



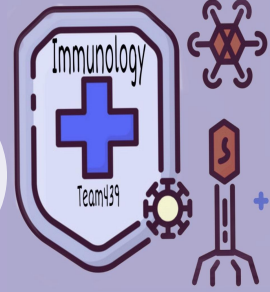
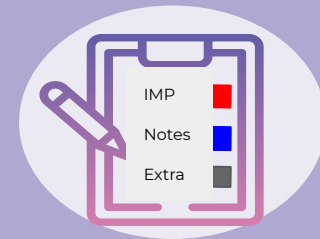
# Hypersensitivity reactions

Revised & Approved  
by:

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# Objectives

01

To know that hypersensitivity reactions are over and excessive immune responses that can be harmful to body in four different ways

02

To be familiar with inflammatory processes in Type I hypersensitivity reaction that mediates allergic inflammation

03

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

04

To know that Type III hypersensitivity reactions are mediated by immune complexes and cause vasculitis

05

To describe Type IV hypersensitivity is a purely cell mediated immune response associated with chronic inflammation



In other words : over reaction

# What is hypersensitivity?

types of immune reactions

desirable reaction

Protective immunity

undesirable reaction:  
Hypersensitivity

types of hypersensitivity



All causes tissue damage

Immediate

Delayed

IgG or IgM

**Type I:**  
IgE Ab

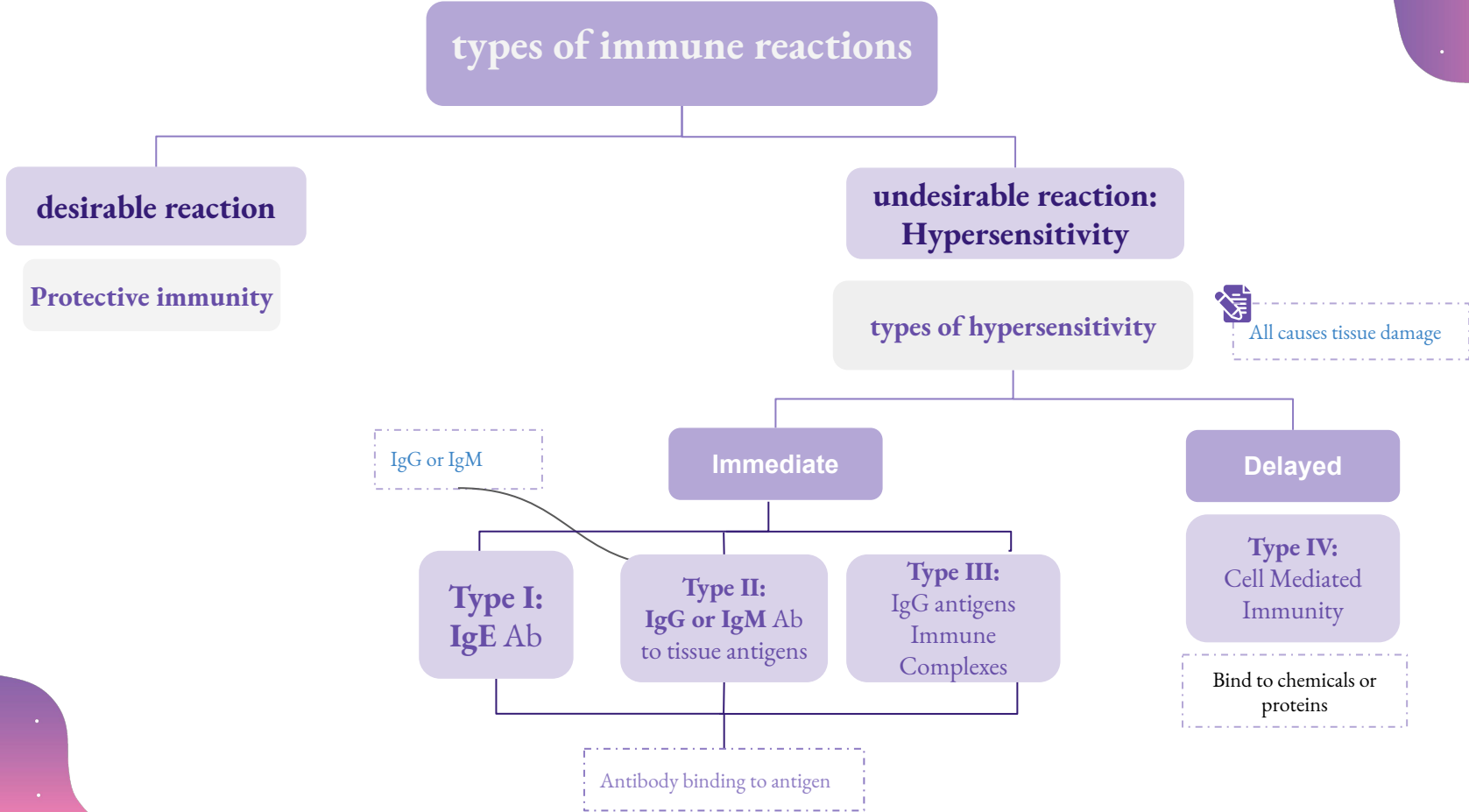
**Type II:**  
IgG or IgM Ab  
to tissue antigens

