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ОБЩАЯ НОЗОЛОГИЯ

Учебно-методическое пособие
для студентов 3 курса факультета по подготовке специалистов
для зарубежных стран, обучающихся на английском языке
по специальности «Лечебное дело», медицинских вузов

GENERAL NOSOLOGY

Teaching workbook
for students of the faculty for training specialists for foreign countries,
studying in English on specialty «General medicine»
of higher medical education institutions

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Предназначено для студентов 3 курса факультета по подготовке специалистов для зарубежных стран, обучающихся на английском языке по специальности «Лечебное дело», медицинских вузов.

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CONTENTS

LIST OF ABBREVIATION

AMS — acute mountain sickness

ARS — acute radiation sickness

ATP — adenosine triphosphate

CMS — chronic mountain sickness

CNS — central nervous system

CO_2 — carbon dioxide

CRS — chronic radiation sickness

DNA — deoxyribonucleic acid

Gy — Gray

HA — high altitude

Hb — hemoglobin

ICD — international classification of diseases

IR — ionizing radiation

NADPH — nicotinamide adenine dinucleotide phosphate

O_2 — oxigen

RBC — red blood cell

TPP — typical pathological process

UV — ultraviolet

INTRODUCTION TO THE DISCIPLINE «PATHOLOGICAL PHYSIOLOGY». GENERAL DOCTRINE ABOUT DISEASE. GENERAL ETIOLOGY AND PATHOGENESIS

Pathophysiology (from the Greek: ***pathos*** — illness, suffering; ***physis*** — nature and ***logos*** — teaching, science) — the basic fundamental integrative biomedical science that studies the most common patterns of occurrence, development and outcome of the disease.

The main subjects of pathophysiology study are:

1) the causes and mechanisms of the functional and biochemical abnormalities underlying the disease;

2) mechanisms of adaptation and restoration of disturbed functions in disease (recovery mechanisms).

Object of the pathophysiology study includes three components:

- illness and disease states;
- typical pathological processes;
- typical forms of pathology of organs, tissues and systems.

As a theoretical foundation of medicine, pathophysiology binds the basic theoretical disciplines (biology, biochemistry, biophysics, physiology, genetics, etc.) to the disciplines of clinical profile:

- *biology* — pathological processes often begin at the cell level;
- *biochemistry* — the changes in biochemical processes underlie in the pathological condition
- *biophysics* — reveals the connection between the physical mechanisms underlying the organization of living objects and biological characteristics of their life;
- *physiology* — to be able to found the pathological functions needs to understand the functions of the healthy tissues, organs and systems of the body.

Pathophysiology is closely related to the morphological sciences (anatomy, histology, pathological anatomy), as it cannot be dysfunction without disturbing the structure.

The main task of the pathophysiology as a fundamental medicobiological science — to provide new knowledge about the nature of disease and pathogenetic mechanisms of recovery (sanogenesis).

History of pathophysiology

In one of the earliest printed medical publications «De naturali parte medicinae» («On natural part of medicine», 1542, J. Fernely) indicates that the occurrence of the disease is accompanied by the transition of the body to the world of qualitatively new, peculiar laws. In this regard, the field of medicine that studies the life features of a sick organism, the author has designated as pathology.

Term and content of the pathophysiology foundations were formed by the beginning of the XVIII century.

Claude Bernard (1813—1878 yy.) researched the processes of internal secretion, the founder in endocrinology; introduced the concept of «internal environment» of the body. Find out the blood and lymph as «internal environment» for all cells are the source from which cells receive nutrients and to which they give the products of their metabolism.

Development of experimental physiological direction in the pathology is inextricably linked with the name of a prominent Russian scientist V.V. Pashutin, widely regarded as the father of Russian pathophysiology. **Viktor Vasilyevich Pashutin (1845–1901 yy.)** created the first pathophysiology schools. He had the first in Russia scientific works of endocrine glands activity and studied the problems of metabolism impairments.

The founder of the second school was Russian pathophysiologists **A. B. Fokht.** Was one of the greatest experimenters. The range of scientific interests A. B. Fokht was extremely wide: problems of pathology of the cardiovascular system, kidneys, respiratory system, digestive system. He was one of the first Russian scientists have raised questions about the need for extensive study of the endocrine glands.

Founder of comparative pathology is **I. I. Mechnikov**. He initiated the comparative pathology of inflammation, the theory of cellular and humoral immunity, the doctrine of phagocytosis and formulated biological (phagocytic) theory of inflammation. The first time established a link of inflammation with immunity, in mechanisms of which phagocytosis also plays a significant role.

Cohnheim J. was a creator of the theory of vascular inflammation. The first time described in detail the entire set of changes in vascular tone and blood flow with exudation and emigration.

Scientific interests of **G. N. Sakharov** focused mainly on problems of immunity, allergies, cytotoxins, endocrinology, constitution, infectious diseases, etc.. In 1904, discovered the phenomenon of serum anaphylaxis and described the tissue changes characteristic of hyperergic inflammation (phenomenon Arthus — Sakharov).

A. A. Bogomolets (1881–1960 yy.) developed and introduced into clinical practice antireticuloendothelial cytotoxic serum. He had research in the field of endocrine pathology pathophysiology of tumor growth, circulation, physiology of aging, immunology.

N. N. Anichkov (1885–1965 yy.) first in Russia introduced the practical lessons in pathophysiology. Main areas: pathology of cardiovascular system, physiology and pathology of the RES, anoxia, gastrointestinal pathology.

Andrei Dmitrievich Ado had fundamental studies in the mechanisms of allergic reactions, the pathogenesis of inflammation and immunity; studies of autoimmune process; selected a new class of virus-induced «intermediate» antigens.

Rudolf Wirchov introduces term «pathological physiology» to medical terminology; study the nature of the disease; create the theory of cellular pathology, cellular theory of inflammation.

S. S. Khalatov (1884–1951 yy.) first pointed to the importance of local deposits of cholesterol in the origin of a number of pathological processes; proved the role of disorders of cholesterol metabolism in the development of atherosclerosis.

P. N. Vesyolkin created the doctrine of fever, pathogenesis of hemotransfusion complications and traumatic shock. He studied the pathophysiology of the heat exchange disorders.

Research activities **I. R. Petrov** was devoted to the study of mechanisms of the damaging effect of electric current, oxygen deficiency, pathogenesis of shock (trauma, burns, electric) and radiation sickness.

N. N. Sirotinin had experimental studies of anaphylaxis research on the problem of oxygen starvation and adaptation to hypoxia; studied in comparative evolutionary pathology of infection, immunity and allergy

A. M. Chernuh studied common problems of nosology, sanogenesis, theory of inflammation and microcirculation, experimental therapy; created the original doctrine of the neurovascular regulation of cell activity in various pathological processes (inflammation).

U. Kennon formulated the principle of homeostasis.

P. D. Gorizontov had fundamental research on the pathogenesis of radiation sickness; classic work on the problem of stress and the regulation of hematopoiesis.

A. D. Speranskii developed the doctrine of decisive role of the nervous system (trophic function) in the mechanisms of origin, development and outcome of disease.

G. N. Kryzhanovsky was a creator the theory of generating mechanisms of neuro-pathological syndromes. Was the founder of study of determinant.

L. A. Orbely formulated the position of the adaptive-trophic role of the sympathetic nervous system, that under the damaging effects activates the higher parts of the central nervous system, mobilizes energy, stimulates the cardiovascular system, enhances muscle performance, activates immunological mechanisms and other processes.

Hans Selye identifying the term «stress»; was at the forefront of modern concepts of unified neuroimmune-endocrine regulation of body functions in health and disease.

V. V. Parin founder of new scientific trends in physiology, medicine and biology, and one of the founders of space biology and medicine.

Basic studies of **F. Burnet** are devoted ecology of viruses, their relationship with «host», mechanism of viral replication, their variability. Is the author of clonal-selection theory of immunity and discoverer of immune tolerance phenomenon; for the latest discovery received the Nobel Prize (1960).

The methods of pathophysiology

Scientific facts and positions obtained using different methods, are the basis for the development of specific and general concepts and theories of pathology in humans. The results of these developments consider and used in solving actual fundamental and applied problems in medicine and biology. The main methods are:

1) modeling:
- physical:
  - ✓ on biological objects;
  - ✓ on artificial systems;
- formalized:
  - ✓ intellectual;
  - ✓ mathematical;
  - ✓ computer;

2) clinical examination;
3) theoretical analysis;
4) medical thinking.

Modeling

The main method of pathophysiology is to model of diseases, pathological processes, states and reactions. This method is used for creating theoretical (logical) models of pathogenesis, carry out mathematical and computer modeling of diseases.

Physical or material modeling on real physical objects (animals, their organs, cells, etc.). Models of pathological processes, conditions, reactions and diseases imitable in animals are used to study the etiology and pathogenesis of human diseases, the development of methods of diagnosis, treatment and prevention. Experiment on animals made under strictly justified need; using optimal species and number of animals; with the use of painkillers. To study the pathological processes in living subjects use the following methods of the experiment:

a) the method of removal or damage (off) of any organ with subsequent analysis showed symptoms compared with the clinical picture of the humans disease in which detected the lesion of corresponding organ.

b) the method of inclusion (on) — introduction of various substances, the excess of which leads to the development of a disease (for example, to study hyperthyroidism the introduce the thyroid hormones);

c) the method of stimulation (for example, stimulation of the vagus nerve occurs bradycardia);

d) the method of isolated organs — the nature and extent of damage of a particular organ (heart, lungs, liver, and others.) and its contribution to the development of circulatory failure, respiratory, digestive, etc.;

e) the method of parabiosis — connection of two animals (parabiont) through the bloodstream and lymphatic system to study the mutual humoral influences (hormones and other metabolites);

f) the method of tissue culture — isolation and fractionation the cellular elements of the various organs and tissues to study their role in the regulation of hematopoiesis and immunopoiesis, mechanisms of cells malignization, the establishment of mechanisms damaging effect on cells of various pharmacological agents, etc .;

g) the method of comparative pathology — the study of the evolutionary aspect of the development features and course of various pathological processes (inflammation, hypoxia, fever, etc.).

Modeling of pathological processes of human in animals has a number of shortcomings due to significant species differences of vital processes in animals and humans, as well as important role of social factors in the occurrence, development and outcome of human diseases. Also used modeling of human pathology using artificial physical systems — artificial heart, kidney, blood, lung ventilation apparatus, cardiopulmonary bypass, etc.

Formalized (non-material, virtual) modeling of diseases. It is realized as logical, mathematical, computer, etc. Logic modeling is used in learning process of future specialists. Logical modeling of diseases and pathological processes, as well as the patient followed by actual confirmation of the assumptions made are widely used in clinical practice and research.

The formation at students the basics of medical thinking is achieved in the course of their analysis of specific pathophysiological experimental or clinical data, in solving professional medical problems (situation tasks) in the classroom. This simulates behavior of the doctor, modeling the disease and patient as a whole to develop methods of diagnosis of the disease, as well as the strategy and the specific treatment regimens of the patient.

Computer modeling (e.g., pathological processes or effects of therapeutic interventions) is often carried out by modern computers and programs.

Methods of clinical examination

The availability of modern equipment and the latest examination technology allows in a human patient focused study the dynamics of the state of various organs and systems, structural changes in them, biochemical and electrophysiological parameters of functioning the body as a whole.

Obligatory conditions for the implementation of such studies are their safety for the patient and the well-reasoned need.

Obtained from the direct study of patient data allow:

1. to made the accurate diagnosis of the disease;

2. to evaluate the effectiveness (or ineffectiveness) of treatment;

3. examine the characteristics and patterns of occurrence, development and outcome of disease in humans;

4. provide material for a scientific explanation of the etiology and pathogenesis of diseases and pathological processes.

Methods of theoretical analysis

Theoretical analysis and development on this basis of scientific ideas, concepts, hypotheses and theories related to the solution of fundamental and applied problems in medicine and biology — the most important method of pathophysiology.

The result is the formation of a system based views on the causes and mechanisms of the origin, development and outcome of disease, disease states and pathological processes, principles and methods for their detection, treatment and prevention the theoretical propositions in medicine and biology.

Medical thinking

Medical thinking is one of the most delicate and difficult types of modeling in medicine: predictive modeling of the patient and his disease.

Having examined and listening to the sick person, examining results of various studies (biochemical, functional etc.) the doctor creates a model of the patient and his disease. With this in mind, it models the scheme of further diagnostic search methods (strategy, algorithm) of treatment and prevention disease in individual patients.

Part of pathophysiology

Pathophysiology as an academic discipline includes three main sections:

1. general nosology;
2. doctrine about typical pathological process;
3. doctrine about typical form of tissue, organs and system pathology.

First two are the part of general pathophysiology, last — systemic pathophysiology.

General nosology

Norm — it is the biologic optimum of functioning and developing of the organism.

Health — is a condition of total physical, spiritual and social well-doing, but not only the absence of disease and physical defects (World Health Organization, 1946). The health is the life of the human, who is able to work and adapted to the changes of environment (I. Petrov). By N. Zaiko — the health is the normal condition of organism, its structure and functions correspond to each other and its regulatory systems are able to support the homeostasis.

Pre-disease — condition of the body with the weakening of some sanogenetic mechanisms and their complexes preceding and promotes the development of the disease.

Disease — it is a qualitatively new process of life with disturbance of normal activity of the human organism under the influence of injurious agents accompanied by structural, metabolic and functional changes with limitation of adaptation, ability to work.

Table 1 — Differences between health and disease

Health	Disease
Wide range of variation of functions	Narrowing range of variation of functions
Sufficient amount of functional reserves	Reducing the amount of functional reserves
Lack of strong linkages between functions	Presence of hard linkages between functions
Optimum adaptation to changing conditions of functioning	Reduced adaptation to changing conditions of functioning

There are subjective criteria of the disease (patient complaints of malaise, pain, various functional impairment, etc.) and objective (results of a study with laboratory and instrumental methods), allowing to identify abnormalities and to establish the typical symptoms (signs) of the disease.

Semiology (sémeion = sign, symptom) — the study of symptoms and signs of diseases.

Symptoms — subjective feeling of disease.

Signs — objective parameters of changed functions and structures of body systems.

Classification of diseases

Classification may follow various principles: cause, localization, mechanisms of development, age, sex, type of dysmetabolism, professional aspects, clinic duration and others.

Clinical classification of the diseases is based on the clinical forms, localization, duration of processes, types of diseases current (acyclic, cyclic).

According to duration:

✓ flash-like (several minutes — several hours);

✓ acutest (several hours — 3–4 days);

✓ acute (5–14 days);

✓ sub acute (15–35–40 days);

✓ chronic (several months and years).

Etiological classification is based on a cause: heredity or acquired, infectious noninfectious, traumatic, toxical etc.

Topography-anatomic classification of the diseases corresponds with the main physiological systems (pulmonary, cardiac, renal diseases etc.).

The International Classification of Diseases (ICD) applied the following criteria:

- reason (hereditary, infectious etc.);
- main link in the pathogenesis of the disease (degeneration, hypertension, immunopathological condition, endocrinopathy, etc.);
- main localization of the diseases (diseases of blood, respiratory system, heart, liver, etc.);
- patient's age (newborn illness, childhood diseases, diseases elderly and senile age);
- basic principles of treatment (surgical, therapeutic disease).

There are four stages of disease:

1. Latent period (incubation period for infectious diseases). It lasts from the moment of impact disease agent on the body until the first signs of the disease. During this period start numerous protective reactions aimed at removing the causes of diseases and compensation of the damages. The initial period for different types of the disease may be very short (eg, mechanical trauma, acute intoxications) or very long (metabolic diseases, tumors, certain infections).

2. Prodromal period. The first signs of the disease are appear (initially nonspecific), followed by the deployment of clinical manifestations characteristic of this disease.

3. Period of expressed manifestations (specific signs of the disease).

4. Outcome of the disease.

Outcome of the disease may be:

• recovering;
• transition in chronic form;
• relapses;
• complication;
• death.

Recovering may be complete and incomplete

Complete recovering — is characterized by the absence of symptoms and normalization of impaired functions.

Incomplete recovering — persist dysfunction (in varying degrees of severity) of individual organs and their regulation. One expression of incomplete recovery is a relapse (return) of the disease, as well as its transition a chronic state.

The study of mechanisms involved in recovery from disease to health is **sanogenesis** (sanos — health).

Classification of sanogenetic mechanisms:

1. Primary:
✓ adaptive;
✓ protective;
✓ compensatory;
2. Secondary:
✓ protective;
✓ compensatory;
✓ terminal.

Adaptation — changes in the structure and metabolism, conducive to the optimal functioning of the body in the new environment (in case of damage). Maintains the homeostasis and prevents damage under the action of environmental factors.

Compensation — restructuring of the relationship between the elements of the system, aimed at ensuring full (sufficient) function, at damage of specific

structures responsible for the implementation of this function in norm. Compensation eliminates the consequences of the damage.

Distinguish 3 main ways of sanogenesis:

1. Immediate (unstable, «alarm») protective compensatory reactions that occur in the first few seconds and minutes after exposure (protective reflexes - vomiting, coughing, sneezing, etc .; release of adrenaline and glucocorticoids in stress reactions etc.);

2. Relatively stable protective and compensatory mechanisms act throughout the disease (initiation of reserve capabilities, including regulatory systems (eg switching to a high level of thermoregulation, increasing the number of red blood cells, etc.); processes of neutralization of poisons; reaction from the system of active connective tissue);

3. Stable protective compensatory reactions: immunity, compensatory hypertrophy, reparative regeneration and other structural compensation persist for many months or years after undergoing the disease.

Main features of sanogenesis:

- ✓ it's a dynamic complex of mechanisms;
- ✓ it's a complex of physiological and pathophysiological mechanisms;
- ✓ it's develop in action to the organism extreme stimulant;
- ✓ mechanism of sanogenesis are affected during all pathological process;
- ✓ it's direct to repairing autoregulation of organism.

The transition to a chronic form means that the disease progresses slowly, with long periods of remission (months or even years). Such a course of the disease is determined by the virulence of the pathogen and mainly reactivity of organism. So, in old age, many diseases become chronic (chronic pneumonia, chronic colitis).

Relapse (in roman recidivus) — is a renewed or aggravation the symptoms of disease after their elimination or easing.

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

Complication — is pathological process, condition or reaction, developing on the basic disease background, but it is not obligatory for disease (appendicitis can by complicated by peritonitis, myocardial infarction — arrhythmia).

Death may be:

- natural;
- premature:
  - ➢ the violent death,
  - ➢ death as a result of disease.

