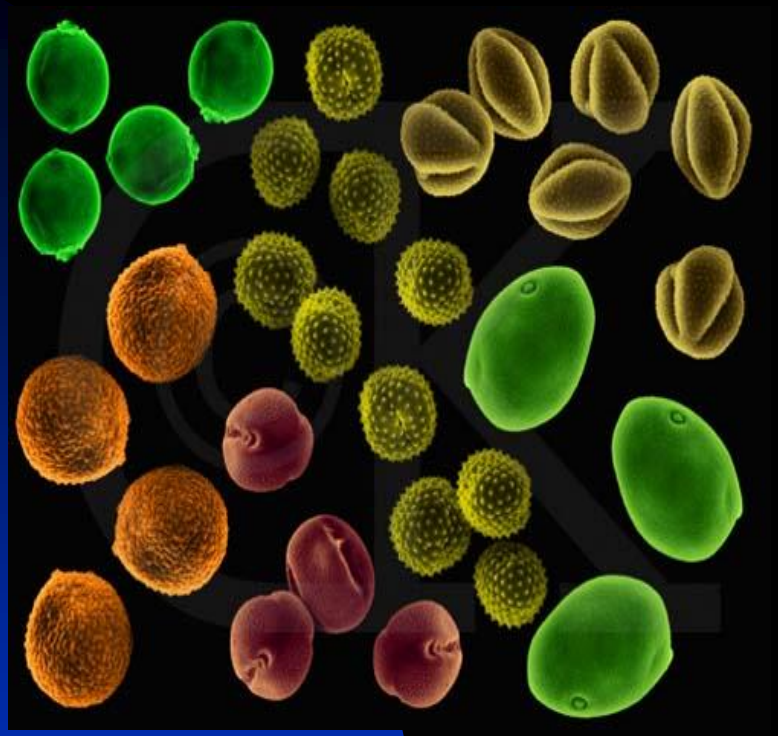
Hypersensitivity

Jun Dou(窦骏)

Department of Pathogenic biology and Immunology,
School of Medicine, Southeast University

Immunopathology

- The immune system has evolved powerful mechanisms to protect the body from harmful pathogens.
- These same mechanisms, **when poorly controlled**, can cause extensive tissue damage.
- Immunopathologies can arise from responses against:



Nonself antigens or Self antigens

PAMPs and damage/danger-associated molecular patterns (DAMPs)

Terminology

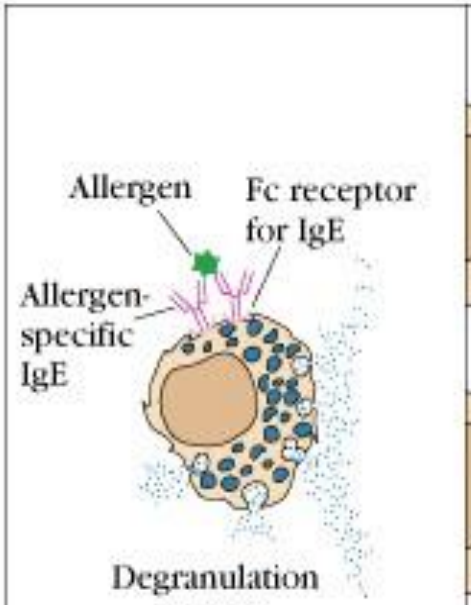
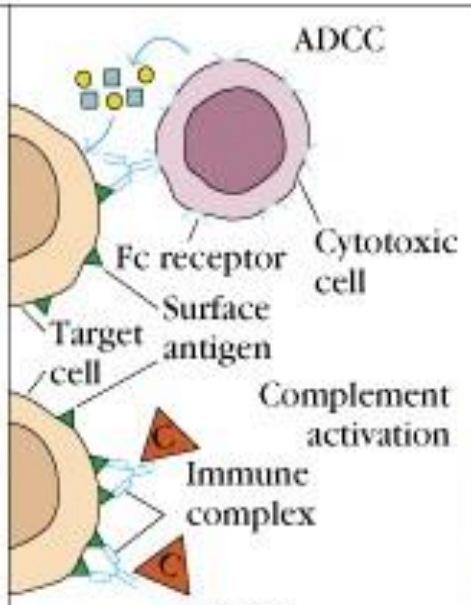
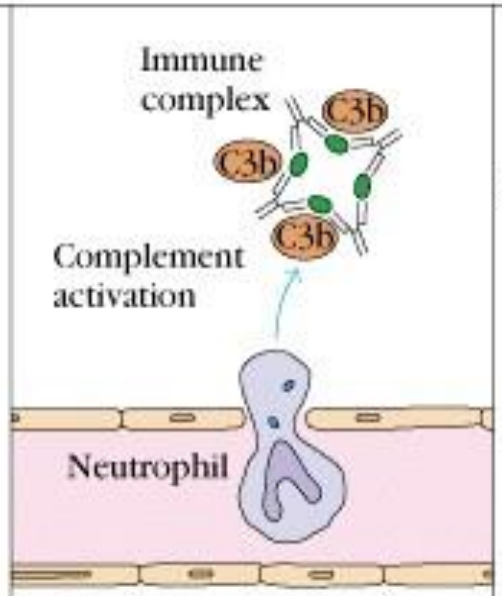
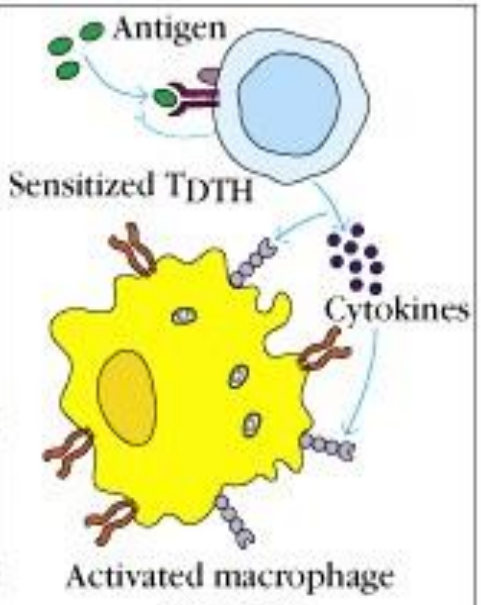
- Hypersensitivity.
  Immediate
  Delayed
- Allergy
- Anaphylaxis
- Allergen
- Allergins
- Wheal and flare reaction (red and swollen)
- Asthma
- Atopy Dermatitis
- Mast cells and Basophils

- Hapten
- Desensitization
- Antibody-dependent cell-mediated cytotoxicity (ADCC)
- Graves disease
- Goodpasture's syndrome
- Immune complex disease (ICD)
- Arthus reaction
- Serum Sickness
- Contact hypersensitivity
- Tuberculin type hypersensitivity
- Granulomatous hypersensitivity

Overview of Hypersensitivity

- There are two categories and four types of hypersensitivities.
- Categories are based on the speed of a reaction
- **Immediate**
  - Antibody mediated
- **Delayed**
  - T cell mediated
- All hypersensitivity reactions are **secondary** responses

Hypersensitivity Gell and Coombs Classification

 **Type I**	 **Type II**	 **Type III**	 **Type IV**
IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
Ag induces crosslinking of IgE bound to mast cells and basophils with release of vasoactive mediators	Ab directed against cell surface antigens meditates cell destruction via complement activation or ADCC **or phagocytosis**	Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils	Sensitized T_{DTH} cells release cytokines that activate macrophages or T_C cells which mediate direct cellular damage
Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema	Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia	Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulnephritis, rheumatoid arthritis, and systemic lupus erythematosus	Typical manifestations include contact dermatitis, tubercular lesions and graft rejection

Type I Hypersensitivity

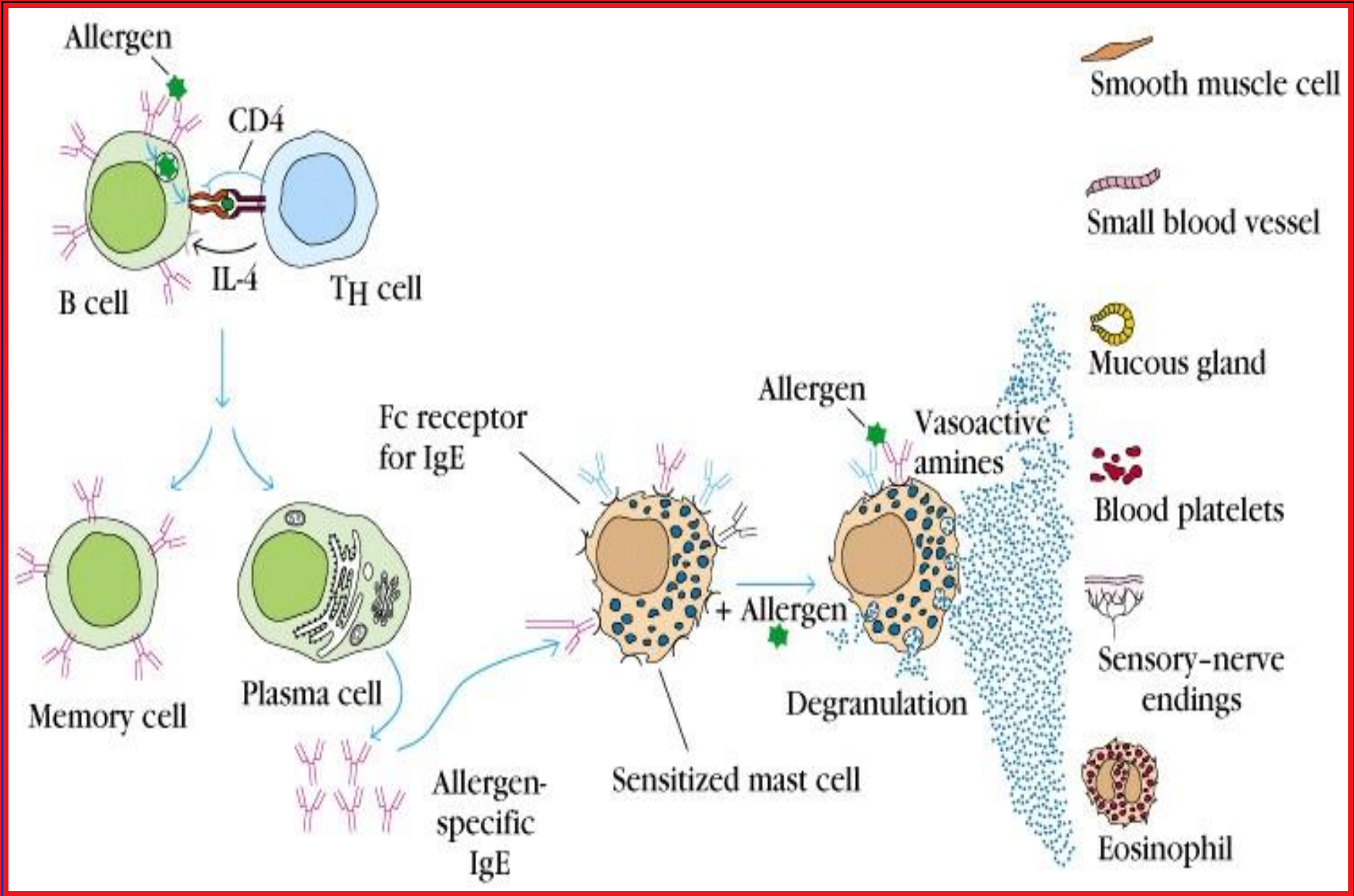
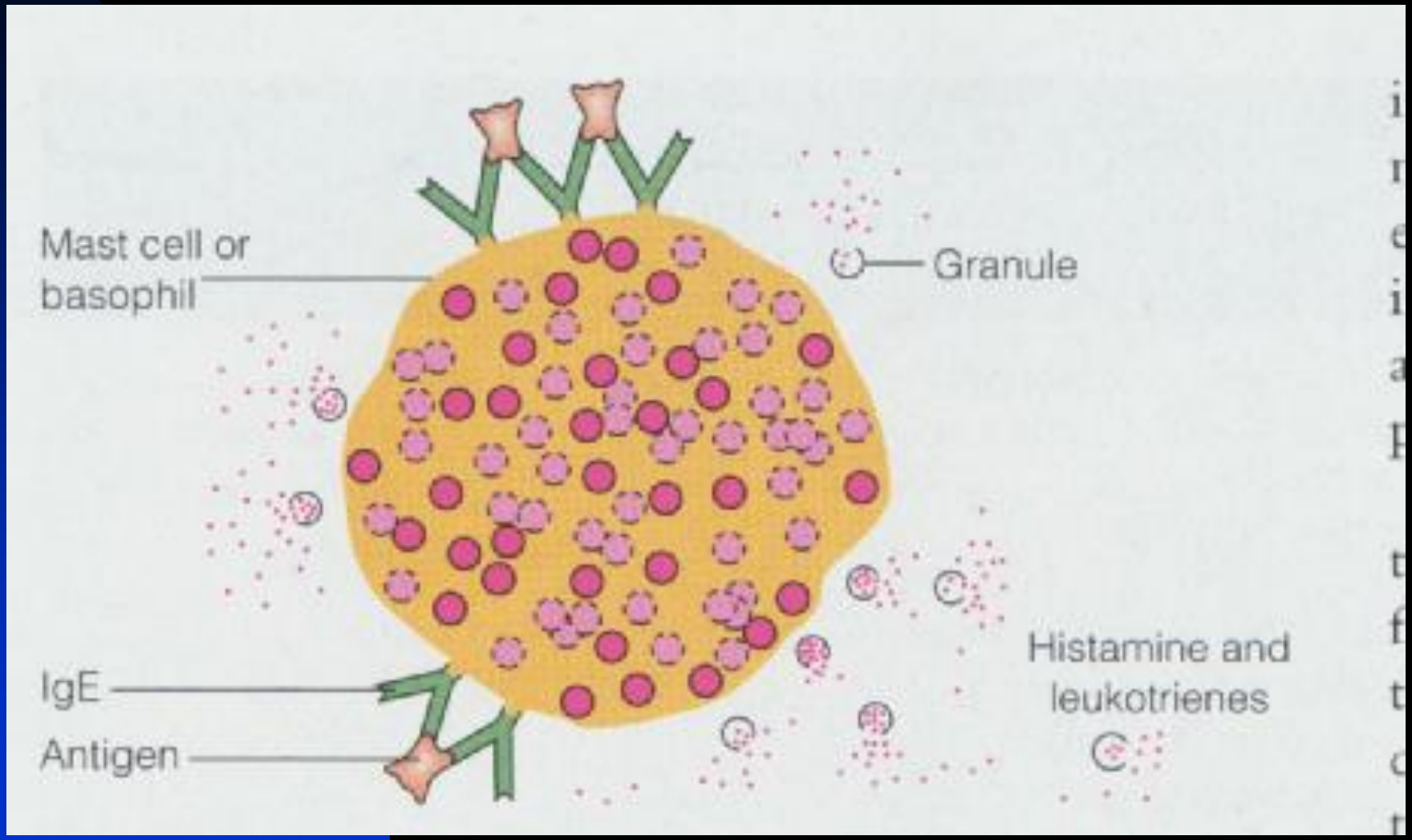


Figure 13-5 part 1 of 2 Immunobiology, 7ed. (© Garland Science 2008)

