

Hypersensitivity reaction

Is the immune system always acting in correct manner?

Did you hear about killing by friend fire during battles?

Did you know that renal failure particularly among Children may develop after Streptococcal tonsillitis?

Why physicians always asking their patients when prescribing antibiotics for drug allergy?

What happen if you allergic to penicillin and take it?

Why bee stings are dangerous when thousands of them attack you?

Hypersensitivity or Allergy

Hypersensitivity is an immune reaction to innocuous (non harmful) antigens that results in tissue injury and/or disease

Hypersensitivity reactions are harmful antigen-specific immune responses in which the immune system pass their border of self recognition or their **defense task** into **destructive task**

Atopy: the genetic predisposition to synthesize inappropriate levels of IgE specific for external allergens

An antigen that causes allergy is an allergen.

Allergens are harmless environmental antigens.

These Ags when enter the body stimulate immune system to produce IgE antibodies.

Examples : pollen, dust mites, mold, pet dander, fruits, gluten, eggs, fish.....

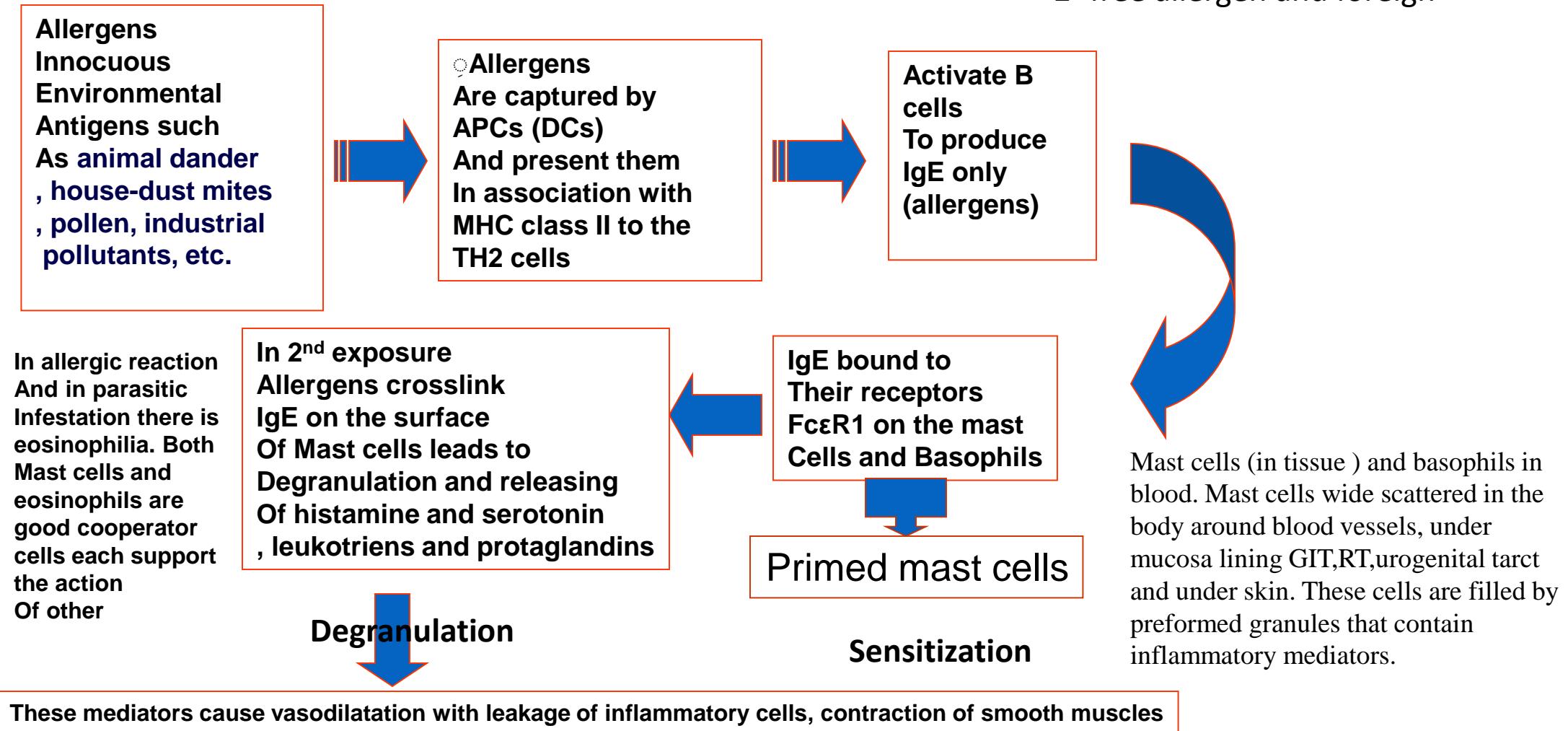
There are 4 types of HSRs

- 1-Type I or IgE mediated hypersensitivity or anaphylactic reaction.
 - 2- Type II or cytolytic hypersensitivity. (IgM and IgG)
 - 3- Type III or immune complex Hypersensitivity. (IgM and IgG)
 - 4- Type IV or Delayed Type or cell mediated Hypersensitivity.
- The first three reactions are Antibody mediated while the fourth is cell mediated reaction

