PATHOPHYSIOLOGY OF IMMUNE SYSTEM. ALLERGY

If before researchers took an interest only in the defensive role of the immunity, at present a great attention is paid to the deficiency and pathology of the immune system itself. Immune system activity is disturbed in all pathological processes and diseases. Defects of the immune system make the organism helpless against the microorganisms and other pathogenic factors.

The immune system recognizes heterologous substances and promotes neutralization of their action. But occasionally the immune response to the heterologous antigens resembling those of the host may lead to repeal of the tolerance against the organism's own antigens and development of immunopathological processes. Or frequently «error in recognition» is observed, that is, the immune system reacts to the indifferent and even useful factors as if to the harmful ones and mobilizes its defensive functions against them.

Disturbances in the immune system functions have a bearing even on the development of the malignant tumors.

The pathological processes connected with disturbances in the activity of the immunocompetent (lymphoid) tissue, that is, immunopathological states and reactions include:

1.Immunity deficiency states.

2.Pathological tolerance.

3.Transplantation disease ("graft-versus-host" reaction).

4.Allergic reactions.

5.Autoimmune processes.

*The pathological states which are connected with the weakness of the organism's immune system, are called immunity deficiency states.*

The congenital and acquired immunity deficiency states are distinguished.

The congenital immunity deficiency syndromes include hereditary and congenital deficiencies connected with delay of lymphoid tissue's development to different extent (hypoplasia, aplasia). But the acquired immunity deficiencies are caused by the diseases in the period of individual development or drugs.

The congenital immune deficiency syndromes are divided into 3 groups - syndromes of the cellular, humoral and mixed immunity deficiency.

I. Syndromes of the cellular immunity deficiency:

1) Mac-Kusic's syndrome-achondroplasia;

2) Di George's syndrome- thymic hypoplasia.

II. Syndromes of the humoral immunity deficiency:

1) Bruton's syndrome-X-linked agammaglobulinemia;

2) West's syndrome-IgA deficiency.

III. Syndromes of the mixed immunity deficiency:

1) Glanzmann-Riniker syndrome-Swiss type agammaglobulinemia;

2) Louis-Bar syndrome-ataxia telangiectasia.

Syndromes of the cellular immunity deficiency are characterized by underdevelopment of the thymus gland and the zones of the peripheral lymphoid tissue that depend on this gland. They are accompanied by different developmental defects. The sick children die of developmental defects or complications of the infectious diseases.

In the patients with syndromes of the humoral immunity deficiency bacterial infections go on especially severe; in bronchi, lungs, gastrointestenal tract, skin, etc. pyodestructive changes occur which frequently lead to the development of sepsis. Bruton's syndrome is connected with hypoplasia of zones in plasmacyte cells of the peripheral lymphoid tissues (lymph nodes, spleen) whose activity depends on B lymphocytes.

In syndromes of the mixed immunity deficiency thymus gland as well as peripheral lymphoid tissue, are hypoplastic, and therefore, cellular and humoral immunity are weakened at the same time.In such children, besides the weakness of the immune system, different developmental defects and malignant mesenchymal tumors are observed.

 The main clinic signs of the syndromes of primary immunity deficiency are connected with weakness of the organism's resistance against infectious diseases. Even the microbes with weak pathogenicity easily may cause diseases in them. They fall ill frequently and severely (inflammatory diseases of the respiratory and urogenital systems, gastrointestenal diseases accompanied by diarrhea).Inflammatory diseases often lead to bacterial complications (pneumonia, meningitis, sepsis).Physical underdevelopment of the organism, otitis, sinusitis, conjunctivitis, pyodermia are observed.

The sick children die of infectious diseases or malignant tumors in first years of life.

Acquired immunity deficiency occurs frequently in adult persons and may be primary (disease of the immune system itself) or secondary (as a result of different diseases or some methods of treatment).

The primary acquired immunity deficiency is caused by the special disease of viral etiology connected with the weakness of the immunity, that is, AIDS (acquired immunodeficiency syndrome) which was initially recognized in US in 1981 (and is wide spread also in the Central Africa). But its infecting agent, that is, HIV (human immunodeficiency virus) or LAV (lymphoadenopathic virus) was described previously (1974).It belongs to the group of retroviruses of the subfamily of lentiviruses.

6-8 weeks (seldom 8-9 month) after the infection antibodies against HIV appear, and only beginning from this moment infection of the organism may be revealed by the up-to-date methods. Ratio between infected persons (positive test to the antibodies) and those that fall ill ranges from 50:1 to 100:1.

Transmission of HIV infection occurs by one of the following 3 routes:

1. Sexual contact. Most cases of AIDS in the industrialized world like US occur in homosexual or bisexual males while heterosexual promiscuity seems to be the dominant mode of this infection in Africa and Asia.

2. Parenteral transmission-occurs in 3 groups of high risk populations: a) intravenous drug abusers by sharing needles, syringes, etc.; b) hemophiliacs who have received large amounts of factor VIII concentrates from pooled blood components from multiple donors; c) recipients of blood and blood products who have received multiple transfusion of whole blood or components like platelets and plasma. 3. Perinatal transmission. HIV infection occurs from infected mother to the newborn during pregnancy transplacentally, or in immediate post-partum period trough contamination with maternal blood, infected amniotic fluid or breast milk.

So, HIV penetrates into the organism with blood and its derivates, with cells during transplantation of tissues and organs, blood transfusion, with sperm and saliva through injured mucous membrane or skin.

In the pathogenesis of AIDS weakness of the cellular immunity is of great importance. The number of T-lymphocytes (especially that of T-helpers) is sharply decreased. Because viruses of AIDS selectively enter T-helper cells and damage them. This leads to weakness of the organism's immunity and favourable conditions are formed for development of the infectious diseases (even of those caused by the microorganisms with the weak pathogenecity).The patients usually die of secondary infectious diseases.

As for the WHO, AIDS is defined as the existence of at least two major signs associated with at least one minor sign, in the absence of known secondary cause of immunosuppression.

Major signs are: weight loss of >10% of body weight, chronic diarrhea of >1 month's duration, prolonged fever (intermittent or continuous) of >1 month.

Minor signs are: recurrent oropharyngeal candidiasis, persistent generalized lymphadenopathy, persistent cough for >1 month, generalized pruritic dermatitis, recurrent herpes simplex infection.

But this definition does not cover the now well established role of HIV in the etiology of AIDS. It has been modified, and AIDS is classified on the basis of etiologic agent and the natural history of disease as regards its clinical manifestatioins:

1. infectious mononucleosis-like syndrome or acute seroconversion illness;
2. AIDS-related complex (ARC) or pre-AIDS;
3. full-blown AIDS.

The average survival after the onset of full-blown AIDS is 18-24 month.

The secondary acquired immunity deficiency is caused by a number of diseases, especially viral, bacterial and parasitical infections, vast burns, renal and hepatic insufficiency, disturbances of metabolism. They arise also as a result of some methods of treatment. Leukosis, malignant lymphoma (lymphogranulomatosis, lymphosarcoma, reticulosarcoma), sarcoidosis, thymoma, malignant tumors result in the secondary weakness of the immune system. Since formation and development of T as well as B lymphocytes are disturbed, cellular, as well as humoral immunity reactions are weakened.