Type I anaphylactic reactions



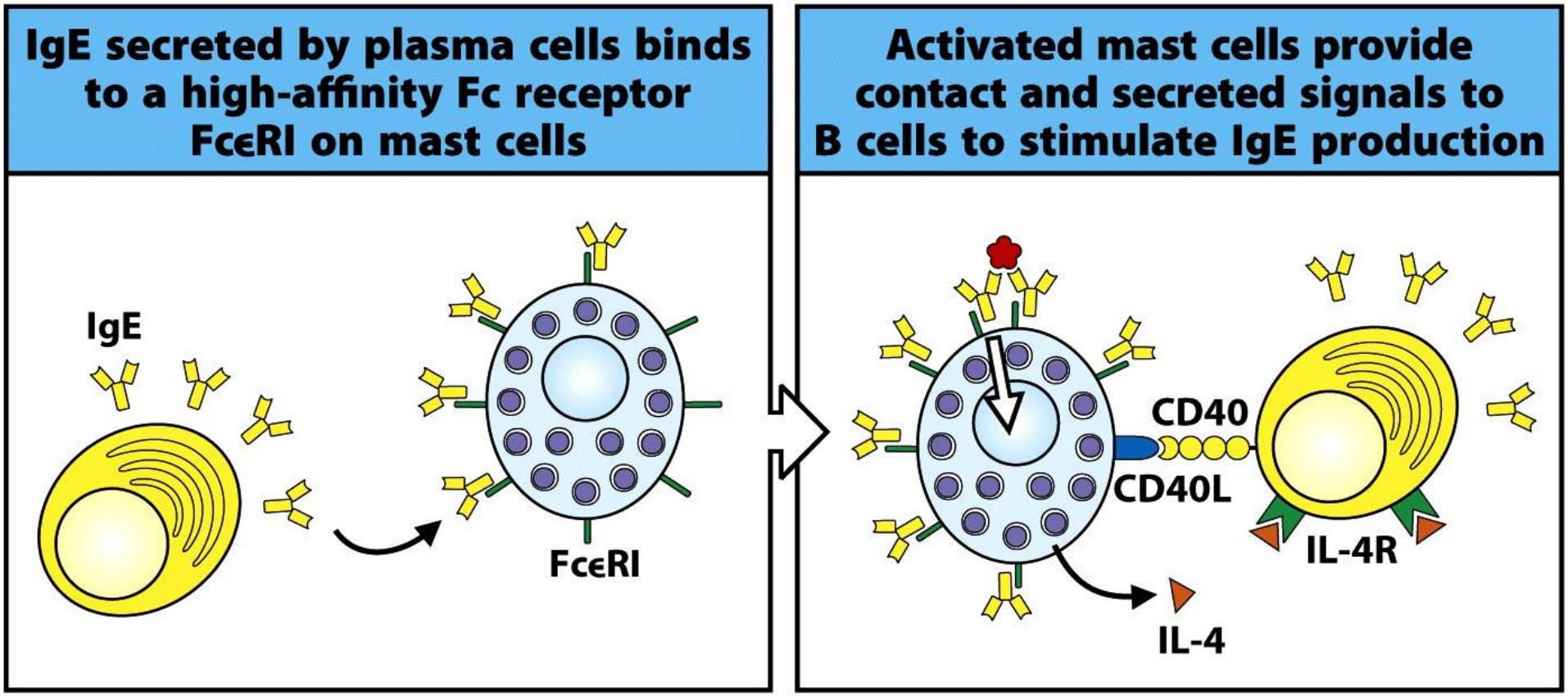


Figure 13-6 Immunobiology, 7ed. (© Garland Science 2008)

What makes these agents allergens? Chemistry? Mimicry? Adjuvant?

Why are some pollens allergenic while others (e.g. pine) are not?

Why are some people allergic?

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

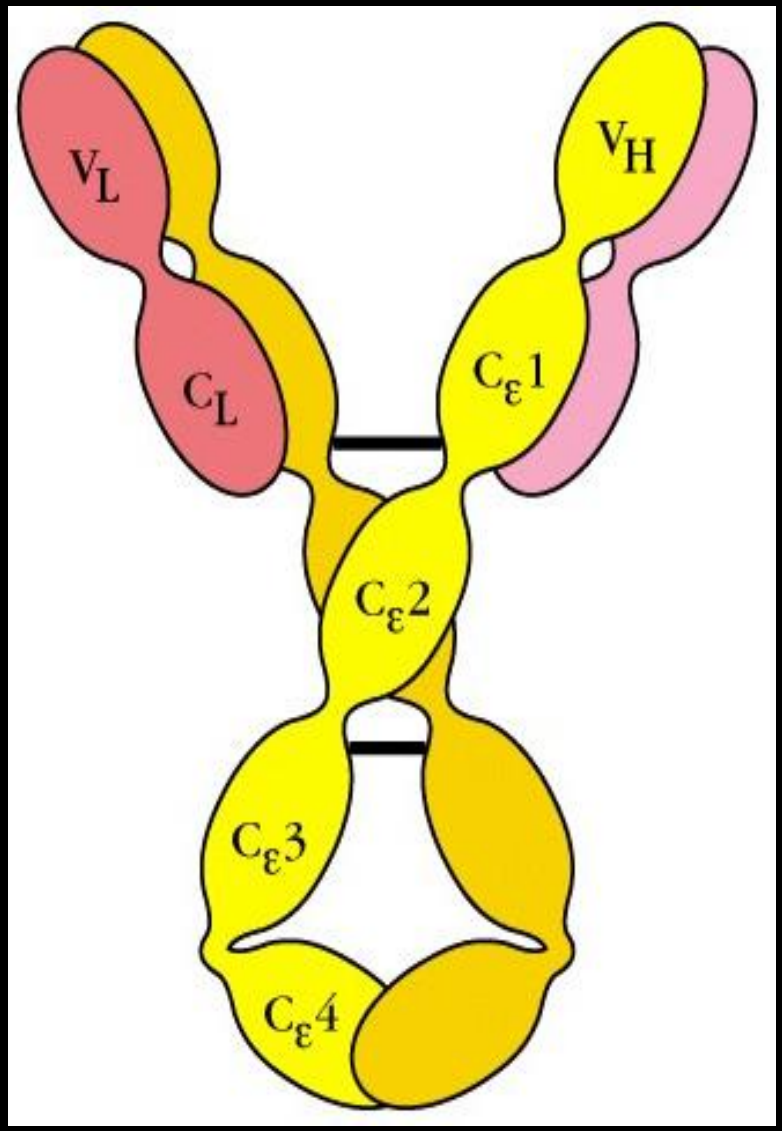
Fun fact(e.g.): square mile of ragweed produces 16 tons of pollen per season.

Atopy

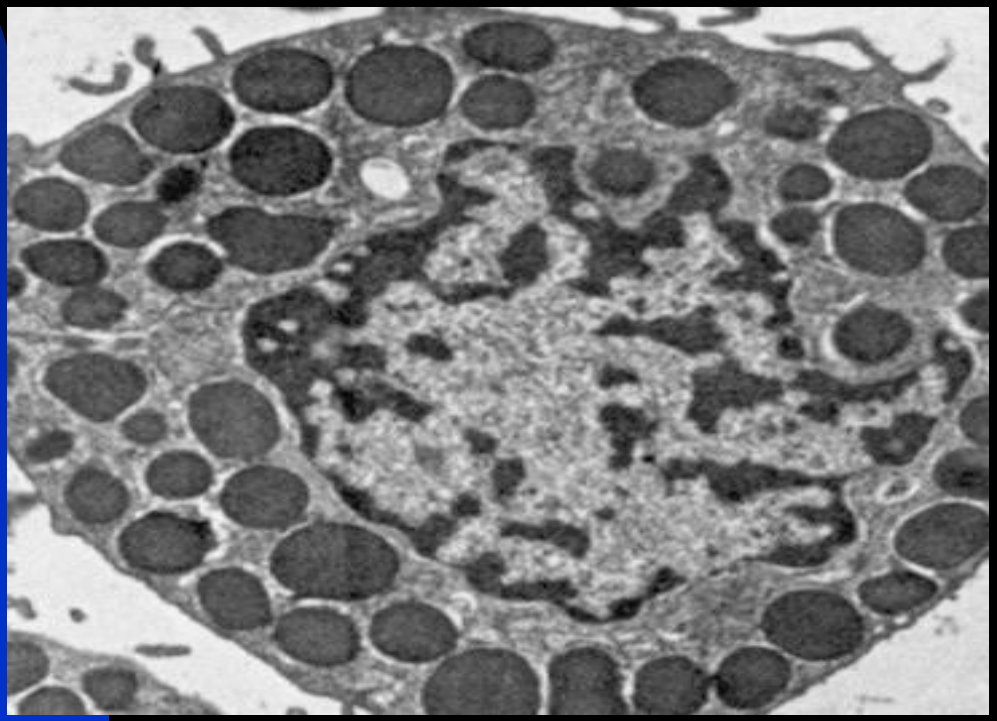
- Hereditary predisposition to HS reactions against environment antigens. (nonparasitic antigens) IgE.
- Increased: IgE , eosinophils, hay fever,
- eczema, asthma.
- Genetic basis:
  - Locus for cytokines
  - Locus for beta chain of high affinity IgE receptor
  - HLA?

IgE, Mast Cells and Basophils.

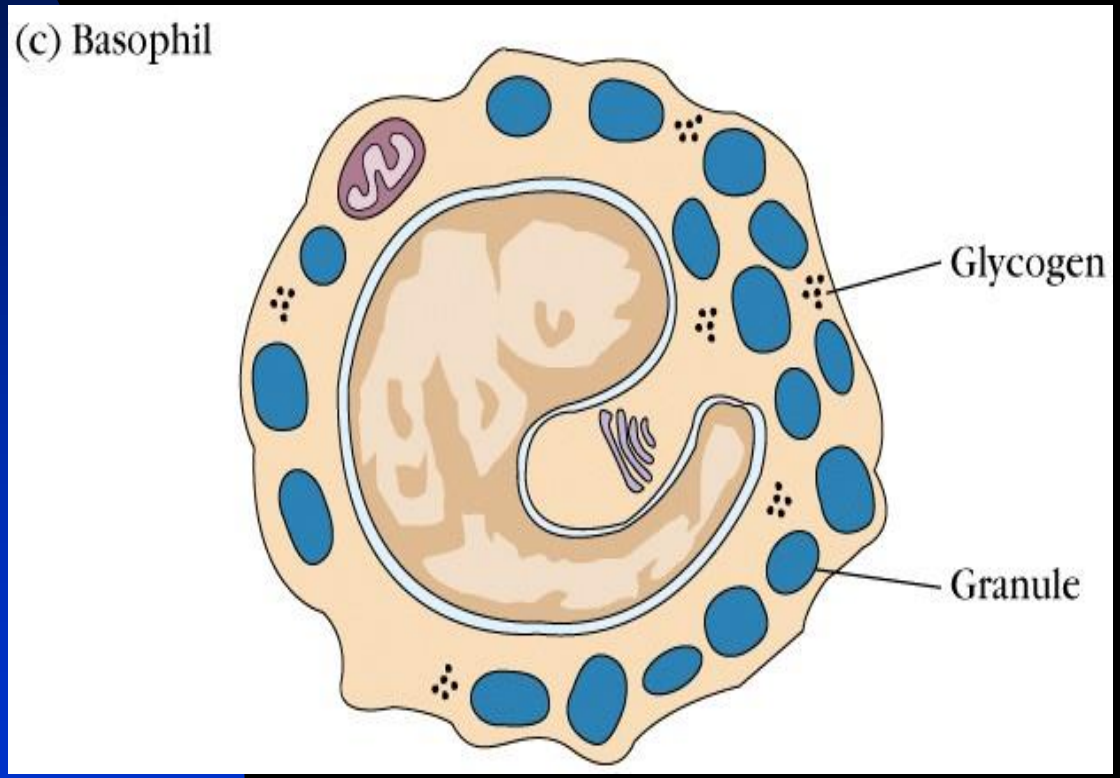
- IgE: 190.000 kd
- Fc receptor for IgE.



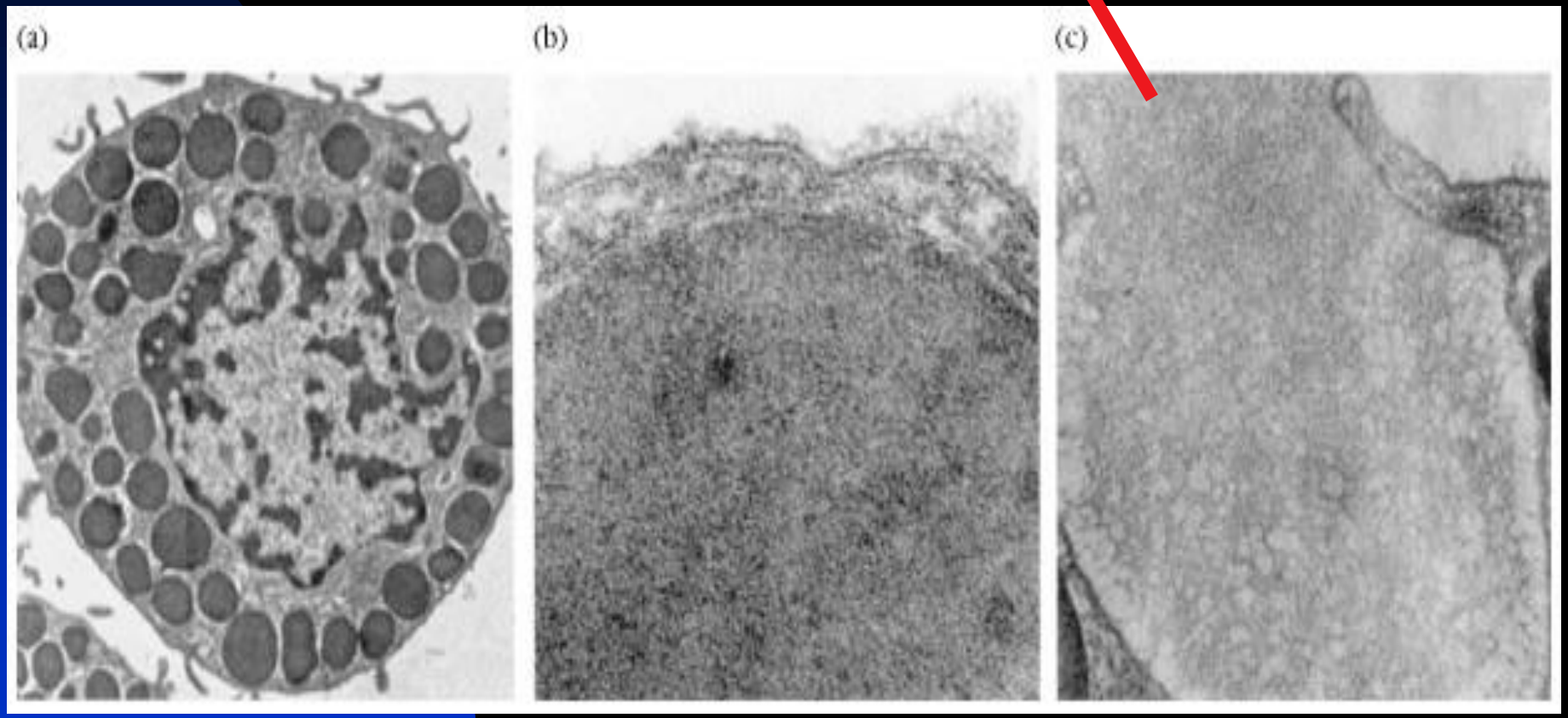
- **Mast cells in Tissues**
  - Near blood and lymph vessels
  - Mucous membranes.
    - 10,000 per mm^3 in skin.
  - Cytokine producers



