Chapter 3
Hypersensitivity

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Gel and Coombs classification of hypersensitivities.

<table>
<thead>
<tr>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>Type IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE Mediated</td>
<td>IgG/IgM Mediated</td>
<td>IgG Mediated</td>
<td>T cell</td>
</tr>
<tr>
<td>Classic Allergy</td>
<td>rbc lysis</td>
<td>Immune complex Disease</td>
<td>Delayed Type</td>
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<tr>
<td></td>
<td></td>
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<td>Hypersensitivity</td>
</tr>
</tbody>
</table>
TYPE I Hypersensitivity
Classic allergy

• Mediated by IgE attached to Mast cells.
  • The symptoms resulting from allergic responses are known as anaphylaxis.
    • Includes: Hay fever, asthma, eczema, bee stings, food allergies.
Allergens

- Allergens are nonparasite antigens that can stimulate a type I hypersensitivity response.

- Allergens bind to IgE and trigger degranulation of chemical mediators.
Allergens

Table 16-1 Common Allergens Associated with Type I Hypersensitivity

<table>
<thead>
<tr>
<th>Proteins</th>
<th>Foods</th>
<th>Insect products</th>
<th>Mold spores</th>
<th>Animal hair and dander</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreign serum</td>
<td>Nuts</td>
<td>Bee venom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccines</td>
<td>Seafood</td>
<td>Wasp venom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plant pollens</td>
<td>Eggs</td>
<td>Ant venom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rye grass</td>
<td>Peas, beans</td>
<td>Cockroach calyx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ragweed</td>
<td>Milk</td>
<td>Dust mites</td>
<td></td>
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<tr>
<td>Timothy grass</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birch trees</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td></td>
<td></td>
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<tr>
<td>Sulfonamides</td>
<td></td>
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<tr>
<td>Local anesthetics</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Salicylates</td>
<td></td>
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</tr>
</tbody>
</table>
Characteristics of allergens

- Small 15-40,000 MW proteins.
- Specific protein components
  - Often enzymes.
- Low dose of allergen
- Mucosal exposure.
- Most allergens promote a Th2 immune.
Allergens

Dermatophagoides pteronyssinus (common dust mite)
Allergen is easily aerosolized and inhaled. Der P1 breaks down components of tight junctions which helps it to cross mucosa.
Atopy

- **Atopy** is the term for the genetic trait to have a predisposition for localized anaphylaxis.

- Atopic individuals have higher levels of IgE and eosinophils.
Genetic Predisposition
Type I hypersensitivity

- Candidate polymorphic genes include:
  - IL-4 Receptor.
  - IL-4 cytokine (promoter region).
  - FcεRI. High affinity IgE receptor.
  - Class II MHC (present peptides promoting Th2 response).
  - Inflammation genes.
Mechanisms of allergic response

**Sensitization**

Repeated exposure to allergens initiates immune response that generates IgE isotype.

Th2 cells required to provide the IL-4 required to get isotype switching to IgE.
Mechanisms of allergic response

Sensitization

Th2/B cell interaction

Busse and Lemanske. NEJM Feb 2001. 344:350
Mechanisms of allergic response

Sensitization

• The IgE can attach to Mast cells by Fc receptor, which increases the life span of the IgE.
• Half-life of IgE in serum is days whereas attached to FcεR it is increased to months.
Mechanisms of allergic response

**Fcε receptors (FcεR)**

**FcεR1**

- high affinity IgE receptor found on
  - mast cells/basophils/activated eosinophils.

- Allergen binding to IgE attached to FcεR1 triggers release of granules from cell.
Mechanisms of allergic response

FcεRI

(a) FcεRI:
High-affinity IgE receptor

[Diagram of FcεRI structure with annotations]
Mechanisms of allergic response
Effector Stage of Hypersensitivity

Secondary exposure to allergen

- Mast cells are primed with IgE on surface.
- Allergen binds IgE and cross-links to activate signal with tyrosine phosphorylation, Ca++ influx, degranulation and release of mediators.
Early mediators cause immediate symptoms e.g., histamine (preformed in granules), leukotriene C4 and prostaglandin D2, are quickly made. 2' mediators
Mediators of Type I Hypersensitivity

