Hypersensitivity reactions

TEACHING OBJECTIVES

1. Understand the classification of hypersensitivity reactions
2. Know the diseases associated with hypersensitivity reactions
3. Understand the mechanisms of damage in hypersensitivity reactions
4. Know the methods for diagnosing conditions due to hypersensitivity
5. Know the modes of treating disease due to hypersensitivity and their rationale

Hypersensitivity Reactions

- Undesirable (damaging, discomfort producing and sometimes fatal) reactions produced by the normal immune system.
  - require a pre-sensitized (immune) state of the host.
  - Gell and Coombs classification:
    - four types: type I, type II, type III and type IV
    - based on the mechanisms involved and time taken for the reaction.
    - Frequently, a particular clinical condition (disease) may involve more than one type of reaction.

Hypersensitivity Reactions

1. Immediate hypersensitivity reactions

- result from an AMI based interaction (antibody- antigen)
- take minutes to hours to develop after first encounter with antigen

Type I. Type II. and Type III.

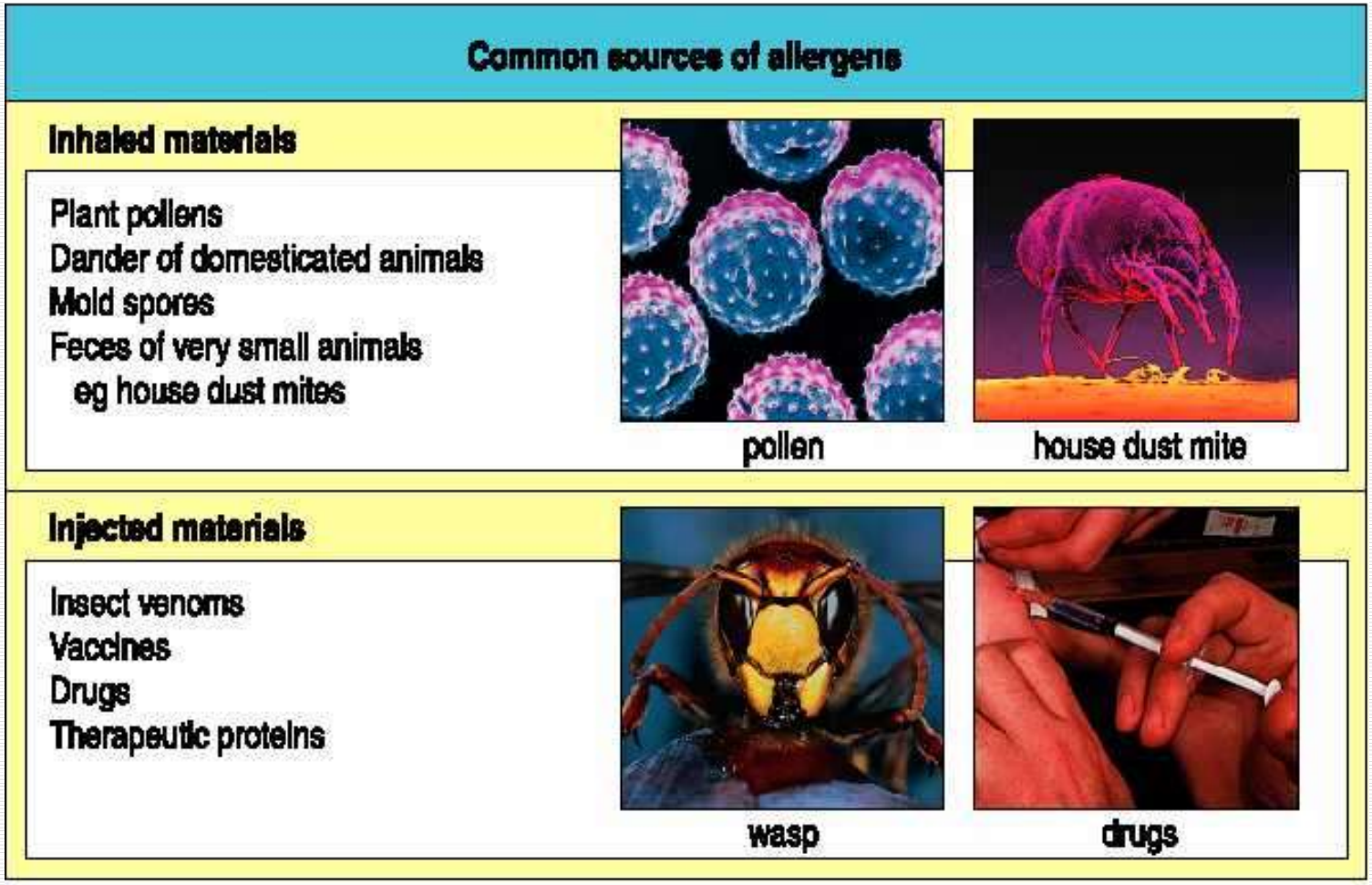
2. Delayed hypersensitivity reactions

- result from an CMI based interaction (cell-cell)
- symptoms do not develop for days after exposure to antigen

