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ОБЩАЯ ПАТОФИЗИОЛОГИЯ

Учебно-методическое пособие для иностранных студентов,
обучающихся на английском языке

В двух частях

Часть 1

GENERAL PATHOLOGICAL PHYSIOLOGY

Teaching workbook for foreign students educated in English

In two parts

Part 1

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Цель учебно-методического пособия — углубить и закрепить знания студентов при изучении общей патологической физиологии.

Составлено в соответствии с типовой учебной программой по патологической физиологии для студентов медицинских вузов, обучающихся на английском языке, утвержденной Министерством здравоохранения Республики Беларусь 7 июля 2009 г.

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CONTENTS

THE LIST OF ABBREVIATION

ACTH — adrenocorticotropic hormone
ADCC — antibody-dependent mediated cytotoxity
ADH — antidiuretic hormone
AMP — adenosine monophosphate
ATP — adenosine triphosphate
a/v O_2 — oxygen arterial venous ratio
BTK — Buton's tyrosine kinase
C_{3a}, C_{5a} — complement components
CDC — centers for disease control
CGD — chronic granulomatous disease
CMV — cytomegalovirus
CNS — central nervous system
CTL — cytotoxic T-lymphocytes
CVID — common variable immunodeficiency
DIC — disseminated intravascular coagulation
DNA — deoxyribonucleic acid
e. g. — from Latin *exampli gratia* meaning «for example»
Er — erythrocytes
ESR — erythrocyte sedimentation rate
etc. — from Latin *et cetera* meaning «an so on» «and other things»
FAT — factor of thrombocyte activation
Hb — hemoglobin
HIGM1 — hyperimmunoglobulinaemia M type1
HIV — human immunodeficient virus
HLA — human leukocyte antigens
HSCT — hematopoietic stem-cell transplantation
IDDM — insulin-dependent diabetes mellitus
i. e. — from Latin *id est* meaning «that is»
Ig — immunoglobulin
Il — interleukin
IVIG — intravenous immunoglobulin
Le — leucocytes
LT — leukotreine
MAC — mycobacterium avium complex
MHC — major histocompatibility complex
MoAb — monoclonal antibody

MODY 1,2,3,4 — maturity onset diaberes of the young
NADPH — nicotinamiddinucleatide phosphate
NBT — Nitroblue tetrazolium
NIDDM — non-insulin-dependent diabetes mellitus
NK — natural killer
NS — nervous system
P_AO_2 — oxygen partial pressure in alveolar air
P_aO_2 — oxygen partial pressure in arterial blood
PCP — pneumocystis carinii pneumonia
Pg — prostaglandin
PGL — persistent generalized lymphadenopathy.
PID — pelvic inflammatory disease
PML — progressive multifocal leukoencephalopathy
PMN — polymorphnuclear neutrophils
P_VO_2 — oxygen partial pressure in venous blood
RNA — ribonucleic acid
S_aO_2 — arterial blood oxygen saturation
SCID — severe combined immune deficiency
SCIDS — severe combined immunodeficiency syndrome
TNF — tumor necrosis factor
Tr — trombocytes
TrA2 — tromboxan A2
WAS — Wiskott-Aldrich syndrome
WHO — World Healthcare Organization
XHIM — X-linked hyper-IgM syndrome
XLA — X-linked agammaglobulinemia
XTP — X-linked thrombocytopenia
γ-IFN — gamma-interferon

GENERAL DOCTRINE ABOUT DISEASE

«The main pathological physiology aim is to teach students to ability to use natural history knowledge close by the diseased man bed»

S. P. Botkin

Pathological physiology is a science studying the concrete mechanism and the general laws of occurrence, development and outcome of diseases and pathological processes.

Pathophysiology: pathology from Greek *pathos* is a «disease», «suffering» *logos* is a «doctrine», a «science» **physiology** from Greek *physis* is a «nature», *logos* is a «doctrine», a «science».

The subject matter and the content of pathological physiology

The research object of pathological physiology is a diseased organism.
The research subject of pathological physiology is:
1) finding out of general and private mechanisms of occurrence, development and outcome of pathological processes and disease;
2) studying of typical pathological processes.

The pathological physiology problems:
➤ study of the vital functions impairment basic regularity in the pathology conditions;
➤ the facts working out and the facts analysis and synthesis;
➤ the diseases etiology extended and advanced study;
➤ the advanced study and the effective methods of early diseases diagnostics, treatment and prophylaxis introduction;
➤ the pathological processes experimental models creation;
➤ the clinical pathological physiology development.

The pathological physiology methods:
1) The modelling methods:
➤ the physical;
➤ modelling on biological objects;
➤ on artificial systems;
➤ on artificial systems;
➤ the intellectual modelling;
➤ the mathematical modelling;
➤ the computer modelling.
2) The clinical research methods.
3) The theoretical analysis method.
4) The medical thinking.

Scientifics and scientific works

V. V. Pashutin (1845–1901). He was busy with the metabolism impairments problems. The 1st in Russia scientific works of the endocrine glands activity study belong to him. He created the 1st pathological physiology schools of thought.

I. G. Savtchenko (1862–1932). He is a founder of the path physiologist's school of thought in Kazan (the immunologic research school). He proved on himself the oral vaccination against cholera possibility.

A. A. Bogomolets (1881–1960). He carried out the endocrine pathology researches, the tumor growth researches, the blood circulation researches, the ageing physiology researches, the immunology researches. He worked out and introduced in the clinical practice the anti – reticular – endothelial cytotoxic serum.

N. N. Anichkov (1885–1965). He was the 1st in Russia who introduced the pathological physiology practical studies. The main schools: the cardiac vascular system pathology, physiology and pathology of the reticular endothelial system, the oxygen starvation, the gastrointestinal tract pathology.

P. V. Veselkin. He carried out the thermal exchange impairments researches. He is a founder of fever doctrine, the posttraumatic complications and traumatic shock.

S. Chalatov (1884–1951). He was the 1st who specified the meaning of the local cholesterol deposits in origin of pathological processes line and proved the role of cholesterol exchange impairments in the atherosclerosis development.

A. M. Chernuch (1916–1982). He made a great contribution to the common nosology and sanogenesis problems study, the inflammation and microcirculatory theory, the experimental therapy questions.

G. N. Krydganovskiy. He is a founder of the generative mechanisms of neuropathologic syndroms theory. He is a founder of the determinant doctrine.

V. A. Negovskiy. He worked in the resuscitation area. He organized the 1st laboratory of the terminal conditions problems research.

Nosology (from Greek *nosos* is a «disease») is a doctrine about disease.

General nosology *includes* 3 components:
 — Nosology;
 — General etiology;
 — General pathogenesis.

General nosology examines the following questions:
 — the pathology concepts (disease, health) definition;
 — the diseases nomenclature and classification;
 — the diseases occurrence, development and current types.

The general nosology basic concepts

Norm is a set of the organism various properties expressing the specific genotype optimum realization in the given individual.

Health is a condition of the complete physical, spiritual and social well-being of the organism, supporting it's the most adequate participation in various types of public labor activity, and it is not only the diseases and physical defects absence.

Disease is a process arising due to the pathogenic factors influence. It is expressed in the complex of the functional and metabolic changes, the adaptability impairment, the capacity for work and socially necessary activity limitation.

Classification of disease:
1) The types of disease current: acyclic, cyclic.

2) Disease variants according to the current duration:
— *flash-like* disease (from several minutes till several hours);
— the acutest disease (from several hours till 3–4 days);
— acute disease (5–14 days);
— sub acute disease (15–35–40 days);
— chronic disease (some months and years).

Periods and outcomes of disease

Predisease is an organism vital activity on the brink of health and disease. Predisease can be revealed in case of loading, functional and other tests.

The predisease phases:

The 1st phase is characteristic of the nonspecific complaints prevalence at the practically safe capacity for work, the homeostasis impairment occurs on the information and energy processes level.

The 2nd phase is characteristic of the metabolic and structural changes.

It is a predisease in its clinical sense when there is a change of the etiologic factors to the pathogenic.

Periods and outcomes of disease:
1) Latent period (incubation):
➢ is a time between the moment of pathogenic agent action and the manifestation of the 1st disease symptoms;
➢ there is an exhaustion of primary sanogenic mechanisms;
➢ in infection disease this period is called incubation. Incubation period is caused by exhaustion of sanogenic mechanisms and pathogenic organism accumulation.

2) Premonitory period. It is presented by the first non-specific signs of disease: indisposition, increase in temperature, fever, headache.

*3) Period of clinical manifestations. I*t is presented by the specific symptoms for this disease.

4) Period of recovery. It is characterized by the absence of symptoms and normalization of impaired functions.

5) Death is the most negative disease outcome. *Death can be:* natural, premature (the violent death, death as a result of disease).

The main pathological physiology concepts

Complication is a pathological process, a condition or a reaction, developing on the basic disease background, but it is not obligatory for disease.

Acute condition (aggravation) is a chronic disease stage described of the increased available symptoms or the new symptoms occurrence.

Relapse (from Roman *recidivus*) is a disease symptoms renewed or aggravation after their elimination or easing.

Remission (in roman *remission* is a reduction, easing) is a temporary easing (the incomplete remission) or an elimination (the complete remission) of the disease manifestations.

Pathological process is a naturally arising set of pathogenic and adaptive changes in organism in reply to the pathogenic factor action

Pathological condition is a stable deviation of the structural, functional, biochemical properties of tissues, organs and systems from norm, arising under the injuring factor action and poorly varying in time

Reactivity is a totality of species, sex, age, constitution and individual features. Reactivity determines the character of organism reaction on physiologic and pathologic factors.

The classification of body constitution is shown in the table 1.

Table 1 — Classification of body constitution

According to Sigo	– respiratory; – digestive; – muscular; – cerebral
According to Bogomoleths	– asthenic; – fibrous; – lipomatous; – hydropic
According to Krechmer	– athletic; – picnic; – asthenic
According to Chernorutsky	– asthenic; – normosthenic; – hyperthenic
According to Hippocratus	– impetious; – rapid; – inert; – weak
According to Pavlov	– impetious; – rapid; – inert; – weak

Etiology (from Greek *aetia* is a «reason», *logos* is a «doctrine») — is a doctrine about reasons and conditions of the pathological processes and diseases occurrence and development. This term was introduced by Democrit (470–460 B. C.), the founder of the casual school in medicine. The reason (the etiologic factor) causing the given disease and giving the specific features to it.

The reason classification:

1) by origin:
 — exogenous (mechanical, physical, chemical, biological, psychogenic);
 — endogenous (hereditary and constitutional).
2) by the action intensity:
 — extreme;
 — usual;
 — indifferent.

Condition (from Roman conditio is a «condition») is a factor promoting, interfering or modifying action of the etiologic factor. The condition by itself cannot cause disease.

The condition classification

1) by origin:
— exogenous — ecological, household, social;
— endogenous — sex, age, the body constitution, resistency, the higher nervous activity type.

Conditions can have hereditary character, conditions can be formed during the pre-natal period and the extrauterine period of life.

2) according to the influence on organism:
— positive;
— negative (conditions can aggravate the association between cause and effect, promote the disease occurrence).

Pathogenesis

Pathogenesis (from Greek pathos is a «suffering», *genesis* is a «development») is a doctrine about the pathological processes and the concrete diseases mechanism and development.

Each disease has its own pathogenesis, but four pathogenic components are common (non-specific) for all pathological processes: typical pathological processes (reactions), pathologic systems, pathologic dominant, vicious circle.

Typical pathological processes: impairments of local blood circulation, inflammation, allergy, hypoxia, tumor, stress, shock.

Typical pathological reactions are non-specific impairments of basic processes in organism.

Specificity of pathological process is determined by quantity, time and non-specific reactions «turn on» in these processes, e. g. typical pathological reaction on injury: information impairments (also pathological system formation,

impairment of reproduction processes, impairment of energy supply, and impairment of generation, transformation and realization of excitation).

Pathological system is a functional totality of single cell, tissue, system or organism reaction results from pathogenic factor action on organism. It is characterized by prolonged self-sustaining activity and depression of adaptive protective mechanisms. It has in its base information process impairment and results in aggravation in imbalance between diseased organism and environment.

Vicious circle is characterized by the next moment: the end point result of pathological process become a cause of increase in primary chain of pathological process (e. g. rennin mechanism in arterial hypertension).

Sanogenesis (from *Latin sanitas* — health, from Greek *gennon* — origin) is a dynamic complex of protective adaptive mechanisms of physiologic and pathologic character resulting from extreme irritant action on organism. This process is functioning during the pathological process duration (from predisease up to recovery). It remain impaired self-control of organism.

The idealistic and metaphysical theories of the disease etiology

Monocausalism (from Roman *mono* — «one», *causa* — «cause») — is a mechanic study. It admits only the role of cause and refutes the role of condition in disease occurrence.

Conditionalism (from Roman *condition* — «condition») — is a study, which refutes causality in disease occurrence. It substitutes the category of cause for the sum of equivalent conditions (equalent according to the role).

Constitutionalism is a study, which admits the role of the body constitution in disease occurrence.

Polyetiologism is an etiology school according to which the organism body constitution features have the crucial importance for the disease occurrence and current.

The factors theory is a theory recognizing the plurality of reasons and conditions, their mutual influence.

The civilization diseases. Authors of the given school attribute the universal value to the social factors in the pathological processes development.

Holism (from Greek *holos* is the «whole», «everything») is a doctrine according to which human life is controlled by some «integrity factor» on which health and disease depend.

Terminal conditions

It is a reversible organism function decrement preceding the biological death, when the protectively-adaptive complex of mechanisms are insufficient to eliminate the consequences action of the pathogenic factor on organism.

The characteristic features of terminal conditions is an inability of the dying organism to revert to the normal state independently, without help from the outside even if the etiologic factor action has stopped.

The leading mechanism of terminal conditions is hypoxia.

Terminal conditions: preagony, terminal pause, agony, clinical death, postreanimation encephalopathy.

Preagony:
➢ characterize by the higher nervous system structures inhibition, it manifestates by the twilight state, sometimes with the medullary vasomotor centre excitation;
➢ decrease in reflex activity, the alive eye reflexes;
➢ the arterial blood pressure is decreased, the peripheral arteries pulse is weak filling or it is not probed at all;
➢ the aerobic exchange prevails.

Terminal pause:
➢ the respiratory termination, the acute cardiac activity to the temporary asystole;
➢ apnea has temporary character (from several minutes till 3–4 hours);
➢ terminal pause can be absent (in case of the electric current injury);
➢ terminal pause is distinctly expressed in case of the dying because of the blood loss and asphyxia.

Agony

Agony (from Greek *agonia* is a «struggle») is a terminal condition preceding clinical death, it is characterized by the deep higher nervous system functions impairment with the medulla oblongata simultaneous excitation. The consciousness is absent, sometimes it quickly clears up, the eye reflexes and the external irritants reaction disappear. There is a sphincter relaxation.

The main agony sign is the 1st inhale occurrence after the terminal pause period. At the beginning there is a weak respiration, then it increases in depth and reaches the maximum, gradually weakens and absolutely stops.

The axilliary muscles participate in respiration — there are muscles of neck and face — the gasping respiration appears (from English *gasping* is a convulsive, spasmodic).

The agonal respiration occurrence testifies about the brain hypoxia. It is associated with the cortex inhibition influence on the sub cortical centers, the diencephalon and the brain steam. This brain centers disinhibition leads to the temporary vital functions activation.

The metabolism changes sharply, there is a catabolism prevalence of synthesis:
— the sharply increased glycolysis;
— the increased lactic acid level in tissues and organs;
— the sharply increased macroergic phosphates disassimilation.

From the organs of sense side the sense of smell dies ahead of the other.

After bradycardia, the temporary asystoly and the substantial decrease in the arterial blood pressure there is some increase in the arterial blood pressure (up to

30–40 mm Hg) as a result of the renewal and a little increase of the cardiac contractions. However, these manifestations are often short-term.

Clinical death (mors clinicalis) is a terminal condition coming after the cardiac activity and respiration stoppage and proceeding before the higher nervous system structures irreversible changes.

The absence of the external life signs (consciousness, reflexes, respiration, cardiac contractions), but organism as the whole has not died yet, the energy substratum is still in tissues and metabolic processes proceed.

The clinical death duration is defined:

— by the time which is experienced by the brain cortex in case of the blood circulation and respiration stoppage;

— the mild neurons, synapses destruction begins from the moment of clinical death, but even 5–6 minutes after clinical death these damages are still irreversible (it is explained by the high nervous system plasticity);

— usually the clinical death duration does not exceed 3–4 minutes in minimum, 5–6 is a maximum.

Biological death is an irreversible organism activity stoppage. It is an inevitable final stage of the organism individual life.

The biological death absolute signs: cadaveric cooling, the livores mortis occurrence, cadaveric rigidity, putrefaction.

CELL INJURY

Cell pathology is presented by 3 basic parts:
1. Cell pathology as awhole (dystrophy, necrosis, hypertrophy).
2. The sub cellular structures and components pathology (lysosomal, chromosomal, peroxisome diseases).
3. The intercellular interaction and cellular co-operation impairment.

