

**IMMUNITY**

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**Advanced Immunopharmacology**

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**IMMUNITY**

# Definition of Immunity:

* It is the natural or acquired resistance of the body to a certain disease or pathogenic organism or foreign particles produced by Immune system.
* It is the defense system of the body that produces resistance or response against any foreign particles or micro-organisms.

*“Lymphocytes are the cornerstone of immune system”*

# Functions of Immune System:

Functions of immune system are as follows;

* Scavenge dead, dying body cells
* Destroy abnormal (cancerous)
* Protect from pathogens & foreign molecules: parasites, bacteria, viruses

# Lines of Defense against Foreign Pathogens:

The Immune System has three lines of defense against foreign pathogens:

1. Physical and Chemical Barriers (Innate Immunity)
2. Nonspecific Resistance (Innate Immunity)
3. Specific Resistance (Acquired Immunity)

## Physical and Chemical Barriers (Innate Immunity):

Physical and chemical barriers form the first line of defense when the body is invaded.

### Physical Barriers:

* The **skin** has thick layer of dead cells in the epidermis which provides a physical barrier. Periodic shedding of the epidermis removes microbes.
* The **mucous membranes** produce **mucus** that trap microbes.
* **Hair** within the nose filters air containing microbes, dust, pollutants
* **Cilia** lines the upper respiratory tract traps and propels inhaled debris to throat
* **Urine** flushes microbes out of the urethra
* **Defecation** and **vomiting** -expel microorganisms.

### Chemical Barriers:

* **Lysozyme**, an enzyme produced in **tears**, perspiration, and saliva can break down cell walls and thus acts as an antibiotic (kills bacteria)
* **Gastric juice** in the stomach destroys bacteria and most toxins because the gastric juice is highly acidic (pH 2-3)
* **Saliva** dilutes the number of microorganisms and washes the teeth and mouth
* **Acidity** on skin inhibit bacterial growth
* **Sebum** (unsaturated fatty acids) provides a protective film on the skin and inhibits growth
* **Hyaluronic acid** is a gelatinous substance that slows the spread of noxious agents

## Nonspecific Resistance (Innate Immunity):

The second line of defense is **nonspecific resistance** that exist prior to exposure to the microbe(antigen), it includes:

* Host defenses such as barrier to infectious agent (e.g. skin and mucous membrane)
* Certain cells (e.g. natural killer cells)
* Certain proteins (e.g. the complement cascade and interferons)
* Phagocytosis
* Inflammation

### Phagocytic cells:

Phagocytic cells ingest and destroy all microbes that pass into body tissues.

For example:

* Macrophages are cells derived from monocytes (a type of white blood cell)
* Macrophages leave the bloodstream and enter body tissues to patrol for pathogens

**Inflammation** is a localized tissue response that occurs when your tissues are damaged and in response to other stimuli. Inflammation brings more white blood cells to the site where the microbes have invaded. The inflammatory response produces swelling, redness, heat, pain.

**Fever** inhibits bacterial growth and increases the rate of tissue repair during an infection.

## Specific Resistance (Acquired Immunity):

The third line of defense is **specific resistance,** this system relies on **antigens**, which are specific substances found in foreign microbes

* Most antigens are proteins that serve as the stimulus to produce an **immune response**.
* The term "antigen" comes from anti-body generating substance
* Adaptive immunity occurs after exposure to an agent, improves upon repeated exposure, and is **Specific**
* It is mediated by antibody produced by B lymphocytes and by two types of T lymphocytes:
* **Helper T cells**
* **Cytotoxic T cells**
* Cells involve in adaptive immunity have **long-term memory** for a specific antigen
* Adaptive immunity can be **active or passive**

# Main components of Innate and Adaptive immunity

Table 1. Main components of Innate and adaptive immunity

|  |  |  |
| --- | --- | --- |
|  | Humoral Immunity | Cell-Mediated Immunity |
| Innate Immunity | Complement & neutrophils | Macrophages and natural killer cells |
| Adaptive Immunity | B cells and antibodies (made by plasma cells) | Helper T cells and cytotoxic T cells |

* The **cell-mediated arm** consists primarily of T lymphocytes (e.g, helper T cells and cytotoxic T cells)
* The **antibody mediated arm** consists of antibodies(immunoglobulins) and B lymphocytes that can differentiate into plasma cells

