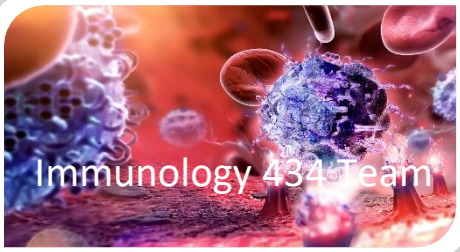

Lecture 5:

Hypersensitivity

Objectives:

- To know that hypersensitivity reactions are over and excessive immune responses that can be harmful to body in four different ways.
- To be familiar with inflammatory processes in Type I hypersensitivity reaction that mediates allergic inflammation
- 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
- To know that Type III hypersensitivity reactions are mediated by immune complexes and cause vasculitis.
- Describe Type IV hypersensitivity is a purely cell mediated immune response associated with chronic inflammation.

Done by:

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Nada Alamri Talal AlHoshan

Lamyaa Al.thwadi Lama Alkahtani

Mashael Hussein

Motivation Quote

بعد المسافة لا يهم، الخطوة الأولى فقط هي الأكثر صعوبة

Red = Important Notes Orange = Further Explanation gray = Additional Notes Green = Examples

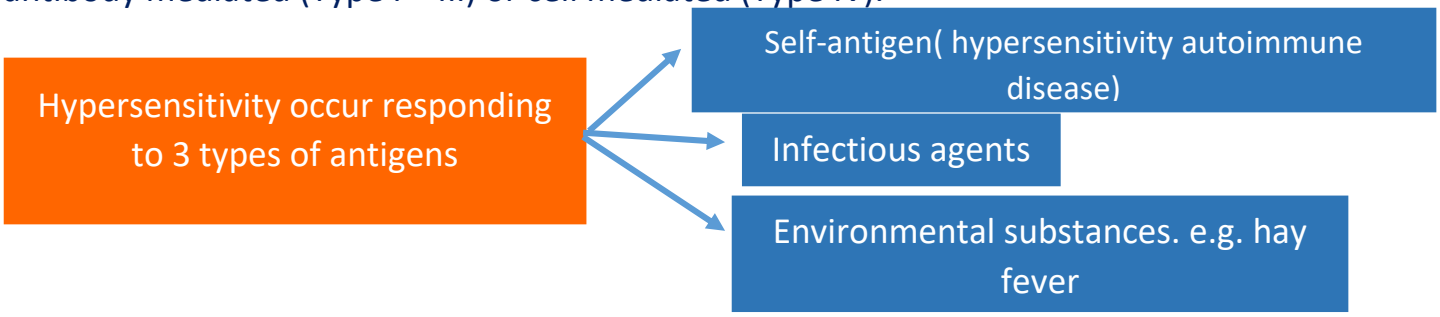
Navy: boys notes Purple: girls notes

Table of Contents

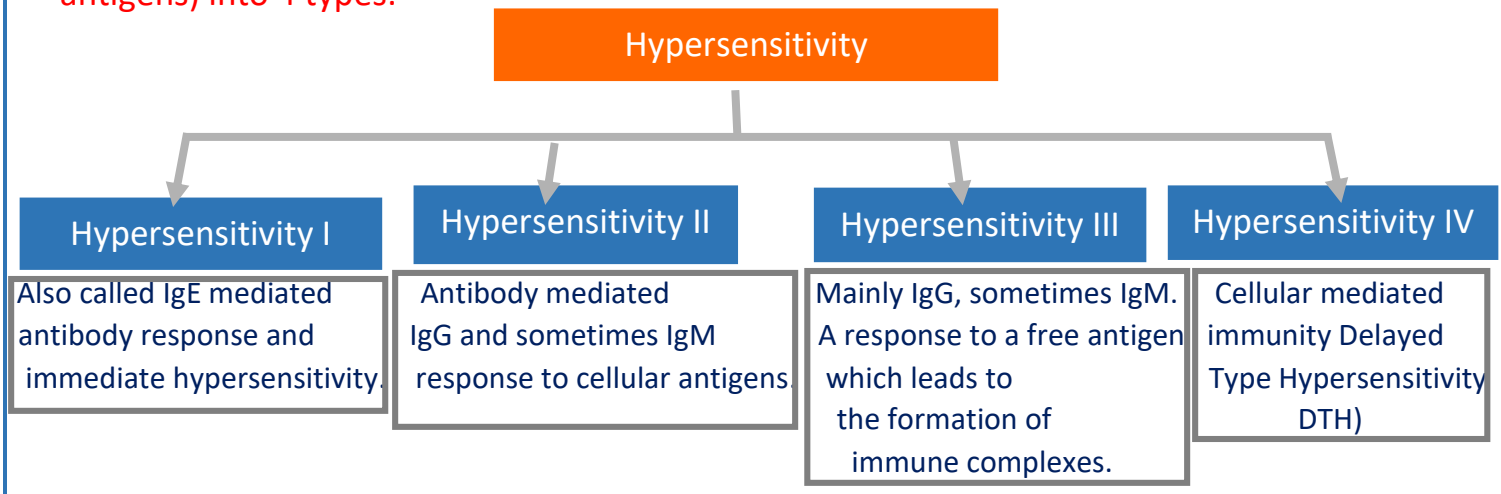
What is hypersensitivity?

