

Hypersensitivity Reactions

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Learning Objectives

By the end of this lecture you will be able to:

- ① List the four types of hypersensitivity reactions
- ② Describe the mechanism of each hypersensitivity reaction
- ③ Understand the clinical manifestations and managements of some hypersensitivity reactions

Hypersensitivity reactions

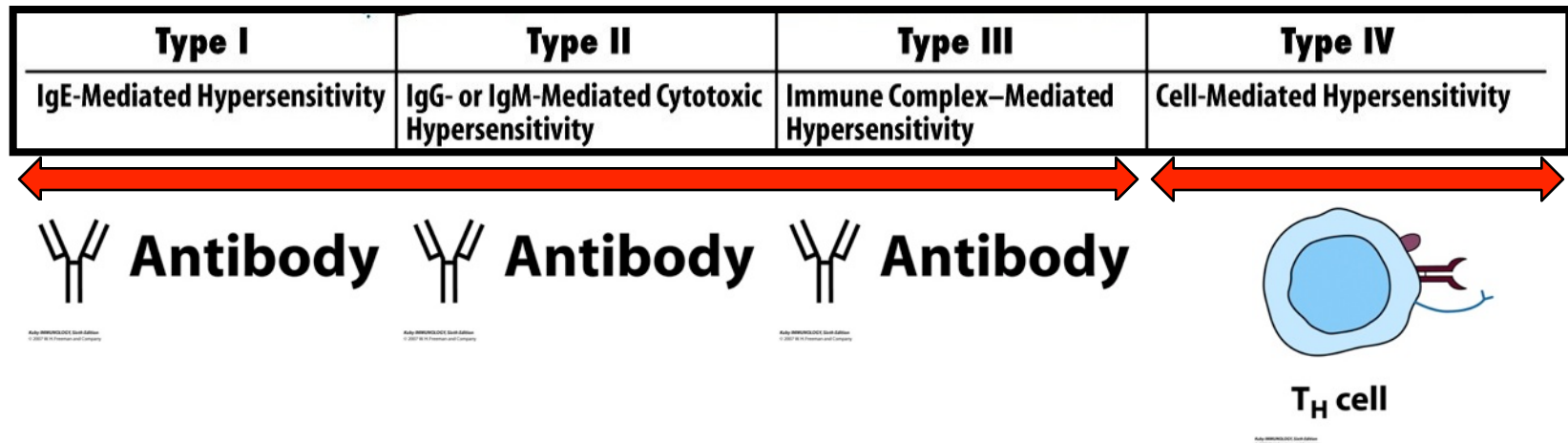
- Excessive or inappropriate reaction of the immune system
- Resulting from repeated or prolonged exposure to antigens
- Sometimes lead to host tissue damage



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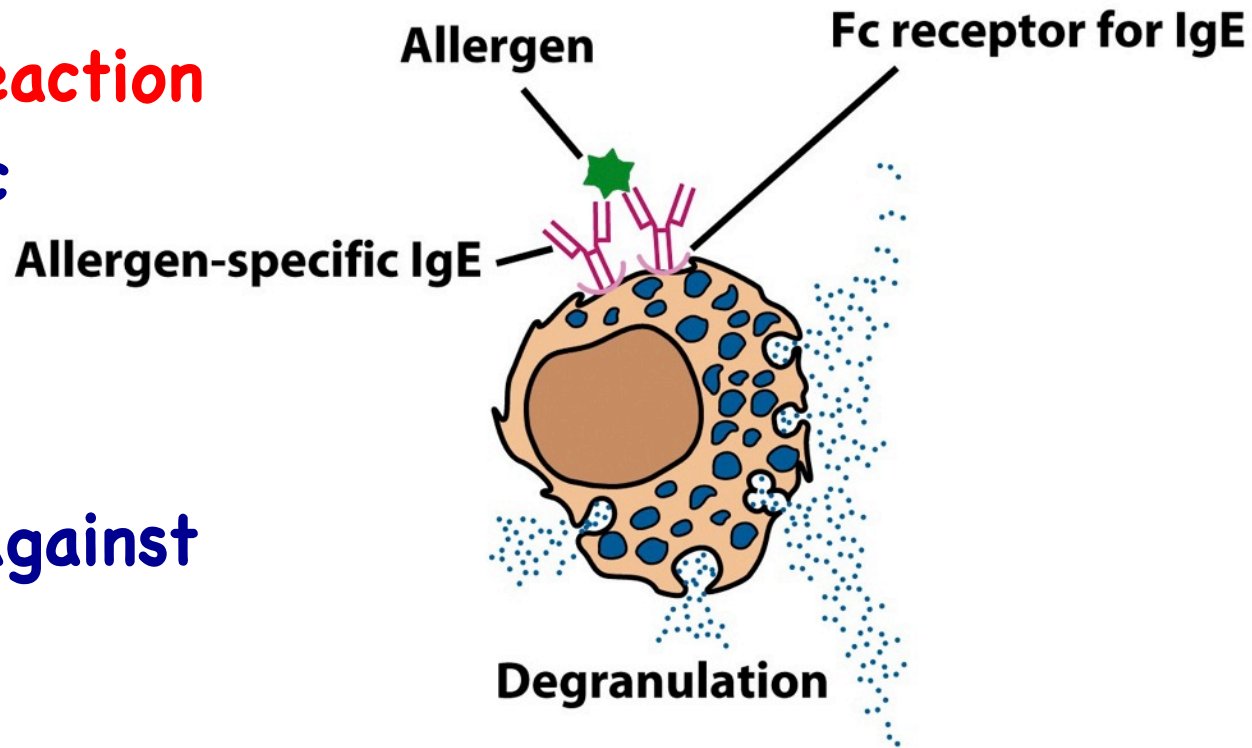
Hypersensitivity reactions

- They cause injury by the release of substances that attract and activate cells and molecules of inflammation
- The reactions are classified into four types depending upon the mechanism that underline the tissue damage



Type I

- Is an **Immediate Hypersensitivity Reaction**
- Also called Allergic reaction
- Characterized by production of IgE against proteins commonly present in the environment



Immediate Hypersensitivity Reaction

- Occurs within minutes to hours of Ag exposure
- Allergens are relatively harmless antigens commonly found in the environment

Allergen cross-linkage of cell-bound IgE

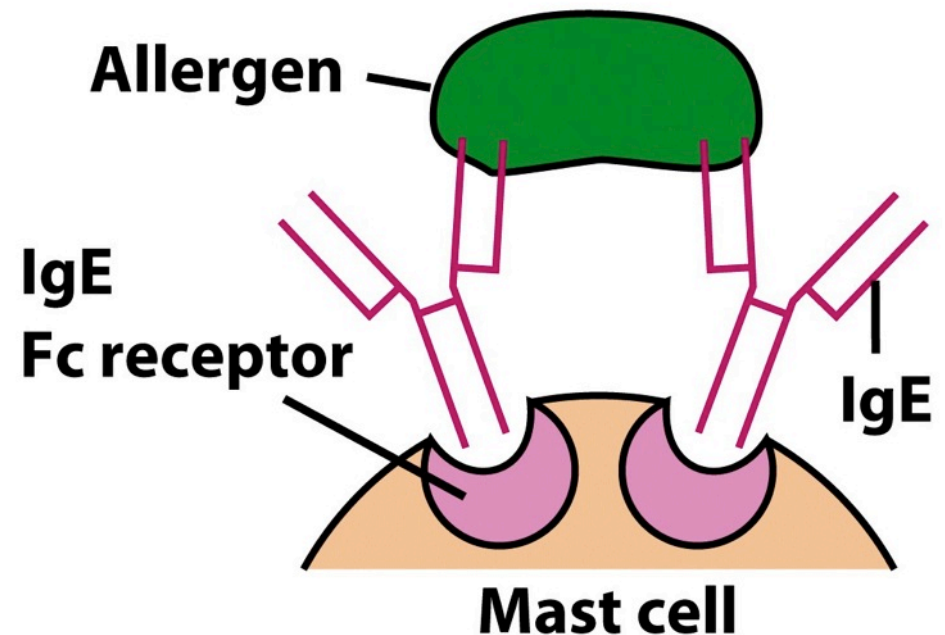


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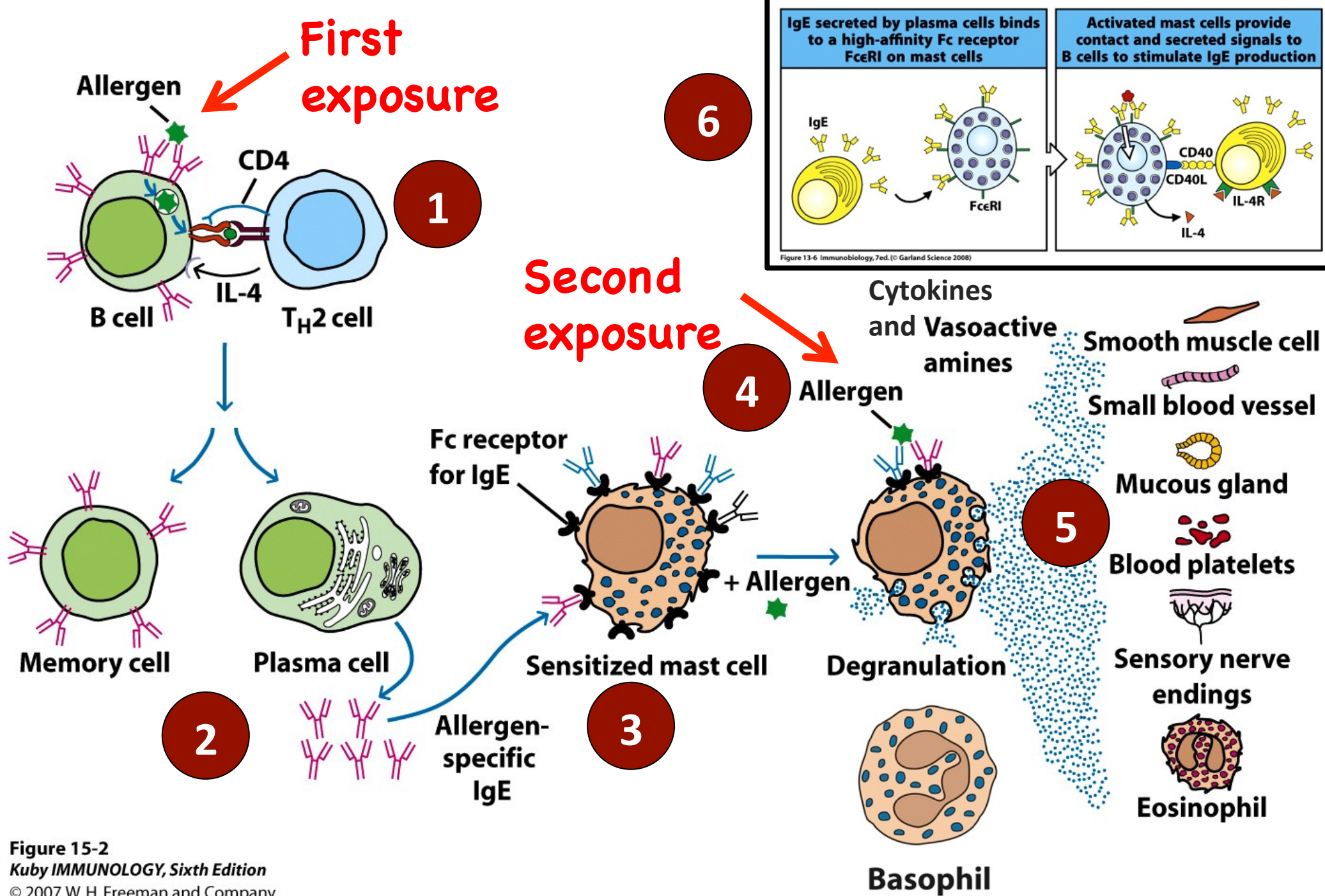


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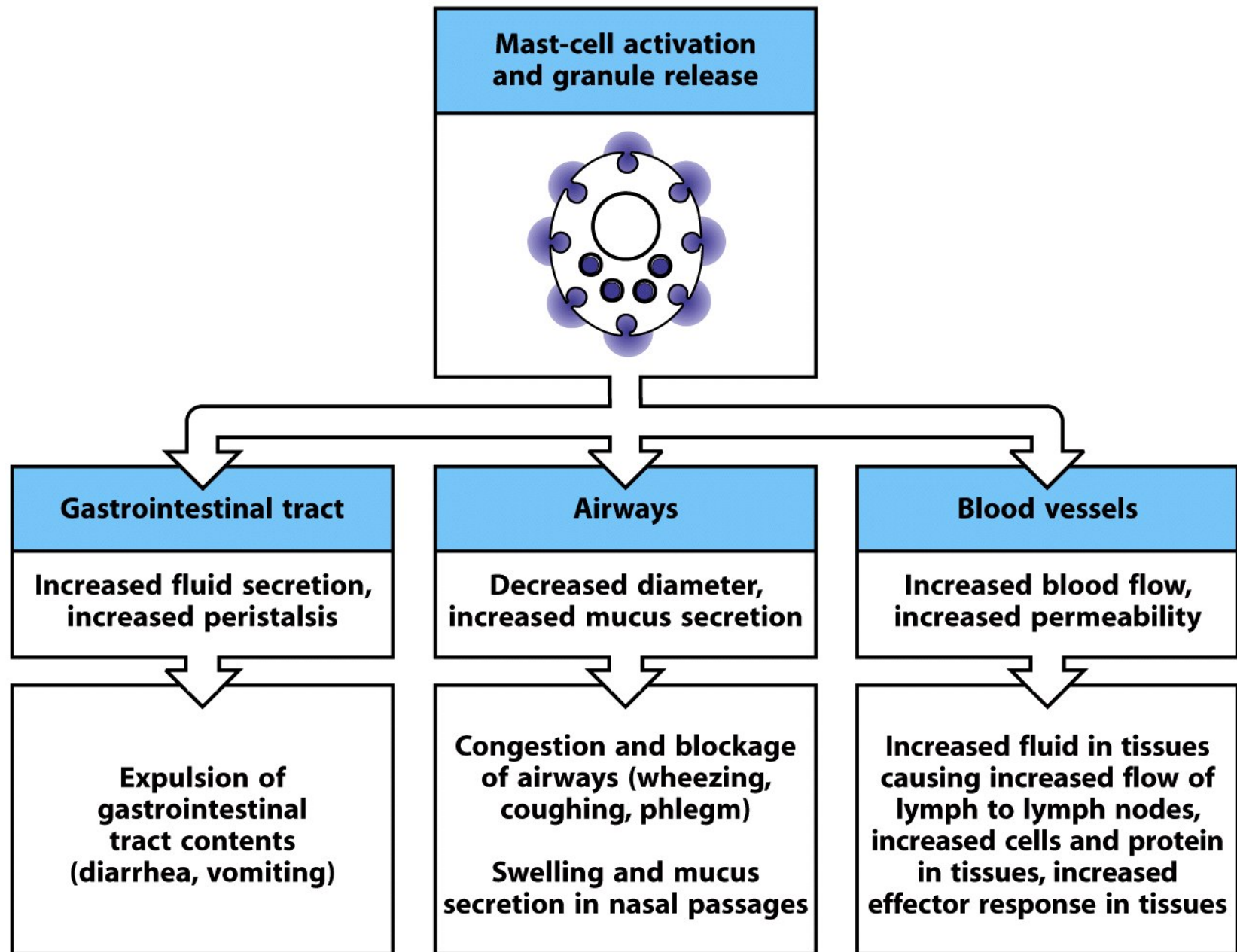


