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Учреждение образования
«Гомельский государственный медицинский университет»

Кафедра патологической физиологии
Обсуждено на заседании кафедры
Протокол №7 от 30.08.2017

МЕТОДИЧЕСКАЯ РАЗРАБОТКА
Для проведения занятия со студентами
3 курса ФПСЗС, обучающихся на английском языке
по патологической физиологии

Тема: **Иммунопатологические процессы**

Theme: **Immunopathological processes**

Время 3 ак. часа

Actuality of the theme. Immune insufficiency is to be considered as an anomalous condition of immune system. The displays of these insufficiencies are quite various: rise of sensitivity to bacterial and viral infections, development of autoimmune diseases. Its clinical displays are determined by defeating of a certain link of immune response. Diagnostic of immune insufficiency is complicated, because there are no specific symptoms, or clear parallelism between clinical symptoms and laboratory confirmation. Illness masks and has manifestation similar various clinical symptoms.

Learning goals of the lesson: To study etiology and pathogenesis of primary and secondary forms of immunodeficiency states (IDS). To study mechanisms of allergy development. Consider mechanisms for failure of immunological tolerance as a factor of initiation of self-damage to body tissues.

Educational goals of the lesson: formation of scientific outlook and theoretical basis of future specialists on the basis of fundamental knowledge and the latest achievements of pathological physiology.

Objectives of the lesson:

1. To know main clinical and diagnostic criteria of IDS; manifestations and basic principles of IDS treatment. To know etiology and pathogenesis of HIV infection, clinical manifestations of AIDS.
2. To know etiology and general pathogenesis of allergic reactions.
3. To know I, II, III, IV, types of allergic reactions according to Jell and Coombs classification, be to be able to explain mechanisms of their formation.
4. To know basic principles of diagnosis, prevention and treatment of allergic diseases.
5. To know the main reasons for failure of natural immunological tolerance, pathogenesis of autoimmune diseases.

To repeat the following questions from related disciplines to ensure absolute mastery of the material:

1. Structure of hematoparenchymal barriers; effector cells of immune system (course of histology, cytology and embryology disciplines).
2. Structure and functions of immune system, types of immunity; characteristic of immunocompetent cells, mechanisms of immune response; structure and characteristics of immunoglobulins (microbiology, virology and immunology disciplines);

Control questions of the lesson:

1. Hereditary and acquired immunodeficiencies (ID): causes, mechanisms of formation and manifestation of ID.
2. Principles of diagnostics and immunotherapy of ID.
3. Allergy: definition, etiology, classification, stages of allergic reactions.
4. Allergic reactions type I: pathogenesis and main clinical manifestations
5. Allergic reactions type II: pathogenesis and clinical manifestations.
6. Allergic reactions type III: pathogenesis and clinical manifestations.
7. Allergic reactions type IV: pathogenesis and clinical manifestations.
8. Autoimmune diseases: definition, classification, mechanisms of violation of immune tolerance and occurrence of immune autoaggression.

Calculation of study time

Total study time 3 ac.hours

№ п/п	Contents	Calculation of study time
1.	Introduction. Motivational characteristic of the theme	3 minutes
2.	Written control of students on the topic of the lesson	15 minutes
3.	Interviews with students about the topic of the lesson	60 minutes
4.	Self-managed student work	15 minutes
5.	Summing up the results of the lesson	5 minutes
6.	Decision of situational tasks	20 minutes
7.	Task for the next lesson	2 minutes

Additional materials:

IMMUNE SYSTEM

There are two types organs of immune systems - central (or primary) and peripheral (or secondary).

The central organs of the immune system are bone marrow and thymus - a place of lymphopoiesis

The peripheral organs of the immune system include:

1. Lymph nodes, lymph ducts, and spleen.
2. Mucous-Associated Lymphoid Tissue
3. Skin-Associated Lymphoid Tissue

The cells of immune system::

1. Antigen presenting cells: are macrophages, dendritic cells of types 1 and 2, B-lymphocytes.
2. Regulatory cells: T-inducers of T-helper cells type 1, 2 and 3, the natural regulatory T cells.
3. Effector cells: plasma cells (differentiated from B cells), cytotoxic T cells with the phenotype of CD8 + (or T-killer cells); effector T cells of inflammatory with the phenotype CD4 + (or T-lymphocytes, responsible for delayed-type hypersensitivity); neutrophils, eosinophils, basophils, mast cells, natural killer cells (NK-cells), macrophages.
4. Memory cells: memory T cells with phenotype CD8 +; memory T cells with the phenotype of CD4 +; long-lived plasma cells; memory B cells.

The molecules of immune system:

1. The antigen presenting, antigen-recognition and antigen-binding molecules (a set of these molecules is unique to each organism for each lymphocyte clone for each specific immune response)
 - free immunoglobulin: IgM, IgG, IgA, IgE, IgD;
 - antigen presenting molecule: human leukocyte antigens (HLA I and II), and molecules CD1 (a, b, c, d, e);
 - immunoglobulin receptors of B cells to recognize and bind antigen (B cellular receptors - BCR);
 - T-cell receptors to recognize and bind antigen (T cellular receptors - TCR);
2. Adhesion molecules mediate interactions between cells and ligands in direct contact:
 - the superfamily of immunoglobulin-like molecules;
 - integrins;
 - selectins;
 - mucins;
 - superfamily of receptors to tumor necrosis factor and nerve growth factor - TNF / NGF (or a molecule that mediate apoptosis);
 - Link-family (components of the extracellular matrix).
3. Immunocytokines are hormones of the immune system, acting more with para- and autocrine, at least - with endocrine effects:
 - interleukins - ILs;
 - colony-stimulating factors -CSFs;
 - interferons - IFNs;
 - tumor necrosis factors - TNFs;
 - transforming grows factors -TGFs;
 - chemokines et al.
4. Combined group of different inflammatory mediators including complement proteins, acute phase proteins, prostanoids and leukotrienes, proteolytic enzymes, and others.

Stage of immune response

1 endocytosis, processing and presentation of antigen

2 antigen recognition

3 signal transduction and lymphocyte activation

4 clonal expansion of lymphocytes

5 maturation of effector cells and memory cells

6 effector activity

Immunopathology:

- Allergy
- Autoimmune disease
- Immunodeficiency

HYPERSENSITIVITY

Hypersensitivity is an **excessive** immunologic reaction to an antigen that results in a pathologic response after **reexposure to the same** antigen.

Allergy, autoimmunity and alloimmunity are hypersensitivity response; the difference is the source of antigen to which the hypersensitivity is directed.

Allergy is a typical immune pathological process, that is characterized by change in hypersensitivity to allergen, injury of self-structures, cell and organ functions, associated with decrease in adaptive abilities of organism and its vital ability impairments.

Autoimmunity occurs when tolerance to one's self-antigens breaks down and antibody is formed against one's own antigens. Self-antigens are recognized as foreign in autoimmunity, and host tissues are destroyed by autoantibodies.

Alloimmunity is the development antibodies against antigens from an individual of the same species. It is observed during immunologic reactions against transfusions, grafted tissue, or a fetus during pregnancy.

Classification and characteristic of allergens.

By origin and nature: Endogenic, Exogenic

Endoallergens: natural (primary) and acquired

Natural (inherent) isolated tissues from immune system: crystalline lens, nervous system, colloid of thyroid, female and male gonads

Acquired (secondary) endoallergens are formed from normal proteins after damage its structure by environment infectious and noninfectious nature.

Exoallergens: infectious and noninfectious

Infectious: viruses, bacteria, fungi and parasites and product of their activity

Noninfectious: home, drugs, epidermal, pollen and food (animal and vegetable nature)

Exoallergens by penetration into organism:

- respiratory (pollen, dust, aerosol...)
- alimentary (foody allergens)
- contact (drug unctures, cosmetic creams, staining agents, tars...)
- parenteral (drugs, insect poisons...)
- transplacental (some antibiotics, proteins...)