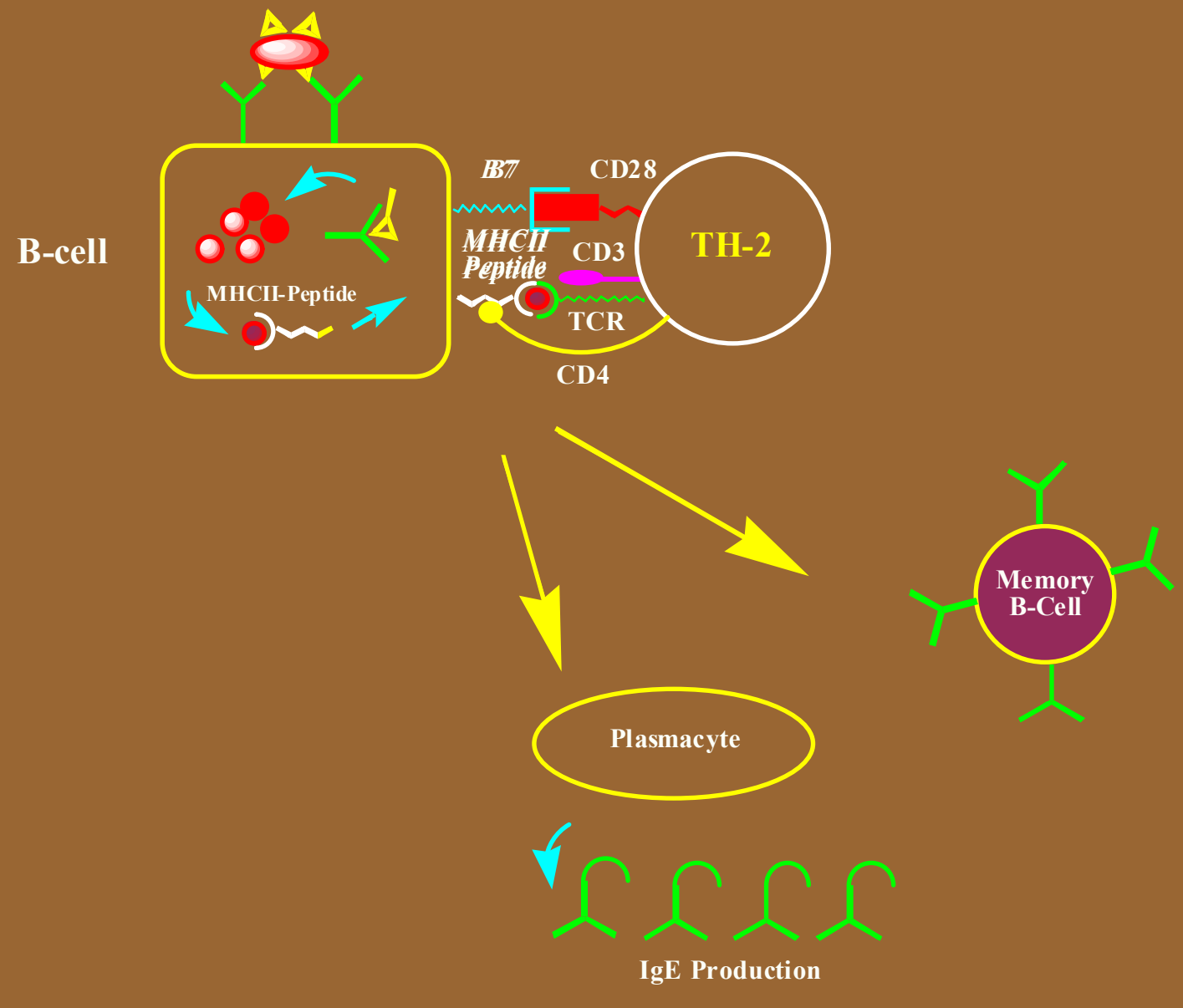
Type IV

Hypersensitivity Reactions

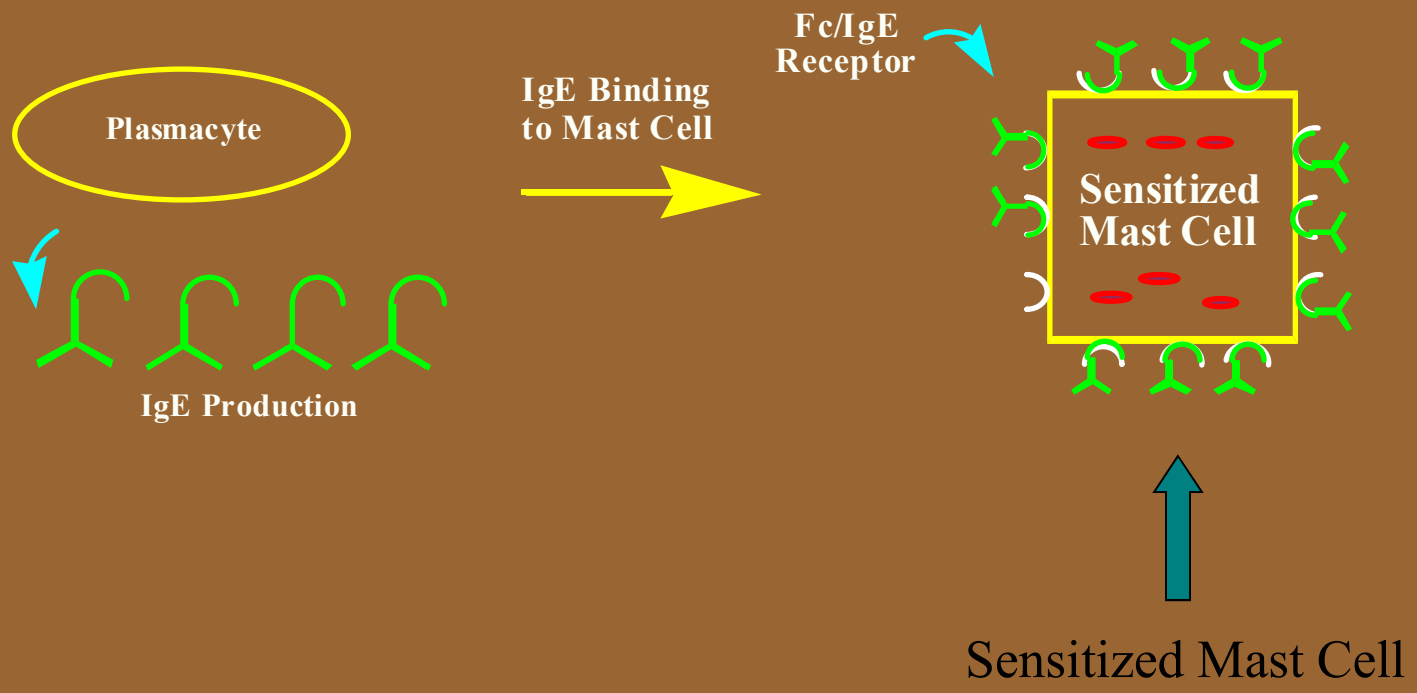
Figure 10.1a



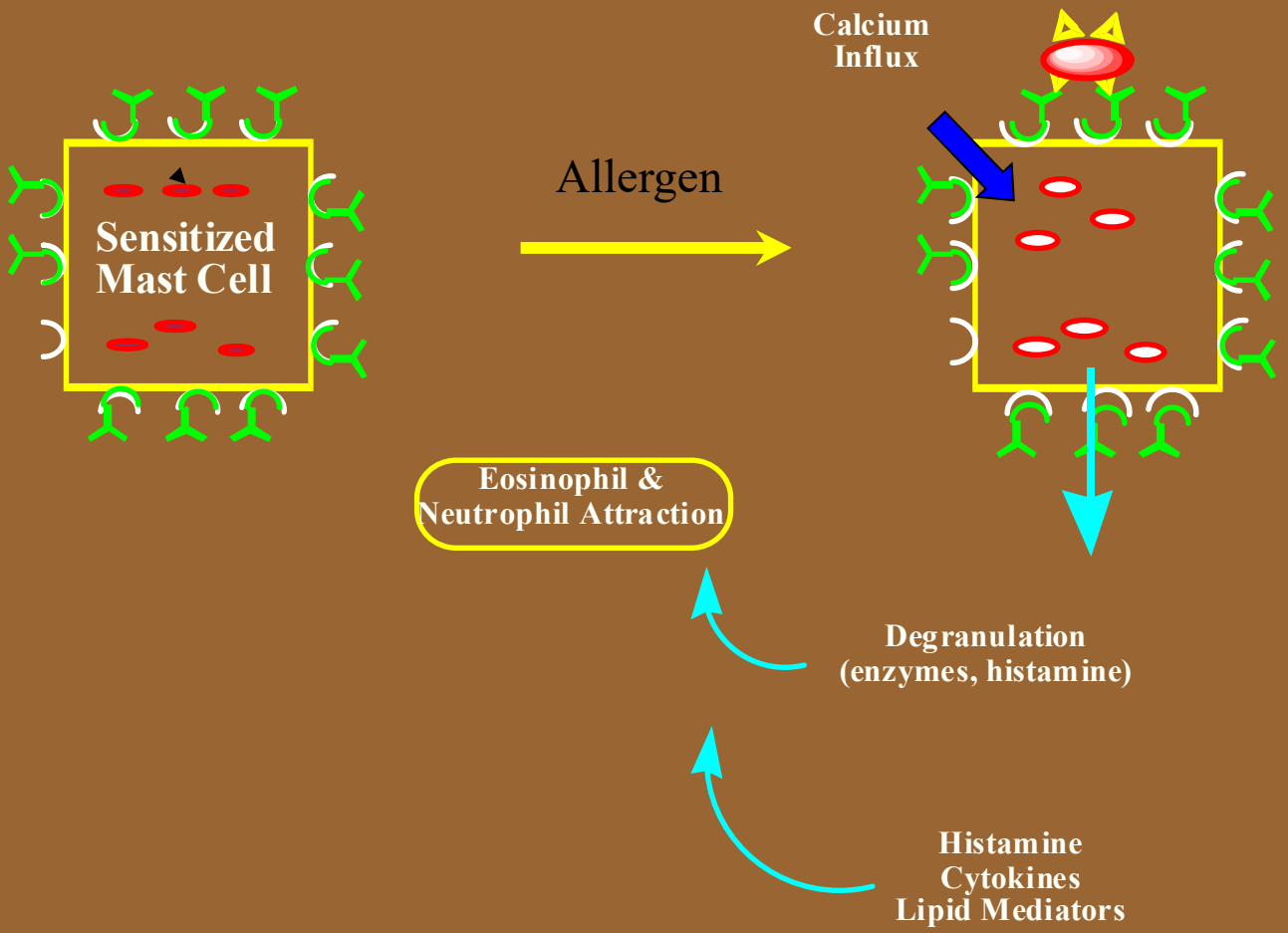
Type I Hypersensitivity: Sensitization



Type I Hypersensitivity: Sensitization

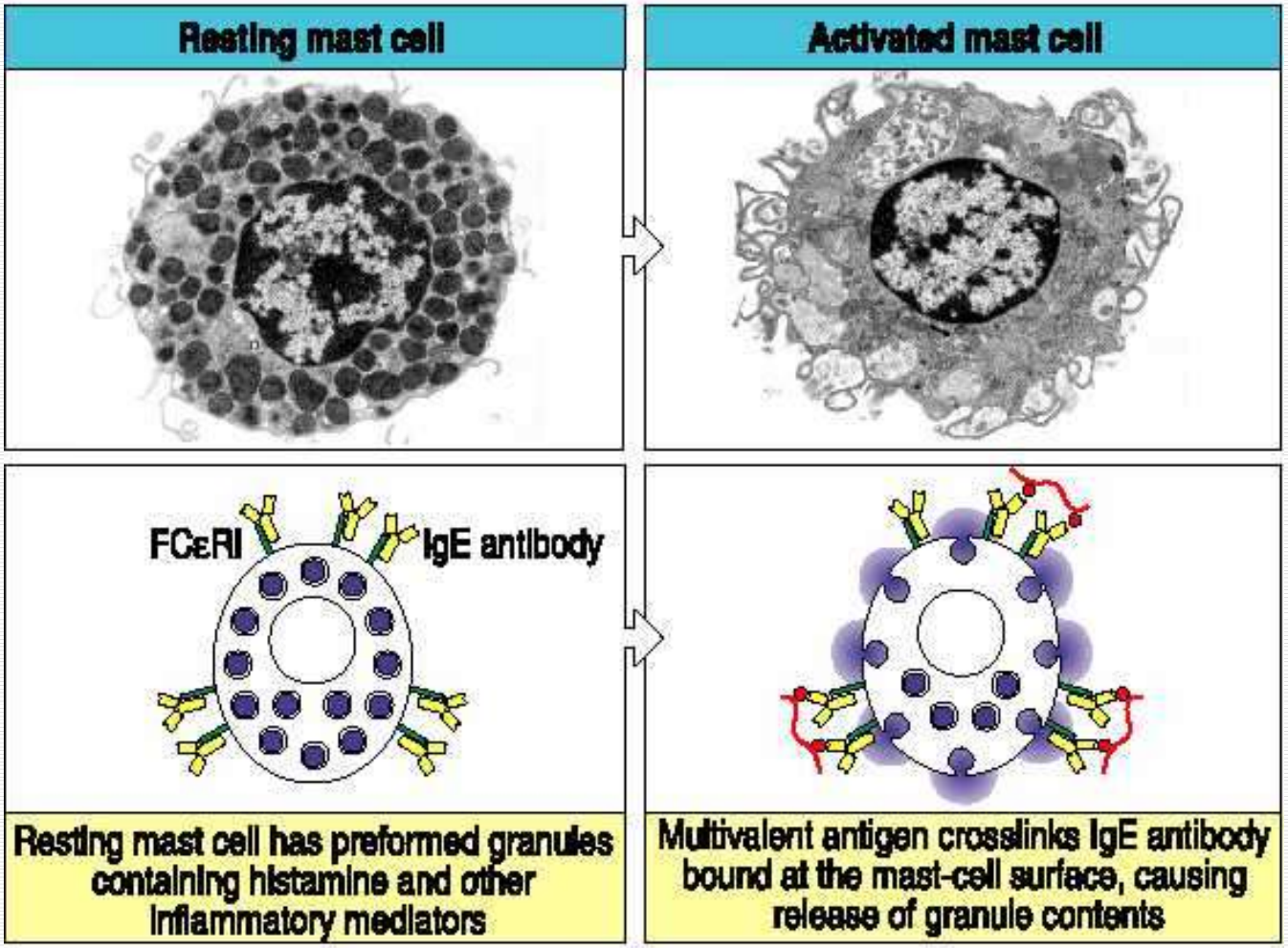


Type I Hypersensitivity: Effector



Type I Hypersensitivity

Figure 7.24



Type I Hypersensitivity

Preformed Mediators:

1. stored in granules in mast cells

1. Histamine - most important mediator in humans, although a similar function is performed by serotonin in other species, e.g., rodents

    - most of the characteristics of anaphylaxis can be mimicked in humans by injection of histamine alone

    - present in granules at very high concentrations as an electrostatic complex with heparin. After fusion of the granules histamine is released from the heparin complex by ion-exchange effects

    - stimulates contraction in most smooth muscle, vasodilation and permeability in post-capillary venules, drop in blood pressure

2. Preformed Mediators:

1. Eosinophil chemotactic factor - attracts and prevents further migration of eosinophils and neutrophils

2. Neutrophil chemotactic factor - attracts and prevents further migration of neutrophils

3. Degradative enzymes including: Arylsulfatase - inactivates leukotrienes chymase - degrades proteins N-acetylglucosaminidase - degrades heparin

2. Causes and Results

- for humans can result from, bee or wasp sting, seafood, nuts.

- can also result from **cross** linking of drug to self protein (i.e., penicillin, insulin)

- can result in asthma, hay fever, systemic or localized anaphylaxis

