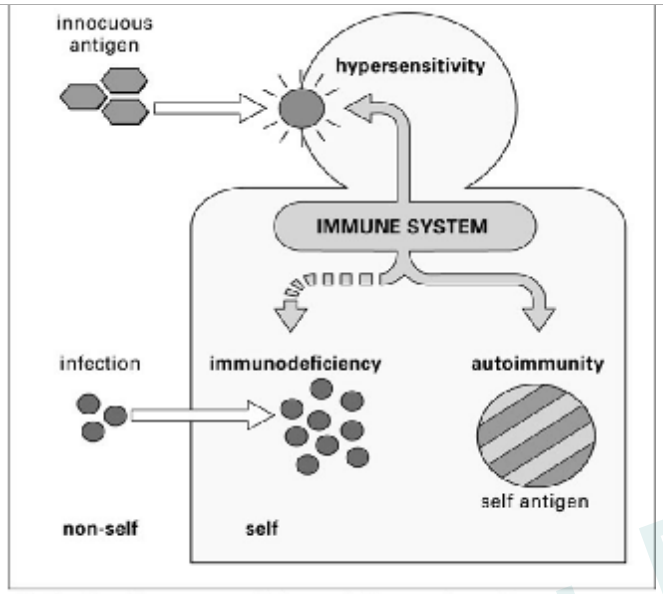
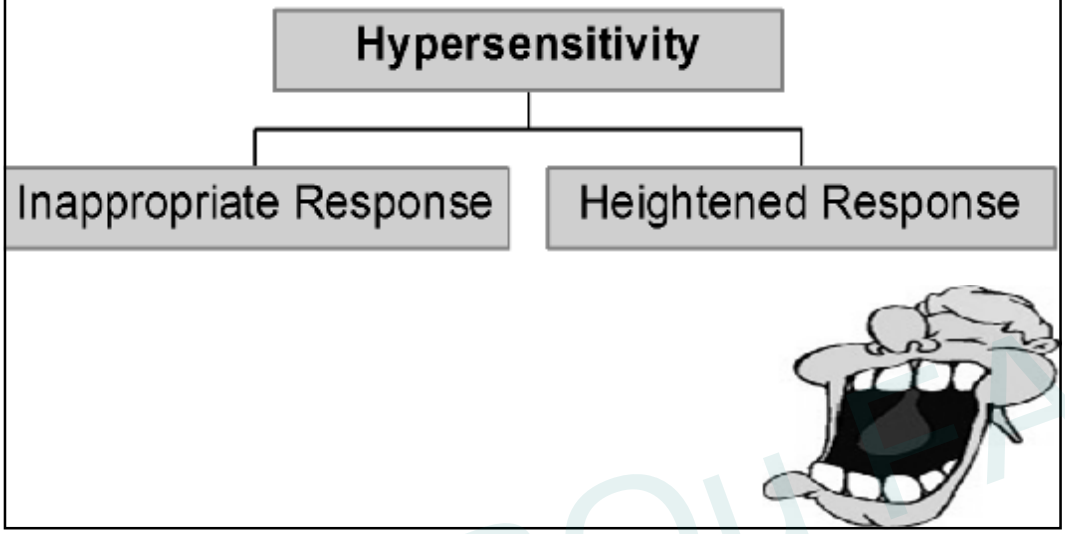
Inappropriate immunity

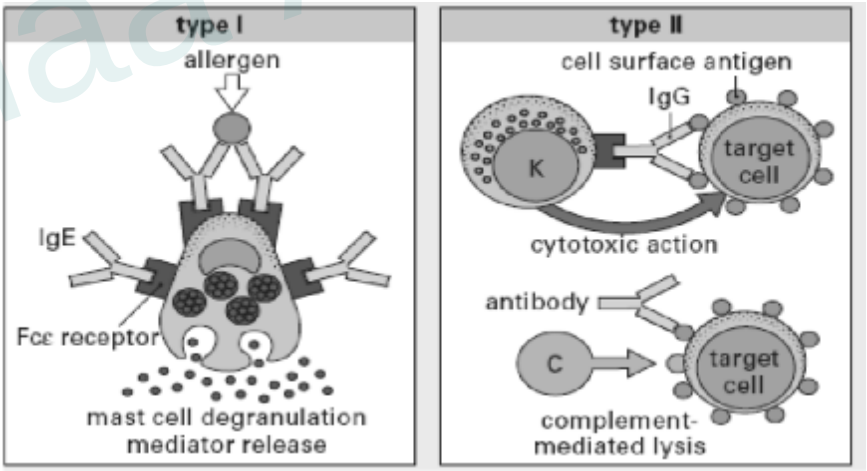


Hypersensitivity Reactions

Hypersensitivity is an immune reaction to innocuous antigens that results in tissue injury and/or disease



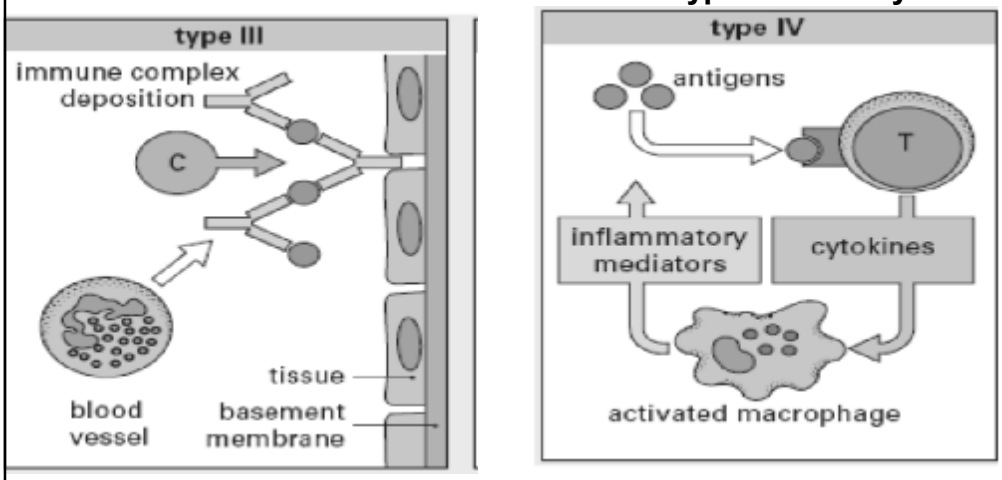
Gel and Coombs classification of hypersensitivity



type I: mast cells bind IgE via their Fcε receptors.on encountering allergen the IgE becomes cross-linked, inducing degranulation and release of mediators that produce allergic reactions.

type II: antibody is directed against antigen (non soluble) on an individual's own cells (target cell) or foreign antigen, such as transfused red blood cells. This may lead to cytotoxic action by NK cells, or complement-mediated lysis.

Gel and Coombs classification of hypersensitivity



type III: (soluble Ag) immune complexes are deposited in the tissue. Complement is activated and polymorphs are attracted to the site of deposition, causing local tissue damage and inflammation.

type IV: antigen-sensitized T cells release cytokines following a secondary contact with the same antigen. Cytokines induce inflammatory reactions and activate and attract macrophages, which release inflammatory mediators.

