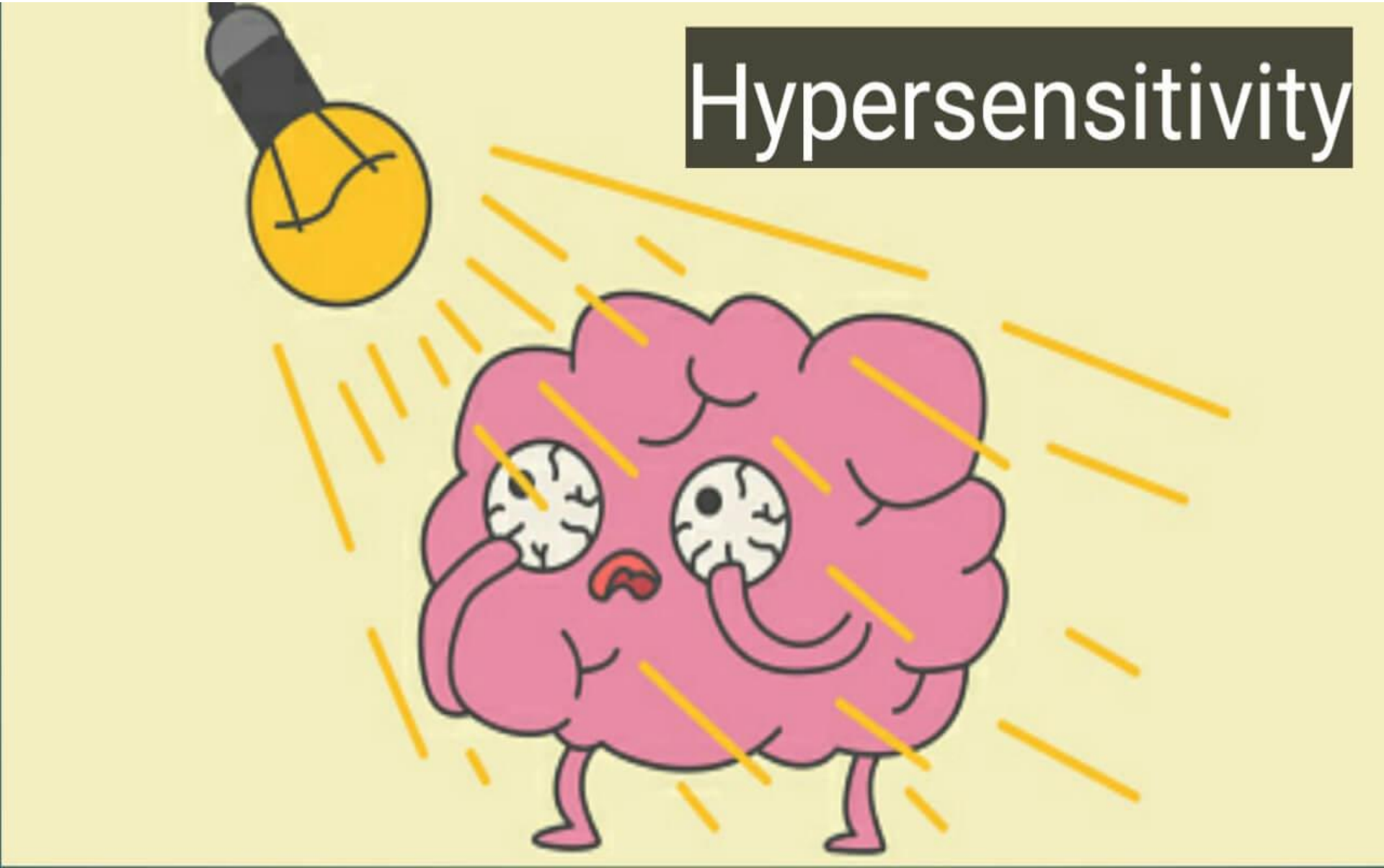
Hypersensitivity



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Learning outcomes

- By the end of this lecture the students will be able to :

1. Recognize types of hypersensitivity
2. Clarify the mechanism of type I hypersensitivity
3. Define pharmacologically active mediators of type I hypersensitivity
4. Define diagnostic tests and treatment of type I hypersensitivity.
5. Compare type II, III and IV hypersensitivity
6. Define the clinical types of hypersensitivity

Lecture Outline

Hypersensitivity: definition and types

- type I, mechanism, diagnosis and treatment
- Comparison of type II,III and IV Hypersensitivity
- Various clinical types of hypersensitivity

Case Scenario

Four days after birth, a female neonate with the blood type AB, Rh(D) **positive** was admitted to hospital due to **jaundice**. Her mother, 39 years old, had a normal vaginal delivery and had a history of gravida 4 para 2.
The mother had no previous history of blood , plasma, or any blood products transfusions .
The newborn was apathetic and had been crying loudly when they were admitted.
The results of the seroanalysis revealed a **strong positive result (+++) on the direct Coombs test, a total bilirubin of 46.1 mg/dL, and a direct bilirubin of 1.1mg/dL.**

- State the diagnosis of this case?
- clarify the underling mechanism?

Hypersensitivity

Definition

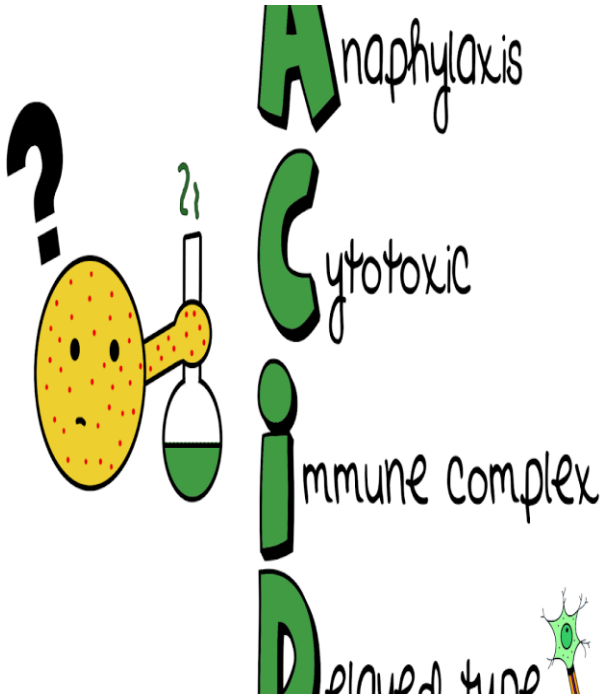
Hypersensitivity refers to undesirable (damaging, discomfort-producing and sometimes fatal) reactions produced by the normal immune system.

