Hypersensitivity

Definition: Any exaggerated immune response against a foreign antigen leading to harmful effects.

Types:

-Type I (immediate).

- Type II (cytotoxic).

- Type III (immune complex).

- Type IV (delayed or cell-mediated)**.**

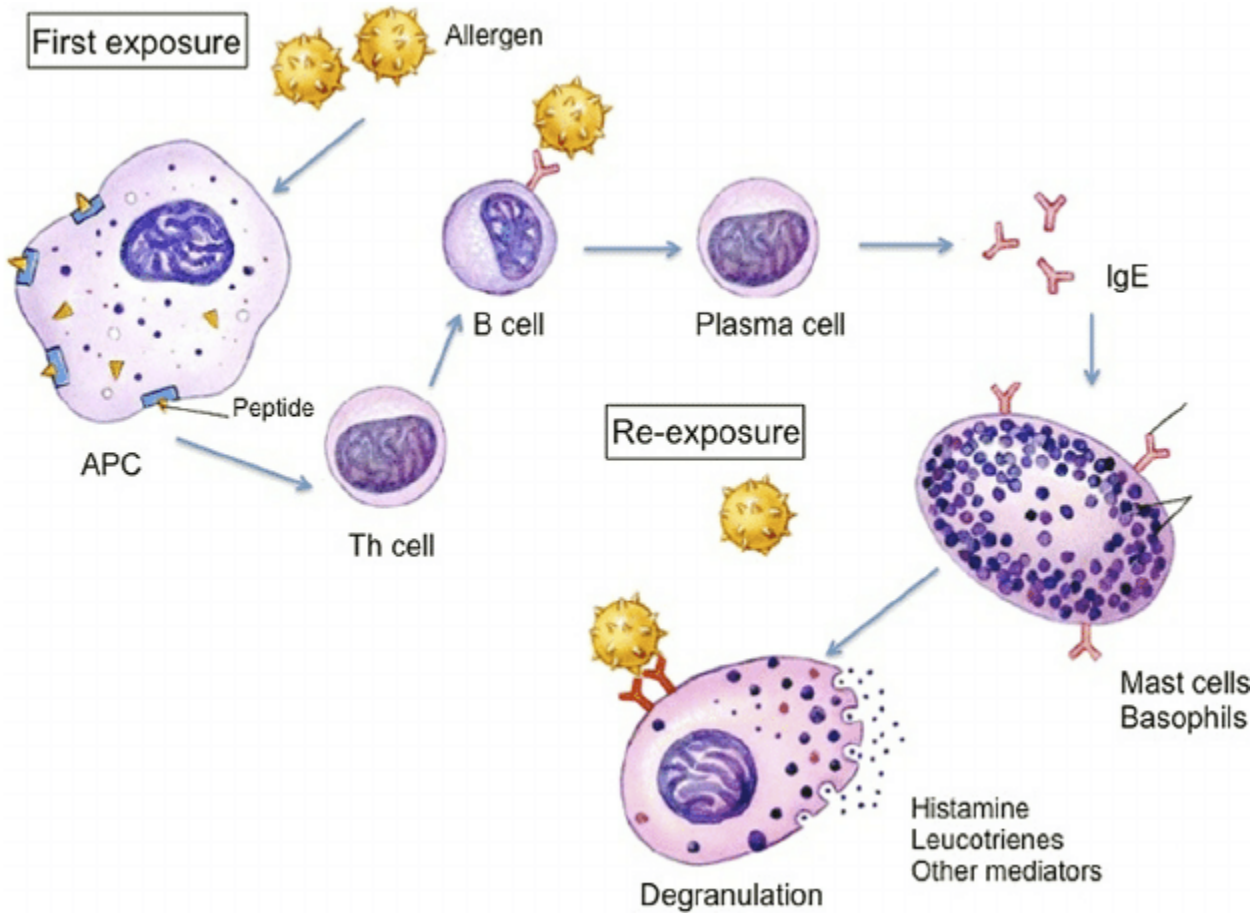
TYPE I (IMMEDIATE) HYPERSENSITIVITY

- Type I hypersensitivity reactions are exaggerated immune responses to harmless environmental antigens.
- They are mediated by IgE.
- Either Localized or systemic reaction.
- The antigens that stimulate it are called allergens.

