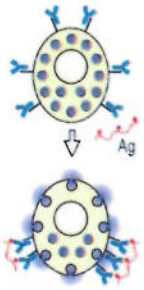
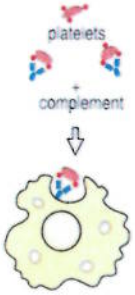
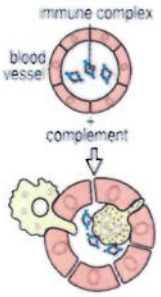
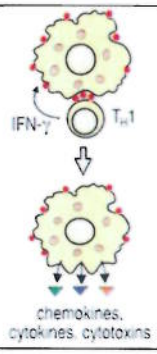
Lecture 20: Hypersensitivities

General Features of Hypersensitivity Disorders

- Inappropriate, exaggerated immune response to an antigen by a pre-sensitized individual
- **All** have three phases: i)sensitization, ii) activation, and iii) effector.
- can develop in the course of expected humoral or cell-mediated immune response
- consequences include localized tissue damage or systemic damage, possibly death
- early (acute) and late (prolonged) phases of responses

Overview of Hypersensitivities:

	Type I	Type II	Type III	Type IV
Recognition	IgE	IgG or IgM	IgG>IgM	T_{H1} – MHC II
Antigen	Soluble	Cell surface protein (Altered)	Soluble	Soluble → altered protein.
Effector	**Mast**-cell: histamine TNFα Eosinophil reactive compounds	**Complement Activation**: cell killing & inflammation NK -**ADCC**	C3a/C5a→ inflammation & tissue damage (**neutrophil**)	**Macrophage activation.**
				
Examples	Allergies, asthma, systemic anaphylaxis	Drug allergies (e.g. penicillin)	Arthus reaction (local), serum sickness (systemic)	Contact dermatitis

(images from Janeway, 6th edition)

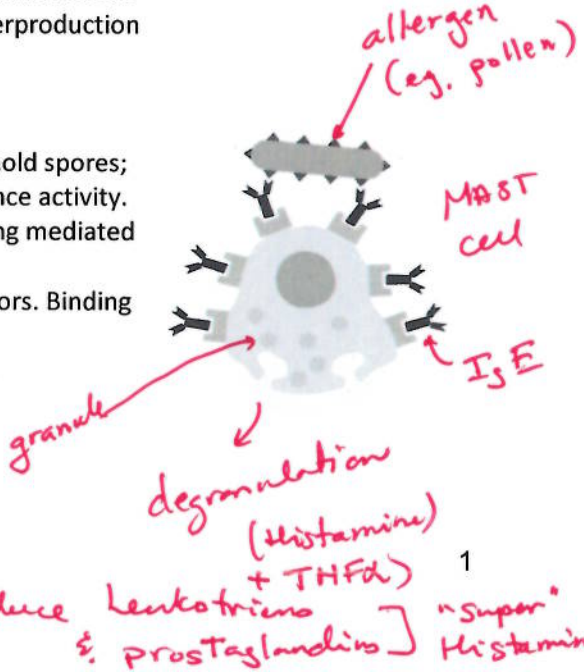
Type I Hypersensitivity reactions

Overview:

- Allergy: disease following a response to an otherwise innocuous antigen
- Quick response - within minutes of exposure
- Entry routes and dosages of allergen determine manifestation of illness
- Familial tendencies are common – genetic component - overproduction of IL-4.

Components of Type I Hypersensitive response

1. Allergens: proteins; pollen; drugs; foods; insect products; mold spores; animal hair/dander. Protease activity of allergen may enhance activity.
2. Antibodies: IgE, generally in mucosal tissues; IgE cross-linking mediated by multivalent antigen (allergen)
3. Early response effector cells: mast cells - have FcεR1 receptors. Binding of antigen causes granulation – mediators released.
4. Later effector cells: eosinophils, neutrophils, macrophages, lymphocytes



Pharmacologic Mediators:

Early Phase (minutes to hours):

	Product	Effects
Inflammation	Histamine,	Increase in vascular permeability. Increase in fluid flow, smooth muscle contraction.
	Leukotrienes/ prostaglandins	Prolonged inflammatory response. Mucus production, increased vascular permeability, smooth muscle contraction.
Cytokines	TNFα (Mast cells)	Increase in vascular permeability. Increase in fluid flow.