Hypersensitivity

Classification

Hypersensitivity reactions are classified into four types:

- **type I, type II, type III (immediate reactions)**
- **type IV (delayed reactions)**



Type I Hypersensitivity

- **Allergens:**
  - **Inhalants**: Pollen grains, Fungal allergens
  - **Injectants**: drugs
  - **Contact**: Antiseptic spray
  - **Ingestants**: egg, fish

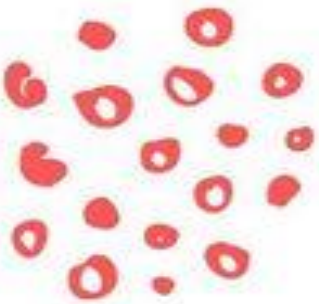
Type I hypersensitivity immediate.

The reaction may involve:

- Skin (urticaria and eczema)
- Eyes (Conjunctivitis)
- Nasopharynx (rhinorrhea, rhinitis),
- Bronchopulmonary tissues (asthma)
- Gastrointestinal tract (gastroenteritis).

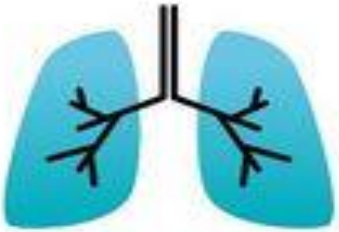
Antibody is **reactant**
Antigen is **allergen**

Signs of anaphylaxis

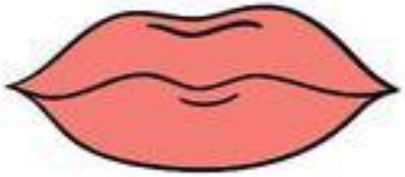


Rash (hives)