Some methods of treatment (radiotherapy, corticosteroids, immunodepressants, thymectomy, drainage of the thoracic lymphatic duct, etc.) weaken activity of the immune system.Occasionally antilymphocytic cytotoxic sera are used to weaken the immune system.

It is known that organism does not develop immune reactions against its own numerous antigen. But under certain conditions organism may not produce antibodies also against heterologous antigens.

*The state of organism's inability to the immune response is called the immunogenic tolerance (Lat. tolerantia). Immunogenic tolerance is the state of the organism's reactivity to certain antigen which causes immunogenic reaction in other organisms of the same species.*

Example for specific acquired immune tolerance is loss of ability of tissues of mouse of one pure line to reject skin transplant of the mouse of another pure line, if the mouse-recipient in its embryonal period had received splenic cells of the mouse-donor. This state is called ''transplantation immunity'' and is explained as a result of entering of transplantation antigens into recipient's organism with the splenic cells. These antigens block up the cellular reaction rejecting the transplant. The organism loses the ability to recognize the transplant as the heterologous one, and grafting becomes successful.

Thus, the organism ceases to differ from its own one the antigens with which it was in contact in the embryonic period.

Tolerance possesses specificity. The organism, tolerant to one antigen, does not lose the ability to react to another one.

The study of immune tolerance is of great importance to elucidate the problems of immunogenic pathology and transplantology.

The following types of the immunogenic tolerance are distinguished:

1. Physiological tolerance-is the tolerance of the immunocompetent system to the antigens of the own proteins and cells of the organism. According to the clonal-selective hypothesis of Burnet and Fenner (1948) mechanism of the physiological tolerance is connected with destruction, elimination and absence of those clonal cells of the immunocompetent system which were exposed to the massive influence of the antigens of the own proteins and cells of the organism in the period of the embryonic development (when the immunocompetent system was not sufficiently mature yet).

2. Isolation tolerance-is a form of the physiological tolerance. It is extended to the antigens of some components of tissues of the brain, eyes, testicles, thyroid gland which are isolated from the immunocompenent system by hematotissular (hematoencephalic, hemato-ophthalmic, hematothyroid, etc.) barriers. Breach of the isolation leads to onset of autoimmune diseases.

3. Induced (artificial, medicinal) tolerance –is reproduced by the way of suppression of activity of different cells of the immunocompetent system using ionizing radiation, high doses of cytostatics, immunodepressants. Induced tolerance is applied for the purpose of increasing success of transplantation of organs and tissues, treatment of allergic reactions, autoimmune pathological processes.

4.Transplantation tolerance or transplantation immunity-is a form of the pathological tolerance. It consists of loss of ability of tissues to reject the graft of the animal belonging to the same species, but to another line.

5. Pathological tolerance-is incapability of the organism to the immune response, that is, the state of the organism's areactivity to certain antigen which causes immunogenic reaction in other organisms of the same species. The organism's immunocompetent cells ''tolerate'' heterologous antigens, those of bacteria, viruses, parasites, cells of the malignant tumors or graft. The basic mechanisms of the development of the pathological tolerance are:

a) immunity deficiency states;

b) increased activity of T-lymphocytes-suppressors which leads to inhibition of T-lymphocytes-killers and plasmatic cells (B-lymphocytes);

c) inhibition or blockade of cellular immunity reactions to the proper antigen (usually to that of tumor cells or cells of the graft).

When the high doses of antigens administered into organism in the form of solution (microbial polysaccharides), in the immune system antibodies are not synthesized against them. This is called immune paralysis or Felton's syndrome and is explained by the following way. Antigen particles in the form of solution easily enter the immunocompetent cells and damage them. Since the immunocyte clones sensitized against other antigens are not damaged, the organism loses the ability to response only to the antigens which has caused the immune paralysis.

Transplantation disease or ''graft-versus-host'' reaction develops when a great mass of donor's tissues containing immunocompetent cells of bone marrow, leukocytic mass is transplanted to the recipient. Decreased activity of the «host»s immunocompetent system (influence of radiation, immunodepressants, organism's immaturity, etc.) aggravates this reaction.

Transplantation disease is characterized by affection of recipient' s immunocompetent system organs, that is, development of peculiar immunity deficiency state as well as lesion of skin, digestive tract, liver.

Graft-versus-host reaction manifests itself by necrotic and dystrophic affection of above-mentioned organs and tissues, anemia, lymphopenia thrombocytopenia, nausea, vomiting, diarrhea, enlarged liver. In infants, besides, physical development is delayed. Therefore, in adults this state is called «homologous disease» (as a result of homotransplantation of immunocompetent system cells), and in newborns- runt disease or runt syndrome.

 Experimentally runt disease is reproduced by the way of intravenous (not intracutaneous or intraperitoneal) injection of 5-15 millions of immunocompetent splenic cells of adult mouse into a newborn mouse of another strain. The signs set in 6-7 days later. The baby mouse does not thrive, it grows slowly, the skin is dry and thin, the hair falls out, diarrhea develops accompanied by emaciation, the liver and spleen are enlarged, the lymphoid tissue is atrophied, occasionally ascites may be observed. The animal becomes a runt and perishes within 4 weeks. The cause of the disease is the immune conflict between the cells that were administered and the recipient's cells.

 The animals which receive homologous tissue (for example, splenic cells) and become tolerant are changed into a kind of immunogenic chimeras. Such chimeras are diovular twins each of which has blood groups of both of them. This state develops in the intrauterine period when the twins exchange blood cells through placental circulation.

 *Allergy (Gr. allos- other, ergon-work) is heightened and qualitatively altered sensitivity of the organism to the action of infectious agents or other substances of antigenic nature (allergens). Allergy is the pathological form of the immunogenic reactivity.*

 At the beginning of our century prince Albert in Monaco could not bathe in the Mediterranian Sea in the period of increase of number of jelly- fish Physalia. Usually from contact with them his skin was covered by rash. In 1902 Porter and Richer, who were invited into his yacht, established that extract of these jelly-fish were exsessively toxic for ducks and rabbits.

In Paris these scientists began to study tentacles of Actinaria. When determining the toxic dose of extracts some dogs did not die during 4-5 and more days, but showed the strongest sensitivity and died several minutes later after administration of small doses of the extract. They called this phenomenon anaphylaxis (Gr.ana – negation; phylaxis- guarding). Anaphylaxis is a state of increased susceptibility or hypersensitivity following a repeated parenteral injection of a foreign protein.

In an year Arthus proved that anaphylaxis was caused also by repeated injections of the substances which are completely harmless when injected once. At present it is known that irritation from the bite of insects is frequently caused not by poison(which such creations as mosquito do not have), but by our own hypersensibilization to the antigens of their saliva.

In 1905 Sakharov observed anaphylaxis in guinea-pigs.

The term allergy was first used by Pirquet in 1906 to designate hyper- as well as hyporeactive states. But now this term means only hyperergy. The reaction caused by the repeated (resolving) injection of the heterologous protein was called by Bezredka (1912) anaphylactic shock.

