ALLERGY

I. MOTIVATION OF THE PURPOSE.

Allergy is one of the most important problems of general pathology and clinical medicine. Allergy underlies or accompanies many human diseases. Therefore, knowledge of the etiology, pathogenesis, prevention and treatment basics of allergies is absolutely necessary for a doctor of any specialty.

II. PURPOSE OF THE SELF-TRAINING.

As a result of self- training, the student should know:

- definition and essence of the basic concepts and terms of allergology;
- principles of allergic reactions classification;
- be able to explain the general patterns of occurrence and development of allergic reactions;
- be able to explain the mechanisms of different types of allergic reactions clinical manifestations development;
- principles of prophylaxis and pathogenetic therapy of allergic reactions;
- get acquainted with the content of practical work and be ready to perform them.

III. INITIAL LEVEL OF KNOWLEDGE.

For understanding the topic "Allergy" you need to know:

- mechanisms of cellular and humoral immunity formation;
- mechanisms of biologically active substances formation and release;
- biochemical, physico-chemical, vascular and cellular changes in the inflammation focus.

IV. THEME STUDY PLAN.

1. Allergy, definition, differences between allergies and immunity. Conditions for the allergic reactions occurrence.
2. Allergens. Exogenous (infectious, non-infectious), endogenous (primary, secondary). Mechanisms of the endogenous allergens formation.
3. Classification of allergic reactions.
4. General mechanisms of the allergic reactions development. Active and passive sensitization. Immune, pathochemical and pathophysiological stages. Desensitization (specific and nonspecific).
5. Mechanisms of immediate hypersensitivity (anaphylactic) reactions development, clinical forms (atopic bronchial asthma, allergic rhinitis, allergic conjunctivitis, hives, anaphylactic shock, angioedema (Quincke's edema)).
6. Mechanisms of tissue-specific (or cytotoxic) hypersensitivity development, clinical forms (autoimmune hemolytic anemia, thrombocytopenia, allergic drug-inducing agranulocytosis, postinfarction myocarditis, myasthenia).
7. Mechanisms of immune complexes hypersensitivity development, clinical forms (serum sickness, Arthus phenomenon, exogenous allergic alveolitis, glomerulonephritis).
8. Mechanisms of delayed type hypersensitivity development, clinical forms (allergic contact dermatitis, infectious and allergic diseases: tuberculosis, leprosy, brucellosis, syphilis, protozoal diseases, fungal diseases of the skin and lungs).
9. Mechanisms of antireceptor allergic reactions development.

10. Autoimmune and autoallergic diseases, mechanisms of their development.

11. The biological significance of allergic reactions. Pathophysiological basis for the prevention and treatment of allergic diseases.

V. LITERATURE:

1. Lecture notes.
2. Additional material of the Pathophysiology Department.

VI. QUESTIONS FOR SELF-CONTROL.

1. Allergy: definition, principles of allergic reactions classification.
2. Causes and conditions of allergic reactions occurrence. Allergen classification.
3. Stages of allergic reactions development, their characteristics.
4. The sensitization, the general mechanisms of development, types.
5. Stages of allergy. Characteristics of biologically active substances released in the pathochemical stage.
6. Desensitization, types, ways of formation.
7. Comparative characteristics of the most common mechanisms of immediate and delayed types of allergic reactions development.
8. Special features for development mechanisms anaphylactic (IgE-mediated, immediate) reactions, clinical forms.
9. Special features for development mechanisms of antibody-dependent cytotoxic hypersensitivity hypersensitivity, clinical forms.
10. Special features for development mechanisms of immune complex-mediated hypersensitivity, clinical forms.
11. Special features for development mechanisms of cell-mediated (delayed type) hypersensitivity, clinical forms.
12. Special features for development mechanisms of antireceptor (noncytotoxic or stimulatory) hypersensitivity, clinical forms.
13. Atopic diseases. Signs and mechanisms of atopy development.
14. Mechanisms of endoallergen formation and autoallergy development.
15. Mechanisms of the pseudo-allergic reactions development, their difference from the true allergic reactions.
16. The biological significance of allergies.
17. Pathophysiological basis for the prevention and treatment of allergies.