Dizziness, confusion



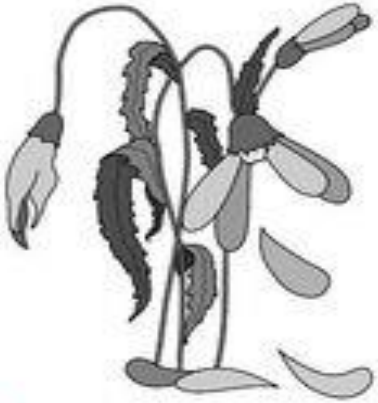
Chest tightness, difficulty breathing



Swelling of lips, tongue

Rapid heartrate

Cough, wheezing



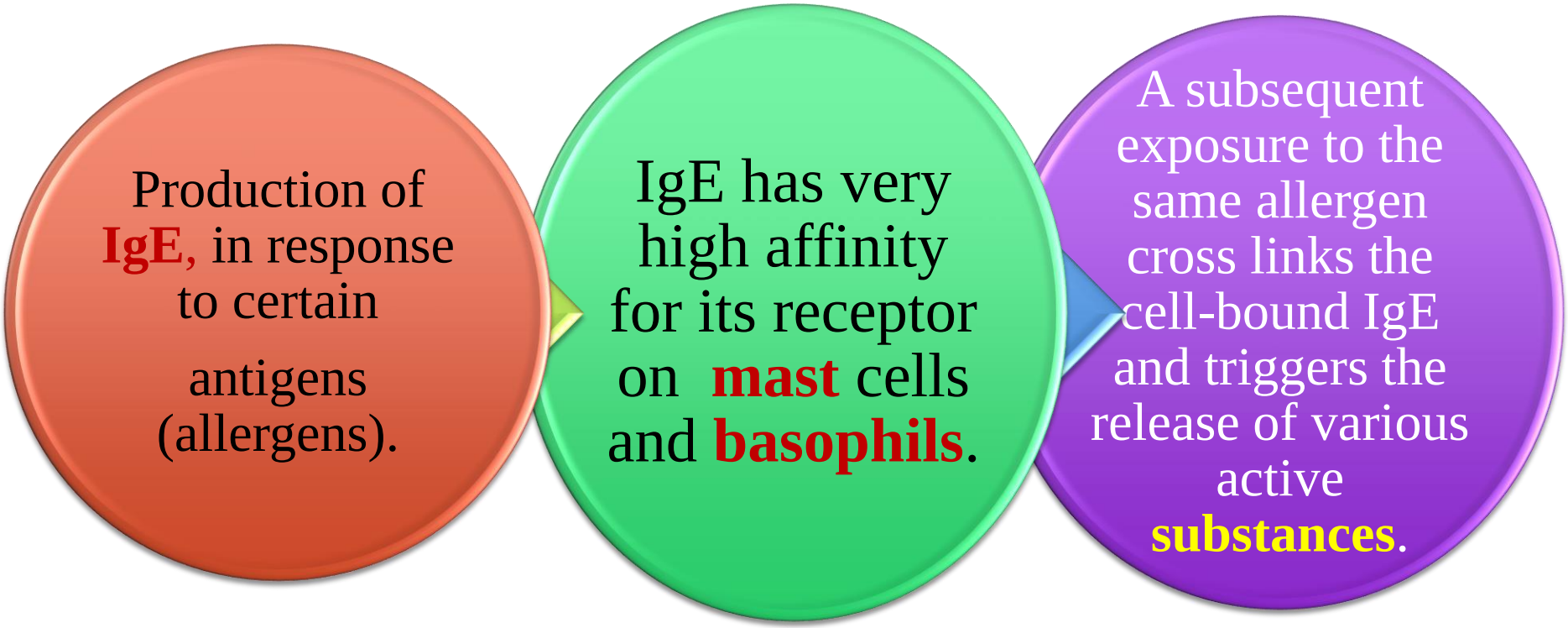
Weakness, faint pulses

Pale, sweaty, clammy

Nausea, vomiting

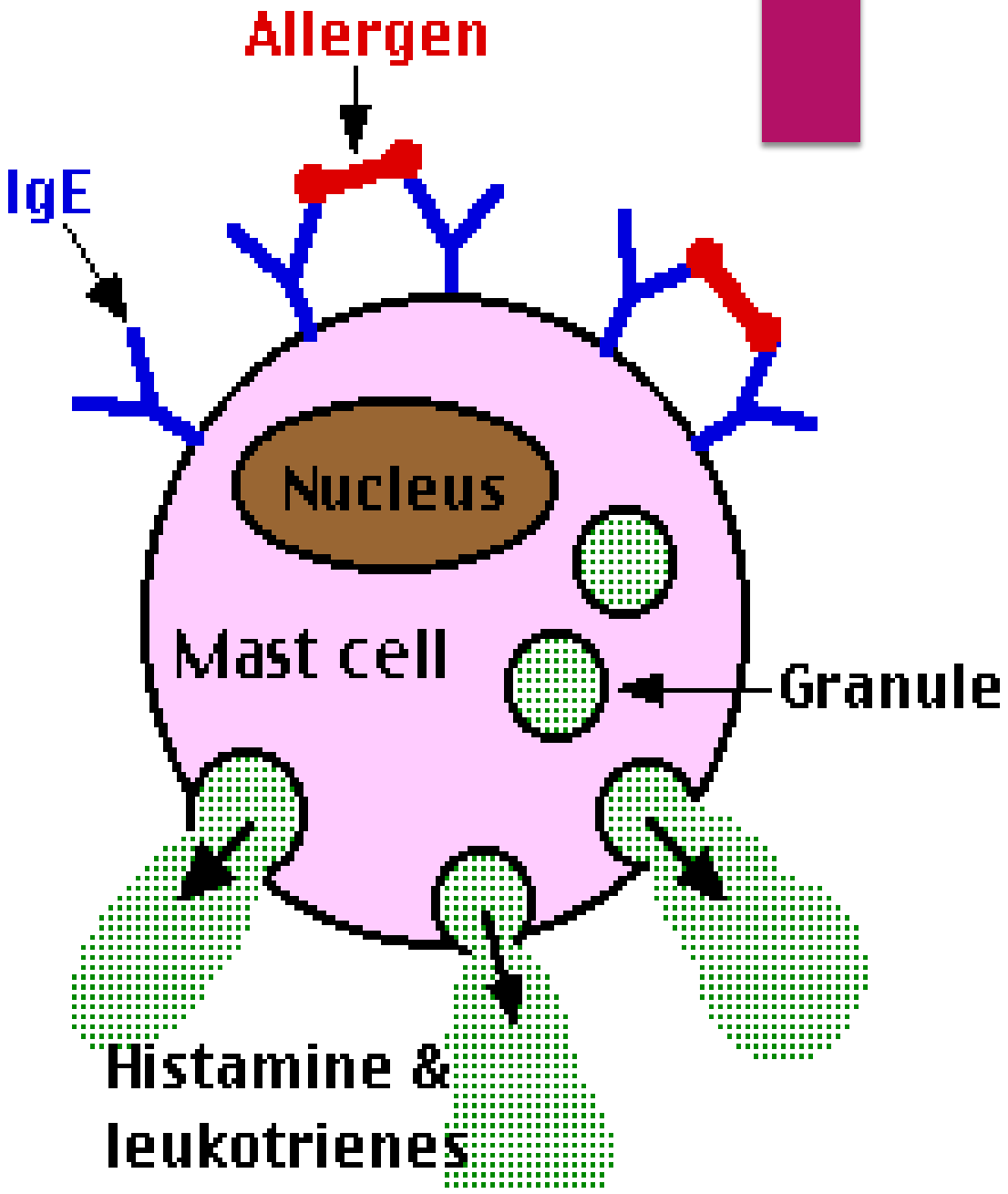
northernpdx

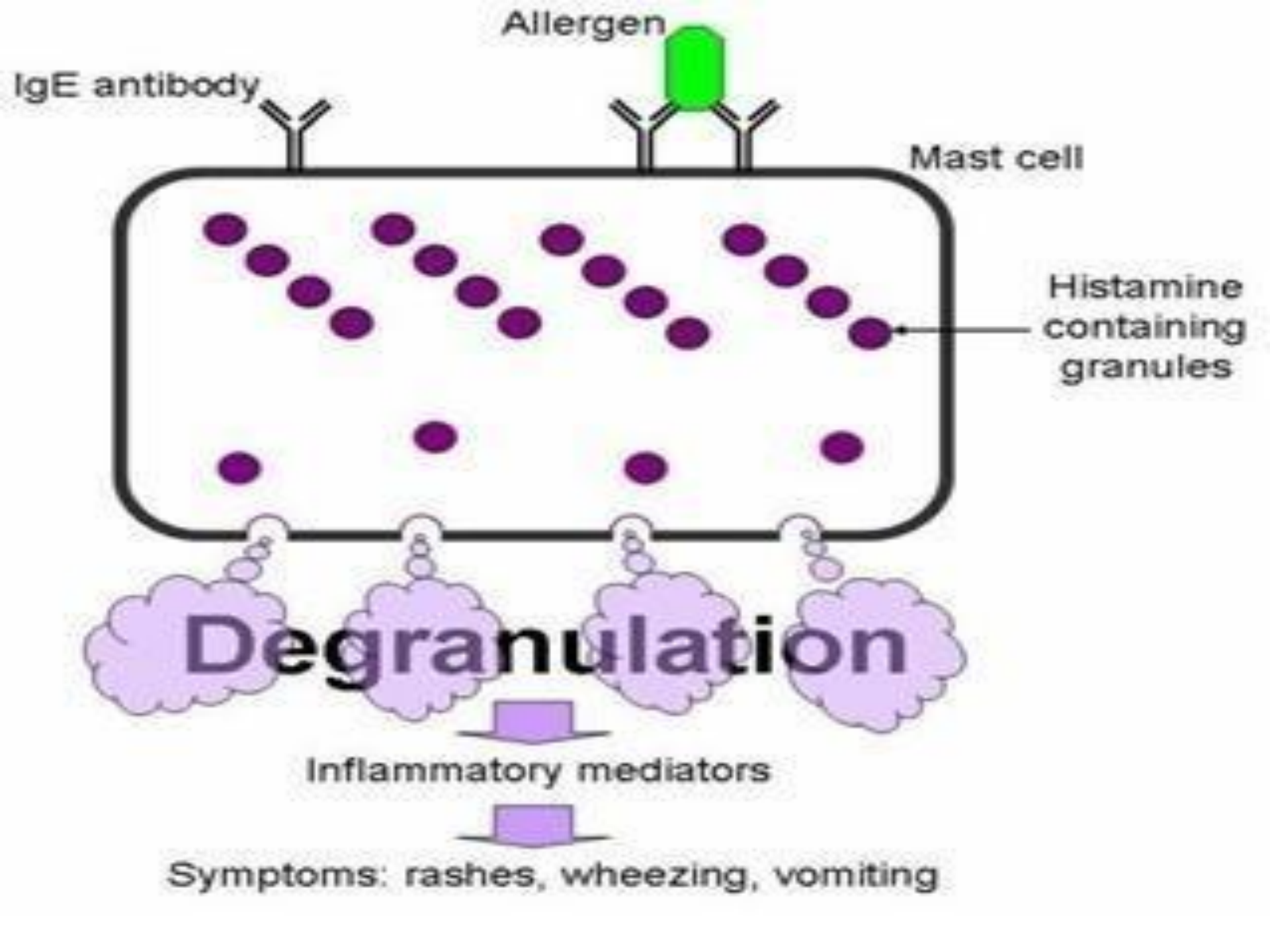
The mechanism of reaction involves



Cross-linking of **allergen** to **IgE (**binde to-Fc-receptor on mast cell**)** is important in mast cell **triggering**.