Types of the cell damage:
1. Primary cell damage is caused by the direct injuring factor influence on organism.
2. Secondary cell damage is a consequence of the primary injuring influence on tissues and organism.

The etiologic factors classification:
1) *by nature*:
— physical (mechanical, temperature, radial);
— chemical (toxins, acids, alkali, drugs);
— biological (viruses, bacteria);
— psychogenic (the brain neurons injury).
2) *by origin:*
— exogenous;
— endogenous.

The cell alteration mechanisms:
1) the energy supplying impairment;
2) the membrane and the enzymes system injury;
3) ion and water imbalance;
4) the genetic program realization impairment and the genetic information change;
5) the intracellular mechanisms of functions control impairment.

Mechanisms of the cell energy supply impairments:
а) the ATP resynthesis impairment as a result of deficiency of the metabolism substratum, oxygen, the enzymatic activity and the mitochondria pathology;
б) pathology of the transport energy systems;
в) the energy utilization mechanisms impairment.

The membrane system and the enzyme kinetic properties impairment:
— an increase in lipid peroxidation;
— a decrease in lysosomal hydrolyzing enzime;
— the macromolecule spatial structure modification;
— the membrane reparation processes impairment;
— the membrane injury by amphiphilous compounds;
— hyperhydration of cells, the membrane overdistension and rupture.

Ionic imbalance:
— the transmembrane transfer of K^+, Na^+, Ca^{2+}, Mg^{2+}, Cl^- change and the ionic ratio change in cytosol;
— an increase in intracellular Na^+ is a hyperhydration;
— a decrease in intracellular liquid and proteins is a hypohydration;
— the electric physiologic properties change.

Change of the nuclear structure and size
Nuclear pathology. *Polyploidy* is an increase in chromosomes number up to the value divisible by the haploid number of chromosomes (3n, 4n, 5n, etc.).
Aneuploidy is a chromosomes number change nondivisible by the haploid number of chromosomes (2n+1, 2n-1).

Activity of functional nuclear condition is characterized by chromatin distribution:
Heterochromatin is a slow-acting, condensed. It is located in the peripheral part of nucleus.
Euchromatin is an active, non-condensed. It is located in the central part of the nucleus.
Change of nucleus shape:
1) deformation with cytoplasmic inclusions;
2) evaination of nucleus in cytoplasm;
3) nuclear polymorphysm.

Change of nuclear number:
— *akaryote;*
— variant of norm (Er, Tr);
— pathology (fragments of tumor cells, cell death);
— *multinucleate cell* — an increase in number of nuclei;
— cell fusion, pathology of mitosis.
«Nucleus satellites» (karyomere, small nucleus) — nucleus-like formation with its own membrane locating near intact nucleus in cytoplasm.
Change of size and number of nucleolus:
— an increase in in number and size of nucleolus testifies about;
— an increase in their activity.
Nucleolus segregation testifies about the complete nucleolus transcription arresting.

Nuclear inclusions

Cytoplasmic. They are limited by membrane and they are parts of cytoplasm located in nucleus.
True. They are located in nucleus and conforming cytoplasm substances.
Virus-induced. They are viral inclusions:
a) inclusions in karyoplasm of viral matrix;
b) inclusions of protein peptides in in-nuclear virus generation;
c) «reactive inclusions» in response to virus-induced cytoplasm injury.

Apoptosis

Apoptosis is a biochemical specific type of cell death.
It is characterized by activation of non-lysosome endogenous endonucleases, which split nuclear DNA on small fragments.
Meta-structure changes in apoptosis and necrosis are shown in the picture 1.
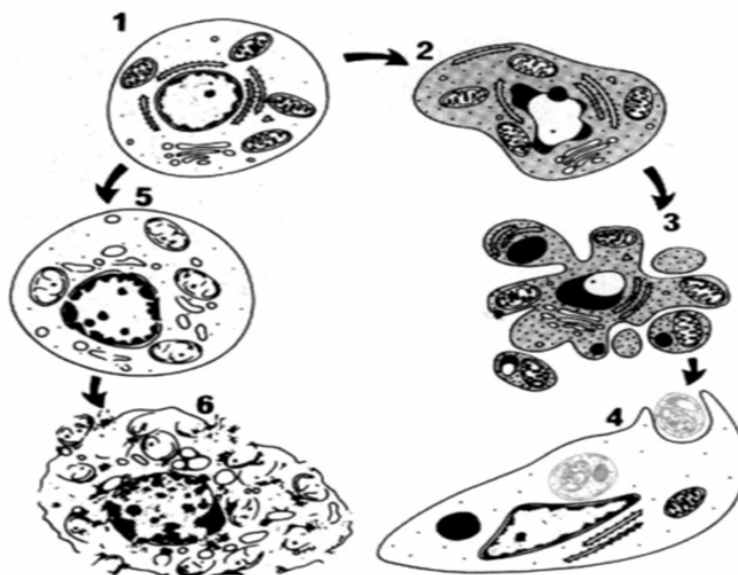
Picture 1 — Meta-structure changes in apoptosis and necrosis:
1 — intact cell; 2 — the beginning of apoptosis; 3 — fragmentation of apoptotic cell;
4 — phagocytosis of apoptotic bodies by the surrounding cells;
5 — death of incellular structures in necrosis; 6 — cell membrane destruction

Morphologically apoptosis is a cell death of single disorderly located cells. It is associated with the formation of rounded bodies surrounding by membrane («apoptotic bodies»). Apoptotic bodies are phagocyted by the surrounding cells.

Apoptosis takes part in physiologic and pathologic processes:
— cell destruction in embryogenesis;
— death of the immune system cells;
— elimination of cells during the proliferation;
— hormone-dependent organ involution;
— endometrium rejection in menstrual cycle;
— follicle atresia in menopause;
— regress of breast gland after the lactation arrest.

THE ROLE OF IMMUNE SYSTEM IN PATHOLOGY. AUTOIMMUNE MECHANISMS OF DISEASES

Allergy is a typical immune pathological process. It 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.

Stages of allergic reaction: immunologic, pathochemical, pathophysiological.

Classification of allergens: expogenous, endogenous.

Classification

1) Classification of Medic reaction (Cooke, 1930).

2) According to occurrence duration:
— immediate type (in 15–20 minutes, no longer than 6 hours);
— delayed type (in 6 hours, maximum 24, 48, 72 hours).

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

In immediate hypersensitivity (*hypersensitivity of type I*), the immune response releases vasoactive and spasmogenic substances that act on vessels and smooth muscle and proinflammatory cytokines that recruit inflammatory cells.

In antibody-mediated disorders (*hypersensitivity of type II*), secreted antibodies participate directly in injury to cells by promoting their phagocytosis or lysis and injury to tissues by inducing inflammation. Antibodies may also interfere with cellular functions and cause disease without tissue injury.

In immune complex-mediated disorders (*hypersensitivity of type III*), antibodies bind antigens and then induce inflammation directly or by activating complement. The Le that are recruited (neutrophils and monocytes) produce tissue damage by release of lysosomal enzymes and generation of toxic free radicals.

In cell-mediated immune disorders (*hypersensitivity of type IV*), sensitized T-lymphocytes are the cause of the cellular and tissue injury.

Anti-receptor (*hypercencitivity of type V*).

The hypersensitivity of type I (anaphylactic type)

It is a rapidly occurring reaction that results from the combination of an offering antigen with antibody (IgE) previously bound to the surface of mast cells.

Cells of hypersensitivity type I: mast cells, basophils.
Antibodies of Hypersensitivity type I: IgE (regains), IgG.

Pathogenesis

First exposure to offending allergen stimulates IgE production by plasma cells derived from B-cells. IgE binds to IgE Fc-receptors on cell membrane of mast cells. Individual is prone to hypersensitivity of type I.

Reexposure to same antigen (allergen) resulting in allergen fixes to IgE bound on surface of mast cell and causes cross-linking of adjacent IgE molecules. It causes a series of reactions that results in release of primary and secondary antigens.

The mediators of hypersensitivity of type I are showen in the table 2.

Table 2 — The mediators of hypersensitivity of type I

Primary	
Histamine	Increase in vascular permeability, dilation of arterioles and venules, smooth muscle contraction, increase in mucose secretion
Eosinophilic chemotactic factor	Chemotaxis of eosinophils
Neutrohilic chemotactic factor	Chemotaxis of neutrophils
Basophilic kallekreine	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	Bronchal 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 smooth muscle vessels
Lysosomal enzymes of granulocytes and oxydants	Cell injury

The hypersensitivity of type II (antibody-dependent)

It is a hypersensitivity reaction in which antibodies are formed against target antigens that are either normal or altered cell membrane components.

The types of hypersensitivity (type II)

Complement mediated cytotoxy: antibody reacts with cell surface antigen. Complement fixes antigen-antibody complex. It results in cell lysis or phagocytosis by macrophages.

ADCC: cell type that bear FC-receptors for IgG and cause lysis of target cells coated with IgG (or IgE in case of parasites) after interaction between Fc-receptors of killer cells Fc-portion of antibody coating the target cells.

Antibody mediated cellular dysfunction: antibodies directed against cell surface receptors impair or dysregulate cellular functions without causing cell injury or inflammation.

The mediators of hypersensitivity of type II are shown in the table 3.

Table 3 — The mediators of hypersensitivity of type II

Mediator	Biologic activity
Activated components C_{4b2a3b}	Immune fixation to phagocytes, activation of phagocytosis, granule oxydation
C_{3a}, C_{5a}–anaphylotoxins	Neutrophil, eosinophil, monocyte chemotaxis
C_{567}	Neutrophil selective chemotaxis
C_{5678}	Slow injury of cell membrane, release of lysosomal enzymes
Oxydant	Lipid peroxidation, cell membrane injury
Lysosomal enzymes	Opsonized cell injury

Hypersensitivity of type III

It is a hypersensitivity reaction in which antigen-antibody (immune) complexes are formed. It results inactivation of complements and accumulation of neutrophils. All these result in acute inflammatory reactions in tissue.

Pathogenesis. Immune complexes are initiated by exogenous antigen (e. g. bacteria, viruses), endogenous antigen (e. g. DNA). Pathogenic immune complexes are formed in circulation and deposites in tissues (circulating immune complexes) at extra-vascular sites where antigens has been previously planted (*in situ* immune complexes).

Immune complexes activate complement and cause neutrophil accumulation at the site of immune complex deposition. It results in acute inflammatory reaction.

The mediators of hypersensitivity of type III are showen in the table 4.

Table 4 — The mediators of hypersensitivity of type III

Injury of cell and no-cell structure	Membrane attack complex, enzymes of phagocytes and destructed cells, active forms of oxygen and free radicals
Induction of inflammatory reactions in the zone of allergy	Chemotactic factors, LTB_4, TNF, kinins, C_{3a} complement factor, anaphylotoxins, C_{4b2a3b}, C_5, C_{5b67}
An increase in vascular and basement membrane permeability	histamine, serotonin, LTD_4, LTC_4, C_{3a}, C_{5a}
Activation of thrombus formation	Hageman's factor, TrA_2

Cell-Mediated type IV of hypersensitivity

The cell-mediated type of hypersensitivity is initiated by antigen-activated (sensitized) T-lymphocytes. It includes the delayed type hypersensitivity reactions mediated by CD4$^+$ T cells, and direct cell cytotoxicity mediated by CD8$^+$ T-cells. It is the principal pattern of immunologic response not only to a variety of intracellular microbiologic agents, such as Mycobacterium tuberculosis, but also to many viruses, fungi, protozoa and parasites. So-called contact skin sensitivity to chemical agents and graft rejection are other instances of cell mediate reactions. In addition, many autoimmune diseases are now known to be caused by T-cell–mediated reactions.

The mediators of hypersensitivity of type IV are shown in the table 5.

Table 5 — The mediators of hypersensitivity of type IV

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

The present-day of immunotherapy
— use of vaccines from allergen-specific allergovaccination;
— use of antibodies (anti-IgE, anti-Il);
— serotherapy.

There are three ways of vaccine working out: use of usual vaccines per os, which are using parenteral; constructing of special vaccines, use of carrying agents.

IMMUNE DEFICIENCIES

Classification
Immunodeficiences are classified into:
➢ *primary* immunodeficiency disorders (almost genetically determined);
➢ secondary immunodeficiency states (arising as complications of infections, malnutrition, aging, side effects of immunosupression, irradiation, chemotherapy for cancer and other autoimmune disorders).

Primary immunodeficiency occurs as a result of a genetic defect. Primary immunodeficiency may involve one type of T- or B-cell, all the T cells (DiGeorge syndrome), or all the B-cells (Bruton's agammaglobulinemia). Most commonly, one Ig (usually IgA or IgG) is missing. Individuals with selective Ig deficiency may have an increased susceptibility to certain infections or may be asymptomatic. Severe cases of IgG deficiency may be treated with replacement

injections. Typically, selective IgA deficiency is not treated because patients may develop IgG antibodies to administered IgA, which may cause anaphylaxis. With total B-cell deficiency, the missing Ig can be provided to the individual by intravenous administration. Infants with primary T-cell deficiency have severely impaired ability to fight infection because T-cells are required not only for cellular immunity but humoral immune responses as well. If the pluripotential bone marrow stem cells are dysfunctional, T- and B-cells and all other white blood cells may be deficient. This condition is called severe combined immunodeficiency syndrome (SCIDS). SCIDS used to be fatal in early childhood, but treatment with harvested stem cells is yielding promising results.

Primary immunodeficiency may also occur if an individual is born without certain MHC proteins. Without these proteins, dysfunctional self-antigen presentation to the T-cells occurs, leading to a failure of T-cell immune function. This condition usually causes death in early childhood.

Chronic granulomatous disease (CGD)

CGD is a rare congenital immunodeficiency (approximately one case per 250 thausand 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 (i. e. neutrophils, eosinophils, monocytes and macrophages).

Clinical findings. 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;
— cutaneousand hepatic abscesses;
— osteomyelitisand septicemia.

These severe infections usually become apparent during the 1st year of life and are caused predominantly by Staphylococcus aureus, Aspergillusspecies, enteric gram-negative bacteria, Serratia marcescens and Burkholderia (Pseudomonas) cetacean.

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, biliarysystem, ureters or bladder.

Biochemistry. While all CGD patients share the severe defect in the respiratory burst, there is substantial heterogeneity in the molecular mechanisms responsible.

The enzyme that catalyzes the respiratory burst, NADPH oxidase, consists of at least four subunits (designated phoxfor phagocyte oxidase): gp91phox and

p22phox (the two subunits of a low-potential flavocytochrome termed flavocytochrome 558that is the redoxcenter of the oxidase), p47phox and p67phox (the two cytosolic oxidasecomponents).

CGD is caused by a defect in any one of these four components.

Genetics. Mutations in the gp91phoxgene (CYBBon chromosome Xp21.1) cause the X-linked recessive form of the disease that affects about 70 % of CGD patients.

The remaining 30 % of patients have mutations in the genes encoding: p47phox–NCF1on chromosome 7q11.23 (about 25 % of cases), p67phox–NCF2on chromosome 1q25 (about 2 % of cases), p22phox–CYBA on chromosome 16q24 (about 3 % of cases).

Deletions, insertions, splice site defects, nonsense mutations, missense mutations and, in rare cases, regulatory mutations have been identified in the four types of CGD at the molecular genetic level.

Most CGD patients have mutations unique to their families and the diversity of these mutations and the multiple genes affected provides a partial explanation for the genetic, biochemical and clinical heterogeneity of CGD.

Analysis of NADPH oxidase expression on neutrophils. Monoclonal antibody (MoAb) 7D5 can be used to define cytochrome 558 expression on the surface membrane of neutrophils, CD32 MoAb to the common Fc receptor for IgG is used as a control.

Analysis of NADPH oxidase activity on neutrophils from a carrier. NBT slide test: showing normal blue oxidized pigment deposition and dysfunctional transparent cells without the capacity to oxidize. The formazan upon cell activation: this is indicative of maternal carriership of disease.

CGD disease management. Prophylactic antibiotics active inside phagocytes, most often co-trimoxazole (or a macrolide when hypersensitive).

Monitor lung function to detect early deterioration.

Prescribe rules to prevent exposure to disease-transmitting conditions: no hairy pets (fungi), no turtles or snakes (Salmonella spp.), no wood chipping, or exposure to dusty areas, no extreme gardening (fungi, mycobacterial strains).

Bone marrow transplantation should be considered when prophylactic measures and life style changes do not improve the condition; checkHLA-typing in the family for an HLA-matched donor.

Family screening for carriership and eventual prenatal screening.

DiGeorge syndrome

Severe T-cell deficiency with:
— less than 50 T-cells/10^9l (CD3+,CD45RA+,CD62L+);
— low mitogenproliferation;
— cardiac defects;
— hypocalcemia.
However, 40 % of children with 22q11 deletion have no heart malformation.

Transcription factors direct the development:

— TBX1 (T-box family). Homozygous knockouts in mice and zebra fish are lethal but features of DiGeorgesyndrome.

— Presented evidence that TBX1 mutations explain most findings in DiGeorge syndrome.

Thymus development and thymocytematuration intricate cross-talk: no thymus development no lymphocyte development and vice versa.