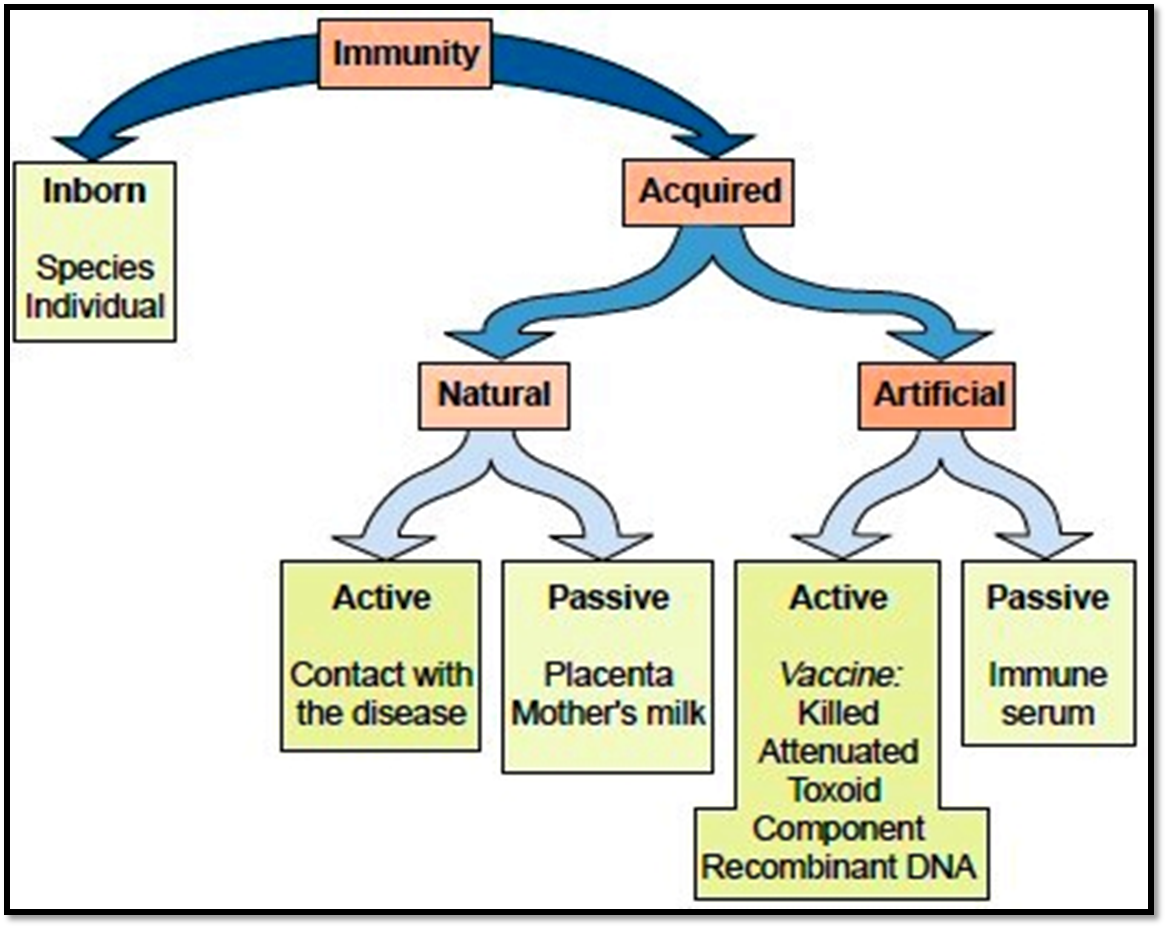
# Steps in an immune response:

Steps involved in an immune response are;

* When an antigen is detected by a macrophage, this causes the T-cells to become activated. The activation of T-cells by a specific antigen is called **cell-mediated immunity**. The body contains millions of different T-cells, each able to respond to one specific antigen.
* The T-cells secrete **interleukin 2.** Interleukin 2 causes the proliferation of certain **cytotoxic T cells** and **B cells**.
* From here, the immune response follows 2 paths: one path uses cytotoxic T cells and the other uses B cells.

# Cytotoxic T Cell Pathway:

* The cytotoxic T cells are capable of recognizing antigens on the surface of infected body cells.
* The cytotoxic T cells bind to the infected cells and secrete **cytotoxins** that induce apoptosis (cell suicide) in the infected cell and **perforins** that cause perforations in the infected cells.
* Both of these mechanisms destroys the pathogen in the infected body cell.



# Characteristics of active and passive immunity:

Table 2. Characteristics of active and passive immunity

|  |  |  |  |
| --- | --- | --- | --- |
|  | Mediators | Advantages | Disadvantages |
| **Active immunity** | Antibody and T cells | Long duration (years) | Slow onset |
| **Passive immunity** | Antibody only | Immediate availability | Short duration (months) |

# Major functions of T Cells and B Cells:

Table 3. Major functions of T Cells and B Cells

|  |  |
| --- | --- |
| Antibody-Mediated Immunity (B Cells) | Cell-Mediated Immunity (T Cells) |
| * Host defense against infection (opsonize bacteria, neutralize toxins and viruses) | * Host defense against infection (especially M. tuberculosis, fungi and virus infected cells) |
| * Allergy (hypersensitivity) (e.g. hay fever, anaphylactic shock) | * Allergy (hypersensitivity e.g. poison oak) |
| * Autoimmunity | * Graft and tumor rejection * Regulation of antibody response (help and suppression) |

# Difference between Innate and Acquired immunity:

## Characteristics of Innate immunity:

1. Acts within minutes
2. Exists prior to exposure to the microbe(antigen)
3. Does not improve after exposure to an antigen
4. It has no memory cells
5. Its mediators destroy microbes and secrete cytokines
6. Non specific

For example:

* Respiratory cilia: elevate mucus-containing trapped organisms
* Low pH in stomach: retard growth of microbes

## Characteristics of Acquired immunity:

1. Highly specific
2. Requires several days before becoming effective
3. Occurs after exposure to an antigen
4. Improves on repeated exposure
5. It is characterized by long-term memory
6. Its mediators present antigens to CD4-positive helper T cells

For example:

* IgG passed from mother to fetus during pregnancy
* IgA passed from mother during breast feeding

# Anti-Bodies:

* **Antibodies** are globulin proteins (**immunoglobulins** [Ig]) are Y-shaped proteins that circulate through the blood stream and bind to specific antigens, thereby attacking microbes
* The antibodies are transported through the blood and the lymph to the pathogen invasion site
* The body contains millions of different B cells, each able to respond to one specific antigen
* They make up about 20% of the protein in blood plasma
* Blood contains 3 types of globulins **[Alpha, beta and Gamma]** basedon their electrophoretic migration rate
* Antibodies are **gamma globulins**

