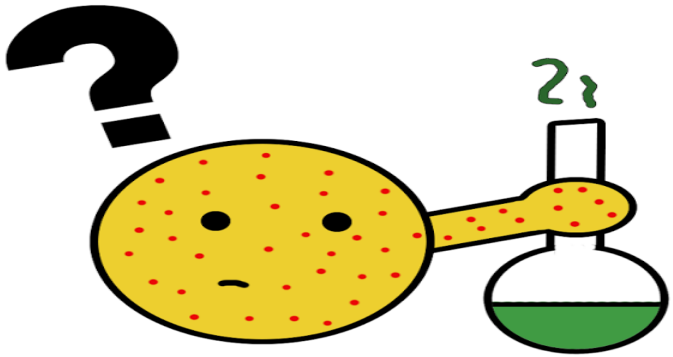
Hypersensitivity

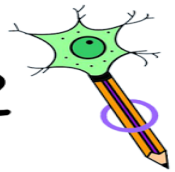


Anaphylaxis

Cytotoxic

immune complex

Delayed type



MEDiCOWESOME 2013

By: Dr. Suzan Yousif

Classification

- **Coombs and Gell classification**

1-Type I - anaphylactic(atopic, or immediate)

2-Type II - cytotoxic (antibody-dependent)

3-Type III - immune complex

4-Type IV - delayed or cell-mediated

TYPE I HYPERSENSITIVITY

- Type I hypersensitivity is also known as **immediate** or **anaphylactic** hypersensitivity.

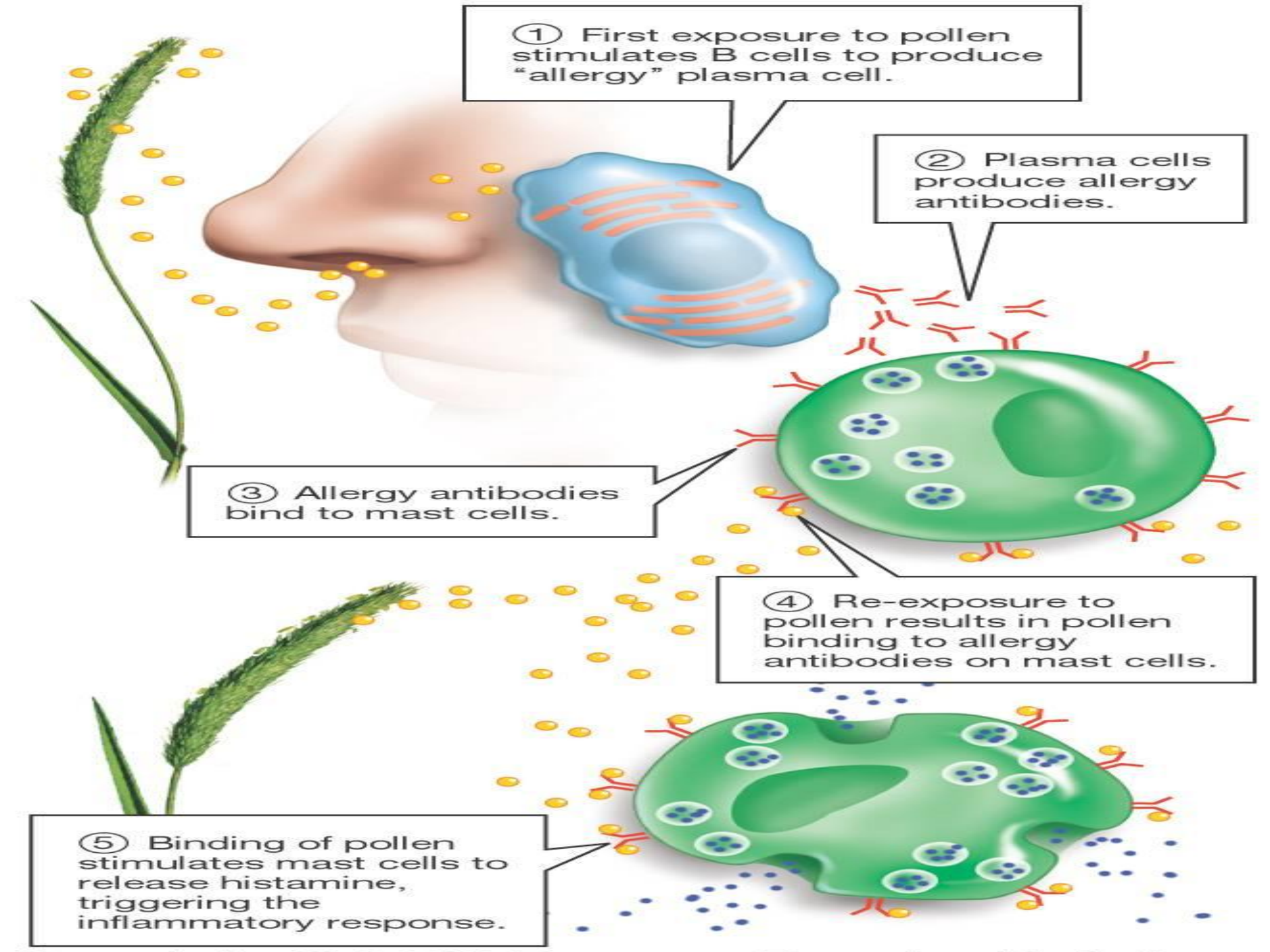
- The reaction may involve skin (urticaria and eczema), eyes (conjunctivitis), nasopharynx (rhinitis), bronchopulmonary tissues (asthma) and gastrointestinal tract (gastroenteritis)

