Hypersensitivity

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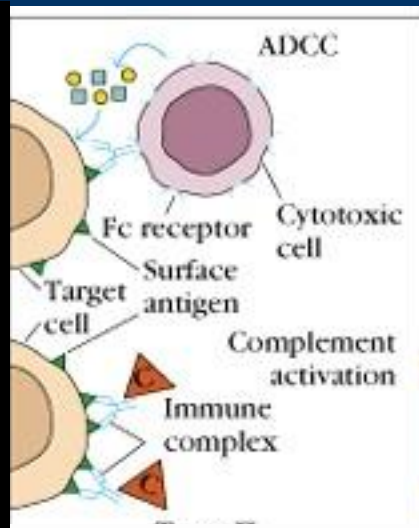
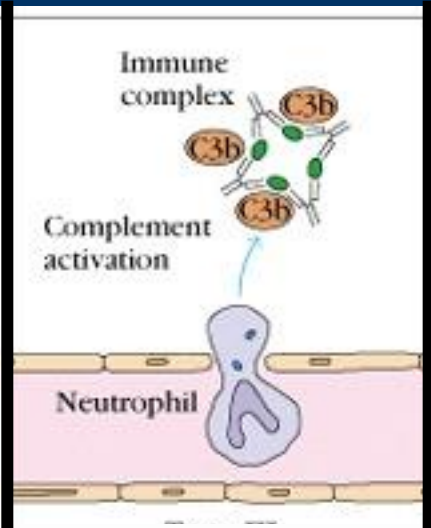
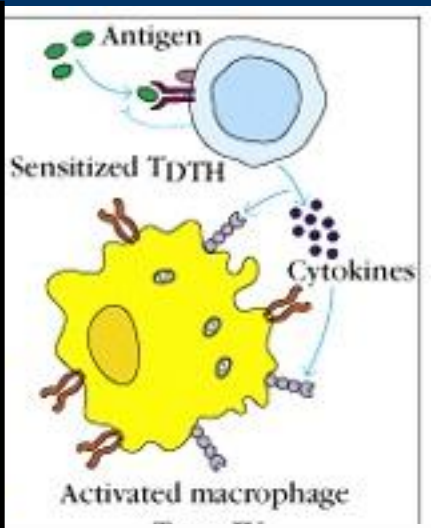
Gel and Coombs classification of hypersensitivities.







Type I	Type II	Type III	Type IV
IgE Mediated	IgG/IgM Mediated	IgG Mediated	T cell
Classic Allergy	rbc lysis	Immune complex Disease	Delayed Type Hypersensitivity

TYPE I Hypersensitivity
Classic allergy

- Mediated by IgE attached to Mast cells.
- The symptoms resulting from allergic responses are known as **anaphylaxis**.
  - Includes: Hay fever, asthma, eczema, bee stings, food allergies.

Allergens

- Allergens are nonparasite antigens that can stimulate a type I hypersensitivity response.
- Allergens bind to IgE and trigger degranulation of chemical mediators.

Allergens

TABLE 16-1 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

In the US ---
36 million people
said to have hay fever!

Characteristics of allergens

- Small 15-40,000 MW proteins.
- Specific protein components
  - Often enzymes.
- Low dose of allergen
- Mucosal exposure.
- Most allergens promote a Th2 immune.

Allergens

Dermatophagoides pteronyssinus
(common dust mite)

Example: Der P1

Der P1 is an enzyme allergen
from the fecal pellets
of the dust mite.

Der P1 Allergen

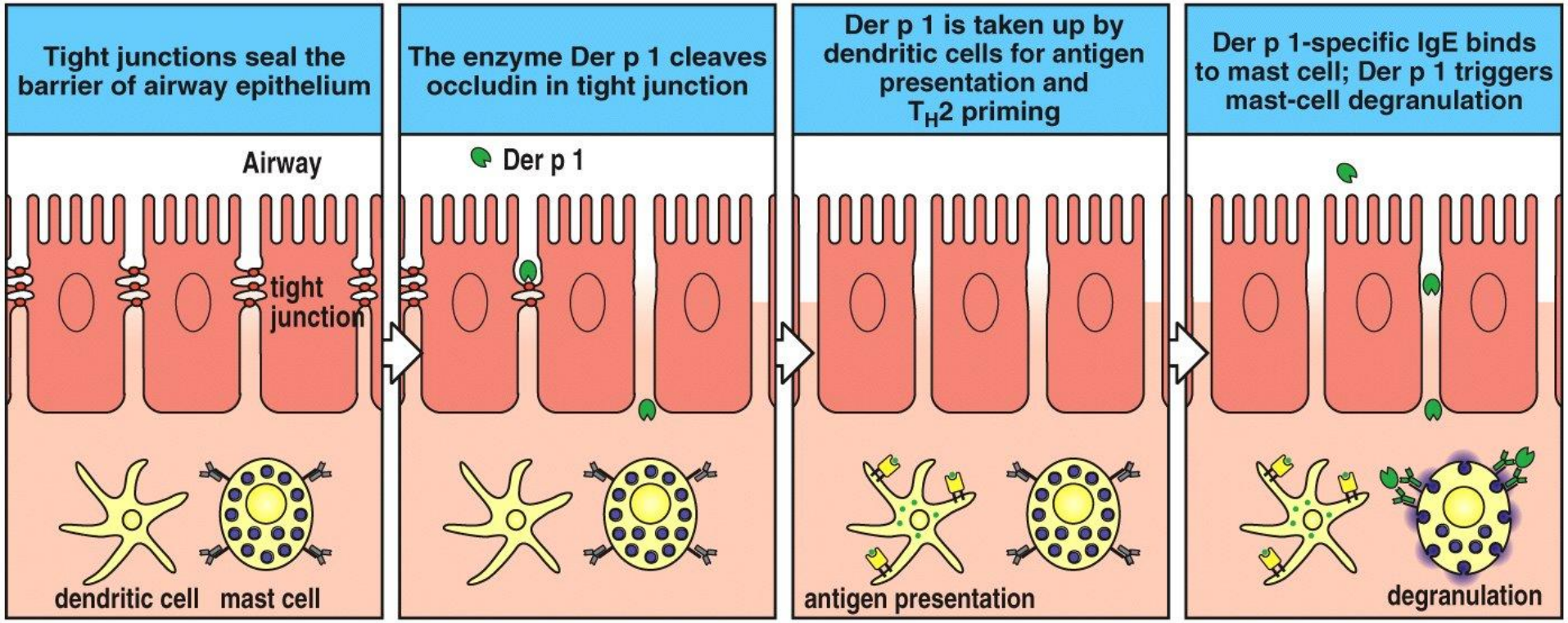


Figure 12-5 Immunobiology, 6/e. (© Garland Science 2005)

Allergen is easily aerosolized and inhaled.
Der P1 breaks down components of tight junctions which helps it to cross mucosa.