A normal immune response is a protective reaction. Hypersensitivity an overreaction to a certain condition.

Undesirable reactions (Hypersensitivity) can happen to both types of adaptive immunity: either antibody mediated (Type I – III) or cell mediated (Type IV).



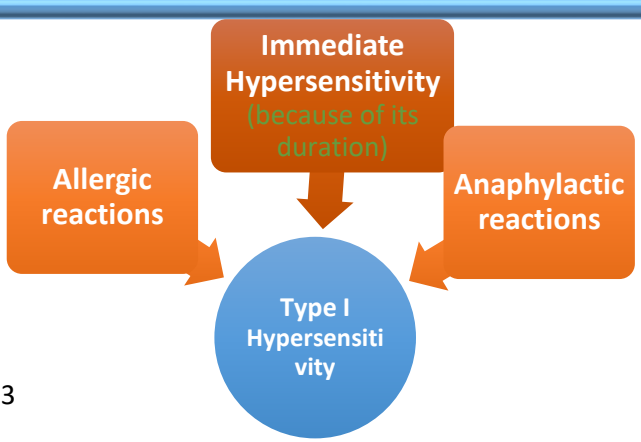
Hypersensitivity responses is classified by the responding mechanisms (not the responding antigens) into 4 types:



Hypersensitivity Type I

Type I Hypersensitivity:

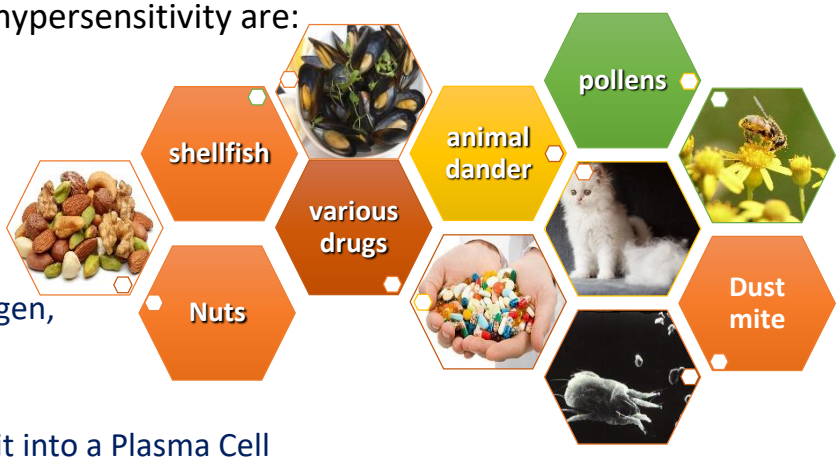
- Antibody type: IgE
- Occurs within minutes to hours
- Cellular components:
- Mast cells, basophiles & eosinophils



- Antigens: Also known as allergens
  (Antigens with low molecular weight & highly soluble

Allergens:

Most people will not react to these allergens but some individuals **atopic** respond by producing large amounts of **Ig E** antibodies
Non-allergic individuals respond to these allergens by producing **Ig G** antibodies
Some of the allergens involved in type I hypersensitivity are:



Type I reactions:

Sensitization phase:

(Antigen presenting cell APC) takes the antigen, processes it, degrades it, then presents it with association of class II MHC. T Helper 2 comes in contact with the B Cell and turns it into a Plasma Cell or a Memory Cell. Plasma Cells then produce IgE antibodies specific for that type of allergen. Then, the IgE antibody attaches to a Mast Cell which has receptors for this antibody. Mast Cells are said to be synthesized when they are bound to an antibody.

Challenge phase:

Occurs when we have a subsequent encounter with the similar antigen
it will bind to the Ig(Antigen) and lead to degranulation of the mast cells
making produce a large amount of its mediators which cause what we see in allergic patient
(sneezing, muscle contraction, mucus production,..etc)
(subsequent contact with allergens)

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)

Mechanism of type I hypersensitive response:

What distinguishes a type I hypersensitive response from a normal humoral response is that

IgE

- IgE is present in very **Low level in serum** In most people
- It's half life in serum is only **2-3 days**
- In the bound state the half-life is **3 weeks**.