Incidence

DiGeorge syndrome is common:

— estimated incidence 25/100 thousand newborns.

But DiGeorge syndrome with severe immunodeficiency is uncommon:

— estimated incidence 0,2/100 thousand newborns;

— (SCID 1.5/100 thousand newborns).

Mode of presentation

Among 100 patients:

— 64 % had heart malformations.

— Of those diagnosed as infants, 92 % had heart malformation.

— One patient presented as «SCID» with failure to thrive and CMV pneumonitis.

DiGeorge syndrome is more than immunodeficiency, heart malformation, and hypocalcemia:

— Heart-outlet malformations: truncus, VSD, Fallot, PA, IAA.

— Thymus: aplasia, dysplasia, immunodeficiency.

— Parathyroids: aplasia, dysplasia, hypocalcemia.

— Palate: cleft palate and velopharyngeal dysfunction.

— Face: minor characteristic anomalies.

— Brain: cognitive and behavioral changes.

IgA deficiency (IgAD)

Selective IgA deficiency (IgAD).

Overview:

— Less than 0,05 g/l serum IgA and concomitant lack of secretory IgA.

— Most common form of primary immunodeficiency in the western world affecting 1/600 individuals.

— Most individuals with IgAD are not prone to infections.

— Anti-IgA antibodies developing 30 % of patients.

— Simultaneous IgG subclass deficiency (IgG2) in less than 5 % of patients.

— Development of CVID in less than 5 % of patients during 20 year follow-up.

Etiology

Genetic predisposition:

— HLA.

Idiopathic.

Drug induced:
  — anti-rheumatic;
  — anti-epileptic.
Chromosomal aberrations:
  — chromosome 18.

Clinical management
Treatment only if the individual has symptoms.
Prophylactic or periodic antibiotics.
Immunoglobulin therapy can be beneficial:
— with low levels of IgA if the patient has high levels of anti-IgA antibodies.
Follow-up of Ig-levels: CVID may develop later in life.
Autoimmune diseases connected to IgAD:
— IDDM.

Severe combined immune deficiency

Genetically determined complete block in T-lymphocyte development. Approximately1:100 thousand births. Non-distinct diseases:
  — early diagnosis can be life saving;
  — emergency treatment: usually allogeneic hematopoietic stem-cell transplantation.

Clinical findings:
The onset of infection during the 1st few months after birth.
Usual symptoms include:
— recurrent oral candidiasis;
— interstitial pneumonitis;
— recurrent diarrhea episodes;
— failure to thrive.
Every infant with one of these man if estations should be investigated for a severe immune deficiency

Laboratory evaluation:
— lymphopenia (more than 90 % of cases);
— absence of a thymic shadow on chest X-ray.

Diagnosis:
— T-cell lymphopenia can be masked by the presence of maternal T-cells;
— associated immunological abnormalities: (variable) low NK-and/or B-cell counts;
— to be excluded: HIV infection and DiGeorge syndrome.

Treatment
— Allogenic stem-celltransplantation is a curative procedure. Chance of success dependson:
а) compatibility between donor and recipient;
в) clinical status at diagnosis.

— Emergency treatment to be performed by a specialized pediatric transplantation unit.

— Alternative therapies, i. e. enzymatic substitution [ADA] or gene therapy is being investigated.

Wiskott-Aldrich syndrome management

Patients with milder forms of WAS may profit from infectious prophylaxis (immunoglobulins, antibiotics).

— Trauma-preventive measures to limit the risk of life-threatening bleeding complications.

— HSCT which is curative.

— HSCT indicated if a matched donor is available, with excellent results if performed early.

— HLA-non-identical HSCT has been successful and is considered in severe forms and absence of amatched donor.

Clinical:

— Main clinical findings: bleeding, eczema, susceptibility to infections.

— Immunodeficiency may be progressive.

— Autoimmune phenomena are common (hemolytic anemia, vasculitis).

— Substantial risk for lymphoma and lymphoproliferative disease.

— Marked variability of clinical manifestations.

— Occasionally only XTP.

Laboratory:

— Low platelets, which are of small size (microthrombocytopenia).

— Immunological findings: diminished T-cell alloresponsiveness, dysgammaglobulinemia, low isoagglutinin titer.

Diagnosis:

— Congenital microthrombocytopenia in combination with persistent eczema in a male patient.

— Mutational sequence analysis is broadly available and is useful to confirm the clinical diagnosis, to investigate carrier status in females, and to perform prenatal diagnosis.

X-linked agammaglobulinemia

Epidemiology and genetics:

— A rare primary immunedeficiency: one case per 250 thousand males.

— Inheritance: X-linked.

Genetics: mutations of the BTK gene.

Clinical features

Onset of symptoms within the 1st year of life, after disappearance of passively-acquired maternal antibodies.

Bacterial infections are the predominant manifestations of XLA.

Types of infections include:
— ear/nose infections (*H. influenzae or St. pneumoniae*);
— bronchitis / pneumonia (*H. influenzaeor, St. pneumoniae*);
— skin infections (*Staphylococcus or Pseudomonas*);
— gastrointestinal infections (*Giardialamblia, Campylobacter*);
— meningitis (*H. influenzaeor, St. pneumoniae*);
— septicemia (*H. influenza St. pneumoniae or Pseudomonas*).
Opportunistic infections (*P. carinii, Cryptosporidium*) are rare.

Astoviral infections, increased susceptibility to enteroviral infections are well recognized.

Laboratory evaluation:
— Absent / low serum IgG, IgA, and IgM. A few patients may have normal levels of one or two Ig isotypes at diagnosis; in rare cases XLA patients may have near-normal Ig levels.
— Defective antigen-specific antibody response to vaccines.
— Normal circulating T-cells; B-cells are severely decreased (usually less than 1 %). The percent age of circulating B-cells, rather than the extent of the Ig defect, is a better indicator of XLA.

Diagnosis:
A diagnosis of XLA is suspected in a male with low/absent levels of Ig, absence of circulating B-cells, and normal T-cell counts. In the case of a positive family history, this immunological phenotype allows a definite diagnosis of XLA.

In sporadic cases, a definitive diagnosis is provided by one of the following findings:
— mutation of BTK gene sequence;
— absence of BTK mRNA or of BTK protein.

XLA management:
— IVIG: 400 mg/kg/21 days.
— Aggressive/timely antibiotic treatment for acute infections.
— Prolonged antibiotic administration may be necessary.
— Regular monitoring of lung function.
— Chest physiotherapy if necessary.
— Regular monitoring of liver function to control Ig safety.

X-linked hyper-IgM syndrome

Epidemiology and genetics:
— *A rare primary immunodeficiency*: (less than 1 case per 1 million males).
— *Inheritance:* X-linked.
— *Genetics:* mutations of the CD40 ligand (CD40L) gene/
— Other names: CD40L deficiency, hyper IgM type 1 (HIGM1).

Clinical features:
— Increased occurrence of bacterial and opportunistic infections.

— Pneumocystis carinii (P. jerovici), pneumonia (PCP) is common in the 1st years of life.

— Increased risk of Cryptosporidium infection.

— High incidence of liver/biliary tract disease.

— Increased occurrence of gastrointestinal and liver tumors.

— High mortality rate (~40 % by age 20 years), if not treated properly.

Laboratory evaluation:

— Low serum IgG and IgA — normal to increased IgM (defective class switch recombination).

— Normal T- and B-cell counts.

— Normal in vitro response to mitogens, but response to antigens is often diminished

— Frequent occurrence of neutropenia.

Diagnosis

Diagnosis is base reduced/absent expression of CD40L by CD4+ T-cells upon in vitro activation.

Definitive diagnosis is provided by mutational sequence analysis.

XHIM management:

— IVIG, 400 mg/kg/21 days.

— Trimethoprim-sulfametoxazole to prevent PCP.

— Use filter-sterilized water (to prevent Cryptosporidium infection).

— Azithromycin (or paromomycin) to prevent cryptosporidiosis.

— Nitazoxanide can be used to treat Cryptosporidium infection.

— Regularmonitoring of liver function.

— Consider stem-cell transplantation, especially if HLA-matched family donor is available.

Human immunodeficient virus

HIV-results in the infection disease associated with primary impairment of the immune system and secondary immunedeficiency occurrence. It is characterized by activation of opportunistic pathogens. The disease is phase. Period of HIV-infection clinical manifestations is called AIDS. HIV was found by L. Montanie in France and R. Gallo in the USA in 1983.

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

Classification System for human immunodeficient virus infection by centers for disease control

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.

Classification system for HIV-infected adults and adolescents is shown in the table 6.

Table 6 — Classification system for adults and adolescents with human immunodeficient virus by centers for disease control

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

Note. # — for symptomatic conditions; * — for AIDS-indicator conditions.

Classification system by centers for disease control: symptomatic Conditions (category B)

Category B symptomatic conditions are defined as symptomatic conditions occurring in an HIV-infected adolescent or adult that meets at least one 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;
— PID;
— cervical dysplasia (moderate or severe)/cervical carcinoma in situ;
— hairy leukoplakia, oral;
— idiopathic thrombocytopenic purpura;
— constitutional symptoms, such as fever (more 38,5 °C) or diarrhea lasting more then one month;
— peripheral neuropathy;
— herpes zoster (shingles), involving more or equal two episodes or more or equal one dermatome.

Classification system by centers for disease control: AIDS-indicator conditions (Category C):

— bacterial pneumonia, recurrent (more or equal 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 (more than 1 month duration);
— cytomegalovirus disease (other than liver, spleen or nodes);
— encephalopathy, HIV-related;
— herpes simplex: chronic ulcers (more than 1 month duration) or bronchitis, pneumonitis or esophagitis;
— histoplasmosis, disseminated or extrapulmonary;
— isosporiasis, chronic intestinal (more than 1 month duration);
— Kaposi sarcoma;
— burkitt lymphoma, immunoblastic or primary CNS;
— 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);
— PML;
— salmonella septicemia, recurrent (non-typhoid);
— toxoplasmosis of brain;
— wasting syndrome due to HIV (involuntary weight loss more than 10 % of baseline body weight) associated with either chronic diarrhea (more or equal 2 loose stools per day more or equal 1 month) or chronic weakness and documented fever more or equal 1 month.

Clinical staging of HIV/AIDS and case definition by World Healthcare Organization

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 one through four, 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 more or equal 15 years.

Clinical staging of HIV/AIDS for adults and adolescents by World Healthcare Organization

Primary HIV Infection:
— Asymptomatic.
— Acute retroviral syndrome.
— Clinical Stage 1.
— Asymptomatic.
— Persistent generalized lymphadenopathy.

Clinical Stage 2:
Moderate unexplained weight loss (less than 10 % of presumed or measured body weight).
Recurrent respiratory infections (sinusitis, tonsillitis, otitis media and pharyngitis).
— Herpes zoster.
— Angular cheilitis.
— Recurrent oral ulceration.
— Papular pruritic eruptions.
— Seborrheic dermatitis.
— Fungal nail infections.

Clinical Stage 3:
— Unexplained severe weight loss (more than 10 % of presumed or measured body weight).
— Unexplained chronic diarrhea for more than 1 month.
— Unexplained persistent fever for more than 1 month (>37,6 °C, intermittent or constant).
— Persistent oral candidiasis (thrush)
— Oral hairy leukoplakia
— Pulmonary tuberculosis (current).
— Severe presumed bacterial infections (e. g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia).
— Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis.
— Unexplained anemia (Hb less than 8 g/dL).
— Neutropenia (neutrophils less than 500 cells/µL).
— Chronic thrombocytopenia (Tr less than 50 thousand cells/µL).

Clinical Stage 4:
— HIV wasting syndrome, as defined by the CDC.
— Pneumocystis pneumonia.
— Recurrent severe bacterial pneumonia.
— Chronic herpes simplex infections (orolabial, genital or anorectal site for more than 1 month or visceral herpes at any site).
— Esophageal candidiasis (or candidiasis of trachea, bronchi or lungs).
— Extrapulmonary tuberculosis.
— Kaposi sarcoma.
— Cytomegalovirus infections (retinitis or infection of other organs).

— CNS toxoplasmosis.
— HIV encephalopathy.
— Cryptococcosis extrapulmonary (including meningitis).
— Disseminated nontuberculosis Mycobacteria infection.
— PML.
— Candida of the trachea, bronchi or lungs.
— Chronic cryptosporidiosis (with diarrhea).
— Chronic isosporiasis.
— Disseminated mycosis (e.g., histoplasmosis, coccidioidomycosis, penicilliosis).
— Recurrent non-typhoidal Salmonella bacteremia.
— Lymphoma (cerebral or B-cell non-Hodgkin).
— Invasive cervical carcinoma.
— Atypical disseminated leishmaniasis.
— Symptomatic HIV-associated nephropathy.
— Symptomatic HIV-associated cardiomyopathy.

Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis)

Pathogenesis

➤ gp 120 HIV binds CD4+ protein-receptor on the surface of T-cells, macrophages, monocytes, astrocytes, endotheliocytes, sperm cells.

➤ progressive decline in CD4+ T–lymphocytes and a reserval of the normal 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 (FC receptors).

➤ the immune system inhibition results in AIDS-definding 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), the time from HIV-infection up to AIDS (about 10 years).

Treatment:
— inhibitors of reverse transcriptase;
— inhibitors of viral proteins.

INFLAMMATION

Inflammation (from Roman *inflammatio, from Greek phlogosis —* «inflammation»*) —* is the most often met typical pathological process.

Inflammation is a numerous process, which was perfected in evolution as an adaptive organism reaction in response to the local tissues injury.

It manifests by:

1) injury of tissues (alteration);
2) the microcirculation impairment with the vascular permeability increase;
3) exudation;
4) emigration of Le;
5) proliferation.

Etiology of inflammation causes:
— exogenous;
— endogenous.

The inflammation reaction development depends on:
1) the location of the phlogogen agent action;
2) the inflammation beginnings location;
3) the organism reactivity definds;
4) the inflammation beginnings;
5) the inflammation clinical course;
6) the inflammation outcomes.

The inflammation classification

— Infectious.
— Non-infectious (aseptic).

According to the local reactions and clinical presentations intensity:
— normergic;
— hyperergic;
— hypoergic (anergic).

According to the main components intensity:
— exudative;
— proliferative (productive);
— the interstitial inflammation;
— on the basis of immunity;
— with the pointed condylomas and polyps formation *(the polypous inflammation).*

According to the development quickness and duration:
— acute;
— chronic.

The inflammation local signs:

1. *Redness (rubor)* it is associated with the arterial hyperemia development,

increase in oxyhemoglobin arterial flow, increase in the blood flow rate, the venous blood arterialization.

2. *Heat (calor)* increase in the redox processes intensity.

3. *Swelling (tumor)* develops in case of the increased exudation and edema.

4. *Pain (dolor)*.

The nociceptors irritation by the chemical mediators of inflammation as a result of:

— the hydropic fluid compression;

— of ionic imbalance (H^+ and K^+ extracellular accumulation);

— the sensitive nervous endings and fibers injury by enzymes.

5. *Loss of function (functio laesa):*

— change of metabolism;

— change of the organ and tissue regulation;

— the structural impairments.

Common clinical manifestations of inflammation

Begins in response to the *pyrogens* action:

— *positive value* (it activates phagocytosis, the antibody genesis, the bacteriostatic and bacteriologic activity);

— *negative value* (hyperpyrexia leads to the higher NS-impairment, critical decrease in temperature leads to the cardiovascular system impairments).

Leukocytosis results from leukopoiesis stimulation.

The protein fractions change:

— hypoalbuminemia;

— hyperglobulinemia;

— an increase in α- and β-globulins;

— an increase γ-globulins.

The acute phase proteins production under the action of interleukins, and ESR-acceleration results from:

— disproteinemia;

— the physical-chemical parameters change;

— the Er adhesion and aggregation activation.

Normal ESR level:

— in women — 2–15 mm/hour;

— in men — 1–10 mm/hour;

— in newborn — 2 mm/hour.

In physiologic conditions ESR increases in pregnancy (in the 2nd part), in case of the intensive physical activity.

ESR level depends on:

— Change of the different blood proteins fractions correlation.

— Increase of the lowly dispersed proteins (globulins, fibrinogen) in inflammation processes and some infectious diseases leads to ESR change —

the weak charged lowly dispersed proteins absorbs on the negative charged Er, also proteins decrease the Er surface charge and promotes the erythrocytes closing in and increase the erythrocytes sedimentation rate.

— Volume, number and diameter of Er.

— Increase in volume, number and diameter of Erleads to the ESR decrease.

— Decrease in volume, number and diameter of Er leads to the ESR increase.

Blood cholesterol level and blood lecithin level:

— the cholesterol adsorbing on Er leads to the ESR increase;

— lecithin decreases ESR.

Change of the Ers relative density:

— hypercapnia (asphyxia, cardiac decompensation), ESR decrease because of the Er diameter increase and decrease in the Er relative density.

Blood viscosity:

— hydremia leads to increase in ESR;

— increase of blood viscosity (dehydration) leads to decrease in ESR.

Some drugs and therapy exert influence on ESR:

— the nonspecific and specific irritant therapy, vaccine therapy, blood transfusion, chronic ingestion of soda lead to increase in ESR;

— ingestion of salicylic preparations, mercurial and calcic preparations, diuretics, sleeping — draughts, antimalarial drugs lead to decrease in ESR.

