

Hypersensitivity Reactions

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Reference
Kuby Immunology 8th Edition
Chapter 15

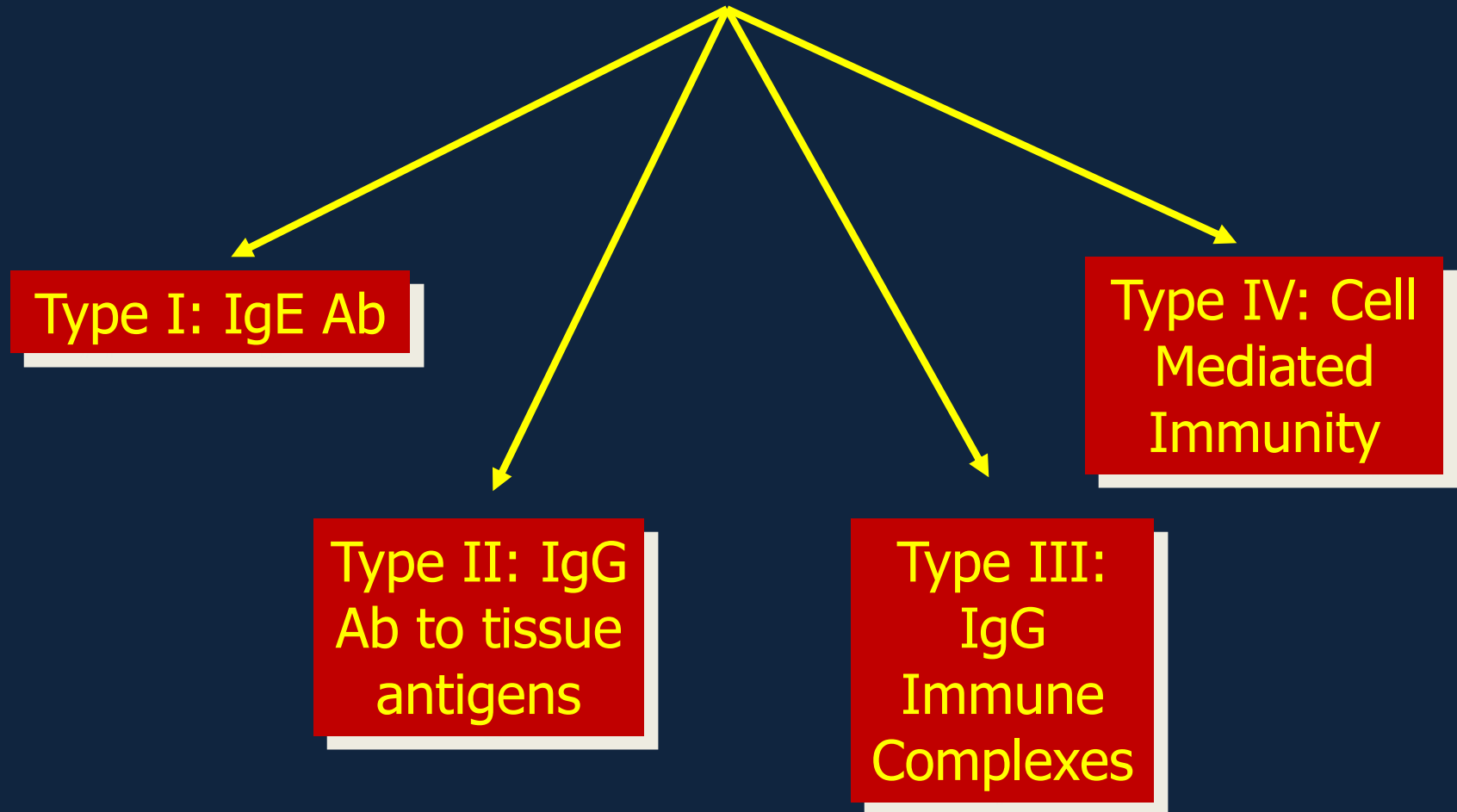
Objectives

- To know that hypersensitivity reactions are over and excessive immune responses that can be harmful to body in four different ways
- To be familiar with inflammatory processes in Type I hypersensitivity reaction that mediates allergic inflammation
- To recognize that Type II hypersensitivity deals with immune responses against antigens that are integral part of cell membrane and are usually associated with autoimmune disorders
- To know that Type III hypersensitivity reactions are mediated by immune complexes and cause vasculitis
- To describe Type IV hypersensitivity is a purely cell mediated immune response associated with chronic inflammation

What is hypersensitivity?

- **Protective immunity**: desirable reaction
- **Hypersensitivity**: undesirable reaction
- Undesirable responses can be mediated by
 - ***Antibody binding*** to antigens (Types I-III)
 - ***Cell mediated reaction*** to chemicals or proteins (Type IV)

Gel and Coombs Classification



Type I: Immediate Hypersensitivity

- Most people will not react to these allergens but some individuals “**atopic**” respond by producing large amounts of **IgE in response to those otherwise harmless substances**
- **Non-allergic** individuals respond to these allergens by producing **IgG** antibodies

Type I Hypersensitivity

- Also termed as:
Immediate Hypersensitivity

Allergic reactions

Anaphylactic reactions are **severe** and **rapidly progressing** systemic forms which can be quickly **life threatening**

