AZERBAIJAN MEDICAL UNIVERSITY
DEPARTMENT OF MEDICAL MICROBIOLOGY and IMMUNOLOGY

Lesson 21.

Immunopathology. Immunodeficiency. Hypersensitivity reactions and their types. Autoimmune diseases. Skin-allergic reactions, their application in microbiological diagnosis

FACULTY: General Medicine
SUBJECT: Medical microbiology - 1

Discussed questions:

1. Information on the pathology of the immune system: hypersensitivity and immunodeficiency.

2. Immune deficiencies: congenital (primary) and acquired (secondary).

2.1. Congenital defects:

- Deficiency of T-lymphocytes.
- Deficiency of B-lymphocytes.
- Deficiency of T- and B-lymphocytes.
- Lack of complement system.
- Phagocyte deficiency.

2.2. Acquired immune deficiencies:

- Deficiency of B-lymphocytes.
- T-lymphocyte deficiency (acquired immune deficiency syndrome).

3. Autoimmune diseases.

4. Hypersensitivity reactions:

- Type I (anaphylactic type) hypersensitivity reaction: anaphylaxis, atopy, drug allergy.
- Type II (cytotoxic) hypersensitivity reactions.
- Type III (immune complex) hypersensitivity reactions. Arthurian phenomenon, serum sickness.
- Type IV (delayed) hypersensitivity reactions. Infectious allergies, contact allergies, drug allergies.
- *In vivo* and *in vitro* allergy tests and their application.

Purpose of the lesson:

- To inform students about immunopathology, primary and secondary immune deficiencies, hypersensitivity reactions (allergic reactions), their application in microbiological diagnostics.

Immunopathology.

- **Autoimmune diseases**
- **Immunodeficiencies**
- **Hypersensitivity reactions**

Immunodeficiencies

Immune deficiencies can be congenital and acquired.

Immune deficiency in any of the 4 main components that make up the immune system:

1. B-lymphocyte system (antibodies),
2. T-lymphocyte system,
3. complement system,
4. it can develop as a result of disorders occurring in phagocytes.

Clinically, opportunistic or recurrent infections are more typical at this time.

Recurrent infections caused by pyogenic bacteria, mainly B-lymphocyte deficiency,

Recurrent fungal, viral, or protozoan infections are typical for T-cell deficiency.

Autoimmune diseases

- In the elderly, tolerance is usually observed against antigens that have been exposed during the embryonic period and are known as "native".
- In some cases, tolerance is lost and an immune response is formed by the immune system against the body's own antigens, in other words, an autoimmune disease is formed.
- In the pathogenesis of autoimmune diseases, the interaction of the components of the immune system with their own healthy cells and seeds is stopped. Autoimmune diseases are sometimes referred to as immune complex diseases. Many diseases whose pathogenesis is based on autoimmune processes are known (autoimmune thyroiditis, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus (SLE) etc.).

Hypersensitivity reactions

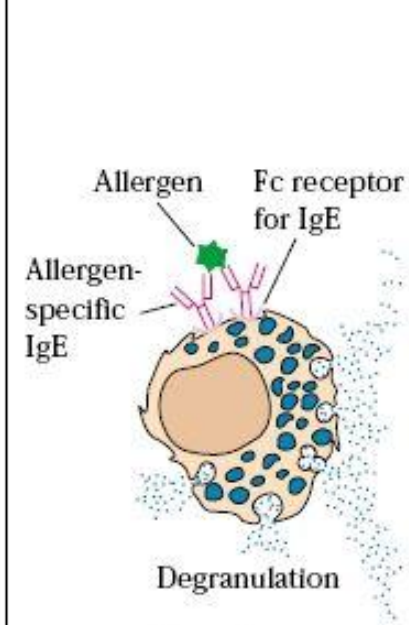
- When the immune response results in unusual, dangerous reactions for the body, the terms hypersensitivity (in English, hypersensitivity) or allergy (lat., allos-foreign, ergone-effect) are used.
- The clinical manifestation of these reactions is typical and characteristic in different individuals and occurs in individuals with high sensitivity to these antigens as a result of contact with specific antigens.
- As a result of the first contact of an individual with an antigen, sensitization occurs, and then repeated contacts with the same antigen cause the formation of allergic reactions.

Hypersensitivity reactions

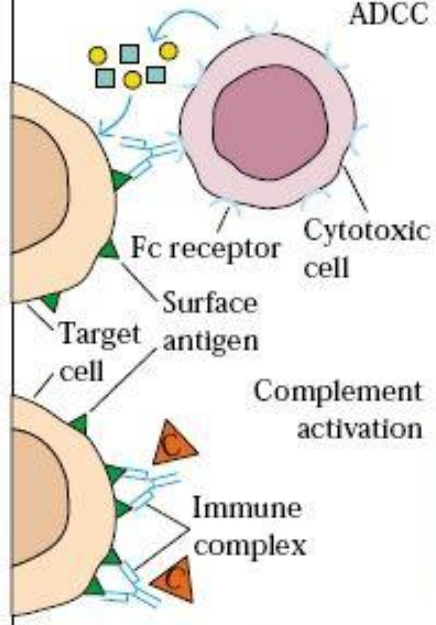
Hypersensitivity reactions are divided into 4 types.

Types I, II and III are activated by antibodies (B-lymphocytes). Type I reactions are related to IgE, and type II and III reactions are related to IgG.

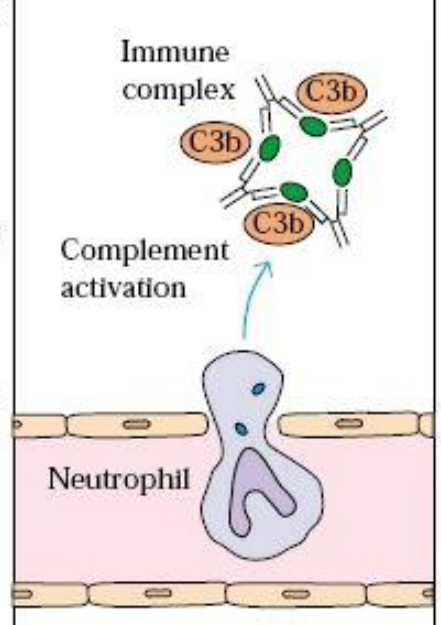
Type IV reactions are related to sensitized T-lymphocytes.