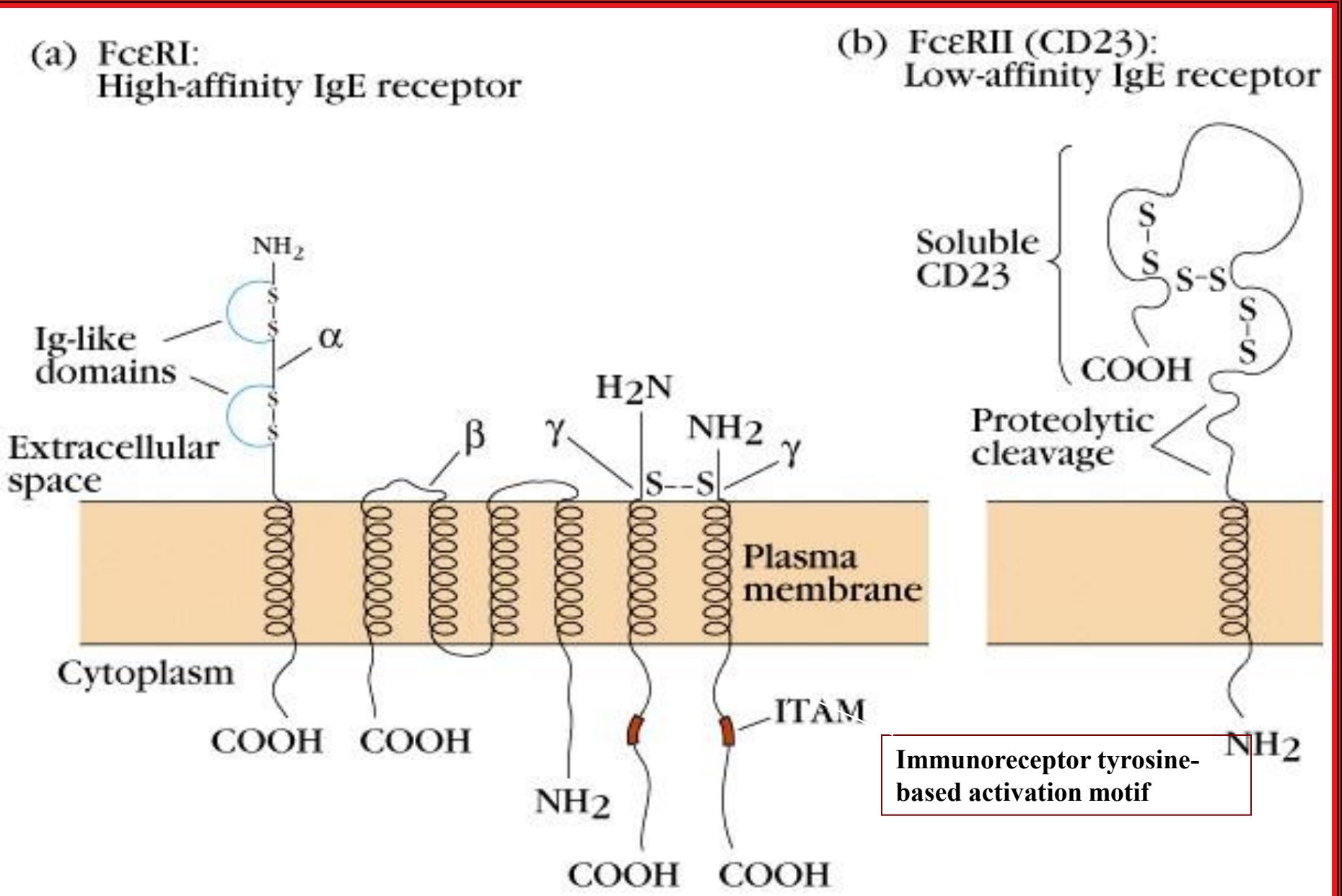
- **Basophils in blood.**
  - **(1% WBCs)**
  - **Stain with basic dyes, granules.**



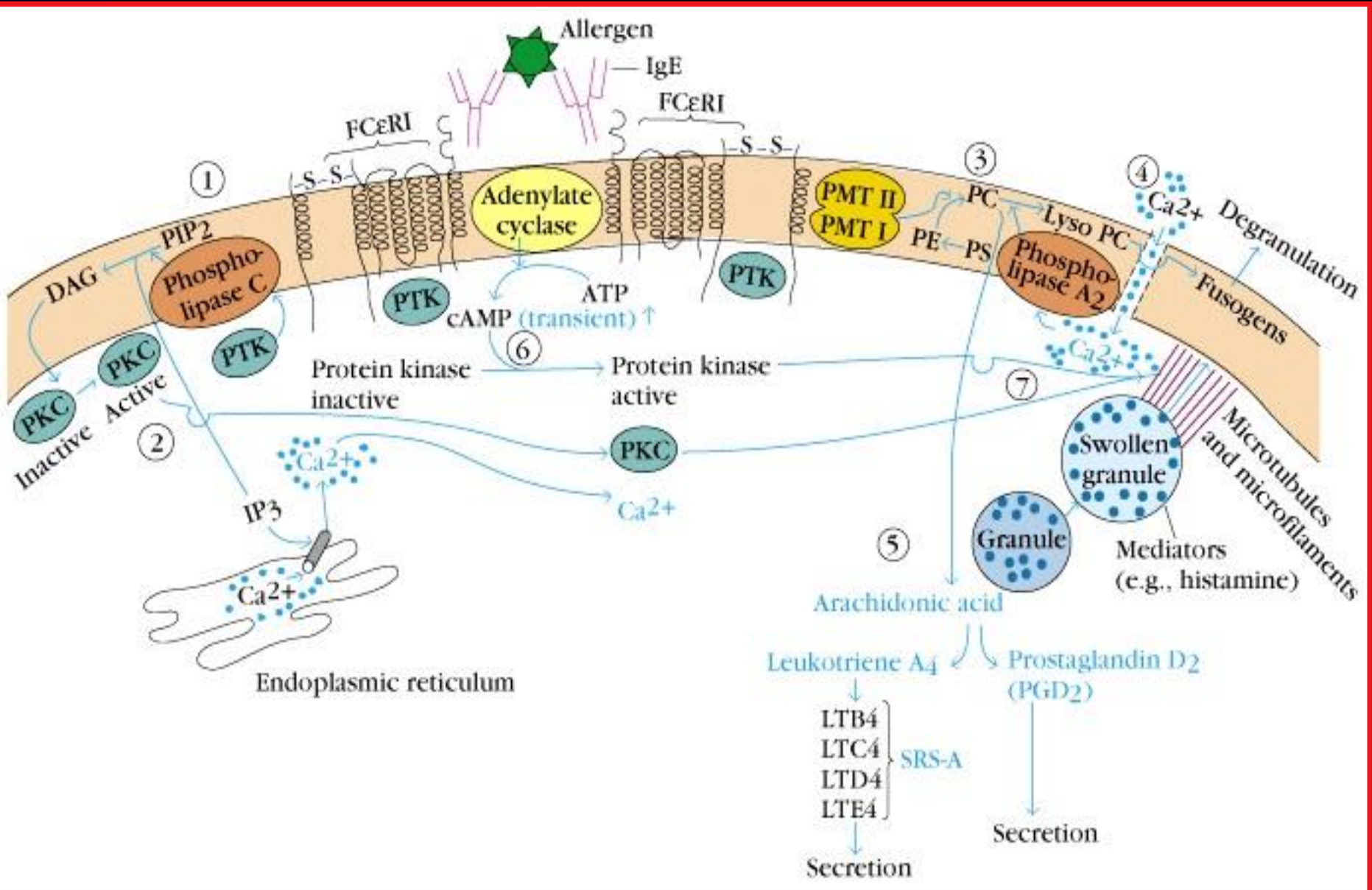
Mast Cells and Degranulation

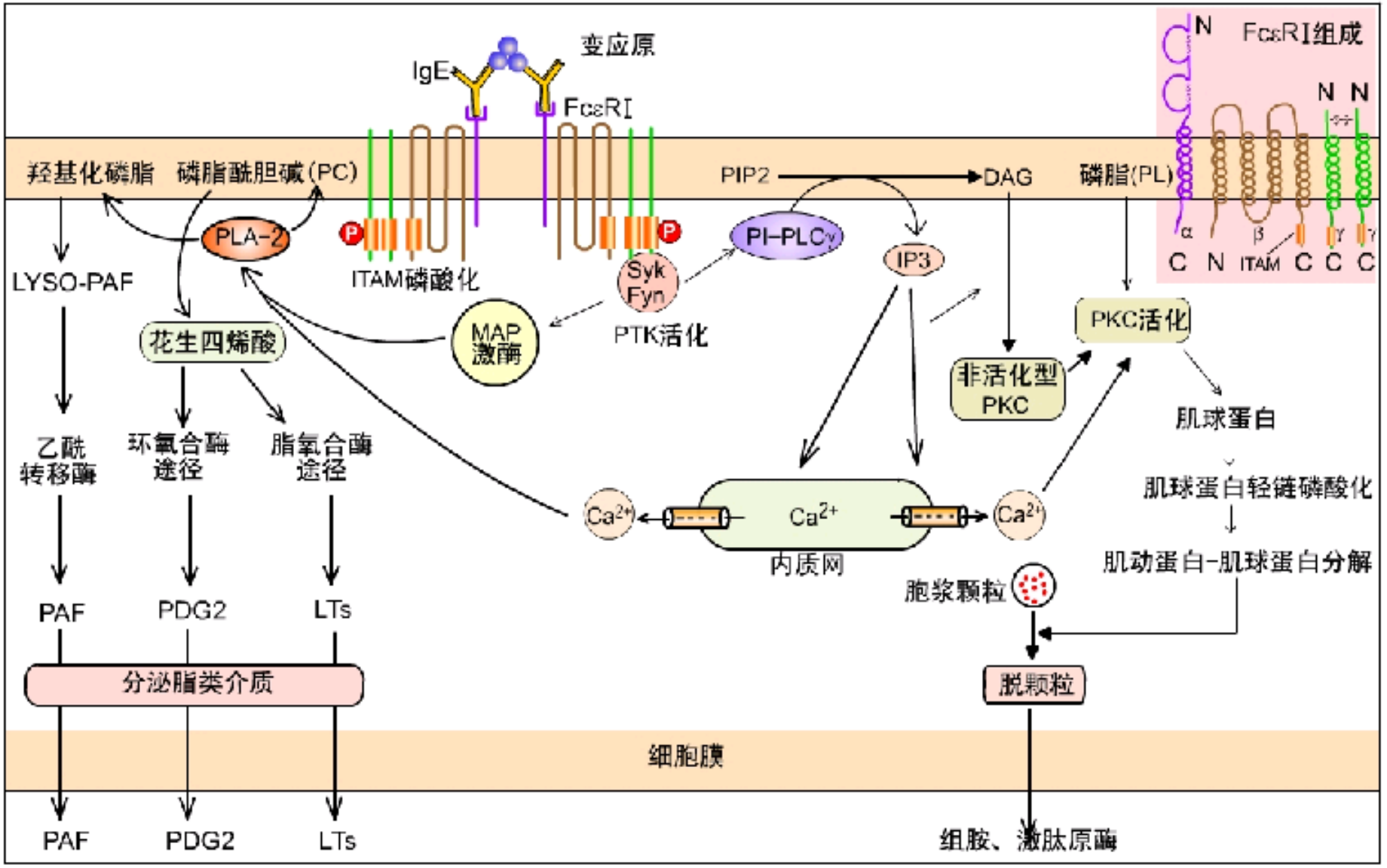


IgE Fc Receptors



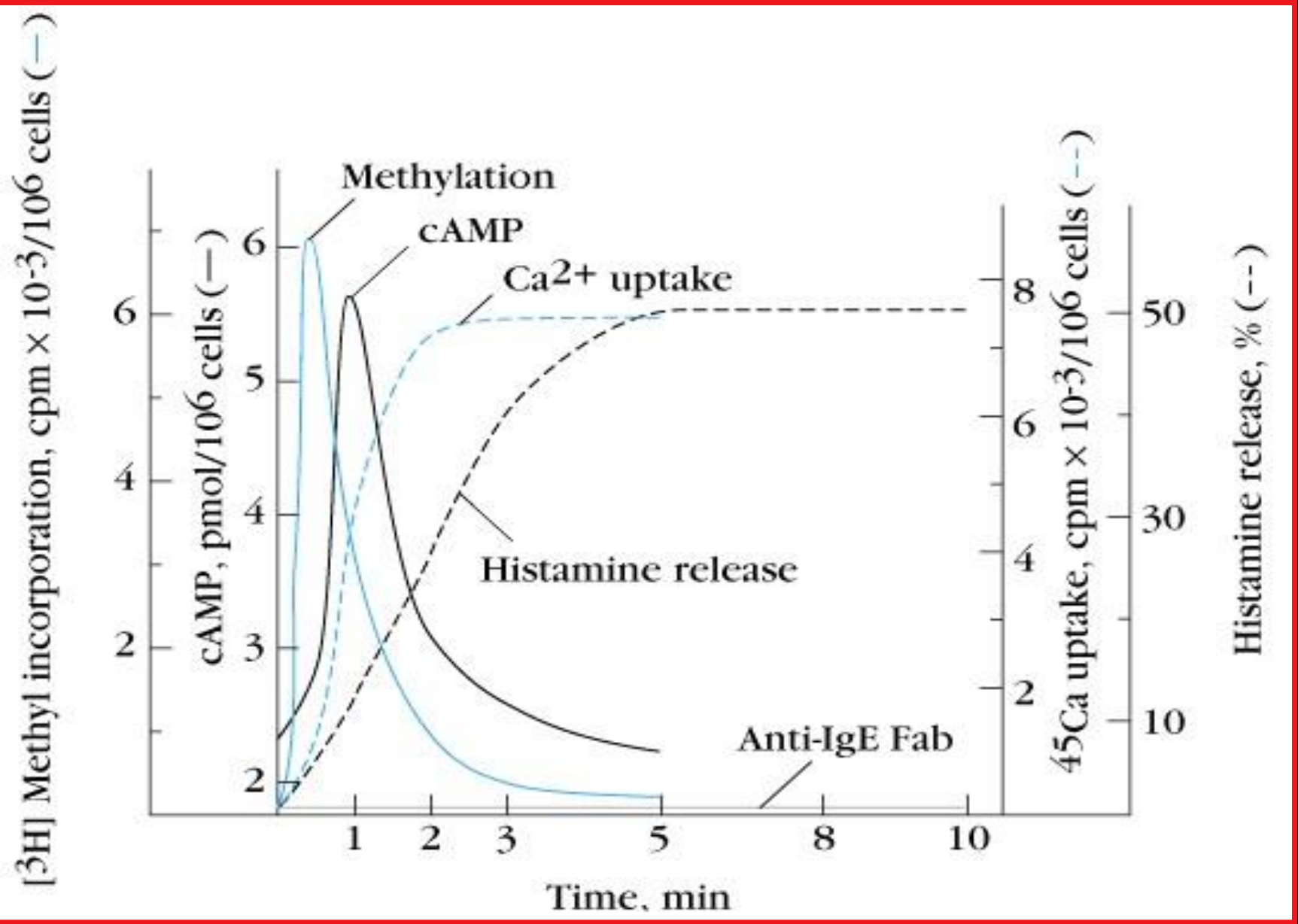
Mast cell activation & degranulation





致敏靶细胞脱颗粒、释放和合成生物活性介质机制

Mast cell activation & degranulation



Histamine

- Most of the biologic effects of histamine in allergic reactions are mediated by the binding of histamine to **H1 receptor**.
- This binding induces contraction of intestinal and bronchial smooth muscles, increased permeability of venules, and increased mucus secretion by goblet cells.