Mechanism:

The allergic reaction first requires sensitization to a specific allergen (usually harmless) and occurs in genetically predisposed individuals. The allergen is either inhaled, Contacted or ingested and is then processed by an antigen-presenting cell (APC), such as a dendritic cell, macrophage, or B-cell. The antigen-presenting cells then migrate to lymph nodes. The production of IgE is under the control ofTh2 cells

- These TH2 cells then release IL-4.
- IL-4 act on B cells to promote production of antigen-specific IgE (class switching from IgM to IgE).
- IgE has very high affinity for its receptor (Fc) on mast cells and basophils.
- A subsequent exposure to the same allergen cross links the cell-bound IgE and triggers the release of various active substances. Cross-linking of IgE Fc-receptor is important in mast cell degranulation.


First exposure
Allergen
B cell
Plasma cell
IgE
Peptide
APC
Th cell
Re-exposure
Mast cells
Basophils
Histamine
Leucotrienes
Other mediators
Degranulation

These **mediators** include :

a- Preformed mediators: Histamine and platelet activating factor (PAF) are the mediators of symptoms and signs seen during the early phase, which occurs within 15-20 minutes of exposure to the allergen. The signs include the wheal , flare reaction , oedema and increased vascular permeability.

b- Newly formed mediators: The leukotrienes and prostaglandins, which take several hours to be synthesized, cause the symptoms seen during the late phase. The late phase typically occurs 5-6 hours after allergen contact . The symptoms of the late phase is the same as those of early phase, but persist longer.

Clinical Examples:

1- Anaphylaxis

- This is a generalized (systemic) form of type I hypersensitivity characterized by vasodilatation and smooth muscle contraction resulting in pallor, hypotension, edema, wheezing, cyanosis, nausea, itching, urticaria, loss of consciousness and may end in death.
- The condition may occur after a short time (5-20 minutes) due to previous sensitization by foreign antigens, e.g. penicillin, foreign serum, insect venom or ruptured hydatid cyst.

2- **Atopy**

This is a localized form of Type I hypersensitivity which usually develops in susceptible individuals as a result of exposure to:

- Inhalant allergens; e.g. plant pollens, house dust, house dust mites, mold spores.
- Ingestant allergens; e.g. foods (such as milk, fish, egg, strawberries, etc...).
- Contactant allergens; animal fur, feathers, hair, etc The manifestations of atopy may be bronchial asthma, allergic rhinitis, hay fever, conjunctivitis, urticaria and gastrointestinal disorders, e.g. diarrhea.

Diagnosis

1- The cutaneous test (prick test, puncture test): Routine diagnosis in diseases (atopic or anaphylactic): A single drop of concentrated aqueous allergen extract placed on the skin which is then pricked lightly with a needle point at the center of the drop. After 20 minutes the reaction is graded and recorded.

2. Measurement of levels of total IgE and IgE specific for a particular allergen.

Management of anaphylactic shock.

1. Anaphylactic shock is an emergency which must be dealt with immediately by administration of adrenaline, corticosteroids together with oxygen inhalation.
2. Administer drugs that counteract inflammatory mediators: Antihistamines neutralize histamine.
3. Treat asthma with a corticosteroid and a bronchodilator.
4. Epinephrine neutralizes many mechanisms of anaphylaxis**:** Relaxes smooth muscle. and reduces vascular permeability**.**

II. Management of atopy

1. Avoidance of the responsible allergen.

2. **Specific Immunotherapy :**This involves injecting the patient, over time, with gradually increasing doses of the responsible allergen. The aim of immunotherapy is shifting the immune response from Th2 to Th1 response .

As a result of this treatment , specific IgE level decrease and IgG titters rise .

3. Drugs that block the release of the mediators or counteract their effects, e.g. antihistaminic, corticosteroids and anti-leukotrienes.

4. Monoclonal anti-IgE antibodies: These antibodies attach to the Fc portion of IgE and prevent it from attaching to mast cells.