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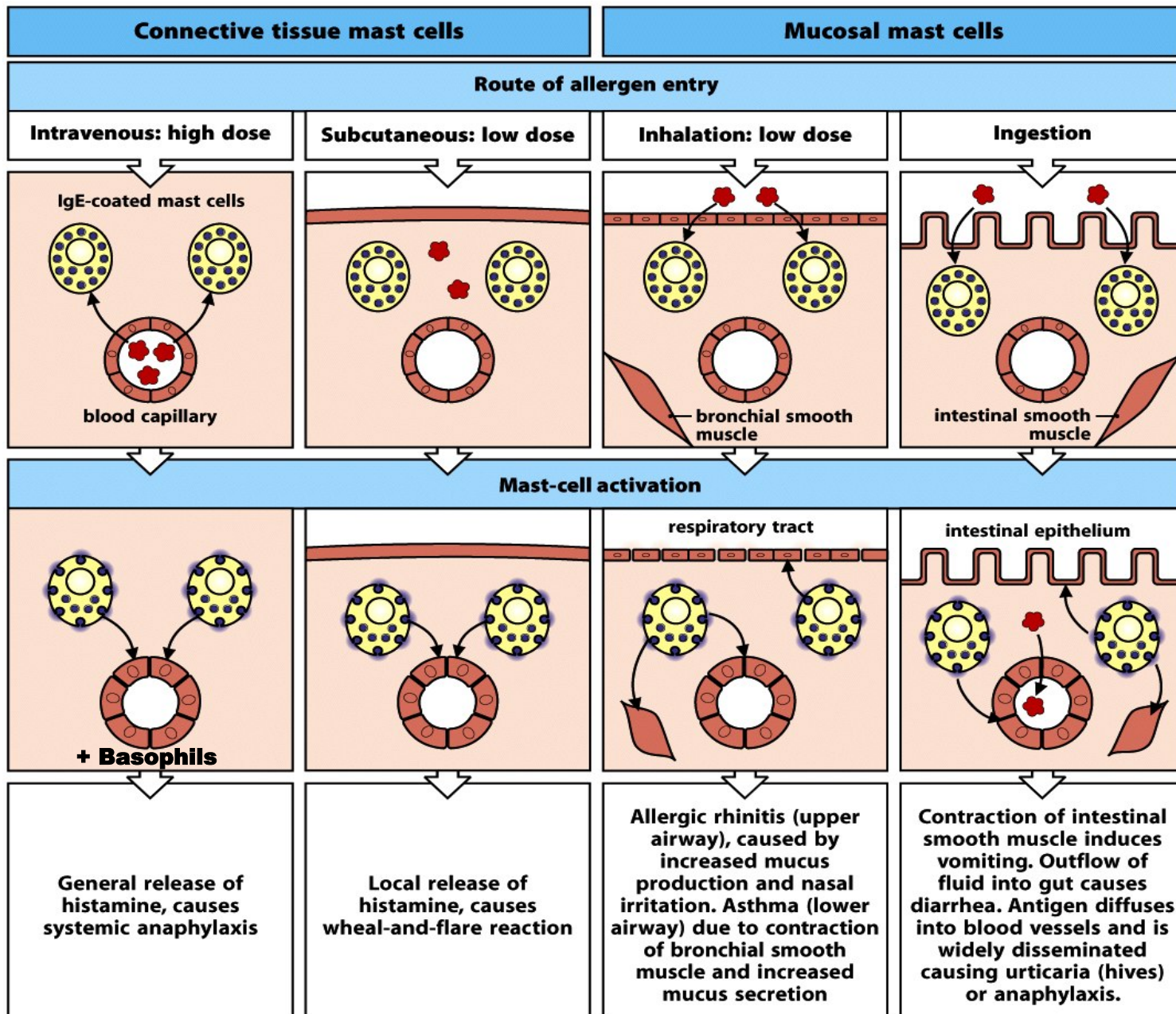


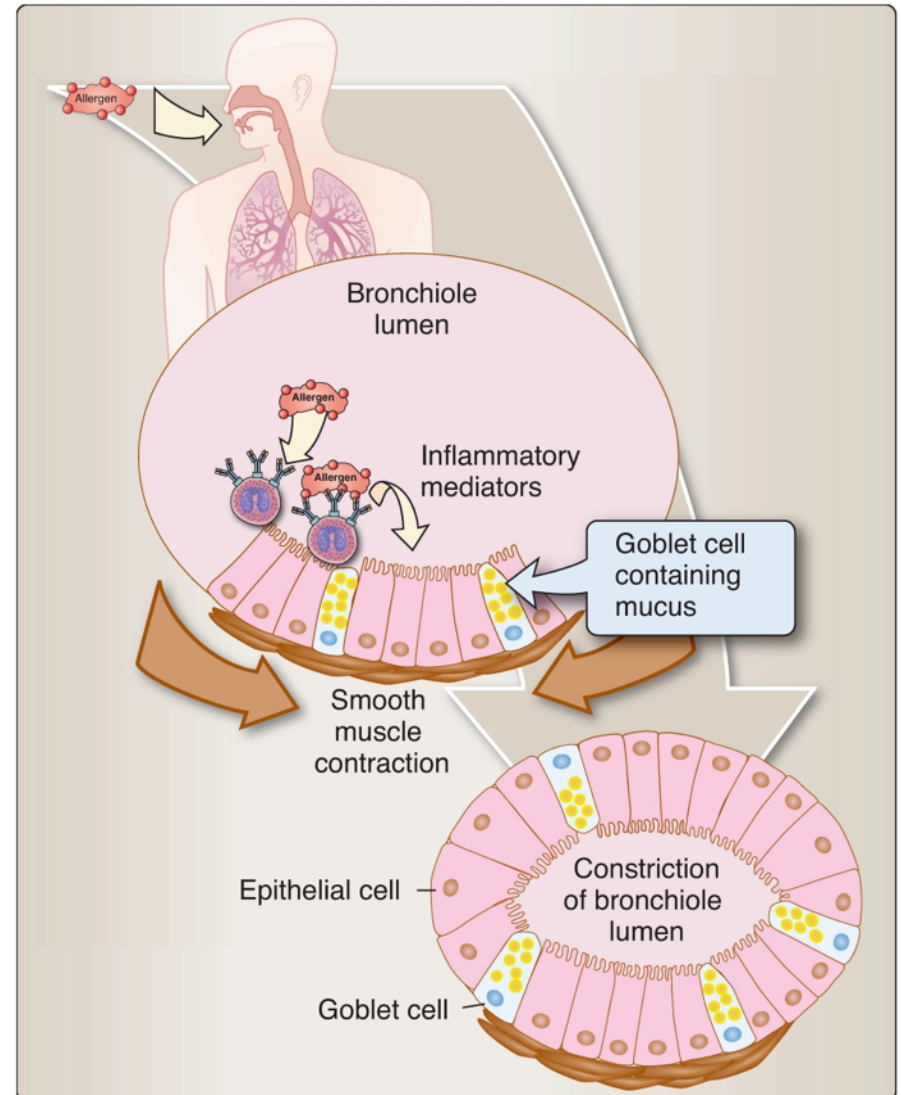
Figure 13-15 Immunobiology, 7ed. (© Garland Science 2008)

Immediate Hypersensitivity Mediators

Mediator		Effects
AUTACOIDS	Histamine	Vascular permeability and bronchospasm
	Leukotrienes	Vascular permeability and bronchospasm
	Prostaglandins	Vascular permeability and bronchospasm
	Bradykinins	Vascular permeability and bronchospasm
CYTOKINES	IL-1 & TNF- α	Systemic anaphylaxis and increase of CAMs expression
	IL-4 & IL-13	Increase IgE production

Localized Type I reactions

- Mast cells accumulate in tissues such as respiratory passages, intestinal walls, and skin
- Inhaled allergens cause allergic asthma



Immediate and Late responses

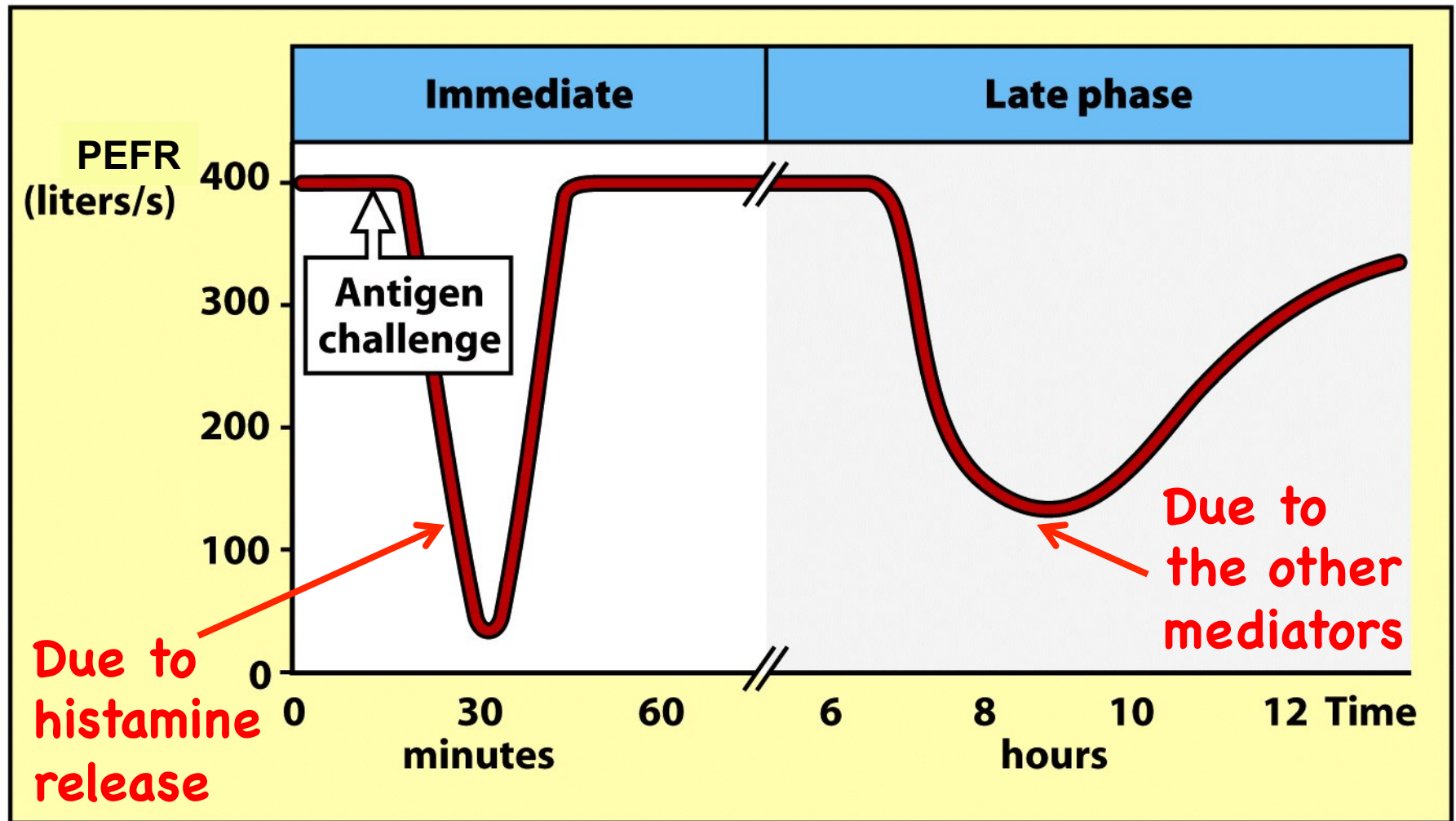


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Acute and chronic asthma

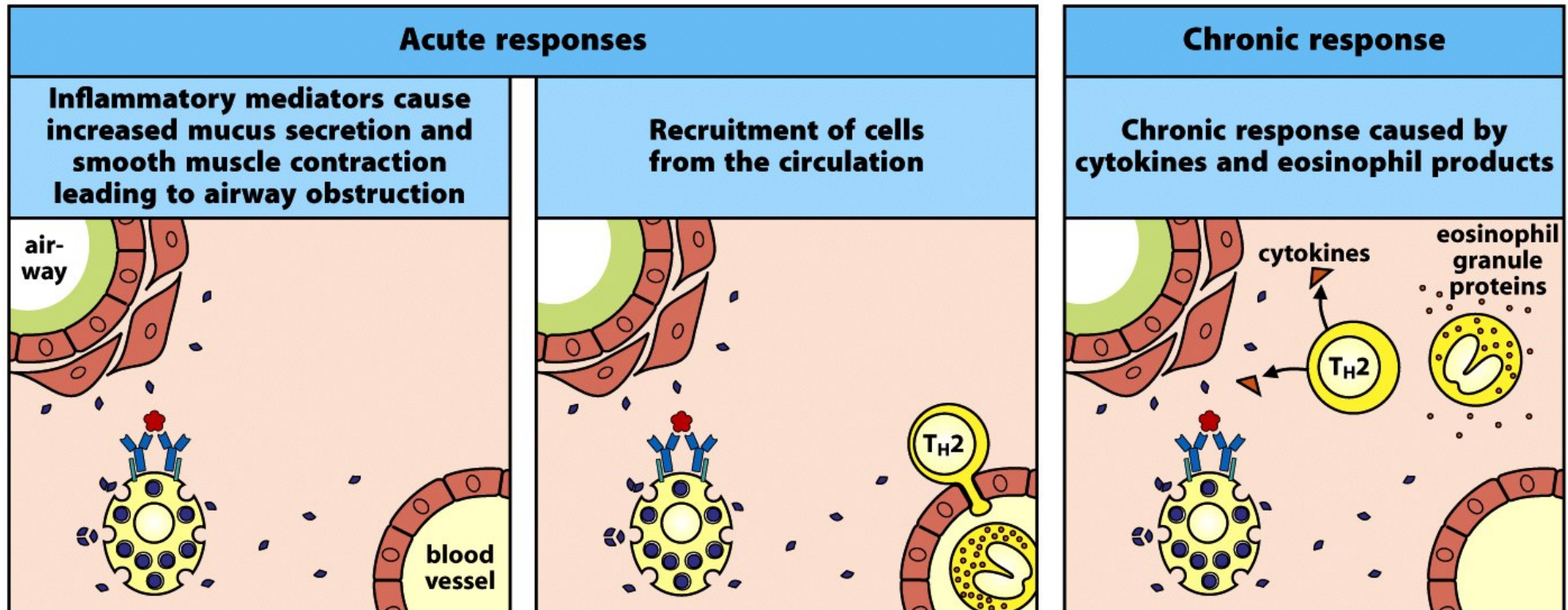
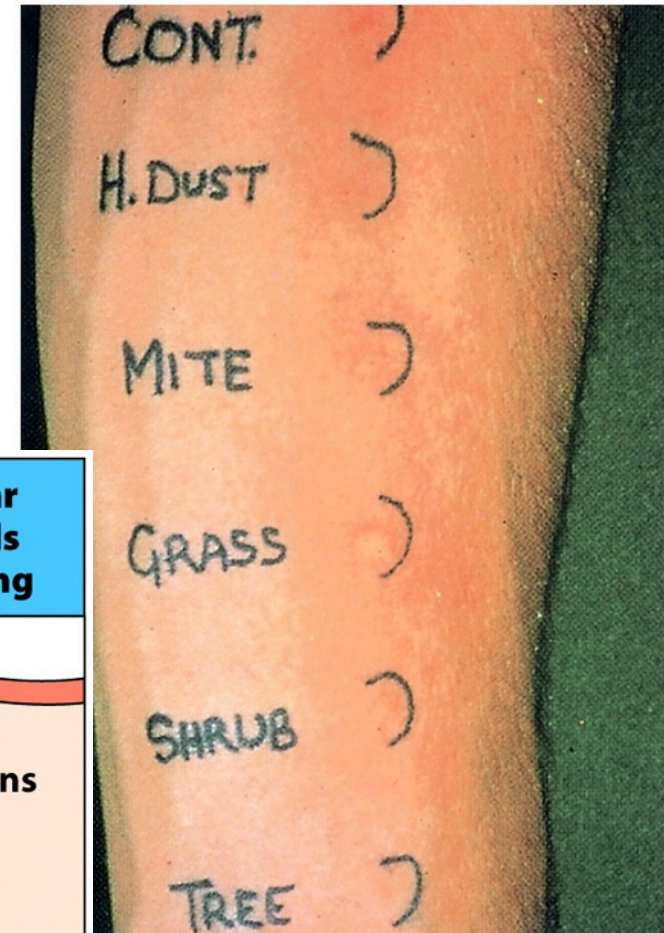
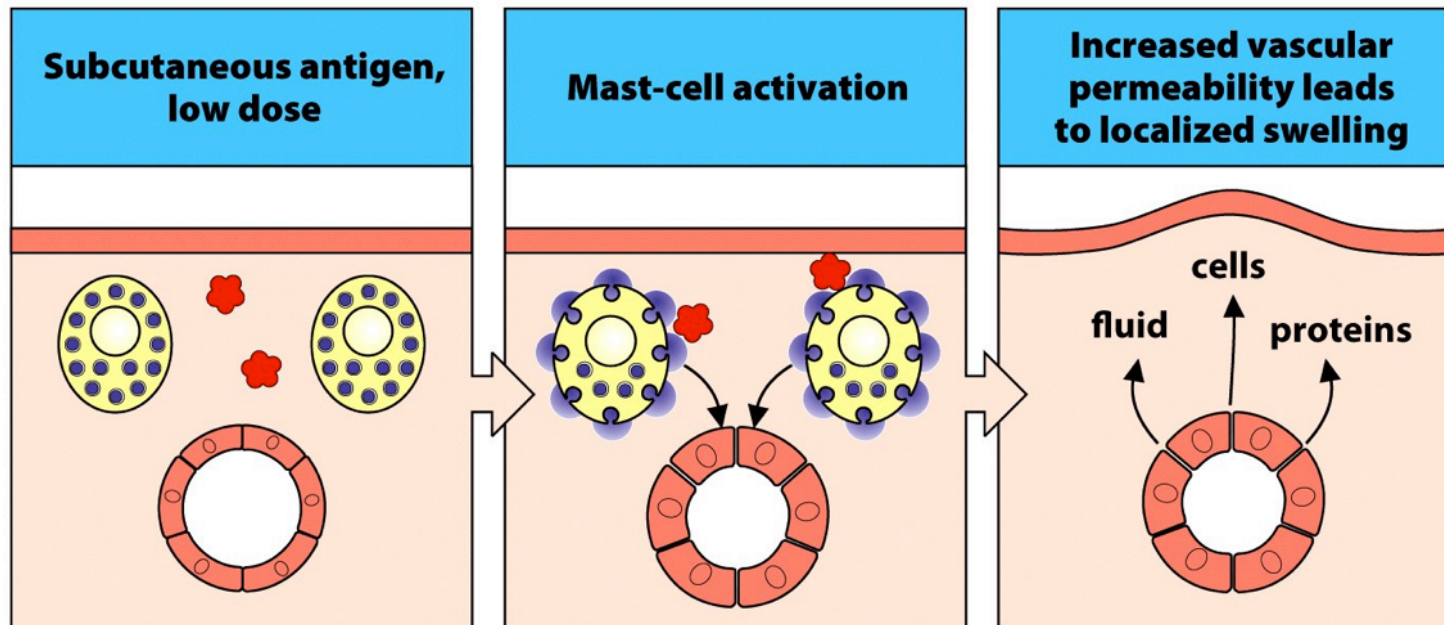


