Hypersensitivity - an inappropriate immune response that causes damage to the individual

- Type I hypersensitivity - mediated by IgE
- Type II hypersensitivity - mediated by IgG
- Type III hypersensitivity - mediated by immune complexes
- Type IV hypersensitivity - cell-mediated

Immediate hypersensitivity - Types I, II and III
Delayed hypersensitivity - Type IV

**What makes an antigen to be an allergen?**

**Type I hypersensitivity = allergic reactions**
- Mast cells and basophils possess receptors for the Fc region of IgE (FcεRI). Eosinophils but ONLY after activation!!
- IgE produced in response to an antigen (allergen) binds to mast cells and basophils.
- If antigen cross-links this IgE on the cell surface, the FcεRI are cross-linked—resulting in degranulation of the cell and release of vasoactive mediators (histamine, leukotrienes, prostaglandins, cytokines etc).

**TABLE 15-1**

<table>
<thead>
<tr>
<th>Common allergens associated with type I hypersensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proteins</strong></td>
</tr>
<tr>
<td>Foreign serum</td>
</tr>
<tr>
<td>Vaccines</td>
</tr>
<tr>
<td><strong>Foods</strong></td>
</tr>
<tr>
<td>Nuts</td>
</tr>
<tr>
<td>Seafood</td>
</tr>
<tr>
<td>Eggs</td>
</tr>
<tr>
<td><strong>Plant pollens</strong></td>
</tr>
<tr>
<td>Peas, beans</td>
</tr>
<tr>
<td>Milk</td>
</tr>
<tr>
<td><strong>Insect products</strong></td>
</tr>
<tr>
<td>Bee venom</td>
</tr>
<tr>
<td>Wasp venom</td>
</tr>
<tr>
<td><strong>Drugs</strong></td>
</tr>
<tr>
<td>Cockroach calyx</td>
</tr>
<tr>
<td>Dust mites</td>
</tr>
<tr>
<td><strong>Molds</strong></td>
</tr>
<tr>
<td>Spores</td>
</tr>
<tr>
<td><strong>Animal hair and dander</strong></td>
</tr>
<tr>
<td>Lysozyme</td>
</tr>
<tr>
<td><strong>Latex</strong></td>
</tr>
</tbody>
</table>

**Features of inhaled allergens that may promote the priming of T<sub>h</sub>2 cells that drive IgE responses**

- **Protein**
- **Enzymatically active**
- **Low dose**
- **Low molecular weight**
- **Highly soluble**
- **Stable**
- **Contains peptides that bind host MHC class II**
- **Required for T-cell priming**
1) The allergen enters the body and is recognized by IgE on a B-lymphocyte
2) The B-lymphocyte then proliferates and differentiates into plasma cells
3) The plasma cells produce and secrete IgE which binds to receptors on mast cells and basophils.
4) Allergen cross reacting with IgE on mast cell.
5) The next time the allergen enters the body, it cross-links the Fab portions of the IgE bound to the mast cell.
6) This triggers the mast cell to degranulate and releases its histamine and other inflammatory mediators.
7) The inflammatory mediators are now able to bind to receptors on target cells which leads to dilation of blood vessels, constriction of bronchioles, excessive mucus secretion, and other symptoms of allergy.

**RECAP:**

**Effector Mechanisms**

- **Immediate Allergic Reaction** – caused by mast cell degranulation and release of pre-stored chemical mediators
- **Late-phase response** – involves the recruitment of Th2 cells, eosinophils, and basophils

**TABLE 15-3**

<table>
<thead>
<tr>
<th>Class of mediator</th>
<th>Examples</th>
<th>Biological effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzyme</td>
<td>Trypsin, chymase, collagenase, and others</td>
<td>Renostral connective tissue matrix</td>
</tr>
<tr>
<td>Toxic mediator</td>
<td>Histamine, heparin</td>
<td>Toxic to parasite; increase vascular permeability, cause smooth muscle contraction</td>
</tr>
<tr>
<td>Cytokine</td>
<td>IL-6, IL-13</td>
<td>Stimulate and amplify T and B cell response</td>
</tr>
<tr>
<td>Cytokine</td>
<td>IL-4, IL-5, GM-CSF, TNF, GM-CSF</td>
<td>Promote eosinophil production and activation</td>
</tr>
<tr>
<td>Cytokine</td>
<td>IFN-γ, GM-CSF</td>
<td>Promote mononuclear cell activation, stimulate cytokine production</td>
</tr>
<tr>
<td>Chemokine</td>
<td>CC12, 40, 41</td>
<td>Affects monocytes, macrophages, and neutrophils</td>
</tr>
<tr>
<td>Chemokine</td>
<td>Leukotrienes, C5a, C6, C7</td>
<td>Cause smooth muscle contraction, increase vascular permeability, stimulate eosinophil activation</td>
</tr>
<tr>
<td>Lipid mediator</td>
<td>Phospholipase A2, Arachidonic acid</td>
<td>Activates mast cells, eosinophils, and neutrophils</td>
</tr>
</tbody>
</table>

**Figure 15-4a**

*High-affinity IgE receptor*

**Figure 15-4b**

*FceRI: High-affinity IgE receptor*
Response: depends on how the allergen entered the body!!!