- The reaction may cause a range of symptoms from minor inconvenience to death.
- The reaction usually takes 15 - 30 minutes from the time of exposure to the antigen.
- sometimes it may have a delayed onset (10 - 12 hours).

- Immediate hypersensitivity is mediated by **IgE**.
- The primary cellular component in this hypersensitivity is the **mast cell** or **basophil**.
- The reaction is amplified and/or modified by platelets, neutrophils and eosinophils.
- A biopsy of the reaction site demonstrates mainly **mast cells** and **eosinophils**.

Mechanism:

- The mechanism of reaction involves preferential production of IgE, in response to certain antigens (**allergens**).
- IgE has very high affinity for its receptor on mast cells and basophils.
- A subsequent exposure to the same allergen cross links the cell-bound IgE and triggers the release of various pharmacologically active substances like histamine, heparin tryptase, chymase, and monocyte chemotactic factors.


① First exposure to pollen stimulates B cells to produce "allergy" plasma cell.
② Plasma cells produce allergy antibodies.
③ Allergy antibodies bind to mast cells.
④ Re-exposure to pollen results in pollen binding to allergy antibodies on mast cells.
⑤ Binding of pollen stimulates mast cells to release histamine, triggering the inflammatory response.

Allergens

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

Contents of the Mast Cell Granules

Active agent	Activity
Histamine	Increases vascular permeability; elevates level of cyclic AMP
Heparin	Anticoagulation
Serotonin	Increases vascular permeability
Chymase	Proteolysis
Hyaluronidase	Increases vasuclar permeability
Eos. Chem. Factor	Chemoattraction of eosinophils
Neut. Chem. Factor	Chemoattraction of neutrophils
Platelet Agg. Factor	Aggregates platelets

Localized anaphylaxis

Target organ responds to direct contact with allergen.

- Digestive tract contact results in vomiting, cramping, diarrhea.
- Skin sensitivity usually inflamed area resulting in itching.
- Airway sensitivity results in sneezing and rhinitis OR wheezing and asthma.

Systemic anaphylaxis

- Systemic vasodilation and smooth muscle contraction leading to severe bronchiole constriction, edema, and shock.

- Similar to systemic inflammation.

Treatment for Type I

- Pharmacotherapy Drugs.
  - Non-steroidal anti-inflammatories
  - Antihistamines block histamine receptors.
  - Steroids
  - Theophylline OR epinephrine -prolongs or increases cAMP levels in mast cells which inhibits degranulation.