Mast Cell degranulation is preceded by increased **Ca++ influx**, which is a crucial process.




Allergen
IgE antibody
Mast cell
Histamine containing granules
Degranulation
Inflammatory mediators
Symptoms: rashes, wheezing, vomiting

Mediators of Immediate Hypersensitivity

Preformed mediators in granules:

histamine	bronchoconstriction, mucus secretion, vasodilatation, vascular permeability
Tryptase	proteolysis
ECF-A	attract eosinophil and neutrophils

Newly formed mediators:

leukotriene B4	basophil attractant
leukotrieneC4, D4:	same as histamine (1000x more potent)
prostaglandins	edema and pain

Diagnostic tests for immediate hypersensitivity

- **Skin** (prick and intradermal) tests.

- **Measurement of IgE antibodies** by ELISA.

Treatment

A- Avoidance of exposure.

B- Symptomatic treatment.

C- Immunotherapy

A- Avoidance of exposure.

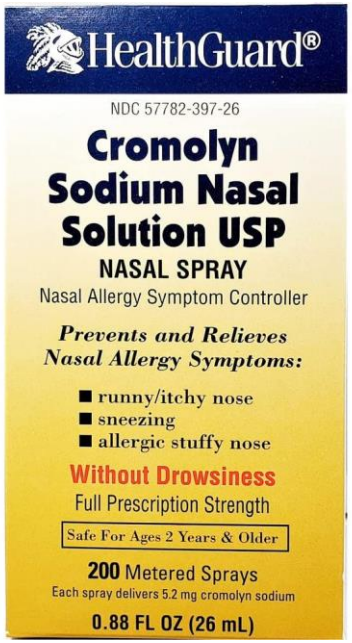
For **dust mite** allergens: Cover mattresses and pillows with dust mite **resistant covers.**

For **fungal** allergens: removing indoor **plants** (which promote mold growth), drying or removing wet carpets.

B- Symptomatic treatment

1. Antihistamines which block histamine receptors.

2. Chromolyn sodium inhibits mast cell degranulation, by inhibiting Ca++ influx.



B- Symptomatic treatment

- **leukotriene receptor blockers**
- **inhibitors of the cyclooxygenase**
- **Late onset allergic symptoms**, particularly bronchoconstriction, which is mediated by leukotrienes, or short term relief from bronchoconstriction is provided by **bronchodilators** (inhalants).

C- Immunotherapy

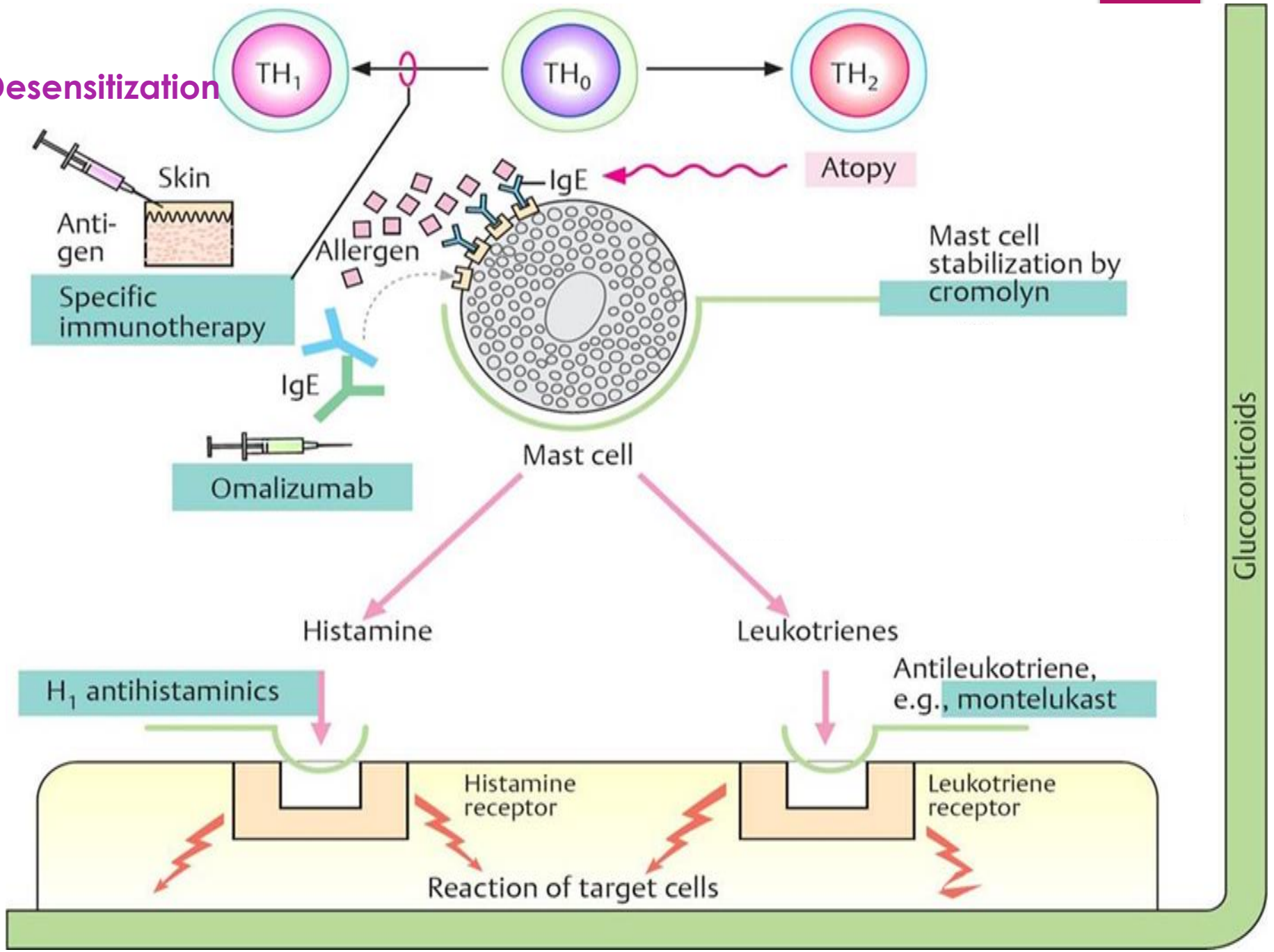
Desensitization

- Administration of gradually **increasing** doses of allergen extracts at **regular** intervals over a period of years (starting with a very small dose), given to patients by injection, drops, or tablets under the tongue (sublingual).