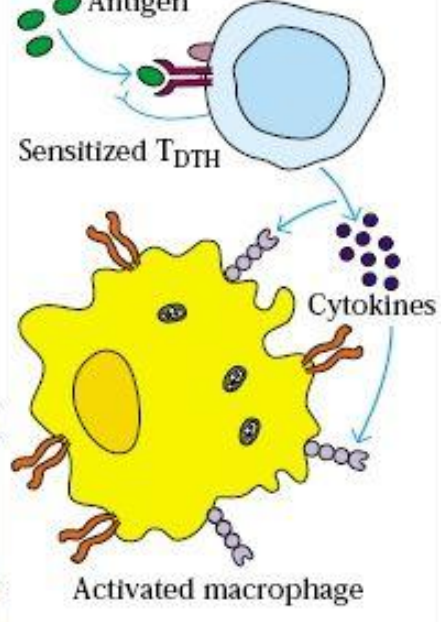
Type I



Type II



Type III



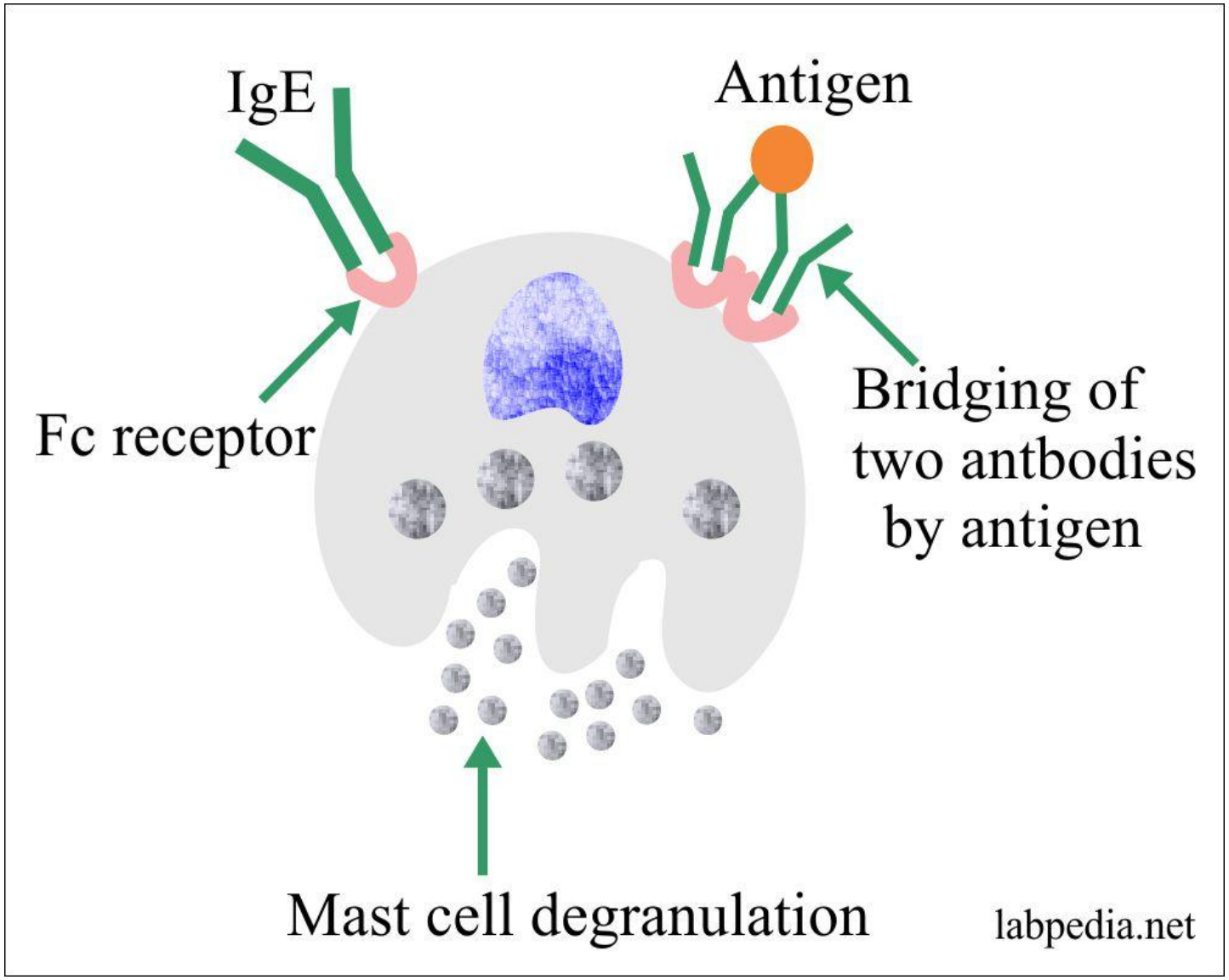
Type IV

IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
Ag induces crosslinking of IgE bound to mast cells and basophils with release of vasoactive mediators	Ab directed against cell surface antigens meditates 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 T_H1 cells release cytokines that activate macrophages or T_C cells which mediate direct cellular damage
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, glomerulnephritis, rheumatoid arthritis, and systemic lupus erythematosus	Typical manifestations include contact dermatitis, tubercular lesions and graft rejection

