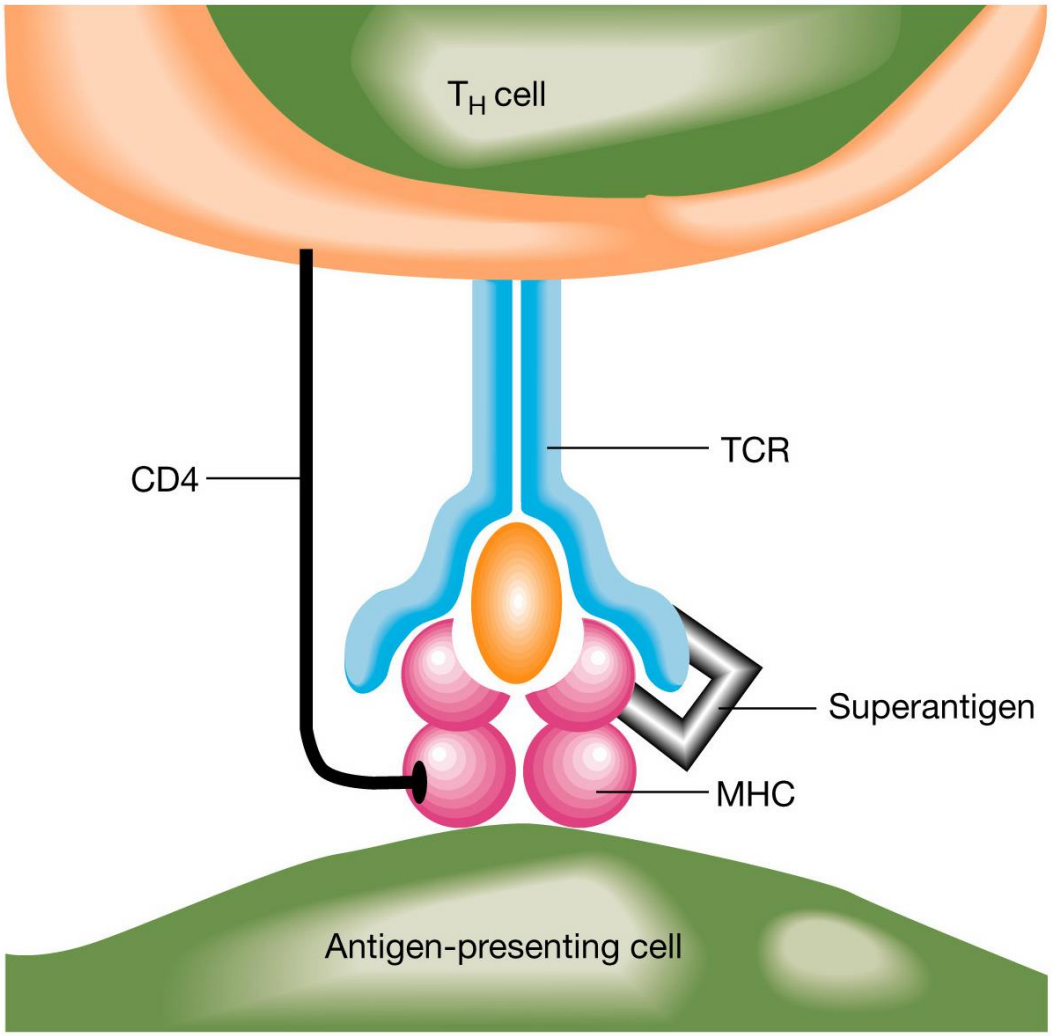
**When the antigen binds to the antibody, the B cell first acts as an APC (antigen presenting cells ).**

**The bound antigen is endo-cytosed and complexed with MHC II and then surface expressed**

**The surface expressed complex interacts with and activates $T_H$ cells that produce the cytokines interleukin 4 & 5**

**IL4 and 5 stimulates the B cells to produce identical memory B cells and antibody secreting plasma cells that secrete the same antibody**

# Superantigens




**Bacterial superantigens act by binding to both the MHC protein and the TCR at positions outside the normal binding site**

**Superantigens can interact with large numbers of cells, stimulating massive T-cell activation, cytokine release and systemic inflammation**

**Superantigens** (SAgs) are a class of antigens that cause **non-specific activation of T-cells** resulting in polyclonal T cell activation and massive cytokine release. SAgs are produced by some pathogenic viruses and bacteria most likely as a defense mechanism against the immune system.

# Antibodies

# *AKA* Immunoglobulins

**found in serum, blood, bodily secretions and milk**

**5 classes**

**IgG IgA IgM IgD and IgE**

# 5 Classes of Antibodies

**IgG:** Immunoglobulin G is a type of antibody. Each IgG has two antigen binding sites. Representing approximately 75% of serum antibodies in humans, IgG is the most common type of antibody found in the circulation.

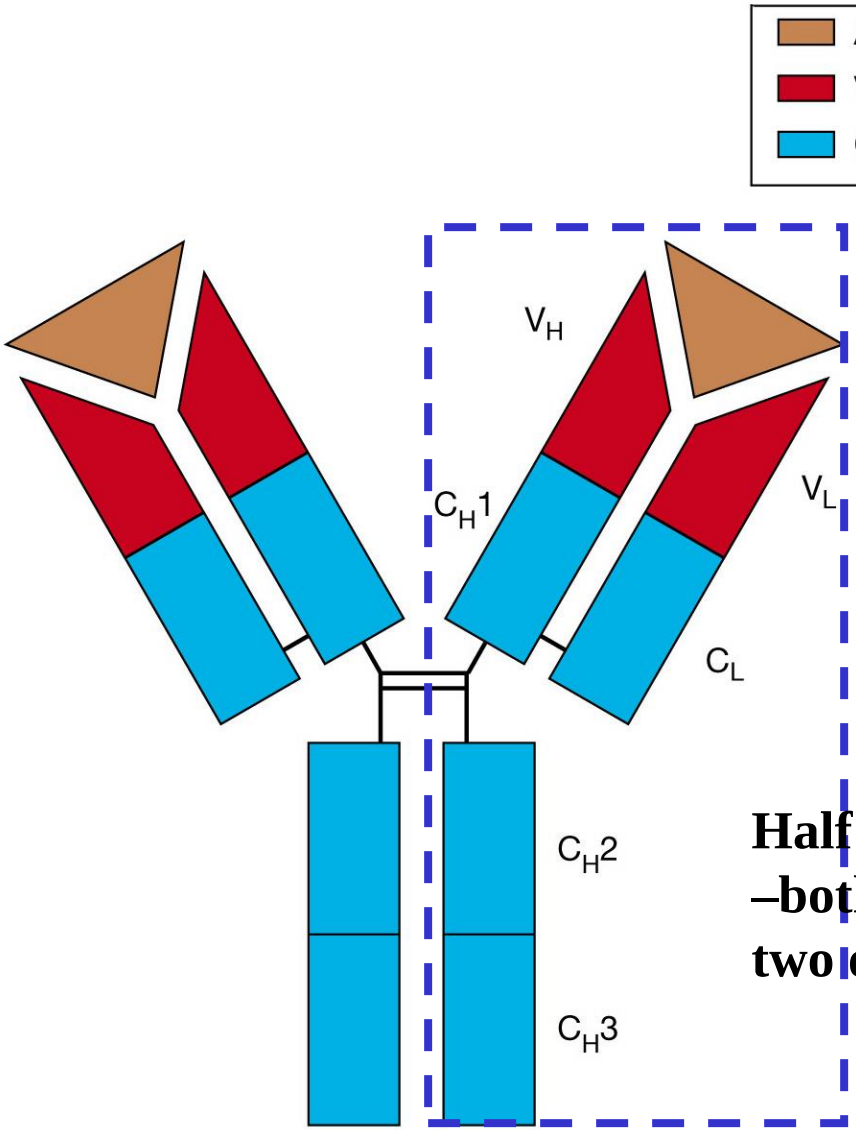
**IgM:** Immunoglobulin M, or **IgM** for short, is a basic antibody that is produced by B cells. **IgM** is by far the physically largest antibody in the human circulatory system. It is the first antibody to appear in response to initial exposure to an antigen.