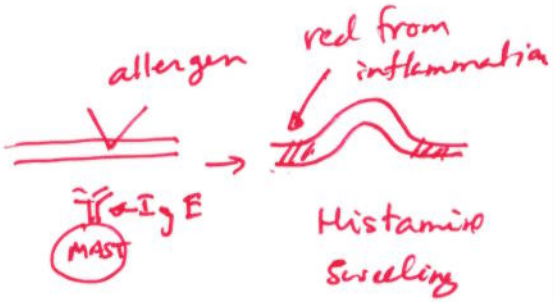
Late phase (48 hrs-days):

Profound inflammation, tissue damage from peroxidases, sustained edema from TNFα.

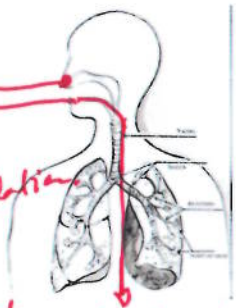
Types of Hypersensitivity I Reactions:

Local Reactions:

1, Wheal-and-flare [localized edema raising tissue (Wheal) with surrounding inflammation (flare)]



2. Hay fever
(Runny nose, sneezing)



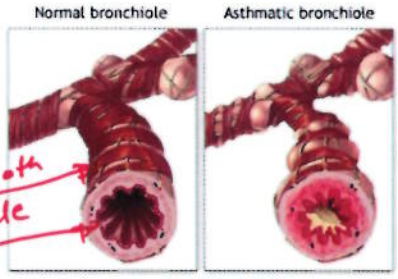
3. Food Allergy
(Diarrhea, vomiting)

- fluid in GI tract (histamine, TNFα)
- Smooth muscle contraction

GI tract.

4. Broncial asthma: Airways narrow, breathing difficult
   - Smooth muscle contraction
   - Mucus/fluid flow into bronchiole

Chronic asthma: Permanent damage from prolonged response, Mast cells more sensitive → degranulation.

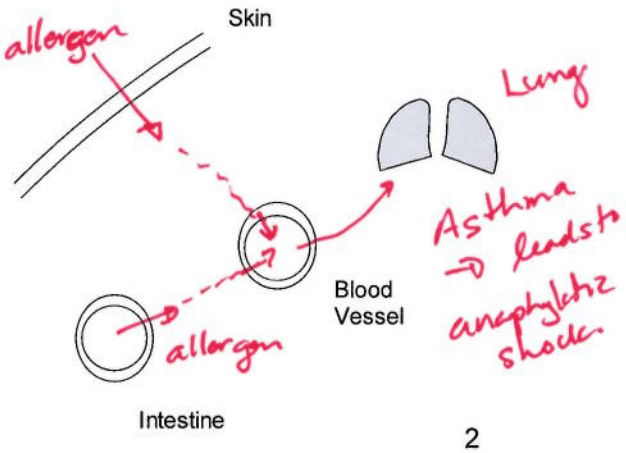


Systemic anaphylaxis:

Anaphylaxis: *Greek origin – ana – opposite phylaxis – prevention. "against protection"*

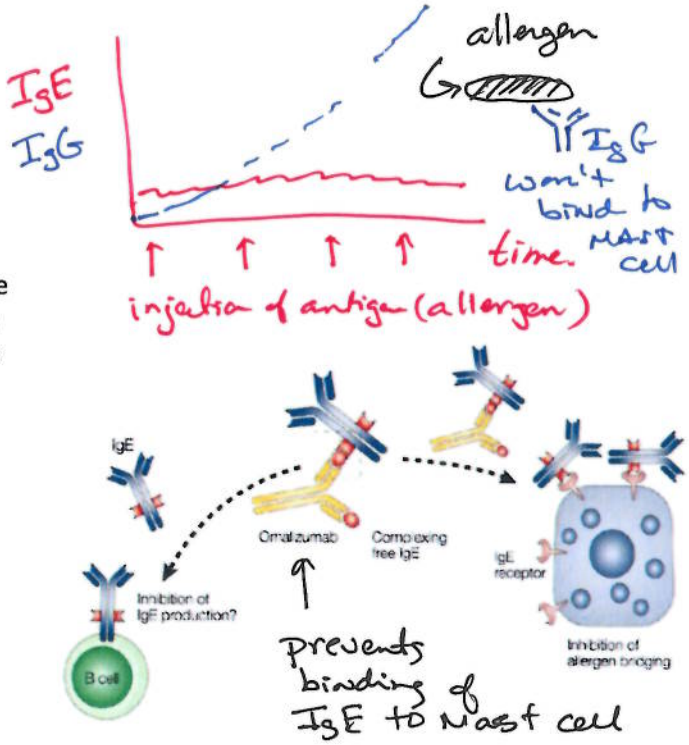
Sudden (minutes to 1-2 hrs) and profound reaction, can be fatal (hives, itching, throat constriction, difficulty breathing, decreased blood pressure).

