Hypersensitivity - an inappropriate immune response that causes damage to the individual

Type I hypersensitivity - mediated by IgE

Type II hypersensitivity - mediated by IgG

Type III hypersensitivity - mediated by immune complexes

Type IV hypersensitivity - cell-mediated

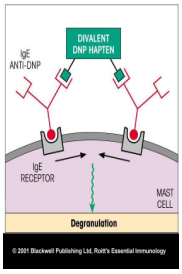
Immediate hypersensitivity - Types I, II and III

Delayed hypersensitivity - Type IV

What makes an antigen to be an allergen?

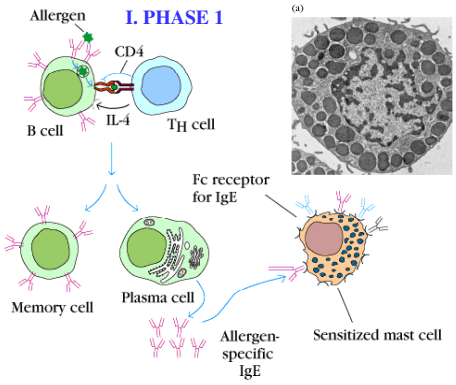
Features of inhaled allergens that may promote the priming of T_H2 cells that drive IgE responses	
Protein	Only proteins induce T-cell responses
Enzymatically active	Allergens are often proteases
Low dose	Favors activationof IL-4-producing CD4 T cells
Low molecular weight	Allergen can diffuse out of particle into mucus
Highly soluble	Allergen can be readily eluted from particle
Stable	Allergen can survive in desiccated particle
Contains peptides that bind host MHC class II	Required for T-cell priming

Figure 12-3 Immunobiology, 6/e. (© Garland Science 2005)



Type I hypersensitivity = allergic reactions

- **Mast cells and basophils possess receptors for the Fc region of IgE (FcεRI). Eosinophils but ONLY after activation!!**
- **IgE produced in response to an antigen (allergen) binds to mast cells and basophils.**
- **If antigen cross-links this IgE on the cell surface, the FcεRI are cross-linked– resulting in degranulation of the cell and release of vasoactive mediators (histamine, leukotrienes, prostaglandins, cytokines etc).**



Kuby Figure 16-2

TABLE 16-1 COMMON ALLERGENS ASSOCIATED WITH TYPE I HYPERSENSITIVITY

Proteins
- Foreign serum
- Vaccines

Plant pollens
- Rye grass
- Ragweed
- Timothy grass
- Birch trees

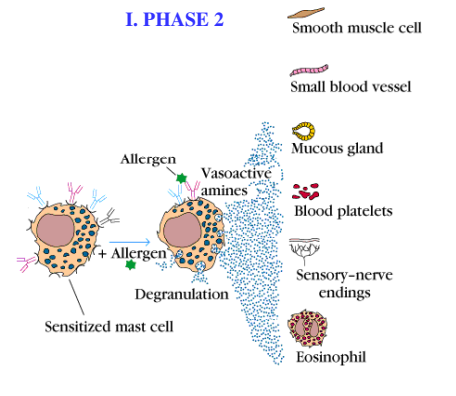
Drugs
- Penicillin
- Sulfonamides
- Local anesthetics
- Salicylates

Foods
- Nuts
- Seafood
- Eggs
- Peas, beans
- Milk

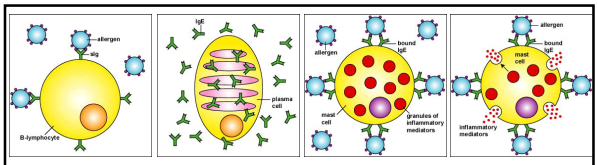
Insect products
- Bee venom
- Wasp venom
- Ant venom
- Cockroach calyx
- Dust mites

Mold spores

Animal hair and dander



Kuby Figure 16-2



RECAP:

1) The allergen enters the body and is recognized by sIg on a B-lymphocyte
2) The B-lymphocyte then proliferates and differentiates into plasma cells
3) The plasma cells produce and secrete IgE which binds to receptors on mast cells and basophils.
4) Allergen cross reacting with IgE on mast cell.
5) The next time the allergen enters the body, it cross-links the Fab portions of the IgE bound to the mast cell.
6) This triggers the mast cell to degranulate and releases its histamine and other inflammatory mediators.
7) The inflammatory mediators are now able to bind to receptors on target cells which leads to dilation of blood vessels, constriction of bronchioles, excessive mucus secretion, and other symptoms of allergy.