Atopy

- **Atopy** is the term for the genetic trait to have a predisposition for localized anaphylaxis.
- Atopic individuals have higher levels of IgE and eosinophils.

Genetic Predisposition
Type I hypersensitivity

- Candidate polymorphic genes include:
  - IL-4 Receptor.
  - IL-4 cytokine (promoter region).
  - FcεRI. High affinity IgE receptor.
  - Class II MHC
    (present peptides promoting Th2 response).
  - Inflammation genes.

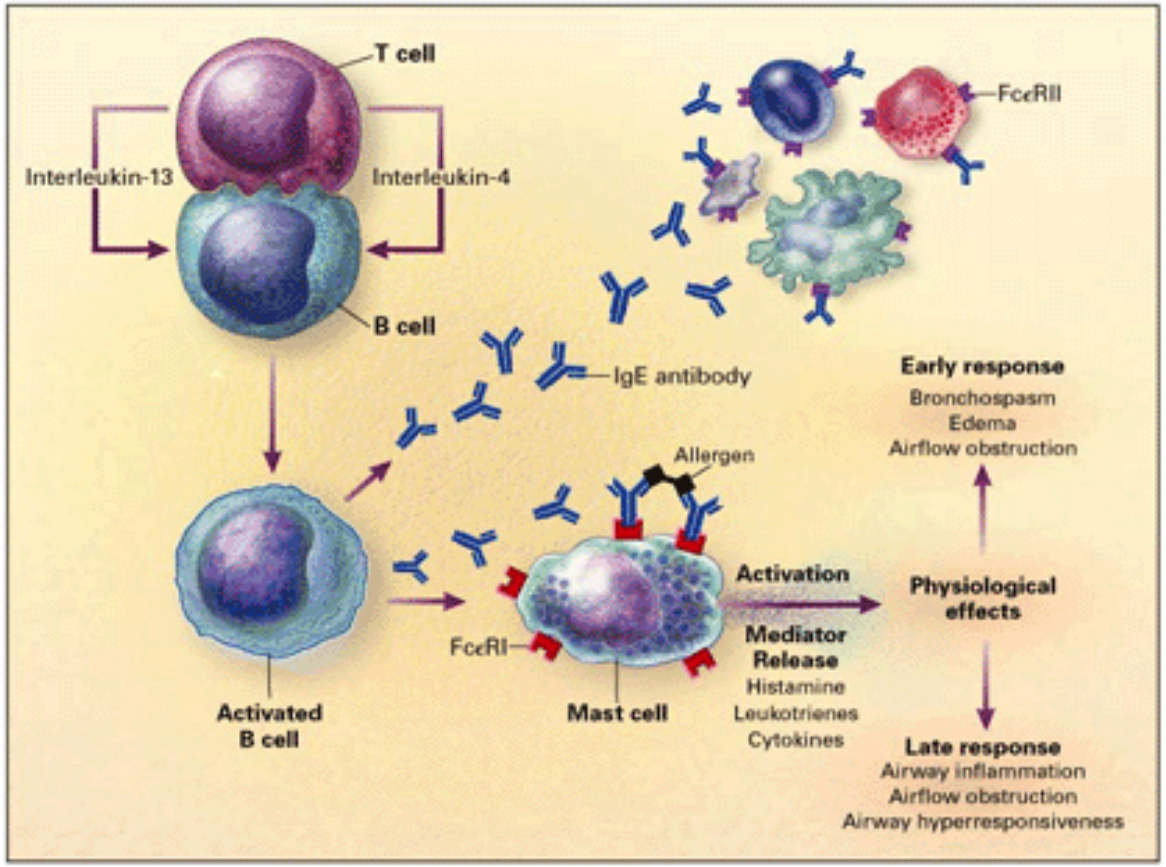
Mechanisms of allergic response

Sensitization

Repeated exposure to allergens initiates immune response that generates IgE isotype.

Th2 cells required to provide the IL-4 required to get isotype switching to IgE.

Mechanisms of allergic response
Sensitization
Th2/B cell interaction



IL-4

IL-4R

CD40

Drive B cell Activation and IgE isotype switch.

Busse and Lemanske NEJM Feb 2001. 344:350

Mechanisms of allergic response

Sensitization

- The IgE can attach to Mast cells by Fc receptor, which increases the life span of the IgE.
- Half-life of IgE in serum is days whereas attached to FcεR it is increased to months.

Mechanisms of allergic response
Fc ε receptors (FcεR)

