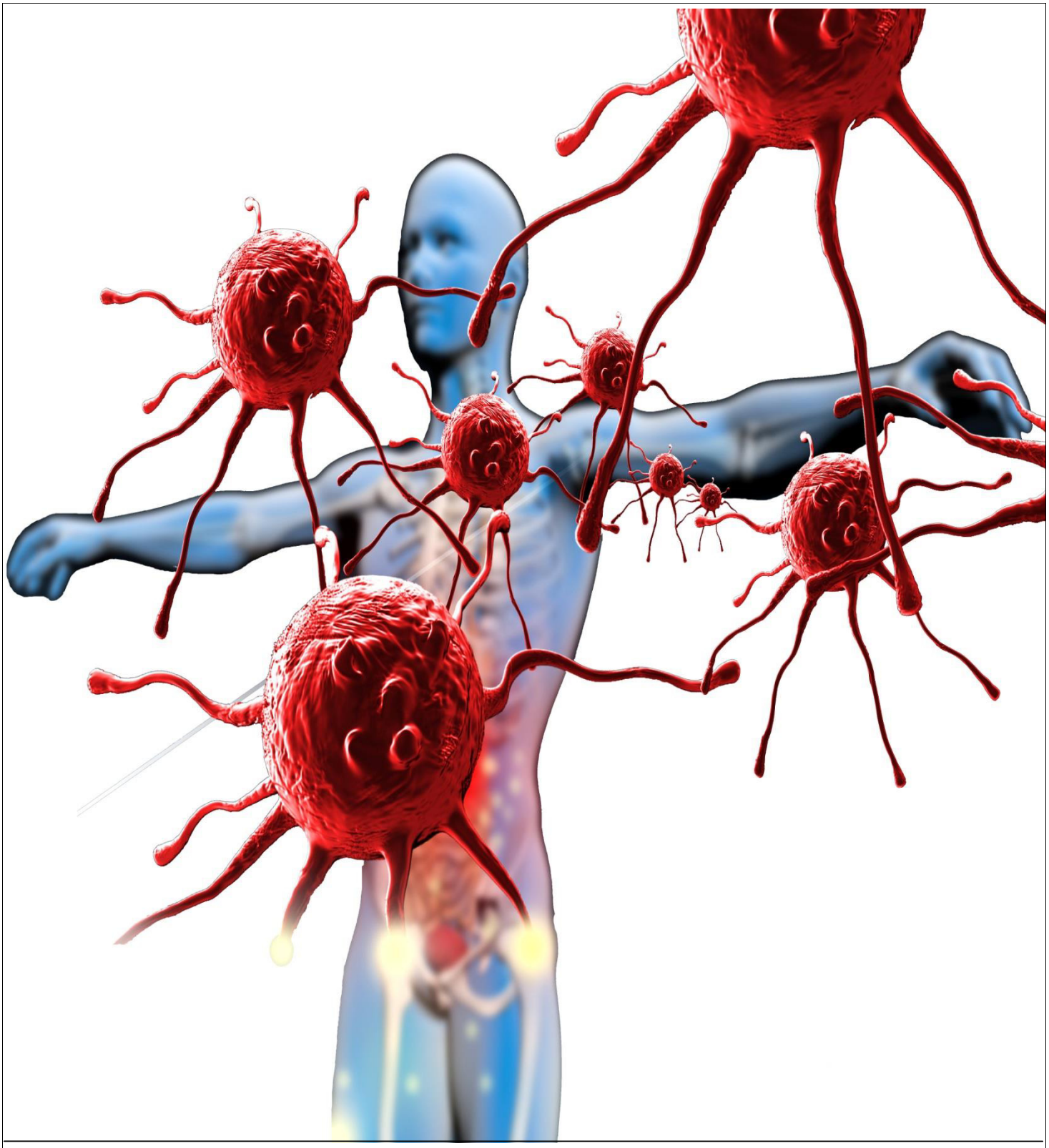

IMMUNOLOGY

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#16

By Mohanned Nawaiseh

Hypersensitivity

•this sheet was written according to sec1&2

•I've rearranged a lot and a lot of information here and there and I've rephrased a lot of things as well, so please don't be confused when referring to the original recording

•also, this sheet needs 2 hours studying; if you finished it in less than that you're awesome.

