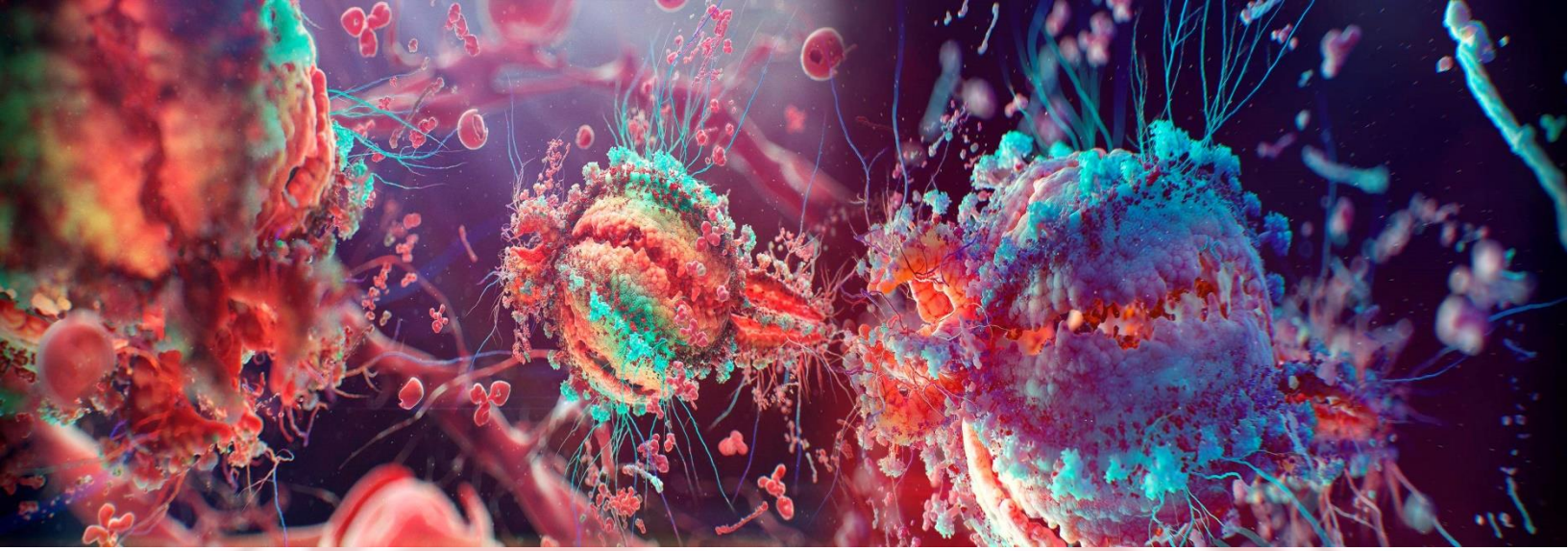

Immunology

Lecture (12)

Part 2

Done by:
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Today we will talk about hypersensitivity reactions
Hypersensitivity reactions – 'over reaction' of the immune system to harmless environmental antigens.

So we can understand from this definition that there are antigens don't cause immune system reaction but sadly our body considers it as a harmful antigen.

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

We will take some examples of how can hypersensitivity cause death in some cases.

Hypersensitivity reactions require a pre-sensitized (immune) state of the host.
What is the mean of pre-sensitized?
Exposed at least once, it is very unlikely for the immune system to produce allergy reactions in the first exposure to the antigen.
We can see the symptoms at the second exposure.
And we should know that the strength of the allergy reaction increases with time, so the third exposure will be stronger than the second exposure.

Allergen: the antigens that give rise to immediate hypersensitivity.
We should focus on the(immediate) word in the definition.

Types of Hypersensitivity Reactions
There are 4 types of hypersensitivity reactions:

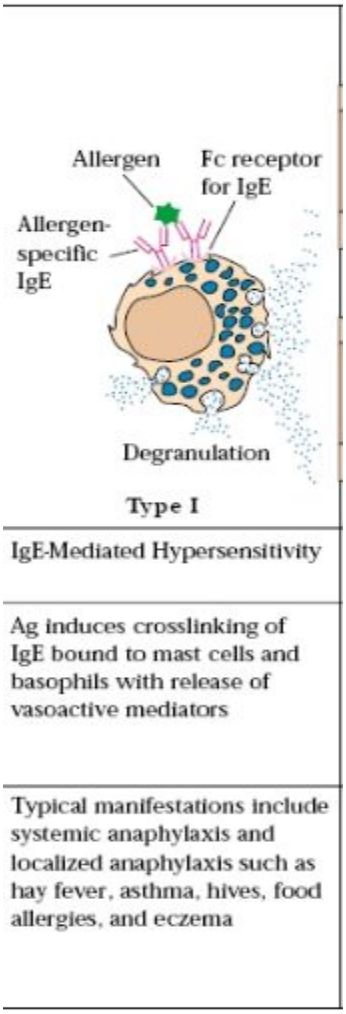
- **Type I: classical immediate hypersensitivity (most famous type)**
- **Type II: cytotoxic hypersensitivity, from the name we can figure out that there is cell lysis.**
- **Type III: immune-complex mediated hypersensitivity**
- **Type IV: cell-mediated or delayed hypersensitivity**

Types I, II and III are antibody-mediated
Type IV is cell-mediated, and because it is a cell-mediated so it takes a long time for the reaction, so we call it delayed hypersensitivity.

Now we talk about each of them in details.

Type I: Immediate hypersensitivity

Look at this picture



What is the antibodies and cells that play a role in this type?

- **Mast cell and IgE.**

So, we have a receptor on the mast cell and we call it Fc receptor for IgE when this receptor binds with IgE this will lead to degranulation of mast cell, this will release histamines and other mediators.

This mechanism needs IgE and we said that IgE has the least percentage from other antibodies.

But when the antigen enters the body, this will lead to producing IgE, and by the time we will have more amount of IgE, this will lead to increase the reaction by time.

Some diseases from this type:

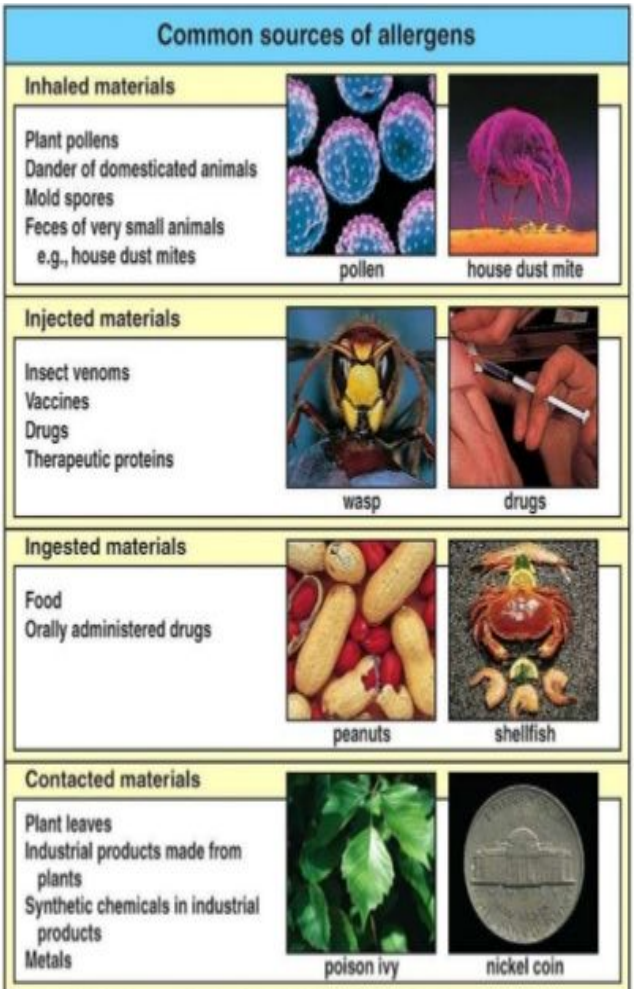
1. **System anaphylaxis**
2. **Fever**
3. **Asthma**
4. **Hives**
5. **Food Allergies**
6. **Eczema**

We will take in the details:

- **An antigen (allergen) reacts with cell fixed antibody (IgE) leading to release of soluble molecules (mediators).**

- **Soluble molecules cause the manifestation of disease**
- **Systemic life-threatening; anaphylactic shock (the worst)**
- **Local atopic allergies; bronchial asthma, hay fever and food allergies**

You should study these sources very well.



Pathophysiology

First exposure to the allergen: Allergen stimulates the formation of an antibody (IgE type). Ig E fixes, by its Fc portion to mast cells and basophils

The second exposure to the same allergen: It bridges between IgE molecules fixed to mast cells leading to activation and degranulation of mast cells and release of mediators.