**IgD:** Immunoglobulin D (**IgD**) is an antibody isotype that makes up about 1% of proteins in the plasma membranes of immature B-lymphocytes where it is usually co-expressed with another cell surface antibody called IgM.

**IgA:** Immunoglobulin A is an antibody that plays a crucial role in the immune function of mucous membranes. The amount of IgA produced in association with mucosal membranes is greater than all other types of antibody combined.

- **IgE:** Immunoglobulin E (**IgE**) are antibodies produced by the immune system. If you have an allergy, your immune system overreacts to an allergen by producing antibodies called Immunoglobulin E (**IgE**). These antibodies travel to cells that release chemicals, causing an allergic reaction. Immunoglobulin E (**IgE**) are antibodies produced by the immune system.

# Antibodies consist of 2 heavy chains and 2 light chains that are linked by a disulfide bond




**The variable regions of the antibody bind antigen**

**Half of a complete antibody –both halves are joined by two disulfide bonds**

# The steps in antibody production

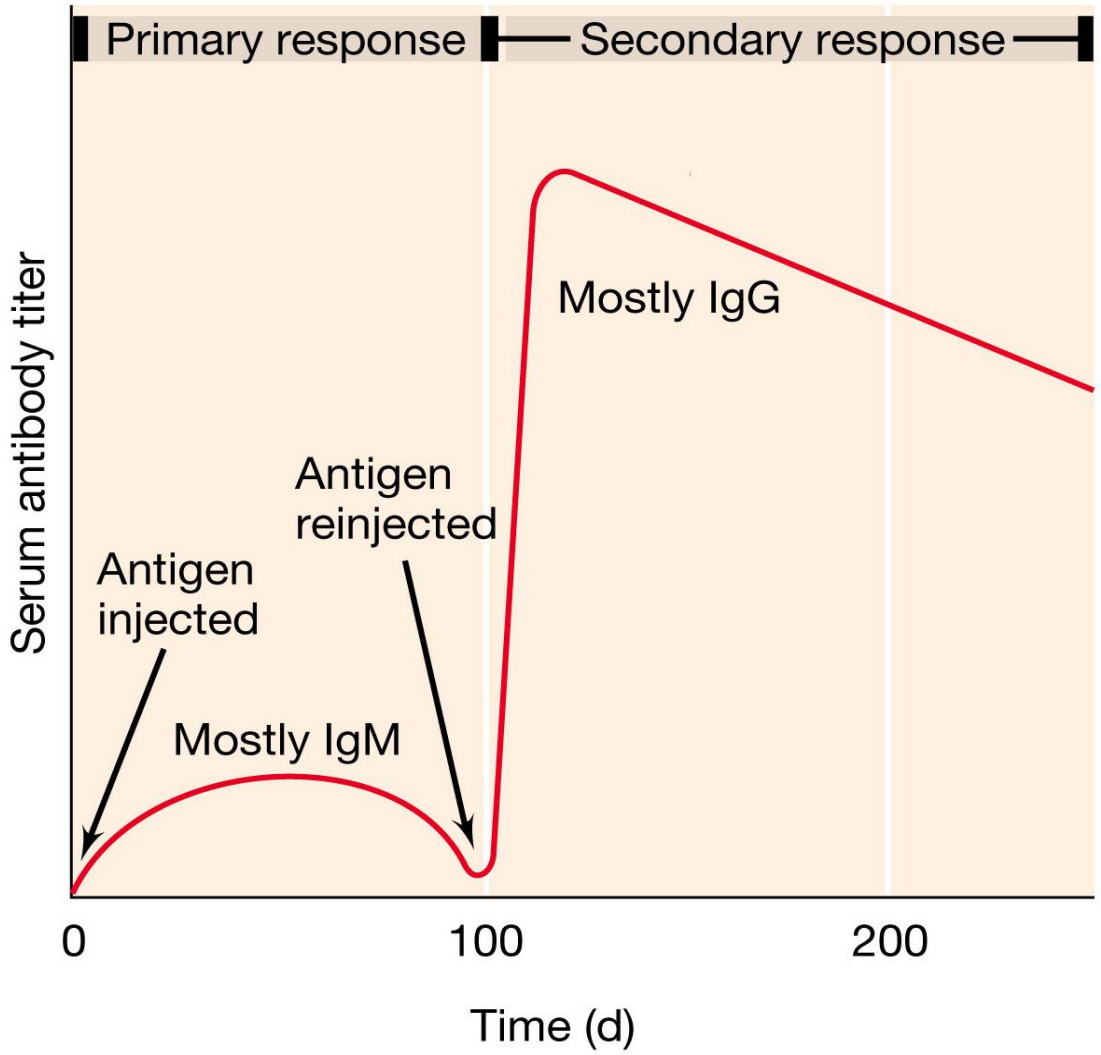
**Antigens are spread via the blood and lymphatic circulatory system to lymphoid organs such as spleen (blood) and lymph nodes (lymph)**

1. **if antigen delivered intravenously, the antigens enter the spleen**
2. **if antigen delivered subcutaneously, intradermally, topically or intraperitoneally, the antigen enters the lymph nodes**

**Antibodies are formed in these lymphatic tissues. Each antigen stimulated B cell multiplies and differentiates to form**

1. **antibody secreting plasma cells—short lived (< week) secrete IgM**
2. **memory cells—long lived—upon exposure to the antigen again these cells immediately convert to plasma cells and produce IgG in high amounts without the aid of helper T cells**

# The Primary immune response is mediated by IgM the secondary immune response is stronger and mediated by IgG



# Acquired Immunity

**Natural active immunity – immunization is a natural outcome of infection**

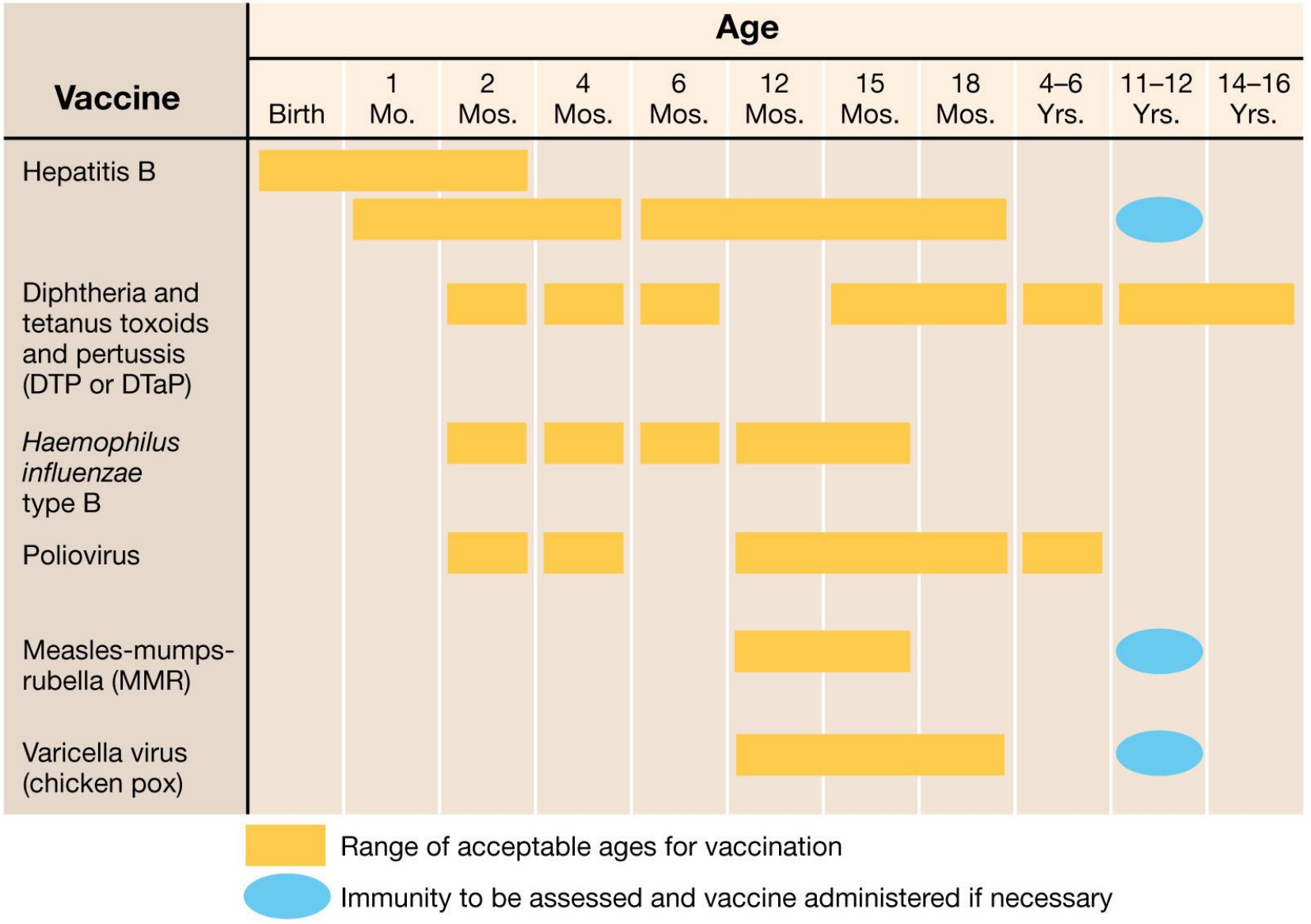
**Artificial active immunity—individual purposely exposed to an antigen to induce the formation of antibodies**