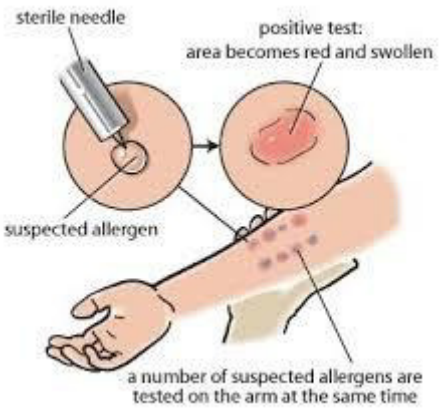
First, we are going to talk about 3 allergy tests

1) Skin testing 2) Specific IgE serum test 3)skin patches

♦skin testing

Sometimes In the clinic, before giving the patient IV injection we have to do this test to avoid anaphylactic shock. Same applies for patient with suspected allergy to some antigens (for example cat's fur) we do this test to confirm.

So what we do here is that, we take a drop of that solution and put it on the patient's skin (on his arm), and then we take a needle and inject the tip of it into that area, by that we make sure we've only introduced a very small amount of that antigen into his arm.



If the patient is allergic to that specific antigen, he'll develop localized inflammatory reaction (10mm in diameter) within minutes (20-30)

But what if the patient is allergic to that needle? Or if the patient has a problem in his normal inflammatory respond? Then false positive or false negative results will appear. To solve this problem we use positive and negative control;

- the positive control is usually a histamine solution.
- the negative control is usually a saline solution.

What we do here is, we put a drop from each control on the patient's skin and then we stick a needle at the middle of each drop; normally at the site of the positive control should come positive (i.e. should develop a localized redness and swelling) and the negative control should come negative, if not then there is a problem and we can't use this test.

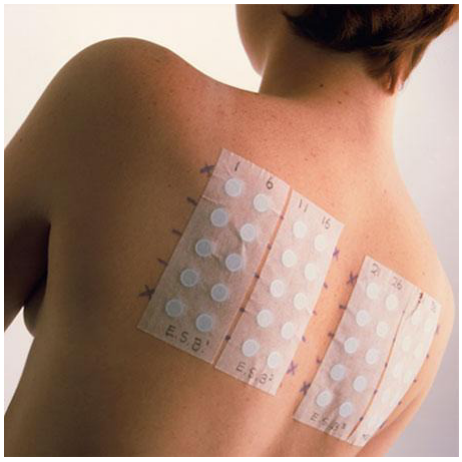
♦ Specific IgE serum test

In this test we are more concerned with the antibodies, so if we for example are suspecting an allergy from "X" antigen, we take a serum sample from the patient and put it on a filter paper, after that we wash it. If the patient has IgE for that specific antigen it will stick on the paper after the wash out process. How to detect those antibodies? We use a radioactive anti IgE and apply them on the paper, after a second wash we put this paper in a gamma counter machine to see how much is still attached there.

Notice that this is a qualitative and a quantitative method; known as radioallergosorbent test (RAST)

♦ Skin patches,

This test is quite simple actually, you take a box patch and stick it on the patient's back, this box patch contains different areas for different antigens, when sticking it on the patient you are actually introducing these antigens on his skin. After several hours –maybe 2 days- you check for any inflammatory reaction to know which one of these antigens is causing it.



Hypersensitivity type 2

This type is associated with autoimmune diseases; it's mediated by (IgG & IgM) and with complement involvement. The destructive effect happens from the complement system after their binding. Most of the times the antigens are part of the tissue or cell membrane, that's why the attack causes a destructive effect for the organs.

Some of the diseases which are associated with Hypersensitivity type 2 (the doctor didn't mention then in sec1)

- Haemolytic Anaemia
- Goodpasture's syndrome: where the basement membrane of the vessels in the lung and kidney is attacked by one's own antibodies
- thrombocytopenia: when those Abs are directed against platelets

Of course since we always have these antibodies, such activation is always there and this is the pathophysiology of autoimmune diseases.

