Chapter 10. Hypersensitivity Reactions

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The purpose of immune response is to eliminate the foreign antigens that have entered into the host. In most instances, immune response leads to only a subclinical or localized inflammatory response which just eliminates the antigen without causing significant damage to the host. However, at times, this response becomes abnormal; leading to an exaggerated inflammatory response that causes extensive tissue damage or sometimes even death.

DEFINITION AND CLASSIFICATION

The term hypersensitivity (HSN) or allergy refers to the injurious consequences in the sensitized host, following contact with specific antigens. Gell and R Coombs classified HSN reactions into four types *(Table 10.1)*.

- **Immediate HSN reactions:** These reactions occur immediately, within minutes to few hours of antigen contact, as a result of an abnormal exaggerated humoral response (antibody-mediated). This can be further classified into three types (HSN type I, II, and III), based on the type of effector mechanisms
- **Delayed HSN reaction:** It occurs after few days of antigen contact, as a result of an abnormal cell-mediated immune response.

Table 10.1. Features of various types of hypersensitivity reactions.

	Type I	***Type II***	***Type III***	***Type IV***
Immune response altered	Humoral	Humoral	Humoral	Cell-mediated

	Type I	***Type II***	***Type III***	***Type IV***
Immediate or delayed	Immediate	Immediate	Immediate	Delayed
The duration between the appearance of symptoms and antigen contact	2–30 minutes	5–8 hours	2–8 hours	24–72 hours
Antigen	Soluble	Cell surface bound	Soluble	Soluble or bound
Mediator	IgE	IgG	Ag-Ab complex	T_{DTH} cell
Effector mechanism	Mast cell degranulation	ADCC Complement-mediated cytolysis	Complement activation and inflammatory response	Macrophage activation leads to phagocytosis or cell cytotoxicity
Abbreviation: ADCC, antibody-dependent cellular cytotoxicity.				

This is also called type IV HSN reaction. It is mediated by a specific subset of T_H cells called delayed hypersensitivity T cells or T_{DTH} cells.

TYPE I HYPERSENSITIVITY REACTION

Type I HSN reaction involves the production of IgE by sensitized B cells following contact with an allergen which in turn induces mast cell degranulation. Type I reaction occurs in various clinical conditions such as anaphylaxis and asthma.

Mechanism of Type I Hypersensitivity

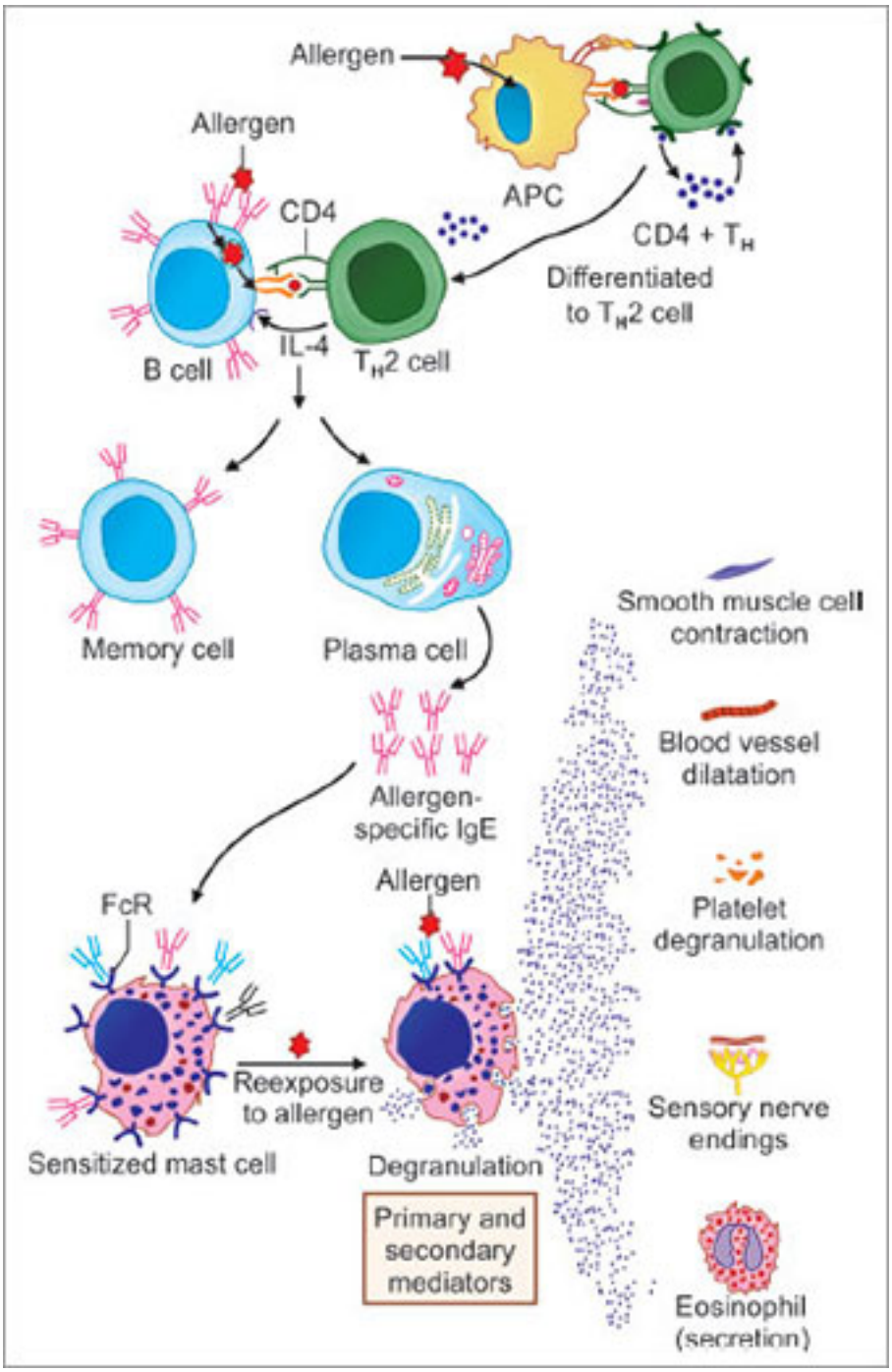
Type I HSN reaction occurs through two phases; the sensitization and effector phases, both occurring with an interval of 2–3 weeks *(Fig. 10.1)*.