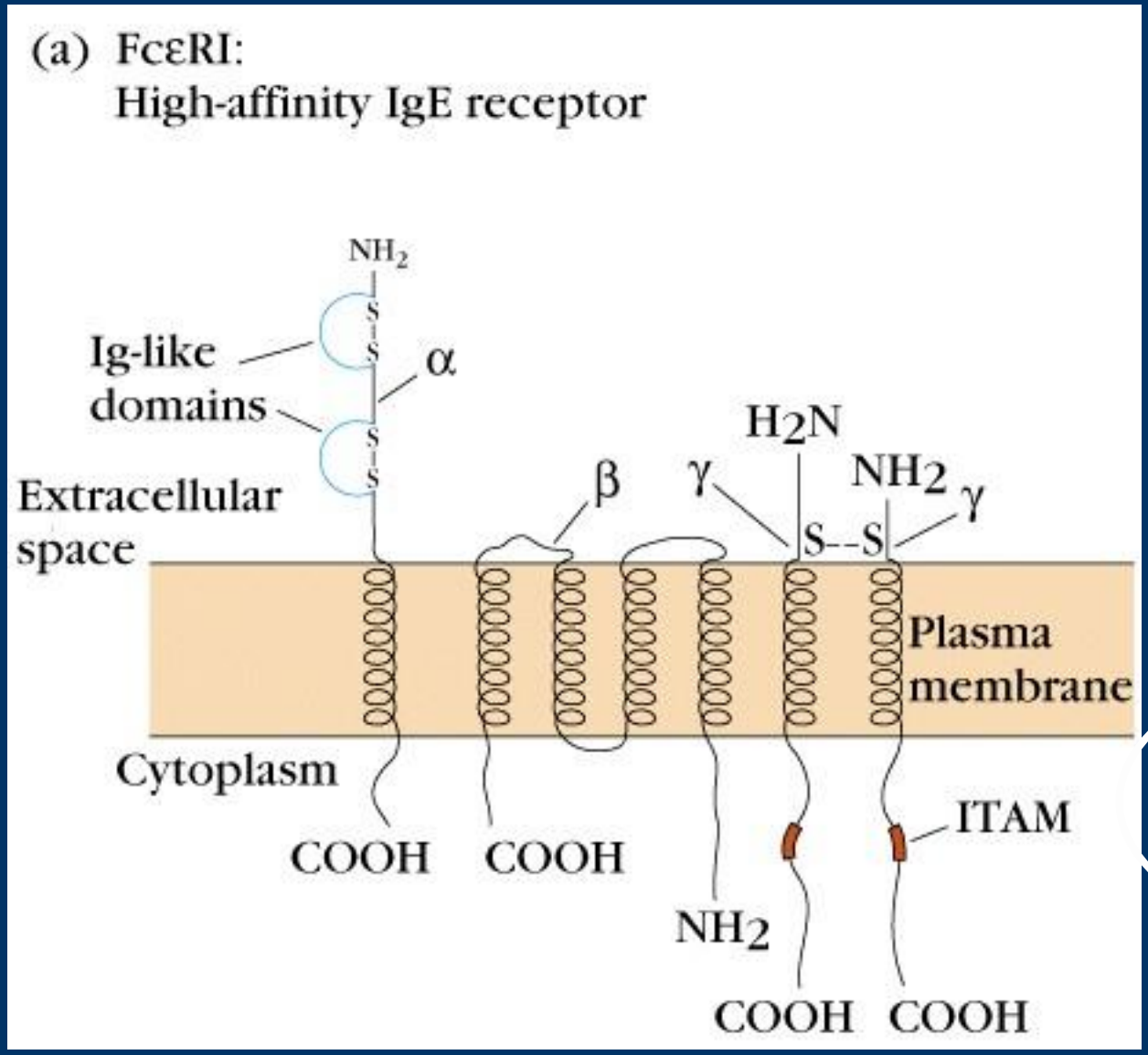
FcεR1

- high affinity IgE receptor found on
  - mast cells/basophils/activated eosinophils.

- Allergen binding to IgE attached to FcεR1 triggers release of granules from cell.

Mechanisms of allergic response

FcεRI



High affinity IgE Fc Receptor

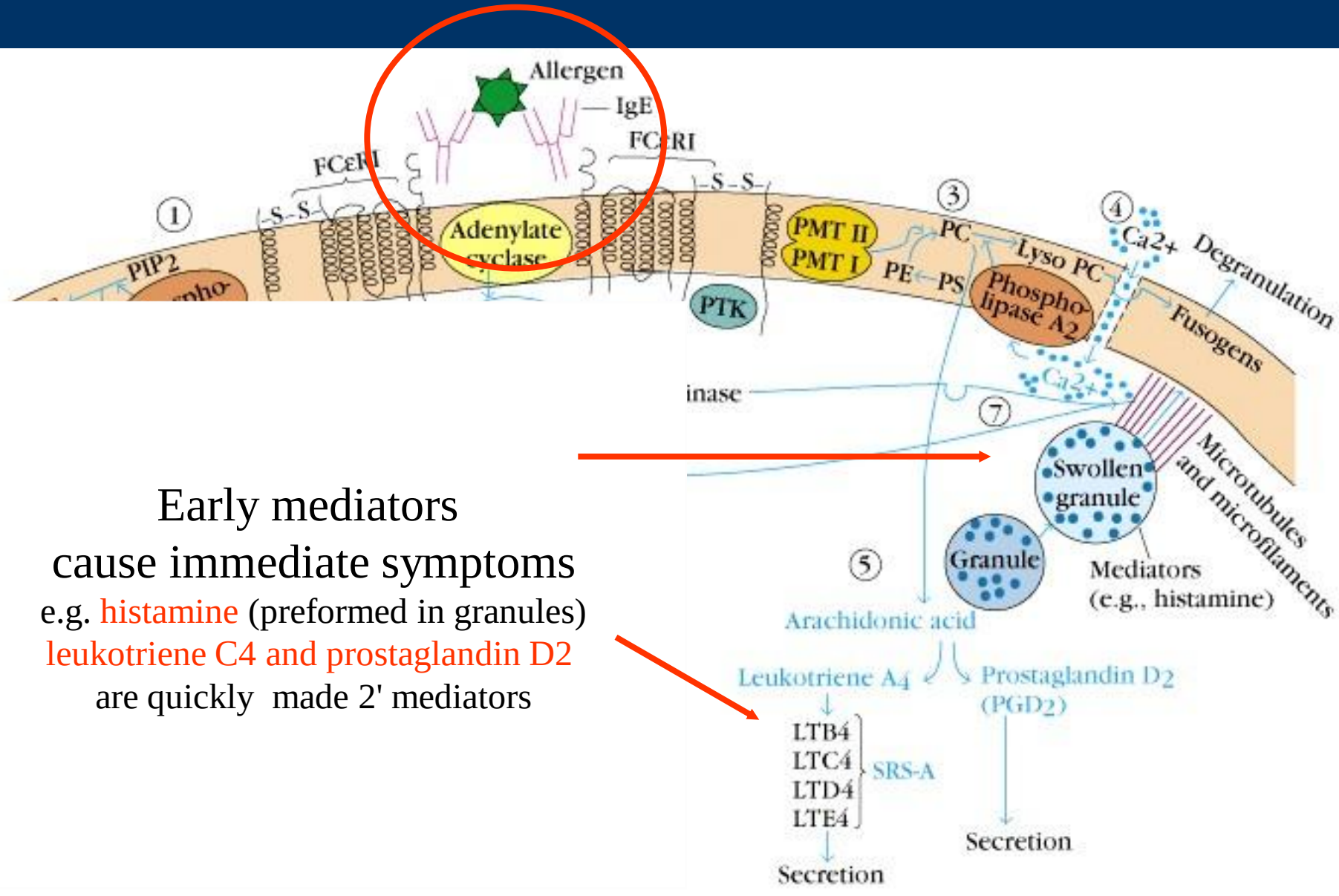
Has ITAM motifs

Mechanisms of allergic response
Effector Stage of Hypersensitivity

Secondary exposure to allergen

- Mast cells are primed with IgE on surface.
- Allergen binds IgE and cross-links to activate signal with tyrosine phosphorylation, Ca++ influx, degranulation and release of mediators.