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Localized Type I reactions

- Skin allergens cause inflammatory response

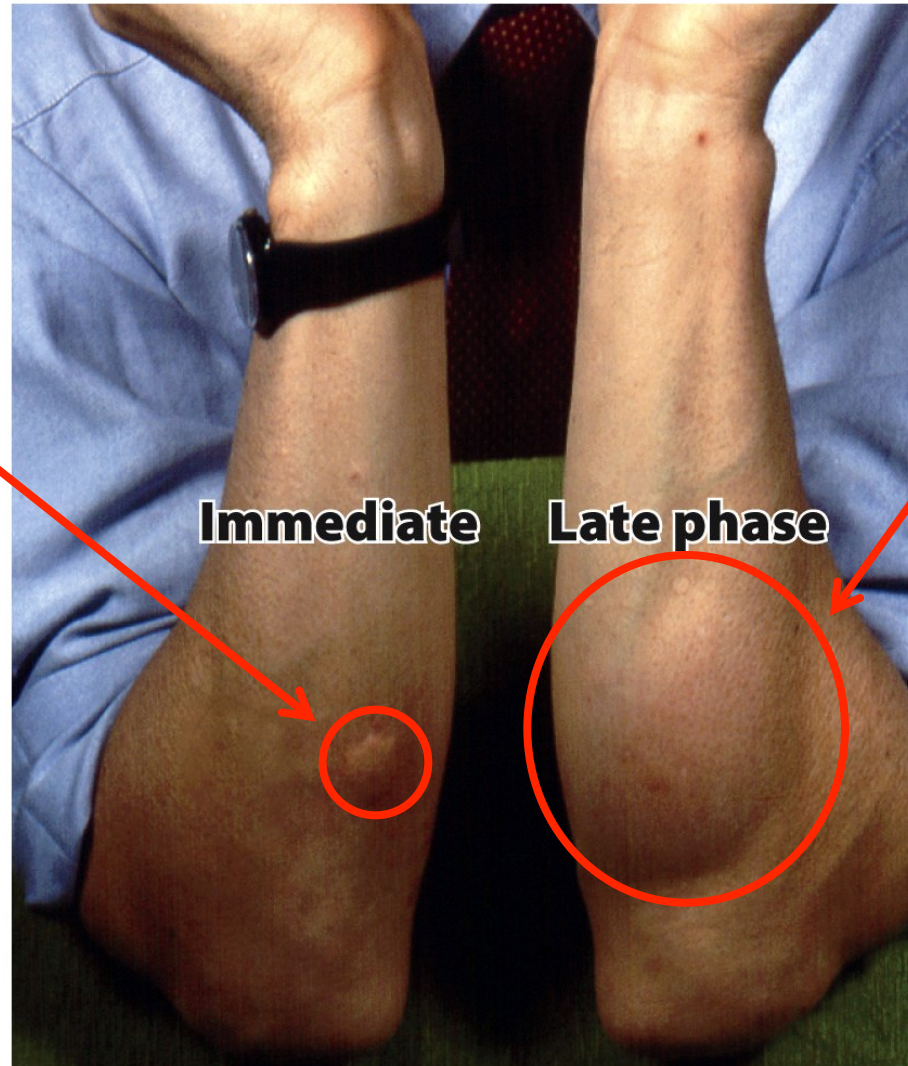


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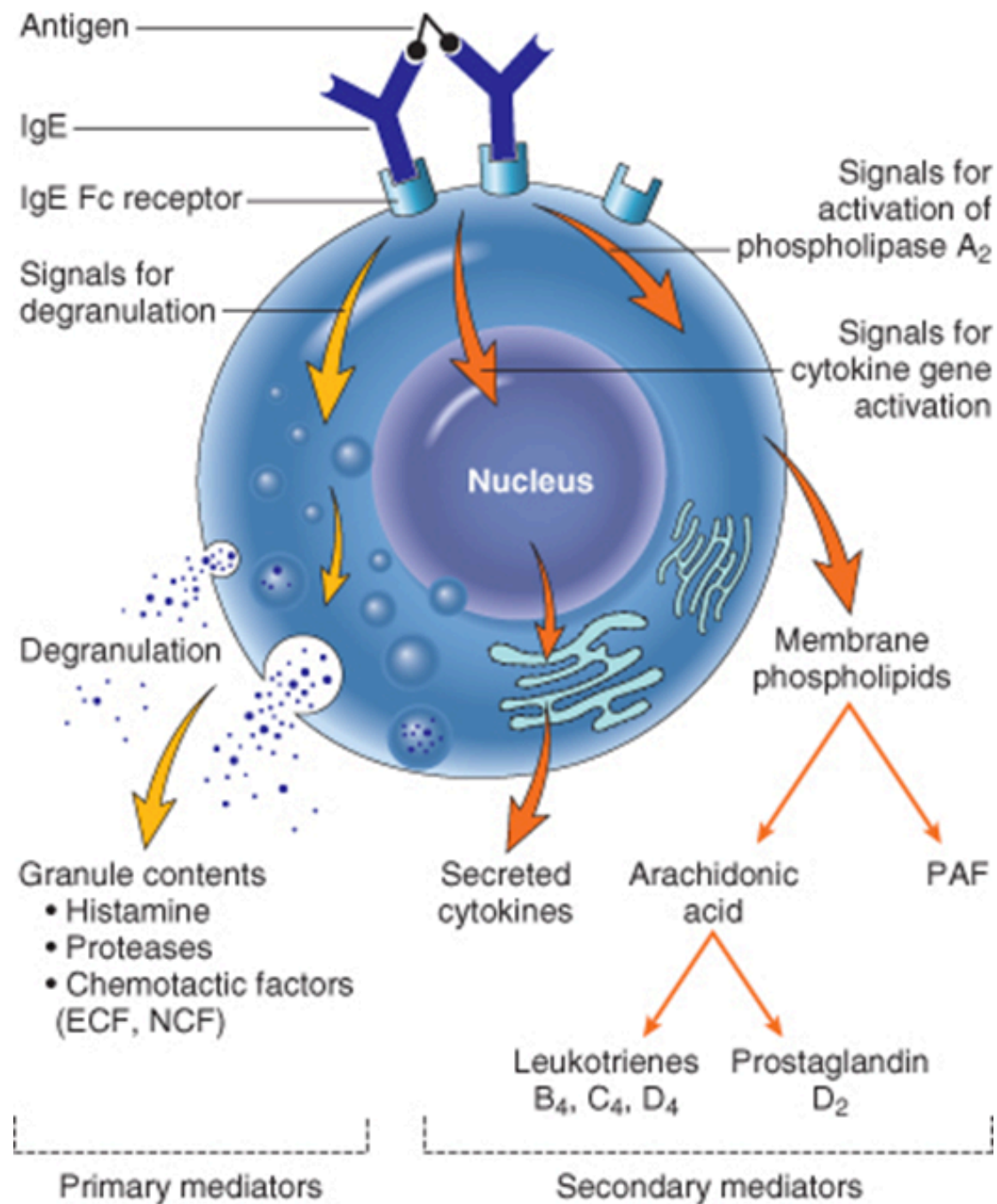
Figure 12.24 part 1 of 2 The Immune System, 3ed. (© Garland Science 2009)

Immediate and Late responses

Wheal and flare
(early-phase)
within 15 minutes
of allergen
challenge



Edema (late-
phase) after 6
hours of allergen
challenge



Systemic Type I reactions **ANAPHYLAXIS**

- Dissemination of some antigens by the bloodstream can result in systemic inflammation (**anaphylaxis**)
- Mediated by systemic release of basophilic and mast cell mediators
- Management: Epinephrine (life saving), H1 and H2 antagonists, Corticosteroids, and Salbutamol

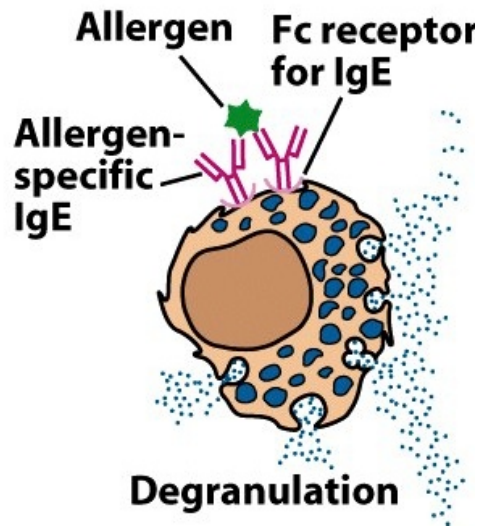
TABLE 15-4**Mechanism of action of some drugs used to treat type I hypersensitivity**

Drug	Action
Antihistamines	Block H₁ and H₂ receptors on target cells
Cromolyn sodium	Blocks Ca²⁺ influx into mast cells
Theophylline	Prolongs high cAMP levels in mast cells by inhibiting phosphodiesterase, which cleaves cAMP to 5'-AMP*
Epinephrine (adrenaline)	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.	

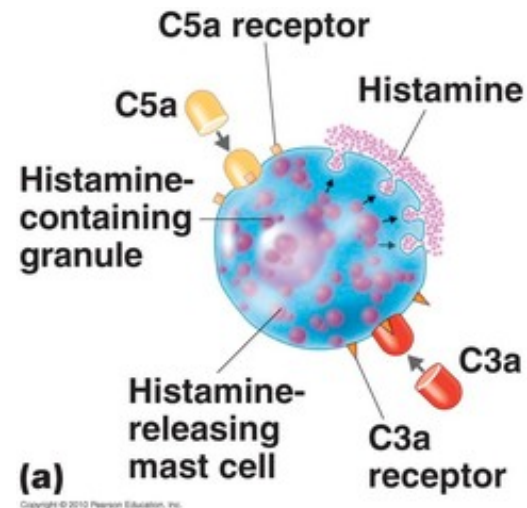
Anaphylactic vs. Anaphylactoid

- An **anaphylactoid** ("allergic-like") reaction is an immediate, systemic reaction that mimics anaphylaxis (release of identical mediators from mast cells and basophils), but differs in that it is NOT an IgE mediated response

Can be caused by drugs e.g. penicillin



Anaphylactic



Can be caused by drugs e.g. morphine

Anaphylactoid

Anaphylactic vs. Anaphylactoid

	Anaphylactic Reaction	Anaphylactoid Reaction
Is sensitization required?	Yes	No
Can reaction occur in first exposure?	No	Yes
How much exposure is needed to start reaction?	Little	Much
Is reaction predicted by allergy skin test?	Yes	No
Can be caused by drugs?	Yes	Yes

Atopy and Hygiene Hypothesis

- Exposure to some infectious agents in childhood drives the immune system towards T_H1 response and non-atopy.
- Children with genetic susceptibility to atopy and living in an environment with low exposure to infectious disease tend to mount T_H2 responses, and will be more susceptible to develop atopic allergic diseases

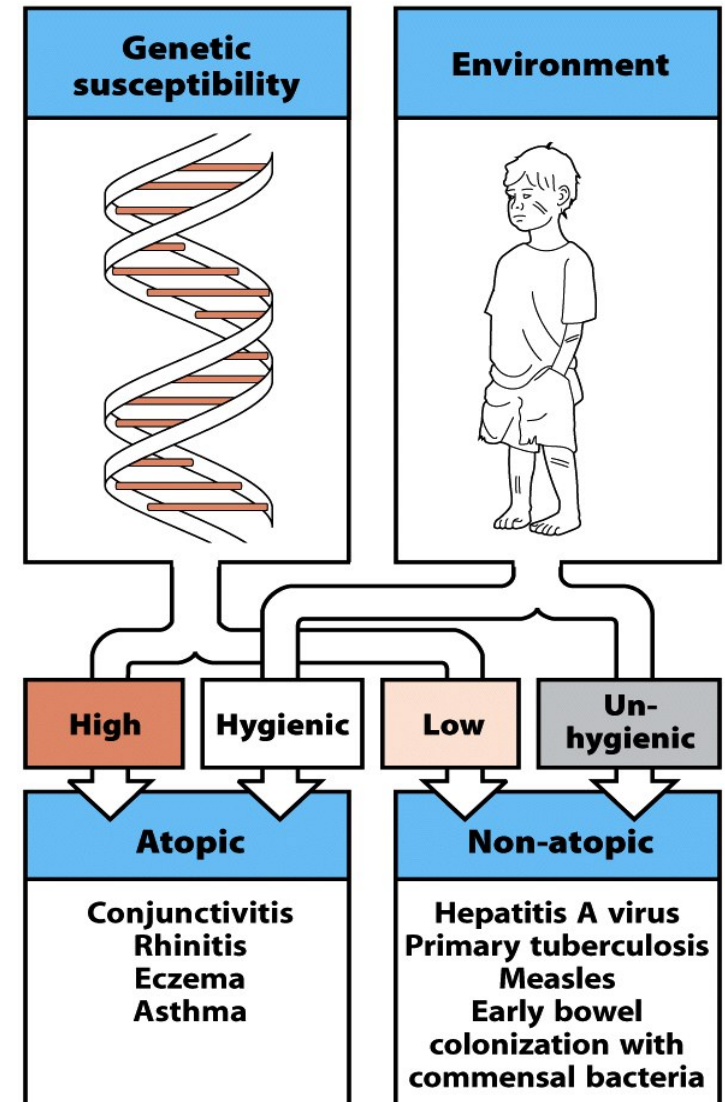
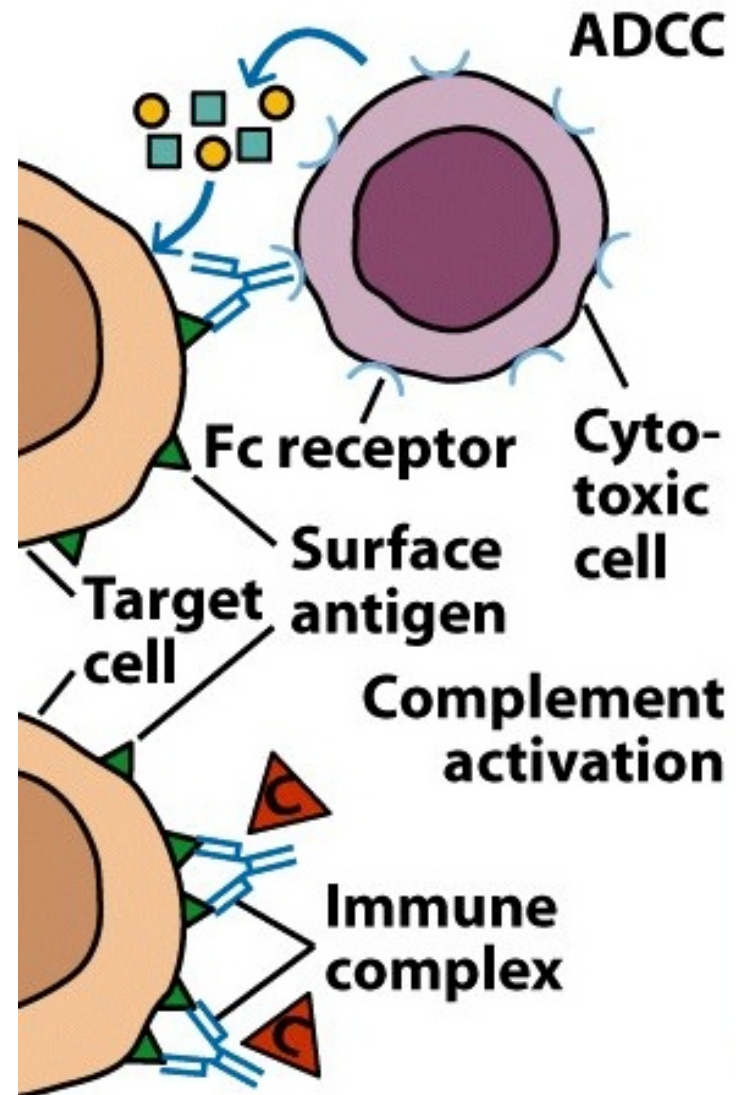