Disenzymemia result from injury of cellular membranes

Also *pain reactions* and *allergization, intoxication* of organism are observed in inflammation.

Components of inflammation

Alteration, exudation and proliferation are referred to the components of inflammation.

Alteration. In latin *alteration* is a change, an injury is a cells structure and functions impairment, an organs impairment, a systems impairment, a metabolism impairment leading to the vital activity impairment.

Primary alteration. It arises in case of the phlogogen factor action and it is characterized by the metabolism impairment, morphological and functional impairments, usually it locates in the inflammation epicenter.

Secondary alteration. It arises as a consequence of the surrounding tissues and the whole organism response (it may arise in case of the phlogogen factor action if the phlogogen factor action continues).

Mostly it marked in the peripheral part of inflammation (around the primary alteration zone).

Primary and secondary alteration are showen in the table 7.

Table 7 — Primary and secondary alteration

Zone of primary alteration	Zone of secondary alteration
Cause	
Phlogogenic agent	Phlogogenic agent; physical chemical factors, metabolic changes in zone of primary alteration; action of inflammation chemical mediators
Localization	
Localization of direct phlogogenic agent action	Periphery of direct phlogogenic agent action, region around the zone of primary alteration
Mechanisms of formation	
Injury and destruction of tissue structure, metabolism impairments (catabolism prevalence), substantial physical chemical changes	Impairments of NS control, axon transport, trophic and plastic factors, vascular tone and blood flow, and action of inflammation chemical mediators
Time of forming	
Strait out after the direct action of phlogogenic action	In some seconds-minutes after the direct action of phlogogenic agent
Maniphestations	
Mostly irreversible	Reversible

Chemical Mediators of Inflammation

Chemical previous cell mediators of inflammation are showen in the table 8.

Table 8 — Chemical previous cell mediators of inflammation

Groups of mediators	Mediators	Sources of mediators	Effects
Vasoactive amines	Histamine	Basophils mast cells	Vasodilation; an increase in vascular permeability; spasm of smooth muscles
	Serotonin	Tr	Itches; granulocyte inhibition; stimulation of monocytes-macrophages and fibroblasts
Lysosomal factors	Proteinases	Granulocytes monocytes-macrophages	Tissue destruction; stimulation of emigration and phagocytosis stimulation of monocytes-macrophages and fibroblasts; proliferation and activation of Le
	Non-enzyme cationic proteins	Granulocytes	Microbicidity; an increase in vascular permeability; mast cell degranulation; adhesion and migration of leukocytes
Neuropeptides	Substance P calcitoninogen related peptide neurokinin A	C-fibers of afferent neurons	Vasodilation; an increase in vascular permeability; mast cell degranulation; spasm of smooth muscles
Neuromediators	Acetylcholine	Cholinergic mediators	Vasodilation; smooth muscle spasm; stimulation of Le

Chemical newly synthesized mediators of inflammation are shown in the table 9.

Table 9 — Chemical newly synthesized mediators of inflammation

Groups of mediators	Mediators	Sources of mediators	Effects
Arachidonic acid metabolites	Prostaglandins	Monocytes-macrophages, granulocytes, Tr	Activation of Le vasodilation pain
	Thromboxanes	Monocytes-macrophages, granulocytes, Tr	Aaggregation of Tr spasm of smooth muscles; activation of granulocytes, Le, an increase in vascular permeability (LTC_4, D_4, E_4); vasodialtion
	Leukotrienes lipoxins	Monocytes-macrophages, granulocytes, Tr	Activation of smooth muscle spasm (LTC_4, D_4, E_4, lipoxins)
Phospholipids	PAF, platelet activating factor	Granulocytes, mast cells, monocytes-macrophages	Smooth muscle spasm; vasodilation; an increase in vascular permeability; activation of Le, aggregation of Tr
Monokines	IL-1, TNF, tumor necrosis factor	Monocytes-macrophages	Activation of Le and other cells; proliferation and activation of lymphocytes; stimulation of phagocytosis; stimulation of proliferation and activation of fibroblasts; stimulation of tissue destruction
Lymphokines	Macrophage activating factor; macrophage inhibiting factor, interleukin-2	T-lymphocytes	Activation and inhibition of granulocytes; stimulation of lymphocytes and granulocytes; activation of NK-cells
Oxygen active forms	Superoxide anion, perhydroxyl-anion, hydroxyl-anion, singlet oxygen, hydrogen dioxide, hypochloride	Granulocytes, monocytes-macrophages	Tissue destruction; granulocyte activation; phagocytosis; stimulation; inhibition of monocytes
The other small molecules	Nitric oxide	Monocytes-macrophages, granulocytes	Tissue destruction, granulocyte activation

Chemical plasma mediators are shown in the table 10.

Table 10 — Chemical plasma mediators

Groups of mediators	Mediators	Sources of mediators	Effects
Kinins	Bradykinin	Plasma interstitial fluid	Increase in vascular permeability; smooth muscle spasm; inhibition of granulocytes; stimulation of lymphocytes and fibroblasts; pain
Factors of blood coagulation	Fibrinopeptides products of fibrin degradation	Plasma	Activation of Le; phagocytosis inhibition
Complement components	C5b–C9 C5a des Arg C5a–C3a	Plasma interstitial fluid	Tissue destruction (C5a–C9); Le activation; increase in vascular permeability (C5a, C3a); smooth muscle spasm

Acute phase response is a system organism protection

Acute phase response is a number of the numerous systemic reactions developing in response to injury, this reactions are caused by the main protective and control organism systems involving (NS, endocrine system and immune system).

This reactions are accompanied by the physiological functions co-ordinate reorganizations, the metabolic resoursces repartition for the injury protecting of organism.

The acute phase response development scheme include:
1. Tissues injury.
2. Inflammation.
3. Activation of Le, fibroblasts, endothelial cells.
4. The mediators secretion.
5. The mediators action on the target cells.
6. The systemic reactions:
— NS — hypothalamus — fever.
— Endocrine system — pituitary gland — adrenocorticotropin.
— Liver — the acute phase proteins.
— Hemopoietic system — bone marrow — leukocytosis, reticulocytosis.
— Immune system — Le activation.

Exudation

Exudation (exsudatio; in roman *ex-sudare* — «sweat») — is a protein containing liquid part of blood transudation through the vascular wall in the inflammatory tissue.

Exudate is a protein containing liquid part of blood transudation through the vascular wall in the inflammatory tissue. Exudate is an inflammatory origin liquid, this liquid effluents from microvessels, containing big amount of protein and, as a rule, blood corpuscles.

It accumulates in tissues and/or body cavities in inflammation.

Triad:

1) vascular reactions and changes of blood circulation in the inflammatory center;

2) exudation (the liquid pat of the blood effluent from the vessel);

3) emigration is a Le exit in the inflammatory center and phagocytal reaction development.

Change of microcirculation in inflammatory center

The short — term spasm
↓
Arterial hyperemia
↓
Venous hyperemia
↓
Prestasis
↓
Stasis
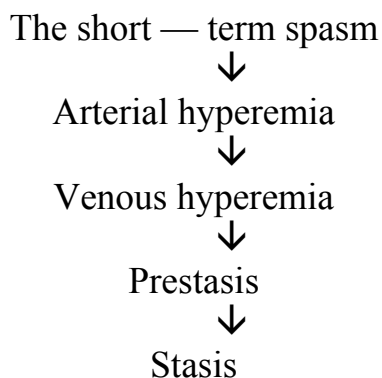
The blood circulation scheme in inflammation is shown in the picture 2.
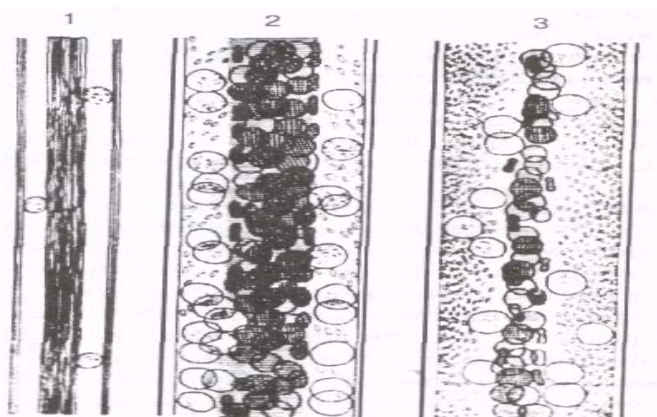
Picture 2 — The blood circulation scheme in inflammation:
1 — axial blood stream, axial plasmatic zone with single Le;
2 — blood flow slowing down in the axial zone; visible Er; краевое стояние Le и Tr;
3 — regional standing of Le, Tr; ↓ axial plasmatic zone

Molecules of the cells adhesion is shown in the table 11.

Table 11 — Molecules of the cells adhesion

Name	Functions
Selectins	Begins the interaction between leukocytes and vessel's endothelium
Adherins	Join l-selectin in the leukocyte and endothelium interaction initiation
Integrins	Join molecules of adhesion on the cell and molecules of the extra-cellular matrix and providing the strong joining
Immunoglobulin super-family	Ligands for integrins

The three stages model of Le adhesion to endothelium:

1. Leukocytic CD15 and E-selectin joining lead to the slowing down and stoppage of neutrophils, when neutrophils rolls on endothelium.

2. Fixed Le is activated because of the interaction with molecules and chemokines of endothelium.

3. Activation of Le leads to the integrins expression on it's surface for joining with ICAM – 1, which induces in case of endothelium activation.

Phagocytosis is a protective and adaptive reaction of organism consists of recognition and active attachment of microorganisms, destroyed cells and foreign particles by phagocytes.

Stages of phagocytosis:

1) approaching;

2) the object attaching to the external membrane and it's submergence consisting of phagosome in cytoplasm;

3) fusion of phagosomes and lysosomes and the phagolysosome forming;

4) ingestion;

5) the object's remains excretion in surroundings.

Acute inflammation:

— intensive clinical course;

— fast recovery (in 1–2 weeks);

— (in dependence on the damaged organ or tissue, the alteration scale and extent).

In case of the normergic type of inflammation in the inflammatory center there is a moderate alteration and tissue destruction, exudative and proliferative changes.

In case of the hyperergic type of inflammation in the inflammatory center alteration and tissues destruction dominate.

Chronic inflammation.

If inflammation from the very outset has persisting and prolonged clinical course, it will called as «*primary-chronic*»

If inflammation clinical course after the acute period has prolonged clinical course, it is called as «*secondary chronic*»

The character of chronic inflammation clinical course:

— Local factors.

— Cellular structure.

— Cytotoxins.

— Chemical mediators of inflammation.

— Character, degree and measure of tissue injury.

— Common systemic factors.

Conditions promoting chronic inflammation:

— Prolonged stimulation of macrophages by citokines, immune complexes, products of microorganism and cell metabolism.

— Activation of angiogenesis in the center of chronic inflammation.

— Migration of PMN Le to the center of inflammation. Le cause matrix destruction of connective tissue, they secrete biologically active substances causing chemotaxis of mononuclear Le to the center of inflammation and activation of them.

Characteristic signs:

— granuloma formation (in tuberculosis, brucellosis or syphilis);

— infiltration of inflammation center predominantly by lymphocytes and monocytes;

— fibrouse capsule formation (subject to foreign body or Calcium salt deposits);

— necrosis in the center of inflammation.

Excess acumulation of activated macrophages in the center of inflammation is characteristic for incomplete phagocytosis. In case of toxoplasmosis, leprae, tuberculosis, organic and non-organic object uptake (dust particles, dextrane molecules).

FEVER

Typical impairments of thermoregulation

Poikilothermous animals

In greek *poikilos* is a changable and *therme* is a heat cold — blooded animals, which body temperature depends on the environment temperature (lamprey, amphibia, reptile).

Poikilothermia is inability to support body temperature on the constant level independently of variations in the environmental temperature. It makes this animals dependent on the climate factors.

The periodically fall of temperature leads to the great number of animals disappearance including the gigantic dinosours.

In age of Reptiles (185–190 millions years ago).

The 1st primitive mammals appear and also the bird — predecessors posessing the isothermal mechanisms sources. Also they were the 1st homothermous (warm — blooded) animals.

Homotherm animals

In greek *homoios* is the same.

Warm-blooded animals are able to support the relatively constant body temperature at the considerable changes of the environmental temperature (mammals, birds, man).

Isothermy

1. It is an ability to support the constant body temperature on the relatively constant level

2. It is a vitally important characteristic, which is acuired by man and higher animals in the evolutional process, which allow to realize the full organism adaptation to the hanging environmental conditions.

3. To meteorological and climate geographical factors

Complete isothermy

1. It is pecuiar to the adult homothermous organisms.

2. Some species of adult mammals possess the ability to periodically loss of homothermy (hibernation).

3. There is a sharply decreased level of metabolic processes in them, and they within certain limits beome *poikilothermous*.

Newborns from all species of mammals have the imperfective system of thermotax and more than adults prone to overcooling or overheating.

In old age the thermotax mechanisms become less perfective, and the temperature factor has more pathogenic influence, than for organism in the prime of life.

Hypothalamus

1. Center of heatformation.

2. Control of the heatformation process (chemical thermotax) is realized by the posterior hypothalamus nuclei activity.

3. Center of heatemission.

4. Processes of physical thermotax (heatemission) are caused by the front hypothalamus nuclei.

Effectors of thermotax

1. Liver — metabolic pocesses associated with exothermal processes.

2. Thyroid gland—thyroid hormones dissociate oxydative phosphorylation $\rightarrow \uparrow$ of free oxydation part $\rightarrow$ great quantity of heat.

3. Adrenal glands — adrenaline$\rightarrow$the blood vessels narrowing $\rightarrow \uparrow$ in heat level in organism.

4. Muscles — muscular work $\rightarrow \uparrow$ quantity of heat.

5. Muscular shivering $\rightarrow$ exertion of fibers, no work $\rightarrow$ energy turn to the heat equivalent.

Organs associated with the heat emission

To the organs associated with the heat emission are related:

1) lungs (heat with the expired air);

2) cardio-vascular system;

3) an increaswe in cardiac rate;

4) an increase in cardiac output;

5) in case of blood vessels dilation.

To these agans are related also:

a) eliminative organs (intestine and kidneys);

в) sudoriferous glands.

Circadian biorhythms of temperature. It is characterized by small acriphases (maximum and minimum peaks are within limits 0,5–0,7 ^{o}C).

Fever
(from Latin *febris*, from Greek *pyrexia*)

It is an etiologic non specific and pathogenic form of typical pathological process, characterized by dynamic reorganization of the thermotax system function in response to the pyrogenic substances action and manifests by increase in temperature of internal environment in higher homothermous animals and man.

«Nucleus» of body is a functional concept, joining internal organs (sometimes sceletal muscles), in which heat production takes place.

«Membrane» of body is a functional concept, it is presented by skin, subcutaneous fat (sometimes sceletal muscles), with the help of which diffusion of heat produced by «nucleus» of body to environment takes place

Etiology of fever

The reasons of fever are **pyrogenes** (from Greek *pyros* is a «fire», *pyretos* **is a «heat»).**

Classification of pyrogenes

Primary (exopirogenes):

— infectious (viruses, mushrooms, bacteria, rickettsia, mono- and multicellular parasites) non-infectious (proteins and protein content substances, lipids and fat content substances, steroids, nucleoproteids, lipopolysaccharides).

Properties of exopyrogenes (*do not cause fever independently):*
— temrmostable;
— non-toxic;
— non-allergenic;
— non-antigenic;
— are haptens;
— tolerance develops at repeated usage;
— cause a number of protective effects;
— there is nagroup specificity.

Secondary endopyrogenes: IL-1, IL-6, IL-8, TNF, gamma-IFN, cationic protein, granulocytic macrophage colony-stimulating factor.

Properties of endogenous pyrogenes
— Cause development of fever.
— Basically they are produced in micro- and macrophages of organism.
— Non-toxic.
— Thermolabile.
— Do not possess specific specificity.
— Tolerance is not formed to them.