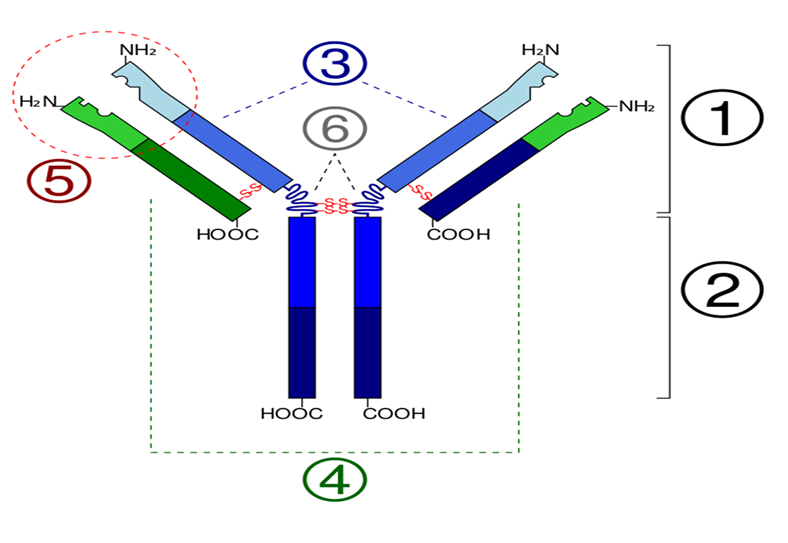
## Types of Antibodies:

There are 5 classes of antibodies (listed from most common to least common) based on differences in their heavy chain:

1. IgG
2. IgM
3. IgA
4. IgD
5. IgE

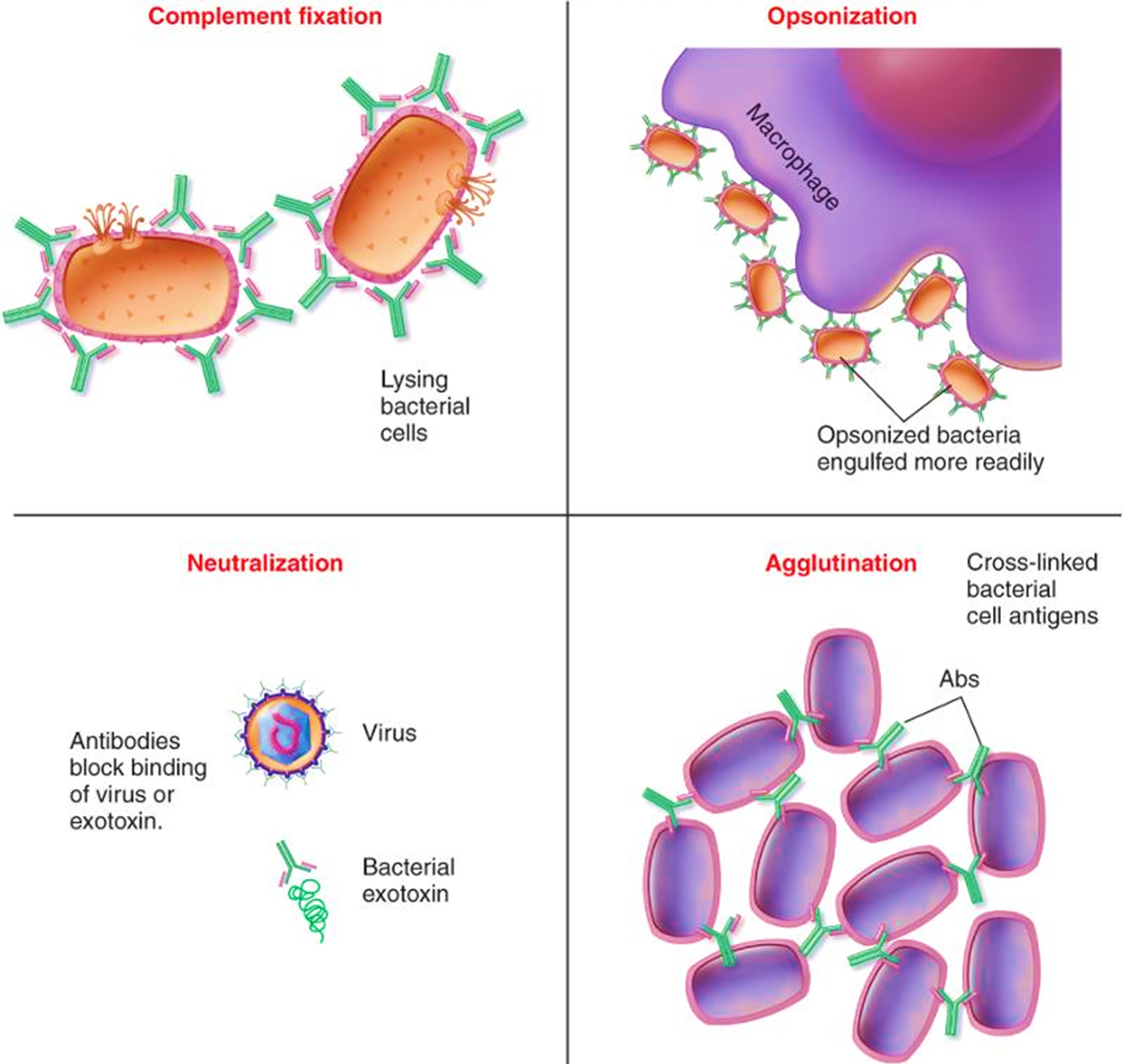
## Antibody Structure:

* The simplest antibody has a Y shaped structure
* Each antibody is made of four polypeptide (protein) chains: 2 **heavy chains**and 2 **light chains**
* The term light and heavy refers to molecular weight; light chain have molecular weight of about 25,000 whereas heavy chains have molecular weight of 50,000 to 70,000
* Both heavy chains are identical to each other and both light chains are identical to each other
* Each contains a **constant** **region** and a **variable** **region**.
* The constant region forms the main part of the molecule while the variable regions forms the antigen-binding site
* Each antibody has 2 antigen-binding sites
* The constant region of the heavy chain is responsible for various **biologic functions (e.g. complement activation and binding to cell surface receptors)**



1. **Fab region**
2. **Fc region**
3. **Heavy chain (blue)**
4. **Light chain (green)**
5. **Antigen binding site (paratope)**
6. **Hinge regions**

## Mechanisms of Antibody Reaction:



## Important functions of immunoglobulins

### IgG:

* Opsonizes bacteria, neutralizes bacterial toxins and viruses, crosses the placenta, fixes complement

### IgA:

* Main antibody in the secretions such as colostrum, saliva, tears and respiratory, intestinal and genital secretions
* Prevent attachment of bacteria and viruses to mucous membranes, does not fix complement

### IgM:

* Produced in the primary response to an antigen, does not cross the placenta, antigen receptor on the surface of B cells, fixes complement

### IgD:

* Found on the surface of many B cells as well as in serum

### IgE:

* Mediates immediate hypersensitivity, defend against worm infections, does not fix complement

# Antigens and Immunogens:

* Toxins or foreign substances that induces an immune response in the body, esp. the production of antibodies
* Antigens include foreign proteins, nucleic acids, lipids, polysaccharides
* Antigens have immunogenicity
* Immunogens are molecules that induce immune response
* Antigens are immunogens and the term are used interchangeably but there are some exceptions (e.g. Penicillins are haptens)
* Haptens are not immunogenic because they cannot activate helper T cells

# Autoimmunity:

* The Immune System defends the body against infections and certain other diseases.
* It consists of different organs, cells and proteins known as Anti-Bodies
* Sometimes the Immune system makes a mistake and attacks the body’s own tissues or organs known as autoimmunity

**Examples of Auto-Immune Diseases:**

* + Type-I Diabetes, Systemic Lupus Erythematosus(SLE)
  + Rheumatoid Arthritis

# Complement System:

* Complement was discovered by Jules Bordet as a heat-labile component of normal plasma that causes the **Opsonization (enhancement of phagocytosis)** and **killing of bacteria**
* The complement system refers to a series of >20 proteins, circulating in the blood and tissue fluids
* These proteins complement (i.e., augment) the effects of other components of the immune system (e.g., antibody)
* Complement is an important component of our innate host defenses
* Complement protein synthesized mainly by the liver

## Role of Complement system:

There are three main effects of complement system:

1. **Lysis** of cells such as bacteria , allografts and tumor cells
2. **Generation of mediators** that participate in inflammation and attract neutrophils
3. **Opsonization** (enhancement of phagocytosis)

## Activation of Complement:

* Most of the proteins are normally inactive,and are proenzymes
* In response to the recognition of molecular components of microorganisms they become sequentially activated in an enzyme cascade
* The activation of one protein enzymatically cleaves and activates the next protein in the cascade
* Activation of complement system can be initiated either by antigen-antibody complex or by a variety of nonimmunologic molecules e.g., endotoxin

## Different Types of Complement Pathways:

* Classical Pathway
* Alternative Pathway
* Mannose-binding Lectin Pathway
* Lytic Pathway

## Role of Complement in Diseases:

* The complement system plays a critical role in inflammation and defense against some bacterial infections.
* Complement may also be activated during reactions against incompatible blood transfusions
* During the damaging immune responses that accompany autoimmune disease
* **Opsonization**: microbes are phagocytized much better in the presence of C3b because there are C3b receptors on the surface of many phagocytes
* C5a and C5,6,7 complex attract neutrophils, C5a also enhances the adhesiveness of neutrophils to the endothelium

## Diseases associated with complement deficiencies:

Table 4. Diseases associated with complement deficiencies

|  |  |
| --- | --- |
| Complement Deficiency | Disease |
| C3 and Factor B | Severe bacterial infections |
| C3b-INA, C6 and C8 | Severe Neisseria infections |
| Deficiencies of early C components C1, C4, C2. | Systemic lupus erythematosus (SLE), glomerulonephritis and polymyositis |
| C1-inhibitor | Hereditary angioedema |