Type I Hypersensitivity

Lipid Mediators:

- formed and secreted after mast cells are activated

1) Leukotrienes B4, C4, D4:

- formerly known as SRS-A, slow reacting substance of anaphylaxis
- arachidonic acid metabolites structurally related to prostaglandins
- contracts bronchioles and increases capillary permeability

2) Platelet-activating Factor (PAF):

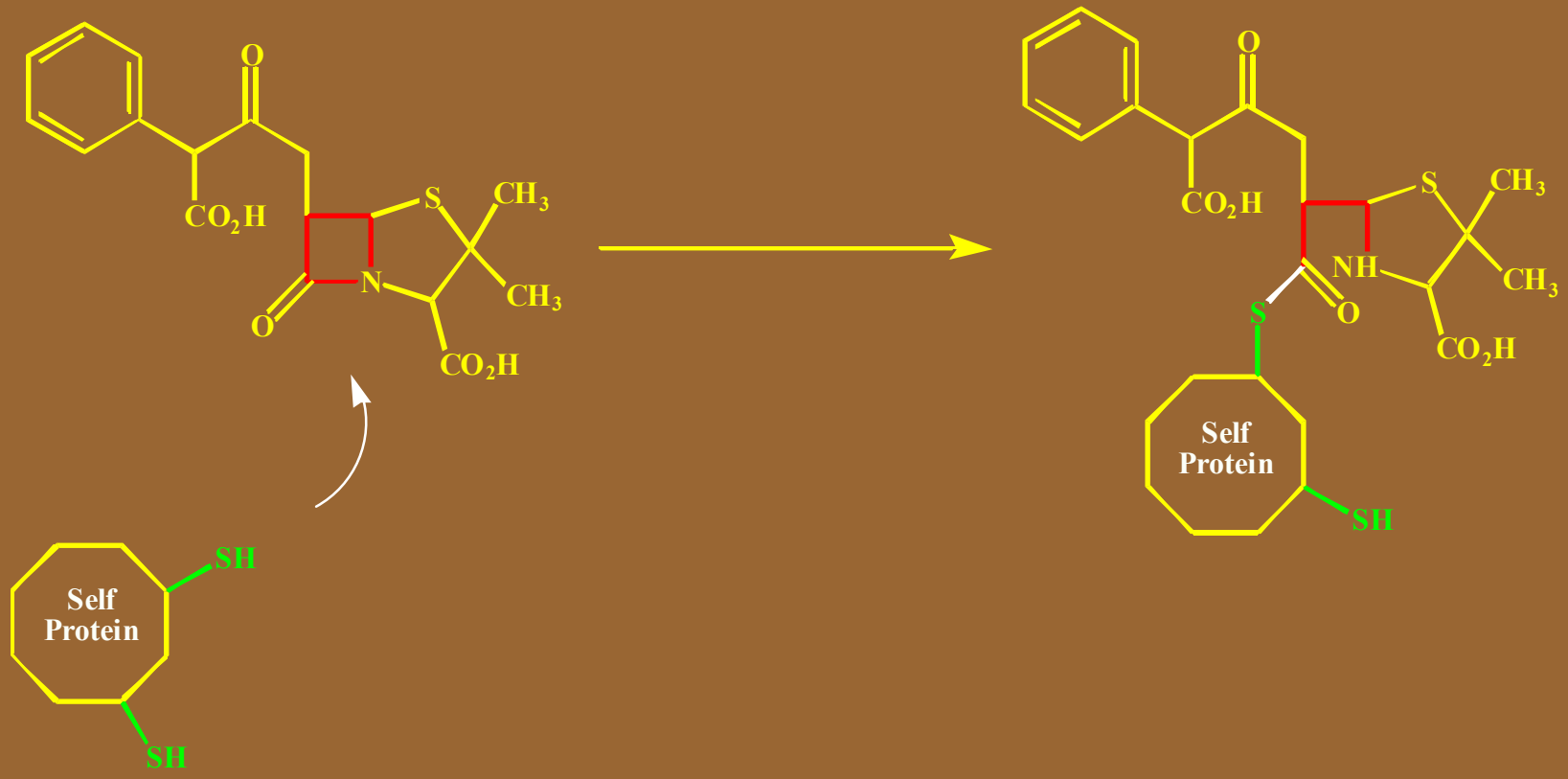
- synthesized from phospholipids in the cell membranes
- active at $l0^{l0}$ M
- potent hypotensive agent
- most potent bronchorestricting agent in asthma and allergic rhinitis (hay fever)
- aggregates and lyses platelets releasing serotonin and other mediators
- promotes eosinophil infiltration
- PAF antagonists represent an active area of research, particularly for drugs to prevent abnormalities in reproduction

3) Prostaglandin D2 and other prostaglandins

Cytokines:

- stimulates production of lymphokines (IL-3, IL-4, IL-5, IL-6, GM-CS~), which stimulate production of leukocytes, more mast cells - stimulates production of bradykiniin, which causes vasodilation, hypotension

Type I Hypersensitivity



Type I Hypersensitivity

Systemic Anaphylaxis:

- most severe and life-threatening type of allergic response
- characteristics:

- generalized flush, palpitations, dizziness, apprehension, urticaria, angioedema and abdominal cramps
- may proceed to dyspnea, seizures, cyanosis, shock, and/or death
- begins 3 to 4 min after administration

- causes:

-xenogenic sera, allergenic extracts, dextrans, therapeutic enzymes, polypeptide hormones, penicillins and cephalosporins.