VII. OBLIGATORY TASKS FOR INDEPENDENT WORK.

1. Make the pathogenesis scheme for allergic reactions of all types with an indication of the prevention and pathogenetic therapy principles specifically for each type of allergy.

ALLERGY

Allergy (from the Greek *allos* – other, *ergon* – act, "other action") – a typical pathological process, qualitatively altered immune response of the organism, occurring in conditions of hypersensitivity to the antigen and accompanied by damage to own tissues and cells and / or changes in their functional state.

The main etiological factor (cause) of allergy is called **allergen**.

The basis of allergy is **sensitization (or immunization)** – the process of acquiring a hypersensitivity to the one or the other allergen by the organism due to the production of allergen-specific antibodies or lymphocytes.

MECHANISMS FOR CONVERTING A PROTECTIVE IMMUNE RESPONSE TO AN ALLERGY (DAMAGE REACTION)

The factors contributing to the transformation of predisposition to allergy into the appropriate disease are:

1. Increased permeability of barriers.

It can be associated with both genetic predisposition and inflammatory processes (for example, in the intestines or respiratory tract). Increased permeability of the skin, mucous membranes and blood-tissue barriers leads to the penetration into the body of those antigens that under normal conditions either do not enter the organism or enter limited.

2. Features of the immune response.

For example, dysfunction of immunocompetent cells, disturbance of the formed antibodies number, imbalance of different Ig classes.

3. Changes in the formation and ratio of various mediators of the immune response.

For example, in patients with allergy, the level of secretion and release of proinflammatory mediators is increased compared with healthy people, and the production of antiinflammatory mediators is reduced.

4. Increased sensitivity of peripheral tissues to allergy mediators.

5. Disturbance of phagocytosis.

ALLERGY CRITERIA:

- genetic,
- immunological,
- functional,
- specific (allergological).

1. Genetic criteria.

It has long been known that predisposition to allergic diseases (especially atopic) can be inherited.

For example:

- in cases of parents angioedema, the disease in children occurs in 50% of cases;
- rate of familial allergic rhinitis ranges from 30 to 80%;
- in patients with bronchial asthma, hereditary predisposition to allergic diseases is detected in 55.3% of cases, and this risk reaches 80%in the presence of allergic diseases in patient kinsmans in ascending, descending and lateral lines;
- cases of identical manifestations of allergy to the same allergens set in monozygotic twins are described.

In this connection, there are special genetic markers for many allergic diseases – risk factors for allergy.

Hereditary predisposition to allergy is presented in the term **"atopy"**, suggested to the **"allergic constitution"** designation – a genetically mediated predisposition to allergic-type reactions. One of its manifestations is the lack of a strict connection between the tendency to the allergic response and a

specific allergen type. In this connection, a typical manifestation of the allergic processes progression is the expansion of the allergens spectrum that cause pathological reactions.

An analysis of the genetic basis of allergy showed that the predisposition to the disease is a polygenic phenomenon, and the number of genes with which this predisposition is linked is rather large.

2. Immunological criteria.

For example:

- decrease in the content of regulatory CD4 + T-lymphocytes (Th) and cytotoxic CD8+ T-cells in the blood;
- increased IgE concentration in serum (IgE level above 20 IU/ml in a child is evaluated as a sign of a possible atopic disease in adulthood);
- ratio of specific and total IgE.

3. Functional criteria (congenital and acquired functional defects).

For example:

- decrease in β-adrenoreceptor activity,
- increased sensitivity of the bronchi to biologically active substances (histamine, acetylcholine),
- decrease in serum histamine binding power – ability to bind free histamine (histaminopexy).

4. Specific (allergological) criteria.

- skin tests – application of allergen extracts at the skin damage area accompanied by an assessment of the local inflammatory reaction (for example: chamber-scarification test (with scratching) and prick-test (pricking the skin to a depth of 1-1.5 mm with a needle or pin containing a small amount of the allergen));
- elimination tests (exclusion of the examined person from contact with the estimated allergen);
- *in vitro* allergy tests (radioallergosorbent test (RAST), Shelley's test, mast cell degranulation reaction, studies on isolated organs, etc.).