Immediate effects

- Histamine
  - Vasodilation with increased fluid into tissues causing increased swelling or fluid in mucosa.
  - Activates enzymes for tissue breakdown.
- Leukotrienes
- Prostaglandins
Immediate vs Late Effects (early mediators)

Early/Late Effect on lung airflow OR Wheezing
Mediators of Type I Hypersensitivity

Primary Mediators

Pre-formed mediators in granules

- Histamine
- Cytokines TNF-$\alpha$, IL-1, IL-6.
- Chemoattractants for Neutrophils and Eosinophils.
- Enzymes
  - tryptase, chymase, cathepsin.
  - Changes in connective tissue matrix, tissue breakdown.
Type I Hypersensitivity

**Secondary mediators**

Mediators formed after activation

- Leukotrienes
- Prostaglandins
- Th2 cytokines - IL-4, IL-5, IL-13, GM-CSF
Continuation of sensitization cycle

- Mast cells control the immediate response.
- Eosinophils and neutrophils drive late or chronic response.

- More IgE production further driven by activated Mast cells, basophils, eosinophils.
Continuation of sensitization cycle

**Eosinophils**

- Eosinophils play key role in late phase reaction.
- Eosinophils make
  - enzymes,
  - cytokines (IL-3, IL-5, GM-CSF),
  - Lipid mediators (LTC4, LTD4, PAF)
- Eosinophils can provide CD40L and IL-4 for B cell activation.
Localized anaphylaxis

- Target organ responds to direct contact with allergen.
- Digestive tract contact results in vomiting, cramping, diarrhea.
- Skin sensitivity usually reddened inflamed area resulting in itching.
- Airway sensitivity results in sneezing and rhinitis OR wheezing and asthma.
Systemic anaphylaxis

• Systemic vasodilation and smooth muscle contraction leading to severe bronchiole constriction, edema, and shock.

• Similar to systemic inflammation.
Treatment for Type I

Pharmacotherapy

• Drugs.
  • Non-steroidal anti-inflammatories
  • Antihistamines block histamine receptors.
  • Steroids
  • Theophylline OR epinephrine - prolongs or increases cAMP levels in mast cells which inhibits degranulation.
Treatment for Type I

- Immunotherapy
  - Desensitization (hyposensitization) also known as allergy shots.
  - Repeated injections of allergen to reduce the IgE on Mast cells and produce IgG.
Treatment for Type I
Effect of allergy shots
Allergen Specific Antibodies

Change in amount of each isotype from more IgE to more IgG.
TYPE II Hypersensitivity
Antibody mediated cytotoxicity
Blood Transfusion reactions

Innocuous antigens on red blood cells.

EXAMPLE: ABO blood group antigens
Antibody against rbc antigen binds and mediates killing of rbcs via C’or ADCC causes systemic inflammation.

ABO Blood Groups

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Blood-group phenotype</th>
<th>Antigens on erythrocytes (agglutinins)</th>
<th>Serum antibodies (isoagglutinins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA or AO</td>
<td>A</td>
<td>A</td>
<td>Anti–B</td>
</tr>
<tr>
<td>BB or BO</td>
<td>B</td>
<td>B</td>
<td>Anti–A</td>
</tr>
<tr>
<td>AB</td>
<td>AB</td>
<td>A and B</td>
<td>None</td>
</tr>
<tr>
<td>OO</td>
<td>O</td>
<td>None</td>
<td>Anti–A and anti–B</td>
</tr>
</tbody>
</table>

Quex: Why do we have antibodies to these innocuous antigens even before we get blood transfusion?
TYPE II
Antibody mediated cytotoxicity

Drug reactions

• Drug binds to rbc surface and antibody against drug binds and causes lysis of rbcs.
• Immune system sees antibody bound to "foreign antigen" on cell. ADCC
TYPE II
Hemolytic disease of newborn

Rh factor incompatibility

- IgG abs to Rh an innocuous rbc antigen
  - Rh\(^+\) baby born to Rh\(^-\) mother first time fine. 2nd time can have abs to Rh from 1st pregnancy.
  - Ab crosses placenta and baby kills its own rbcs.
  - Treat mother with ab to Rh antigen right after birth and mother never makes its own immune response.
TYPE II
Rh factor incompatibility

DEVELOPMENT OF ERYTHROBLASTOSIS FETALIS (WITHOUT RHOGAM)
- Placenta
- Maternal circulation
- RBCs with Rh antigen
- 1st Pregnancy

Mother
- Delivery
- Rh-specific B cell
- IgM
- Memory cell

2nd Pregnancy
- Memory cell
- Plasma cells
- IgG
- IgG anti-Rh Ab crosses placenta and attacks fetal RBCs causing erythroblastosis fetalis

PREVENTION (WITH RHOGAM)
- Mother (treated with Rhogam)
- B cell
- Rhogam
- Prevents B-cell activation and memory cell formation
TYPE III
Antigen antibody immune complexes. IgG mediated

Immune Complex Disease

• Large amount of antigen and antibodies form complexes in blood.