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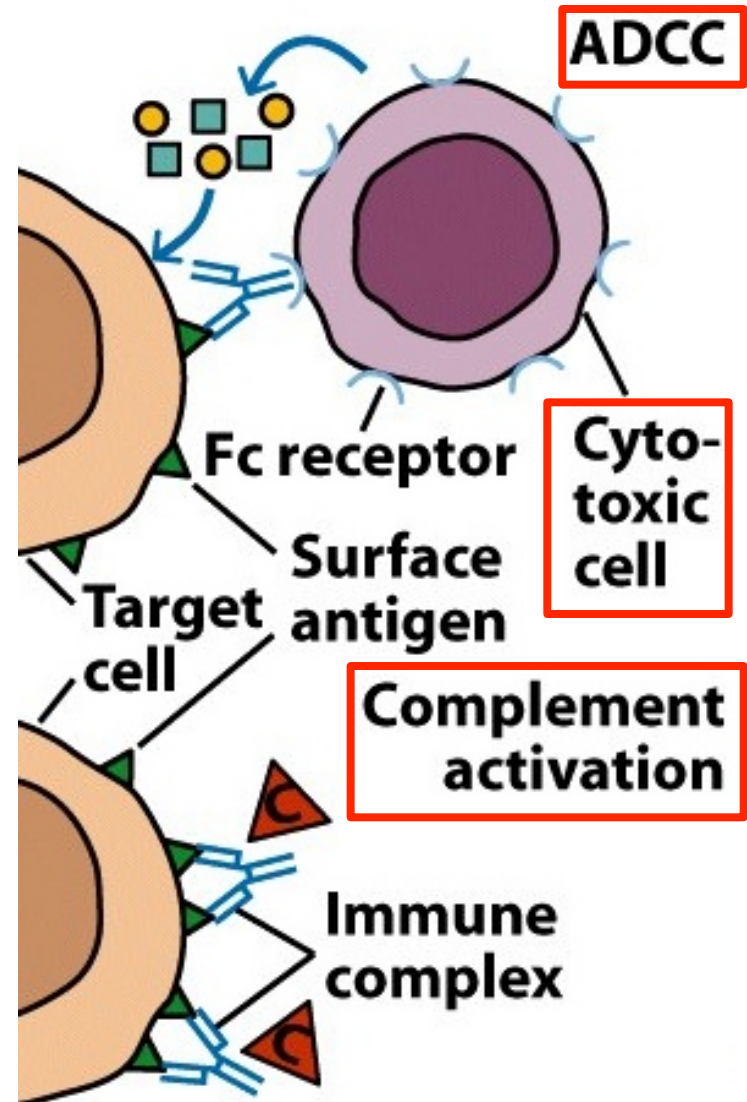
Type II

- Is an **Antibody-Mediated Cytotoxic Reaction**
- Mediated by IgG and IgM binding to specific cells or tissues **surface**
- The damage is restricted to the cells and tissues bearing this antigen



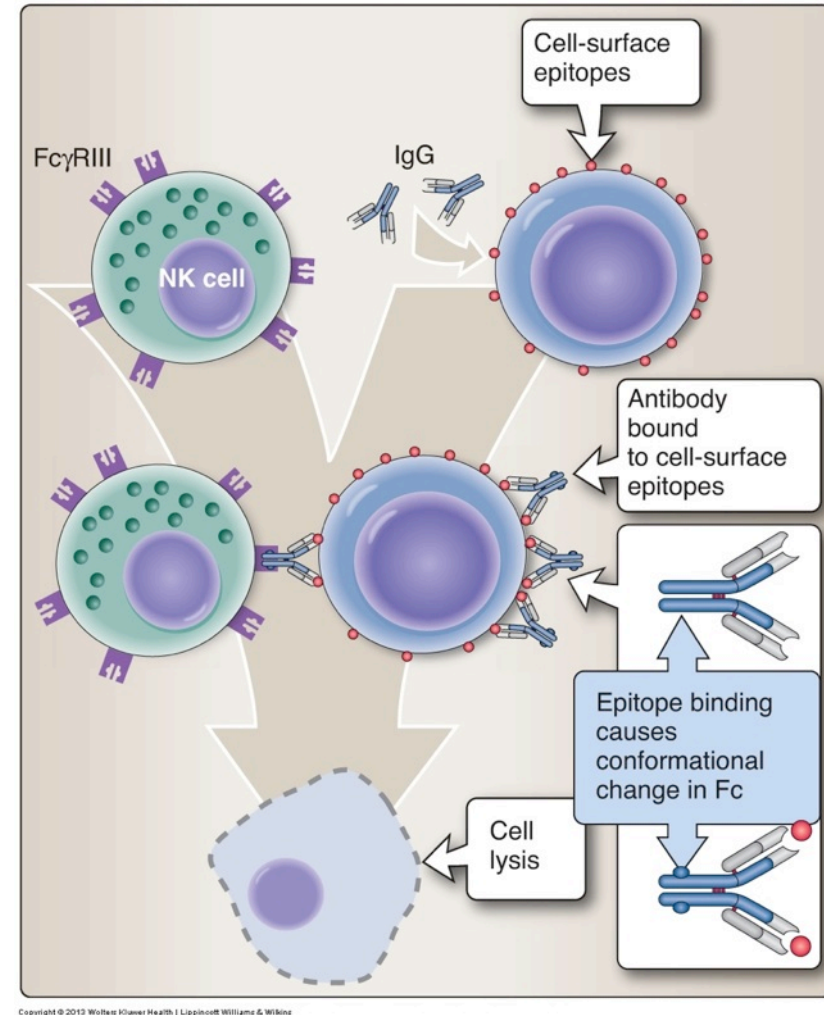
Antibody-Mediated Cytotoxic Reaction

- Antibody directed against cell **surface** or tissue antigens
- also interacts with the Fc receptor (FcR) on a variety of **effector immune cells** (e.g. NK, MΦ, PMN)
- or can activate **complement** cascade where MAC is formed and **C3b** can deposit on target cells



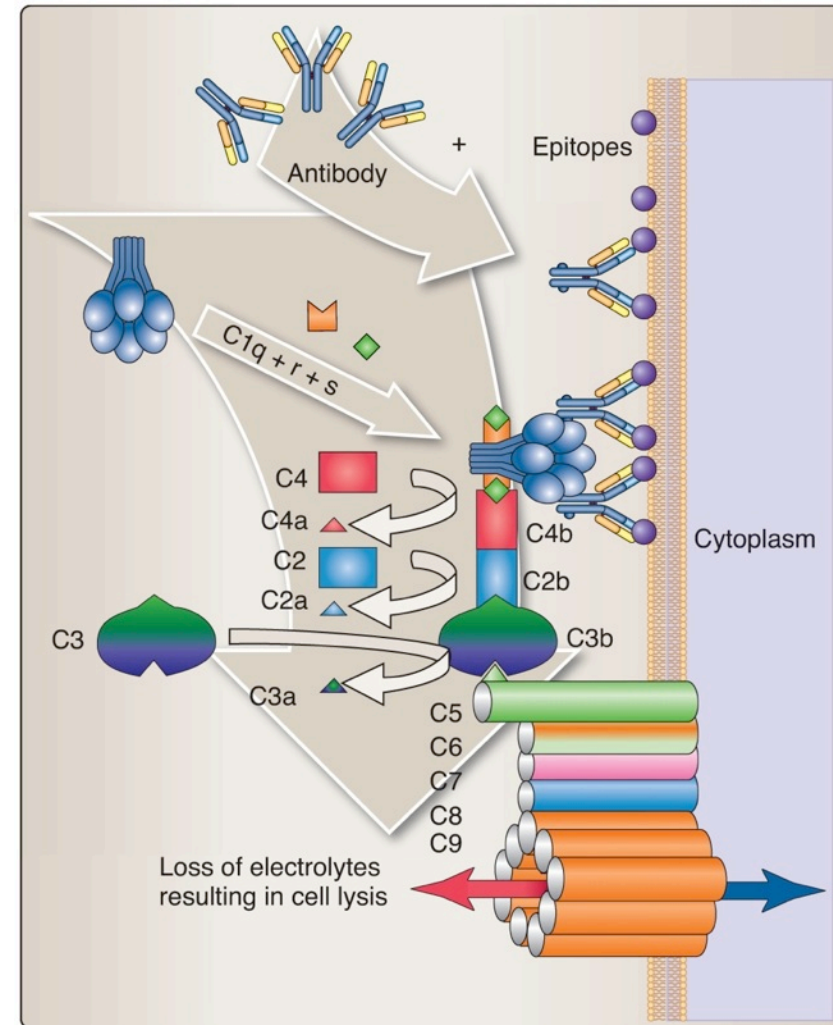
FcR-Mediated Mechanism

- ① Antibodies (may also be auto-reactive) generated against surface antigens
- ② They also bind to FcR on effector cells
- ③ Effector cells include NK cell, Macrophage, Neutrophil
- ④ NK cell will kill target cells by **ADCC**
- ⑤ Macrophages and neutrophils will undergo **phagocytosis or frustrated phagocytosis**



Complement Pathway-Mediated

- ① Auto-reactive antibodies generated against surface antigens
- ② C1 binds to auto-reactive IgG and IgM on target cell or tissue
- ③ Classical complement pathway is initiated on target cell or tissue
- ④ **MAC formation**



CR-Mediated Mechanism

- ① C3b deposit on target cell surface
- ② Recognized by CR on macrophages and neutrophils (recruited by C3a and C5a "Chemotaxis")
- ③ Phagocytosis or frustrated phagocytosis