- localized anaphylaxis affects only certain vasodilation smooth muscles most common is hay fever (allergic rhinitis) and asthma (localized bronchial constriction)

- Skin grids are useful for detecting if a person will respond to an allergen; **Risk of sensitizing the individual as well as leading to shock.**

Type I Hypersensitivity

3. Drugs that Affect TYPE I

-Antihistamines	Block Hl&H2 receptors
-Cromolyn Sodium	Blocks Calcium influx
-Theophylline	Prolongs *cAMP* levels (inhibits phosphodiesterases). Degranulation is increased by lowering levels of cAMP
-Epinephrine	Stimulates *cAMP* production through β-adrenergic receptor
-Cortisone	Blocks histamine production, stimulates mast cell cAMP production

Type I Hypersensitivity

Histamine Causes a Wide Array of Effects

- smooth muscle cells - Constriction
- small blood vessels - Vasodilation
- mucous glands - Mucous secretion
- blood platelets
- sensory nerve endings

} Histamine Receptors (H1 and H2 receptors

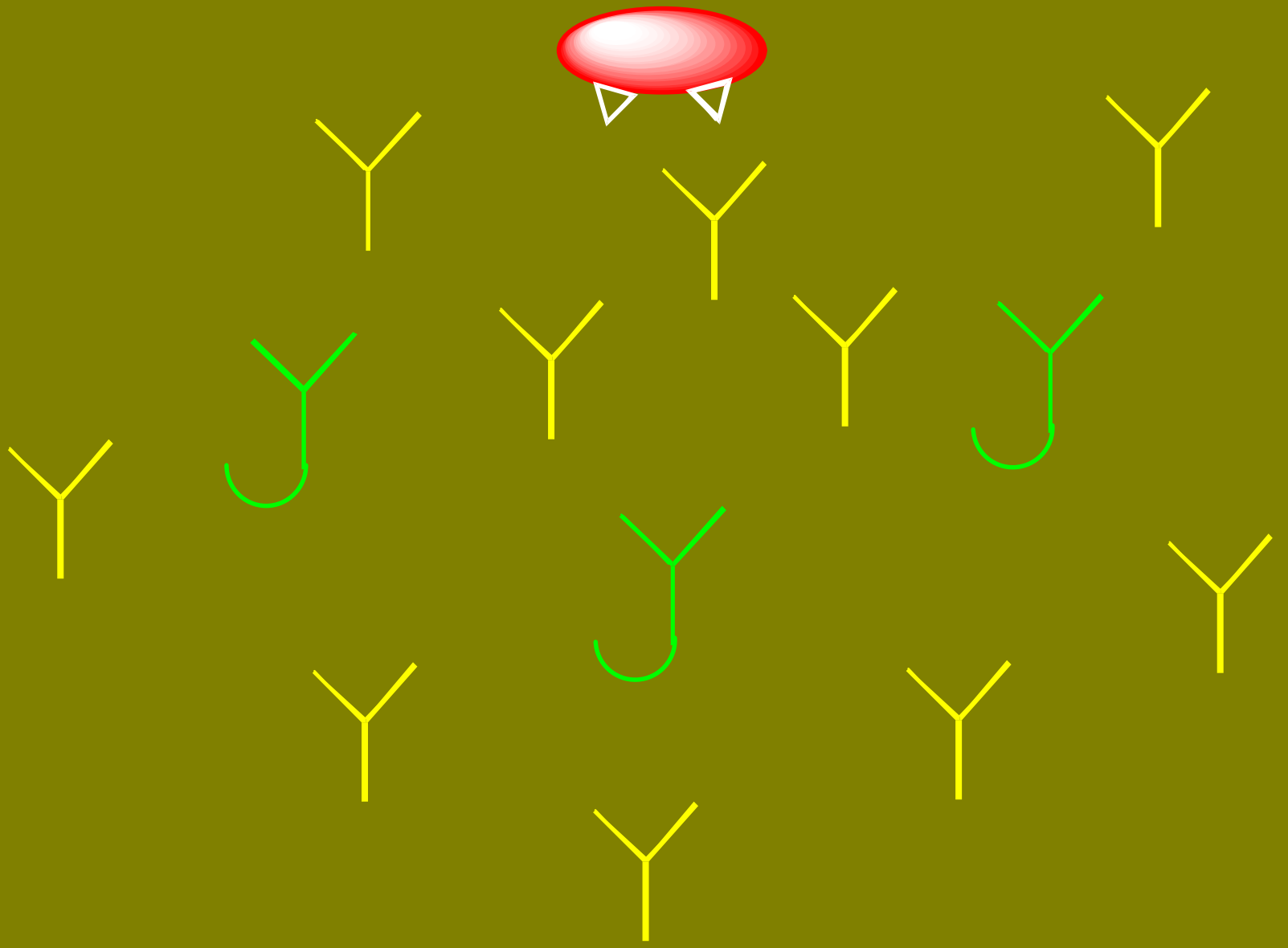
4. Therapeutic Immediate-Hypersensitivity Antigens

- Therapy for allergies based on hyposensitivity

- Typical therapy depends on the injection of known quantities of an allergen in the hope of increasing the amount of IgG over IgE capable of reacting with the allergen

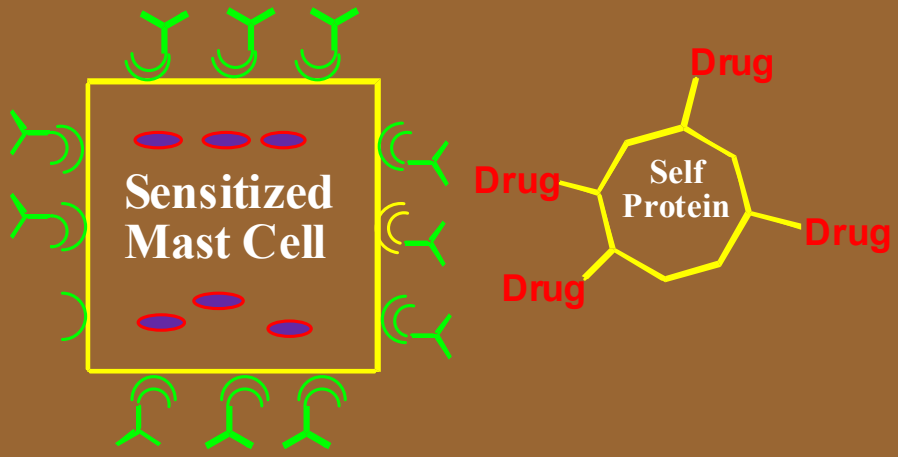
- IgG blocks the binding of the allergen with IgE

Type I Hypersensitivity: Immunomodulation



Hypersensitivity Induced Drug Immunopathology

Type I= Can cause allergic anaphylactic reaction due to allergen complexation with sensitized Mast cell



Type II Hypersensitivity

- The reaction time is minutes to hours
- Mediated by antibodies of IgM or IgG class
- Damage mediated by complement or ADCC
- Endpoint is cell lysis
  - Cells that bind antibodies
    - Foreign cells
    - unfortunate “bystanders” cells binding substances recognizable by antibodies