Tanatogenesis (thanatos — death) — study of signs, conditions, causes and nature of death.

The dying process is divided into a series of successive stages called terminal condition.

Terminal conditions — is a reversible decrement of organism function that 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*:** 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*:** hypoxia.

The main steps of dying are:

• preagony;
• terminal pause;
• agony;
• clinical death.

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 (*in greek *agonia* is a struggle):

• main agony sign is the first inhale occurrence after the terminal pause period;

• at the beginning — respiration is weak, then it increases in depth, reaches the maximum, gradually weakens and absolutely stops; may appear terminal type of breathing;

• bradycardia, temporary asystoly, decrease in the arterial blood pressure may be short-term increase in the arterial blood pressure;

• in metabolism – a prevalence catabolism;

• deep dysfunctions of higher nervous system with simultaneous excitation of the medulla oblongata;

• consciousness is absent, sometimes it quickly clears up;

• eye reflexes and external irritants reaction are disappear;

• sphincter relaxation.

Clinical death

- consciousness is absent;
- absence of pulse and blood pressure;
- absence of breathing;
- widely dilated pupils;
- completely unresponsive to the painful stimulus;
- recovery can occur only with resuscitation.

Postresuscitation disease

This is not a complication of intensive care, it is a form of pathology, with pathogenetic base on fundamentally new totality pathological processes and reactions, whose interaction and characteristic sequence of development define specific features of the clinical course of postresuscitation.

In the postresuscitation period are identified:

- violations of systemic and peripheral hemodynamics, hemostasis disorders, rough disorders of all kinds of metabolism;
- violation of gas exchange function of the respiratory system;
- failure of the liver and kidneys;
- brain dysfunction (encephalopathy).

I period — early postresuscitative (in the experiment, it takes the first 6–8 h in the clinic — 10–12 h), is characterized by rapid dynamics of the restore the functioning of vital organs and systems in combination with the instability of many body functions. Cardiac output first increases and then decreases, develops hypovolemia, increases the total peripheral vascular resistance, instability in blood pressure; violations of regional circulation and microcirculation in the form of blood flow shunt, increased blood viscosity, blood circulation centralization of on the background of hypoperfusion of the peripheral tissues; growing oxygen consumption to vital organs; stored oxygen debt of the body. Oxidized products of metabolism are accumulated (due to ongoing hypoxia), that deepens metabolic acidosis, which further goes into respiratory alkalosis. Identified hyperenzymemia, hormone imbalance, hypercatecholaminemia, endotoxemia, expressed hemostatic disorders (bleeding, microthrombosis), water and electrolytes imbalances. Death can occur from repeated circulatory disorders, heart failure, coagulopathic bleeding, pulmonary and brain edema.

II period (lasting several hours) — the period of temporary and relative stabilization of the main body functions and improve the general condition of the patient. Notes the temporary stabilization of basic functions, but microcirculatory disorders are not fully eliminated. Save metabolic disorders (hypokalaemia, slow fibrinolysis, increased lipolysis, tendency to hypercoagulability), blood volume deficit and widespread violations of acid-base status.

III period (from the end of first – to the beginning of second day) — is the stage of repeated deterioration. To circulatory and anemic hypoxia bind respiratory

(caused by microthrombosis of pulmonary vessels, shunt in the pulmonary circulation). Noted persistent and progressive arterial hypoxemia. Observed recurrence of hypovolemia, deterioration of peripheral circulation, oliguria, metabolic acidosis, increase of catabolic processes, development of severe hypercoagulation and slowing of fibrinolysis. Critical expression reaches damage of parenchymal organs.

IV period — is end stage (2–3 day after resuscitation). During this period, perhaps as improvement, followed by recovery as well as deepening of functional metabolic disorders and structural abnormalities. Appear purulent-septic complications on the background immunosuppression; again grow disorders of peripheral circulation; reduces the blood oxygen capacity due to deepening of anemia; increases the excretion of potassium with urine (due to hypoxic cell damage). Usually develops complete failure of spontaneous breathing occurs or deepening coma.

In the case of a favorable course of the recovery period the consequences of suffering from terminal condition can be observed for a long time (autoimmune brain damage, encephalopathy, etc.), so the patient must be in a year or more to be under a doctor's supervision.

Biological death

Soon after biological death a number of signs of death and postmorten changes appears. They are the followings:

- algor mortis (cooling) — result of heart production stopping in the body and body temperature equal to environment;
- rigor mortis — complete loss of ATP which required to cause separation of myosin and active during relaxation, and muscle is unable to relax until further enzyme activity complete degrades. Usually develops in 2-5 hours after death and kept during 2–3 days;
- livor mortis (Latin: livor — bluish color, mortis — death), postmortem lividity, due to heart stops functioning, heavy red blood cells sink through the serum by action of gravity (starts twenty minutes to three hours after death);
- decomposition — caused by autolysis (breaking down of tissues by the body's own internal chemicals and enzymes) and putrefaction (by bacteria).

The basis of the disease is the pathological process.

Pathological process — is a complex of morphological, biochemical and functional changes developing in tissues at infringement of realization of the genetic program or interaction with the sickly factor of environment.

Differences between the pathological process from the disease:

1) disease is always one main reason (producing a specific etiological factor), the pathological process always polyetiological;

2) same pathological process may cause the different picture of the disease in depending on the location (inflammation of lung — pneumonia, heart muscle inflammation — myocarditis, etc.);

3) disease usually is a combination of several pathological processes (pneumonia has a combination of pathologic processes such as inflammation, fever, etc.);

4) local pathological process can exist without disease (callus).

Slowly current pathological process is a pathological condition.

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.

In some cases, the pathological condition may go back in the pathological process, disease (eg, pigmented skin area under the influence of mechanical, chemical and physical factors can be transformed into a malignant tumor melanosarcoma).

Pathological reaction (function) is inadequate (quantitatively or qualitatively) answer of alive system on physiological irritation. It is an external display of pathological process, symptom of disease, an attribute of presence in the organism of pathological process. Examples: dilation of skin vessels under the influence adrenaline, allergic reactions, inadequate psycho-emotional and behavioral reactions, abnormal reflexes (reflexes Rossolimo, Babinski) etc.).

Within the general nosology develop three important categories of doctrines:

- nosology;
- general etiology;
- general pathogenesis.

Nosology (from Greek: nosos — disease; logos — science) — the doctrine of the disease in the strict, narrow sense of the term or private nosology.

General etiology (from Greek: aitia — reason, logos — science) — the doctrine of causes and conditions of occurrence and development pathological processes, states, reactions, disease, the principles of etiotropic therapy and prevention.

Etiological factors are divided into exogenous and endogenous; acquired, congenital, heredity; according nature –physical (mechanical, thermal, radiation, etc.), chemical (poisons, toxic metabolites, side-effect of medical drugs) and biological (microbes, viruses, parasites, immune), psyco-emotional, social causes.

Factors which increase morbidity are ***risk factors*** (for example, hereditary factors, obesity, arterial hypertension are the risk factors for atherosclerosis).

Condition is a factor promoting, interfering or modifying action of the etiologic factor. The condition cannot cause disease. The difference between conditions and cause is that the cause is one and a lot of conditions. Conditions are not necessary for the disease occurrence and do not give it specificity.

According to origin conditions may be classified as exogenous (ecological, social), endogenous (sex, age, constitution, type of higher nervous activity). They may be formed during prenatal or postnatal period. Distinguish the conditions conducive to effect of cause and preventing it.

The idealistic and metaphysical theories of the disease etiology

1) ***Monocausalism*** (in 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.

2) ***Conditionalism*** (in roman condition — condition) — is a study, which refutes causality in disease occurrence. It substitutes the categorion of cause for the sum of equivalent conditions (equalent according to the role).

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

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

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

6) ***The cevilization diseases*** — the universal value attribute to the social factors in the development of pathological processes.

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

General pathogenesis (pathos — pain, suffering, distress, genesis — origin) — the doctrine of the mechanisms of development and completion of pathological processes, states, reactions and diseases, the principles of pathogenetic therapy and prevention.

Pathogenesis — mechanisms involved in disease onset and diseases development (pathomechanisms).

Pathogenesis of illness always includes 2 processes: damage (pathological changes) and protective reactions and processes (adaptation and compensation).

All events, which are observed in pathogenesis of any disease, are called the links of pathogenesis. Pathogenesis of disease has **main** (leading, keyword, organizing) **link** or many links. As a rule, it (they) act from the beginning to the completion of the process. Identify key link or links of pathogenesis provides carrying out effective pathogenetic therapy and prevention of pathological processes and disease.

In the pathogenesis of diseases and pathological processes is always a start, initial, trigger, **releaser**. This mechanism is largely determines the specificity of disease regardless of act it throughout all disease or starts it. For example knowing that an initial link in the pathogenesis of ischemic renal hypertension is the activation of the renin-angiotensin-aldosterone system allows the physician to block this link using drugs and effectively treat the patient. But after the activation of other links of hypertension pathogenesis of releaser factor may lose the trigger value.

In the pathogenesis of disease can be identified a number of stages or links which are linked by causal-effect relationships. This means that the changes arising in the course of disease are becoming the causes of further violations. Distinguish the followings types of causal-effect relationships:

1) «straight line» (one event is a consequence of the previous and the cause of next);

2) branched types (include the divergence and convergence): divergence — certain events of pathogenesis have many consequences; convergence — different events of pathogenesis lead to the same consequence;

3) «vicious circle» — certain phenomena of pathogenesis through a certain sequence events lead to increased themselves, etiological factor causes the pathologic reactions (process) and then these reactions return to the etiological factor (first agent) and intensify it. This type of causal-effect relationship self-sustained the pathogenesis of disease and worsens its course.

For example, a sharp deterioration in the transport of oxygen in blood loss leads to heart failure, which further impairs the transport of oxygen. There is a «vicious circle».

In the complex chain of causal-effect relationships in the development of disease distinguish local and general changes. There are 4 variants of relationships of local and general processes in the pathogenesis:

1. In response to the local damage to organ or tissue as a result of the general reactions of the organism are mobilized tissue adaptive mechanisms to delimitation of the lesion (eg, granulation shaft during inflammation, the barrier function of the lymph nodes). Consequently, the main parameters of homeostasis (body temperature, leukocyte count and leukocytic formula, erythrocyte sedimentation rate, metabolism) may not be changed.

2. Local process through the receptor system and entry of biologically active substances into the blood and lymph systems causes the development of generalized reactions, and certain changes in the main parameters of homeostasis. In this case, activates adaptive response aimed at preventing the development of common pathological changes in the body.

3. Generalization of the local process in severe cases can lead to failure of adaptive and protective reactions, and ultimately — to the general intoxication, sepsis, or death.

4. Local pathological changes in organs and tissues may develop secondarily on the basis of primary generalized process (eg skin leukemids in some types of leukemia, etc.).

In the development of almost any of disease can be distinguished specific and nonspecific mechanisms of its formation.

Nonspecific mechanisms include typical pathologic processes such as inflammation, disorder of lymphocirculation, fever, thrombosis, the generation of reactive oxygen species, increase membrane permeability etc..

Specific mechanisms include activation the systems of cellular and humoral immunity, which provides specific protection in the fight against foreign objects in the body.

Pathological system — it is a functional summation of reactions single cells, organs, tissues, systems and organism, which appear in the action to organism a pathogenic factor.

Pathological system characterized by:

✓ long-term self-sustained activity;

✓ depression adaptation and protective mechanisms;

✓ based on disorders of information process;

✓ lead (in case of long-term existence) to increasing a disbalance by sick organism and environment;

✓ many PS are developed on the basis of the vicious circles or pathological dominant.

Typical pathological processes

Typical pathological process (TPP) is a standard, answer of the organism, generated during evolution, on action of the damaging (injuring) agents with distinct prevalence of a protective component.

The basis of each TPP is logically developing complex of reactions and processes of damage, destruction, protection, compensation, reparation and adaptations that occur in response to the pathogenic agent. TPP have characteristic features:

• Polyetiology. TPP caused by a large number of causes of different nature (physical, chemical, biological) and origin (exogenous and endogenous, infectious and non-infectious), realizing their pathogenic effect in a variety of environments. For example, inflammation may be caused by mechanical trauma and various chemical agents; microorganisms; excess in the blood and tissues of metabolites (lactic salts, uric acid) etc.

• Monopathogenetic. TPP have standard, stereotypical, common mechanisms of development. For example, inflammation, regardless of its cause, features of development and localization in the body, in the pathogenesis involves complex of mechanisms of typical alterations, vascular reactions and changes in local blood circulation, fluid exudation and emigration of leukocytes, phagocytosis and cell proliferation.

• Complexity. The mechanism of the development of TPP — a complex of interconnected changes: damage and simultaneously developing protection processes, compensation, reparation and adaptation (adaptation).

• Standardness of manifestations. TPP are manifested typical for them standard features. Thus, the inflammatory process of any origin characterized by general (leukocytosis, fever, dysproteinemia et al.) and local (pain, redness, swelling of tissue, increasing its temperature and function disorder) signs. Standard manifestation of TPP due to the fact that it is based on the typical mechanisms of development.

Typical forms of pathology of organs, tissues and systems

Typical forms of pathology of organs, tissues and systems are also components of individual diseases.

Various typical forms of pathology developing in a particular tissue or organ, accompanied by a number of specific for tissues or organs, pathological and adaptive changes. Set of interrelated changes is referred to as the standard (typical) form of pathology of the tissue or organ.

Example. The typical form of pathology — anemia. A variety of reasons can cause hemolysis, violation of RBCs formation and maturation, their loss with bleeding and hemorrhage. But all these states are characterized by a necessary changes — decrease in the amount of hemoglobin per unit blood volume. Such typical, stereotyped form of RBCs pathology is referred to as «anemia». In turn, anemia as typical form of erythrocytes system pathology may be a component of various diseases (e. g., leukemia, kidney failure, radiation sickness, atrophic gastritis, etc.). Typical form of pathology organs and tissues also include cardiac arrhythmias, respiratory failure, nephritic syndrome, uremia, liver failure, leukemia, hyperthyroid condition, syndromes of neurogenic disorders of movement and/or sensitivity, neuroses, and several others.

As a TPP the typical forms of pathologies of organs and tissues have a number of characteristic features of polyetiology, monopathogenetic, complex process of damage and adaptation, standardness of manifestations, including as a component in the pathogenesis of many concrete disease.

PATHOGENIC EFFECTS OF ENVIRONMENTAL FACTORS ON THE HUMAN BODY

In the medical literature pathogenic environmental factors are called «devastating effect» (I. M. Sechenov), «extraordinary stimulus» (I. P. Pavlov), «stressors» (H. Selye), «extreme factors». Among them distinguish mechanical, physical, chemical, biological and social pathogenic factors.

The degree of pathogenicity of any environmental factors is relative and depends on the conditions of the body existence.

DAMAGING EFFECT OF MECHANICAL FACTORS

Mechanical factors may have both local and general damaging effect on the body. The effect of their pathogenic action determined by the strength of this action (kg / cm2) (tension, compression) or in the form of kinetic energy of the mass moving at a certain speed (mV2 / 2g) (kick, falling, bullet or other gunshot wound). Damaging effect of mechanical factors also depends on the state of reliability, strength or resistance of damaged structures.

Stretching — resistance to deformation and the ability to restore the initial state. Pathological processes and initial condition of the tissues effect on the elasticity of the tissues (eg, inflammation reduce elasticity and increase the risk of rupture, muscle at rest, more stretchable than a shrinking).

Compression — small in strength, but long-acting factors of compression can lead to soft tissue necrosis, atrophy (eg due to pressure of tumors).

As a result of prolonged pressure on the human body, soon after the liberation (decompression) arises — crush syndrome.

Crush syndrome

Crush syndrome develops as a result of crushing long limbs (usually lower) by ground, heavy objects, wreckage after earthquakes, blockages in the mines, etc., with duration of compression more than 4 hours. Prolonged (for 8–24 hours) stay in the affected one position (coma, poisoning, severe alcohol intoxi-

cation) can develop positional compression syndrome. In this case, own body weight press on the limbs.

Three pathogenetic factors are important in the development of crush syndrome:

1. painful stimulus;

2. traumatic toxemia due to absorption of toxic products of tissues autolysis from the lesion;

3. plasma and blood loss (edema and hemorrhage in the area of crushed or long ischemic tissues).

Clinical severity depends on degree and duration of limb compression, volume and depth of the lesion, and combined damage to other organs and structures (traumatic brain injury, injury to the internal organs, bones, joints, blood vessels, nerves, etc.).

By severity there are four clinical forms of crush syndrome:

1) light (crush the individual segments less than 4 hours) — minor symptoms, the prognosis is favorable;

2) moderate (crush of both legs less than 6 hours) — there is a moderate impairment of renal function;

3) heavy (crush of both legs about 6 hours) — characterized by significant hemodynamic disorders. Possible death in the early and intermediate period;

4) extremely heavy (crush both legs more than 6 hours) — rapidly progressing clinical manifestations, patients die in the first or second day after the injury.

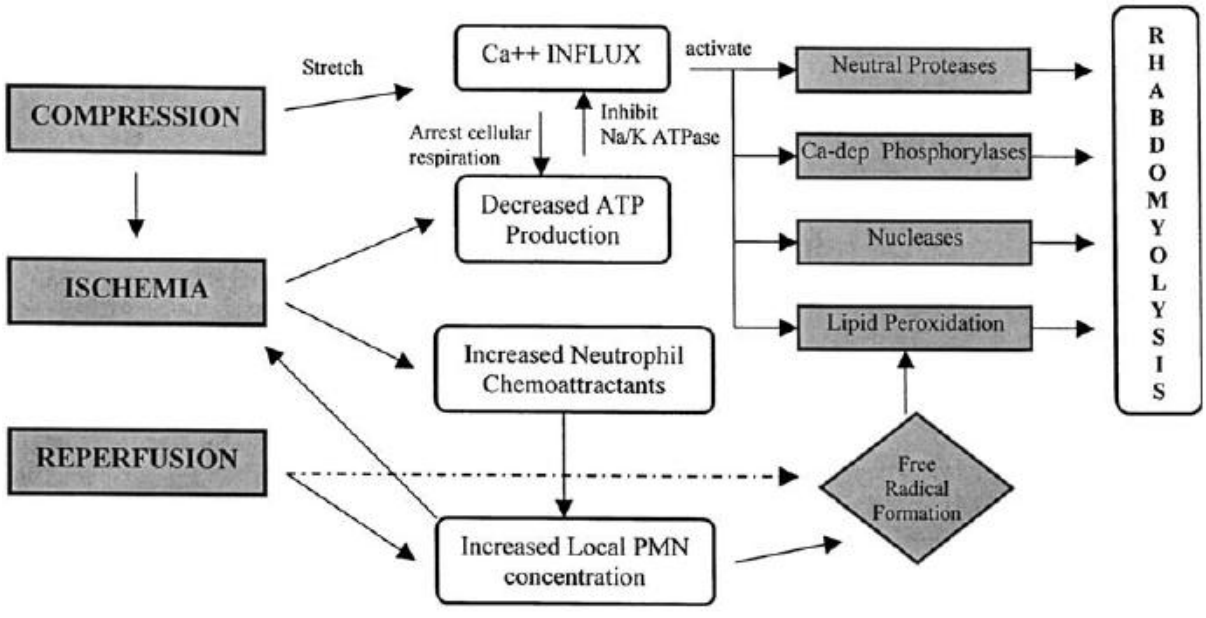

Figure 1 — The pathogenesis of rhabdomyolysis (Malinoski D. J., 2004)

Three are 3 periods in the clinical picture:

I period (initial or early) — hemodynamic disorders (in 1–3 days after release from compression). After a few hours appear local changes in the compressed limb.