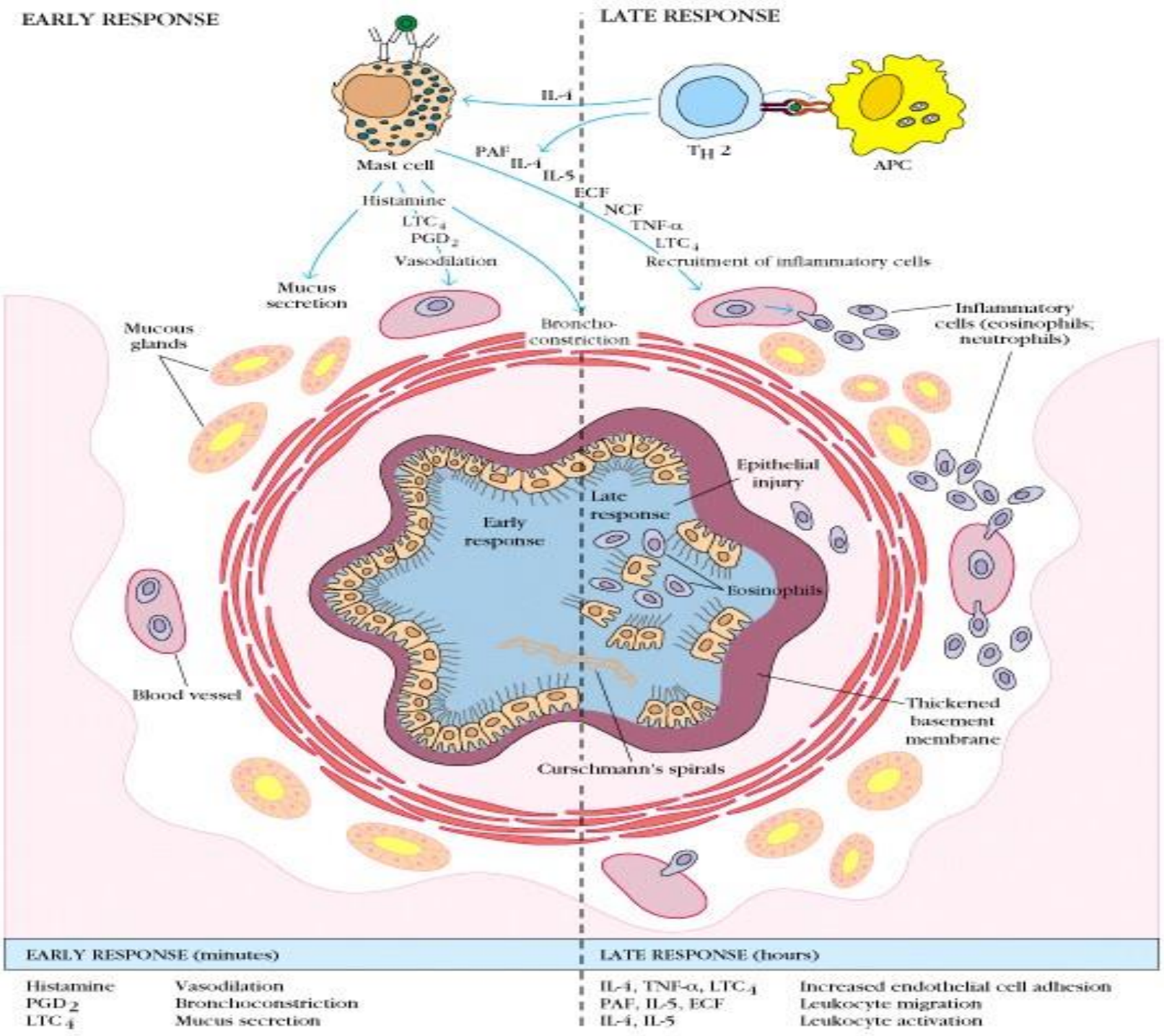
- Interaction of histamine with **H2** receptor increases vasopermeability and dilation, and stimulates exocrine glands.

- Binding of histamine to H2 receptor on mast cells and basophils **suppresses** degranulation; thus, histamine exerts **negative feedback** on the release of mediators.

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)

Early And Late



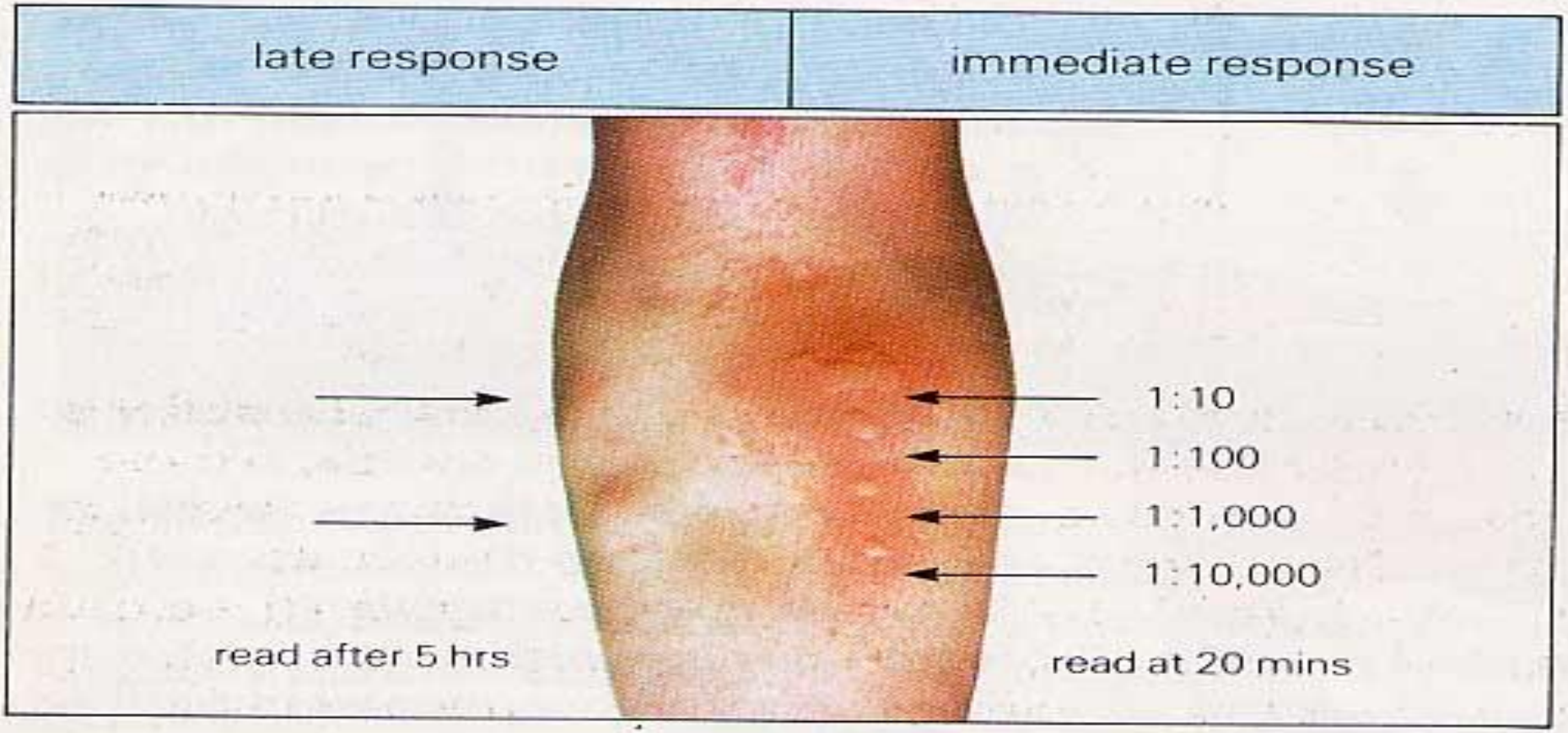


Fig.19.24 Skin prick tests with grass pollen allergen in a patient with typical summer hay fever. Skin tests were performed 5 hours (left) and 20 minutes (right) before the photograph was taken. The tests on the right show a typical end point titration of a Type I immediate wheal and flare reaction. The late phase skin reaction (left) can be clearly seen at 5 hours, especially where a large immediate response has preceded it. Figures for allergen dilution are given.

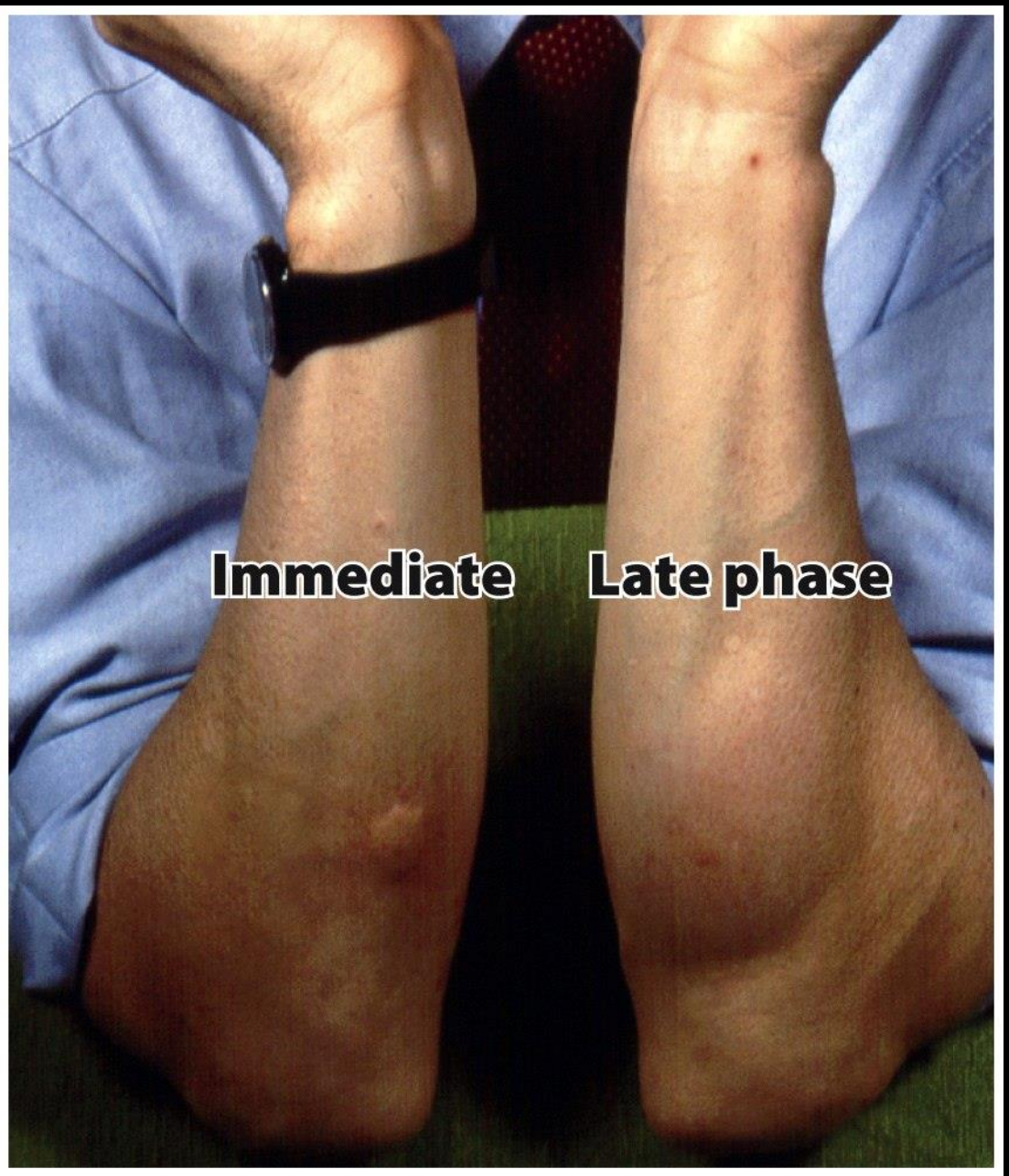


Figure 13-14 part 2 of 2 Immunobiology, 7ed. (© Garland Science 2008)

Systemic Anaphylaxis

Disseminated mast cell activation

in response to:

Direct injection of antigen (*e.g.* bee stings)

Rapid absorption of antigen from GI tract

Small molecules that modify self proteins, permitting induction of T_h response (*e.g.* penicillin)

- **Widespread vasodilation**
- **Catastrophic loss of blood pressure**
- **Constriction of airways**
- **Pulmonary edema** **DEATH**

Consequences of Type 1 Reactions

- Systemic Anaphylaxis
- Localized Anaphylaxis
  - Allergic Rhinitis or hay fever.
  - Asthma. 5% of population, 4.8 million, 2000 deaths, $12 billion
  - Increase in African-American children. Why?

    Allergic vs Intrinsic
  - Food Allergies
    - Atopic urticaria or hives
  - Atopic Dermatitis. Allergic eczema.

Therapy for Type I Hypersensitivity

- **Avoidance**
- **Anaphylactic shock treated by immediate injection of epinephrine (adrenergic receptors on smooth muscle)**
- **Antihistamines (initial phase)**
- **Corticosteroids**
- **Desensitization**
  - **Escalating allergen dosage**
  - **Induction of IgE to IgG class switch?**

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.

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	Attracts monocytes, macrophages, and neutrophils
Lipid mediator	Prostaglandins D_2, E_2 Leukotrienes B4, C4	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

Approaches to treatment of allergy

Target step	Mechanism of treatment	Specific approach
T_H2 activation	Induce regulatory T cells	Injection of specific antigen or peptides Administration of cytokines, e.g., IFN-γ, IL-10, IL-12, TGF-β Use of adjuvants such as CpG oligodeoxynucleotides to stimulate T_H1 response
Activation of B cell to produce IgE	Block co-stimulation Inhibit T_H2 cytokines	Inhibit CD40L Inhibit IL-4 or IL-13
Mast-cell activation	Inhibit effects of IgE binding to mast cell	Blockade of IgE receptor
Mediator action	Inhibit effects of mediators on specific receptors Inhibit synthesis of specific mediators	Antihistamine drugs Lipooxygenase inhibitors
Eosinophil-dependent inflammation	Block cytokine and chemokine receptors that mediate eosinophil recruitment and activation	Inhibit IL-5 Block CCR3

Treg:
nTreg,
iTreg

Figure 13-25 Immunobiology, 7ed. (© Garland Science 2008)

Type II Hypersensitivity Reactions

- Initiated by IgG binding to cell surface or extracellular matrix molecules.
- Three different effector mechanisms.
- Activation of complement
  - Direct cell lysis via membrane attack complex
  - Susceptibility to phagocytosis

Local inflammatory responses

Examples include: transfusion reactions, drug binding to red blood cell membranes, Rh reaction in **Rh^- mothers**.