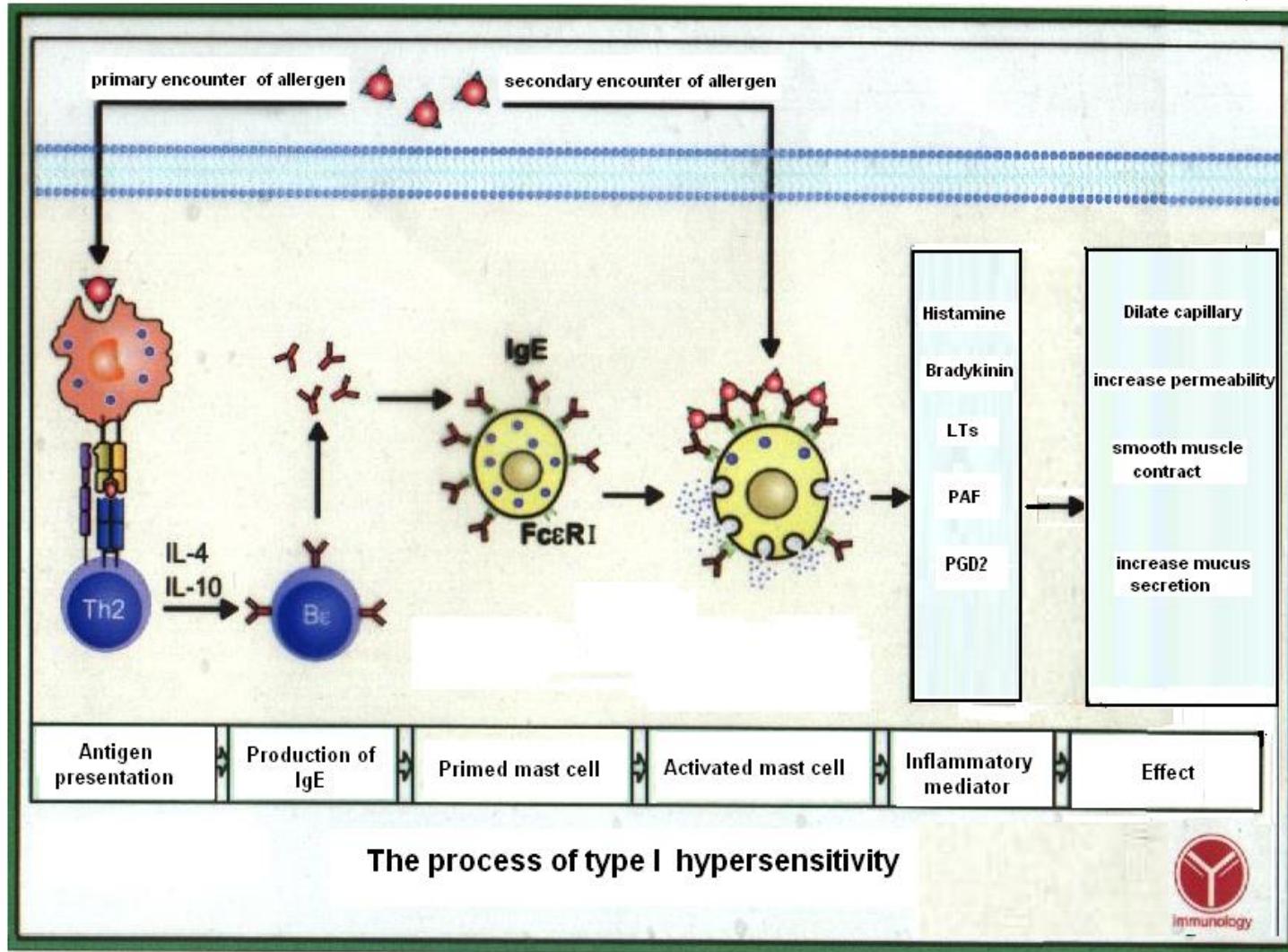
These reactions cause

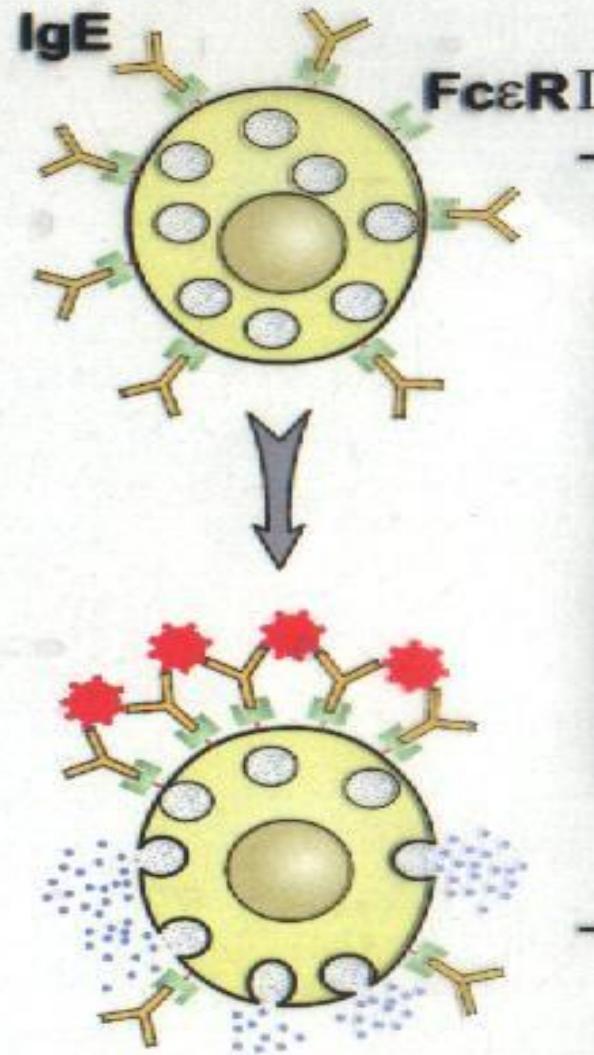
- 1- HSRs
- 2- Autoimmune diseases
- 3- Graft rejection

Mechanism of Type I HR



Mechanism of Type I HR

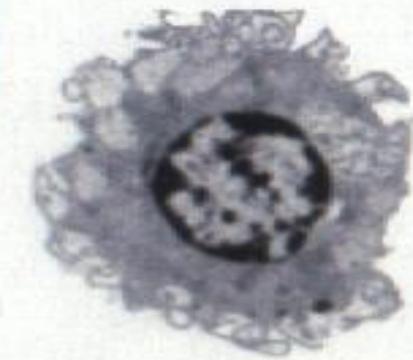




Resting mast cells



Activated mast cells



Activation of mast cells mediated by IgE



Immunology

Common diseases of type I hypersensitivity

1- Systemic like anaphylaxis or anaphylactic shock fatal (emergency case= Hypotension, Bronchospasm, urticaria shock and death). This condition can develop by (Penicillin and cephalosporins drugs, anaesthetic drugs, bees)-Adrenaline injection.

2- Localized allergies like

Hay fever (allergic rhinitis)

Asthma

food allergy- diarrhea

Eczema

Urticaria



Urticaria

Hay Fever Symptoms

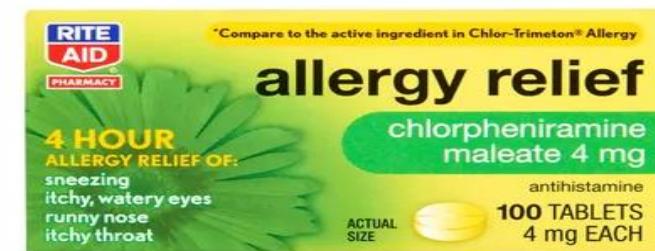
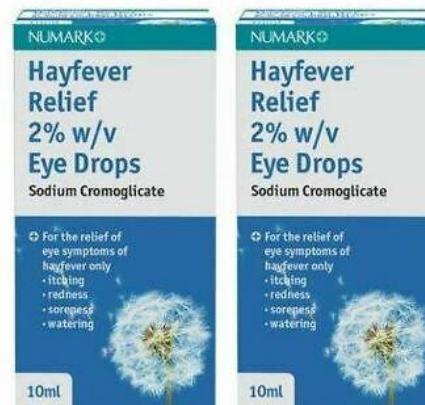
Top Medicines to Help with Hay Fever

Allergy Tablets
Chlorphenamine (Piriton) tablets are commonly used for quick relief from hay fever. Non-Drowsy products like Cetirizine (Zirtek, Piriteze) and Loratadine (Clarityn) provide all day protection.

Adult Nasal Drops
Ortivine 10ml.

Eye Drops
Sodium Cromoglycate (Opticrom) - regular use to prevent and treat hayfever. A preservative free version is also available for people

Nasal Spray
For adults and children, Beclomethasone (Beconase) helps reduce inflammation in the sinuses.



Lab.Diagnosis

- 1-Intradermal skin test: Injection of various allergens intradermally and after 20 minutes looking for erythema.
- 2- Measurement of IgE by ELISA

Treatment

- 1- Avoidance exposure to the allergens.
- 2- Desensitization therapy: small amounts of allergens are administered for several times which inhibit synthesis of IgE and produce tolerance to that allergen.
- 3- Drugs like corticosteroids like **Dep-Medrol (methylprednisolone IM)** (which are anti-inflammatory but cause suppression of the immunity. H-1 antihistamines like diphenylhydramine prevent binding of histamine to their H-1 receptors. Beta agonists like **epinephrine (adrenaline)** and salbutamol which inhibit mast cells degranulation, Alpha antagonists like methoxamine (vasoconstriction to elevate B.P) and **phenylephrine (decongestant)**



Skin allergy test

Type 2 HR (Cytolytic/Cytotoxic HR)

This type of HR results from Abs (IgG or IgM) that mistakenly react with self Ags on the **surface of body cells or basement membrane** which results in cell destruction by one of the following mechanisms:

Mechanisms

- A) Cytotoxic (Destruction without inflammation or Destruction with inflammation)
- B) Non cytotoxic (cell dysfunction) no cell damage.
- A) Cytotoxic (Destruction without inflammation)