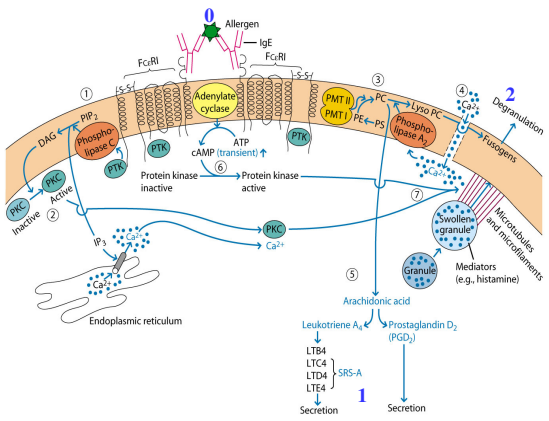


TABLE 16-3 PRINCIPAL MEDIATORS INVOLVED IN TYPE I HYPERSENSITIVITY

Mediator	Effects
Primary	
Histamine	Increased vascular permeability; smooth-muscle contraction
Serotonin	Increased vascular permeability; smooth-muscle contraction
Eosinophil chemotactic factor (ECF-A)	Eosinophil chemotaxis
Neutrophil chemotactic factor (NCF-A)	Neutrophil chemotaxis
Proteases	Bronchial mucus secretion; degradation of blood-vessel basement membrane; generation of complement split products
Secondary	
Platelet-activating factor	Platelet aggregation and degranulation; contraction of pulmonary smooth muscles
Leukotrienes (slow reactive substance of anaphylaxis, SRS-A)	Increased vascular permeability; contraction of pulmonary smooth muscles
Prostaglandins	Vasodilation; contraction of pulmonary smooth muscles; platelet aggregation
Bradykinin	Increased vascular permeability; smooth-muscle contraction
Cytokines	
IL-1 and TNF-α	Systemic anaphylaxis; increased expression of CAMs on venular endothelial cells
IL-2, IL-3, IL-4, IL-5, IL-6, TGF-β, and GM-CSF	Various effects (see Table 12-1)

Effector Mechanisms

- Immediate Allergic Reaction – caused by mast cell degranulation
- Late-phase response – involves the recruitment of Th2 cells, eosinophils, and basophils

Class of product	Examples	Biological effects
Enzyme	Tryptase, chymase, cathepsin G, carboxypeptidase	Remodel connective tissue matrix
Toxic mediator	Histamine, heparin	Toxic to parasites Increase vascular permeability Cause smooth muscle contraction
Cytokine	IL-4, IL-13	Stimulate and amplify T_H2 cell response
	IL-3, IL-5, GM-CSF	Promote eosinophil production and activation
	TNF-α (some stored preformed in granules)	Promotes inflammation, stimulates cytokine production by many cell types, activates endothelium
Chemokine	CCL3 (MIP-1α)	Attracts monocytes, macrophages, and neutrophils
Lipid mediator	Leukotrienes C4, D4, E4	Cause smooth muscle contraction Increase vascular permeability Stimulate mucus secretion
	Platelet-activating factor	Attracts leukocytes Amplifies production of lipid mediators Activates neutrophils, eosinophils, and platelets

Figure 12-12 Immunobiology, 6/e. (© Garland Science 2005)

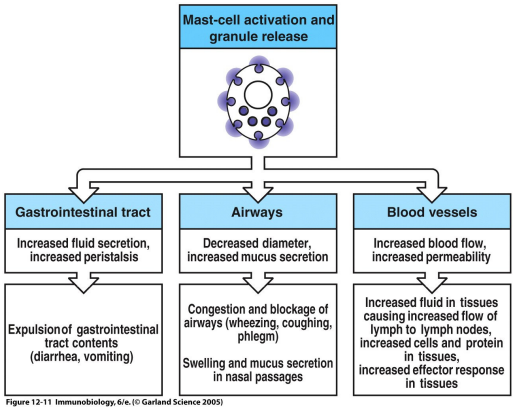


Figure 12-11 Immunobiology, 6/e. (© Garland Science 2005)

Localized allergic reactions - symptoms depend on the location of mast cell/basophil degranulation

- **Skin ---> eczema**
- **Nasal mucosa ---> allergic rhinitis (hay fever)**
- **Respiratory tract ---> asthma**
- **Gastrointestinal tract ---> vomiting, diarrhea (food allergies)**

Systemic allergic reaction = systemic anaphylaxis

- Systemic vasodilation results in an acute loss of blood pressure.
- Bronchoconstriction causes asphyxiation.
- Death can occur within minutes.

Epinephrine counteracts the effects of allergic mediators on smooth muscle and vasculature.

-Due to histamine, prostaglandins, and other preformed mediators that cause rapid increase in vasc. Permeability and contraction of smooth muscle

Late-Phase Reaction by inducing synthesis and release of mediators including leukotrienes, chemokines, and cytokines from activated mast cells

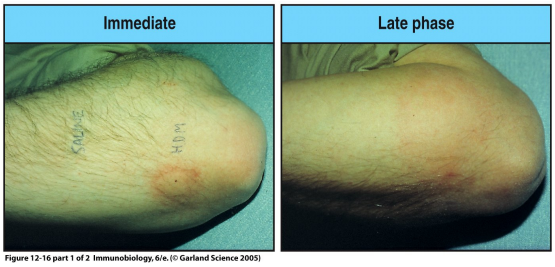


Figure 12-16 part 1 of 2 Immunobiology, 6/e, (© Garland Science 2005)

Causes of allergic reactions (factors predisposing to IgE responses):

Characteristics of the antigen

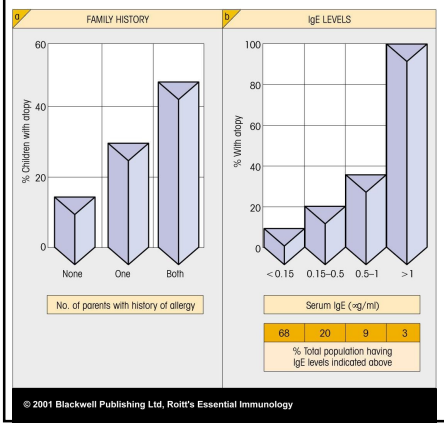
- **Certain antigens are more likely to induce IgE responses (e.g. ragweed pollen)**

Mode of presentation of the antigen

- **Dosage, adjuvant may influence the IgE vs IgG response**

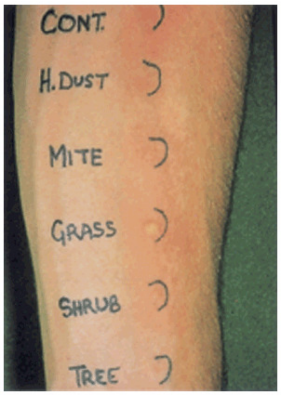
Genetics of the individual

- **Certain mouse strains are more likely to make IgE responses**
- **Parents with allergies are more likely to have children with allergies**



Blame it on your parents!!!!