It becomes pale, cyanotic fingers, rapidly increases swelling, the skin becomes woody density. Peripheral vascular pulsation is not defined. Progressively increase the symptoms of endogenous intoxication, plasma loss, hemoconcentration, creatinemia, proteinuria, cylindruria. Period is characterized by hemodynamic instability. General condition deteriorates with rise of local changes.

II period (intermediate) — acute renal failure (from 3–4 to 8–12 days). Swelling of the affected limb is enhanced by formation of bubbles with clear or hemorrhagic content, appear dense infiltrates with local and sometimes even total necrosis of the entire limb. Haemoconcentration replaced hemodilution, anemia increases sharply reduced urine output, up to anuria. In the blood, increases the amount of residual nitrogen, urea, creatinine, potassium, the picture of uremia. Body temperature increased. The patient's condition rapidly deteriorating, intensified slacknessand confusion, there is a vomiting and thirst, jaundice of the sclera and skin. The fatality rate in this period is 35 %.

III period (late period or local complications) begins in a 3–4 week. Normalized hemodynamic parameters, renal functions are restored. In uncomplicated cases, limb edema and pain end at the end of month. Perhaps the development of local (infection of open injuries) and general complications (generalization of infection with sepsis).

PATHOGENIC ACTION OF ACCELERATION

In biology and medicine are the following types of acceleration:

1. Rectilinear acceleration — overload occurs when increasing or decreasing the speed without changing the direction.

In relation of vector to longitudinal axis of the body distinguish overload:

- longitudinal positive — from the head to the feet;
- longitudinal negative — from the feet to the head;
- positive transverse — from the chest to the back;
- negative transverse — from the back to the chest;
- positive sideward — right to left;
- negative sideward — left to right.

2. The radial and centripetal — occurs when changing the direction of the body motion, for example when the banking by plane, rotations of human in a centrifuge.

3. The angular acceleration — occurs when a non-uniform motion of a body in a circle, ie, by increasing or decreasing angular velocity.

Action of acceleration manifested by offset of soft tissue, organs in the direction of the inertial forces of deformation; unusual afferent impulses to the central nervous system, leading to the breakdown of its regulatory role. The

leading place in the genesis of physiological changes during overload belongs to blood and tissue fluid.

In the action acceleration are distinguished:

• compensatory phase: increased frequency of heart rate, increased blood pressure, increased cardiac output and regional blood flow, increase lung ventilation, increased oxygen consumption, oxygen tension in the tissues of the brain, enhancing the function of several endocrine glands;

• decompensatory phase: the breakdown of compensation, bradycardia, arrhythmia, disorders of cardiac conduction, drop in blood pressure, impaired redox processes, disorders of the regulatory function of nervous and endocrine systems.

EFFECTS ON THE BODY BAROMETRIC PRESSURE CHANGES

Effect of reduced barometric pressure (hypobaria)

People found hypobaria while climbing in the mountains, on the ascent to altitude in leaky aircraft, spacecraft during accidents, in pressure chambers.

At an altitude 3000–4000 meters (corresponding barometric pressure 530-460 mm Hg) is an expansion of gases and increase their pressure in enclosed and semi-cavities of the body, leads to irritation of the walls of the receptors, causing pain (especially eardrums and the mucous membranes of the middle and inner ear, maxillary and frontal sinuses).

At an altitude 9000 meters or more (which corresponds to 225 mmHg or below) occur symptoms of decompression. This is due to the transition of oxygen, and especially nitrogen dissolved in body fluids to a gaseous state. Formed bubbles of free gas (gas emboli), are spread by the vessels in different parts of the body, causing embolism. This in turn leads to the development of tissue ischemia. Especially dangerous are embolism of coronary artery and cerebrovascular disease.

High altitude (HA):

• High altitude: 1500 to 3500 m — high-altitude illness common with abrupt ascent to above 2500 m;

• Very high altitude: 3500 to 5500 m — most common range for severe high-altitude illness;

• Extreme altitude: 5500 to 8850 m — progressive deterioration of physiologic function eventually overcomes acclimatization.

Acute mountain sickness (AMS)

Acute mountain sickness is caused by reduced air pressure and lower oxygen levels at high altitudes. Barometric pressure falls as altitude increases. As the barometric pressure decreases, the partial pressure of oxygen decreases proportionately. This condition is referred to as hypobaric hypoxia. It lead to:

• increased pulmonary ventilation;

• increasing the oxygen capacity of blood (ejection of RBCs from blood depot (spleen, liver), in prolonged state of hypoxia increased erythropoiesis);

• increase in the minute volume of circulating blood, acceleration of blood flow;

• at the tissue level — increased capillarity; increased myoglobin; improving the system of regulation of redox processes, and others.

Excess hypoxia stimulates the respiratory center as a result is hyperventilation with decreases in the blood CO_2, it lead to respiratory alkalosis develops, disturbed regulation of respiration. During waking mind takes the signals to breath. During sleep, when the mind control is weakened, there is a Cheyne–Stokes periodic breathing (respiration stopped on 10–15 seconds (due to a lack of CO_2), after which the respiratory movements renewed, first increasing in depth (due to increased concentration of CO_2 during apnoe), then decreasing.

Hypocapnea shifts HbO_2 dissociation curve to left (increases alveolar O_2 uptake and inhibits release of O_2 to tissues) it leads to hypoxia deepening.

Risk factors of acute mountain sickness are rate of ascent, individual susceptibility, preexisting cardiopulmonary disease, physical exertion, obesity.

Symptoms of AMS occur in 6–36 H after ascent. There are headache, dizziness, fatigue, malaise, disturbed sleep, anorexia, nausea, vomiting, shortness of breath. In humans, the most sensitive and susceptible to hypoxia are the brain tissue and the tissue of pulmonary alveoli. It is the cause of development edematous processes in the brain and lung alveoli.

Hypoxic mechanisms of pulmonary and brain edema:

1. The increase of pressure in the blood vessels and capillaries due to their spasm, water retention in the body and blood stagnation in the venous system.

2. Increasing the permeability of capillary wall leads to the exit of the liquid plasma components into the intercellular space.

3. Increased permeability of the cell membrane (hypoxia violates selective permeability of cell membranes, resulting in begins equalization of ion concentration inside and outside the cell: the cell loses K^+ ions and overloaded by Na^+, Ca^{2+} ions).

4. Decrease in plasma oncotic pressure of leads to blood concentration.

Manifestations of brain edema:

- change in mental status; e.g., confusion;
- photophobia;
- hallucinations;
- ataxia (discoordination);
- coma;
- can cause death from brain herniation.

Manifestations of pulmonary edema are progressive: initial nonproductive cough, progressive dyspnea, tachypnea and tachycardia, production of pink, frothy sputum, due to weakness the patient tries to lie, but due to suffocation forced

to sit; severe hypoxemia, patchy infiltrates on chest x-ray. It leads to progress of hypoxia, lethargy, coma and death.

Chronic mountain sickness (CMS, Monge's disease)

Occurs in high altitude natives or long-term residents (> 2500 m). May be primary CMS (acclimatized individuals) and secondary (individuals with conditions; e.g., obesity, neuromuscular disorders, chronic lung disease).

Chronic hypoxia leads to excessive erythropoiesis (erythrocytosis with Hct > 58 %), decreased partial pressure of O_2 in the air is associated with pulmonary hypertension, leading to cor pulmonale, reduced exercise tolerance, dyspnea, headache, anorexia, inability to concentrate, memory loss.

Explosive decompression

Explosive decompression occurs usually at fast depressurization of the aircraft at high altitude (more than 16 km above sea level).

Pathogenesis:

1) per second there is decrease in ratio of end atmospheric pressure to the initial in more than 2 times;

2) partial pressure of oxygen in the inhaled air reduced to below 16 mm Hg, and in the alveoli — less than 6.5 mm Hg .;

3) barometric pressure is equalized with the sum of pressures of water vapor (47 mm Hg or more) and carbon dioxide (30 mmHg or more).

All this leads to the fact that the oxygen content in the tissue close to zero, and breathing switches from oxygen to nitrogen. Is attached multiple gas embolism of tissues and organs (rapid formation of gas bubbles, mainly nitrogen, due to a sharp decrease in its solubility in tissue and interstitial fluid). There is effect of «boiling» blood, intercellular and even intracellular fluids, leading to rupture of blood vessels, lungs and other organs.

On the background of excess afferentation with huge receptor field and mechanical limit excursions of the lungs, heart and blood vessels rapidly difficult and depressing respiration, heart work, blood return to the heart, reduced blood pressure and increased venous and cerebrospinal fluid pressure. Already within 1–2 minutes after the onset of explosive decompression the heart stops, develops collaptoid state, lost consciousness, convulsions and death occurs.

Effect of increased barometric pressure (hyperbaria)

There are two main types of hyperbaric: natural and artificial.

Artificial hyperbaric carried out with different purposes occurs when the human or experimental animal stay in the pressure chamber (eg, hyperbaric oxygenation).

Natural hyperbaric — is a compression of the body when submerged under water (while diving to great depths, divers and caisson work). When submerged under water, for every 10 meters per person acts additional 1 atmosphere.

High hydrostatic pressure suppresses biochemical reactions occur with an increase in volume of the final products. However, the main pathogenic effect is associated with increased dissolved gases in body fluids (saturation). When submerged under water increases the amount of dissolved nitrogen. Especially active are saturated with nitrogen organs rich in fat (adipose tissue and nerve dissolved in 5 times more nitrogen than blood). At the same narcotic effect of nitrogen manifest at a barometric pressure more than 0.6 MPa. Oxygen at elevated pressure more 0.2–0.4 MPa becomes toxic.

Decompression Sickness (Caisson disease)

Decompression associated with the sudden decrease in pressures during underwater ascent, usually occurring during free or assisted dives.

There are three periods (stages):

1 period — dive (during the transition from normal to increased pressure). When submerged under water at a depth of 20–40 m compressed surface vessels, chest, lungs, increased blood circulation in the internal organs (including the lungs, heart, brain), accompanied by overstretching the walls of their blood vessels (up to rupture), impression of eardrums (up to rupture). There are possible displacement and compression of the internal organs, as well as lung tissue ruptures, the occurrence of air embolism and even death.

2 period — saturation (the period of constant high saturation of liquids and gases tissues a result of increased their solubility). Risk of development of lung barotrauma and air embolism enhanced. Dissolved in plasma, tissues nitrogen (especially in nerve and fat) causes initially euphoria, then — anesthesia and finally — the toxic effect. Toxic effect of nitrogen and oxygen are manifested the development of headache, dizziness, disorders of the cardiovascular system (in the form of bradycardia, reduce of volume flow velocity), damage of the airway epithelium, their alveolar surfactant layer (up to pulmonary edema), intestinal mucosa, inhibition of erythropoiesis, the development and progression of metabolic acidosis, seizures, necrobiosis, necrosis and even death .

3 period — desaturation (during ascent or decompression, characterized by the formation and an increase in gas, especially nitrogen, bubbles in the extracellular and intracellular fluids). Develops when the body passing from high blood pressure to normal atmospheric pressure.

During infringement of ascent rules develops caisson disease.

Faster the diver ascends with depth more rapidly, in large quantities, and larger formed gas bubbles (especially nitrogen and helium), because it moves from the dissolved gaseous state. The gas accumulates in the form of bubbles in the blood, extracellular fluids, fat and nerve tissues.

Manifestations:

- bends pain in large joints;

- chokes cough, substernal pain;
- marbling of skin; skinny bends – cutaneous, itchy rash;
- lymphedema;
- spinal cord: ascending paresthesia (tingling), ascending paralysis, loss of bowel and bladder control;
- bleeding froth from mouth, nose;
- headache, confusion, sensory and motor deficits;
- in worst case convulsions, coma, death.

DAMAGING EFFECT OF SOUND AND NOISE

Noise

Harmful to health boundary volume is 80 dB.

Distinguish specific and non-specific effect of noise on the human body.

Specific effect of noise — dysfunction of the auditory analyzer, due to prolonged spasm of sound-perceiving apparatus resulting in the disruption of metabolic processes and as a consequence is degenerative changes in the endings of vestibular-cochlear nerve cells and Corti organ.

Non-specific effects of noise:

• entering of excitation in the cerebral cortex of the brain. In the initial stages develops protective inhibition of the central nervous system with impaired mobility and balance of excitation and inhibition. In the future, there is a depletion of nerve cells and, consequently, irritability, emotional instability, memory loss, reduced attention and working capacity;

• excitation of the hypothalamus, which is realized by the type of stress reaction;

• entering of excitation in the spinal cord is switched on its autonomic nervous system centers, which causes a change in the functions of many organs.

Ultrasound

Ultrasound 0151 inaudible to the human ear elastic waves with a frequency above 20 kHz. Sound pressure in the ultrasonic wave can vary ± 303,9 kPa (3 bar).

The biological effect of ultrasound is due to:

• mechanical effect: negative pressure promotes the formation of microscopic cavities in the cells, followed by rapid slamming them, which is accompanied by intense hydraulic beats and ruptures — cavitation;

• physico-chemical effect: cavitation leads to depolarization and degradation of molecules, causing them to ionization that activates chemical reactions, normalizes and accelerates tissue metabolism;

• heat effect of ultrasound mainly due to the absorption of acoustic energy. When the ultrasound intensity 4 W / cm 2, and its exposed for 20 seconds the temperature of tissue at a depth of 2–5 cm is increased at 5–60 °C.

A positive biological effect in tissues causes ultrasound of low (up to 1.5 W/cm^2) and secondary (1.5–3 W/cm^2) intensity. High-intensity ultrasound (3–10 W/cm^2) has a damaging effect: violates the capillary blood flow, causing destructive changes in the cells, leading to local overheating of tissues.

The nervous system is most sensitive to ultrasound: selectively are affected peripheral nerves, broken transmission of nerve impulses in the synapses. As a result, there is vegetative polyneuritis and paresis, raises the threshold of excitability of the auditory, vestibular-cochlear and visual analyzers, sleep disorder, irritability, fatigue.

DAMAGING EFFECT OF THERMAL ENERGY

Action of high temperatures

Action of high temperatures can cause burns, burns disease and overheating.

Burns injury

Burns (thermal) — local tissue damage as a result of fire, flammable liquids, steam, heated solids.

Mechanism of burns associated with the development of inflammatory reactions at the site of agent action and the thermal coagulation of proteins, leading to cell death and tissue necrosis.

The depth of burn injury is classified as follows:

1st degree — Superficial burns involving only the epidermis. The skin will be red and hypersensitive.

2nd degree — burns involving the epidermis and part of the dermis, location for collagen, elastic fibers and sweat glands and hair follicles. The skin is red, blistered and swollen, painful (due to damage of sensory nerves). These burns may heal without grafting.

3rd degree: 3a — partial or complete necrosis of malpighian (sprout) skin layer; 3b – complete necrosis of the skin in the full thickness. The sensory nerves are destroyed; therefore, all sensation to pinprick is lost in the affected areas.

4th degree — full thickness burns that destroy both layers of the skin and underlying structures, including fascia, muscle and bone.

The location of burn injury is a factor in determining the severity and outcome. Burn injury to the face, neck, hands, feet, perineum, respiratory system and crossing major joints are associated with complications, functional loss and handicap.

Burns disease

Burns disease — functional disorders of internal organs and systems developed due to extensive (more than 10–15 % of the body surface) and deep burns.

There are four periods of development burn disease:

1. Burn shock — in extensive and deep burns over 15 % of the body surface (in children and elderly even smaller areas). In the first 12–36 hours, in a zone of burning sharply increases capillary permeability, which leads to significant release of fluid from the vessel into the tissue. At the site of injury evaporates large amounts of edematous fluid, blood volume is decreased. Leading pathogenetic factors: hypovolemia, pain stimulation and increase vascular permeability.

2. General toxemia — develops due to autointoxication by decay products of burns site tissue (denatured protein, biologically active amines, polypeptides, et al.) and the production of specific burns autoantibodies (in skin identified burns autoantigens specific for this type of injury).

3. Septicotoxemia (secondary infections).

4. Reconvalescence (recovery).

Overheating

Overheating (hyperthermia) — a temporary increase in body temperature due to the accumulation of excess heat (with a loss of heat transfer processes and the effect of high environmental temperature).

The causes of overheating:

- environmental factors: high ambient temperature (ambient temperature about 33 °C stops heat loss from the body surface due to convection and radiation of heat; at higher temperature, the heat loss is possible only due to the evaporation of sweat from the skin surface); high humidity (development of overheating even at 33–34 °C due to cessation of sweating or evaporation of sweat); water deficit in the body and due to its loss with sweat;
- the presence of agents impeding implementation of the mechanisms of heat transfer of the body;
- uncoupling of oxidation and phosphorylation in the mitochondria.

Increase in body temperature accompanied by:

- sharp acceleration of respiratory movements (irritation of the respiratory center of the heated blood) develops heat dyspnea;
- acceleration of heart rate and blood pressure;
- due to water loss through sweating occurs blood clots, disturbed electrolyte metabolism, increased erythrocyte hemolysis;
- damage to various tissues leads to the accumulation of decay toxic their;
- due to destruction of VII, VIII, X, and other plasma factors disrupted blood clotting.

Overexertion of thermoregulation mechanisms leads to their depletion, followed by inhibition of central nervous system, respiratory depression, heart function and decreases in blood pressure and as a result — a deep hypoxia.