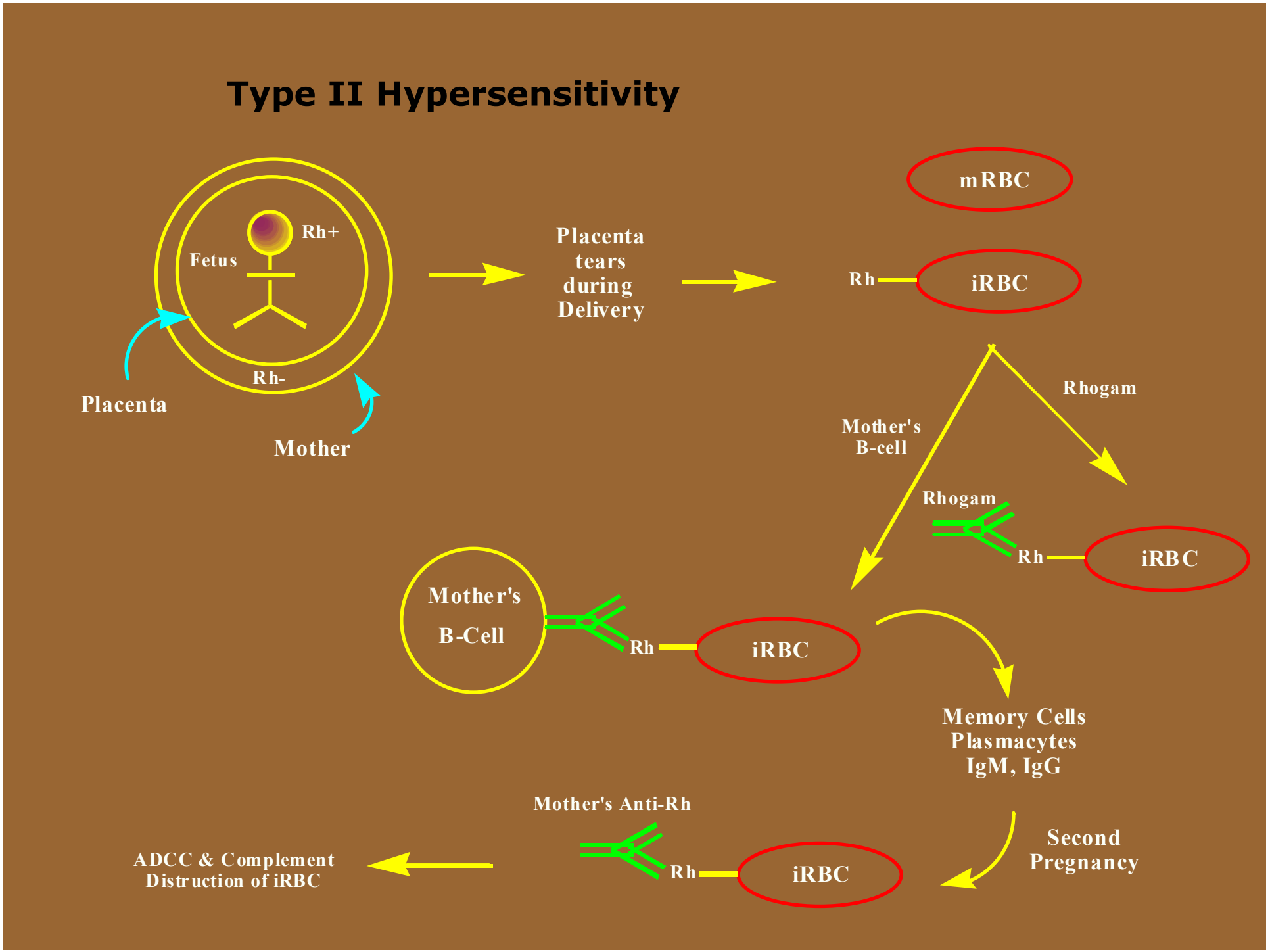
Type II Hypersensitivity

• Antibodies react with foreign antigens on surface of blood cells - Blood groups are sugars connected to lipid (glycolipid) or protein (glycoprotein); have antibodies to groups that are lacking.

Blood Group	**Serum Abs (IgM)**
A	anti-B
B	anti-A
AB	none
O	anti-A anti-B

• Blood cells deemed to be foreign are removed by ADCC
• Reason for blood transfusion reaction

• Other blood antigen Rhesus blood group (Rh(D); 85% are RhD+ and 15% are RhD-) results in Rh incompatibility (erythroblastosis fetalis); treatable with RhoGam.


Type II Hypersensitivity
Fetus
Rh+
Rh-
Placenta
Mother
Placenta tears during Delivery
mRBC
Rh
iRBC
Mother's B-cell
Rhogam
Rhogam
Rh
iRBC
Mother's B-Cell
Rh
iRBC
Memory Cells
Plasmacytes
IgM, IgG
Second Pregnancy
Mother's Anti-Rh
Rh
iRBC
ADCC & Complement Distruction of iRBC

Rho(D) Immune Globulin (RhIG)

Antigen Source Human erthrocytes with Rho(D) surface antigen.

Production Process

RhoD- men or sterile women are immunized with Rho(D) cells in order to produce anti-Rho(D) antibodies.

The antibodies are harvested from plasma collected from these donors.

Type III Hypersensitivity a.k.a immune complex hypersensitivity

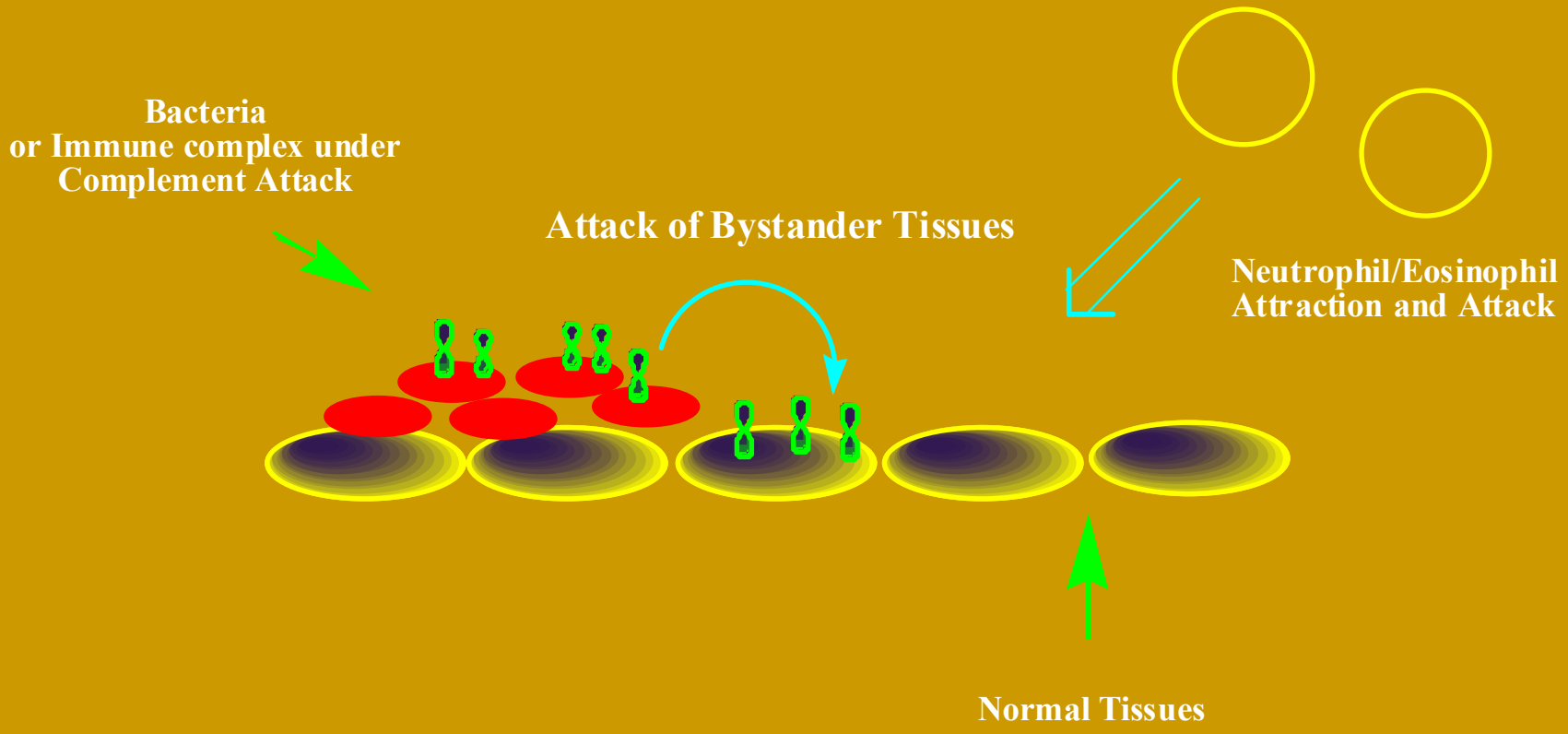
- mediated by soluble immune complexes
  - mostly of IgG class, sometimes IgM
  - The antigen may be exogenous (chronic bacterial, viral or parasitic infections), or endogenous (non-organ specific autoimmunity:
    - The antigen is soluble and **not attached** to the organ involved.
    - Primary components are soluble immune complexes and complement (C3a, 4a and 5a).
- Damage is caused by platelets and neutrophils.
- Reaction may take 3-10 hours after exposure to the antigen

Type III Hypersensitivity

1. Mechanism

- Large immune complexes are formed from complement
- Complexes are deposited on blood vessel walls or tissues
- Mast-cells bind the complement at specific receptors and are activated
- Neutrophils are attracted to the site leading to tissue damage