- **vaccination**
- **immunization**

**Artificial passive immunity—individuals receive antibodies that play no role in the antibody production process used to cure a person suffering from a disease**

**Natural passive immunity—newborns receive IgG from mothers that pass through the placenta and receive IgA through colostrum**

# Immunization schedule for infants and children



# Available vaccines for infectious diseases in humans

| Disease | Type of vaccine used |
|---|---|
| **Bacterial diseases** | |
| Anthrax | Toxoid |
| Diphtheria | Toxoid |
| Tetanus | Toxoid |
| Pertussis | Killed bacteria (*Bordetella pertussis*) *or* acellular proteins |
| Typhoid fever | Killed bacteria (*Salmonella typhi*) |
| Paratyphoid fever | Killed bacteria (*Salmonella paratyphi*) |
| Cholera | Killed cells or cell extract (*Vibrio cholerae*) |
| Plague | Killed cells or cell extract (*Yersinia pestis*) |
| Tuberculosis | Attenuated strain of *Mycobacterium tuberculosis* (BCG) |
| Meningitis | Purified polysaccharide from *Neisseria meningitidis* |
| Bacterial pneumonia | Purified polysaccharide from *Streptococcus pneumoniae* |
| Typhus fever | Killed bacteria (*Rickettsia prowazekii*) |
| *Haemophilus influenzae* meningitis | Conjugated vaccine (polysaccharide of *Haemophilus influenzae* conjugated to protein) |
| Lyme disease | Recombinant membrane protein of *Borrelia burgdorferi* |
| **Viral diseases** | |
| Yellow fever | Attenuated virus |
| Measles | Attenuated virus |
| Mumps | Attenuated virus |
| Rubella | Attenuated virus |
| Polio | Attenuated virus (Sabin) or inactivated virus (Salk) |
| Influenza | Inactivated virus |
| Rabies | Inactivated virus (human) *or* attenuated virus (dogs and other animals) |
| Smallpox | Cross-reacting virus (vaccinia) (Section 16.12) |
| Hepatitis A | Recombinant DNA vaccine |
| Hepatitis B | Recombinant DNA vaccine *or* inactivated virus |
| Varicella (chickenpox) | Attenuated virus |

# Autoimmunity

 The normal immune system must be able to distinguish between **self and non-self**.

  Autoimmunity – is a breakdown of tolerance

  Immunity against self antigens (autoantigens) is called autoimmunity

  Autoimmunity results from a "loss of self tolerance"

 Tolerance –**the mechanisms to prevent self reactivity**.

  It is the lack of immune responsiveness to an individual's own tissue antigens

  Autoimmune diseases are chronic inflammatory responses directed against components of the body (self)

# Factors that induce autoimmunity

Include a combination of

A) Genetic

B) Hormonal &

C) Environmental Factors

**(A) Genetic Factors:** HLA gene (human leucocyte Antigen Gene)

 There is a strong association of some diseases with certain HLA gene.

 These genes are required to **encode proteins responsible** for presentation of processed antigen to CD4/8 T cells e.g., Rheumatoid Arthritis occur predominantly in person carrying HLA - DR4

 Ankylosing Spondylitis is more likely to occur in people carrying HLA - B27

# Non-HLA Gene

There are certain genes besides HLA which show association with auto immune diseases .e.g.,

- Genes associated with thymic antigen presentation.
- Genes associated with antigen clearance (complement proteins)
- Genes associated with tolerance induction (CTLA-4, Fas-FasL)

E.g. , Polymorphism in cytotoxic T-lymphocyte associated antigen (CTLA) – 4 is associated to several autoimmune diseases such SLS (Systemic Lupus Scleroses)

# Hormonal Factors

- Hormones play an important role in autoimmune diseases. It has been observed that 90% all autoimmune diseases occur in women and it is due to some facts;
  - Studies have shown that estrogen can stimulate auto-antibody production e.g., Demonstrated in SLE (Systemic Lupus Erythematosus) -prone mice
  - Females have a slightly higher cortisol secretion than males
  - Testosterone seems to be protective against several types of autoimmune diseases, eg. SLE, diabetes, MS (Multiple Sclerosis) etc

- Another factor involved for females having higher ratio of autoimmune diseases is;
  - Ability of pregnant women to modify their immune system during pregnancy to keep the fetus.

# Environmental Factors

- **Drug-induced autoimmunity:** There are certain drugs which can bind with normal protein and make them immunogenic and induce autoimmunity
- For example; **Procainamide** - leads to changes in central tolerance in thymus and changes in peripheral T-cell reactivity and induces SLS.

- **Chemical-induced autoimmunity:** There are certain chemicals which induce autoimmunity.
- For example; Heavy metals (i.e. mercury, silver, or gold)- can lead to autoantibody expression