Treatment for Type I

- Immunotherapy
  - Desensitization (regular administration of gradually increasing doses of allergen extracts over a period of years)
  - Repeated injections of allergen to reduce the IgE on Mast cells and produce IgG.

TYPE II HYPERSENSITIVITY
cytotoxic

- Type II hypersensitivity is also known as **antibody-dependent** hypersensitivity and may affect a variety of organs and tissues.
- In type II hypersensitivity, the antibodies produced by the immune response bind to antigens on the patient's own cell surfaces.
- The antigens recognized in this way may either be intrinsic ("self" antigen, innately part of the patient's cells) or extrinsic (absorbed onto the cells during exposure to some foreign antigen, possibly as part of infection with a pathogen

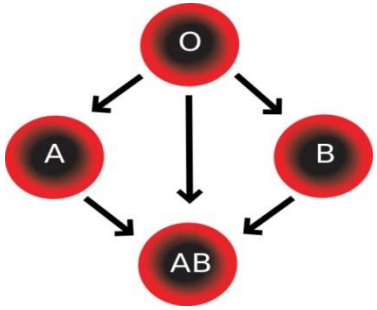
- IgG and IgM antibodies bind to these antigens to form complexes that activate the classical pathway of complement activation for eliminating cells presenting foreign antigens

- As a result mediators of acute inflammation are generated at the site and membrane attack complexes cause cell lysis and death. The reaction takes hours to a day.

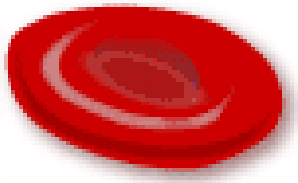
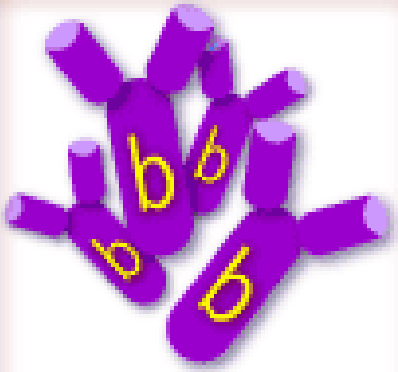
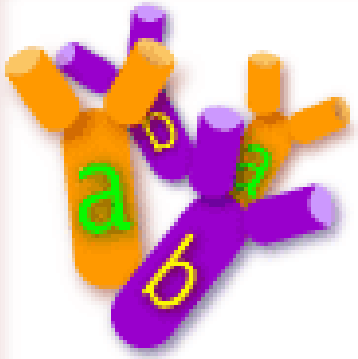
Examples

- **Autoimmune haemolytic anaemia**
- **Pernicious anemia**
- **Immune thrombocytopenia**
- **Transfusion reactions**
- **Hashimoto's thyroiditis**
- **Graves' disease**
- **Myasthenia gravis**
- **Hemolytic disease of the newborn**