FcεRI Triggers Release of Mediators



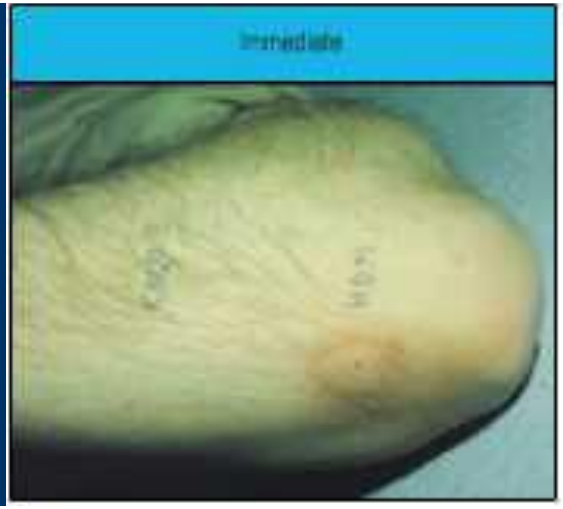
Early mediators
cause immediate symptoms
e.g. histamine (preformed in granules)
leukotriene C4 and prostaglandin D2
are quickly made 2' mediators

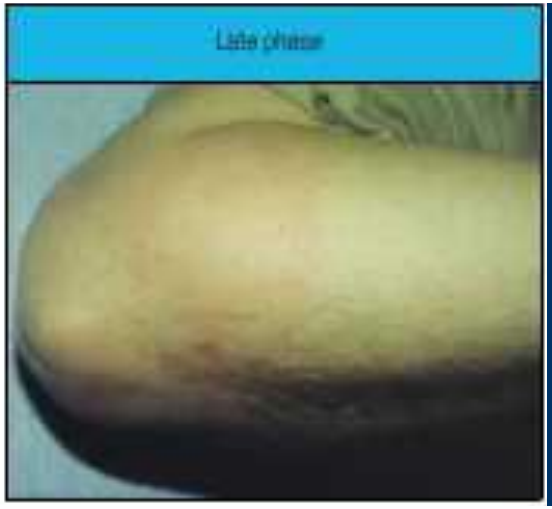
Mediators of Type I Hypersensitivity
Immediate effects

- Histamine
  - Constriction of smooth muscles.
    Bronchiole constriction = wheezing.
    Constriction of intestine = cramps-diarrhea.
  - Vasodilation with increased fluid into tissues causing increased swelling or fluid in mucosa.
  - Activates enzymes for tissue breakdown.
- Leukotrienes
- Prostaglandins

Immediate vs Late Effects

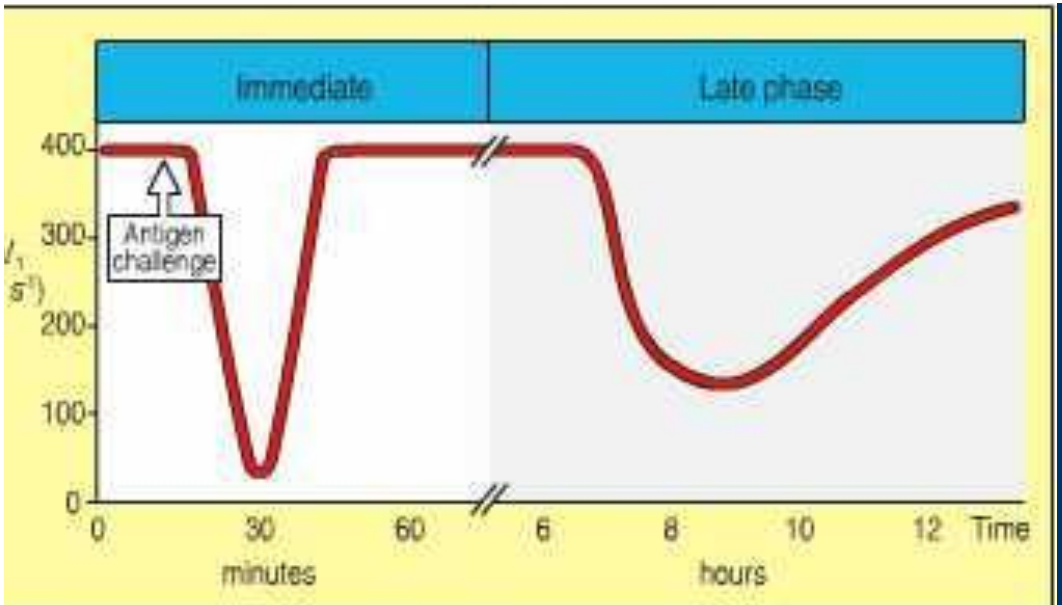
(early mediators)





Early/Late

Effect on lung airflow
OR
Wheezing



Mediators of Type I Hypersensitivity

Primary Mediators

Pre-formed mediators in granules

- Histamine
- Cytokines TNF-α, IL-1, IL-6.
- Chemoattractants for Neutrophils and Eosinophils.
- Enzymes
  - tryptase, chymase, cathepsin.
  - Changes in connective tissue matrix, tissue breakdown.

Type I Hypersensitivity

Secondary mediators

Mediators formed after activation

- Leukotrienes
- Prostaglandins
- Th2 cytokines- IL-4, IL-5, IL-13, GM-CSF

Continuation of sensitization cycle

- Mast cells control the immediate response.
- Eosinophils and neutrophils drive late or chronic response.

- More IgE production further driven by activated Mast cells, basophils, **eosinophils.**

Continuation of sensitization cycle
Eosinophils

- Eosinophils play key role in late phase reaction.
- Eosinophils make
  - enzymes,
  - cytokines (IL-3, IL-5, GM-CSF),
  - Lipid mediators (LTC4, LTD4, PAF)
- Eosinophils can provide CD40L and IL-4 for B cell activation.

Localized anaphylaxis

Target organ responds to direct contact with allergen.