Heat stroke

Heat stroke — is acute hyperthermia with a rapid rise in body temperature or prolonged exposure to high environmental temperature.

Manifeatations: core temperature exceeding 40 °C, cessation of sweating, rapid pulse, rapid respiration, hypotension, CNS symptoms predominate: unsteady gait, confusion, combative behaviour, reduced consciousness, convulsion and coma.

Death in heat stroke occurs from paralysis of the respiratory center.

Action of low temperatures

Effect of low temperatures can cause supercooling (hypothermia), frostbite and chronic lesions of the cold — cold neurovasculitis.

Supercooling (hypothermia)

Primary hypothermia: Excessive exposure to cold, wind, snow ,water, or altitude.

Secondary hypothermia: patient becomes cold in normal environmental temperature, secondary to underlying condition such as trauma, myxedema, sepsis. Elderly, alcoholic, and chronically ill have impaired heat generation owing to reduced lean body mass, impaired mobility, inadequate nutrition, reduced shivering; also, impaired vasoregulatory responses and ability to sense temp extremes. Medications that may altering central thermoregulation (dopaminergic tone) are phenothiazines, barbiturates, lithium, α-blockers).

In the pathogenesis of hypothermia distinguish the following phase:

1. Compensation. Reaction intended to limit heat transfer: a reflex spasm of blood vessels, decreased sweating, slow breathing. Increase heat production: muscle tremors (chills), strengthening the processes of glycogenolysis in the liver and muscles, increased blood glucose, increased basal metabolic rate.

2. Decompensation. Develops under the long-term low temperatures. Reduced body temperature, muscle tremors stopped, reduced oxygen consumption and intensity of metabolic processes, dilate peripheral blood vessels. As a result, inhibition of functions of the cerebral cortex, subcortical and bulbar centers, reduces blood pressure, slows the heart rate, progressively weakens and reduces the incidence of respiratory movements. Gradual fading all vital functions. Death occurs from paralysis of the respiratory center.

Stages of hypothermia:

- Mild Hypothermia — individual response to cold varies. In general, body temperatures from 33° to 35 °C constitute mild hypothermia. In this temperature range, the casualty is in an excitation (responsive) stage. The casualty will usual-

ly remain conscious, however, they may start to exercise poor judgment or have irrational behavior. The body's natural defense mechanism, shivering, will eventually diminish. The body will attempt to retain and generate heat by increasing heart rate, blood pressure, and cardiac output. The respiratory rate will increase, which, in the long run, only cools the body more by breathing in cold air and losing moisture through respirations.

- Moderate Hypothermia — moderate hypothermia occurs when the core temperature is between 30–33°C. Cognitive abilities become more difficult and the patient becomes stuporous and does not respond to painful stimuli. Shivering is replaced by progressive muscular rigidity. In the initial excitation phase, heart rate, blood pressure, and cardiac output all rise. With decreasing temperatures, these all decline. The patient in this stage is at risk for lethal cardiac dysrhythmias.
- Severe Hypothermia — when the core temperature is below 30°C, the patient is in severe hypothermia. The casualty will be unconscious with no response to pain. Pupils dilated. Vital signs will be barely detectable or non-detectable. Without immediate and intensive treatment, this patient will die.

Hibernation — is artificial decrease in body temperature in medical practice under anesthesia achieved by physical effects used to reduce the body's need for oxygen and prevention of the temporary cerebral ischemia.

Frostbite

The most susceptible body parts are those areas farthest from the body's core, such as the hands, fingers, feet, toes.

Depending upon wind velocity and air temperature, the exposure time necessary to made frostbite varies from a few minutes to several hours. The degree of cold injury, just like burn injuries, in many cases will not be known for at least 24 to 72 hours. There are four degrees of frostbite injury (identical to burn injuries) based on physical findings.

1st degree — superficial injury. The first signs - burning, tingling, followed by numbness of the affected area. Then there are itching and pain of varying severity, edema develops. After a few days may be a slight peeling. Full recovery occurs in 5–7 day after frostbite.

2nd degree — involves all the epidermis and superficial dermis. After warming intense and prolonged pain, itching, burning sensation. In the initial period there pallor, cooling, loss of sensitivity, formation of bubbles filled with clear content. Full restoration of the skin integrity occurs within 1–2 weeks, granulation and scars are not formed.

3rd degree — involves the epidermis and dermis layers and frozen skin is stiff with restricted movement. Long-term intense pain. Formed at the initial stage of bubbles filled with bloody contents, their bottom blue-purple, is not sensitive to stimuli. There is a destruction of all skin elements with the development of granulation tissue and scarring. Nails do not grow again or grow de-

formed. Rejection of dead tissue ends in 2–3 weeks, after which comes the scarring that lasts up to 1 month.

4th degree — frozen tissue involves full thickness through dermis with muscle and bone involvement. No bubbles develop at much edema, loss of sensitivity indicate the frostbite 4th degree.

EFFECTS OF ULTRAVIOLET RADIATION

Ultraviolet (UV) irradiation comprises three distinct spectra: A (320–400 nm), B (290–320 nm), and C (200–290 nm).

UVA penetrates to the deeper dermis, formation of pigment by converting of tyrosine to melanin.

UVB penetrate the epidermis and are nearly fully absorbed in the upper dermis. UVB wavelengths have strong general stimulating effect, vitamin-antirachitic action (synthesis of cholecalciferol). Mechanism common stimulating and photochemical actions: UV radiation excites atoms, enhancing their reactivity, which leads to increased activity of chemical reactions in the cells, providing a stimulating effect on the metabolic and trophic processes. Ultimately, the enhanced growth and tissue regeneration, increases the body's resistance to the action of infectious and toxic agents, improves physical and mental performance.

UVC is absorbed by atmospheric ozone. Pronounced bactericidal action.

Pathogenic effect of excessive UV exposure:

- skin lesions it causes photochemical burn, with the development of erythema and Blistering skin reactions, fever, headache, common painful condition. Pathogenic effect is associated with activation of lipid peroxidation, resulting in damage to the membrane, disintegration of protein molecules, cell death;
- defeat of conjunctiva (photoelectric ophthalmia) manifested its redness and swelling, burning sensation and «sand» in the eyes, lacrimation, photophobia pronounced;
- can provoke an aggravation of some chronic diseases (rheumatism, stomach ulcer, tuberculosis, etc.);
- due to increased melanin formation and degradation of proteins increases the body's need for essential amino acids, vitamins, calcium and other salts;
- excessive UV radiation in the wavelength range area C can lead to inactivation of cholecalciferol — to its conversion into indifferent or even harmful substances;
- prolonged excessive UV exposure can promote the formation of peroxy compounds and epoxy compounds having a mutagenic effect, and induce occurrence of basal cell and squamous cell carcinomas of the skin, especially in people with fair skin;
- effects on the nervous system mediated through the irradiated skin

capillaries in blood proteins and cholesterol. Excitation occurs in the autonomic centers of the hypothalamus and basal ganglia, increased body temperature, increased and then drop in blood pressure, drowsiness, collapse and death from paralysis of the respiratory center.

THE DAMAGING ACTION OF LASER RADIATION

Lasers — a device for obtaining narrow beam of monochromatic light energy of high intensity. It is successfully used for the treatment of numbers diseases (eye diseases, tumor, etc.). The action of laser radiation is measured in hundreds of thousand parts of second, so, despite the fairly deep penetration of laser beams into the body (20–25 mm), the sensation of pain does not arise. The greatest sensitivity to laser radiation has pigmented tissue.

Effect of laser radiation on the cell:

• free radical mechanism: the direct damaging effect of laser radiation on the cell associated with the excitation of atoms and ultimately to damage of protein molecules;

• thermal effects associated with absorption by tissue energy of infrared radiation and heat inactivation of protein;

• cavitation effect is due to a rapid rise in temperature to level at which evaporation of the liquid portion in cell. There is a «blast effect» (cavitation) due to the momentary formation of a microcavity with elevated pressure (up to tens or hundreds of atmospheres), and propagating from her shock wave, disruptive a tissue. This effect is at the heart of the laser scalpel;

• biological — inactivation of enzymes and changes in their specific activity.

EFFECT OF ELECTRIC CURRENT ON THE BODY

Features of electric damaging effect:

- tissue damage throughout the path;
- irritating vast number of receptors;
- cause biological effects, chemical, mechanical, thermal damage.

Pathway of the current through the body:

- vertical pathway parallel to the axis of the body is the most dangerous. It involves all the vital organs; central nervous system, heart, respiratory muscles, in pregnant women the uterus and fetus;
- horizontal pathway from hand to hand: the heart, respiratory muscles and spinal cord;
- pathway through the lower part of body — local damage.

Table 2 — Pathophysiologic Effects of Different Intensities of Electrical Current

Current intensity	**Probable effect**

1 mA	Tingling sensation; almost not perceptible
16 mA	Maximum current a person can grasp and «let go»
6–9 mA	«Let-go» current for an average adult
3–5 mA	«Let-go» current for an average child
16–20 mA	Tetany of skeletal muscles
20–50 mA	Paralysis of respiratory muscles; respiratory arrest
50–100 mA	Threshold for ventricular fibrillation
> 2 A	Asystole
15–30 A	Common household circuit breakers
240 A	Maximal intensity of household current

Mechanism of action:

Specific action — manifested by passing current through the body, resulting effects are caused by the redistribution of ions.

Nonspecific action — due to other forms of energy, which is converted into electricity outside the body (flame and electric arc radiation, light, ultraviolet, infrared radiation).

Specific action:

• Biological effect is stimulation of skeletal and smooth muscle, glandular tissue, nerve receptors and conductors.

• Electrochemical action includes:

✓ electrolysis;

✓ polarization of cell membranes;

✓ accumulation in some parts of positively charged ions, occurrence of acid reaction and coagulation of proteins (coagulation necrosis), on other negatively charged ions are accumulated, there is alkaline reaction, swelling of colloids, there colliquative necrosis;

✓ movement of protein molecules;

✓ the accumulation of toxic products of electrolysis;

✓ dissolved gases pass in the gaseous state;

✓ plating of skin during contact of body with metals.

• The thermal effect due to the conversion of electrical energy into thermal energy, with a large amount of heat release in the tissues. Manifestations:

✓ «pearl beads» occur during melting of the bone with the release of calcium phosphate;

✓ «current signs» — areas of coagulated epidermis having a circular or oval shape, gray-white, solid consistency

✓ fringed roll elevation with retraction in the center;

✓ branching pattern of red color is due to paralysis of the blood vessels. Such changes are observed on the skin, if the temperature at the point of passage of the current does not exceed 120 °C;

✓ burns are formed at higher temperature, the current passes through the

tissue, it may damage the underlying tissue until carbonization.

• Mechanical effect due to significant thermal and mechanical energy high voltage currents. The combined action of heat and mechanical energy has an explosive effect.

Complications

• postraumatic myositis with rhabdomyolysis;

• acute/delayed-onset central and peripheral nervous system complications (very often);

• sepsis;

• psychiatric complications.

Immediate death may occur from:

• Current-induced ventricular fibrillation.

• Asystole.

• Respiratory arrest secondary to:

— paralysis of the central respiratory control system;

— paralysis of the respiratory muscles.

THE DAMAGING EFFECTS OF IONIZING RADIATION

Mechanisms of action of ionizing radiation

Etiological factors of radiant disease are the various forms of ionizing radiation of high energy (α-, β-, γ- rays, X-radiation, etc.). Their general property is an ability to penetrate in biological medium and ionize atoms and molecules.

Intensity and duration of injury depends on form of radiation, dose, time factor and type of molecular or supramolecular target, which occurs on the pathway of radiation.

The external irradiation is such one, when a source of it is located out of organism. The internal (incorporated) irradiation is the one, when radioactive materials enter inside.

1. The primary action of IR

Direct effect of radiant energy is a damage of the macromolecules of organism by radiation itself. Eventually, intramolecular alterations happen. Any type of molecules may be a target — organic macromolecules as DNA, lipids, phospholipids, enzymes, proteins, vitamins, hemoprotein, etc.

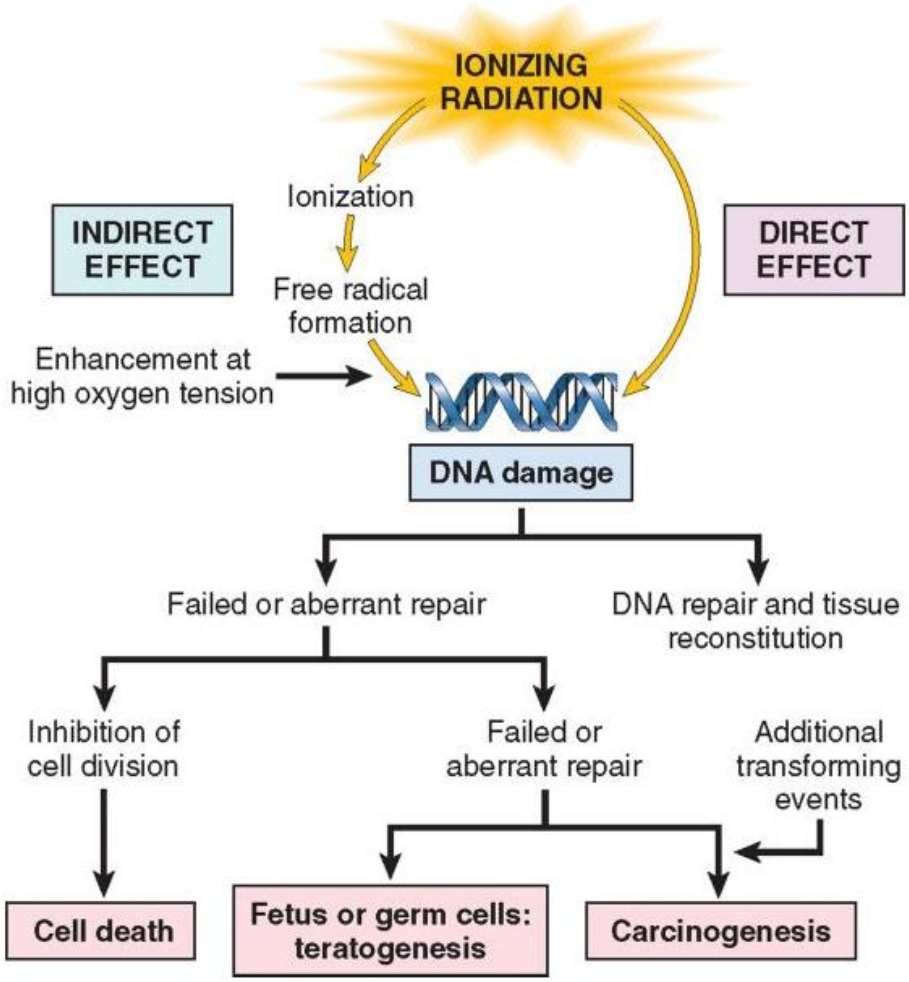

Figure 2 — Effects of ionising radiation (V. Kumar, 2010)

Indirect effect is a damage of macromolecules by the water radiolysis products. Ionization of water molecules is the most significant of all primary radiochemical transformations. The first products are the ionized water molecules H_2O^+ and H_2O^-. Then free hydrogen and hydroxyl radicals are formed (H^*, OH^*), which initiate a chain of father reactions and new products are formed (peroxide of hydrogen $H_2O_2{}^*$, hydroperoxide $HO_2{}^*$, atomic oxygen O^* etc.). The water radiolysis products biochemically are very active and cause extensive nonenzymatic oxidation.

2. Action of IR on cells

Cellular reaction to the action of IR:

- temporary blocking of mitosis;
- complete suppression of mitosis;
- interphase cell death;
- mitotic cell death.

By radiosensitive include actively dividing and undifferentiated cells: hematopoietic bone marrow cells, germ cells of the testes, skin and intestinal

epithelium. In spite of differentiation, high radiosensitivity has lymphocytes. Radioresistant cells include brain, muscles, liver, kidneys, cartilage, ligaments.

3. Action of IR at the organism level:

Immediate consequences:

- Radiation sickness from external exposure:
- ✓ Acute radiation sickness.
- ✓ Chronic radiation sickness.
- Radiation sickness from internal exposure.
- Local action of IR (radiation burns, cataracts, necrosis).

Long-term consequences: may develop after 10–20 years or more after total body irradiation or local.

Distinguished somatic consequences (occur in irradiated organism):

• *non-tumor forms* — reduced life expectancy, hypoplastic state in hematopoietic tissue, mucous membranes of digestive system, respiratory tract, in the skin; sclerotic processes (cirrhosis, nephrosclerosis, arteriosclerosis, cataract beam), and dishormonal states (obesity, hypophysial cachexia, diabetes insipidus);

• the development of *tumors*, radiation leukemia.

Genetic consequences (as a result of damage to reproductive cells) may occur loss of zygote or embryo, the birth of individuals with inherited abnormalities or carrying mutant genes. «The genetic load» can be transmitted from generation to generation.

Acute radiation sickness (ARS)

In total, single, uniform irradiation of the organism in a dose of 1 Gray.

There are 4 form of ARS:

1. Bone marrow form (1–10 Gy).
2. Intestinal form (10 to 20 Gy, the death at 7–10 days).
3. Toxemic form (20–80 Gy, the death at 4–7 days).
4. Cerebral form (more than 80 Gy, the death at after 1–3 days, and during the actual exposure — «death under the beam»).

Bone marrow form

Depending on the dose there are four degrees of severity:

I — mild (1–2 Gy);

II — medium (2–4 Gy);

III — severe (4–6 Gy);

IV — extremely severe (more than 6 Gy).

The disease is characterized by 4 phases:

1) ***Primary acute phase reaction*** occurs in the first minutes or hours after exposure. Duration of phase 1–3 days.

Manifestations:

- excitation, headache, general weakness;
- dyspeptic disorders (nausea, vomiting, loss of appetite);
- lability of the autonomic functions — fluctuations in blood pressure, heart rhythm;
- activation of the pituitary-adrenal system, enhanced secretion of adrenal hormones;
- at doses of 8–10 Gy seen the development of shock-like state with a decrease in blood pressure, transient loss of consciousness, fever, diarrhea development;
- peripheral blood: leukocytosis with a left shift, absolute lymphopenia.

2) ***Phase of the imaginary clinical well-being*** — including in the pathological process of defense mechanisms. Duration depends on the radiation dose and ranges from 10–15 days to 4–5 weeks. For very severe defeat this phase is absent.

