Hypersensitivity Reactions
(Types I, II, III, IV)

April 15, 2009
Inflammatory response - local, eliminates antigen without extensively damaging the host’s tissue.

*Hypersensitivity* - immune & inflammatory responses that are harmful to the host (von Pirquet, 1906)
<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 Hypersensitivity</td>
<td>IgG- or IgM-Mediated Cytotoxic Hypersensitivity</td>
<td>Immune Complex-Mediated Hypersensitivity</td>
<td>Cell-Mediated Hypersensitivity</td>
</tr>
<tr>
<td>Ag induces cross-linking of IgE bound to mast cells and basophils with release of vasoactive mediators.</td>
<td>Ab directed against cell surface antigens mediates cell destruction via complement activation or ADCC.</td>
<td>Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils.</td>
<td>Sensitized T_H1 cells shown above release cytokines that activate macrophages or T_C cells that mediate direct cellular damage. T_H2 cells and CTLs mediate similar responses.</td>
</tr>
<tr>
<td>Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema.</td>
<td>Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia.</td>
<td>Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus.</td>
<td>Typical manifestations include contact dermatitis, tubercular lesions, and graft rejection.</td>
</tr>
</tbody>
</table>

**Figure 15-1**
*Kuby IMMUNOLOGY, Sixth Edition*  
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<table>
<thead>
<tr>
<th>Cell - Type I</th>
<th>Activated function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basophil</strong></td>
<td>Produce effector molecules</td>
</tr>
<tr>
<td></td>
<td>Capable of ingesting foreign Particles</td>
</tr>
<tr>
<td></td>
<td>Association with parasite infection</td>
</tr>
<tr>
<td><strong>Mast cell</strong></td>
<td>Release of granules containing histamine and other active agents</td>
</tr>
</tbody>
</table>

Figure 1-4 part 3 of 3 Immunobiology, 6/e. (© Garland Science 2005)
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mast cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Origin of precursor</td>
<td>CD34+ hematopoietic progenitor cells</td>
</tr>
<tr>
<td>Major site of maturation</td>
<td>Connective tissue</td>
</tr>
<tr>
<td>Cells in circulation</td>
<td>No</td>
</tr>
<tr>
<td>Mature cells recruited into tissues from circulation</td>
<td>No</td>
</tr>
<tr>
<td>Mature cells residing in connective tissue</td>
<td>Yes</td>
</tr>
<tr>
<td>Proliferative ability of mature cells</td>
<td>Yes</td>
</tr>
<tr>
<td>Life span</td>
<td>Weeks to months</td>
</tr>
<tr>
<td>Major development factor (cytokine)</td>
<td>Stem cell factor</td>
</tr>
<tr>
<td>Expression of FcεRI</td>
<td>High levels</td>
</tr>
<tr>
<td>Major granule contents</td>
<td>Histamine, heparin and/or chondroitin sulfate, proteases</td>
</tr>
</tbody>
</table>
Type I hypersensitivity response

- Allergen
  - B cell
    - CD4
    - IL-4
  - TH2 cell
    - Allergen
      - Memory cell
      - Plasma cell
      - Fc receptor for IgE
      - Allergen-specific IgE
      - Sensitized mast cell
      - Degranulation
        - Vasoactive amines
          - Smooth muscle cell
          - Small blood vessel
          - Mucous gland
          - Blood platelets
          - Sensory nerve endings
          - Eosinophil

Figure 15-2
Kuby IMMUNOLOGY, Sixth Edition
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IgE

Normal serum level = 0.0003 mg/ml

No hinge region
Additional domain

Binds to mast cell

V_L, C_L, C_E1, C_H2, C_H3, C_H4
**FcεRI: High-affinity IgE receptor**

- **NH₂**
- **α**
- **β**
- **γ**
- **γ-Intracellular signal trans.**
- **Link**
- **Binds Fc region of IgE**