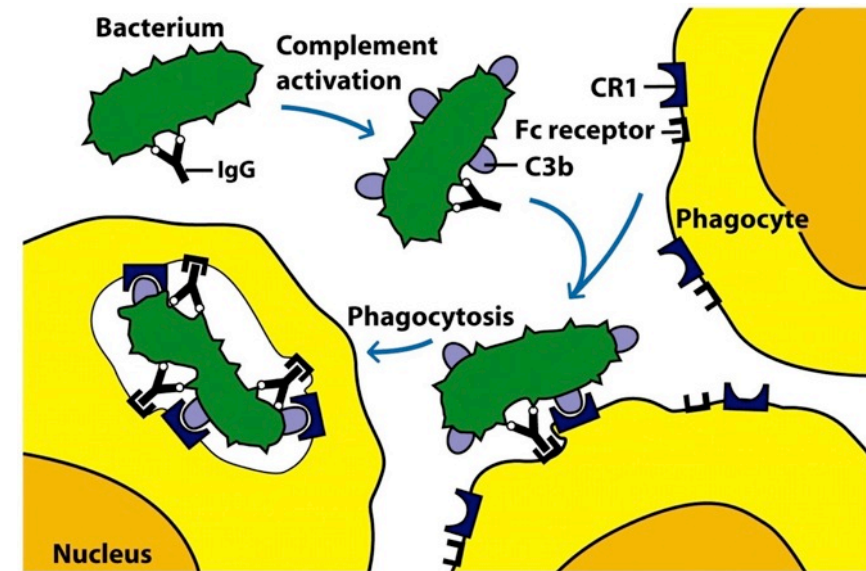
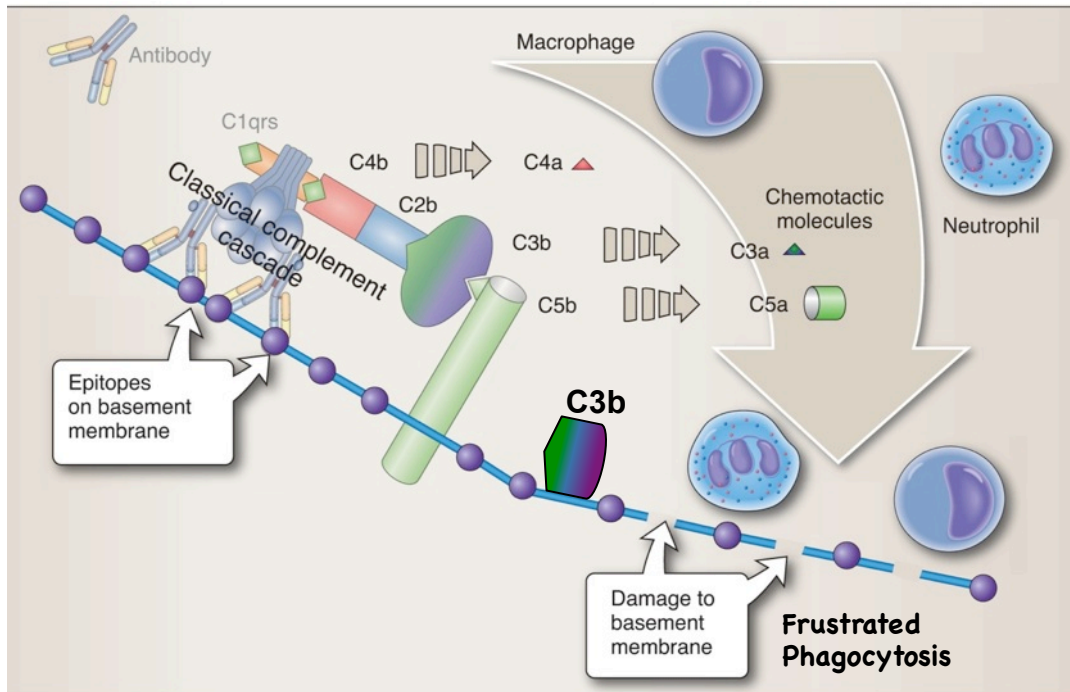
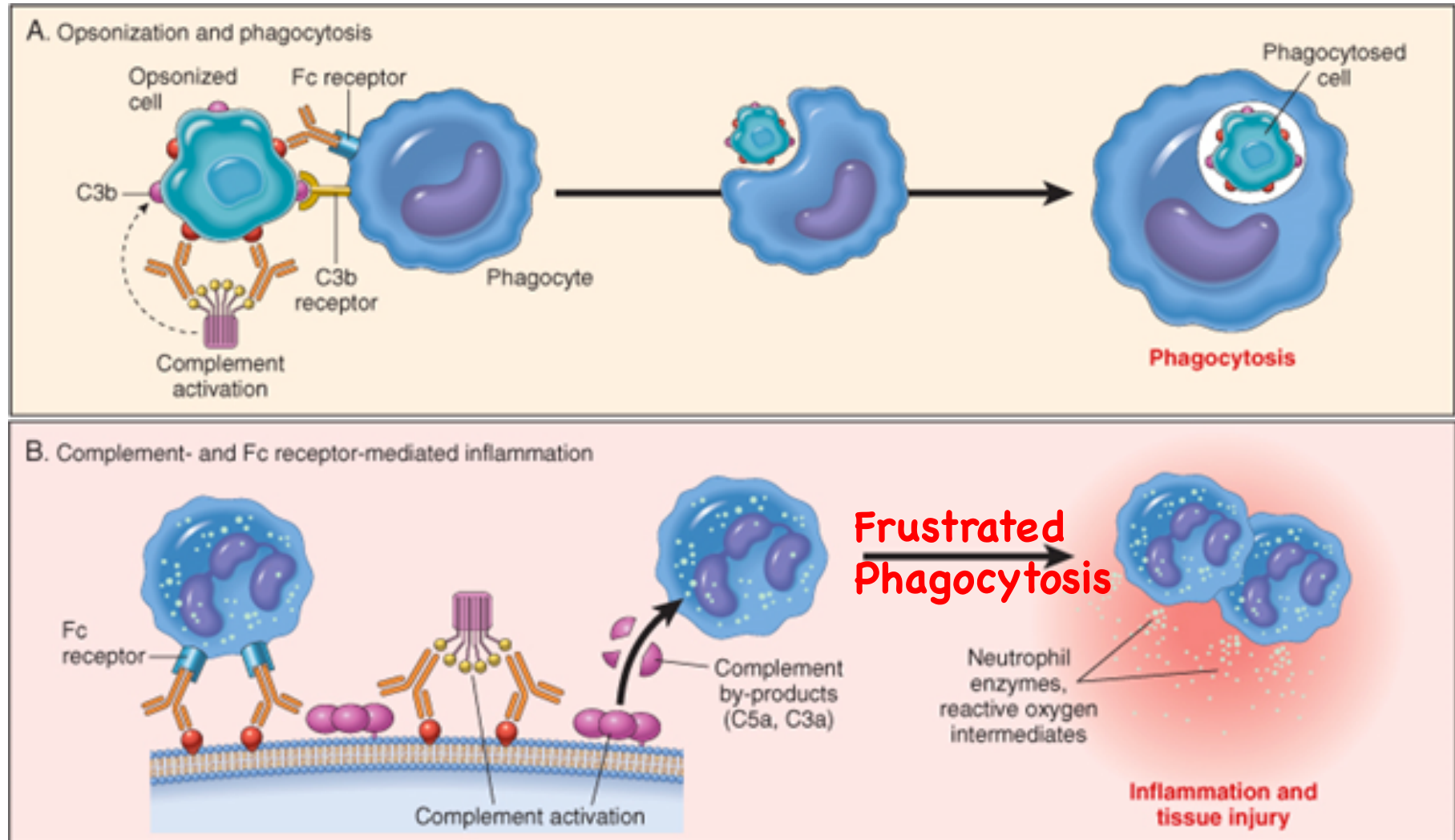
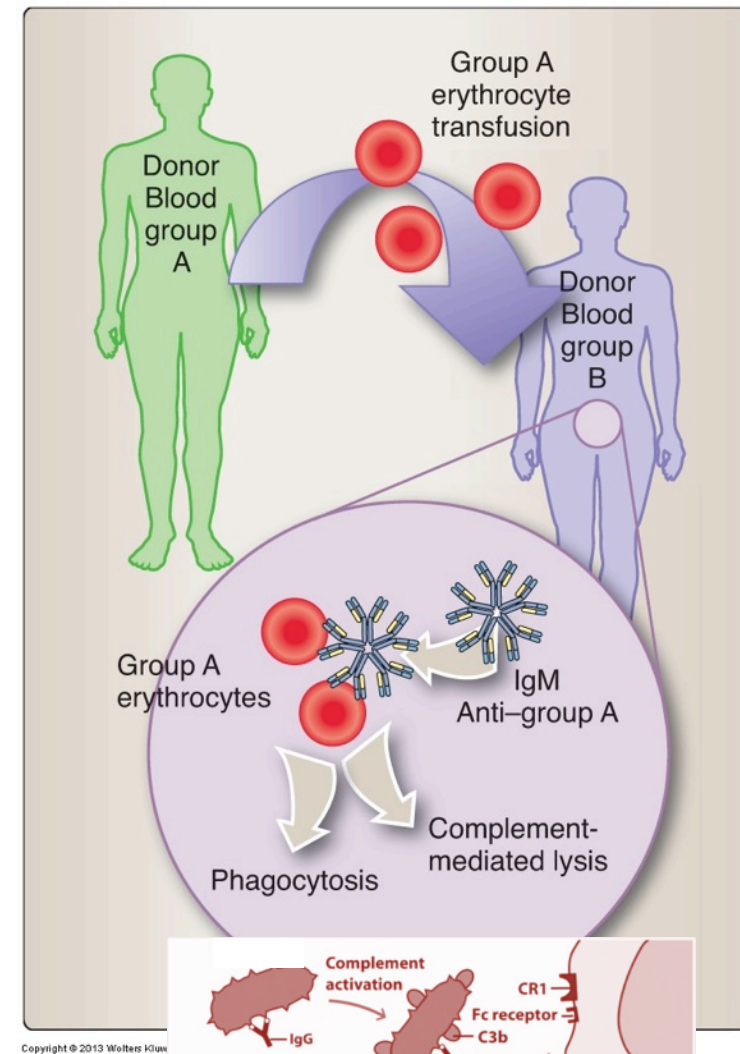
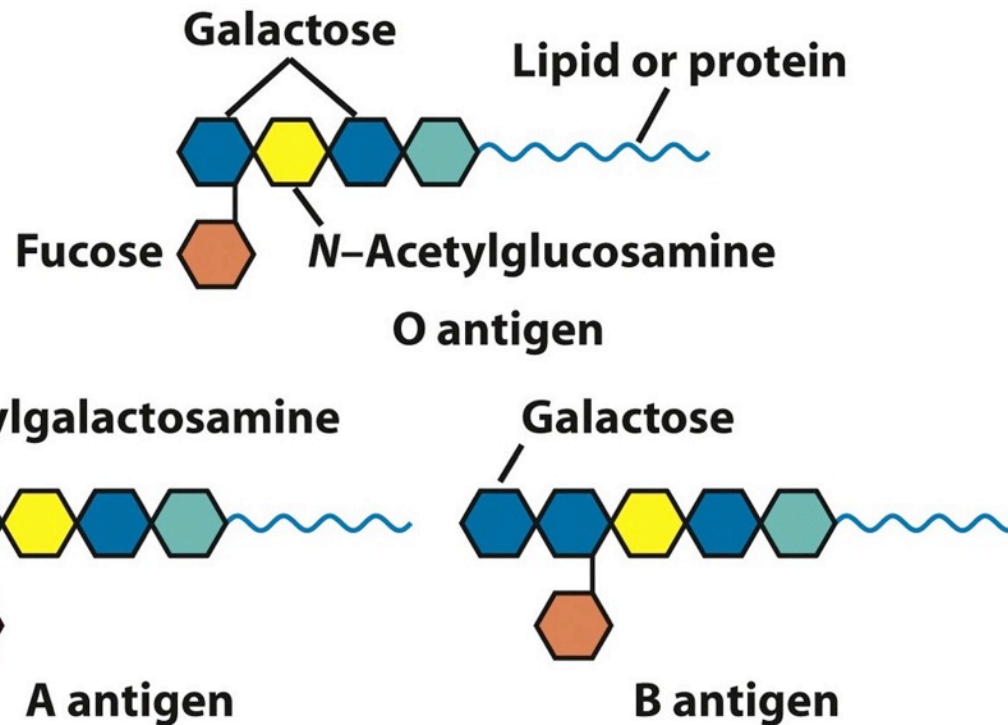


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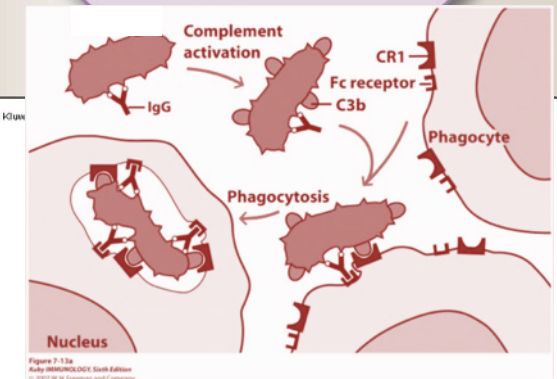
Damage mechanisms



Transfusion Reaction



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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

Hemolytic disease of the newborn (HDN)

Also known as: Erythroblastosis Fetalis

Rh⁻ mother
bearing an
Rh⁺ fetus

Second fetus
dies

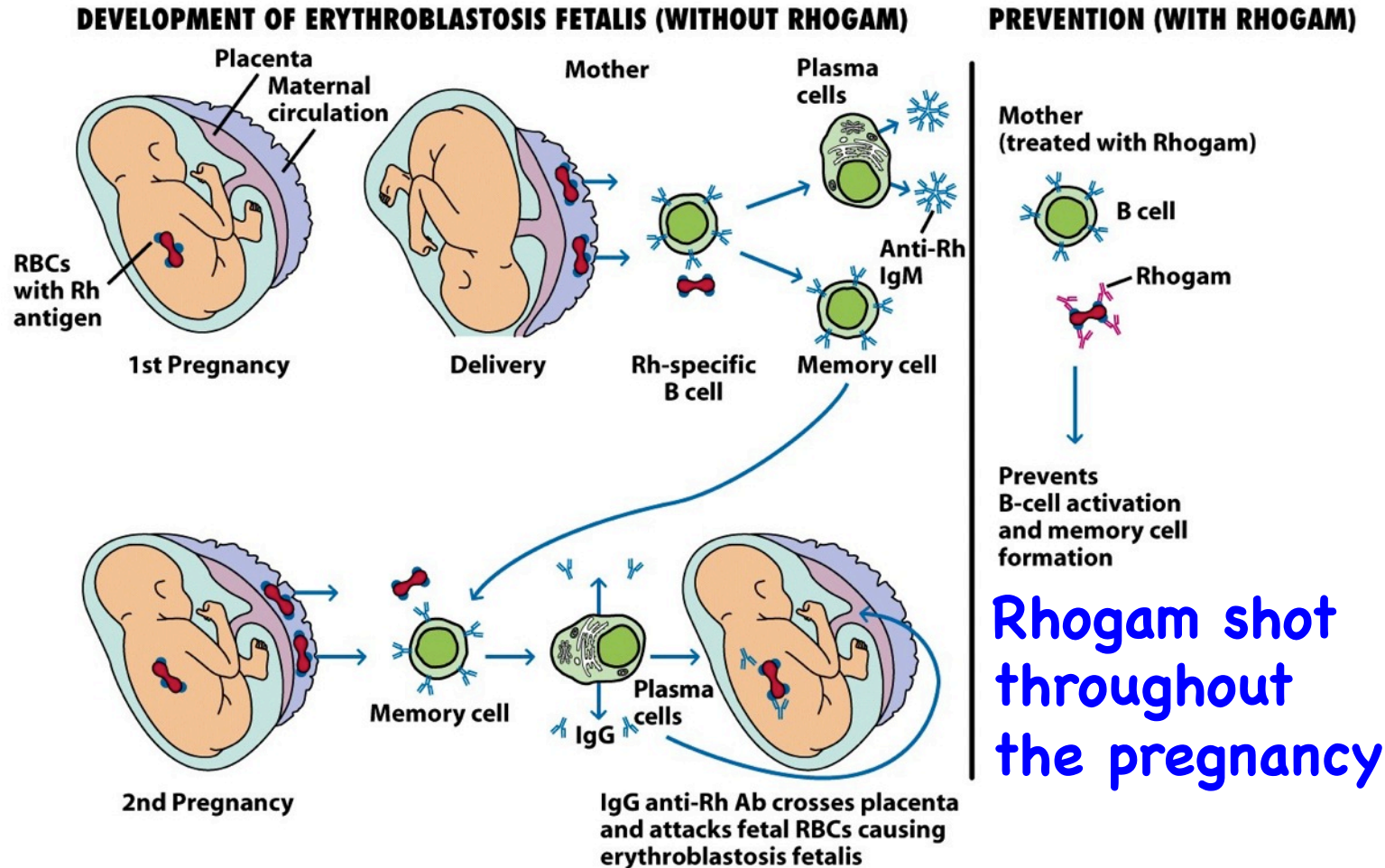
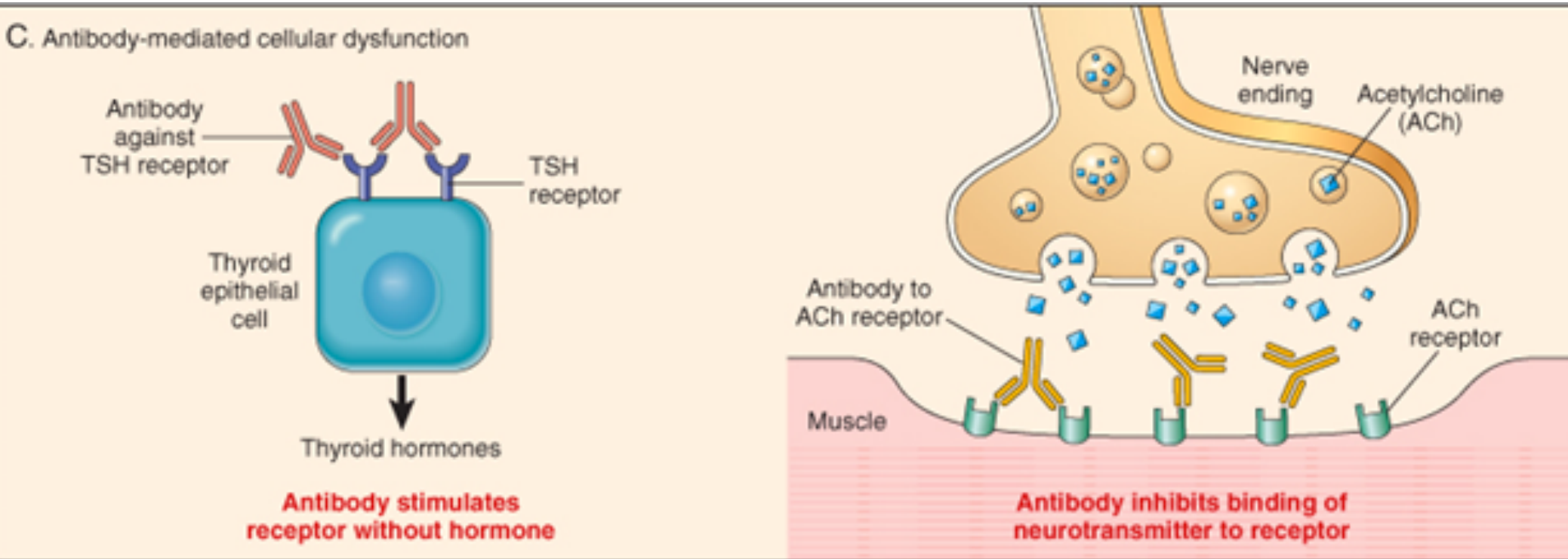


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Type II-like Autoimmune diseases