♦Here are some conditions which are explained by hypersensitivity type2;

- it's not actually an autoimmune disease, it happens **in incompatible blood transfusion**, when the (anti-A and anti-B) antibodies attacks the antigens on the transfused blood cells causing fatal outcomes.

- **Rh-incompatibility**; again, it happens when antibodies attacks antigens on the transfused blood cells. You may not have the complementary system activated in this condition, mainly because the D antigens on the RBCs membrane are scattered away from each other. So what happens here is an opsonization reaction rather than cell lysing, and then these RBCs get phagocytosed in the spleen.

Hypersensitivity type 3

Occurs when immune complexes (antigen-antibody complexes) that are not adequately cleared by innate immune cells accumulate, giving rise to an inflammatory response and attraction of leukocytes (forming a granuloma). As expected, the antibodies are usually IgG & IgM but unlike Hypersensitivity type2 the antigen is not a part of the tissue or the cell e.g. streptococcal glomerulonephritis; its antigens circulate in the blood stream, after their reaction with human Abs they settle in the kidney; the complementary activation and the following damage happens there causing glomerulonephritis.

So as you can see the poor kidney has nothing to do with the antibody and it doesn't even express the antigen, but yet it's the site where all the destruction happens. That's why we call it immune complex disease,

The prototype of Hypersensitivity type 3 is known as **arthus reaction**

Arthus reaction

It Is a local type III hypersensitivity reaction, most commonly seen after intradermal injection of an antigen.

The experiment was first made by repeatedly giving subcutaneous injections to a rabbit(can also be done by injecting the antigens intradermally and injecting its specific antibodies intravenously), it has been noticed that at first when giving the first injection- i.e introducing the antigen for the first time- nothing happened! Later on after several injections an inflammatory reaction has been developed at the site of injections. The same reaction will be developed in human when given the same vaccine intramuscularly.

What's the explanation? At first the body has formed antibodies against the antigen, later on –in the second injection- those antibodies traveled through the circulation reaching the newly introduced antigens and start attacking them forming immune complexes, their deposit at the site of the second injection causes an inflammatory reaction.

Now, why these immune **complexes do settle down?**

4Reasons

•Certain **concentration** of Abs and Ags &the **size of the complex**, remember from sheet7 the curve which shows the zone of equivalence, as you recall; when the **concentration** of Ags =Abs the formed complexes will be precipitated. Keep in mind if Ags >Abs then the complexes will be water soluble and do not precepetate.
Size of the complex; if it's too large(especially with excess Abs) it'll be phagocyted, if it's too small it'll not bind easily with each other, so only moderate and intermediate complexes will precipitate and have an actual effect.

•**Charge**: for example, antibodies **against DNA** has got a Predilection to settle in the basement membrane on the small vessels in the kidney, that's why in autoimmune diseases like in **lupis**; antibodies against DNA settle in the kidney causing glumeronephritis, the patient may die only from **renal failure**.

•Inherited **deficiency** of some **complementary components**, like in C2 C1 C4 causing a decrease in the clearance of those complexes thus help in their precipitation

•**Hemodynamic**; in small vessels, where the flow is delayed. so the kidney , joints and skin are more susceptible to this complement system precipitation.

<Glumeronephritis: can also be caused by hypersensitivity type 2 against RBCs and platelets. >

Serum sickness

• Describes a delayed immune system response, either to certain kinds of medications or Antidotes (given to a person whom has been bitten by a snake or has been exposed to rabies) Serum sickness is similar to an allergy, in that the body mistakenly identifies a protein from the antiserum or medication as harmful antigens and activates the immune system to fight it off

• It is manifested by fever, joint pain, malaise and renal problems. It is usually resolves by itself.

• Serum sickness will usually develop within 7 to 10 days after initial exposure, but sometimes it can take as long as 3 weeks.

If you are exposed again to the substance, serum sickness tends to develop faster (within 1 to 4 days), and only a very small amount of the substance may cause an intense response

•Serum sickness is considered the prototype of hypersensitivity type2

Antidote:

It's a substance which can counteract a form of poisoning (e.g. snake or scorpion venom) , usually manufactured by injecting the toxin into an animal in small doses and extracting the resulting antibodies from the animal's blood. We use horses mainly, although it is possible to use another human being for this process.

