Hypersensitivity

- **Hypersensitivity**: An adaptive immune response which occurs in an inappropriate or exaggerated way, resulting in tissue damage or some other detrimental response in the host.
- **Allergen**: Any antigen that elicits a hypersensitivity reaction
From “Immunobiology” by Janeway and Travers
**Type I Hypersensitivity**

- Often called “immediate hypersensitivity”
- “Atopy” = increased tendency of certain individuals to type I hypersensitivity
- Allergens often environmental
- Mild to fatal manifestations
- Mechanism primarily involves production of IgE and degranulation of mast cells

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Common allergens</th>
<th>Route of entry</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic anaphylaxis</td>
<td>Drugs, serum, venoms, certain foods</td>
<td>intravenous</td>
<td>Oedema, vasodilation Circulatory Collapse Death</td>
</tr>
<tr>
<td>Wheal and Flare</td>
<td>Insect bites, allergy testing</td>
<td>subcutaneous</td>
<td>Local vasodilation Local oedema</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>Pollens, Dust mite faeces</td>
<td>inhaled</td>
<td>Oedema and irritation of nasal mucosa</td>
</tr>
<tr>
<td>(Hay Fever)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchial asthma</td>
<td>Pollens, Dust mite faeces</td>
<td>inhaled</td>
<td>Bronchial restriction Airway inflammation</td>
</tr>
<tr>
<td>Food Allergy</td>
<td>Shellfish, milk, eggs, fish, wheat</td>
<td>oral</td>
<td>Vomiting, diarrhoea pruritis (itching)</td>
</tr>
</tbody>
</table>
IgE-mediated response to bee venom

What is IgE?

- Monomeric immunoglobulin
- ~0.002% total serum Ig
- Elevated in atopic conditions (and parasitic infestations)

From Roitt’s Essential Immunology™ 11th edition
Why IgE?: $T_H^1$ vs $T_H^2$ response

What are mast cells?

- Derived from myeloid progenitor
- Resident in mucosal and epithelial tissues
- Contain granules containing histamine, heparin, TNF-α, proteases and other degradative enzymes and inflammatory mediators.
- Have high affinity IgE receptors (FcεRI) on surface
Allergies have two phases:
Phase 1 = Sensitization

- Binding of allergen to IgE bound to mast cells results in activation and degranulation
- Note: Non-immunological stimuli can also cause mast cell degranulation (e.g., opiates)
Mast cells produce IL-4 to further stimulate IgE production

Degranulation of Mast Cells releases...

- Chemoattractants: e.g., chemokine CCL3, PAF (neutrophils, eosinophils, basophils)
- Inflammatory mediators: e.g., histamine, TNF-α (vasodilation & vascular permeability)
- Spasmogens: e.g., histamine, leukotrienes, prostaglandins (bronchial smooth muscle contraction)
Allergic reactions consist of an early and late phase

- Direct consequence of degranulation of preformed mediators by mast cells (histamine, prostaglandins)
- 6-8 hours later, caused by substances produced by mast cells AFTER IgE-mediated activation (leukotrienes, chemokines)

Physical manifestation will depend on where mast cells activated
Acute anaphylaxis

- Occurs when allergen enters bloodstream (insect stings, injected drugs, rapidly absorbed food)
- Widespread activation of tissue mast cells
- ↑ vascular permeability, fluid leaves blood vessels, tissues swell, BP↓ drastically (anaphylactic shock)
- Airways constrict, epiglottis swells
- Treatment = adrenalin (tightens junctions between endothelia cells, relaxes bronchial smooth muscle, stimulates heart)

Heredity of Atopy

- The greater the parental history of allergy, the greater the likelihood of the children being atopic
- If one monozygotic (identical) twin is atopic, there is ~55% chance that the other will be also. (c.f., ~30% for dizygotic twins, and about 17% for the general population)
Are allergies on the rise?

- Australian hospital admissions for anaphylaxis, angioedema, and urticaria for the periods 1993-1994 to 2004-2005 analysed*.
- Found a continuous increase in the rate of hospital admissions for angioedema (3.0% per year), urticaria (5.7% per year), and anaphylaxis (8.8% per year).
- Particularly steep increase for food-related anaphylaxis among children < 5 years.

*The Journal of Allergy and Clinical Immunology (2007) Vol 120, p878-884

Why?

- Hygiene Hypothesis: Let them eat dirt
- We need exposure to everyday microorganisms to prime our $T_{H1}$ response
- Lack of exposure to parasites means our $T_{H2}$ pathway instead acts against innocuous allergens
### Strategies for treatment*

<table>
<thead>
<tr>
<th>Target step</th>
<th>Mechanism of treatment</th>
<th>Specific approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>T(_{H2}) activation</td>
<td>Reverse T(<em>{H2}/T(</em>{H1}) balance</td>
<td>Injection of specific antigen or peptides</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Administration of cytokines, e.g., IFN-(\gamma), IL-10, IL-12, TGF-(\beta)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use of adjuvants such as CpG oligodeoxynucleotides to stimulate T(_{H1}) response</td>
</tr>
<tr>
<td>Activation of B cell to produce IgE</td>
<td>Block co-stimulation</td>
<td>Inhibit CD40L</td>
</tr>
<tr>
<td></td>
<td>Inhibit T(_{H2}) cytokines</td>
<td>Inhibit IL-4 or IL-13</td>
</tr>
<tr>
<td>Mast-cell activation</td>
<td>Inhibit effects of IgE binding to mast cell</td>
<td>Blockade of IgE receptor</td>
</tr>
<tr>
<td>Mediator action</td>
<td>Inhibit effects of mediators on specific receptors</td>
<td>Antihistamine drugs</td>
</tr>
<tr>
<td></td>
<td>Inhibit synthesis of specific mediators</td>
<td>Lipoxygenase inhibitors</td>
</tr>
<tr>
<td>Eosinophil-dependent inflammation</td>
<td>Block cytokine and chemoxine receptors that mediate eosinophil recruitment and activation</td>
<td>Inhibit IL-5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Block CCR3</td>
</tr>
</tbody>
</table>