They increase protective properties of organism: increase in phagocytosis, glucocorticoids production, tissue regeneration, the hepatic detoxicative function, improve processes of microcirculation.
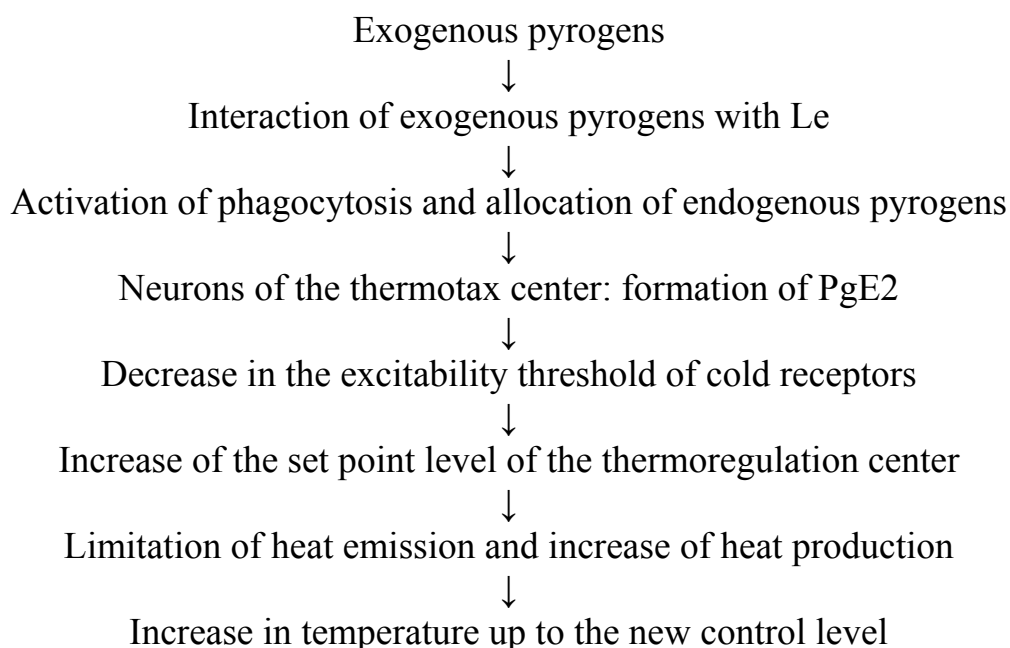
Secretion of endogenous pyrogens does not lead to death of phagocytes.

Factors determining the occurance of feverish process (according to A. D. Ado, 1994)

1. Condition of reactance (excitability) of temperature thermal centers and peripheral thermoreceptors.

2. Activity of synthesis and transport mediators of fever (acetylcholine, serotonin, peptides and others.).

3. Changes of number and structure of Le in blood of the patient during the disease.

4. Speed of formation and allocation of endopyrogenes.

5. Permeability of hematoencephalic and histohaematic barrier.

6. Specific immunologic and allergic stage of the patient's organism, caused by the condition of the immunocompetent system including production of antibodies, activity of lymphocytes and macrophages.

7. Non-specific reactance of endocrine and immunocompetent systems.

8. Besides the degree of the body temperature increase in various diseases depends on the increasing introduction of the CNS substances: caffeine, phenamin, etc.

«Set point» is a mechanism, which localizes in neurons of preoptic area of hypothalamus and controls the body temperature. The higher limit of the body temperature is 37 ºC (37,5 ºC in intestines).

Pathogenesis of fever

Exogenous pyrogens

↓

Interaction of exogenous pyrogens with Le

↓

Activation of phagocytosis and allocation of endogenous pyrogens

↓

Neurons of the thermotax center: formation of PgE2

↓

Decrease in the excitability threshold of cold receptors

↓

Increase of the set point level of the thermoregulation center

↓

Limitation of heat emission and increase of heat production

↓

Increase in temperature up to the new control level

There are three stages of the feverish reaction development according to criteria of the temperature change:

1. Stage of increase in temperature (st. incrementi).
2. Stage of the temperature standing on a high level (st. fastigii).
3. Stage of temperature decrease (st. decrementi).

The onset of fever can be:

Acute (during several hours) — for example, meningococcus meningitis, ornithosis, leptospirosis

Gradual (during several days) — for example, typhoid fever, paratyphus

According to degree of the body temperature increase:

1) subfebrile (up to 38 °C):
— low (up to 37,5 °C);
— high (from 37,6 up to 38 °C).
*2) febrile* (more than 38 °C):
— moderate (up to 39 °C);
— high (up to 41 °C);
*3) hyperpyretic* (more than 41 °C).

Types of the temperature curves in fever

Passing type (*febris ephemera*). It is a unitary short-term «candle» of temperature in some hours. This type is described, for example, in severe form of a pseudo-tuberculosis and lactostasis.

Constant type (*febris continua*). It is characterized by heat, without the acute daily fluctuations (no more than 1 degree). It is observed in croupous pneumonias, abdominal and epidemic typhus, Q fever, pseudo-tuberculosis.
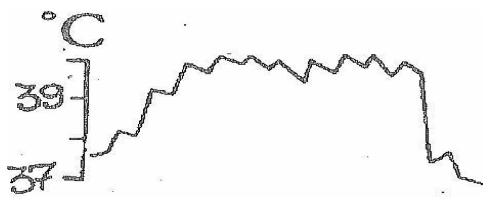
Aperient (*febris remittens*). It is similar to the temperature curve of constant type, but has a little more expressed range of daily fluctuations (1–3 degrees), and does non fall to the norm temperature. So it occurs in the end stage of abdominal typhus, and sometimes it is present during all the disease. In a similar way it precedes bronchus pneumonia, tuberculosis, exudative pleurisy, various virus infections and aseptic fevers.
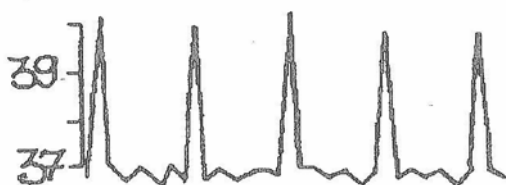
Alternating (*febris intermittens*). This form has great ranges with decrease in the morning temperature up to norm and below, fluctuations (3–4 degrees). It is observed in acute hepatitis, tuberculosis and sepsis. It is often characterized by separate short-term attacks of increase in temperature (paroxysm), periods of apyrexy separated from each other. It can repeat every day in malaria attacks (febris guotidiana), or to come in day on the third (febris tertiana) — in Pl.vivax infection, in two days on the fourth (febris guartana) — with Pl. malaria.
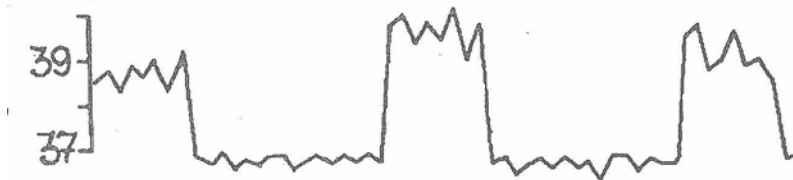
Returnable type (*febris recurrens*) — correct alternation of the periods of pyrexia and apyrexia lasts for some days. E. g. returnable typhus: in this case dependence of the temperature curve on the activator is well visible. Spirochete is phagocyted by macrophages. Also it made multiple copies in them. In due course multiplied spirochetes break through the phagocytic barrier and flood blood: to it there corresponds the next attack of fever lasts during 6–8 days then the temperature critically decreases and there comes the period of apyrexy which lasts for 6–8 days too. Returnable fevers accompany borreliosises. Aseptic returnable fever is observed in lymphogranulomatosis when the febrile and apyrexic periods alternate and last for 3–10 days. Periodic granulocytopenia is accompanied by episodes of fever each 3 weeks.
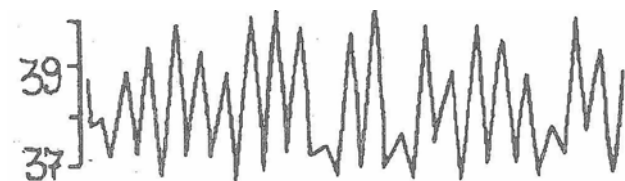
Exhausting, hectic (*febris hectica*) — it is characterized by long current and greater daily fluctuations in temperature (up to 3–5 degrees). It is observed in sepsis, local and system infections**,** for example**,** severe progressing tuberculosis, malignant tumours, quite often in hectic fever there is a distortion of a daily rhythm to morning peaks and evening recession of temperature.
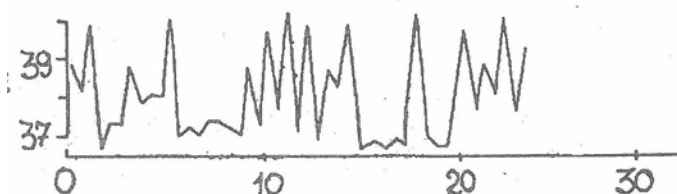
Wrong, atypic (*febris irregularis seu atypica*) — it is characterized by infringement of a daily rhythm, there are rises in temperature in the mornings

and recessions by the evening (febris inversa), or 2–3 rises and falling, or irregular fluctuations of temperature in a day. It is mainly observed in sepsis.

Wavy or undulating (*febris undulans*) — it is characterized by gradual increase of the body temperature up to high values and then gradual decrease down to subfebrile (sometimes normal). The cycle repeats through 2–3 weeks. It is observed in infectious (brucellosis, visceral leishmaniasis) and non-infectious (lymphogranulomatosis).

Feverish curves according to A. P. Kazantsev:

1. Acute wavy fever (febris undulans acuta) — unlike undulating, it is characterized by rather short-term waves (3–5 day) and absence of remission between waves — in the form of of some fading waves. Meets at ornithosis, abdominal typhus, mononucleosis.

2. Reccurent (febris recidiva) — unlike a returnable fever, it is characterized usually by one relapse developing various terms (two day – some months). It is observed at leptospirosis, a pseudo-tuberculosis.

Positive value of fever
— Interfere duplication of microorganisms.
— Fever increases the immune answer.
— Fever promotes development of some protective factors.
— The general adaptable syndrome develops.
— Fever is often the first and the unique sign of disease.
— The artificially created fever.

Negative value of fever
— An increase in the cardiovascular system loading (especially in persons with this system impairments).
— In case of the critical body temperature decrease the undesirable manifestations of three fever development stages are possible.
— The nervous system inhibition.
— The mediated frustration of functions, organs and systems.
— The expresses 5–7 days time fever switches off spermatogenesis for 3–4 weeks.

Features of termotax in newborns
The small size of the newborn body, newborns provide the needs in thermogenesis by means of the untrembling mechanism which cannot be found without special measuring instruments. The superficial layer of the body has small thickness and the isolating layer of fat is rather thin. Newborns allocate

cytokines and answer them with a true fever development. Healthy newborns are rather persistent to overcooling. Instability of newborns to overheating is defined by the limiting mechanisms.

Endogenous anti-pyrogenic system

— *Arginine-vasopressin.* Its introduction into some hypothalamic structures decreases fever.

— *Intermedin hormone (α-MSH).* Its introduction to experimental animals ↓ certainty decreased fever

Effect of its introduction to experimental animals increases the anti-pyretic effect of paracetamol introduction in 25 000 times.

Catecholamines. Introduction of adrenaline and noradrenalin causes decrease in the body temperature in feverish conditions.

Introduction of serotonin leads to increase in body temperature.

Glucocorticoids:
— Its inductors (corticotrophin releasing hormone and corticotropin).
— Inhibite synthesis of pyrogenic cytokins (Il-6 and TNF).

Malignant hyperthermia

It is an extraordinarily type of overheating.

Condition developing in operations under general narcosis with introduction of the depolarizing muscle relaxant.

In basis there is a genetically caused defect of synaptic membranes leading to the sharply increase of its permeability.

It develops in 1 of 60 000 cases of the general anesthesia with using of the depolarizing muscle relaxants.

Pathogenesis of malignant fever

Under the action of depolarizing muscle relaxants Ca^{2+} ions are released from sarcoplasmic reticulum, and cascade of hyper-metabolic reactions are started:
— activation of muscle cell retractive elements;
— rapid ATP destruction;
— dissociation of oxidative phosphorylation and glucose free radical oxidation;
— excess of CO_2 and lactate;
— an increase heat emission;
— an increase in the body temperature up to 43 $^{\circ}$C, man is kind of boiled in his own body.

Depolarizing muscle relaxants have bi-phase effect in synaptic gap: at the beginning they cause shirt-time muscle contraction and then relaxation, because of impulsing impairment from nerve to muscle. Muscle contraction is dozens of minutes prolonged in case of the listed above defect.

Hyperthermia

It is a typical pathological form of the thermal metabolism impairment developing in organism of man as a result of the heat content sharp increase not connected with fever and manifests by the nucleus of the body temperature increase above 38 ºC and organs and systems impairment.

Differ between fever and hyperthermia is shown in the table 12.

Table 12 — Differ between fever and hyperthermia

Criterion	Fever	Hyperthermia
Etiology	Pyrogenic substances	High temperature of environment, factors which prevent realization of heat emission mechanisms, disconnectors of oxidative phosphorylation in mitochondria
The main chain of pathogenesis	Safety of the organism thermotax mechanisms	Breakdown of the thermotax mechanisms
Change of thermal control	Controllable passage of the thermotax system on more high level	Non-controllable increase of the body temperature
Biochemical processes	It activates the oxidative phosphorylation process, it increases synthesis of ATP, it mobilizes the organism protective reactions	Blockage of ATP synthesis occurs, break up of ATP takes place, excess production of heat takes place
Manifestations on the temperature increase stage	Shivering and moderate stimulation of functions (in case of the body temperature increase on 1 °C, puls increases on 8–10 ictuses per minute and respiratory movements increase on 2–3 times per minute)	The acute sweating, sence of heat, the acute pulse and respiration increase (on 10–15 movements) in case of the body temperature increase on 1 °C
Dependence on the surrounding temperature	The body temperature level doesn't depend on the environment temperature	There is a direct dependence between the body temperature and the environment temperature
Influence of warming	The body temperature does not change	The body temperature increases
Influence of overcooling	The body temperature does not change	The body temperature decreases
Anti-pyretic usage	It decreases the body temperature	It doesn't influence the body tempeature

TYPICAL FORMS OF MICROCIRCULATION IMPAIRMENTS

Microcirculation impairments

Microcirculation is a well-ordered blood and lymph circulation in microvessels, transport of plasma and blood form elements, transport of fluids in intersticium. Microcirculation is presented by arterioles, capillaries and venules (diameter 2–200 mcm).

Microcirculation is organized by terminal arteriole → metarteriole → capillary → postcapillary venule. Arteriovenular anastomosis joints arterioles directly with venules (or small artery with veins — juxtacapillary blood flow).

Functions of microcirculation: metabolic, transport, support of the blood pressure level, nutritient, thermal control, protection.

Causes of microcirculatory impairments
1) impairments of icentral and local blood circulation;
2) change in blood volume and viscocity;
3) injury of the microcirculatory vascular wall (atherosclerosis, inflammation).

Typical forms of microcirculation impairments
1) vascular;
2) intravascular;
3) extravascular.

Intravascular impairments

Causes: decrease in rate of blood and lymph flow, high increase in rate of blood flow, impairment of blood flow laminarity, high increase in extra-capillary blood flow.

Transmural impairments

Causes: impairment of blood vessel permeability: increased permeability of blood vessels, decreased permeability of blood vessels; impairment of emigration.

Mechanisms:

— *an increase in vascular permeability results from*: formation of endothelial gaps, cytoskeletal reorganization, increased transcytosis, direct endothelial injury, acidosis, activation of hydrolases;

— *a decrease in vascular permeability results from:* thickening of vascular wall, impairments of the in-cell process providing;

— *emigration impairments results from:* increase in Le emigration, exit of Er and Tr results in hemorrhagies.

Extravascular impairments

Causes: increased flow of interstitial fluid; decreased flow of interstitial fluid.

Mechanisms: an increased flow of intestinal fluid results from: inflammation, allergy, tumor growth, venous hyperemia, stasis; *a decreased flow of the*

intestinal fluid results from: hypo-hydration (diarrhea, plasmorrhagia, a decrease in lymph production, a decrease in fluid filtration, an increase in fluid reabsorption).

The low rate of filtration results from a decrease in hydrostatic capillary pressure, the density of capillary bed and the permeability of capillary wall. The lowering of lymph flow may result from the low interstitial hydrostatic pressure, high hydrostatic pressure in lymphatic vessels and impaired contraction of endothelial cells forming lymphatic capillaries.

Capillary trophic insufficiency:
1) impairment of blood and lymph circulation;
2) fluid and blood particle transport impairment through the capillary wall;
3) decrease in interstitial fluid outflow;
4) impairment of metabolism in tissues and organs.

Consequences: dystrophy, impairment of organ function, tissue function and vital ability of organism.

Sludge-phenomenon

Sludge is an aggregation, adhesion of Er and blood separation.

Etiology: impairment of central and local blood circulation, an increase in blood viscosity, injury of microcirculatory vessels' wall.

Mechanisms of sludge

1) activation of form blood elements, release of pro-aggregate factors;
2) removal of negative charge on the surface of form blood elements, neutralization of their surface charge by cations or protein molecules;
3) attaching of protein micelles to the surface of form blood elements and potentiation of their sedimentation on the vascular walls.

The listed above results in:
4) formation of conglomerates of form blood elements;
5) separation of blood plasma and aggregates of blood form elements.

Types of sludge: classic, dextrane, amorphous (picture 3).
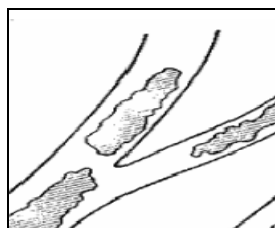
classic   dextrane   amorphous

Picture 3 — Types of sludge

Consequences: impairment of blood flow in organs, impairment of trans-capillary blood form element flow, dystrophy of organs and tissues, hypoxia, acidosis.

Lymph circulation impairments

Lymph circulation failure is a condition in which lymphatic vessels are not doing their main function — the implementation of a permanent and effective drainage of the interstitium.