TYPE II: CYTOLYTIC (CYTOTOXIC) HYPERSENSITIVITY

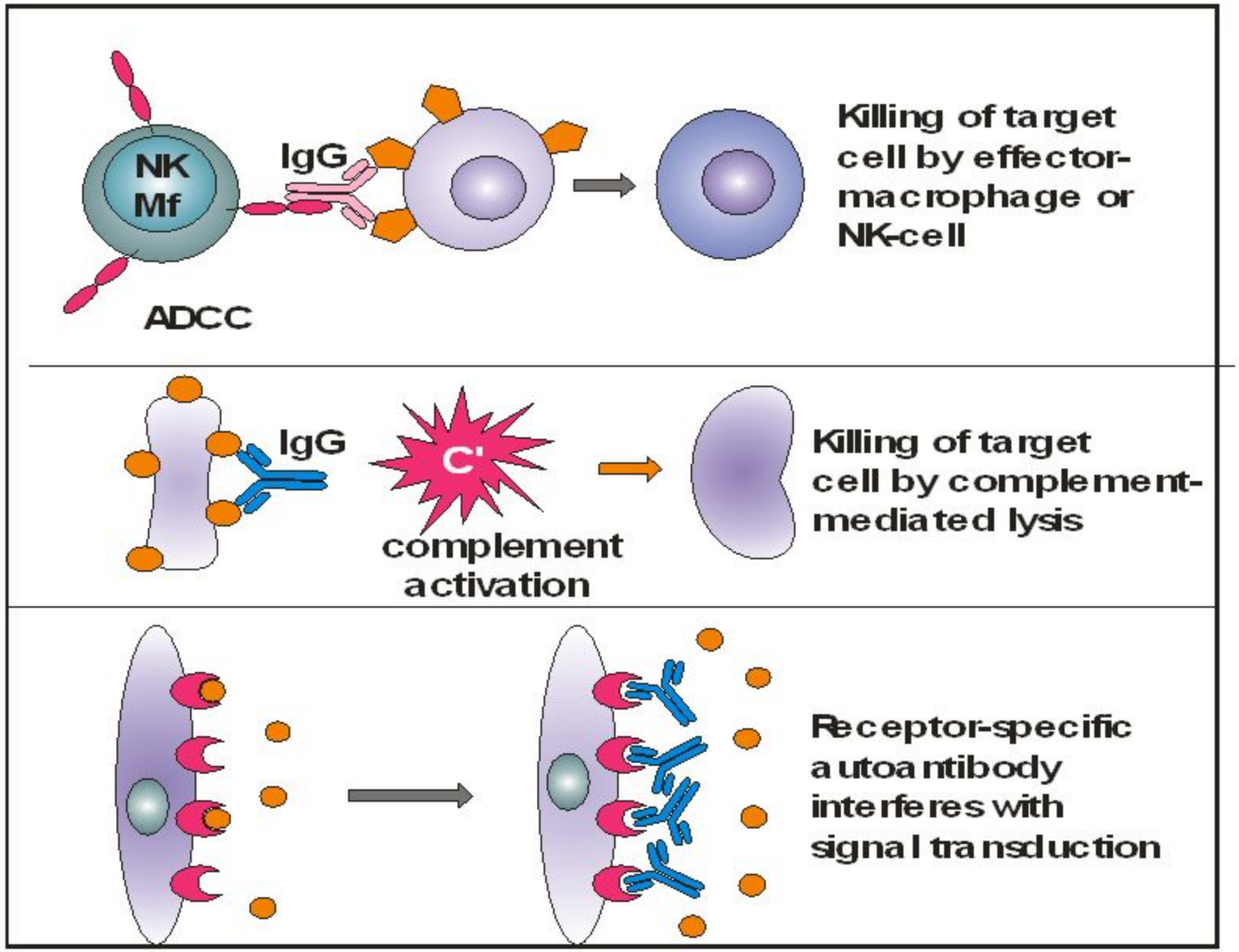
These occur when an antibody (IgG or 1gM) react with antigen on the cell surface. This antigen is a part of the cell membrane or it is a circulating antigen (or hapten) that attaches to the cell membrane. This cell may then be destroyed by one of the following destructive processes:

a- The complement is fixed to the antigen antibody complex in the cell membrane. Lysis of target cells occurs via the activated complement.

b- Opsonization of target cells.

c- Lysis of target cells by antibody-dependent cell-mediated cytotoxicity (ADCC) through the action of natural killer (NK) cells, polymorphs or macrophages.

MECHANISMS OF TYPE II HYPERSENSITIVITY REACTIONS



Examples of Cytolytic (Cytotoxic) Reactions

1.Transfusion reactions due to blood group (ABO or Rh) incompatibility.