Using the above criteria allows to predict the sensitization possibility in the examined person, confirms the allergic nature of the process. But the main criterion that gives information about the etiology of allergies in each concrete case is the "antigen-antibody" reaction, which is the basis of allergic tests – tests of specific diagnostics of allergic diseases .

An important and most constant criterion for allergopathology is the identification of eosinophilia, which in most cases indicates sensitization of the organism. However, it should be considered that the blood eosinophils content may also vary due to other causes (malignant tumors, blood system diseases, parasitic invasions).

ETIOLOGY OF ALLERGIC REACTIONS AND DISEASES

The possibility of an allergic disease in a concrete individual is determined by:

- antigen character;
- antigen properties;
- antigen amount (at the first and repeated contacts);
- antigen entrance way into organism;
- features of the organism's immunological reactivity.

Allergens properties:

1. Relatively low molecular weight.
2. The ability to sorb or aggregate into small corpuscles and in this form to penetrate (diffuse) into the secrets of the mucous membranes and integumentary tissues, without visible tissues injury.
3. High solubility and ability to easily permeate into the organism fluids.
4. Chemical stability *in vivo* (allergens are not metabolized, at least quickly).
5. Protease-enzymes most often become allergens among proteins. Non-proteinaceous substances themselves are not allergens, but they are able to form chemical compounds with the organism's own proteins, thereby acquiring the properties of full allergens. Such substances are called haptens.
6. Allergens show their effect in extremely small doses. *For example,* a clinically significant total dose of ragweed pollen allergens can be as low as 1 μg per year.

There are several different classifications of allergens.

Types of allergens, depending on the ability to cause allergies:

- complete allergens (macromolecules),
- incomplete antigens – **haptens** – low molecular weight substances (drug metabolites, simple chemicals – iodine, bromine, chromium, nickel), which become antigens only after combination with the organism tissues proteins to form so-called complex (or conjugated) antigens.

Types of allergens depending on the chemical structure:

- proteins,
- protein-polysaccharide complexes (serum, tissue, bacterial allergens),
- polysaccharides;
- compounds of polysaccharides with lipoids – lipopolysaccharides (house dust allergen, bacterial allergens).

Types of allergens depending on the origin:

- endoallergens (organism's own proteins):
  - primary (natural, congenital);
  - secondary (acquired);
- exoallergens – allergens that enter the organism from the environment:

Primary endoallergens – tissue antigens, normally isolated from the immune system influences. Only after contact with the immune system due to the conforming barriers damage, they begin to be perceived as foreign.

Examples of primary endoallergens:

- brain,
- eye lens,
- thyroid gland colloid,
- testes.

Secondary endoallergens are the own organism's initially normal proteins, which acquire the properties of foreignness as a result of the disturbance of their structure under the action of various environmental factors.

Secondary endoallergens are divided into:

- infectious (formed from normal tissue under the action of infectious agents);
- non-infectious (formed from normal tissues under the influence of cold, burns, radiation energy, etc.).

Exoallergens by origin are divided into:

- infectious:
  - microorganisms (viruses, bacteria, fungi, parasites);
  - metabolic products of microorganisms;
- non-infectious:
  - industrial,
  - domestic,
  - medicinal,
  - epidermal,
  - pollen,
  - food (animal and vegetable origin).

Exoallergens, depending on the entrance way into organism are divided into:

- respiratory (pollen, dust, aerosols, etc.);
- alimentary (food allergens);
- contact (low molecular weight substances that can enter the body through the skin and mucous membranes, — medical ointments, cosmetic creams, dyes, resins, etc.);
- parenteral (drugs and insect's poisons – bees, mosquitoes, etc.);
- transplacental (some antibiotics, protein drugs, etc.).

The most frequent etiological factors leading to the allergy development are the following:

1. Infectious agents.
2. Pollen plants.
3. House dust.
4. Food products.
5. Insect allergens.
6. Medicinal products.
7. Chemicals, metals.

Among **infectious agents**, the most active are fungal allergens, less active are bacterial, viral, parasitic allergens.

Features of infectious allergies:

- increasing in organism's sensitization due to the action of the bacteria structural elements acting as **adjuvants** – substances that enhance the immune response when administered with an antigen (for example, during vaccination);
- increasing in other allergens entrance into the organism and the polysensitization development.