**Type III:**  
IgG antigens  
Immune  
Complexes

**Type IV:**  
Cell Mediated  
Immunity

Bind to chemicals or  
proteins

Antibody binding to antigen



# Type I: Immediate Hypersensitivity

01

Most people will not react to these allergens (antigen causing allergy) but some individuals “atopic” respond by producing large amounts of IgE in response to those otherwise harmless substances

Because of the genetic background of individual that leads to respond in abnormal way to allergens

02

Non-allergic individuals respond to these allergens by producing IgG antibodies

They have two ways to respond to these allergens :  
1-ignore them  
2-producing IgG Abs

## Anaphylactic reaction:

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

# Type I: Immediate Hypersensitivity

## Features

Antibody response	-allergic ( <b>atopic</b> ): <b>igE</b> *Occurs within minutes to hours and may lead to <b>anaphylactic shock</b> -non-allergic (non-atopic) : <b>igG</b> *most people	<b>Atopic</b> >have allergy <b>non-allergic ( non-atopic)</b> > have no allergy
Cellular components (involved)	mast cells basophiles & eosinophils	
Antigens (allergens)	low molecular weight and highly soluble e.g pollens, dust mite, animal dander, nuts, various drugs	

## Clinical Examples

**Injected allergns: hymenoptera** (bees, wasps, ants,) sting venom ( a poisonous substance) enters the blood stream causing systemic inflammation & Anaphylactic shock

There is a reaction has similar symptoms of anaphylactic shock called “**anaphylactoid reaction**”

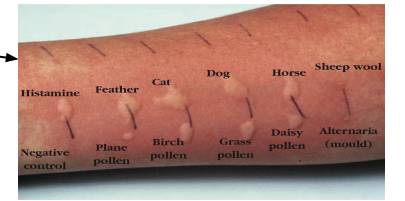
**The difference between them :** 1) non-IgE mediated

May result from :