Classification of allergic reaction (Cooke, 1930):

According to occurrence duration:

Immediate type (in 15–20 minutes, no longer than 6 hours)

Delayed type (in 6 hours, max 24, 48, 72 hours)

Pathogenic classification (by P. Gell and K. Coombs, 1963)

1. hypersensitivity type I (Immediate type, anaphylactic, reagin type)
2. hypersensitivity type II (Immediate type, cytotoxic)
3. hypersensitivity type III (Immediate type, immune complex)
4. hypersensitivity type IV (Delayed type, cell-mediated)

Stages of allergic reaction:

1. immunologic,
2. pathochemical,
3. pathophysiological

General signs of allergy:

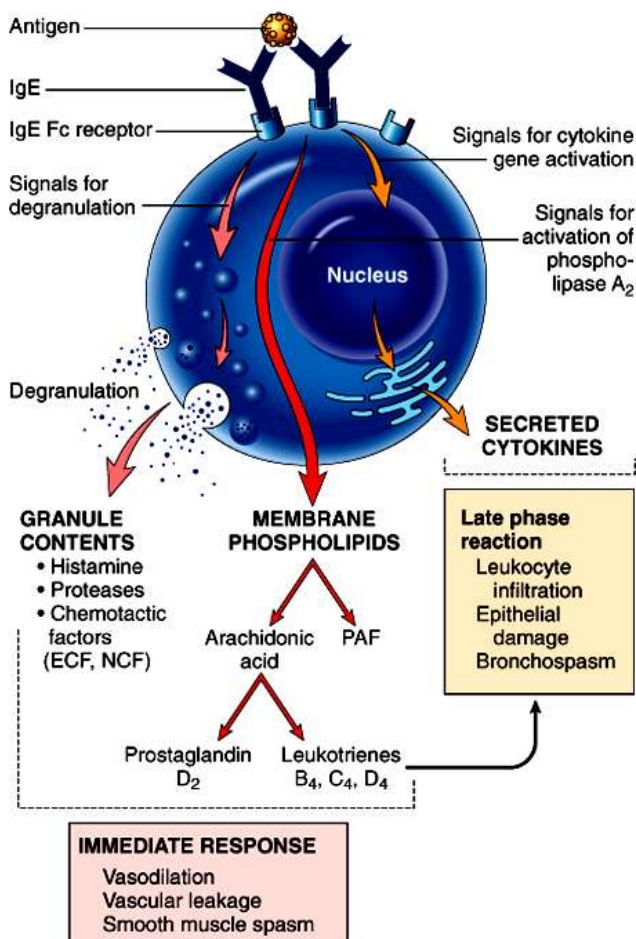
- damage of own structure of organism

- inadequate reactions on allergen
- hyperergic answered
- decrement of adaptive possibility of organism
- local or generalized reactions
- possible to develop nonimmune disorders

Criteria of allergic condition:

- 1. Genetic:**
 - aptitude for allergy may be inheritance (30-40%)
 - relation with HLA system
- 2. Immunologic:**
 - tendency to decreasing a level of CD4 (helpers)
 - decreasing a level of CD8 (cytotoxic lymphocytes)
 - increasing a level of Ig E
- 3. Functional:**
 - predisposing factors: inherent and acquired functional defects
 - atopy associated with decreasing of activity β -adrenoreceptors
 - increasing a sensitivity bronchus to acetylcholine and histamine
 - eosinophilia
 - decreasing a histaminepeptic activity in serum (hystaminopexia) in norm =10-24 mkg/ml
- 4. Specific (allergologic):**
 - skin tests
 - elimination tests
 - allergologic tests in vitro
 - PACT
 - Shelly tests
 - Reaction of degranulation of mast cells
 - Examinations on isolated organs

HYPERSENSITIVE TYPE 1



Hypersensitive type I, IgE mediated. Anaphylactic. Humoral/Immediate, reagin type

Cells: mast cells, basophils

Target cells 1st order: mast cells, basophiles – these cells have the most ability to bind with IgE-antibodies. One basophile can fixed 3000- 300 000 molecules of IgE

Target cells 2nd order: macrophages, monocytes, eosinophils, thrombocytes and lymphocytes, but ability to bind with IgE less.

Antibodies: IgE, IgG₄

Figure 1 Pathogenesis of hypersensitive type 1

Pathogenesis:

Sensibilization: First exposure to offending antigen (allergen) stimulates IgE production by plasma cells derived from Bcells. IgE binds to IgE Fc receptors on cell membrane of mast cells.

1. Immune stage: Reexposure to same antigen (allergen) resulting in allergen fixes to IgE bound on surface of **target cells** (mast cell) and causes cross-linking of adjacent IgE molecules. It causes a

series of reactions that result in release of primary and secondary mediators.

2. **Pathochemical stage:** release of primary and secondary mediators

Mediators of hypersensitivity type I

Mediator	Biologic activity
Primary	
histamine	increase in vascular permeability, dilation of arterioles and venules, smooth muscle contraction, increase in mucose secretion
eosinophilic chemotactic factor	chemotaxis of eosinophils
neutrophilic chemotactic factor	chemotaxis of neutrophils
basophilic kallikrein	bradykinin formation
heparin	anti-coagulant and anti-complement activity
Newly synthesized	
LTC ₄ , LTD ₄	smooth muscle contraction, increase in vascular wall permeability
LTB ₄	chemotaxis of neutrophils and eosinophils
PgD ₂	smooth muscle contraction, increase in vascular wall permeability
FAT	Tr aggregation, mediator release, smooth muscle contraction
TrA ₂	Tr aggregation, smooth muscle contraction
Secondary	
PgF ₂	smooth muscle contraction, increase in vascular permeability, stimulation of mediator release from mast cells
PgE ₂	bronchial smooth muscle relaxation, inhibition of mediator release from mast cells
Bradykinin and leukokinin	increase in vascular permeability, dilation of arterioles and precapillaries, smooth muscle contraction, stimulation of neutrophil, monocyte, eosinophil chemotaxis
Serotonin	smooth muscle contraction, increase in vascular wall permeability, spasm of renal, cardiac, pulmonary vessels, dilation of vessels
Lysosomal enzymes of granulocytes and oxydants	cell injury

FAT – factor activation of t thrombocytes; LT – leucotrien; Pg – prostaglandin; Tr – tromboxan

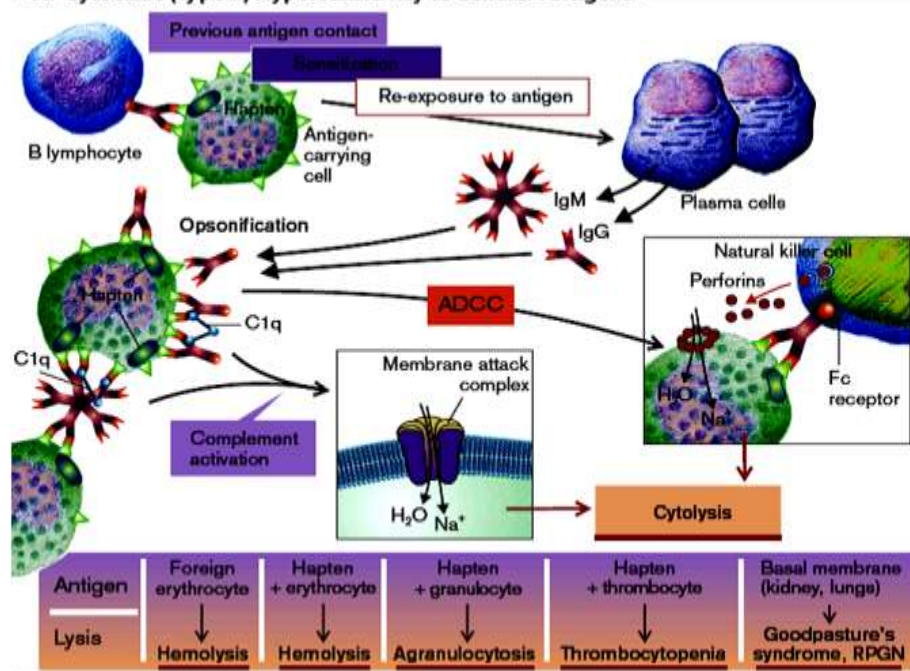
3.

4. **Pathophysiological stage:**

Allergy: allergic rhinitis, asthma, urticaria, food allergies, anaphylactic shock

HYPERSENSITIVE TYPE 2

A. Cytotoxic (Type II) Hypersensitivity to Cellular Antigens



Hypersensitive type II.
Cytotoxic. Tissue specific.
 Humoral/Immediate.
Antibodies: IgG_{1,2,3} or IgM

Figure 2 Pathogenesis of hypersensitive type 2

Pathogenesis:

Antibodies are formed against target antigens that are either normal or altered cell membrane components.

1. **Immune stage. 3 main way realized immune stage:**

Complement dependent cytotoxicity. Two Mechanisms:

- Direct lysis by complement activation
- Lysis by opsonization (C3b) - often involves RBCs

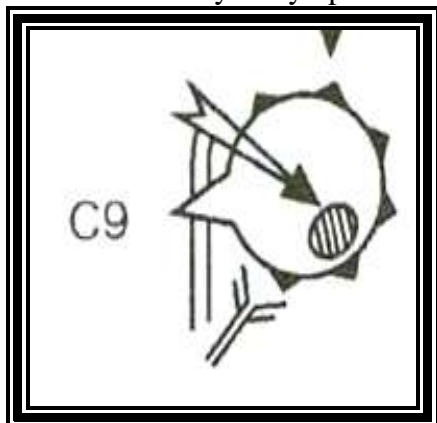


Figure 3 Complement dependent cytotoxicity

Examples: Transfusion reactions, erythroblastosis fetalis, autoimmune hemolytic anemia, autoimmune thrombocytopenia, certain drug reactions

Antibody-dependent cell-mediated cytotoxicity (ADCC): Monocytes, neutrophils, eosinophils, or NK cells recognize cells by Fc portion of IgG bound to cell and kill cell without phagocytosis

Example: Goodpasture's syndrome

Antibody-dependent phagocytosis:

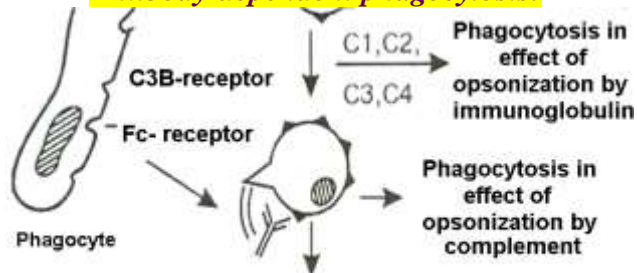


Figure 4 Antibody-dependent phagocytosis

Mechanism of phagocytosis is dependent by bound allergen to phagocytes by Fc-receptor. Activated phagocytes are absorbed target cells and destroy it with lysosomal enzymes

2. Pathochemical stage:

Mediators of Hypersensitivity type II

Mediator	Biologic activity
activated components C_{4b}2a3b	immune fixation to phagocytes, activation of phagocytosis, granule oxydation
C_{3a}, C_{5a} —anaphylotoxins	neutrophil, eosinophil, monocyte chemotaxis
C₅₆₇	neutrophil selective chemotaxis
C₅₆₇₈	slow injury of cell membrane, release of lysosomal enzymes
oxydant	lipid peroxidation, cell membrane injury
lysosomal enzymes	opsonized cell injury

3. Pathophysiological stage:

Allergy: Immediate drug reaction. **Autoimmunity:** Hemolytic anemia, Graves disease.