Epinephrine ('epi-pen') relaxes SMC, restores vascular integrity.



Treatment Strategies for Allergies

- Environmental - limit exposure to allergen
- Drugs – Antihistamines, mast cell stabilizers, corticosteroids (reduce inflammation), leukotriene inhibitors.
- Hyposensitization - slow, prolonged immunization with allergen appears to reduce sensitivity. This probably involves a change in antibody production from IgE to IgG, i.e. class switching is from IgM→IgG instead of IgM→IgE. IgG inhibits IgE activation of mast cells.
- Immunotherapy - administration of humanized anti-IgE monoclonal antibodies (Omalizumab – clinically approved). Binds to CH_3 domain of IgE.



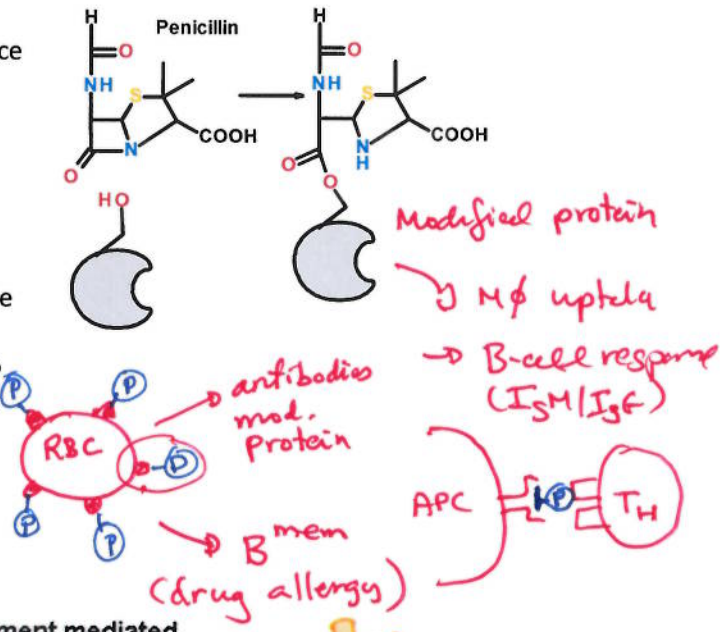
Hypersensitivity II (IgM + IgG/Macrophage/NK)

Cell surface antigen

- Antibody-mediated destruction of cells.
- Binding of specific antibody to antigen on the surface of a cell facilitates its destruction.
- Basis of several autoimmune diseases.

2A. Sensitization:

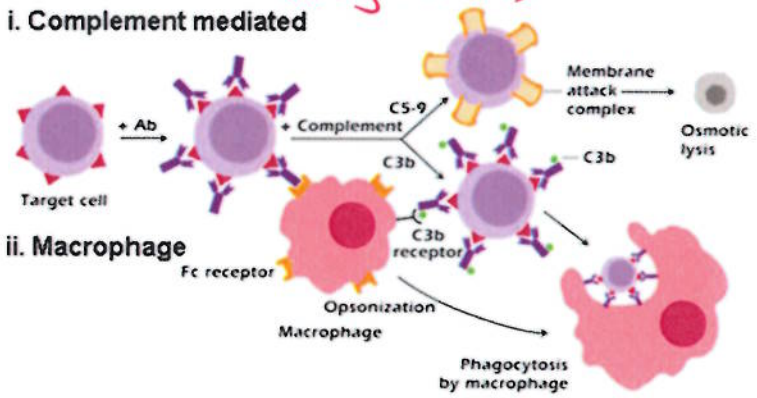
- Modified proteins on surface of cells generate a B-cell response via C3b enhanced phagocytosis by macrophages & T_{H2} response.
- Drug-induced Reactions: Drugs adsorb to cell membrane proteins and act as hapten-carrier conjugates; blood cells most commonly affected. Most Ab are directed to the modified protein, and thus the reaction subsides as antigen in eliminated.
  - Cross-reactivity is a possibility, leading to chronic conditions.
  - Presence of B-memory cells can lead to rapid response for subsequent uses of the drug.