The mechanism of development of allergic reactions is based on the immune changes. But immune reactions serve for defence of the organism from the heterologous factors, whereas the defensive function of allergy is disputable.

The following facts are in favour of defensive significance of allergy:

1. identity of the mechanisms of immunity and allergy;
2. decontamination and removal of antigens from the organism in allergy;
3. evolution of allergic reactions which manifest themselves completely only in warm-blooded animals and reach the highest stage of development in human beings; they may be regarded as favourable reactions directed to the preservation of the species.

Community of etiologic factors (antigenic stimulant), aims (liberation of the organism from "alien") and mechanisms (components of the immunocompetent system) of allergy and immunity exists. But there are also substantial differences:

1. Allergy may be caused by factors which do not give rise to immunogenic reactions (cooling, ionization, etc).
2. In allergy participate the classes of antigens (reagins) rarely taking part in immunity.
3. The main distinctive difference is that in all cases of allergy the own cells and tissues of the organism are damaged.

So, if the specific reaction of the organism to the antigen is not accompanied by the injury, it is immune reaction, if the damage is caused, it is allergy. In other words, allergy is the immune reaction which is accompanied by the damage to the tissues of the organism.

Depending on its reactivity and the antigen's quantity the organism may respond to the same antigen by immune, as well as allergic reactions. For instance, in the blood of the most people which are treated by penicillin, the immune bodies against this antibiotic are found, but not in all of them the allergic reactions are observed.

Some scientists tried to prove that the antigens causing immune and allergic reactions differed. For example, Ascarides antigen stimulates synthesis of immunoglobulin E in the human organism and causes development of allergic reaction. But a large amount of even weak antigenic substances also may cause a strong allergic rections.

Idiosyncrasy is hypersensitivity of the organism to the nutrients and drugs.

This term is connected with the concept of disease of Greek and Roman physicians which explained the essence of diseases by dyscrasia. At present the unusual reactions to the nutrients and drugs that are realized by the participation of the immune mechanisms are regarded as food allergy and drug allergy . But a large group of these reactions that are connected with deficiency of certain enzymes in the organism, and not by the immune mechanisms, are called ''hereditary enzymopathies''.

Allergic reactions are caused by the substances of antigenic character which are called allergens, and sometimes, by the substances of non- antigen nature which are called haptens.

The haptens differ from ordinary allergens by their small molecules. They cannot exert the antigenic action and acquire the allergen properties only after being bound by the organism's proteins(conjugate or complex allergens). Haptens include some drugs , chemical elements (bromine, iodine, nickel, etc),a number of complex organic compounds of non- protein nature (vital activity products of microorganisms, polysaccharides), etc.

 The allergens are divided into 2 large groups:1)exoallergens, 2) endoallergens.

 According to the site of penetration into the organism the following groups of exoallergens are distinguished:

1)respiratory

2)alimentary

3)parenteral

4)contact

5)transplacental

 According to their origin infectious and non-infectious allergens are distinguished. The infectious allergens include bacterial (bacteria and the products of their vital activity), viral, fungous, etc. Non- infectious allergens are divided into the following groups:

1. domestic(domestic dust, library dust);
2. epidermal (wool, hairs, epidermic cells);
3. medicamentous (antibiotics, sulfanilamides);
4. chemical substances of industrial origin (ursol, benzene, formol);
5. pollen (of grass, flowers, trees);
6. food (yolk, honey, coffee, chocolate).

The endoallergens (autoallergens) are divided into 2 groups:

1)natural (primary) allergens;

2)acquired (secondary) allergens.

 The natural endoallergens are unchanged proteins of some tissues of the organism itself (lens, nervous tissue, follicles of the thyroid gland, ovaries). When the physiological isolation of these tissues is disturbed (as a result of injury), in immunocompetent cells autoantibiodies are formed which act against their proteins.

The special inhibitory factors (immunorepressors) prevent formation of antibodies against own proteins of the organism in immunocompetent cells. But the autoallergens are exception. They are not in contact with immunocompetent cells since the embryonal period. Therefore, in the organism there are not the specific immunorepressors of these tissue proteins, and in the following periods of the life the cells of the immune system receive them as "heterologous''.

 The acquired endoallergens are pathologically changed tissues. They may be infectious and non-infections. Non-infectious autoallergens are formed under the influence of the physical (cold, burns, radiation), chemical and other factors on the organism's tissues. Some drugs also cause formation of autoallergens (the organism's proteins acquire antigenic properties after binding them).

 The infectious autoallergens may be simple or complex. The simple autoallergens are the proteins which are altered under the influence of viruses on the cells. The antibodies against these antigens may react only with them, and cannot be bound neither by cell, nor by viruses separately.

 The complex autoallergens are combinations (or conjugates) of the infectious agent with tissue proteins (tissue+ microbe, tissue+toxin). The antibodies against these autoallergens may be bound with the complex itself, as well as with the microbe forming its part.

 Allergy is the general reaction of the organism. Symptom- complex of allergic and anaphylactic reactions is the following: decrease of arterial pressure, bronchospasm, inflammation of mucous membranes, dilatation of blood vessels, disturbances in water and salt metabolism, eczematous changes in the skin, diarrhea, vomiting, leukopenia, eosinophilia, irritation of the vegetative(especially sympathetic) nervous system, etc.

So, in allergy together with the local reactions, the general reactions occur. The allergic reaction occurring in any point of the body is manifestation of the general reaction.

 A state of balance in the immune responses (humoral or cell- mediated ) is essential for protection against endogenous and exogenous antigens. Hypersensitivity is defined as a state of exaggerated immune response to an antigen. These are different classifications of allergic hypersensitivity reactions.

 Depending upon the rapidity and duration of the immune response, two distinct forms of allergic reactions are recognized (R.Cook,1930):

1. Immediate type in which on administration of antigen the reaction occurs immediately (within seconds to minutes). Immune response in this type is mediated largely by humoral antibodies (B- lymphocytes). Immediate type of hypersensitivity includes anaphylactic shock, Overy's phenomenon, Arthus' phenomenon, Schultz- Dale phenomenon, non-infectious form of the bronchial asthma, pollinosis, urticaria, Quincke's edema, serum, sickness, etc.
2. Delayed type in which the reaction is slower in onset and develops within 24-48 hours and the effect is prolonged. It is mainly mediated by cellular response (T-lymphocytes). Delayed type includes allergic reactions of bacterial origin (tuberculin reaction), contact dermatitis, transplant rejection, autoallergic reactions and diseases.

The immediate type allergic reactions differ from the delayed type allergic reactions by the following signs:

1. The immediate type allergic reactions appear in several (up to 20) minutes after the contact of the sensitized organism with allergen. But for the delayed reactions this period is 6-48 hours.
2. The mechanism of the immediate type allergic reactions is connected with the antibodies freely circulating in the blood, whereas such antibodies are not found in the delayed type allergic reactions.
3. The immediate type allergic reactions are connected with B-lymphocytes, and the delayed type reactions-with T-lymphocytes.
4. It is possible to produce the state of hypersensitivity causing the immediate type allergic reaction passively by the way of transfusion of the blood serum from the sensitized organism into the healthy organism. But to produce the delayed type allergic reactions by the way of passive sensitization lymphocytes, the cells of the lymphoid organs or exudate cells must be transfused.
5. The delayed type allergic reactions are connected with the cytotoxic or lytic action of the allergens on the sensitized leukocytes whereas such changes are not characteristic of the immediate type allergic reactions.
6. The allergens of the delayed type allergic reactions exert toxic action on the isolated tissue cultures of the sensitized organism. This is not characteristic of the immediate type allergic reactions.
7. Usually antihistaminic preparations do not stop the development of the delayed type allergic reactions.
8. The passive transmission of the delayed type allergic reaction in the man is conditioned by existence of Laurence's transferring factor in the sensitized lymphocytes.

