Hypersensitivity

Special Thanks to Farrah Mendoza

What is hypersensitivity?

FYI - Protective immunity: Is a desirable reaction

It is not protective. It is more than what we want! Basically, our immune system is exaggerating!

Hypersensitivity :

Is an undesirable damaging reaction produced by excessive immune reactions.

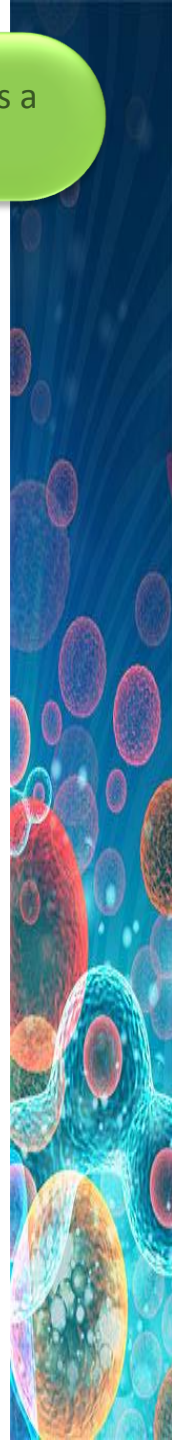
Undesirable responses can be mediated by:

Type I, II, II are mediated by **Antibodies**

Type IV *are mediated by* ***Cell mediated reactions*** to chemicals or proteins

*It responds to **3** different types of antigen:*

- Infectious agents
- Environmental substances **e.g. hay fever**
- Self antigen (hypersensitivity autoimmune disease) **e.g. rheumatoid arthritis**



Types of hypersensitivity

4 Types of hypersensitivity responses are classified by **GEL AND COOMBS** according to *the responding mechanisms*, but NOT *the responding antigens.*

	Type I Hypersensitivity	Type II Hypersensitivity	Type III Hypersensitivity	Type IV Hypersensitivity
Types of mediation & responding mechanism	IgE (Immediate reaction)	IgG, IgM (Antibody to body's self antigen)	IgG (Immune complex)	Cell Mediated Immunity

Gel & Coombs are names of the two scientists that classified the types of hypersensitivity.

Type I: Immediate Hypersensitivity

Type I is termed as : Immediate Hypersensitivity / Anaphylactic reactions / Allergic reactions

Non-allergic	Allergic
Most people are non-allergic	Some people are allergic and they are called "atopic"
They respond to allergens by producing **IgG** antibodies	They respond to allergens by producing **IgE** antibodies

Occurs within minutes to hours

Antigens: Also known as allergens have *low* molecular weight & are *highly* soluble

Cellular component:
- Mast cells
- basophiles
- eosinophils

Antibody type:
IgE
An antibody that is present in minute amounts in the body but plays a major role in allergic diseases

Dander is skin cells that fall from the body of various **animals**, similar to dandruff.

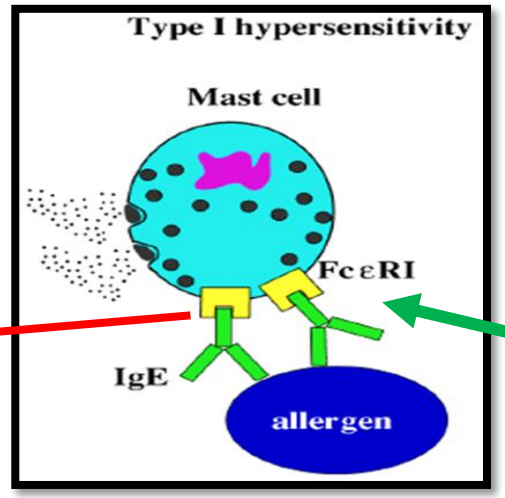
What allergens causes Type I hypersensitivity?
Pollens, dust mites, animal dander, nuts, shellfish, various drugs, etc.

Type I Reactions

Type I reactions occur in **two phases:**

1-Sensitization phase: **First** contact with allergens.

2-Challenge phase: **Subsequent** contact with allergens. (Re-exposure to allergens)



Special receptor for **IgE** to bind with

The Mechanism Of Reaction

What distinguishes a Type I hypersensitive response from a normal humoral response is **that the plasma cells secrete IgE**.

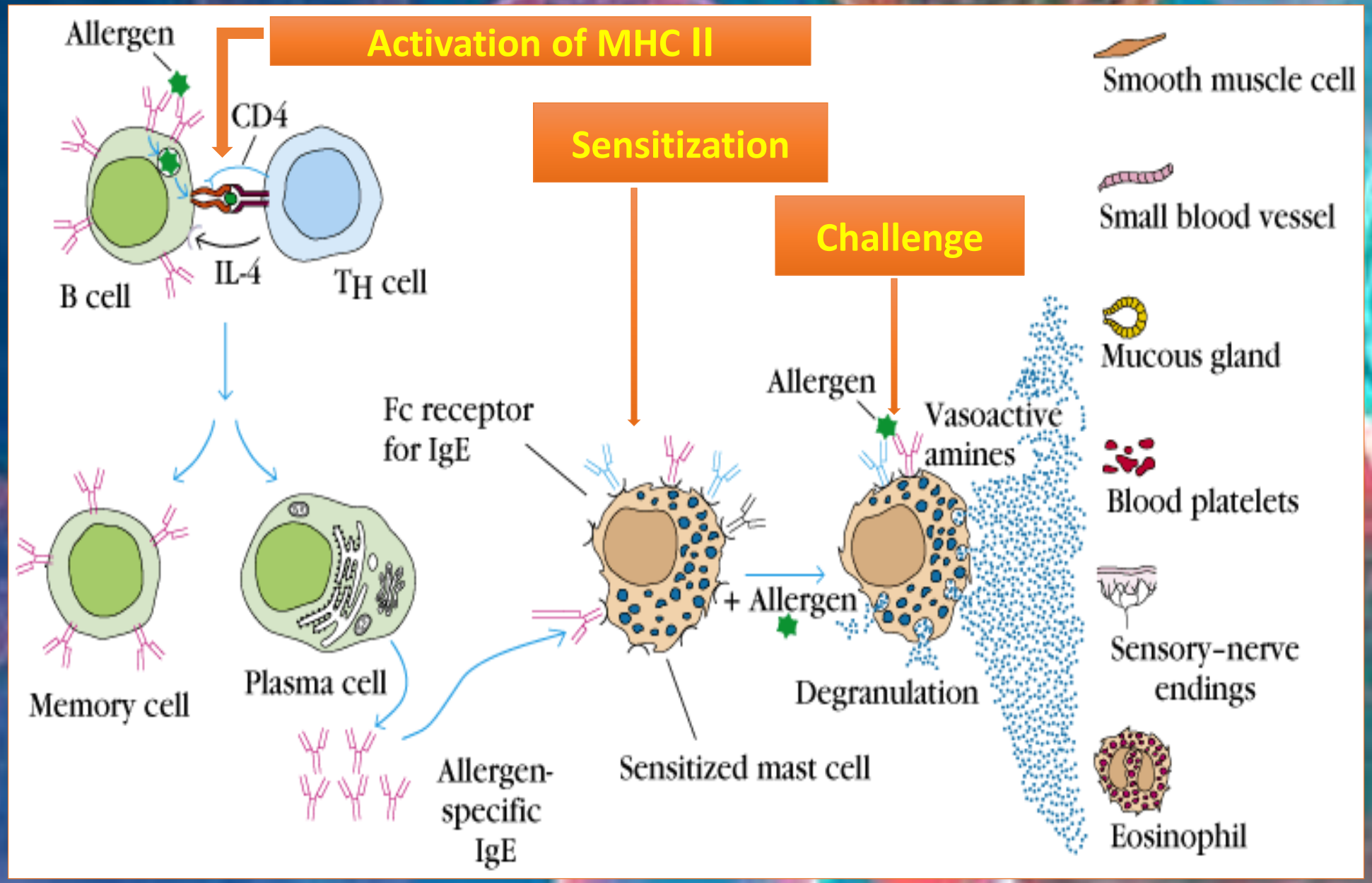
- **Unbound IgE** is present in very low levels in serum in most people, and its half life in serum is only 2-3 days
- **Most** of the body's **IgE** is **bound** to high affinity receptors (**IgE Fc**), *and its half-life is* 3 weeks.