Alloimmunity: Transfused blood cells, hemolytic disease of the newborn

HYPERSENSITIVE TYPE 3

Hypersensitive type III. Immune complex. Humoral/Immediate.

Antibodies: IgG_{1,2,3} or IgM

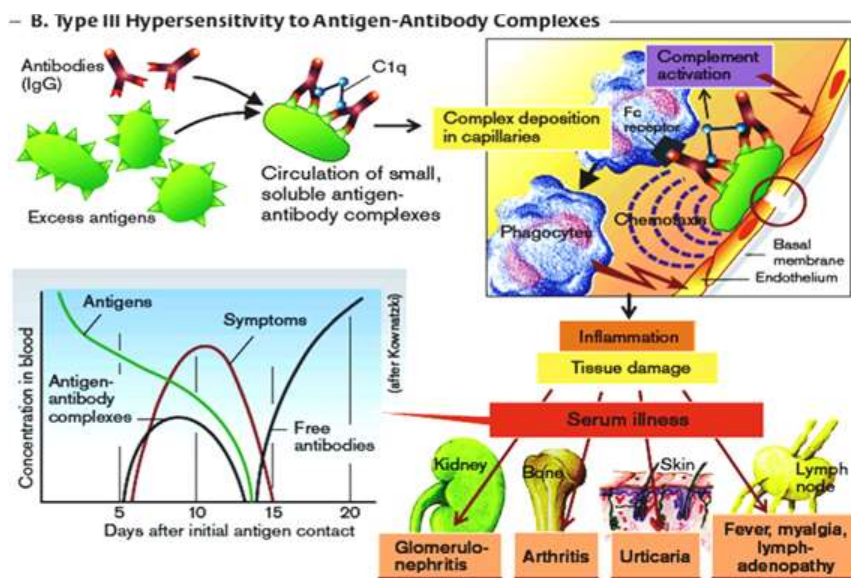


Figure 5 Pathogenesis of hypersensitive type III.

Pathogenesis:

Antigen-antibody (immune) complexes are formed.

1. Immune stage:

Pathogenic immune complexes (if contain of **antigen more than antibodies**) are formed in circulation and deposits in tissues (circulating immune complexes), activate complement and cause neutrophil accumulation at the site of immune complex deposition and result in acute inflammatory reactions in tissue.

2. Pathochemical stage:

Mediators of Hypersensitivity type III

Mediator	Biologic activity
Membrane attack complex, enzymes of phagocytes and destructed cells, active forms of oxygen and free radicals	Injury of cell and no-cell structure
Chemotactic factors, LTB_4 , TNF, kinins, C_{3a} complement factor, anaphylotoxins, C_{4b2a3b} , C_5 , C_{5b67}	Induction of inflammatory reactions in the zone of allergy
histamine, serotonin, LTD_4 , LTC_4 , C_{3a} , C_{5a}	An increase in vascular and basement membrane permeability
Hageman's factor, Tr_{A2}	Activation of thrombus formation

3. Pathophysiological stage:

Allergy: Arthus reaction, that of allergic alveolitis.

Autoimmunity: Serum sickness, celiac disease, glomerulonephritis, systemic lupus erythematosus, vasculitis.

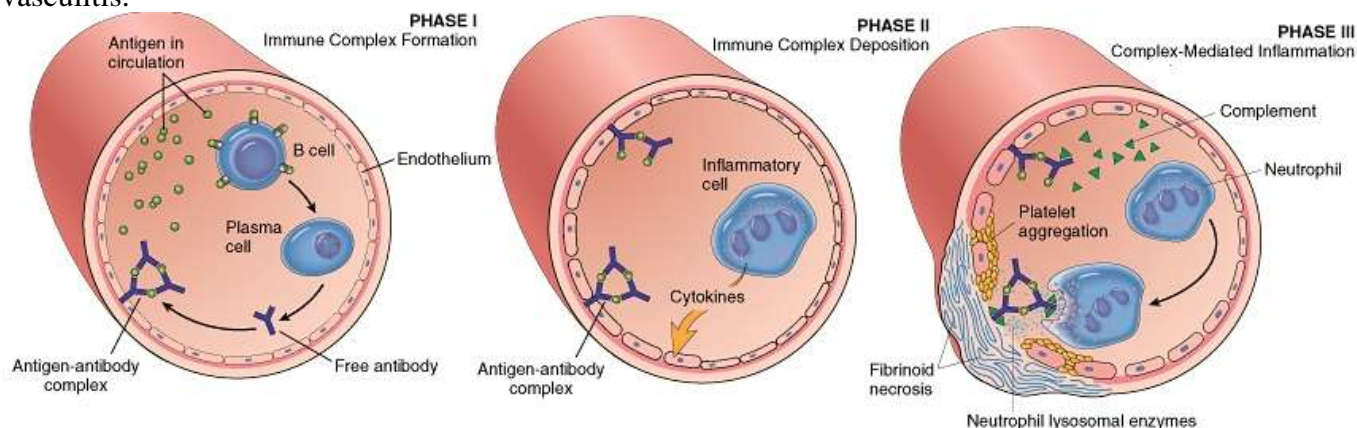


Figure 6 Schematic illustration of the three sequential phases in the induction of systemic type III (immune complex) hypersensitivity.

Serum sickness

Serum sickness is an immune complex-mediated hypersensitivity reaction characterized by fever, rash, arthritis, arthralgia, and other systemic symptoms. Von Pirquet and Schick first described and popularized the term serum sickness at the turn of the 20th century, using it to describe patients who had received injections of heterologous (nonhuman) antitoxins for the treatment of diphtheria and scarlet fever. Classic serum sickness is now rarely seen, because the use of foreign proteins is limited to antitoxins such as those used to treat botulism, diphtheria, rabies, and snake, scorpion, and spider venom. A similar syndrome, serum sickness-like reactions (SRLR), occurs after the administration of a medication.

HYPERSENSITIVITY TYPE IV.

Cell-mediated. Cellular/Delayed.

Pathogenesis:

It is the principal pattern of immunologic response to a variety of intracellular microbiologic agents, such as *Mycobacterium tuberculosis*, and many viruses, fungi, protozoa, and parasites.

Immune stage:

Effectors:

Th1 cells --> activate macrophages (DTH)

Th2 cells --> activate eosinophils

CD8 T cells --> directly cytotoxic

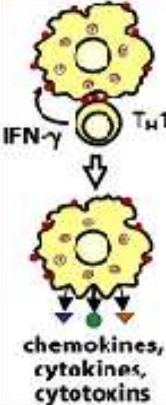
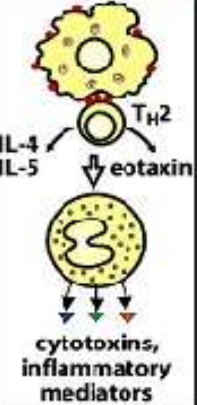
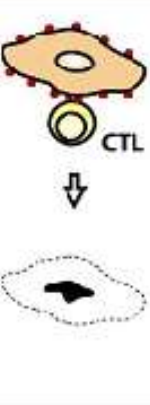
Type IV			
Immune reactant	Th1 cells	Th2 cells	CTL
Antigen	Soluble antigen	Soluble antigen	Cell-associated antigen
Effector mechanism	Macrophage activation	IgE production, eosinophil activation, mastocytosis	Cytotoxicity
			
Example of hypersensitivity reaction	Contact dermatitis, tuberculin reaction	Chronic asthma, chronic allergic rhinitis	Graft rejection

Figure 7 Pathogenesis of hypersensitivity type IV

Delayed type hypersensitivity reactions mediated by CD₄⁺ T cells, and direct cell cytotoxicity mediated by CD₈⁺ T cells.