# Bacterial / viral infections causing Autoimmunity:

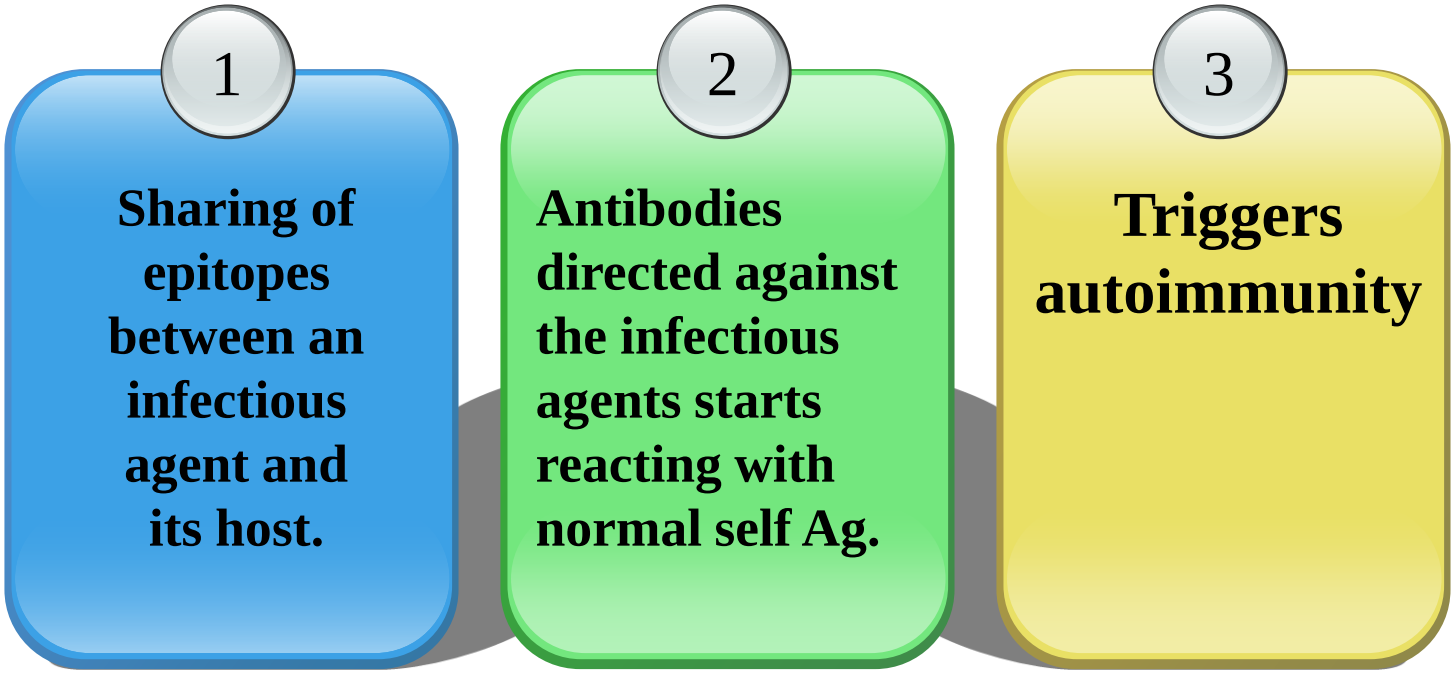
- Normally the immune system provides protection against bacteria and viruses. However, the immune system may lose the ability to distinguish “self” from “non-self”
- Leads to pathogenesis of several important conditions such as multiple sclerosis and rheumatoid arthritis
- A possible mechanism is “molecular mimicry” that is similarity between human and pathogen protein.
- For example; HBV can induce Multiple Sclerosis Coxsackie virus B3 can induce Myocarditis.

# Mechanisms of Autoimmunity

## A) Molecular mimicry

- Viruses and bacteria possess **antigenic determinants** that are **very similar, or even identical**, to normal host cell components.
- This phenomenon, known as molecular mimicry, occurs in a wide variety of organisms.
- Molecular mimicry may be the initiating step in a variety of autoimmune diseases.
- Molecular mimicry present in a wide variety of human and pathogen proteins e.g.,
  - Human cytomegalovirus IE2 protein and HLA-DR (Human Leukocyte Antigen – antigen D Related) molecule
  - Poliovirus VP2 pro and Acetylcholine receptor
  - Papilloma virus E2 protein and Insulin receptor
  - Rabies virus glycoprotein and Insulin receptor

# Mechanism of Molecular Mimicry




**Epitopes:** The part of an antigen molecule to which an antibody attaches itself.

## B) Alteration of Normal Proteins

- Drugs can bind to the normal proteins and modify their nature which results in the newer antigen for the antibodies and immune response occurs.
  - Example: Procainamide - induced SLE (Systemic Lupus Erythematosus).

## C) Release of "Sequestered antigens"

 Some antigens in the body are hidden from cells of the immune system.

 These regions are known as immunologically privileged sites. e.g., sperm, CNS, uveal tract of eye etc.

- When antigens from immunologically privilged sites enter into the ciruclation.
- Both humural and cell mediated responces may occur to these self antigenes e.g.,
- Aspermatogensis
- Encephalitis &
- Endopthalmitis
- Intracellular antigens are also new to immune system.
- Radiations/chemicals also can damage the cells and cause release of sequestered substances.

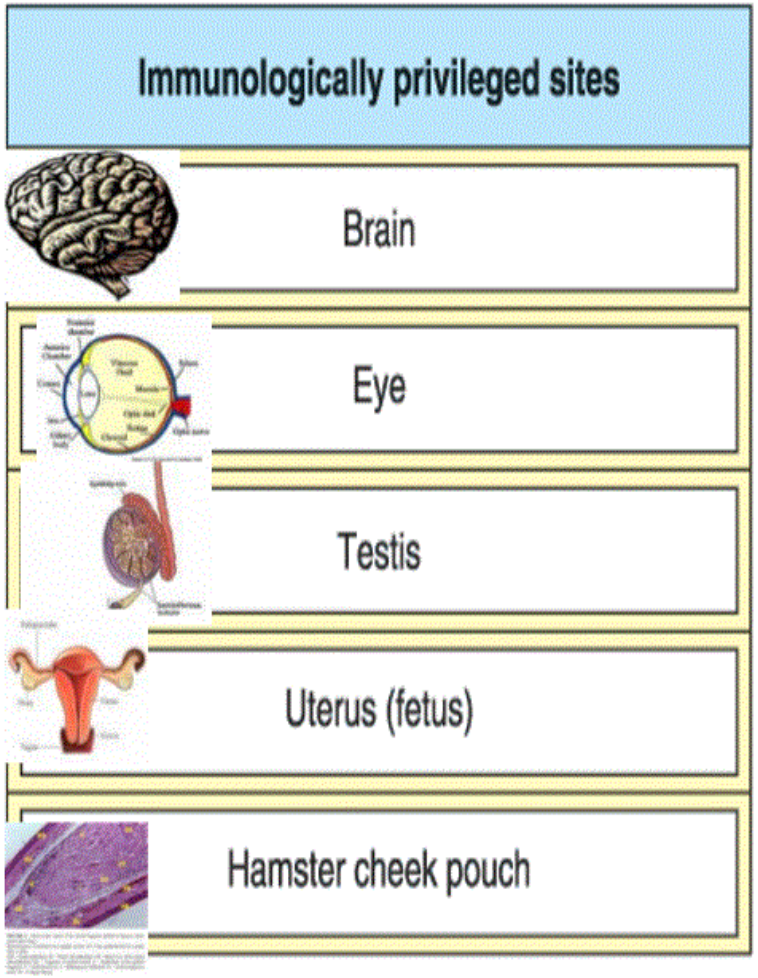



Fig 13.35 © 2001 Garland Science

# Autoimmune Diseases

Autoimmune diseases are **chronic inflammatory responses** directed against components of the body (self).

 Autoimmune disease are broadly divided into **organ-specific** and **systemic.**

**Organ specific** - Organ specific means the auto-immunity is directed against a component of one particular type of organ.

**Systemic**- the auto-immunity is directed against an antigen that is present at many different sites and can include involvement of several organs.