* Avoidance/reduction of allergen = safest and most effective method

### Strategies for treatment 2: Worms as therapy?

![Image of worms and text](image_url)
Type II Hypersensitivity

- also known as antibody-dependent cytotoxic hypersensitivity
- occurs when antibody binds to either self antigens or foreign antigens on cells
- Cell death occurs from phagocytosis, NK cell activity, or complement-mediated lysis
- Pathology occurs when the destruction of the tissues leads to illness in the host

**Immune reactant:** IgG antibody

**Antigen:** Cell- or matrix-associated antigen, Cell-surface receptors

**Effector mechanism:** Complement, FcR cells (phagocytes, NK cells), Antibody alters signaling

**Examples:** Some drug allergies (e.g., penicillin), transfusion reaction, autoimmune hemolytic anemia, Graves' disease, (agonist), Myasthenia gravis (antagonist)
Examples of Type II reactions

- Reactions against blood cells and platelets (certain drug reactions, transfusion reactions, haemolytic disease of the newborn)
- Hyperacute graft rejection (from a few minutes to 48h after transplantation)
- Reactions against tissue antigens (Myasthenia Gravis)

Hypersensitivity Type III

- Also known as immune-complex (IC) disease
- Caused by the deposition of immune complexes (antigen/antibody/C) in blood vessels and tissues
- Different clinical conditions depend on the varying routes of antigen delivery and the site of complex deposition
Types of Type III reactions

<table>
<thead>
<tr>
<th>Route of Ag delivery</th>
<th>Resulting disease</th>
<th>Site of IC deposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous (high dose)</td>
<td>Vasculitis</td>
<td>Blood vessel walls</td>
</tr>
<tr>
<td></td>
<td>Nephritis</td>
<td>Renal glomeruli</td>
</tr>
<tr>
<td></td>
<td>Arthritis</td>
<td>Joint spaces</td>
</tr>
<tr>
<td>Inhaled</td>
<td>Pneumonitis</td>
<td>Alveolar/capillary interface</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Arthus reaction</td>
<td>Perivascular area</td>
</tr>
</tbody>
</table>

What causes immune complexes to deposit?

- ICs (Ag/Ab/C) are usually cleared by binding to CR1 receptors on erythrocytes (RBCs)
- ICs bound to RBCs are transported to liver and spleen for removal by fixed tissue macrophages
- ICs accumulate where Ab production is continuous (e.g., chronic infection) or complement is deficient
Serum Sickness

- Occurs when foreign serum proteins are introduced (passive immunisations, anti-venins)
- Long-lasting nature of serum proteins => prolonged Ab production and formation of ICs
- ICs deposit in kidneys, blood vessels and joints => nephritis, vasculitis & arthritis
- Symptoms occur 7-10 days after administration and disappear with no lasting effect once IC are cleared

Time course of serum sickness

From “Immunobiology” by Janeway and Travers
Type IV hypersensitivity

- Also known as delayed-type hypersensitivity (DTH)
- Mediated by T cells and macrophages (antibody independent)
- Reactions develop hour to days after contact with antigen
- Skin reactions are histologically different to those caused by Ig-mediated hypersensitivities

Contact hypersensitivity (CHS)

- Also known as contact dermatitis
- Antigens are simple chemicals (haptens)
  - nickel
  - plant material (e.g., poison ivy)
  - topically applied drugs
  - soaps and cosmetics
- Initial contact sensitizes
- Second contact leads to erythema, itching, eczema or necrosis of the skin within 12-48h
Mechanism of CHS

From "Immunobiology" by Janeway and Travers

CHS to poison ivy

Pentadecacatechol

Figure 13-31: Immunobiology, 5th ed. (c) Garland Science 2008

Figure 19-36: The Immune System, 2nd ed. (c) Garland Science 2003
**Tuberculin-type DTH**

- First noticed in the late 19th century
- Injection of “tuberculin” intradermally to sensitive individuals causes redness and swelling within 12-18 h, reaching maximum intensity after 24-48h
- Forms the basis for today’s TB skin tests (Mantoux and Heaf tests)

**The tuberculin reaction**

- Mediated by $T_{\text{H}1}$ cells that recognise mycobacterial peptides expressed on MHCII molecules on local macrophages and dendritic cells
- Activated $T_{\text{H}1}$ cells release cytokines and chemokines that recruit fluid, proteins and other leukocytes to the area
The 4 Hypersensitivities: an overview

<table>
<thead>
<tr>
<th>Type</th>
<th>Manifestations (examples)</th>
<th>Effector Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Atopy (anaphylactic shock, asthma, hives, drug allergies)</td>
<td>IgE, mast cells</td>
</tr>
<tr>
<td>II</td>
<td>Cytotoxic antibody (haemolytic anaemia, Rh incompatability)</td>
<td>IgG, IgM, complement</td>
</tr>
<tr>
<td>III</td>
<td>Ag-Ab complexes (serum sickness glomerulonephritis)</td>
<td>IgG, antigen, complement</td>
</tr>
<tr>
<td>IV</td>
<td>Cell-mediated (contact dermatitis)</td>
<td>T cells, macrophages</td>
</tr>
</tbody>
</table>

Brilliant marketing?