1. Pathochemical stage:

Mediators of Hypersensitivity type IV

Mediator	Biologic activity
Mediators, effect on lymphocytes	
Factors of transmission	Factors are responsible for Delayed type Hypersensitivity, cytotoxic action and blast-transformation
Factors of transformation: mitogenic, blastogenic	Factors determining mitogenic and blastogenic activity, non-specific involvement of lymphocytes in allergic reaction
IL-1	Stimulation of T-lymphocyte proliferation influenced by mitogens and antigens
IL-2	Promotes T-lymphocyte proliferation in CTL, helper activity in

	respect of B-lymphocytes
Mediators, effect on phagocytosis	
Macrophageal chemoattractant protein (MCP)	Stimulate concentration of macrophages in allergic alteration region.
Macrophageal inflammatory protein (MIP)	Transform macrophages (monocytes) in active form, activate endothelium
Factor of chemotaxis (FC)	Stimulate chemotaxis of macrophages and granulocytes
Mediators, effect on target cells	
Lymphotoxine (TNF-p)	Cytotoxic effect
Interferon - a (IFN-a)	Antiviral effect, enhance cytotoxicity of lymphocytes, activate macrophage and NK
Interferon - y (IFN-y)	Antiviral effect stimulate immune reactions (enhance of antibodies productions, cytotoxicity of lymphocytes, phagocytosis by macrophage)
Factor of inhibition of proliferation	Inhibited of cells proliferation
Factor of inhibition of cloning	Inhibited of clonal cells growth

2. Pathophysiological stage:

Allergy: Contact dermatitis.

Autoimmunity: Hashimoto thyroiditis, rheumatoid arthritis.

Alloimmunity: Graft rejection. Seldom: particular disorder is associated with a single mechanism.

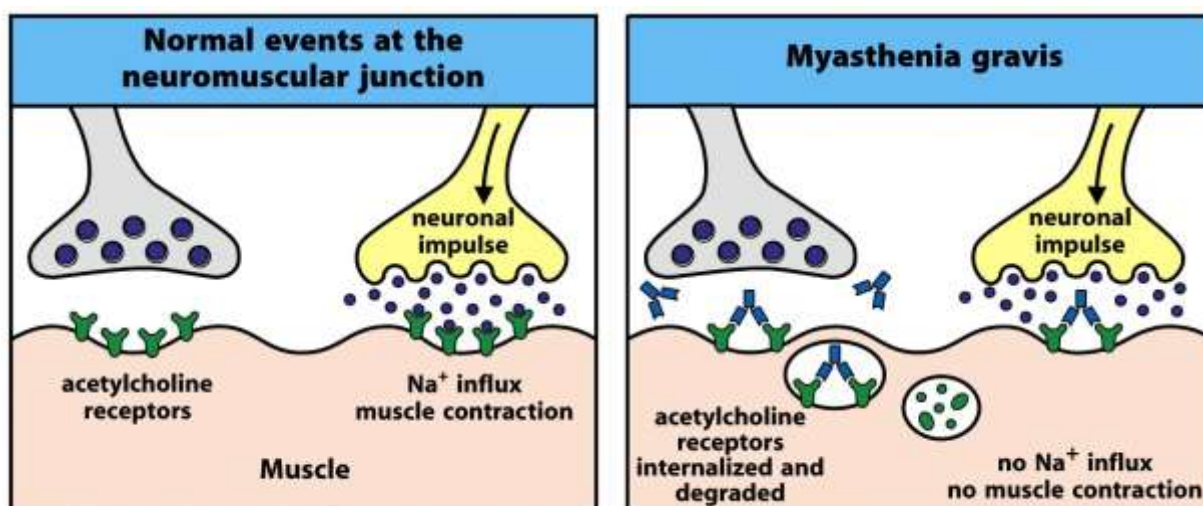


Figure 14-22 Immunobiology, 7ed. (© Garland Science 2008)

Figure 9 Pathogenesis of myasthenia gravis

HYPERSENSITIVITY TYPE V (S.Sell 1978): the immune response is developed against receptors, hormones, metabolites, or clotting factors.

AUTOIMMUNE DISEASE

Disease deterministic by auto-antibodies and cytotoxic lymphocytes directed to auto antigens

Main mechanism:

- Mutation of immunocompetent cells
- Hereditary or acquired pathological disbalance among immunocompetent cells (pathological over proliferation of «forbidden» clones or deficiency of normal lymphocytes)
- Primary or secondary changes in system «idiotypic – anti idiotypic», namely in system of autoregulation of immune response (appearance of «forbidden» class immunoglobulin or pathological disbalance of its normal forms)

Autoantigens:

- average (proteins and other macromolecules)

- «sequestered» (isolated) are in tissues, inaccessible to lymphocytes (brain, crystalline lens, nervous system, colloid of thyroid, female and male gonads)
- **modified** (appears in damage, mutations, oncology transformations)

Autoantibodies:

1. Natural or physiological
2. Antibodies-attestor
3. Aggressive or pathogenic

Pathogenesis of autoimmune disorders has 2 stages:

1. **Inductive stage**, failure of immune auto tolerance.

Mechanism of immune tolerance:

- 1) **Clonal deletion (or «clonal abortion»)** – it is a death of immunocompetent cell in case of negative selection in thymus or marrow. Arrive at apoptosis of T- and B- lymphocytes, that have high specific antigen determination receptors to autoantigens
- 2) **Clonal anergy** – areactivity of lymphocytes, that have B-cells receptors to solute autoantigens in low concentrations. After contact with antigen lymphocytes save vitality, but this cells not response to signal from antigen specific receptors – this cells functional inactive.
- 3) **T-cells mediated immunosuppression.** For saving tolerance peripheral autoreactive T lymphocytes must be destroyed by apoptosis or stay anergic by effect of cytokines Th2 supression

2. **Effector stage.** Its proceed by one or several types of hypersensitive (II, III, IV or V type P.G.H. Gell и P.R.A. Coombs)

Pathogenic class of autoimmune disease:

1. **Class A. Primary autoimmune disease with genetic burden.** For involved organs may be organospecific (autoimmune thyroiditis), intermediate (autoimmune pathology of liver and gastro – intestinal tract) and organonspecific (collagenoses).
2. **Class B. Secondary autoimmune disease (f.e. alcohol liver cirrhosis, chronic radiation sickness)**
3. **Class C. Autoimmune disease that base on genetic defect of complement** (some forms of hereditary hemolytic anemias).
4. **Class D. Autoimmune disease with slow viruses and prions** (Alzheimer disease).
5. **Class E. Combined forms**

PSEUDOALLERGIC REACTIONS

Stages:

1. **Pathochemical** (mediators same in true allergic reaction: histamine, leucotrien, products of complement activation, kallikrein-kinins system)
2. **Pathophysiological** (clinical signs: urticae, Quincke's disease, bronchismus, anaphylactic shock)

Type of pseudoallergic reactions:

1. **Reaction with releasing mediators of allergy** (histamine ...) **from mast cells, in action of environment factors.** IgE independent activators of mast cells: antibiotics, myorelaxantes, opiates, polysaccharides, x-ray contrasts drugs, anaphylatoxin (C3a, C5a), neuropeptides (substances P), ATP, IL-1, IL-3; mechanical irritation (urticarial dermographism), physical factors (cold urticaria), ultraviolet radiation (sun urticaria), physical activity (cholinergic urticaria); nutritive: fish, tomatoes, egg protein, strawberry, chocolate.
2. **Reaction with metabolism disturbances of polyunsaturated fatty acids (at first arachidonic acid).** Depression of COG lead a metabolism of arachidonic acid in lipoxygenase way. As a result over amount of leucotrien. Example: effect of aspirin or other nonsteroid anti-inflammatory drugs.
3. **Reactions with uncontrolled activation of complement.** Hereditary deficiency of first component of complement (inherent angioneurotic Quincke's edema) or activation of complement on alternative way in case of activity by cobra venom, bacterial lipopolysaccharines, thrombolytic drugs,

narcotic analgesics, some enzymes (trypsin, plasmin, kallikrein...). Activation a complement system lead to formation C3a, C5a, that cause release a mediators from mast cells, basophiles and thrombocytes.

Alloimmune graft rejection

Alloimmunity occurs when an individual's immune system reacts against of the tissues of other members of the same species. Transplantation of organs is commonly complicated by an alloimmune response against donor antigens. The primary mechanism of the rejection of transplanted organs is a type IV, cell-mediated reaction. Because HLA antigens are the principle targets of the recipient this greatly enhances the possibility of a successful graft.

Transplant rejection is classified as hyperacute, acute, or chronic depending on the amount of time that elapses between transplantation and rejection. Hyperacute rejection usually occurs in recipients having preexisting IgG or IgM antibody to antigens in the graft. As circulation to the graft is reestablished, antibody binds to the grafted tissue and activates the inflammatory response. This response initiates the coagulation or blood clotting cascade that results in cessation of blood flow in into the graft.

Acute rejection is a cell-mediated immune response that occurs approximately 2 weeks after the transplantation. The recipient develops an immune response against unmatched HLA antigens and shows an infiltration of lymphocytes an macrophages characteristic of type IV hypersensitivity reaction. Chronic rejection occurs after months or years of normal function. It is characterized by slow progressive organ failure. Chronic rejection may be caused by inflammatory damage to endothelial cells lining blood vessels. It is likely a result of a weak immunologic reaction against minor histocompatibility antigens on the grafted tissue.

