Use + Share + Adapt

{ Content the copyright holder, author, or law permits you to use, share and adapt. }

- **Public Domain – Government**: Works that are produced by the U.S. Government. (USC 17 § 105)
- **Public Domain – Expired**: Works that are no longer protected due to an expired copyright term.
- **Public Domain – Self Dedicated**: Works that a copyright holder has dedicated to the public domain.
- **Creative Commons – Zero Waiver**
- **Creative Commons – Attribution License**
- **Creative Commons – Attribution Share Alike License**
- **Creative Commons – Attribution Noncommercial License**
- **Creative Commons – Attribution Noncommercial Share Alike License**
- **GNU – Free Documentation License**

Make Your Own Assessment

{ Content Open.Michigan believes can be used, shared, and adapted because it is ineligible for copyright. }

- **Public Domain – Ineligible**: Works that are ineligible for copyright protection in the U.S. (USC 17 § 102(b)) *laws in your jurisdiction may differ

{ Content Open.Michigan has used under a Fair Use determination. }

- **Fair Use**: Use of works that is determined to be Fair consistent with the U.S. Copyright Act. (USC 17 § 107) *laws in your jurisdiction may differ

Our determination **DOES NOT** mean that all uses of this 3rd-party content are Fair Uses and we **DO NOT** guarantee that your use of the content is Fair.

To use this content you should **do your own independent analysis** to determine whether or not your use will be Fair.
Classification of Immune Mediated Tissue Injury: Gell Coombs Classification

Mechanisms of Immune-Mediated Disorders

(4- types)
J. Fantone: Host Defense
2/17/09
10:00-12:00am
The four types of hypersensitivity reaction

**Type I**
- Allergen
- IgE
- Fc receptor
- Mast cell degranulation
- Mediator release

**Type II**
- Cell surface antigen
- IgG
- Target cell
- Cytotoxic action
- Antibody
- Complement
- Target cell
- Complement mediated lysis

**Type III**
- Immune-complex deposition
- Complement
- Blood vessel
- Tissue basement membrane

**Type IV**
- Antigens
- Activated macrophage
- Inflammatory mediators
- Lymphokines
Type I Anaphylactic Type

- **Prototype Disorders**
  - Allergic rhinitis
  - Allergic asthma
  - Anaphylaxis (insect venom)

- **Immune Mechanisms**
  - IgE-Mast cells
  - Vascular permeability
  - Eosinophils
Type II, Cytotoxic Type

- **Prototype Disorders**
  - Hemolytic reactions
  - Goodpastures Syndrome
  - Myasthenia Gravis
  - Grave’s Disease (hyperthyroidism)

- **Immune Mechanisms**
  - IgG
  - Complement
  - Phagocytic cells
  - ADCC
Type III, Immune Complex Disease

- Prototype Disorders
  - Post-streptococcal glomerulonephritis
  - Vasculitis
    - Polyarteritis nodosa

- Immune Mechanisms
  - Ab-Ag reactions
  - Complement
  - Neutrophils
  - Fibrin, hemorrhage
Type IV, Cell-Mediated (Delayed) Hypersensitivity

• Prototype Disorders
  – Poison Ivy
  – Tuberculosis (granulomatous inflammation)
  – Cytotoxic T-cell
    • Dr. King’s lectures

• Immune Mechanisms
  – T-lymphocytes
  – Monocyte/macrophage
Antibody-Mediated Cell and Tissue Injury: IgE Mediated Hypersensitivity Reactions

Objectives:

To understand the pathophysiologic mechanisms associated with Type I anaphylactic hypersensitivity reactions
Objectives (cont.)

- The role of IgE-mediated Mast cell degranulation in Type I reactions
- The primary effector mediators released during Mast cell stimulation
- The pathologic changes observed in tissues associated with anaphylactic hypersensitivity reactions
- The modulatory role of eosinophils in these reactions
- To correlate the effect of mediators on target organs with the clinical expression of anaphylactic reactions
Clinical

- Type I reactions are usually the result of exposure to environmental allergens in genetically susceptible individuals.
- 1/10 persons in USA affected to varying degrees.
- Genetics not clearly defined, although there is a familial association.
- Atopy: a genetic predisposition for developing IgE responses to many antigens.
- Local or systemic symptoms.
Clinical (cont.)