Type I

IgE-mediated hypersensitivity

IgE-mediated hypersensitivity (Type I)

❖Due to allergens that induces IgE

❖IgE binds to surface of mast cells and basophils and eosinophils ***(sensitization)***

❖ Second exposure leads to cross linking IgE on cell membrane (Degranulation of these cells) very rapid, **occurring within 30 minutes of the encounter**

❖**Mediators released ⇒ systemic or localized reactions** itching to swelling ,breathing difficulties, shock or death

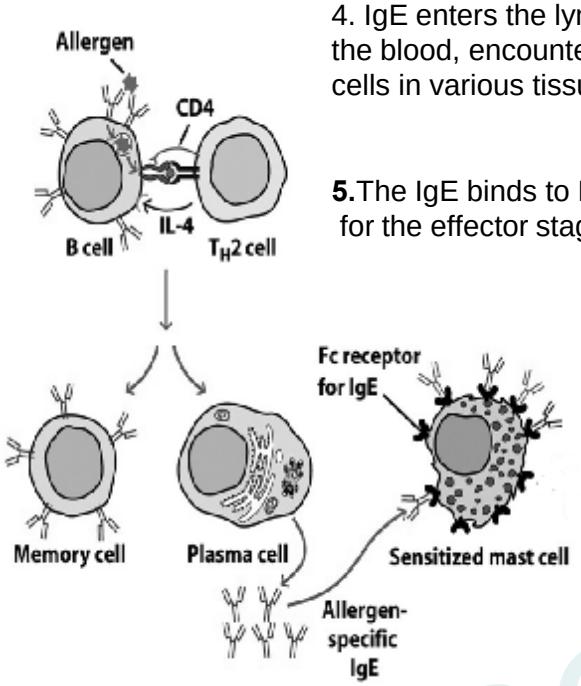
Sensitization Stage of Type I Hypersensitivity

1. Allergen breaches the mucosal barrier, is taken up by dendritic cell which conveys it to the local lymph node.

2. Naive T cells recognizing peptide-MHC presented by dendritic cell are activated and, differentiate into Th2 effectors that supply help to allergen-specific B cells.

3. The Th2 cells supply **cytokines(IL-4)** that influence differentiating plasma cells to switch to **IgE production.**

Sensitization Stage of Type I Hypersensitivity



4. IgE enters the lymphatics and recirculates through the blood, encountering basophils in the blood / mast cells in various tissues.

5.The IgE binds to FcεR on these cells, sensitizing them for the effector stage of type I hypersensitivity

Effector Stage

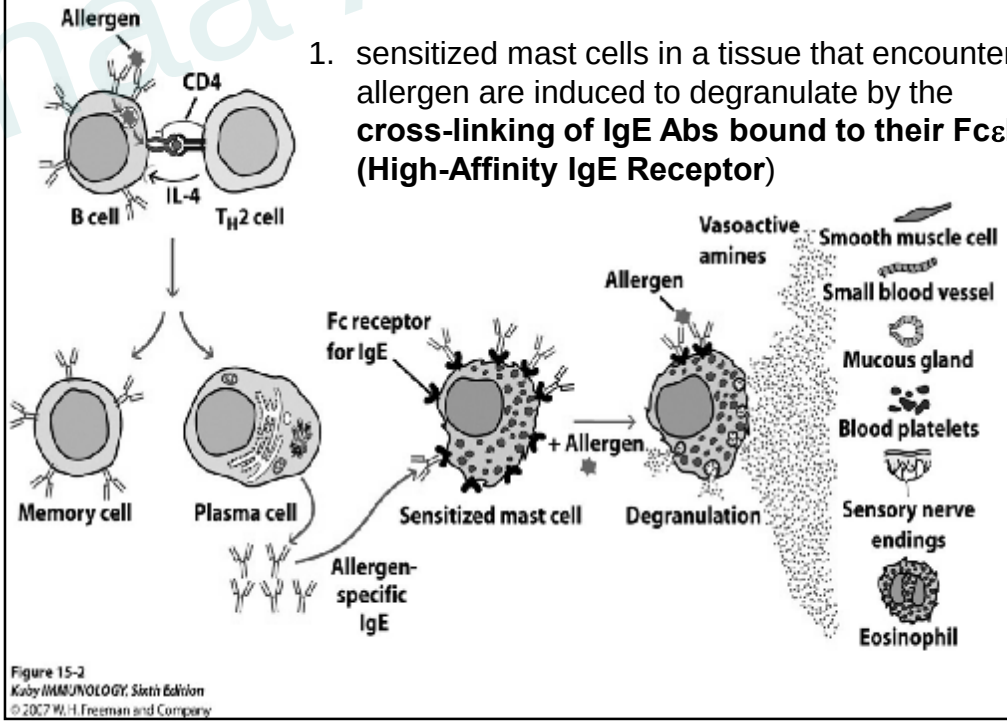
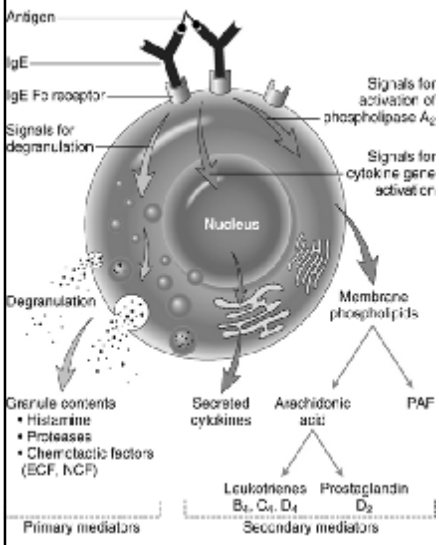


Figure 15-2
Kuby IMMUNOLOGY, Sixth Edition

1. sensitized mast cells in a tissue that encounter allergen are induced to degranulate by the **cross-linking of IgE Abs bound to their FcεIR (High-Affinity IgE Receptor**)

Effector Stage



2. releasing histamine and other mediators.

3.The mast cell breaks down, and enzymatic digestion of its membrane components generates mediators such as PAF(platelet activating factor).

4. Chemotactic factors released during mast cell activation encourage the extravasation of additional immune system cells from the,circulation, including eosinophils and sensitized basophils.

5. all these molecules combine to produce the indicated physiological signs of an allergic response.

Effects of Mast cell degranulation

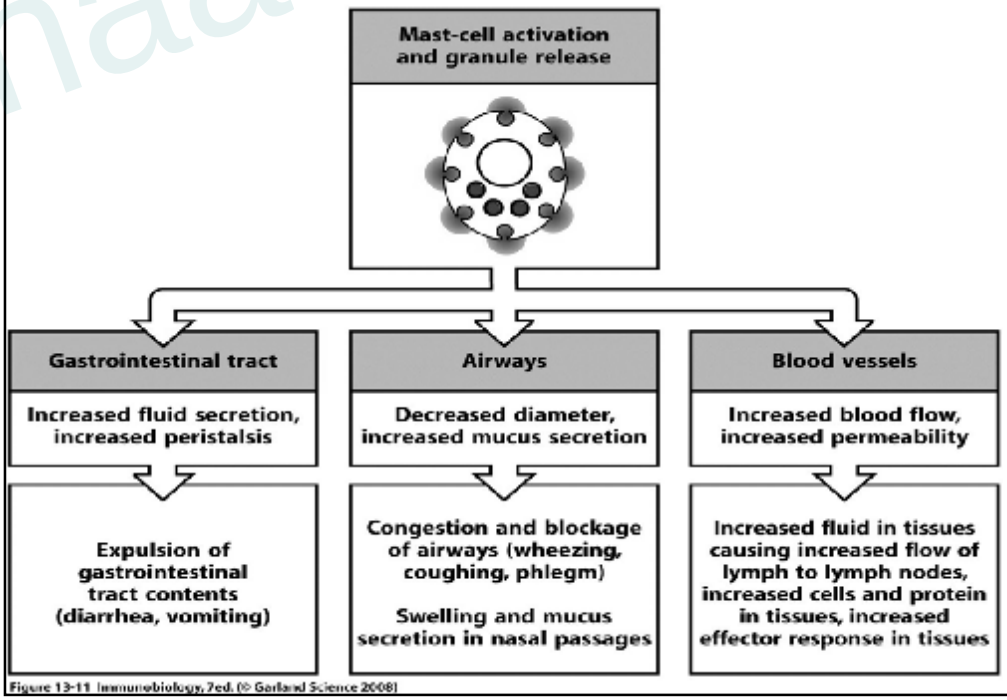
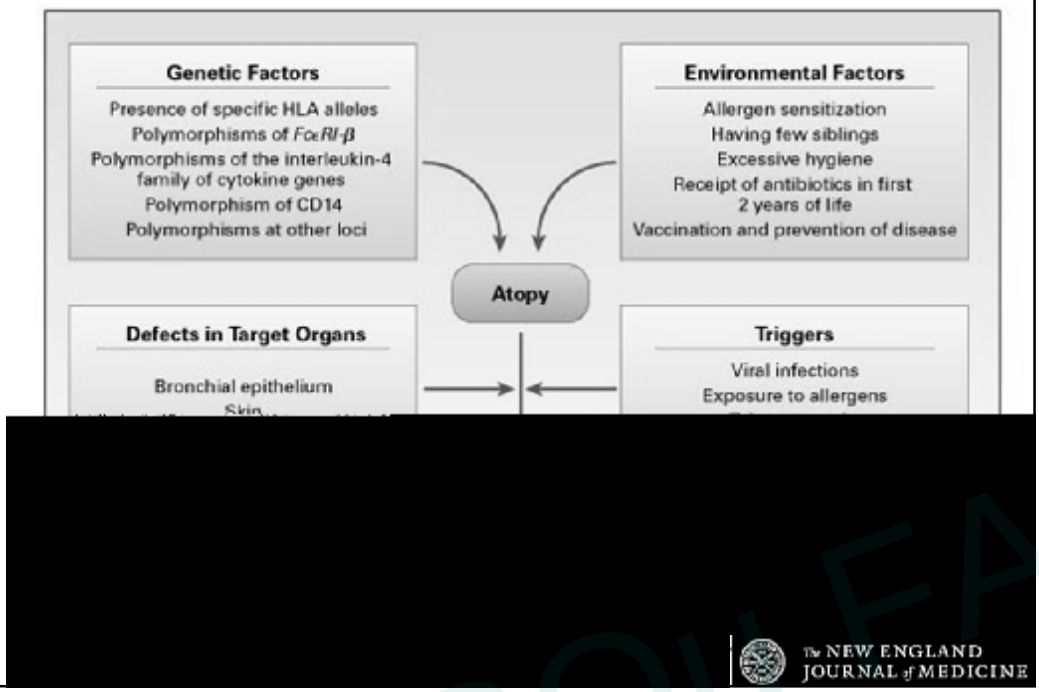