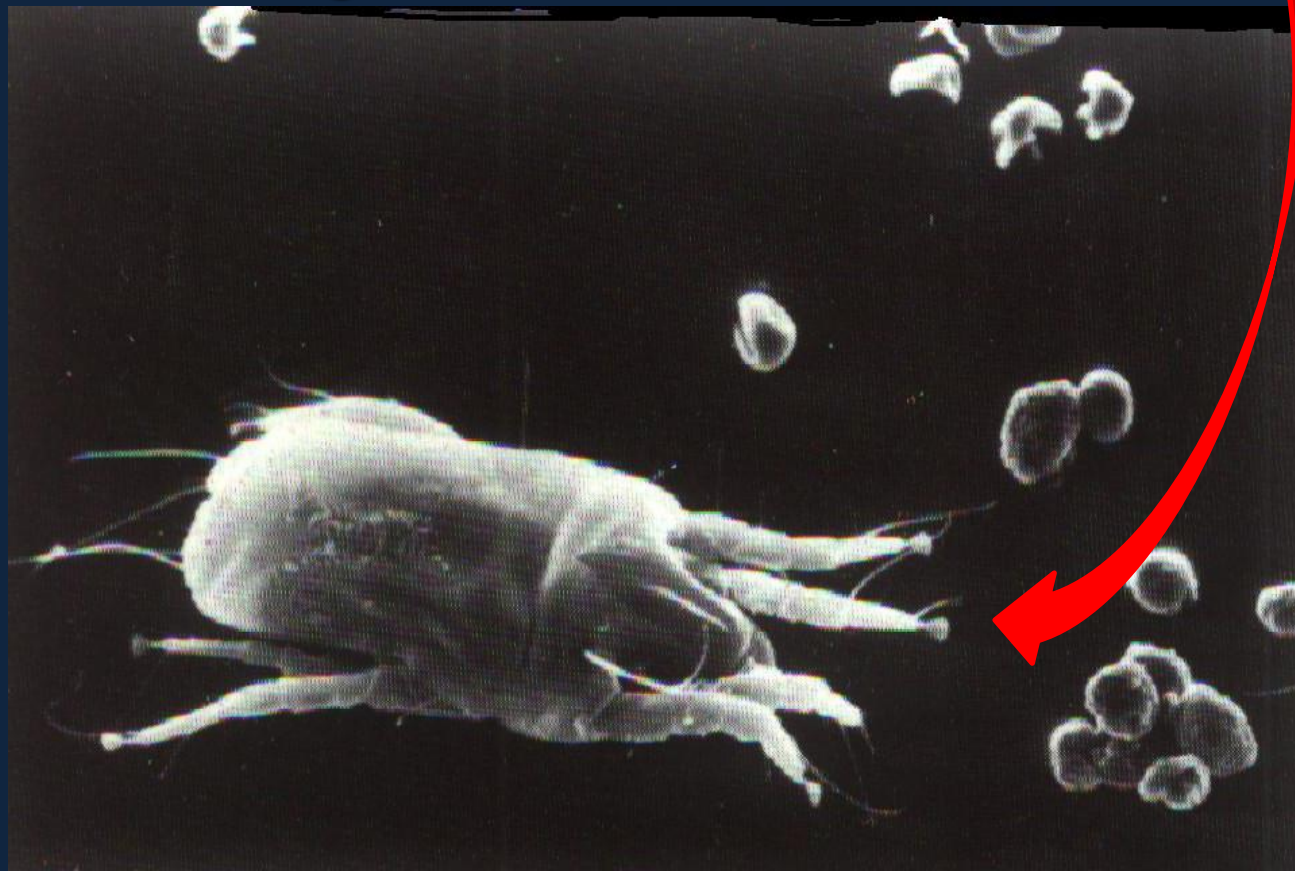
(Occurs within minutes to hours)

Features

- Antibody type: IgE
- Cellular components:
Mast cells, basophiles & eosinophils
- Antigens:
Also known as allergens
(antigens with low molecular weight & highly soluble)

Allergens

- Some of the allergens involved in type I hypersensitivity are: pollens, dust mite allergens, animal dander, nuts, shellfish, various drugs etc



