Hypersensitivity

Immunopathology

1) An overactive immune response

Hypersensitivity

2) Failure of appropriate recognition

Autoimmune diseases

Hypersensitivity

What is Hypersensitivity?

Harmful **antigen-specific immune responses** , occur when an individual who has been **primed** by an antigen **subsequently encounters the same antigen**, produce **tissue injury** and **dysfunction**

Terminology - Hypersensitivity

- **Allergen：** A substance that causes an allergic reaction

- **Atopy：** **G**enetic predisposition to synthesize inappropriate levels of IgE specific for external allergens

- **Sensitization:** Repeated exposure to allergens initiates immune response that generates antibody isotype.

Types of Hypersensitivity

Gel and Coombs classification of hypersensitivities

1. **Type I Hypersensitivity**
2. **Type II Hypersensitivity**
3. **Type III Hypersensitivity**
4. **Type IV Hypersensitivity**

- Types I, II and III - antibody mediated
- Type IV - cell mediated

Type I Hypersensitivity /

Immediate-type hypersensitivity

Type I hypersensitivity

Characteristics

- Occur quickly
- Mediated by serum IgE
- Systemic and regional tissue dysfunction
- Genetic predisposition

COMPONENTS IN TYPE I HYPERSENSITIVITY

Allergen：

- Pollen, dust mite, insects etc
- Selectively activate CD4 (Th2) cells and B cells

IgE：

- Produced by mucosal B cells in the lamina Propria
- Special affinity to the same cell
- IL-4 is essential to switch B cells to IgE production

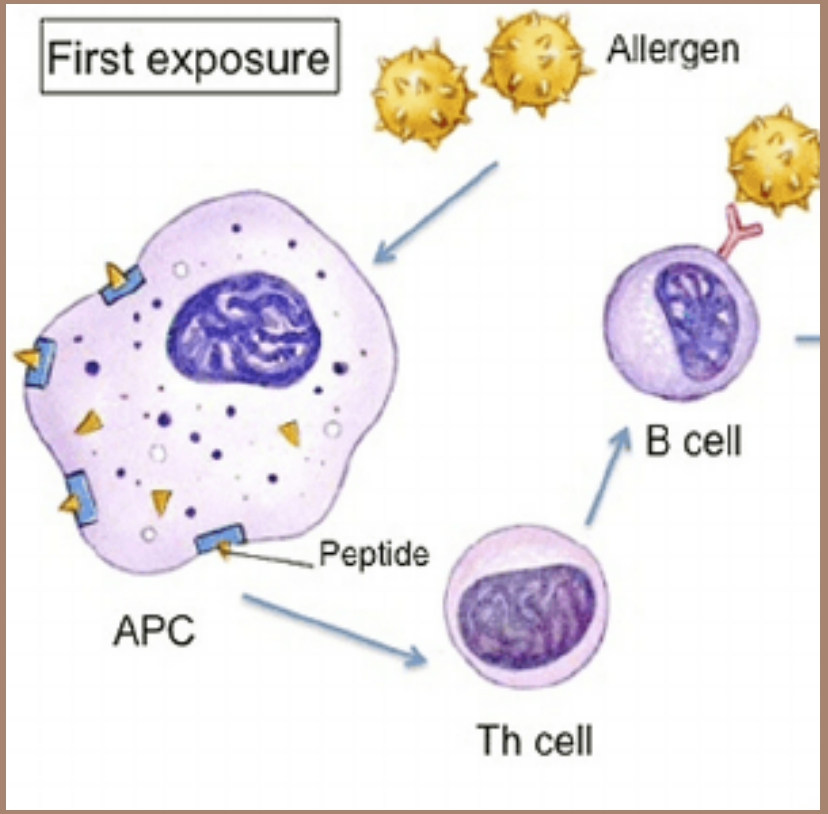
Pathogenic mechanisms

Priming stage

First exposure to allergen

Allergen stimulates formation of antibody (IgE type)

IgE fixes, by its Fc portion to High affinity receptor of the IgE on mast cell, Basophils & eosinophils