# Autoimmunity Classification

Can be classified into clusters that are either

***organ-specific*** or ***systemic***

| Organ-specific autoimmune diseases | Systemic autoimmune diseases |
| --- | --- |
| Type I diabetes mellitus | Rheumatoid arthritis |
| Goodpasture's syndrome | Scleroderma |
| Multiple sclerosis | Systemic lupus erythematosus<br>Primary Sjögren's syndrome<br>Polymyositis |
| Graves' disease<br>Hashimoto's thyroiditis<br>Autoimmune pernicious anemia<br>Autoimmune Addison's disease<br>Vitiligo<br>Myasthenia gravis | |

Figure 13-1 Immunobiology, 6/e. (© Garland Science 2005)

# Tissues of The Body Affected By Autoimmune Attack


**Thyroid**
Hashimoto's Thyroiditis
Graves Disease

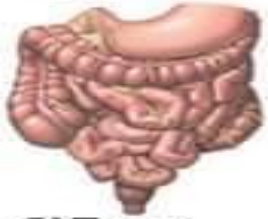
**Triggers**
1. Stress
2. Hormones
3. Metals
4. Food Antigens
5. Pesticides & Poisons

**Brain**
Multiple Sclerosis
Autism
Guillain-Barre Syndrome
Psychological

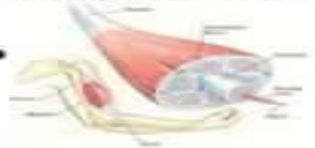
**Blood**
Leukemia
Lupus
Hemolytic
Dysglycemia

**Autoimmune Disorder**

**Bones**
Rheumatoid Arthristis
Ankylosing Spondylitis
Polymyalgia Rheumatica



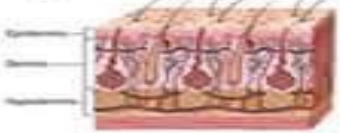
**GI Tract**
Celiac
Chron's Disease
Ulceratic Colitis



**Muscles**
Fibromyalgia
Muscular Dystrophy

**Nerves**
Peripheral Neuropathy
Diabetic Neuropathy

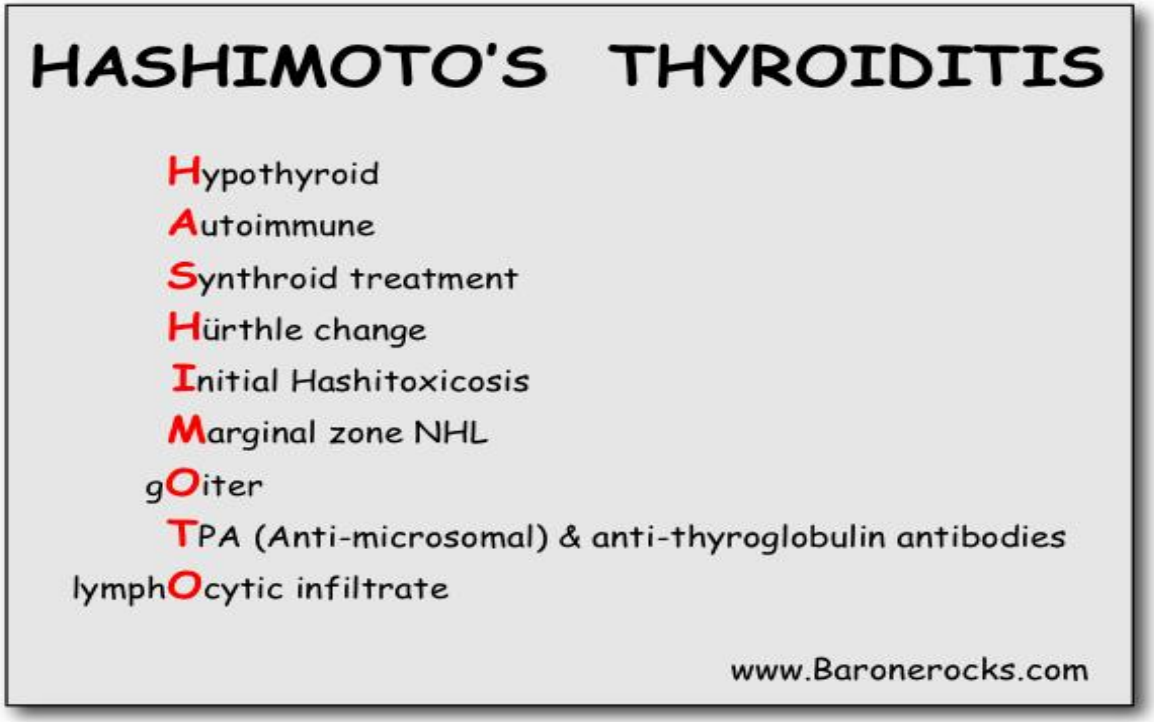
**Lungs**
Asthma
Wegener's Granulomatosis



**Skin**
Eczema
Psoriasis
Scleroderma
Vitiligo

# Organ specific

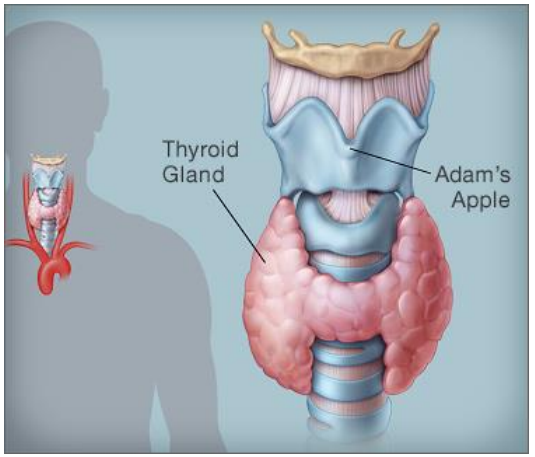
Damage is confined to the organ against which the immune response is mounted. e.g.,

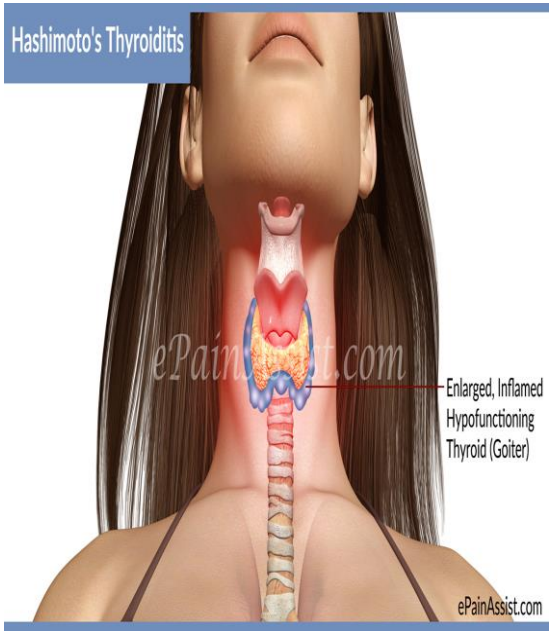


# Hashimoto's Thyroiditis

Organ specific disease affecting the **thyroid gland**.

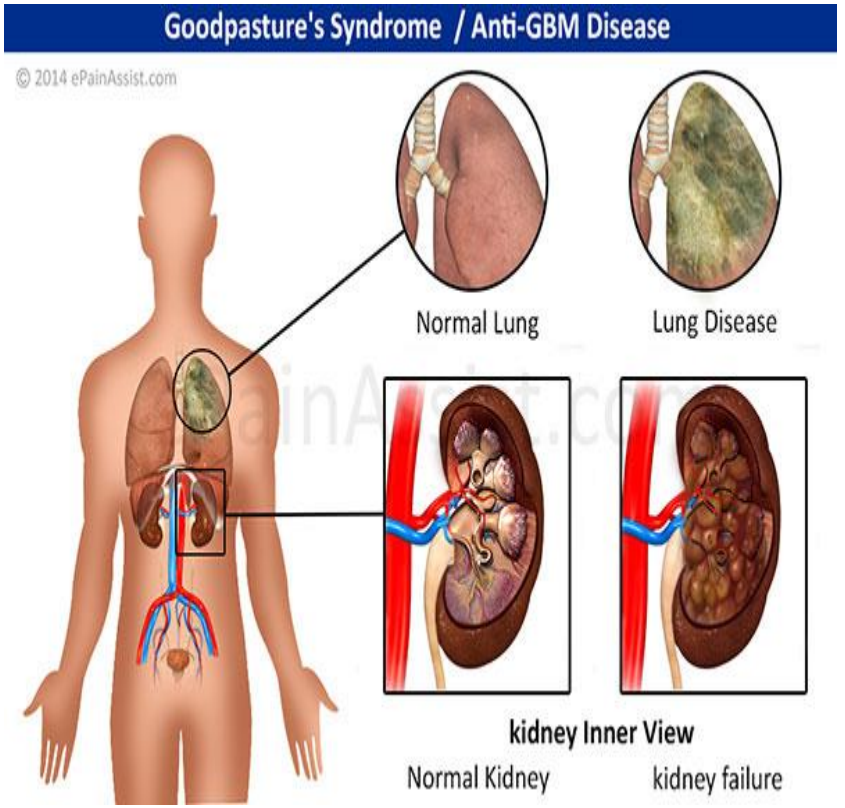
- Most often seen in women 30 to 40 years old, may be **genetic predisposition**.
- Common cause of **hypothyroidism**.
- Causes diffuse hyperplasia (Thick benign) in the gland resulting in development of a **goiter**.
- Thyroid autoantibodies are formed against Thyroid Proxidase (TPO) & thyroglobulins cause gradual destruction of follicles in the thyroid gland.
- Interferes with iodine uptake and leads to decreased production of thyroid hormones (hypothyroidism).