IMMUNODEFICIENT STATES

Immunodeficient states — group of independent diseases and related syndromes, which common signs is a insufficiency and inability of organism to resist the foreign antigenic aggression.

Immunodeficiencies are classified into:

- *primary* immunodeficiency disorders (almost genetically determined)
- *secondary* immunodeficiency states (arising as complications of infections, malnutrition, aging, side effects of immunosuppression, irradiation, chemotherapy for cancer and other autoimmune disorders).

By level of disorders and localization of defect (phenotype classification):

1. Disorders of humoral immunity
2. Disorders of cell component and thymus functions
3. Combination ID (SCID)
4. Defects in phagocytosis
5. Defects in complement system
6. Defects in IL-system and cooperation of cells in immune response
7. IDS with inherited metabolic disorders
8. Small (minor) ID

Clinical "masks" of ID

- Recurrent and chronic disease (sinusitis, otitis, pneumonia, infections of urinary tract, pyelonephritis). Very high probability of ORL-organs diseases: otitis, sinusitis.
- Foci of infection of various localization (pyoderma, otitis, etc..)
- Recurrent purulent-inflammatory diseases
- Recurrent herpes skin and mucous membranes
- Sepsis and septic conditions in infant.
- Children with ID more prone to allergic, autoimmune diseases, neoplastic processes
- Chronic diarrhea and gastroenteropathy unclear origin;
- Long-term subfebrilitet and fever of unknown origin;
- Malabsorption syndrome;
- Recurrent fungal infections of the mucous membranes in the mouth, intestines, lungs;
- Lymphadenopathy, tonsillitis; hypoplasia of lymph nodes;

- Thymomegalia; hyperplasia or hypoplasia of the thymus gland;
- Atopic dermatitis with pyoderma, urticaria and swelling Kwinke, allergic diseases, complicated infections;
- **Hepatomegaly, splenomegaly;**
- Inadequate response to conventional methods of treatment and prevention of recurrence of the disease and vaccines (BCG, etc..)
- Signs of fatigue, tiredness, weakness, sleep disturbances;
- **Autoimmune diseases;**
- Lymphoma and myeloproliferative diseases, malignant tumors.

Typical association between the type of immunodeficiency, the agent and clinical manifestations:

I. Deficiency of humoral (B-level) immunity.

1. Deficiency of IgG, IgM.

Cause: extracellular pyogenic bacteria (streptococci, staphylococci, Haemophilus); viruses (enterovirus, Herpes zoster); protozoa (Pneumocystis, etc.)

Clinical and laboratory signs: defect of opsonization and killing of microorganisms, recurrent infections of lung, central nervous system, gastric and intestines.

2. Deficiency of secretory IgA.

Cause: extracellular pyogenic bacteria (streptococci, staphylococci), Haemophilus influenzae, Gram-negative bacteria, fungi, Giardia.

Clinical and laboratory signs: recurrent infections of mucous, respiratory tract, stomach, and intestines.

II. Deficiency of cellular (T-cell) immunity.

Cause: intracellular bacteria (Mycobacteria, Listeria, Legionella, Salmonella, Nocardia, Chlamydia); fungi (Candida, Histoplasmosis, Mucor mycosis), DNA viruses (herpes simplex virus, varicella zoster virus, cytomegalovirus, papova), protozoa (Toxoplasmosis, Cryptosporidiosis, Pneumocystis).

Clinical and laboratory signs: reduced number of T-lymphocytes and defect of intracellular killing of pathogens, frequent severe infection of lung, central nervous system, stomach, intestines, and skin.

III. Deficiency of phagocytes.

Cause: Gram-negative enteric and pyogenic bacteria (E.coli, Pseudomonas, Klebsiella, Staphylococcus), fungi (Candida, Aspergillus, Mucor mycosis).

Clinical and laboratory signs: impaired chemotaxis, oxygen-dependent metabolism, phagocytosis; septicemia, pneumonia, bacterial endocarditis, anorectal abscess.

PRIMARY IMMUNODEFICIENT STATES

B cell immunodeficiencies:

Deficiency of humoral immunity

1. ↓ resistance to infections caused by capsular bacteria: staphylo-, strepto-, pneumo-, gonococcus, **Pseudomonas aeruginosa** patients suffer from recurrent bacterial infections (especially by encapsulated bacteria because antibodies are critical for the opsonization and clearance of these microbes), although immunity to most viral and fungal infections is normal.
2. ↑ incidence of viral infections, ORL-organs and respiratory system
3. More often develop skin lesions, rarer – GIT
4. Cellular immunity is relatively preserved
5. Autoimmune syndrome, allergic reactions
6. Clinical manifestations - after 6-9 months, after the disappearance of maternal immunity

X-linked Agammaglobulinemia

Occurs in 1 in 10^3 to 10^6 males (X chromosome-linked).

The first type of immunodeficiency was described by Bruton in 1952. For the last forty years 50 variants of different primary immunodeficiencies were identified. As a rule, they are genetically determined monogenic diseases, autosomal recessive transmission trait or X-linked, sometime autosomal-dominant transmission trait (C1 inhibitor deficiency), sometime with unknown transmission trait.

X-linked agammaglobulinemia, also referred to as **Bruton's agammaglobulinemia**, is an **X-linked recessive chromosome defect** caused by genetic mutation of a B cell-specific tyrosine kinase. The defect leads to a B cell maturation disorder characterized by **arrested B cell development at the pre-B cell stage**. Recurrent respiratory tract infections are the most common clinical manifestations of the **resulting IgG deficiency**. Meningitis, pyoderma, and sepsis may also occur. These infections are typically caused by capsule-forming pyogenic bacteria, such as staphylococci, pneumococci, and streptococci. One-third of these cases are associated with seronegative oligoarthritis. Patients with X-linked agammaglobulinemia usually respond well to intravenous IgG replacement.

Selective IgA deficiency.

Occurs once in every 400 to 2,000 individuals. However, its incidence varies across racial and ethnic lines.

An abnormally **low concentration of IgA** in bodily secretions is, by far, one of the most common forms of humoral immunodeficiency. The incidence of the defect may be sporadic or familial. Selective IgA deficiency is commonly associated with an atopic disposition (elevated IgE) and HLA types B8 and DR3. **Around 50% of the patients remain asymptomatic. IgA deficiency is mainly associated with recurrent respiratory tract infections, but may also occur in autoimmune diseases like systemic lupus erythematosus (SLE) and sprue.**

Hyper-IgM syndrome

Hyper-IgM syndrome is characterized by the arrested development of B cells at the IgM level (*switching defect*). There is an abundance of circulating m+ and d+ B cells, but hardly any g+ or a+ B cells. The defect is X-chromosome-linked and recessively inherited. Since it is based on mutations in the gene of the CD40-ligand, CD40 is no longer able to mediate class switching in B cells. Recurrent respiratory tract infections are the main clinical features of IgG and IgA deficiencies. Besides the characteristic B cell pattern, thrombopenia and neutropenia may also be observed. IgG and antibiotic administration is the treatment of choice.

Common variable immunodeficiency (CVID)

- CVID has an estimated prevalence of about 1:50,000. The typical patient is between 20 and 40, and males and females are equally affected. About 20% of patients are diagnosed in childhood. CVID is a heterogeneous group of diseases all associated with inadequate immunoglobulin production. Low levels of immunoglobulin G (IgG), immunoglobulin A (IgA) and/or immunoglobulin M (IgM). Recurring infections involving the ears, eyes, sinuses, nose, bronchi, lungs, skin, GI tract, joints, bones, CNS, parotid glands, etc. These infections respond to antibiotics but recur upon discontinuation of the medications. Bronchiectasis can occur from severe and recurrent lung infections. Nodular lymphoid hyperplasia of the GI tract.

T cell immunodeficiencies:

DiGeorge syndrome

22q11.2 deletion syndrome affects between 1 in 2000 and 1 in 4000 live births. DiGeorge syndrome results from the deletion of some unidentified genes that map to chromosome 22q11. DiGeorge syndrome is an example of a T-cell deficiency that derives from **failure of development of the third and fourth pharyngeal pouches**. The latter gives rise to the thymus, the parathyroids. Thus these patients have a **variable loss of T-cell-mediated immunity (congenital thymic aplasia or hypoplasia), tetany (due to parathyroid hypoplasia gives rise hypocalcemia (50%)), and congenital defects of the heart and great vessels**, palatal abnormalities (50%), hypertelorism, hearing loss (both conductive and sensorineural), learning difficulties (90%) but broad range

Combined immunodeficiencies:

Severe combined immunodeficiency disease (SCID)

Approximately 1:100,000 births.

Severe combined immunodeficiency disease (SCID) — genetically determined common variable defects in both humoral and cell-mediated immune responses. Immunologically these patients are characterized by cell-mediated and humoral immunity advanced impairments, presented by lymphopenia, particularly T-lymphocytes.

