

# Immunology lecture 19

**Remember that: type II hypersensitivity is responsible for most of consequences of autoimmune diseases.**

## **Type III hypersensitivity reaction:**

- This is mediated by antibodies (the antibodies can be IgM or IgG).
- Usually involves complement activation and there is a lot of neutrophils in the site of the inflammation.
- The mechanism of type III hypersensitivity is immune-complex mediated.
- We get antigen with antibody, and the antigen can be a self-antigen or it can be a foreign antigen depending on the situation and on the disease itself.
- Type III hypersensitivity is similar to type II in such aspects as: complement activation and involvement of IgM and IgG antibodies.

***The difference between type II and type III hypersensitivity is that:***

- The antigen in case of type II hypersensitivity is part of the tissue which is injured, for example: the antigen is part of RBCs membrane, platelets or the basement membrane of lung and so on.
- In the case of type III hypersensitivity the tissue which is injured has a nothing to do with the antibody or the antigen.

The antigen is not part of tissue which is injured.
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***Mechanism of tissue damage in type III hypersensitivity reaction:***

- 1- Exposure to antigen leads to the synthesis of antibodies.
  - 2- formation of antigen-antibody complexes that circulate in the blood , and they usually precipitate in tissues, and wherever they precipitate they produce complement activation and consequently produce tissue damage.
- For example: if immune-complexes settle in the basement membrane of the kidney, the kidney has a nothing to do with antigen or with antibody.

The antigen is not part of the kidney (it might be a DNA), and the antibody combines with the antigen in the blood (outside the kidney), and they just precipitate in the kidney producing inflammation there.

- in the SLE (systemic lupus erythematosus) the antigen could be DNA and the antibody interact with DNA forming immune-complexes which circulate in the blood and they settle in the basement membrane of the kidney producing inflammation there, (so the antigen is not part of the tissue that is involved in the inflammation) and that's the difference between type II and type III hypersensitivity reactions.

### **Why we have precipitation?**

-We know that antibody will interact with antigen forming immune-complex that will get bigger and forming lattice then we get precipitation.

### **The magnitude of type III hypersensitivity reaction depends on certain factors:**

#### **1-The size of immune-complexes:**

- Large-sized immune-complexes will be recognized quickly by macrophages as foreign bodies and they will be engulfed.

-Small-sized immune-complexes remain in the solution without a problem.

-Intermediate-sized immune-complexes are difficult to remove by phagocytosis and they will precipitate (are the one that causes type III hypersensitivity reaction).

- The size has something to do with deposition of immune-complexes in the blood vessels.

#### **2-the charge:**

-We have positively charged immune-complexes they will attach to negatively charged areas and vice versa.

Charged cationic antigens have tissue-binding properties, particularly for the glomerulus, and help to localize complexes to the kidney.

### **3-hemodynamic factors:**

-as the blood passes through the blood vessels it will reach a small network of capillaries where the movement of blood is slowed down and this allows the immune-complexes to precipitate at the terminals, and these networks are present in the kidneys, abundantly in glomeruli.

Renal Glomeruli: are networks of capillaries that perform the first step of filtering the blood.

-Very often, manifestations of immune-complex diseases are related to the kidneys.

-Also the symptoms may present in the joints or the skin.

- Systemic manifestations of immune-complex diseases are also present like fever, malaise ...etc.

### **4-deficiency of complement:**

*HOW can deficiency of complement predispose to immune-complex diseases?*

-as we know, C3b binds to immune-complexes and splits Fc-Fc interactions preventing them from precipitating or if had already interacted and precipitated then it splits them and solubilizes them , and by this way it prevents lattice formation and precipitation of immune-complexes.

-by deficiency of complement there is an increase in the chance of precipitation of immune-complexes.

-Complement deficiency also increases the predisposition for development of autoimmune diseases.