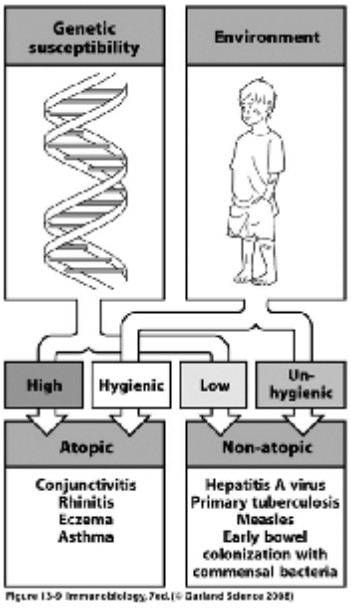
Figure 13-11 Immunobiology, 7ed. (© Garland Science 2008)

Factors Influencing the Development of Atopy and Allergic Inflammation



Genetics and Environment are important for the development of allergies

The "hygiene hypothesis" of allergy induction contends that too clean of an environment and lack of infections during childhood (along with a genetic susceptibility) promote a bias of the immune system toward T_H2 and IgE



Atopy: a increased tendency toward type I hypersensitivity (IgE allergies)

Allergens

- Are an antigen that gives rise to immediate hypersensitivity

TABLE 15-1 Common allergens associated with type I hypersensitivity

Proteins	**Foods**
Foreign serum	Nuts
Vaccines	Seafood
	Eggs
Plant pollens	Peas, beans
Rye grass	Milk
Ragweed	
Timothy grass	**Insect products**
Birch trees	Bee venom
	Wasp venom
Drugs	Ant venom
Penicillin	Cockroach calyx
Sulfonamides	Dust mites
Local anesthetics	
Salicylates	**Mold spores**
	Animal hair and dander
	Latex

Table 15-1

Allergens

Aero-allergens

Food allergens

Pollen

Animals

Latex

House dust mite

Cockroach

The characteristics of inhaled allergens

Features of inhaled allergens that may promote the priming of T_H2 cells that drive IgE responses	
Protein, often with carbohydrate side chains	Only proteins induce T-cell responses
Enzymatically active	Allergens are often proteases
Low dose	Favors activation of 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 13-3 Immunobiology, 7ed. (© Garland Science 2008)

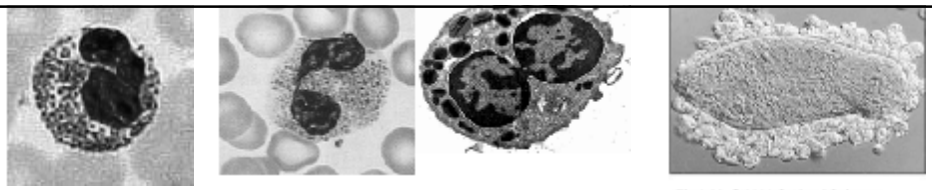


Fig 9.33 © 2001 Garland Science

Cytokine-activated **Eosinophils** have Fcε receptors (FcεR)

Compounds Released from Eosinophils

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
	Matrix metalloproteinase-9	Matrix protein degradation
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
	TGF-α, TGF-β	Epithelial proliferation, myofibroblast formation
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 13-13 Immunobiology, 7ed. (© Garland Science 2008)

Cytokine-activated **Eosinophils** have Fcε receptors (FcεR)

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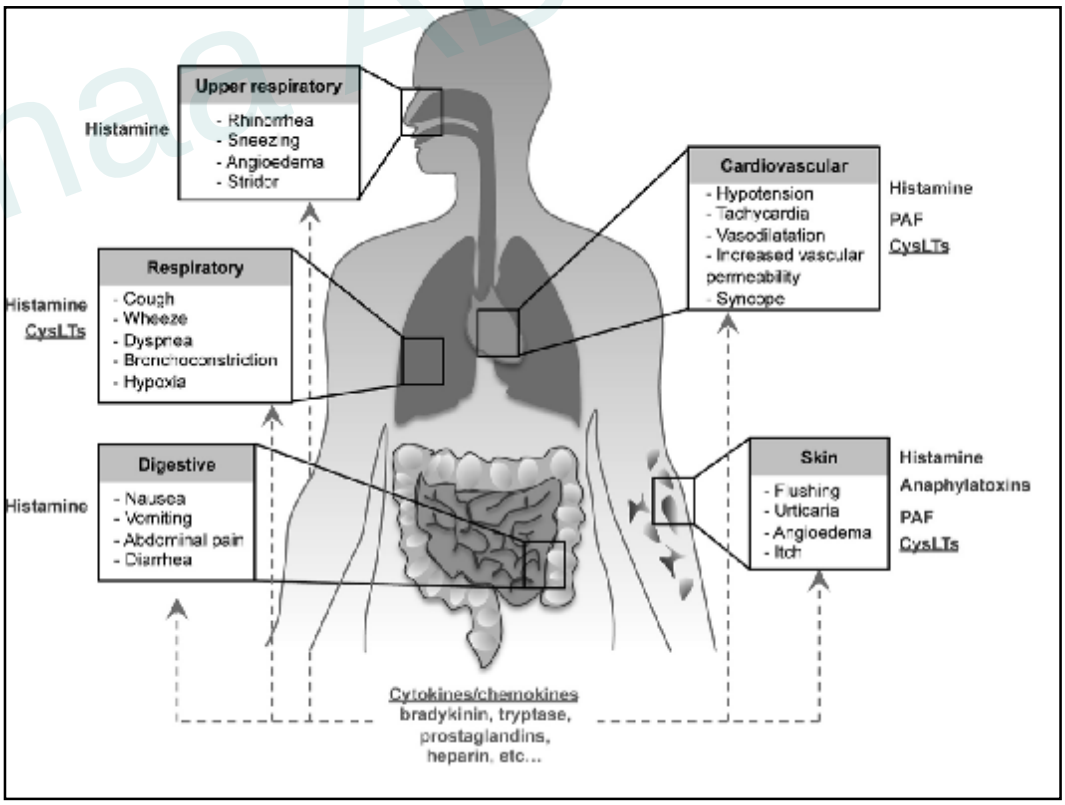
Figure 13-13 Immunobiology, 7ed. (© Garland Science 2008)