- **IgE** binds with **high affinity** to **Fc** receptors on the surface of "tissue" mast cells and "blood" basophils.
- *Mast cells and basophils coated by* **IgE** *are said to be sensitized.*

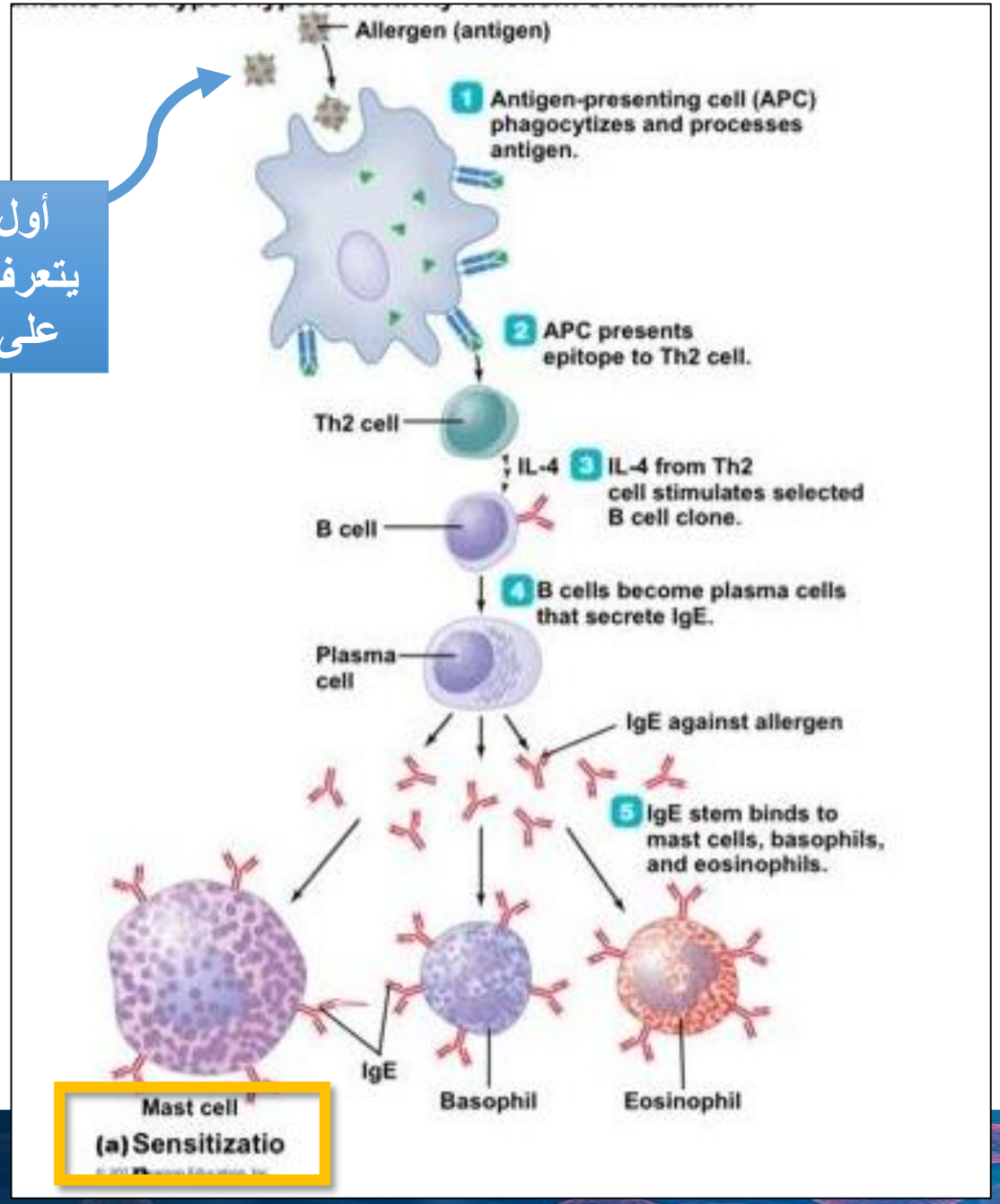
When the body is exposed to the same allergens, the **IgE** on the membrane of sensitized mast cells and basophils are cross-linked*. This results in the degranulation of these cells, which rapidly releases a variety of mediators.

Cross-link: Allergen is attached to 2 receptors at the same time, when this happens, histamine is released.

Type I: Immediate Hypersensitivity



أول مرة
يتعرف الجسد
على الجسم



1-Sensitization phase:

First contact with allergens.

Sensitization is a learning process in which repeated administrations of a stimulus results in the progressive amplification of a response.