Forms of lymph circulation failure are related:
1. Mechanic lymph circulation failure. The lymph flow is inhibited because of the organic (compression by tumor, scar, lymphatic node or vessel extirpation) or functional (an increase in blood pressure in large blood vessels, spasm of lymphatic blood vessels).

2. Dynamic lymph circulation failure (the volume of interstitial fluid transudation exceeds the possibility of lymphatic system to effective tissue drainage).

3. Resorptive lymph circulation failure. It results from the structural changes in interstitial tissue, accumulation of proteins and pathologic protein disposition in interstitium.

The main clinical and pathophysiological manifestations of lymph circulation failure in the acute stage are edema, protein accumulation and fibrosis. The main manifestation in chronic stage is sclerosis.

IMPAIRMENTS OF LOCAL BLOOD CIRCULATION

Peripheral or organic blood circulation is a blood circulation in the limits of a single organ.

Typical forms of local blood circulation impairments are: arterial hyperemia, venous hyperemia, ischemia, stasis, embolism

Arterial hyperemia

Arterial hyperemia is characterized by a local deposition of the blood flow rate through the organ or tissue from a dilation of arterial vessels.

Arterial hyperemia is classified into:

1) physiologic — an increase in rate of blood flow results from the increased organ or tissue needs;

2) pathologic — results from the outrageous action of environmental factors. It does not meet the requirements of the cell metabolic activity.

There are the following types of arterial hyperemia depending on the etiologic factors and mechanisms:

1) angioneurotic (neuroparalytic);

2) neurotonic:

— post-ischemic;

— inflammatory;

— collateral;

— on a base of arteriovenous shunts;

— vacuum.

Angioneurotic (neuroparalytic) results from atrophy of sympathetic fibers (injury of sympathetic fibers, blockage of sympathetic ganglions and adrenergic fibers).

Neurotonic results from the increase in parasympathetic drive or sympathetic cholinergic vasodilating fibers in case of their center irritation by tumor, scar and others.

Clinical manifestations of arterial hyperemia and their mechanisms:
1. Redness — reduction of deoxygenated hemoglobin in the capillary bed.
2. Increased temperature — increased inflow of warm arterial blood.
3. Vessel pulsation.
4. Slight swelling — mild accumulation of fluid in the interstitial space resulted from an increase in filtration rate.
5. Increased number of functioning capillaries — an increase in capillary hydrostatic pressure.
6. Increased arteriole diameter and blood flow rate — metabolic mechanism.
7. Increased lymphatic outflow — mild elevation of interstitial hydrostatic pressure.

Venous hyperemia
Venous hyperemia is characterized by a local deposition of blood and a decrease in blood flow rate through the organ or tissue resulting from a delay or cessation of blood outflow by the venous vessels.

Venous hyperemia is classified into the ***local*** and ***general***.

General venous hyperemia results from: acute impairments (myocardial infarction, acute myocarditis), chronic impairments (heart malformations, cardiac ischemic disease, cardiac amyloidosis).

Venous hyperemia can be stagnant, passive and active.

Acute venous hyperemia results in cell compression → dystrophy → necrosis.

Chronic venous hyperemia results in tissue atrophy and sclerosis → induration of organ.

Causes and mechanisms of venous hyperemia are:
1. Compression — tumor, swelling tissue, scar or tourniquet.
2. Obstruction by thrombus or embolus.
3. Heart failure.
4. A decrease in venous wall elasticity combined with vein extension and constriction.
5. Venous valves failure.

Clinical manifestations and their mechanisms:
1. Cyanosis: accumulation of deoxygenated Hb in the capillary bed.
2. Edema: an elevation of hydrostatic pressure in veins and capillaries.
3. Decreased local temperature — a decrease in the rate of metabolic process and reduced inflow of warm arterial blood.

4. Increased diameter of venous vessels and decreased blood flow.

5. Decreased lymphatic outflow — compression of lymphatic capillaries caused by high interstitial hydrostatic pressure.

6. Decreased capillary blood flow and stasis.

Consequences of venous hyperemia: hypoxia, hypotrophy, hypoplasia, sclerosis and necrosis. Venous hyperemia is one of the major predisposing factor of thrombosis.

Ischemia

Ischemia is an imbalance between the supply and demand of the organ or tissue for blood. It implies insufficient oxygen and nutrients delivery and inadequate removal of metabolites

According to etiology and mechanism ischemia is classified into:
— angiospastic (reflex);
— compression;
— obstruction;
— redistributive.

Mechanisms of ischemia:

1. Obstruction or compression of arterial vessels or capillaries by tumor, scar, tourniquet, atherosclerotic plaque, thrombus, embolus, cell aggregates or vesicles of gases.

2. An increase in blood viscosity: polycytemia, massive hemoglobinemia or myoglobinemia.

3. Spasm of arterial vessels: increased sympathetic drive, accumulation of adrenaline, angiotensin II, thromboxane, LT, endothelin, serotonin.

4. Increase in metabolic demand outpacing the blood supply.

5. Rapid lowering of the systemic blood pressure as in shock or collapse.

6. Combination of the listed above.

Clinical manifestations and mechanisms:

1. A decrease in diameter and number of visible vessels.

2. Pallor: reduction in the amount of hemoglobin.

3. A decrease or disappearance of pulsation.

4. A reduction of lymph output de to a decrease in interstitial pressure caused by reduction of water filtration from capillaries into interstitium.

5. A decrease in local temperature due to a reduced blood inflow and decreased rate of oxygen-depended metabolism.

6. A reduction in diameter of arterioles and precapillaries, a decreased capillary bed and low blood flow velocity.

The consequences of ischemia: coagulation necrosis or infarct, apoptosis. Moderate ischemia can result in hypotrophy, atrophy and sclerosis.

Stasis

*Stasis i*s a cessation of blood flow in microcirculatory bed.

Types of stasis: true, ischemic, venous-congestive

True stasis begins with cell aggregation and cell adhesion to the vessel wall and is followed by hemodynamic changes.

Thrombosis

Thrombosis is a lifetime blood clotting partially or completely inhibiting blood flow.

The permissive conditions are the following:

1) local — impairment of vascular wall integrity, lowering of blood flow;

2) general — in blood flow change property, imbalance between coagulation and anti-coagulation;

3) sex, age, climate, body constitution, diseases, trauma, surgical operations.

Types of thrombus

1) According to the structure: white, red, combined, hyaline.

2) According to etiology: marantic , septic, tumoral.

Also thrombus is classified into: progressive, local, obstructive, partial.

Marantic thrombus. It develops in case of organism exhaustion (dehydration and hemoconcentration). It develops in old people in superficial veins of extremities and sinuses of *dura mater.*

Tumor thrombus. It results from tumor growing up in the vein lumen and growing in direction of blood flow. Thrombi result from hematologic diseases: polycytemia, leukemia.

Septic thrombus. It results from inflammation process in veins' wall and surrounding tissue (periphlebitis, phlebitis, thrombophlebitis, bacteria in thrombus).

Outcomes of thrombosis

Outcomes of thrombosis are: aseptic lysis, septic lysis, organization (appearance of fibroblasts on the 5th day), vascularization, canalization, petrifaction, abruption are referred to the outcomes of thrombosis.

Embolism

Embolism occurs when an embolus migrates from one part of the body (through the blood and lymph circulation) and causes a blockage (occlusion) of a blood vessel in another part of the body. The term was coined by Rudolph Carl Virchow in 1948.

Embolism is classified into **exogenous** and **endogenous.**

Exogenous embolism

Air embolism, on the other hand, is usually caused by exogenic factors. This can be the rupture of alveoli, and inhaled air can be leaked into the blood vessels. Other more-common causes include the puncture of the subclavian vein

by accident or during operation where there is negative pressure. Air is then sucked into the veins by the negative pressure caused by thoracic expansion during the inhalation phase of respiration. Air embolism can also happen during intravenous therapy, when air is leaked into the system (however this iatrogenic error in modern medicine is extremely rare).

Gas embolism is a common concern for deep-sea divers because the gases in our blood (usually nitrogen and helium) can be easily dissolved at higher amounts during the descent into deep sea. However, when the diver ascends to the normal atmospheric pressure, the gases become insoluble, causing the formation of small bubbles in the blood. This is also known as decompression sickness or the Bends. This phenomenon is explained by Henry's Law in physical chemistry.

Septic embolism is a type of embolism that is infected with bacteria, resulting in the formation of pus. These may become dangerous if dislodged from their original location. Like other emboli, a septic embolism may be fatal.

Parasitic embolism results from: helminthism, ascaridiasis.

Embolism of pulmonary vessels is often observed in ascaridiasis. Embolism of lymphatic vessels is often meets in elephantiasis.

Endogenous embolism

Thromboembolism is a combination of thrombosis and its main complication, embolism. It classified into the venous and arterial thromboembolism.

Arterial — thrombi in the left heart, aorta.

Venous — v. femoralis, blood vessels of the small pelvis.

The most dangerous type of thromboembolism is pulmonary embolism (with the pulmo-coronary reflex), that is, blockage of the main artery of the lung or one of its branches. It can be fatal.

Fat embolism caused by physical trauma, bone fracture. Fat embolism is often a complication of crush-syndrome.

Amniotic fluid embolism is an obstetric emergency. It is results from pathologic labor and incorrect obstetric care. It can result in DIC syndrome (disseminated intravascular coagulation).

Tissue embolism is an embolism of small fragments of tissues, tumor cells and chorion villi.

Cell embolism. This type of embolism reminds tissue embolism.

The direction of the embolus can be one of two types:

— *anterograde;*

— *retrograde.*

In *anterograde* embolism, the movement of emboli is in the direction of blood flow. In *retrograde* embolism, however, the emboli move in opposition to the blood flow direction; this is usually significant only in blood vessels with low pressure (veins) or with emboli of high weight.

Paradoxical (venous to arterial) embolism. In paradoxical embolism, also known as crossed embolism, an embolus from the veins crosses to the arterial blood system. This is generally found only with heart problems such as septal defects (holes in the cardiac septum) between the atria or ventricles.

Embolism of the systemic blood circulation: pathological processes in pulmonary veins, left heart, arteries of the systemic blood circulation.

Embolism of the pulmonary blood circulation: the drift of emboli from the right heart and veins of the systemic blood circulation. It is characterized by emergency, rapid development of clinical manifestations, dyspnea, and high decrease in arterial blood pressure, inhibition of cardiac activity.

Portal embolism. Portal embolism is observed in pathology of intestinal veins (enterocolitis, intestinal obstruction). It is a rare and dangerous to life pathology, leading to venous hyperemia of intestines, a big amount of blood is accumulated in the abdominal cavity. It can be fatal.

TYPICAL FORMS OF CARBOHYDRATE METABOLIZM IMPAIRMENTS

Carbohydrates were found out by K. E. Shmidt in 1884. It is a large group of compounds, including sugars and starch, that contain carbon, hydrogen, and oxygen and have the general formula $Cx(H_2O)y$.

There are 5 pathway of glucose metabolism in cell:

1) depot of glycogen;

2) glycolisis. The conversion of glucose by a series of ten enzyme-catalysed reactions to lactic acid. Glycolysis takes place in the cytoplasm of cells and the first nine reactions (converting glucose to pyruvate) from the first stage of cellular respiration;

3) aerobic respiration in which food stuffs (carbohydrates) are completely oxidized by atmospheric oxygen, which the production of maximum chemical energy from the foodstuffs;

4) free fat acids and triglycerides;

5) glucose.

Impairments of carbohydrate metabolism are:

— impairments of digestion and absorption;

— impairments of synthesis, depot and glycogenolysis;

— impairments of interstitial metabolism;

— control impairments of carbohydrate metabolism.

Hypoglycemia. It is a syndrome testifying about a decrease in blood glucose level (lower than 3,3 mmol/l).

Hypoglycemia testifies about the blood glucose level control impairments.

Mechanisms of hypoglycemia:
— a decrease in blood glucose inflow;
— an increase in glucose utilization bytissues and blood outflow;
— combnation of 1st and 2nd mechanisms.

Types of hypoglycemia:
— alimentary;
— insulin;
— contra-insulin hormone insufficiency;
— glycogenic;
— hepatic;
— diabetes insipidus;
— enzymopathia;
— autoimmune;
— essential;
— hypoglycemia in patients with diabetes mellitus.

Symptoms of hypoglycemia results from central and peripheral NS impairments:
— in abrupt decrease in blood glucose level caused by hyperadrenalinemia, an increase in sympathetic system activity;
— cerebral symptoms prevail in more slow decrease in glucose level.

Hyperglycemia. Hyperglycemia is defined as an increase of capillary blood glucose level above N (more than 6,1 mmol/l).

Types of hyperglycemia:
1) physiologic (compensatory);
2) pathologic (impairments of active hormonal homeostasis):
— alimentary;
— neurogenic;
— convulsive;
— endocrine;
— insulin.

Diabetes mellitus. *Diabetes mellitus* is clinically and genetically heterogeneous disease, which is characterized byn a chronic multihormonal frustration of all metabolism types (metabolic disease N 1) and gradual defeat of all organs and systems.

Etiologic classification of diabetes mellitus:
1) type I (beta-cell destruction usually resulting in absolute insulin defficiency):
— autoimmune diabetes — WHO (immune mediated);
— essential diabetes;
2) type II (it results from the primary insulin resistency with relative insulin deficiency up to predominantly secretory defect with insulin resistency or without it — WHO);

3) other specific types of diabetes:

— genetic defects of beta-cell function;

— genetic defects in insulin action;

— disease of exocrine pancrease;

— endocrinopathias;

— diabetes induced by medicines or chemicals;

— infections;

— usual forms of the immune mediated diabetes;

— unusual forms of immune-mediated diabetes;

— gestation diabetes.

Specific types of diabetes

1. Genetic defects of beta-cell function. Diabetes results from the specific gene drefects which are related to this group. Diabetes occurrence is associated with monogenic defect of beta-cell function.

— MODY 1,2,3,4 — it is diabetes of adults in youth;

— mitochondrial gene mutation (mutation of DNA 3243).

For the 1st time the point mutation of mtx DNA was opened in MELAS-syndrome (mitochondrial myopathy, lactate-acidosis, encephalopathy, stroke like syndromes, diabetes associating with sensory loss or without loss of hearing).

— The other forms of diabetes mellitus type II, which are caused by mutant or abnormal insulin (Chicago, Angeleno insulin, impairment of proinsulin conversion into insulin resulting in intermediate forms of insulin. Intermediate forms of insulin possess only 5–10 % of intact insulin biologic activity).

2. Genetic defects of insulin action:

— resistency to insulin type A;

— lipoatrophic diabetes, etc.

3. Diseases of exocrine pancreas (pancreatitis, trauma, neoplasia, fibrocalculous pancreas pathology, pancreatectomy, hemochromatosis, etc.)

4. Endocrinopathias (acromegaly, Cushing's syndrome, pheochromocytoma, glucogonoma, hyperthyroiditis, somatostatinoma).

5. Diabetes mellitus induced by medicines or chemical substances:

— glucocorticosteroids, thyroid hormones, α- and β-adrenergic agonists, a nicotinic acid;

— vacor-remedy for struggle against rodents;

— nitrozamines, nitrozurea;

— pentomidin-remedy for pneumocystic carinii infection treatment;

— cyanides.

6. Viral infections.

Viral infections influence diabetes mellitus occurance. Viral infections associate with beta-cell destruction: Coxaci B4, cytomegalovirus, congenital rubella, epidemic parotitis.

7. The unusual forms of insulin-mediated diabetes: physical inactivity syndrome — CNS autoimmune disease (antibodies to glutamate decarboxylase,

systemic lupus erythematous (antibodies to insulin receptor), pigment papillary dystrophy of skin, acantosis nigricans — pigment papillary dystrophy of skin (antibodies to insulin receptor).

8. The other genetic syndromes: Down's syndrome, Turner's syndrome, Cleinfelter's syndrome, Laurence-Moon-Bardet-Biedl — insulin defect, a decrease or beta-cell absence.

9. Gestation diabetes.

It is defined as diabetes that occurs in a previously non-diabetic pregnant woman. Although this type of diabetes often resolves after delivery, approximately 50 % of affected women will not revert to the non-diabetic state after the pregnancy is over. Even in those who do, the risk of developing type II diabetes after about 5 years is higher than normal.

Causes of gestational diabetes. The increased energy demands during pregnancy and the continually high levels of estrogen and growth hormone are believed to be the causes of gestational diabetes. Growth hormone and estrogen stimulate insulin release and may result in the oversecretion of insulin, leading to decreased cellular responsiveness. Growth hormone also has some anti-insulin effects, for example, the stimulation of glycogenolysis, the breakdown of glycogen, and the breakdown of adipose tissue. Adinonectin, a plasma protein derived from adipose tissue, plays a role in regulating insulin concentration and resistance; reduced levels of this substance also may contribute to the impaired glucose metabolism and hyperglycemia, wich are seen in gestational diabetes. Women who develop gestational diabetes may have subclinical problems with glucose control even before diabetes develops.