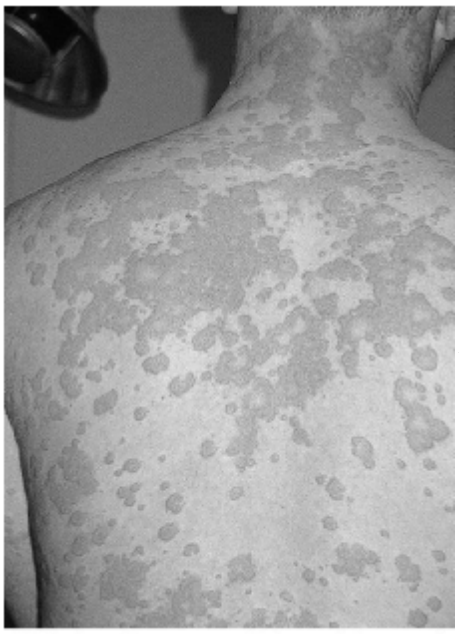
IgE-mediated allergic reactions

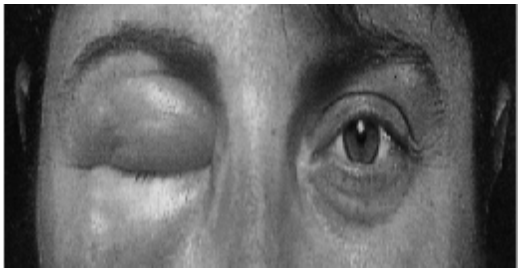
Syndrome	Common allergens	Route of entry	Response
Systemic anaphylaxis	Drugs Serum Venoms Food, e.g. peanuts	Intravenous (either directly or following oral absorption into the blood)	Edema Increased vascular permeability Laryngeal edema Circulatory collapse Death
Acute urticaria (wheal-and-flare)	Animal hair Insect bites Allergy testing	Through skin Systemic	Local increase in blood flow and vascular permeability
Seasonal rhinoconjunctivitis (hay fever)	Pollens (ragweed, trees, grasses) Dust-mite feces	Inhalation	Edema of nasal mucosa Sneezing
Asthma	Danders (cat) Pollens Dust-mite feces	Inhalation	Bronchial constriction Increased mucus production Airway inflammation
Food allergy	Tree nuts Shellfish Peanuts Milk Eggs Fish Soy Wheat	Oral	Vomiting Diarrhea Pruritis (itching) Urticaria (hives) Anaphylaxis (rarely)

Figure 13-2 Immunobiology, 7ed. (© Garland Science 2008)



Generalized urticaria





Anaphylactic response to bee sting

Treatment Of hypersensitivity typel

✓Avoidance – very difficult

✓ Antihistamines – most common for mild forms such as hay fever

✓Corticosteroids – essential for chronic conditions such as Asthma

✓Bronchodilators

✓Cromoglycate – stabilises mast cells

✓Sympathomimetics – e.g. adrenalin in anaphylaxis

✓Lipoxygenase antagonists

✓Desensitisation - low but increasing dose of allergen to induce high affinity, mature IgG rather than IgE – competes for allergen

Type I Hypersensitivity:
Late-Phase Reactions

- Caused by pharmacologic/vasoactive mediators -> induce local inflammation….**causes tissue damage**
- Occurs 4-6 hrs after initial rxn; can persist 1-2 days
- TNF-α and IL-1 increase CAM's on endothelia → promote tethering/migration of:
  - Neutrophils
  - Eosinophils
  - Monocytes
  - Basophils

Cytokines from Mast cells also contribute!

- Eosino's exhibit Fc receptors for IgE -> triggers degran.
- Neutro's release lytic enzymes, PAF, leukotrienes

Type I Hypersensitivity:
Regulatory factors

- The following factors influence IgE response to allergens:
  - Level of Ag dose
  - Mode of antigen presentation
  - Relative presence of T_H1 and T_H2 titres
    - T_H2's release IL-3,4,5, and 10
    - T_H1's release IFN-γ
- Atopic vs non-atopic individuals express qualitatively different Type I responses to allergens…
  - Atopic responses involve T_H2 → production of IgE from B cells
  - Non-atopic responses involve T_H1 → production of IgM or IgG

Type I Hypersensitivity:

Detecting allergies

Skin tests- injections or scratchings

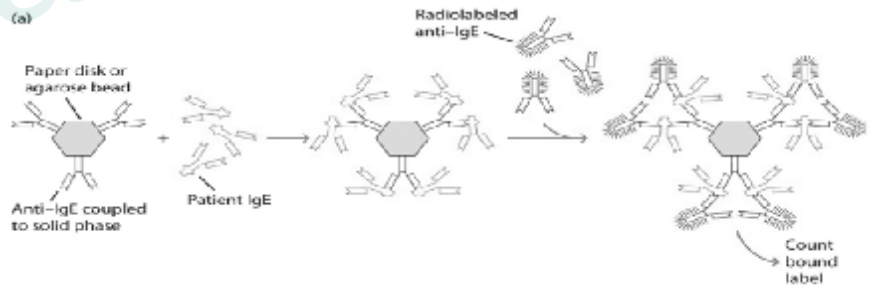
- -Stim local Mast cells
- -Produces P-K rxn (wheal and flare)
- -Inexpensive and quick
- -May sensitize one to new Ag's
- -May stim late-phase rxn in some

Immunoassays for serum IgE

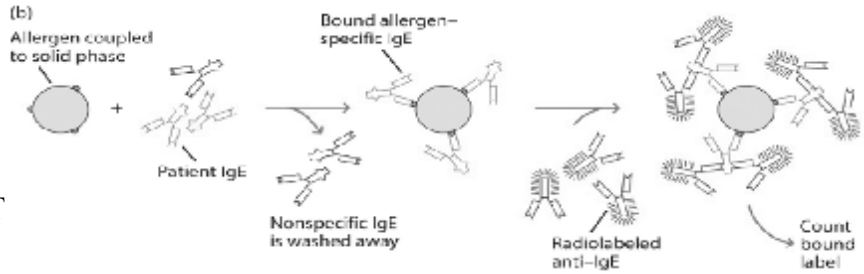
- -Radioimmunosorbent test (RIST)
- -Radioallergosorbent test (RAST)

Immunoassays for IgE

RIST



RAST



Type I Hypersensitivity:

Treatment methods

Immunotherapy

- Antibody therapy
  - Injected monoclonal anti-IgE Ab binds free and mIgE on B cells
- Hyposensitization
  - Repeated injections of allergen causes a shift in Ig response

Drug treatments

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.

Antibody-mediated cytotoxicity
Type II Hypersensitivity

Type II Hypersensitivity
antibody-mediated cytotoxicity

- Occur when damage to the host tissues is caused by cellular lysis induced by the direct binding of antibody **to cell surface antigens.**
- Antibodies involved are mainly the IgM or IgG.
- In some cases of type II HS, the pathological antibodies attack leukocytes or red blood cells, so-called "**mobile cells."**
- In other cases, the antibodies bind to cells that are "**fixed"** as part of a solid tissue.