Pathogenic mechanisms

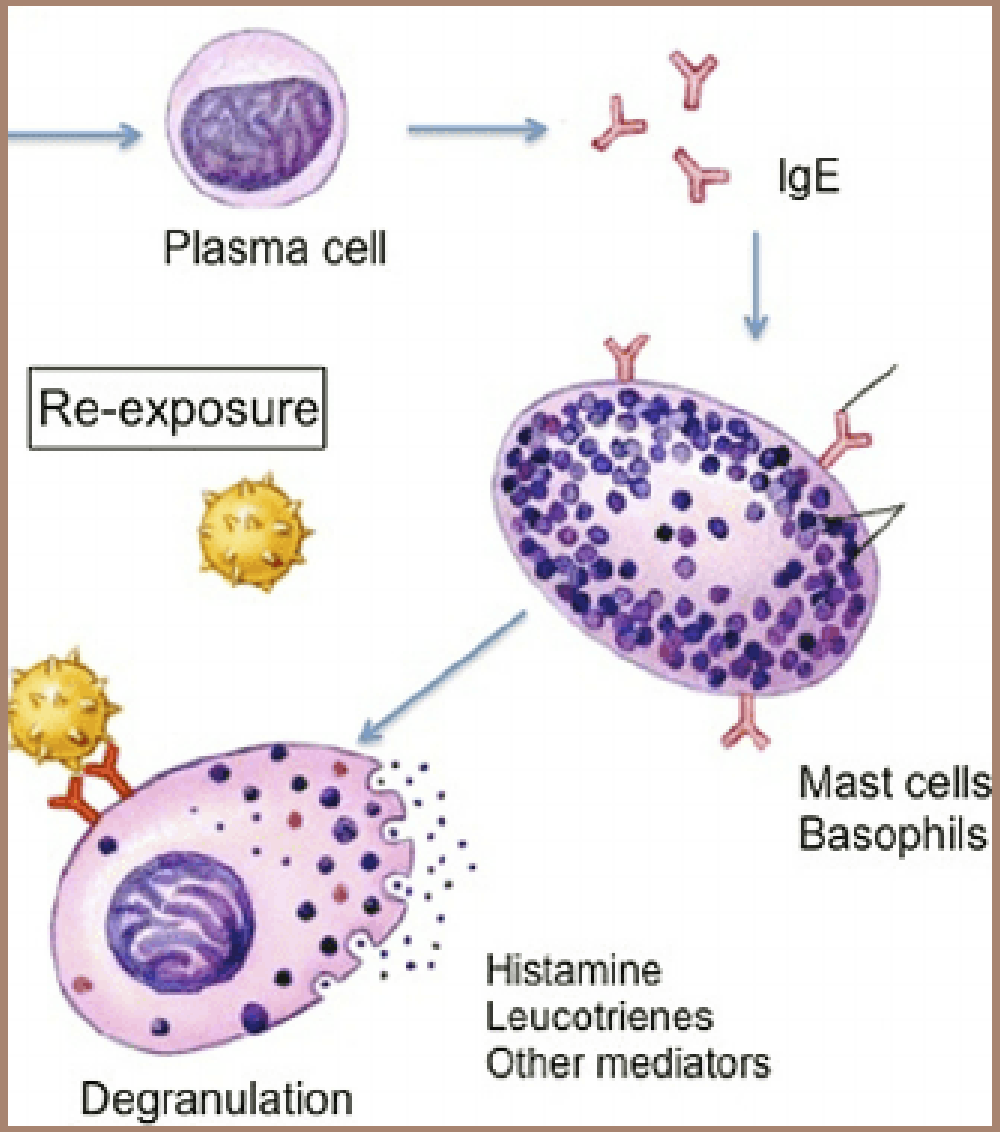
Activating stage

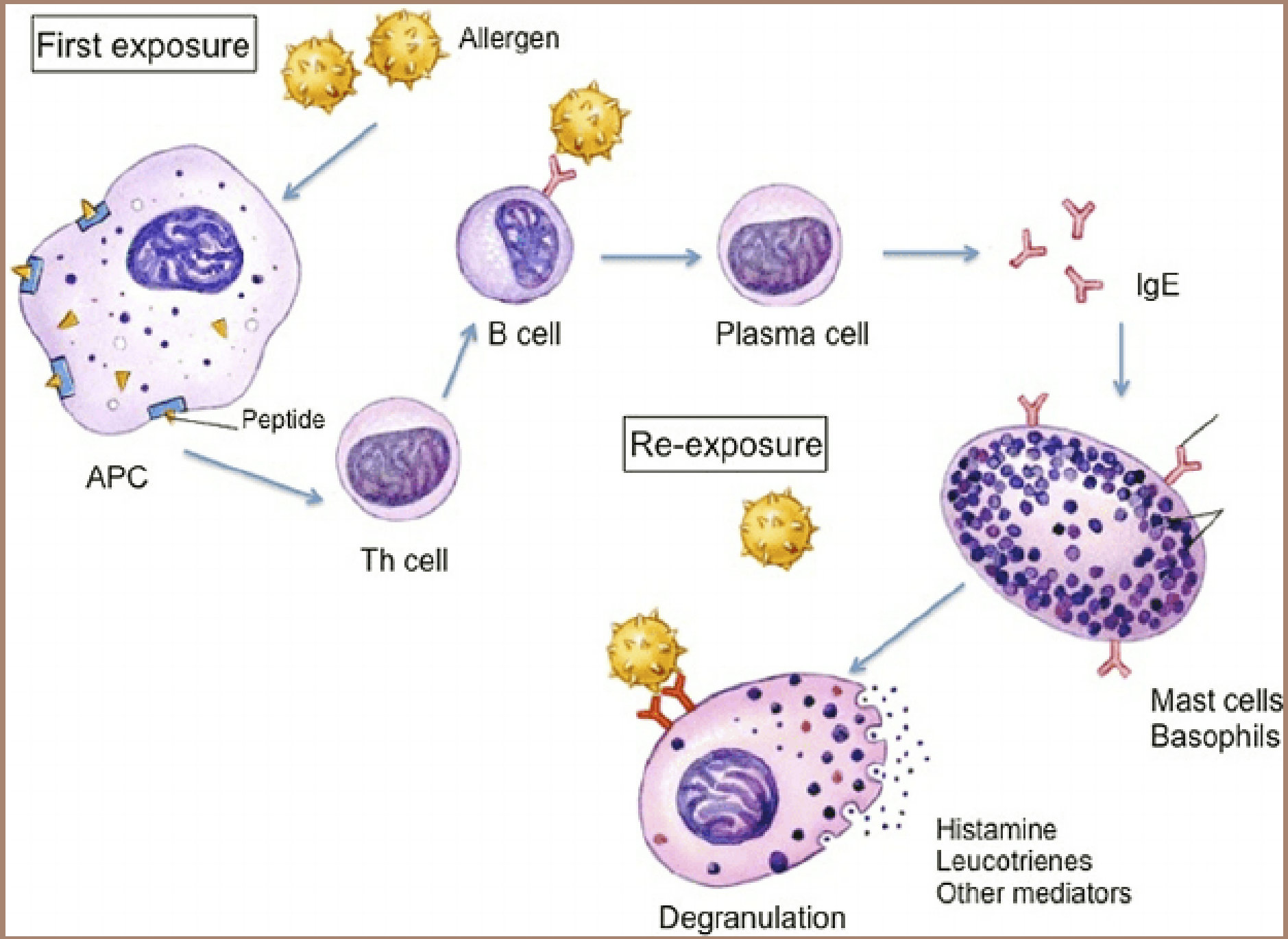
Second exposure to the same allergen

Bridges between IgE molecules fixed to mast cells

Activate and degranulate mast cells

Release of mediators




First exposure
Allergen
B cell
Plasma cell
IgE
Peptide
APC
Th cell
Re-exposure
Mast cells
Basophils
Histamine
Leucotrienes
Other mediators
Degranulation

IgE

Effect stage：

Immediate/early phase response

- Mediated by histamine
- Start within seconds
- Last several hours

Late-phase response

- Mediated by new-synthesized leukotrienes, cytokines, and chemokines, which recruit and activate eosinophils and basophils.
- Take up 8-12hours to develop
- Last several days

Mediators derived from mast cells

Three classes

1) Preformed mediators stored in granules

histamine

2) Newly sensitized mediators:

leukotrienes, prostaglandins, platelets activating factor

3) Cytokines produced by activated mast cells, basophils

TNF, IL3, IL-4, IL-5 IL-13, chemokines

These mediators cause

- smooth muscle contraction
- mucous secretion
- bronchial spasm
- Vasodilatation
- vascular permeability
- oedema

Effect of biological mediators

Histamine

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

Effect biological mediators

Leukotrienes

- Contract bronchial smooth muscles

Platelet activating factor (PAF)