Mechanism: inflammatory reaction in response to the infection action => increasing in permeability of the mucous membranes and skin.

Allergic diseases (for example, seasonal rhinitis, rhinoconjunctivitis) caused by **plant pollen** are called **pollinosis**.

The most common pollen allergens:

- birch,
- *Phleum (timothy),*

- *Poa* (meadow-grass, bluegrass, tussock, speargrass),
- *Dactylis glomerata* (also known as cock's-foot, orchard grass, or cat grass),
- *Festuca pratensis* (also known as meadow fescue),
- *Artemisia* (wormwood, southernwood, tarragon, sagewort, common mugwort, big sagebrush, etc.),
- *Ambrosia* (ragweeds)

House dust – has a very complex composition and includes:

- organic matters of origin animal (wool, dandruff, feathers),
- plant components (pollen),
- microbial origin substances (fungi, bacteria), etc.

The main component of house dust, which determines its allergenic properties, is the microscopic mites of the *Dermatophagoides* family, spreading most better at high temperatures and humidity.

The most common food allergens:

- chicken eggs,
- cow's milk,
- seafood (bivalve, squids, shrimps),
- nuts (peanuts),
- grasses (porridges, flakes, flour products made from wheat and rye),
- legumes (peas, beans).

The most common insecticidal allergens are:

1. Insect's poisons:
   - hymenoptera (wasps, bees, bumblebees, ants, etc.),
   - bloodsucking dipterans (mosquitoes, midges, mosquitoes, gadflies, etc.),
   - hemiptera (bedbugs).
2. Scales and metabolic products of insects (including the clothing moth).

Drug allergy are most often associated with the following drugs and their metabolic products in the organism:

- antibiotics (penicillins, cephalosporins, etc.);
- sulfonamide drugs (for example, diuretics);
- nonsteroidal anti-inflammatory drugs;
- local anesthetics;
- vitamins (thiamine and others);
- enzyme drugs (streptokinase, etc.);
- components of serums, vaccines and blood drugs;
- hormones (insulin, adrenocorticotropic hormone, thyroid stimulating hormone, etc.);
- muscle relaxants;
- cytostatics (cisplatin, cyclophosphamide, cytarabine, etc.).
- opiates, etc.
- polysaccharides
- dextrans.

Signs of a drug allergy:

- appearance of unusual effects of the drug;
- appearance of these effects from small doses of the drug;
- appearance of these effects a few days after the first contact with the drug.

The most common chemical allergens:

- turpentine,
- epoxy resins,
- dyes,
- varnishes, etc.

Significant contingents of workers in the mining and metallurgical industries, residents of large industrial regions are exposed to **metal allergens**. The impact of metals such as chromium, nickel, cobalt, manganese (electric welding, foundry and mining production) leads to the development of allergic dermatoses, and allergic diseases of the respiratory organs.

GENERAL PATHOGENESIS OF ALLERGIC REACTIONS

The pathogenesis of any allergic reaction can be divided into 3 stages:

I. Stage of immune reactions (immunological).

It begins with the first contact of the organism with the allergen and consists in the formation and accumulation of allergic antibodies (or sensitized lymphocytes) in the organism. As a result, the organism becomes sensitized – it becomes more sensitive to a specific allergen. Repeated entrance of a specific allergen results in its complexation with *antibodies* (an "antigen–antibody" complex is formed) or *sensitized lymphocytes* (an "antigen–sensitized lymphocyte" complex is formed), which determine the next stage of an allergic reaction.

II. Stage of biochemical reactions (pathochemical).

Its essence consists in the liberation of pre-existing and the formation of newly synthesized biologically active substances (mediators of allergy) as a result of complex biochemical processes triggered by the "antigen–antibody" or "antigen–sensitized lymphocyte" complexes.

III. Stage of clinical manifestations (pathophysiological).

It represents the organism's response to the mediators formed in the previous stage, including those that cause damage to cells, tissues and organs.