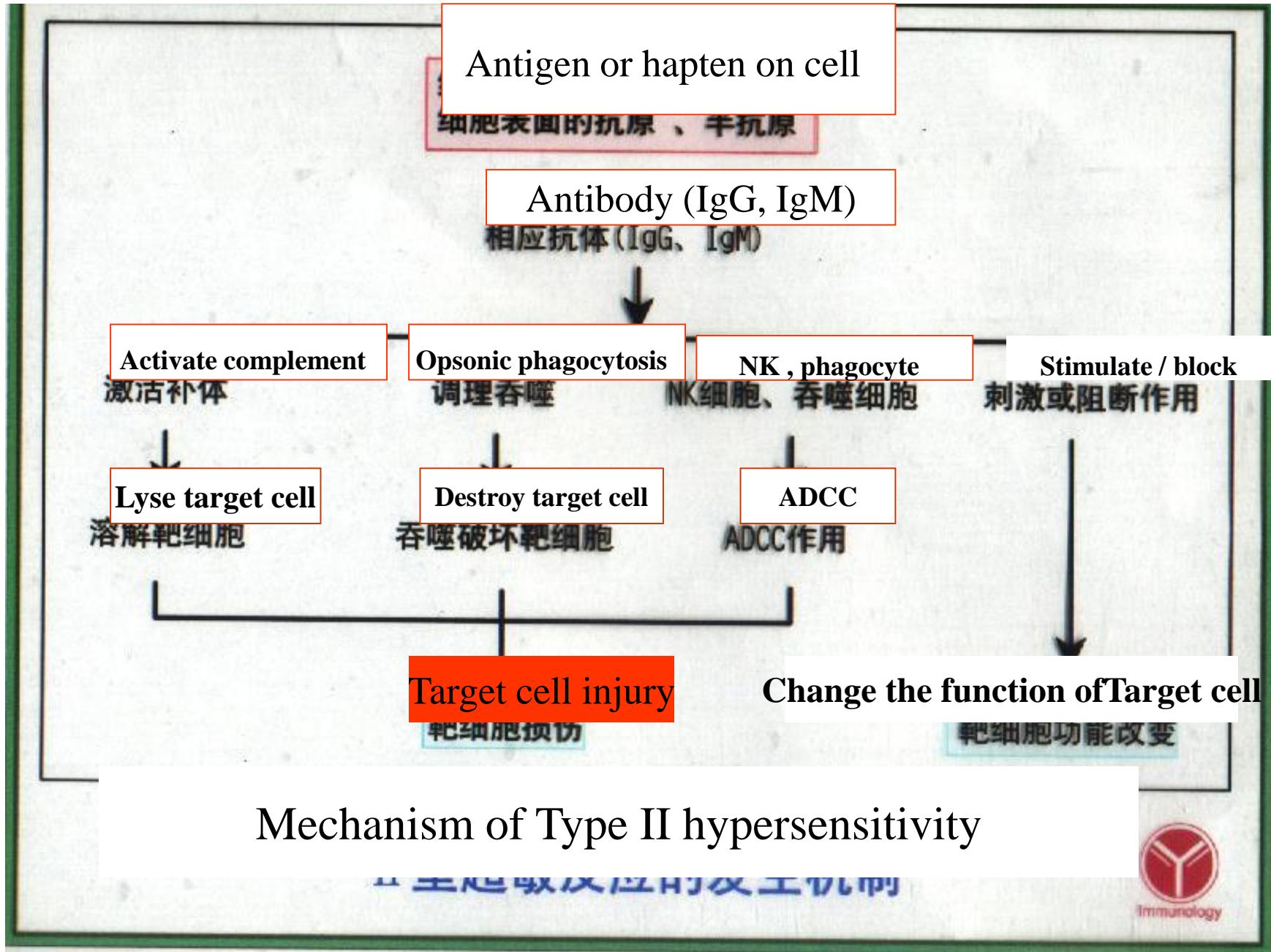
1- Abs like IgG and IgM bind with Ag on the surface of the cells will activate C.S by Classical pathway (**complement activation**).

2- Coated Abs act as opsonin and engulfed by neutrophils (**phagocytosis**).

Killed by ADCC by NK cells (Neutrophils, macrophages and eosinophils can also perform (**ADCC**).

Examples

- 1- ABO incompatability
- 2- Hemolytic disease of new born
- 3- Autoimmune hemolytic anemia (penicillin act as a hapten binds to surface of RBCs ---Abs ----lysis of RBCs



Cytotoxic (Destruction with inflammation)

Antigens on basement membrane will activate C.S-----C3a and C5 a -----inflammation-mast cells degranulation----Histamine---Vasodilation and C5a attract neutrophils (become frustrated because can not engulf B.M) release O₂ radical species and lysozymes -----tissue damage (inflammation)

Examples

- 1- Acute rheumatic fever (Antibodies against M protein of Str.pyogen will cross react with heart muscle).
- 2- Goodpasture syndrome (autoantibodies formed against collagen IV in the basement membrane in Kidney --- Glomerulonephritis (Complement activation)).
- 3- Graft rejection: Abs from recipient will bind with Ag on the cells of donors.
- 4- Pemphigus vulgaris---- Autoantibodies against desmosomes ----loss cell to cell adhesion----vesicle formation



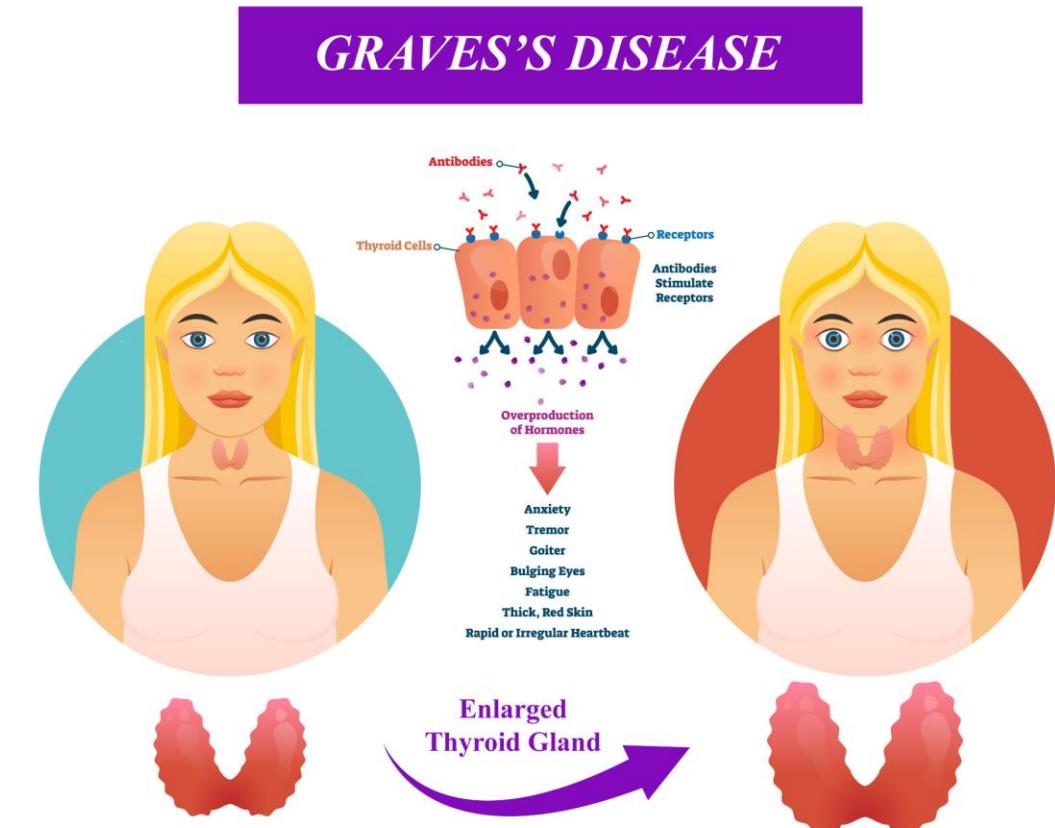
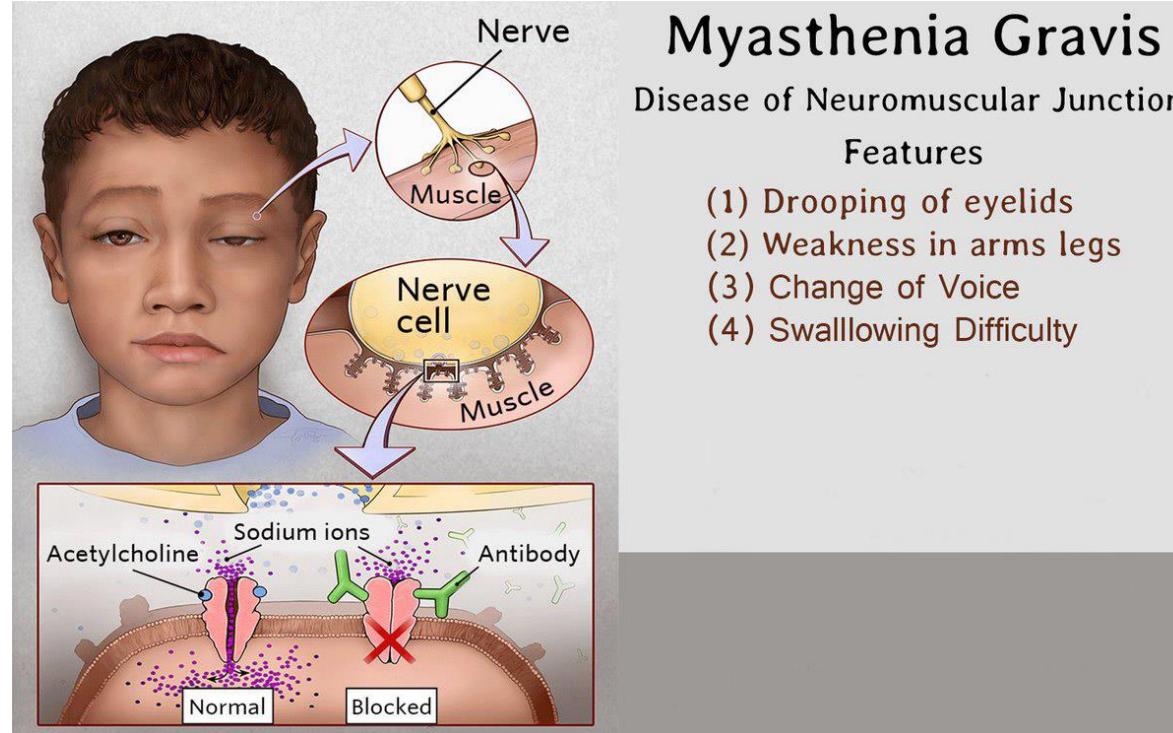
B- Non cytotoxic (cell dysfunction)

Autoantibodies bind to their receptors on cells cause either blocking (inhibition) so less production or overactivate the cell to produce excess product.