2 B/C. Activation & Effector Functions.

i. Complement-mediated Reactions

- Specific antibody binds to antigen on target cell membrane
- **C1q** of the classical pathway binds to the Fc region of specific antibody, triggering the complement cascade that leads to **lysis** of target cell
- Phagocytes can bind Ab-Ag complex directly via C3b receptors.
- Mediators released by phagocytes cause inflammation and tissue damage

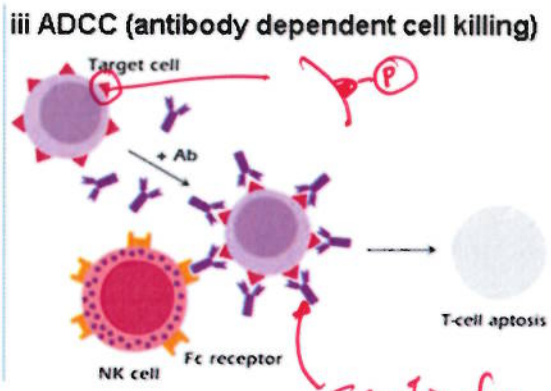


ii. Macrophage munching of opsonized target cell (and C3b opsonized antibodies), via C3b and Fc receptors.

iii. Antibody-Dependent Cell-mediated Cytotoxicity (ADCC)

- Specific antibody binds to antigen on target cell.
- NK cells bearing Fc receptors bind to the specific antibody (**phagocytosis does not occur.**)
- NK cells kill by:

ADCC
a) Granzyme & perforin → apoptosis of cell
b) Fas & FasL



Specific for modified protein ∴ no effect after drug is removed

Type III Hypersensitivity (Neutrophil)

3A Sensitization:

- Binding of antibody **(IgG>IgM)** to antigen (formation of immune complex) in **solution** causes IC deposition in tissues kidney, skin, joints, heart, brain, small blood vessels

3B/C Activation and Effector:

- Complement activation.
- Release of the **anaphylatoxins C5a and C3a** result in increased vascular permeability and recruitment and activation of neutrophils that release proteases and inflammatory mediators while attempting endocytosis of complex.
- Severity and nature depends on the **quantity, size and distribution** of immune complexes.

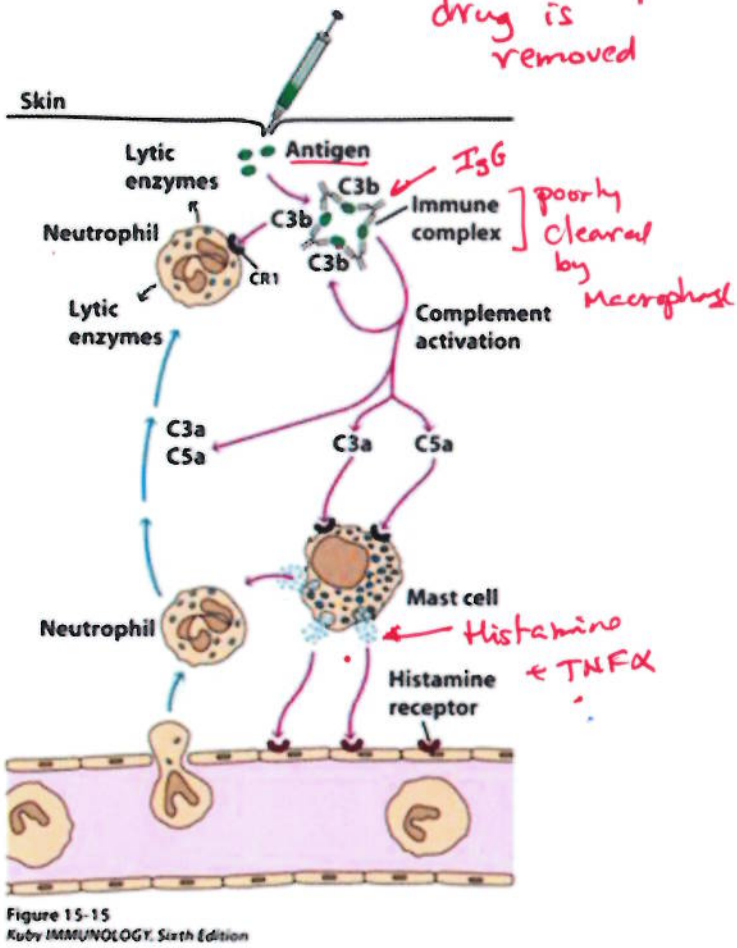


Figure 15-15
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Localized reaction: ***Arthus reaction*** Local

- Immune complexes accumulate near site of antigen introduction (e.g., insect bite, injection, inhalation of bacterial or fungal spores)
- Inflammation, localized tissue damage, and necrosis occur over 4-8 hours
- This disorder comprises many occupational diseases:
  - Farmer's lung: allergy to spores of bacterium on rotting hay, pulmonary inflammation
  - Pigeon breeder's, cheese washer's, maple bark stripper's, paprika worker's, thatched roof worker's diseases

Systemic reaction: e.g., **serum sickness**

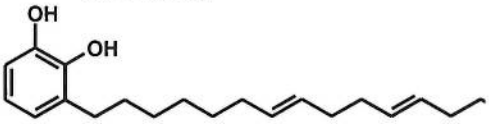
- Response to foreign protein such as Ig (Ig therapy for treatment of various disorders)
- Immune complexes are formed after repeated prolonged administration and deposited in tissues
- Symptoms: fever, joint pain, rash.