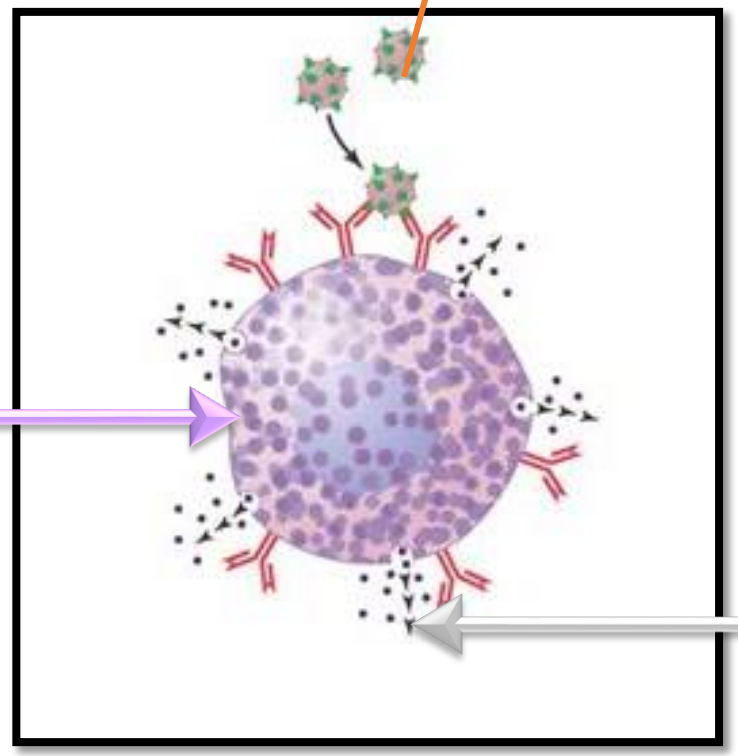
أي: الجسم يتعرض للجسم الغريب لأول مرة إلى أن يتعلمها، وهذا يؤدي إلى رد فعل الجسم للحسايات.

2-Challenge phase:

Subsequent contact with allergens.

(Re-exposure to allergens)

Subsequent exposure to allergen



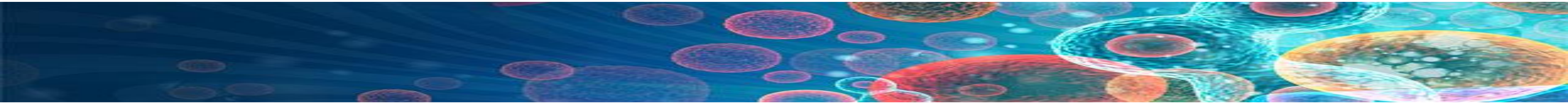
Sensitized mast cell, basophil, or eosinophil

Sensitized mast cell, basophil, or eosinophil

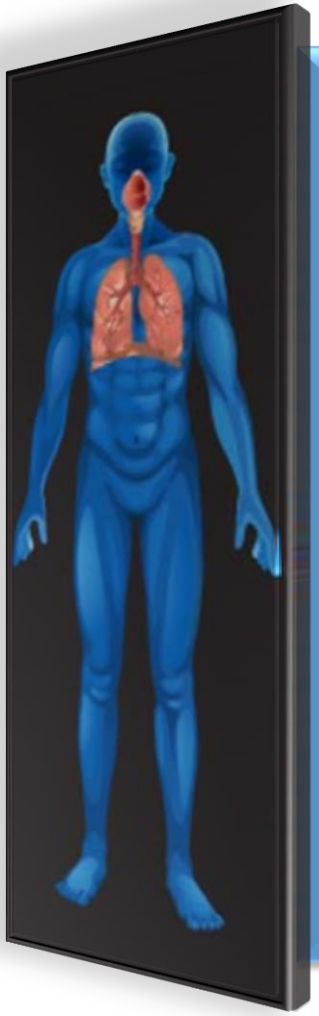
دخل الأليرجين للجسم للمرة الثانية وارتبط مع اثنان من الـ receptors، مما أدى إلى إطلاق الـ histaminesالذي هو السبب الرئيسي لرد فعل الجسم للحساسية

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)



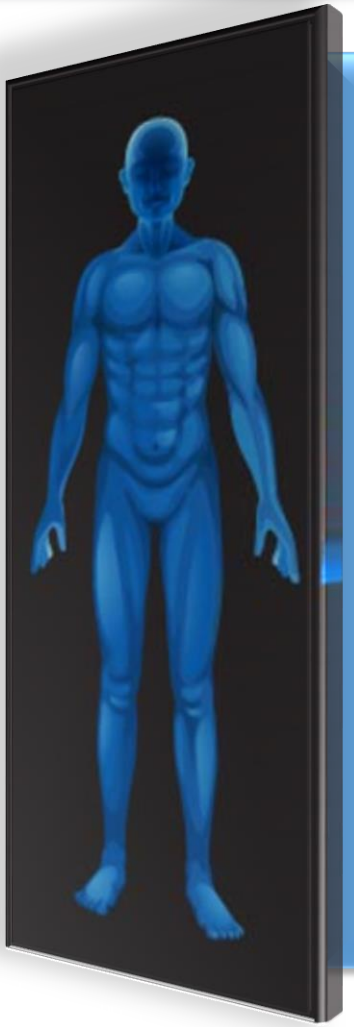
Allergy is a systemic disorder



Allergies that affect the Respiratory system are:

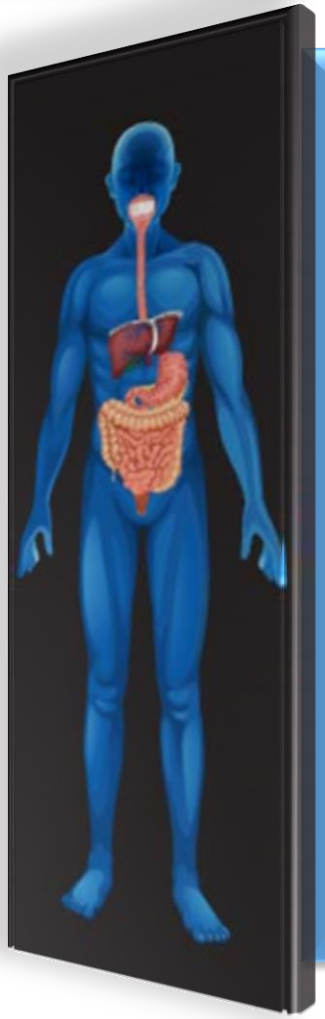
- Allergic Rhinitis
- Asthma

(nose, pharynx, and lungs)



Allergies that affect the Skin:

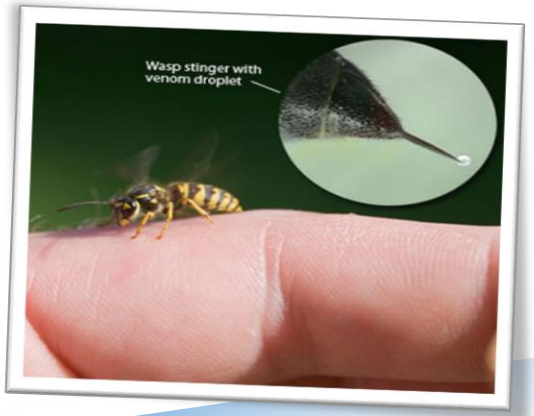
- Eczema
- Urticaria
- Allergic Dermatitis



Food allergies that affect the Digestive system cause an effect on:

- Oesophagus
- Stomach

Injected allergens:



1. Bee sting venom enters the blood stream.
2. Systemic inflammation.
3. Anaphylactic shock ⟶ life threatening.

However, even though Anaphylactic reactions are part of Type I hypersensitivity, it is **not** IgE mediated.