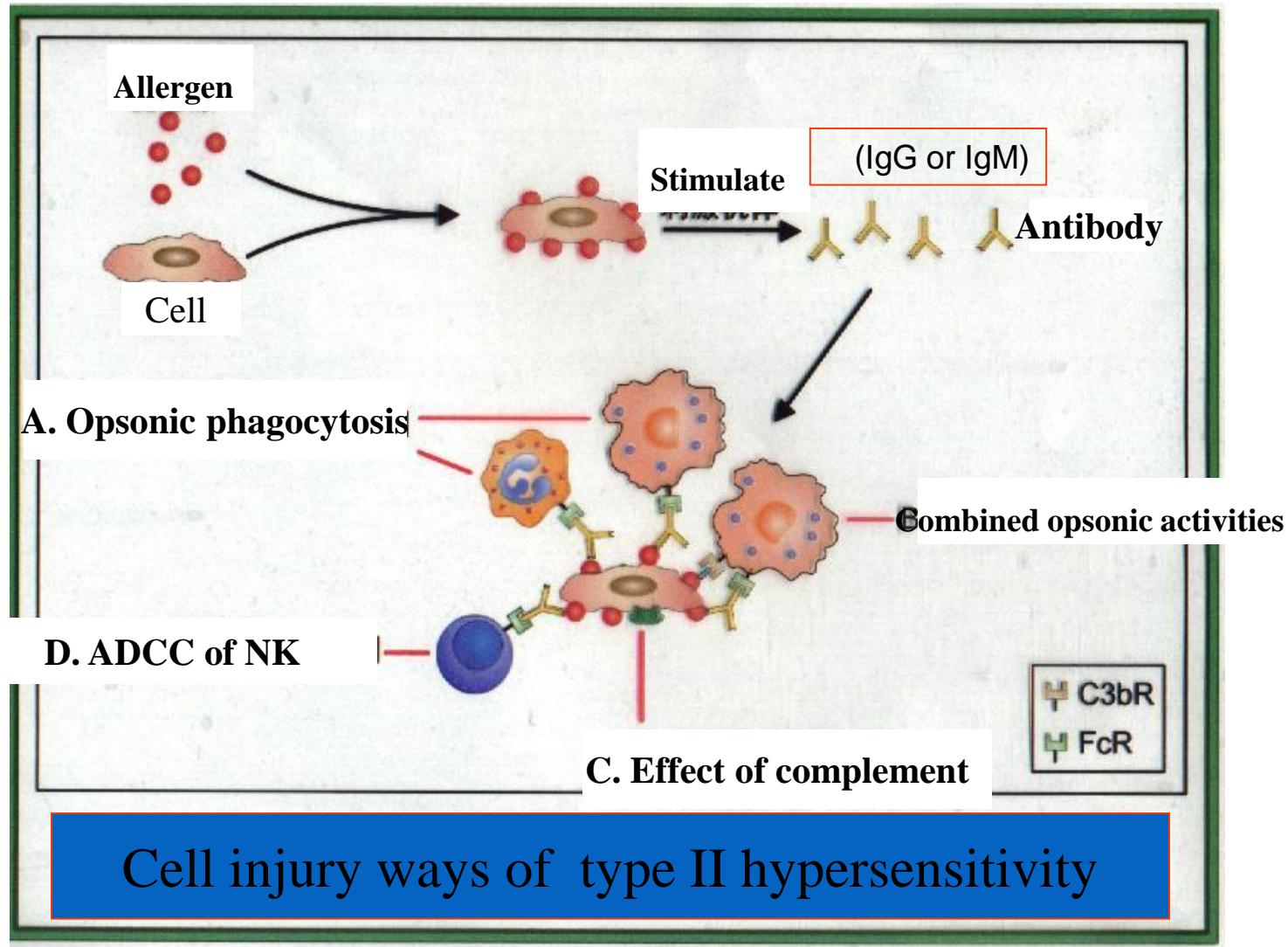
Examples

1- Graves disease (hyperthyroidism) (Anti-TSHR) (Both T3 and T4 will be high while TSH low

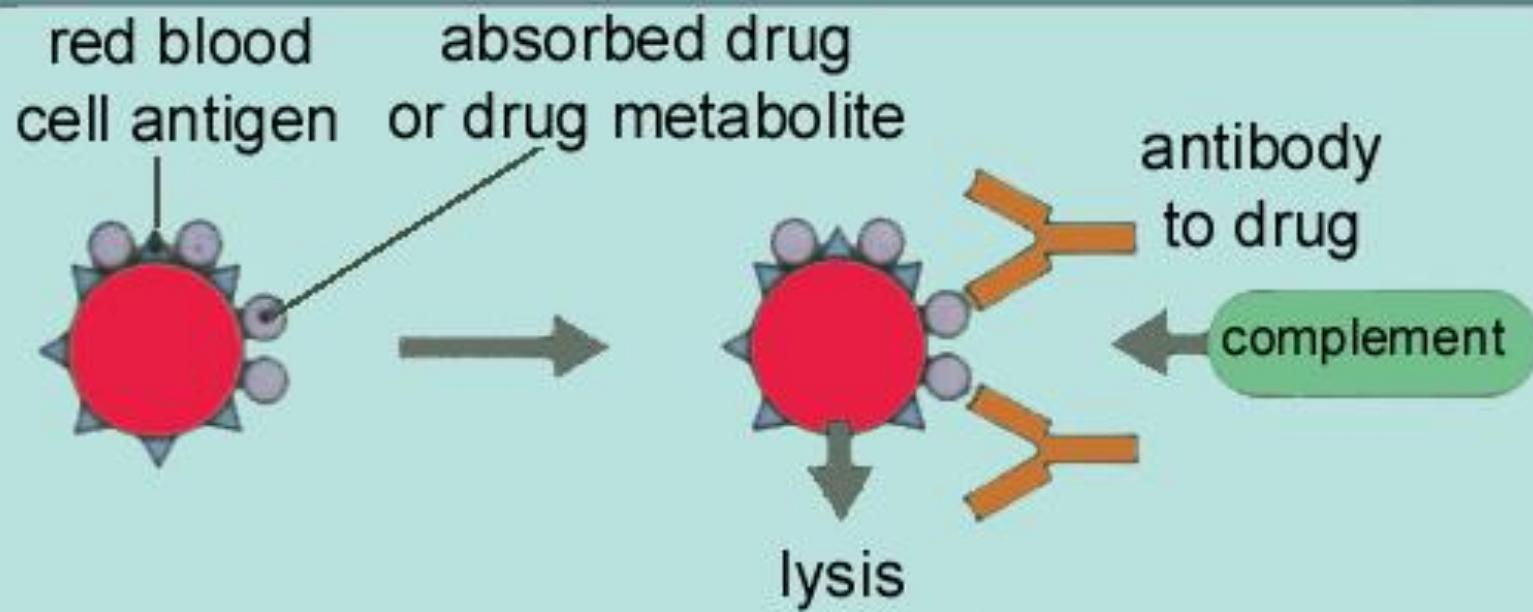
2-Myasthenia gravis (Autoantibodies against ACHR----No muscle contraction