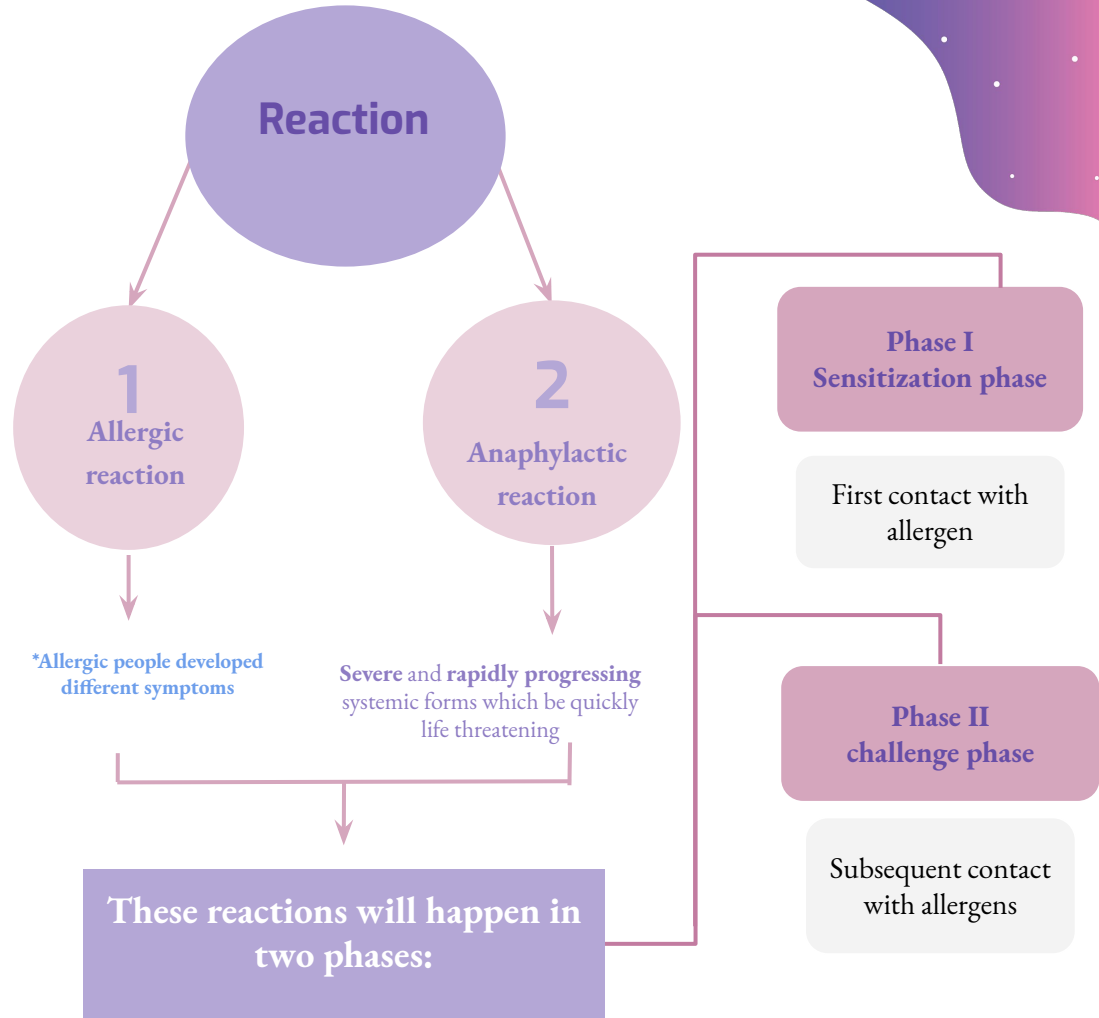
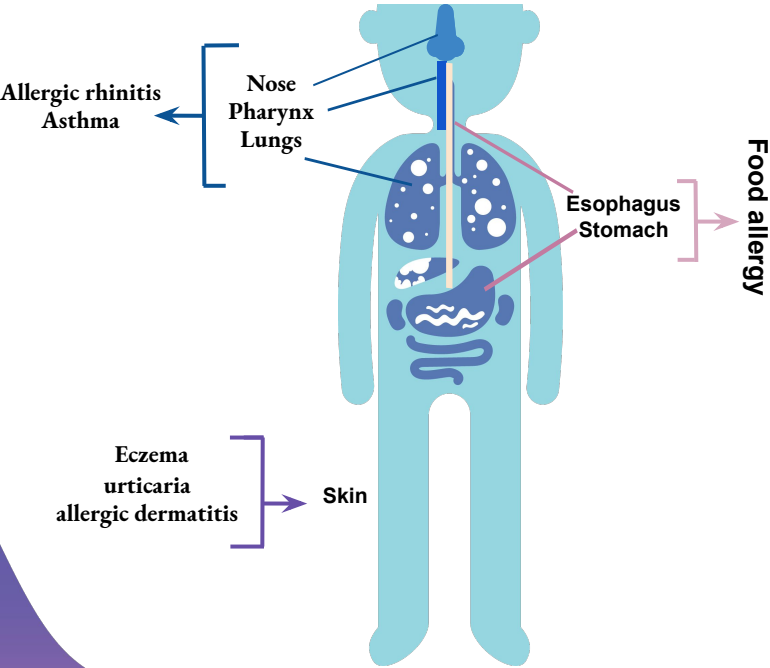
- 1) constrast media ( *مثل الأشخاص اللي تعرضون للأشعة المقطعية CT* )
- 2)local anesthetic