- **Classic form** initially described in Swiss infants. Isolated block in maturation of lymphoid cells in safety of other hematopoietic lines. It is presented by lymphopenic agammaglobulinemia, thymus aplasia, congenital thymus dysplasia, presented by T and B lymphocytopenia with agammaglobulinemia. The remaining case of SCID is inherited as autosomal-recessive, or X-linked (75% of diseased are boys).

- The most common cases of autosomal recessive SCID is a **deficiency of the enzyme adenosine deaminase (ADA)**. Although the mechanisms by which ADA deficiency causes SCID are not entirely clear, it has been proposed that deficiency of ADA leads to accumulation of deoxyadenosine and its derivatives (e.g., deoxy-ATP), which are particularly toxic to immune lymphocytes, especially those of T-lineage. Hence there may be a greater reduction in the number of T-lymphocytes than of B-lymphocytes.

- **Reticular dysgenesis**. Defect in maturing of all lymphoid and myeloid cells (erythrocytes and megakaryocytes are intact). The cause is unknown. The clinical course of infection process is flash-like, enough in early death.

The main clinical symptoms are presented in the first months of life and include severe persistent polyorganitis potentially lethal infectious process with the severe physical delay. Patients with SCID are extremely susceptible to recurrent, severe infections by a wide range of pathogens, including *Candida albicans*, *P. carinii*, *Pseudomonas*, cytomegalovirus, varicella, and a whole host of bacteria.

Wiskott-Aldrich syndrome.

The incidence is about 4-10 in 1 million live births. There is no geographical factor.

Wiskott-Aldrich syndrome was linked in 1994 to mutations in a gene on the short arm of the X chromosome, which was termed Wiskott-Aldrich syndrome protein (*WASP*). It was later discovered that the disease X-linked thrombocytopenia was also due to *WASP* mutations, but different ones from those that cause full-blown Wiskott-Aldrich syndrome. Furthermore, the rare disorder X-linked neutropenia has been linked to particular mutations of the *WASP* gene. Wiskott-Aldrich syndrome is caused by altered expression of CD43, a glycoprotein that forms an important part of the cytoskeleton. Defective actin bundle formation in T cells and thrombocytes can be visualized by electron microscopy. It is characterized by **thrombocytopenia, eczema, and immunodeficiency**, ending in **early death**, only boys are diseased (sometimes these boys live up to 10 years). Lethal outcome is caused by infections, hemorrhages and malignant lymphomas.

Ataxia-telangiectasia (Louis-Bar syndrome)

The incidence world-wide is estimated to be between 1 in 40,000 and 1 in 100,000 people.

It is an autosomal recessive disorder beginning in early childhood, caused by neuronal degeneration predominantly in the cerebellum, and the subsequent development of telangiectasias in the conjunctiva and skin (ataxia refers to poor coordination and telangiectasia to small dilated blood vessels, both of which are hallmarks of the disease). Pathogenic association of these events is not revealed. The ataxia-telangiectasia locus is identified on chromosome 11p22-23 has been identified as a large gene.

Signs and symptoms:

- **Ataxia** (difficulty with control of movement) that is apparent early but worsens in school to pre-teen years. Involuntary movements. Dysarthria (slurred, slow, or distorted speech sounds)
- **Oculomotor apraxia** (difficulty with coordination of head and eye movement when shifting gaze from one place to the next)
- **Telangiectasia** (dilated blood vessels) over the white (sclera) of the eyes, making them appear bloodshot. These are not apparent in infancy and may first appear at age 5–8 years. Telangiectasia may also appear on sun-exposed areas of skin.
- **Immunodeficiency**: recurrent sinusitis and pulmonary infections

- Increased incidence of cancer (primarily, but not exclusively, T-cell leukemia, T-cell lymphoma, gliomas and carcinomas have been reported in some)
- Diabetes in adolescence or later

Defects in phagocytosis

Congenital Neutropenias

Severe neutropenia, defined as an absolute neutrophil count of less than 500 cells per cubic millimeter, suppresses inflammation and increases susceptibility to recurrent and severe bacterial and fungal infections. Descriptions of patients with infections and neutropenia appeared early this century, but in 1930, Roberts and Kracke showed that neutropenia can precede infection. Soon thereafter, neutropenias were subdivided into asymptomatic neutropenias and those associated with bone marrow insufficiency.

Defects of Adhesion

The process of aggregation and attachment of neutrophils to endothelial surfaces is mediated by a group of molecules called integrins and selectins and that these molecules are essential for a normal inflammatory response.

Leukocyte adhesion deficiency type 1 is an autosomal recessive disorder resulting from a lack of β_2 integrin adhesion molecules on neutrophils. There are three β_2 integrins, which have different α chains but a common β chain, called CD18. Defects in CD18 account for the loss of β_2 integrin and the clinical findings in patients with the disorder. Neutrophils are unable to aggregate, they do not bind to intercellular adhesion molecules on endothelial cells, a step that is necessary for their egress from the vasculature and transport to sites of inflammation. As a result, even when there is no infection, the neutrophil count is about twice the normal level.

Clinical features: recurrent infections (gram-negative enteric bacteria, *S. aureus*, candida species, and aspergillus species) of the oral and genital mucosa, skin, and intestinal and respiratory tracts.

The second type of leukocyte adhesion deficiency is a defect of carbohydrate fucosylation and is associated with growth retardation, dysmorphic features, and neurologic deficits.

Defects of Signaling

- *pathogen* is triggers to production of *interleukin-12* by *dendritic cells and macrophages*.
- *dendritic cells and macrophages* in turn induces the secretion of *interferon- γ* by T cells and natural killer cells
- *interferon- γ* activates *macrophages and neutrophils*
- *macrophages and neutrophils* produce tumor necrosis factor α and activate NADPH oxidase, which promotes ***killing of the pathogen*** by increasing the production of hydrogen peroxide.

The *interferon- γ receptor* consists of a ligand-binding chain and a ***signaling chain*** (also called the R1 and R2 chains, respectively).

Mutations have been identified in the genes for both chains of this receptor, with both autosomal recessive and autosomal dominant inheritance. Children with a mutation that causes complete loss of the ligand-binding chain have severe disease that begins in early infancy. The main features are disseminated atypical mycobacterial disease or fatal BCG infection after vaccination an inability to form granulomas and the absence of a response to high doses of interferon gamma.

Interleukin-12 also has two chains. A mutation in the gene increases susceptibility to mycobacterial disease and can form mature granulomas.

Defects of Intracellular Killing

The responses of phagocytes to pathogens include phagocytosis, proteolytic destruction within granules, and damage induced by hydroxyl radical, superoxide, and hydrogen peroxide generated by NADPH oxidase. Patients with defects in intracellular killing of microbes have increased susceptibilities to specific pathogenic bacteria and fungi that result in atypical and often muted inflammatory responses.

In 1967, a specific defect in the intracellular killing of bacteria was identified and traced to the oxidative metabolism of phagocytes.

Chronic granulomatous disease CGD

CGD is a rare congenital immunodeficiency (1 case per 250 000 individuals).

Inheritance:

- X-linked recessive form (70% of all CGD cases — majority male patients).
- Autosomal recessive form (remaining 30% – males/females affected equally).

Cause: profound defect in burst of oxygen consumption that normally accompanies phagocytotoxic killing of bacteria and fungi by all myeloid cells (ie. neutrophils, eosinophils, monocytes, and macrophages).

Signs and symptoms:

As a result of the failure to activate the respiratory burst in their phagocytes, the majority of CGD patients suffer from severe recurrent infections, the most common of which include: pneumonia, lymphadenitis, cutaneous and hepatic abscesses, osteomyelitis and septicemia

These severe infections usually become apparent during the first year of life and are caused predominantly by catalase-positive microorganisms, which destroy their own hydrogen peroxide, including *S. aureus*, *Burkholderia cepacia*, aspergillus species, nocardia species, and *Serratia marcescens*. Infections with catalase-negative organisms, such as *Streptococcus pneumoniae*, are rare. In addition, CGD patients have diffuse granulomas (presumably caused by microbes) that can become sufficiently large to cause obstructive or painful symptoms in the esophagus, stomach, biliary system, ureters, or bladder.

Defects in the Formation and Function of Neutrophil Granules

Myeloperoxidase Deficiency

Deficiency of myeloperoxidase is the most common inherited disorder of neutrophils. About half of those affected have a complete deficiency of myeloperoxidase; the rest have structural or functional defects in the enzyme. Myeloperoxidase, the principal component of azurophilic (primary) granules, catalyzes the formation of hypochlorous acid (bleach) from hydrogen peroxide and chloride ion; hypochlorous acid is then converted to chlorine. Hypochlorous acid has ability to kill microorganisms. The mutations in the gene encoding myeloperoxidase are heterogeneous and can result in either transcriptional or post-transcriptional defects.

The Chédiak–Higashi Syndrome

Case reports by Chédiak and Higashi were published in the early 1950s, but the first cases were described in 1943.