Blood Transfusion reactions



The ABO Blood System

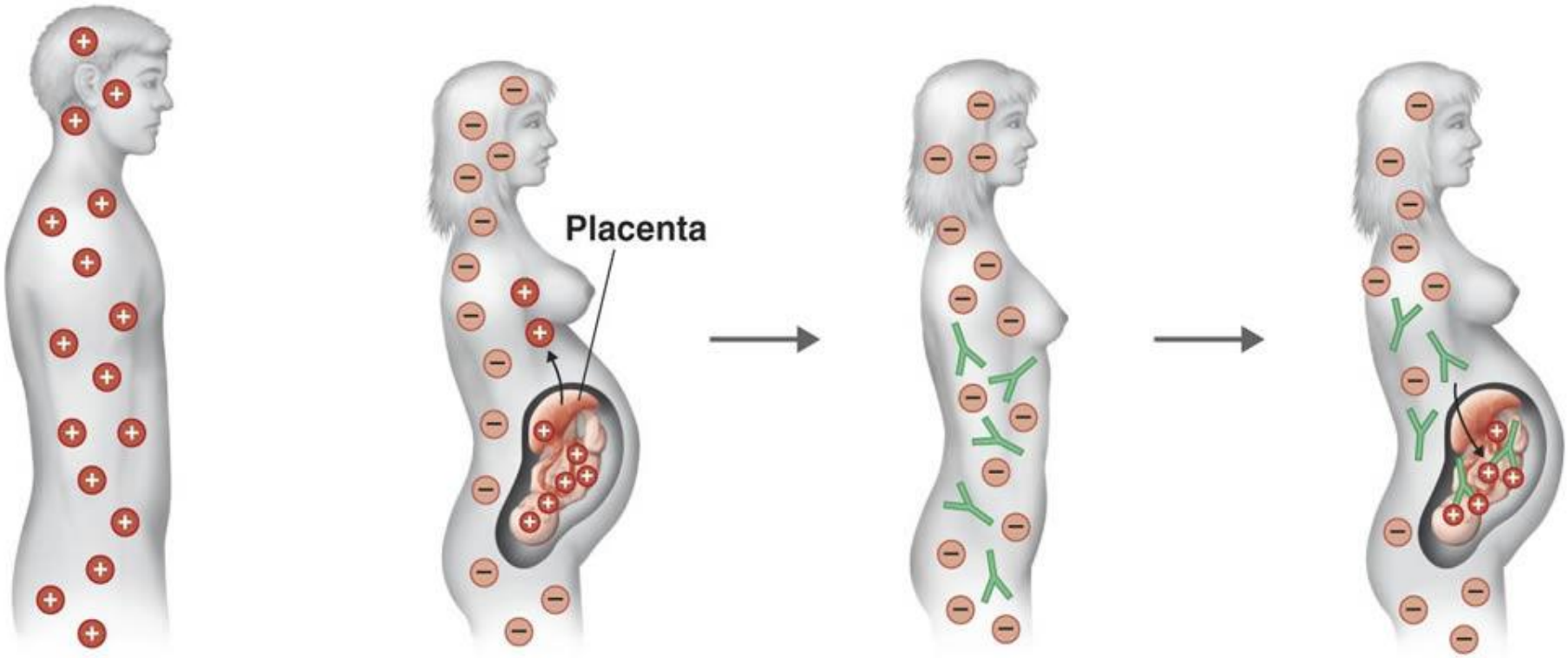
Blood Type (genotype)	Type A (AA, AO)	Type B (BB, BO)	Type AB (AB)	Type O (OO)
Red Blood Cell Surface Proteins (phenotype)	 A agglutinogens only	 B agglutinogens only	 A and B agglutinogens	 No agglutinogens
Plasma Antibodies (phenotype)	 b agglutinin only	 a agglutinin only	NONE. No agglutinin	 a and b agglutinin

Hemolytic disease of newborn

Rh factor incompatibility

- IgG abs to Rh an innocuous RBC antigen
  - Rh^+ baby born to Rh^- mother first time fine. 2nd time can have abs to Rh from 1st pregnancy.
  - Ab crosses placenta and baby kills its own rbcs.
  - Treat mother with ab to Rh antigen right after birth and mother never makes its own immune response.

Rh factor incompatibility



1. Rh^+ father.
2. Rh^- mother carrying her first Rh^+ fetus. Rh antigens from the developing fetus can enter the mother's blood during delivery.
3. In response to the fetal Rh antigens, the mother will produce anti-Rh antibodies.
4. If the woman becomes pregnant with another Rh^+ fetus, her anti-Rh antibodies will cross the placenta and damage fetal red blood cells.