## Diagnosis of allergy

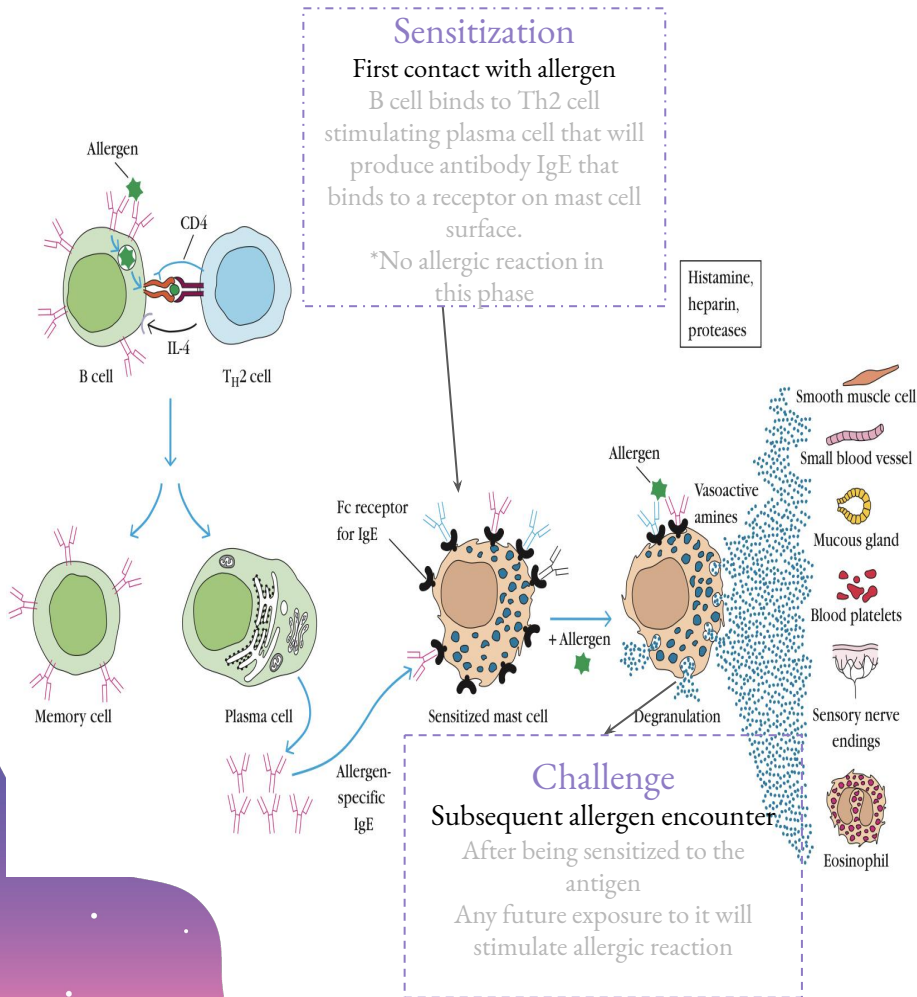
- Skin prick test (SPT) putting a small amount of allergens on the skin then prick the skin with a needle and wait for 15-20 minutes to see if there is a reaction
- Specific IgE Measurement by testing IgE in the serum
- Elimination /Provocation test (Food allergy) avoiding type of food every day until expose the type which cause the allergy