- Agglutinate and activate platelets to release histamine

Eosinophil chemotactic factor（ECF-A）

Bradykinin

- Vasodilator function

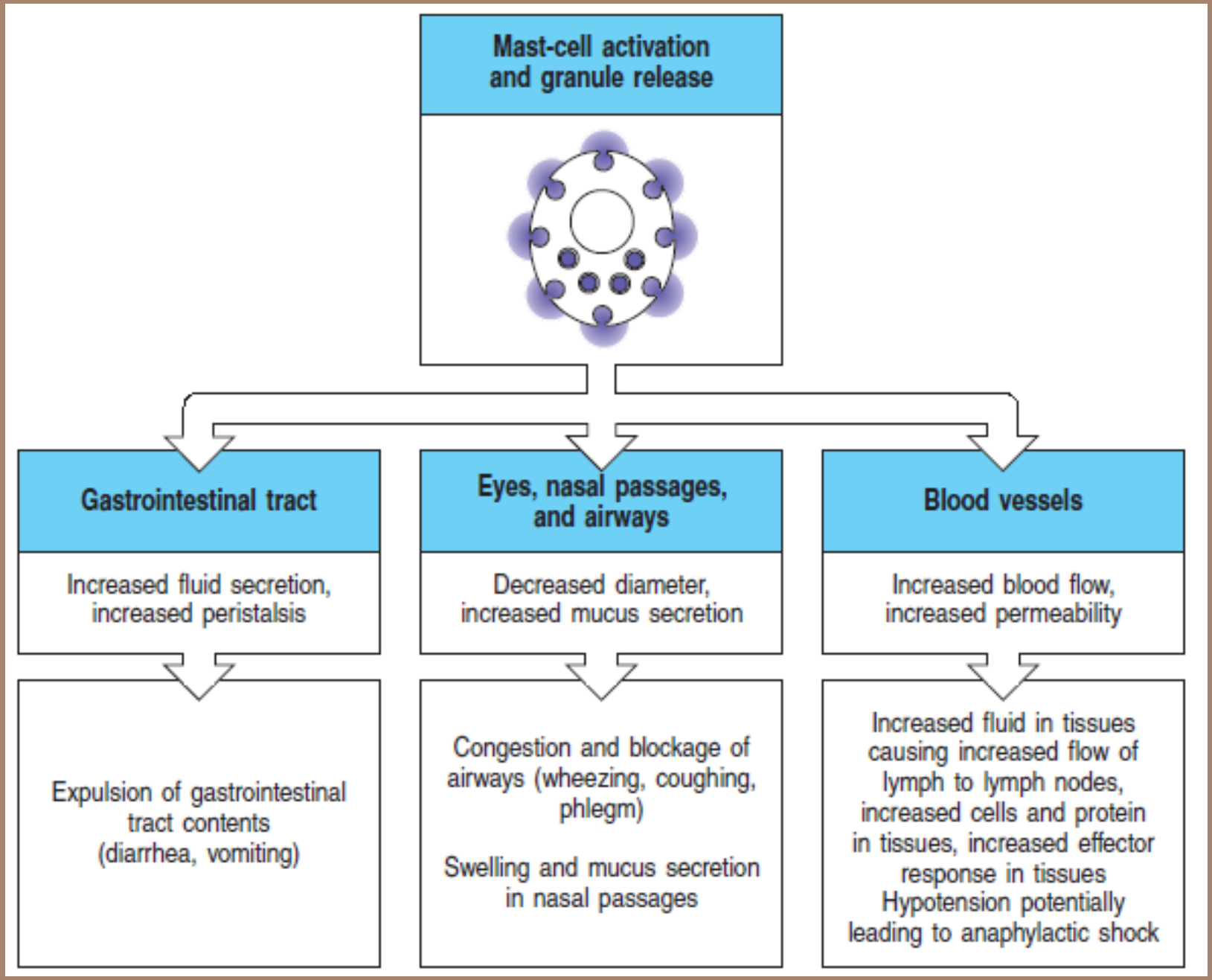
Prostaglandins

Localized anaphylaxis

Target organ responds to direct contact with allergen

- Digestive tract contact - vomiting, cramping, diarrhea.
- Skin sensitivity - inflamed area resulting in itching.

- Airway sensitivity – sneezing, rhinitis, wheezing and asthma.

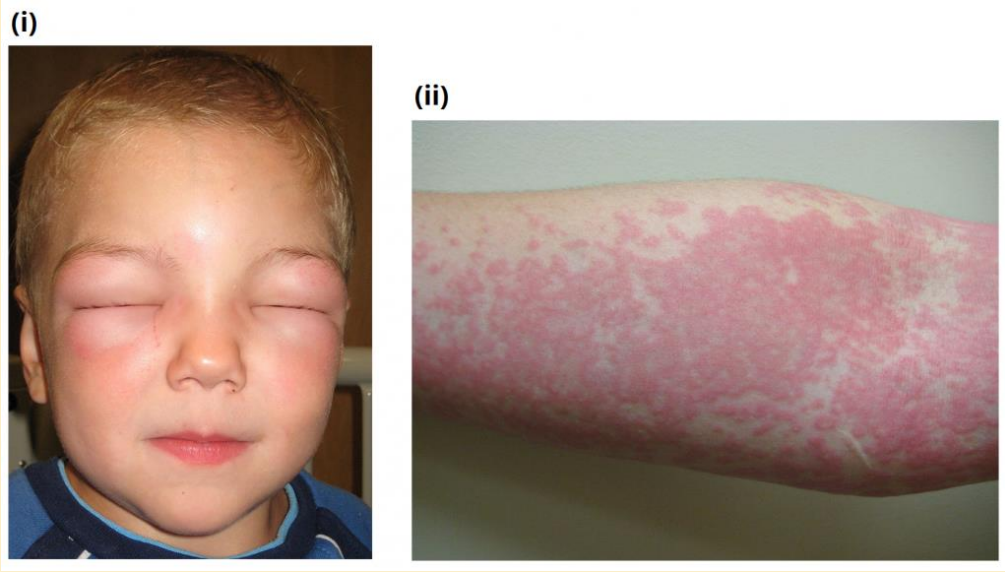


Mast-cell activation has different effects on different tissues.

Systemic anaphylaxis

- Systemic vasodilatation and smooth muscle contraction leading to

  - severe bronchiole constriction
  - oedema
  - shock



Diagnosis

1) History taking for determining the allergen involved

2) Skin tests:

Intradermal injection of battery of different allergens

A wheal and flare (erythema) develop at the site of allergen to which the person is allergic

3) Determination of total serum IgE level

4) Determination of specific IgE levels to the different allergens

Management

1) Avoidance of specific allergen responsible for condition

2) Hyposensitization:

Injection gradually increasing doses of extract of allergen

- production of IgG blocking antibody which binds allergen and prevent combination with IgE

3) Drug Therapy:

corticosteroids injection, epinephrine, antihistamines

Management

Treatments for allergic disease		
Target step	**Mechanism of treatment**	**Specific approach**
In clinical use		
Mediator action	Inhibit effects of mediators on specific receptors Inhibit synthesis of specific mediators	Antihistamines, β-blockers Lipoxygenase inhibitors
Chronic inflammatory reactions	General anti-inflammatory effects	Corticosteroids
T_H2 response	Induction of regulatory T cells	Desensitization therapy by injections of specific antigen
IgE binding to mast cell	Bind to IgE Fc region and prevent IgE binding to Fc receptors on mast cells	Anti-IgE antibodies (omalizumab)