**Extracellular space**

**Cytoplasm**

**Plasma membrane**

**Ig-like domains**

**COOH COOH**

**ITAM**

**Figure 15-4a**

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Initiation of degranulation

(a) Allergen cross-linkage of cell-bound IgE

(b) Antibody cross-linkage of IgE

(c) Chemical cross-linkage of IgE

(d) Cross-linkage of IgE receptors by anti-receptor antibody

(e) Enhanced Ca\(^{2+}\) influx by ionophore that increases membrane permeability to Ca\(^{2+}\)

Figure 15-5
*Kuby IMMUNOLOGY, Sixth Edition*
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Late phase: allergic inflammation

- Smooth-muscle-cell activation and hyper-reactivity for contraction, and release of chemokines and pro-inflammatory cytokines

- Eosinophil activation and release of mediators, chemokines and pro-inflammatory cytokines

- Increased endothelial-cell adhesion and inflammatory-cell transmigration

- Histamine

- Mast cell

- Basophil

- DC

- T-cell activation and proliferation by IgE-facilitated and non-IgE-facilitated presentation of allergens by inflammatory DCs

- Allergic rhinitis and asthma
  - \( T_{h2} \)-cytokine-mediated induction of increased mucus production
  - Local production of IgE
  - \( T_{h1} \)-cell-mediated induction of bronchial epithelial-cell apoptosis

- Atopic dermatitis
  - \( T_{h1} \)-cell-mediated induction of keratinocyte apoptosis
  - \( T_{h1} \)-cell-mediated epithelial-cell activation, and release of chemokines and pro-inflammatory cytokines

---

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRIMARY</strong></td>
<td></td>
</tr>
<tr>
<td>Histamine, heparin</td>
<td>Increased vascular permeability; smooth muscle contraction</td>
</tr>
<tr>
<td>Serotonin (rodents)</td>
<td>Increased vascular permeability; smooth muscle contraction</td>
</tr>
<tr>
<td>Eosinophil chemotactic factor (ECF-A)</td>
<td>Eosinophil chemotaxis</td>
</tr>
<tr>
<td>Neutrophil chemotactic factor (NCF-A)</td>
<td>Neutrophil chemotaxis</td>
</tr>
<tr>
<td>Proteases (tryptase, chymase)</td>
<td>Bronchial mucus secretion; degradation of blood vessel basement membrane; generation of complement split products</td>
</tr>
<tr>
<td><strong>SECONDARY</strong></td>
<td></td>
</tr>
<tr>
<td>Platelet-activating factor</td>
<td>Platelet aggregation and degranulation; contraction of pulmonary smooth muscles</td>
</tr>
<tr>
<td>Leukotrienes (slow reactive substance of anaphylaxis, SRS-A)</td>
<td>Increased vascular permeability; contraction of pulmonary smooth muscles</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>Vasodilation; contraction of pulmonary smooth muscles; platelet aggregation</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>Increased vascular permeability; smooth muscle contraction</td>
</tr>
<tr>
<td>Cytokines</td>
<td></td>
</tr>
<tr>
<td>IL-1 and TNF-α</td>
<td>Systemic anaphylaxis; increased expression of CAMs on venular endothelial cells</td>
</tr>
<tr>
<td>IL-4 and IL-13</td>
<td>Increased IgE production</td>
</tr>
<tr>
<td>IL-3, IL-5, IL-6, IL-10, TGF-β, and GM-CSF</td>
<td>Various effects (see Table 12-1)</td>
</tr>
</tbody>
</table>

Table 15-3
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Factors in the development of allergic diseases

- Geographical distribution
- Environmental factors - climate, air pollution, socioeconomic status
- Genetic risk factors
- “Hygiene hypothesis”
  - Older siblings, day care
  - Exposure to certain foods, farm animals
  - Exposure to antibiotics during infancy
- Cytokine milieu