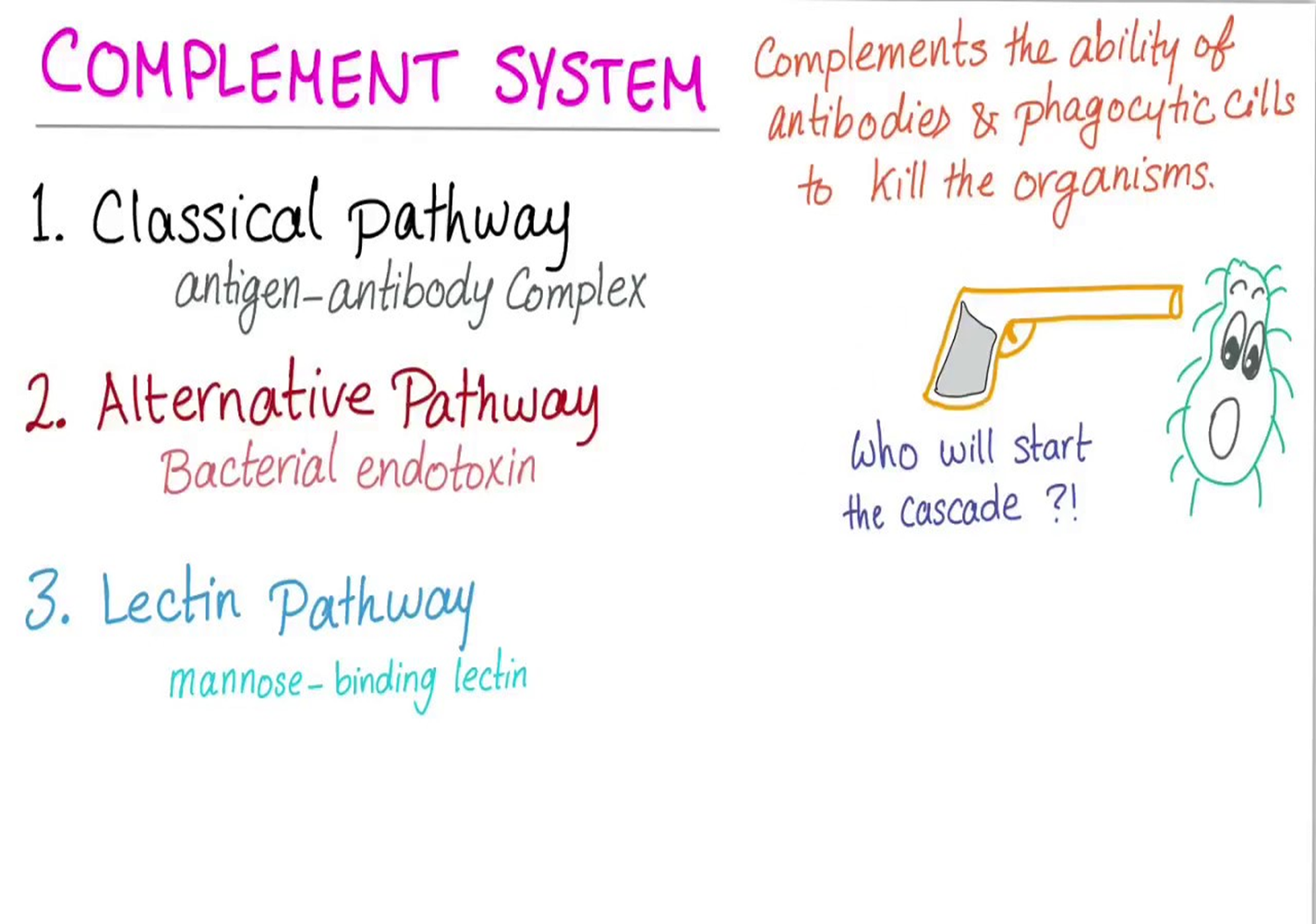
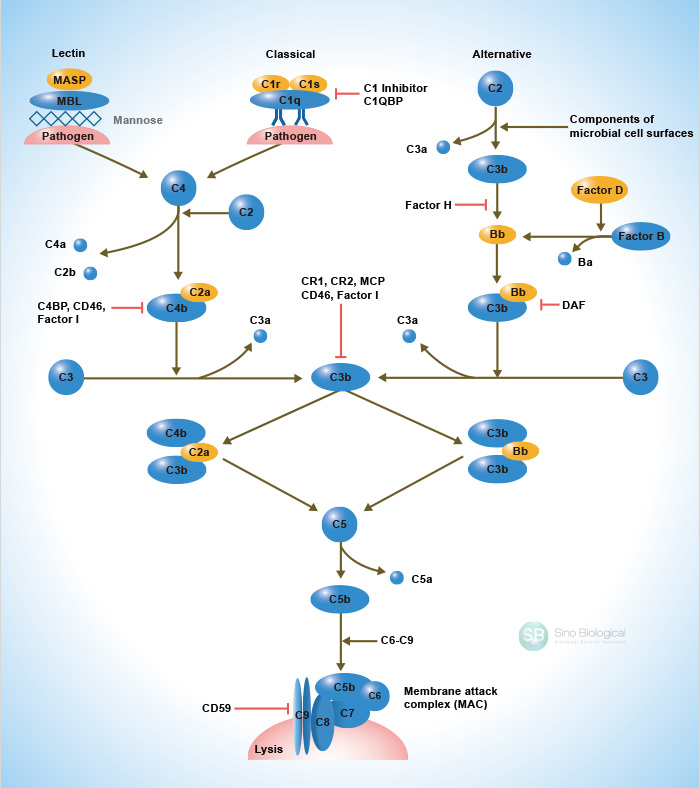


Table 5. Classic and Alternative pathways

|  |  |
| --- | --- |
| Classic Pathway | Alternative Pathway |
| * Specific acquired immunity * Initiated by antibody * Interaction of all components | * Non-specific innate immunity * Bacterial endotoxin, capsule * C1, C4, C2 are by-passed |