The most important mediator is histamine, there are other mediators such as Newly sensitized mediators: leukotrienes, prostaglandins, platelets activating factor, Cytokines produced by activated mast cells, basophils e.g. TNF, IL3, IL-4, IL-5, IL-13, chemokines.

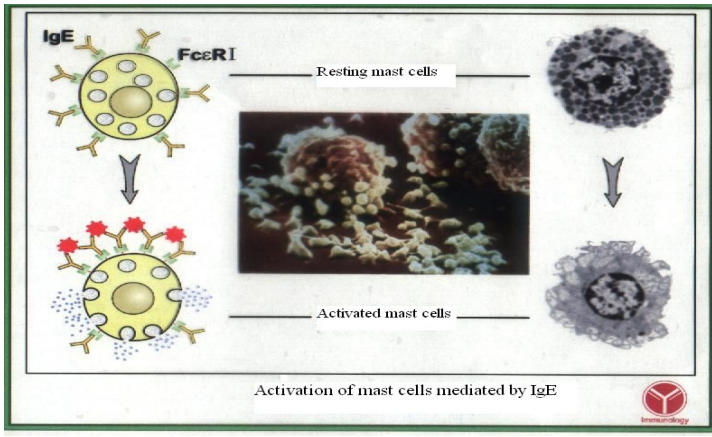
These mediators cause:

1. **smooth muscle contraction**
2. **mucous secretion and bronchial spasm**
3. **vasodilatation**
4. **vascular permeability and edema**

So, patients with asthma have bronchoconstriction.

Look at this picture, which contains mast cell before and after the binding with IgE.

So, this reaction requires allergen, IgE to bind with the mast cell for the granulation, this leads to the release of histamine.
IgE binds with FcεRI.



Anaphylactic shock

It is the worst type from them,

What is the meaning of shock?
Pre death stage (hypotension, weak pulse rate, swelling, unconsciousness and death)

Allergens:
Drugs: penicillin
serum injection: anti-diphtheritic or anti-tetanic serum (antitoxins) we give them as a vaccination.
Anaesthesia or insect venom, sometimes we hear that there is a patient died in the operation from the hypersensitivity for Anaesthesia, or from snake or scorpion venom.

We can treat the anaphylactic shock by epinephrine (IV), corticosteroids injection, and antihistamines.
We should start with epinephrine to get back the pulse and blood pressure, then we should give the patient fluids (for blood pressure), and antihistamine/corticosteroids to work against the hypersensitivity mechanism.

Penicillin is the most famous drug to create a hypersensitivity reaction, so we say :

“never give penicillin without an allergic test”

What do we mean by allergic test?
An allergy test is an exam performed by a trained allergy specialist to determine if your body has an allergic reaction to a known substance.

Should we do this test every time we give the drug for the patient?
Yes, we should, in some cases when we want to prevent rheumatic fever we give the patient multi injection of penicillin, so every time we give penicillin we should do this test, and maybe if you don't do this step for one time, this will lead him to hypersensitivity and death.
The hypersensitivity reaction maybe for the adjuvants substances with penicillin such as procaine.

In the past, some people used to treat this reaction by increasing the dose of allergen, then decrease it, so the body will not create a reaction,

"يعني اذا في حد كان عنده حساسية من الذهب وكل ما يلبس خاتم ذهب بصير عنده حساسية بنعالجها بانه نزيد كمية الذهب يعني بنخليه يابس اساور ب ايده ف بتزيد الحساسية الشوي بس بكون الجسم تعود على الذهب شوي ل هيك بس نزيح الاساور بصير الجسم متعود على الخاتم لحاله وهيك بتختفي الحساسية"

We don't use this method now because it can cause anaphylactic shock and death.

Atopy

- **The local form of type I hypersensitivity**
- **Exposure to certain allergens that induce production of specific IgE**

Allergens :

1. **Inhalants: dust mite faeces, tree or pollens, mould spores.**
2. **Ingestants: milk, egg, fish, choclate**
3. **Contactants: wool, nylon, animal fur**
4. **Drugs: penicillin, salicylates, anaesthesia insect venom**

- **There is a strong familial predisposition to atopic allergy**
- **The predisposition is genetically determined**
- **Allergic rhinitis, allergic asthma, atopic dermatitis are the most common manifestation of atopy. Allergic gastroenteropathy is rare. These manifestations may coexist in the same patients at different times. Atopy can be asymptomatic.**

Allergic rhinitis: also known as hay fever, is a type of inflammation in the nose which occurs when the immune system overreacts to allergens in the air. Signs and symptoms include a runny or stuffy nose, sneezing, red, itchy, and watery eyes, and swelling around the eyes.

allergic asthma: It is characterized by variable and recurring symptoms, reversible airflow obstruction, and easily triggered bronchospasms. Symptoms include episodes of wheezing, coughing, chest tightness, and shortness of breath.