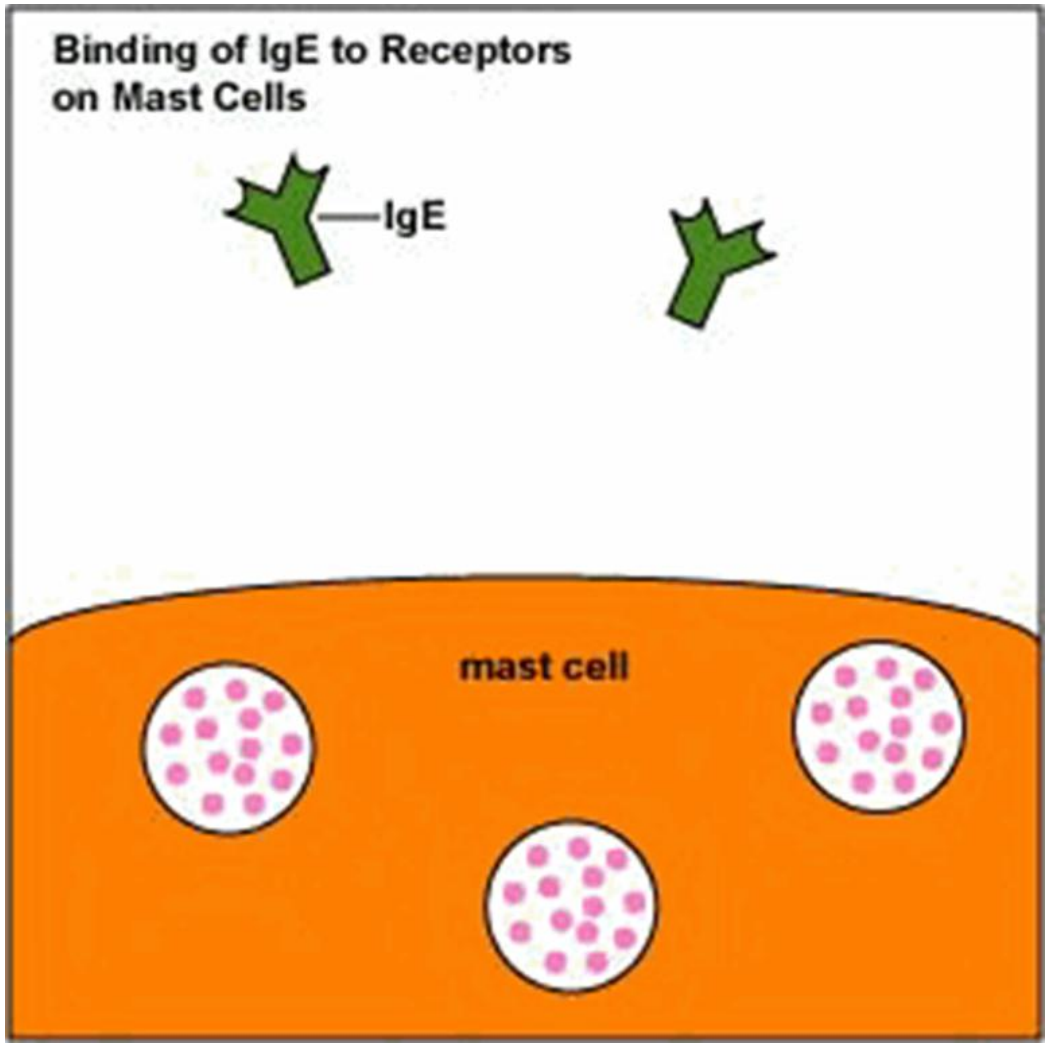
Type I (anaphylactic type) hypersensitivity reactions

- An immediate hypersensitivity reaction occurs under the influence of a number of mediators released as a result of the combination of antigen with IgE on the surface of cells.
- The process is formed as a result of the induction of IgE antibodies by the antigen and their binding to the surface of basophils and immune cells through the Fc fragment. This situation is called sensitization.
- Repeated contact with the same antigen and its combination with IgE on the surface of basophilic or immune cells results in the release of biologically active mediators from these cells within 1 minute (immediate reaction).

Type I (anaphylactic type) hypersensitivity reactions



Type I (anaphylactic type) hypersensitivity reactions



Clinical signs of type I hypersensitivity

- Clinical signs of type I sensitivity are in various forms, for example, atopy, allergic rhinitis, or Quincke's edema, allergic eczema, allergic rhinitis, allergic conjunctivitis, or hay fever, allergic asthma, etc. who can manifest.
- However, the most severe form of sudden type hypersensitivity manifests as anaphylaxis. At this time, severe bronchospasm and hypotension (shock) can be life-threatening.