Local, including visible, **manifestations of an immediate type allergy are determined by:**

1) dilatation of blood vessels (redness);
2) increase in the vascular wall permeability (edema, rash – blisters, stains, etc.);
3) smooth muscles spasm (during the bronchospasm – dyspnea, asphyxia);
4) hyperproduction of nasal, bronchial mucus and other secrets (runny nose, sneezing, nasal congestion, impaired smelling, coughing, wheezing, lacrimation, diarrhea);
5) irritation of nerve endings (itching, pain).

Common allergy manifestations include:

- fever,
- changes in the number and functional activity of blood cells,
- changes in the activity of blood formation and immunopoesis,
- changes in organism metabolism, etc.

AUTOIMMUNE DISORDERS

Normally, in every organism there are antibodies, B-and T-lymphocytes, directed against the own tissues antigens (autoantigens). The presence of autoantigens, most autoantibodies and autoreactive lymphocytes is not a pathological phenomenon.

Types of autoantigens:

- **natural/common** (include the widest range of proteins and other macromolecules of which the human organism is built),
- **"sequestered"** (they are present in tissues inaccessible to lymphocytes: brain, lens of the eye, thyroid colloid, testicles),
- **modified** (i.e., formating during damage, mutations, tumor degeneration).

Some antigens (for example, proteins of the myocardium and renal glomeruli) are cross-reacting with some microbial antigens (in particular, antigens of β-hemolytic streptococcus).

Types of autoantibodies directed against autoantigens:

- **natural or physiological** (they make up the majority, cannot damage own tissues when interacting with autoantigens);
- **"witnesses"-antibodies** (they correspond to the immunological memory against autoantigens that have ever been formed due to random tissue damage);

- **aggressive** or **pathogenic** (they can cause damage to the tissues against which are directed).

If there are a number of conditions, an **autoimmune process** can be triggered under the action of autoantigens, autoantibodies and autoreactive lymphocytes. This promotes the immune inflammation development accompanied by the involved tissues destruction, formation of fibrosis and vascular neoplasm. It ultimately leads to the loss of the organs function.

Autoimmune process is an immune inflammation directed against normal (unaltered) antigens of own tissues and caused by the formation of autoantibodies and autoreactive lymphocytes (i.e., autosensitization).

The most important additional conditions for the activation and maintenance of the autoimmune process:

- chronic viral, prion and other infections;
- pervasionof pathogens with cross-reacting antigens;
- hereditary or acquired molecular structure anomalies of the most important structural and regulatory molecules of the immune system (including molecules involved in the apoptosis control);
- individual features of the constitution and metabolism, predisposing to the sluggish character of inflammation;
- elderly age.

Contingently, the pathogenesis of autoimmune disorders can be divided into two stages:

- inductive,
- effector.

Inductive stage – associated with the failure of immunological self-tolerance. Tolerance to the organism's own antigens is a natural state in which the destructive activity of the immune system is directed only to external antigens. The processes of organism aging from an immunological point of view are due to the gradual failure of this tolerance.

Mechanisms that control the maintenance of long-term self-tolerance:

- clonal deletion,
- clonal anergy,
- T-cell mediated immunosuppression.

Clonal deletion is a form of central tolerance that is formed in the course of negative selection by apoptosis of T-lymphocytes (in the thymus) and B-lymphocytes (in the bone marrow), which have highly specific antigen-recognition receptors to autoantigens.

Clonal anergy is a form of central tolerance in which cells, mainly B-lymphocytes, become functionally inactive.

However, some T- and B-lymphocytes often avoid negative selection and can be activated during presence of some additional conditions. The listed factors may contribute to this:

- pervasion of pathogens with cross-antigens or polyclonal activators,
- shift of the cytokine profile in the Th1 direction,
- prolonged inflammatory process with the entry into the blood and tissues of many mediators that can modify autoantigens in the focus, etc.

If the first two mechanisms (clonal deletion and anergy) are ineffective, a peripheral mechanism – T-cell mediated immunosuppression is activated to maintain tolerance.

T-cell mediated immunosuppression is a form of peripheral tolerance aimed at activating apoptosis in peripheral autoreactive T-lymphocytes or their anergy under the suppressive influence of the Th2 profile cytokines.