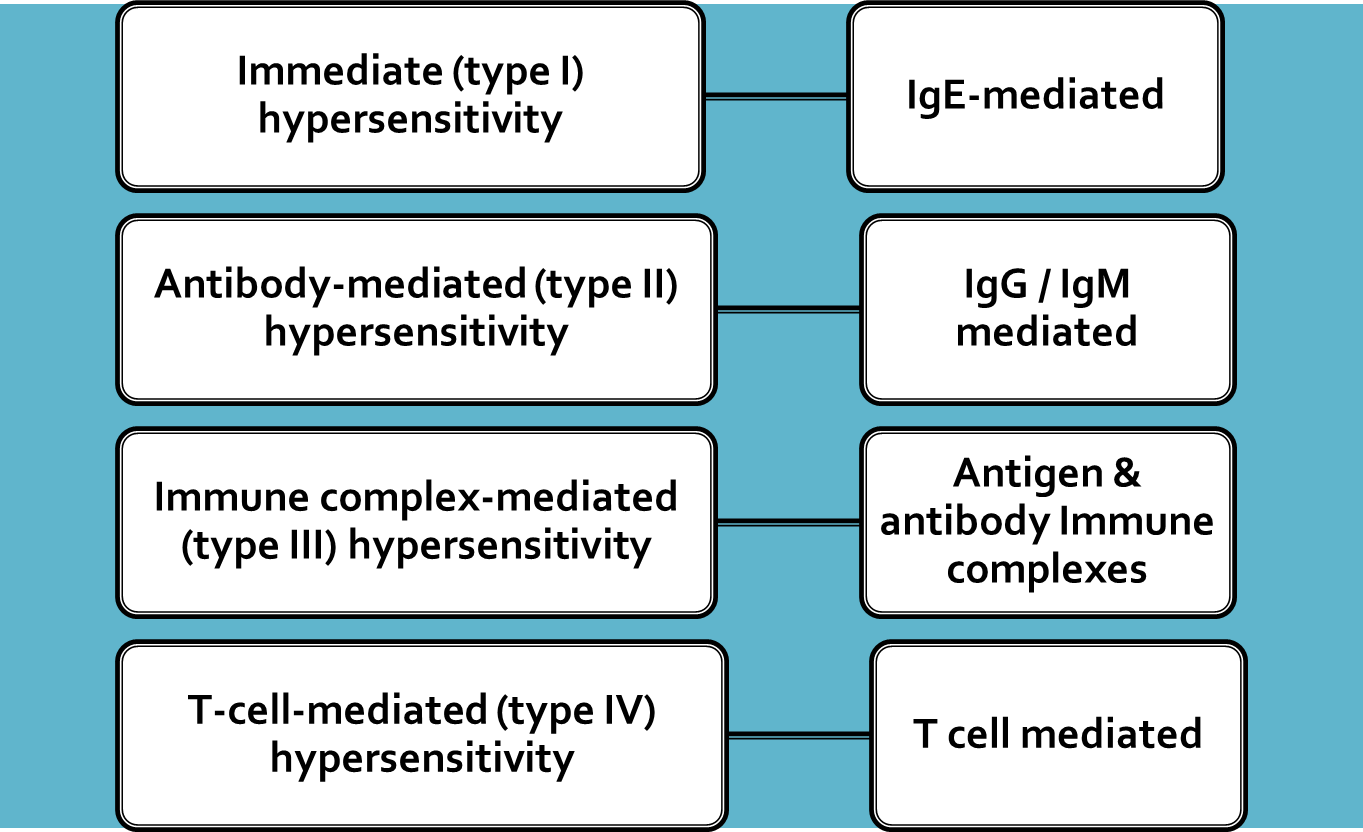


# Hyper-Sensitivity:

* Hypersensitivity reactions (HR) are immune responses that are exaggerated or inappropriate against an antigen or allergen
* Hypersensitivity immune responses are capable of causing tissue injury and diseases that are called “hypersensitivity diseases”
* Hypersensitivity reactions occur in response to external stimuli(antigen) whereas autoimmune reactions occur in response to internal stimuli(antigens)
* The term **allergy** is often equated with hypersensitivity

# Classification of hypersensitivity

Coombs and Gell classified hypersensitivity reactions into four forms:



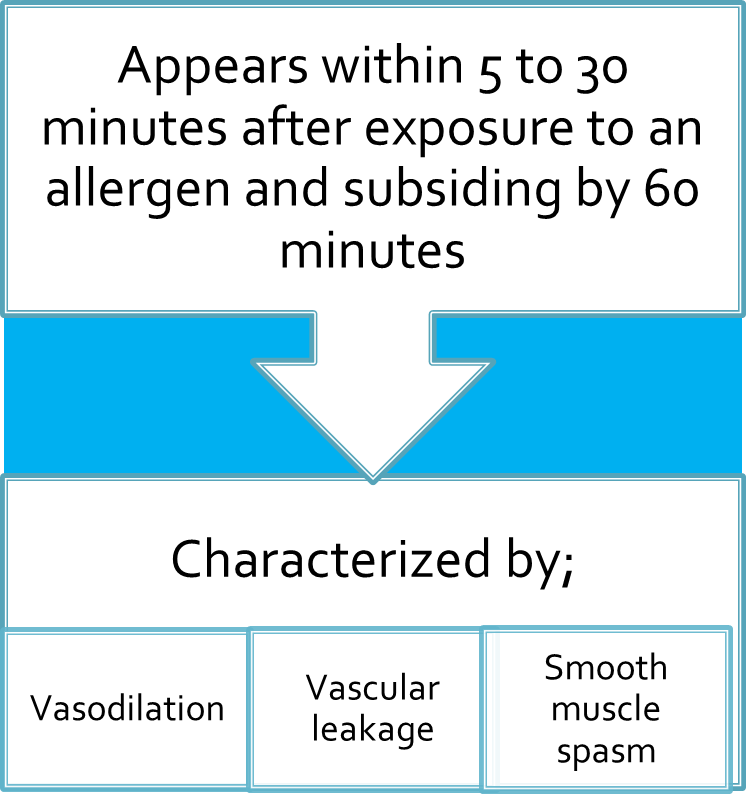
## Type I or Anaphylactic Response:

Anaphylactic Responses mediated by IgE antibodies that are produced by the immune system in response to environmental proteins (allergens) such as pollens, animal danders or dust mites. These antibodies (IgE) bind to mast cells and basophils, which contain histamine granules that are released in the reaction and cause inflammation bronchial asthma, allergic rhinitis, allergic dermatitis, food allergy, allergic conjunctivitis, and anaphylactic shock may take place.

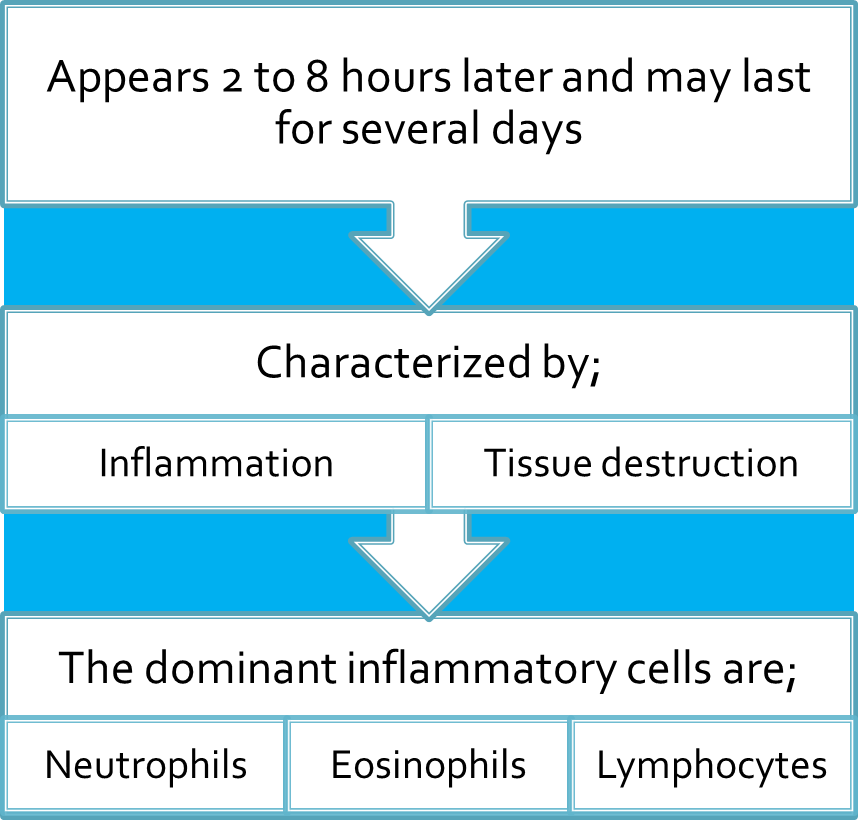
### Common allergens:

* Skin contact (Pollen,latex,animal scratches,poison plants)
* Injection (bees sting)
* Ingestion (medication,nuts)
* Inhalation (pollen,dust,animal dander)