- **Antibody-dependent cell-mediated cytotoxicity (ADCC)**
  - **Effector cells expressing Fc receptors: neutrophils, eosinophils, macrophages, natural killer cells (NK)**
- **Anti-receptor Ab, Autoimmune reactions**

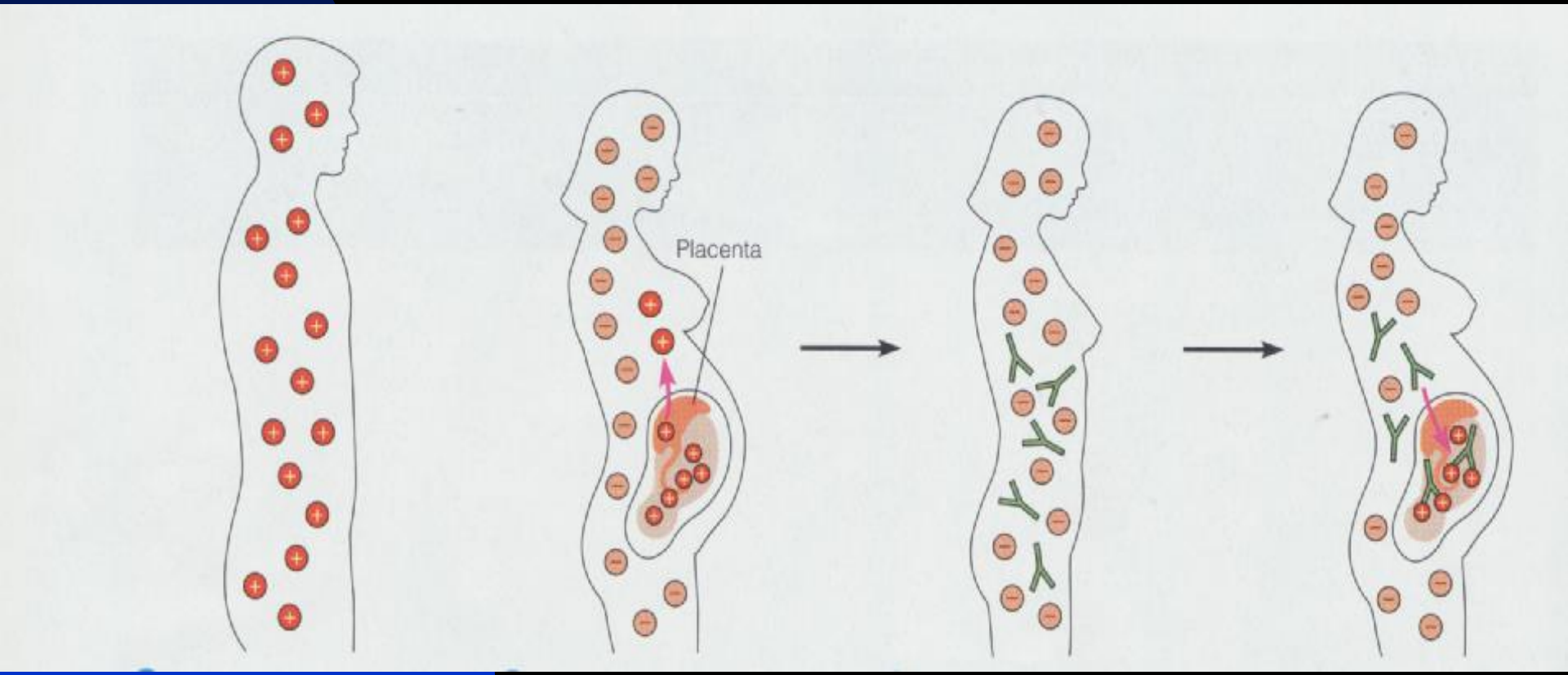
Type II cytotoxic reactions

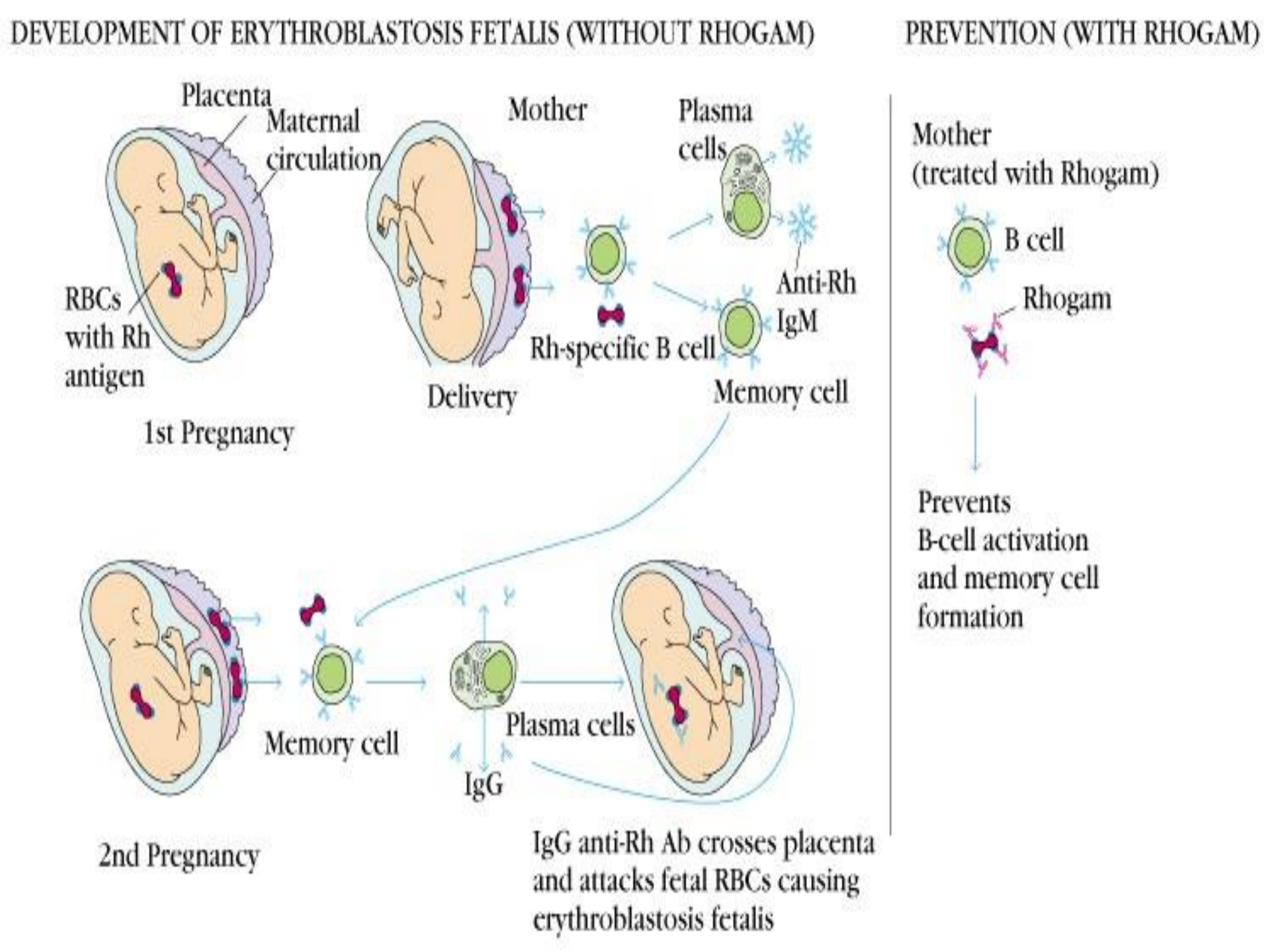
- ABO blood groups

Blood group	Blood cell antigen	Plasma Antibody	Can receive
AB	A and B	Neither	A, B, AB, O
B	B	Anti A	B, O
A	A	Anti B	A, O
O	None	Anti A and Anti B	O

Type II cytotoxic reactions

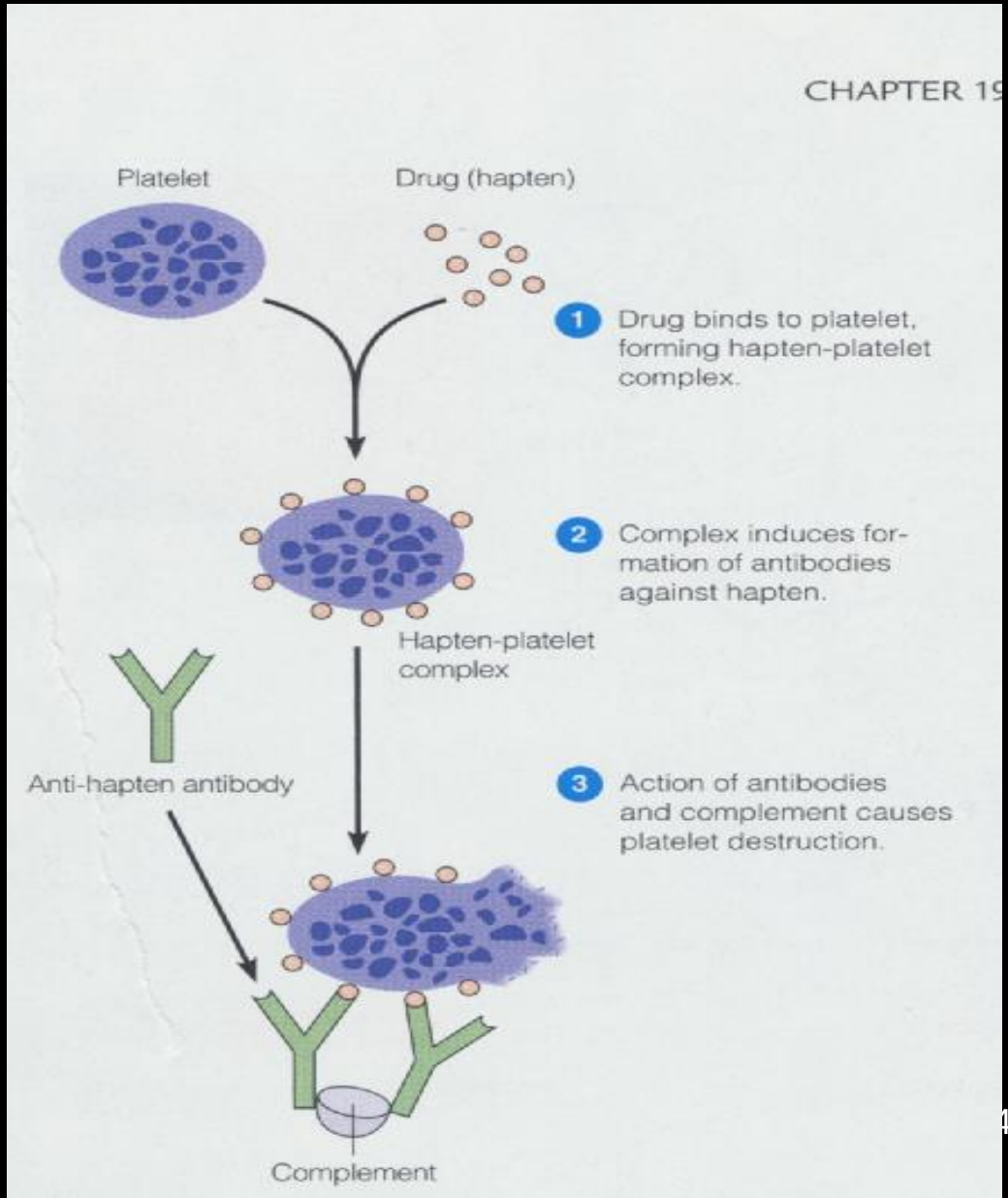
- Hemolytic disease of the newborn




DEVELOPMENT OF ERYTHROBLASTOSIS FETALIS (WITHOUT RHOGAM)
PREVENTION (WITH RHOGAM)
Placenta
Maternal circulation
RBCs with Rh antigen
1st Pregnancy
Mother
Delivery
Plasma cells
Anti-Rh IgM
Rh-specific B cell
Memory cell
Memory cell
Plasma cells
IgG
2nd Pregnancy
IgG anti-Rh Ab crosses placenta and attacks fetal RBCs causing erythroblastosis fetalis
Mother (treated with Rhogam)
B cell
Rhogam
Prevents B-cell activation and memory cell formation