TYPE II HYPERSENSITIVITY /

ANTIBODY-DEPENDENT CYTOTOXICITY

Common disease of type II hypersensitivity

- Rheumatic heart Disease
- Transfusion reaction: mismatch of ABO blood group, severely destroy RBC
- Hemolytic disease of newborn
- Autoimmune hemolytic anemia
- Hyper acute rejection in allogenic organ transplantation
- Goodpasture syndrome
- Hyperthyroidism or hypothyroidism—receptor diseases

Components involve in Type II hypersentivity

1. Surface antigen on target cells

Target cells: Normal tissue cell, changed or modified self tissue cells

Antigen : Blood group antigen,

Self-antigen modified by physical factors or infection

2. Antibody, complement and modified self-cell

Activate complement —— Lyse target cells

Opsonic phogacytosis —— Destroy target cells

Mf、NK、 T —— ADCC

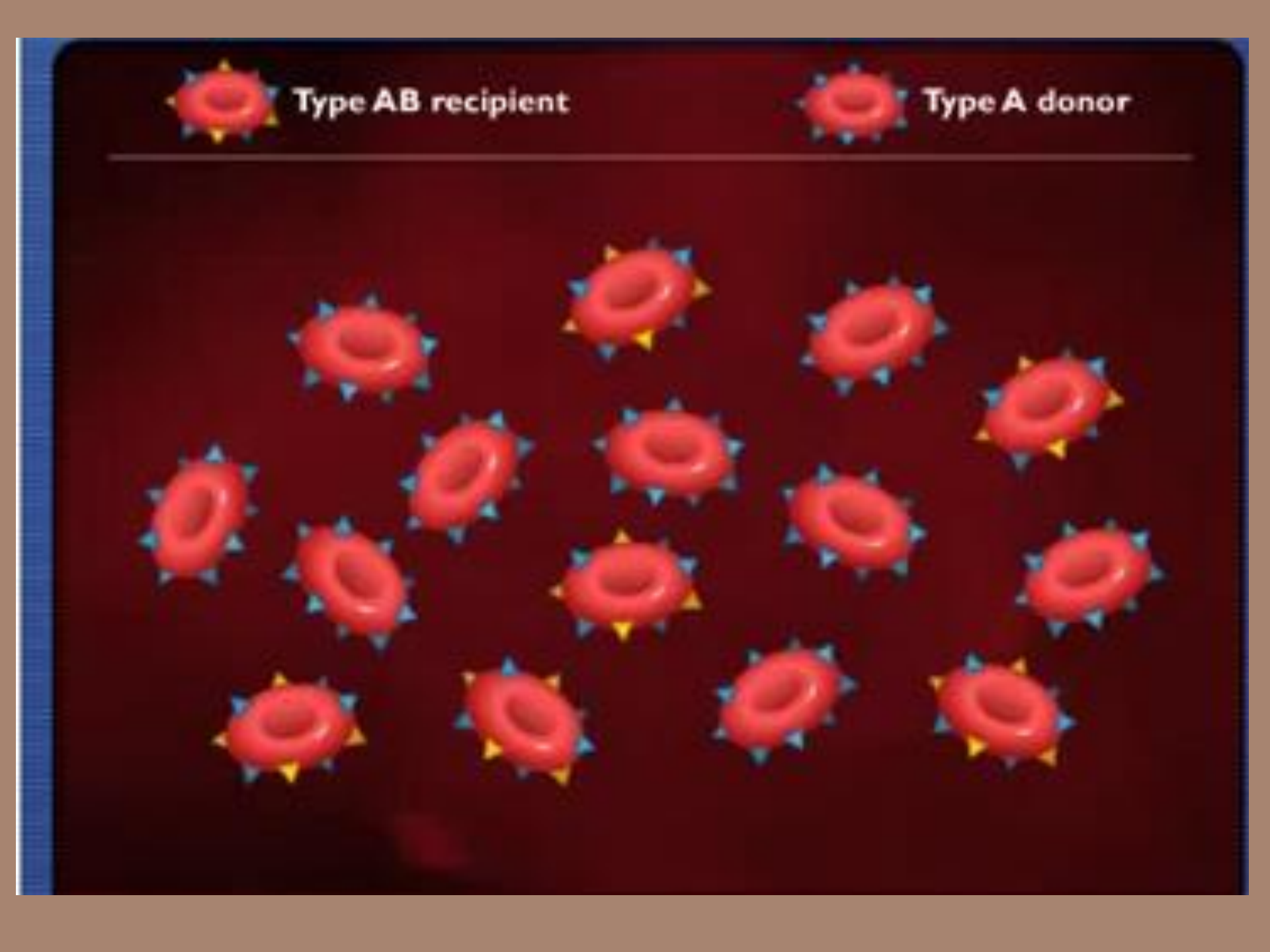
Mechanism of injury

Type II hypersensitivity (antibody-dependent cytotoxicity)

Complement-dependent red blood cell lysis. Occurs for example in haemolytic transfusion reactions (HTR) caused by ABO incompatibility

Antibody-dependent red blood cell degradation. Occurs as the result of binding of antibodies to the red cell membrane that fail to activate complement but promote macrophage uptake as in HDN caused by Rh incompatibility.

Antibody-dependent cell-mediated cytotoxicity (ADCC). Occurs as a result of cytotoxic antibodies become fixed on the surface of effector cells and subsequent antigen binding induce perforin-dependent or granzyme-dependent cell lysis of the cell bearing the antigen.