Atopic dermatitis (AD), also known as atopic eczema, is a type of inflammation of the skin (dermatitis). It results in itchy, red, swollen, and cracked skin.

There is familial tendency, when you ask the patient about his/her family history of allergy, he'll say yes.

Diagnosis

1. **History taking for determining the allergen involved**
2. **Skin tests: Intradermal injection of the battery of different allergens. A wheel and flare (erythema) develop at the site of allergen to which the person is allergic**
3. **Determination of total serum IgE level**
4. **Determination of specific IgE levels to the different allergens.**

How we can know that this person has a hypersensitivity reaction type I?

1. **The symptoms connected with triggered.**

The patient knows that if he/she eat, drink or smell a specific thing this will lead to the reaction.

2. **Family history can help**

3. **Some reactions associated with a specific route (IV route is the most dangerous one)**

4. **Check IgE levels in the blood, if there is an allergy it will be high, we can use a specific test for a specific allergen by looking for a specific IgE.**

5. **Also, we can use a skin test**

If anyone has an allergy, there are two results

Become more sever

recovery

Management

1. **Avoidance of specific allergen responsible for the condition**
2. **Hyposensitization: Injection of gradually increasing doses of extract of an allergen**
   - **production of IgG blocking antibody which binds the allergen and prevents combination with IgE**
   - **It may induce T cell tolerance**
3. **Drug Therapy: corticosteroids injection, epinephrine, antihistamines**
   - **Long-acting antihistamine**
   - **Anti leukotrienes**
   - **anti-interleukins**
   - **corticosteroids**
4. **Humanized anti-IgE monoclonal antibodies that neutralize IgE antibodies and prevent them from binding to FcεRI on mast and basophile cells**

If anyone has anaphylactic shock, we use epinephrine shot in the heart. (it's life-saving)

Now we will talk about type II: Cytotoxic or Cytolytic Reactions

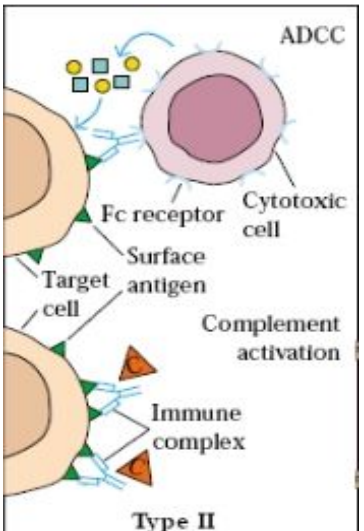
Look at this picture

You can see ADCC (Antibody-dependent cellular cytotoxicity) in this picture, so natural killer cells play an important role in this reaction.

So it's IgG-mediated cytotoxic hypersensitivity

- **An antibody (IgG or IgM) reacts with antigen on the cell surface**
- **This antigen may be part of the cell membrane or circulating antigen (or hapten) that attaches to the cell membrane**
- **Cell lysis results due to :**

1. **Complement fixation to antigen-antibody complex on the cell surface. The activated complement will lead to cell lysis**



Type II
IgG-Mediated Cytotoxic Hypersensitivity
Ab directed against cell surface antigens meditates cell destruction via complement activation or ADCC
Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia

2. **Phagocytosis is enhanced by the antibody (opsonin) bound to cell antigen leading to opsonization of the target cell**
3. **Antibody depended on cellular cytotoxicity (ADCC):**
    - **Antibody coated cells: e.g. tumour cells, graft cells or infected cells can be killed by cells possess Fc receptors**
    - **The process differs from phagocytosis and independent of complement**
    - **Cells most active in ADCC are: NK, macrophages, neutrophils and eosinophils**

So when IgG/IgM bind with the cell membrane this will lead to the destruction of the cell by complement pathway, ADCC and phagocytosis.