According to the pathogenetic classification true allergic reactions and pseudoallergy are distinguished. True allergic reactions are hypersensitivity reactions the developmental mechanism of which is connected with the immune changes. By their immune mechanisms the true allergic reactions are divided into 2 groups:

1. Hymergic reactions-their development depends on interaction of allergen with antibody. Since their antibodies are synthesized with participation of B-lymphocytes, they are called ''B-lymphocyte-linked reactions.'' According to immunoglobulin class of their antibodies they are divided into A, C, E, M-globulin reactions.
2. Kytergic reactions-develop as a result of combination of allergen with sensitized lymphocytes. They are called T-lymphocyte-linked reactions.

Pseudoallergy is the state of hypersensitivity of the organism which is not connected with the immunity.

Type I-anaphylactic type reactions or atropy (Gr. atopos-strange) or reagin type cell injuries or immediate type allergic reactions.

This type includes 2 subtypes:

1.Reagin-is connected with production of IgE-class antibodies (reagin) and underlies atopic diseases (atopic bronchial asthma, pollinosis, urticaria,Quincke's edema, allergic conjunctivitis, allergic rhinitis, etc.).

2.Anaphylactic-is connected mainly with IgC4 –antibodies and is observed in anaphylactic shock.

TypeII-cytotoxic type reactions or reactions of cytolysis-is connected with formation of IgG1,2,3 and IgM. This type reactions cause injury to the cells by combining humoral antibodies with cell surface antigens (blood cells being affected more commonly, but also those of kidneys, liver, brain, spleen, sperm): autoimmune hemolytic anemia, transfusion reactions (posttransfusion shock), hemolytic disease of the new-born, idiopathic thrombocytopenic purpura, myasthenia, etc.

The II type allergic reactions differ from autoallergy by the fact that in these reactions antibodies are produced in common way, circulate in the blood and then act upon the own cells of the organism, whereas in autoallergy antibodies are formed in the own cells of the organism and they are absent in the circulating blood.

Type III-immune complex type reactions or precipitin type or Arthur’ type reactions-result from formation of immune complexes by direct antigen-antibody combination as a result of which the complement system gets activated, causing cell injury.

Depending on the distribution and location of antigens typeIII reactions may be local or general (systemic). Examples of local immune complex diseases are Arthur’ phenomenon, farmer’s lung (allergic alveolitis in response to bacterial antigen from mouldy hay).

Examples of circulating immune complex diseases are: various forms of glomerulonephritis, collagen diseases (polyarteritis nodosa, selerodermia, rheumatoid arthritis, systemic lupus erythematosus), serum sickness, anaphylactic shock, etc.

Type IV-cell-mediated or T-lymphocyte dependent or tuberculin type or delayed type reactions- are connected with formation of sensitized lymphocytes (T-effectors). Stimulated by the antigens, lymphocytes produce lymphokines.

The IV type reactions include allergic reactions of bacterial origin (tuberculin reaction), contact dermatitis, transplant rejection, autoallergic reactions and diseases.

TypeV-receptor-mediated or stimulating type (but later inhibiting and blocking effects on activity of receptors were also revealed).Antigens of this type reactions are neuromediators (for example, acetylcholine), hormones (insulin, thyrotropic hormone) and their structural analogues. Contacting with B-lymphocytes, these biologically active substances initiate their transformation into plasmatic cells and activate synthesis of IgG by them.

Examples of stimulating effects of these antibodies are imitation of effect of thyrotropic hormone (development of the hyperthyroid state) and stimulation of cytotoxic action of T-lymphocytes-killers against own cells of the organism. Inhibiting action of antibodies-suppression of effects of insulin and acetylcholine as a result of their interaction with structures of receptors of these hormone and neuromediator.

Usually in the mechanisms of development and clinical manifestations of allergic reactions not one, but several (or all) types of hypersensitivity are realized. For instance, the I and III types-in atopic bronchial asthma and anaphylactic shock, the III and IV types-in autoimmune diseases.

In the pathogenesis of allergy sensibilization (sensitization) is of great significance. Sensibilization is hypersensitivity of the organism to the antigen. It consist of formation of antibodies and sensitized lymphocytes in the organism which the antigen has entered for the first time.The state of sensibilization of the organism cannot be identified with the allergic reactions. Because such an organism is practically healthy, and allergic reactions occur only when the antigen enters the sensitized organism repeatedly.

By the method of formation active and passive sensibilization are distinguished. Active sensibilization is formed when allergen enters the organism by the natural ways or is introduced into the organism artificially. To create the passive sensibilization in the experiment the blood or lymphoid cells of the actively sensitized animal is administered into the blood flow of the healthy animal of the same species.

So, the active sensibilization is formed with participation of the own immune system of the organism, whereas the passive sensibilization is connected with humoral antibodies or immune cells (immunocytes) which are introduced into the organism in the ready form.

By the active way the allergic reactions may be caused not sooner than 7-8 days after the first entrance of the antigen. The allergic reaction (anaphylactic shock) proceeds more severely at the end of the second week of the sensibilization. In the passively sensitized organism the antibodies spread in the body and are fixed in the cells during 24-28 hours, and at the end of this period allergic reactions occur.

According to the number of types of antigens taking part in the process, the following types of sensibilization are distinguished:

1. monovalent sensibilization-hypersensibility of the organism only to one type of antigen;
2. polyvalent sensibilization-hypersensibility of the organism to several allergens at the same time;
3. cross-sensibilization-in the organism sensitized by one allergen, hypersensibility to another type of allergen is formed.

The following three stages of allergy are distinguished:

I - the stage of immune reactions or immunogenic stage;

II - the stage of biochemical reactions or pathochemical stage;

III - the stage of clinical manifestations or pathophysiological stage.

These stages are closely connected, and each preceding stage prepares the ground for the next one. Thus, at the stage of immune reactions allergen first enters the organism, antibodies or sensitized lymphocytes are formed. At the end of this stage combination of the antibodies with the allergens that enter the organism repeatedly, starts off the stage of pathochemical changes. The essence of the second stage is characterized by formation of biologically active substances, that is, allergic mediators. The character of the pathophysiological changes at the third stage, in its turn, is determined by the pathogenic action of the allergic mediators on the cells, tissues and organs.

At the first stage of allergy the type of allergic reaction is determined by the character of the antibody synthesized in the organism. So, immediate type is connected with the formation of humoral antibodies, and delayed type- that of immune cells with special antibodies or receptors.