TYPE III HYPERSENSITIVITY
immune complexes

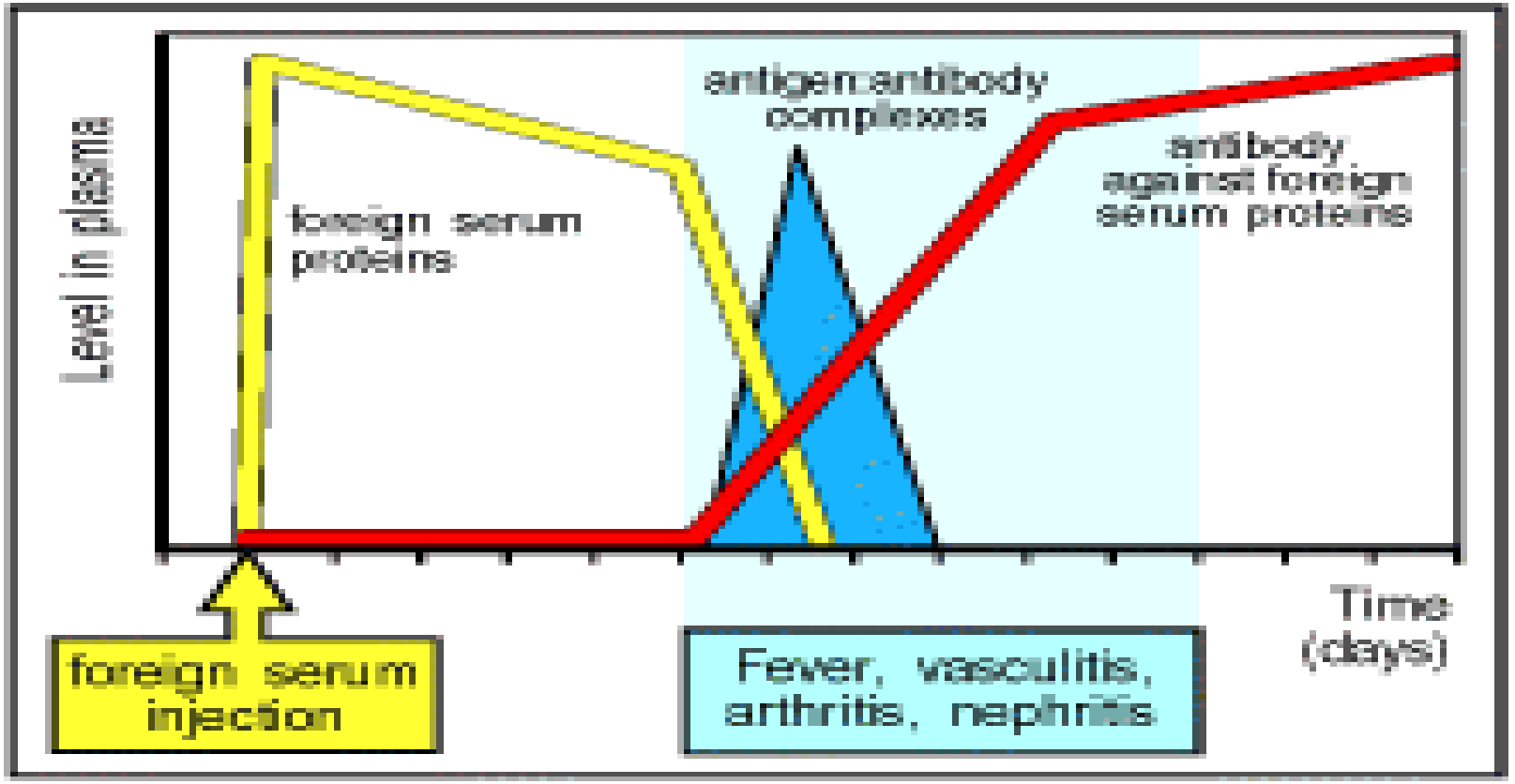
- Large amount of antigen and antibodies form complexes in blood.
- If not eliminated can deposit in Kidneys, Joints, Lung, Skin and trigger inflammation.
- PMNs and macrophages bind to immune complexes via FcR and phagocytize the complexes.
- If unable to phagocytize the immune complexes can cause inflammation via C' activation.

Examples of Human Immune Complex–Mediated Diseases

Disease	Antigen involved	Clinicopathologic manifestations
Systemic lupus erythematosus	DNA, nucleoproteins, others	Nephritis, arthritis, vasculitis
Polyarteritis nodosa	Hepatitis B virus surface antigen	Vasculitis
Poststreptococcal glomerulonephritis	Streptococcal cell wall antigen(s); may be "planted" in glomerular basement membrane	Nephritis
Serum sickness	Various proteins	Arthritis,vasculitis, nephritis

Serum sickness

- Is a disease caused by the injection of large doses of a protein antigen into the blood and characterized by the deposition of antigen-antibody complexes in blood vessel walls, especially in the kidneys and joints.