### **5- RBCs:**

They clear immune-complexes from the serum because they have CR1 (complement receptor 1) on their surfaces, and when they go through the

blood stream they will pick up anything with C3b or C4b on its surface, then they go to the reticulo-endothelial system (in spleen and liver) where the antigens are cleared by macrophages there.

-remember: CR1 is the receptor for C3b and C4b.

-The prototype for localized type III hypersensitivity reactions is:

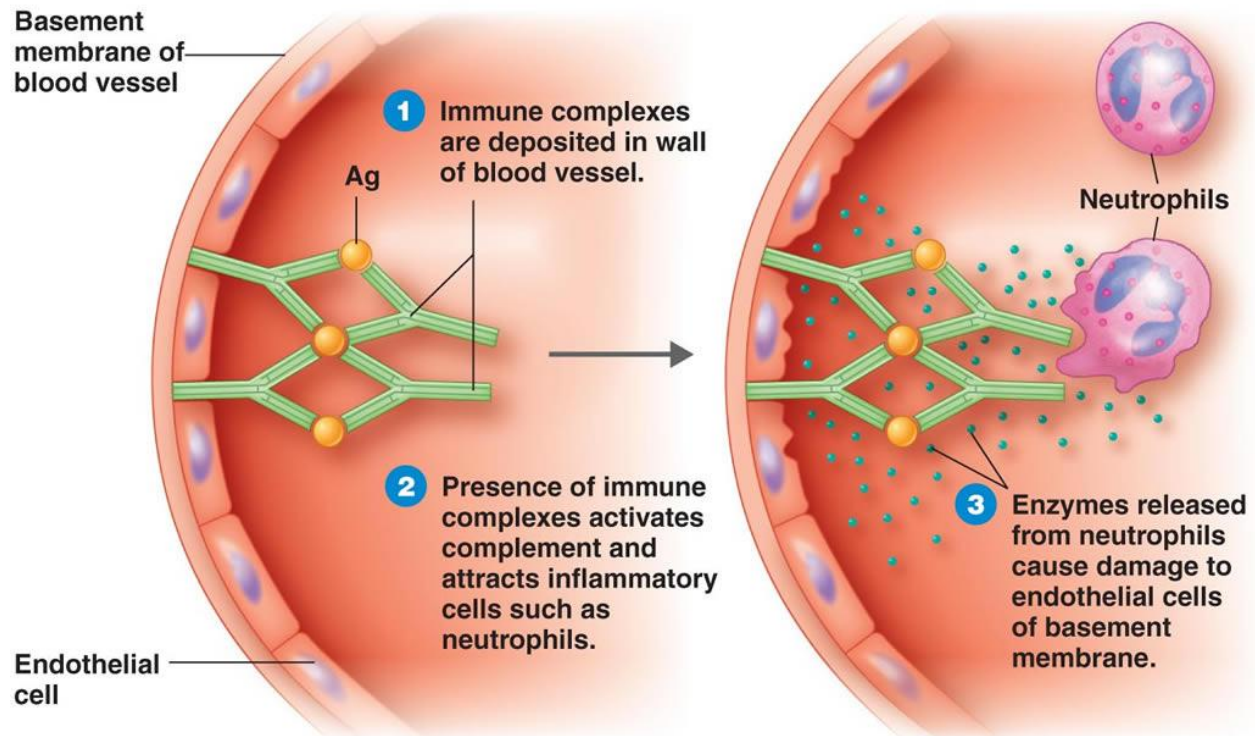
Arthus reaction: formation of immune-complexes at a localized site.
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- The other reactions are done experimentally on animals.

### **Method of Arthus reaction:**

- 1- We inject the antigen into the skin in one place.
- 2- We inject the antibody for that antigen intravenously in another place.  
(So we inject the antigen and the antibody in separate places).  
the antibody will circulate in the blood till it reaches to the area where the injection of the antigen took place, so there will be diffusion of the antibody through the blood vessels towards the antigen, then immune-complexes get deposited in vessel walls at the site of injection causing complement activation, that leads to inflammation (vasculitis) and sometimes necrosis at the area of injection of the antigen.