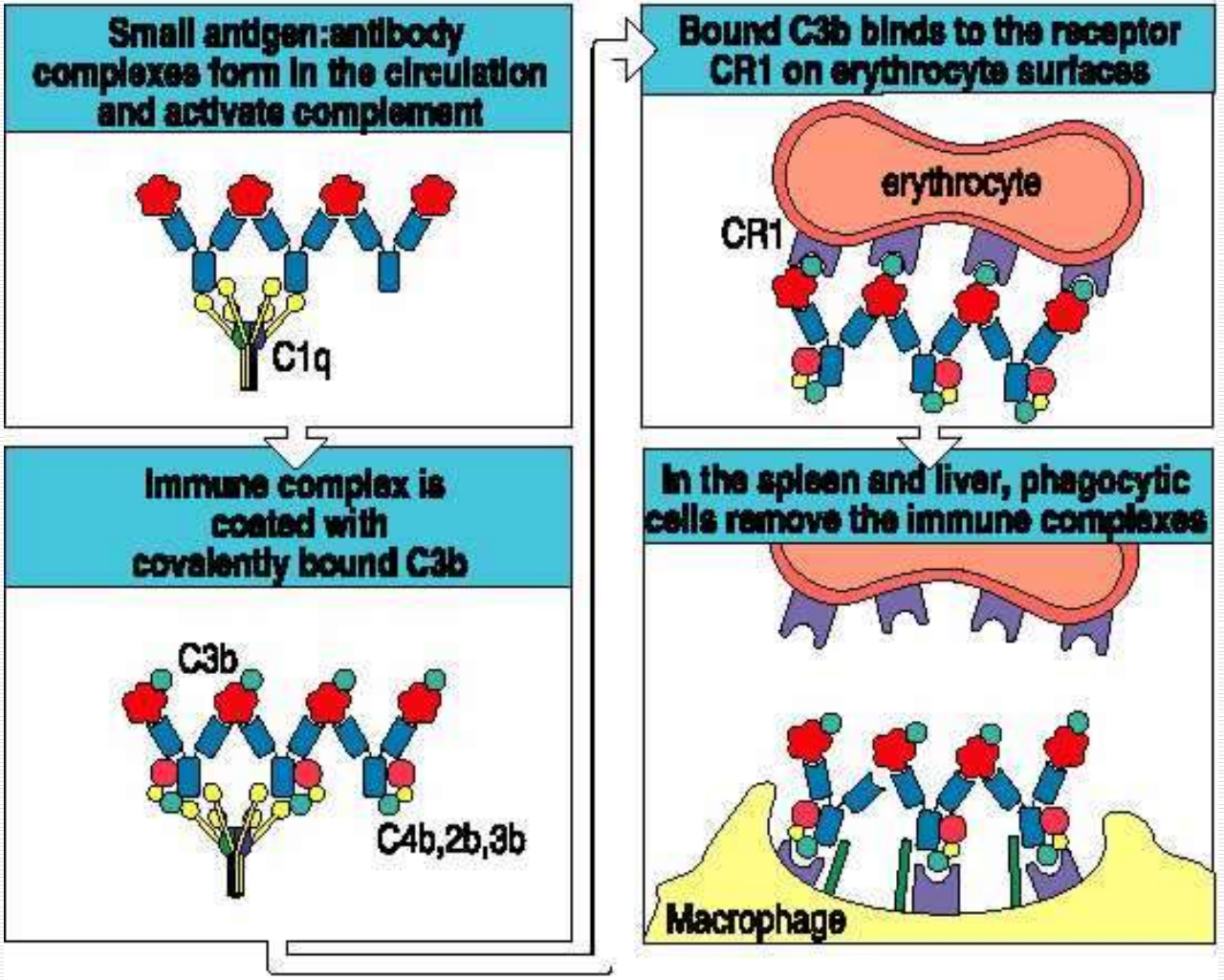
Type III Hypersensitivity



Examples: Serum Sickness, Arthus Reaction, Rheumatic Fever, Rheumatoid Arthritis Farmer' and Pigeon's Lung