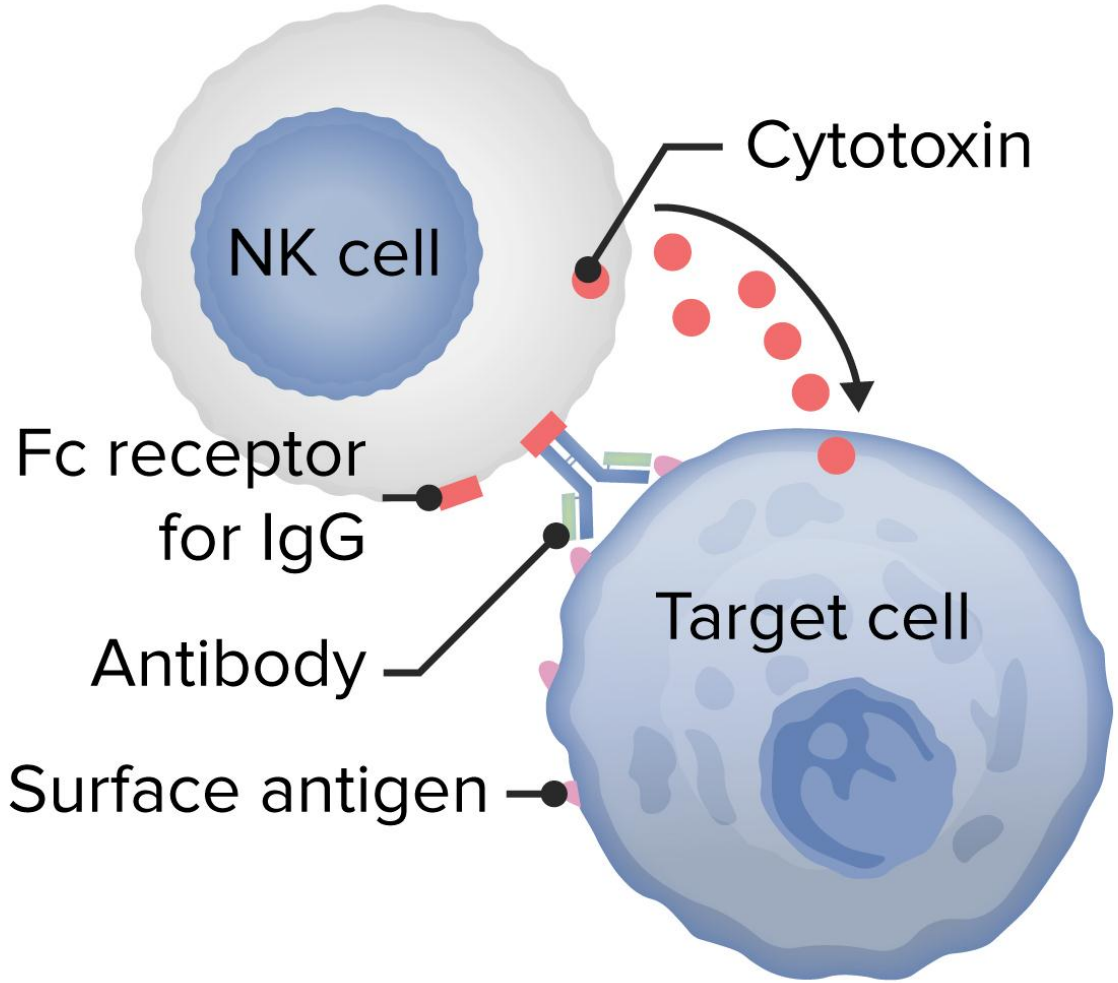
Desensitization

- It has been determined that the introduction of small doses of allergens into the body results in the weakening or loss of hypersensitivity.
- Since the antigen-IgE complex is formed in a small amount at this time, not enough mediators are produced for the formation of strong allergic reactions. This situation, which is the opposite of sensitization, is called desensitization. It is possible to prevent systemic anaphylaxis through it.
- This method (Bezredko method) allows to prevent allergic reactions during the use of some medicines, especially immune serums.

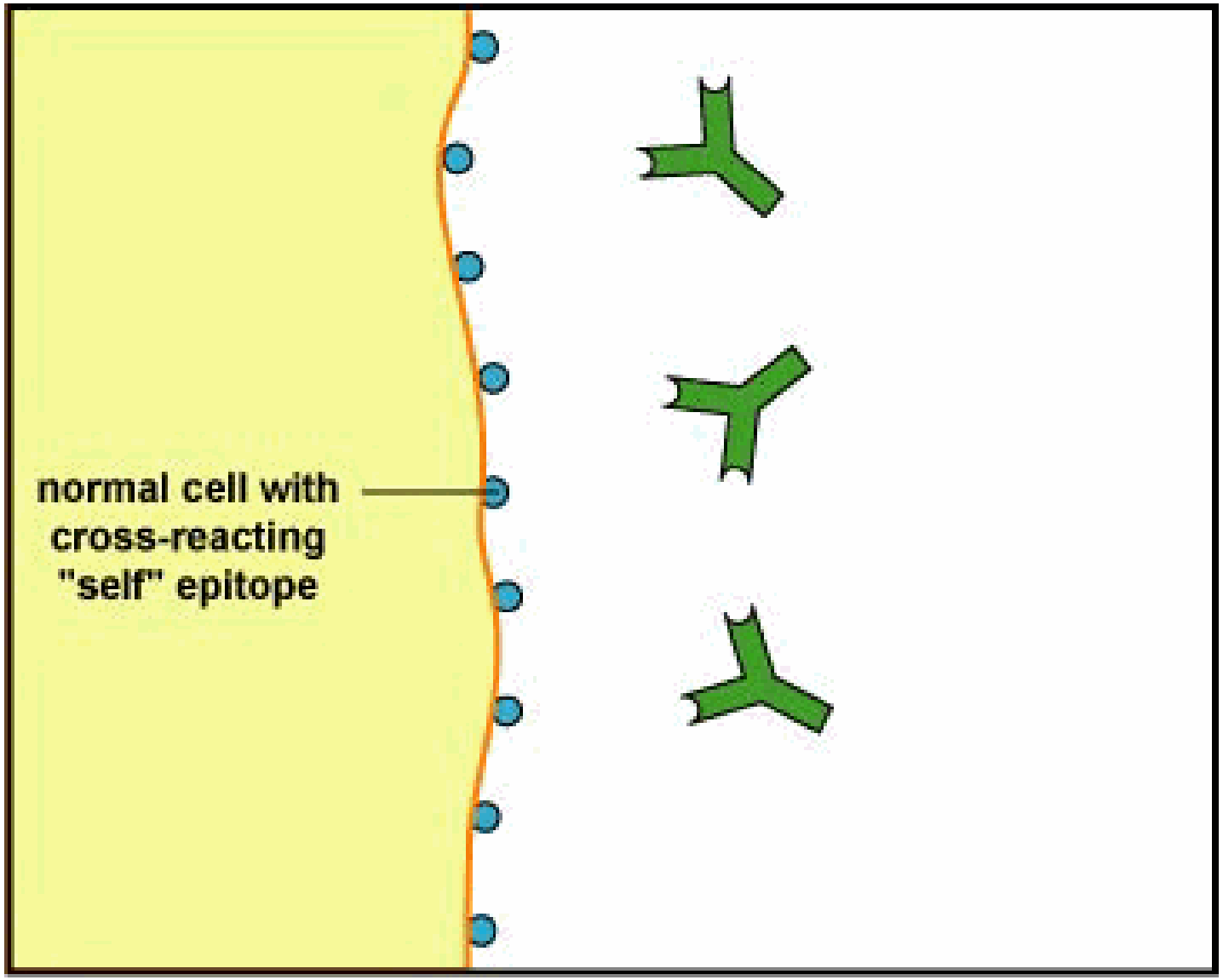
Type II (cytotoxic type) hypersensitivity reactions

- Cytotoxic type hypersensitivity occurs as a result of the combination of antibodies formed against cell membrane antigen with this antigen and activation of complement.
- The antibody (IgG) binds to the antigen through the Fab-fragment, and to the complement through the Fc-fragment. This leads to the production of the complement membrane binding complex and damage to the cell membrane.
- As a result, hemolytic anemia-type complement-mediated lysis occurs, as in blood transfusion reactions incompatible with the ABO system or the Rhesus factor.