Depositions of these immune-complexes on vessel walls activates complement and attracts inflammatory cells like neutrophils.
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-It appears in a matter of hours, within 2-3 hours.

-Remember: in type I hypersensitivity the reaction occurs in minutes (immediate), but in type II and III the reaction needs hours before we get the symptoms of the disease.

## Other examples of type III hypersensitivity:

### 1-Serum sickness:

- Is an allergic reaction that develops due to the injection of antiserum that contains proteins derived from non-humans (animal sources).

-when we inject human antiserum our immune-system doesn't recognize them as foreign proteins, because humans' proteins are similar.

Serum: is the component that is neither a blood cell (serum does not contain white or red blood cells) nor a clotting factor; it is the blood plasma not including the fibrinogens. Serum includes all proteins not used in blood clotting (coagulation) and all the electrolytes, antibodies, antigens, hormones, and any exogenous substances (e.g., drugs and microorganisms).wiki

Antiserum: is blood serum containing antibodies that we use in passive immunization for many diseases.

- Passive immunization: we inject prepared antibodies.

- Active immunization: we inject an antigen in a way that doesn't produce a disease, and we allow the immune-system to produce antibodies against that antigen.

- Pool human serum: is the collection of humans' serums (from many people).

Because most of us were infected in the past or vaccinated, we have many antibodies against different diseases (like tetanus).

- we can use the collection of our serums that contain antibodies against many of diseases as antiserum for passive immunization of an infected patient who is not immunized against this infection.

- we use pool human antiserum for passive immunization for common diseases that affect many of us, like: tetanus , diphtheria, hepatitis B ....etc

- tetanus: is a disease that classically follows a puncture wound but can follow a skin trauma by an object contaminated with spores of clostridium tetani like soil.

For example: after an accident you may develop compact fracture that may be contaminated with soil which contain spores.

These spores will vegetate under the appropriate anaerobic conditions (necrotic tissues), from this location clostridium tetani releases its exotoxin which is called tetanospasmin that causes tetanus.

So if we have a patient who suffers from tetanus we clean the wound then treat him with antibiotics like penicillin and also by human antiserum that contains antibodies that neutralize tetanus toxin (from previous

vaccination), but we should use the pool human antiserum, not only from one person.

**-now, let's assume that we have a patient who was bitten by a snake, and as we know most of us were not bitten by a snake, and that means we do not have antibodies for the venom.**

**-so how can we get antiserum in this case?**

- By injection of antigen (venom) in repeated small doses (so we won't kill the animal) into a horse (or any other big animal), and the immune-system of the horse will produce antibodies against this venom, then we take the serum from the horse that contains antibodies specific for the injected venom.

- Now we can use this antiserum for this patient.

-Now, we take the horse antiserum, and then we inject it into the affected patient.

-the antibodies of the antiserum start to circulate in the blood but they will drop gradually, because they will be distributed in the body and some of them will be catabolized while others will neutralize the venom (and you will survive).

But at the same time the proteins in the antiserum will be recognized as foreign proteins and the body will produce antibodies against them, this does not happen when we use a human antiserum because we have similar proteins unlike animals. (the proteins in the antiserum are treated as antigens)

-the human antibodies will bind to the horse's proteins and produce immune-complexes that get bigger and larger in magnitude until they reach the right size and magnitude when they reach to zone of equivalence, then precipitate in different tissues like; skin, renal glomeruli and joints where they activate the complement and produce the symptoms.

-when you give the patient this antiserum you are saving his life from the venom but at the same time you are inducing serum sickness because of the foreign proteins (antigens) of the horse. But we have to save his life.

### ***Symptoms of serum sickness:***

- 1- Skin rashes.**
- 2- Glomerulo-nephritis (represented by hematuria, proteinuria).**
- 3- Arthritis.**
- 4- Fever.**
- 5- Not feeling well.**

-but eventually the immune-complexes are going to be cleared by reticulo-endothelial system, and then they will disappear because we have a certain amount of the antigens but we are still producing antibodies, so now we have free antibodies rising.