Type II-Antibody-Mediated Cytotoxic Hypersensitivity



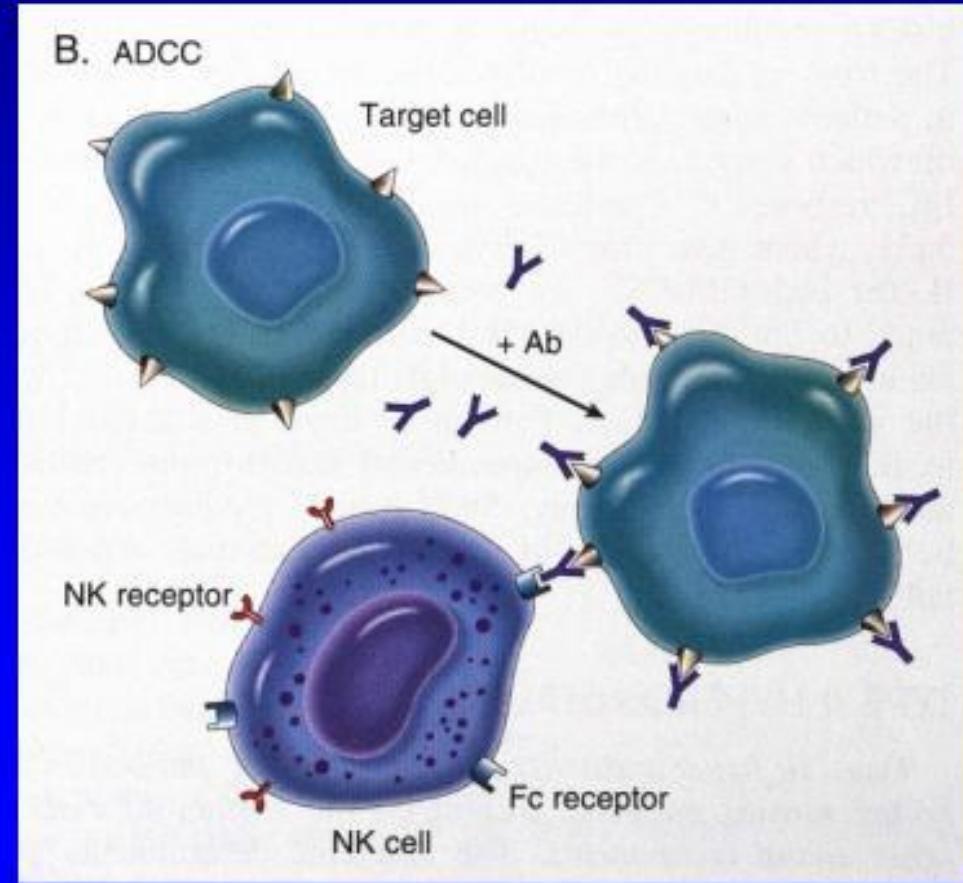
Drug-induced reactions to red cells



Type II Hypersensitivity Reactions

2. *Antibody-Dependent Cell Mediated Cytotoxicity*

- IgG antibody coats cells
- NK cells, PMN's, Eos, and macrophages bind via Fc receptors and induce cell damage



Type III HSR or soluble immune complexes

This occurs when

- 1- Soluble Ags (intrinsic or extrinsic)
- 2- Soluble Abs (IgG or IgM)
- 3- One of them should be excess (either excess of Ag (more common) or excess of Abs)

When there is little Abs and an excess of Ags or reverse leading to **small immune complex** formation which **deposit** in **tissue**

Normally these soluble immune complexes removed by RES like Macrophages but our body can not remove Ics in certain situations

1- Overwhelming infections (pathogen invade body in high quantities)

2- Persistent of infection like (HBV)

3- Self antigens (autoantibodies against self antigens)

Mechanisms

Immune complexes (one of them access)----Circulation in blood (not removed by macrophages)----deposited in tissues----activation of CS by classical pathway-----C3a and C5a production-----degranulation of mast cells---Histamine---Vasodilation. C5a attract neutrophils which bind via Fc portion of IgG and IgM on basement membrane- become frustrated ---release lytic enzymes ---tissue damage. Platelets aggregate making microthrombi which clog small capillaries---hypoxia-ischemia-necrosis. This reaction called fibrinoid necrosis (Ics+complement+fibrin+ necrotic tissue)

Examples of Local type III HSR

1- Arthus reaction

Repeated injection of insulin at one site leads to development of erythema. Insulin hormone was prepared in horses so associated with foreign horse protein which make antibodies in human. Repeated insulin injection (excess of Ags) will produce soluble Ics which deposited locally at the site of injection leading erythema reaction as mentioned above. This local type III HSR was discovered first by Arthus so called Arthus reaction.

2- Pneumonitis (Farmer lungs)

Examples of systemic type III HSR

1-Serum sickness

Anti-tetanus Abs were prepared in horses (so associated with horse proteins) and the body will make Abs that leads to IC formation in blood circulation and can deposit in various body tissues. Its self limited.

2- Systemic lupus erythematosus

Autoantibodies against cell components like anti-histone Abs, anti-ds DNA -----soluble Ics---deposit in skin rash (butterfly rashes), joint (arthritis), Kidney (glomerulonephritis)

3- Rheumatoid arthritis

IgM against Fc of IgG ---Immune complexes –deposition in synovial membrane –Inflammation.

4- Post Streptococcal glomerulitis, HBV glomerulonephritis.

So what are the key players of Type III HSR?

- 1- Immune complexes (Free Ag and Ab one of them is in excess)
- 2- Complement activation
- 3- C3a and C5a
- 4- Mast cells and neutrophils

Examples of different hypersensitivity reactions against one antigen

Penicillin ---Allergen---IgE ---Type I HSR

Penicillin attaches to RBCs surfaces (modification of surface Ag) that make antibodies-Lysis– Type II HSR

Penicillin binds with carrier proteins (soluble Ag) + Abs---Ics- --deposition in tissue ----Type III HSR

Penicillin engulfed by cells like APCs----TH1 cells- Type IV HSR



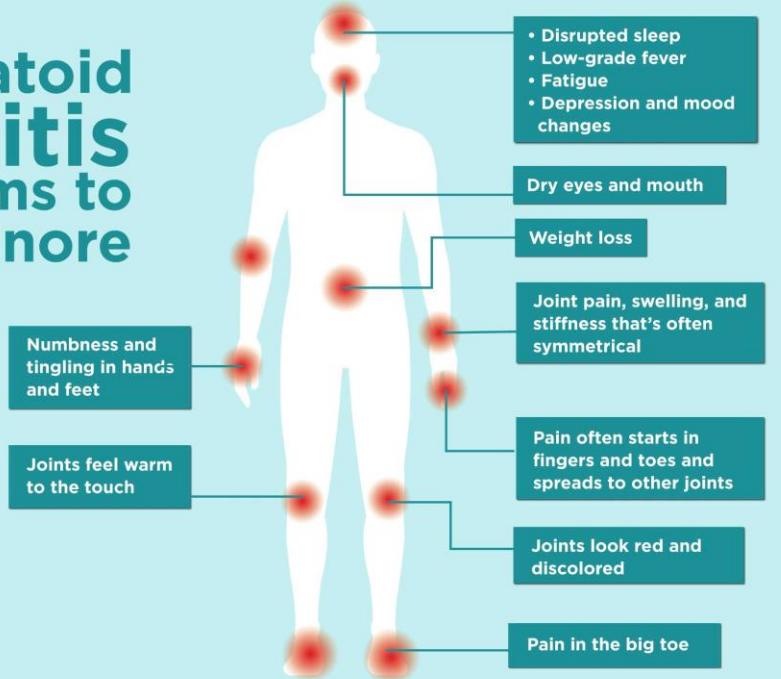
Arthus reaction



Butterfly rashes of SLE



Rheumatoid Arthritis symptoms to never ignore



Complication of Systemic Lupus Erythematosus (SLE)



Mouth and nose ulcers



Skin butterfly rash and red patches

Heart

- endocarditis
- atherosclerosis
- inflammation of the fibrous sac

Lungs

- pleuritis
- pneumonitis
- pulmonary emboli
- pulmonary hemorrhage

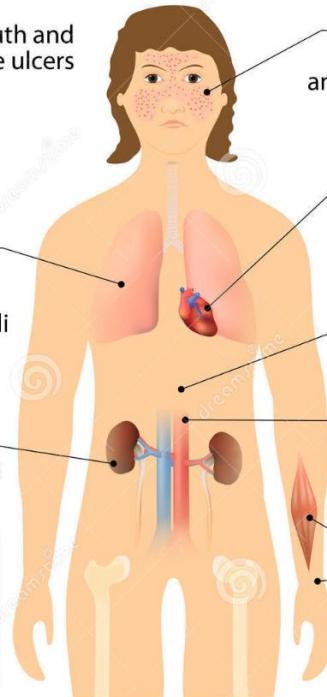
Blood

- anemia
- high blood pressure

Kidneys

- blood in the urine

Hair loss
High fever
Abnormal headache



Muscle and Joints

- pain and
- arthriticsches
- swollen joints



Examples of Type 3 Hypersensitivity

Localized forms:

- 1- **Arthus reaction:** If an Ag injected subcutaneously into an individual that already has precipitating Abs, then acute inflammation will develop at the site of injection within several hours.