- Digestive tract contact results in vomiting, cramping, diarrhea.
- Skin sensitivity usually reddened 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

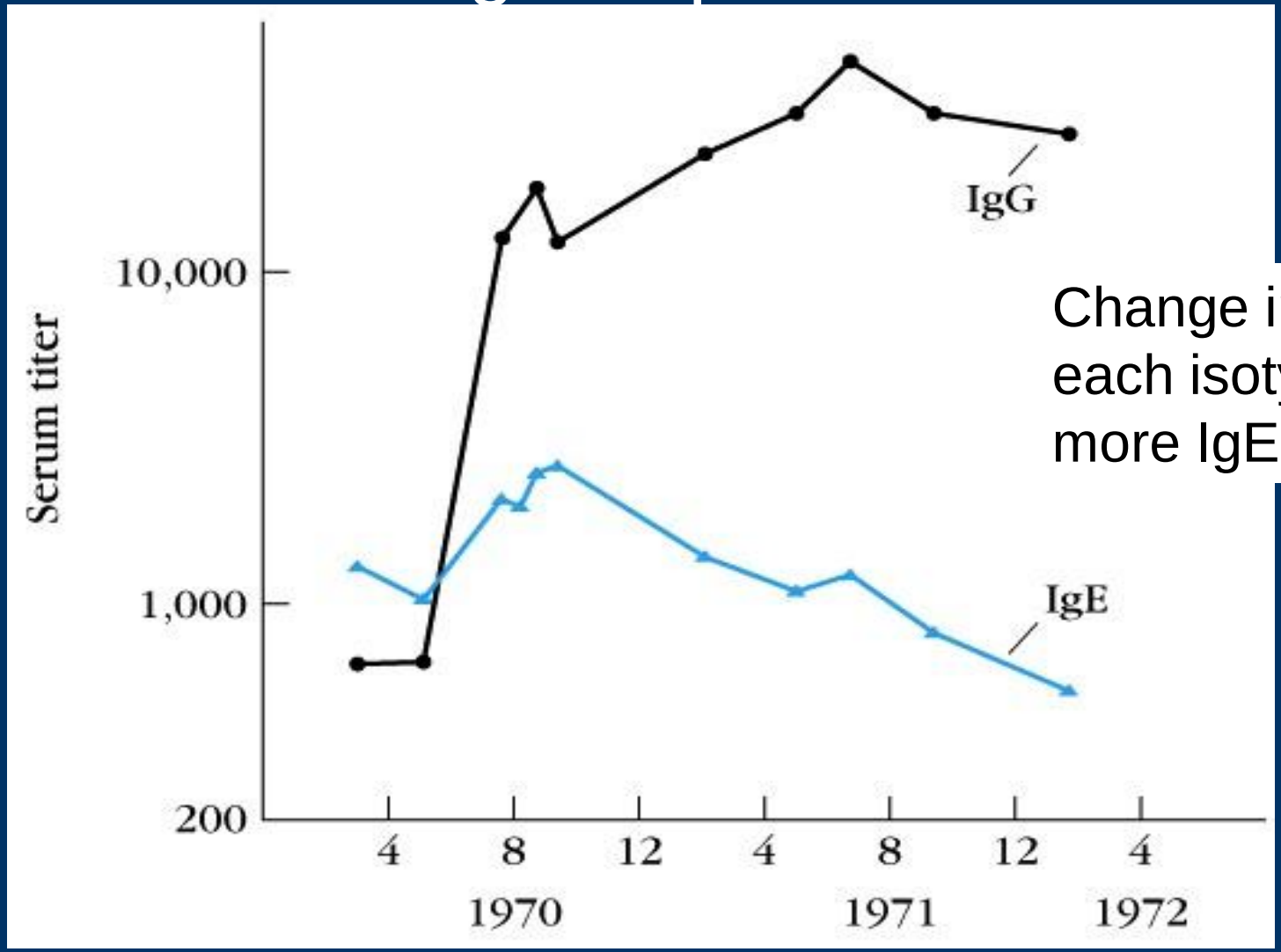
Pharmacotherapy

- 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 (hyposensitization) also known as allergy shots.
  - Repeated injections of allergen to reduce the IgE on Mast cells and produce IgG.

Treatment for Type I
Effect of allergy shots
Allergen Specific Antibodies

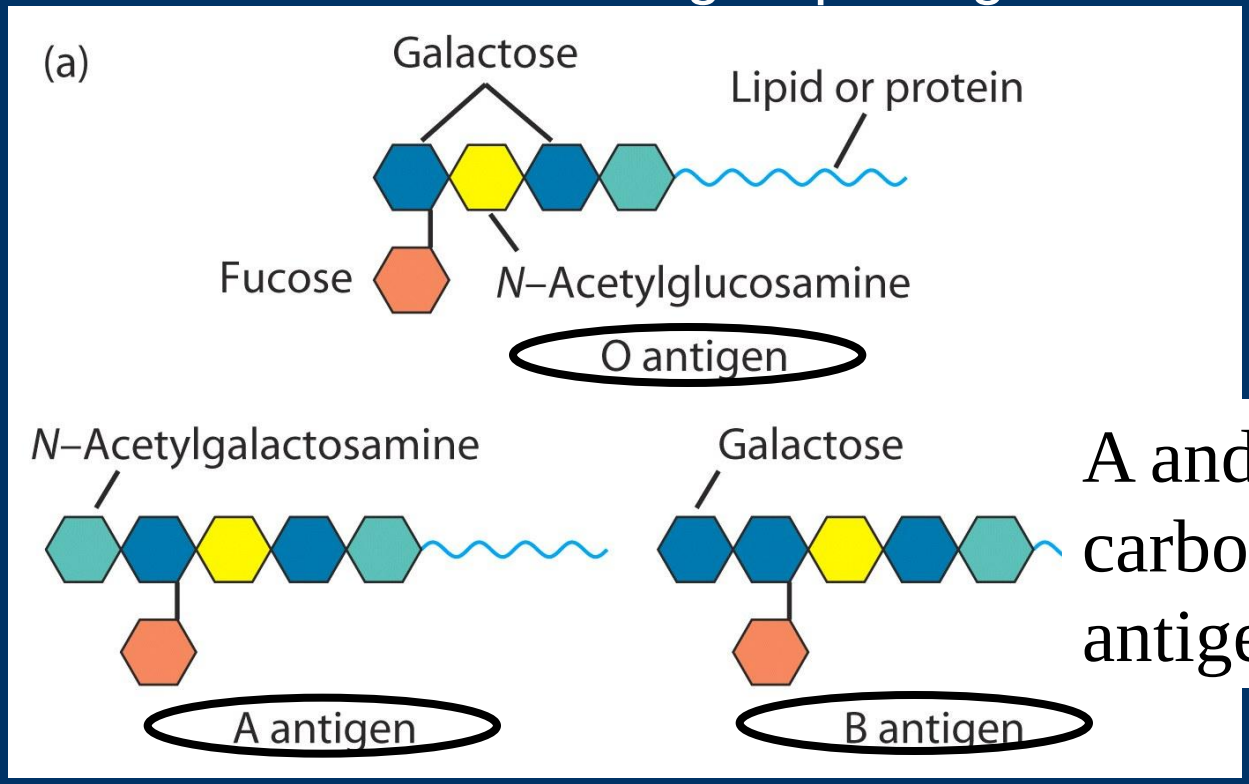


Change in amount of each isotype from more IgE to more IgG.