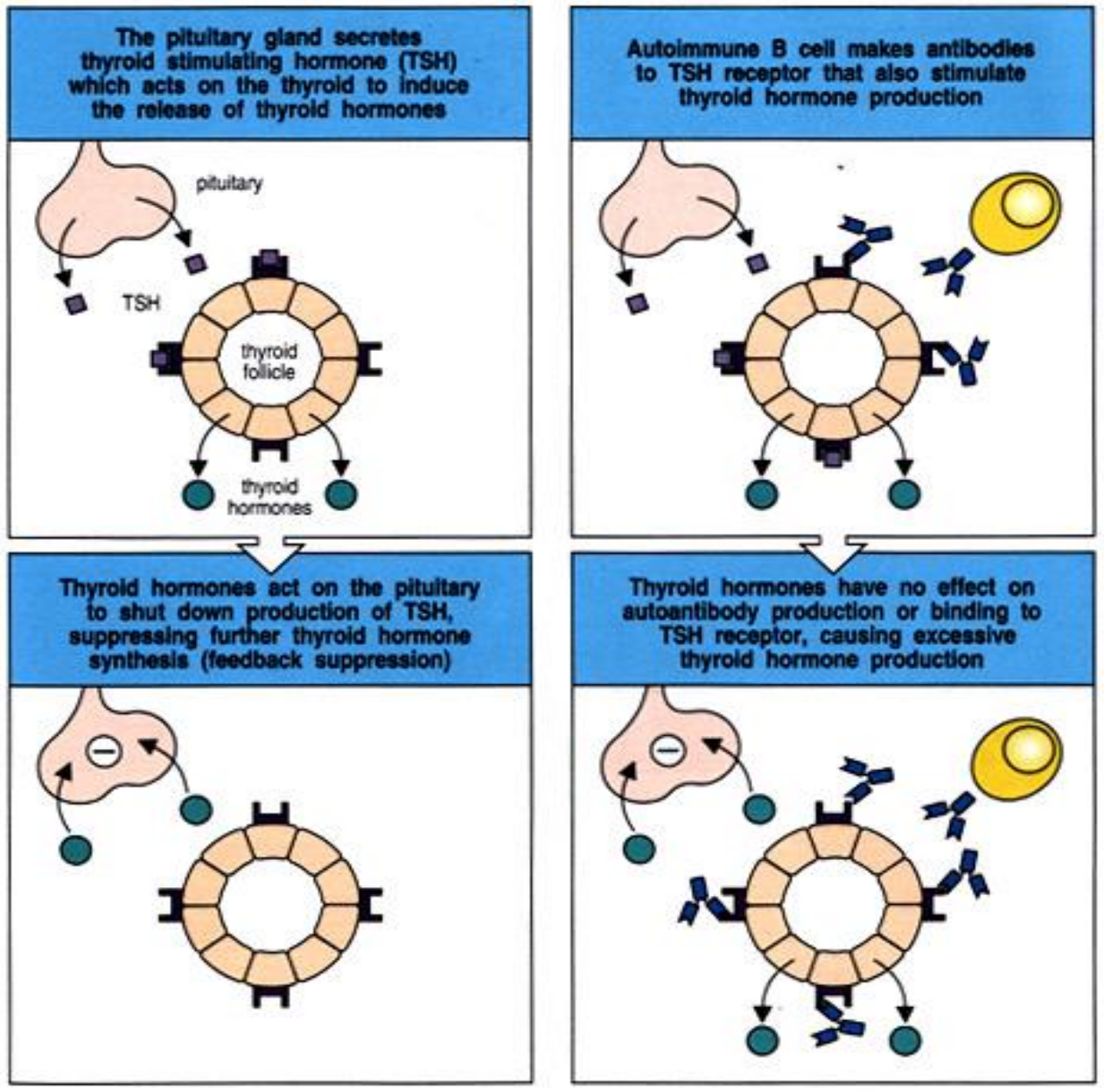
Type II cytotoxic reactions

- **Drug-induced cytotoxic reactions**



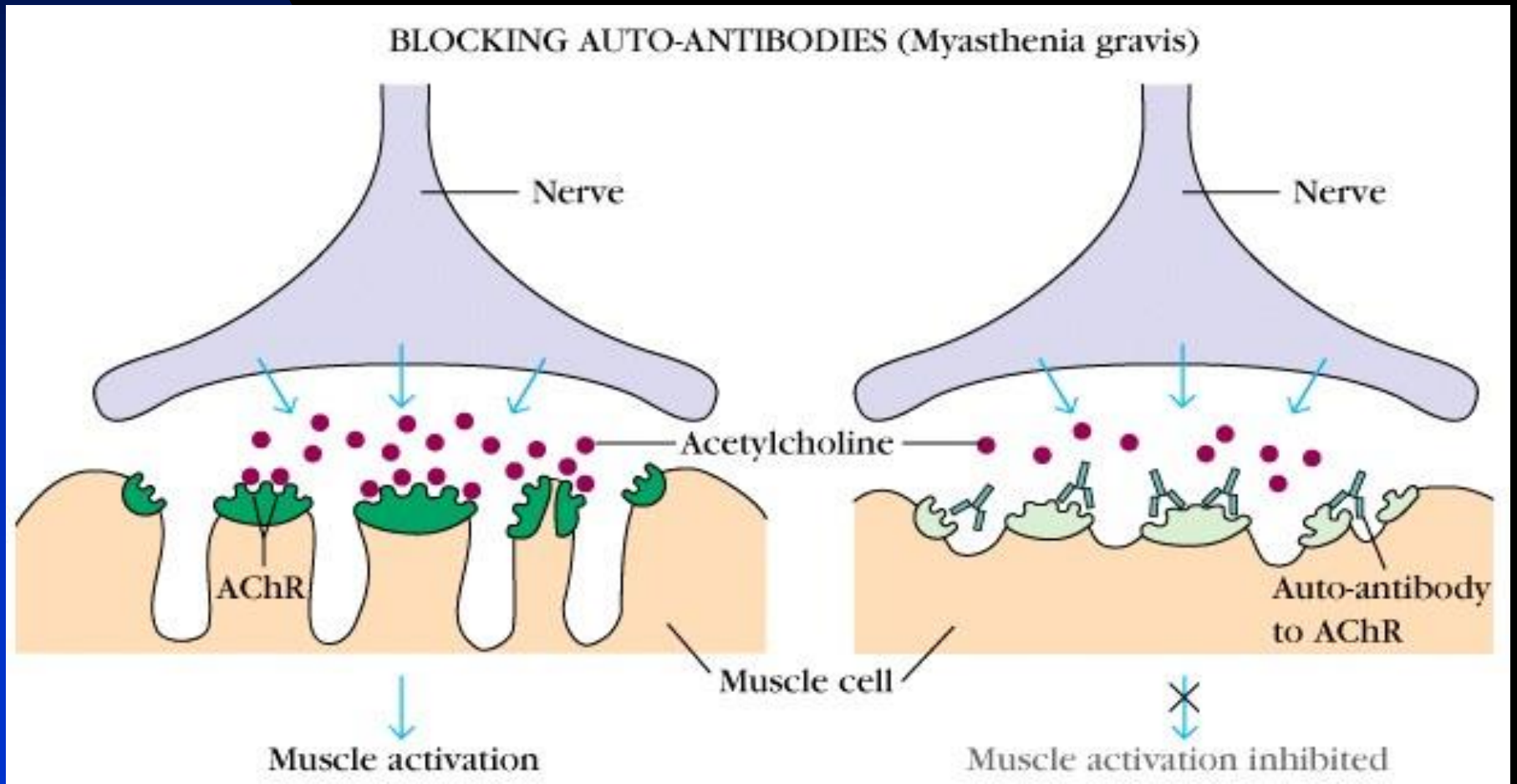
Graves' Disease :A type II hypersensitivity reaction involving receptor binding

- Antibodies to thyroid stimulating hormone (TSH) receptor stimulate thyroid hormone production.
- Block of TSH feedback inhibition
- Result is excessive thyroid hormone production



Myasthenia Gravis:A type II hypersensitivity reaction involving receptor binding

- Autoantibodies to chain of acetylcholine receptor found at neuromuscular junction block neuromuscular transmission. Antibodies also drive degradation of AChR. Patients develop progressive weakness and eventually die.

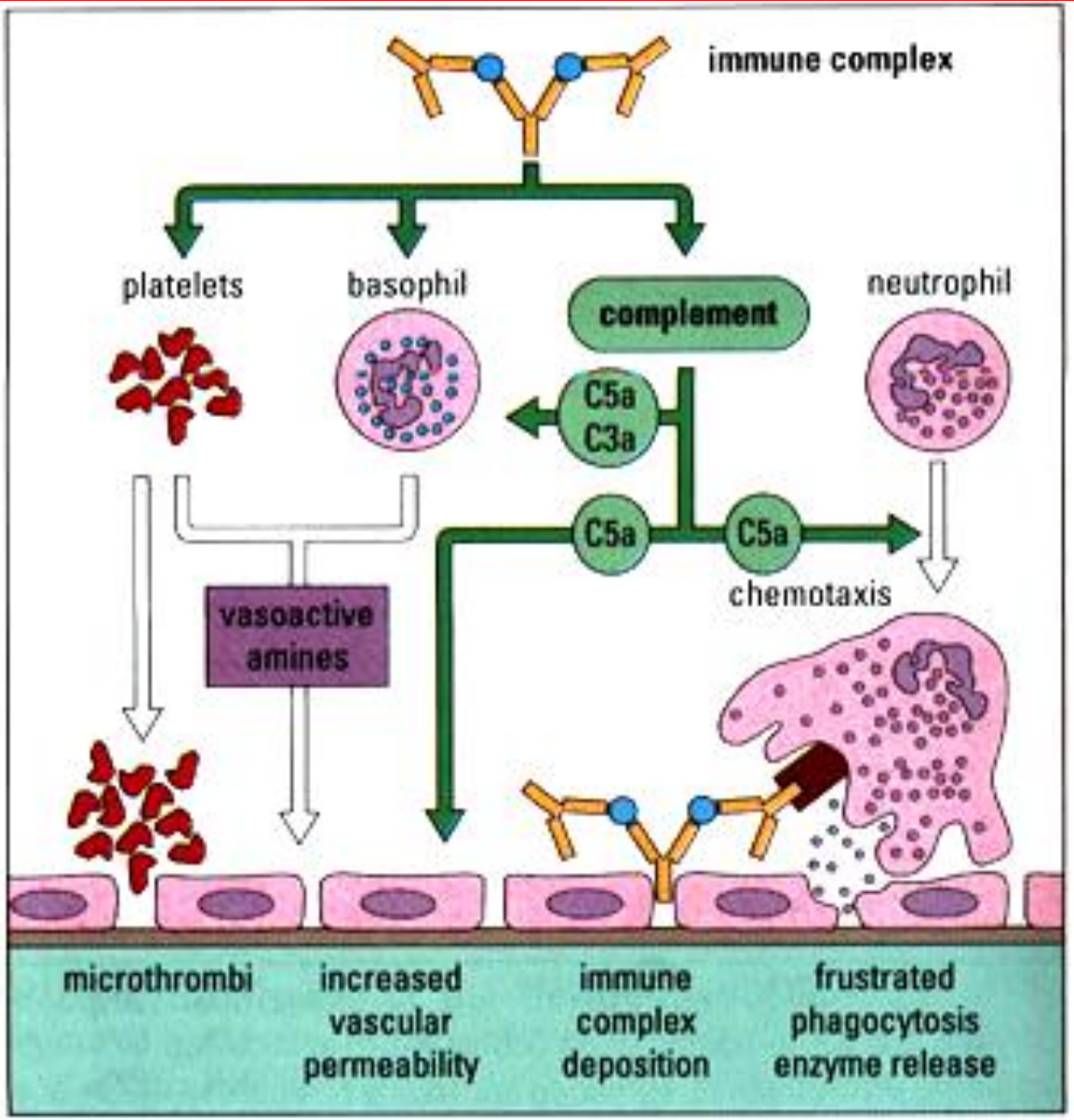


Type III - Immune Complex Disease

Syndrome	*Autoantigen*	*Consequence*
Post-streptococcal glomerulonephritis	Streptococcal antigen	Transient nephrotic syndrome
Polyarteritis nodosa	Hepatitis B surface antigen	Systemic vasculitis
Systemic lupus erythematosus (SLE)	DNA, histones, ribosomes, etc.	Glomerulonephritis, vasculitis, arthritis

Type III Hypersensitivity

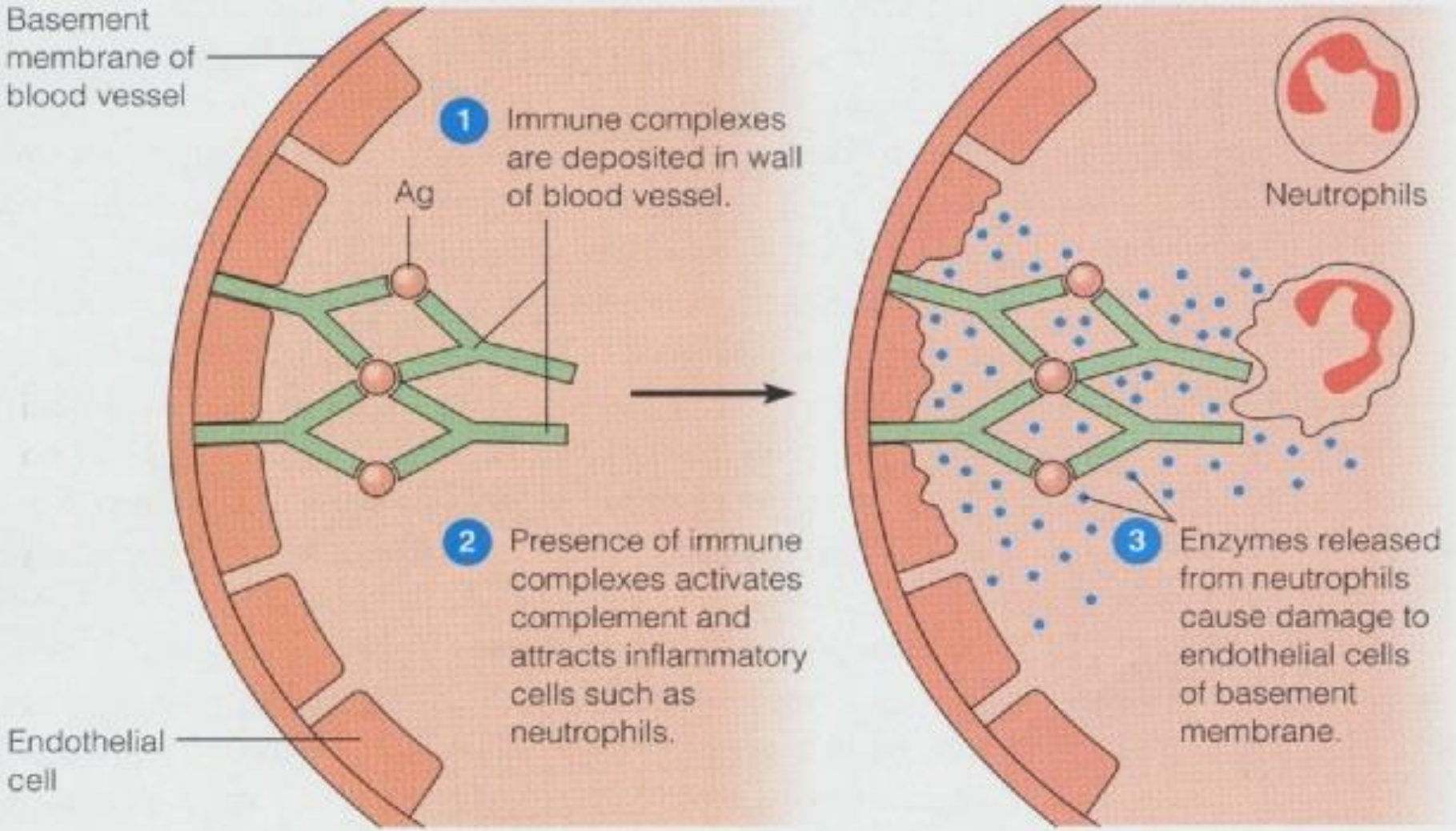
- Allergen is soluble.
- Lots of it.
- Immune complex
- mediated
  - Activate platelets (in man) and basophils via Fc receptors, followed by release of vasoactive amines



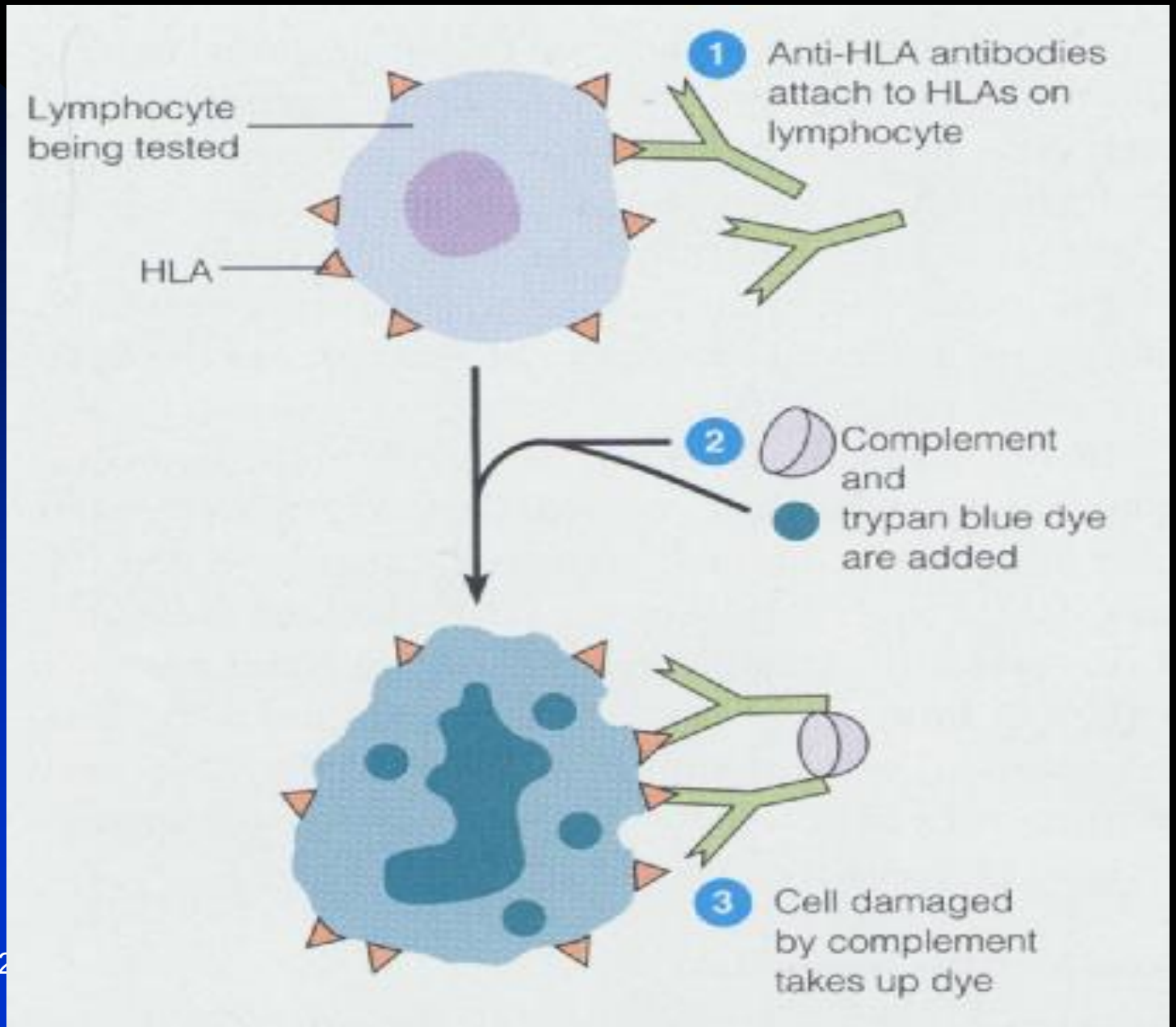
- Activate complement, releasing C3a and C5a, which activate basophils, and attract **neutrophils** (C5a)

- **Examples**
  - Serum sickness following antibody treatment
  - Autoimmune reactions (*e.g.* arthritis, nephritis)
  - Farmers lung etc.