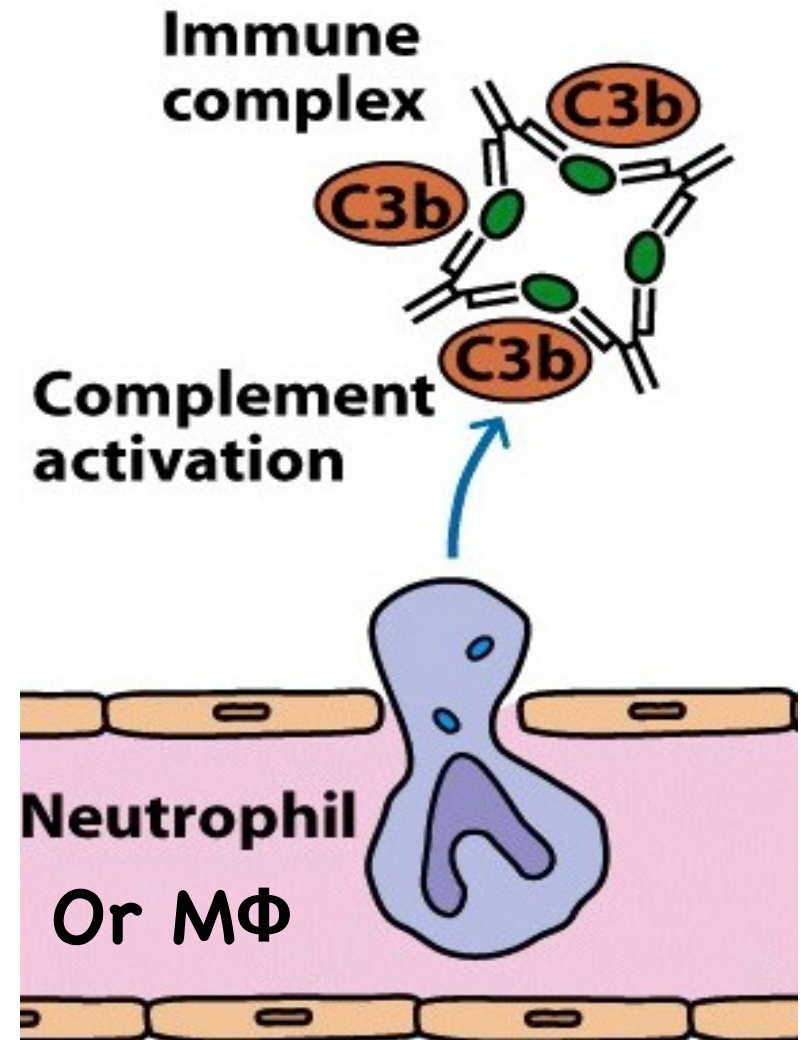
Graves disease

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Myasthenia gravis

Type III

- Is an **Immune Complex Reaction** to prolonged Ag exposure
- Mediated by large amounts of immune complexes (Ab-soluble antigens)
- The damage depends upon the site of complex deposition



Clearing Immune Complexes

- Immune complexes can damage tissues
- C3b coats immune complexes
- RBC have capability of binding C3b coated complexes and carrying them to liver and spleen to be cleared

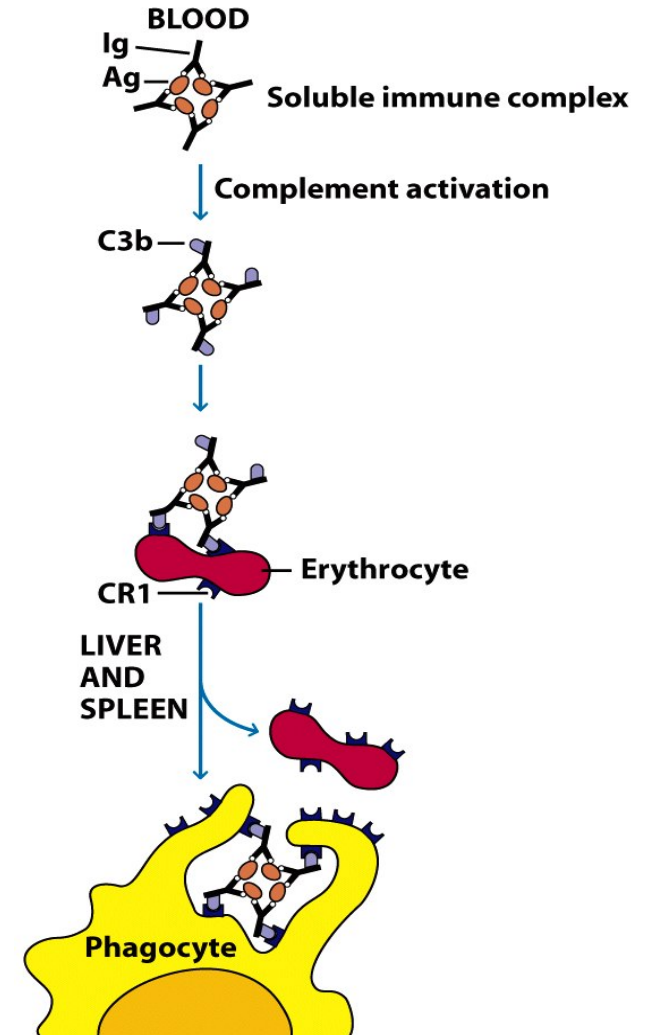
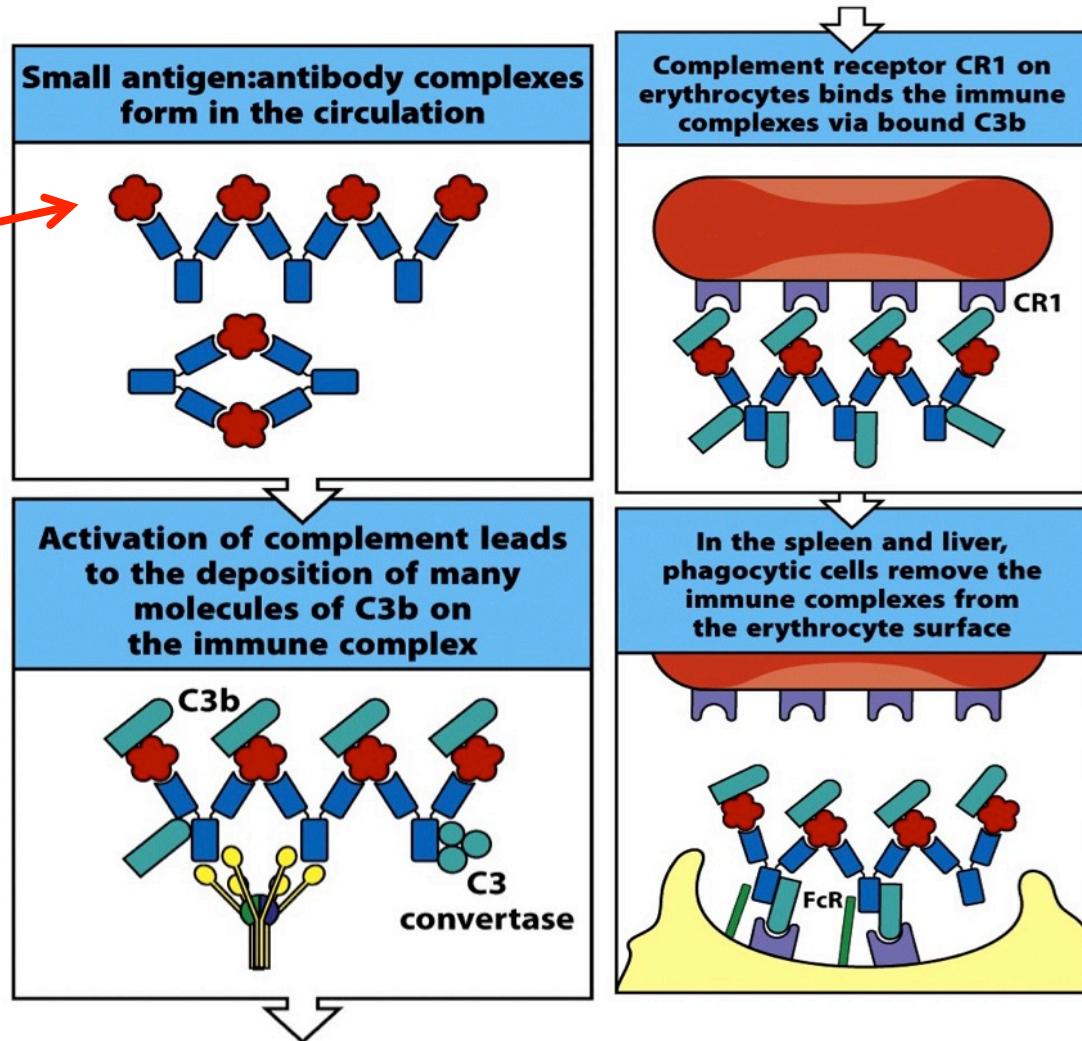


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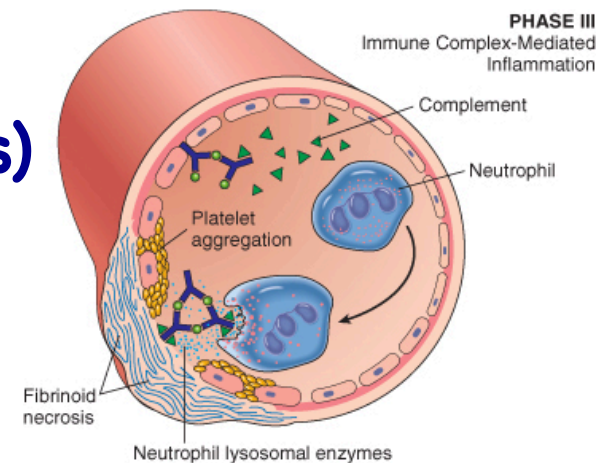
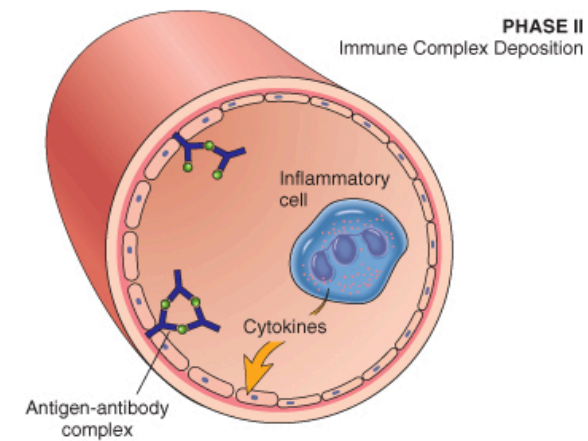
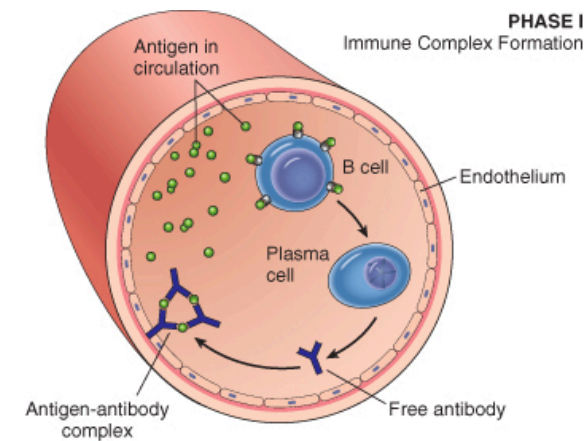
Clearing Immune Complexes

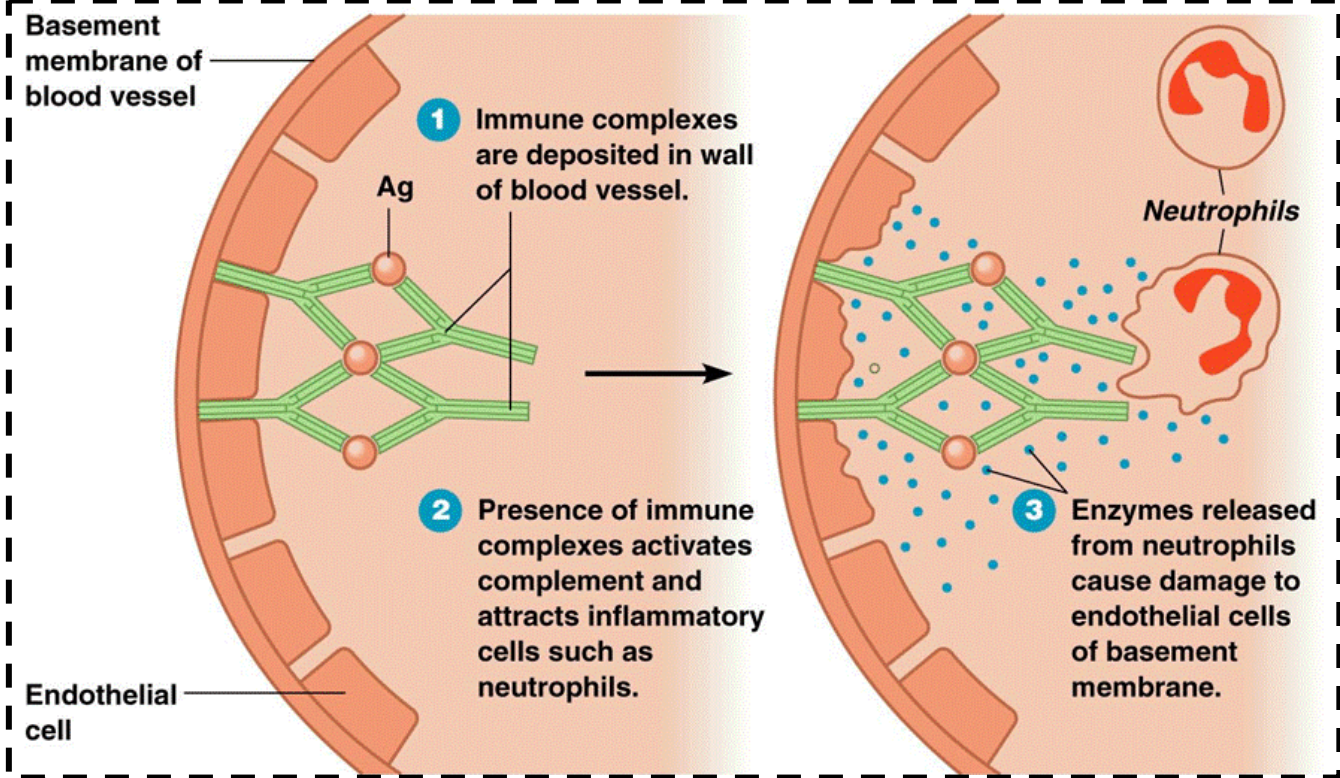
Virus Particle
Bacterial Toxin
Self Antigen



Systemic Immune Complex Reaction

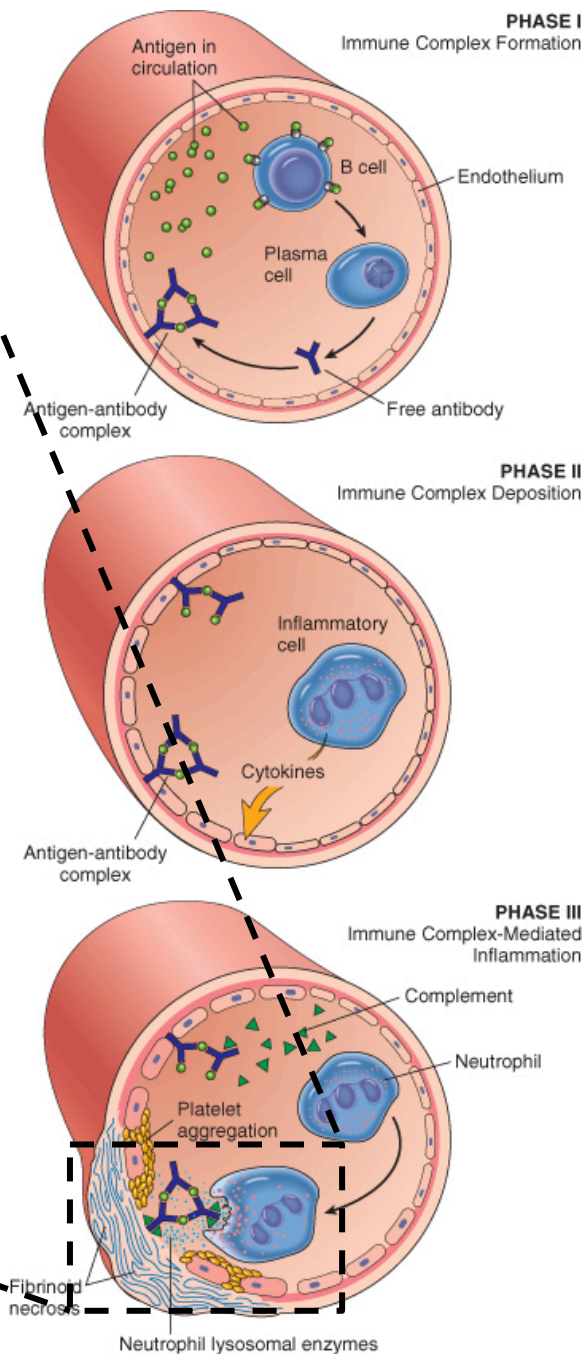
- Presence of large amount of antibodies in the serum against soluble antigen
 - Serum sickness
 - HAMA response
 - Autoimmune diseases (SLE, RA)
 - Drug reactions (penicillin, sulfonamides)
 - Infectious disease





systemic vasculitis

- Recruitment of neutrophils and Mφ
- Frustrated phagocytosis (IL-1, TNF- α)
- Platelets aggregation