# Goodpasture's Syndrome

- An uncommon and life-threatening hypersensitivity disorder believed to be an autoimmune process related to **antibody formation in the body**.
- Goodpasture's syndrome is characterized by **renal** (kidney) disease and **lung hemorrhage**.
- Antibodies react with antigens in the glomerular basement membrane of the kidney, results in **severe necrosis**.
- Antigen in kidney is similar to antigen found in lungs, resulting in antibody reacting with lung tissue resulting in **pulmonary hemorrhage**.



# Autoimmune Hemolytic Anemia

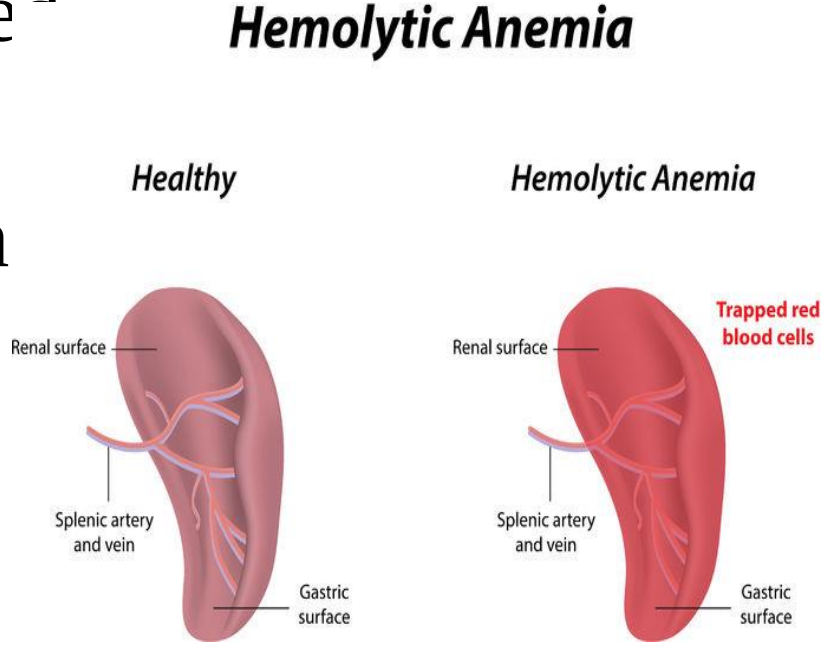
- Self Ag: Red blood cells (RBC's)

 Can be associated with **systemic lupus erythematosus**

 Mechanisms of Ab-mediate ] destruction;

 Opsonization and digestion by macrophage

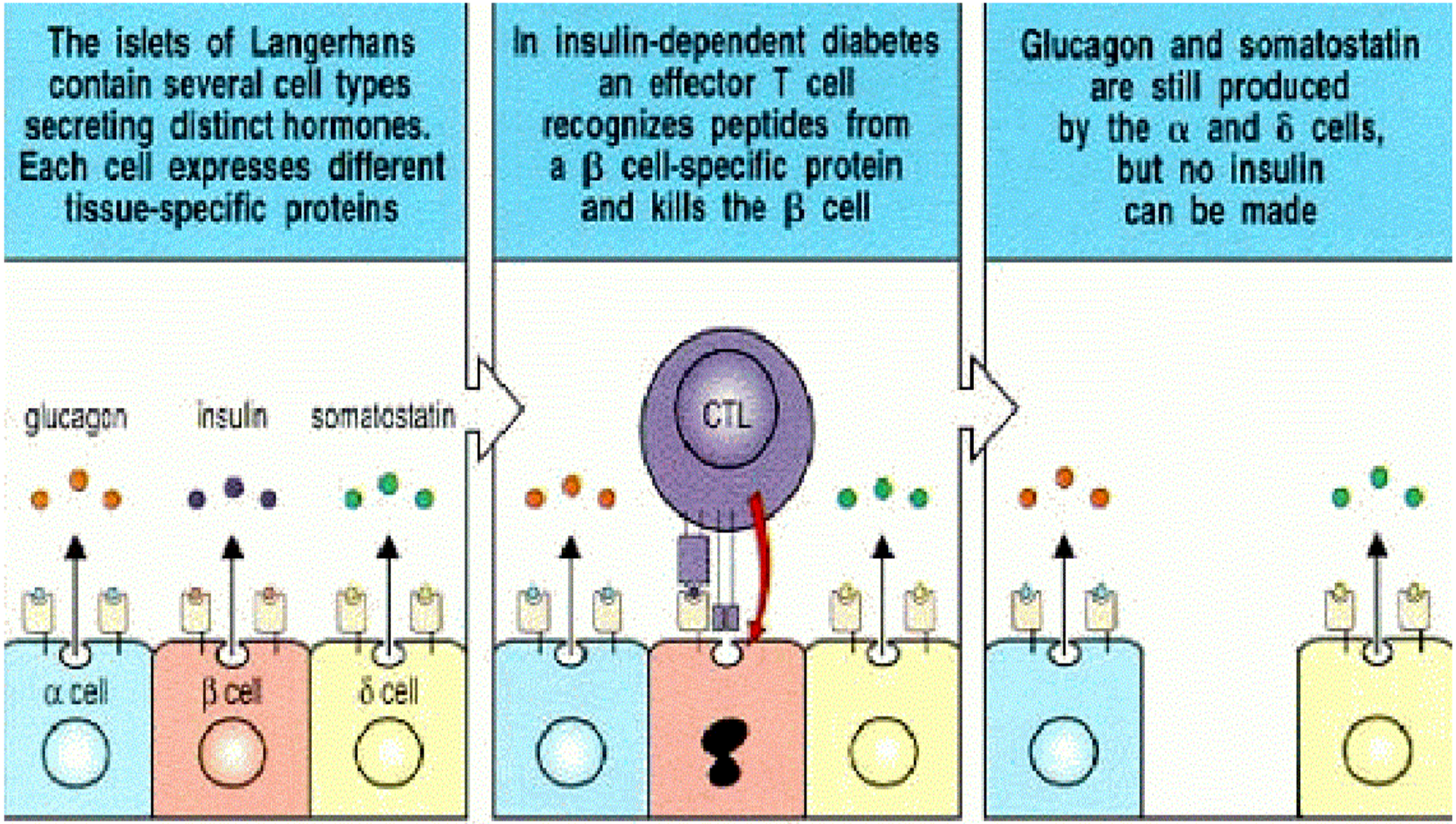
 Complement cascade and lysis of RBC



# Insulin Dependent Diabetes Mellitus

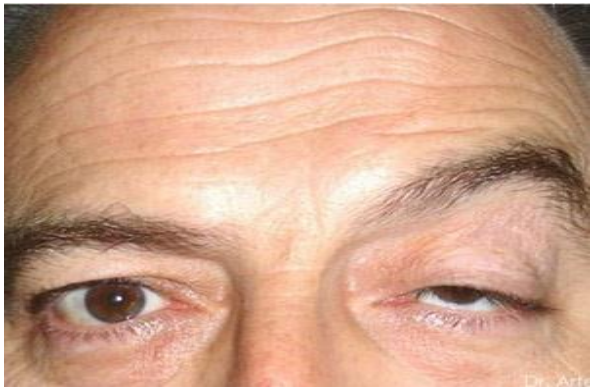
- **Self Ag:** insulin-secreting **β-islet cells** of pancreas
- More specifically this is islet cell enzyme, glutamic acid decarboxylase
- Type I, Juvenile-onset (insulin-dependent diabetes mellitus; IDDM)
- Abs, T cells, adhesion molecules, Decrease serum cytokine inhibitors, sustained expression of cytokines including TNF-α, IFN-γ, IL-1
- **Symptoms**: ↓ insulin → abnormalities in glucose metabolism → ketoacidosis, thirst, polyuria, vision disturbances
- **Late stages:** progressive atherosclerotic vascular lesions → arterial obstruction, renal failure, blindness