Type III immune complex reactions

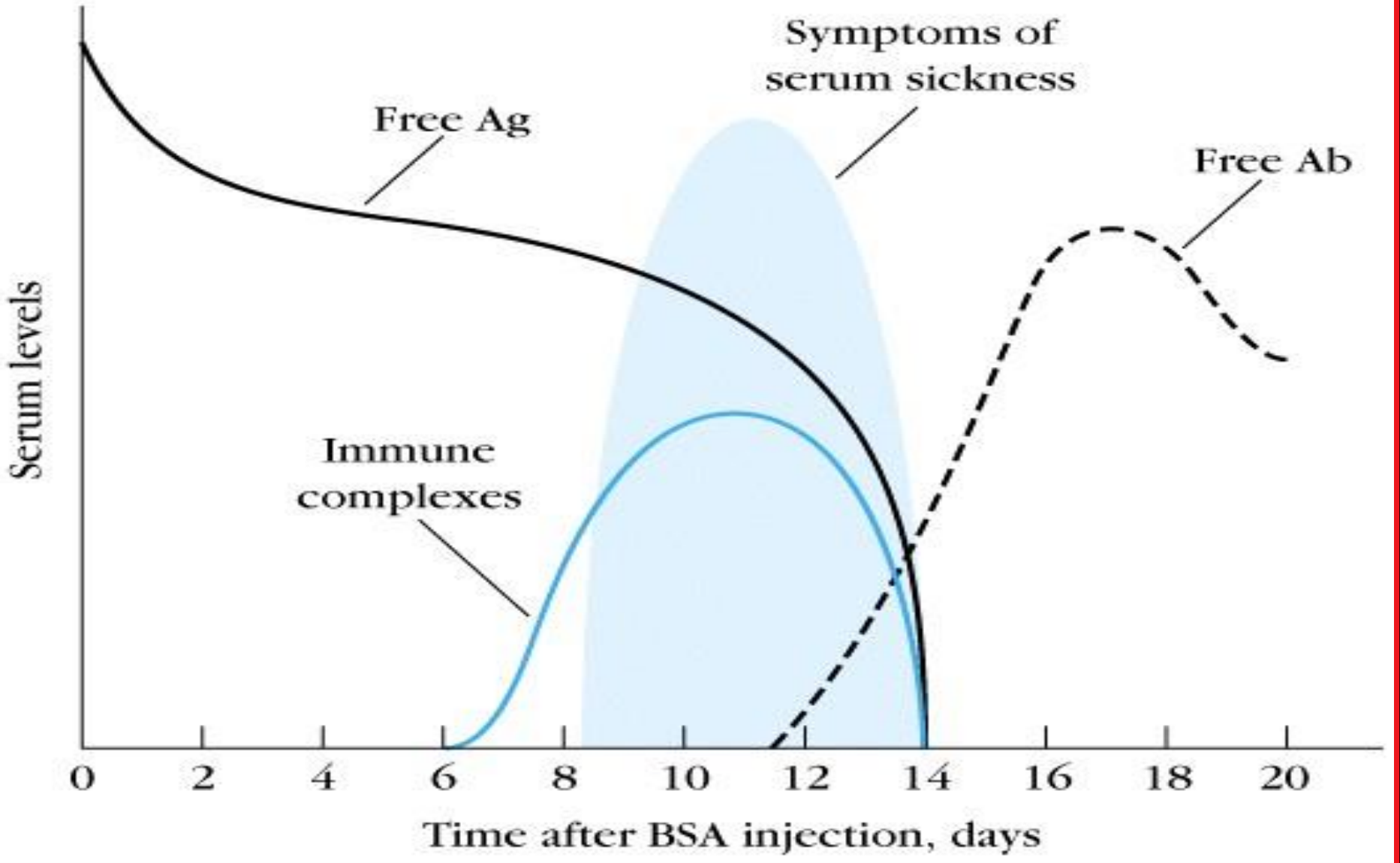


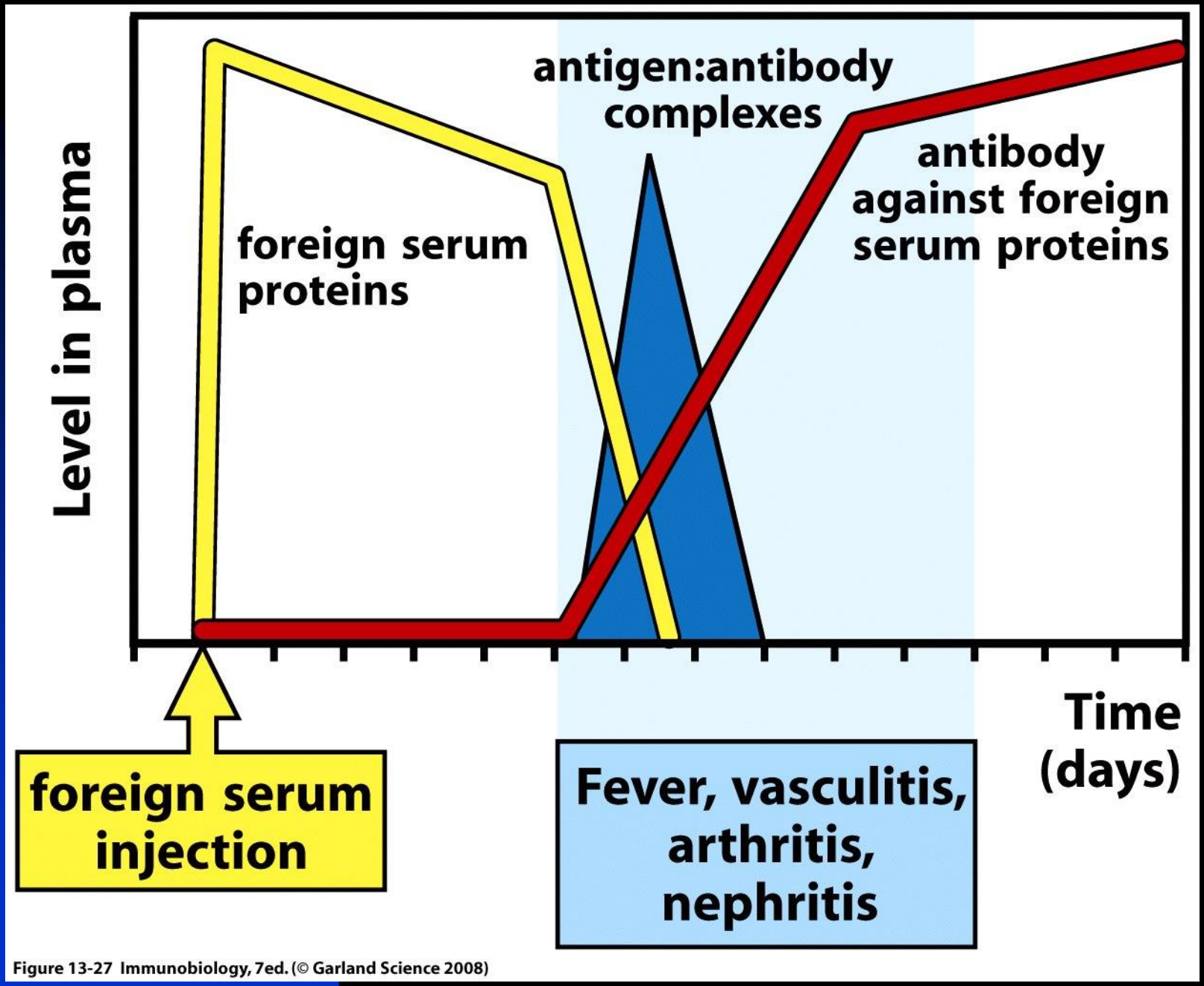
HLA complex


Lymphocyte being tested
HLA
1 Anti-HLA antibodies attach to HLAs on lymphocyte
2 Complement and trypan blue dye are added
3 Cell damaged by complement takes up dye

Localized and Generalized

Type III reactions: Arthus reaction, Serum Sickeness.





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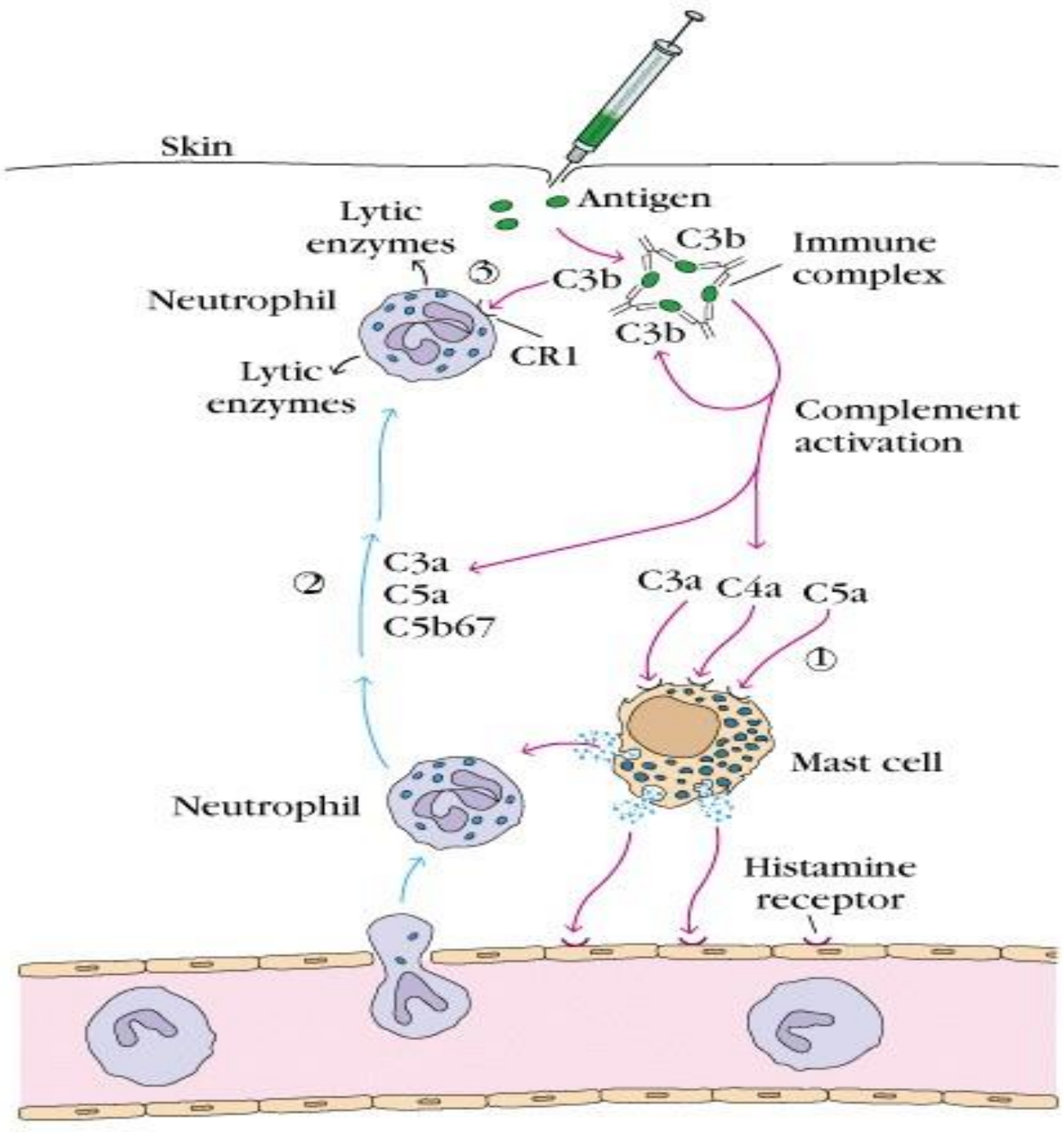
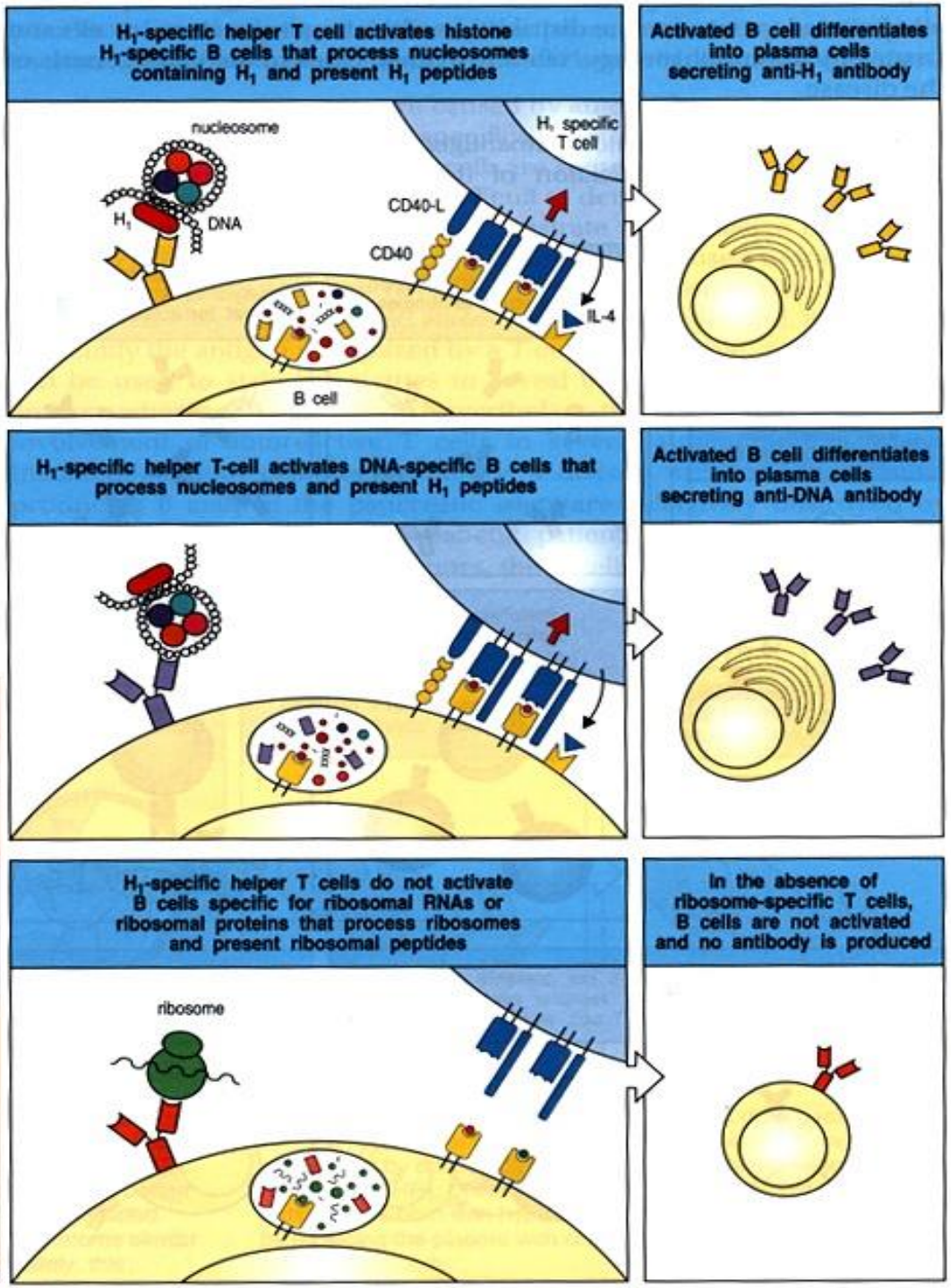