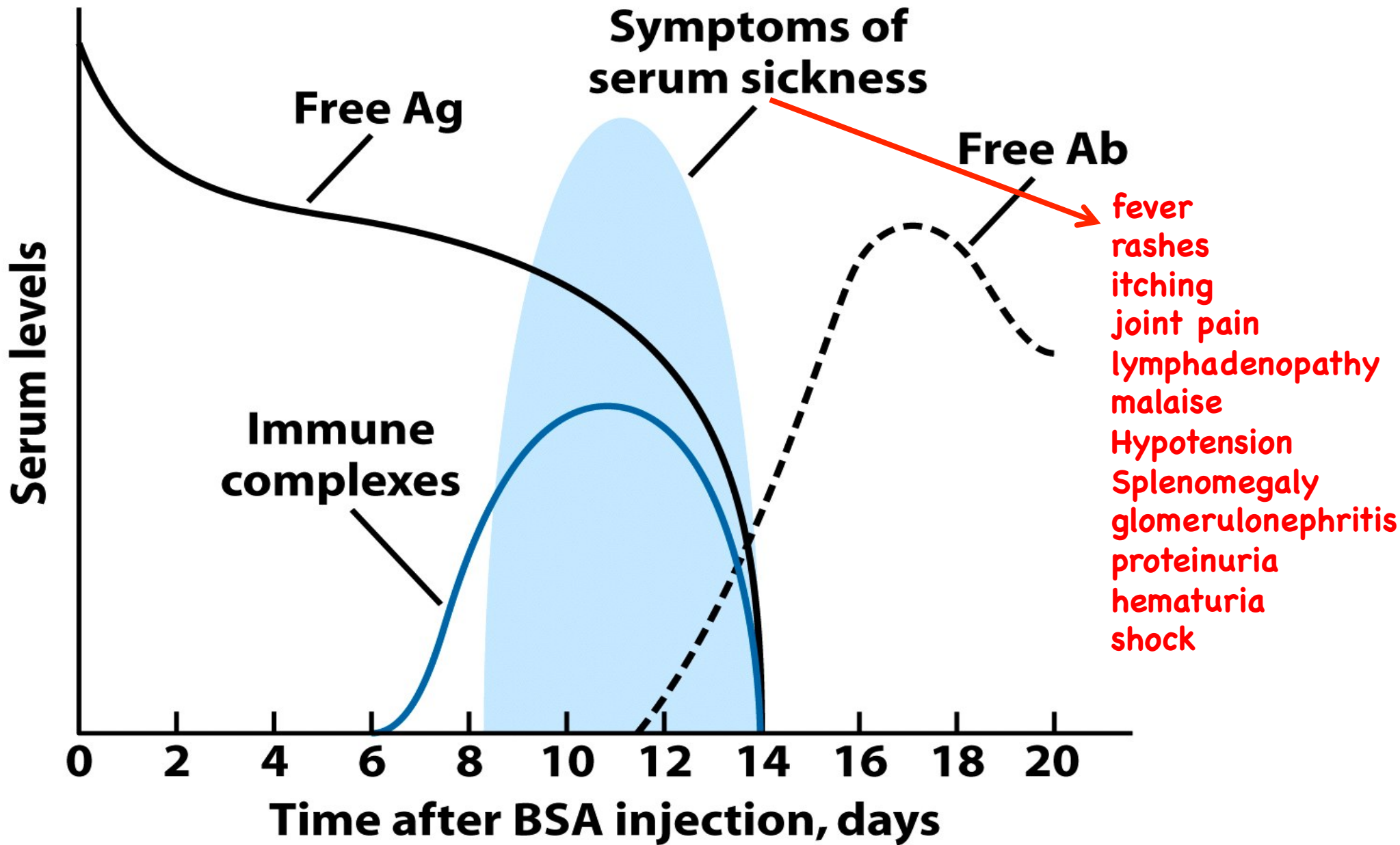
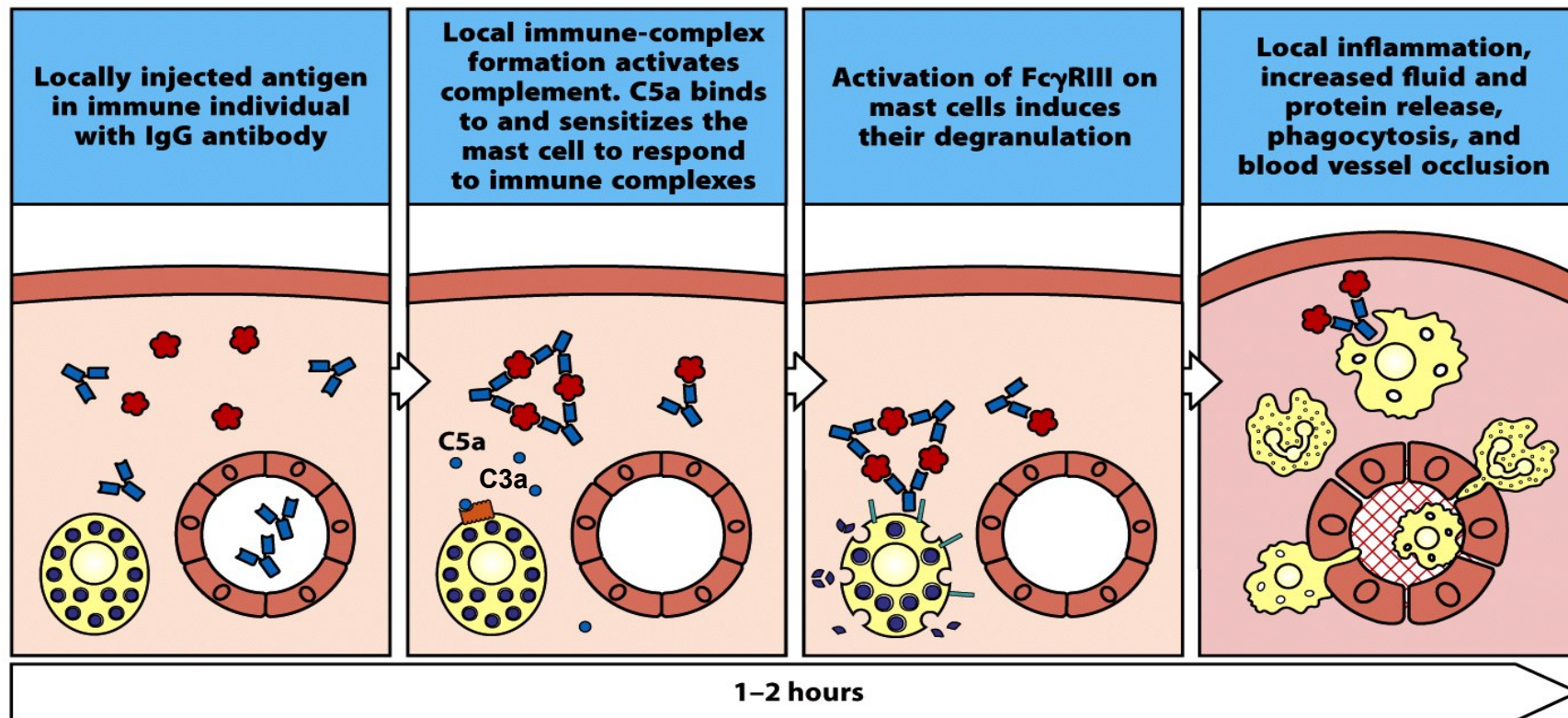


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Local Immune Complex Reaction

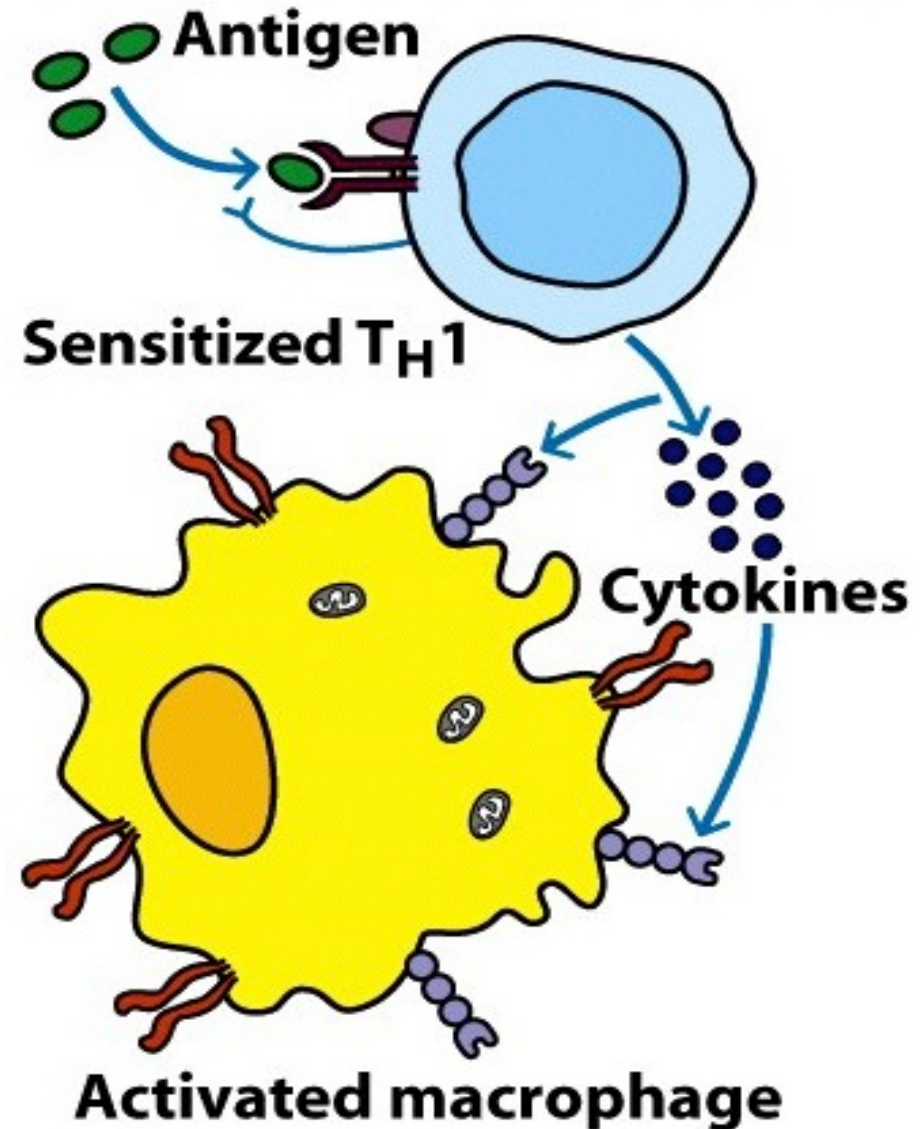
- Injection of antigen intradermally or subcutaneously into a body that has high level of antibody for that antigen (e.g. Arthus reaction, Bug bites)



**local
vasculitis**

Type IV

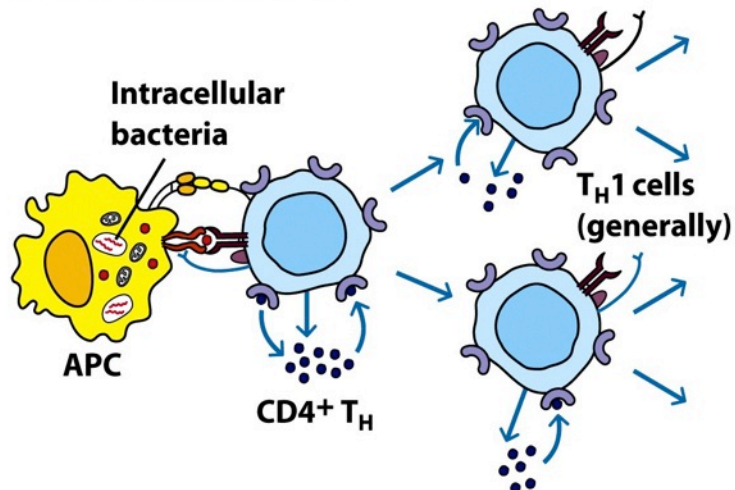
- Is a **Delayed-Type Hypersensitivity (DTH) Reaction**
- It is a T-cell mediated inflammatory response (no Ab involved)
- Ag-specific effector T cells lead to MΦ activation



Delayed-Type Hypersensitivity

- Can be elicited against exogenous or endogenous antigens (autoimmune T cells)

Sensitization phase

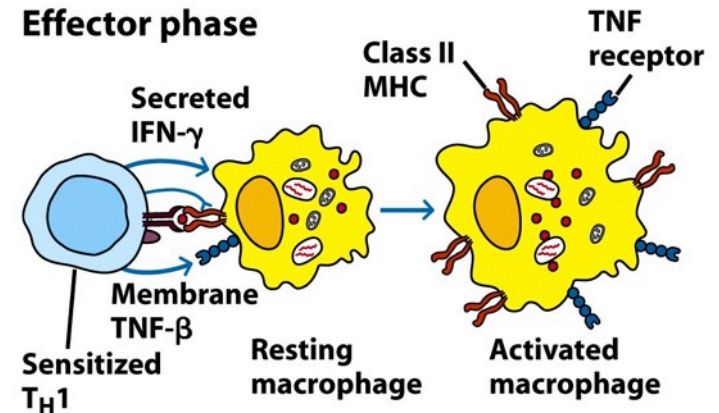


Antigen-presenting cells: Macrophages
Langerhans cells

DTH-mediating cells:
T_H1 cells generally
CD8 cells occasionally

Figure 15-17a
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Effector phase



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

Figure 15-17b
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Delayed-Type Hypersensitivity

- Three variants of Type-IV reactions:
 - Contact hypersensitivity (48-72 hours)
 - Tuberculin-type hypersensitivity (48-72 hours)
 - Granulomatous hypersensitivity (21-28 days)
- The local response is also accompanied by a variety of systemic immune responses, such as T cell proliferation and synthesis of cytokines including (IFN- γ)

Contact hypersensitivity

- Reaction at the point of contact with allergen
- Seen following contact with agents such as nickel, chromate, rubber, and pentadecacatechol



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Poison oak
(*Toxicodendron radicans*)

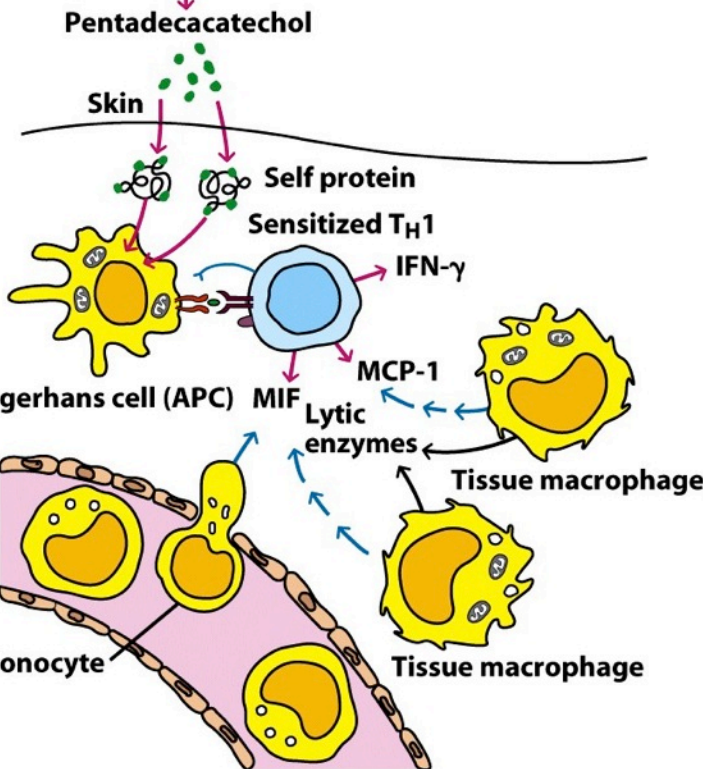


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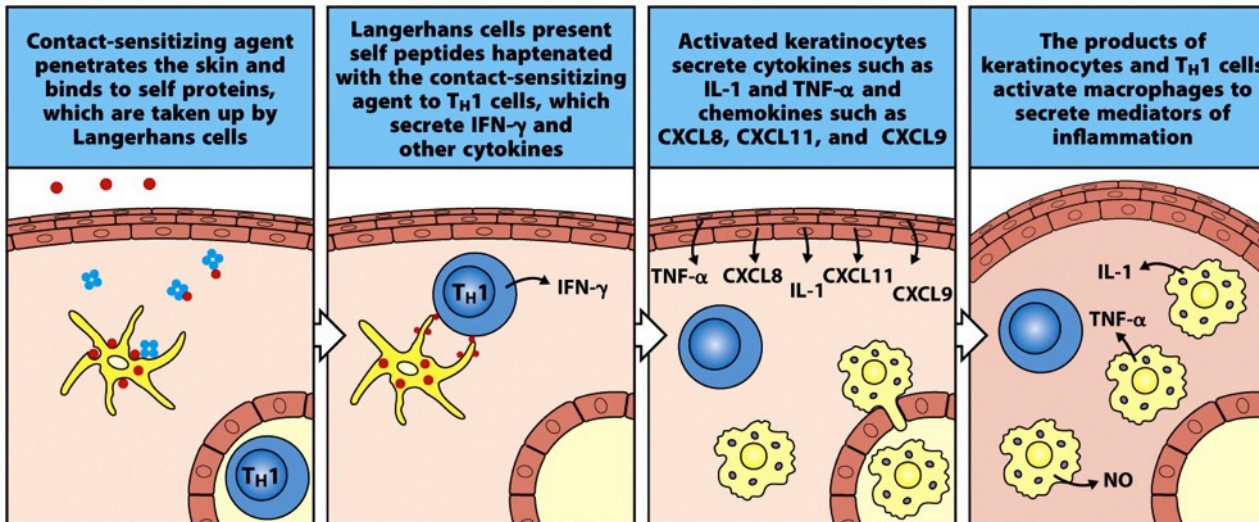