- The Chédiak–Higashi syndrome is an autosomal recessive disorder of all lysosomal granule-containing cells. The mutated gene in the Chédiak–Higashi syndrome, *LYST*, encodes a cytoplasmic protein involved in vacuolar formation, function, and transport of proteins. All cells containing lysosomes have giant granules. In neutrophils, the large granules result from the abnormal fusion of primary (azurophilic) granules with secondary (specific) granules and the fusion of the giant granules with phagosomes is delayed, contributing to the impaired immunity. Hair also has giant inclusions. Partial ocular and cutaneous albinism; recurrent bacterial infections, especially of *S. aureus* and beta-hemolytic streptococcus; platelet dysfunction with easy bruising; and severe periodontal disease.

Defects in complement system

Complement Deficiency

Neutrophil-mediated adhesion, chemotaxis, and phagocytosis of foreign substances opsonized by iC3b is severely impaired in this rare hereditary disease. Virtually no neutrophils infiltrate the sites of inflammation. The patients develop life-threatening sepsis. The severity of the disease is dependent on the degree of impaired surface expression of complement receptors CR3 and CR4 and LFA-1. Other clinical features of this immunodeficiency syndrome are described in the table.

Complement Deficiencies	
Complement proteins	Deficiency-associated manifestations
C1-C4	SLE, pyogenic infections (e.g., pneumococcal sepsis)

C3, FH, F1	Pyogenic infections, glomerulonephritis
C8	Infections, especially by <i>Neisseria</i> spp. (gonococci, meningococci); sclerodactyly
CR3, CR4, LFA-1	Gingivitis, delayed decidualization of the umbilical cord, recurrent sepsis

SECONDARY IMMUNODEFICIENT STATES

Iatrogenic disorders are caused by some form of medical treatment. Cancer chemotherapeutic agents suppress blood cell formation in the bone marrow. Immunosuppressive corticosteroids for treatment of individuals with transplants or autoimmune diseases depress B and T cell formation. The consequence of these therapies for cancer and immunosuppression is manifested as a progressive increase in infections with opportunistic microorganisms.

Traumatized burn victims are susceptible to severe bacterial infections because of decreased neutrophil function and complement levels. Burn victims also have increased suppressor cell function, which may increase antigen-specific suppression.

A relationship between emotional stress and depressed immune function seems to exist. Many lymphoid organs are innervated and can be affected by nerve stimulation. Also, lymphocytes have receptors for many hormones such as neurotransmitters and can respond to changing levels of these chemicals with increased or decreased function.

The main causes of secondary immunodeficiency

1. Protozoa and helminthic invasions (toxoplasmosis, leishmaniasis, trichinellosis)
2. Bacterial infection (tuberculosis, staphylococcus, pneumococcus)
3. Viral acute and persistent infections (measles, rubella, herpes, chicken pox, chronic hepatitis B, HIV)
4. Eating Disorders: protein-energy malnutrition, exhaustion, loss of protein through the intestines and kidneys.
5. Malignant neoplasms especially a lymphoproliferative
6. Autoimmune Diseases
7. states that lead to a loss of immune cells and immunoglobulins (bleeding lymphoma)
8. Exogenous and endogenous intoxication (immunosuppressants, corticosteroids, drugs)
9. Immunodeficiencies after exposure to physical agents (ionizing radiation)
10. Violation of neurohumoral regulation
11. Immunodeficiency senile

Deficiency of some nutrients can lead to the development of some secondary ID:

- Lack of iron disturbed phagocytic ability of neutrophils,
- lack of vitamin A - reduces the number of some lymphocyte subpopulations;
- Lack of vitamin B6 and folic acid disturbed cellular immunity,
- Zinc deficiency reduces the ratio of T-helper and cytotoxic lymphocytes.

Classification of secondary immunodeficiencies:

1. By Type:

- Violations of T-cell
- Violations of humoral
- Violations of effector factors
- Combined defects

2. By current :

- Acute ID
- Chronic ID

3. By prevalence

- "Local" ID (ID, mainly affecting the local immune mechanisms (mucosa, skin, and others.))
- System ID.

4. By severity:

- mild
- medium
- heavy

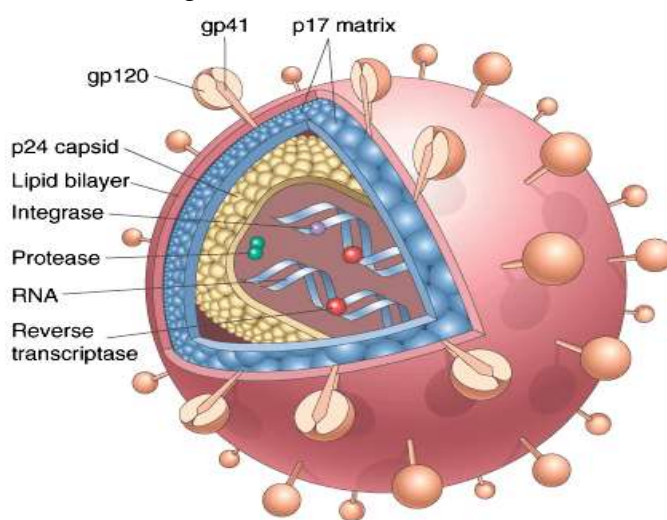
HIV (human immunodeficiency virus)

HIV results in the infection disease associated with primary impairment of the immune system and secondary immune deficiency occurrence. It is characterized by activation of opportunistic pathogens. HIV was found by L. Montanier in France and R. Gallo in the USA in 1983.

Etiology: HIV is different in structure from other retroviruses. It is roughly spherical with a diameter of about 120 nm. It is composed of two copies of positive single-stranded RNA that codes for the virus's nine genes enclosed by a conical capsid composed of 2,000 copies of the viral protein p24. The single-stranded RNA is tightly bound to nucleocapsid proteins, p7, and enzymes needed for the development of the virion such as reverse transcriptase, proteases, ribonuclease and integrase. A matrix composed of the viral protein p17 surrounds the capsid ensuring the integrity of the virion particle.

This is, in turn, surrounded by the viral envelope that is composed of two layers of phospholipids taken from the membrane of a human cell when a newly formed virus particle buds from the cell. Embedded in the viral envelope are proteins from the host cell and about 70 copies of a complex HIV protein that protrudes through the surface of the virus particle. This protein, known as Env, consists of a cap made of three molecules called glycoprotein (gp) 120, and a stem consisting of three gp41 molecules that anchor the structure into the viral envelope. This glycoprotein complex enables the virus to attach to and fuse with target cells to initiate the infectious cycle. Both these surface proteins, especially gp120, have been considered as targets of future treatments or vaccines against HIV.

The RNA genome consists of at least seven structural landmarks (LTR, TAR, RRE, PE, SLIP, CRS,



and INS), and nine genes (*gag*, *pol*, and *env*, *tat*, *rev*, *nef*, *vif*, *vpr*, *vpu*, and sometimes a tenth *tev*, which is a fusion of *tat* *env* and *rev*), encoding 19 proteins. Three of these genes, *gag*, *pol*, and *env*, contain information needed to make the structural proteins for new virus particles. For example, *env* codes for a protein called gp160 that is broken down by a cellular protease to form gp120 and gp41. The six remaining genes, *tat*, *rev*, *nef*, *vif*, *vpr*, and *vpu* (or *vpx* in the case of HIV-2), are regulatory genes for proteins that control the ability of HIV to infect cells, produce new copies of virus (replicate), or cause disease.

There are two varieties, HIV-1 and HIV-2; the latter is most common in Africa.

There are four stages of **viral biocycle**:

- primary infection of host cell in blood mucosa
- cytokine activation of cell; transcription of HIV genome; transport of viral RNA to cytoplasm; reverse transcriptase-mediated synthesis of proviral DNA
- synthesis of HIV proteins, assembly of virion core structure
- budding and release of mature virion

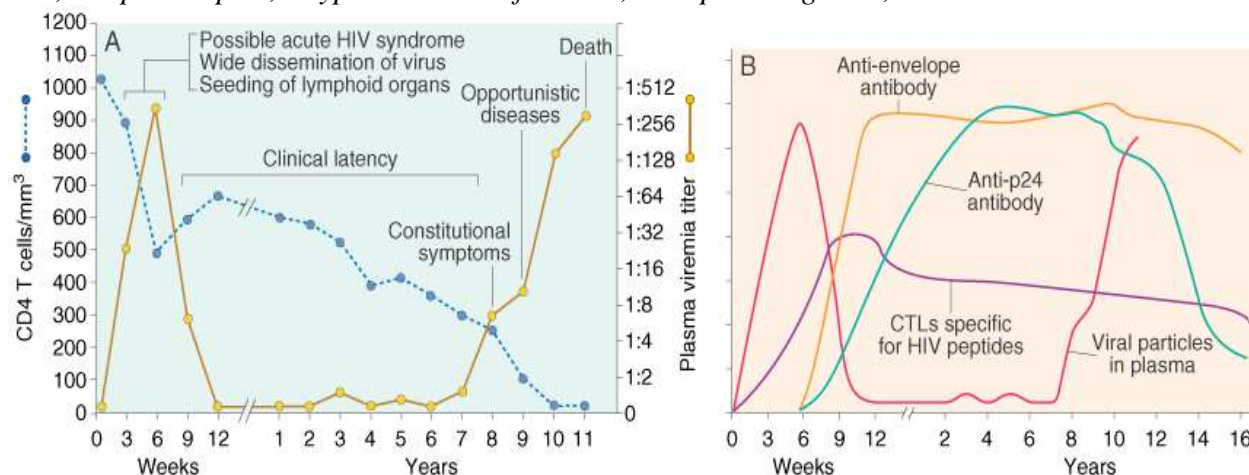
Pathogenesis

➤ gp120 HIV binds CD4 protein-receptor on the surface of T cells, macrophages, monocytes, astrocytes, endotheliocytes, sperm cells.