Type I reactions occur in two phases

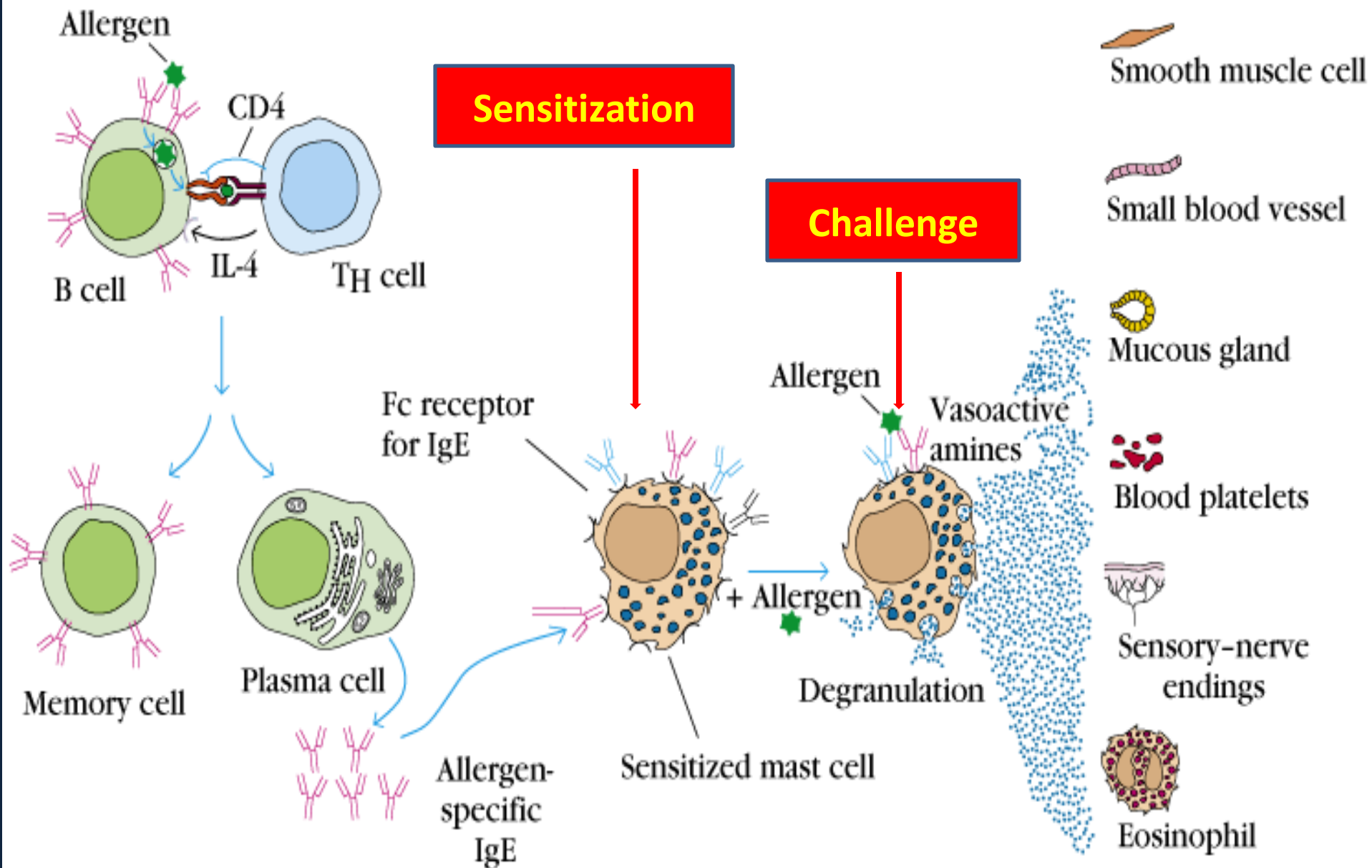
- **Sensitization phase**

First contact with allergens

- **Challenge phase**

Subsequent contact with allergens

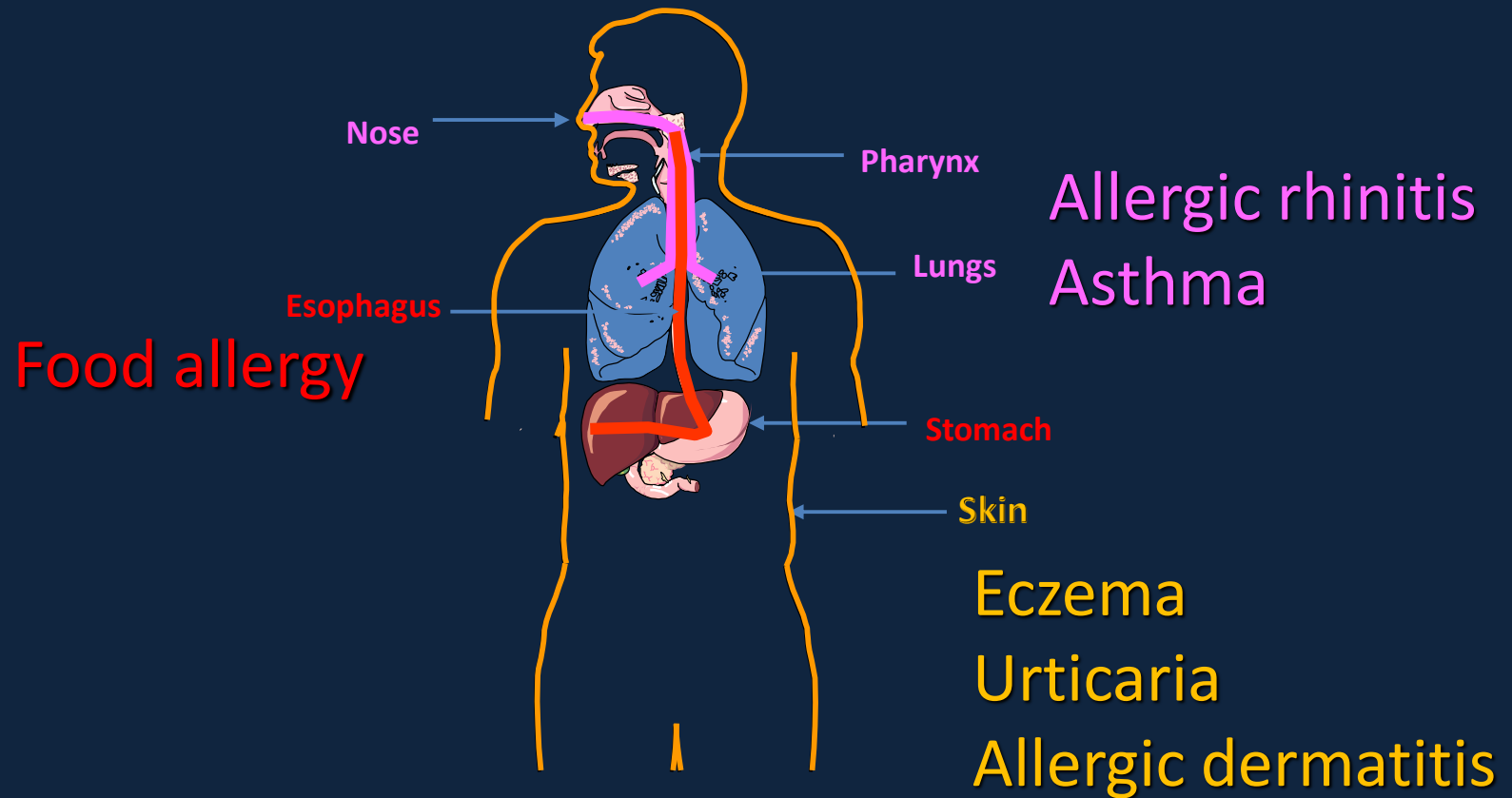
Type I Hypersensitivity (Immediate)



Primary and Secondary Mediators

Mediator	Effects
PRIMARY	
Histamine, heparin	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)

Allergy is a systemic disorder



Allergy: Rhinitis, Eczema & Conjunctivitis



* Injected allergens:

Hymenoptera (bees, wasps, ants) sting venom enters the blood stream

→ Systemic inflammation

→ Anaphylactic shock
(life - threatening)



❖ Anaphylactoid reactions:-

Are non - IgE mediated
may result from contrast media or
local anesthetics

Diagnosis of Allergy

Skin Prick test

1. Skin prick test (SPT)
2. Specific IgE measurement (RAST)
3. Elimination / Provocation test (Food allergy)

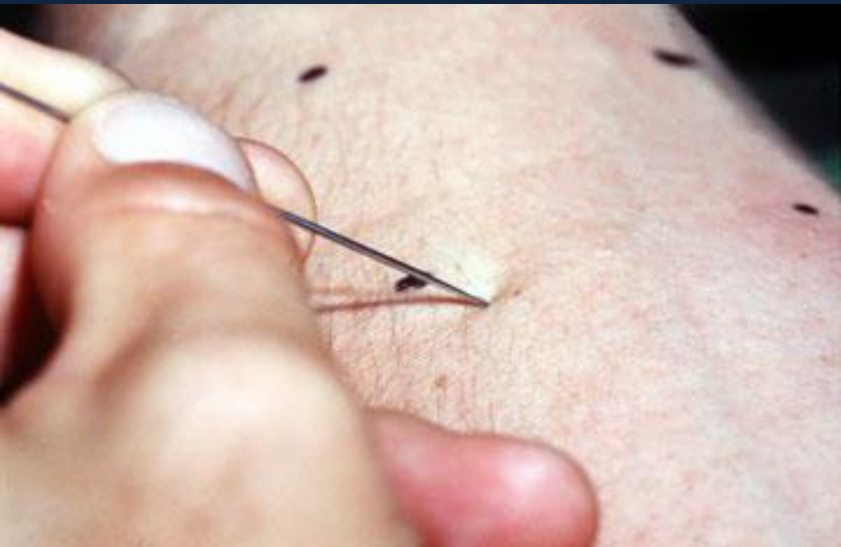


Figure 15-10
Kuby IMMUNOLOGY, Sixth Edition
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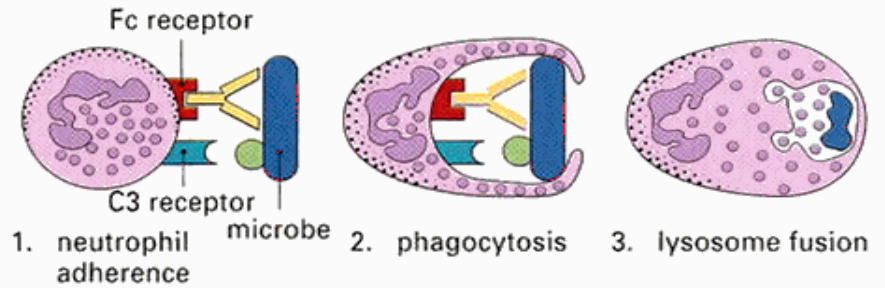
Type II Hypersensitivity Reactions

- Features:-

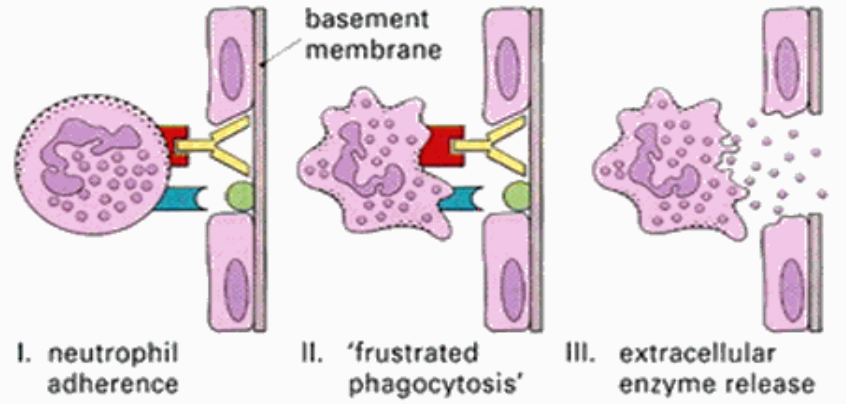
- IgG (or IgM)
 - Antigens: bound to cell membranes
 - (Self antigens)
 - Exogenous antigens (microbial)
- Complement activation (Invariable)

Type II Damage

Normal antimicrobial action

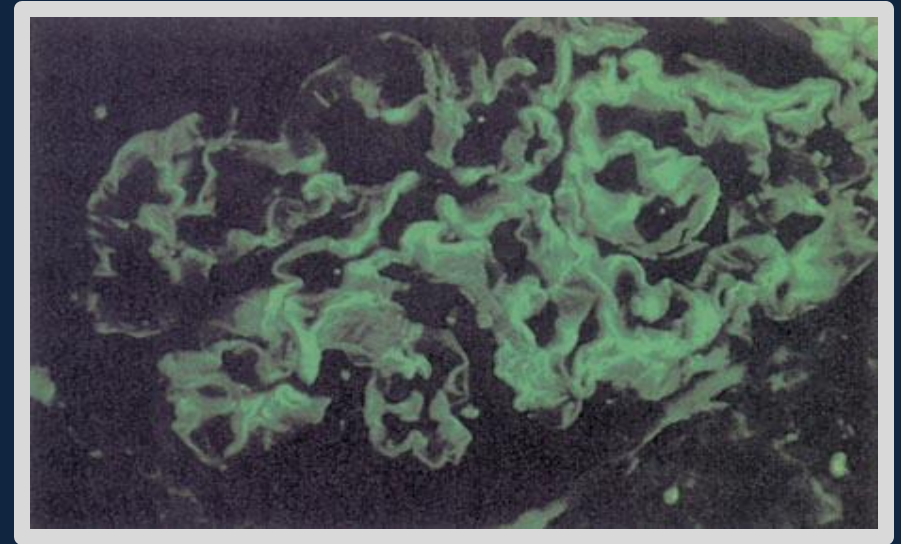


Type II hypersensitivity reaction



Clinical examples:

Glomerulonephritis
(anti-glomerular
basement membrane)



Mis-matched blood
transfusion



Diagnosis

- Detection of antibodies and antigens by Immunofluorescence in tissue biopsy specimens e.g. kidney, skin etc.