Figure 16.10



Kuby Figure 16-10

-Due to histamine, prostaglandins, and other preformed mediators that cause rapid increase in vasc. Permeability and contraction of smooth muscle

Late-Phase Reaction by inducing synthesis and release of mediators including leukotrienes, chemokines, and cytokines from activated mast cells

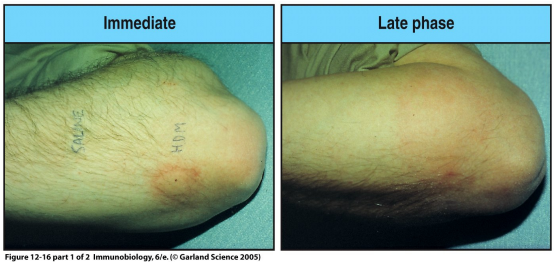


Figure 12-16 part 1 of 2 Immunobiology, 6/e, (© Garland Science 2005)

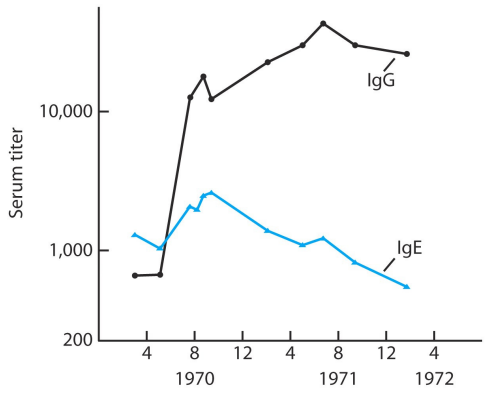
Therapeutic approaches - Allergen immunotherapy

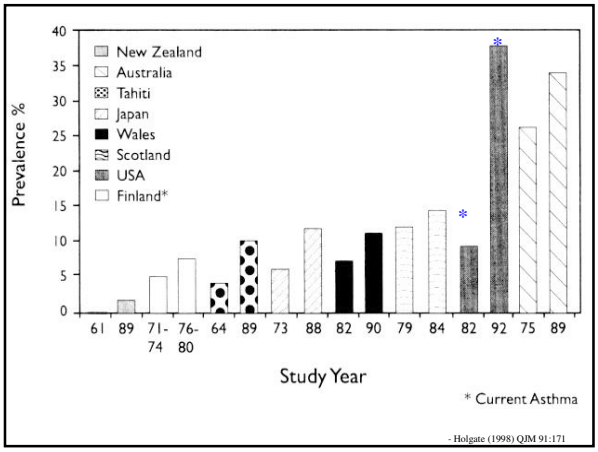
- **The practice of administering gradually increasing quantities of an allergen extract to an allergic subject to ameliorate the symptoms associated with subsequent exposure to the causative allergen.**

- Introduced in 1911

"The mechanisms of immunotherapy are complex....newer studies suggest that immunotherapy acts by modifying T-cell responses either by immune deviation [shift from Th2 to Th1], T-cell anergy, or more likely both." - WHO, 1998.

Risk: systemic anaphylaxis (potentially fatal)



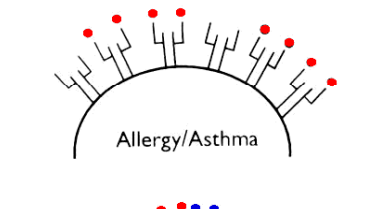


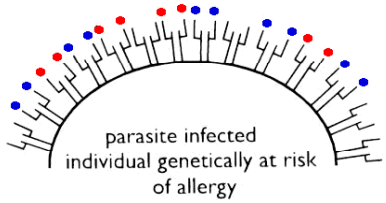
- Holgate (1998) QJM 91:171

- In 1975, Godfrey (Clin. Allergy 5:201) investigated the occurrence of allergy and asthma in Gambian school children.

- Showed their association with urban dwelling, higher socioeconomic status and lower total circulating IgE levels.

- Suggested that in the rural setting, parasite infection was protective against the development of allergy and asthma.





- Holgate (1998) QJM 91:171

Children in Caracas, Venezuela treated with antihelminthic drugs - Lynch et al (1993) J. Allergy Clin. Immunol. 92:404.

	Change in parasite load	Change in reactivity to house dust mite
Treatment group	68% --> 5%	17% --> 68%
Control group	43% --> 70%	26% --> 16%

1) **Exposure to infectious diseases in early childhood**
2) **Environmental pollution**
3) **Allergen levels**
4) **Dietary changes**

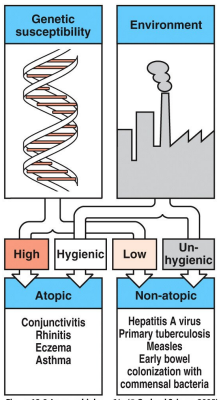


Figure 12-9 Immunobiology, 6/e. (© Garland Science 2005)