Type AB recipient
Type A donor

TYPE III HYPERSENSITIVITY

Characteristics

- Arise with soluble antigens
- The pathology is caused by the deposition of antigen:antibody aggregates, or immune complexes, in tissues and sites
- PMNs and macrophages bind to immune complexes via FcR and phagocytize the complexes

Characteristics

- If not eliminated - deposit in capillaries or tissue , joints
- If unable to phagocytize the immune complexes can cause inflammation via C’ activation ---> C3a C4a, C5a

C3a, C5a (anaphylotoxins)

attract phagocytes and mast cells

binding to complement receptors on the surface of

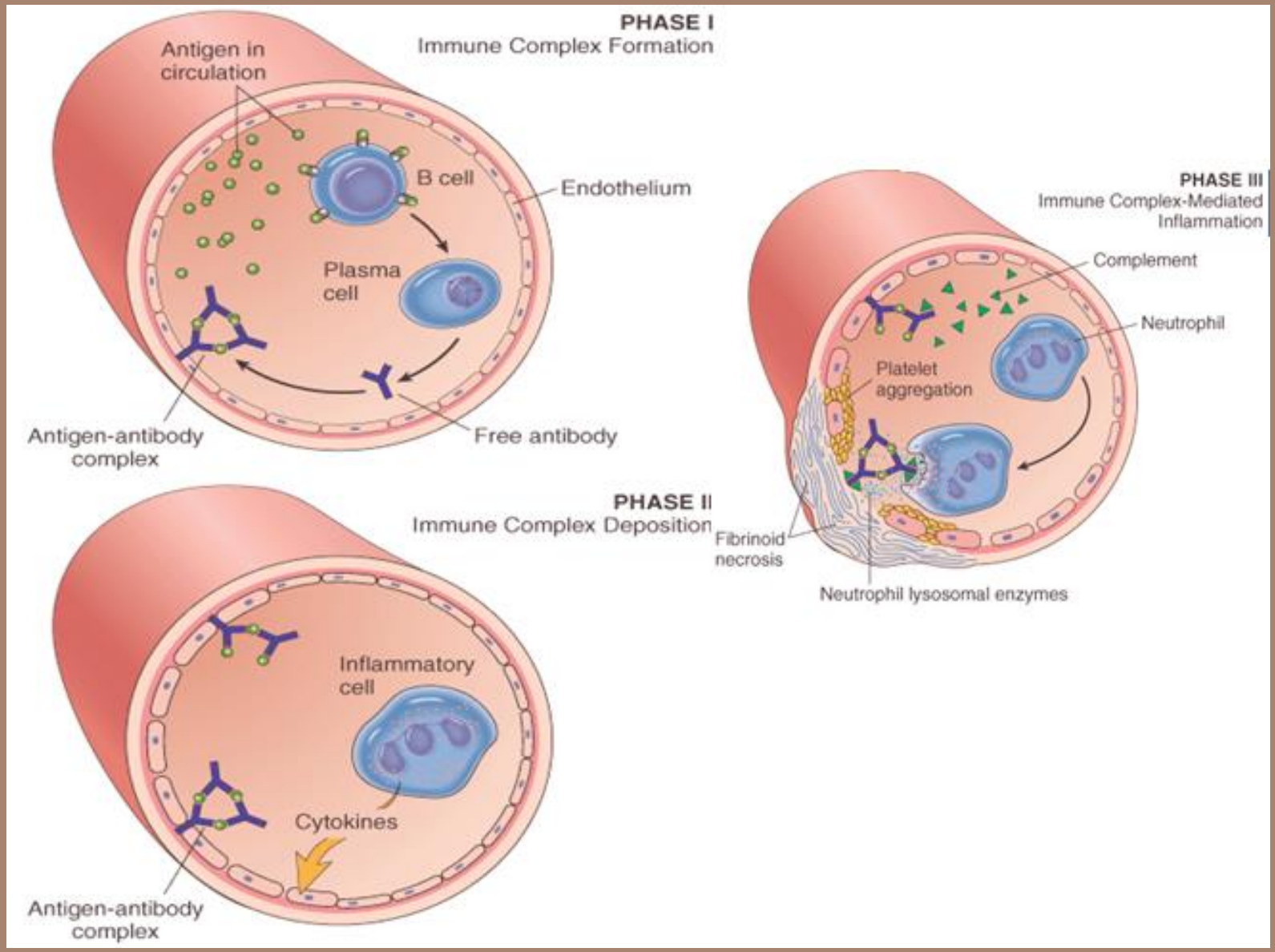
such cells

degranulation

inflammatory reaction

vasodilation, increased vascular permeability

Pathogenesis of Type III HST



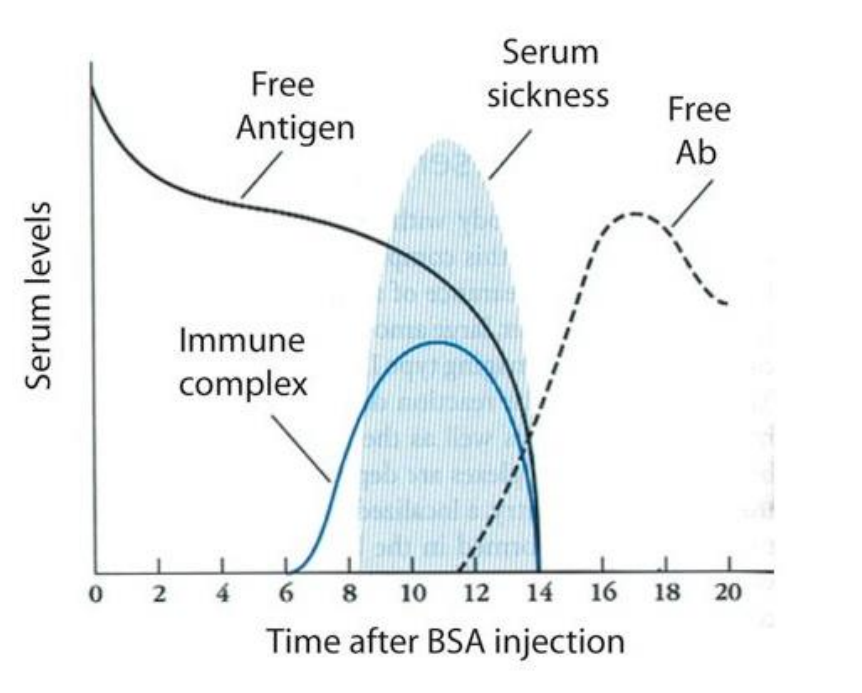
Localized disease

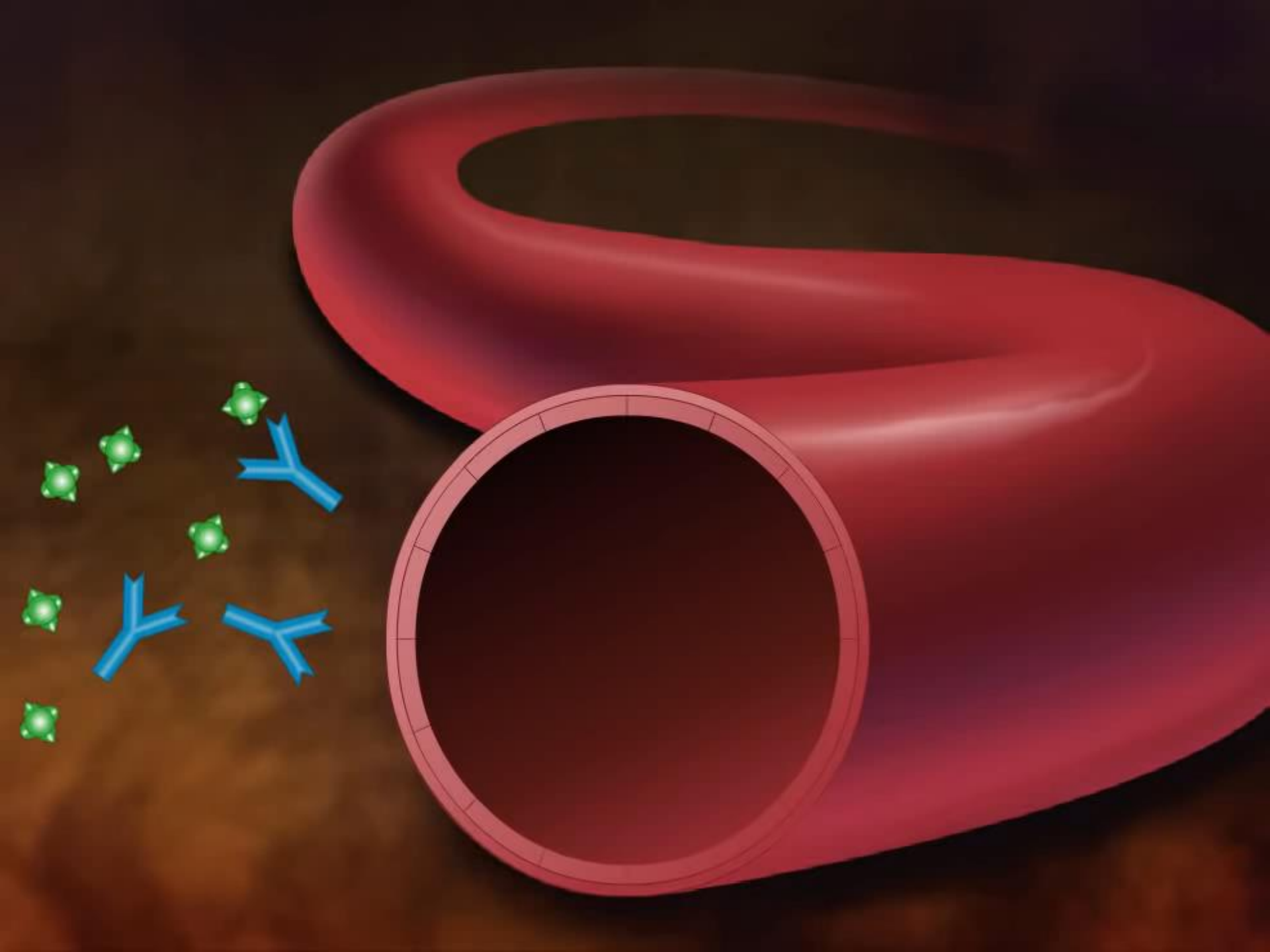
- Arthus Reaction

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

Systemic disease

- Serum sickness occur when a patient is injected with a large amount of antitoxin





Common disease of type III hypersensitivity

1. **Local immune complex disease**

Arthus reaction： Experimental local reaction,

Necrotic vasculitis

2. **Acute systemic immune complex disease**

Serum sickness

↓

systemic tissue injury ,fever, arthritis, skin rash

3. Chronic immune complex disease

SLE

Rheumatoid arthritis： RF+IgG →Deposit on synovial membrane

TYPE IV HYPERSENSITIVITY /

DELAYED-TYPE HYPERSENSITIVITY / DTH

Characteristics

Interaction of primed T cells and associated antigen

↓

Infiltration of Mononuclear Cells

↓

Inflammatory response

Type IV / Delayed type hypersensitivity

- Delayed is relative because DTH response arise 24-72 hours after exposure rather than within minutes.

Mechanism of type IV hypersensitivity

- Formation of effector and memory T cells
- Inflammation caused by effector T cells

Inflammation and tissue injury mediated by CD4 (Th1)