Sensitization Phase

This occurs when an individual is exposed for the first time to the sensitizing or priming dose of an allergen.

- In susceptible individuals, very minute doses can be sufficient to sensitize the host cells
- The antigenic peptides are presented by antigen-presenting cells to the CD4 helper T cells
- Activated T_H cells are differentiated into T_H2 cells which in turn secrete interleukin 4 (IL-4)
- IL-4 induces the B cells to differentiate into IgE producing plasma cells and memory cells
- Secreted IgE migrates to the target sites, and coat on the surface of mast cells. Such sensitized mast cells (coated with IgE) will be waiting for interaction with the subsequent antigenic challenge.

Fig. 10.1. Mechanism of type I hypersensitivity reaction.



Effector Phase

When the same allergen is introduced subsequently (shocking dose), it directly encounters with the IgE antibodies coated on mast cells.

- IgE cross-linkage initiates the mast cell activation and degranulation. Granules in turn release several pharmacologically active chemical mediators that lead to various manifestations of type-1 reaction

- **Degranulation occurs in two phases**: Mast cells undergo degranulation in two phases

  1. Primary mediators: The preformed chemical mediators which are already synthesized by mast cells are immediately released, e.g. histamine and serotonin

  2. Secondary mediators: The mast cells synthesize them following stimulation by allergen and release, e.g. prostaglandins and leukotrienes.

- **Pharmacological actions:** The chemical mediators perform several pharmacological actions, such as bronchial and other smooth muscle contraction, increased vascular permeability, and vasodilation

- **Symptoms:** These actions in combinations, produce symptoms such as breathlessness, hypotension, and shock leading to death at times.

Manifestations of Type I Reaction

There are various manifestations of type I HSN reaction.

- **Systemic anaphylaxis:** It is an acute medical emergency condition, characterized by severe dyspnea, hypotension, and vascular collapse leading to death at times

  - A wide range of allergens such as penicillin have been shown to trigger anaphylaxis in susceptible humans

  - Epinephrine (adrenalin) is the drug of choice for systemic anaphylactic reactions.

- **Localized anaphylaxis (Atopy):** Here, the reaction is limited to a specific target tissue or organ, mostly the epithelial surfaces at the entry sites of allergen. They almost always run in families (i.e. inherited). Examples include:

  - *Allergic rhinitis (or hay fever):* Exposure to airborne allergens with the conjunctiva and nasal mucosa leads to conjunctival watering, sneezing, and coughing

  - *Asthma:* Exposure to allergens to lower respiratory mucosa results in contraction of bronchial smooth muscles, bronchoconstriction, and dyspnea

  - *Food allergy:* The food allergens (e.g. nuts, eggs, seafood, etc.) can stimulate the mast cells lining the gut mucosa to cause GI symptoms such as diarrhea and vomiting

  - *Atopic dermatitis* (allergic eczema): Characterized by erythematous skin eruptions

  - *Drug allergy* by various drugs such as penicillin, sulfonamides, etc.