Generalized forms:

1-Serum sickness:

Patients received large doses of equine antitetanus serum developed a characteristic reaction about 10 days later which caused generalized vasculitis with erythema, edema and urticaria of the skin then subsided within few days. This reaction is called serum reaction.

- 2- **Glomerulonephritis:** this associated with many viral and bacterial infections
- 3- **Henoch-Schonlein purpura (IgA-Ag immune complexes deposit in blood vessels of skin (skin rashes), Kidney (glomerulitis), joints (arthritis) in abdomen (pain))**
- 4- **Systemic lupus erythematosus:** Autoimmune disease type III HR in which autoantibodies (autoreactive B cells) are formed against autoantigens like DNA and nucleoprotein-Immune complexes –precipitation on Blood vessels of various tissues-vasculitis. Antinuclear antibody (ANA test used for diagnosis of lupus)
- 5- **Rheumatoid arthritis:** Chronic inflammatory autoimmune disease in which autoantibodies (anti IgG Abs) are formed which attack IgG –immune complex-joint (Rheumatoid factor)

Diagnosis

- Examination of the tissue biopsies for the presence of IgG and complement by Immunofluorescence.
 - Detection of immune complexes in the serum.
 - Depletion the level of complement especially C3 and C4
- Treatment by giving anti-inflammatory drugs

Type IV Hypersensitivity

Due to the excessive activation of **Cytotoxic T lymphocytes and Th1 cells** which secrete high levels of cytokines (inflammatory cytokines) that harm the tissue. The effect develops after **2-3 days** (therefore it is called **delayed type hypersensitivity reaction**). This kind of reaction is mainly generated as a **defense mechanisms against intracellular pathogens**.

Characters

- 1- Delayed (1-2 days)**
- 2- No antibody participation**
- 3- Sensitization is required**
- 4- Cell mediated (Th1 and CD8 cells)**
- 5- Chemicals like soap, plants, jewelers (nickel), hair dyes.....---act as hapten**

Role of CD8 cells in Type IV HSR

Hapten combined with skin protein presented by MHC-I then migrate to L.N to meet the specific T cytotoxic cells (This cell will be activated upon receiving two signals, primary signal= MHC-I and TCR with CD8, secondary signal = B-7 and CD28 + Cd40 and CD40 L). Activated CD8 cell will undergoes proliferation (clonal expansion) and become effector or sensitized cells against that particular chemical substance as well as becomes memory cells. These effector CD8 cells leave L.N and enter circulation (This process takes several days) and this is the first exposure (**sensitization stage**).

In second exposure (**effector phase**) to the same chemical substance plus hapten present by MHC-I to sensitized CD8 cells which become activated only by primary signal then secrete perforins and granzymes that kill the cells and after 1-2 days vesicular lesions (blisters) will appear in the skin.

Role of T H1 cells in Type IV HSR

Sensitization phase

The same mechanism but will presented by MHC-II and secrete IL-12 which activate and proliferate TH1 cells in L.N (sensitized or effector cells as well as memory cells).

Second exposure to the same chemical, TH1 cells will accumulate at the site and secrete IL-2, IFN-gamma and TNF beta which

1- Attract lymphocytes

2- Attract macrophages which become activated due to IFN gamma---release free O₂ radicals and NO ---tissue damage (granuloma formation)

Examples of Type IV HSR

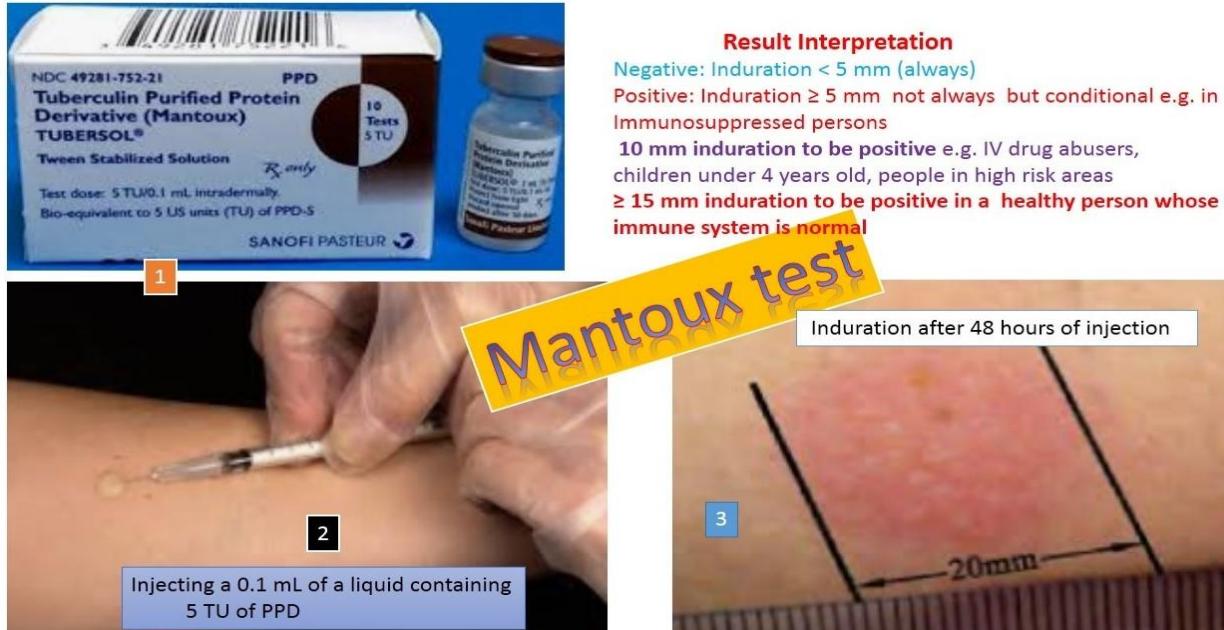
1- Type 1 diabetes mellitus

2- Graft rejection (Type II, III and IV)