Consequences of gestational diabetes. Gestational diabetes can negatively affect the pregnancy by increasing the risk of congenital malformations, stillbirths, and large-for-date babies, which can result in problems during delivery. Gestational diabetes is routinely tested for during prenatal medical examinations. Good obstetrical outcomes are dependent on good maternal glycemic control as well as pre-pregnancy weight. Women who have gestational diabetes usually are treated with diet, insulin, or both, as necessary. The use of oral anti-hyperglycemic agents such as sulfonylurea (glyburide) instead of insulin for pregnant women unable to achieve glycemic control with diet alone has been investigated. Findings suggest glyburide may be as effective as insulin in reducing obstetric complications, without increasing the risk of congenital malformations, although further studies are required to ensure the safety of this or other agents.

Diabetes mellitus type I

It is characterized by impairments of carbohydrate metabolism, which are caused by beta-cell destruction, and ketoacidosis aplitude. It is characterized by absolute insulin deficiency and absolute or relative excess of contra-insulin hormones.

Autoimmune diabetes mellitus is characterized by beta-cell destruction resulting from autoimmune or immune process.

Essential diabetes mellitus is characterized by beta-cell destruction and a decrease in beta-cell number. Etiology and pathogenesis are unknown.

Key link in pathogenesis: progressive beta-cell destruction of pancreas islets.

Diabetes mellitus type I is HLA-associated.

Auto-antibodies spectrum in diabetes mellitus type 1:

— antibodies to pancreatic islets, to insulin, to glutamate decarboxilase, cytoplasmic antibodies and others;

— organospecific — antibodies to thyroglobulin, peroxidase of thyroid gland, gastric parietal cells, hemopoietin, adrenal gland cortex cells, antilymphotoxic antibodies, IgG and IgA;

— non-organospecific — anti-nuclear, mitochondrial, antibodies to smooth muscle fibers, fibroblasts;

— post-receptor;

— combined (most often).

Diabetes mellitus type II

Carbohydrate metabolism impairments associated with insulinresistency and defect in insulin secretion or primary impairments of insulin secretion and moderate insulinresistency.

Classification of insulin resistency:

1) According to etiology:

— abnormalities of beta-cell secretory product: abnormality of insulin molecule, block in proinsulin transformation into insulin;

— clinical antagonists of insulin: an increase of contra-insulin antagonists (growth hormone, cortisole, catecholamines and others), non-hormonal insulin antagonists, defect of insulin receptor, post-receptor defects.

2) According to pathogenesis:

— primary (befor insulin therapy);

— secondary (reaction on insulin therapy).

3) According to defect localization:

— pre-receptor;

— receptor.

It is characterized by relative insulin secretion. Age of onset is more than 50 years. It is not directly HLA-associated. It is not characterized by hereditary predisposition. 90 to 100 % concordance in homozygous twins (type I — 50 % concordance in twins).

Clinical course is stable, ketoacidosis is not characteristic (insulin inhibits lipolysis and creats conditions for acetyl Co-A utilization in lipogenesis and steroid genesis).

Clinical features of type II: insulinresistency, obesity, hyperlipidemia type IV and V, hypertension, hyperuricemia, nephropathia, accelerated atherosclerosis.

Comparative characteristic of diabetes mellitus type I and II is shown in the table 13.

Table 13 — Comparative characteristic of diabetes mellitus type I and II

	Type I (previously IDDM)	Type II (previously NIDDM)
Clinical	Weight onset more than 20 years; normal; decreased blood insulin; anti-islet cell antibodies; ketoacidosis is common	Onset more than 50 years; obese; normal or increased blood insulin; no anti-islet antibodies; ketoacidosis rare
Genetics	50 % concordance in twins; HLA-D linked	90 to 100 % concordance in twins; no HLA association
Pathogenesis	Autoimmunity, immunopathalogic mechanisms, severe insulin deficiency	Insulin resistance, relative insulin deficiency
Islets cells	Insulin early, marked atrophy and fibrosis, beta-cell depletion	No insulitis, focal atrophy and amyloid deposits, mild beta-cell depletion

Pathogenesis of diabetes mellitus. Absolute or relative insulin deficiency results in energy starvation of muscular and fat tissue. It is characterized by an increase in contra-insulin hormone secretion. All these result in carbohydrate, lipid and protein metabolism impairments:

1) Carbohydrate metabolism:
— in muscles, liver — a decrease in glycogenesis;
— a decrease in glucose income in fat tissue;
— glycogenolisis in muscles and liver, which is influenced by glucagon and adrenaline;
— hyperglycemia;
— lactacidemia.

2) Protein metabolism:
— prevalence of catabolic processes (particulary in muscles);
— an increase in amino acid and urea blood level;
— loss of nitrogen.

3) Lipid metabolism:
— a decrease in fat depot;
— an increase in fat level in liver;
— an increase in contra-insulin hormone level;
— an increase in very-low-density-lipoprotein production in liver.

4) Water-electrolyte metabolism:
— loss of potassium and sodium;
— polyuria, dehydration.

Clinical manifestations
Type I: polyuria, polydypsia, polyphagia, ketoacidosis, hyperglycemia, glucosuria, weight loss, muscle weakness, ketonemia, ketonuria, increased suspectability to infections.

Type II: obesity, polydypsia, polyuria, weakness, weight loss, hyperglycemia, dehydration, hyperosmolar non-ketonic coma.

Complications

Acute metabolic complications in diabetes mellitus: hyperosmolar coma, hypoglucemic coma, ketotic coma, lactacidemic coma.

Chronic complications in diabetes mellitus associated with micro- and macroagiopathic abnormalities:

1) circulatory abnormalities:
— atherosclerosis;
— cardiomyopathy (with no apparent coronary arteries pathology);
2) retinopathy;
3) diabetic nephropathy;
4) diabetic neuropathy (peripheral polyneuropathy, radiculopathy, autonomic neuropathy);
5) diabetic foot ulcers.

HYPOXIA

Hypoxia is a typical pathological process resulting from the insufficient biologic oxidation. It is characterized by the impairment of energy supply and plastic processes in organism.

Causes of hypoxia are:
— a decrease in oxygen supply (exogenous hypoxia);
— a decrease in gas exchange function (respiratory);
— a decrease in blood oxygen capacity (haemic);
— a decrease in rate of blood flow (circulatoric);
— microcirculation impairments (microcirculatory);
— a decrease in primary intensity and efficiency of biologic oxidation (primary tissue);
— over-utilizing hypoxia;
— severe hypoxia or a combination of 2 and more types (combined).

Classification of hypoxia

1) According to causes and mechanisms:
— exogenous: normobaric, hypobaric;
— endogenous: respiratory, circulatoric, haemic, histotoxic, overutilizing, substrate, combined.

2) According to respiratory system reaction:
— at the input of respiratory system: hypoxic, hyperoxic, hyperbaric;
— in the respiratory system: respiratory, circulatoric, haemic.

3) According to the severity: moderate, severe, critical (lethal).

4) According to clinical manifestations:
— latent;

— compensate;
— sub-compensate;
— decompensate;
— terminal.
5) According to localization:
— local;
— general.
6) According to the rate of occurrence:
— flash-like;
— acute;
— sub-acute;
— chronic.

Resistance to hypoxia

The most resistant to hypoxia are: bones, cartilages, ligaments, tendons. There are no significant morphologic changes in these tissues even in conditions of severe hypoxia.

Changes in skeletal musculature are revealed in 100–120 minutes.

Morphologic changes and function impairments are revealed in liver and kidneys in 20–30 minutes.

Consequences of hypoxia are determined by the degree of injury and time of their development.

Nervous system processes are the least resistant to hypoxia. Its different parts' resistance to hypoxia varies. Resistance of nervous cells decreases in the following line: peripheral nerve ganglions, spinal chord, medulla oblongata, cerebellum, cerebral cortex.

Cessation of cerebral cortex oxygenation causes profound structural and functional changes in 2–3 minutes, in medulla oblongata — in 8–12 minutes, in ganglions of the vegetative nervous system — in 50–60 minutes.

Pathways of glucose utilization in cells:
1) anaerobic glycolysis in cytoplasm;
2) aerobic glycolysis in mitochondria;
3) hexose mono-phosphate shunt.

Types of hypoxia, etiology and pathogenesis

Hyperoxemic hypoxia. It results from the increase in gas pressure, increase in oxygen concentration in the inhaled air.

Pathogenesis: 1) an increase in oxygen pressure in tissues results in mitochondria destruction; 2) systemic enzymopathia; 3) free radical formation; 4) change of in-cell protein synthesis; 5) morphologic changes in pulmonary tissue.

Exogenous hypoxia. Exogenous hypoxia results from the decrease in oxygen transport from lungs to periphery, because of arterial hypoxemia.

Arterial hypoxemia results in oxygen transport inhibition, because of the decrease in Hb oxygen saturation.

Types of exogenous hipoxia are: normobaric, hypobaric.

Hypobaric hypoxia results from the decrease in atmosphere barometric pressure (e. g. mountain disease, altitude sickness, caisson disease).

Normobaric hypoxia can result from displace of oxygen by the inert or anesthetic gases, such as nitrous oxide and ethylene, or oxygen is consumed by combustion in closed place.

Respiratory hypoxia. It results from insufficiency of oxygen transport from atmosphere into the blood plasma as a consequence of external respiration impairments.

Mechanisms of gas exchange insufficiency

1) alveolar hypoventilation;
2) impairments of ventilation perfusion ratio;
3) impairments of pulmonary perfusion;
4) impairment of alveolar capillary diffusion;
5) pathological venous shunts in lungs.

Circulatory hypoxia:
1) heart failure and decrease in vascular tone;
2) hypovolemia results from the acute massive blood loss;
3) loss of plasma results from burns, cholera (secretory diarrhea);
4) a decrease in blood volume (a decrease in blood depot, myocardial contractibility and pump function).

Haemic hypoxia. It results from the decrease in blood oxygen capacity (anemia), deficiency of circulating Er and low concentration of Hb and the decrease in Hb affinity to oxygen, inhibition of oxygen transport.

It influences pH, CO_2, electrolyte concentration and physical chemical parameters of Er.

There are the following mechanisms influencing Hb affinity to oxygen:
— hem-hem interactions;
— Bor's effect;
— influence of 2,3-diphosphoglycerate.

The most important of the acquired Hb impairments are: methaemoglobin and carbon monoxide poisoning. Carbon monoxide poisoning inhibits the ability of Hb to release the oxygen bound to it. Methaemoglobin is an abnormal version of Hb which accumulates in the blood.

Histotoxic hypoxia. It results from the decrease in ability of the tissue to use oxygen even through the supply is normal or greater than normal. It develops due to disabled oxidative phosphorylation enzymes.

Over-utilizing hypoxia is due to increase in the demand of tissues for oxygen. It results in deficiency of macroergic compounds and cell hyperfunction.

Substrate hypoxia is due to substrate deficiency (glucose), which is necessary for biologic oxidation. It results in a decrease in ATP level, impairments of plastic processes andmetabolism.

Combined hypoxia. It results from factor action impairing two and more mechanisms of oxygen supply or oxygen utilizing. It is observed in severe hypoxia in case of oxygen transport impairments.

Acute blood loss results in haemic or hemodynamic hypoxia.

The Types of hypoxia are showen in the table 14.

Table 14 — Types of hypoxia

Parameters of oxygen regimen in organism	Norm	Exogenous	Respiratory	Circulatoric	Haemic	Histotoxic
P_AO_2	100–110 mm Hg	↓*	N, ↑	N	N	N
P_aO_2	85–95 mm Hg	↓	↓*	N	N	N
S_aO_2	96–98 %	↓	↓	N	N, ↓	N
P_VO_2	35–40 mm Hg	↓	↓	↓	N	↑
a/v O_2	~ 6 (Vol%)	N	N	↑*	N	↓*
Oxygen blood capacity	~ 16–25 (Vol %)	N, ↓	N	N	↓*	N

Note. * — change with the diagnostic role in this type of hypoxia; ↓ — a decrease; ↑ — an increase; N — normal.

Mechanisms of extreme adaptation
— an increase in alveolar ventilation;
— tachycardia, an increase in cardiac output;
— an increase in circulating blood volume;
— redistribution of blood flow with the increase in cerebral and coronary blood flow;
— an increase in blood oxygen capacity because of the change in Hb properties and release of Er from the depot;
— an increase in association of oxidation and phosphorylation;
— glycolysis activation;
— a decrease in organ and tissue functioning.

Mechanisms of long-term adaptation
— a decrease in metabolic processes and the demands of oxygen;
— an increase in gas exchange function (an increase in alveoli and capillary number, an increase in activity of respiratory musculature);
— myocardial hypertrophy;
— an increase of Hb and Er blood level;
— inhibition of control system reactions on different stimuli.

Oxygen-hemoglobin dissociation curve. Progressive increase in the percentage of Hb bound with oxygen as blood pO_2 increases, which is called the *percent*

saturation of Hb. Because the blood leaving the lungs and entering the systemic arteries usually has a pO_2 of about 95 mm Hg, one can see from the dissociation curve that the *usual oxygen saturation of systemic arterial blood averages is 97 %.* Conversely, in normal venous blood returning from the peripheral, the pO_2 is about 40 mm Hg, and *the saturation of Hb averages is 75 %.*

Treatment and prevention of hypoxia

Etiotropic principle: 1) exogenous hypoxia — normalization of pO_2 in inhaled air; 2) add of carbon dioxide in inhaled air; 3) endogenous hypoxia — elimination of pathologic process or disease.

Pathogenic principle: decrease in acidosis, ion or electrolyte imbalance; decrease in membrane destruction, membrane injury by enzymes; an increase in activity of biologic oxidation.

Symptomatic principle: getting rid of discomfort sense inhibiting the health state.

Sanogenic principle: prevention of hypoxia.

Stages of adaptation

— extreme adaptation;
— transient stage;
— stable long-term adaptation;
— deadaptation.

Levels of adaptation to hypoxia

1) An increase in oxygen consumption results from:
— hyperventilation and an increase in cardiac output;
— an increase in Er number in blood;
— an increase in blood oxygen capacity.
2) An increase in oxygen transport in cells
— opening of arteriole and post-capillary sphincters;
— an increase in ATP in-cell level;
— mobilization of reserve capillaries;
— a decrease in oxygen diffusion;
— an increase in oxygen tension gradient.
3) An increase in oxygen utilizing cell abilities:
— an increase in cytochromoxidase sensitivity to oxygen;
— an increase in mitochondrion number;
— an increase in energy consumption in anaerobic glycolysis.

EXTREME CONDITIONS

Extreme conditions are the conditions occure under the influence of extreme pathogenic factors and characterized by the limiting effort of organism protective reactions.

Classification of extreme conditions:
1) According to clinical course:
— acute;
— subacute;
— chronic.

2) According to the occurrence rate:
— flash-like (the 1st 10 minutes);
— immediate (the 1st day);
— delayed (weeks, months, years).

Features of extreme conditions:
1) extreme conditions are characterized by the occurrence of pathological reactions aggravating the frustrations in organism («vicious circles»);
2) extreme conditions have a set of similar metabolism and physiological function changes;
3) extreme conditions can be autonomous reversible;
4) extreme conditions demand urgent and effective medical actions.

*Similarities to terminal conditions***:**
— extreme conditions and terminal conditions are the boundary conditions between life and death;
— there is a real threat of organism destruction in extreme and terminal conditions;
— extreme conditions i case of the adverse development pass into terminal conditions.

Differences between extreme and terminal conditions:
— extreme conditions are less severe, than terminal conditions;
— extreme conditions usually precede the development of terminal conditions;
— some forms of extreme conditions can be autonomous reversible;
— terminal conditions without the emergency help of a doctor result in organism destruction (death);
— the effective methods of extreme condition treatment is the pathogenic factor elimination and blockage of the basic pathogenic mechanisms.

Shock

Shock is a typical pathological process caused by extreme agents of the external and internal environment and representing a complex of pathological and protectively-adaptive reactions in the form of CNS over-excitation and braking, hypotension, hypoperfusion, organ and tissue hypoxia and metabolism impairments.

Classification of shock:

1. Pain shock:

— exogenous or traumatic (in mechanical damages, burns, cold injuries, surgical interventions);

— endogenous (cardiogenic, nephrogenic).

2. Humoral shock shock (hetero-transfusion, hemolytic, anaphylactic, hormonal, toxic).

3. Psychogenic shock.

Classification according to V. K. Kulagin:

1. *Receptive*:

— mental;

— painful;

— electric.

2. *Traumatic*:

— in mechanical trauma;

— operational;

— wound;

— hemorrhagic;

— compressional;

— burnt.

3. *Toxic*:

— endotoxic;

— exotoxic;

— anaphylatic;

— septic.

4. *Ischemic*:

— declamping shock;

— in thrombosis or embolism of large vessels.

5. *Neurogenic (centrogenic):*

— in paralysis of vasomotor center;

— in «spinal» shock.

6. *Mixed*.

The general pathogenesis of shock (stage of compensation) is showen in the table 15.

Table 15 — The general pathogenesis of shock (stage of compensation)

Organs and systems	Changed functions
Nervous and endocrine systems	Psychologic and motor excitation; activation of sympathetic-adrenal system, hypereflexia of the hypothalamus-pituitary-adrenal gland system, thyroid gland
Cardiovascula system	Tachycardia, hypertensive reactions, arrhythmia, blood circulation centralization, impairments of organ- tissue microcirculation
Lungs	Tachypnea with hypercapnia
The blood system and hemostasis	A decrease in circulating blood volume, an increase in blood viscosity, hypercoagulative-thrombotic condition
Liver	Activation of glycogenolysis, a decrease in detoxication
Kidneys	Oligouria, uremia

The general pathogenesis of shock (stage of decompensation) is shown in the table 16.