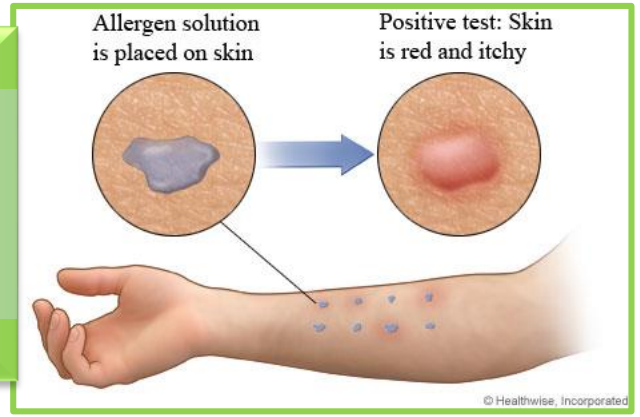
Not only bee stings, it can also result from: Contrast media **OR** local anesthetics.

Contrast media: a substance introduced into a part of the body in order to improve the visibility of internal structures during radiography.

أي: مادة تعطى للمريض لكي تظهر نتائج الأشعة السينية بشكل جيد وواضح، فهذه المادة قد تسبب حساسية للجسم.

How to diagnose allergies?

Skin prick test (SPT)



Specific IgE measurement (RAST)

radioallergosorbent test (RAST) is a blood test used to determine the substances a subject is allergic to.

Elimination or Provocation test (Food allergy)

أكثر طريقة تأخذ وقت:
يستبعد الطبيب أنواع مختلفة من الطعام الذي قد يسبب الحساسية للشخص، ثم يراقب الطبيب نتائج المريض على مدى أسابيع إلى أن يحدث حساسية فيعرف الطبيب ماذا أكل وما سبب الحساسية

Type II Hypersensitivity

Before understanding how Type II reacts, we have to know a few things:

Reaction time is minutes to hours.

They are known as cytotoxic hypersensitivity. They are ENDOGENOUS, therefore they may affect various organs and tissues.

What does this mean?

The antibodies produced by the immune response bind to antigens on the patient's own cell surfaces and components of extracellular matrix (complement-mediated lysis).

يعني الأنتاي بوديز يرتبطون مع الأنتيجنز حق الجسم نفسه، مثل الأنتيجينز على خلايا الدم مما يؤدي إلى تحلل الخلية.

Phagocytes and NK cells may also play a role (ADCC)(Antibody-Dependent Cell-mediated Cytotoxicity).

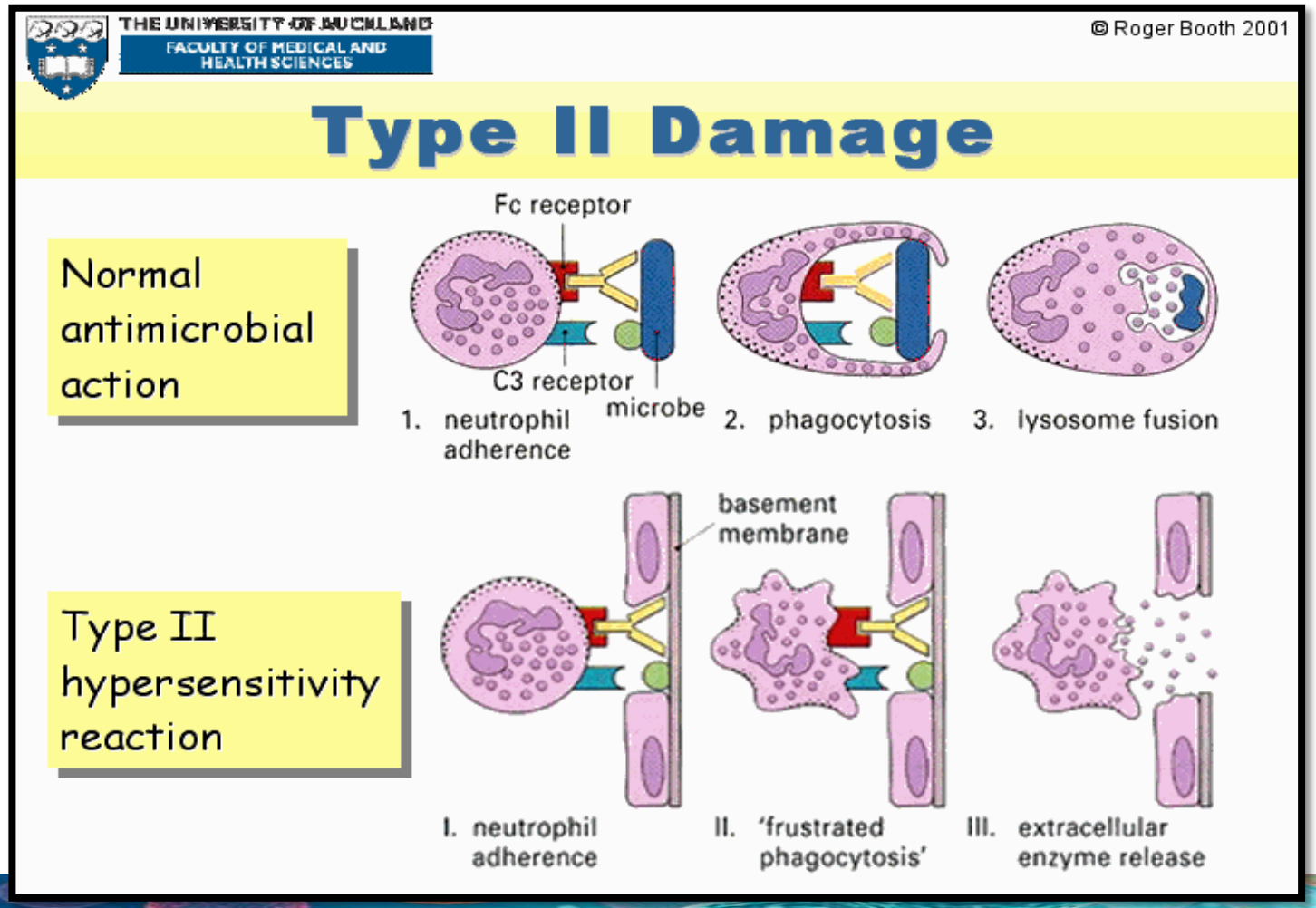
Examples to Type II hypersensitivity: Drug-induced hemolytic anemia, granulocytopenia, and thrombocytopenia.