Type III: Immune complex hypersensitivity

- When an antigen reacts with an antibody the product they form is called an **immune complex** which is capable of inducing an inflammatory response
- Immune complexes are deposited in tissues like kidneys (nephritis), joints (arthritis) or blood vessels (vasculitis)

Type III Hypersensitivity (immune-complex mediated)

- Features

Antibody (IgG/ or IgM) + Antigen (soluble)



- Immune – Complex formation

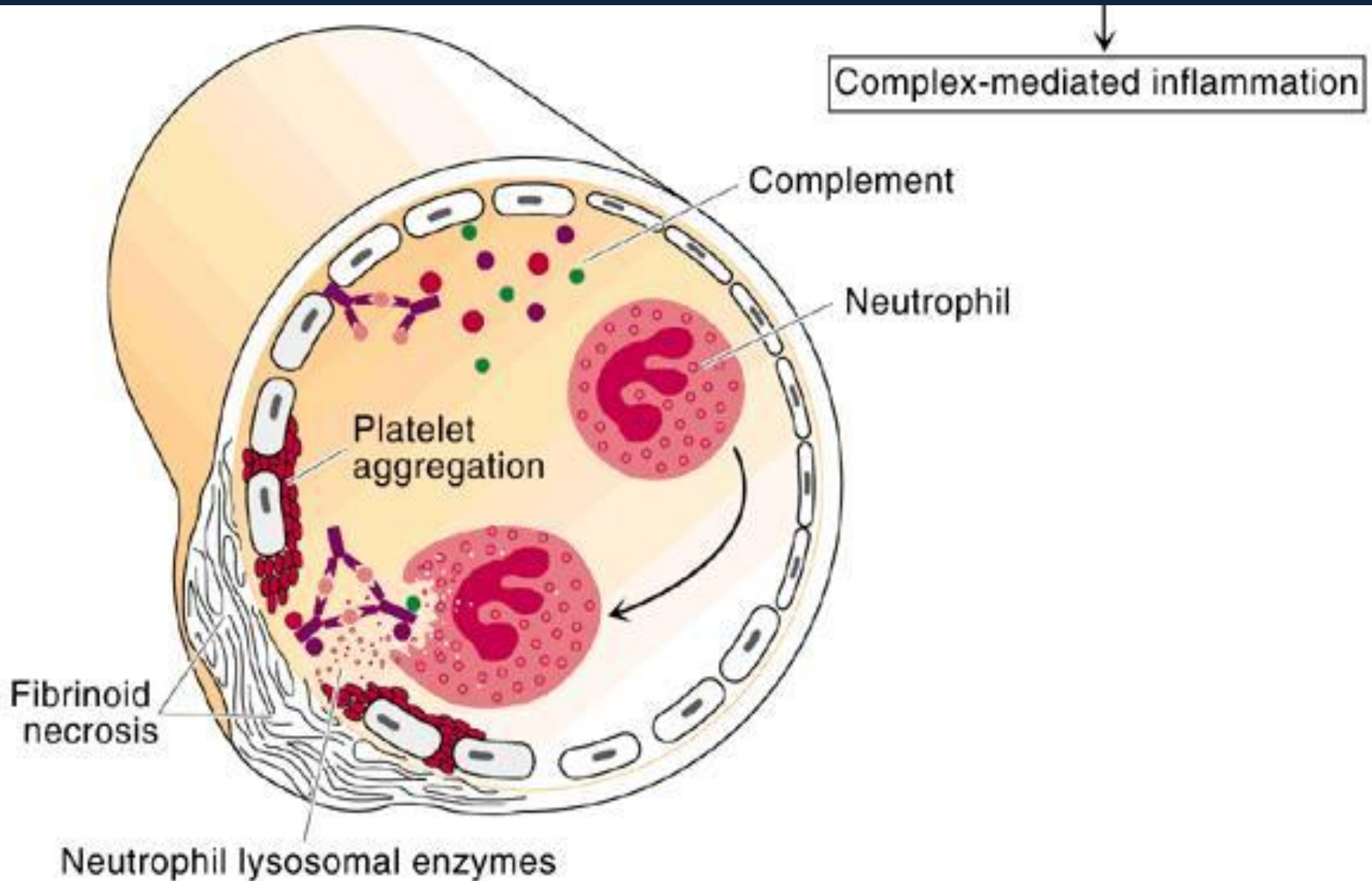


- Complement activation



- Attraction of inflammatory cells

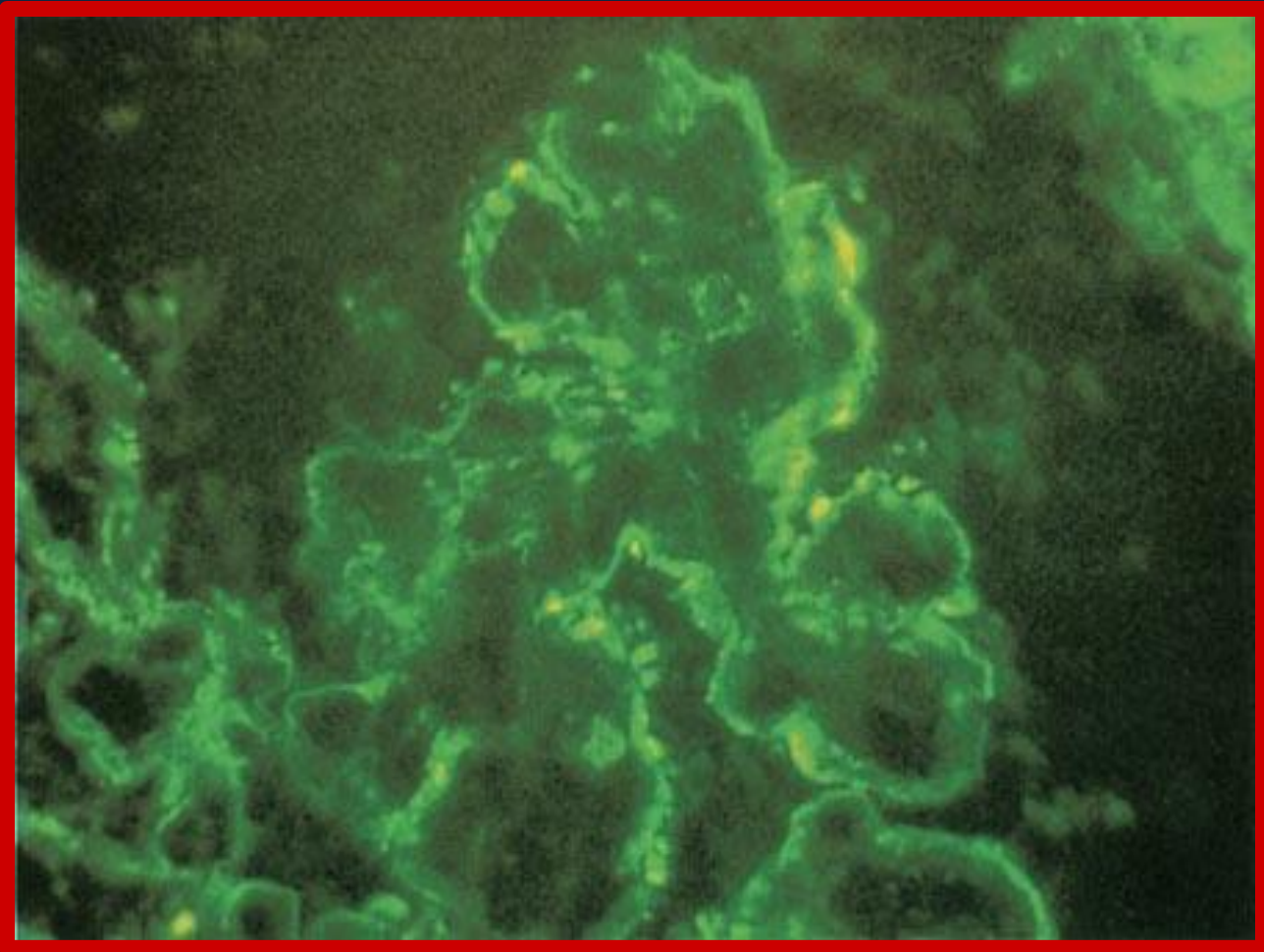
Type III Reactions



Type III Hypers. Reactions

Clinical examples:

Glomerulonephritis: Rheumatoid arthritis, SLE



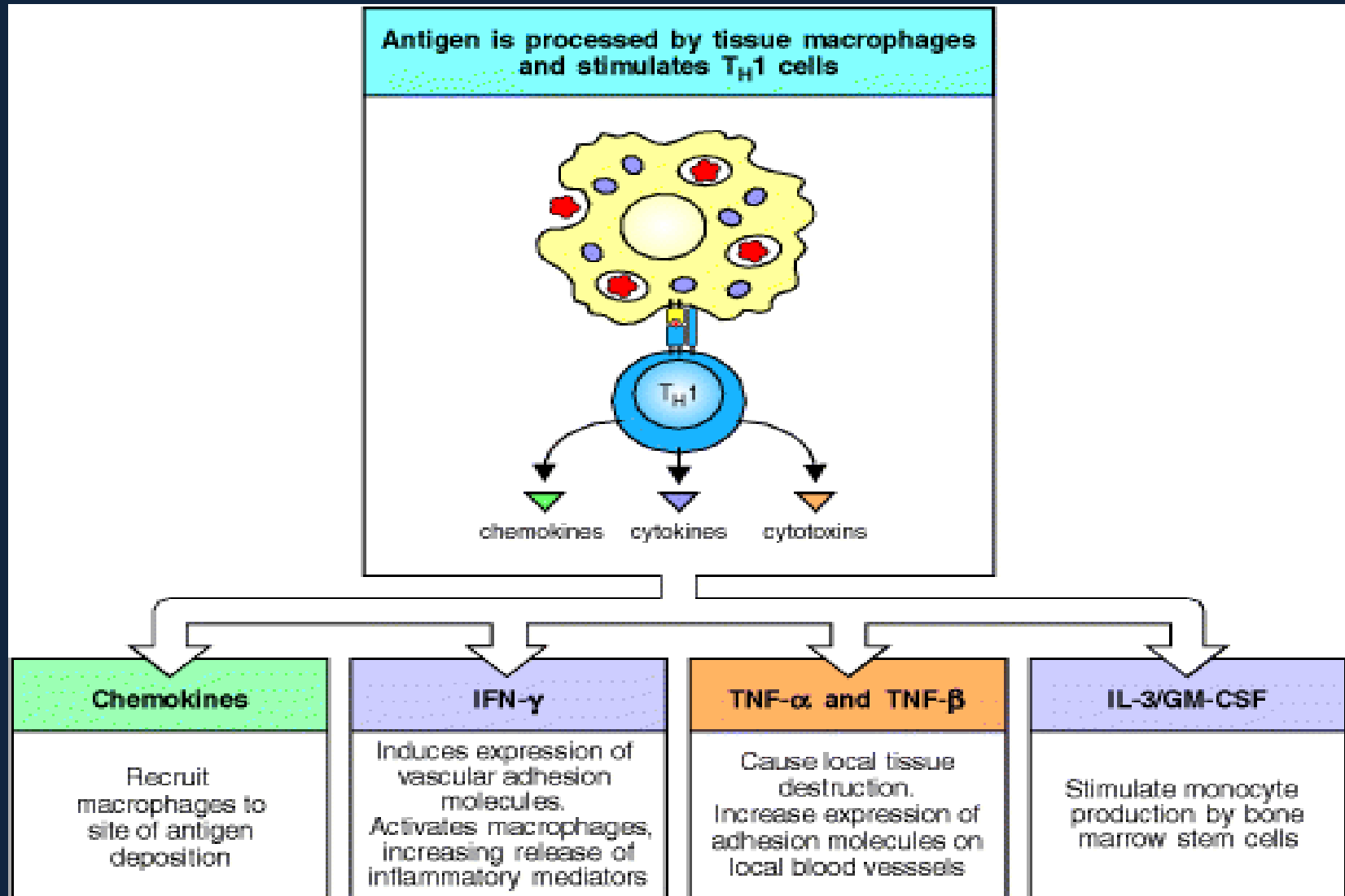
Diagnosis of Type III Hypers. Reactions

Demonstration of specific immune
complexes in the blood or tissues by:
Immunofluoresence

Type IV hypersensitivity reactions (Delayed Hypersensitivity)

- Features
- Cell mediated immune response
 - Antigen dependent T cell (**CD4 generally and CD8 occasionally**) activation via MHC Class I or II
- Activated macrophages
- Delayed onset (2-4 days)