Antibody-dependent cellular cytotoxicity



Type II (cytotoxic type) hypersensitivity reactions



Type III (immune complex type) hypersensitivity reactions

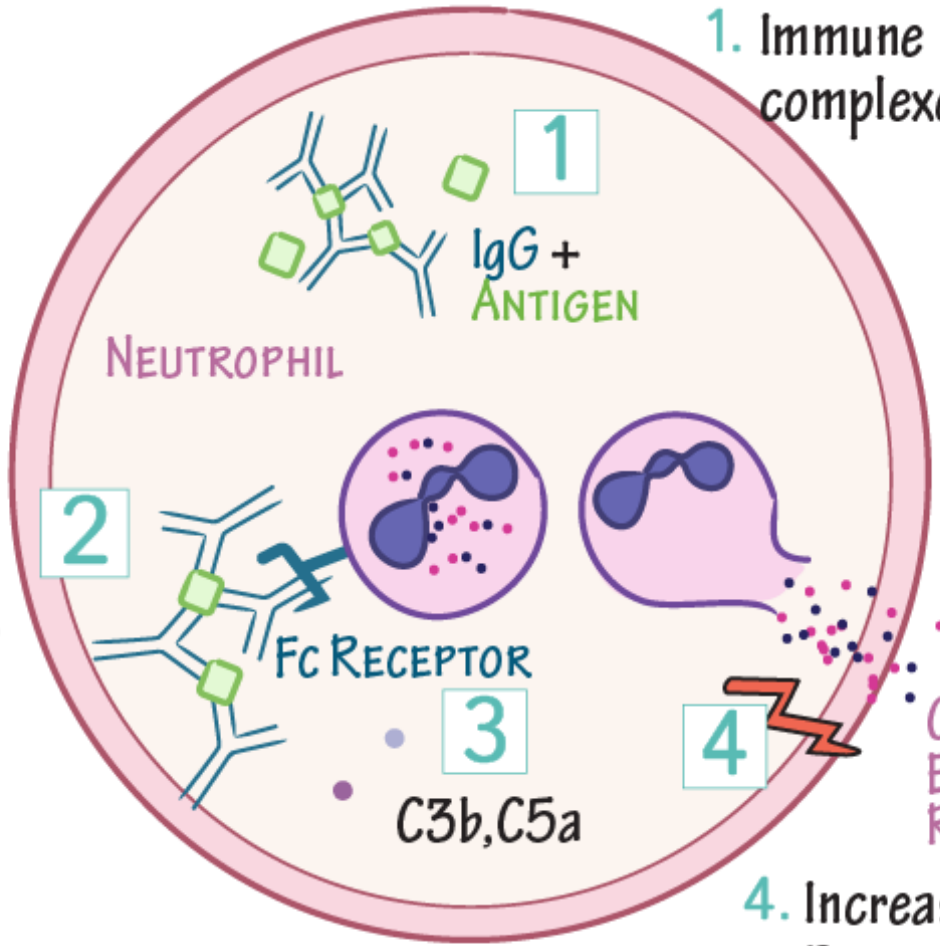
- Immune complex-type hypersensitivity is characterized by antigen-antibody complexes causing inflammatory processes in tissues.
- Normally, immune complexes are removed from the body through the reticuloendothelial system, but sometimes they are retained in the body and cause a number of diseases in the tissues.
- In persistent bacterial and viral infections, immune complexes can accumulate in organs, such as the kidney, causing damage. In autoimmune disorders, "native" antigens (autoantigens) can induce the synthesis of autoantibodies.

Type III (immune complex type) hypersensitivity reactions

- It is observed that the latter combine with the relevant antigens, or form deposits as complexes in organs, especially joints (arthritis), kidneys (nephritis) or blood vessels (vasculitis).
- Deposition of immune complexes in tissues, for example, on the wall of blood vessels, activation of the complement system and chemotaxis of neutrophils to these parts is accompanied by inflammation and tissue damage (e.g., vasculitis).
- Type III hypersensitivity reactions include Arthus phenomenon and serum sickness.

IMMUNE COMPLEX-MEDIATED

IgG Antibody-Antigen Complexes



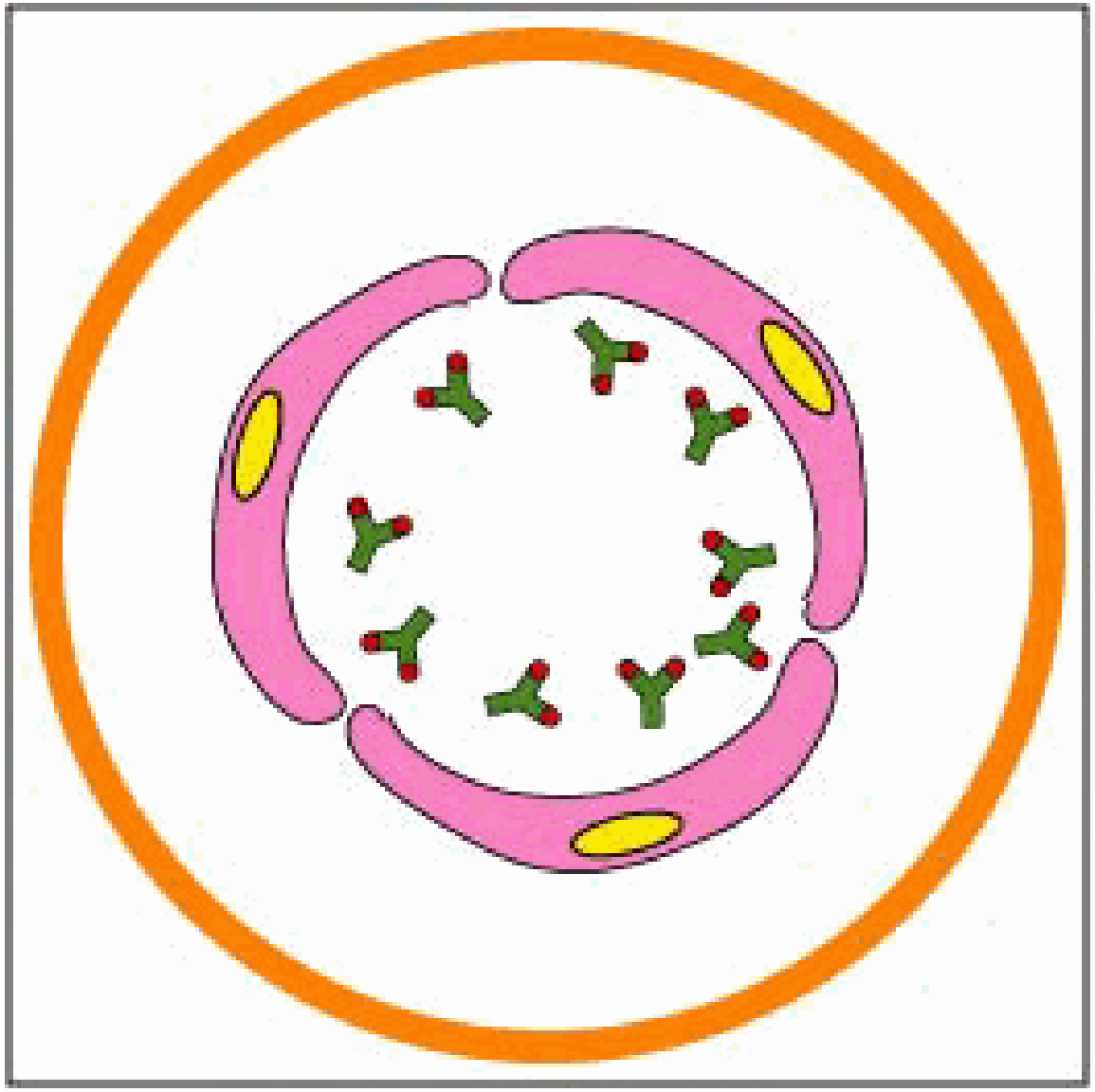
1. Immune complexes form.