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Tuberculin-type hypersensitivity

- Induced by injection of soluble Ag from intracellular organisms such as *Mycobacterium tuberculosis* e.g. Tuberculin test (PPD test)

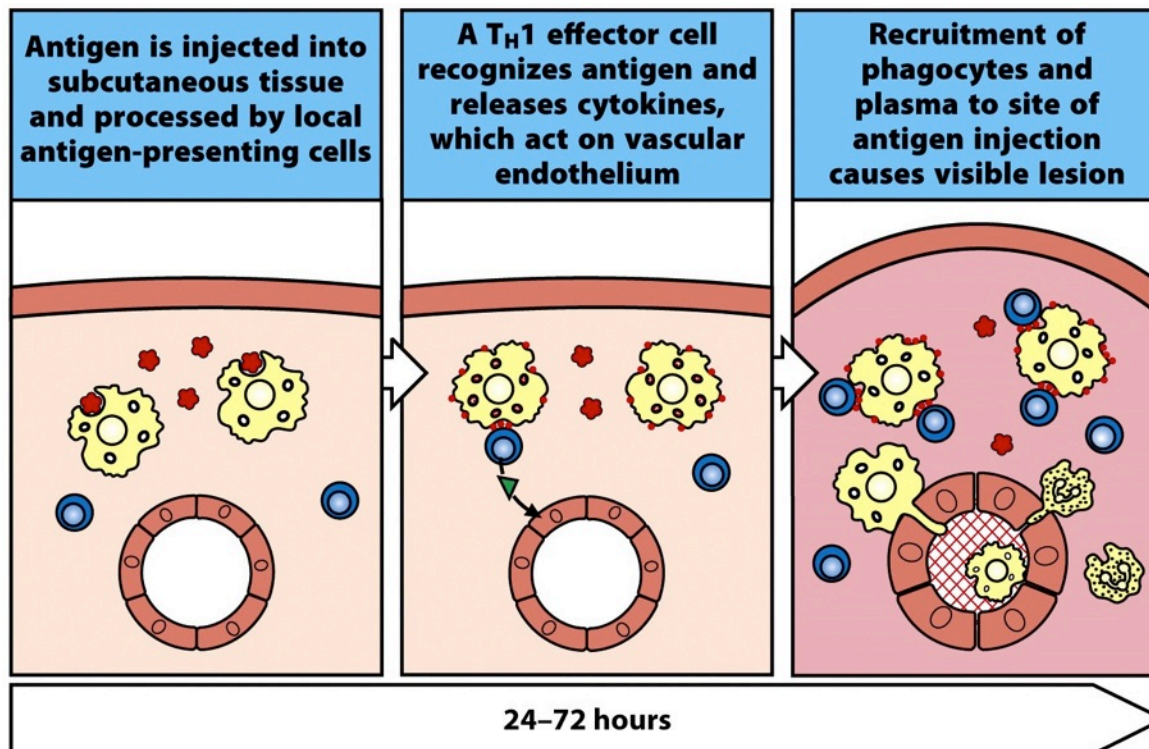


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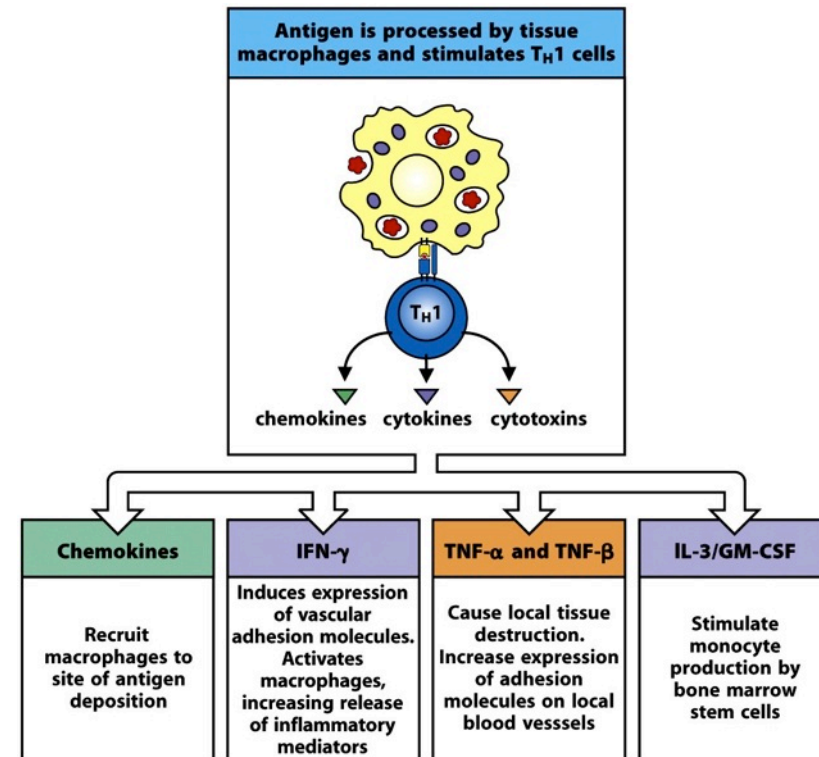


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Granulomatous hypersensitivity

- The most important form of Type-IV reactions
- Persistence of intracellular organism within MΦ
- Particles cannot be destroyed by MΦ
- Chronic stimulation of T cells and release of cytokines lead to the formation of epithelioid cell granuloma (central collection of epithelioid cells and MΦ surrounded by T cells)

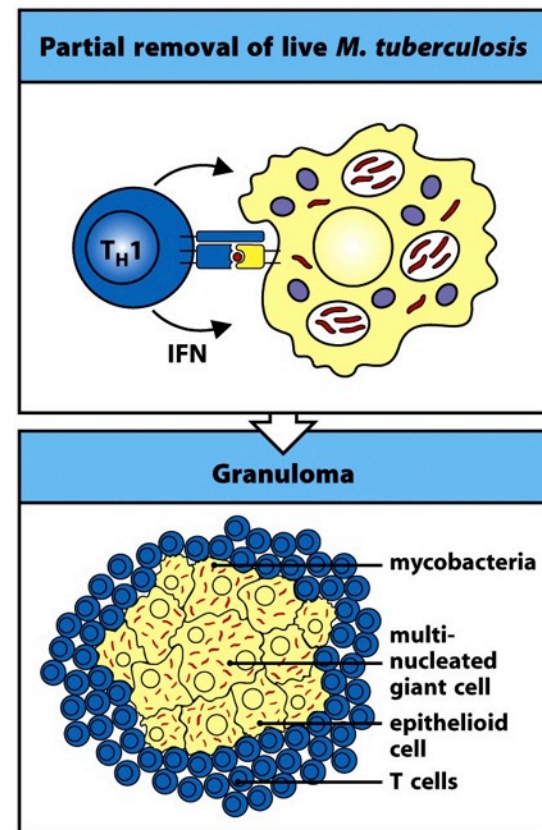
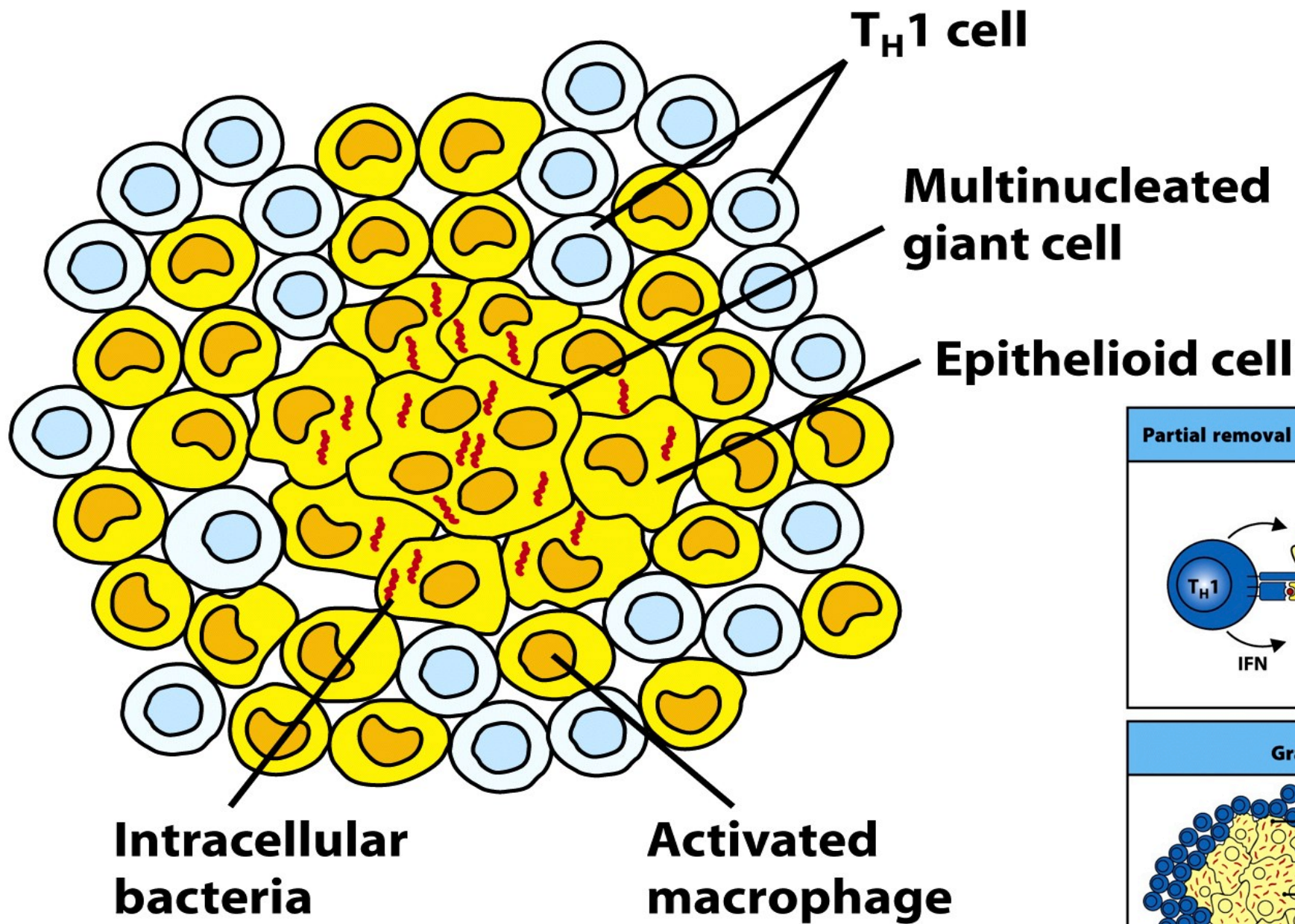


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TABLE 15-5**Penicillin-induced hypersensitive reactions**

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_H1 cells	Contact dermatitis

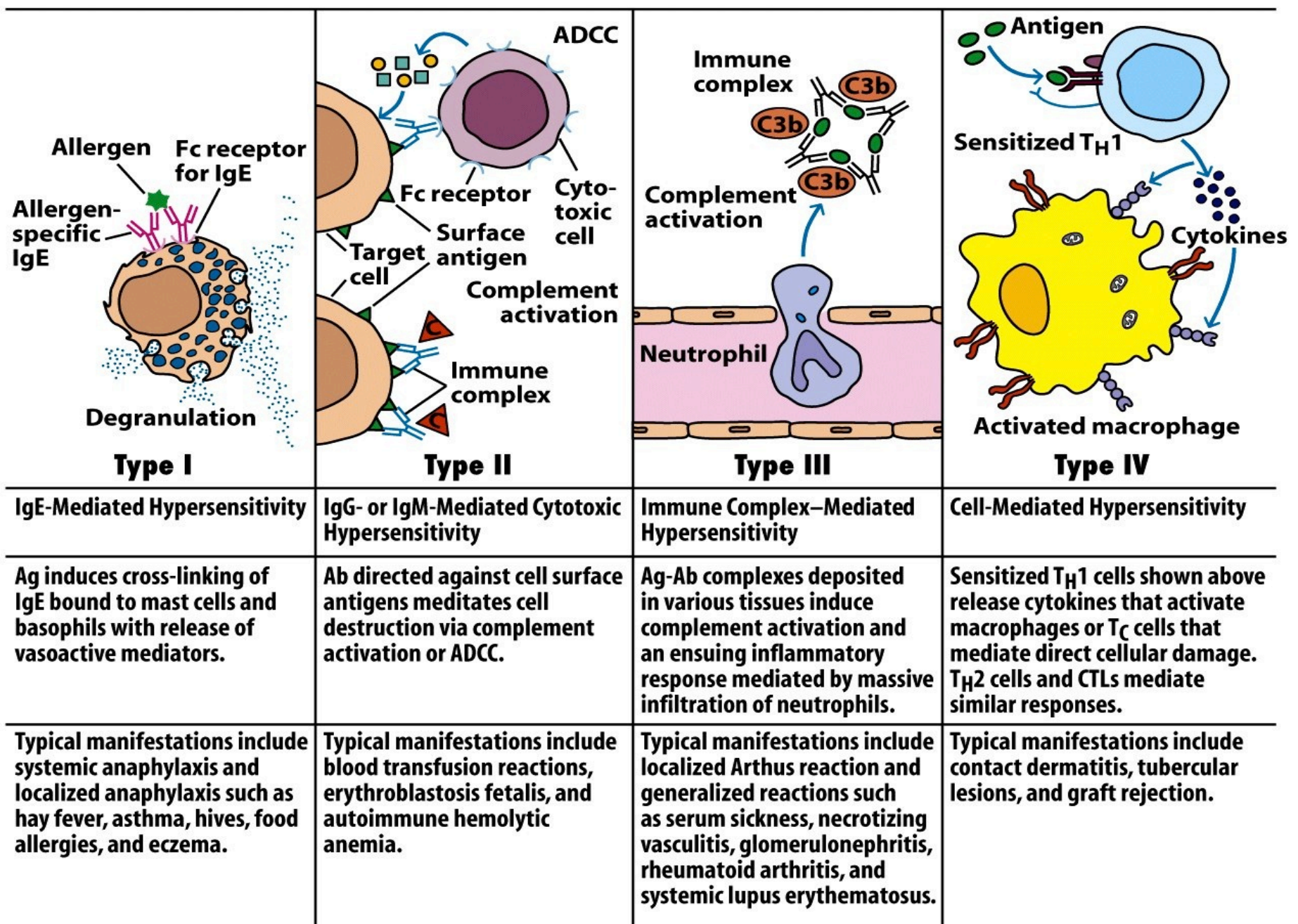


Figure 15-1
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You are now able to:

- ✓ List the four types of hypersensitivity reactions
- ✓ Describe the mechanism of each hypersensitivity reaction
- ✓ Understand the clinical manifestations and managements of some hypersensitivity reactions