1. Autoimmune diseases, e.g. autoantibodies to an individual's own red blood cells are present in autoimmune hemolytic anemia. Autoantibodies to other tissues, e.g. kidney and skin may be produced in certain diseases and lead to tissue damage of the respective organs.

3. Drug reaction: drug may become attached to a cell surface. Antibodies to the drug reacting at the cell surface lead to destruction of the cell in presence of complement.

4. In graft rejection; cytotoxic reactions are one of the mechanisms of tissue damage.

TYPE III: IMMUNE-COMPLEX HYPERSENSITIVITY REACTIONS

- When antibodies combine with their specific antigen, immune complexes are formed. Normally, they are effectively removed by the reticuloendothelial system (macrophages).

- Small soluble immune complexes are formed, especially when there is antigen excess. These complexes, being very small, may escape phagocytosis and become deposited in tissues (especially in joints and kidneys) leading to tissue damage.

Mechanism of Tissue Damage:

1. The first step is the formation of soluble immune complexes that are formed of antigen and IgG or IgM.

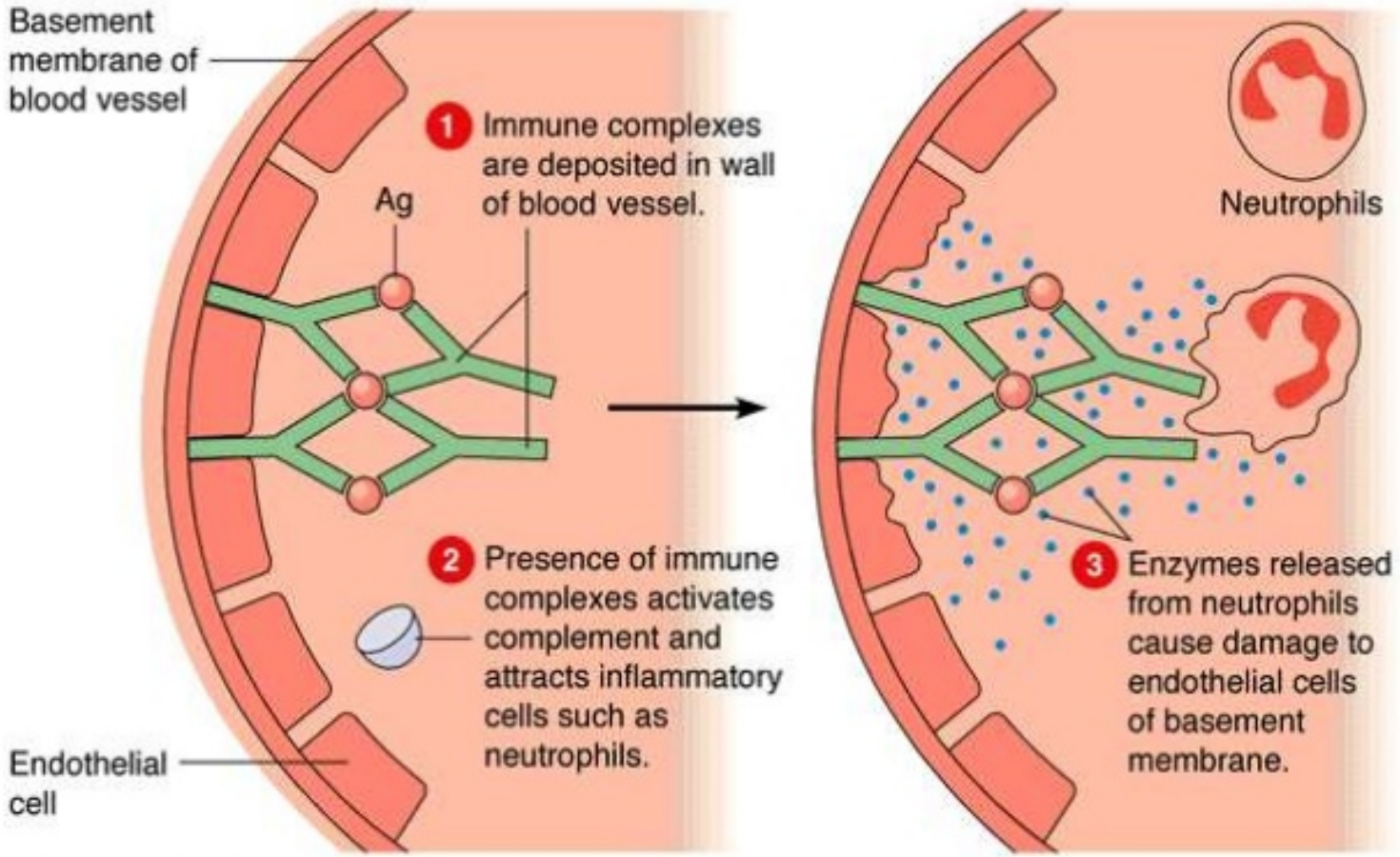
2. These immune complexes penetrate the endothelium of blood vessel walls and become deposited on the vascular basement membrane.