2. Complexes deposit on vessel wall (or tissues).

3. Complement & Neutrophil activation, inflammation.

4. Increased Permeability -> Tissue damage.

Type III (immune complex type) hypersensitivity reactions



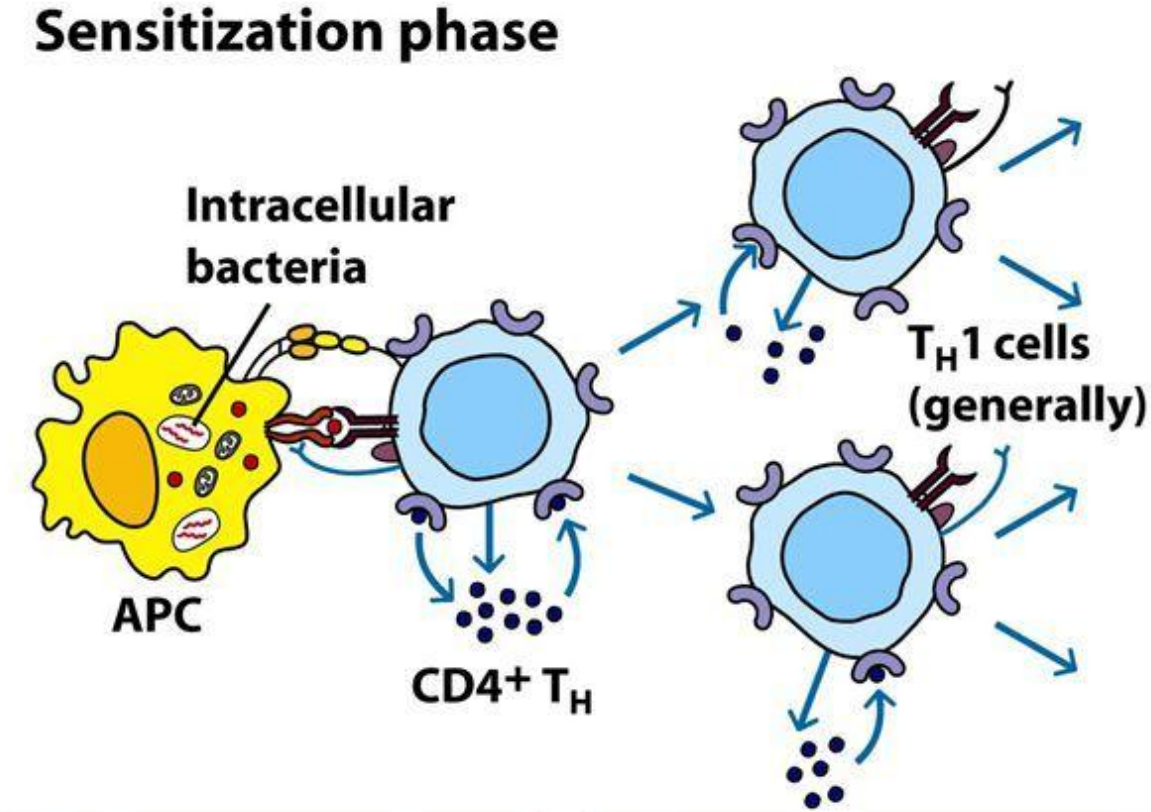
Type IV (delayed type) hypersensitivity reactions

- Delayed-type hypersensitivity (DTH) reactions are associated with T-helpers (CD4) and cytotoxic T-lymphocytes. DTH is a lymphoid-macrophage reaction and develops as a result of immune activation of macrophages by the effect of lymphocytes sensitized by allergen.
- Immune inflammation mechanisms are based on DTH: the antigen enters the body, undergoes phagocytosis by macrophages, breaks into small parts, and its fragments appear on the surface of macrophages in association with class II MHC. Antigen-II class MHC complex interacts with antigen-specific receptors on the surface of Th-lymphocytes. Th-lymphocyte activation and clonal proliferation occur due to IL1 produced by macrophages and IL2 synthesized by lymphocytes.

Type IV (delayed type) hypersensitivity reactions

- Sensitization - T-lymphocytes sensitized to the allergen are formed in the body
- The allergen is recognized by sensitized T-lymphocytes upon re-introduction.
- This leads to the synthesis of cytokines by sensitized T-lymphocytes.
- Due to the effect of cytokines, macrophages are activated and migrate to the area where the antigen is located.
- Destruction and elimination of allergen by macrophages.
- Infiltration and granuloma consisting of lymphocytes and macrophages are formed in the area where the allergen is located.

Type IV - Hypersensitivity



Antigen-presenting cells: Macrophages Langerhans cells

DTH-mediating cells: T_H1 cells generally CD8 cells occasionally

Allergological diagnostic methods

- Due to the activation of cellular immunity in many infectious diseases, a state of high sensitivity to pathogens and their toxins develops. Allergic tests used in the diagnosis of infectious diseases are based on this phenomenon.
- Allergy tests allow to reveal the state of high sensitivity in the body.
- Allergens are used for this purpose. Allergens used in the diagnosis of infectious diseases consist of the filtrate of the purified broth culture of the respective microorganisms, and sometimes from killed microorganisms or antigens prepared from them.

Allergic tests

- Allergy tests are specific, but these reactions also give positive results in people who have had the disease or who have been vaccinated.
- Allergic tests used in immunodiagnostics are divided into two groups: in vivo and in vitro.
- In vivo allergic tests include skin-allergic tests. These tests are performed on directly examined patients, and allow to detect immediate and delayed hypersensitivity (ITH and DTH).