The signs and course of the allergic reaction depend on the type of the immunoglobulin ( IgA, IgD, IgE, IgG, IgM) which reacts with the antigen causing this reaction and its following abilities:

1. to combine with antigen (this ability is highest in IgM and lowest in IgG);
2. to penetrate into tissue (large molecular IgM penetrates the tissues with difficulty);
3. to accumulate in tissues(from this viewpoint the activity of IgE is the highest).

The main part of the IgE usually accumulates in tissues. It combines easily with basophils and mast cells, but its blood concentration is comparatively low.

According to the changes caused by them in the organism, incomplete antibodies, reagins, dermatosensitizing antibodies, etc. are distinguished. Antibodies which do not react to antigen in the precipitation and agglutination tests are called incomplete antibodies. They are determined by the antiglobulin sera.

The antibodies which react in the following dermato-allergic test of Praustnitz-Kustner are called reagins. The blood serum of the patient with atopy is injected intracutaneously to the healthy man, and a day later to the same area the investigated allergen is injected. If the patient’s blood serum contains reagin type antibody, edema and hyperemia are observed in the site of injection. The most of reagins belong to the class of IgE (non-precipitant) and a small amount-to the class of IgG.

Usually a number of allergens cause formation of the humoral and cellular antibodies in the organism at the same time, and therefore, the most of the allergic reactions are of mixed character.

The general mechanism of type I (atopic) reactions is the following. When the allergen enters the organism, in the cells of the immune system reagin type antibodies are synthesized. They are fixed mainly in the mast cells and basophils. So, in the organism sensibilization to the allergen is formed. The allergen that repeatedly enters the organism, is combined with reagin. Under the influence of these combinations from mast cells and basophils different allergic mediators are liberated.

In type II (cytotoxic) reactions antibodies react to the cells having antigenic determinants.

Under the influence of antigens causing type III (immune complex type or Arthus’ type) reactions precipitant antibodies (mainly immunoglobulins A and M) are synthesized which react with corresponding antigens in blood and intercellular fluid. The microprecipitates that are formed, are accumulated in the vascular wall and perivascular spaces. The microcirculation is disturbed and in tissues damages of different character (up to necrosis) occur. In these reactions the complement system, lysosomic enzymes, superoxide radicals, kallikrein-kinin system take part.

In the mechanism of type IV (delayed) reactions the free antibodies do not participate. Under the influence of allergens causing these reactions the antibodies bound with immune system cells, that is, sensitized T lymphocytes are formed, which are combined with antigens by their special type antibodies or receptors. Sensitized T lymphocytes accumulate in the same areas where the allergens repeatedly entering the organism, are situated. In the T lymphocytes a number of biologically active substances ( lymphokines) are synthesized which cause cell injury, draw phagocytes into the process, accelerate chemotaxis and phogocytic activity of macrophages and polymorphocellular cells. Some of them exert cytotaxic action and weaken cellular activity. Lawrence's transferring factor, when administered into non-sensitized organism, causes the state of passive sensibilization.

The allergen-antibody complexes activate the complement system and the proteolytic enzymes in the blood (trypsinogen, plasminogen, kallikreinogen), degranulate the most cells and promote liberation of biologically active substances, that is, the second stage of allergy begins.

Mediators, on the one hand, stimulate defensive reactions of the organism, on the other hand, exercise pathogenic influence on the organism. Their pathogenic actions result in typic injuries and manifestations of diseases which are characteristic of allergic reactions.

Activation of the mast cells and basophils is one of the main processes in the pathogenesis of the immediate type allergic reactions. Some of the mediators (histamine, serotonin, eosinophil chemotactic factor) are freely in the cells and are immediately excreted, other mediators (heparin, aryl sulphatase A, galactosidase, peroxidase, superoxide dysmutase) are situated in cellular granulations and are excreted by the way of diffusion.

A number of mediators (slow-reacting substance of allergy - SRSA, thrombocyte - activating factor) are synthesized only in the period of activation of the cells. These are called the primary anaphylactic mediators. They influence vascular wall and blood cells cause chemotaxis of eosinophils and neutrophils. From the activated mast cells the secondary mediators of allergy (phospholipase D, aryl sulphatase B, histaminase, SRSA) are liberated.

Liberation of mediators is a complicated process. For instance, in the liberation of histamine IgE takes part. Cyclic guanosine monophosphate (GMP) accelerates this process, and cyclic adenosine monophosphate (AMP) suppresses it.

In the pathogenesis of immediate type allergic reactions (type I) mainly the following mediators take part:

1. Histamine - causes spasm of smooth muscle fibers, increases capillary permeability, hydrophilic properties of interstitital substance of the loose connective tissue, promotes formation of edema, urticaria, petechial hemorrahage.
2. Serotonin - has not much significance in human allergic reactions. But the drugs acting against serotonin are successfully applied in the treatment of a number of allergic diseases (especially urticaria, dermatitis).
3. Slow reacting substance of allergy (SRSA) - is the mixture of several leukotrienes (especially leukotriene D4). Though leukotrienes cause the spasm of isolated smooth muscle preparations more slowly than histamine, but antihistamine preparations cannot prevent spasm caused by these mediators.
4. Eosinophil chemotactic factor.
5. Neutrophil chemotactic factor.
6. Heparin - delays blood coagulation and decreases complement system activity. It is activated after being liberated from the mast cells.
7. Thrombocyte - activating factor - is synthesized in basophils; accelerates aggregation of thrombocytes, causes liberation of histamine and serotonin from thrombocytes, increases vascular wall permeability.
8. Aryl sulphatases - are enzymes causing hydrolysis of sulfoethers. Their amount is large in eosinophils.
9. Phospholipase D - is in human eosinophils; decreases activity of thrombocyte - activating factor.
10. Histaminase - is in human eosinophils and neutrophils.
11. Anaphylatoxin - accelerates liberation of histamine from mast cells. The pathophysiological changes in the blood circulation of the healthy guinea - pig when the blood serum of the guinea - pig with anaphylactic shock is transfused, is explained by the action of the anaphylatoxin.
12. Prostaglandins - cause lysis of mast cells and liberation of allergic mediators.

In the pathogenesis of cytotoxic type allergic reactions (type (II) other types of allergic mediators take part:

1. Complement system - is activated by allergen-antibody complexes formed in these reactions. The biologically active products formed in the process of complement’s activation cause development of inflammatory processes in the tissues. Under the influence of its active enzymes in cell membranes channels are formed through which water and salts easily pass.

2. Superoxide radicals-as a result of decreased superoxide dysmutase activity in pathological processes, a large amount of superoxide radicals are accumulated in tissues. They destroy membrane lipides and damage cell membranes.

3. Lysosomic enzymes-are excreted from phagocytic cells and participate in the mechanism of cell injury (acid phosphatase, ribonuclease, cathepsins, collagenase, elastase).

In the immune complex type reactions (type III) also increased amount of mediators accelerating phagocytosis play a principal part, proteolytic processes are accelerated. In these reactions the following mediators take part:

 1) complement system;

 2) lysosomic enzymes;

 3) superoxide radicals;

 4) histamine;

 5) serotinin;

 6) kinins (bradykinin, kallidin)-are in the kininogen and are activated under the influence of kallikrein. They cause spasm of smooth muscle fibers of bronchi, dilate the vessels, accelerate chemotaxis of leukocytes, increase permeability of microcirculatory system vessels, cause pain.