- Most common form - allergic rhinitis
  - Also
    - Certain types of asthma
    - Atopic dermatitis (eczema)
    - Certain gastrointestinal food allergies

- Allergens
  - Pollens, molds, house dust mite, animal dander
Pathophysiology

Induction and effector mechanisms in Type I Hypersensitivity

- Antigen presentation
- IgE production
- Mast cell activation
- Mediator release
- Clinical effects

Antigen

- Processing and presentation

- APC
- TH
- B_e

- IL-4, IL-5, IL-6
- IFN_y

- GM-CSF, TNF_a
- IL-8/9, inflammatory cell activation

- Preformed and newly formed mediators

- Pharmacological effects:
  - Blood vessels
  - Airways etc.
  - Cell infiltration

- Clinical effects:
  - Asthma
  - Eczema
  - Hay fever

- Feedback effects:
  - On the immune system

Source Undetermined
Sensitization to Ag

B-cell proliferation with production of IgE (IL-4 driven process)

IgE binds to surface of mast cell or basophil

Second Ag challenge

Multivalent Ag binds IgE on mast cells: crosslinking IgE

Degranulation and release of preformed mediators

De novo synthesis of mediators
Degranulation and release of preformed mediators

- Histamine
- Chemotactic factors
- Proteases

De novo synthesis of mediators

- Leukotrienes (C4, D4, E4)
- Prostaglandins
- Platelet activating factor
- Cytokines

Smooth muscle: bronchial, GI, vascular
Vascular endothelium
Secretory glands (e.g. mucous)
Eosinophils
Resting mast cell shows granules containing serotonin and histamine.

Activated mast cell.

Multivalent antigen crosslinks bound IgE antibody causing release of granule contents.
Effects of Mediators in Anaphylaxis: Reversible Response

- Histamine - vascular permeability, vasodilation (post-capillary venule), smooth muscle contraction
- Chemotactic Factors
- Cytokines
- Lipid mediators
Effects of Mediators in Anaphylaxis: Reversible Response (cont.)

- Lipid Mediators: Arachidonic acid metabolites
  - Leukotriene C4, D4, E4 - smooth muscle contraction
  - Prostaglandins - vasodilation
Effects of Mediators in Anaphylaxis: Reversible Response (cont.)

- Lipid Mediators: PAF - platelet activating factor - low molecular weight lipid
  - Acetylated glycerol ether phosphocholine (AGEPC)
  - Activates phagocytic cells
  - Smooth muscle contraction
Role of Eosinophils in Anaphylaxis:

• Normal levels 2 to 3% circulating leukocytes
• Type 1 response: up to 10%+ circulating leukocytes
• Secretory products include:
  – NADPH oxidase-derived oxidants
  – Prostaglandins and Leukotrienes (LTC4)
  – Major basic protein (MBP): cytotoxic
  – Cytokines
  – others
Pathologic Changes Associated with Anaphylactic Reactions: Reversible

• Symptoms depend on target organ: skin
  – Gross: swelling, wheal and flare response
    • early response: preformed mediators
    • late response: synthesized mediators
  – Light microscopic: edema, eosinophils
  – Electron microscopic: edema, endothelial cell gaps
# Immediate and late skin reactions

<table>
<thead>
<tr>
<th>late response</th>
<th>immediate response</th>
</tr>
</thead>
<tbody>
<tr>
<td>(at 5 hours)</td>
<td>(at 20 minutes)</td>
</tr>
</tbody>
</table>

![Image of skin reactions](image.png)

- At 5 hours:
  - 1:10
  - 1:100
  - 1:1000
  - 1:10000

- At 20 minutes:
Pathologic Changes Associated with Anaphylactic Reactions: Reversible

- Mucous and serous glands
  - Increased secretion
- Bronchial and GI smooth muscle
  - Contraction
**Therapeutic Approaches**

- Avoid antigen
- **Mediator antagonists**
  - anti-histamines: receptor antagonist
  - leukotriene inhibitors: lipase inhibitors, receptor antagonists
  - functional: sympathetic stimulants
- **Inhibit mast cell degranulation**
  - cromolyn
- **Non-specific anti-inflammatory agents**
  - corticosteroids
- **Immunotherapy** ("allergy shots")
## Comparison of Skin Tests

<table>
<thead>
<tr>
<th>Hypersensitivity Type</th>
<th>Time</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Minutes</td>
<td>Wheal: edema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flare: vasodilation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eosinophils</td>
</tr>
</tbody>
</table>
Diagnosis