- Abnormal cellular response
 - (**Granuloma formation**)

Mediators released by T_{DTH} cells



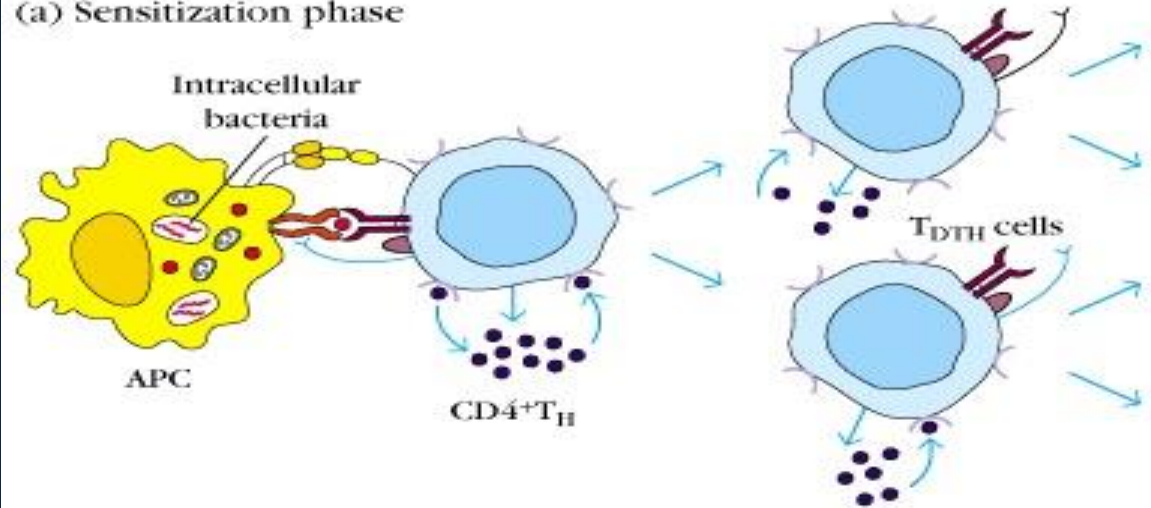
Development of DTH Response

Sensitization phase:
1-2 week period

Effector phase:
24-72 hours

Effector cells
(activated macs)
act non-specifically

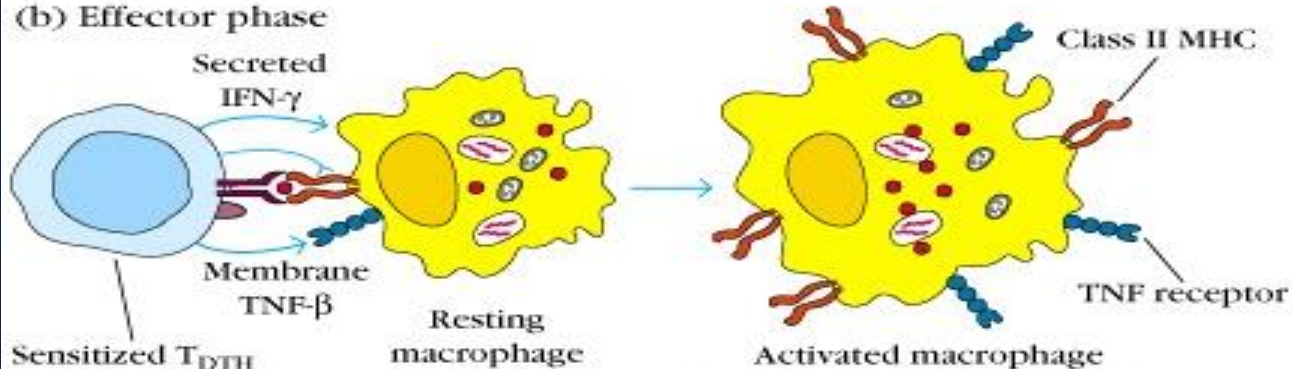
(a) Sensitization phase



Antigen-presenting cells:
Macrophages
Langerhans cells

T_{DTH} cells:
T_H1 cells (generally)
CD8+ cells (occasionally)