3. Complement is activated and C3a and C5a (anaphylatoxins) are released:

a. These anaphylatoxins react with receptors on mast cells and basophils, causing release of vasoactive amines (e.g. histamine), which increase vascular permeability.

b. C5a, is also chemotactic for neutrophils which infiltrate the area. In an attempt to engulf the immune complexes, these phagocytic cells degranulate and release lysosomal enzymes that destroy the basement membrane.

4. Platelets are aggregated with two consequences; they release vasoactive amines and form microthrombi which cause local ischemia and further tissue damage .


Basement membrane of blood vessel
1 Immune complexes are deposited in wall of blood vessel.
Ag
2 Presence of immune complexes activates complement and attracts inflammatory cells such as neutrophils.
Endothelial cell
Neutrophils
3 Enzymes released from neutrophils cause damage to endothelial cells of basement membrane.
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Examples of Immune-Complex-Mediated Reactions

1. Serum Sickness

This syndrome is considered to be a systemic immune-complex disease. It occurs following injection of large amount of foreign serum (e.g. horse antitetanic or antidiphtheritic serum), The antigen is slowly cleared from the circulation, while antibody production begins. These antibodies react with remnants of antigens still present.

Immune complexes are formed, which may become deposited at various sites causing the manifestations of the disease. Typical serum sickness results in fever, urticaria, arthralgia, lymphadenopathy, and splenomegaly, which develop a few days to 2 weeks after injection of the foreign serum or drug.

2. Arthus reaction

This is a form of local immune complex disease due to repeated subcutaneous injection of low dose of a foreign antigen, e.g. insulin and rabies vaccine. The reaction occurs at the site of antigen injection. Immune complexes are deposited in the walls of blood vessels, complement is activated, and the previously mentioned inflammatory response is initiated resulting in local erythema, oedema and necrosis.

3. Post-streptococcal glomerulonephritis.

4. Viral infections: e.g. hepatitis B.

5. Autoimmune diseases: e.g. rheumatoid arthritis and systemic lupus erythematosus (SLE).

Therapeutic Measures

1.Anti inflammatory drugs e.g. antihistaminics and corticosteroids.

2. Suppression of the immune response by corticosteroids and immunosuppressive drugs.

3. Removal of offending complexes via plasmaphoresis (exchanging the patient's plasma with normal plasma, thereby removing the immune complexes)

TYPE IV: CELL MEDIATED (DELAYED) HYPERSENSITIVITY

It is an exaggerated cell mediated immune response that damages host cells. The main cell involved is the activated T-lymphocyte (Th1). Antibody and histamine play no role in this type. The response is delayed (starts hours or days after contact with the antigen

Mechanism:

Th1 cells recognize antigens and release pro-inflammatory cytokines. These act on the vascular endothelium leading to increase vascular permeability and leakage of fluid into the tissues. They also attract and activate monocytes, macrophages as well as more T cells. These inflammatory reactions lead to local tissue damage. Cytotoxic T cells may also play a role .

Examples:

1. **The tuberculin skin test reaction** is the classic clinical example of delayed hypersensitivity by intradermal injection of purified protein derivative

2**. Contact dermatitis**

The manifestations of cell mediated hypersensitivity occur after sensitization with chemicals, plant materials, topically applied drugs and some cosmetics. In all cases, the small molecules acting as haptens enter the skin, attach to body proteins, which are taken up by APCs in the skin (Langerhan's cells) to be presented to T cells.

3.Granuloma formation :Cell-mediated hypersensitivity reactions are seen in a number of chronic infectious diseases, especially those caused by intracellular bacteria, e.g. mycobacteria.

4. Autoimmune diseases.

5. Graft rejection