Manifestations:

- patients feel satisfactory becomes visible clinically signs disappear;
- in the gonads can atrophy, inhibition in early stages of spermatogenesis;
- in the small intestine and skin atrophic changes;
- neurological symptoms quenched;
- peripheral blood: progress lymphopenia on the background of leucopenia, decreased reticulocyte count and platelets;
- in the bone marrow develops devastation (aplasia).

3) ***Phase height of disease***: a sharp deterioration of health. Duration phase from several days to 2–3 weeks. When irradiated over 2.5 Gy possible death.

Manifestations:

- weakness, increased body temperature;
- appear bleeding and hemorrhage in the skin, mucous membranes, gastrointestinal tract, brain, heart and lungs;
- reduced body weight;
- hypoproteinemia, hypoalbuminemia, elevated levels of residual nitrogen and reduction of chlorides;
- infection a result of decrease immunity;
- peripheral blood: leukopenia, thrombocytopenia, anemia, ESR increase;
- bone marrow: picture of devastation with initial signs of recovery.

4) ***Recovery phase***: gradual normalization of disturbed functions. Duration 3–6 months, in severe cases, 1–3 years, can become chronic.

Manifestations:

- general condition significantly improved;
- normal temperature;
- disappear diarrhea and hemorrhagic manifestations;

• after 2–5 months normalizes the function of sweat and sebaceous glands, hair growth renewed;

• Peripheral blood: recovered blood counts and metabolism.

Intestinal form

10–20 Gy, death at 7–10 days.

Manifestations: nausea, vomiting, bloody diarrhea, increased body t, there may be full pseudoileus and bloating. Develop hemorrhages and deep leukopenia with a complete lack of lymphocytes, the picture of sepsis. Death is a result of dehydration, accompanied by loss of electrolytes and protein, shock.

Toxemic form

20–80 Gy, death at 4–7 days.

Manifestations: hemodynamic instability in the intestine and liver, vascular paresis, tachycardia, hemorrhage, severe intoxication and meningeal symptoms, oliguria and hyperasotemia.

Cerebral form

More than 80 Gy, death after 1–3 days, and during the actual exposure – «death under the ray».

Manifestations: convulsively paralytic syndrome, blood circulation, lymph circulation in the central nervous system, vascular tone and thermoregulation, digestive and urinary systems, a progressive decrease in blood pressure. Cause of death — cell death of the cerebral cortex, neurons of hypothalamic nuclei.

Chronic radiation sickness (CRS)

CRS caused by prolonged exposure of the organism in small doses after a total dose of 0.7–1 Gy.

Forms of CRS:

1. Total external irradiation or diffuse distribution of isotopes causes a form with detailed clinical syndrome.

2. Clinical syndrome with lesion of certain organs and systems from internal and external irradiation.

Period of development:

1. Initial period — unstable leukopenia, asthenia signs, vegetative-vascular instability.

2. Extended period — lack of physiological regeneration and functional changes in the nervous and cardiovascular systems.

3. Recovery period, the prevalence of reparative processes.

Features: the gradual development of a long wavy current.

Severity:

• light (grade I): poorly expressed neuro-regulatory disorders of organs and

systems, unstable moderate leukopenia and thrombocytopenia;

• moderate (grade II): add functional impairment of NS, cardio-vascular system and gastrointestinal tract, and progress leukopenia lymphopenia, thrombocytopenia, hypoplasia of bone marrow;

• severe (grade III): atrophic processes in the gastrointestinal mucosa, add infectious-septic complications, anemia, severe hypoplasia of hematopoiesis, hemorrhagic syndrome and circulatory disorders.

Radiation sickness from internal exposure

Radiation sickness from internal exposure — an independent nosological form, a chronic disease caused by the gradual accumulation of radioactive elements are α, β, γ emitters.

There are three main types of radionuclides distribution: skeletal, reticuloendothelial and diffuse.

By the skeletal type distributed mainly radionuclides of alkaline earth group elements (calcium, strontium, barium, radium) accumulated in the mineral part of the skeleton.

Reticuloendothelial type of distribution is typical for nuclides of rare earth elements — zinc, thorium, americium, transuranic elements.

The diffuse type distributed alkali elements — potassium, sodium, cesium, rubidium, hydrogen nuclides.

«Organotropic» radionuclides selectively accumulate in certain organs (such as isotopes of iodine concentrates in the thyroid gland, in the kidney — uranium, radioactive lead and beryllium).

Manifestations: syndromes of general and local lesions in areas dominating penetration of radioactive substances in the body, their removal and accumulation.

PATHOGENIC EFFECTS ON THE BODY OF CHEMICAL FACTORS

Damaging effect on the body of chemical substances and compounds (poisons) found both in industry (industrial poisoning) and at home (household poisoning).

Arising under the influence of diverse chemical the biological effects can be classified as follows:

• local irritant (damaging) effects;

• total specific (toxic) effects (eg, the effect of botulinum toxin on nerve terminals in the muscles);

• general non-specific action (eg, the occurrence of hypoxia of many tissues, organs and systems with damaged lungs, heart, etc.);

• mutagenic effects;

• carcinogenic effect;

• teratogenic effects.

The main way of chemicals penetration are: through the skin barrier, through the respiratory tract, per os, parenteral.

Features of the toxic effect of chemicals determined by:

• species (structure);

• ability to form complexes;

• dose;

• duration of action;

• features of metabolism;

• place of absorption, accumulation and excretion;

• ability to provide local and / or systemic damaging effect, specific and / or non-specific;

• ability to provide local damage to cellular and tissue structures, or cause systemic changes.

BIOLOGICAL FACTORS INFECTIOUS PROCESS

Infectious process — developed in the course of evolution typical pathological process that occurs in the interaction of microorganism with the macroorganism, under adverse conditions, external and / or internal environments.

The main types of infectious process:

• ***bacteremia, viremia*** — the presence in the blood of bacteria and / or viruses with no evidence of their reproduction;

• ***sepsis*** — severe generalized form of infectious process caused by the multiplication of microorganisms in the blood (sometimes in other body fluids);

• ***septicopyemia*** — infectious process characterized by the development of secondary purulent lesions in various organs and tissues in patients with sepsis;

• ***mixed infection*** — infectious process caused simultaneously by two or more agents;

• ***reinfection*** — the recurrence of infectious process caused by the same organism after the patient's recovery;

• ***superinfection*** — re-infection by the same pathogen until the period of recovery;

• ***secondary infection*** — infection process that develops against the backdrop of existing (primary) infectious disease, caused by other microorganisms.

Character and severity of infectious process depends on the following factors:

• basic properties of the infectious agent;

• pathogenicity and virulence;

• features of the interaction of microorganisms and macroorganism;

• tropism of microorganisms to certain tissues of macroorganism;

• initial state macroorganism (especially the immune system);

• condition of the environment.

PSYCHOGENIC PATHOGENIC FACTORS IATROGENIC DISEASES

There are the following types of psychosomatic and somatopsychic disorders:

• ***Psychosomatic disorders*** — somatic disorders arising from impact of the complex of psychosocial factors (hypertension, coronary artery disease, gastric and duodenal ulcer, neurodermatitis).

• ***Nosogenic disorders*** — pathological reactions to stressful factors of the disease and its consequences.

• ***Iatrogenic disease.***

• ***Somatogenic disorders*** — mental disorders that develop as a result of neurotoxic effects somatic disease.

• ***Mental disorders complicating somatic pathology*** (eg, alcoholism, eating disorders).

• ***Somatoform disorders*** — mental disorders manifested by somatic complaints that are not objectively confirm the presence of somatic disease.

• ***Dissociative (conversion) disorders*** of movement and sensation — mental disorders manifest violation of motor and sensory functions that mimic organic pathology and cannot be explained by structural damage to the nervous system.

Common signs of psychosomatic disorders:

• chronic course;

• significant role of mental stress in manifestation, development and course of the disease;

• personal characteristics of the patient, determining emotional lability, difficulties in interpersonal relationships, and others;

• lack effectiveness of traditional methods of somatic pathology treatment;

• positive effect of pharmacotherapy and psychotherapy.

Iatrogenic diseases

Iatrogenesis — (from the Greek iatros — doctor; genesis — origin) — is any unwanted or adverse effects of preventive, diagnostic and therapeutic interventions or procedures that lead to disturbances of body functions, controlling habitual activity, disability or death; complications of medical interventions, which developed as a result of the error and correct doctor's actions (according to ICD-10).

Classification by iatrogenic A.P. Krasilnikov:

1. Psychogenic «diseases of the word» — careless remarks and misunderstood of medical worker about the health, insight the patient's own medical history and special medical literature, listening to public lectures.

2. Drugs: pharmacological negative effects (for example, a hypoglycaemic shock after insulin injection); drug intoxication, including toxic, mutagenic, oncogenic, teratogenic, embryotoxic, immunosuppressive effect; drug allergies,

drug intolerance of pseudoallergic nature; drug dependency; drug psychoses; incompatibility of simultaneously administered drugs; vaccination reactions and complications.

3. Traumatic: surgical manipulation and occasional medical injuries, burns (radiation, thermal, chemical), and consequences of injuries.

4. Infectious: intrahospital (hospital, nosocomial) infections, abscess formation with intramuscular injections, etc.

5. Mixed.

THE ROLE OF HEREDITY IN PATHOLOGY. PATHOLOGICAL PHYSIOLOGY OF INTRAUTERINE PERIOD

HEREDITARY DISEASES

Genetically determined diseases — the diseases, which are caused by genetic factors. Their transmission to descendants may be limited in the case of impaired reproductive capability of the patient.

Hereditary diseases — are diseases transmitted to the next generations which are based on structural changes in DNA.

Congenital diseases — disease and developmental abnormalities which are manifested just after the birth. May be hereditary and non-hereditary.

The etiology of hereditary diseases

Causes of hereditary diseases are factors which may cause mutation — mutagens. A risk factor for the emergence and implementation of the mutation action is the failure of repair systems (genetically determined or acquired) or a violation of the regulation of gene activity (epigenetic mechanisms).

Mutations

Mutation — is a strong spasmodic change of genetic apparatus (not connected with cell division or usual recombination of chromosomes) and is a material basis of genetically determined diseases.

Etiology

Mutagens — are etiological factors, which cause a mutation.

By etiology distinguish spontaneous and induced mutations.

Spontaneous (or natural) are called mutations arising spontaneously due to natural conditions of the external and internal environment. For example hormonal factors (endocrine diseases mother diabetic embryo- and fetopathy); somatic maternal disease (cardiovascular, respiratory, digestive, urinary and other systems); endogenous chemical mutagens which are formed in the body during metabolism — peroxides and free radicals (automutagenes). «Overripeness» of germ cells: are basis on processes that lead to desynchronization of ovulation and fertilization. Age of parents: it is known that mothers aged 35 years and under 17 years has increased frequency of gametic genomic mutations. There is a relationship between the father's age older than 40 years and the frequency of monogenic diseases.

Induced mutation — a mutation caused by special direction of the impact of physical (ionizing radiation), chemical (pesticides, industrial connections (formaldehyde, benzol and other); drugs (cytostatic drug, connections of mercury, arsenic and other)) and biological mutagens (DNA and RNA viruses: measles, chickenpox, mumps, infectious mononucleosis, rubella).

Feature of chemical mutagens consists in that their effect is dependent in dose and cell cycle stage. The higher dose of the mutagen, the stronger the mutagenic effect. The most sensitive to mutagens step of DNA synthesis (S-phase).

Classification of mutation

By etiology: spontaneous and induced.

By type of mutated cells: gametic, somatic, mosaic.

By value: favourable, pathogenic, neutral.

By levels of genetic material organization: gene, chromosome, genome.

Gene mutations

Gene mutations (point mutations) — mutation involving a change in a single nucleotide base within a gene.

1. By the nature of the changes:

- deletion is a loss of segment of DNA;
- duplication is doubling of segment of DNA;
- inversions are a turn of segment of DNA on 180º;
- insertion is an insertion of additional segment of DNA;

• transversion is replacement in DNA of purine basis on pyrimidine or vice versa.

2. On the consequences: neutral, regulatory, dynamic, missense mutations, nonsense mutations.

Missense mutation — altering the coding sequence resulting in substitution of one functional codon for another.

Nonsense mutation — altered DNA codes for a stop codon that causes premature termination of protein synthesis.

Chromosomal mutations are structural alterations of chromosomes:

- deletion is a loss of area of chromosome;
- duplication is doubling of separate area of chromosome;
- inversions are a turn of separate areas of chromosome on 180º;
- translocation is a change of position.

Genome mutation (polyploidy, aneuploidy) are changing the number of the structurally unchanged chromosomes in a genome.

Polyploidy — is multiplying the complete set of chromosomes multiple of the haploid (3n, 4n, 5n). Causes of polyploidy are double fertilization or absence of the 1st meiotic division. Result in the lack of viability of organism and are reason of spontaneous abortions and stillborn.

Aneuploidy — a change of amount of chromosomes is in one or a few pair not-multiple haploid (2n + 1, 2n-1). It is most widespread class of mutations, the basic forms of chromosomal illnesses.

Monosomy — the presence of only one of the two homologous chromosomes (Turner syndrome).

Trisomy — presence of three gomologic chromosomes in cariotype (21 — Down syndrome, 13 — Patau syndrome, 18 — Edwards syndrome).

Antimutagens

Antimutagens — a substance capable of suppressing spontaneous and inducing mutagenesis.

Antimutational mechanisms

1. Neutralization mutagen prior to contact with the DNA (e.g. by increasing the activity of enzymes detoxifying mutagens).

2. Enhancing the stability of DNA to mutagens (duplication of the structural elements of the genome, the matrix principle of biosynthesis, the ability to repair, regulation of gene activity.

3. Prevents the conversion of indirect mutagens in the true.

Examples of antimutagens: amino acids (arginine, histidine, methionine), enzyme (peroxidase, NADPH oxidase, catalase, glutamineperoxidase), some medicaments (sulfonamides, interferon, antioxidants), Vitamins E, C, A, K.

Classification of hereditary diseases

There are hereditary, congenital, familial and sporadic diseases.

Congenital diseases — are conditions that already exist at birth. Congenital diseases may be caused by hereditary and non-hereditary factors (birth defects that occur due to teratogenic effects of external factors, congenital infections). At the same time, not all hereditary diseases are congenital.

Family diseases — are diseases among family members (including family members from two to several generations). They can be hereditary and non-hereditary.

Working classification of hereditary diseases (E. D. Goldberg, 2009):

- single gene diseases;
- chromosome diseases;
- multifactorial diseases;
- genetic diseases of somatic cells;
- diseases exhibited atypical inheritance.

Single gene disorders — caused by a mutation of a single gene.

Chromosomal diseases — caused by chromosome and genome mutations.

Multifactorial diseases — a hereditary predisposition.

Diseases exhibited atypical inheritance — caused by such phenomena as mitochondrial genetics, genomic imprinting, uniparental disomy, triplet repeat expansion.

Mitochondrial disease —— a heterogeneous group of diseases characterized by genetic and structural-biochemical defects of mitochondria, violation of tissue respiration. The main causes of mitochondrial disease include mutations of mitochondrial genes, nDNA gene mutation required for mitochondria, violation of intergenomic interaction, which may cause a phenomenon of depletion (depletion of mtDNA copy number), as mtDNA synthesis is under the control of nDNA.

Genomic imprinting refers to an epigenetic mark that distinguishes parental alleles and results in a monoallelic, parental-specific expression pattern in mammals. Genomic imprinting also subjects mammals to a greater genomic risk because a mutation in one allele (either genetic or epigenetic) can result in the absence of one or more gene products. The most well-known conditions include Prader-Willi syndrome, Angelman syndrome, Beckwith-Wiedemann syndrome, Silver-Russell syndrome.

Uniparental disomy occurs when a person receives two copies of a chromosome, or part of a chromosome, from one parent and no copies from the other parent.

Triplet repeat expansion occurs during multiple stages of human development in different cell types, and is sensitive to the gender of the parent who transmits the repeats. As the triplet repeat expands with successive generations there is increasing dysfunction of the gene and worsening of the clinical symptoms. An example is Huntington disease, fragile-X syndrome.

Monogenic diseases — are determined by a single mutant gene and occur in a particular action (often specific) and obligatory environmental factor (pollution physical and chemical factors, nutrients, supplements, drugs). Examples: lactose intolerance, lack of α1-antitrypsin.

The clinical picture of a specific monogenic hereditary disease can vary. Genetic causes of the polymorphism can be the phenomenon of interaction of main genes and modifiers genes, as environmental factors.

Genetic heterogeneity (genocopy) can be determined by mutations in different genes (interloci heterogeneity) or multiple allelism of individual particular gene (intralocus heterogeneity). Interloci heterogeneity is known for hereditary forms of epilepsy (about 20 genes including mitochondrial). Along with genocopies can occur phenocopies of gene diseases.

Phenocopies — those diseases, which are caused by environmental factors and have a clinical picture similar to known hereditary diseases.

The opposite condition, when the mutant genotype of the individual do not develop the disease as a result of environmental influences (drugs, diet, etc.), is defined as ***normocopying***.

The phenomenons of gene expression variability are including penetrance and expressivity.

Penetrance — is the probability of phenotypic manifestations of the abnormal gene, the ability of the gene to be realized in a sign. It shows the percentage of the abnormal gene carriers reveals a pathological phenotype. Incomplete penetrance is determined by genotypic environment of the gene, ie, a person can be the abnormal gene carrier, but the gene is not manifested due to the modifying effect of other genes.

Expressiveness — a severity of manifestations of the abnormal gene. For example, in six-fingered the sixth finger may be short as a weak manifestation of inherited sign.

Polygenic disease — are determined by many genesб the result of interaction of normal or modified (mutated genes), each of which alone does not lead to the development of the disease). Individual becomes ill by polygenic disease when the «threshold of the disease».

Single gene disorders

Autosomal Dominant Disorders

Marfan syndrome is an autosomal dominant connective tissue disorder involving the cardiovascular, skeletal and ocular systems, the integument, lungs and dura. In 90–93 % of cases is caused by mutations in FBN1. Main manifestations include aortic aneurysm and dissection, ocular lens dislocation and long bone overgrowth, usually associated with normal intelligence.

Autosomal Recessive Disorders

Phenylketonuria (PKU) is an autosomal recessive metabolic genetic disorder characterized by a mutation in the gene for the hepatic enzyme phenylalanine hydroxylase (PAH). This enzyme is catalyzes the conversion of phenylalanine to tyrosine. The absence of PAH leads to accumulation of phenylalanine and tyrosine to become an essential amino acid. Clinical manifestations are postnatal growth retardation, moderate to severe mental retardation, recurrent seizures, hypopigmentation, and eczematous skin rashes.