⇩

Release chemokines and cytokines

⇩

IFN-γ, TNF-α, & TNF-β cause tissue destruction & inflammation

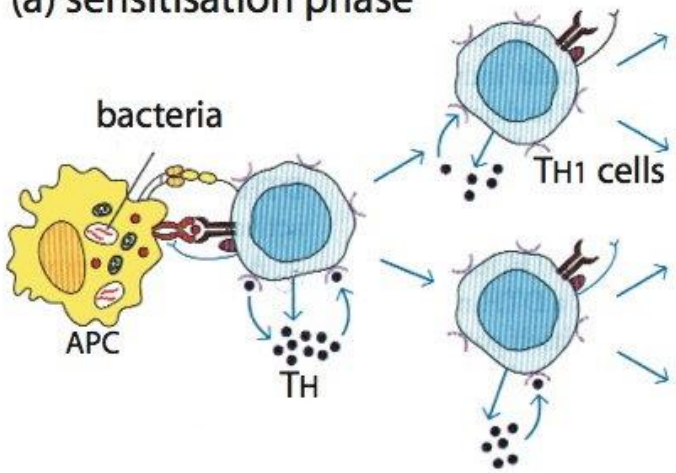
IL-2 activates T cells and CTLs

Chemokines – do macrophage recruitment

IL-3, GM-CSF for increased monocyte/macrophage

Pathogenesis of type IV hypersensitivity

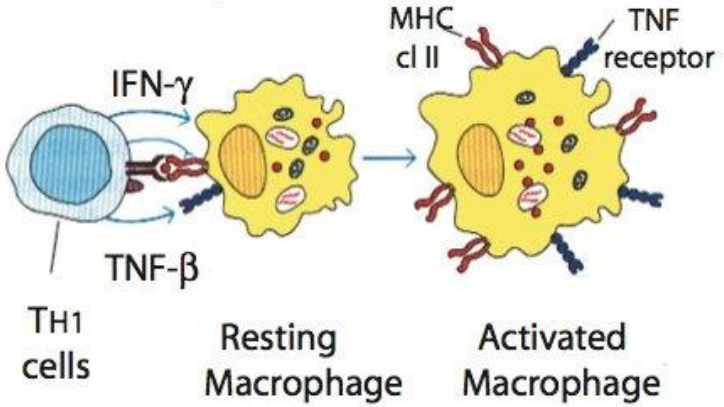
(a) sensitisation phase



APCs:
Macrophages

DTH Cells:
TH1

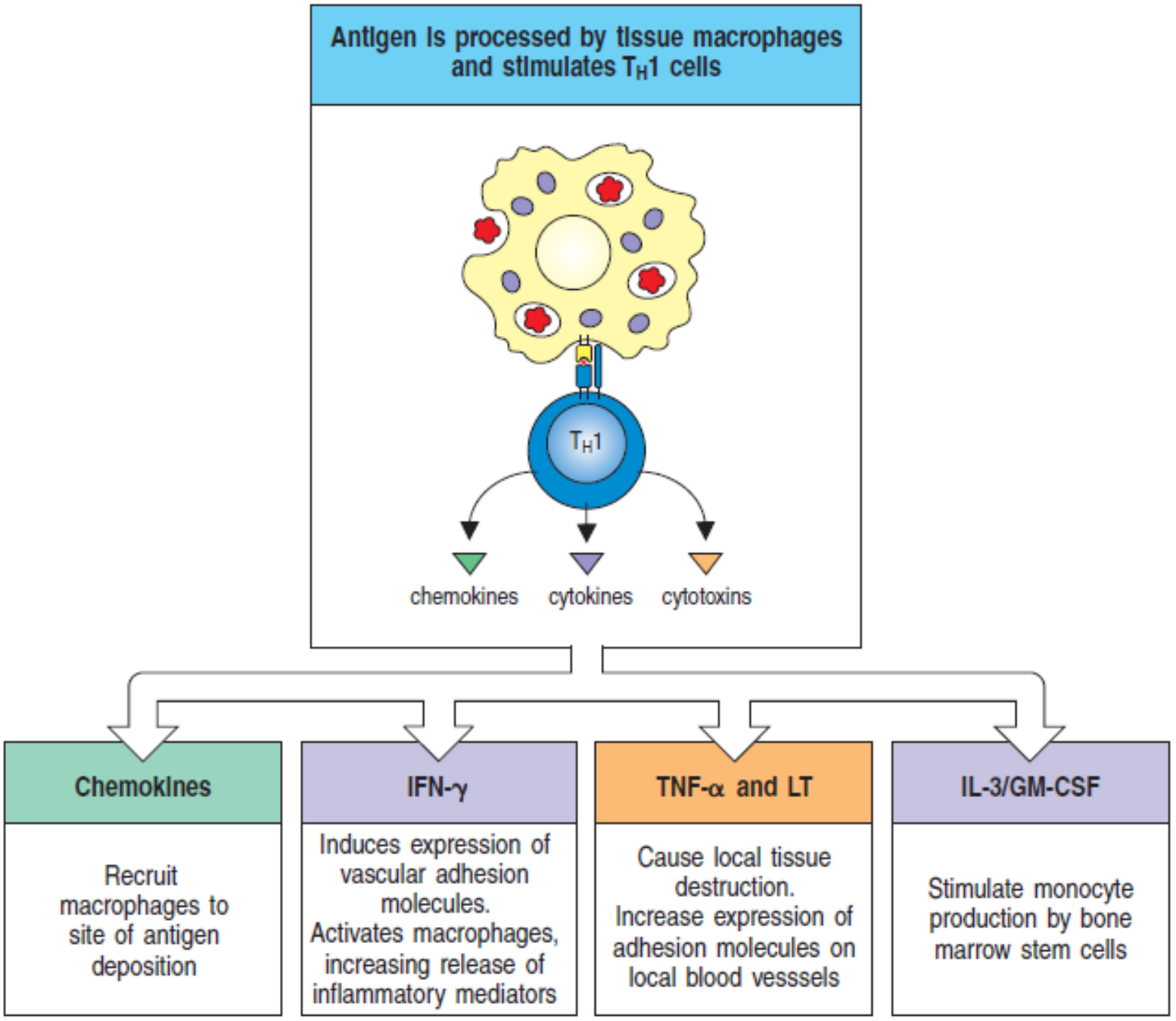
(b) effector phase



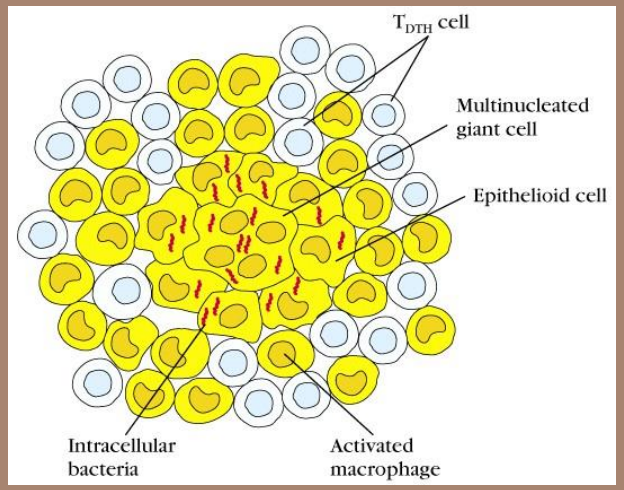
TH1 products:
IFN-γ, TNF-β, IL-2, IL-3, IL-8, MCAF, MIF

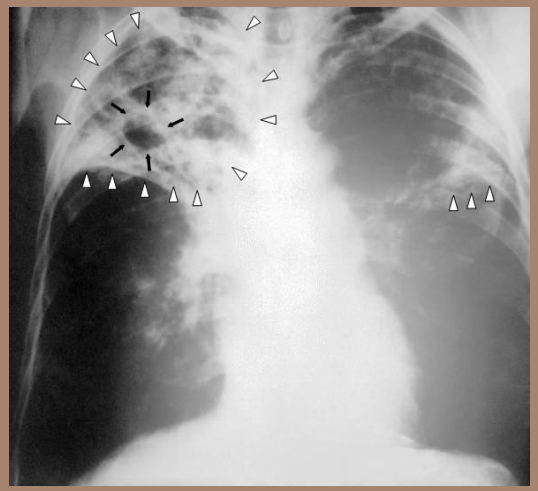
Macrophage activation:
MHC cl II, TNF receptor, oxygen radicals, nitric oxide