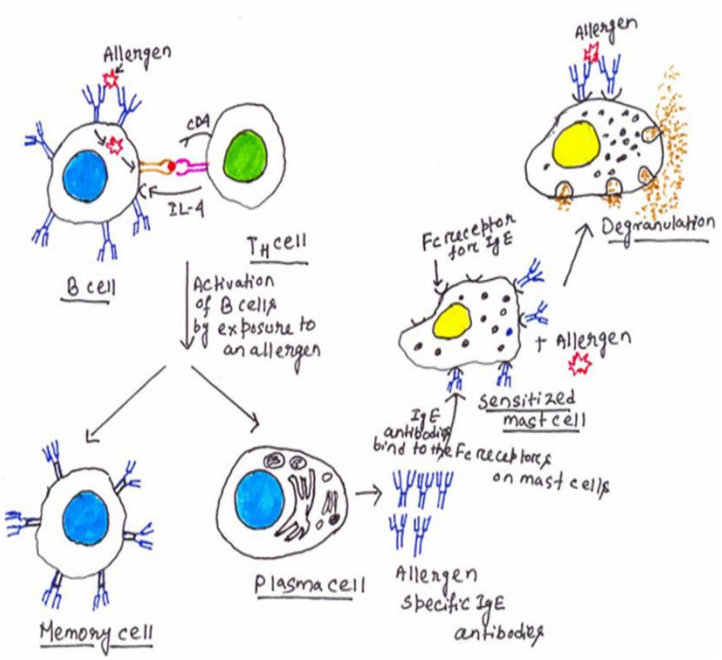
But much of the IgE in the body is bound to **high receptors** (IgE Fc) **affinity**

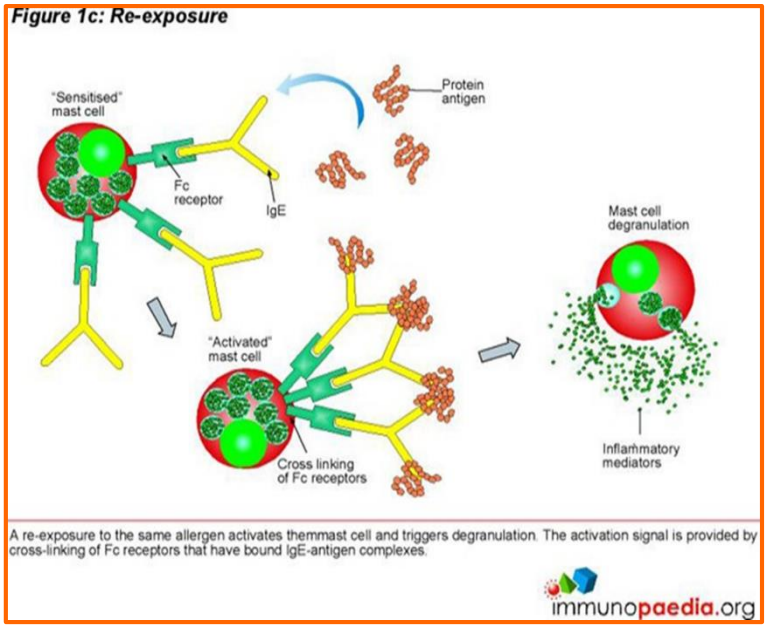
the plasma cells secrete IgE.

1) IgE bind with high affinity to Fc receptors **on the surface of** tissue mast cells and blood basophils.

2) Mast cells and basophils coated by IgE are said to be sensitized during Sensitization phase

3) A later exposure to the same allergen cross-links the membrane-bound IgE on sensitized mast cells and basophils causing degranulation of these cells to rapidly release a variety of mediators. (During Challenge phase).





Check this video it's might be long but so helpful **23minutes**

Check this video **1:45**

Allergy (Type I Hypersensitivity) is a systemic disorder:

Type I hypersensitivity is a systemic disorder that can affect:

a) Digestive system: food allergy. (Nuts, strawberries)

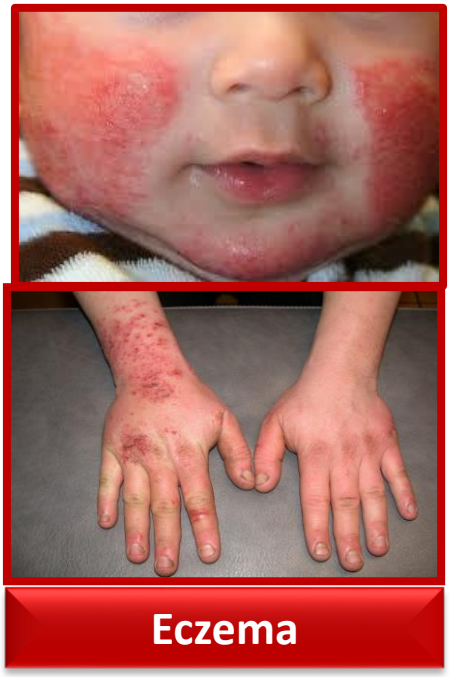
b) Respiratory system: Allergic Rhinitis and Asthma

c) Skin: Eczema, Urticarial, and Allergic Dermatitis.

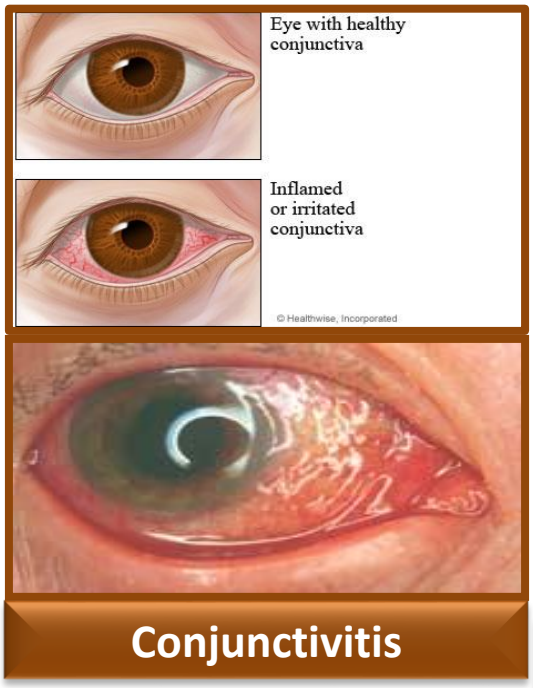
Some allergens are injected into the body such as a bee sting. The bee's venom gets into the bloodstream and may cause systemic inflammation, leading to an anaphylactic shock, which is fatal.