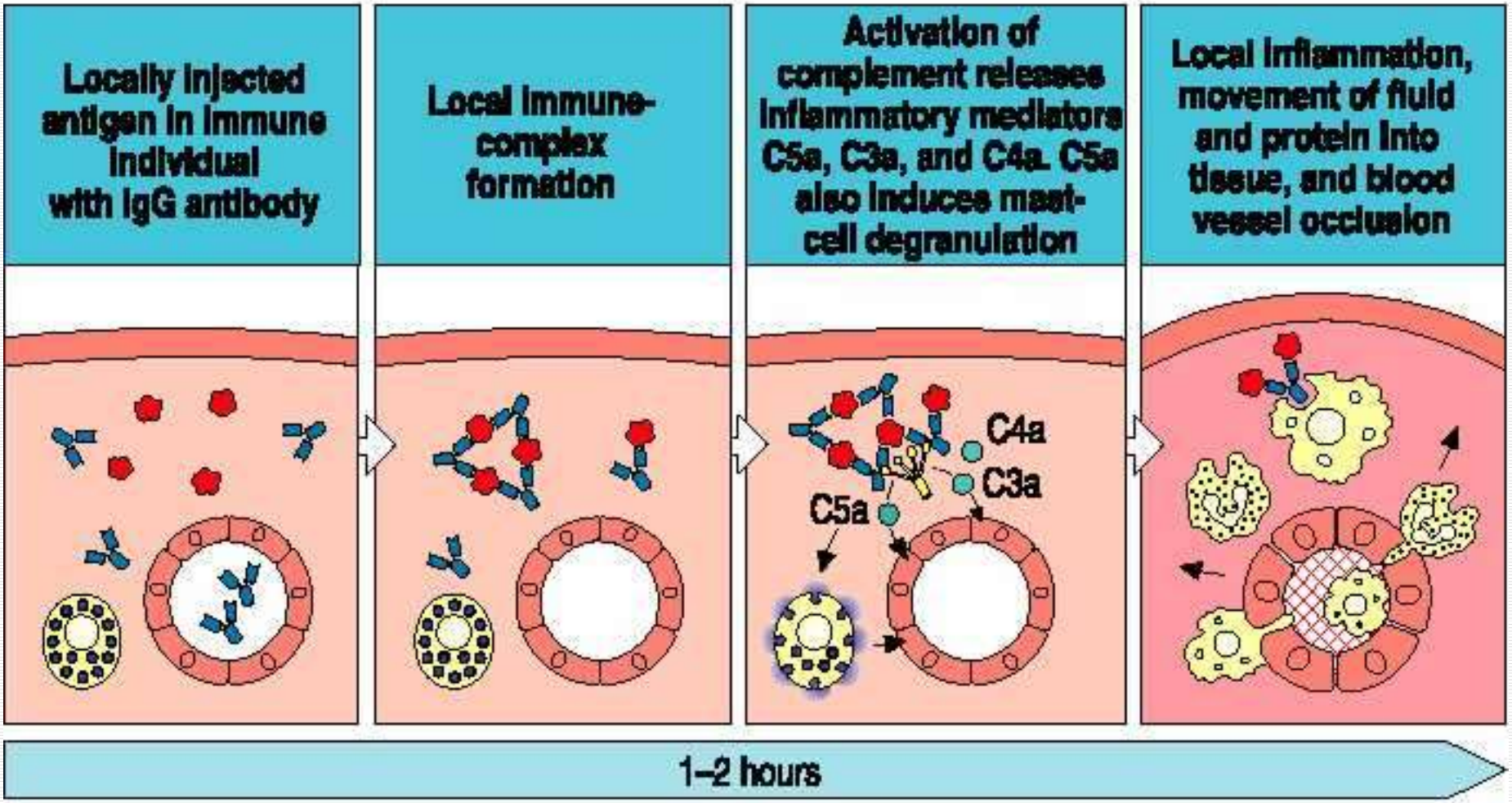
Type III Hypersensitivity

Figure 7.37



Type III Hypersensitivity

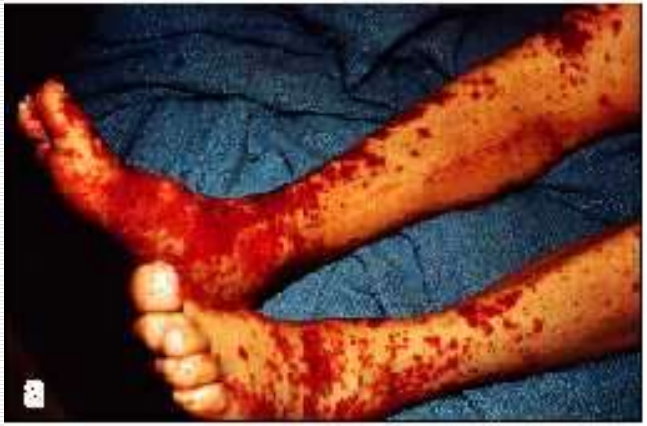
Figure 10.29

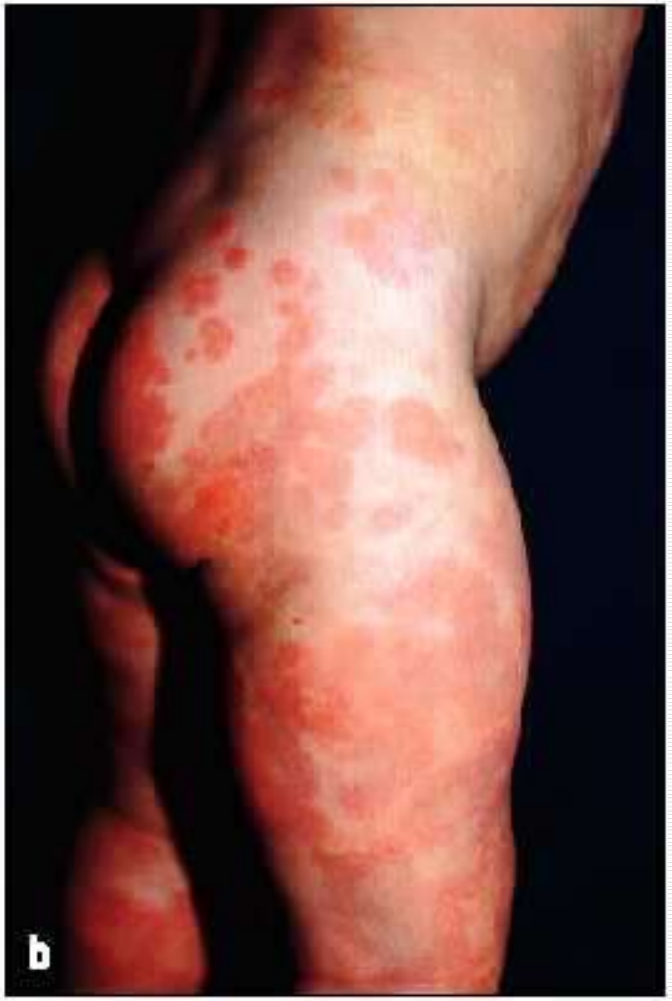


Type III Hypersensitivity

Figure 10.30

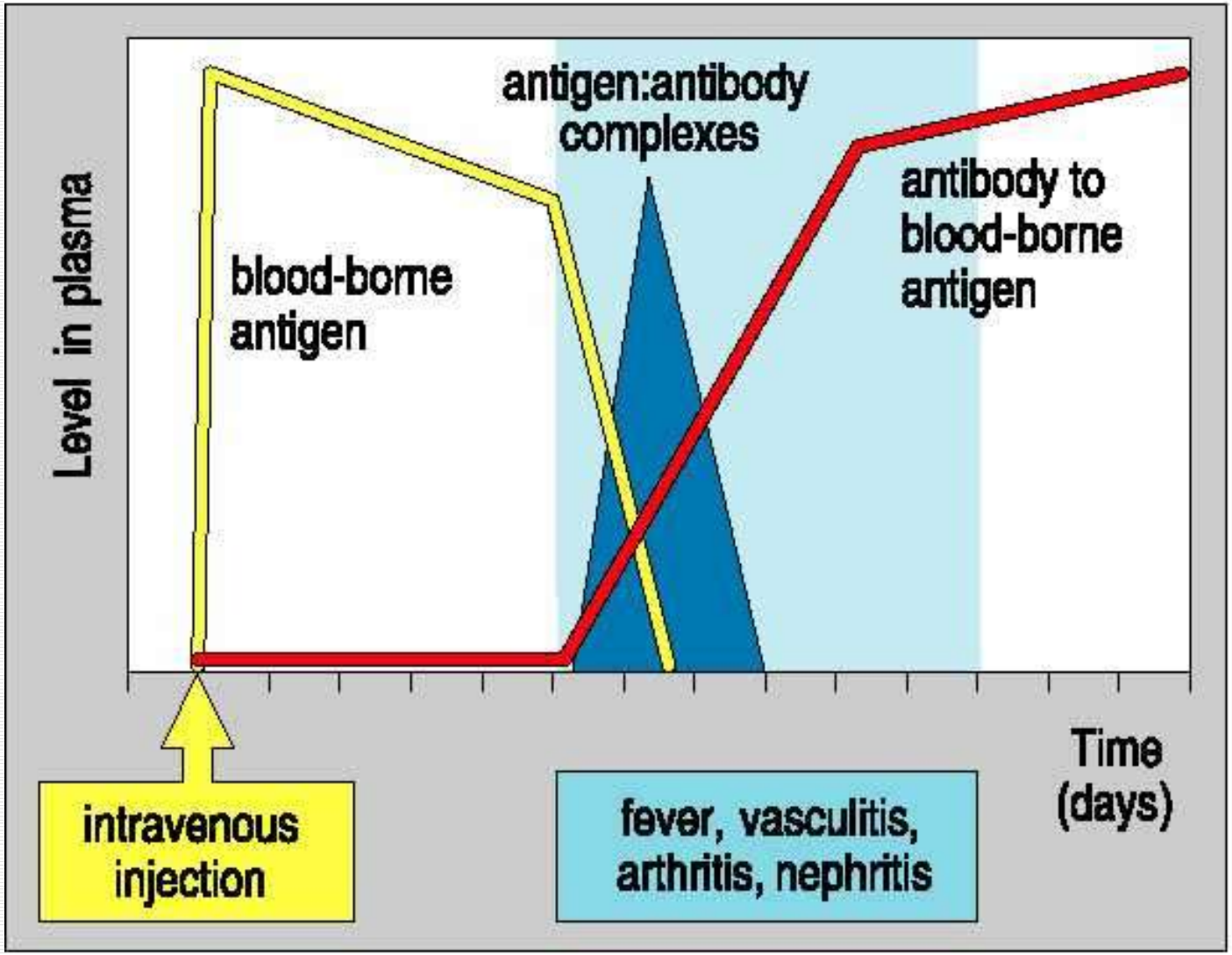
Route	Resulting disease	Site of immune-complex deposition
Intravenous (high dose)	Vasculitis	Blood vessel walls
	Nephritis	Renal glomeruli
	Arthritis	Joint spaces
Subcutaneous	Arthus reaction	Perivascular area
Inhaled	Farmer's lung	Alveolar/capillary interface





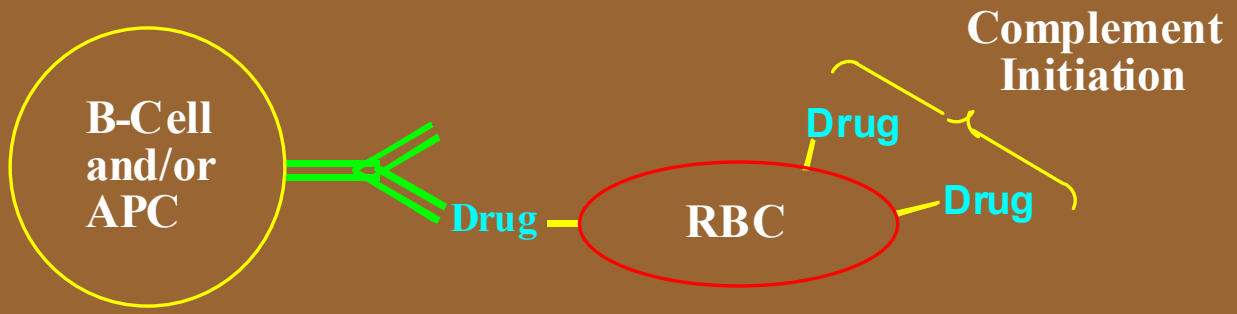
Type III Hypersensitivity

Figure 10.31



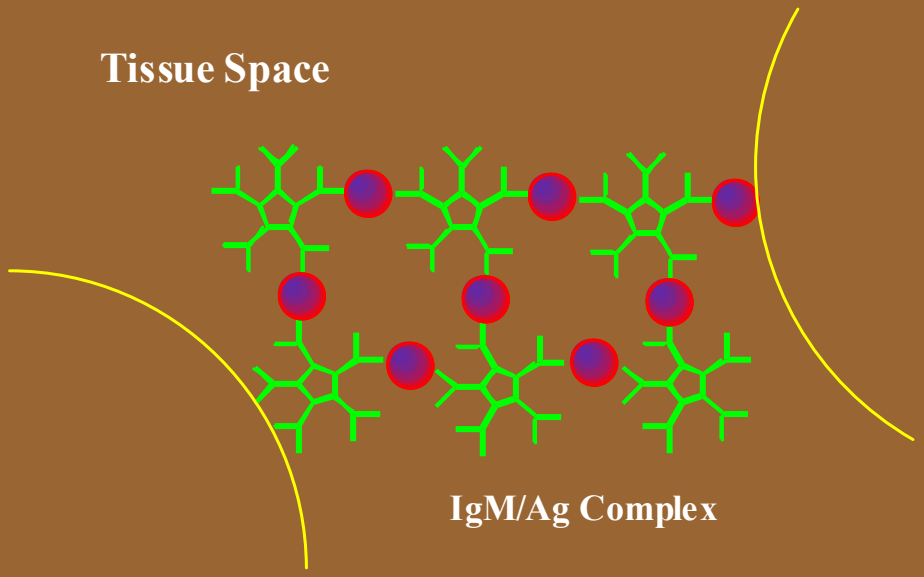
Hypersensitivity Induced Drug Immunopathology