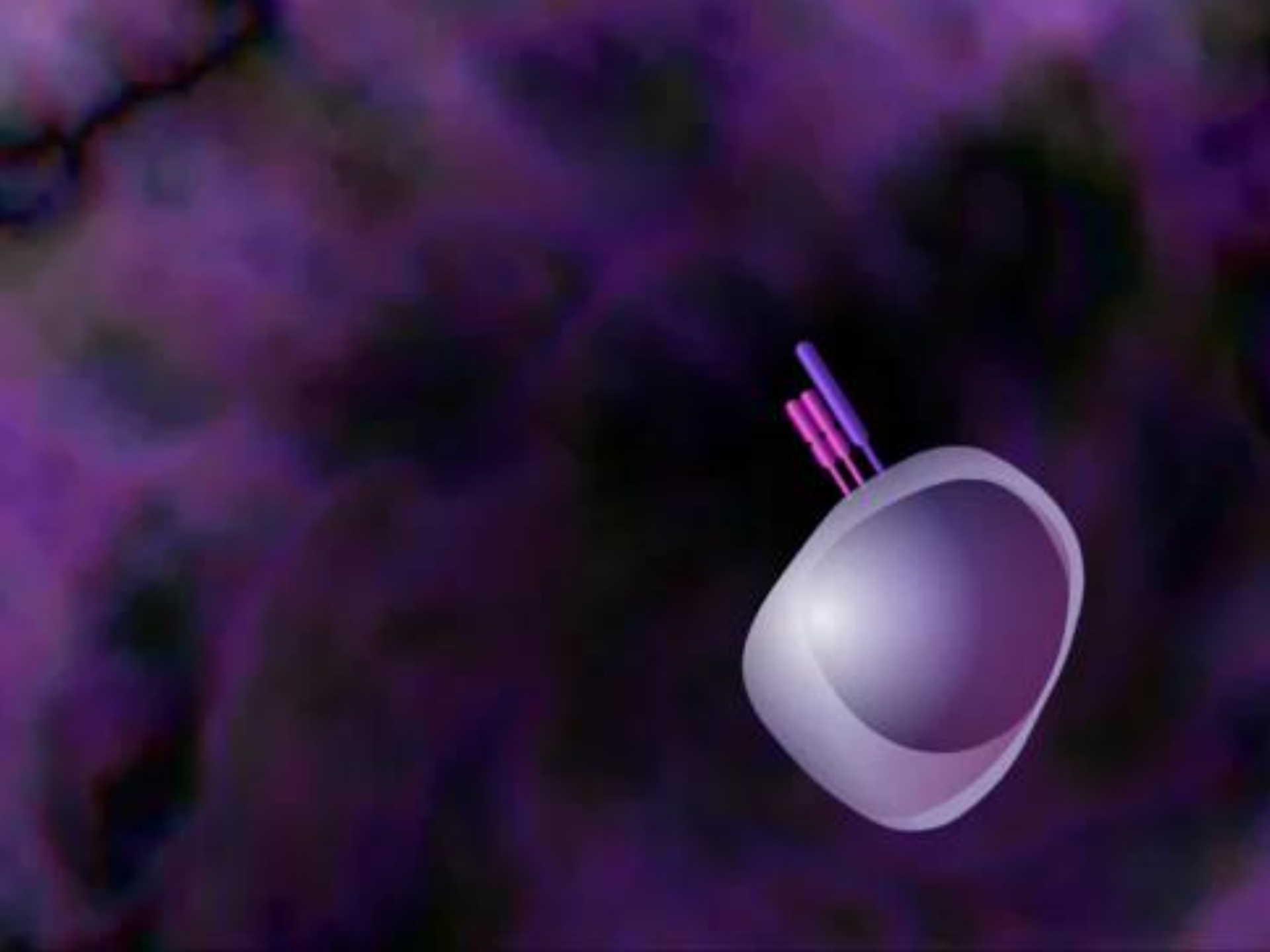
Goldsy RA et al. Immunology 5th Ed, 2003, p 384


Antigen is processed by tissue macrophages and stimulates T_H1 cells
T_H1
chemokines
cytokines
cytotoxins
Chemokines
Recruit macrophages to site of antigen deposition
IFN-γ
Induces expression of vascular adhesion molecules. Activates macrophages, increasing release of inflammatory mediators
TNF-α and LT
Cause local tissue destruction. Increase expression of adhesion molecules on local blood vesssels
IL-3/GM-CSF
Stimulate monocyte production by bone marrow stem cells

- Immune injury mainly caused by infiltration of mononuclear cells and lymphocytes
- Inflamed area becomes red and fluid filled & can form lesion.
- Continued exposure to antigen can cause chronic inflammation and result in granuloma formation







Common disease of type IV hypersensitivity

1) Contact dermatitis :

Paint, drugs

Manifest Red rash, papules, dermatitis

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.	

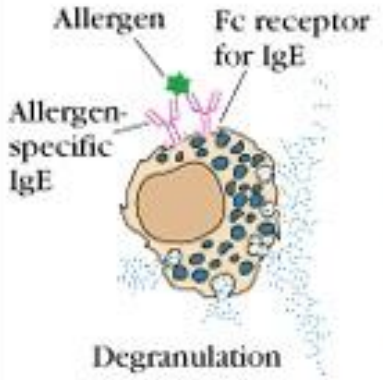
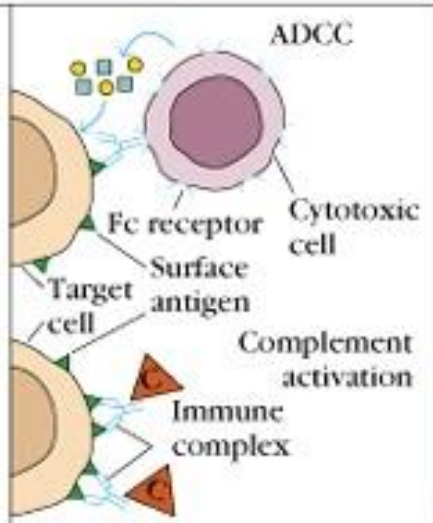
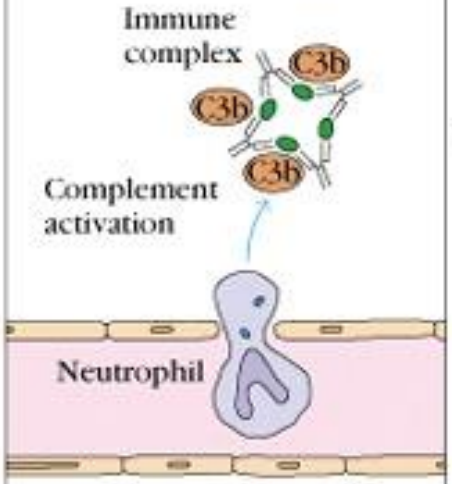
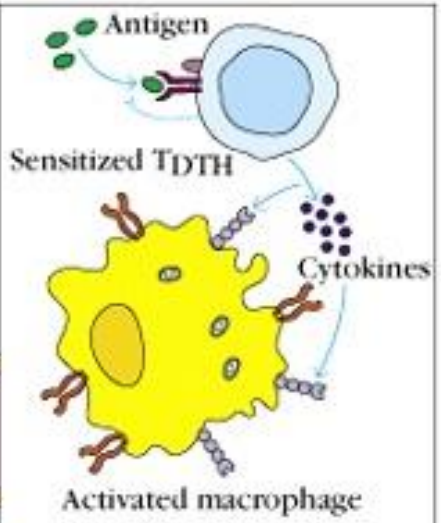
Common disease of type IV hypersensitivity

2) Infectious delayed type hypersensitivity

Tuberculin test

Summary

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**	 **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	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