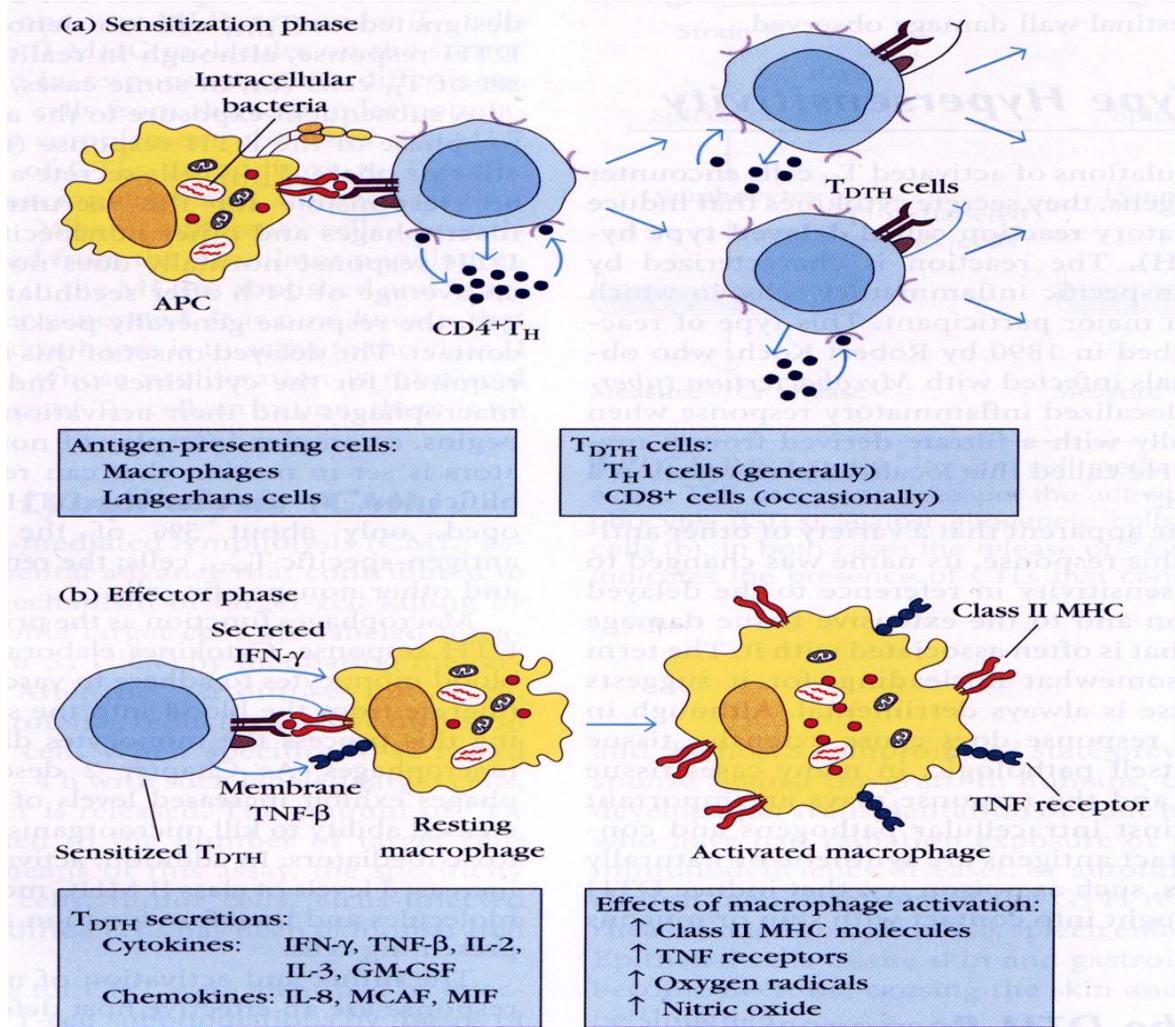
3- Tuberculin skin test

4-Lepromin skin test

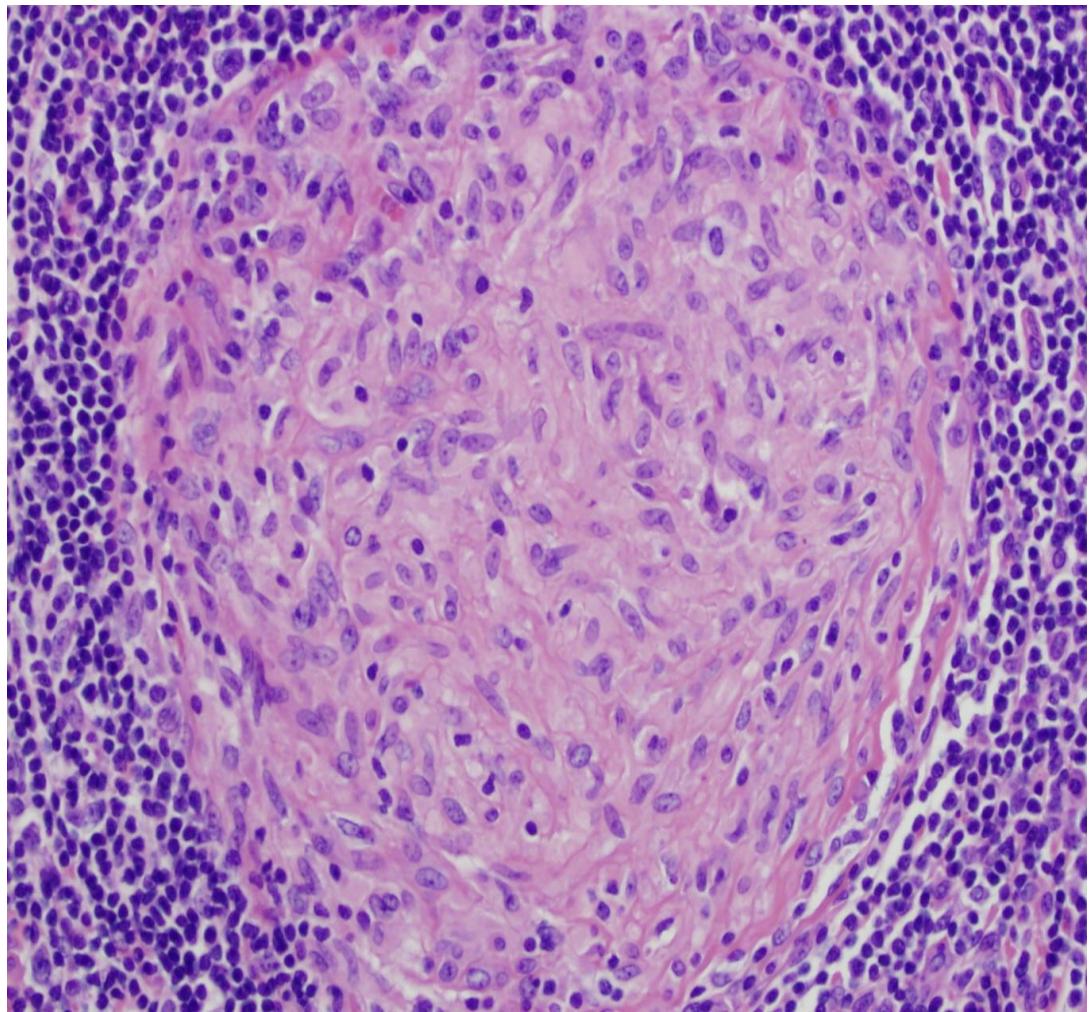
5- T.B



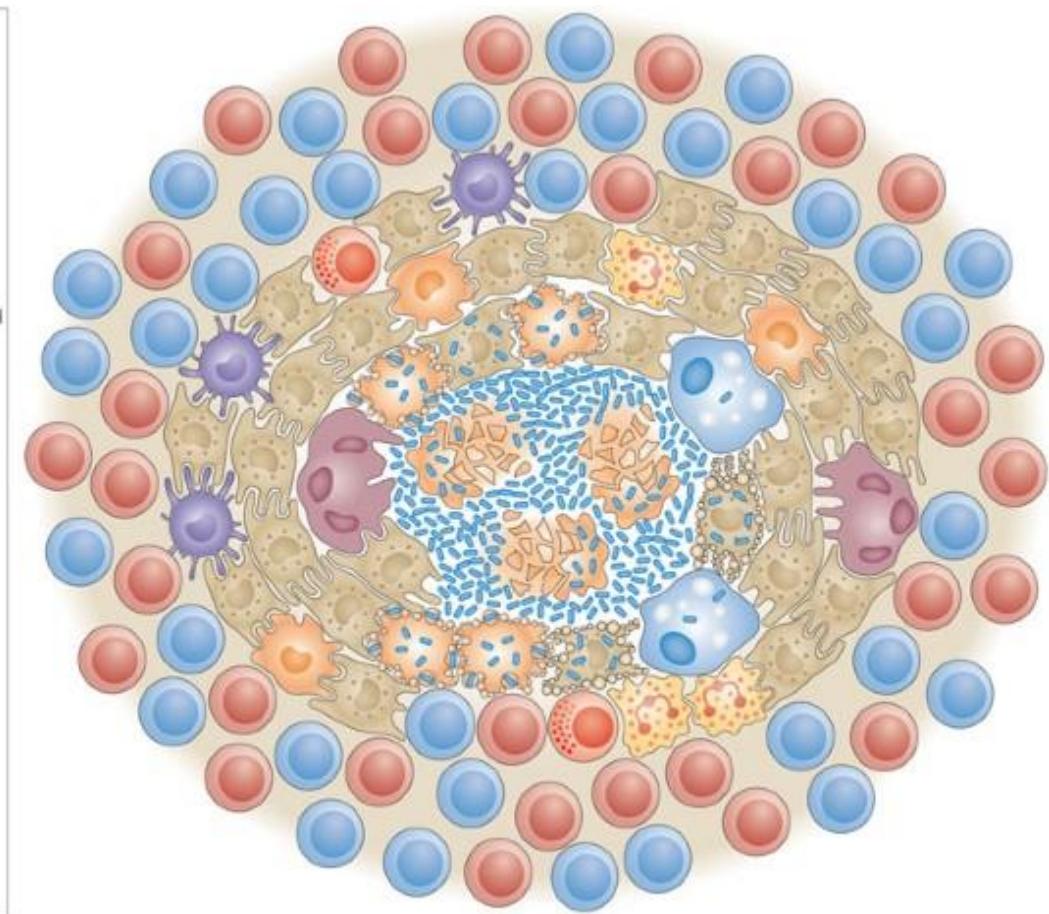
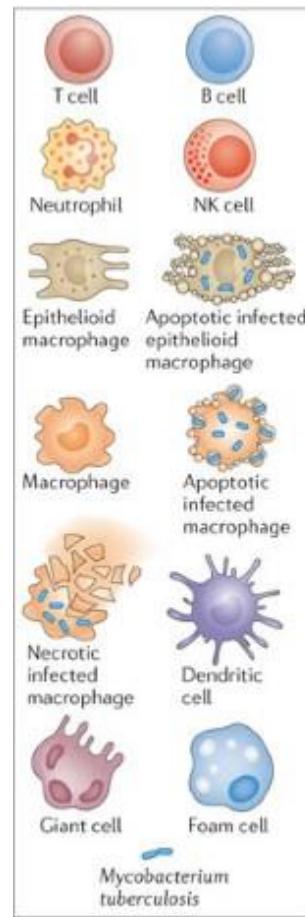
Mantoux test (Tuberculin skin test)