Clinical Conditions

1. **Transfusion reaction due to ABO incompatibility (this explanation is from the internet)**

The A and B antigens are the most immunogenic; hence transfusion of an ABO-incompatible unit causes the recipient antibodies to interact with the donor RBC surface antigens, triggering complement activation and resulting in the acute intravascular hemolysis of the transfused donor RBCs.
Complement activation causes various pro-inflammatory effects via the release of active C3a and C5a subcomponents. These are anaphylatoxins which cause histamine and serotonin release from mast cells, increase vascular permeability causing a capillary leak syndrome and stimulate smooth muscle contraction. These translate clinically into the classical symptoms of flushing, hypotension and bronchospasm, respectively.
Experimental evidence supports a central role for cytokines in the pathophysiology of hemolytic transfusion reactions. Tumour necrosis factor (TNF) appears to be the most commonly identified mediator of intravascular coagulation and end-organ injury although other cytokines have been implicated including interleukin (IL)-8, monocyte chemoattractant protein, and IL-1 receptor antagonist.
Ultimately, the complement cascade terminates with activation of the membrane attack complex (MAC) leading to cytolysis. The released hemoglobin tetramers complex with haptoglobin and are removed by the liver, causing haptoglobin depletion. Residual free hemoglobin circulates in the plasma or gets converted to oxidized methemoglobin in the blood, imparting a reddish or brownish color, respectively.
Small, unbound hemoglobin dimers are also filtered by the glomerulus which causes hemoglobinuria. This heme pigment causes acute kidney injury directly or via tubular obstruction or vasoconstriction. In practice, this heme-induced acute tubular necrosis requires a secondary factor like dehydration, nephrotoxin use or sepsis to translate into significant renal insufficiency.
The hemoglobin is taken up by the renal tubular cells, degraded and the iron is stored as hemosiderin. When these renal tubular cells are sloughed in the urine 3-10 days later, hemosiderinuria becomes detectable.

Tissue factor is expressed on monocytes and endothelial cells and can precipitate disseminated intravascular coagulation (DIC). The exposure of RBC stroma and cytokine activation may also feed the consumptive coagulopathy. In rare cases, the above events may culminate into multi-organ failure.

2. **Rh-incompatibility (Haemolytic disease of the newborn)**

Watch this video https://www.youtube.com/watch?v=0nOc-441XUI

3. **Autoimmune diseases: The mechanism of tissue damage is cytotoxic reactions e.g. SLE, autoimmune haemolytic anaemia, idiopathic thrombocytopenic purpura, myasthenia gravis, nephrotoxic nephritis, Hashimoto's thyroiditis**
4. **A non-cytotoxic Type II hypersensitivity is Graves's disease**
    - **It is a form of thyroiditis in which antibodies are produced against TSH surface receptor**
    - **This lead to mimic the effect of TSH and stimulate cells to overproduce thyroid hormones**
5. **Graft rejection cytotoxic reactions: In hyperacute rejection, the recipient already has performed antibody against the graft**

6. **Drug reaction (type II):**
    - **Penicillin may attach as haptens to RBCs and induce antibodies which are cytotoxic for the cell-drug complex leading to haemolysis**
    - **Quinine may attach to platelets and the antibodies cause platelets destruction and thrombocytopenic purpura**

So penicillin can cause two hypersensitivity reaction:
1- if the penicillin cause mast cell degranulation by IgE, Type I
2-Penicillin may attach as haptens to RBCs and induce antibodies which are cytotoxic for the cell-drug complex leading to haemolysis, Type 2

In type 1 and 2 There are certain cells destroyed after Antibodies bound to them

Type 1 ---- IgE binds to mast cell this will release histamine
Type2------ IgG/IgM bind to a target cell and destroy it

Type III: Immune Complex Mediated Reaction

- **When antibodies (IgG or IgM) and antigen coexist immune complexes are formed**
- **Immune complexes are removed by reticuloendoth. Syst.**
- **Some immune complexes escape phagocytosis**
- **Immune complexes deposited in tissues on the basement membrane of blood vessels and cause tissue injury**