# ALLERGY IS A SYSTEMATIC DISORDER



# Primary and secondary mediator



Mediator	Effects
<b>Primary</b>	<b>*Immediately release</b>
Histamine, heparin	Increased vascular permeability; smooth muscle contraction
Serotonin (rodents)	Increased vascular permeability; smooth muscle contraction
Eosinophil chemotactic factor (ECF-A)	Eosinophil chemotaxis
Neutrophil chemotactic factor (NCF-A)	Neutrophil chemotaxis
Proteases (tryptase, chymase)	Bronchial mucus secretion; degradation of blood vessel basement membrane; generation of complement split products
<b>Secondary</b>	<b>*Not produce until the mast cells/ basophils is activated</b>
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- $\alpha$	Systemic anaphylaxis; increased expression of adhesion molecules on venular endothelial cells
IL-4 and IL-13	Increased IgE production
IL-3, IL-5, IL-6, IL-10, TGF- $\beta$ , and GM-CSF	Various effects (see text)

# Type II Hypersensitivity Reactions

<p><b>Features</b></p>	<p>Antibody</p>	<p>IgG (or IgM) Both can activate the complement system</p>	<p>Hypersensitivity 2 is <b>antibody-dependent</b> process in which specific antibodies bind to antigens, resulting in tissue damage or destruction -For tissue antigen, not free antigen. -usually associated with autoimmunity</p>
	<p>Complement activation</p>	<p>Invariable ( constant)</p>	
	<p>Antigens (allergens)</p>	<p>-Exogenous antigens: (microbial) -bound to cell membranes: (<b>Self antigens</b>)</p> <p><i>In the normal condition, neutrophils attack microbes as antimicrobial action</i></p> <p><i>But in type II, neutrophils attack the basement membrane like blood vessels</i></p>	<p><b>Cellular antigen</b></p> <p><b>Normal antimicrobial action</b></p> <p>1. neutrophil adherence 2. phagocytosis 3. lysosome fusion</p> <p><b>Type II hypersensitivity reaction</b></p> <p>I. neutrophil adherence II. 'frustrated phagocytosis' III. extracellular enzyme release</p>
<p><b>Clinical Examples</b></p>	<ul style="list-style-type: none"> <li>● Mismatched blood transfusion (RBCs of Donor will be Attacked by the immune response of The Recipient)</li> <li>● Glomerulonephritis (anti-glomerular basement membrane) Producing antibodies against glomerular basement &gt; renal failur</li> </ul>		
<p><b>Diagnosis of allergy</b></p>	<p>Detection of antibodies and antigens by immunofluorescence in tissue biopsy specimens e.g. kidney, skin etc.</p>		



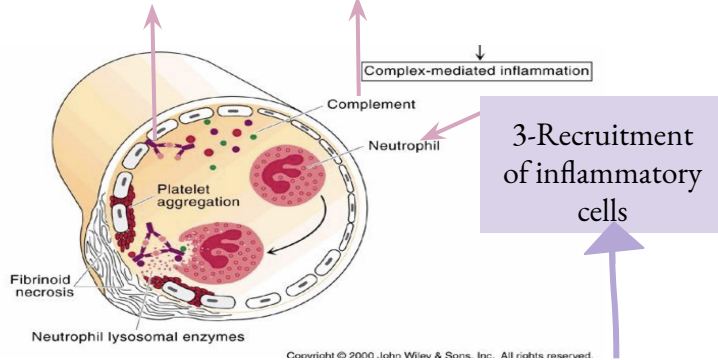
# Type III Hypersensitivity (immune-complex mediated)

Features	Antibody	IgG or IgM
	Complement activation	<p>It is activated after formation of <b>immune-complex</b> (antigen react with antibody) which is capable of inducing an inflammatory response</p> <p>Immune-complexes are deposited in tissues like:</p> <ul style="list-style-type: none"> <li>Blood Vessels (vasculitis)</li> <li>Kidneys (nephritis)</li> <li>Joints (arthritis)</li> </ul>
	Antigen	Free <b>Soluble</b> antigen
Clinical examples	<ul style="list-style-type: none"> <li>● Glomerulonephritis</li> <li>● Rheumatoid Arthritis</li> <li>● Systemic Lupus Erythematosus (SLE)</li> </ul>	<p>Type II: was for tissue antigens (cellular antigens).  <b>Type III: for free antigens.</b></p> <p>Factories made an anti-Immunoglobulin with fluorescent dye, they put it on the slide which it may have antigen that cause hypersensitivity. If that gene is present, then all the slide will be fluorescent.</p>
	Diagnosis	Immuno-complexes detection in blood/tissue using Immunofluorescence