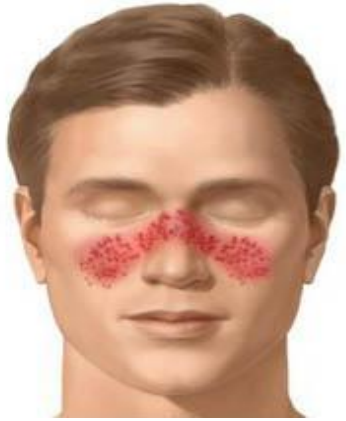


Systemic Lupus Erythmatosus

- The disease is characterized by the presence of autoantibodies , which form immune complexes with autoantigens and are deposited within the kidney glomeruli

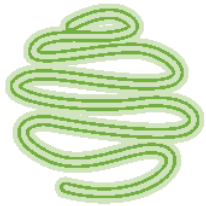
- The resulting type III hypersensitivity is responsible for the glomerulonephritis

  (Inflammation of blood capillary vessels in the glomeruli)



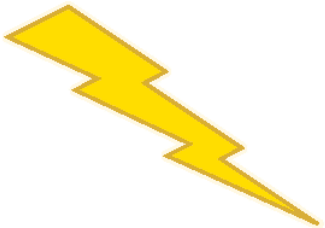
Butterfly rash

1. Genes



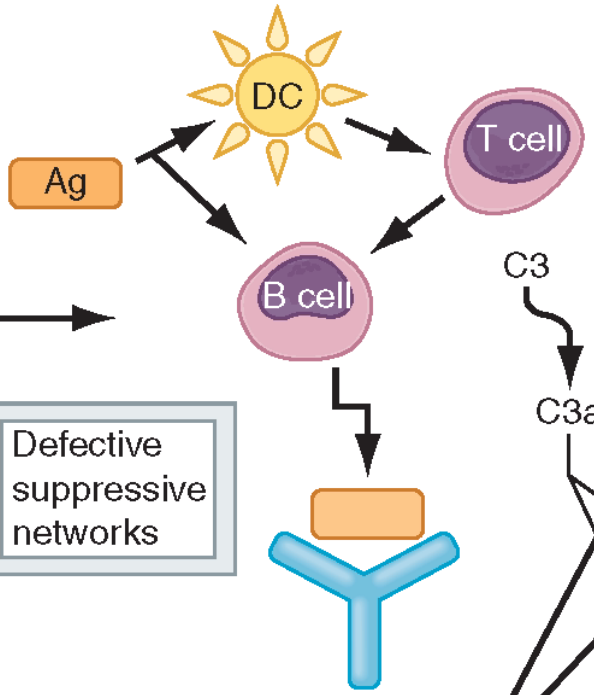
C1q,C2,C4
HLA-D2,3,8
MBL
FcR 2A,3A,2B
IL-10
MCP-1
PTPN22

Environment



UV light
Gender
?Infection
?EBV
Others

2. Abnormal Immune Response

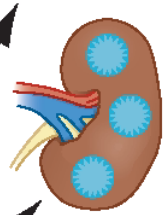


3. Autoantibodies Immune Complexes

C3

C3a

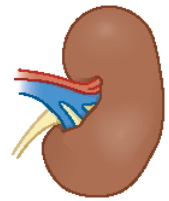
4. Inflammation

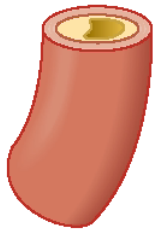


Rash
Nephritis
Arthritis
Leukopenia
CNS dz
Carditis
Clotting
Etc.

Chr. inflam.
Chr. oxid.

5. Damage





Renal Failure
Atherosclerosis
Pulm fibrosis
Stroke
Damage from Rx
Etc.