• If not eliminated can deposit in capillaries or joints and trigger inflammation.
TYPE III

Immune Complexes

• PMNs and macrophages bind to immune complexes via FcR and phagocytize the complexes.

BUT

• If unable to phagocytize the immune complexes can cause inflammation via C’ activation ---> C3a C4a, C5a and "frustrated phagocytes".
TYPE III

Immune Complex Disease

"Frustrated Phagocytes"

• If neutrophils and macrophages are unable to phagocytize the immune complexes, these cells will degranulate in the area of immune complex deposition and trigger inflammation.

• Unable to eat -------try to digest outside cell.
TYPE III
Immune Complex Disease

Localized disease

• Deposited in joints causing local inflammation = arthritis.
• Deposited in kidneys = glomerulonephritis.
TYPE III
Immune Complex Disease

- Serum sickness from large amounts of antigen such as injection of foreign serum.

Serum sickness is usually transient immune complex disease with removal of antigen source.
Mast Cell Mediators

• Preformed
  • Vasoactive amines: histamine
  • Neutral proteases: tryptase, chymase
  • Acid hydrolases: β-hexoseaminidase
  • Proteoglycans: heparin, chondroitin sulfate

• Newly formed
  • Eicosanoids: PGD$_2$, LTC$_4$
  • Cytokines: TNF$_\alpha$, IL-4, IL-5, IL-6
Mast Cell Tryptase

- Tetrameric serine protease
- Found only in mast cells, not basophils
- Peaks in 1 hour and remains elevated 4-6 hours in serum following release in anaphylaxis
- Alpha isoform is predominant in blood: most mastocytosis patients with systemic disease have total tryptase levels that are elevated (> 20 ng/ml) and are at least 10-fold greater than their β tryptase level.
Histamine

• Produced almost exclusively by basophils and mast cells (3-8 pg/cell)

• Immediate pharmacologic effects:
  – pruritus (H1)
  – ↑ vascular permeability/vasodilatation (H1)
  – smooth muscle contraction  (H1)
  – gastric acid secretion (H2)
Injection of Histamine in the Skin: The Triple Response

- Local erythema - $H_1$ (and some $H_2$)-mediated arteriolar dilatation
- More widespread flare from antidromic release of Substance P from sensory nerves
- Wheal produced by increased vascular permeability
Acute Phase Allergic Reaction:

- Occurs within seconds to minutes of IgE receptor activation (mast cell mediator release) and resolving within an hour
- Intense pruritus, edema, erythema
- Almost all effects can be replicated with histamine
Late Phase Allergic Reaction:

- A delayed inflammatory response (peaking at 4-8 hrs and persisting up to 24 hrs) following an intense acute phase reaction
  - Skin: erythema, induration, burning
  - Lungs: airway obstruction poorly responsive to bronchodilators
  - Nose/eyes: erythema, congestion, burning
- Histology: mast cell degranulation followed by influx of first neutrophils and eosinophils followed by mononuclear cells
- Major portion of effects replicated by TNFα
Therapy of Allergic Disease

- Inhibition of IgE synthesis:
  - Immunotherapy

- Inhibition of IgE binding to receptor:
  - Monoclonal anti-IgE (Xolair (Omalizumab))

- Inhibition of mast cell mediator release:
  - Topical corticosteroids
    - Cromolyn, nedocromil
  - Inhibition of mediator action:
    - Antihistamines
    - Leukotriene receptor antagonists
    - Topical and systemic corticosteroids
Gell and Coombs Classification

- Type I (IgE-mediated)
- Type II (Fc and complement-mediated)
- Type III (Immune complex-mediated)
- Type IV (Delayed-type hypersensitivity)
Type II Hypersensitivity Reactions: Mechanisms of Tissue Damage