# Hypersensitivity III reactions

1-Free antigens binding to antibodies which cause

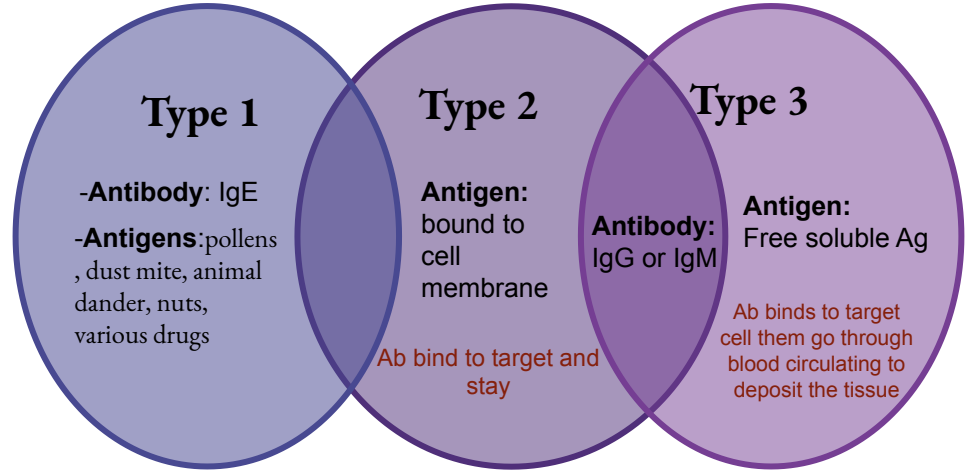
2-Complement activation



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in the normal state, phagocytes (neutrophils/macrophages) will clear out the immune-complexes after the immune reaction. But in type III reaction, the immune-complexed will be bigger in size so it will be hard for phagocytosis the complexes

# Comparison between immediate hypersensitivity



# Type IV Hypersensitivity

Known as delayed type hypersensitivity-**DTH** (2-4 days ; 48h-72h) and cell-mediated hypersensitivity

Features	Antibody	No antibodies (cell-mediated)
	Cells involved	Generally CD4 and occasionally CD8 - CD activates macrophages via Th1
	Antigen	Presented to T cells by APCs (involving both MHC classes)

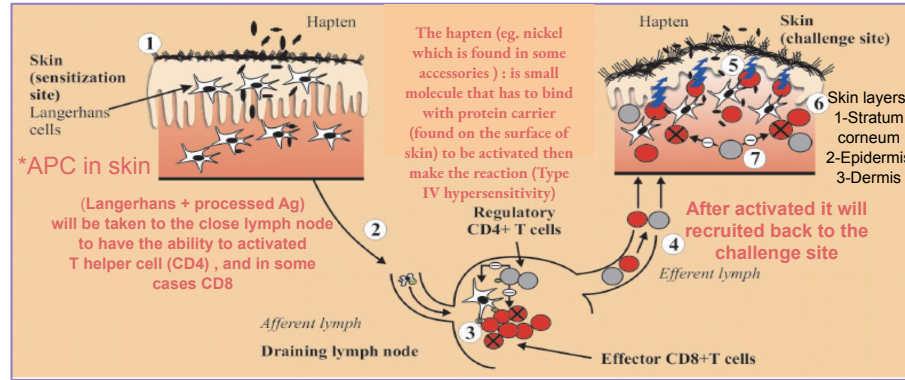
Clinical examples

## Contact dermatitis

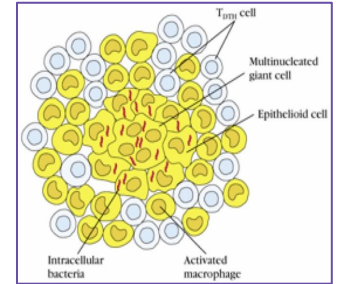
\*Not to be mixed with Type I allergic dermatitis