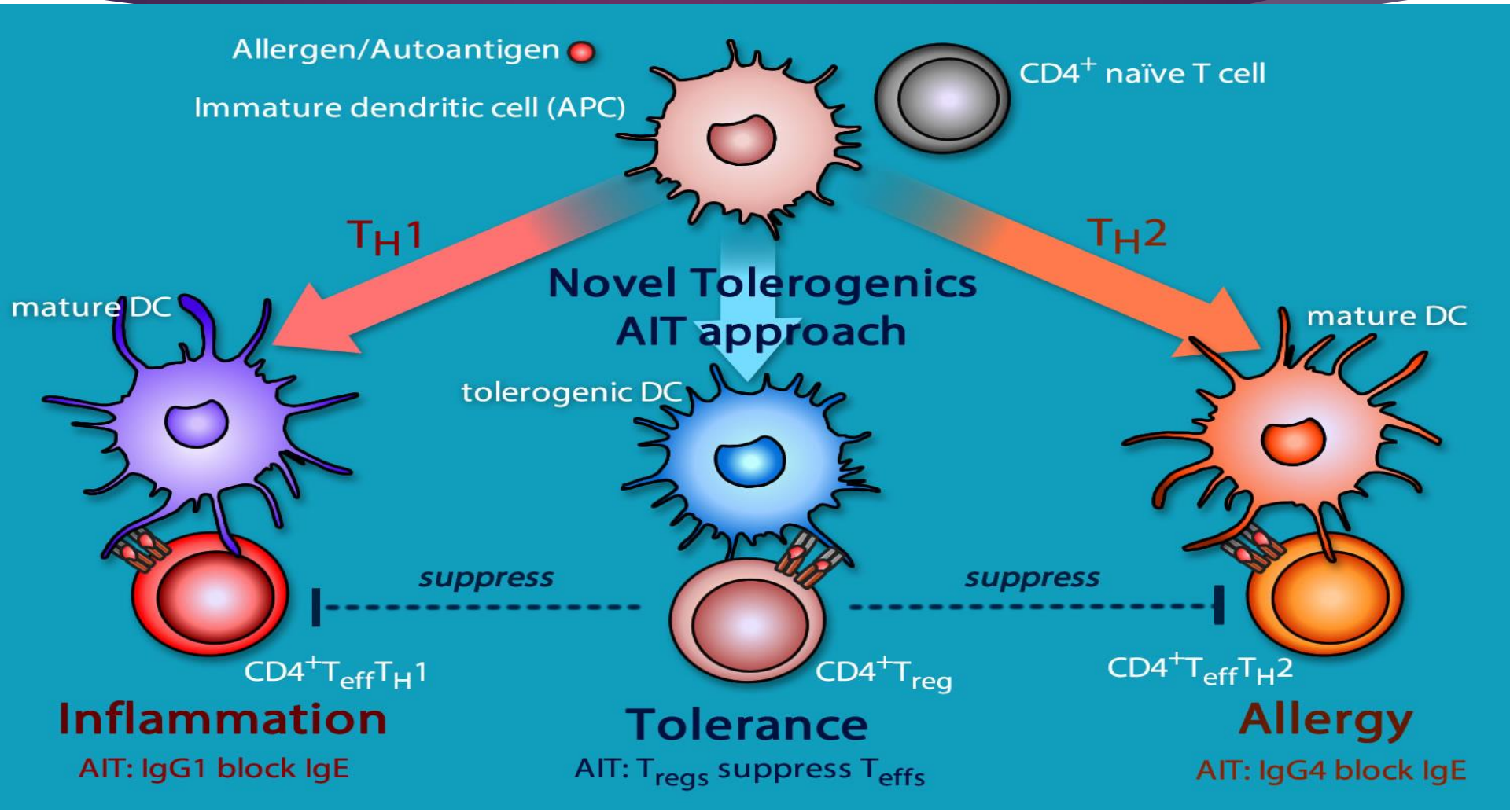
Mechanism

- It is possible to teach the immune system to **tolerate** the allergen and causes the production of **'regulatory'** immune cells, which:
  - Stop the production of **IgE**
  - Rise in allergen-specific **IgG4** antibodies with blocking activity through the inhibition of allergen-induced-IgE mediated release of inflammatory mediators from mast cells.

Desensitization



Cross regulation between TH1 and TH2



Type II hypersensitivity

» 1- Incompatible blood transfusion.

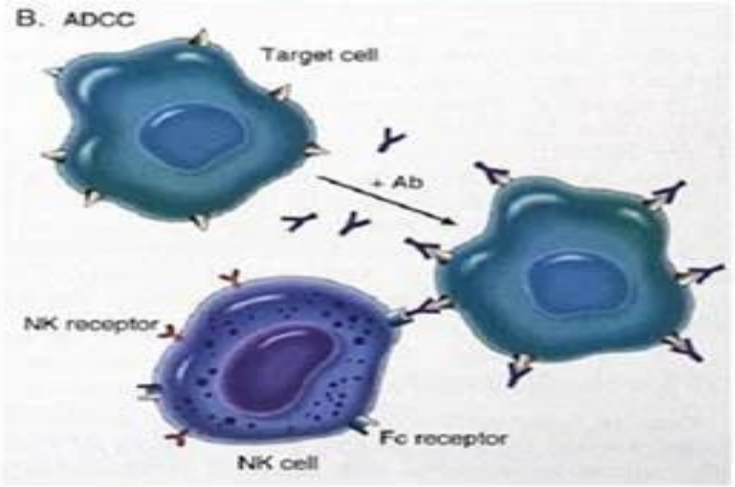
- ABO: **intravascular** haemolysis (**complement**): Manifestations: nausea, fever, rigors, back pain.