TYPE IV HYPERSENSITIVITY

Delayed type hypersensitivity

- DTH response is from:
  - Th1 cells release cytokines to activate macrophages causing inflammation and tissue damage.
  - Continued macrophage activation can cause chronic inflammation resulting in tissue lesions, scarring, and granuloma formation.
- Delayed is relative because DTH response arise 24-72 hours after exposure rather than within minutes.
- Unlike the other types, it is not antibody mediated but rather is a type of cell-mediated response.

Stages of Type IV DTH

Sensitization stage

- Memory Th1 cells against DTH antigens are generated by dendritic cells during the sensitization stage.
- These Th1 cells can activate macrophages and trigger inflammatory response.

Stages of Type IV DTH

Effector stage

- Secondary contact yields what we call DTH.

Th1 memory cells are activated and produce cytokines.which cause tissue destruction, inflammation.

- Inflamed area becomes red and fluid filled can form lesion.
- Continued exposure to antigen can cause chronic inflammation and result in granuloma formation.

Delayed type hypersensitivity (DTH)

DTH can be the result of Chronic infection or Exposure to some antigens.

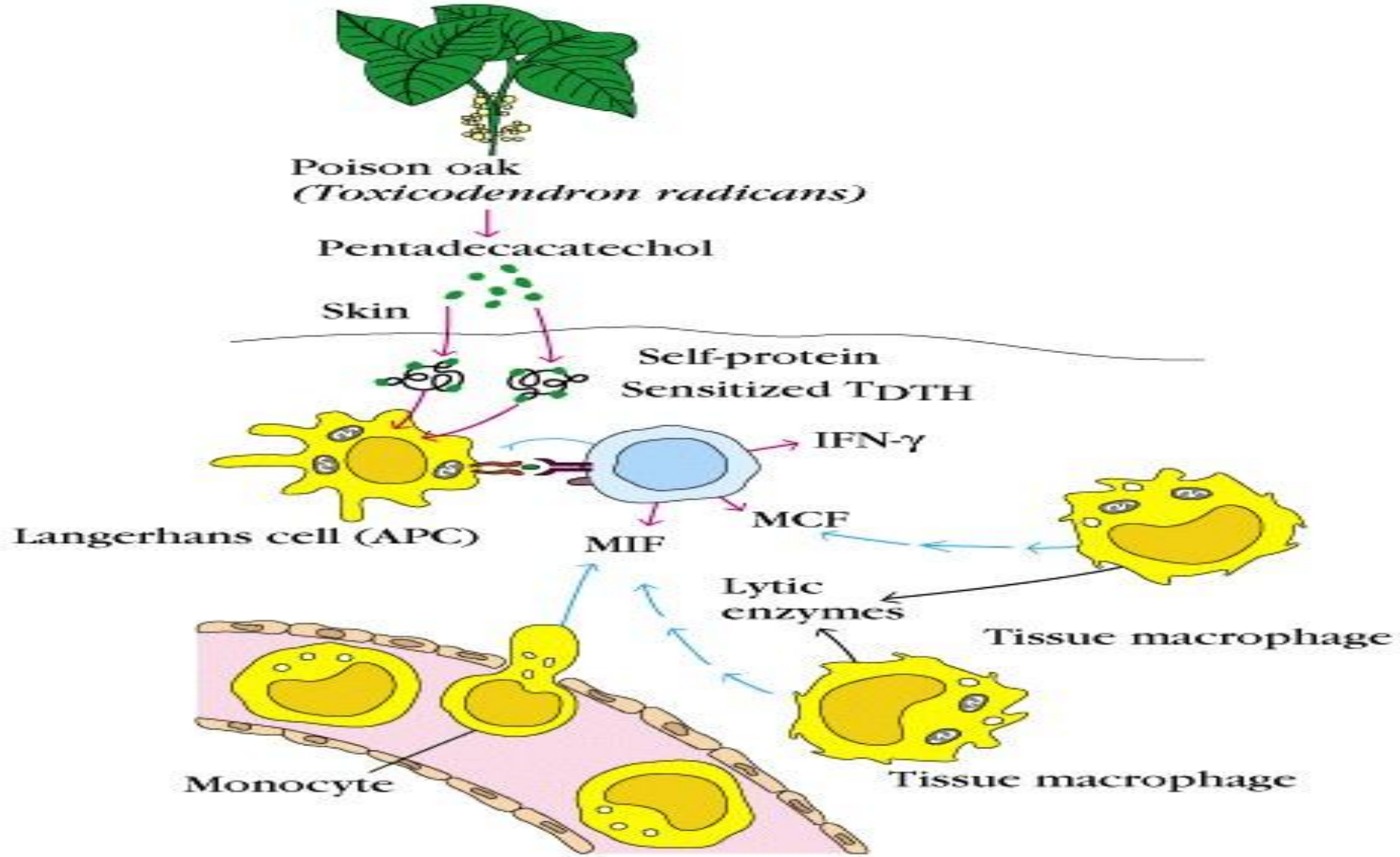
TABLE 14-3 INTRACELLULAR PATHOGENS AND CONTACT ANTIGENS THAT INDUCE DELAYED-TYPE HYPERSENSITIVITY