## Pathophysiology of Contact dermatitis:



## Granuloma formation



Diagnosis

1-Delayed skin test (Mantoux test/Tuberculin test) The Mantoux skin test consists of an intradermal injection of 0.1 ml of PPD tuberculin (Tuberculin Purified Protein Derivative) for 24-72 hours then measure the diameter of the reaction

2- Patch test (used for contact dermatitis) It's done to see if a particular substance is causing allergic reaction or not. In this test, allergens are applied to patches (زى اللصاق اللي في الصورة) then placed on your skin for 48-72 hours. During this time you should avoid bathing or sweating.

3- Lymphocyte transformation test Take Sample of blood on slide, add the antigen and wait to see if, the blood will recognize that antigen or not



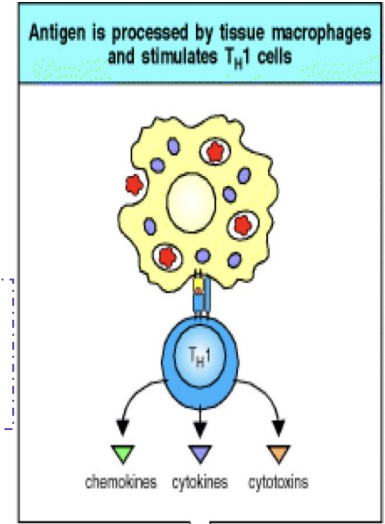
# Reaction Phases Of delayed hypersensitivity (type IV):

# Mediators released by T-DTH

**Phase I (1-2 weeks) > Sensitization phase**

CD4+ Th1 (generally) or CD8+ (occasionally) are activated by APCs like (macrophages and langerhans) via MHC Class I or II and become T-DTH (delayed type T cell).

\*Not to be mixed with challenge phase in hypersensitivity I



**Phase II (24-72 hours) > Effector phase**

Sensitized T-DTH secretes chemical mediators to (activate macrophages) that act non-specifically  
Chemical mediators are:

- Chemokine
- IFN- $\gamma$
- TNF  $\alpha$  &  $\beta$
- IL-3/GM-CSF

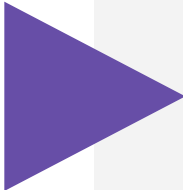
More Details about chemical mediators

**Macrophage activation increases the following:**

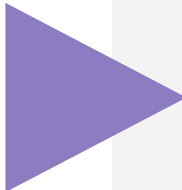
- MHC Class II
- TNF receptors
- ROS
- Nitric Oxide

<b>Chemokines</b>	<b>IFN-<math>\gamma</math></b>	<b>TNF-<math>\alpha</math> and TNF-<math>\beta</math></b>	<b>IL-3/GM-CSF</b>
Recruit macrophages to site of antigen deposition	Induces expression of vascular adhesion molecules. Activates macrophages, increasing release of inflammatory mediators	Cause local tissue destruction. Increase expression of adhesion molecules on local blood vessels	Stimulate monocyte production by bone marrow stem cells

## Take home message :



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.



Hypersensitivity reactions are undesirable, excessive, and aberrant immune responses associated with disorders such as allergy, autoimmunity and chronic inflammation.



# Quiz

Question 1: The cause of allergy

A - antibodies

B- allergens

C- T cells

D- all of them

Question 2: Antibody type in hypersensitivity II

A -IgE

B-IgM

C-IgG

D- IgG & IgM

Question 3: how we can diagnose type II hypersensitivity:

A - Immunofluorescence

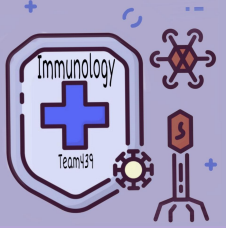
B- patch test

C- prick test

D- RAST

Question 4: which one considered as cell mediated hypersensitivity

A - Type I hypersensitivity B-Type II hypersensitivity C-type III hypersensitivity D-Type IV hypersensitivity



# team leaders

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