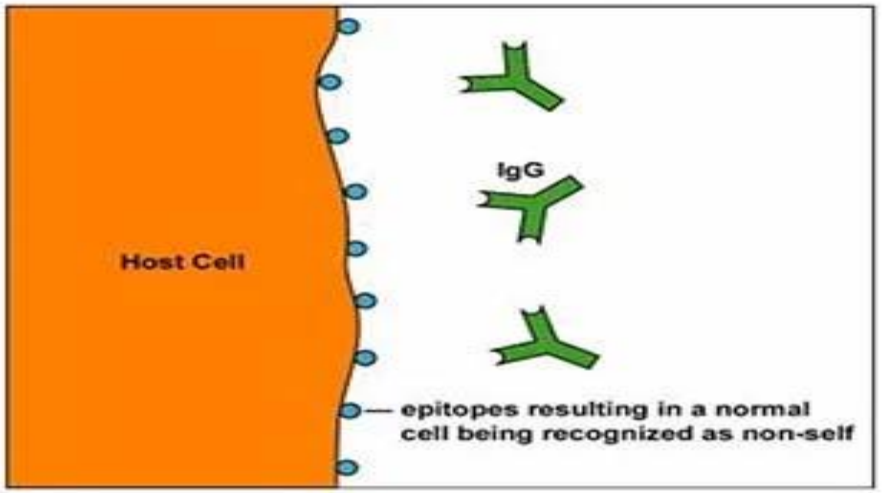
» 2- Erythroblastosis faetalis:

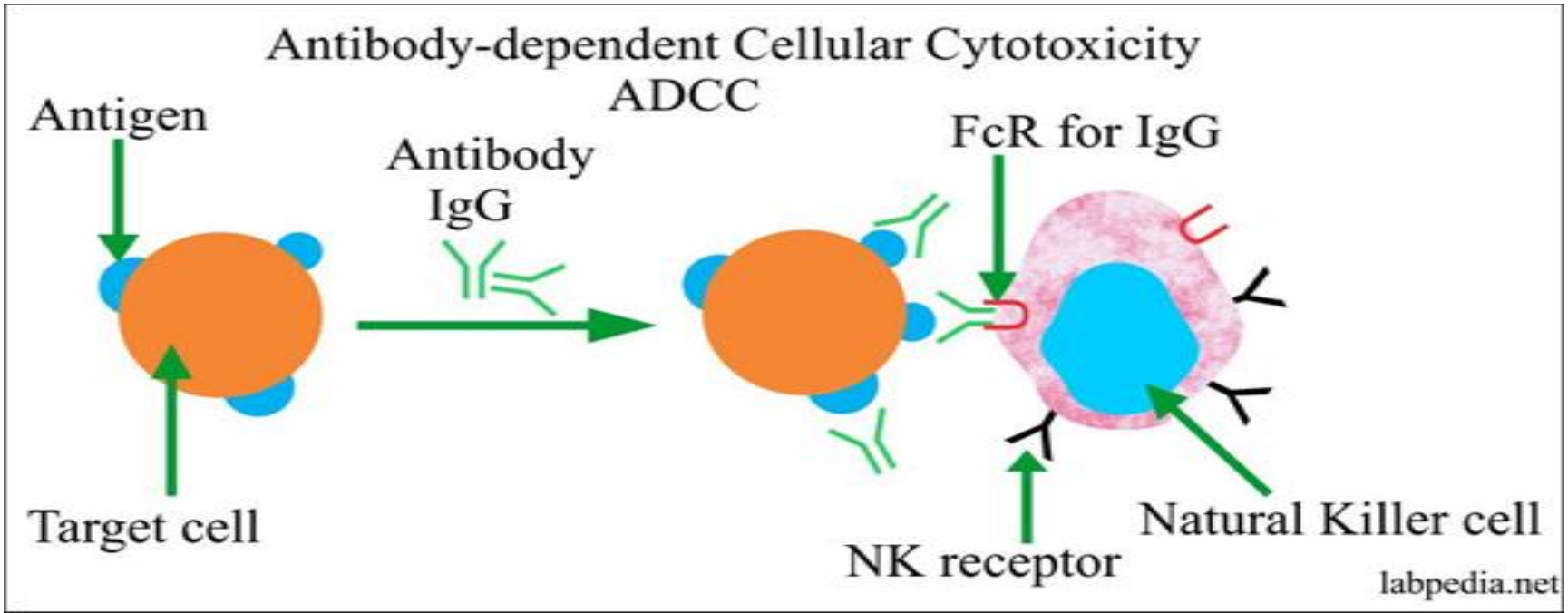
- RH: **extravascular** hemolysis (phagocytic cells).
- When mother (Rh **negative**) gives birth to Rh **positive** infant, at time of birth, fetal blood may enter to maternal circulation and produce **antibody** against Rh antigen.
- At **2nd birth**, the antibody will cross the placenta and become attached to Rh antigen on the surface of RBCs of the fetus and **extravascular haemolysis** occur and the infant show anemia and jaundice at first day then hepatosplenomegally and bilirubin encephalopathy.