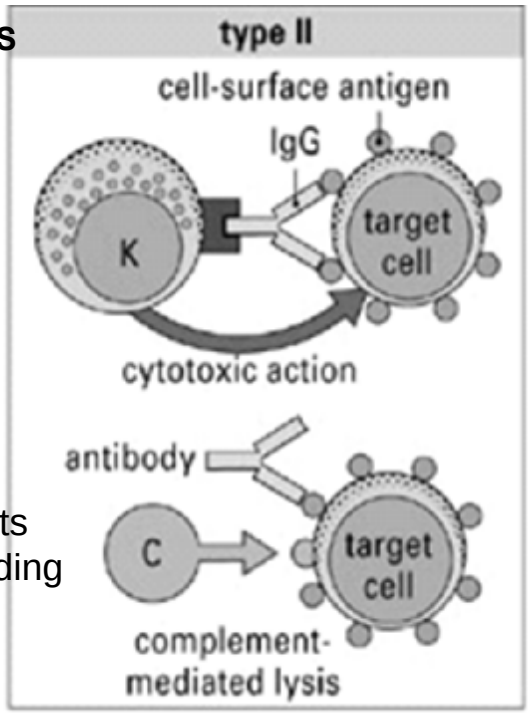
Mechanisms underlying type II HS

• ADCC (antibody-dependent cell-mediated cytotoxicity)

• Complement activation

•(the target is mobile) Phagocytosis

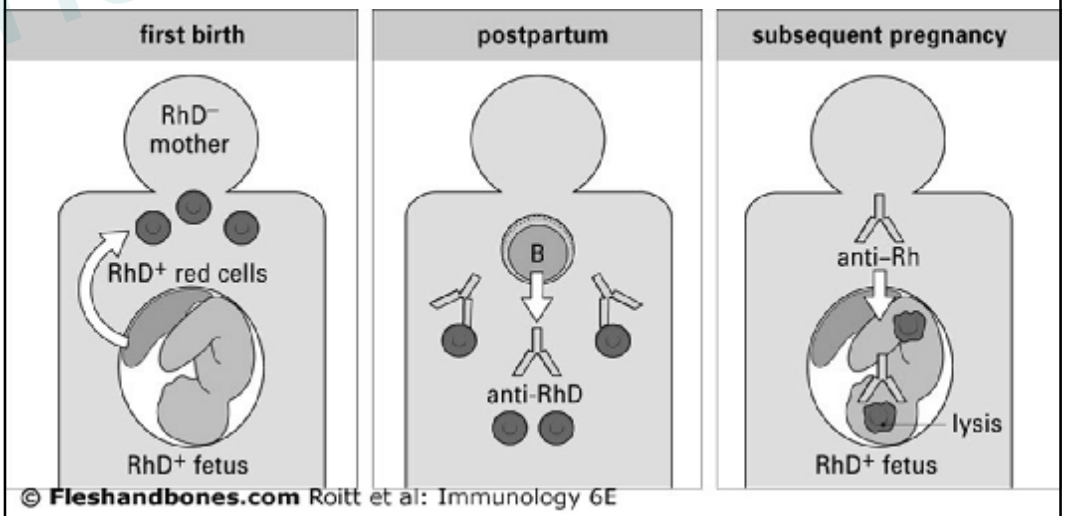
•(the target is fixed) phagocyte releases the contents of its lysosomes externally, leading to tissue damage

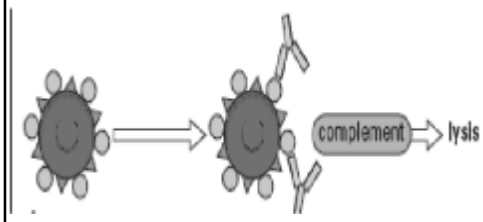


Examples of Type II Hypersensitivity Reactions

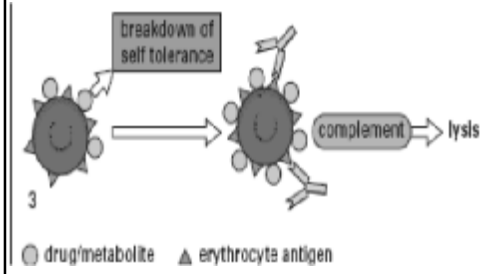
- Autoimmune hemolytic anemia
- Goodpasture's syndrome
- Pemphigus
- Pernicious anemia (if autoimmune)
- Transfusion reactions
- Rheumatic fever
- Hemolytic disease of the newborn
- Drug Induced hemolytic Anemia
- Autoimmune thrombocytopenia

Haemolytic disease of the newborn





The drug adsorbs to cell membranes.Antibodies to the drug bind to the cell and complement mediated lysis occurs.



Drug adsorbed onto cell membranes, breakdown of self tolerance
formation of antibodies to other blood group antigens on the cell surface.

Immune Complex-Mediated

Type III hypersensitivity Reactions

Hypersensitivity Type III

(Immune Complex) Reactions

- is triggered by a soluble antigen circulating in serum, capable of forming large immune complexes (IC) with IgM or IgG antibodies in the circulation.
- Antibody-Antigen immune complexes are deposited in organs, activate complement, and cause inflammatory damage.

When do ICs trigger Hypersensitivity reactions?

✓ The individual has a complement deficiency that leads to inefficient removal of ICs.

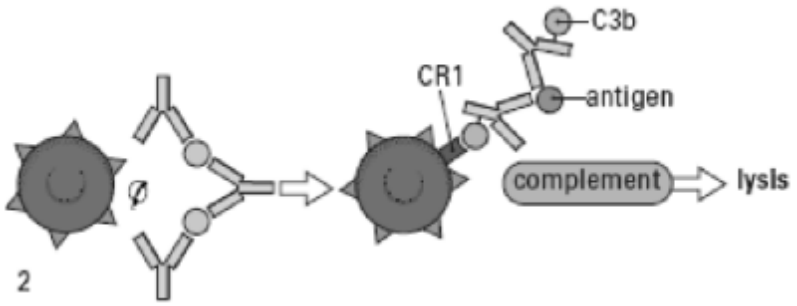
✓ The individual has a competent immune system, the sheer quantities of antibody and antigen present may generate damaging ICs

✓The type III HS reaction is a clinical complication of the pathogen Infection
✓exposure to tumor antigens cause type III HS symptoms.

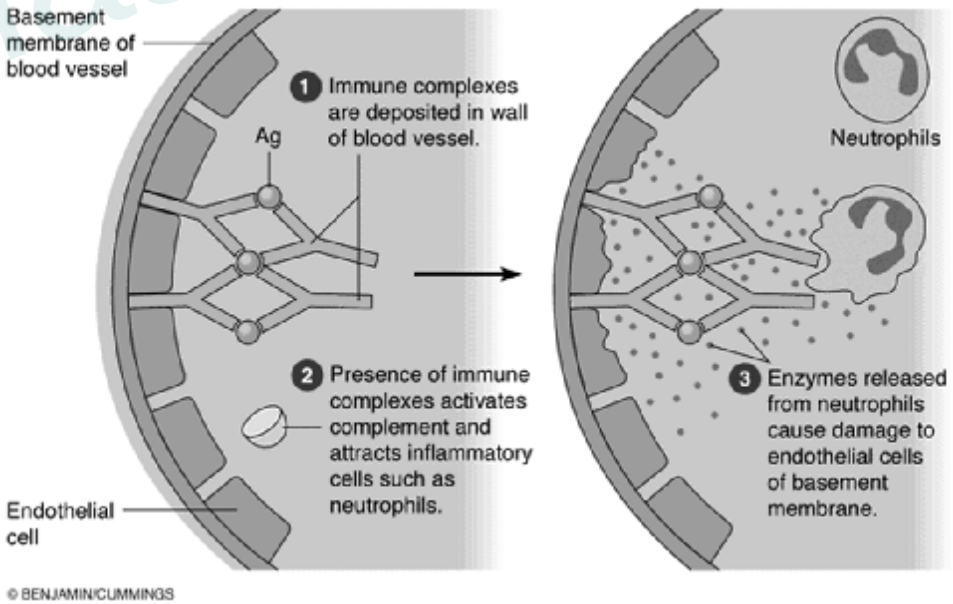
✓Some drug “allergies” may also be due to type III HS reactions. In this case, the symptoms persist as long as the drug the individual is taking.

✓Type III HS is also often found in patients expressing autoantibodies.

drug “allergies” due to type III HS reactions.