Skin
Antigen
Lytic enzymes
C3b
Immune complex
③
C3b
Neutrophil
C3b
CR1
Lytic enzymes
Complement activation
②
C3a
C5a
C5b67
C3a
C4a
C5a
①
Mast cell
Neutrophil
Histamine receptor

Systemic Lupus Erythematosus (SLE)

- Multiple B cells with different specificities can receive help from
- a single autoreactive T cell when the B cells recognize constituents



Circulating Immune Complexes and Pathogenesis

Autoimmune Diseases

- Systemic lupus erythematosus
- Rheumatoid arthritis
- Goodpasture's syndrome

- **Drug Reactions**
  - Allergies to penicillin and sulfonamides
- **Infectious Diseases**
  - Poststreptococcal glomerulonephritis
  - Meningitis
  - Hepatitis
  - Mononucleosis
  - Malaria
  - Trypanosomiasis

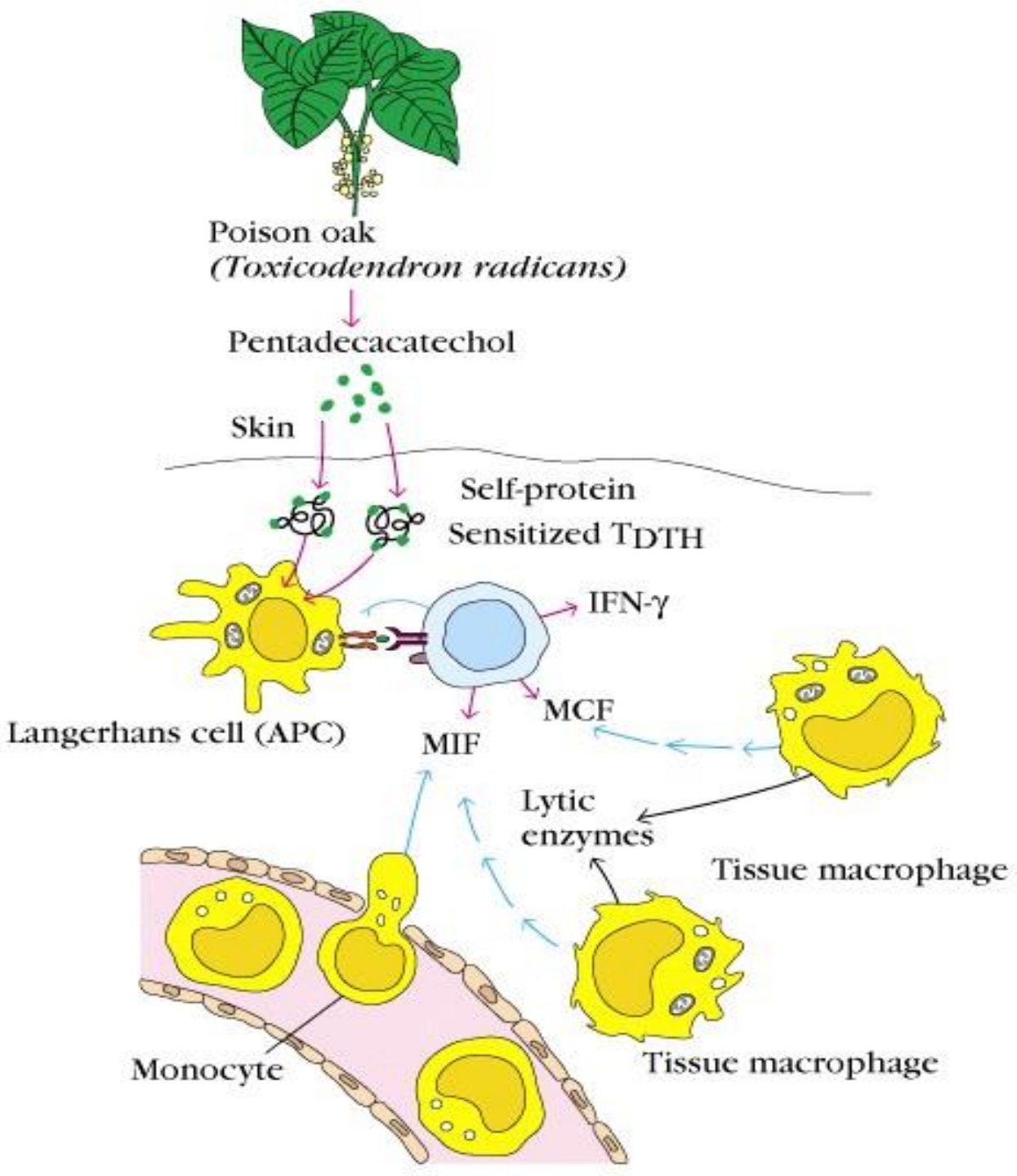
Type IV Hypersensitivity

(Delayed Type Hypersensitivity)

- **Mediated by memory T cells**
  - **Requires previous exposure**
  - **Time scale 24-72 hours**
  - **Requires antigen processing, presentation to specific T cells which must traffic to local site.**

- **Primarily mediated by Th1 cells producing IFN-γ**
- **Examples**
  - **Tuberculin test**
  - **Contact hypersensitivity (*e.g.* pentadeca-catechol in poison ivy reacts with self proteins in the skin, generating modified peptides).**

Type IV Hypersensitivity Contact Dermatitis



TYPE IV HYPERSENSITIVITY

Delayed-type Hypersensitivity (DTH)

- **T cell-mediated response**
- **$CD4^+$ cells recognize antigen and proliferate and make cytokines to attract and activate mononuclear phagocytes.**

- **T cell mediated. $CD4^+$TH1, class II MHC.**

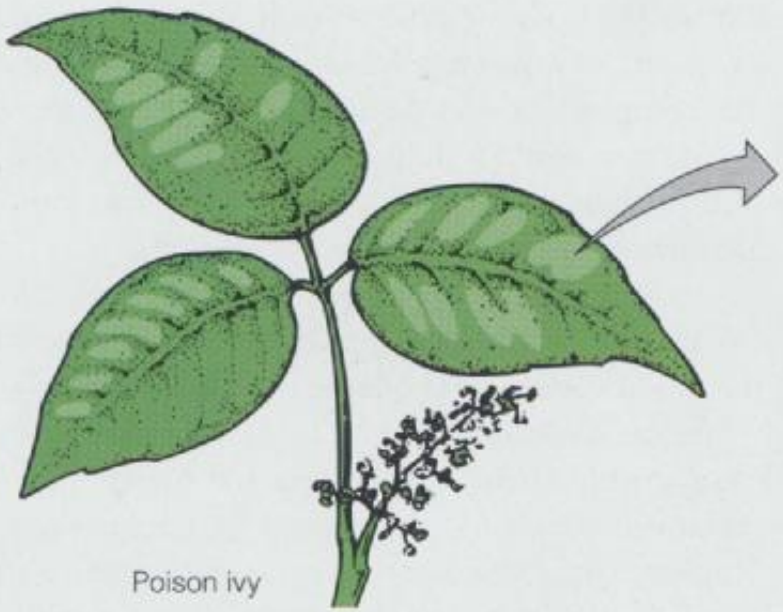
- **Important for defense against intracellular pathogens**
- **Cytokines: IFN-γ, MIF, TNF.**
- **IL-3, GM-CSF (Hematopoiesis)**
- **Manifestations:**
- **TB skin test,**
- **Infections: Mycobacteria, Listeria, Brucella, Salmonella, Leishmania**

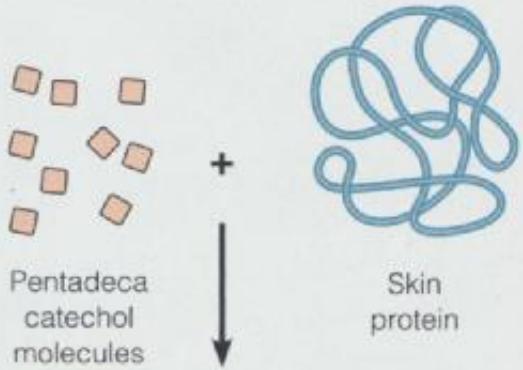
Type IV - T cell mediated disease

Syndrome	Autoantigen	Consequence
Insulin-dependent diabetes mellitus	Unknown pancreatic β cell antigen (GAD?)	β-cell destruction
Rheumatoid arthritis	Unknown synovial joint antigen	Joint inflammation and destruction
Experimental autoimmune encephalomyelitis (EAE), multiple sclerosis	Mylein basic protein (MBP), proteolipid protein (PLP)	Brain invasion by CD4 T cells, paralysis

Fig. 22.3 Clinical and patch test appearances of contact hypersensitivity. The eczematous area is due to sensitivity to the rubber component of this individual's undergarment (left). The suspected allergen may be confirmed by applying it, in a weak, non-irritant concentration to a patch of skin (patch test). An eczematous reaction (right) induced between 48 and 72 hours, confirms the allergen.

Type IV cell mediated reactions





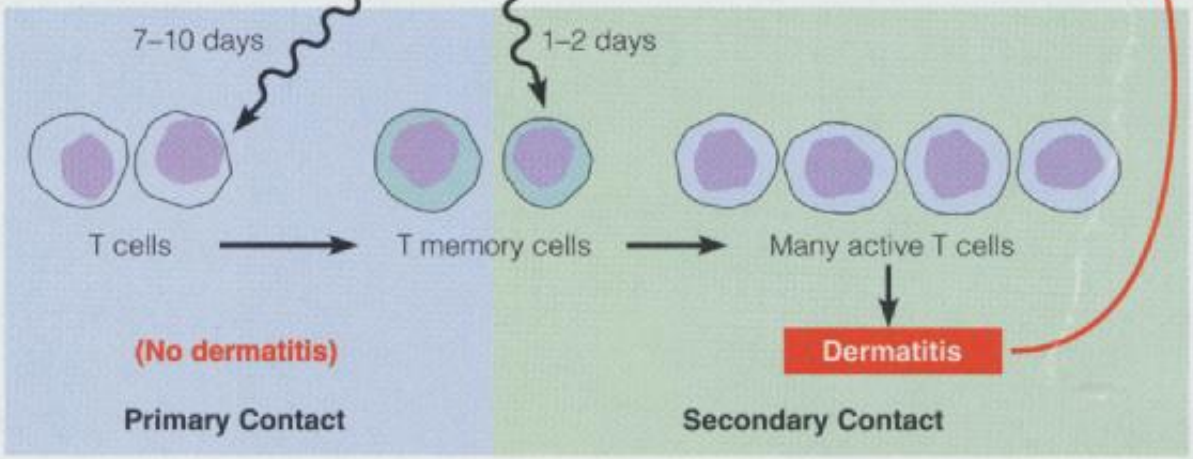


FIGURE 19.7 The development of an allergy (allergic contact dermatitis) to catechols from the poison ivy plant. The catechols are haptens that must combine with skin proteins to provoke an immune response. The first contact with poison ivy sensitizes the susceptible person, and subsequent exposure results in contact dermatitis (shown in the photo inset).

■ How does a hapten cause an allergic reaction?

Hypersensitivity Summary

- Inappropriate secondary reactions.
- Type I to IV. **Overlap in reality.**
- **Immediate：** Type I.
- IgE, Degranulation
- Type II. Ab mediated cytotoxicity.
- Type III. Immune Complex
- **Delayed：**
- Type IV. T cells and Cytokines.

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

Summary

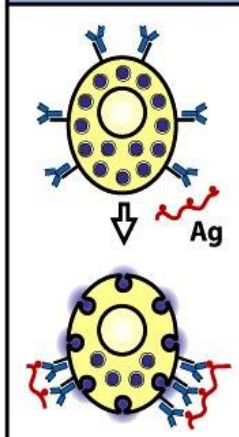
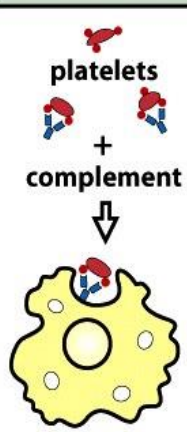
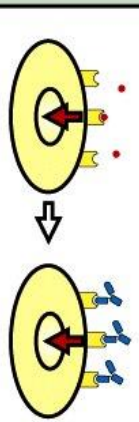
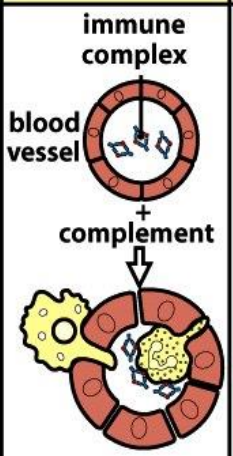
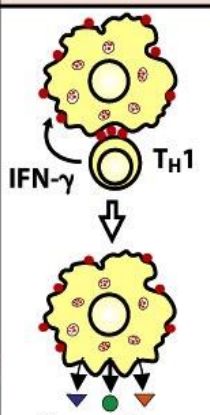
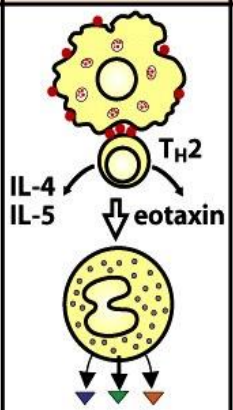
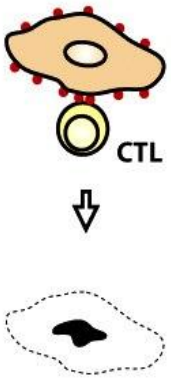
	Type I	Type II		Type III	Type IV		
Immune reactant	IgE	IgG		IgG	T_H1 cells	T_H2 cells	CTL
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Cell-surface receptor	Soluble antigen	Soluble antigen	Soluble antigen	Cell-associated antigen
Effector mechanism	Mast-cell activation	Complement, FcR^+ cells (phagocytes, NK cells)	Antibody alters signaling	Complement, phagocytes	Macrophage activation	IgE production, eosinophil activation, mastocytosis	Cytotoxicity
							
Example of hypersensitivity reaction	Allergic rhinitis, asthma, systemic anaphylaxis	Some drug allergies (e.g. penicillin)	Chronic urticaria (antibody against FCεRIα)	Serum sickness, Arthus reaction	Contact dermatitis, tuberculin reaction	Chronic asthma, chronic allergic rhinitis	Graft rejection

Figure 13-1 Immunobiology, 7ed. (© Garland Science 2008)

Concepts:

1. Graves disease and Myasthenia Gravis
2. Goodpasture's syndrome
3. Immune complex disease (ICD)
4. Arthus reaction
5. Serum sickness
6. Contact hypersensitivity
7. Asthma and Degranulation

Questions:

1. What is mainly mechanism in IgG antibody-mediated cytotoxic hypersensitivity ?
2. What is mainly mechanism in immune complex-mediated hypersensitivity ?
3. What is mainly mechanism in cell-mediated hypersensitivity ?
4. What is mainly mechanism in IgE antibody-mediated hypersensitivity ?