Some people carry a pen that contains adrenalin to stop the allergic reaction.

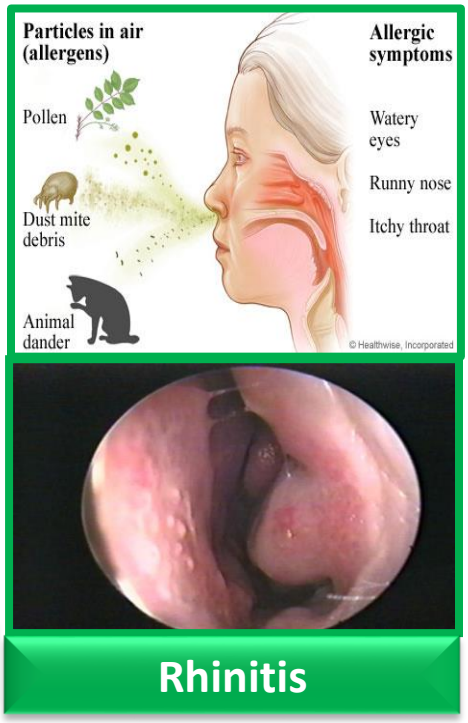
Anaphylactic reactions: has the same symptoms of anaphylaxis, but has nothing to do with type I hypersensitivity and IgE. It results of contrast media (radiology procedure) or as a result of a certain type of local anaesthetic substances.



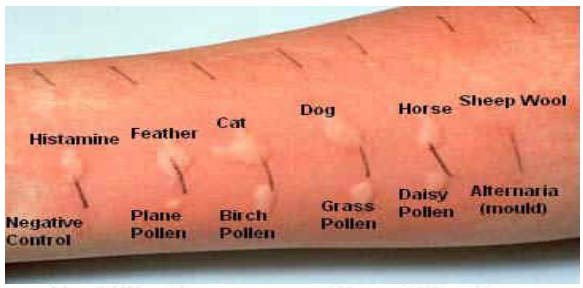
Eczema



Conjunctivitis



Rhinitis



Food allergy
Elimination / Provocation test

Skin prick test
SPT

Diagnosis of Allergy

RAST
Specific IgE measurement

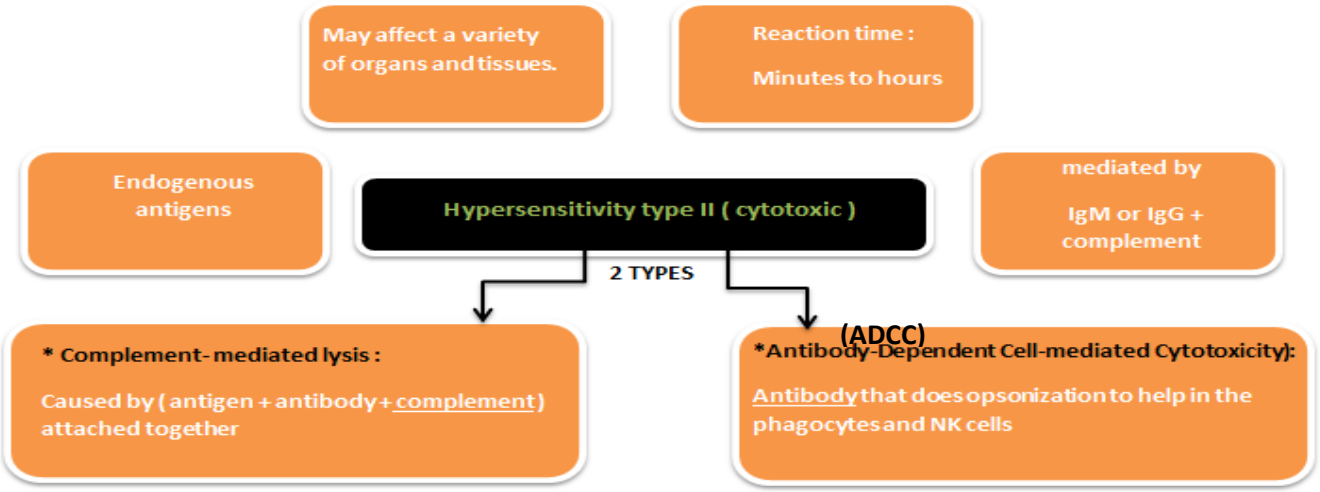
For more information watch this video

Note

- Skin Prick Test (SPT): Placing droplets of suspected allergens on the forearm of the patient, leaving it for 15 minutes, then checking which drop is reacting.
- Specific IgE Measurement (RAST): in laboratories. A sample of serum blood is taken from the patient and is analyzed for specific IgE or certain allergen.
  - The best treatment is to avoid getting in contact with allergens.