Gene	Nature of polymorphism	Possible mechanism of association
IL-4	Promoter variant	Variation in expression of IL-4
IL-4 receptor α chain	Structural variant	Increased signaling in response to IL-4
High-affinity IgE receptor β chain	Structural variant	Variation in consequences of IgE ligation by antigen
MHC class II genes	Structural variants	Enhanced presentation of particular allergen-derived peptides
T-cell receptor α locus	Microsatellite markers	Enhanced T-cell recognition of certain allergen-derived peptides
ADAM 33	Structural variants	Variation in airway remodeling
β_2-Adrenergic receptor	Structural variants	Increased bronchial hyperreactivity*
5-Lipoxygenase	Promoter variant	Variation in leukotriene production†

Figure 12-8 Immunobiology, 6/e. (© Garland Science 2005)

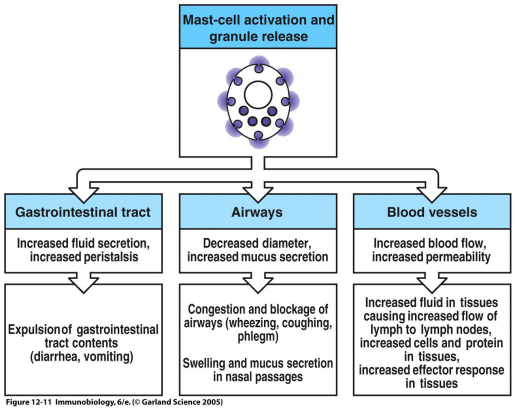


Figure 12-11 Immunobiology, 6/e. (© Garland Science 2005)

Class of product	Examples	Biological effects
Enzyme	Tryptase, chymase, cathepsin G, carboxypeptidase	Remodel connective tissue matrix
Toxic mediator	Histamine, heparin	Toxic to parasites Increase vascular permeability Cause smooth muscle contraction
Cytokine	IL-4, IL-13	Stimulate and amplify T_H2 cell response
	IL-3, IL-5, GM-CSF	Promote eosinophil production and activation
	TNF-α (some stored preformed in granules)	Promotes inflammation, stimulates cytokine production by many cell types, activates endothelium
Chemokine	CCL3 (MIP-1α)	Attracts monocytes, macrophages, and neutrophils
Lipid mediator	Leukotrienes C4, D4, E4	Cause smooth muscle contraction Increase vascular permeability Stimulate mucus secretion
	Platelet-activating factor	Attracts leukocytes Amplifies production of lipid mediators Activates neutrophils, eosinophils, and platelets

Figure 12-12 Immunobiology, 6/e. (© Garland Science 2005)

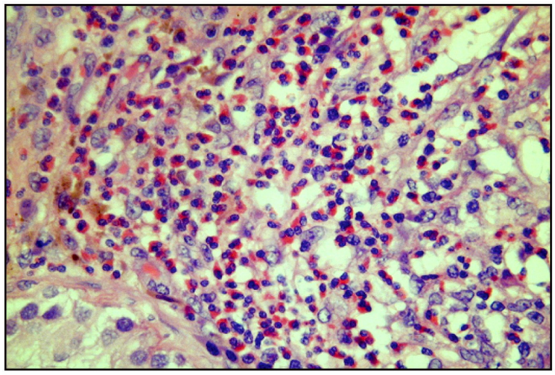


Figure 12-13 Immunobiology, 6/e. (© Garland Science 2005)

Eosinophils

- Eosinophils express FcεRI only after activation
- On activation – release toxic granule proteins and free radicals which can kill microorganisms and parasites
- On activation – synthesis of chemical mediators such as prostaglandins, leukotrienes, and cytokines which amplify the inflammatory response

Class of product	Examples	Biological effects
Enzyme	Eosinophil peroxidase	Toxic to targets by catalyzing halogenation Triggers histamine release from mast cells
	Eosinophil collagenase	Remodels connective tissue matrix
Toxic protein	Major basic protein	Toxic to parasites and mammalian cells Triggers histamine release from mast cells
	Eosinophil cationic protein	Toxic to parasites Neurotoxin
	Eosinophil-derived neurotoxin	Neurotoxin
Cytokine	IL-3, IL-5, GM-CSF	Amplify eosinophil production by bone marrow Cause eosinophil activation
Chemokine	CXCL8 (IL-8)	Promotes influx of leukocytes
Lipid mediator	Leukotrienes C4, D4, E4	Cause smooth muscle contraction Increase vascular permeability Increase mucus secretion
	Platelet-activating factor	Attracts leukocytes Amplifies production of lipid mediators Activates neutrophils, eosinophils, and platelets

Figure 12-14 Immunobiology, 6/e. (© Garland Science 2005)

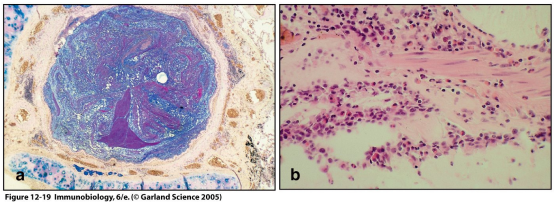


Figure 12-19 Immunobiology, 6/e. (© Garland Science 2005)

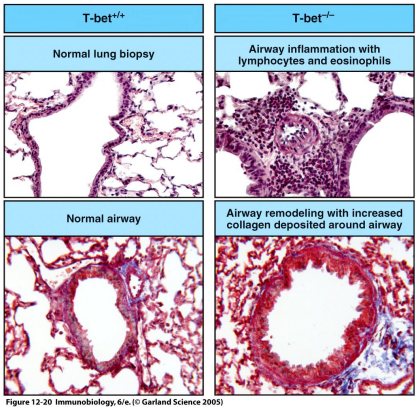
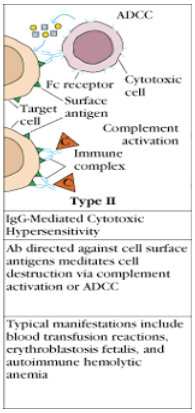


Figure 12-20 Immunobiology, 6/e. (© Garland Science 2005)



Type II (antibody-dependent) hypersensitivity = IgG-mediated destruction of cells

Occur in any circumstance in which cells are exposed to high levels of cell-reactive IgG antibody.