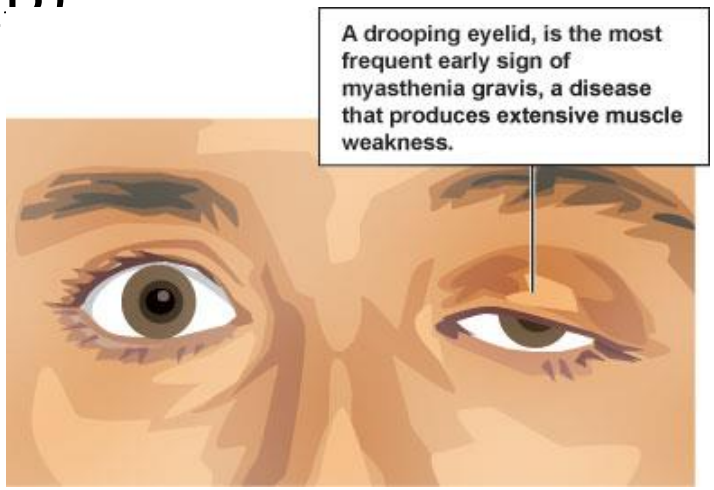
# Insulin Dependent Diabetes Mellitus



# Myasthenia gravis

- In normal individuals, acetyl choline (ACh) is produced at **motor nerve terminals**.
- When released, it interacts with ACh receptors on post synaptic membrane of the muscle, ultimately **activating contractile machinery.**
- In Myasthenia gravis (B and C), **Auto Antibodies** are produced against ACh receptors which can activate complement and cause damage to post synaptic membrane (B) or the ACh receptors are internalized and destroyed (C).
- The net result is loss of ACh receptors.





# Neuromuscular disorder

- Caused by auto Abs against acetylcholine receptors (ACh).
- Weakness and fatigue of voluntary muscles.
- Difficulty in swallowing, breathing, can lead to death.

# Systemic-auto-immune Diseases

Systemic Diseases- the auto-immunity is directed against an antigen that is present at many different sites and can include involvement of several organs.

# Systemic Lupus Erythematosus (SLE)

**Self Ags:** DNA, Nucleohistones

**Causes:** a) Genetic predisposition b) Environmental causes & c) Drug interactions

Ag-Ab complexes are deposited in kidneys and vascular tissue.

**Trigger Type III hypersensitivity.**

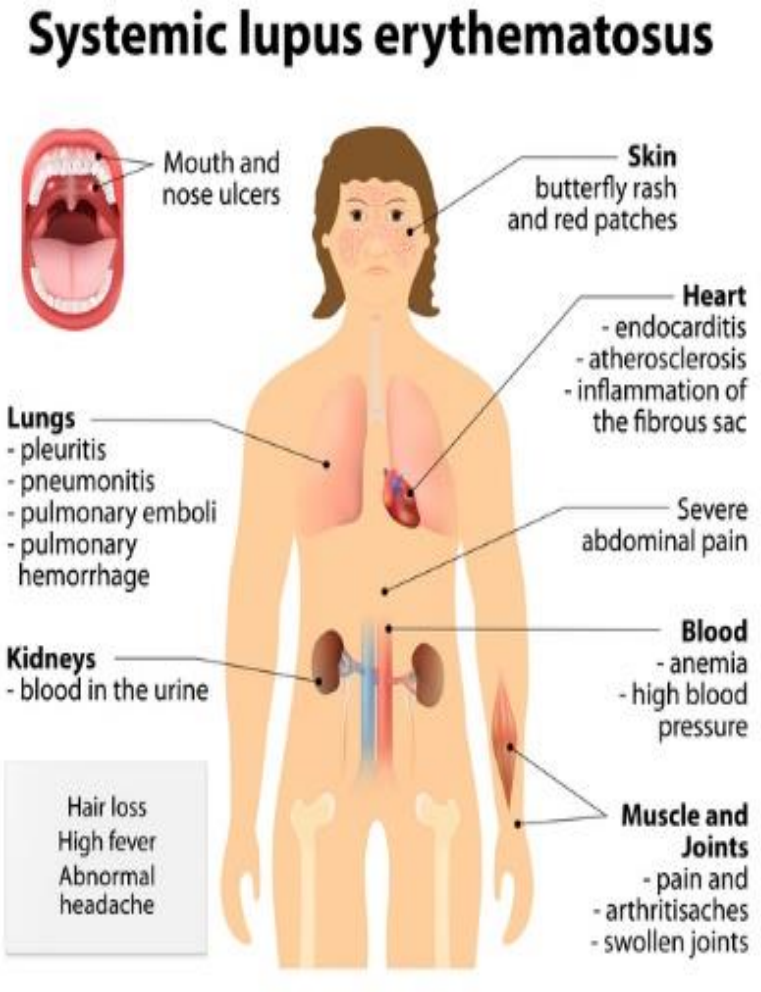
Severe damage to kidneys, vascular tissue.

Renal involvement very common.

Caused by deposition of immune complexes in kidney tissue.

Leads to renal failure, most common cause of death.

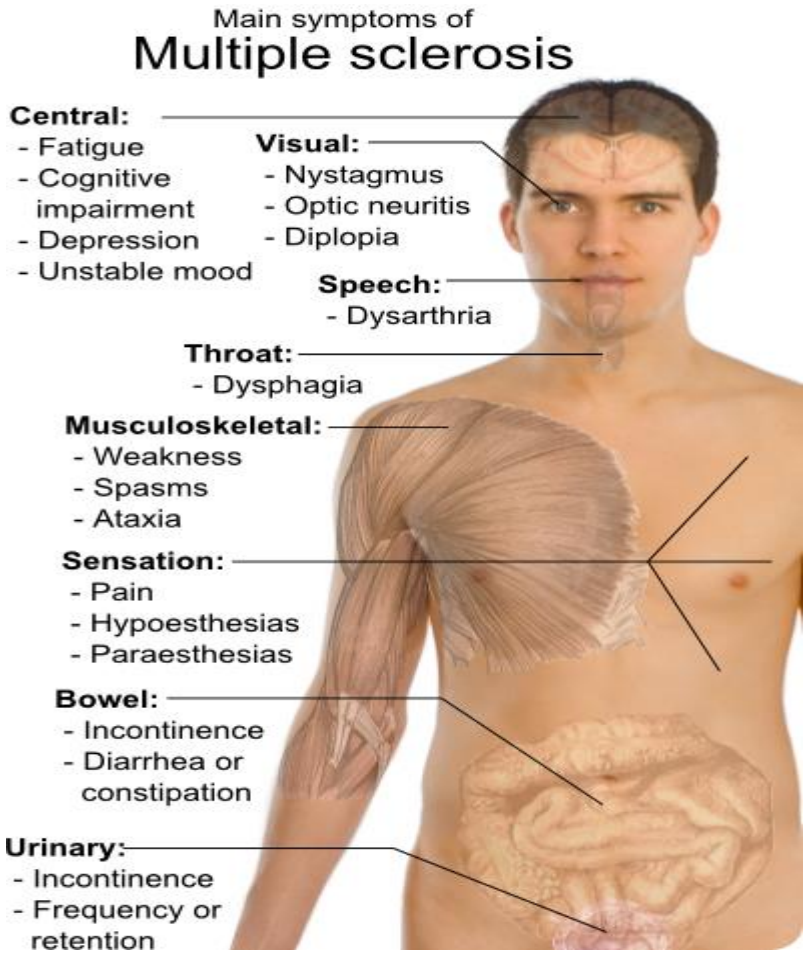
Other systemic effects: a) Cardiac b) Central nervous system & c) Hematologic abnormalities.