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

- Systemic (anaphylactic shock)
- Asthma
  - Classification by immunopathological phenotype can be used to determine management strategies
- Hay fever (allergic rhinitis)
- Allergic conjunctivitis
- Skin reactions
- Food allergies
Diseases in Humans (I)

• **Systemic anaphylaxis** - potentially fatal - due to **food ingestion** (eggs, shellfish, peanuts, drug reactions) and **insect stings** - characterized by airway obstruction and a sudden fall in blood pressure.
Diseases in Humans (II)

Bronchial asthma

• Chronic inflammation
  – Intermittent & reversible airway obstruction
  – Chronic bronchial inflammation with eosinophil infiltration
  – Bronchial smooth muscle hypertrophy and hyperreactivity

• Dominated by the presence of eosinophils, CD4+ T lymphocytes (Th2), and a large proportion of CD4+ NKT cells expressing an invariant T cell receptor that recognizes glycolipid antigens.
Asthma

Normal Airway

- Muscle
- Lining

Airway in Person with Asthma

- Swelling
- Mucus
- Tight Muscles
Mediators and treatment of asthma

- Anti-IL-13 - reduce mucus overproduction and eosinophilia
- Anti-chemokine receptors: CCR3, CCR4, CCR8 on Th2 cells.
- Anti-RANTES or -eotaxin abs to prevent recruitment of eosinophils
<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihistamines</td>
<td>Block $H_1$ and $H_2$ receptors on target cells</td>
</tr>
<tr>
<td>Cromolyn sodium</td>
<td>Blocks $Ca^{2+}$ influx into mast cells</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Prolongs high cAMP levels in mast cells by inhibiting phosphodiesterase, which cleaves cAMP to 5’-AMP*</td>
</tr>
<tr>
<td>Epinephrine (adrenaline)</td>
<td>Stimulates cAMP production by binding to $\beta$-adrenergic receptors on mast cells*</td>
</tr>
<tr>
<td>Cortisone</td>
<td>Reduces histamine levels by blocking conversion of histidine to histamine and stimulates mast-cell production of cAMP*</td>
</tr>
</tbody>
</table>

*Although cAMP rises transiently during mast-cell activation, degranulation is prevented if cAMP levels remain high.
Diseases in Humans (III)

• **Upper respiratory tract**
  – Allergic rhinitis (hay fever) - reactions to plant pollen or house dust mites in the upper respiratory tract - mucosal edema, mucus secretion, coughing, sneezing, difficult in breathing - also associated with allergic conjunctivitis. Some evidence that asthma can develop in patients who have allergic rhinitis. Treatment - antihistamines

• **Gastrointestinal tract**
  – Result from release of mediators from intestinal mucosal and submucosal mast cells following sensitization through the g.i. route of exposure - enhanced peristalsis, increased fluid secretion from intestinal cells, vomiting, and diarrhea. This is not the same as an anaphylactic response. Reactions usually begin in childhood - often remit in late childhood or in adulthood.

• **Skin**
  – Urticaria (wheal and flare) - mediated by histamine.
  – Eczema - late-phase reaction to allergen in the skin - inflammation - can be treated with steroids.
Urticaria
Atopic Eczema

Copyright Slice of Life & Suzanne S. Stensaas - obtained from PEIR, Dept. of Pathology, UAB
Radioallergosorbent Test (RAST)

Allergen coupled to solid phase + Patient IgE → Bound allergen–specific IgE

Nonspecific IgE is washed away → Radiolabeled anti-IgE

Count bound label

Figure 15-11b
Kuby IMMUNOLOGY, Sixth Edition
© 2007 W.H.Freeman and Company
1st study of allergen-specific immunotherapy:

Noon, L.  Prophylactic inoculation against hay fever
Lancet I, 1572-1573 (1911)
Desensitization/Allergen-Specific Immunotherapy

Subcutaneous or sublingual administration

Figure 15-12
Kuby IMMUNOLOGY, Sixth Edition
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February 24, 2009. Eating a tiny bit of peanut flour every day may increase peanut tolerance in children who are allergic to peanuts, a new study shows.

