Immunologic mechanisms of tissue damage
(hypersensitivity reactions)

Although the immune system generally is protective, the same immunologic mechanisms that defend the host may at times result in severe damage to tissues & occasionally may cause death. This inappropriate immune response is termed hypersensitivity or allergy. Gell & Coombs (1963) have classified hypersensitivity reactions into four major types:

- **Type I**: Anaphylaxis H.S.
- **Type II**: Antibody-dependent cytotoxic H.S.
- **Type III**: Immune-complex mediated H.S.
- **Type IV**: Cell-mediated (delayed) H.S.

**Type I hypersensitivity:** Which is also referred to as:

- Anaphylaxis H.S. →◊ (A Latin- word opposite to prophylaxis).
- Immediate H.S. →◊ (The reaction occurs within minutes after exposure to Ag).
- Atopy →◊ (A hereditary predisposition to the development of immediate hypersensitivity reaction against common environmental antigens).

This reaction results from the release of pharmacologically active substances from mast cells & basophils following interaction between Ag & Ab which present on surface of these cells. The reaction may be mild & localized one, e.g. allergic conjunctivitis, or it may be severe generalized reaction, e.g. anaphylactic shock.
Requirements of anaphylaxis:

1- IgE: It is referred to as:

Reagenic Ab, Homocytotropic Ab

IgE is named so because it possesses specific receptors on Cell membrane of mast cell & basophiles.

IgE receptors:

- Fc epsilon receptor I (FcεRI)
  These are high affinity IgE receptors expressed on cell Membrane of Basophils & mast cells (Langerhans cells).

- Fc epsilon receptor II (FcεRII) CD23
  These are low affinity IgE receptors Expressed on: T & B lymphocytes, monocytes, eosinophil, & platelets.

2- Allergenes: These are antigens capable of stimulating type I H.S. responses in allergic individuals, & they include:

  a- Inhalants → animal danders, plant pollens, fungal spores, houst dust, houst dust mites (dermatophagiodes).

  b- Ingestants → (foods, drugs ... etc.) egg albumin, fish, cheese, Nuts, milk, food additive, penicillin, aspirin.

  c- Contactants → pollen, food, drugs ... e

3- Mast cells & Basophils

They represent a major source of potent chemical mediator implicated in a wide spectrum of inflammatory & immunological processes.

In addition, they express membrane receptors (FcεRI) that specifically bind the Fc portion of IgE (binding site) Ab.

Immediate H.S. reactions are mediated or initiated when allergen molecule crosslink the Fab components of adjacent IgE molecule on the
surface of mast cells & basophils → degranulation of the cells & release vasoactive amines.

**Complements are not involved** in this type of reaction.

4- **Intra-cellular biochemical events (mast cell degranulation):**
The initial exposure to an allergen results in production of specific IgE & its ultimate fixation to mast cells & basophils; subsequent exposure to the allergen will trigger an Ag-Ab reaction on the cell membrane. A critical step is the bridging of adjacent membrane-bound IgE molecules by the allergen (one allergen molecule crosslink two adjacent FAB components of IgE on mast cells). This is followed by:

a- Influx of calcium ions into the mast cells.

b- Cytoplasmic phosphodiesterase is activated,

c- Increase level of 3,5 GMP & decreased level of cAMP.

d- Solublization & release of mediators stored in mast cells & basophils.
Mast cell & basophil mediators of atopic disease

(vesoactiveamines):

1- Preformed (stored) mediators:
   - Histamine
   - ECF-A
   - Eosinophil chemotactic factor of anaphylaxis

2- Synthesized mediators
   - PAF
   - SRS-A
   - Bradykinin
5- Vasoactive amines:

a- Histamine:
- It causes smooth muscle contraction of human bronchioles.
- It increases permeability of capillaries (vasodilatation).
- It increase secretions by nasal & bronchial mucous glands.
- max. Reaction 1-2 min → Duration 10 min.
- Responsible for symptoms of hay fever, angio-oedema, bronchospasm of acute anaphylaxis.

b- ECA-A (Eosinophil Chemotactic Factor of Anaphylaxis)
- preformed in basophils & mast cells.
- causes influx of eos. to area of allergic inflammation. (eosin Phil chemotaxis)

* role of eosinophils in allergy: They control allergic reactions by releasing histaminase and arylsulfatase, which degrade two important mediators, histamine and SRS-A, respectively. Eeosinophils may therefore reduce the severity of type I response.