Immune Complex Mediated Hypersensitivity



Immune Complex Mediated Hypersensitivity diseases

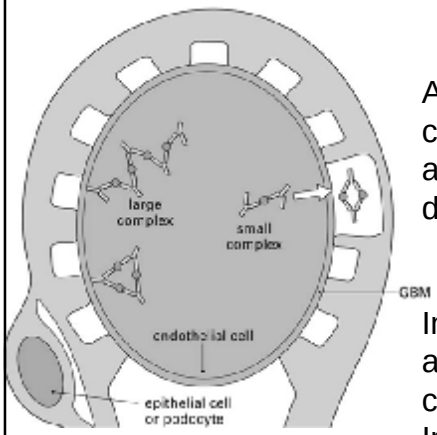
- ❖Acute glomerulonephritis
- ❖Systemic lupus erythematosus
- ❖Rheumatoid arthritis
- ❖Progressive systemic sclerosis
- ❖Dermatomyositis

Type III HS reactions

Example	Pathological Ab Directed Against	Deposition of ICs
Arthus reaction	Subcutaneously injected Ag	Localized
Serum sickness	Toxins, environmental Ag, drug Ag, Ag of persistent pathogen	Systemic
SLE	Host DNA nucleoproteins, clotting factors, other self-proteins	Systemic
RA	Host IgG	Systemic

systemic lupus erythematosus (SLE)

In many diseases, complement activation causes: tissue damage; increased inflammation



Autoimmune diseases where immune complexes deposit in tissues and there activate complement, causing damage and destruction of host cells.

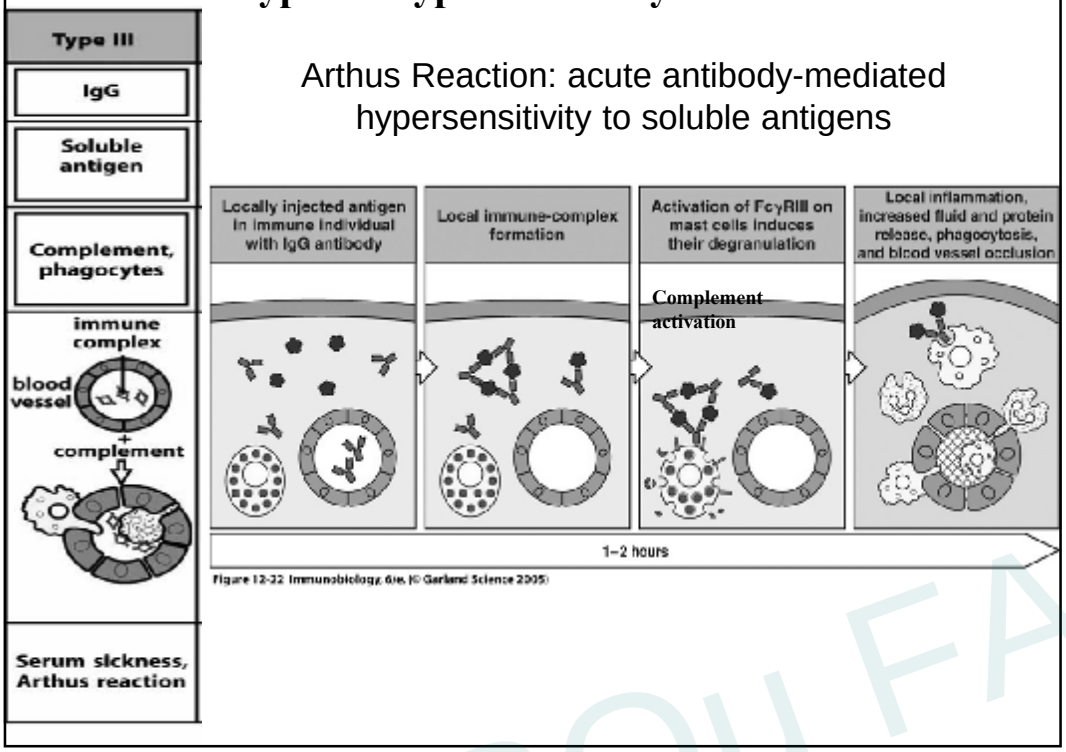
In SLE, autoantibodies are generated against cell contents including DNA, cytoplasmic proteins, and mitochondria. Immune complexes deposit in capillary beds in organs such as skin, kidney, joint, and brain where they activate complement.

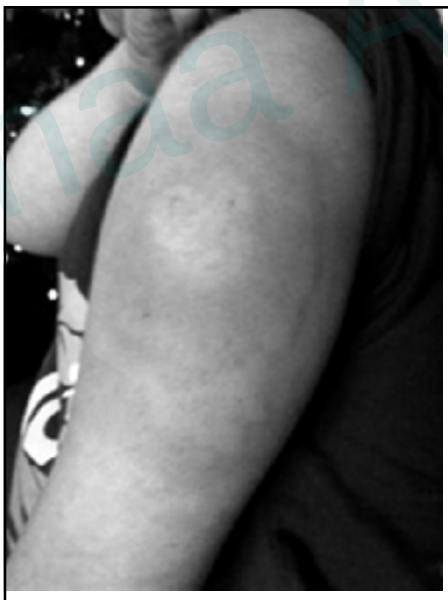
Arthus reaction

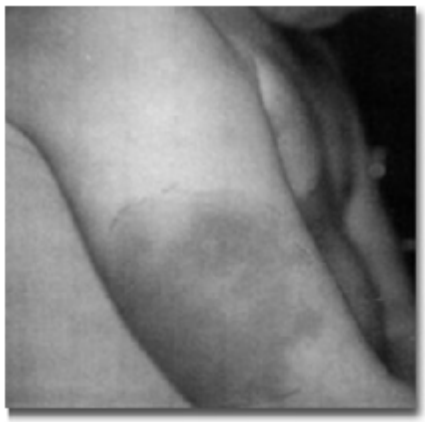
- Takes place at a local site in and around the walls of small blood vessels.Frequently demonstrated in the skin.
- An animal is immunized repeatedly until it has appreciable levels of serum antibody (mainly IgG).
- Following subcutaneous or intradermal injection of the Ag a reaction develops at the injection site :edema ; hemorrhage, severe pain, induration, necrosis; depending on the amount of Ag injected.
- a peak after 4–10 hours, then wanes and is usually minimal by 48 hours.

Type III hypersensitivity

Arthus Reaction: acute antibody-mediated hypersensitivity to soluble antigens





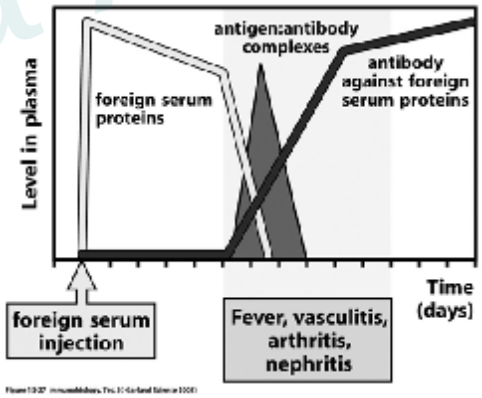


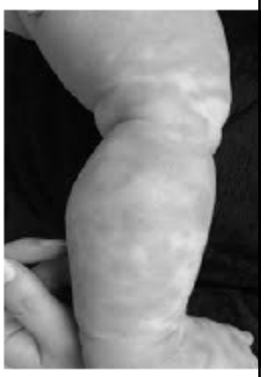
Exaggerated local (Arthus-type) reactions are rare following receipt of a diphtheria- or tetanus-containing vaccine

Serum sickness

- **injections of foreign antigen**
- circulating ICs deposit in the blood vessel walls; tissues : increased vascular permeability; inflammatory diseases glomerulonephritis and arthritis.
- Was a complication of serum therapy, in which massive doses of Abs were given for diseases (diphtheria).
- Horse anti-diphtheria serum was usually used, and some individuals made Abs against the horse proteins.
- commonly studied in rabbits by giving them an IV injection of a foreign soluble bovine serum albumin (BSA).
- After about 1 week Abs are formed, enter the circulation; complex with antigen.