Hypersensitivity Type II

CHECK ME!! CHECK ME!!



IgG (sometimes IgM)

*the antigen that affects the cell is bound to the cell membrane, it could be (self - antigen / exogenous [microbe] then attached itself to the membrane)

Normal action:

When a microbe enters, the antibody and the complement (innate system) attach to the microbe to help the phagocytic cell in the elimination of that microbe

Hypersensitivity action:

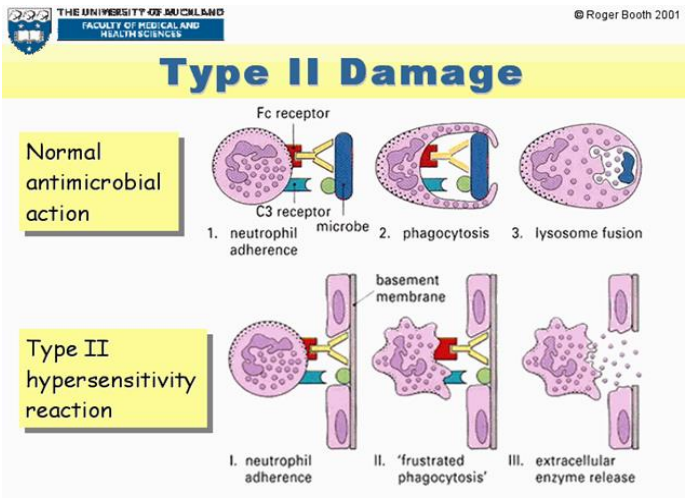
if the person is atopic, the phagocytic cell damages the tissue of the patient (frustrated phagocytosis) because the antigen is attached to the cell membrane.

Clinical examples:

- Mismatched blood transfusion
- B/Glomerulonephritis
  (anti-glomerular basement membrane)

Diagnosis :

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



Hypersensitivity Type III

CHECK ME!!

What is immune complex??

It is antigen + antibody + complement = immune complex = inflammatory response

antigen is soluble not attached to the organ involved

- Antigens: may be exogenous (chronic bacterial, viral or parasitic infections)
- Endogenous (non-organ specific autoimmunity: e.g., systemic lupus eythematosus, SLE)

IgG class, IgM may also be involved

Primary Complements (C3a, 4a and 5a)

Immune complexes are deposited in tissues like
Kidneys (nephritis)
Joints (arthritis)
Blood vessels (vasculitis).
The reaction may take 3-10 hours after exposure to the antigen.

The damage is caused by platelets and neutrophils.

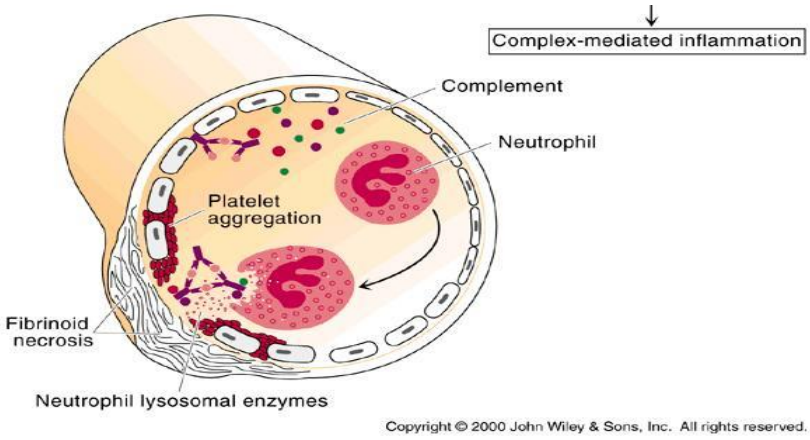
Mechanism of type III Hypersensitivity reaction:

Antibody (IgG/ or IgM) + Antigen (soluble) activities basophils or other immune cells that produce mediators

Like histamine or serotonin which increase vascular permeability than they contact with the endothelial cells making the neutrophils secrete the digesting chemicals damaging the surrounding cells.

Immune Complex Diseases:

- Glomerulonephritis
- Rheumatoid Arthritis
- Systemic Lupus Erythematosus (SLE)



Diagnosis: Detection of immune complexes by Immunofluorescence

Hypersensitivity Type IV

Reaction involves sensitized T-cells and the release of mediators

Also called cell mediated hypersensitivity (T-cell mediated)
Another name for it is delayed type hypersensitivity as it requires 4-5 days to be initiated

T-cells involved: CD4+/CD8+ (occasionally)
Type of CD4+ (T-Helper cell): Type 1 as it's cell mediated *reminder TH2 is activated in humoral immunity*
MHC class: 1 OR 2 activated when T-cells are sensitized