Each child went home with instructions to eat 5 mg of peanut flour mixed with yogurt each day, gradually adding more peanut flour over the next six weeks.
Protective role of IgE

Copyright © 2003, Elsevier Science (USA). All Rights Reserved.
Type II hypersensitivity

- Mediated by abs directed towards antigens present on cell surfaces or the extracellular matrix (type IIA) or abs with agonistic/antagonistic properties (type IIB).

- Mechanisms of damage:
  - Opsonization and complement- and Fc receptor-mediated phagocytosis
  - Complement- and Fc receptor-mediated inflammation
  - Antibody-mediated cellular dysfunction
Examples: autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura

Kumar et al. Robbins and Cotran Pathologic Basis of Disease
Examples: pemphigus vulgaris, Goodpasture syndrome
Kumar et al. Robbins and Cotran
Pathologic Basis of Disease. Elsevier
2005
Examples: Graves disease (hyperthyroidism), myasthenia gravis

Kumar et al. Robbins and Cotran Pathologic Basis of Disease
Non-autoimmune type II reactions

- Transfusion reactions (ABO incompatibility)
- Hemolytic disease of the newborn (erythroblastosis fetalis)
DEVELOPMENT OF ERYTHROBLASTOSIS FETALIS (WITHOUT RHOGAM)

1st Pregnancy
- Placenta
- Maternal circulation
- RBCs with Rh antigen

Delivery
- Mother
- Plasma cells
- Anti-Rh IgM

Rh-specific B cell
- 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 hypersensitivity (immune complex disease)

Mechanisms of Ab deposition

Effector mechanisms of tissue injury

Serum sickness - a transient immune complex-mediated syndrome
Arthus reaction

Peaks @ 4-8 hours
Visible edema
Severe hemorrhage
Can be followed by ulceration

Figure 15-15
Kuby IMMUNOLOGY, Sixth Edition
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Formation of circulating immune complexes contributes to the pathogenesis of:

• Autoimmune diseases
  – SLE (lupus nephritis), rheumatoid arthritis
• Drug reactions
  – Allergies to penicillin and sulfonamides
• Infectious diseases
  – Poststreptococcal glomerulonephritis, meningitis, hepatitis, mononucleosis, malaria, trypanosomiasis
WAIT FOR US!

RIGHT, START CLEANING UP!

MUNCH!

—OH! NO... MACROPHAGES!

MUNCH! MUNCH!

AARRGH!
Killer T lymphocytes

Type IV hypersensitivity (DTH)

Kumar et al. Robbins and Cotran Pathologic Basis of Disease. Elsevier 2005
<table>
<thead>
<tr>
<th>Intracellular bacteria</th>
<th>Intracellular viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Herpes simplex</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></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intracellular fungi</th>
<th>Contact antigens</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pneumocystis carinii</em></td>
<td>Picrylchloride</td>
</tr>
<tr>
<td><em>Candida albicans</em></td>
<td>Hair dyes</td>
</tr>
<tr>
<td><em>Histoplasma capsulatum</em></td>
<td>Nickel salts</td>
</tr>
<tr>
<td><em>Cryptococcus neoformans</em></td>
<td>Poison ivy</td>
</tr>
<tr>
<td><em>Intracellular parasites</em></td>
<td>Poison oak</td>
</tr>
<tr>
<td><em>Leishmania sp.</em></td>
<td></td>
</tr>
</tbody>
</table>
Autoimmune diseases mediated by direct cellular damage

Top - Goldsby et al, Figure 20-1 - Hashimoto’s thyroiditis
Bottom - Goldsby et al, Figure 20-3 - Type I diabetes
Sensitization phase

Intracellular bacteria

APC

CD4+ T\textsubscript{H}

T\textsubscript{H}1 cells (generally)