Both sensitization and effector phases of Type IV hypersensitivity reaction



H and E stained tuberculous lesion



Schematic diagram of tuberculous lesion

Delayed-type hypersensitivity (DTH) (e.g., tuberculin skin test)

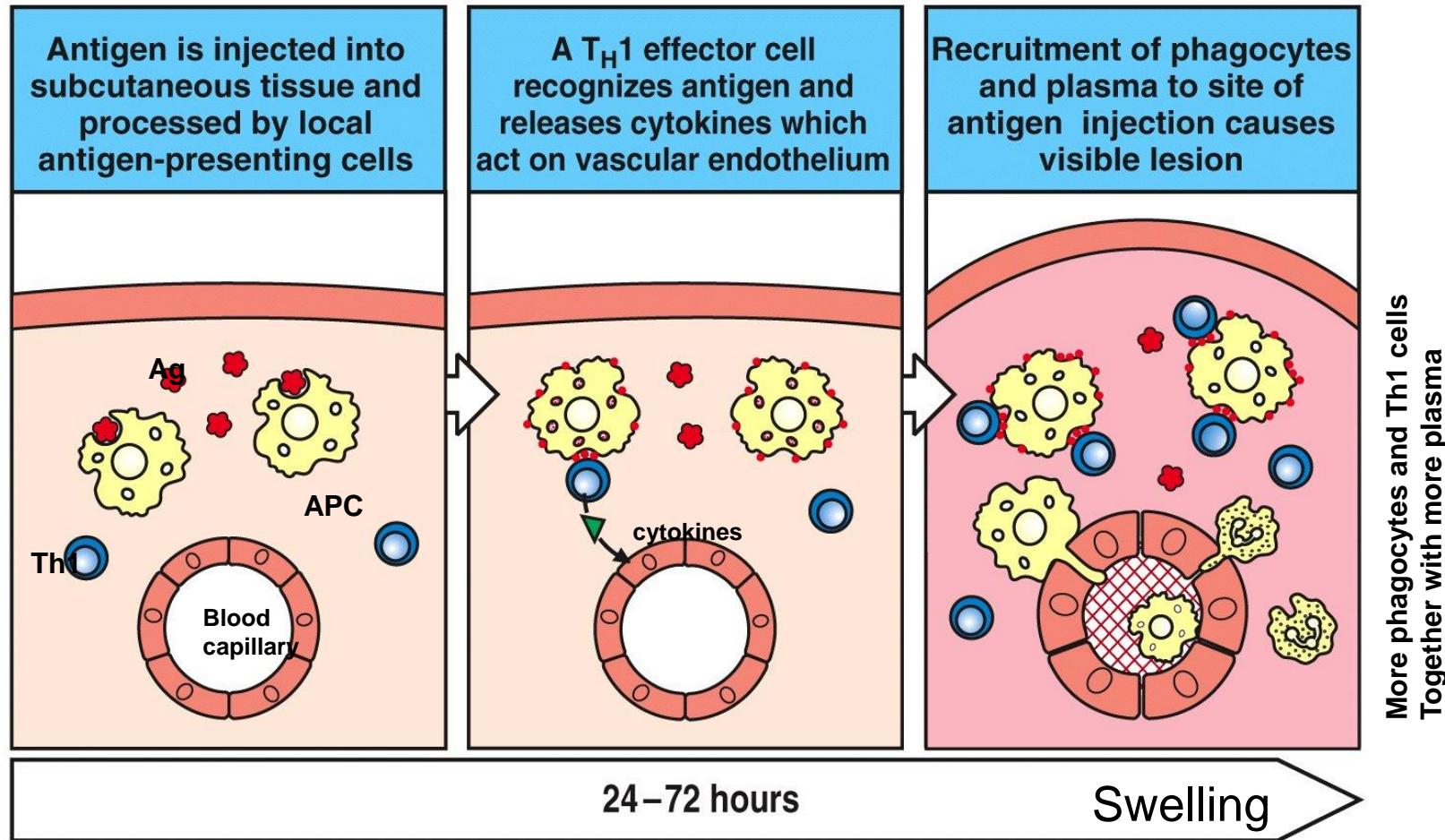


Figure 12-25 Immunobiology, 6/e. (© Garland Science 2005)

DTH as a result of a contact-sensitizing agent*

Like chemicals such as formaldehyde or some stains

Contact Dermatitis

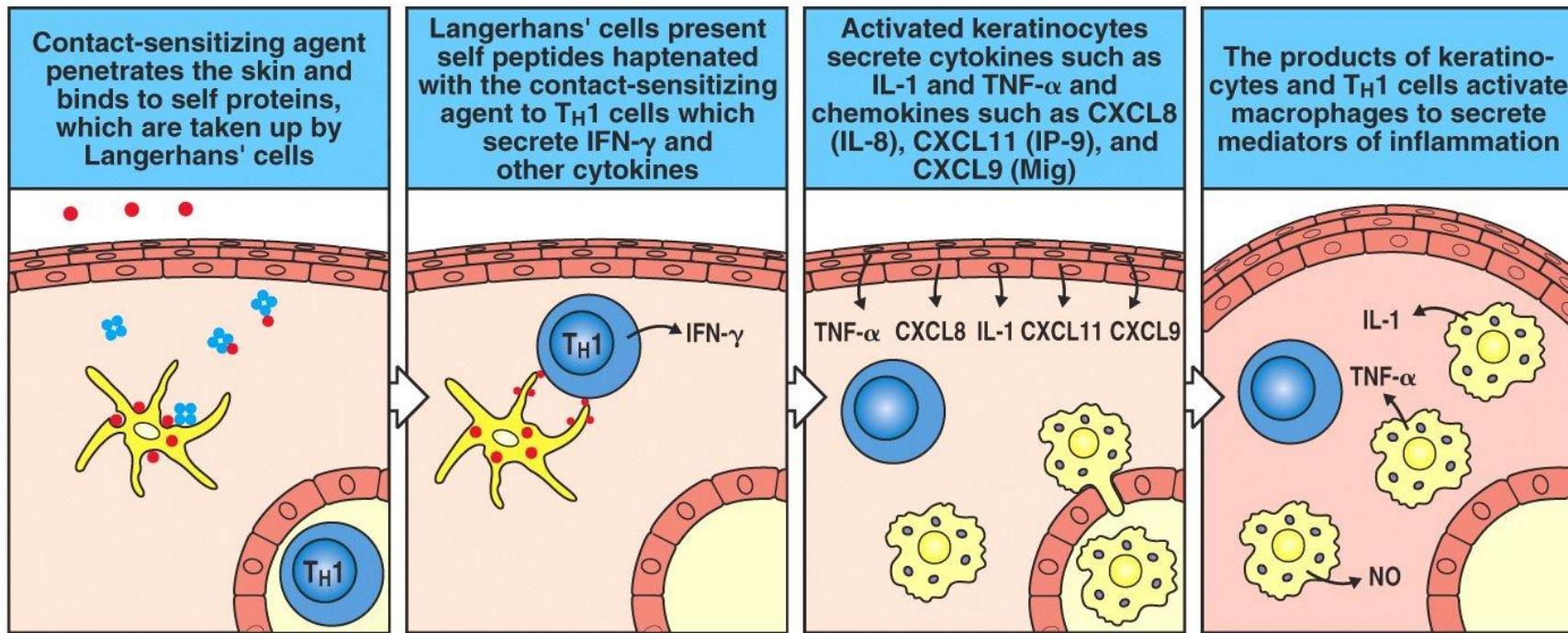


Figure 12-27 Immunobiology, 6/e. (© Garland Science 2005)

*a contact-sensitizing agent is usually a small molecule that penetrates the skin then binds to self-proteins, making the protein “look” foreign