- The symptoms will disappear by the time that we clear up all immune-complexes.

### **2-post-streptococcal glomerulo-nephritis (PSGN):**

-When we get an infection by certain M types of streptococcus pyogenes, either in the skin or in the throat. (Usually rheumatic fever results from throat infection while glomerulo-nephritis can result from skin infection or throat infection).

-in this case We get infection by streptococcus pyogenes, then our immune-system will produce antibodies (against the bacteria's antigens), that circulate in the blood till they meet the antigens and combine with them to produce immune-complexes that settle in the kidneys producing glomerulo-nephritis.

-Once the antigen is cleared then the symptoms will disappear and everything will be fine.

-PSGN Mainly occurs in the children.

- PSGN does not recur but rheumatic fever does recur and that's why we put the patients with rheumatic fever under antibiotic therapy until the age of 20 or 22.

-PSGN only happens once and it does not produce any permanent damage to the kidney and the patient recovers and he never gets the disease again.



-PSGN is a type III hypersensitivity reaction secondary to the infection by streptococcus pyogenes, because the antigen of streptococcus is the one involved with the antibody in the kidney.

-many of the glomerulo-nephritic diseases are actually immune-complex diseases.

-Rheumatic fever is a type II hypersensitivity reaction because the antigen of the heart is involved with the antibody due to cross reactivity.

### **3-Rheumatoid arthritis:**

- is actually cell-mediated.

- But still some people believe that, someone who gets rheumatoid factor in the joint cavity activates complement, and produce inflammation in the joint.

(**Rheumatoid factor:** is immune-complex that is formed in the joint cavity by a combination between the antigen which is IgG and the antibody which is IgM).

-rheumatoid arthritis is type IV hypersensitivity reaction if it is cell mediated.

-rheumatoid arthritis is type III hypersensitivity reaction if it is mediated by immune-complexes.

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### **Type IV hypersensitivity:**

-is cell-mediated.

-blood cells like T-lymphocytes, macrophages and cytokines (to help them work) are the factors that are involved in pathogenesis of type IV hypersensitivity reaction.

-if you get the production of antibodies by chance in this type they have no consequences even complement has nothing to do with this type.

-The prototype for type IV hypersensitivity reaction is granuloma or tuberculin test.

## ***Tuberculin test:***

- We use PPD (purified protein derivative).

-tuberculin: is a mixture of proteins from mycobacteria (the ones we need) that is probably contaminated with other structural components of mycobacteria (not pure, that's why we don't use it anymore, we use PPD instead).

## **How can we get PPD?**

1-We collect proteins from mycobacteria (tuberculin).

2-We purify these proteins because they are contaminated with other components of mycobacteria.

## **Method of tuberculin test:**

1- We inject PPD intradermally.

2- We tell the patient to come back after 2 days. Because as you know type IV hypersensitivity is the delayed type of hypersensitivity reaction, because the cells need a long time to prepare themselves and to migrate to the site of the injection.

- Usually the appearance of the symptoms from type IV hypersensitivity reaction needs 24-48 hrs.

- If the tested patient comes back and he has an induration (hard swelling at the site of injection (the hardness is due to accumulation of the cells like macrophages and T-lymphocytes)) with erythema around it, this indicates positive test.

-In the wheel and flare of type I hypersensitivity reaction, the swelling is soft and like a gel, Due to extravasations of fluids (made of fluids).

-If the patient shows reaction to PPD, the patient is allergic to mycobacteria tuberculosis, because he has been exposed at some stages of his life to the antigen of mycobacteria.

- If the antigen persists and goes on and on, this induration will become granuloma.

- Granuloma: is specialized type of chronic inflammation that contains macrophages, T-lymphocytes and giant langhans cells, caseation and fibrosis.
- Granuloma is not limited only to TB also it occurs in other diseases like sarcoidosis, leprosy, allergic pneumonitis ....etc.
- tuberculoma is the granuloma of TB.