# Multiple Sclerosis (MS)

**Attacks the CNS and causes neurological disabilities.**

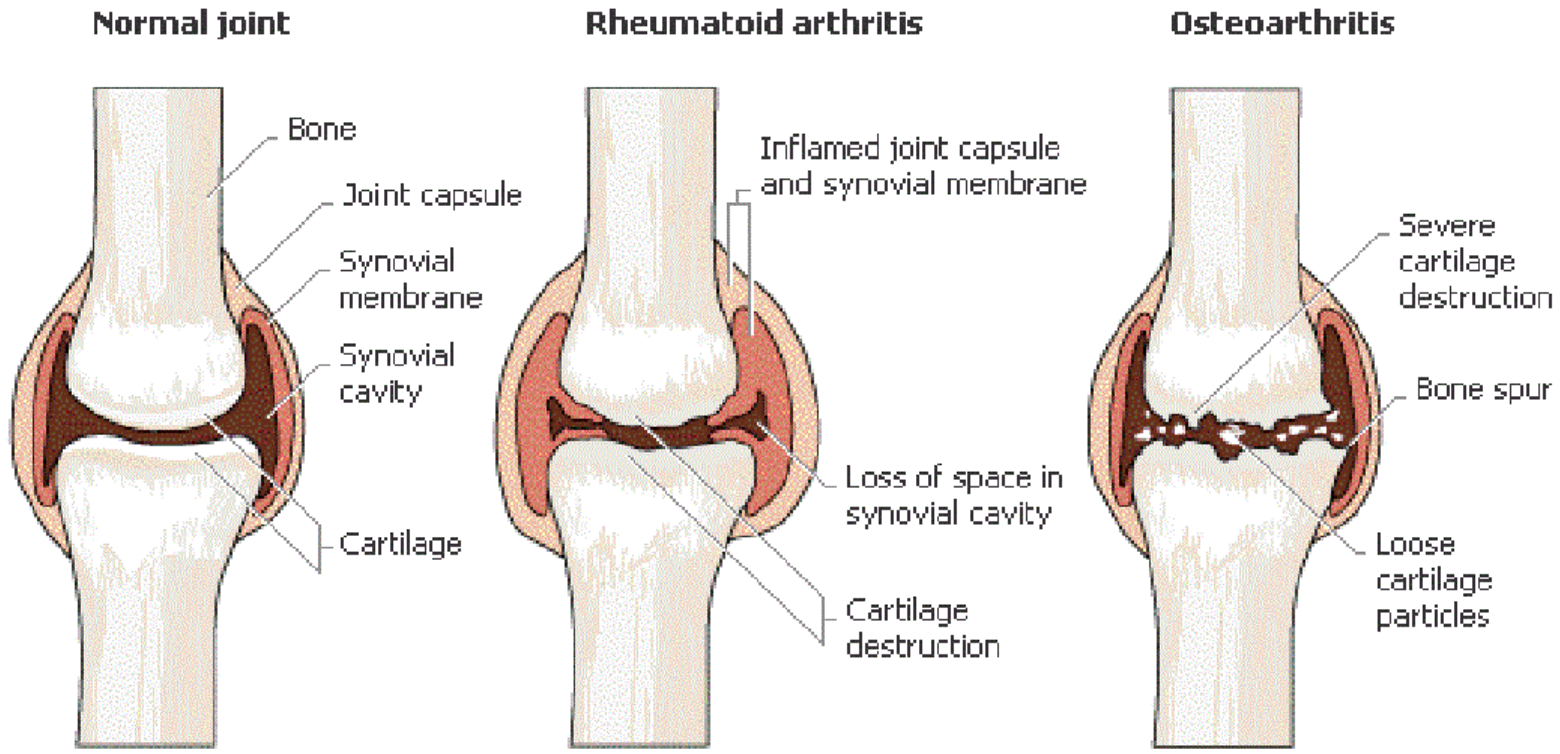
- Degenerative disease of the **myelin sheath.**
- Myelin basic protein (**MBP**) and proteo-lipid protein (**PLP**) are considered as antigens. Some viral infections are also considered responsible.
- Myelin sheath damage is initiated by **increased migration of auto-reactive T cells across the BBB**, leading to inflammation and formation of hardened scar tissue ("sclerotic plaques") in various areas of the CNS.
- Demyelination along the axons disrupts nerve conduction.
- It could be mild such as numbness in limbs or severe such as paralysis or loss of vision.
- Genetic influence is important here.
- Risk is higher in women than men.



# Rheumatoid Arthritis

- Self Ag: Cartilage
- TNF genes, Epstein–Barr virus Infection (EBV)
- Chronic inflammatory disease primarily affecting the joints, but can affect heart, lung and blood vessels.
- Women are proven to it three more times than men.
- Typically strikes at ages between 20 and 40, but can occur at any age.
- The three major symptoms of arthritis are joint pain, inflammation, and stiffness.

 Auto Abs against Fc portion of IgG often called rheumatoid factor.  Abs against collagen.  Immune complexes deposited in joints.  Complement activation leads to inflammation---Type III hypersensitivity.



# Treatment of Autoimmune Diseases

# Methods of Treatment:

I. **Current Therapies-** Aimed at reducing symptoms by providing non-specific suppression of the immune system

II. **Experimental Therapeutic Approaches-** try to induce specific immunity

- Note: Immunosuppression mechanism should be adapted with caution as opportunistic bacteria can take benefit.

# Current Therapies

- **Immunosuppressive drugs**
  - -Corticosteroids (Prednisone),
  - -Antimetabloites (Azathioprine, methotrexate- inhibit DNA synthesis), slows the proliferation of lymphocytes
- **Cyclosporin A -** Blocks signal transduction mediated by the TCR (inhibits only antigen-activated T cells while sparing non activated ones)
- **Thymectomy-** Removal of thymus from patients with myasthenia gravis
- **Plasmapheresis** - Removes antigen-antibody complexes for a short-term reduction in symptoms.

# Experimental Therapies

 **T-cell Vaccination-**Autoimmune T-cell clones elicit regulator T-cells that are specific for the TCR on the autoimmune T- cells - results in suppression of the autoimmune cells

 **Peptide Blockade of MHC molecules-** A synthetic peptide is used to bind in place of the regular peptide on the MHC- induces a state of clonal energy in the autoimmune T-cell

 **Monoclonal-Antibody Treatment-** Monoclonal antibody against the IL-2 receptor blocks activated TH- cells

- Blockage of preferred TCRs with monoclonal antibodies
- Monoclonal antibody against an MHC molecule that is associated with autoimmunity while sparing the others.

 **IgG Dose Treatment**

# Any Questions

- Tumor necrosis factor TNF
- **Ankylosing spondylitis** is a type of arthritis that affects the spine. **Ankylosing spondylitis** symptoms include pain and stiffness from the neck down to the lower back. The spine's bones (vertebrae) fuse together, resulting in a rigid spine. These changes may be mild or severe, and may lead to a stooped-over posture.

- **Myocarditis** Cardiac inflammation stains purple. **Myocarditis** is uncommon and can be caused by a viral infection or a self-directed immune response (this is when the persons own immune system attacks the body, such as in autoimmune diseases like rheumatoid arthritis or lupus).