Destruction via:
- complement-mediated lysis
- opsonization
- ADCC

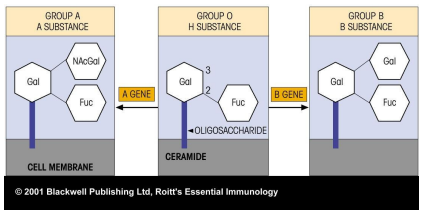
Examples include:
- transfusion reactions
- Rh syndrome

Blood group antigens:

- Represent difference in terminal sugar residues on red cell glycoproteins

A = terminal N-acetylgalactosamine (NAcGal)
B = terminal galactose (Gal)
O = no terminal residue

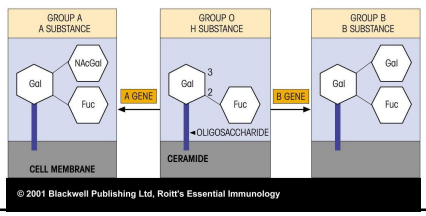
- Cross-react with antigens present on intestinal microorganisms.



Type O individuals have antibodies to A and B groups
Type A individuals have antibodies to the B antigen
Type B individuals have antibodies to the A antigen
Type AB individuals no antibodies

Type O = universal donor (cells cannot be destroyed by antibodies in recipients)

Type AB = universal recipient (have no antibodies that could destroy transfused cells)



Rhesus (Rh) incompatibility

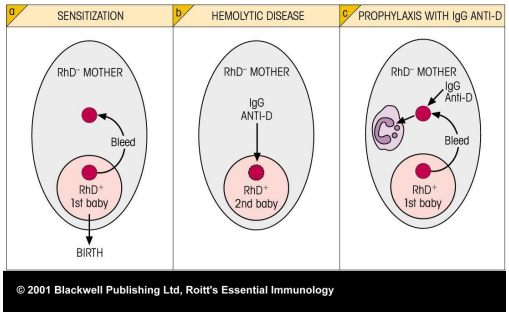
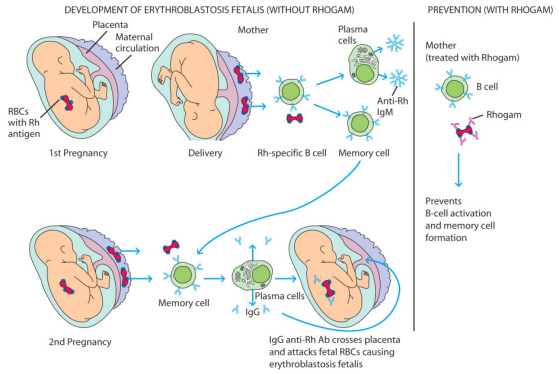


Figure 16-15



Drug-induced hemolytic anemia:

- Some drugs bind to erythrocyte proteins and create novel epitopes

- An individual may make an IgG response to the novel epitopes

- The resulting IgG antibody may mediate complement-mediated lysis of red cells - leading to hemolytic anemia

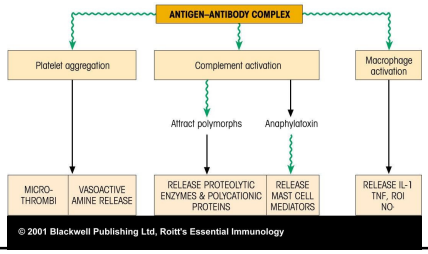
Treatment - cease using the drug

Type III hypersensitivity = immune complex-mediated hypersensitivity

- Binding of antibody to soluble antigen creates immune complexes.

- Immune complexes are normally removed from circulation (remember, C3b binding to receptors on erythrocytes).

- High levels of immune complexes may result in adverse effects as a result of complement activation and localized inflammation.

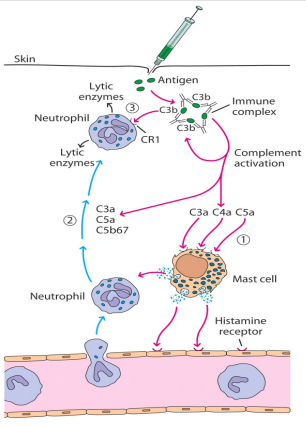


Localized Type III reaction (Arthus reaction)

- Injection of antigen into the skin of an individual with high levels of antibody to the antigen (eg: insect bites [types I and III possible]).

- Intense localized inflammatory reaction characterized by influx of neutrophils.