 In the pathogenesis of delayed type allergic reactions (type IV) the lymphokines, that is, the mediators liberated from lymphocytes, play a main part:

1. Migration inhibiting factor- causes accumulation of macrophages in the damages areas, increases their ability to break down the bacteria and accelerates formation of granuloma.
2. Lawrence’s transferring factor- the state of sensibilization in the healthy animal when the blood of sensitized animal is transfused, is connected with this factor.
3. Mitogenic factors- for instance, lymphocytic mitogenic factor causes proliferation and blast transformation of lymphocytes.
4. Chemotactic factors (of macrophages, neutrophils, eosinophils, basophils, granulocytes).
5. Lymphotoxin- its different types in small doses inhibit proliferation of corresponding cells, whereas in large doses damage all the cells.
6. Interferon- inhibits penetration of viruses into cells.
7. Cutaneous reactivity factor- causes inflammatory reaction in animals in the site of subcutaneous injection.
8. Factor accelerating endogenous pyrogens formation- accelerates synthesis of pyrogen substances in macrophages.

Besides lymphokines, in the pathogenesis of delayed type allergic reactions lysosomic enzymes also take part, and kallikrein- kinin system is activated. Apparently, histamine does not participate in the pathogenesis of these reactions. Therefore, antihistamine preparations do not exercise therapheutic action in the delayed type allergic reactions.

Mediators of the receptor- mediated reactions (type V) are neuromediators (acetylcholine, etc.) hormones (insulin, thyrotropic hormone, etc.), other biologically active substances and their structural analogues.

The stage of clinical manifestations or pathophysiological stage is characterized by the functional disturbances which appear in the organism under the influence of the allergen - antibody complexes and biologically active substances. These changes form the basis of clinical manifestations of the allergic diseases. Depending on the type of disease, at the pathophysiological stage allergic inflammations of different localizations, hemodynamic disorders, spasm of smooth muscle fibers, etc. are observed.

As a result of pathogenic action of the allergic mediators different changes occur in cells, as well as in tissues and organs. Allergic injury of separate cells are well studied on the blood cells, connective tissue cells, etc. The response reaction of each damaged cell is determined by its physiological properties. For instance, in the nervous tissue excitation or inhibition, in smooth muscle myofibrils- contractura occur, in capillaries-exudation and emigration are strengthened, in granular leukocytes (basophils, etc.) and mast cells- degranulation is observed (they swell and throw out their granulations).

The tissues and organs may be damaged directly under the influence of allergen- antibody complexes or as a result of disturbed neurohumoral regulation of activity of the organs.

The general expression of the pathophysiological stage of allergic reactions is the reaction of the organism as a whole, different allergic diseases or allergic syndromes.

Anaphylactic reactions occur in all warm-blooded animals. In cold-blooded animals only under certain conditions ( artificial increase of body temperature) anaphylaxis-like changes may be observed.

Anaphylaxis is the opposite of prophylaxis. It is defined as a state of rapidly developing immune response to an antigen to which the individual is previously sensitized. The response is mediated by humoral antibodies of Ig E type or reagin antibodies.

The clinical examples of anaphylaxis may be of 2 types: general (systemic) and local.

Examples of systemic anaphylaxis are: administration of antisera (for instance, ATS-anti-tetanus serum) or drugs (penicillin), sting by wasp or bee.

Local anaphylaxis is common, affecting about 10% of population. About 50% of those conditions are familial with genetic predisposition.

Local type includes anaphylaxis of internal organs and of the skin; bronchial asthma due to allergy to inhaled allergens like house dust, hay fever (seasonal allergic rhinitis) due to pollen sensitization of conjunctiva and nasal passages, food, allergy to injected allergens like fish, cow’s milk, etc., angiedema (angioneurotic edema) or Quincke’s edema (an autosomal dominant inherited disorder, characterized by laryngeal edema, edema of eyelids, lips, tongue and trunk), cutaneous anaphylaxis due to contact of antigen with skin characterized by urticaria, wheal and flare, Overy’s phenomenon.

In man anaphylactic shock may occur under the influence of medicinal preparations and prophylactic vaccines. One can say that all the drugs and prophylactic vaccines may cause sensibilization and anaphylactic shock in the human organism. Most of them are haptens, that is, they acquire the antigen properties after being combined with the organism’s proteins. But the preparations of the protein and polypeptide nature are full- bodied antigens.

The repeated administration of antitoxic sera, homologous gamma- globulins, hormones of polypeptide origin and antibiotics into the organism, sometimes- sting of poisonous insects may cause anaphylactic shock in man.

In the development of anaphylaxis 3 periods are distinguished:

I - sensitization( sensibilization);

II - resolving period (anaphylactic shock);

III - desensitization.

To produce anaphylaxis, the animal (frequently- guinea-pig) is first sensitized, that is, rendered hypersensitive.

 For active sensibilization a small amount (10 ml) of horse serum (as a heterologous protein) is administered parenterally (often subcutaneously). The state of hypersensitivity develops 10-14 days (latent or incubation period) later during which time in the organism of guinea-pig antibodies against horse serum antigens are formed. The state of hypersensitivity is retained for a long time (up to 2 years).

 To produce passive sensibilization the guinea-pig is administered the serum of actively sensitized animal intravenously. The state of hypersensitivity develops 18-24 hours later (during which time antibodies of donor’s blood serum are fixed in the tissues and cells of recipient).

 To produce the second stage of anaphylaxis (anaphylactic shock ) at the end of the latent period a second (resolving ) injection is made, that is, the dose of antigen (anaphylactogen) about 10 times larger than the first (sensitizing) dose is injected in the animal’s blood (intravenously).

 The first symptoms of anaphylactic shock in guinea-pig appears 0.5-1 minutes after the resolving injection. The animal becomes restless, rubs its muzzle with paw and bristles up the whole body begins to twitch convulsively. Several minutes after the beginning of the attack the guinea-pig falls on a side, tonic and clonic spasms develop, involuntary urination and defecation occur, respiration becomes intermittent and gradually slows down and the animal usually dies of aspyxia within 5-10 minutes.

 Other phenomena in anaphylactic shock are: severe circulatory disorders (sharp drop in blood pressure), dyspnea, diminished oxidative processes, lowered body temperature, acidosis, decreased erythrocyte sedimentation rate, leukopenia and eosinophilia, disappearance of complement from the blood and increased permeability of vascular endothelium. Disfunction of the nervous system is particularly noticeable (general excitement followed by depression and convulsions).

 Autopsy of guinea- pigs killed by anaphylactic shock reveals greatly distended, air- filled lungs, which do not collapse and cover the heart that for some time continues to contract. The direct cause of asphyxia is contraction of the smooth muscles of the bronchi resulting in constriction of their lumens, which leads to retention of the air and distention of the lungs.