Serum Sickness (immune complexes in the blood)

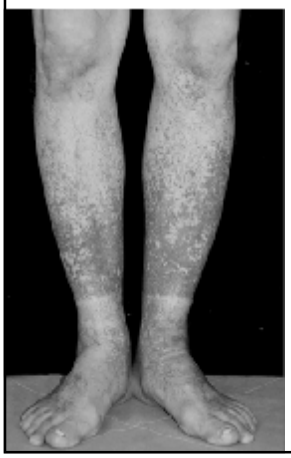




Symptoms are delayed while a primary immune response develops (quickly if the response is a secondary response).

Symptoms : fever, rash, arthritis, glomerulonephritis..

Usually, serum sickness is self-limiting.



A 61-year-old man was bitten by a snake 10 days before visiting our dermatology clinic. He received antivenom immediately after the accident.
He had severe painful erythematous swelling of the right hand and forearm. After intermittent infusion of high dose antivenom he developed fever and arthralgia on multiple large joints with skin rash. On examination, there were multiple non-blanchable, painful purpuric macular patches on both his lower legs and feet. Laboratory tests showed that anti-nuclear antibody, C3, C4, and urinalysis were all within the normal range, except for a mild thrombocytopenia (platelets, 133×10^9 L). Skin biopsy showed leukocytoclastic vasculitis.
The condition, known as serum sickness, that results from the injection of foreign protein or serum. Our patient received antihistamines and systemic corticosteroids and the skin rash resolved after 2 weeks.

Type Ⅳ Hypersensitivity (Cell-Mediated)

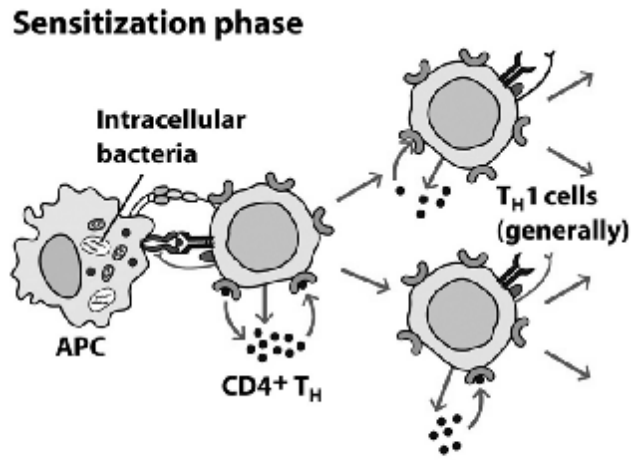
Type IV Hypersensitivity

- Delayed-Type or Cell-Mediated Hypersensitivity
- occurs at about 24–72 hours after exposure of a sensitized individual to an antigen.
- Type IV HS are distinguished by the infiltration of Th1 and macrophages at the site of exposure.

Type IV Hypersensitivity

- DTH reactions have been exploited as a means of determining whether an individual has been previously exposed to a pathogen.
- The skin prick test for tuberculosis is an example of such a test, in which redness and swelling at the site of an injection of a small amount of *M. tuberculosis* antigen indicates that the individual has previously been infected with the bacterium.
- Similar tests can be used to determine prior infection with organisms causing diphtheria or brucellosis

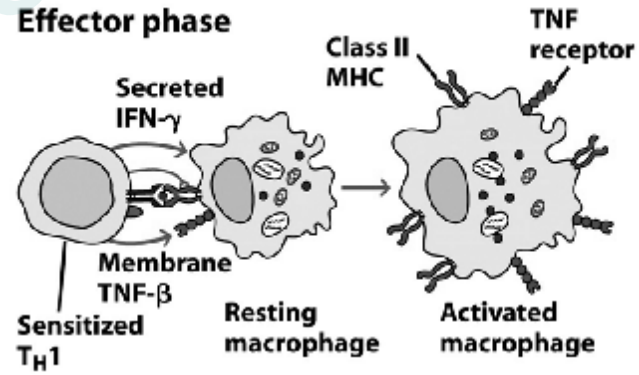
Type IV Hypersensitivity



Antigen-presenting cells: Macrophages Langerhans cells

DTH-mediating cells: T_H1 cells generally CD8 cells occasionally

Type IV Hypersensitivity



T_H1 secretions:
Cytokines: IFN-γ, TNF-β, 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

The DTH reaction used to test the functionality of an individual's T cells. The yeast *Candida albicans* is so prevalent in our environment that virtually everyone has experienced at least one infection with this organism in childhood.

DTH test using *Candida* antigen should provoke redness and swelling at the site of testing in virtually all individuals.

A patient that fails to mount a DTH response during this test likely has a deficit in T cell function and may be suffering from an acquired immunodeficiency.

Type IV hypersensitivity

Examples

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

TABLE 15-6 Intracellular pathogens and contact antigens that induce delayed-type (type IV) hypersensitivity

Intracellular bacteria	**Intracellular viruses**
Mycobacterium tuberculosis	Herpes simplex virus
Mycobacterium leprae	Variola (smallpox)
Listeria monocytogenes	Measles virus
Brucella abortus	
Intracellular fungi	**Contact antigens**
Pneumocystis carinii	Picrylchloride
Candida albicans	Hair dyes
Histoplasma capsulatum	Nickel salts
Cryptococcus neoformans	Poison ivy
Intracellular parasites	Poison oak
Leishmania sp.	

Table 15-6
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Delayed-type hypersensitivity (DTH)

(e.g., tuberculin skin test)

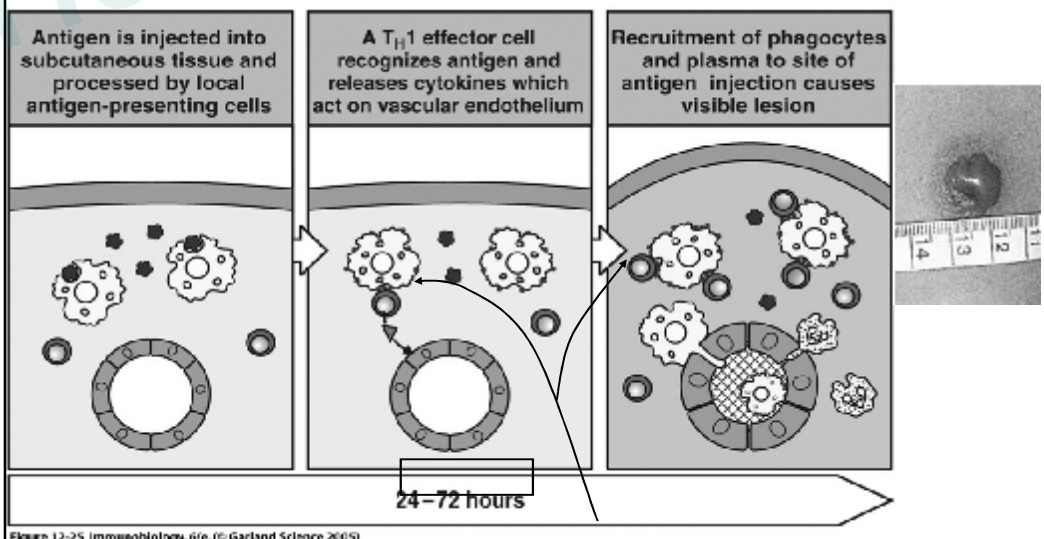


Figure 12-25 Immunobiology, 6/e. (© Garland Science 2005)

T_H1 from a previous immunization (memory)

Contact hypersensitivity (CHS)

or

allergic contact dermatitis

❖ an immune response to a chemically reactive **hapten** that has bound to **self proteins** in the uppermost layers of the skin.

❖ The alteration of self proteins by the binding of the CHS antigen generates a “nonself” entity that can be thought of as a *neo-antigen* (“new” antigen).

❖ Most neo-antigens are thus basically hapten–carrier complexes.

❖ the hapten are usually derived from *xenobiotics*, a class of non-living entities with biological effects.
Examples of xenobiotics can be found among drugs, metals, and industrial and natural chemicals.

.contact hypersensitivity reaction

- **has two stages : sensitization and elicitation**

Sensitization

➢ takes 10–14 days.

➢ the hapten combines with a protein and is internalized by epidermal Langerhans’ cells, which leave the epidermis and migrate lymphatics to the regional lymph nodes.