1. Soluble Ag
2. Ag-Ab complex
3. Complement activation
4. Production of complement byproducts (C3a, etc)
5. Chemotaxis
6. Mast cell degranulation
7. Vascular endothelium effects



Generalized Type III reactions:

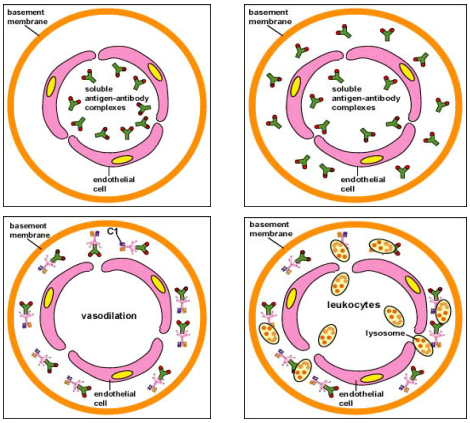
- (sytemic lupus erythematosus, Rheumatoid arthritis)

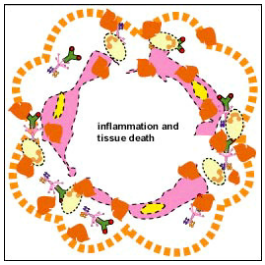
- injection of antigen intravenously into an individual with high levels of antibody to the antigen.

- e.g. injection of horse antitoxins into an individual previously sensitized to horse immunoglobulin

-"serum sickness" - various symptoms including fever, rashes and sometimes glomerulonephritis as a result of immune complex deposition in the kidneys; vasculitis (deposition in arteries) or arthritis (deposition on synovial joints)

-Damage of tissue due to enzymes from "angry" cells





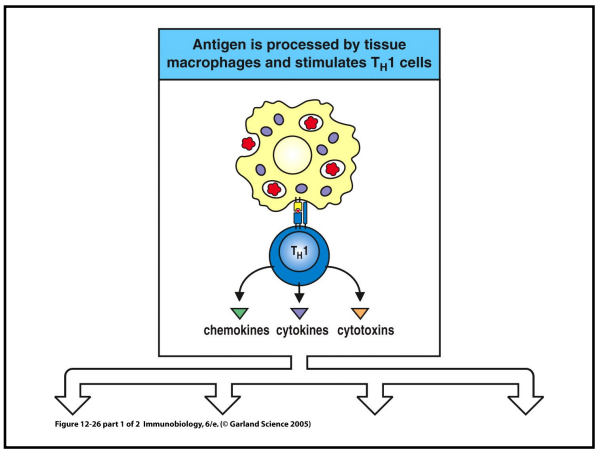
- Large quantities of soluble Ag-Ab complexes form in the blood and are not completely removed by macrophages.
- These Ag-Ab complexes lodge in the capillaries between the endothelial cells and the basement membrane.
- These Ag-Ab complexes activate the classical complement athway leading to vasodilation and attraction of leukocytes to the area.
- The leukocytes discharge their killing agents and promote massive inflammation.
- This can lead to tissue death and hemorrhage.

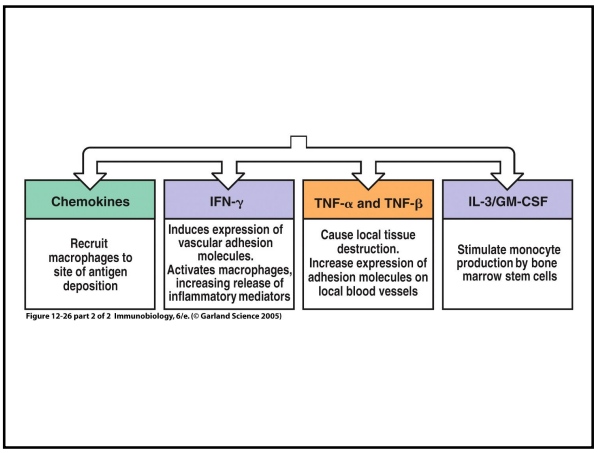
- **Type IV. Hypersensitivity Type IV (delayed-type hypersensitivity, DTH)**
  - Macrophages
  - Th1 T cells (DTH)
  - Cytokines
  - Examples: contact dermatitis (formaldehyde, nickel, cosmetics, jewelry, poison oak, poison ivy)

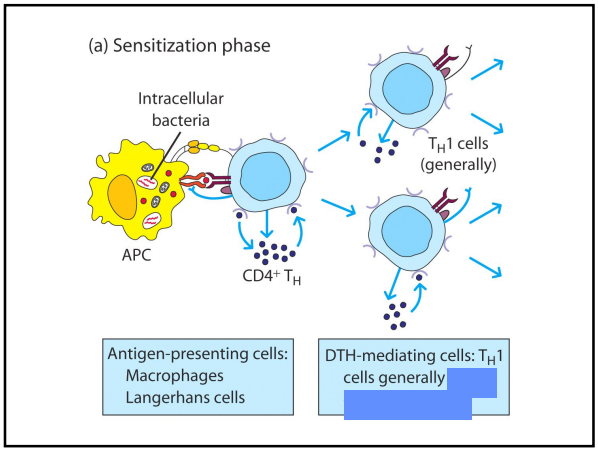
Type IV hypersensitivity reactions are mediated by antigen-specific effector T cells