Type IV Hypersensitivity – DTH delayed type hypersensitivity (T_{H1} + Macrophages) :

4A. Sensitization phase

First exposure: antigen is captured by APCs (likely dendritic cells); presented by MHC II to $CD4^+$ T_H cells, which differentiate into a T_{H1} subset (T_{DTH}; antigen-specific **memory** T cells)

- Time frame: 1-2 weeks after primary contact with antigen
- Triggered by:
  - hapten-like molecules (chemicals)



  - Metal ions (nickel chromium)
  - foreign tissue grafts

4B. Activation phase

Re-exposure to antigen, which is recognized by sensitized, antigen-specific T_{DTH} cells in skin. Activated by D.C. and macrophages in skin.

- T_{DTH} cells secrete cytokines,
  i. **MCP-1:** monocyte chemotactic protein
  ii. **MIF:** macrophage migratory inhibitory factor
  iii. **IFN-γ:** recruits and activates macrophages
- Time frame: 1-3 days after *secondary* contact with antigen

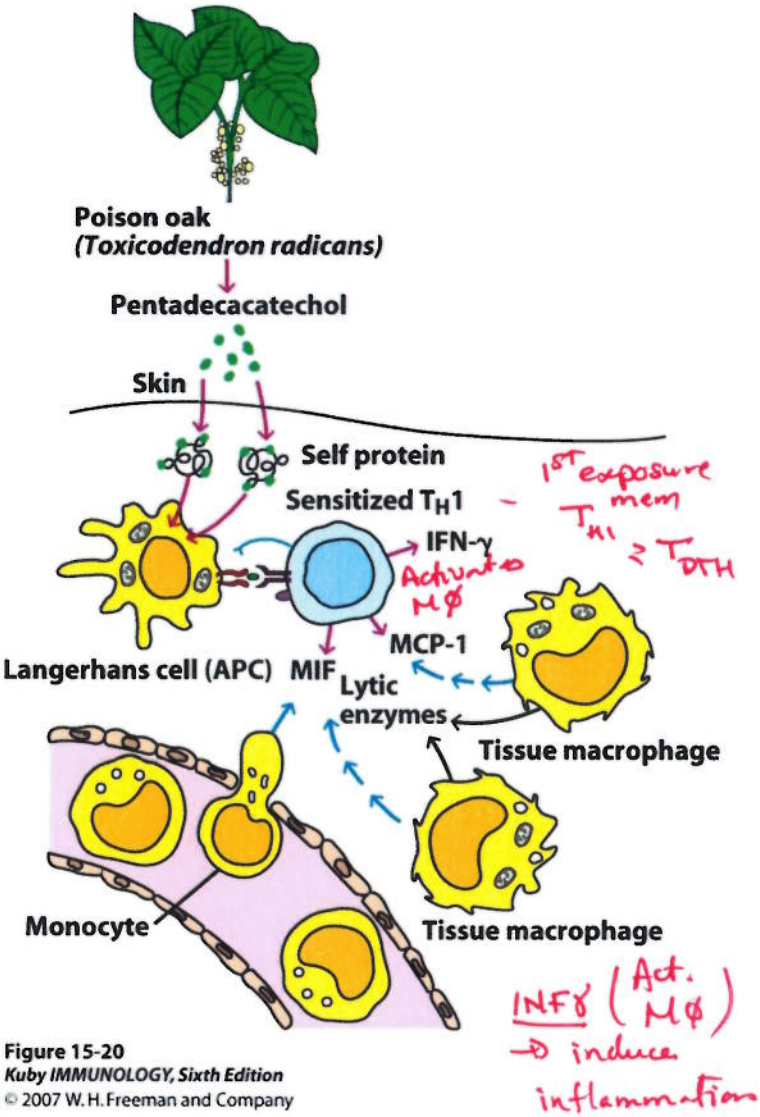


Figure 15-20
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4C. Effector phase

Principal effector cells – monocytes recruited, they then become macrophages

- Phagocytosis
- Lytic enzymes,
- reactive oxygen species like NO
- TNF-α

If antigen persists, then activity of the macrophage is prolonged. Phagocytosis continues. Degradative enzymes and reactive oxygen species from macrophages can leak into surrounding tissue, causing extensive damage. Symptoms can last for weeks and become chronic.