• Skin test - most frequently used
Serologic Tests: RAST - Radioallergosorbent Test - Specific IgE

Bead with Ag (Ab) + Patient’s serum (Ab) → Anti-human IgE
RIST - Radioimmunosorbent Test - Total IgE

Bead + Anti human IgE

+ Patient’s serum (Ab)

Anti-human IgE
Summary: Type I Reaction

- Antibody: IgE
- Effector Cells: Mast Cell & Eosinophil
- Complement: No
- Reaction: Minutes
Antibody-Mediated Cell and Tissue Injury

(Type II and Type III Reactions)
The four types of hypersensitivity reaction:

**Type I**
- Allergen
- IgE
- Fc receptor
- Mast cell degranulation and mediator release

**Type II**
- Cell surface antigen
- IgG
- Target cell
- Cytotoxic action
- Antibody
- Complement
- Target cell-mediated lysis

**Type III**
- Immune-complex deposition
- Complement
- Blood vessel
- Basement membrane

**Type IV**
- Antigens
- T cell
- Inflammatory mediators
- Lymphokines
- Activated macrophage
Pathophysiology

• Cytotoxic or Type II Reactions: Binding of Antibody (IgG or IgM) with cell membrane or tissue antigens
  – Red blood cell membrane antigens - hemolytic anemias
  – Platelet antigens - thrombocytopenia cell membrane - petechial hemorrhage
  – Basement Membrane - Goodpasture’s syndrome
    • Kidney - proteinuria
    • Lung - hemorrhage
Mechanisms

- Opsonin dependent phagocytosis
- Complement-dependent Ab lysis
- Antibody-dependent cell cytotoxicity
Rh Incompatibility in Newborn: Hemolytic Anemia

Pregnant woman Rh-

Sensitized during birth of Rh+ First child

forms circulating IgG antibody (Anti-D)

IgG crosses placenta

hemolysis

Preventative Therapy: Block sensitization by giving mother anti-D (Rho) Immunoglobulin within 72 hours after first birth or abortion
Mechanisms (cont.)

• Antibody directed to tissue antigens: examples
  – Goodpasture’s syndrome: antigen = basement membrane of kidney and lung
  – Dermatitis Herpetiformis: antigen = epidermis basement membrane reticulin
  – Bullous Pemphigoid: antigen = epidermis basement membrane
  – Pemphigus vulgaris: antigen = epidermis keratinocyte membranes
Goodpasture’s Syndrome

- Hemoptysis
- Pulmonary infiltrates
- Renal failure
- Anemia
Pathology

- Circulating ant-GBM antibodies
- Light microscopy: frequently neutrophils, hemorrhage
- Immunofluorescence: immunoglobulin and complement deposition; linear immunofluorescence
- Electron microscopy: no electron dense deposits
Goodpastures Syndrome: Anti-GBM Disease

- Antibody binds to glomerular basement membrane epitope

- Complement activation:
  - C3b deposition
  - C3a + C5a

- Proteases

- Reactive oxygen metabolites

- PMN recruitment

- Tissue injury

- Lung: hemorrhage, hemoptysis, alveolar infiltrates

- Kidney: proteinuria, hematuria, renal failure
Goodpastures Syndrome: Anti-GBM Disease

+ complement → C3a, C5a
→ PMNs
→ proteases
→ oxygen metabolites
→ tissue injury

Lung: hemorrhage, hemoptysis, alveolar infiltrates

Kidney: proteinuria, hematuria, renal failure
glomerulus

J. Fantone
Damage mechanisms

normal antimicrobial action

1. neutrophil
2. phagocytosis
3. lysosome fusion

type II hypersensitivity reaction

4. neutrophil
5. 'frustrated phagocytosis'
6. extracellular enzyme release
Goodpastures Syndrome

- Linear antigen distribution
- Linear antibody + complement distribution
- Linear secondary anti-human antibody to IgG or complement containing a fluorescent marker
Mechanisms (cont.)