TYPE II Hypersensitivity
Antibody mediated cytotoxicity
Blood Transfusion reactions

Innocuous antigens on red blood cells.

EXAMPLE: ABO blood group antigens



A and B carbohydrate antigens

ABO Blood Groups

Genotype	Blood–group phenotype	Antigens on erythrocytes (*agglutinins*)	Serum antibodies (*isohemagglutinins*)
AA or AO	A	A	Anti–B
BB or BO	B	B	Anti–A
AB	AB	A and B	None
OO	O	None	Anti–A and anti–B

Antibody against rbc antigen binds and mediates killing of rbcs via C'or ADCC causes systemic inflammation.

Quex: Why do we have antibodies to these innocuous antigens even before we get blood transfusion

TYPE II
Antibody mediated cytotoxicity

Drug reactions

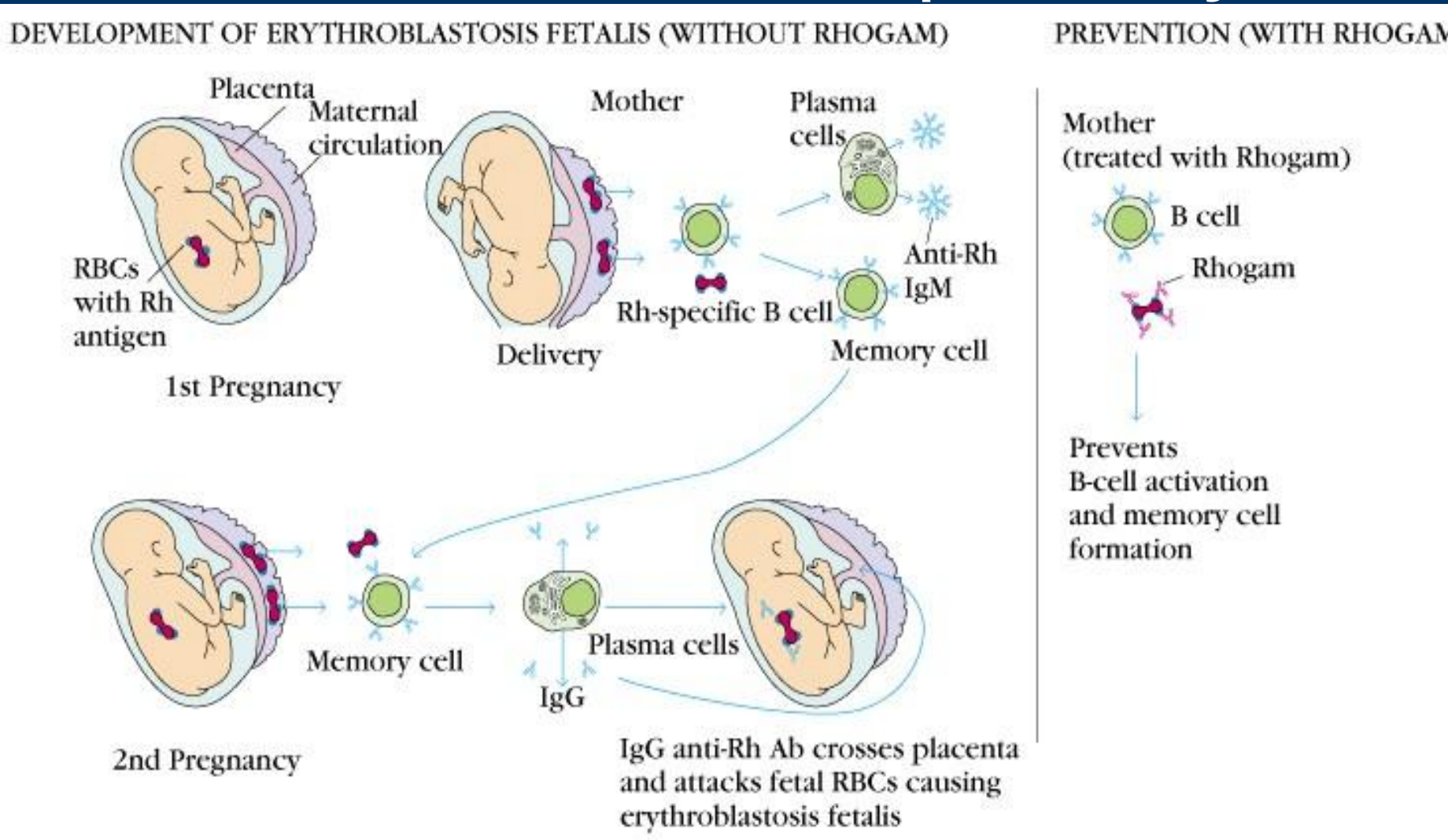
- Drug binds to rbc surface and antibody against drug binds and causes lysis of rbcs.
- Immune system sees antibody bound to "foreign antigen" on cell. ADCC

TYPE II
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.

TYPE II
Rh factor incompatibility



TYPE III
Antigen antibody immune complexes. IgG mediated

Immune Complex Disease

- Large amount of antigen and antibodies form complexes in blood.
- If not eliminated can deposit in capillaries or joints and trigger inflammation.

TYPE III
Immune Complexes

- PMNs and macrophages bind to immune complexes via FcR and phagocytize the complexes.

BUT

- If unable to phagocytize the immune complexes can cause inflammation via C’ activation ---> C3a C4a, C5a and "frustrated phagocytes".

TYPE III
Immune Complex Disease
"Frustrated Phagocytes"

- If neutrophils and macrophages are unable to phagocytize the immune complexes these cells will degranulate in the area of immune complex deposition and trigger inflammation.
- Unable to eat -------try to digest outside cell.

TYPE III
Immune Complex Disease

Localized disease

- Deposited in joints causing local inflammation = arthritis.
- Deposited in kidneys = glomerulonephritis.