If all these mechanisms are ineffective, the development of autoimmune disorders begins. To a large extent, autoimmune pathology (as well as tumor progression) is the apoptosis deficiency (congenital

or acquired). A lethal hereditary disease with a defect in the gene encoding Fas (one of the specialized receptors for the apoptosis induction), which manifests by a lymphoproliferative syndrome with systemic symptoms typical of autoimmune diseases, is described. A significant role in the pathogenesis of many forms of autoimmune pathology is belonged to slow viral and prion infections, which probably can modify the processes of apoptosis and expression of the most important regulatory molecules. Lately, the role of Th17 in the development of autoimmune diseases is investigating.

One of the central aspects of the autoimmune diseases pathogenesis is the presence of any molecular abnormalities. For example, in rheumatoid arthritis and a number of other pathologies, a defect of the Fc-region glycosylation of own IgG-class antibodies was found when a deficiency of sialic acid and galactose is registering. Abnormal IgG molecules form conglomerates between each other with strong immunogenic properties that induce an autoimmune response. The presence of molecular abnormalities of the genes responsible for the synthesis of the Th2-profile cytokines, leads to the fact that the autoimmune response that has begun does not end with the restoration of self-tolerance.

Autoimmune diseases often develop in the so-called immunologically privileged organs:

- brain (multiple sclerosis),
- eye lens (sympathetic ophthalmia),
- thyroid colloid (Hashimoto's thyroiditis),
- testicles (immunological infertility).

When autoantigens from these organs appear in unusual places (for example, in case of tissue barriers injury) and there are any additional conditions for enhancing their immunogenicity (Th2-cytokine deficiency, presence of adjuvants, etc.), the autoimmune process is activated.

The effector stage of any autoimmune process develops by one or more often by several (II, III, IV or V) types of hypersensitivity:

Type II: autoimmune hemolytic anemia, pernicious anemia, pemphigus vulgaris, chronic idiopathic urticaria, severe myasthenia *(myasthenia gravis)*, autoimmune thyroiditis, etc.;

Type III: systemic lupus erythematosus, systemic vasculitis, etc.;

Type IV: rheumatoid arthritis, multiple sclerosis, etc .;

Type V: immune-mediated (type 1) diabetes mellitus, Graves' disease, etc.

The clinical symptomatology of autoimmune diseases is characterized by a chronic progressive course with destructive manifestations in the target organs.

Pathogenetic classes of autoimmune diseases:

Class A. Primary autoimmune diseases with hereditary predisposition:

- organ-specific diseases (for example, autoimmune thyroiditis);
- intermediate (for example, autoimmune pathology of the liver and gastrointestinal tract);
- organ-specific (collagenosis).

Class B. Secondary autoimmune diseases (for example, liver alcoholic cirrhosis, chronic radiation sickness).

Class C. Autoimmune diseases based on complement genetic defects (for example, some forms of hereditary hemolytic anemia).

Class D. Autoimmune diseases associated with slow viral and prion infections (for example, encephalomyelitis vilujensis, Alzheimer's disease, etc.).

Class E. Combined forms.

Diagnosis is based on the identification of specific autoantibodies and autoreactive T-lymphocytes, histological and other special studies.

Treatment of autoimmune diseases is associated with attempts to restore self-tolerance, the prescription of anti-inflammatory anti-mediator drugs, including corticosteroids, as well as gene therapy.

PSEUDOALLERGIC (NON-IMMUNOLOGICAL) REACTIONS – a large group of reactions that do not have an immunological stage, but manifest by clinically symptoms that are similar to true allergic reactions. In other words, antibodies or sensitized lymphocytes are not involved in the development of pseudo-allergic reactions.

In this way, pseudoallergy has **only two stages: pathochemical and pathophysiological.** During the pathochemical stage of pseudoallergic reactions, the same mediators are released as in the case of true allergic reactions (histamine, LT, complement activation products, kallikrein-kinin system), which explains the similarity of clinical symptoms.

The main manifestations of pseudoallergic reactions are:

- urticaria,
- angioedema,
- bronchospasm,
- anaphylactic shock.

According to pathogenesis, the following types of pseudoallergic reactions are distinguished:

1. Reactions associated with the release of allergy mediators from mast cell.
2. Reactions associated with disturbanced metabolism of polyunsaturated fatty acids.
3. Reactions associated with uncontrolled activation of complement.