- Complement-mediated cytolysis
- Antibody-dependent cell-mediated cytotoxicity (ADCC)
Type II Reactions

Normal anti-microbial action:
- Fc receptor
- C3 receptor
- Microbe

1. Neutrophil
2. Phagocytosis
3. Lysosome fusion

Hypersensitivity reaction:
4. Neutrophil
5. 'Frustrated phagocytosis'
6. Extracellular enzyme release
Type II Hypersensitivity Reactions: Examples of Diseases

- Transfusion reactions
- Hemolytic disease of the newborn (Rh incompatibility)
- Hyperacute graft rejection
- Drug-induced hemolytic anemia
Transfusion Reactions
Hemolytic Disease of the Newborn
Hemolytic Disease of the Newborn

<table>
<thead>
<tr>
<th>sensitization</th>
<th>no sensitization</th>
<th>haemolytic disease of the newborn</th>
</tr>
</thead>
<tbody>
<tr>
<td>A  Rh⁻</td>
<td>B  Rh⁻</td>
<td>deaths per 1000 live births</td>
</tr>
<tr>
<td></td>
<td>anti-D</td>
<td>year</td>
</tr>
</tbody>
</table>
Mechanisms Of Drug Hypersensitivity

1A: Blood cell antigen with adsorbed drug or drug metabolite and antibody to drug. Lysis mediated by complement.

1B: Immune complex of drug and antibody with adsorbed complex. Lysis mediated by complement.

2: Breakdown of self-tolerance with antibodies to blood group antigens. Lysis mediated by complement.
Gell and Coombs Classification

- Type I (IgE-mediated)
- Type II (Fc and complement-mediated)
- Type III (Immune complex-mediated)
- Type IV (Delayed-type hypersensitivity)
Type III Hypersensitivity
Mechanisms of Tissue Injury

- *In situ* activation of complement
- Anaphylatoxin-mediated activation of mast cells and phagocytes
- Complex-mediated phagocytosis and release of phagocyte granule enzymes and cytokines into the local microenvironment
Type III Hypersensitivity

Examples of Diseases

• Arthus reaction
• Hypersensitivity pneumonitis
• Immune complex-mediated glomerulonephritis
• Serum sickness
The Arthus Reaction

- Occurs with introduction of antigen into an individual with high titer antibody
- Requires both complement & phagocytes
- Peaks at 3-6 hours after exposure
- Histology: massive influx of neutrophils, edema, sometimes necrosis
Hypersensitivity Pneumonitis Syndromes and Associated Antigens

- Farmer’s lung (thermophilic actinomycetes)
- Malt worker’s lung (Aspergillus spores)
- Pigeon fancier’s disease (avian proteins)
- Cheese washer’s lung (Penicillium spores)
- Furrier’s lung (fox fur)
- Laboratory technician’s lung (rat urine proteins)
A Dominant Role for Mast Cell Fc Receptors in the Arthus Reaction:

Sylvestre et al, 1996, Immunity 5:387
A: Control γ-/-; B: Control γ+/-; C: Control W/Wv; D: W/Wv reconstituted with γ-/- mast cells or E: γ+/- mast cells
Serum Sickness

- Fever, rash, joint pain, lymphadenopathy, occasionally glomerulonephritis
- Timecourse: days to weeks after introduction of foreign antigen
- Causes: allogeneic serum, drugs, infections, autoimmune disorders
Serum Sickness Reactions
Serum Sickness Reactions
Common Locations of Vascular Involvement
Autoimmune Glomerulo-nephritis
Gell and Coombs Classification

- Type I (IgE-mediated)
- Type II (Fc and complement-mediated)
- Type III (Immune complex-mediated)
- Type IV (Delayed-type hypersensitivity)
(a) Sensitization phase

Intracellular bacteria

APC

CD4⁺ T_H

T_H1 cells (generally)

Antigen-presenting cells: Macrophages, Langerhans cells

DTH-mediating cells: T_H1 cells generally CD8 cells occasionally
(b) Effector phase

Sensitized $T_H^1$

Membrane TNF-β

Secreted IFN-γ

Resting macrophage

Activated macrophage

Class II MHC

TNF receptor

$T_H^1$ secretions:
- Cytokines: IFN-γ, TNF-β, IL-2, IL-3, GM-CSF
- Chemokines: IL-8, MCAF, MIF

Effects of macrophage activation:
- ↑ Class II MHC molecules
- ↑ TNF receptors
- ↑ Oxygen radicals
- ↑ Nitric oxide
Serum Sickness

Systemic immune complex disease

Large amounts of antigen such as injection of foreign serum.