X-Linked Disorders

Vitamin D-resistant rickets — is X-linked dominant caused by mutations in phosphate regulating endopeptidase homolog X-linked, FGF23, and dentin matrix acidic phosphoprotein gene respectively. Typical signs are observed from the first months of life: radiological signs of defective mineralization on cartilage growth plates (rickets) and bones (osteomalacia) and alterations of the phosphocalcic homeostasis in spite of a satisfactory vitamin D status. The clinical phenotype combines bone deformities, mainly at the lower limbs.

Hemophilia A — X-linked recessive disorders with a deficiency of factor VIII (antihemophilic globulin). It is characterized by hematoma type of bleeding. Recurrent bleeding in the large joints (hemarthrosis) lead to ankylosis. Large inter- and intramuscular, retroperitoneal hematoma with subsequent destruction of the soft tissues, severe and frequent spontaneous bleeding, persistent recurrent gastrointestinal bleeding and kidney.

Chromosomal disease

Cri du chat syndrome — chromosome 5p deletion syndrome, 5p minus syndrome or Lejeune's syndrome, is a rare genetic disorder due to a missing part of chromosome 5. The syndrome gets its name from the characteristic cry of affected infants, which is similar to that of a meowing kitten, due to problems with the larynx and nervous system. About 1/3 of children lose the cry by age 2. Other symptoms may include feeding problems (due to difficulty swallowing and sucking); low birth weight and poor growth, growth retardation; microcephaly; severe cognitive, speech, and motor delays, behavioral problems such as hyperactivity, aggression, tantrums, and repetitive movements.

Down syndrome

Down syndrome is the most common of the chromosomal disorders. Approximately 95 % of affected individuals have trisomy 21 (due to nondisjunction), 4 % of cases robertsonian translocation t(14; 21)(q10; q10), 1 % of cases — mosaicism. Manifestations: mental retardation, epicanthic folds, flat facial profile, macroglossia, Simian crease, combined atrial and ventricular septal defects (major factor affecting survival in early childhood). Persons have increased risk of Hirschsprung's disease, duodenal atresia, leukemia, Alzheimer's disease

by 35 years of age in most cases. All males are sterility; females have a 50 % chance of having a child with Down syndrome.

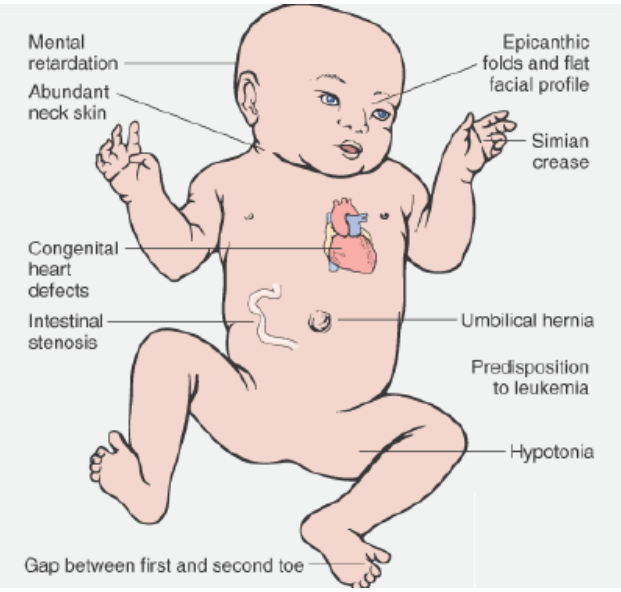

Figure 3 — Trisomy 21: Down syndrome (Kumar V., 2005)

Edwards syndrome

More than half born die by 2 months of age, survival beyond 1 year is rare. Trisomy 18 is due to non-disjunction in approximately 80 % of cases, mosaicism in 10 %, translocation in 5 %, and trisomy 18 plus sex chromosomal aneuploidy in 5 %. Manifestations: craniofacial dysplasia (micrognathia, short neck, low-set malformed ears, unilateral cleft lip and palate, dolichocephaly — long narrow cranium); skeletal malformations (radial aplasia, camptodactyly (crossed, flexed fingers), foreshortened dorsiflexed great toe); obligatory cardiopathy (ventricular septum defect and valvular defects); intestinal and renal malformations.

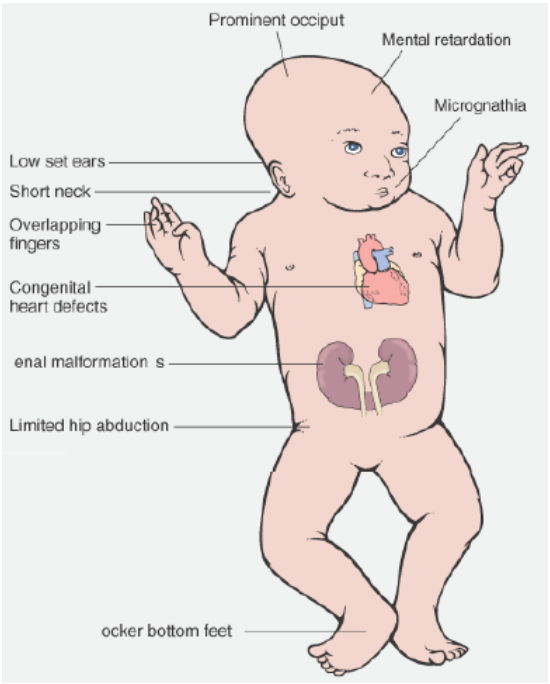

Figure 4 — Trisomy 18: Edwards syndrome (Kumar V., 2005)

Patau syndrome

In most cases is found trisomy 13 caused by non-disjunction, in approximately 20 % of cases translocation of chromosomes 13 and 14, mosaicism is found in less than 10 %. Clinical signs: facial dysplasia (bilateral cleft lip and palate, microphthalmos, coloboma, microtia, hypertelorism). Cerebral symptoms (rhinencephalon (absence of the olfactory bulb) holoprosencephaly (fusion of the frontal lobes)), internal malformations of kidneys, urogenital tract and heart, polydactyly (supernumerary fingers), rocker-bottom feet.

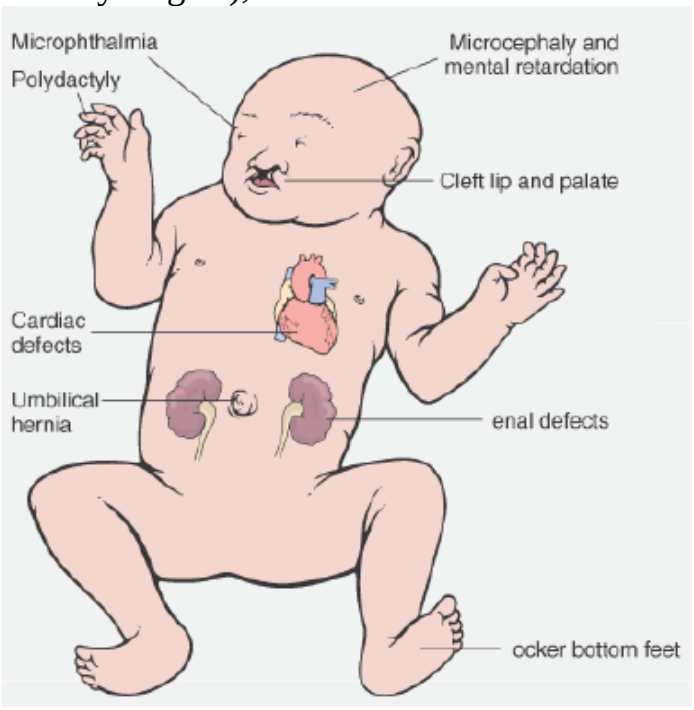

Figure 5 — Trisomy 13: Patau syndrome (Kumar V., 2005)

Klinefelter syndrome

Around 80 % are 47,XXY, 10 % are mosaic, and the remainder is 48,XXYY, 48,XXXY, 49,XXXYY, and 49,XXXXY. Manifestations: patients are phenotypic males, sex chromatin-positive, may be eunuchoid; typically hypospadia and small testes with tubular dysgenesis, patients are sterile due to azoospermia or oligospermia.

Turner syndrome

Turner syndrome is a monosomy of sex chromosomes. 45, X/O (usually is nondisjunction of the paternal gamete). Clinical signs: swelling of the hands and feet at birth, skin fold in the neck, short stature (140 cm), patients are phenotypic females with rudimentary ovaries, leading to primary amenorrhea (infertility) failure of breast development, and a low hairline on the back of the neck; congenital heart disease, sometimes reduced mental development.

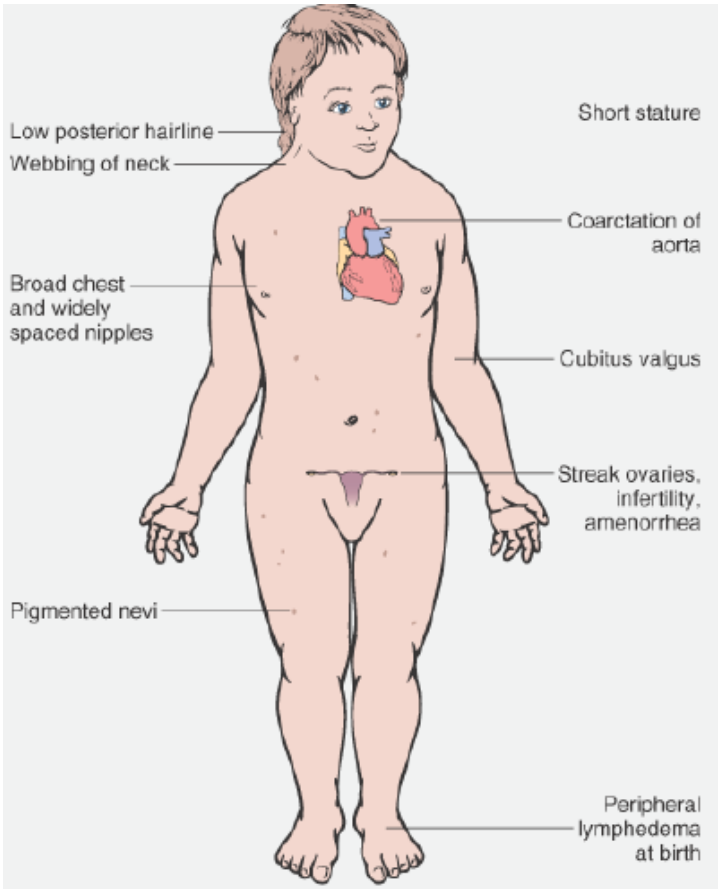

Figure 6 — Turner syndrome (Kumar V., 2005)

The pathogenesis of genetic diseases

The pathogenesis of genetic diseases associated with the primary effect of the mutant allele. The pathogenesis of genetic diseases can be summarized as follows: the mutant allele — a pathological primary product (qualitative or quantitative) — a chain of subsequent biochemical processes — cells — organs — body.

The primary effect of any (nuclear and mitochondrial) mutant alleles can be shown in four variants:

1) quantify excessive synthesis of the polypeptide chain (protein);

2) synthesis of abnormal primary structure of the polypeptide chain (protein);

3) absence of synthesis of the polypeptide chain (protein);

4) quantitatively insufficient synthesis of the polypeptide chain (protein).

In an excess amount of produced protein the pathogenesis of the disease will generally is caused by hyperproduction of gene activity. Example: at primary hemochromatosis is synthesized excessive amount of globin, resulting in overload of red blood cells by hemoglobin and, respectively, by iron → increased blood clotting, developed hemosiderosis of parenchymal organs.

Abnormal protein leads to functional disturbances in the system. Example: sickle cell anemia — replacement of hydrophilic glutamic acid to hydrophobic valine in the globin structure alter the functional properties of hemoglobin (reduced solubility, increased polymerization) → it crystallizes in insufficient oxygen → erythrocytes become sickle-shaped and are aggregate thrombosing capillaries etc.

Absence of production of the primary product is expressed in the accumulation of toxic precursor-products. For example, phenylketonuria.

Insufficient production of the normal primary product. Example: hypocatalasemia (low levels of catalase in blood) is accompanied by recurrent infections, ulceration of gums and oral mucosa.

Mutations in the genes of the morphogenetic controlling lead to congenital malformations (polydactyly, Holt–Oram syndrome, Laurence–Moon syndrome). The initial link of congenital malformations is associated with impaired cell differentiation. Programmed in the genome, cell differentiation, and then organogenesis is implemented by changing the activation and inactivation of certain genes in a strictly limited time intervals (relative to ontogenesis). If the primary product of the morphogenetic gene is abnormal, do not follow the differentiation of cells that necessary for further proper development of organ.

Pathogenesis of congenital malformations

Ways of teratogenic effects realization. All kinds of damaging effects by primary mechanism can be divided into two groups:

1) genetic injury;

2) epigenetic effects through non-genetic molecular structure of cells, ie, all types of violations of the metabolism dynamics or molecular structures on post-genetic level.

All types primary genetic and epigenetic disorders in teratogenesis realized in one of the six stages of germ development:

1) violation of cell viability;

2) violation of determination;

3) cell proliferative disorder;

4) violation of differentiation;

5) violation of organization and intercellular interactions;

6) violation of migration of cells and cell layers.

It is assumed, that the primary molecular mechanism of teratogen action completely determines cell stage at which occurs realization of damage.

Critical periods of development

Critical periods of development — are periods of heightened sensitivity of embryos to the action of endogenous and exogenous damaging factors. Critical periods coincide with the periods of the most intensive organs formation and mainly associated with the periodicity of manifestation of morphological nuclear activity.

There are three groups of the external environment actions:

1) damaging effects resulting in death or pathology;

2) modifying effects causing non-pathological abnormalities — mutations;

3) determinate action of the environment, provide normal development and influence on the body resistance (oxygen supply, power, temperature, etc.).

Critical periods are associated with the following events:

1. Determination of new phases of development (activation of new part of genetic information, which ensures the development of organism to next step).

2. Change the type of trophic and intensification of metabolism.

3. Reduction of regulatory activity.

4. Slowing process of growth structures, leading to a transition to a new stage of development.

Critical periods are characterized high metabolic activity and promoted sensitiveness to the action of damaging factors.

Congenital malformations associated with critical periods of development are due to:

1) violation of the cell division (growth disturbances of individual germs);

2) violations of cell migration (change of the spatial relationship of organs and tissues);

3) abnormal lines of cell and tissue differentiation (appearance of abnormal structures or atypical ratio of normal);

4) break of correlations between cellular components, the rudiments of organs and tissues;

5) changes in the physiological processes of cell death (lack of «reverse development» of the embryo provisory structures);

6) violation of metabolic processes (very significant, but may pass without the expressed morphological violations).

In human ontogenesis are several critical periods of development:

1. Development of germ cells (ovogenesis and spermatogenesis). Genome mutations can cause the formation of defects and make development impossible.

2. Fertilization (1^{st} day). This period may be violation of cytoplasm segregation, of blastomeres determination and their subsequent differentiation.

3. Implantation (7–8th day of embryogenesis). There is a change on histiotrophic nutrition. Die about 30 % of embryos. In this period the axial buds and ovoimplantation is developed. The process of implantation can be violated due to:

• abnormalities of uterus structure of (infantilism, bicornuate or arcuate uterus, walls in uterus);

• endometrial trauma (the inner layer of uterus) as a result of induced abortion, and inflammatory diseases (chronic endometritis);

• metrofibroma;

• uterine scar after cesarean section and other operations.

Stress, emotions, heavy physical activity by pregnant can blocked implantation.

4. Formation of placenta (3–12th week). Changing type of nutrition to hematotrophic. Die about 25 % of the embryos.

5. Histogenesis and organogenesis (from 3rd week to 8–9th), stage of intensive growth of brain (15–20th week). Hazards during this period can cause a variety of abnormalities (cardiovascular, respiratory and other systems), which is associated with heterochronic anlage. The fetus take new reflexes, formed anlage of cerebral cortex, forming medullary hematopoiesis, activates metabolism. In this stage can be malformations of central nervous system. However, brain, endocrine, and reproductive systems of the fetus can be damaged at any stage of development.

6. Formation of main functional systems (20–24th week) — damage arising due to the fact that material of many organs is in determination of cell differentiation. At this time, actively growing pregnant uterus. Hazards include abnormalities of placenta location, such as low-lying.

7. Perinatal period — from full 22 weeks (154 days) of fetal life to 7 full days after birth. Dangerous for the fetus are the last weeks of fetal life, when there is a dissociation between the relatively rapid increase in fetal weight and stop of placenta growth. Disorders of pregnancy can cause by complications such as recurrent threatened miscarriage, late gestoses, placental insufficiency, and placental abruption.

8. Newborn period.

In pathophysiology are marked 5 critical periods:

1. First week of pregnancy — pre-implantation period of embryogenesis or tube.

2. From 3 to 9 weeks — a period of great organogenesis.

3. 3 months pregnant, during which the formation of the placenta are end and its function is characterized by a high activity.

4. 20–24 weeks time of formation of fetal functional systems.

5. From full 22 weeks, when there is dissociation between the relatively rapid increasing a fetal weight and stopping of placenta growth, to the first 8 day after birth — period of adaptation to new external environment, with which it occurs after birth.

Typical manifestations of antenatal pathology are congenital malformations — rough anatomical changes in organs and tissues (or organ systems), leading to dysfunctions.

Depending on the timing of fetal pathology occurrence distinguish the following its forms: gametopathy and kymatopathy (blastopathy, embryopathy, fetopathy).

Prenatal period is the period of fetus development beginning with the moment of fertilization to the birth of the child. Normally, prenatal period lasts for 40 weeks (280 days). Born a child earlier 38th week is premature; if more than 42 weeks — overmature.

Prenatal period is subdivided into 2 periods:

• progenesis (gametogenesis) — period of maturation of ovum and sperm;

• kymatogenesis — period of development fertilized ovum.

There are several periods in the kymatogenesis:

• blastogenesis — from the 1st to 15th day;

• embryogenesis — from the 16th day to full 8 week (56 days);

• fetogenesis — from 9 to 40 week.