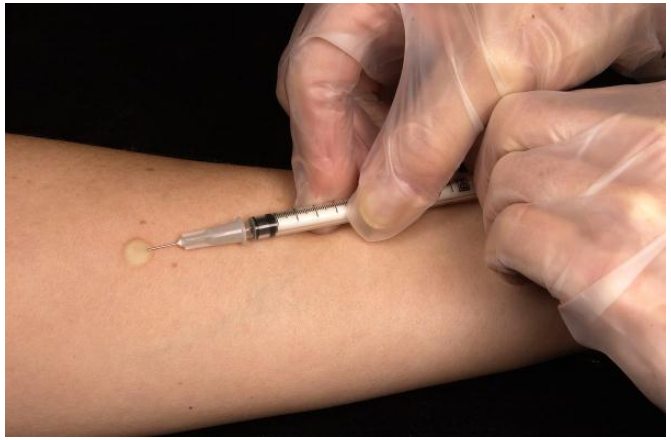
Skin-allergic tests

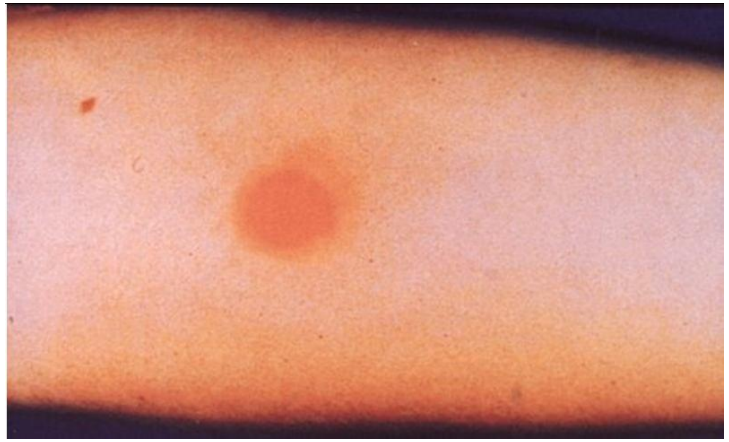
- Allergens are usually injected intradermally or rubbed onto the scarified skin surface.
- In the intradermal method, an amount of 0.1 ml of the allergen is injected into the skin of the front surface of the skin by means of a special needle. When the reaction is positive, after 24-48 hours, a papule (redness and swelling) is formed at the place where the allergen was injected (DTH).
- By measuring the diameter of the papule, a conclusion is made about the intensity of the reaction.

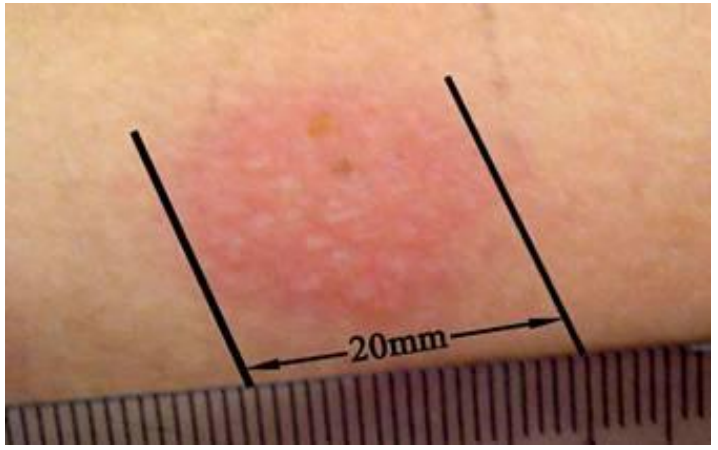
Skin-allergic tests

- Allergens of non-microbial origin (plant pollen, household dust, etc.) are mainly injected by rubbing on the scarified skin surface, or intradermally, as well as by means of an injection (prick test) passing through an allergen drop placed on the skin surface. The result of the reaction is evaluated after 20 minutes (ATH) and 24-48 hours (DTH).
- Determination of DTH by means of a skin-allergic test can be used to determine tuberculosis (Mantu test), brucellosis (Burne test), leprosy (Mitsuda test), tularemia, actinomycosis, etc. used in the diagnosis of diseases.