Type II (Cytotoxic) Hypersensitivity

Antibody Dependent Cell Mediated Cytotoxicity







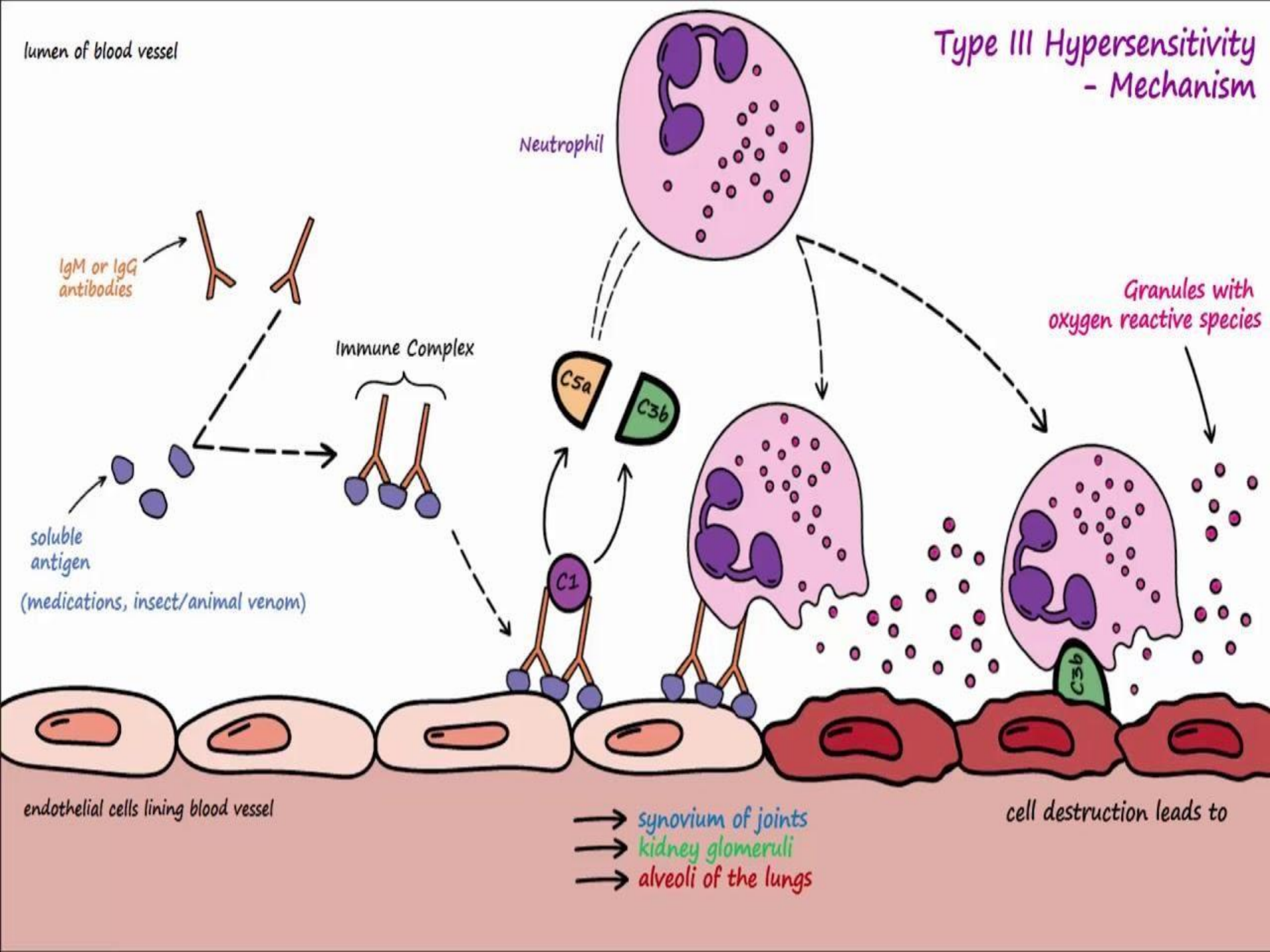
Type III hypersensitivity

Arthus reaction:

- **localized** inflammation of the small vessels (i.e., vasculitis) near the injection or bite site. immune complexes are formed around and within the blood vessels of the skin. Subsequently, activation of the **complement** cascade enhances the local **inflammation**.
- Most individuals present with **redness**, **swelling**, and **pain**. It can also subsequently lead to induration localized to the affected area.

Serum sickness:

- **Systemic** reaction to proteins in **antiserum** derived from **animal** source.
- Symptoms often include a **rash**, joint **pain**, **fever**, and **lymphadenopathy**.


Type III Hypersensitivity - Mechanism
lumen of blood vessel
Neutrophil
IgM or IgG antibodies
Immune Complex
C5a
C3b
Granules with oxygen reactive species
soluble antigen
(medications, insect/animal venom)
C1
C3b
endothelial cells lining blood vessel
synovium of joints
kidney glomeruli
alveoli of the lungs
cell destruction leads to

Type IV Hypersensitivity

- **Tuberculin reaction**

which peaks **48** hours after the injection of antigen (PPD or old tuberculin).

The lesion is characterized by induration and erythema.

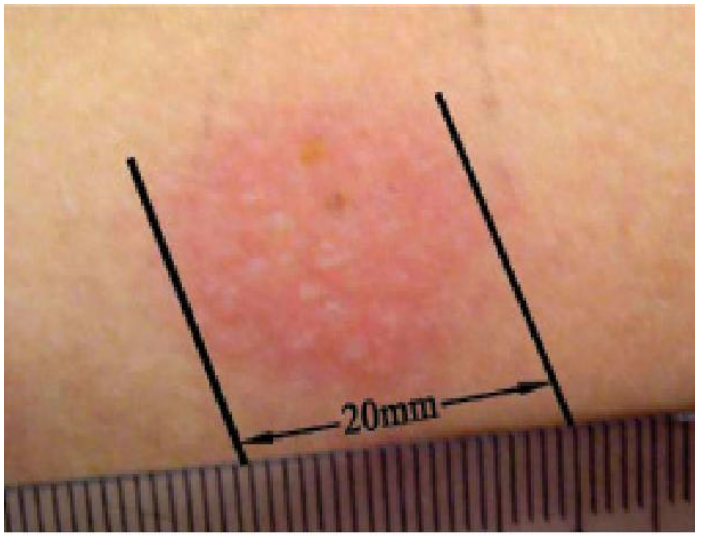


Figure 1: Skin manifestations after 72 hours of a test performed

Mechanism

- CD4+ helper T cells recognize antigen in a complex with Class II MHC.
- CD4+ T cells secrete IL-2 and interferon gamma, further inducing the release of other Th1 cytokines, thus mediating the immune response:
- Activated CD8+ T cells destroy target cells on contact.
- chemokines such as IL-8, monocyte chemotactic and activating factor (MCAF) that collectively lead to macrophage activation and production of hydrolytic enzymes which lead to the development of a **local** tissue reaction which is usually maximal in 48-72 h.

Type IV - Hypersensitivity

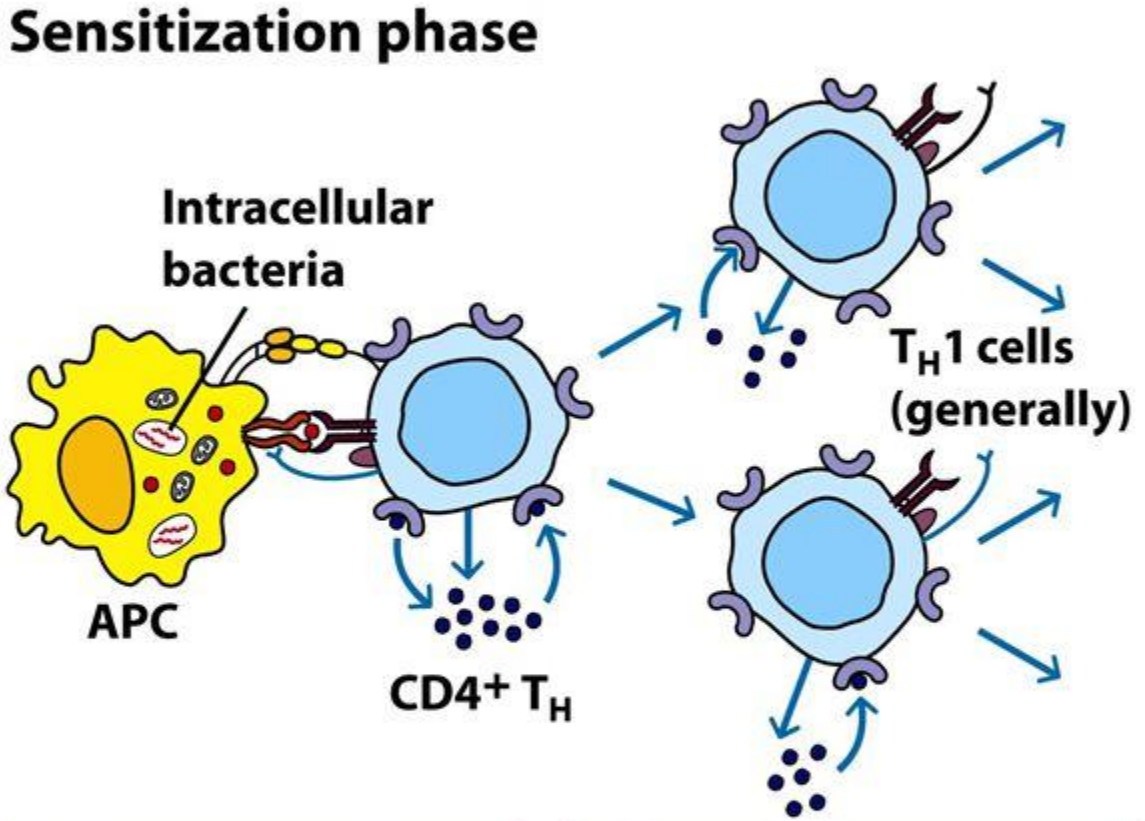
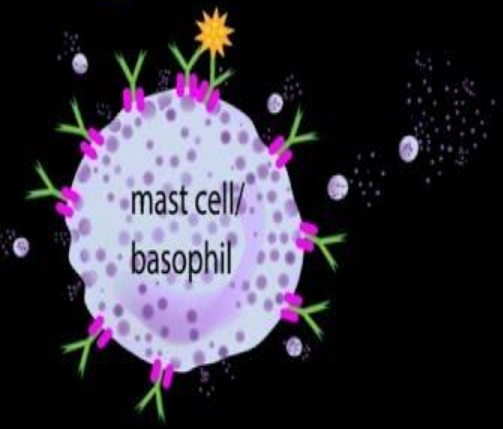