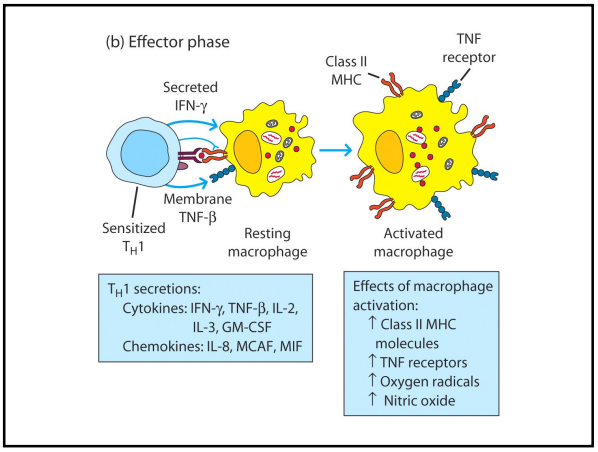
Syndrome	Antigen	Consequence
Delayed-type hypersensitivity	Proteins: Insect venom Mycobacterial proteins (tuberculin, lepromin)	Local skin swelling: Erythema Induration Cellular infiltrate Dermatitis
Contact hypersensitivity	Haptens: Pentadecacatechol (poison ivy) DNFB Small metal ions: Nickel Chromate	Local epidermal reaction: Erythema Cellular infiltrate Vesicles Intraepidermal abscesses
Gluten-sensitiveenteropathy (celiac disease)	Gliadin	Villous atrophy in small bowel Malabsorption

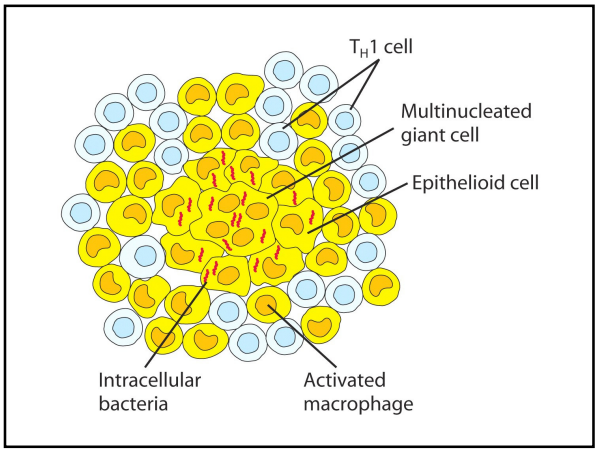
Figure 12-24 Immunobiology, 6/e. (© Garland Science 2005)

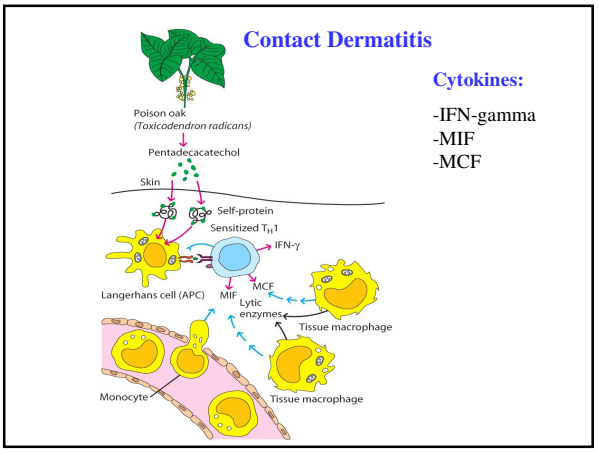

Antigen is processed by tissue macrophages and stimulates T_H1 cells
T_H1
chemokines
cytokines
cytotoxins
Figure 12-26 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)


Chemokines
Recruit macrophages to site of antigen deposition
IFN-γ
Induces expression of vascular adhesion molecules. Activates macrophages, increasing release of inflammatory mediators
TNF-α and TNF-β
Cause local tissue destruction. Increase expression of adhesion molecules on local blood vessels
IL-3/GM-CSF
Stimulate monocyte production by bone marrow stem cells
Figure 12-26 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)


(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


(b) Effector phase
Secreted IFN-γ
Membrane TNF-β
Sensitized T_H1
Resting macrophage
Class II MHC
TNF receptor
Activated macrophage
T_H1 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


T_H1 cell
Multinucleated giant cell
Epithelioid cell
Intracellular bacteria
Activated macrophage


Contact Dermatitis
Poison oak
(Toxicodendron radicans)
Pentadecacatechol
Skin
Self-protein
Sensitized T_H1
IFN-γ
Langerhans cell (APC)
MIF
MCF
Lytic enzymes
Tissue macrophage
Monocyte
Tissue macrophage
Cytokines:
-IFN-gamma
-MIF
-MCF

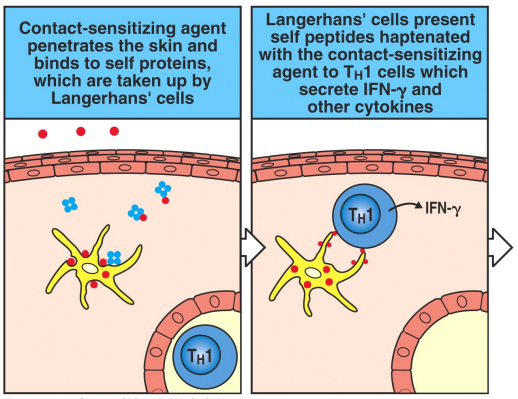


Figure 12-27 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

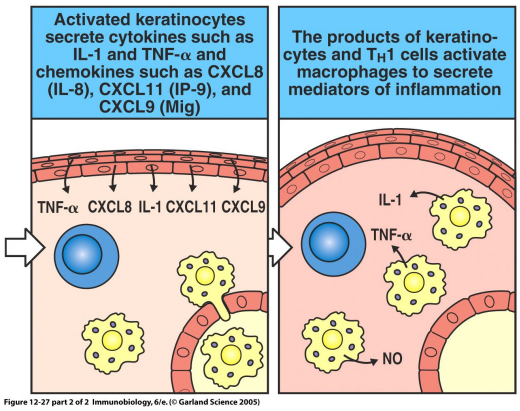


Figure 12-27 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

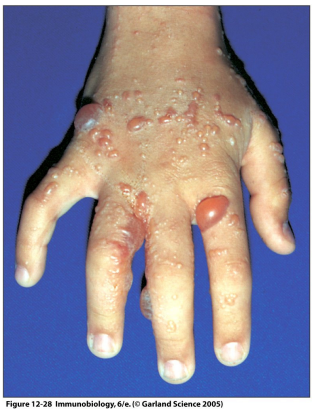


Figure 12-28 Immunobiology, 6/e. (© Garland Science 2005)