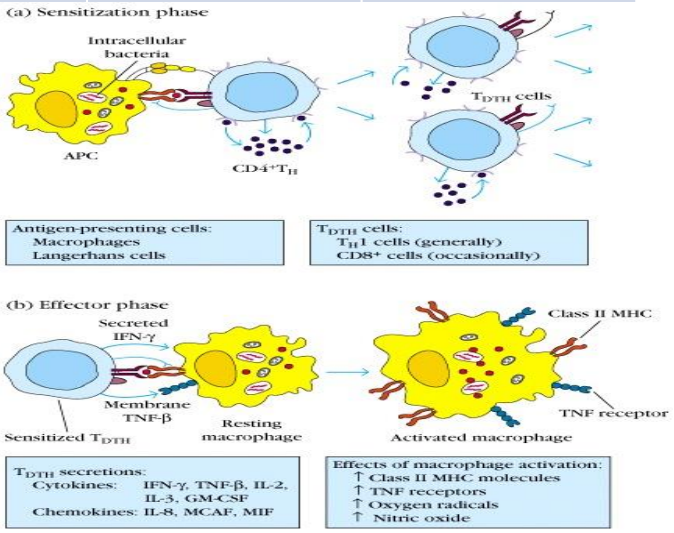
cytokines	chemokines	Cytotoxins
IFN-Gamma: activates macrophages which increases the release of inflammatory mediators IL-3/GM-Csf: stimulates production of monocytes form bone marrow cells	Recruit macrophages to site of antigen deposition	TNF_alpha&beta Local tissue destruction It also increases expression of local adhesion molecules

Sensitization phase 1-2 weeks

APCs process the antigen and then present the antigen to T-cells *Tdth: this usually involves CD4+ type 1/ CD8+ *sometimes*

Effector phase 24-72 hours

Tdth interacts with the resting macrophage which leads to the activation of the macrophage.



Mechanisms of Delayed Type Hypersensitivity:

-Like Type I, Type IV has two phases:

1- Sensitization phase: (takes from 1 to 2 weeks)

-APC degrades and processes the antigen, then presents it to the T Helper Cell. This leads to the formation of the Delayed Type Hypersensitivity Cell. (TDTH)

2- Effector Phase: (takes from 24 to 72 hours).

-It is called delayed hypersensitivity because it takes much longer time to finish the reaction than other types.

-TDTH interacts with resting Macrophages, leading to its activation, resulting in:

a) Increased class II MHC molecules → Very effective activated lymphocyte.

b) Increased TNF receptors

c) Increased Oxygen radicals

d) Increased Nitric Oxide

→ Important for antimicrobial activities.

Clinical examples

A) Allergic Contact Dermatitis.

-Pathophysiology of allergic contact Dermatitis:

Langerhans Cells (APC in the skin) uptakes Hapten (Low molecular weight antigens), processes it, then presents it with association of class II MHC. Then it takes it to a lymph node to come in contact with a T Helper Cell (sometimes Cytotoxic Cell) and activates it. (This is Sensitization phase). T Helper Cells go to the site of infection (Challenge site), and responds to antigens.

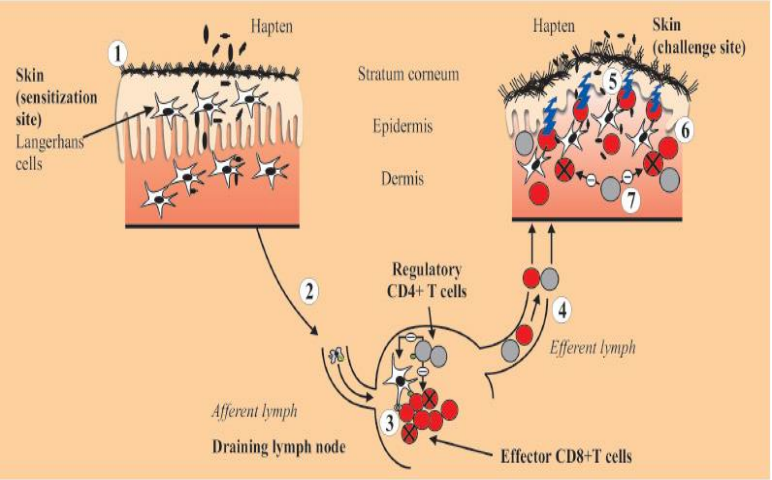
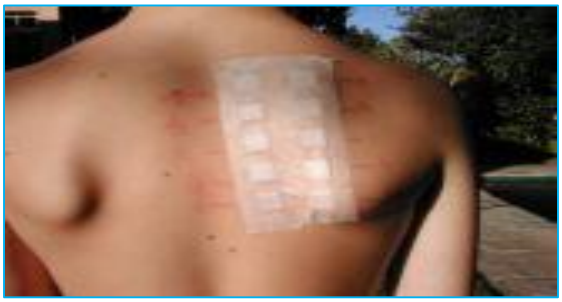


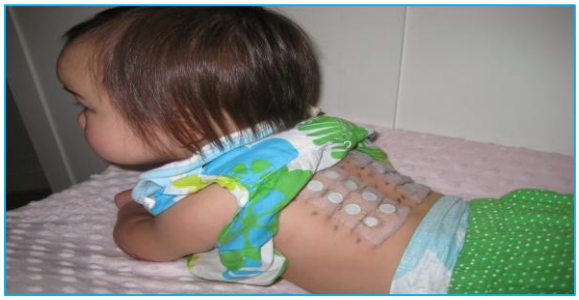
FIGURE 1: **Pathophysiology of allergic contact dermatitis**
Sensitization phase (afferent phase). Haptens penetrate the epidermis (step 1) and are uptaken by epidermal cells including skin DC which migrate to the draining lymph nodes (step 2) where they present haptenated peptides to both CD8+ effector 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).