So in the case of antidote you're actually giving the patient someone's else serum, and using his antibodies as an antidote for your patient, but sometime the body mistakenly recognizes these newly introduced immunoglobulins as a harmful antigens, this

happens after the recovery. The thing is, at first, your body benefits from those immunoglobulin in fighting the venom, but then, your ungrateful body selfishly fight these same immunoglobulins which saved his life.

Let's revise,

- you got **infected with some harmful antigens**, could be from diphtheria, tetanus or snake venom,
- we give **you a serum containing antibodies** to fight these antigens,
- after a while when you **are fully recovered** your body starts producing **antibodies against those immunoglobulns** which helped you in the first place,
- this will form **immune complexes**; those immune complexes will start to deposit into your vessels causing what is known **as serum sickness**

Keep in mind that this sickness is caused by hypersensitivity type 3

In like 2 weeks or something, the concentration of these complexes will decrease due to their distribution in your body and your normal catabolism.

Keep in mind that when your body starts producing antibodies against the antidote you had, those antibody can't be detected in your serum because they'll immediately bind with their antigens

As we said before, the serum is manufactured from horses, but it also can be taken from human beings, you simply take a sample from more than one vaccinated individual and mix them all together → and give this mixture to your patient. This is better because it causes less allergic reaction than animal's serum**. But also keep in mind that there is no vaccine for venoms, so this method is only applied when trying to treat an infection –like TB for example-**

Hypersensitivity type 4

This is the last type of Hypersensitivity, although in wiki there is type 5 :p

Type 4 hypersensitivity is often called " delayed hypersensitivity" as the reaction takes two to three days to develop. Unlike other types, it is not antibody mediated but rather is a type of cell-mediated response (including t-helper, cytotoxic t cells and macrophages)

It deals with intracellular infections, caused by bacteria; especially mycobacteria e.g. TB and some parasites e.g. leishmania. Here, the antigens are taken up by macrophages but they are not being ingested because they are resistant, so they survive inside the macrophages. The macrophages in this case asks for help, by producing IL12 to attract TH1 cells which in turn will attract other macrophages, now these macrophages will accumulate, and some of them will fuse together forming giant cells (langerhans cells)

so all of these cells at the site of the lesion case a necrotic effect in its center → later on this will develop caseation necrosis (granuloma)

•so here as you can see, granuloma is the prototype of type 4 hypersensitivity

Again, this type of hypersensitivity is involved in intracellular antigens and tissue graft injections. It's also the cause of developing some types of allergies;

- rubber or latex gloves; most seen in surgeons
- Cheap jewelry (nickel and chromium); the swelling and redness will appear at the site of contact
- some creams, like(Neomycin antibiotic-wiki)

Another example of hypersensitivity type 4 reaction is a skin test you can do to test for mycobacteria called;

PPD test (purified protein derivative).

To identify mycobacterial antigens, what we do here is actually we give an intradermal injection, wait 2 days then if the patient has an allergy or type 4 hypersensitivity reaction then swelling and induration will appear. In type one the swelling is actually soft because it's mainly fluids, unlike the swelling in type 4, it's actually hard and indurated because it' made mainly of cells (macrophages and t-lymphocytes).

Now a positive PPD test can mean one of three things;

- ♦You are in fact infected with TB
- ♦You had it once and were treated and cured
- ♦You have taken BCG vaccine

Bacillus Calmette–Guérin (BCG)

is a vaccine against tuberculosis

It is prepared from a strain of the attenuated (virulence-reduced) live bovine tuberculosis bacillus, *Mycobacterium bovis*, that has lost its virulence in humans. Because the living bacilli evolve to make the best use of available nutrients, they become less well-adapted to human blood and can no longer induce disease when introduced into a human host. Still, they are similar enough to their wild ancestors to provide some degree of immunity against human tuberculosis.

End of the sheet ☺ done my Mohanned Momani

And a special thanks goes to Raja'i Zurikat and Zakaria W. Shkoukani for giving me their feedback and help in improving this sheet.

عبد الحافظ صالح dedicated to