➤ **progressive decline in CD4 T lymphocytes and CD4/CD8 T lymphocyte ratio.** It is < 1,0 (0,5–0,005). The norm is 1,4–2,0. The absolute CD4 T lymphocyte counts decline (less than 400 cell/μl). The norm is 800–1000 cell/ μl)

➤ HIV-infected monocytes release large quantities of the acute phase reacting cytokines, including IL-1, TNF, IL-6. TNF can contribute to marked fatigue and cachexia. CD8 T cells change their phenotype: express HLA-DR molecules on the background of CD25 absence (CD25 is a receptor to IL-2). So they can not inhibit HIV infection. But on the early stages CD8 T cells inhibit HIV infection by activating B-cells and autoantibody production. These antibodies bind the HIV and increase the cell infection.

➤ the immune system inhibition results in AIDS-depending opportunistic infections: *Pneumocystic carinii*, *Herpes simplex*, *Cryptococcus neoformans*, *Toxoplasma gondii*, *Candida albicans* and others.



There are several stages of HIV infections: incubation (from 1 up to 3 months), primary organism reaction on HIV infection (from 3 weeks up to 3 months), and the time from HIV infection up to AIDS (about 10 years).

CDC Classification System for HIV Infection

The CDC categorization of HIV/AIDS is based on the lowest documented CD4 cell count and on previously diagnosed HIV-related conditions. For example, if a patient had a condition that once met the criteria for Category B but now is asymptomatic, the patient would remain in Category B. Additionally, categorization is based on specific conditions, as indicated below. Patients in categories A3, B3, and C1-C3 are considered to have AIDS.

Table CDC Classification System for HIV-Infected Adults and Adolescents

CD4	A Asymptomatic, Acute HIV, or PGL	B Symptomatic Conditions, #* not A or C	C AIDS-Indicator Conditions*
(1) ≥ 500 cells/ μ L	A1	B1	C1
(2) 200–499 cells/ μ L	A2	B2	C2
(3) < 200 cells/ μ L	A3	B3	C3

Key to abbreviations: CDC = U.S. Centers for Disease Control and Prevention; PGL = persistent generalized lymphadenopathy.

CDC Classification System: Category B Symptomatic Conditions

Category B symptomatic conditions are defined as symptomatic conditions occurring in an HIV-infected adolescent or adult that meets at least 1 of the following criteria:

They are attributed to HIV infection or indicate a defect in cell-mediated immunity.

They are considered to have a clinical course or management that is complicated by HIV infection.

Examples include, but are not limited to, the following: Bacillary angiomatosis; Oropharyngeal candidiasis (thrush); Vulvovaginal candidiasis, persistent or resistant; Pelvic inflammatory disease (PID); Cervical dysplasia (moderate or severe)/cervical carcinoma in situ; Hairy leukoplakia, oral; Idiopathic thrombocytopenic purpura; Constitutional symptoms, such as fever ($>38.5^{\circ}\text{C}$) or diarrhea lasting >1 month; Peripheral neuropathy; Herpes zoster (shingles), involving ≥ 2 episodes or ≥ 1 dermatome.

CDC Classification System: Category C AIDS-Indicator Conditions: Bacterial pneumonia, recurrent (≥ 2 episodes in 12 months); Candidiasis of the bronchi, trachea, or lungs; Candidiasis, esophageal; Cervical carcinoma, invasive, confirmed by biopsy; Coccidioidomycosis, disseminated or extrapulmonary; Cryptococcosis, extrapulmonary; Cryptosporidiosis, chronic intestinal (>1 -month duration); Cytomegalovirus disease (other than liver, spleen, or nodes); Encephalopathy, HIV-related; Herpes simplex: chronic ulcers (>1 -month duration), or bronchitis, pneumonitis, or esophagitis; Histoplasmosis, disseminated or extrapulmonary; Isosporiasis, chronic intestinal (>1 -month duration);

Kaposi sarcoma; Lymphoma, Burkitt, immunoblastic, or primary central nervous system; Mycobacterium avium complex (MAC) or M kansasii, disseminated or extrapulmonary; Mycobacterium tuberculosis, pulmonary or extrapulmonary; Mycobacterium, other species or unidentified species, disseminated or extrapulmonary; Pneumocystis jiroveci (formerly carinii) pneumonia (PCP); Progressive multifocal leukoencephalopathy (PML); Salmonella septicemia, recurrent (nontyphoid); Toxoplasmosis of brain. Wasting syndrome due to HIV (involuntary weight loss >10% of baseline body weight) associated with either chronic diarrhea (≥ 2 loose stools per day ≥ 1 month) or chronic weakness and documented fever ≥ 1 month

WHO Clinical Staging of HIV/AIDS and Case Definition

The clinical staging and case definition of HIV for resource-constrained settings were developed by the WHO in 1990 and revised in 2007. Staging is based on clinical findings that guide the diagnosis, evaluation, and management of HIV/AIDS, and does not require a CD4 cell count. This staging system is used in many countries to determine eligibility for antiretroviral therapy, particularly in settings in which CD4 testing is not available. Clinical stages are categorized as 1 through 4, progressing from primary HIV infection to advanced HIV/AIDS. These stages are defined by specific clinical conditions or symptoms. For the purpose of the WHO staging system, adolescents and adults are defined as individuals aged ≥ 15 years.

Questions for self-control of knowledge:

1. Expand features of immunocompetent cells that are components of different cell populations of immune system.
2. Define the concepts of "affinity" and "avidity."
3. Specify a features of immune response during pregnancy.
4. Describe mechanisms of primary immunodeficiency diseases.
5. What are main causes of secondary immunodeficiency?
6. What is structure of human immunodeficiency virus? Describe mechanisms of interaction immunodeficiency virus with cell.
7. What is opportunistic infection?
8. Define the term "allergy". Indicate correlation between immunity, immunological reactivity, allergy and inflammation. Characterize pseudoallergy reaction.
9. Explain why allergic reaction is a form of abnormal immune response. Which parameters are depended on possibility and severity of allergic reaction?
10. What are causes of allergies?
11. Describe a pathogenetic classification of allergic reactions, in different types of immune tissues damage.
12. What is pathogenesis of local and systemic anaphylactic reactions? Explain the term "atopy."
13. What is pathogenesis and main clinical manifestations of allergic reactions type II? What is antibody-cell cytotoxicity?
14. What are etiology and pathogenesis of allergic reactions type III?
15. What are etiology and pathogenesis of allergic reactions type IV? Give a characteristic of allergens and mediators.
16. What is significance of allergic reactions mediated by T lymphocytes in the problem of graft versus host reaction (GVHD)?
17. Give a description of "Behind a barrier" bodies. What is structure of immune barriers at morphological level?
18. What are main group of autoimmune diseases.
19. What is pathogenesis and main manifestations of SLE? What phase LE-phenomenon and determine nature of its processes.

Tasks for self-managed student work:

1. Anaphylactic shock.
2. Immune regulation of ontogenesis.
3. Wiskott-Aldrich Syndrome

4. Reaction of graft rejection. Disease "graft versus host".
5. Basic principles of diagnostics and therapy of allergic and autoimmune diseases.

Literature

Basis literature:

1. Литвицкий, П. Ф. Патофизиология = Pathophysiology: лекции, тесты, задачи : учеб. Пособие / П. Ф. Литвицкий, С. В. Пирожков, Е. Б. Тезиков. – М. : ГЭОТАР-Медиа, 2016.– 432 с.

Additional literature:

2. Kumar, V. Robbins and Cotran Pathologic basis of disease, 7th Edition / V.Kumar, A.K. Abbas, N. Fausto. — Philadelphia: Elsevier Inc., 2005. — 1629 p. Режим доступа: <http://www.rkmyat.in/up1/34/1629.pdf>. – Дата доступа: 30.08.2016.

3. Кидун, К. А. Общая нозология = General nosology : учеб.-метод. пособие для студ. 3 курса фак. по подг. спец. для зарубеж. стран, обуч. на англ. яз. по спец. «Лечеб. дело», мед. вузов / К. А. Кидун.– Гомель : ГомГМУ, 2015. – 74 с.

4. Кидун, К.А. Test tasks on pathological physiology: Workbook for students of the faculty for training specialists for foreign countries, studying in english on specialty «General medicine», for higher medical education institution In three parts Part 1. General pathophysiology. / К.А. Кидун; под ред. Т.С. Угольник — Гомель: ГомГМУ, 2016. — 108 с.

5. Научная электронная библиотека eLIBRARY.RU [Электронный ресурс] / Научная электронная библиотека. – М., 2005. – Режим доступа: <http://www.elibrary.ru>. – Дата доступа: 26.08.2017.

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