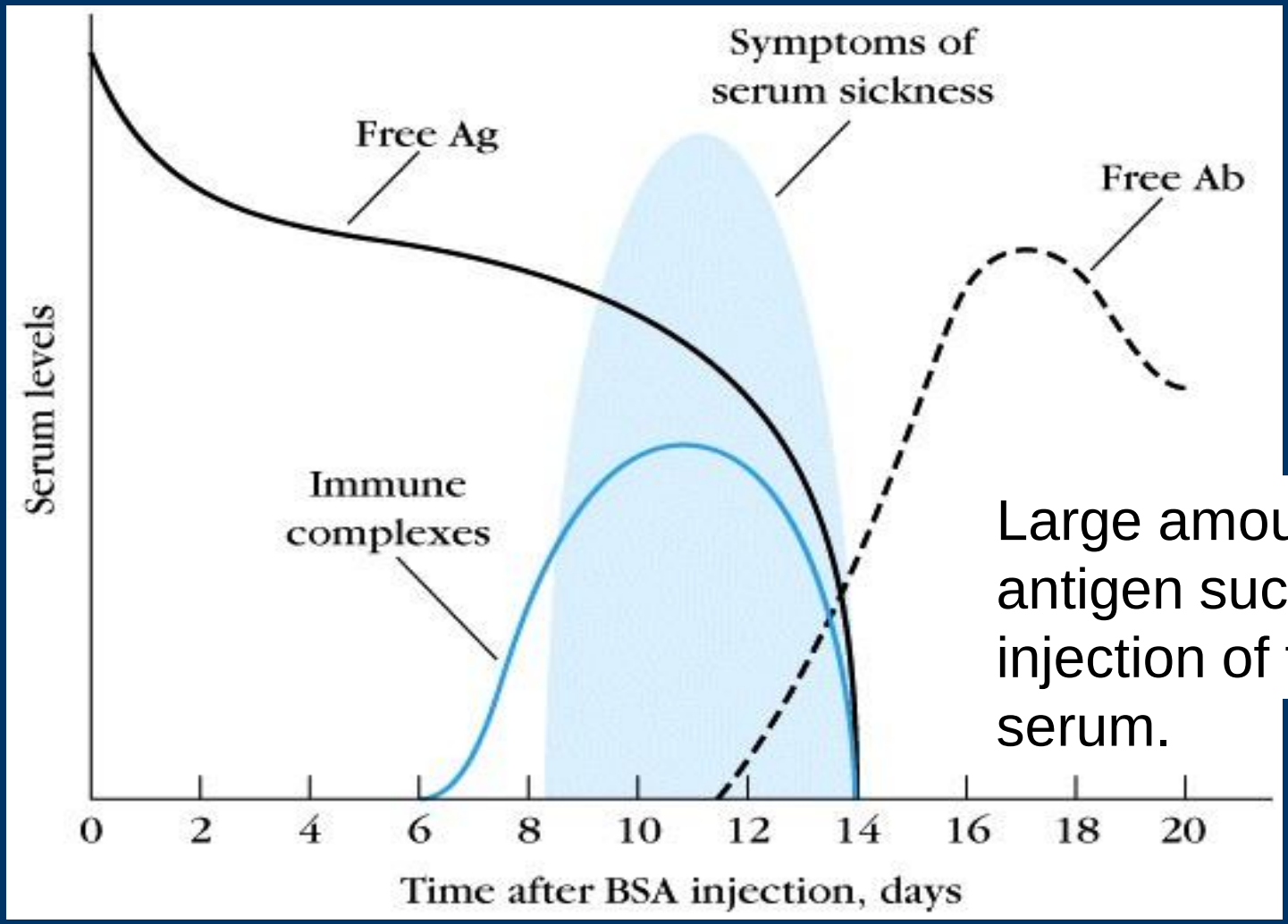
TYPE III
Immune Complex Disease

- Serum sickness from large amounts of antigen such as injection of foreign serum.

  Serum sickness is usually transient immune complex disease with removal of antigen source.

Serum Sickness

Systemic immune complex disease



Large amounts of antigen such as injection of foreign serum.

Days after Antigen Injection

Delayed type hypersensitivity Th1 cells and macrophages

- 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.

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.
  - IFN-γ, TNF-α, and TNF-β which cause tissue destruction, inflammation.
  - IL-2 that activates T cells and CTLs.
  - Chemokines- for macrophage recruitment.
  - IL-3, GM-CSF for increased monocyte/macrophage