**If the patient is positive for PPD, this means one of the following:**

1-this patient may had tuberculosis at some stage of his life, and he was treated and cured.

2-this patient may have been infected by tuberculosis, and the area of the lung that is affected underwent fibrosis and the bacteria is still there but he does not suffer from any disease (most of cases are like that).

*-during the childhood we acquire the disease, but primary TB heals itself and then becomes contained within fibrous capsule within the lung for the rest of your life and have nothing to do with tuberculosis).*

*-Some peoples show reactivation of tuberculosis and this is known as post-primary TB.*

3- This patient may have active disease.

4-the patient is vaccinated.

- Because we were vaccinated during our childhood, if we tested for TB we will show a positive results.

-This vaccine is BCG (Bacillus Calmette–Guérin), that contains a live bacteria that is related to mycobacteria tuberculosis but it's not pathogenic.

In the past this vaccine was given to children at the age of 5-6 years.

But nowadays, we give it to babies during the first month of life (usually within 1-2 weeks after birth)

**Other examples on type IV hypersensitivity:**

**1-contact dermatitis:**

-this happens when you wear some bracelet or a watch that contains certain metals like nickel or when you wear a rubber or latex gloves, the atoms precipitate on your skin and you get type IV hypersensitivity reaction.

- It looks like eczema.

-But contact dermatitis is type IV hypersensitivity, and the inflammation of skin develops at the site of contact with allergen (like: watch, bracelet).

-the symptoms will disappear just by removal of the allergen.

-Eczema is type I hypersensitivity and allergen is ingestible (we eat it). .

### **How can we test for contact dermatitis?**

-By patch test.

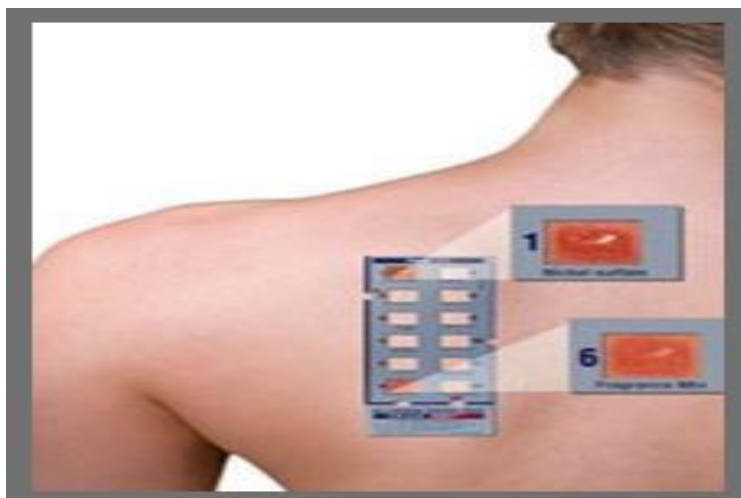
#### **Method of patch test:**

1-We bring a patch that contains many areas; each one has a separate known allergen.

2-We take this patch and we put it on the skin of the patient, and we tell him to come back after day or two.

-When he comes again we take off the patch and we look at the region of skin where the patch was.

- If there is induration and type IV allergic reaction, that means that this patient is allergic to that antigen, also by this way we identify the offending allergen.