B) Tuberculosis Granuloma.

-As a result of persistent antigens.

-T Cells will surround infected cells and continuously activate Macrophages.





Diagnosis of type IV

1. Delayed skin test (Mantoux test)
2. Patch test (Contact dermatitis)

A sheet containing possible allergens are adhered on the back of the patient for 72 hours, then the clinician checks it and sees what type of antigen may trigger a response on the patient.

3. Lymphocyte transformation test

Summary

- Hypersensitivity refers to undesirable damaging reactions produced by the excessive immune reactions. It can occur in response to **3** different types of antigen: Infectious agents, Environmental substances. e.g. hay fever and Self antigen(hypersensitivity autoimmune disease)
  - Type I – allergy
  - Type II – antibodies
  - Type III – immune complex
  - Type IV – T cells
- **Type I hypersensitivity** is the mechanism underlying the classic allergic response. It's also called "immediate" hypersensitivity, which makes sense to any allergy sufferer (as soon as you start petting the cat, you start sneezing). It's caused by an antigen (from an allergen, like cat dander) binding to IgE antibodies that are bound to the surface of mast cells. The antigen bridges the IgE antibodies, triggering release of nasty mediators (like histamine) from the mast cell. The end result: vessels dilate, smooth muscle contracts, and inflammation comes in and makes itself at home.
- **Diagnosis**

1. Skin prick test (SPT)
2. Specific IgE measurement (RAST)
3. Elimination / Provocation test (Food allergy)

- **Type II hypersensitivity** is also called "antibody-mediated" hypersensitivity. Which is kind of misleading, because it's not the only type of hypersensitivity reaction that involves antibodies. Oh well. In this type of hypersensitivity antibodies bind to antigens on a cell surface (any cell surface). Macrophages come in and eat up the cells (they think the Fc fragments of antibodies are yummy). Complement gets activated, inflammation comes in (harming tissue) and cells end up dying. Examples of this type of hypersensitivity include: autoimmune hemolytic anemia, pemphigus vulgaris, Goodpasture syndrome, myasthenia gravis, and Graves' disease.
- **Diagnosis**

  Detection of antibodies and antigens by Immunofluorescence in tissue biopsy specimens e.g. kidney, skin etc.
- **Type III hypersensitivity** is also called "immune-complex-mediated" hypersensitivity. In this one, antibodies bind to antigens, forming complexes. These antigen-antibody complexes circulate (either throughout the whole body, or within one area of the body), get stuck in vessels, and stimulate inflammation, the end result being inflammation-mediated tissue damage and necrotizing vasculitis. Examples of this type of hypersensitivity include: systemic lupus erythematosus, post-streptococcal glomerulonephritis, polyarteritis nodosa, serum sickness, and the Arthus reaction.
- **Diagnosis**

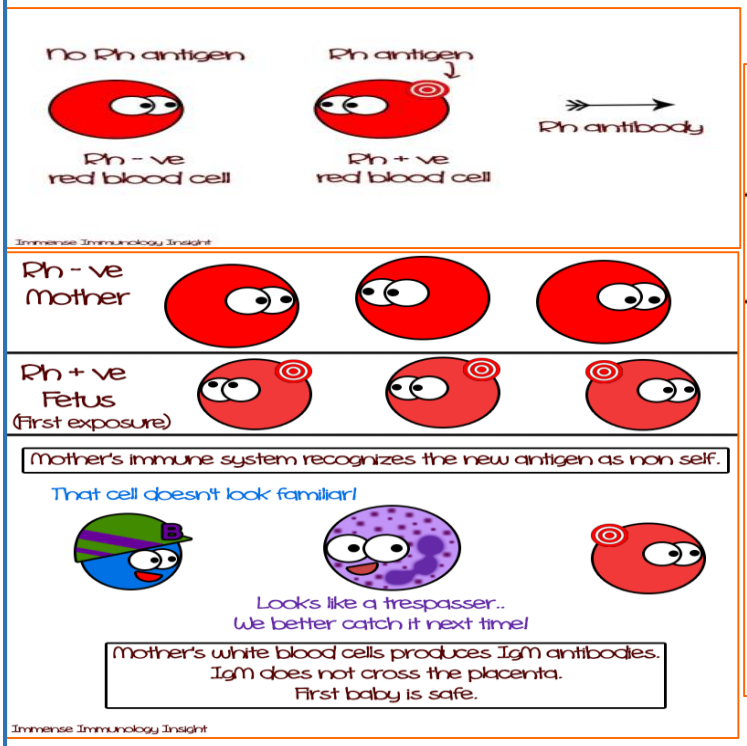
  Demonstration of specific immune complexes in the blood or tissues by: Immunofluoresence