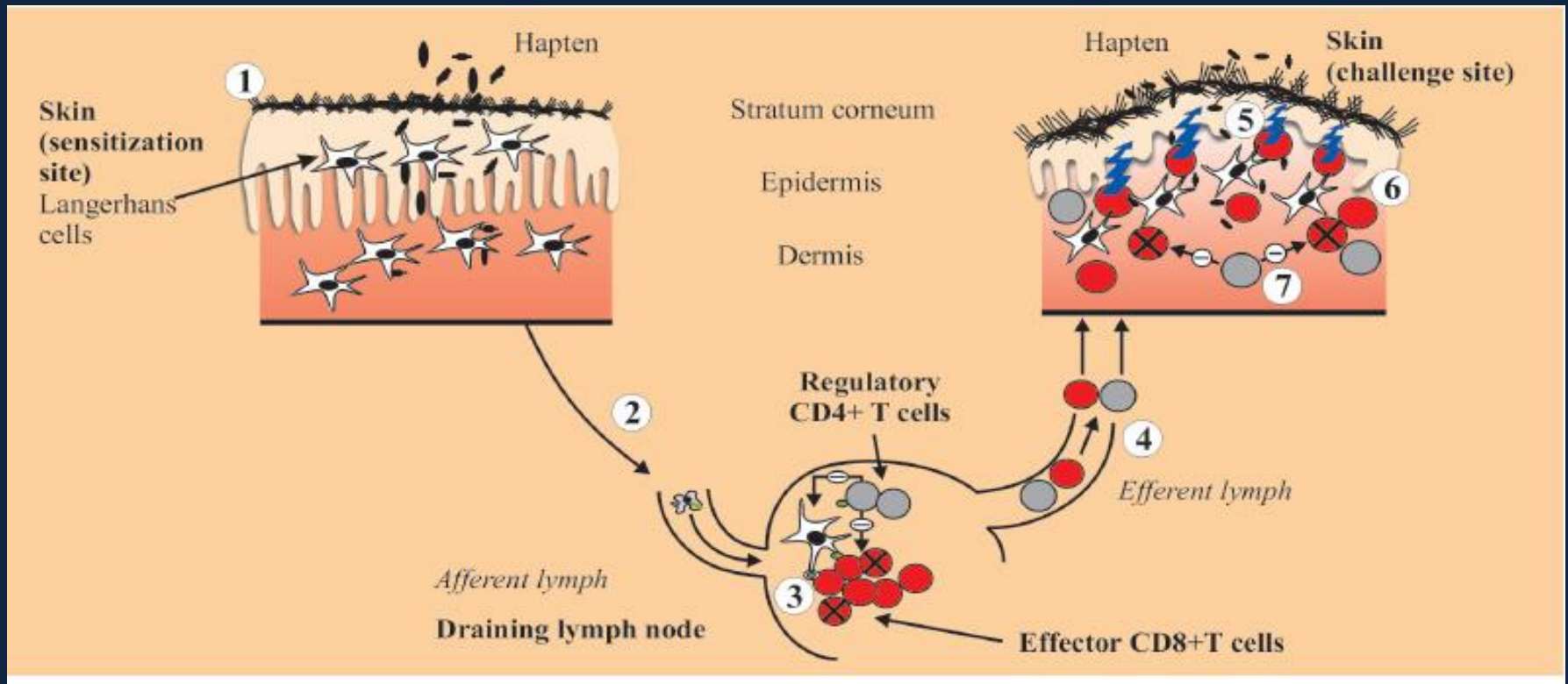
(b) Effector phase



T_{DTH} secretions:
Cytokines: IFN- γ , TNF- β , IL-2,
IL-3, GM-CSF
Chemokines: IL-8, MCAF, MIF

Effects of macrophage activation:
 \uparrow Class II MHC molecules
 \uparrow TNF receptors
 \uparrow Oxygen radicals
 \uparrow Nitric oxide

Pathophysiology of Contact dermatitis.

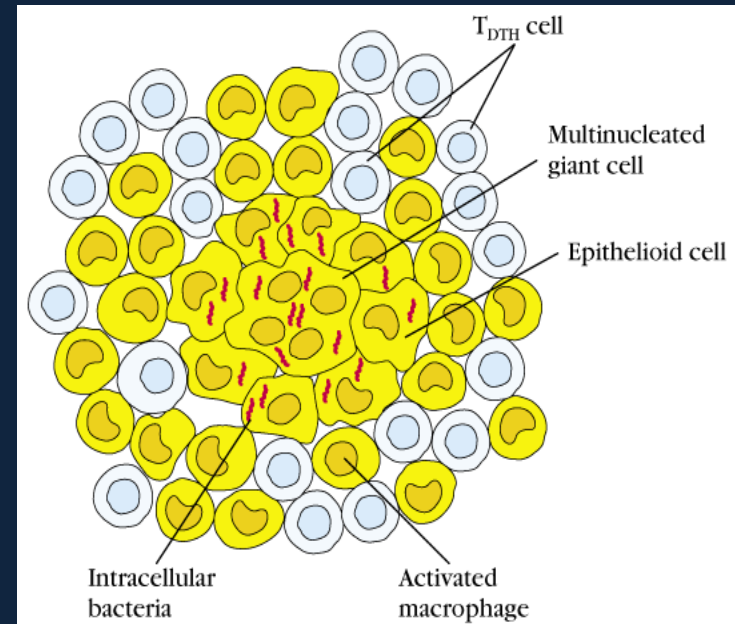


Type IV clinical examples:

Contact dermatitis



TB granuloma
(persistent antigen)



Diagnosis (Type IV)

1. Delayed skin test (Mantoux test)
2. Patch test (Contact dermatitis)
3. Lymphocyte transformation test

Skin Patch Test



Take Home Message

- 1. Type I (IgE), II (IgG) and III (IgG) hypersensitivity reactions are mediated by *antibodies* whereas Type IV hypersensitivity reaction is a *cell* mediated immune response.
- 2. Hypersensitivity reactions are *undesirable*, *excessive*, and *aberrant* immune responses associated with disorders such as allergy, autoimmunity and chronic inflammation.