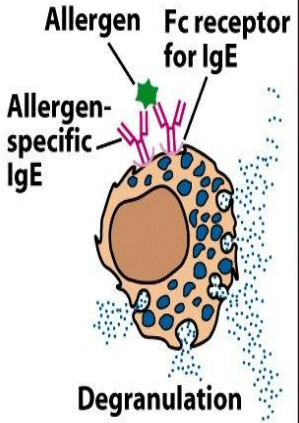
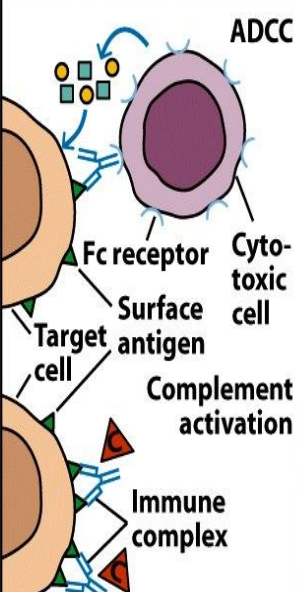
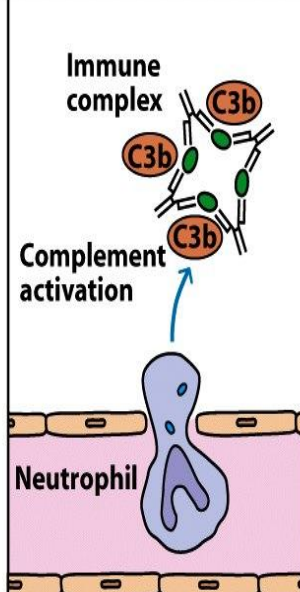
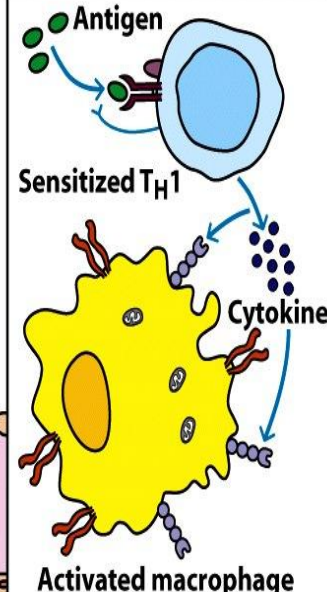
## **2-Allergic pneumonitis:**

- is an allergic reaction that affects the lungs of workers (industrial disease).
- Because those workers are continuously exposed to the site of work, they have continuous supply of certain allergens like moldy hay (molds will release spores that come into your lungs), dropping of pigeons and humidifiers (steam generated by a machine from water to increase humidity).
- Allergic pneumonitis is not like asthma.
- Asthma involves the bronchi and airways passages
- Allergic pneumonitis involves alveoli, and -in acute stages- it may resemble asthma, but when it becomes chronic it leads to fibrosis and destruction of alveoli and eventually leads to respiratory failure.
- Allergic pneumonitis is type IV allergic reaction because the main lesion caused by cells.
- Some say that there is involvement of type III hypersensitivity reaction because in the initial stages you may have production of antibodies against these allergens but they don't play a role in the destructive lesions of allergic pneumonitis.so allergic pneumonitis is really type IV hypersensitivity, because the main lesion is cell-mediated.

## **3-Photo-allergy:**

- in this case the allergen comes in a contact with skin, but only affects the areas that are exposed to the sun light like sun-barrier creams or cosmetics (creams), allergens need sun light to produce allergy.

For example: when you apply sun-barrier cream to the area of the skin that is exposed to sun like your face then, you may develop allergic reaction.

 <p><b>Type I</b></p>	 <p><b>Type II</b></p>	 <p><b>Type III</b></p>	 <p><b>Type IV</b></p>
IgE-Mediated Hypersensitivity	IgG- or IgM-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
Ag induces cross-linking of IgE bound to mast cells and basophils with release of vasoactive mediators.	Ab directed against cell surface antigens mediates cell destruction via complement activation or ADCC.	Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils.	Sensitized TH1 cells shown above release cytokines that activate macrophages or TC cells that mediate direct cellular damage. TH2 cells and CTLs mediate similar responses.
Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema.	Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia.	Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus.	Typical manifestations include contact dermatitis, tubercular lesions, and graft rejection.

**Figure 15-1**  
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Done by : Jamil ennab.

Thanks for Marwan abu ezghareet.

Good luck 😊