Antigen-presenting cells: Macrophages Langerhans cells

DTH-mediating cells: T\textsubscript{H}1 cells generally CD8 cells occasionally

Figure 15-17a
Kuby IMMUNOLOGY, Sixth Edition
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**Effector phase**

- **Sensitized T\_H1**
- **Secreted IFN-\(\gamma\)**
- **Membrane TNF-\(\beta\)**

**Resting macrophage**

- **Class II MHC**
- **Activated macrophage**

**T\_H1 secretions:**

- **Cytokines:** IFN-\(\gamma\), TNF-\(\beta\), IL-2, IL-3, GM-CSF, MIF
- **Chemokines:** IL-8/CXCL8, MCP-1/CCL2

**Effects of macrophage activation:**

- ↑ Class II MHC molecules
- ↑ TNF receptors
- ↑ Oxygen radicals
- ↑ Nitric oxide

*Figure 15-17b*

*Kuby IMMUNOLOGY, Sixth Edition*

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Pentadecacatechol

$$\text{HOH}$$

$$\text{(CH}_2\text{)}_7\text{CH} = \text{CHCH}_2\text{CH} = \text{CH(CH}_2\text{)}_2\text{CH}_3$$

Figure 10-36 The Immune System, 2/e (© Garland Science 2005)
Clinical and patch test appearances of contact hypersensitivity
Tuberculin-type hypersensitivity reaction
DTH in the skin

Uses of tuberculin-type reactions

Demonstration of past infection with a microorganism.
Assessment of cell-mediated immunity.
The importance of TNF-α in the formation of granulomas
Diseases associated with granuloma formation:

- Leprosy
- Tuberculosis
- Schistosomiasis
- Sarcoidosis
- Crohn’s disease
Response to mycobacterial infection

CD95L CD40L CD30L CD40L-1 1BBL OX40L-4 1BB CD27L SolubleMem TNF TNF LTα LTβ Light TRAIL RANKL BAFF APRIL TWEAK EDA GITRL BTLA GITR HVEM

TNF superfamily involvement in granuloma formation and resistance to mycobacterial infection. Reported: Dark gray ligands and receptors are essential for normal granuloma formation and sustained resistance to mycobacterial infection. Pale gray ligands and receptors are required for optimal protective immunity to mycobacterial infection. Unfilled ligands and receptors were not required for normal granuloma formation and expression of protective immunity to mycobacterial infection. Unreported: Ligands and receptors whose function in granuloma formation and resistance to mycobacterial infection has not yet been reported.

Chemokine expression in tissues from *M. tuberculosis*-infected individuals

<table>
<thead>
<tr>
<th>In vivo/ex vivo sample</th>
<th>Chemokines</th>
</tr>
</thead>
</table>
| Pleura                | MIP-1$^\alpha$, MIP-1$^\beta$  
|                       | Mig, RANTES         
|                       | IP-10, MCP-1        
|                       | MCP-1, MIP-1$^\alpha$, MIP-1$^\beta$ |
| BALF                  | IP-10, IL-8         
|                       | MCP-1, MCP-3, MCP-4 
|                       | RANTES              
|                       | MIP-1$^\alpha$       
|                       | Exotaxin            
| Lung                  | MCP-1, MCP-3, MCP-4, IP-10 |
|                       | Eotaxin             
| Alveolar macrophages  | CCR5                
|                       | RANTES              
|                       | MIP-1$^\alpha$       
|                       | MCP-1               
| Plasma                | IL-8, IP-10         
| PBMC                  | MCP-1, RANTES       
|                       | MIP-1$^\alpha$, MIP-1$^\beta$ 
|                       | RANTES              
|                       | MCP-1               
| Cerebral spinal fluid | MCP-1, IL-8         
|                       | MIP-1$^\alpha$       |

Tuberculosis
Sarcoidosis (lymph node)
Skin Reactions

Immediate Arthus DTH