Detection of Type I Hypersensitivity

Type I HSN reaction can be demonstrated by various tests such as:

- Skin prick test

- Detection of total serum IgE antibody by various enzyme immunoassay

- Detection of allergen-specific IgE by various immunoassay formats.

Treatment

Treatment of type I HSN reaction includes:

- Avoidance of contact with known allergens
- **Hyposensitization:** Repeated exposure to increased subcutaneous doses of allergens can reduce or eliminate the allergic response to the same allergen
- Monoclonal anti-IgE antibody
- Drugs such as antihistamines, epinephrine (adrenaline), and cortisone.

TYPE II HYPERSENSITIVITY REACTION

In type II reactions, the host injury is mediated by *antibodies* (IgG or rarely IgM), which interact with various types of antigens, such as:

- Host cell surface antigens (e.g. RBC membrane antigens like blood group and Rh antigens)
- Extracellular matrix antigens, or
- Exogenous antigens absorbed on host cells (e.g. a drug coating on the RBC membrane).

Various clinical conditions where type II HSN reactions occur are as follows:

- Complement-dependent reaction, e.g. ABO or Rh incompatibility, hemolytic anemia (autoimmune or drug-induced)
- Antibody-dependent cellular cytotoxicity (ADCC)
- Antibody-dependent cellular dysfunction, e.g. Graves' disease and myasthenia gravis.

TYPE III HYPERSENSITIVITY REACTION

Type III HSN reactions develop as a result of the excess formation of immune complexes (Ag-Ab complexes) which initiate an inflammatory response through activation of the complement system leading to tissue injury. Type III reactions occur either in localized or generalized forms.

- **Localized or arthus reaction**: It is defined as a localized area of tissue necrosis due to vasculitis resulting from acute immune complex deposition at the site of inoculation of antigen
  - In skin: Following insect bites
  - In lungs: Farmer's lungs, following inhalation of actinomycetes.
- **Systemic reaction:** Here, the small-sized soluble Ag-Ab complexes are carried in circulation and deposited in various distant sites. Examples include:
  - Connective tissue disorders such as systemic lupus erythematosus and rheumatoid arthritis
  - **Serum sickness:** This condition is not seen nowadays, it was seen in the past, following serum therapy, i.e. administration of foreign serum, e.g. horse anti-tetanus serum, to treat tetanus cases.

TYPE IV HYPERSENSITIVITY REACTION

Type IV HSN reactions differ from other types in various ways:

- **Delayed type:** It is delayed-type (occurs after 48–72 hours of antigen exposure)

- **T_{DTH}** *cells:* It is cell-mediated; characteristic cells called T_{DTH} cells (delayed type of hypersensitivity T cells) are the principal mediators of type IV reactions
- **Activated macrophages:** Tissue injury occurs predominantly due to activated macrophages
- **Mechanism:** The type IV HSN reaction occurs in two phases:
  1. *Sensitization phase:* This is the initial phase of 1–2 weeks, that occurs following antigenic exposure. The antigen-presenting cells process and present the antigenic peptides to the helper T cells. T_H cells are differentiated to form T_{DTH} cells
  2. *Effector phase*: The T_{DTH} cells, on subsequent contact with the antigen, secrete a variety of cytokines (e.g interferon-$_{\gamma)}$ which attract and recruit various inflammatory cells (e.g. macrophages) at the site of DTH reaction.
- **Granuloma formation:** Pathology of type IV reaction involves granuloma formation: Granuloma consists of an inner zone of epithelioid cells, typically surrounded by a collar of lymphocytes and a peripheral rim of fibroblasts and connective tissue
- **Common examples** of type IV reaction include:
  - Skin tests such as tuberculin test and lepromin test
  - Contact dermatitis, following exposure to nickel, etc.

EXPECTED QUESTIONS

1. I. Write short notes on:

1. Type I hypersensitivity reaction.
2. Type II hypersensitivity reaction.
3. Immune complex-mediated hypersensitivity reaction.
4. Type IV hypersensitivity reaction.

2. II. Multiple Choice Questions (MCQs):

1. **Type I hypersensitivity is mediated by which of the following immunoglobulins?**
   a. IgA
   b. IgG
   c. IgM
   d. IgE
2. **All are early hypersensitivity reactions,** *except:*
   a. Type I hypersensitivity
   b. Type II hypersensitivity
   c. Type III hypersensitivity
   d. Type IV hypersensitivity
3. **A positive tuberculin test is an example of:**

a. Type I hypersensitivity

b. Type II hypersensitivity

c. Type III hypersensitivity

d. Type IV hypersensitivity

Answers

1. d	**2.** d	**3.** d