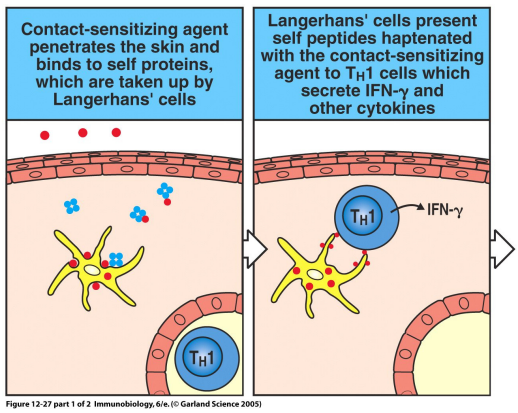


Figure 12-27 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

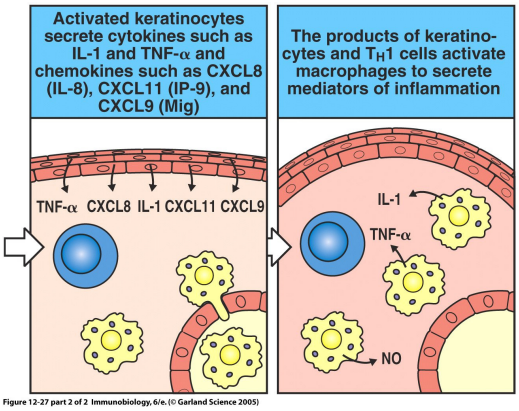


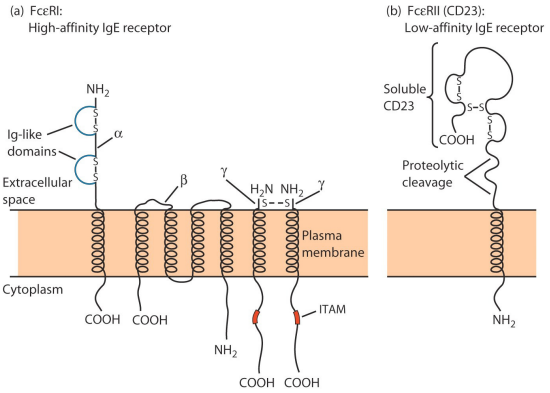
Figure 12-27 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

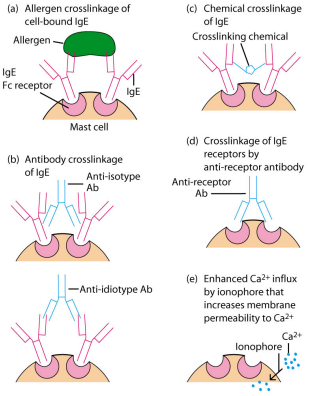
TABLE 16-4 Mechanism of action of some drugs used to treat type I hypersensitivity

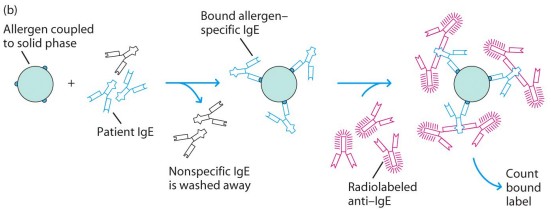
Drug	Action
Antihistamines	Block H_1 and H_2 receptors on target cells
Cromolyn sodium	Blocks Ca^{2+} influx into mast cells
Theophylline	Prolongs high cAMP levels in mast cells by inhibiting phosphodiesterase, which cleaves cAMP to 5′-AMP*
Epinephrine (adrenalin)	Stimulates cAMP production by binding to β-adrenergic receptors on mast cells*
Cortisone	Reduces histamine levels by blocking conversion of histidine to histamine and stimulates mast-cell production of cAMP*

*Although cAMP rises transiently during mast-cell activation, degranulation is prevented if cAMP levels remain high.

The End


(a) FcεRI:
High-affinity IgE receptor
(b) FcεRII (CD23):
Low-affinity IgE receptor
NH2
Ig-like domains
α
Extracellular space
β
γ
H2N NH2
γ
Soluble CD23
COOH
Proteolytic cleavage
Plasma membrane
Cytoplasm
COOH COOH
ITAM
NH2
COOH COOH
NH2


(a) Allergen crosslinkage of cell-bound IgE
Allergen
IgE Fc receptor
IgE
Mast cell
(b) Antibody crosslinkage of IgE
Anti-isotype Ab
Anti-idiotype Ab
(c) Chemical crosslinkage of IgE
Crosslinking chemical
(d) Crosslinkage of IgE receptors by anti-receptor antibody
Anti-receptor Ab
(e) Enhanced Ca2+ influx by ionophore that increases membrane permeability to Ca2+
Ca2+
Ionophore


(b)
Allergen coupled to solid phase
+
Patient IgE
Bound allergen–specific IgE
Nonspecific IgE is washed away
Radiolabeled anti-IgE
Count bound label