Different animals are differently susceptible to anaphylaxis. Rabbits and dogs are less susceptible than guinea pigs; rats and mice can hardly be sensitized. The picture of shock and the character of disfunction of the organs in anaphylactic shock also vary: in guinea pigs the lumens of the bronchi become considerably constricted; in rabbits spasm of the muscles of pulmonary arterioles is most pronounced; in dogs –the circulation in the system of the portal vein is sharply impaired (as a result of spasm of the sphincters in the hepatic veins).

Anaphylactic shock in man is the most dangerous type of allergic reactions. Spasm of bronchioles results in dyspnea (difficulty of expiration), asphyxia. Arterial pressure, body temperature, blood coagulability are decreased. The cold sweat, throbbing headache, noises in the ears, itch are observed. Earlier the beginning of the signs of the shock, more severe its course. The most severe is the course of the anaphylactic shock that begins 3-10 minutes after entering of the allergen into the organism, and it results in the death.

The organism which got over the anaphylactic shock loses its sensibility to the anaphylactogen. This process of terminating the state of hypersensitivity is called desensitization. In the human organism this state lasts 2-3 weeks and then is once again replaced by sensibilization.

Injection of the resolving dose of the allergen into the organism of guinea- pig on the first days of the sensibilization (7-8 days) does not cause the shock and such an animal becomes insensitive to the influence of the anaphylactogen also at the end of the sensibilization period (up to 2 weeks).

Nonspecific desensitization may be produced by various substances acting mainly on the nervous system (ether , chloral hydrate, alcohol, adrenalin, atropine, calcium chloride, ultraviolet and roentgen rays). Their desensitizing effect is unstable.

Specific desensitization is of considerable theoretical and practical interest. It is caused by injection of a small dose of a specific antigen before the end of the latent period or when hypersensitivity has already developed.

Experimental production of desensitized state has served as the basis for preventing phenomena of anaphylaxis in man. So, in diphtheria 4 hours before administration of the main dose of antitoxic serum, a small dose (1-2 ml) of this serum is injected prophylactically, which prevents the development in patient of anaphylaxis during the subsequent administration of a massive dose of antidiphtheria serum for therapeutic purposes.

Overy's phenomenon is produced in guinea- pigs by the way of active and passive cutaneous sensibilization. To produce active cutaneous anaphylaxis the resolving dose of the heterologous protein (white of egg ) is administered subcutaneously into the guinea- pig sensitized by that protein . In the area of injection allergic inflammation develops and capillary permeability sharply increases . To observe the Overy's phenomenon Evans' blue is administered into the blood of the animal and several minutes later the site of injection of heterogenous protein is tinged blue.

Passive cutaneous anaphylaxis is produced by two ways:

1. Blood serum of sensitized animal is administered into the blood of healthy animal. A day later allergen is administered subcutaneously and Evans' blue- into the blood.
2. Blood serum of sensitized animal is administered into the healthy animal subcutaneously. 2 hours later the mixture of allergen and dyestuff is injected into the animal’s blood vessels.

In both cases as a result of the Overy’s phenomenon the area of injection is tinged blue.

Arthus' phenomenon is produced as follows: a rabbit is subcutaneously administered 0.1-1 ml of horse serum every 5-6 days. After the second or third injections the inflammatory reaction (hyperemia, edema, infiltration, emigration of leukocytes) is observed at the site of administration. After 4-5 injections the inflammatory reaction becomes more intensive, the skin and subcutaneous tissues are necrotized. Structural disturbances develop in the walls of the blood vessels, the basic substance of connective tissue, the nerve endings and nerve trunks.

From the pathological point of view Arthus' phenomenon is mixed type reaction, combining the main sign of immediate type and delayed type allergic reactions. Precipitant antibodies play an important part in its development. Precipitins combine with allergen and are converted into immune complexes. Under their influence capillary walls are damaged, as a microcirculatory disorders inflammatory reaction and necrosis occur.

Sometimes allergic reactions resembling Arthus' phenomenon are observed in man.

“ Local” anaphylaxis (Arthus' phenomenon ) may develop only on preliminarily sensitized animals. Anaphylaxis may be transmitted passively, for which purpose a rabbit is administered passively, from another rabbit sensitized with horse serum.

The Schwartzman phenomenon is considered to belong to the same category of phenomena. The filtrate of a broth culture of microbes, for instance, the colon bacilli (0.1-0.2 ml), is administered into the rabbit’s skin 24 hours later the same microbe’s filtrate is administered into vein( 0.1-0.5 ml per 1 kg of the animal’s weight). The animal either soon dies or (when given smaller doses in the second injection) develops hemorrhagic infiltrate at the site of injection which becomes necrotic.

Anaphylactic reaction may be observed also in the isolated organs. For this purpose internal organs of the sensitized animal are removed from the organism and are influenced by the allergen- their smooth muscle fibers sharply contract. For example, in Schultz- Dale reaction isolated part of ileum or horn of uterus of sensitized guinea pig are contracted under the influence of the specific allergen.

The closest to experimental anaphylaxis in man is the serum sickness. It may be caused by the therapeutic injection of heterologous antitoxic serum (against tetanus, diphtheria, botulism, gas gangrene, snake venom) with respect to which the organism happens, at the given moment, to be sensitized (within 7-12 days). It may also set in after the first administration of the serum (within 9-20 days). In these cases the injected antigen causes formation of antibodies which, having accumulated before the antigen was completely eliminated from the organism, react with its remains. Rarely the serum sickness occurs after the treatment with homologous preparations (blood, plasma and its fractions, hormones of peptide origin).

The serum sickness is characterized by rise in body temperature, drop in blood pressure, redness and itching at the site of injection, eruption all over the body, inflammation of the joints, swelling of the lymph nodes, nausea, vomiting, edema of the lips and face. The blood shows leukocytosis which is soon, as in anaphylactic shock, replaced by leukopenia and lymphocytosis. Within several days or weeks these phenomena usually disappear without leaving a trace. Occasionally it results in death.

In the pathogenesis of serum sickness formation of precipitin type antibodies under the influence of heterologous proteins (which break down slowly) play a part. They form immune (antigen- antibody) complexes which are fixed in the endothelial cells of capillaries, lymphocytes, cells of the skin, kidneys, liver and other organs and damage them.

 Man’s increased sensitivity to certain substances underlies a number of special allergic diseases which set in suddenly and run paroxysmal course. These diseases are characterized either by a skin affection taking the form of edema, wheals or eczema, or by irritation of the mucous membranes of the eyes and nose, or by spasm of the blood vessels and smooth muscles . Such diseases include bronchial asthma manifested in attacks of dyspnea resulting from spasm of the smooth muscles and swelling of the mucosa of small bronchi (edema). The allergens causing attack of bronchial asthma gain entrance into the organism through the respiratory tract and may be of various origin - dust, pollen, hair, wool, animal epidermis, drugs, etc.

 Attacks of bronchial asthma in a person formerly affected with it may be provoked also by conditioned reflexes. A patient sensitized to pallen may sometimes have an attack of the disease at the mere sight of a flower.

 Two main clinical pathogenetic forms of bronchial asthma are distinguished noninfectious- allergic (atopic) form and infectious - allergic form. Often atopic form is also complicated by the inflammatory diseases of the respiratory tracts.