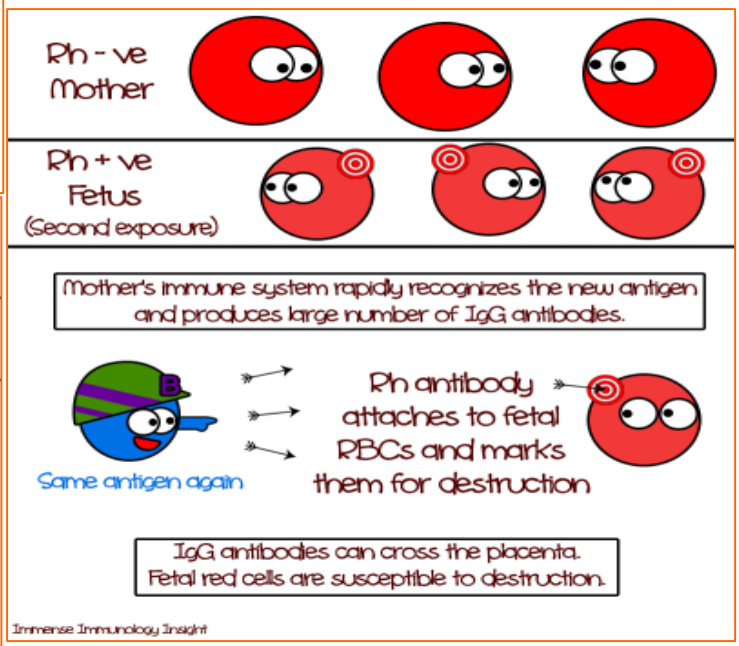
- **Type IV hypersensitivity** is also called "T-cell-mediated" hypersensitivity. This type of hypersensitivity has two subtypes. In one subtype, called delayed-type hypersensitivity, helper T cells secrete cytokines that activate macrophages (which eat the antigen) and induce inflammation (which damages tissue). A good example of delayed-type hypersensitivity is poison ivy. The other subtype, called T-cell-mediated cytotoxicity, involves cytotoxic T cells coming and killing target cells (like the cells of a transplanted organ, or the pancreatic islet cells in a patient with type I diabetes).
- **diagnosis**

1. Delayed skin test (Mantoux test)
2. Patch test (Contact dermatitis)
3. Lymphocyte transformation test

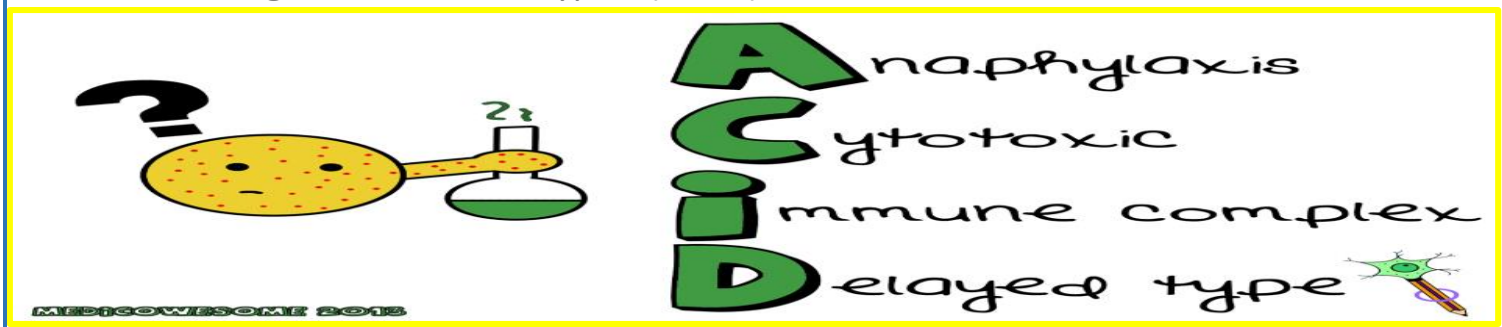
a link that explains hypersensitivity type IV in a story
http://immense-immunology-insight.blogspot.com/2013/11/stages-of-delayed-type-of.html

Hypersensitivity type II & physiology:
In: Blood Transfusion and Rh incompatibility between mother and fetus





Hypersensitivity type (I-IV) & Pharmacology:
In Adverse Drug Reactions [ADR] type B (Bizzar)



MCQS

1 - IgE bind with
A- low affinity
B- high efficacy
C- high affinity

2- Mast cell coated by:
A- IgA
B- IgD
C- IgE

3 - Anaphylactoid reactions mean non - IgE mediated
A- T
B- F

4/ Hypersensitivity type II is mediated by :
A-IgG
B-IgE
C-IgG or IgM
D- IgD & IgE

5/ what is an example on type II hypersensitivity:
A-allergies
B- Rheumatoid arthritis
C-TB granuloma
D- Mismatched blood transfusion

1-C
2-C
3-A
4-C
5-D