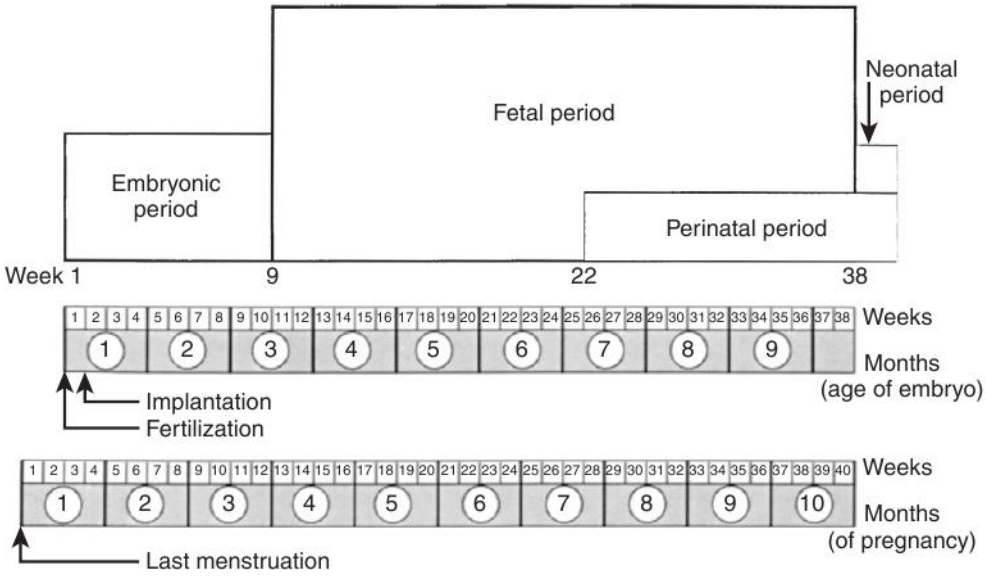

Figure 7 — Human development (From R.A. Polin et al., 2011)

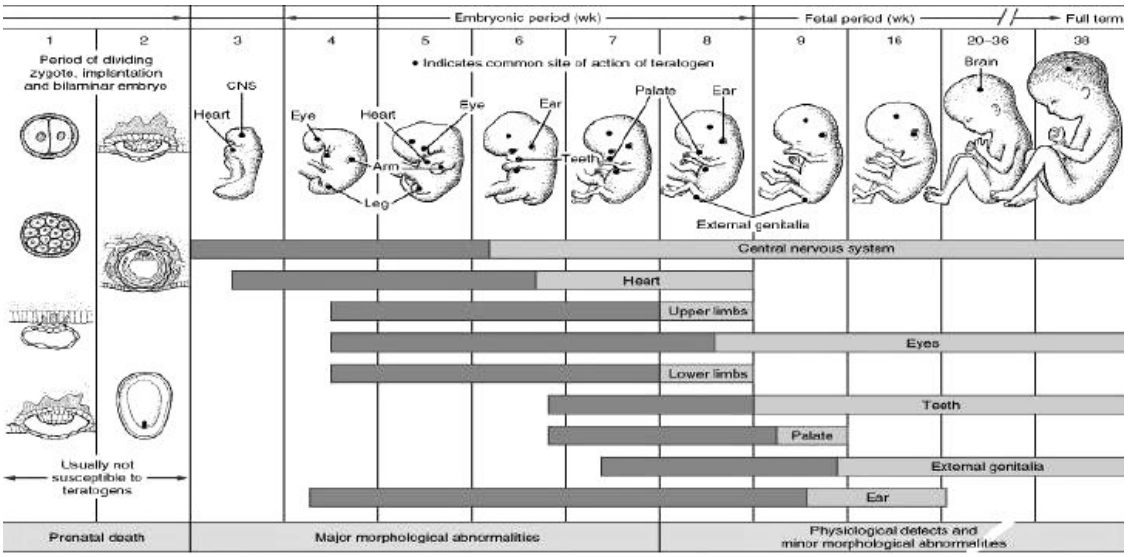

Figure 8 — Schematic illustration of the sensitive or critical periods in prenatal development (From K.L. Moore, 1977)

Gametopathy

It is all kinds of damage to the male and female gametes (ovum and sperm) arising during ovo- and spermatogenesis before fertilization. Gametopathy caused mainly by mutations. Heavy damage of gametes can lead to their death, infertility and miscarriages. Gamete with a defect gene or genes may cause hereditary congenital malformations.

Blastopathy

The main outcomes blastopaty are:

• empty embryo sacs (they are formed due to aplasia or early death embryoblast with subsequent resorption);

• hypoplasia and aplasia extraembryonic organs (amnion, yolk sac);

• twin defects (symmetric and asymmetric, that is, in whole or in part are not separated twins);

• ectopic pregnancy (implantation of the fertilized egg in ovary, fallopian tube, rudimentary uterine horn and internal os of uterus) or violation of the implantation depth (surface, unusually deep).

Most of the embryos, damaged by blastopaty, are eliminated by spontaneous abortion. Twin defects occur as conjoined twins.

Embryopathy

Embryopathy is characterized by impaired formation of organs. It is lead to death of embryo or congenital malformations. The degree of severity of birth defects varies from slight variations in structure of organs to severe changes in many organs, which are fatal.

Microanomalies of development (stigma of dysmorphogenesis) – are morphological changes not accompanied by dysfunction. For example: telangiectasia, freckle, low growth of hair on the forehead or neck deformation ears, mongoloid and antimongoloid slant, epicanthus, arachnodactylia and others.

Congenital malformations include developmental disorders:

• aplasia — complete congenital absence of an organ or its part;

• agenesis — complete congenital absence of an organ and its rudiment;

• hypoplasia — underdevelopment of organ, manifested by deficit of relative weight or size of the organ;

• hypertrophy (hyperplasia) — increase in relative weight (or size) of the organ by increasing the number (hyperplasia) or volume (hypertrophy) of the cells;

• atresia — the complete absence of a channel or a natural orifice;

• stenosis — narrowing channel or orifice;

• non-separation of limbs or their parts, starting with the Greek prefix syn, sym (together), for example, syndactyly — non-separation of fingers;

• ectopy — displacement of organ, its location in an unusual place (for example, location of the kidney in the pelvis, location of the heart out of the chest);

• persistence — saving embryonic structures that normally disappear to a certain period of development. One of the forms of persistence is dysraphia (arrhaphia) — cleft of embryonic fissure (cleft lip, palate, spine, urethra);

• heterotopia — the presence of cells, tissues or whole parts of organ in another organ or in those areas of the organ where they should not be (for example, areas of the pancreas in Meckel's diverticulum);

• hamartia (from the Greek. gamartus — error) — incorrect ratio of tissues, accompanied by the tumorous growth.

Fetopathy

Fetopathy has following features:

1. Rare birth defects in humans caused by teratogens in the fetal period.

2. Any damage in this period entails development of defects at tissue level. In this case, there may be a wrong ratio of tissues in organ or delay of their maturation.

3. The presence of predominantly generalized forms of infections. Characterized by multiple foci, mainly alterative inflammation in parenchymal organs, or the presence of generalized granulomatosis (eg, congenital listeriosis).

4. Infectious and toxic processes are accompanied by severe hemorrhagic diathesis (petechiae on skin and mucous membranes, bleeding in internal organs).

5. A delay of involution and excessive proliferation of cells in the foci of extramedullary hematopoiesis.

6. Hypertrophy and tissue regeneration is mainly due to hyperplasia of mesenchymal elements, which leads to excessive development of connective tissue (eg, in mucoviscidosis — accrementition of elastic and fibrous tissue in pancreas).

Methods of prenatal diagnosis and prevention of congenital diseases

Preventive measures by means medical genetic counseling (MGC), in which the patients or their relatives receive information about hereditary diseases, consequences, probability of inheritance, as well as methods of prevention and treatment.

Periconceptional prevention is aimed at providing optimal conditions for germ cell maturation, their fertilization, formation and implantation of the zygote, early development of the fetus.

It includes:

• MGC, including the study of genealogy, determination of karyotype and leukocyte antigens at spouses.

• Diagnosis of viral and bacterial infections and their timely treatment.

• Exclusion of occupational hazards.

• Diet therapy and vitamin therapy, folic acid (up to 4 mg per day).

Prenatal diagnosis evaluates the fetal condition. There are indirect and direct methods.

Indirect methods (examination of pregnant women) include:

- Obstetrics-gynecology.
- Medical-genetic (genealogical, cytogenetic, molecular-biological).
- Bacteriological and serological.
- Biochemical (tests were screened for alpha-fetoprotein, human chorionic gonadotropin, estriol et al.).

Direct methods (examination of the fetus) are divided into non-invasive and invasive.

The main non-invasive methods is the ultrasound examination (87 % accuracy). Ultrasound screening is carried out in order at least three times during pregnancy: 10–14 weeks of pregnancy — estimated gross malformations, fetal nuchal translucency (3 mm or more — an important marker of chromosomal aberrations in the fetus); 18–21 weeks — identify congenital abnormalities, oligohydramnios and polyhydramnios, fetal hydrops, ventriculomegaly, placental insufficiency etc .; 32–35 weeks — the detection of late manifestations of congenital malformations and functional assessment of the fetus.

Invasive methods include:

- Chorion biopsy and biopsy of the placenta (10–14th week of pregnancy, or 20–22 weeks) performed transabdominal or transcervically — aspiration of chorionic tissue or placenta with a needle under ultrasound guidance.
- Amniocentesis transabdominal (optimally 15–18 weeks) — puncture of the amniotic cavity to obtain amniotic fluid and contained therein fetal cells.
- Cordocentesis (optimally 22–24 weeks) — is a procedure for blood collection from a vein in the umbilical cord of the fetus under ultrasound guidance.
- Fetoscopy — examination of the fetus through an endoscope inserted transabdominal into the cavity of the amnion, biopsy of fetal tissues (liver, spleen, skin, muscle, etc.).

Principles of treatment of congenital diseases.

Common approaches to the treatment of hereditary diseases are similar to the approaches to the treatment of diseases of any etiology:

- symptomatic;
- pathogenetic;
- etiotropic.

Applied to hereditary diseases in a separate group can be identified surgical methods, because sometimes they act as symptomatic therapy, sometimes — pathogenic, sometimes — and the one and the other.

Pathogenetic treatment

- Correction of the exchange at a substrate level (for phenylketonuria prescribes a diet low in phenylalanine).

• Correction of the exchange at the gene product level (compensation product (or adding) for violations caused by abnormal enzyme that does not provide the production of the product, or other biologically active compounds, eg, treatment by thyroxine in hypothyroidism).

• Correction of the exchange at the enzymes level (used for the correction of inherited metabolic diseases in which known functionally abnormal enzyme (enzymopathies)).

• Modifying enzyme activity. Induction of enzyme synthesis can be used to enhance residual enzyme activity by administering drugs. For example, phenobarbital and related drugs stimulate the function of endoplasmic reticulum and synthesis of a specific enzyme. For the treatment of Gilbert syndrome and Crigler-Najjar phenobarbital used to reduce the level of bilirubin in the blood plasma. Inhibition of the enzyme synthesis is used to treat acute porphyria, biochemical basis of which is the increased production of amino levulinate synthase. Hematin inhibits the synthesis of this enzyme and quickly relieves acute attacks of porphyria.

• Compensation for the enzyme

Etiotropic treatment: cell and gene therapy

Etiotropic treatment of hereditary diseases can be carried out at the level of cells or genes.

The term «cell therapy» refers to a method of treatment by transplantation of cells. Transplanted cells retain the genotype of the donor therefore transplant can be viewed as a form of gene therapy, because it leads to a change in the somatic genome.

Gene therapy — a method of treatment by administration of additional genetic information into the cells of the individual at the level of DNA or RNA (genetic engineering structures), or by changes in expression of genes.

Genetic engineering — a set of methods and techniques, including techniques for producing recombinant ribonucleic and deoxyribonucleic acids, by isolation of genes from an organism, implementation of manipulations with genes and introducing ща them to other organisms.

There are currently four areas of etiotropic treatment:

• transplantation of allogeneic cells (cell therapy);

• the introduction of genetically engineered structures in the tissue of the patient (gene therapy);

• transplantation of transgenic cells with the target of genetic engineering design (combination therapy);

• changes in the expression of genes (gene therapy).

Cell therapy

Hematopoietic stem cell transplantation is used as an effective treatment of hereditary metabolic diseases, mainly the lysosomal storage diseases and peroxi-

some. Hematopoietic stem cell transplantation is used in the treatment of the following diseases: Fanconi anemia, primary immunodeficiencies, hemoglobinopathies. Despite numerous clinical trials of cell therapy approved treatment protocols (cell type, quantity, method of administration of the cells, the timing of reintroduction) for particular nosological forms are no.

Gene therapy

Gene therapy by administration of genetically engineered constructs into cells and tissues of the patient (transgenic in vivo) can stimulate the growth of tissue, organ function. In this type of therapy created functionally capable genetic constructs (genetic vector) in the laboratory. These constructions must contain the target gene (or its main part), vector, promoter.

Gene therapy has been tested as presented primarily for the treatment of cardiovascular diseases: coronary heart disease and chronic lower limb ischemia.

Therapeutic angiogenesis in the treatment of critical limb ischemia was carried out by different authors by administering native DNA encoding the protein Vascular endothelial growth factor, gene Fibroblast growth factor, recombinant constructs based on different adenoviruses with genome angiogenin.

Treatment by transgenic cells

Treatment by transgenic cells with the target genetic engineering structure may be called combination therapy. To implement this type of cell gene therapy is necessary to carry out the introduction of the target gene into a cell. Such combination combines the properties of cell vector, gene function and effect of cell therapy.

Transgenic (transfer of genetic material) in vitro directed to somatic target cells, previously isolated from an organism (e.g., resected liver, lymphocyte culture, bone marrow culture fibroblasts, tumor cells).

Finite procedure through gene therapy transgenic somatic cells in vitro - is reimplantation of transgenic target cells. It can be organotropic (liver cells are injected through the portal vein) or ectopic (bone marrow cells are injected through a peripheral vein).

Changes in gene expression as a method of treatment

Changes in gene expression can be achieved by pharmacological modulation or RNA interference.

Today we can talk about three directions:

- increased expression of the gene determining disease;
- increased expression of the normal gene to compensate effect of a mutation in another gene;
- decreased expression of abnormal dominant gene.

THE ROLE OF REACTIVITY, CONSTITUTION AND AGE IN THE DEVELOPMENT OF PATHOLOGY

Reactivity

Reactivity is an ability of whole organism possessing the nervous system to differentiately reacts by the change of vital ability on the action.

Genesis of reactivity

The forming of reaction was due to the evolving of the main characteristics of active creatures:

• ***Reaction*** is a response of organism to determine the action of environmental and intrinsic factors.

• ***Sensitivity*** is an ability to determine the character, force, localization and rate of the agent action on organism.

• ***Irritability*** is an ability to achieve the action of environmental and intrinsic factors and response to it, as a rule, by generalized, low differentiated reaction, e.g. change in metabolism, shape, size and others.

• ***Resistance*** is a stability of organism or its part to the action of specific environmental and intrinsic factors.

Categories of reactivity

According to the type of reaction there are distinguished following form of reactivity:

• ***Normergia*** — it is a norm adequate reactions.

• ***Hyperergia*** (from Greek. hiper — more, ergon — action) — the processes of excitation are dominated. Inflammation is fulminant, with intense symptoms of the disease, acute changes in the organs and systems. F.e. Such as pneumonia, tuberculosis, dysentery occur intensive, rapidly, with strong symptoms, with high fever, a sharp acceleration of ESR, high leukocytosis.

• ***Hypoergia*** (low reactivity) — processes of inhibition are dominated. Hypoergic inflammation is stale, unexpressed symptoms erased, not very noticeable. Distinguish positive (anergy) and negative hypoergia.

✓ Positive hypoergia (anergy) — symptoms reactions decreased (or absent), but this is due to the development of active defense responses (for example, the development of antimicrobial immunity).

✓ Negative hypoergia — symptoms reactions also reduced, but this is due to the fact that the mechanisms that regulate the reactivity of the organism, inhibited, depressed, exhausted, damaged (for example, slow the wound process with flaccid pale granulation, epithelization weak after a long and severe infection).

• Dysergia — is atypical (inadequate) response of the patient to a medicine, the effect of cold (vasodilation and increased sweating).

Factors determining reactivity

Reactivity is determined by many factors and manifests by different changes in vital ability of individual. So, there are several categories of reactivity. Criteria of reactivity forms results from the main biological properties of organism, the character of reaction on action.

Biological properties of organism

There are specific, group, individual types of reactivity according to the main biological properties of organism.

Biological reactivity (specific) — is determined by the specific properties of organism (e.g. atherosclerosis is often observed in people, but it is observed in rabbits. The same is for syphilis. The specific properties of organism reactivity results from the change ability (due to mutation), hereditary fixation of the main specific properties of species.

Group reactivity — it includes age, gender and the body constitution reactivity. E.g. age reactivity — children are more subjected to infection disease, than adult because of immature immune system. Gender reactivity — women are more stable to blood loss, than man. The body constitution. It is known that asthenics are more stable to the prolonged physical and psychological overloads.

Individual reactivity — is determined by hereditary information, individual change ability (mutability). Unlike specific and body constitutional, individual reactivity of organism can be physiologic and pathologic. E.g.: the occurrence of allergic reactions to the factors in single individuals.

According to the level of specificity and organism differentiation there are specific and non-specific reactivity.

Specific reactivity — is an occurrence of immune response on antigen action.

Non-specific reactivity — reactivity reveals itself by the reaction of different factors of the external of the organism, and it's realized with the help of different mechanisms like parabiosis stress, changes of functional condition of the nervous system, the biological barriers, phagocytes (e.g. the activation of phagocytosis of leucocytes in response to contact with foreign cells, non-organic particles, bacteria, viruses and parasites) and others.

Specific and non-specific reactivity can be physiological and pathologic.

Physiological reactivity (primary) the reactions of the healthy organism in normal circumstance of existence, for example, immunity (specific reactivity), and also reactions of the organism on the action of the different factors of the external environment, which do not change homeostasis (non-specific reactivity).

Pathologic reactivity (secondary) reveals itself in the action of the pathogenic factors on the organism. Examples of specific pathologic reactivity are: allergy, immune deficit condition. Example of non-specific pathologic reactivity can be change of reactivity under traumatic shock, narcosis (phagocytosis, sensitivity to medicines).

Immunological reactivity

In ancient Rome, «immune» (immunitas) meant «freed from the payment of taxes».

Also immune become to name people who recover from some contagious disease and stay a resistant to its recurrence.