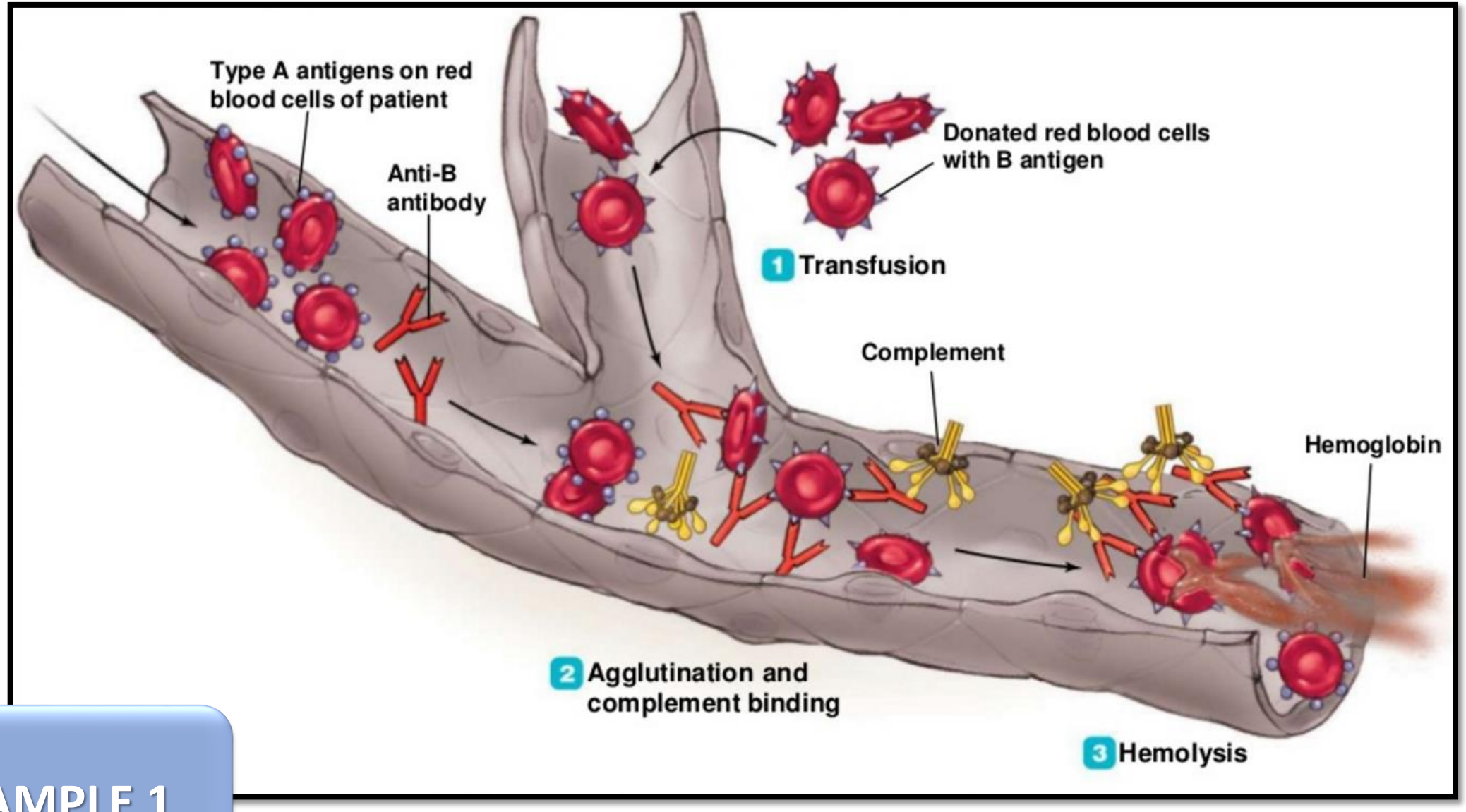
Type II Hypersensitivity Reactions:

Features:

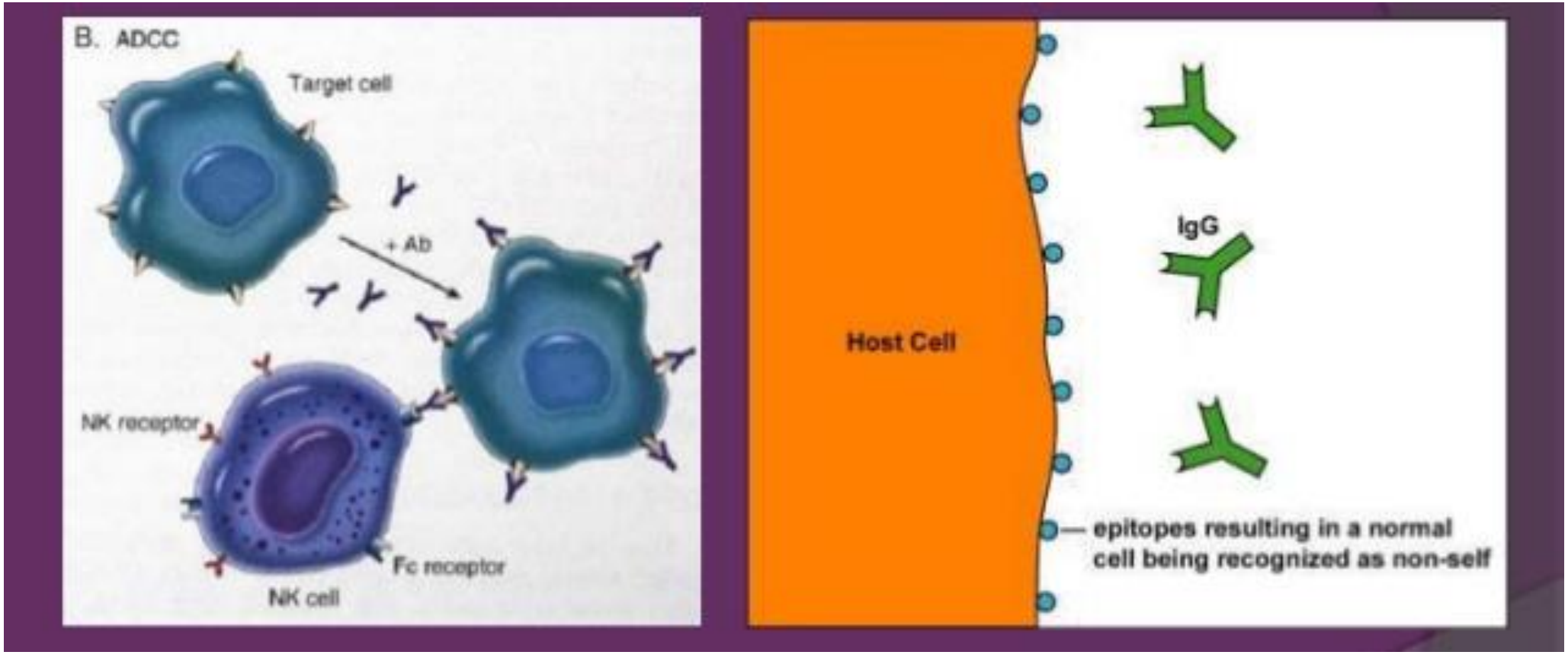
1) Antigens Bound to cell membranes (Self antigens).
2) Exogenous antigens (microbial)
3) Complement activation (invariable).