### The immediate response:



### Late-phase reaction:



## Type II or Cytotoxic-Mediated Response:

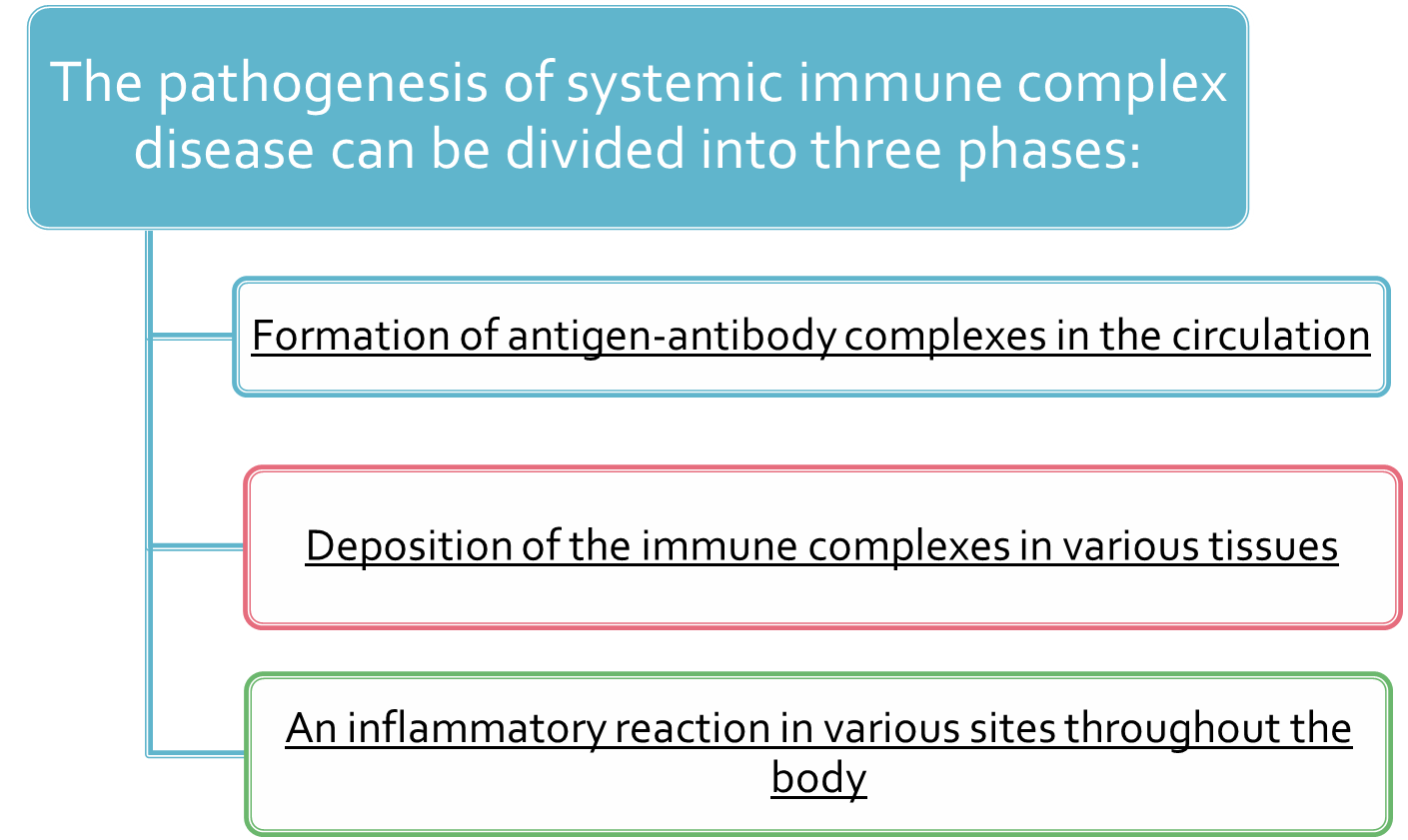
* IgG and IgM mediate cytotoxic-mediated response against cell surface and extracellular matrix proteins
* The immunoglobulins involved in this type of reaction damages cells by activating the complement system or by phagocytosis
* Type II hypersensitivity reactions can be seen in **immune thrombocytopenia, autoimmune hemolytic anemia, and autoimmune neutropenia**

## Type III or Immunocomplex Reactions:

* These are also mediated by IgM and IgG antibodies that react with soluble antigens forming antigen-antibody complexes
* The complement system becomes activated and releases chemotactic agents that attract neutrophils and cause inflammation and tissue damage as seen in vasculitis and glomerulonephritis
* Type III hypersensitivity reactions can classically be seen in serum sickness and Arthus reaction

### Pathogenesis of type III immunity:

* Immune complex hypersensitivity occurs when antigen–antibody complexes induce an inflammatory response in tissues.
* Antigen-antibody (immune) complexes that are formed in the circulation, may deposit in tissues, leading to complement activation and acute inflammation.



### Clinical examples of type III:

Table 6. Clinical examples of type III

|  |  |
| --- | --- |
| Disease | Antigen Involved |
| Systemic lupus erythematosus | Nuclear antigens |
| Post streptococcal glomerulonephritis | Streptococcal cell wall antigen |
| Polyarteritis nodosa | Hepatitis B virus antigens |
| Reactive arthritis | Bacterial antigens (e.g. Yersinia) |
| Serum sickness | Various proteins e.g. foreign serum protein |
| Arthus reaction (experimental) | Various foreign proteins |

### Arthus Reaction:

* A type of local type III hypersensitivity reaction
* A local vasculitis associated with deposition of immune complexes and activation of complement
* Is produced by intradermal injection of an antigen into the skin of a previously immunized individual
* Occur 4–12 hours after injection
* Characterized by severe pain, swelling, induration, edema, hemorrhage, and occasionally by necrosis
* Reported after vaccination against diphtheria and tetanus

## Type IV hypersensitivity reaction:

* Type IV hypersensitivity reaction is also called **delayed type hypersensitivity** reaction because it takes 2 to 3 days for the reaction to develop after exposure to the particular substance.
* Cell-Mediated Type of hypersensitivity is initiated by antigen activated T lymphocytes including; CD4+ T cells and CD8+ T cells.
* Two types of T-cell reactions are capable of causing tissue injury and disease:
* Delayed-type hypersensitivity: initiated by CD4+ T cells
* Direct cell cytotoxicity: mediated by CD8+ T cells

|  |  |  |  |
| --- | --- | --- | --- |
| **Main immune cells involved** | **Important disease** | **Pathologic or Clinical Features** | **Common inducing agents** |
| CD4 (helper) T cells and macrophages | Tuberculosis, coccidiodomycosis | Granuloma | Constituents of bacterim or fungus |
| CD8(cytotoxic) T cells | Contact dermatitis  Steven Johnson syndrome  Toxic epidermal necrolysis | Pruritic  Vesicular rash  Target lesion | Oil of poison oak or poison ivy, topical drugs, soaps, heavy metals jewelry, herpes simplex virus 1, sulfonamides |