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

Type IV DTH
Contact dermatitis

- The response to poison oak is a classic Type IV.
  - Small molecules act as haptens and complex with skin proteins to be taken up by APCs and presented to Th1 cells to get sensitization.
  - During secondary exposure Th1 memory cells become activated to cause DTH.

Contact dermatitis

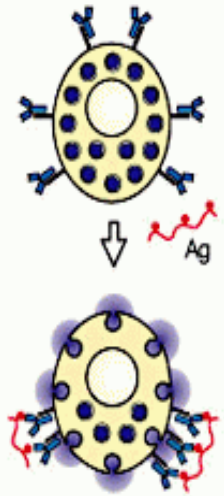
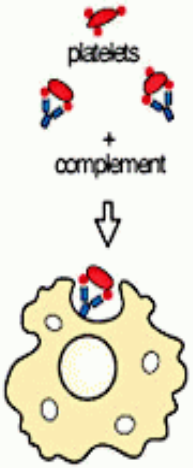
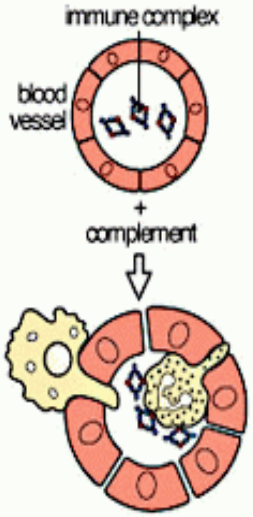
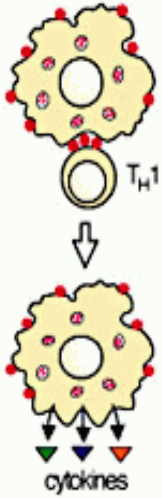
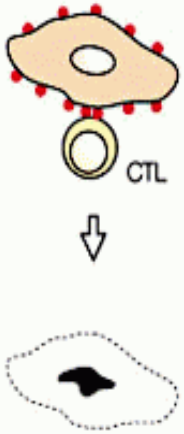


Drug reactions can be any Type of Hypersensitivity

TABLE 16-5 Penicillin-induced hypersensitive reactions

Type of reaction	Antibody or lymphocytes induced	Clinical manifestations
I	IgE	Urticaria, systemic anaphylaxis
II	IgM, IgG	Hemolytic anemia
III	IgG	Serum sickness, glomerulonephritis
IV	T_{DTH} cells	Contact dermatitis

Immune-Mediated Hypersensitivities

	Type I	Type II	Type III	Type IV	
Immune reactant	IgE antibody, T_H2 cells	IgG antibody	IgG antibody	T cells	
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Soluble antigen	Cell-associated antigen
Effector mechanism	Mast-cell activation	Complement, FcR^+ cells (phagocytes, NK cells)	Complement Phagocytes	Macrophage activation	Cytotoxicity
					
Example of hypersensitivity reaction	Allergic rhinitis, asthma, systemic anaphylaxis	Some drug allergies (eg penicillin)	Serum sickness, Arthus reaction	Contact dermatitis, tuberculin reaction	Contact dermatitis