➢ they present processed hapten–protein conjugates in association with MHC class II molecules to CD4+ lymphocytes, producing effector/memory CD4+ T cells

➢ Keratinocytes can be activated by a number of stimuli, including sensitizing agents and irritants. They may express MHC class II molecules and intercellular adhesion molecule-1 (ICAM-1) in the cell membrane.

.contact hypersensitivity reaction

. **Contact Dermatitis**

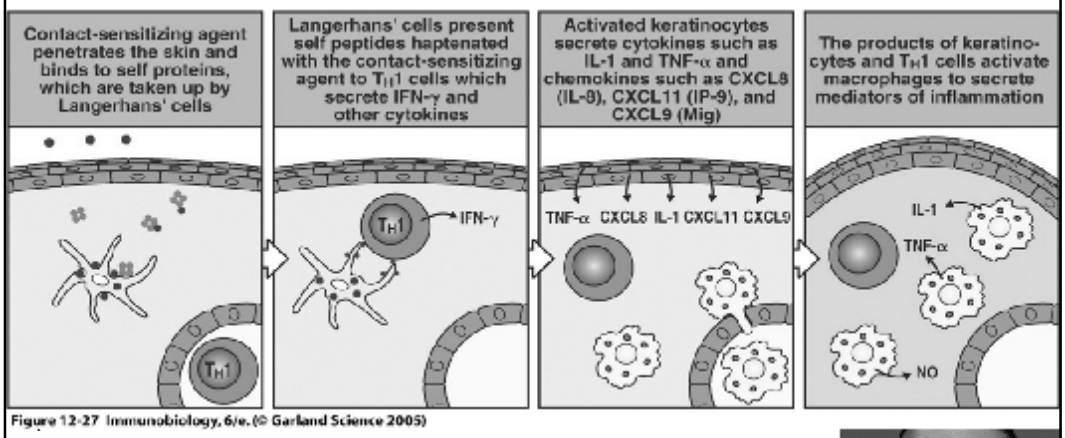


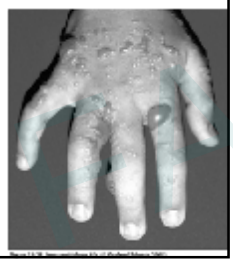
Figure 12-27 Immunobiology, 6/e. (© Garland Science 2005)

Elicitation involves recruitment of CD4+ lymphocytes and monocytes

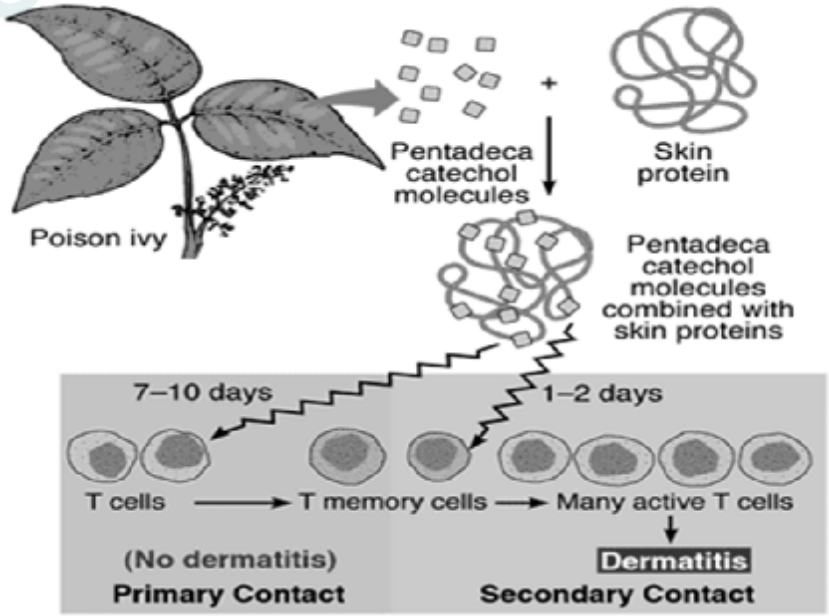
The application of a contact allergen leads to:

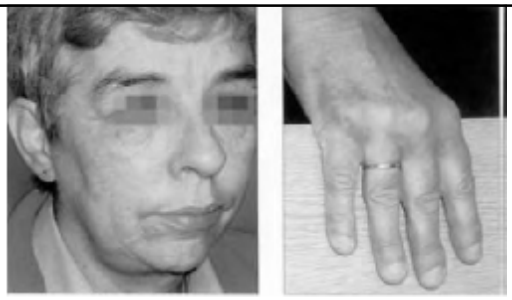
- rapid expression proinflammatory cytokines
- recruitment of effector T cells and monocytes to the site

There is induction of TNF, IL-1β, and GMCSF in Langerhans' cells



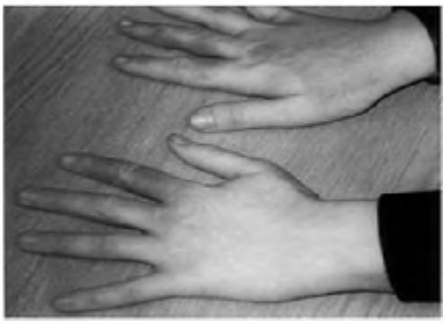
Allergic Contact Dermatitis Response to Poison Ivy Hapten





Irritant CD of face and hands to the disinfectant spray

ACD of the face due to cosmetics



Acute ACD of the hands to latex

granulomatous hypersensitivity

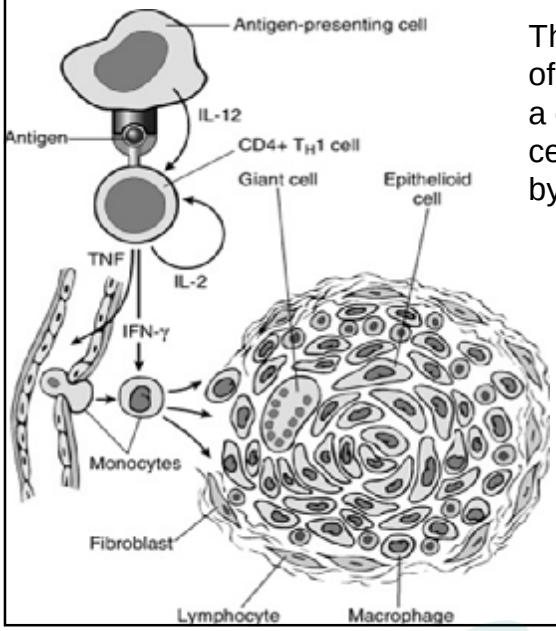
- Granulomatous hypersensitivity causes many of the pathological effects in diseases that involve T cell-mediated immunity.

- It results from the persistence within macrophages of intracellular microorganisms, which are able to resist macrophage killing or other particles that the cell is unable to destroy.This leads to chronic stimulation of T cells and the release of cytokines.

diseases with type IV granulomatous hypersensitivity

- chronic infections (TH1-like T cell responses) tuberculosis, leprosy, and leishmaniasis,
- zirconium and beryllium, sarcoidosis,
- in response to talc, silica, and a variety of other particulate agents, when macrophages are unable to digest the inorganic matter.

granulomatous hypersensitivity



The process results in the formation of **epithelioid cell granulomas** with a central collection of epithelioid cells and macrophages surrounded by lymphocytes.

Delayed hypersensitivity reactions

type	reaction time	clinical appearance	histology	antigen
contact	48–72 hours	eczema	lymphocytes, later macrophages; edema of epidermis	epidermal (e.g. antigen, nickel, rubber, poison ivy)
tuberculin	48–72 hours	local induration	lymphocytes, monocytes, macrophages	intradermal (e.g. tuberculin)
granuloma	21–28 days	hardening (e.g. skin of lung)	macrophages, epithelioid cells, giant cells, fibrosis	persistent antigen or antibody complexes or non-immunoglobulin stimuli (e.g. talc)

Fig. 26.13 The characteristics of type IV reactions comparing contact, tuberculin, and granulomatous reactions.