Localized allergic reactions - symptoms depend on the location of mast cell/basophil degranulation
- Skin → eczema
- Nasal mucosa → allergic rhinitis (hay fever)
- Respiratory tract → asthma
- Gastrointestinal tract → vomiting, diarrhea (food allergies)

Systemic allergic reaction = systemic anaphylaxis
- Systemic vasodilation results in an acute loss of blood pressure.
- Bronchoconstriction causes asphyxiation.
- Death can occur within minutes.

Epinephrine counteracts the effects of allergic mediators on smooth muscle and vasculature.

Causes of allergic reactions (factors predisposing to IgE responses):

Characteristics of the antigen
- Certain antigens are more likely to induce IgE responses (e.g. ragweed pollen)

Mode of presentation of the antigen
- Dosage, adjuvant may influence the IgE vs IgG response

Genetics of the individual
- Certain mouse strains are more likely to make IgE responses
- Parents with allergies are more likely to have children with allergies

Blame it on your parents!!!!

Diagnosis
Therapeutic approaches - Allergen immunotherapy

- The practice of administering gradually increasing quantities of an allergen extract to an allergic subject to ameliorate the symptoms associated with subsequent exposure to the causative allergen.
- Introduced in 1911

“The mechanisms of immunotherapy are complex, newer studies suggest that immunotherapy acts by modifying T-cell responses either by immune deviation [shift from Th2 to Th1], T-cell anergy, or more likely both.” - WHO, 1998.

Risk: systemic anaphylaxis (potentially fatal)

- In 1975, Godfrey (Clin. Allergy 5:201) investigated the occurrence of allergy and asthma in Gambian school children.

- Showed their association with urban dwelling, higher socioeconomic status and lower total circulating IgE levels.

- Suggested that in the rural setting, parasite infection was protective against the development of allergy and asthma.


<table>
<thead>
<tr>
<th>Group</th>
<th>Change in parasite load</th>
<th>Change in reactivity to house dust mite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td>68% → 5%</td>
<td>17% → 68%</td>
</tr>
<tr>
<td>Control group</td>
<td>43% → 70%</td>
<td>26% → 16%</td>
</tr>
</tbody>
</table>
1) Exposure to infectious diseases in early childhood
2) Environmental pollution
3) Allergen levels
4) Dietary changes

Eosinophils
- Eosinophils express FcεRI only after activation
- On activation – release toxic granule proteins and free radicals which can kill microorganisms and parasites
- On activation – synthesis of chemical mediators such as prostaglandins, leukotrienes, and cytokines which amplify the inflammatory response

Inflammation
A rapid, nonspecific reaction triggered in response to tissue damage and/or infection.
Consists of three major events:

1) **Vasodilation** - blood vessels at the site become dilated - results in redness at the site - allows increased blood flow to the area.

2) **Increase in capillary permeability** - results in swelling at the site - allows fluid to move from blood vessels into the tissues at the site.

3) **Accumulation of cells of the immune system** - particularly neutrophils - at the site. These phagocytose bacteria and release lytic enzymes and other substances that damage BOTH invading microorganisms and the cells of the host at the site.

Excess fluid, dead cells and digested material forms pus at the site of infection.

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**Inflammatory mediators**

Factors released by various cells during an inflammatory response which trigger or enhance the inflammatory response.

**Include:**

- Chemokines
- Plasma enzyme mediators of inflammation
- Lipid inflammatory mediators
- Cytokines

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**TABLE 15-3**

<table>
<thead>
<tr>
<th>Effect</th>
<th>IL-1</th>
<th>TNF-α</th>
<th>IL-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endogenous pyrogen fever</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Synthesis of acute-phase proteins by liver</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Increased vascular permeability</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Increased adhesion molecules on vascular endothelium</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fibroblast proliferation</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Platelet production</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Chemokine induction (e.g., IL-8)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Induction of IL-6</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>T-cell activation</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>B-cell activation</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Increased immunoglobulin synthesis</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Macrophage: **Inflammatory Cytokines**

- Produces – PGE, Leukotrienes, PAF, etc
- Cytokines: IL-1, TNF-α, IL-6
  - Action on LIVER:
    - Acute Phase Proteins
      - OPSONINS (C Reactive Protein, MBL, Serum amyloid P)
    - C component synthesis
    - Coagulation proteins (Fibrinogen)
  - Hypothalamus
    - FEVER
    - Hypothalamic-Pituitary-Adrenal (HPA) axis → GC synthesis

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**II. Endothelial damage (Blood Vessels)**

- Activation of Hageman factor
- Clotting cascade
- Thrombin
- Fibrinopeptides + fibrin clot
- Kallikrein
- Bradykinin
- Kininogen
- Kinase

**Clot Removal**

- Activated fibrinolytic system
- Plasmin

**Vascular permeability**

- Neutrophil chemotaxis

**Complement activation**

**III. Membrane phospholipids**

- Phospholipase A
- Lipo-PAF

**Cox-1 and Cox-2**

- Anadonic acid
- Lipoxygenase pathway
- Prostaglandins
- Leukotriene A, C, D, E

**NSAID – Tylenol, Ibuprofen, etc**

- SRS-A
- Neutrophil chemotaxis
- Platelet aggregation
- Endothelial chemotaxis
- Neutrophil activation

**Mast cells/platelets**

**Kinin System**

**Clotting System**

**Clot Removal**

**Macrophage:**

- Inflammatory Cytokines

**Macrophage:**

- Inflammatory Cytokines