Table 16 — The general pathogenesis of shock (stage of decompensation)

Organs and systems	Changed function
Nervous and endocrine systems	Psychologic and motor delay, confused mental state, low efficiency in neuroendocrine control, hyporeflexia
Cardiovascular system	Heart failure, arrhythmia, artrial hypotension and collapse, blood redistribution, capillary-trophic insufficiency
Lungs	Pulmonary failure — «shock lungs»
The blood system and hemostasis	A decrease in circulating blood volume, an increase in blood viscosity, hypercoagulative-thrombotic condition
Liver	Hepatic failure — «shock liver»
Kidneys	Renal failure — «shock kidneys»

The general pathogenic parts of various shock types are:
1. Changes in CNS (excitation, braking, phase conditions).
2. Sharp cardiovascular insufficiency.
3. Oxygen starvation.
4. Distortion of metabolism.
5. Condition of desynchrosis (impairment of biological rhythms).
6. «Stress»-reaction.

3 basic componenst of shock: impairments of control, metabolism, blood supply.

Cardiogenic shock results from severe depression of cardiac performance. It is characterized by a systolic blood pressure lower than 80 mm Hg and cardiac index is lower than 1,8 (L/min)/m^2. Pulmonary edema is usually present. The most frequent cause is myocardial infarction.

Extracardiac obstructive shock is caused by pericardial tamponade and massive pulmonary embolism. Increased pericardial pressure or obstruction of more than 50 to 60 % of the pulmonary vascular bed by thrombus impair ventricular diastolic filling, stroke volume, and cardiac output.

Distributive shock. Distributive shock is caused by profound peripheral vasodilation with inadequate tissue perfusion, although cardiac output may be normal or high. Distributive shock includes *septic, anaphylaxis and neurogenic* shock as well as shock in adrenal insufficiency. Septic shock is the most common cause of death in intensive care units.

Collapse

Collapse (from Latin collapses — «weakened», «fallen», «crash», «falling») — is a form of the acute vascular insufficiency, resulting in change of the vascular channel capacity and circulating blood volume ratio.

Types of collapse (according to I. R. Petrov):
1. Peptone and histamine (only in experiment).

2. Infectionous-toxic (damage of heart and vessels results from infections).

3. Hypoxemic (in conditions of low atmospheric pressure).

4. Orthostatic (it results from the fast change of the body position from horizontal to vertical in patients with a long confinement to bed).

5. Pancreatic.

6. Enterogenic (in «dumping» syndrome).

7. Radiating.

8. Hyperthermal.

9. Reflex and others.

Pathogenesis of collapse:

1. *A rapid decrease in vascular tone is observed in:*

— intoxications;

— reception of medicinal substances;

— radioactive influence;

— impairments of acid-base balance;

— endocrine pathology;

— hypoxia;

— increased irritation depressor reflex zones;

— oppression the pressor cardiovascular motor center.

2. *A decrease in circulating blood volume:*

— absolute (burns, blood loss, etc.);

— relative (right-sided heart failure, an increase in volume of vascular channel).

3. *A decrease in cardiac output:*

— myocardial infarction;

— cardiac tamponade;

— arrhythmias.

Rapid decrease in vascular tone, a decrease in circulating blood volume and cardiac venous inflow, a decrease in arterial and central venous pressure, brain hypoxia, oppression of the organism vital functions.

Clinical manifestations:

— Acute hemodynamic impairments.

— Sudden occurrence of weakness, dizziness, a decrease in the body temperature, fever, thirst, integuments and mucous are pale with cyanotic edema, cold sweat, frequent small pulse. The consciousness is in most cases is safed or blacked out (sometimes can temporarily be lost), arterial blood pressure is 70–60 mm Hg. Sometimes spasms are decreased. Circulating blood volume is decreased.

Differences between shock and collapse are showen in the table 17.

Table 17 — Differences between shock and collapse

Parameters	Shock	Collapse
The name and essence of the process	Nosologic unit	Syndrome, which is not a nosologic unit
Etiology	Shock — «collapse resulting from trauma». It results from exteroreceptor irritation	Collapse — «shock without trauma». It results from inter-receptor irritation because of intoxication
Presence and prevalence of the basic pathogenic link	Changes in CNS are primary	Changes in NS are secondary
Pequliaritiea of clinical course	Phase, rapid development	It is not phase, slow development
Parameters	Shock	Collapse
The severity depends on arterial blood pressure	No	The severity depends on the arterial blood pressure
Consciousness	It is present	It is losed or confused
Change in circularing blood volume	A decrease in circulating blood volume; blood is deposited	Normal or decreased
Narcosis and analgesia	At the beginning it has preventive or treatment role	Its role is negative
Protective adaptive reactions	Primary in CNS, than the whole organism	Dyspnea, an increase in cardiac rate, stimulation of hemopoietic organs, mobilization of blood from the depot

Generality of shock and collapse:
1) development of vascular insufficiency;
2) development of respiratory failure;
3) hypoxia;
4) development of compensatory and pathological reactions.

Faint

Faint — «syncope» (from Greek *synkop* — «reduction», «chopping»).
It is the mildest form of vascular insufficiency.

Faint — sudden, short loss of consciousness owing to the passing ischemia of brain. It occurs reflexly. The leading factor — a decrease in arterial blood pressure down to the level, on which it is not provide sufficient brain perfusion.

The basic parts of faint pathogenesis are:
1. A decrease in arterial blood pressure owing to a decrease of peripheral vascular resistance in vasodilating system (the psychogenic faints caused by hyperactivity of n. vagus).
2. Impairments of cardiac rythm.
3. Hypoxemia.

Coma

Coma (from Greek «coma» — a «deep dream»). However according to etiology and pathogenesis coma essentially differs from dream. Consciousness does not reverse even in intensive nociceptive irritation.

Coma is an extreme condition characterized by the deep CNS neuron oppression, loss of consciousness, loss of various reflexes, absence of reactions on external irritants, deep respiration impairments, impairments of blood circulation and metabolism.

Classification of coma according to origin:

1. *Exogenous* — action of environmental pathogenic agents or deficiency of necessary factors for normal existence of organism:
— traumatic;
— hypothermic (overcooling);
— hyperthermal (heatstroke);
— exotoxic (alcoholic poisoning, medicinal substances, mushrooms);
— alimentary (severe starvation);
— hypoxic;
— radiating.

2. *Endogenous* — impairments of various organs or physiological system activity:
— apoplectic;
— anemic;
— endocrine coma (hypoglycemic, diabetic);
— uraemic;
— hepatic;
— asthmatic;
— asphyxial;
— cholera.

Severity of coma depends on:
1. Degrees of brain function impairments.
2. Degrees of the vital parameter deviations.

We distinguish:
1. Pre-coma condition.
2. Actually coma.

Pre-coma condition (from Latin sopor — «unconsciousness») is characterized by obnubilation: patient is in consciousness, but he is indifferent to everything around, his answers are terse, inadequate.

Actually coma is characterized by:
— complete loss of consciousness;
— absence of reaction to various influences;
— loss of reflexes;
— pathological forms of respiration;

— a decrease in cardiac activity;

— hypotonia;

— a decrease in the body temperature.

Stages of coma:

1) initial — mental anxiety;

2) pre-coma — confusion of consciousness;

3) superficial coma;

4) deep coma — full loss of consciousness, areflexia, vegetative impairments.

TYPICAL FORMS OF TISSUE GROWTH IMPAIRMENTS. NEOPLASMS

Tumor is a typical pathological process characterized by uncontrolled cell proliferation on the different stage of differentiation.

Malignant tumor is the main cause of death in present days.

Synonyms of tumor: neoplasma, blastoma, oncos.

Classical methods of experimental oncology:

— Transplantation of tumor. The 1st in the world transplantation of malignant tumor was made by M. A. Novinski (1876). He transferred cancer and sarcoma from a dog to a puppy. Then cancer and sarcoma were transplanted.

— Tumor induction. Yamagiva and Ichckawa by prolonged crock rubbing in the ear of a rabbit caused pappilloma (chemical tumor induction).

— Tumor explantation – cultivation of tumor out of the organism.

Tumors are classified according to:

— differentiation;

— character of growth, rate of growth;

— metastasis;

— recidivus.

Tumors are classified into benign and malignant.

Benign tumors:

— Mature, well differentiated cells with minor atypism.

— Tumor growth is slow, expansive. Tumor grows moving and squeezing tissues, but not destructing them.

— No metastasis.

— No recidivus after the tumor removal.

Malignant tumors. Tumor from epithelial cells is called cancer Mesenchyma — sarcoma.

It is presented by non-differentiated or low differentiated cells. It is characterized by cataplasia. Tumor growth is rapid: infiltrative and invasive.

— Metastasis.

— Recidivus.

Etiology. The most complete theory is polyetiologic theory of carcinogenesis. Carcinogens: chemical, physical, biological.

Chemical carcinogens:

1) Endogenous chemical carcinogens:
— steroid hormones (estrone);
— bile acids;
— derivatives of thyresine and tryptophan;
— aminoxyphenol (lactic acid in leukemia);
— free radicals and peroxides;
— cholesterol.

Chronic hypoxid and some diseases promote the chemical carcinogen accumulation.

2) Exogenous chemical carcinogens:
— polyaromatic hydrocarbonates (benzpyrene, dibenzpyrene);
— aromatic amines and amides (benzidine);
— amino compounds (aminobenzenazotoluene);
— nitro compounds (dymethylnitrozamine);
— aflotoxins (aflotoxins, sterigmatocystine).

Physical carcinogens. To the physical carcinogens are related: ioning radiation, ultraviolet ray, space radiation.

Biologic factors. The major role belongs to oncogenic viruses (5–15 % of cases):

— RNA- and DNA-viruses.

More than 150 oncogenic viruses are known as DNA-viruses: papoviridae, adenoviridae, herpetoviridae, poxviridae.

Paporaviridae:
1) pa — papilloma Shoup's virus in rabbits;
2) po — polyoma Eddy Stuart's virus in mice;
3) va — vacuolizing virus in monkeys (SV–40).

RNA-virsuses: oncoviridae, spumaviridae, lentiviriadae

Tumor atypism.
The word atypism comes from atipicus — «abnormality».

Anaplasia — is a stable cell differentiation with cell structure and biologic feature change. It is a kind of return to embryonic stage of development:
1) biological (loss of all functions, except proliferation);
2) biochemical (loss of part of enzyme systems);
3) morphological (change of in-cell structures, shape and sizes of the cells and the nuclei).

Cataplasia is an embryonic assimilation.

Types of atypism:

1. Morphologic atypism.

Tissue atypism. It is a change between parenchyma and stoma. It is predominantly characterized by prevalence of parenchyma. It is characteristic of benign tumors.

Cellular atypism. It is manifested by cellular and nuclear polymorphism. It is characteristic of malignant tumors.

2. Antigenic atypism.

There are 5 groups of antigens associated with tumor (according to G. I. Abelev):

— Ag of viral tumors.

— Ag induced by carcinogens.

— Embryonic Ag (oncofetal) → alpha-1,2-fetoprotein.

— Iso-Ag of transplantation type.

— Heterogenic Ag, organospecific Ag usual in other organs (renal Ag in the tumor of liver).

3. Functional atypism.

It means the loss of functions, an increased or perverted function, functioning inadequacy of tumor tissue to control influences (e. g. synthesis of calcitonin by breast cancer cells, ACTH or ADH synthesis by the lung cancer cells).

4. Metabolic atypism.

It means metabolic changes in tumor tissue. It promotes proliferation and adaptation to oxygen deficiency:

— an increase in oncoprotein synthesis — it promotes appearance of specific biologic features; uncontrolled proliferation, loss of the cell clock, immortalization;

— synthesis of embryonal proteins and isoenzymes of some enzymes.

5. Energy atypism.

Change in the pathway of energy supply activation of anaerobic glycolisis in tumor cells. Pasteur's effect is characteristic.

6. Atypism of proliferation:

— uncontrolled proliferation;

— absence of the contract inhibition of proliferation;

— loss of cell clock;

— immortalization.

Protooncogen is a gene of normal genome controlling cell proliferation. Protooncogen can transform to oncogen because of somatic mutation.

Oncogen is a protein promoting cell proliferation and differentiation (nuclear proteins, growth factor). Oncogens can provoke tumor growth because of mutation activated by retroviruses. Many oncogens are known (ras, p53).

Antioncogens can inhibit proliferation of the transformed cells.

Stages of carcinogenesis

Transformation. Protooncogen transforms into the active cellular oncogen resulting from promoter activation (amplification, translocation, insertion, transduction, point mutation).

Immortalization occurs on the early stage of transformation.

Proliferation. Proliferation (activation, promotion). Cell genome is changed in direction of uncontrolled hyperplasia resulting in primary tumor node forming → tumor.

Tumor progression. Accumulation of malignant signs. An increase in tumor malignancy occurs more rapidly than tumor growth rate.

The last stage is an *outcome*.

Metastasis. Metastasis is the movement of tumor cells (the same histologic structure) on the distance from the primary tumor.

Pathways of metastasis: lymphogenous, hematogenous, tissue, combined.

Stages of metastasis (lymphogenous, hematogenous) include: detachment, invasion, tumor cell embolism, tumor cell implantation in capillary wall, extravasation, proliferation of metastatic tumor cell.

Factors determining selectivity of metastasis:
— peculiarities of blood and lymph circulation;
— a decrease in antiblastomic resistency;
— peculiarities of organ metabolism;
— positive chemotaxis.

Metastatic subclone → basement membrane adhesion and invasion → migration through the matrix → vascular basement membrane invasion → tumor cell emboli, adhesion of tumor cell emboli to the vascular basement membrane → migration to the matrix and tumor node forming.

Mechanisms of antiblastomic resistency:
— anticarcinogenic → prevertion of carcinogens' entry in the body, the cell or the nucleus;
— antitransformational → suppression of oncogene expression;
— antinuclear → recognition and killing of a tumor cell.

Cachexia is a condition of abnormally low weight, weakness and general bodily decline associated with chronic disease. It occurs in such conditions as cancer, pulmonary tuberculosis, and malaria.

Treatment
— surgical treatment;
— radiotherapy;
— chemotherapy;
— genetic engineering.

LITERATURE

1. Rubin, E. Pathology / E. Rubin, J. L. Farber // Lippincot Company. — 1994. — 1578 p.

2. Robbins pathologic bases of disease / S. L. Robbins [et all.]. // W. B. Saunders Company. — 1999. — 1425 p.

3. Litvitsky, P. F. Path physiology: educational book: in 2-vol. / P. F. Litvitsky. — M.: GEOTAR-MED, 2002 — Vol. 1, 2. — 752, 808 p.

4. Litvitsky, P. F. Path physiology: educational book / P. F. Litvitsky. — 4th issue, reviewed and improved. — M.: GEOTAR-MEDIA, 2008. — 496 p.

5. Pathological physiology under the editorship of P. F. Litvitsky [Electronic resource]. — Electronic data. (180 Mb). — GEOTAR-MEDIA, 2007. — 1 electronic optical disk (CD–ROM).

6. Pathological physiology: educational book / N. N. Zayko [et all.]; under the editorship of N. N. Zayko and U. V. Byzs. — 4th ed. — M.: MEDpress-inform, 2007. — 645 p.

7. Novitskiy, V. V. Path physiology / V. V. Novitskiy, E. D. Goldberg. — Tomsk: The Publishing house of Tomsk University, 2001.

8. Voiynov,V. A. Path physiology atlas / V. A. Voiynov. — M.: MIA, 2004. — 218 p.

9. Chaitov, R. M. Immunology: educational book / R. M. Chaitov, G. M. Ignatieva, I. G. Sidorovich. — M.: Medicine, 2000 — 432 p.

10. Ugolnik, T. S. Disorders of thermotax. Fever: educational grant on pathological physiology for overseaes students educates in English language / T. S. Ugolnik. — Gomel: GGMU, 2005.— 28 p.

11. The system of hemostasis: physiology, pathophysiology and medical correction: educational methodical grant / E. S. Pitckevich [et all.]. — Gomel: Edicational establishment «Gomel State Medical UIniversity», 2007. — 44 p.

12. Frolov, V. A. General pathophysiology: Electronic course of pathological physiology and additional articles / V. A. Frolov, D. P. Bilibin. — M.: GEOTAR-MEDIA, 2008. — 496 p.

13. The anatomy and physiology of hematopoiesis / C. A. Sieff [et all.]. — WB Saunders, 1998. — 161 p.

14. Shiffman, F. J. Pathophysiology of blood / F. J. Shiffman. Trans. from engl. — M.: «Publishing House BINOM»; SPb.: «Neva dialect», 2000. — 448 p.

15. Tropashko, I. B. Cell injury: methodical recommendations / I. B. Tropashko. — Gomel: GSMU, 2005. — 32 p.