Days after Antigen Injection
Delayed type hypersensitivity
Th1 cells and macrophages

• DTH response is from:
  • Th1 cells release cytokines to activate macrophages causing inflammation and tissue damage.
  • Continued macrophage activation can cause chronic inflammation resulting in tissue lesions, scarring, and granuloma formation.

• Delayed is relative because DTH response arise 24-72 hours after exposure rather than within minutes.
Stages of Type IV DTH

Sensitization stage

- Memory Th1 cells against DTH antigens are generated by dendritic cells during the sensitization stage.
- These Th1 cells can activate macrophages and trigger inflammatory response.
Stages of Type IV DTH
Effector stage

- Secondary contact yields what we call DTH.
- **Th1** memory cells are activated and produce cytokines.
  - IFN-γ, TNF-α, and TNF-β which cause tissue destruction, inflammation.
  - IL-2 that activates T cells and CTLs.
  - Chemokines- for macrophage recruitment.
  - IL-3, GM-CSF for increased monocyte/macrophage
Stages of Type IV DTH

Effector stage

Secondary exposure to antigen

- Inflamed area becomes red and fluid filled can form lesion.
  - From tissue damage there is activation of clotting cascades and tissue repair.
- Continued exposure to antigen can cause chronic inflammation and result in granuloma formation.
Type IV DTH
Contact dermatitis

- The response to poison oak is a classic Type IV.
  - Small molecules act as haptens and complex with skin proteins to be taken up by APCs and presented to Th1 cells to get sensitization.
  - During secondary exposure Th1 memory cells become activated to cause DTH.
Contact dermatitis

Poison oak
(*Toxicodendron radicans*)

Pentadecacatechol

Skin

Self-protein
Sensitized T\(\text{DTH}\)

Langerhans cell (APC)

MIF

MCF

Lytic enzymes

Tissue macrophage

Monocyte

Tissue macrophage

IFN-\(\gamma\)
Delayed type hypersensitivity (DTH)

DTH is a type of immune response classified by Th1 and macrophage activation that results in tissue damage. DTH can be the result of Chronic infection or Exposure to some antigens.

### Table 14-3: Intracellular Pathogens and Contact Antigens That Induce Delayed-Type Hypersensitivity

<table>
<thead>
<tr>
<th>Intracellular bacteria</th>
<th>Intracellular viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Herpes simplex virus</td>
</tr>
<tr>
<td><em>Mycobacterium leprae</em></td>
<td>Variola (smallpox)</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td>Measles virus</td>
</tr>
<tr>
<td><em>Brucella abortus</em></td>
<td>Contact antigens</td>
</tr>
<tr>
<td>Intracellular fungi</td>
<td>Picrylchloride</td>
</tr>
<tr>
<td><em>Pneumocystis carinii</em></td>
<td>Hair dyes</td>
</tr>
<tr>
<td><em>Candida albicans</em></td>
<td>Nickel salts</td>
</tr>
<tr>
<td><em>Histoplasma capsulatum</em></td>
<td>Poison ivy</td>
</tr>
<tr>
<td><em>Cryptococcus neoformans</em></td>
<td>Poison oak</td>
</tr>
<tr>
<td>Intracellular parasites</td>
<td></td>
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<tr>
<td><em>Leishmania sp.</em></td>
<td></td>
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</tbody>
</table>
Granuloma Formation from DTH Mediated by Chronic Inflammation
Drug reactions can be any Type of Hypersensitivity

<table>
<thead>
<tr>
<th>Type of reaction</th>
<th>Antibody or lymphocytes induced</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>IgE</td>
<td>Urticaria, systemic anaphylaxis</td>
</tr>
<tr>
<td>II</td>
<td>IgM, IgG</td>
<td>Hemolytic anemia</td>
</tr>
<tr>
<td>III</td>
<td>IgG</td>
<td>Serum sickness, glomerulonephritis</td>
</tr>
<tr>
<td>IV</td>
<td>$T_{DTH}$ cells</td>
<td>Contact dermatitis</td>
</tr>
</tbody>
</table>