c- HMW-NCF (High Molecular Wt. Neutrophil Chemotactic Factor)

d- Kinin-Generating proteases:

\[
\begin{align*}
\text{Protease enzymes} & \downarrow \text{Cleavage + activation} \\
\text{Hageman factor (XII)} & \\
\text{Plasma kininogen} & \rightarrow \text{Kinin & bradykinin}
\end{align*}
\]
- Smooth muscles contraction of bronchioles.
- ↑ vascular permeability
- ↑ secretion of mucous glands
- Stimulate pain fibers

**e-** PAF (Platelet Activating Factor) -◊ This factor enhances platelet aggregation & release vasoactive amines—◊ increase vascular permeability
—◊ contraction of smooth muscles
—◊ bronchoconstriction

**f-** Arachidonic acid metabolites (*slow reacting substances of anaphylaxis* SRS-A)

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Phospholipids $\xrightarrow{\text{phospholipase A}_2}$ Arachidonic acid

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<th>Oxidation</th>
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<td>5-lipoxygenase</td>
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<td>cyclooxygenase</td>
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Leukotrienes

- LTC4, LTD4, LTE4
- vasodilatation
- bronchoconstriction
- ↑ mucous secretion

Prostaglandins

- PGD2, PGF2, PGE1, PGE2

Clinical manifestations:
Clinical manifestations of immediate H.S. reaction begin very shortly (10-20 minutes) after allergen exposure, & vary greatly in severity &
depending on the target organ or tissue:

**Skin**
urticaria, angioneurotic oedema, atopic dermatitis

**Respiratory system**
Hay fever, asthma, allergic conjunctivitis

**Gastro-intestinal tract**
Vomiting, abdominal pain, diarrhoea

**Urinary tract**
Frequency, dysuria, hematuria

- **Vascular involvement** → CNS → headache, personality disorder

**Factors predisposing to type I H.S.:**
- **Genetic factors** (atopic allergies - hay fever, asthma, food allergy)
  Atopic individuals have IL4-gene coding for high level for IL4
  a- IL4 gene ---- IL4 → ↑ no. Th2
      ↑isotype switching
      ↑IgE level

b- HLA allele at (maternal & paternal) DR loci
e.g. allergy to grass pollen → HLA-DR3
   allergy to rag pollen → HLA-DR2, HLA-DR5

- **Environmental Factors**
Air pollutants (S02, car exhaust, fumes, passive cigarette smoking)
increase permeability of epithelial cells of respiratory tract for allergens.
**Diagnosis:**

- **In Vitro** → **PRIST** (Paper Radio Immunosorbent Test)
- **RAST** (Radio Allergosorbent Test)

These are radioimmunoassay tests to measure total IgE in serum & specific serum IgE respectively

- **In vivo (skin test)**

A series of potential allergens are administered via a scratch test or intradermal, & the injection sites are examined within 15-20 min. for the appearance of wheal (edema) & flare (erythema) reaction.

**Treatment & Prevention:**

1- **Avoidance of responsible allergens.** This can be accomplished easily with food allergies, however it may be difficult with inhalant allergens.

2- **Immunotherapy**

   a- **Desensitization**, **Hyposensitization** (**IgG-blocking Abs**)  
   This involves injecting the patient, over time, with gradually increasing doses of responsible allergens. This stimulates Th1 subsets rather than Th2, cytokines secreted by Th1 including γ-INF causing class switch in B-cell to produce allergen specific **IgG-blocking Abs**, these Abs diffuse in tissues, bind to allergen molecules & the IgG-allergen complex is removed by opsonisation, & no further allergen molecules bind IgE on mast cells.

   b- **Immunotolerance**
   By injecting the patient with synthetic peptides which bind T cell receptors directly & causing T cell anergy (**T cell unresponsiveness**). So T cell
cannot produce help to B cells for further activation.

3- **Drugs**
   a- Anti-histamins → Tavist-D (clemastin fumerate)
   b- Mast cell & basophil stabilizing drugs:
      1- Adrenaline → increase intracellular level of cAMP
      2- Theophylline → inhibits brake down of cAMP by phosphodiesterase
      3- Sodium chromoglycate → inhibits calcium influx
   c- General anti-inflammatory agents → corticosteroids

**Anaphylactoid reactions:**
The clinical manifestations of anaphylaxis can occur in the **absence** of any evidence for an allergen-IgE antibody event.
These reactions are believed to arise through the non-immunologic release of vasoactive & inflammatory mediators from mast cells and basophils in certain susceptible individuals. The **inciting agents** are:
- I.V. radiographic contrast media
- Aspirin
- Venom
- Exercise induce anaphylaxis
- Other causes → idiopathic