IgG or IgM reacts with epitopes on the host cell membrane and activates the classical complement pathway. Membrane attach complex (MAC) causes lysis of the cell afterwards.




Type A antigens on red blood cells of patient
Anti-B antibody
Donated red blood cells with B antigen
1 Transfusion
Complement
Hemoglobin
2 Agglutination and complement binding
3 Hemolysis

EXAMPLE 1



Antibodies react with epitopes on the host cell membrane and NK cells bind to the Fc of the antibodies.
The NK cells then lyse the cell with cytotoxic enzymes.

EXAMPLE 2

Clinical examples of type II Hypersensitivity Reactions:

Glomerulonephritis (anti-glomerular basement membrane).

Mis-matched blood transfusion.

Diagnosis Of Type II Hypersensitivity Reactions :

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

Type III: Immune complex hypersensitivity

1) The antigen may be exogenous or endogens.

2) The antigen is soluble and not attached to the organ involved.

3) Primary components are soluble immune complexes and complement (C3a, 4a and 5a).

4)The damage is caused by platelets and neutrophils.

5) The reaction may take 3-10 hours after exposure to the antigen.

6) Immune complexes are deposited in tissues like kidneys (nephritis), joints (arthritis) or blood vessels (vasculitis).

7) When an antigen reacts with an antibody, they produce an immune complex which is capable of inducing an inflammatory response

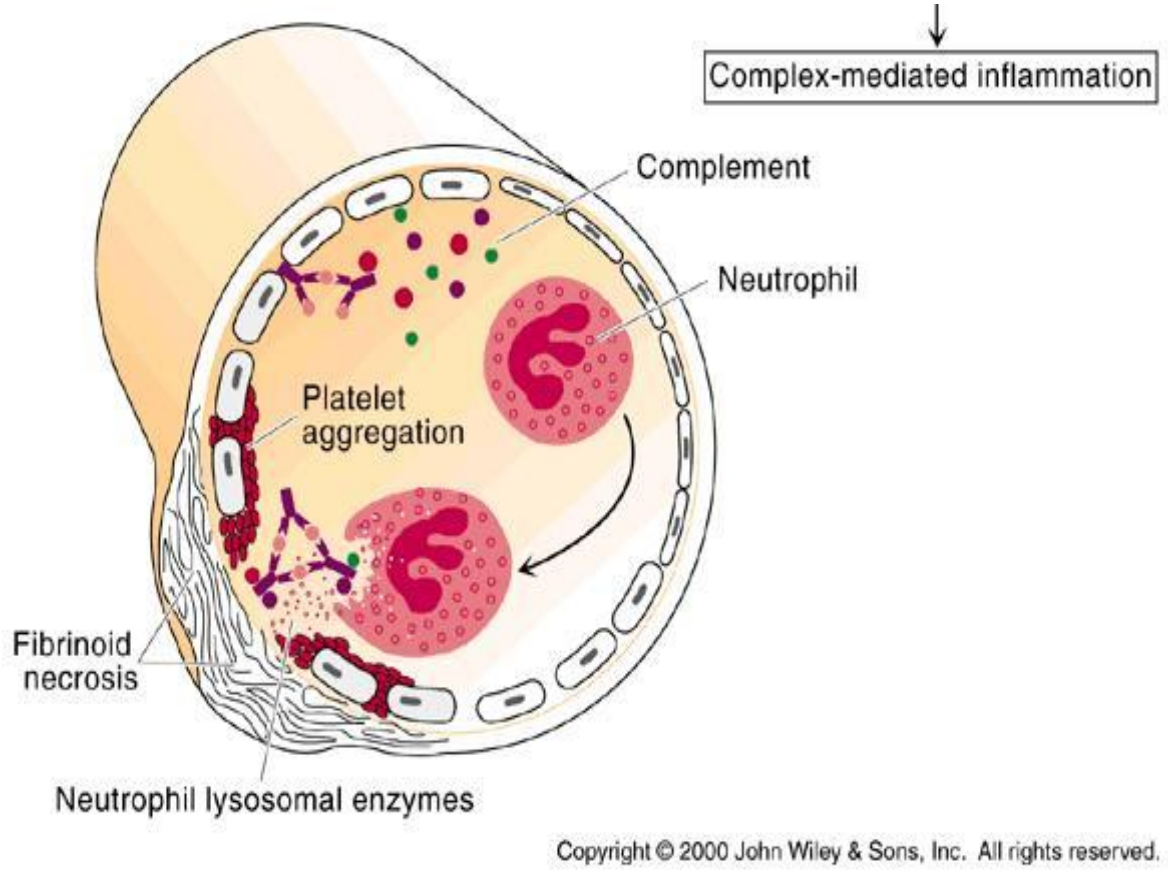
Type III Hypersensitivity (immune–complex mediated):