- Antibody Binds to Cell Receptor (Type V Reactions)
  - Hyperthyroidism (Grave’s Disease): Thyroid follicle cell - IgG antibody binds to thyroid stimulating hormone (TSH) receptor and stimulates cell
  - Myasthenia Gravis: antibody to acetylcholine receptor at neuromuscular synapse antibody blocks neuromuscular transmission (decreased receptors) causing muscle weakness
Antibody to Cell Receptors

A. STIMULATE CELL

B. BLOCK BINDING OF NATURAL LIGAND
GRAVES DISEASE: Hyperthyroidism

TSH → TSH receptor → G → AC → ATP → cAMP → Protein Kinases → Increased T3, T4 production
The four types of hypersensitivity reaction

**type I**
- Allergen
- IgE
- Fc receptor
- Mast cell degranulation
- Mediator release

**type II**
- Cell surface antigen
- IgG
- Target cell
- Cytotoxic action
- Antibody
- Complement
- Target cell
- Complement mediated lysis

**type III**
- Immune-complex deposition
- Complement
- Blood vessel
- Tissue basement membrane

**type IV**
- Antigens
- Inflammatory mediators
- Lymphokines
- Activated macrophage

Source Undetermined
Type III: Immune Complex Mediated Tissue Injury

- Antibody
- Antigen
- Ag-Ab complex
  - Complement activation
    - C5a
  - Monocyte/macrophage activation
    - Cytokines (e.g., TNF, chemokines)
  - Neutrophil influx

J. Fantone
Summary: Immune Complex Mediated Tissue Injury

Neutrophil influx

Phagocytosis of immune complexes

Oxygen metabolites
O2-, H2O2 etc.

Lysosomal enzymes
Proteases etc.

Tissue injury
Pathology of Immune Complex Injury

- Fibrinoid necrosis
- Hemorrhage
- Neutrophils
- Antibody + Complement deposition
- EM: Electron dense deposition
- Granular immunofluorescence
Type III Hypersensitivity: Local I.C. Disease

The Arthus reaction

- Antigen
- Antibody
- Immune complex
- Complement
- Neutrophil
- Neutrophil chemotaxis
- Neutrophil degranulation
- Mast cell degranulation
- Lysosomal enzymes
- Platelet aggregation
- Vasoactive amines
- Endothelial cell retraction

Source Undetermined
Immune Complex-Mediated Hypersensitivity (Type III) (cont.)

- Systemic immune complex disease

  Foreign Ag injected I.V.

  Immune response w/Ab production (IgM, IgG)

  Circulating immune complexes formed

  Tissue deposition w/complement fixation

  Arteritis
  Glomerulonephritis (w/proteinuria)
Immune Complex-Mediated Hypersensitivity (Type III) (cont.)

• Pathology
  – Light microscopy: neutrophils, hemorrhage, edema
  – Electron microscopy: electron dense deposits
  – Immunofluorescence: immunoglobulin and complement deposition, granular immunofluorescence pattern
• Clinical - depends on target organ and/or site of immune complex deposition
  – Synovium - rheumatoid arthritis
  – Kidney - glomerulus
    • Post-streptococcal glomerulonephritis
    • Systemic lupus erythematosus
  – Blood vessel walls - vasculitis
    • Polyarteritis nodosa
    • Early transplant rejection
  – Lung - hypersensitivity pneumonitis
Immune Complex Disease
(post-streptococcal glomerulonephritis)

- Irregular antigen distribution
- Irregular antibody + complement distribution
- Irregular secondary anti-human antibody to IgG or complement containing a fluorescent marker
Immune Complex-Mediated Hypersensitivity (Type III) (cont.)

- Diagnosis
  - Skin tests for Type III reactions

- Therapy
  - Elimination of antigen - as in transfusion reactions, hypersensitivity lung reactions to foreign antigens, and certain drug reactions
  - Corticosteroid and immunosuppressive therapy (cytoxan, cyclosporin)
  - Plasmapheresis
Summary: Type II/III Reaction

- Antibody: IgM & IgG
- Effector Cells: Phagocytic
- Complement: Yes
- Reaction: 6-24 hours
The four types of hypersensitivity reaction

**Type I**
- Allergen interacts with IgE on mast cells.
- IgE binds to Fc receptors on mast cells.
- Mast cell degranulation and mediator release.

**Type II**
- Cell surface antigen binds IgG.
- Antibody-mediated cytotoxic action on target cell.
- Complement-mediated lysis of target cell.

**Type III**
- Immune complex deposition on tissue.
- Complement binds antigens.
- Blood vessel and tissue basement membrane involvement.