Type II= Can cause blood cells that are labelled to be removed by complement or ADCC



Hypersensitivity Induced Drug Immunopathology

Type III= Can cause complement complexation which can lead to innocent bystander reaction in tissues where complexes lodge (i.e., kidney)



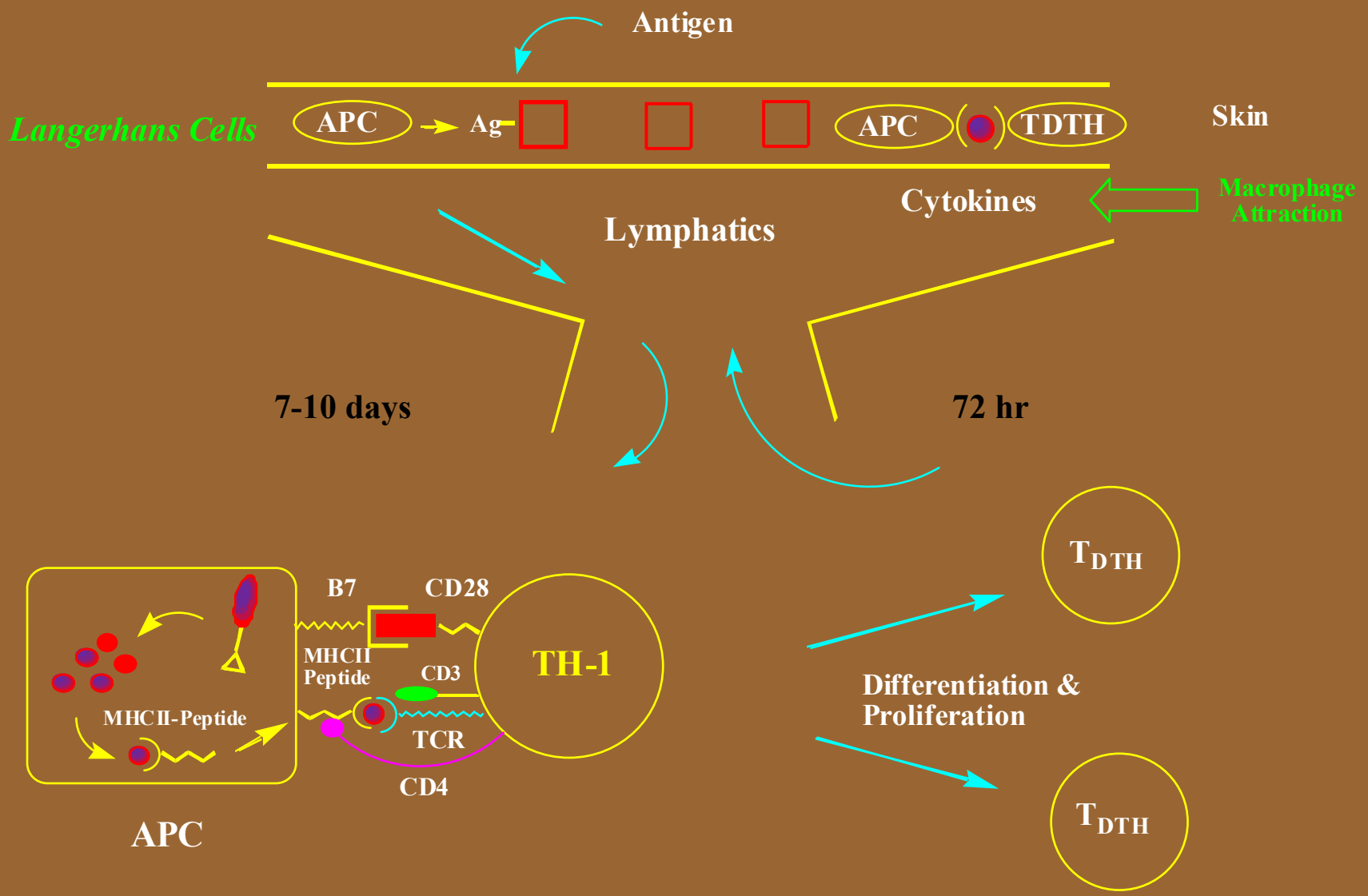
Type IV Delayed Hypersensitivity

- Thought to be a response to tissue harboring bacteria or parasites.

- Occurs most commonly with topical agents which react with the skin (contact dermatitis), such as cosmetics, poison oak, chemicals (e.g., entadecacatechol)

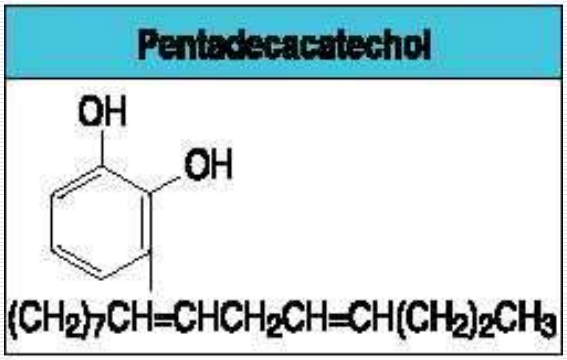
- Development of sensitized T_{DTH} cells, which secrete cytokines capable of activating and attracting macrophages.

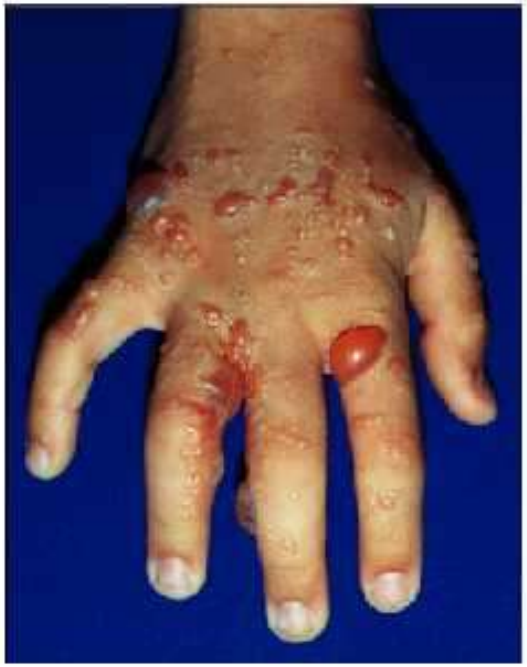
Type IV Delayed Hypersensitivity



Type IV Delayed Hypersensitivity

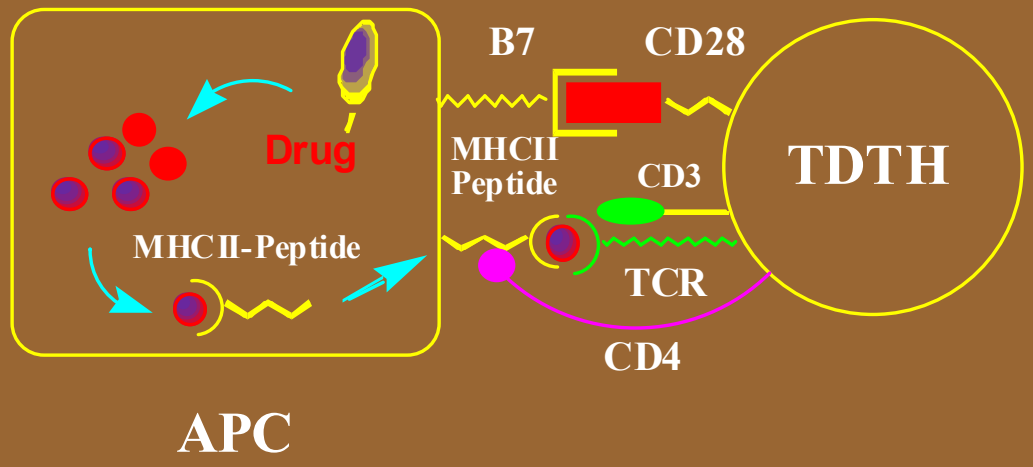
Figure 10.35





Hypersensitivity Induced Drug Immunopathology

Type IV= Can cause tissues to be labelled (i.e., skin) and inducing cytotoxic T cell response



E. Therapeutics Based on Type IV Hypersensitivity

• Type IV hypersensitivity is associated with several diseases and conditions, such as tuberculosis, leprosy, leishmaniasis, deep fungal infections, etc.

• Type IV is also associated with allergic reactions to contact antigens like poison ivy and poison oak

Hypersensitivity Reactions: Take Home Message

1. Allergic or Hypersensitivity reactions result from an non-desirable immune response.

2. Both CMI and AMI are involved in allergic reactions.

3. Complement is an important part of the immune responses ability to combat bacterial infections.

4. Hypersentivity reactions are a major reason for drug induced pathologies.