Stages of Type IV DTH
Effector stage

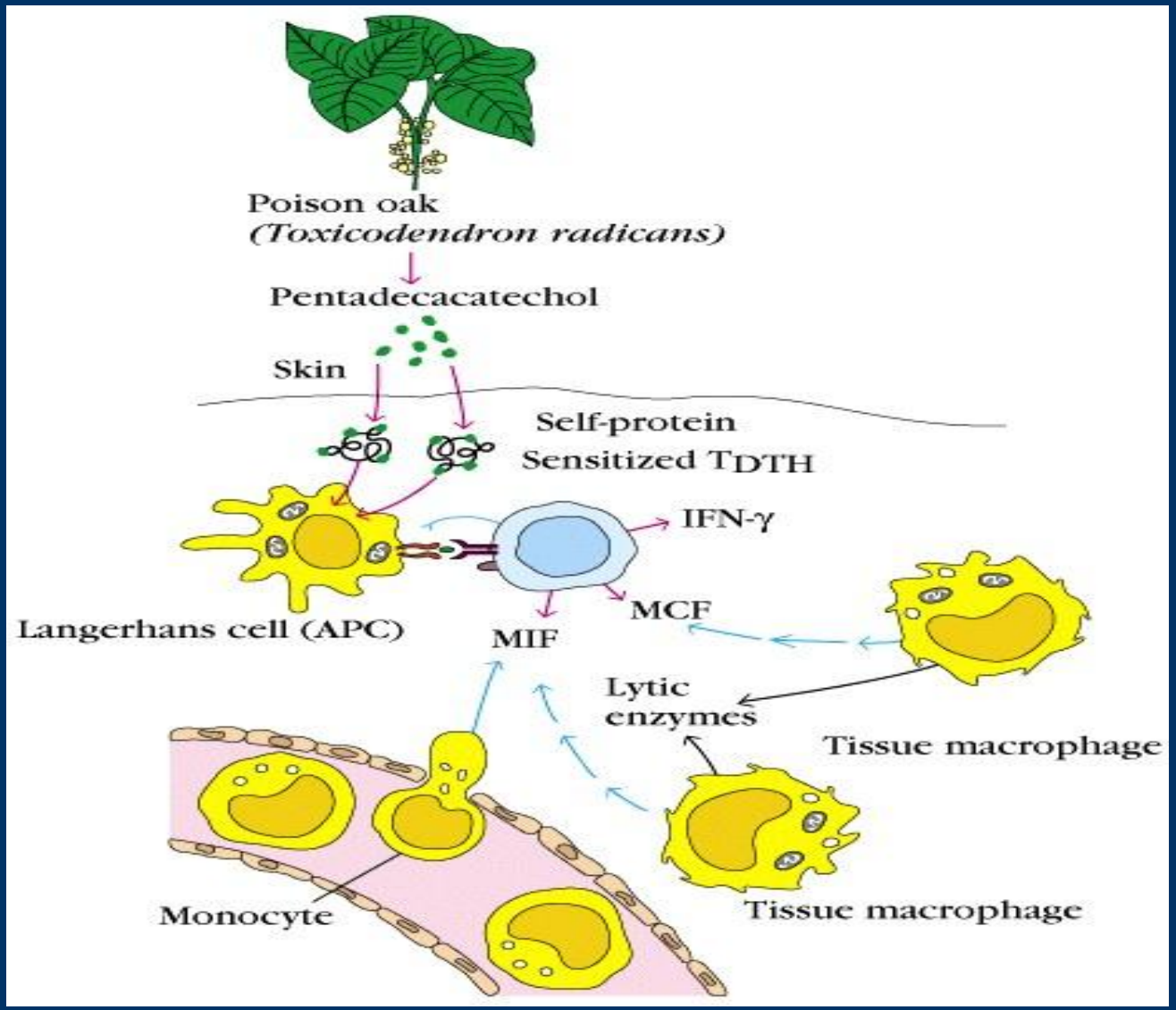
Secondary exposure to antigen

- Inflamed area becomes red and fluid filled can form lesion.
  - From tissue damage there is activation of clotting cascades and tissue repair.
- Continued exposure to antigen can cause chronic inflammation and result in granuloma formation.

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



Delayed type hypersensitivity (DTH)

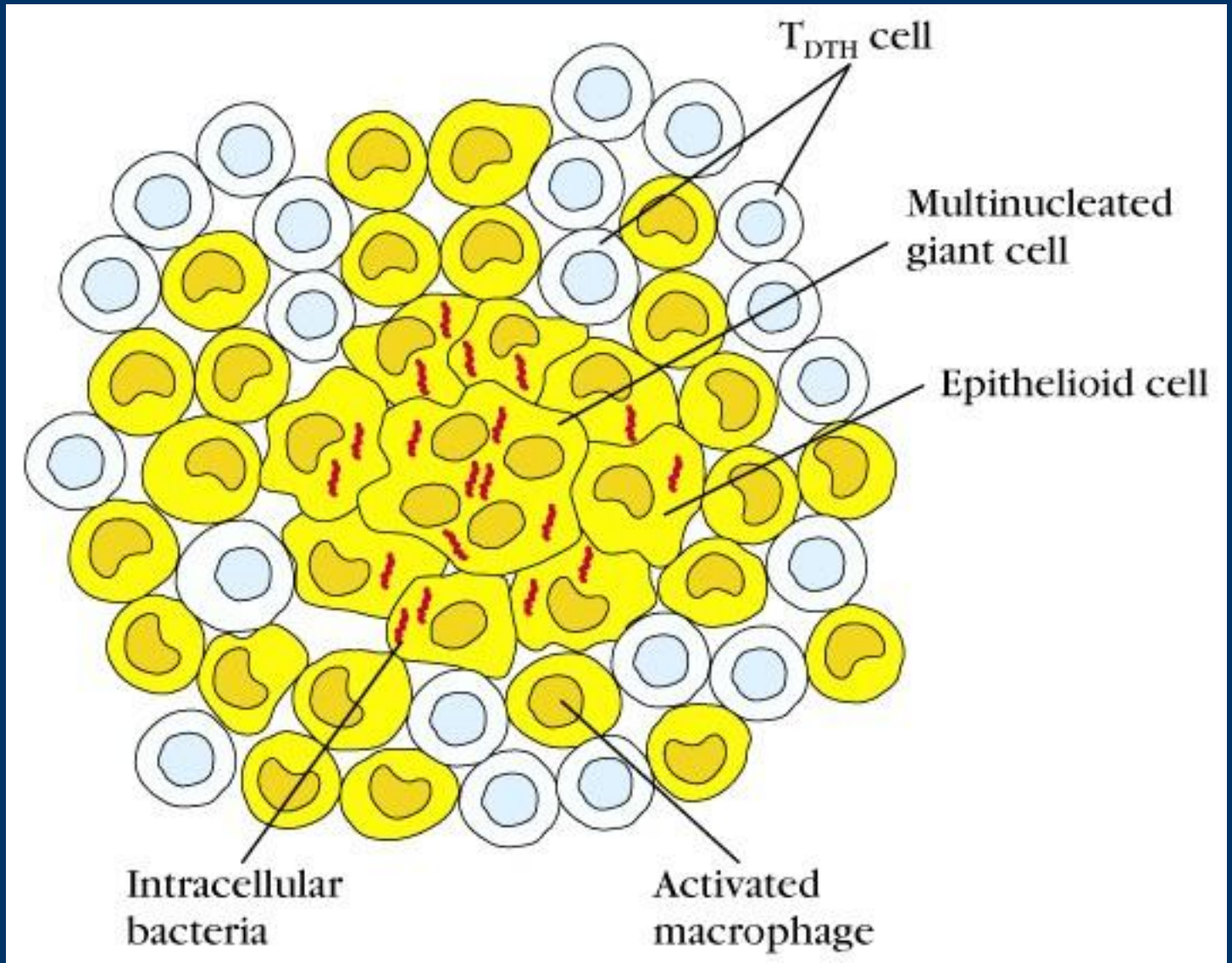
TABLE 14-3 INTRACELLULAR PATHOGENS AND CONTACT ANTIGENS THAT INDUCE DELAYED-TYPE HYPERSENSITIVITY

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.	

DTH is a type of immune response classified by **Th1 and macrophage** activation that results in tissue damage.

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

Granuloma Formation from DTH Mediated by Chronic Inflammation



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