1. Reactions associated with the release of allergy mediators from mast cell.

IgE-independent factors for mast cell activation and degranulation include:

1. Chemicals:
   - food products – histamine liberators (fish, tomatoes, egg white, strawberry, wild strawberry, chocolate);
   - antibiotics,
   - muscle relaxants,
   - opiates,
   - polysaccharides,
   - radiopaque agents,
   - anaphylatoxins (C3a, C5a),
   - neuropeptides (for example, substance P),
   - ATP,
   - cytokines (IL-1, IL-3), etc.
2. Mechanical irritation (dermatographic urticaria)
3. Physical factors:
   - warm and cold energy (cold urticaria),
   - UV-rays (solar urticaria),
   - physical exercises (cholinergic urticaria).

An increase in the blood histamine level can be associated not only with its excessive release, but also with an inactivation disturbances:

- increase in the intestinal mucosa permeability => conditions for the excessive absorption of histamine;
- excessive histamine entering the intestine or its excessive formation in the intestine;
- histaminopexy;
- liver pathology, in particular – toxic hepatitis (for example, against the background of intake of the anti-tuberculosis drug Isoniazid), liver cirrhosis.

Increased bradykinin level can develops in individuals who have been using angiotensin-converting enzyme inhibitors (ACE inhibitors) for a long time (for example, Captopril, Ramipril, etc.). This contributes to the development of urticaria, bronchospasm, rhinorrhea, etc.

2. Reactions associated with disturbanced metabolism of polyunsaturated fatty acids (primarily arachidonic acid).

During cyclooxygenase activity inhibition (the use of non-steroidal anti-inflammatory drugs, for example, acetylsalicylic acid – aspirin), arachidonic acid metabolism shifts towards the lipoxygenase pathway. The result is an excess amount of LT – there is a so-called aspirin form of bronchial asthma occurs.

3. Reactions associated with uncontrolled activation of complement.

This may be due to a hereditary deficiency of the complement C1-component inhibitor (Quincke's congenital angioedema), as well as due to non-immunological activation of complement by an alternative pathway (the effect of cobra poison, bacterial lipopolysaccharides, thrombolytic agents, narcotic analgesics, a number of enzymes (trypsin, plasmin, kallikrein) and etc.)). Activation of the complement system leads to the formation of intermediate products (C3a, C5a), which cause the mediators releasing (primarily histamine) from mast cells, basophils and platelets.

PRINCIPLES OF ALLERGIC DISEASES DIAGNOSTICS

Diagnostics is aimed at identifying the causes and factors contributing to the formation and manifestation of allergic diseases. Specific and non-specific examination methods are used to do this.

Diagnostics always begins with clarifying complaints and collecting allergological anamnesis often allowing to suggeste a preliminary diagnosis, studying the story of life and illness, which the doctor performs during the examination of the patient.

Clinical examination methods include:

- examination by a doctor,
- clinical and laboratory examination methods,
- X-ray methods,
- instrumental methods,
- functional and other examination methods (if it is needed).

The basic principle of the allergic diseases specific diagnosis is the identification of a cause-significant allergen, for which tests are performed *in vivo* and allergen-specific IgE-antibodies or sensitized lymphocytes and products of the specific antigens–antibodies interactions are measured.

Allergy specific screening includes:

- collection of allergological anamnesis;
- skin tests implementation;
- provocative tests implementation;
- laboratory diagnostics.

The collection of allergological anamnesis includes obtaining information from the patient on the following points:

- features of the development and course of the disease;
- hereditary predisposition (family anamnesis of allergies);
- living and housing conditions;
- alimentary and pharmacological anamnesis (association of symptoms with the intake of any food, drugs).

All assumptions must be confirmed by specific tests:

- skin tests,
- provocative tests,
- laboratory tests.

Skin tests (skin testing with allergens *in vivo*):

- prick-tests,
- chamber-scarification tests,
- application tests,
- intradermic tests.

Water-salt extracts of allergens are used for skin testing: plant pollen, house dust, house dust mites, wool, lint, epidermis of animals and birds, food and other products.