Figure 15-17a
Kuby IMMUNOLOGY, Sixth Edition

Overview of Hypersensitivity

Type I

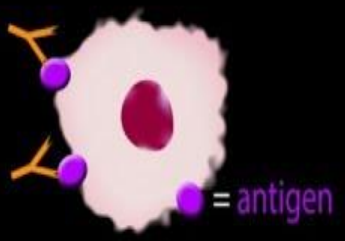
IgE antibodies



- inflammation
- smooth muscle spasms

Type II

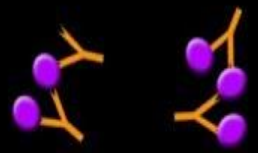
IgG/IgM antibodies



- *cytotoxic*: kill cells by complement, phagocytosis
- interfere with cell functions

Type III

IgG/IgM antibodies



immune complexes

- inflammation

Type IV

T-cells - mediated

- inflammation

Comparison between type-II, III and IV hypersensitivities:

Characteristic	Type-II	Type-III	Type-IV
Antibody	IgG, IgM	IgG, IgM	None
Antigen	Cell-bound	Soluble	Soluble or cell-bound
Response time	Minutes-hours	3-8 h.	48-72 h.

Comparison between type-II, III and IV hypersensitivities:

Characteristic	Type-II	Type-III	Type-IV
Appearance	Lysis and necrosis	Erythema and edema, necrosis	Erythema and induration
Histology	Antibody and complement	Complement and neutrophils	Monocytes, lymphocytes

Comparison between type-II, III and IV hypersensitivities:

Characteristic	Type-II	Type-III	Type-IV
immune reactant	Antibody	Antibody	T-cells
Examples	Incompatible blood transfusion, Erythroblastosis Fetalis, Autoimmune hemolytic anemia.	Arthus reaction, Serum sickness Post streptococcus glomerulonephritis RA SLE	Tuberculin test Eczema MS Type 1 DM

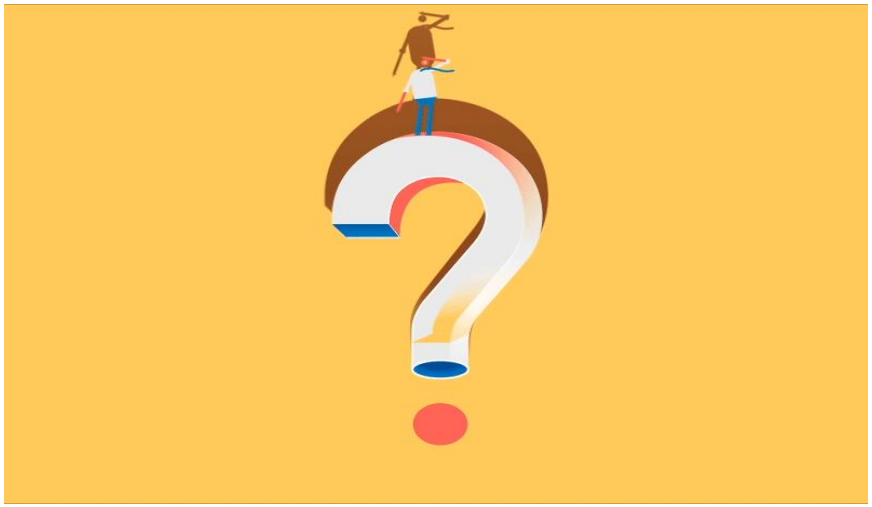
Case Scenario

Four days after birth, a female neonate with the blood type AB, Rh(D) **positive** was admitted to hospital due to **jaundice**. Her mother, 39 years old, had a normal vaginal delivery and had a history of gravida 4 para 2.
The mother had no previous history of blood , plasma, or any blood products transfusions .
The newborn was apathetic and had been crying loudly when they were admitted.
The results of the seroanalysis revealed a **strong positive result (+++) on the direct Coombs test, a total bilirubin of 46.1 mg/dL, and a direct bilirubin of 1.1mg/dL.**

- mention the diagnosis of this case?
- clarify the underling mechanism?

- The following is a property of IgE:

- a-Cross the placenta
- b- Dimer
- c- involved in allergic reactions
- d-Activate complement
- e- pentamer



- Erythroblastosis fetalis is considered :

- a. Type I hypersensitivity
- b. Type II hypersensitivity
- c. Type III hypersensitivity
- d. Type IV hypersensitivity
- e. Immunodeficiency

- Serum sickness is considered one of the types of:

- a. Type I hypersensitivity
- b. Type II hypersensitivity
- c. Type III hypersensitivity
- d. Type IV hypersensitivity
- e. Immunodeficiency

- Basic Immunology : functions and disorders of the immune system , fifth edition ; Abul K. Abbas, Andrew H. Lichtman and Shiv Pillai
- Immunology :7th edition ; David Male, Jonathan Brostoff, David Roth and Ivan Roitt


THANK
YOU
Akbarian