Mechanism

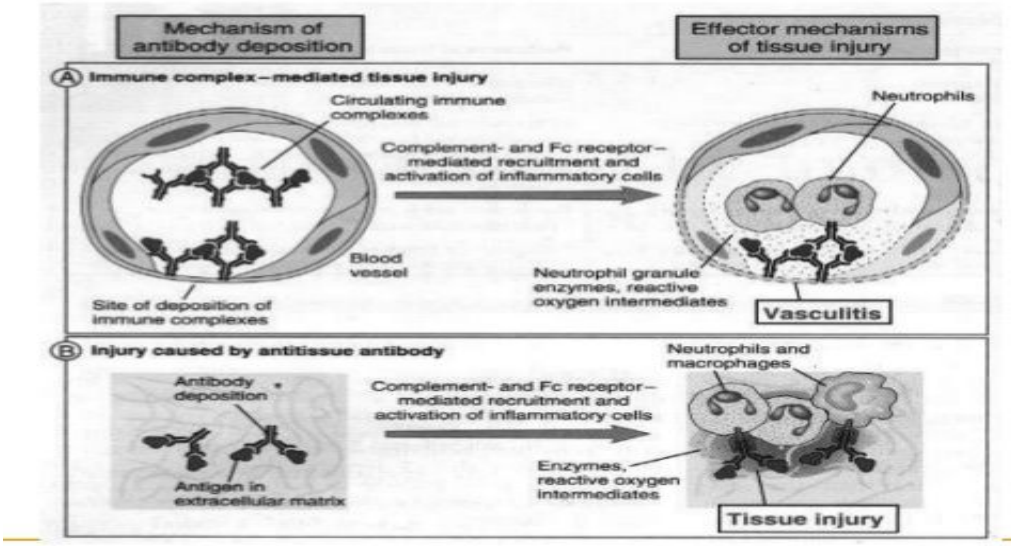
1- antibody should bind with antigen to produce a complex, this complex circulates in the circulation, macrophages destroy this complex, when complex count increases in the circulation, it goes to the basement membrane, so it triggers an inflammatory response, why?
Because macrophages and neutrophils follow this complex and destroy its site.

Immune complexes trigger inflammatory processes:

1. **Immune complexes ----activate the complement------release anaphylatoxins C3a, C5a----- stimulate degranulation of basophils and mast cells-------release histamine -----Histamine increase vascular permeability and help deposition of immune complexes**
2. **Neutrophils are attracted to the site by immune complexes and release lysosomal enzymes which damage tissues and intensify the inflammatory process**
3. **Platelets are aggregated with two consequences**

a- release of histamine
b- a form of microthrombi which lead to ischemia

Look at this picture



Clinical conditions of Type III Hypersensitivity

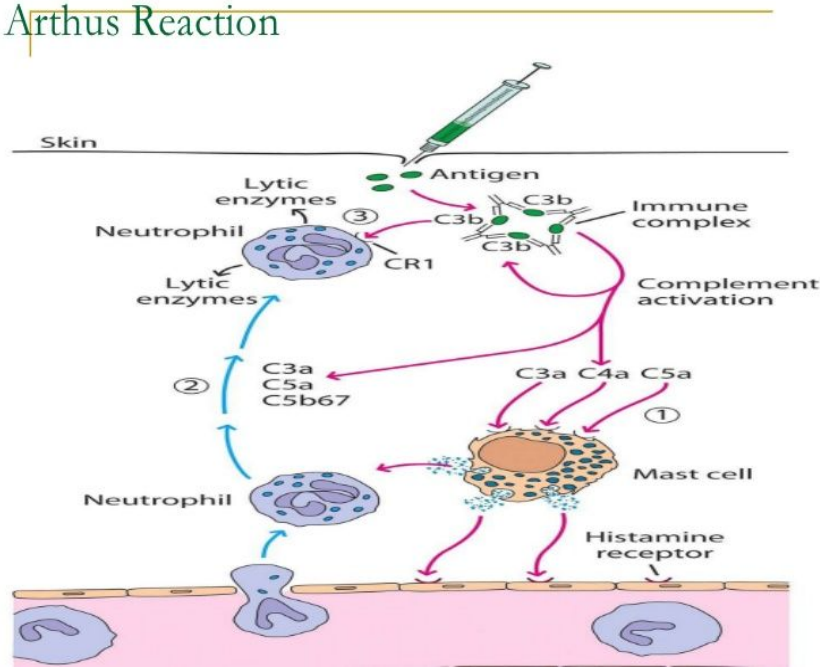
- **Diseases produced by immune complexes are those in which antigens persist without being eliminated as:**

1. **Repeated exposure to extrinsic antigen**
2. **injection of large amounts of antigens**
3. **Persistent infections**
4. **Autoimmunity to self components**

1- Arthus Reaction

- **This is a local immune complex deposition phenomenon e.g. diabetic patients receiving insulin subcutaneously**

1. **Local reactions in the form of edema erythema necrosis**
2. **Immune complexes deposited in small blood vessels Leading to:**
   - **vasculitis**
   - **microthrombi formation**
   - **vascular occlusion**
   - **necrosis**



Watch this video https://www.youtube.com/watch?v=0T_SAXyMs_c
Thank you