The most commonly used are *prick-tests* or *chamber-scarification (scratch or scrape) tests*, which are implemented on the inner surface of the forearms. Tests with negative (with test-control fluid) and positive (with histamine) control are obligatory.

Intradermic tests are more sensitive, but are less specific, they are mainly used to identify sensitization to allergens of bacterial and fungal origin.

Application tests (patch-tests) are implemented using standard sets of chemical allergens for testing – for the diagnosis of allergic contact dermatitis (detection of delayed-type hypersensitivity – type IV reactions).

Provocative tests –

used in case of discrepancy between the anamnesis data and the skin testing results:

- conjunctival,
- nasal,
- inhalation,
- sublingual,
- oral.

Laboratory diagnostics methods *(in vitro)*:

- enzyme-linked immunosorbent assay (ELISA) methods for the specific IgE detection using a chromogenic, fluorogenic, electrochemiluminescent and etc. methods of results registration;
- radioallergosorbent test (RAST) to detect specific IgE;
- molecular allergy diagnostics tests – an innovative method used for mapping allergenic sensitization at the molecular level using purified or recombinant allergens or their's components instead of allergen extracts;
- indirect and direct basophilic test (Shelley's test);
- reaction of histamine specific release from the patient's peripheral blood basophils.

These laboratory diagnostics methods allow to identify only the state of sensitization (the presence or absence of specific IgE-antibodies to allergens without considering clinical manifestations). Methods of laboratory diagnosis are considered as additional measures to clarify the questionable results of *in vivo* testing.

When making a diagnosis, one should rely mainly on the patient's complaints, allergic anamnesis data, patient's examination, skin testing, as well as on the results of laboratory diagnostic methods.

PATHOPHYSIOLOGICAL BASIS FOR THE PREVENTION AND TREATMENT OF ALLERGY

Treatment and prevention of allergic reactions is based on the implementation of **etiotropic, pathogenetic, sanogenetic and symptomatic** principles.

Etiotropic therapy and prevention

In case of **etiotropic therapy** (aimed at allergen eliminating from the organism), measures are taken to remove microbes, parasites, fungi, protozoa (sanation) from the organism and remove abnormal proteins and other allergic compounds.

In case of **etiotropic prophylaxis** (aimed at preventing the contact between the organism and the allergen), measures are taken to prevent the allergens entrance: pollen, dust, animal wool components, organic and inorganic substances, drugs and other allergens. To this end, patients are advised to avoid contact with animals, plants, flowers, which cause allergy to them. In manufacturing, sewage treatment plants, exhaust ventilation, respirators, air humidification, masks, gloves and other devices are used to prevent allergic substances entering into the organism, on the skin and mucous membranes.

Pathogenetic therapy and prevention

Pathogenetic therapy is aimed at breaking the main pathogenesis links of allergy, and **prevention** – at an outrunning blockade of the potential mechanisms of its development. These activities are defined as hypo-or desensitization of the organism. They are aimed at blocking immunogenic sensitizing processes and preventing the formation of allergy mediators and to their neutralization. For this purpose, specific and/or non-specific desensitization is performed.

Specific desensitization is achieved by parenteral repeated administration (as a rule, according to specific schemes) of the same allergen that presumably caused sensitization (the method is designed to form complexes of allergen with AB and a gradual decrease in the content of the appropriate Ig).

Non-specific desensitization is used in cases when a specific one is impossible or ineffective for some reason, or an allergen cannot be identified.

For example:

- in case of immediate type allergic reactions – the use of specific antihistamine or membrane-stabilizing drugs;
- in case of delayed type allergic reactions – the use of immunosuppressants (including glucocorticoids) and immunomodulators, some types of physiotherapeutic influences.

Sanogenetic therapy –

is aimed at the activation of protective, compensatory, reparative, replacement and other adaptive processes and reactions in tissues, organs and the organism generally. For this purpose, multivitamin complexes, adaptogens, immunostimulants are used, carried out non-drug influences: polar bear plunge, physical exertion, fasting, etc.

Symptomatic therapy –

used to prevent or eliminate unpleasant, painful sensations that aggravate the allergy course: headache, dizziness, anxiety, tension, depression, etc. For this purpose, tranquilizers, painkillers, psychostimulants, physiotherapy are used.