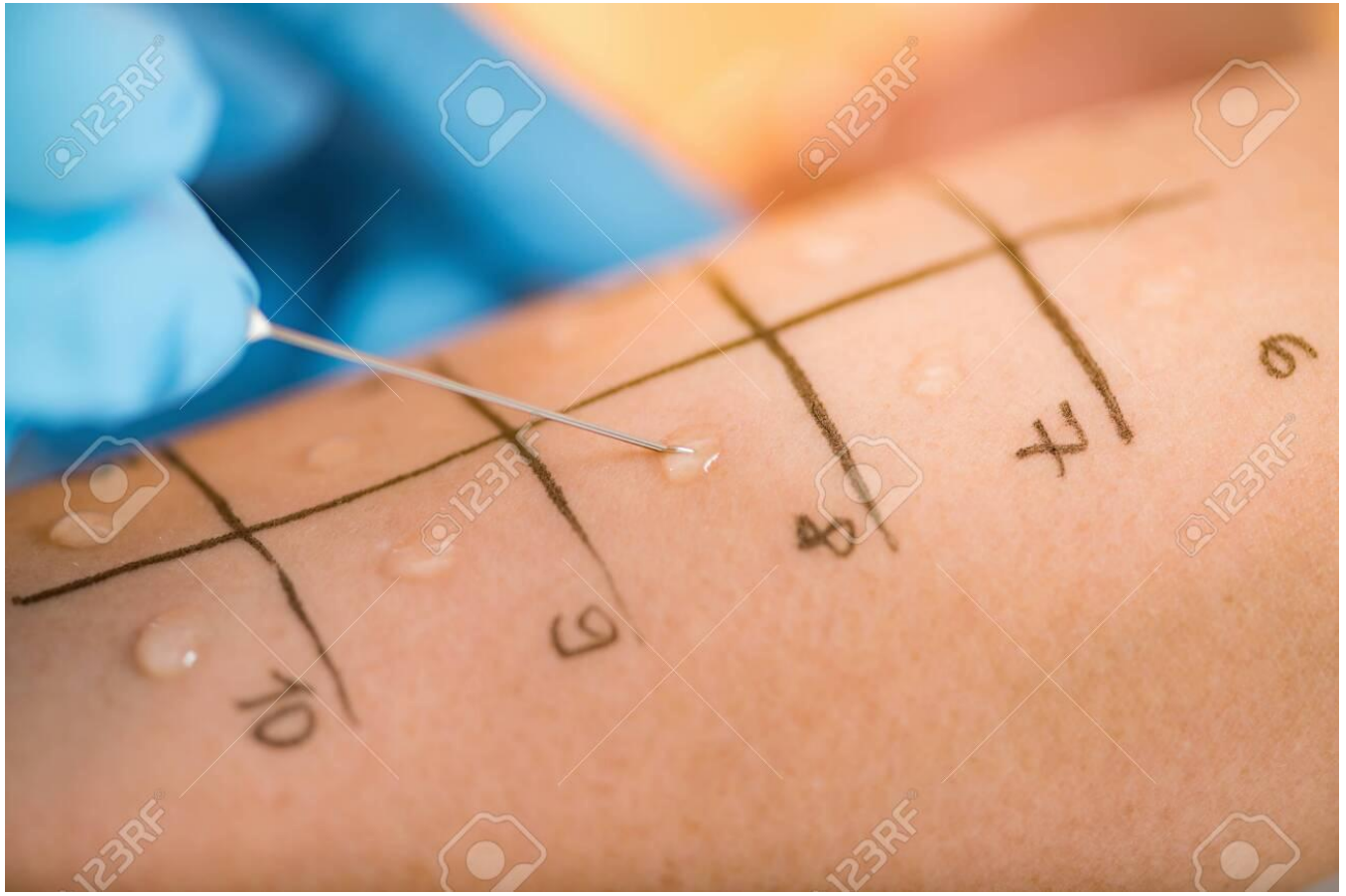
Skin-allergic tests







Skin-allergic test (prick test)

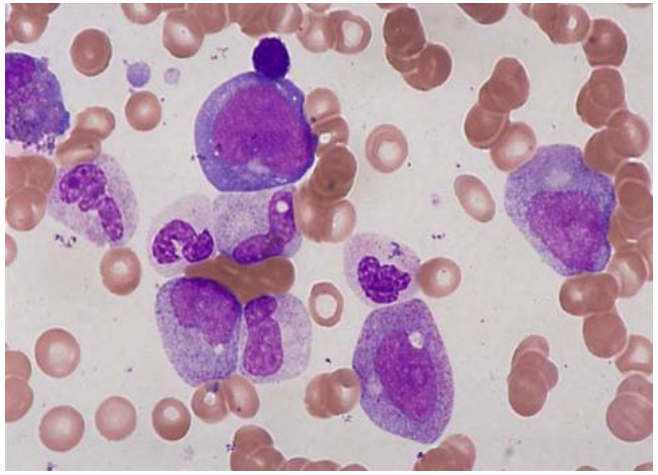


In vitro allergic tests

- In vitro tests are sensitive enough, safe for patients and allow to quantitatively evaluate the level of allergy of the organism.
- Currently, there are various tests to evaluate the sensitization of the organism.
- These tests are based on the reaction of T- and B-lymphocytes, seed basophils, detection of specific IgE in blood serum.

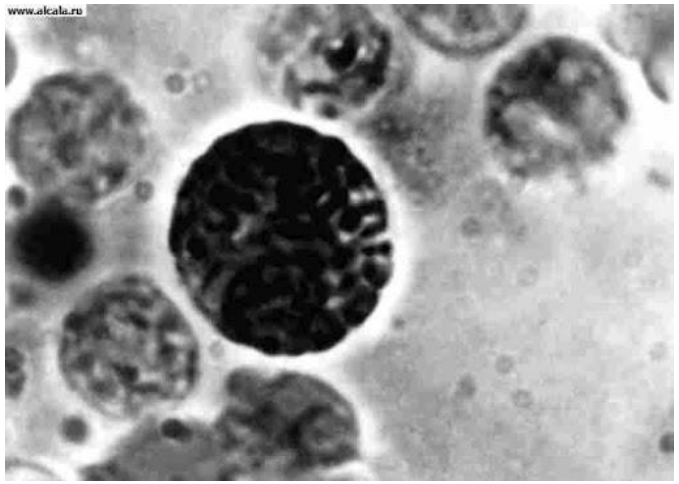
Lymphocyte blasttransformation reaction

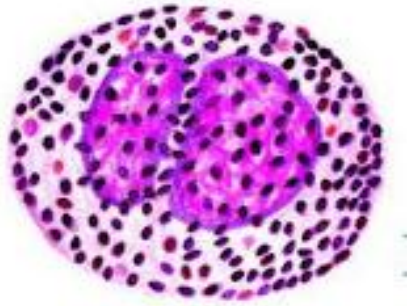
- Lymphocyte blast transformation reaction is based on the transformation of peripheral blood lymphocytes into blast (dividing) cells under the influence of specific and non-specific mitogens.
- Factors causing blast transformation of lymphocytes - mitogens can be specific and non-specific. Allergens that pre-sensitize the organism belongs to specific mitogens, and phytohemaglutinin, koncanavalin A, lipopolysaccharides, etc. to non-specific mitogens.
- To carry out the reaction, the peripheral blood lymphocytes of the examined person are incubated at 37°C for 24-48 hours with the participation of mitogens.
- Then, the percentage of blast cells in the tissues prepared from this mixture and stained by the Giemsa method is evaluated microscopically.



Degranulation test of basophils

- It is based on allergen-induced degranulation of rat basophils pre-sensitized with cytophilic antibodies (IgE) in the patient's serum.
- Rat peritoneal basophils, patient's blood serum and allergen are incubated together to carry out the reaction.
- Then, the number of degranulated basophils in the preparations prepared from this mixture and stained with neutral red is microscopically calculated as a percentage and compared with the control.





In vitro determination of IgE antibodies

- The determination of specific IgE in blood serum is used in the diagnosis of immediate-type hypersensitivity reactions. Determination of IgE is carried out using labeled antibodies.
- If RIM is used, this reaction is called a radioallergosorbent test (RAST).
- However, for this purpose, ELISA or IFR is used more often. The reaction carried out using ELISA is called enzyme-allergosorbent test (EAST): the allergen adsorbed in the solid phase is incubated for a certain time with the patient's blood serum, after washing, an enzyme-enhanced antibody is labeled on it. The specific IgE present in the patient's blood serum combines with the allergen and is stored in a solid phase, and also binds the enzyme-labeled anti-IgE antibodies. The result of the reaction is evaluated as in ELISA.