 Hereditary predisposition is of great importance in the development of the atopic form of the bronchial asthma. Frequently it is observed in several members of the same family. Such an opinion exists that not the concrete forms of allergic diseases are inherited, but the ability to be sensitized under the influence of allergens. However, the probability of manifestation of bronchial asthma in children of diseased parents is higher than that of any other allergic diseases.

 Pollenosis (hay fever) is allergic disease which develops usually during the blooming period (in the spring or beginning of summer). It affects predominantly the persons particularly sensitive to pollen of certain plants (rye, asters, hyacinths, etc), and is characterized mainly by inflammation of the nasal mucosa and than conjunctiva (rhinitis and conjunctivitis). The severe forms of pollenosis are accompanied by the attacks of bronchial asthma.

 Urticaria and Quincke’s (angioneurotic) edema (Bannister’s disease) are characterized by the formation of bubbles on the skin which cause intense itch. Quincke’s edema is one of the main forms of the urticaria. Frequently urticaria is caused by the food allergens. Both these diseases may develop under the influence of the cold air. Action of cold as an allergen is realized by two ways:

1. influence of the low temperature on the skin causes non- specific damage to most cells of the connective tissue and liberation of histamine;
2. the low temperature of the air promotes the change of antigenic properties of the proteins of the skin and formation of autoallergens, against which the specific antibodies are formed in the organism.

Histamine and other mediators dilate the precapillaries, capillaries and venules, increase permeability of their walls. This results in acceleration of exudation in the skin, and the bubbles are formed.

 As distinct from the urticaria, in Quincke’s edema a large amount of exudate is accumulated in the profound layers of the skin and in connective tissue (especially in cheeks, lips, tongue), but in urticaria the receptors are strongly irritated, and this causes excruciating itch.

 The hereditary predisposition plays a great part in the development of the urticaria and Quincke’s edema.

 The bacterial allergies (tuberculin type reactions ) are allergic reactions which develop as a result of repeated entering of bacteria and their vital activity products into the organism. This type of allergy was first observed by Koch (1890). 6-12 hours after the injection of tuberculin (filtrate of broth containing the culture of tubercle bacilli) into the organism of the patient having consumption, at the site of injection hyperemia and swelling occur. These changes reach the maximum level in 24-4 8 hours. This reaction is not observed in persons which are not infected by tuberculosis.

 The bacterial allergic reactions are highly specific and are used even in the diagnosis of the cases which are not revealed by the clinical and laboratory methods (reactions of Pirquet and Mantoux in tuberculosis, Burnet’s reaction in brucellosis, Casoni’s reaction in echinococcosis, etc.)

 Contact dermatitis is the allergic reaction which appears as skin’s hypersensitivity against the substances which do not possess the antigen properties (haptens). The contact dermatitis is caused by chemical elements and drugs (quinine, antibiotics, phenol, benzene, soap, etc), as well as by large-molecular synthetic substances (rubber, materials of the synthetic fibers, etc).

 The contact dermatitis is characterized by inflammation of the superficial layer of the skin. In the inflamed area leukocytes are accumulated, epiderm is degenerated and is easily rejected.

 Transplant rejection is frequently observed in heterotransplantation and even in homotransplan­ta­tion­. Beginning from the first days after transplantation, around the transplanted tissue or organ inflammatory infiltration is developed which consists of lymphoid cells, histiocytes and plasmacytes.

 In a week after the transplantation in the endothelial cells of the graft’s (transplantat’s) capillaries and in basal membranes swelling is revealed, whereas the parenchymal elements are subjected to dystrophy and are necrotized. Then in the large vessels thrombi are formed.

 Autoallergy is a state in which the organism’s immune system fails to distinguish between “self” and “nonself” and reacts by formation of autoantibodies against one’s own tissues. So, autoallergy is the opposite of immune tolerance.

The mechanisms by which the immune tolerance of the organism is broken and autoallergy occurs, may be immune, genetic and microbial. All of these mechanisms may be interacting.

I. Immune mechanisms:

1. polyclonal activation of B cells and generation of celf-reacting B cell clones-B cells may be directly activated by stimuli such as microorganisms and their products leading to bypassing of T cell tolerance;
2. decreased T suppressor and increased T helper cell activity- may lead to high levels of auto- antibody production by B cells contributing to autoallergy;
3. fluctuation of anti-idiotype network control- may cause failure of mechanisms of immune tolerance;
4. sequestered antigen released from tissues- “self- antigen” (autoallergen) which is completely sequestered- may act as “foreign- antigen” if later introduced into the circulation. For instance, in trauma to the testis there is formation of anti-sperm antibodies against spermatozoa. Similar is formation of auto-antibodies against lens crystallin.

II. Genetic factors- there is evidence in support of genetic factors in the pathogenesis of autoallergy, for instance, increased familial incidence of some of the autoimmune disorders was observed.

III. Microbial factors- infection with microorganisms (especially viruses and less often bacteria and mycoplasma) has been implicated in the pathogenesis of autoallergic diseases.

According to their action mechanism, the auto-antibodies are divided into 3 groups:

1. aggressive or damaging auto- antibodies-exert cytotoxic action on the corresponding tissues( they combine with complement);
2. auto-antibodies-“witnesses”- their existence in the blood witnesses damage to one or another tissue, but they do not exert pathogenic action on the organism (they do not combine with complement and do not participate in precipitation test);
3. protective auto- antibodies- take part in the immunity reactions.

Depending upon the type of autoantibody formation, the autoallergic diseases are classified into two groups;

I. Organ specific diseases- the autoantibodies react specifically against an organ or target tissue component and cause its chronic inflammatory destruction. The affected tissues are:

1. endocrine glands – Hashimoto’s thyroiditis, Grave’s disease, insulin- dependent diabetes mellitus, idiopathic Addison’s disease, etc;
2. alimentary tract- autoimmune atrophic gastritis or pernicious anemia, ulcerative colitis, etc;
3. blood cells- autoimmune hemolytic anemia, autoimmune thrombocytopenia, etc;
4. various other tissues and organs-myastenia gravis, autoimmune orchitis, autoimmune encephalomyelitis, primary biliary cirrhosis, chronic active hepatitis, membranous glomerulonephritis, autoimmune skin diseases, etc.

III. Non- organ specific diseases- a number of antibodies are formed which react with antigens in many tissues and thus cause systemic lesions: systemic lupus erythematosus, rheumatoid arthritis, scleroderma, polymyositis, dermatomyositis, polyarteritis nodosa, mixed connective tissue disease, Sjogren’s syndrome (triad of dry eyes, dry mouth and rheumatoid arthritis), Reiter’s syndrome (triad of arthritis, conjunctivitis and urethritis), etc.

A few autoallergic diseases overlap between these two categories.

One must distinguish autoallergic syndromes from autoallergic diseases. Autoallergic syndromes come to being at the certain stage of non-allergic diseases and complicate their course. For instance, in myocardial infarction auto-antibodies are formed against the proteins that pass into the blood from the necrotized areas of the cardiac muscle and damage the healthy parts of the myocardium (postmyocardial infarction syndrome). The infectious hepatitis (acute dystrophy of the liver), burns, radiation sickness and other diseases may be complicated by the autoallergic syndromes.