Antibody (IgG or IgM) + Antigen (soluble) → **Immune Complex formation**

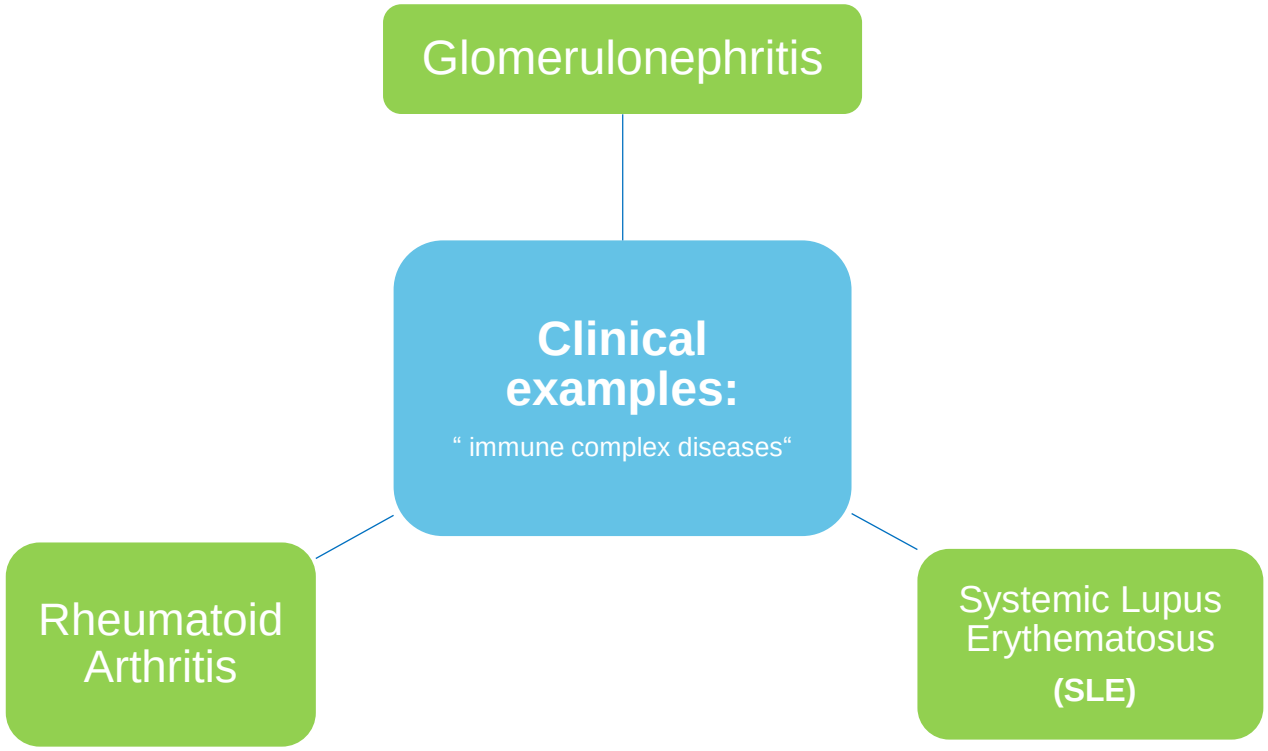
↓

Complement activation → **Attraction of inflammatory cells**

Type III Reactions:

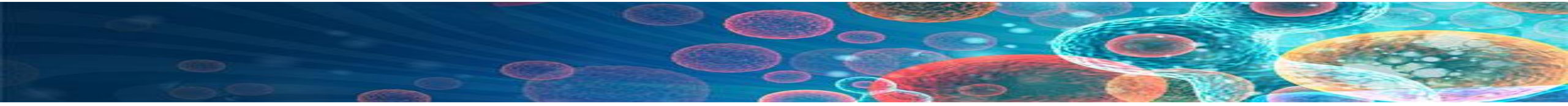


Hypersensitivity III



Diagnosis: By → **IF**

Demonstration of specific immune complexes in the blood or tissues by: **Immunofluoresence “IF”**



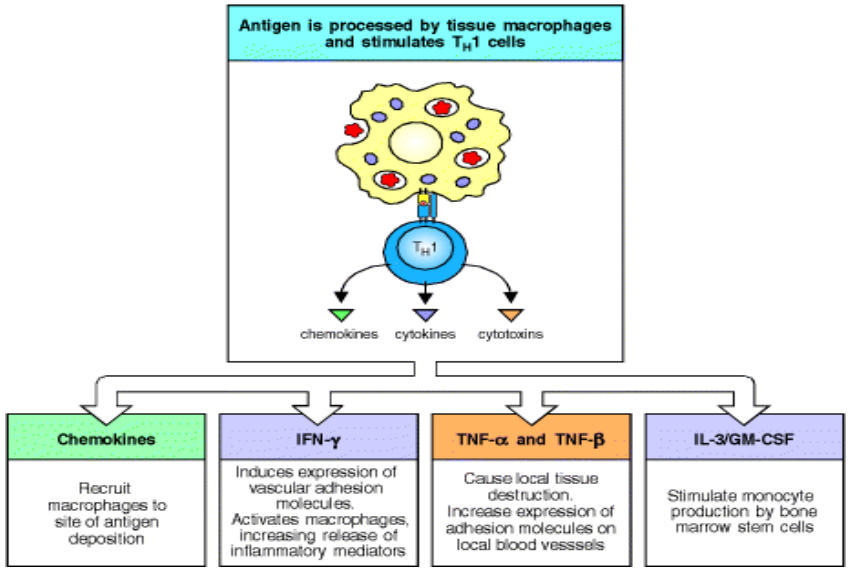
Hypersensitivity IV – Delayed Hypersensitivity

Features:

- Cell mediated immune response
  (= No Humoral response = **No Abs**)
  - 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:

DTH : Delayed Type Hypersensitivity



Hypersensitivity IV

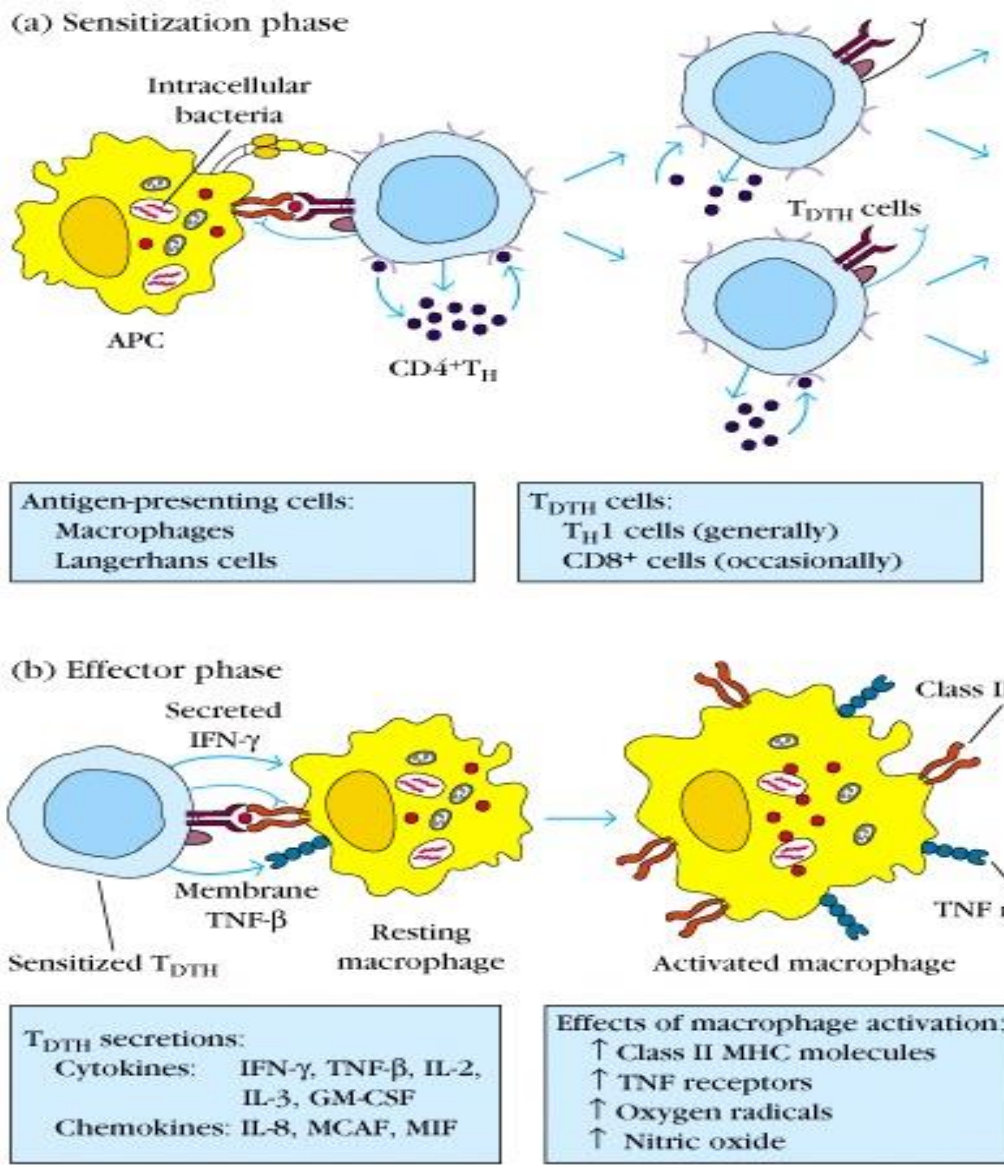
Development of DTH Response:

- **Sensitization phase:**
  1-2 week period

- **Effector phase:**
  24-72 hours

- Effector cells (activated macs) act **non-specifically**

*macs: Macrophages



Hypersensitivity IV

Pathophysiology of allergic contact dermatitis:

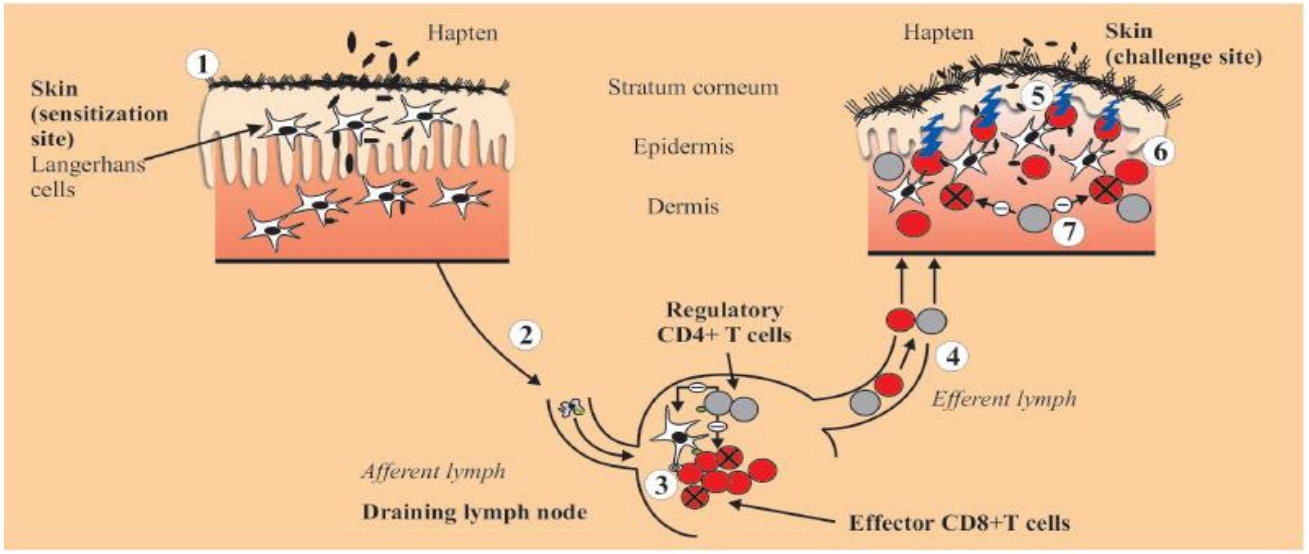
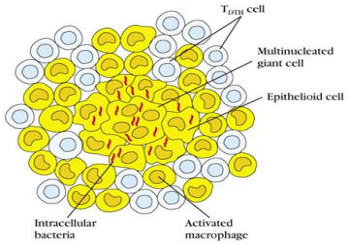


Figure 1: Pathophysiology of allergic contact dermatitis
Sensitization phase (afferent phase). Haptens penetrate the epidermis (step 1) and are uptaken by epidermal cells including skin DC which migrate to the draining lymph nodes (step 2) where they present haptenated peptides to both CD8+ effector T cells and down-regulatory CD4+ T cells (step 3). Specific T cell precursors clonally expand in draining lymph nodes, recirculate via the blood and migrate to tissues including the skin (step 4).
Elicitation phase (challenge phase, efferent phase). When the same hapten is applied on the skin, it is uptaken by epidermal cells, including skin DC and keratinocytes (step 5) which present haptenated peptides to specific T cells. Activation of CD8+ CTLs induces apoptosis of keratinocytes and production of cytokines and chemokines by skin resident cells (step 6). This leads to the recruitment of leucocytes from the blood to the skin. CD4+ T cells may block activation/expansion of CD8+ effectors in lymph nodes during sensitization and in the skin during the elicitation phase of CHS (step 3 and 7).

Clinical examples:

- Allergic contact dermatitis

- **TB granuloma** (persistent antigen)



Hypersensitivity IV

Diagnosis:

Delayed skin test (Mantoux test)

Patch test (Contact dermatitis)

Lymphocyte transformation test

- The tuberculin test:
Mediated by **CD4+ T** cells and takes about **72** hours to develop.

Type	Mediated by	Antibody or lymphocyte induced	Clinical examples	Diagnosis by	Time to react
I	Humoral (Antibody)	IgE	Rhinitis, Eczema, Conjunctivitis,Asthma, Urticaria, Allergic dermatitis, Food allergy	Skin prick test, Specific IgE measurement, Elimination / Provocation test	min-hours
II		IgG + IgM	Glomerulonephritis, Mis-matched blood transfusion, Hemolytic anemia	IF	Min-hours
III		IgG (mostly) + IgM	Glomerulonephritis, Rheumatoid Arthritis, SLE	IF	3-10 h after exposure to Ag
IV	Cell mediated (T cells)	T_H which activate macrophage & T_c	Allergic contact dermatitis, TB granuloma	Delayed skin test (Mantoux test), Patch test (Contact dermatitis) , Lymphocyte transformation test	Sensitization phase: 1-2 week Effector phase: 24-72 h = 1-3 day

← Click here to watch a summarised version of the 4 types of hypersensitivity.

← Click this. It helped me understand the types of reactions.

← Click this. This also helped me understand the types of reactions.

Thank you!

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