**Type IV**
- Antigens interact with T cells.
- Activated macrophage releases inflammatory mediators and lymphokines.
Type IV: Cell-Mediated Immune Reactions

• Objective
  – To define the primary mechanisms involved in contact hypersensitivity and delayed type hypersensitivity reactions
  – To review mechanisms of T-Cell mediated cytotoxicity (see Dr. King)

• Cell Components
  – Mononuclear inflammatory cells: lymphocytes, monocytes/macrophages and antigen presenting cells
# Delayed hypersensitivity reactions

<table>
<thead>
<tr>
<th>DTH type</th>
<th>reaction time</th>
<th>clinical appearance</th>
<th>characteristics</th>
<th>antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>contact</td>
<td>48–72 hours</td>
<td>eczema</td>
<td>infiltration of lymphocytes and, later, macrophages, oedema of epidermis</td>
<td>epidermal: e.g. nickel, rubber, poison ivy usually a hapten</td>
</tr>
<tr>
<td>tuberculin</td>
<td>48–72 hours</td>
<td>local hardening and swelling ± fever</td>
<td>infiltration of lymphocytes, monocytes, and macrophages</td>
<td>intradermal injection used diagnostically: tuberculin, mycobacterial and leishmanial antigens</td>
</tr>
<tr>
<td>granulomatous</td>
<td>4 weeks</td>
<td>hardening e.g. in skin or lung</td>
<td>granuloma containing epithelioid cells, giant cells, and macrophages; fibrosis ± necrosis</td>
<td>persistent Ag or Ag–Ab complexes in macrophages; or 'non-immunological', e.g. talcum powder</td>
</tr>
</tbody>
</table>
Poison ivy

Urushiols on leaf

Contact

Antigen (urushiols) combine with skin proteins

Leaf

Skin

7–10 days

Primary contact

T_{DTH} cells

T_{DTH} memory cells

No dermatitis

1–2 days

Secondary contact

T_{DTH} memory cells

Active T_{DTH} cells

Macrophage activation

Dermatitis
The sensitization phase of contact hypersensitivity

- Hapten
- Epidermis
- Langerhans' cell
- Hapten-carrier complex
- Dermis
- Lymphatic
- Lymph vessel
- Regional lymph node
- Cortex (B cell area)
- Paracortex (T-dependent area)
- Medulla
- Macrophage
- Germinal centre
- Intercitial lymphocytes

Source Undetermined
The elicitation phase of contact hypersensitivity

- Hapten
- Carrier
- ICAM 1
- Class II antigen

- Langerhans' cell
- Venules
- Arteriole
- Lymphatic
- Macrophage

Source Undetermined
Granulomatous Inflammatory Reactions
Macrophage differentiation

- APC → IL-1 → T → IL-2 → T cell proliferation
  - IL-3, IL-6, IFN-α, TNF
  - activation
- Immature macrophage → fusion of cells
- Activated macrophage
- Epithelioid cell
- Multinucleate giant cell
- TNF
Summary: Type IV Reaction

- Antibody: No
- Effector Cells: T-lymphocytes, Monocyte/Macrophage
- Complement: No
- Reaction: 48-72 hours (skin test)
Type IV: T-Cell Mediated Cytotoxicity

(see Dr. King’s presentation)

• Mechanisms
  – CD8+ lymphocyte
  – Antigen expressed with Class I MHC
  – Interleukin-2 clonal expansion
  – Cytotoxic effector cell
    • Recognizes Ag+ class I MHC
T-Cell Mediated Cytotoxicity
(cont.)

• Initiates programmed cell death (apoptosis)
  • Perforins/cytolysins
  • Proteolytic enzymes: granzymes
  • FAS-induced apoptosis: CD8+ T cell: FAS ligand target cell:FAS receptor
• Cytokines
  – Interferon $\gamma$
  – Tumor Necrosis Factor $\alpha$ and $\beta$
The four types of hypersensitivity reaction

**Type I**
- Allergen triggers IgE binding to mast cells.
- Fc receptor mediates mast cell degranulation and mediator release.

**Type II**
- Cell surface antigen binds IgG.
- Cytotoxic action mediated by antibody.
- Complement mediated lysis of target cell.

**Type III**
- Immune-complex deposition on tissue basement membrane.
- Complement activation.

**Type IV**
- Antigens activate T cells.
- Inflammatory mediators and lymphokines released from activated macrophages.
Additional Source Information

for more information see: http://open.umich.edu/wiki/CitationPolicy