Immune reactivity is an important expression of reactivity at all. This concept brings together a number of interrelated phenomena:

1. Human and animal resistance to infectious (infectious) disease, or immunity in the true sense of the word.

2. Reaction of biological tissue incompatibility:

• Heterogeneous or phylogeny — in contact tissue of animals of one species into the body of another (for example, injection of horse serum to rabbit).

• Isogenic — in contact with animal tissues of one immune group to animal of other immune groups within this species. For example, a transfusion of blood another groups to human, organ transplants).

• Individual — transplantation a tissues from one animal to another within one and the same type of immunological groups, when this tissue are abnormal (tumor, exudates, etc.).

• Reaction of interaction embryonic tissues with adult tissues, or with each other.

By origin immunity can be specific and acquired.

Specific immunity — is an inherited feature of this species. For example, cattle are not sick with syphilis, gonorrhea, malaria and many other diseases transmissible to humans.

For long-lived specific immunity is divided into absolute and relative.

Absolute specific immunity — called immunity, which occurs in animals from birth and is so strong that any action of environment can not weaken it or destroy.

For example, any additional effects (hunger, fatigue, chilling injury of the nervous system, etc.) can not cause the disease of poliomyelitis during the infection by the virus of dogs and rabbits.

Relative specific immunity — is less strong, depending on the impact of the environment on each animal.

For example, birds (chickens and pigeons) in normal conditions are immune to anthrax. But you need only weaken the body of these birds by cooled, starvation or injury of central nervous system (removal of cerebral hemispheres, etc.) as they become ill with anthrax.

Acquired immunity — is divided into naturally acquired and artificially acquired. By origin each of them is divided into active and passive.

Naturally acquired

Naturally acquired active immunity — occurs after relevant infectious disease.

Naturally acquired passive immunity (or congenital, or placental immunity) — due to the transition of protective antibodies from the mother's bloodstream

through the placenta into the fetal blood. The fetus gets protective antibodies produced by the mother (measles, scarlet fever, diphtheria and other infections). By passive immunity can transferred with milk.

Artificial acquired immunity is made by man in order to prevent contagious diseases.

Active artificial immunity — is called immunity, achieved by vaccination healthy people and animals by killed or attenuated pathogens microorganisms, attenuated bacterial toxins (anatoxins) or viruses. First artificial active immunization reproduced Jenner by given cowpox vaccine to children. This procedure was called vaccination, and vaccination product — vaccines (lat. vaeca — cow).

Passive artificial immunity — is reproduced by injection artificial human serum containing antibodies against the bacteria and their toxins. Especially effective antitoxic serum against diphtheria, tetanus, botulism, gas gangrene. Also used serum against snake venom (cobra, viper, and others). Sera were obtained mainly from the blood of horses («producers»), which is immunized appropriately toxin.

Antitoxic — immunity is directed to neutralize bacterial toxins in toxic infections (diphtheria, tetanus, botulism, gas gangrene, etc.)

Antibacterial — this immunity, directed to destruction of microbial cells. It manifested by a number of defense mechanisms (antibodies, phagocytosis, tissue reactivity). The antibodies cause the dissolution or agglutination of bacteria or in their presence, the virulent forms of bacteria is transition in avirulent. In various infections antibacterial immunity mechanism is different.

Antiviral immunity. In the mechanism of immunity against viral infections is significant:

1. Development of anti.

2. Phagocytosis of viral particles and other absorbing objects. According to modern concepts, phagocytosis is not a major mechanism of immunity to viral infections.-viral antibodies.

3. Intracellular factors that suppress viral replication of infected cells. Nature and mechanism of action is not yet sufficiently studied.

4. Interferon. Viral infections cause the formation in lymphoid cells special protein — interferon. It inhibits the reproduction of the virus. Effect of interferon is nonspecific.

Immunologic tolerance

Mechanism of immune tolerance:

1) Clonal deletion (or «clonal abortion») — it is a death of immunocompetent cell in case of negative selection in thymus or marrow. Arrive at apoptosis of T- and B- lymphocytes, that have high specific antigen determination receptors to autoantigens

2) Clonal anergy — areactivity of lymphocytes, that have B-cells receptors to solute autoantigens in low concentrations. After contact with antigen lympho-

cytes save vitality, but this cells not response to signal from antigen specific receptors — this cells functional inactive.

3) T-cells mediated immunosupression. For saving tolerance peripheral autoreactive T lymphocytes must be destroyed by apoptosis or stay anergic by effect of cytokines Th2 supression.

Reactivity and biological barriers

Biological barriers — they are special tissue structures, which protect the organism or its separate part from pathogenic influence of the environment and preserve homeostasis. There are two types of the barriers: external and internal.

External barriers: include the skin, the mucous layer which protect the organism from pathogenic influence of the environment, the respiratory organs which hold back harmful materials pressure in atmosphere, the digestive organs (antibacterial action of gastric juice, deprivation of nutrients of antigenic properties), the liver has desintoxicating function, the spleen and the lymphatic nodes, as well as other organs, also have the same function; including mononuclear cells of phagocytes.

Internal barriers the necessary energetic material and prevent the penetration of the foreign and poisonous material arriving from the blood to the organs and tissues.

In 1929 L. S. Stern made a supposition: that there were protective device between the blood and the liquid of the tissue, which she named histo-hematic barriers. Each organ has its own medium because the blood does not contact with the cells of the organs. The functional characteristics of the barriers depend on the morphological and physiological peculiarities, corresponding to the organs and tissues. The peculiarity of each barrier is its selective permeability.

Special barriers a particular group which defend certain organs which are in need of its own strictly constant media. They are hematoencephalic, hematoophthamic, hematotesticucar, hematoplacentar barriers.

The structural elements of the barriers are capillaries, whose endothelium in different organs possesses their own distinctive peculiarities, and that is the principal morphological selective permeability.

In different organs in respect of different materials the barrier function may not be alike. In the study of the penetration of serum proteins into the organs, several types of barriers were shown. Hematoencephalic barrier is mainly present in the vascular walls, the barrier of the thyroid gland has an organisation on the tissue level and with the help of the paranchymatous cells divides the organs into zones where protein does not penetrate. The sarcolemma acts as a barrier in the muscles.

Hematoencephalic barrier has the most difficult organization. Besides having the endothelium and basal membrane it also has argirophil material, the brain layers and glia with astrocytes.

It is known that microorganisms, toxins, medicines, antigens, antibodies do not penetrate into the brain. As to metabolilies, hormones, biologically active materials, the brain acts selectively with respect to them, regulating the penetra-

tion of these materials, these barrier acts selectively, with respect to them regulating the penetration of these materials into the cells of the brain.

The main function of the barrier is the mechanism of dialysis, ultrafiltration, osmosis, as well as the metabolic function of the cells, which are included in the structure of the barrier.

Biological barriers, executing protective and adjusting function, support an optimum composition of medium for the organ and promote a conservation homeostasis to maximum.

Intensive transport through the barrier depends on the functional needs of the organ, hemodynamic, hormonal and nervous effect and also presence and absence of morphological and functional disturbances.

The function of the barrier may change depending on the age, the sex, nervous and hormonal effects and many influences of external and internal media. The functional state of the barrier may change when in sleep and staying awake, tiredness, trauma irradiation with infrared, ultraviolet and X-rays, influence of ultra short and high-frequency waves, ultrasound.

Introduction of alcohol, acetylcholine, histamine, kinines, hialuronidase, agitating the central nervous system, increases the permeability of the barrier in the organism. Materials, with opposite effect, at is lowering permeability, include: catecholamines, salts, calcium, vitamin PP, sleeping medicines.

Permeability of barriers is changed under different pathologic processes, such as trauma, inflammation, alcoholic intoxication, virus infection and others.

Increase of permeability makes the organ more sensitive to poisons, intoxications, intensify tumor growth. In impairment of permeability of the barriers there is possibility of autoimmune damage of the organs (for instance the thyroid gland, the brain). Particular value for developing fetus has the hematoplacental barrier, which defends the fetus in the period of pregnancy. Impairment of permeability of this barrier (virus infection, alcoholic intoxication) can be harmfully reflected in the embryonal development of the fetus, which result in the development of different types of postnatal pathology.

THE ROLE OF THE CONSTITUTION IN PATHOLOGY

Among the factors that play a role in the etiology of diseases, a certain value has the constitution of man (from the Latin constitutio — structure).

Constitution is a set of relatively stable structural and functional characteristics that influence on the reactivity of the organism and its resistance to the action of pathogenic factors.

The founder of the doctrine of the constitution and its connection with the development of disease — Hippocrates, who distinguish people with dry and wet; strengths and weaknesses; sluggish and resilient types of constitution. In addition, he divided people on the temperament to sanguine, choleric, melancholic and phlegmatic.

The main development of the doctrine of the constitution received in the twentieth century.

Classification of the body constitution

The basis of classification in most cases taken different physical characteristics, such as the ratio between height and weight, the length of the trunk and limbs, as well as the size and shape of the chest, the degree of muscle development, etc.. Much less classification of constitutional types is based on the functional features of the nervous system.

C. Sigaud (1914) proposed to allocate 4 type of constitution — respiratory, digestive, cerebral and muscle, depending on the priority of a particular system. Respiratory type is characterized by a long chest with a sharp epigastric angle and moderate development of the abdominal viscera. The digestive type has chest short, obtuse epigastric angle, however, increased the size of the stomach, strongly developed masticatory apparatus, there is a tendency to obesity. People of cerebral type are characterized by a large skull with well developed frontal lobes in combination with delicate thin physique and short limbs. Muscular type of constitution has increased muscle development, proportionate physique, broad chest. According to the Sigaud ideas, formation of the constitution type occurs mainly in children, depending on the training organs and body systems.

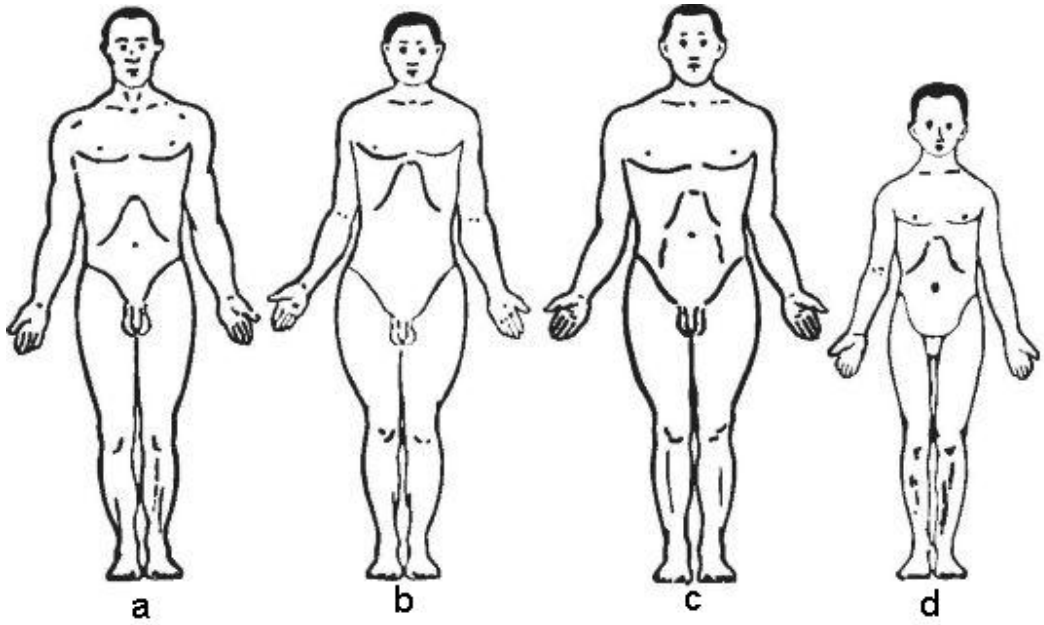

Figure 9 — Types of constitution by C. Sigaud:
a — respiratory; b — the digestive; c — musclar; d — cerebral

German psychiatrist E. Kretchmer (1921) identified three type of constitution — pyknic, shallow (asthenic) and athletics. Picnic is characterized by high body weight due to excess fat deposits, short rib cage, a large protruding belly, long body and relatively short limbs. Asthenic — tall and thin, with long limbs and relatively short trunk, narrow chest. Athlete — people with well-developed muscles, a broad chest and shoulders, narrow hips.

W. Sheldon (1940) based his classification of the degree of development of germ layers derivatives — ectoderm, endoderm and mesoderm, and allocated,

respectively, three constitutional types: endomorphic, ectomorphic and mesomorphic. Characteristics of these types resemble the constitutional types, distinguished E. Kretchmer: endomorphic type similar to picnic, ectomorphic — with asthenic and mesomorphic — the athlete.

In our country the most popular classification of M. V. Chernorutskii (1928), which is allocated on the basis of body features two extreme types — asthenic and hypersthenic and one intermediate — normosthenic.

Asthenic type of constitution is characterized by relatively short body and long limbs, narrow, flat and relatively long chest with a sharp epigastric angle, narrow shoulders, thin, long neck, a small volume of the stomach; the overall longitudinal dimensions substantially prevail over transverse.

In people with type hypersthenic constitution there is an inverse ratio of body size compared to asthenic: relatively long torso and short legs, a short neck, short wide thorax with increased anteroposterior size, large, often protruding belly; in general there is increase the transverse dimensions of the body.

Normosthenic characterized proportionate physique, broad shoulders and convex chest, well muscled.

Chernorutskii study features of metabolism and condition of some of the internal organs from their assigned constitutional types.

Table 3 — Features of metabolism and predisposition to disease in individuals with different types of constitution (by M. V. Chernorutski)

Type of constitution	Features of metabolism	Predisposition to diseases
Asthenics	The predominance of dissimilation processes of assimilation; tendency to increase the basal metabolic rate and alkalosis; accelerated utilization of glucose at the sugar load; cholesterol and lipid levels within normal limits or reduced	Tendency to ptosis of the abdominal organs, peptic ulcer, severe course of pulmonary tuberculosis, hypotension, pathological amenorrhea
Hypersthenics	The predominance of assimilation, the tendency to a decrease in basal metabolic rate and acidosis; impaired glucose tolerance at sugar load; elevated blood lipid and cholesterol	Predisposition to diseases of the cardiovascular system (atherosclerosis, myocardial infarction, hypertension), diabetes mellitus type 2, obesity, gallstones
Normosthenics	Balance of processes of assimilation and dissimilation; parameters of metabolism and physiological processes are close to the average rate	Predisposition to diseases of upper respiratory tract and locomotor system

I. P. Pavlov (1925) identified people with different types of higher nervous activity by taking into account strength, mobility and balance basic nervous processes — excitation and inhibition. He used proposed by Hippocrates classification of temperament — sanguine, choleric, phlegmatic and melancholic.

Sanguine is characterized by a strong balanced mobile type of higher nervous activity; choleric — strong unbalanced mobile; phlegmatic — strong, balanced and inert melancholy – a weak type of higher nervous activity.

Causes and mechanisms of aging

Etiology

At the present time it is impossible to make definitive conclusions about the causes of aging.

Wear and tear theory: Posed by Dr. August Weismann (1982), the theory postulates that the daily grind of life, in particular abuse or overuse, literally wears the body out, leading to disease states. The degeneration of cartilage and eventual grinding of bone on bone is an example of the aging process on body joints, as wear and tear exceed the body's ability to repair.

Waste accumulation theory: This theory proposes that, as we age, our cells accumulate waste products as a consequence of normal metabolic processes in the cells. It is believed that this build-up of toxic «sludge» eventually compromises normal cell functions. Lipofuscin pigments or liver spots, common on aging skin, are an example of this waste material. The brownish pigments consist of oxidized (rancid) fats that accumulate in the skin, as well as in the internal organs of our body, as we age.

Faulty reconstruction theory: Throughout life the body is constantly rebuilding and repairing itself. The Faulty Reconstruction Theory argues that, as we age, the repair process begins to produce faulty reconstruction materials that compromise the repair job and weaken the cell — much like renovating a house with poor quality building supplies that diminish its final structure.

Errors and repair theory: According to this theory, the aging process is, in part, caused by damage to the genetic structure of the DNA, the genetic blueprint of our cells, life-long accumulation of molecular rubbish that, leads to errors in the manufacture of related proteins and helps accelerate the aging process.

Mitochondrial damage theory: The theory postulates that the oxidative processes occurring deep within the mitochondrial membranes eventually damage the organelle, leading to a loss of function. Once mitochondria are lost to the cell, they cannot be replaced, leading to a gradual but inexorable loss of energy and function in cells over time.

The free radical theory of aging was proposed in 1954 by Dr. D. Harman. Aging occurs when cells become permanently damaged from the life-long and unrelenting attack of charged molecular fragments, known as free radicals. The cellular damage inflicted by this uncontrolled oxidative stress inexorably spreads outward to the level of tissues and organs, where it eventually manifests itself as some form of degenerative disease.

Existing on the subject of numerous hypotheses can be divided into two main groups.

The first group of hypotheses suggests that aging is caused by the accumulation of non-renewable damages received by the body over a lifetime. As damaging factors may act radioactive radiation, free radicals and peroxides. It is assumed that the accumulation of certain errors lead eventually to the appearance of new, identifying avalanche increase a process ends with «catastrophic error».

According to the hypothesis of the second group, aging is a genetically programmed process developed in evolution as a tool for limiting the duration of an individual life. From this point of view, the rapid change of the endangered one by one generation contributes to a better adaptability to the conditions of existence and protect the species from extinction to a greater extent than the potential immortality of the individual.

Pathogenesis

There are several variants of mechanisms of age-related changes.

The first variant assumes that the causes of aging, equally and simultaneously act on different elements of the body, leading them to a uniform violation. Accumulated to date experimental data do not support this mechanism of aging.

The second variant selects one link in the body, which by virtue of its weakness or excessive load on it the first down, in the future becoming a driver («pacemaker») age-related changes and causing secondary changes in other, more stable links. On the role of the age driver could claim the hypothalamus, connective tissue, or immune system.

The third variant: aging occurs as a consequence of the activities of certain mechanisms for which generation of age-related changes in other tissues is their normal function («clock») and not the result of any damage.

Progeria

Progeria (Greek. progeros — prematurely aged) — is a rare, fatal genetic condition characterized by an appearance of accelerated aging.

There are progeria in children and adults.

Progeria children is a Hutchinson–Gilford progeria syndrome (HGPS)

The reported incidence of HGPS is 1 in 8 million. Hutchinson–Gilford progeria syndrome had been proposed to be a recessive disorder due to observations of affected individuals found in consanguineous families. However, many cases of progeria suggesting sporadic autosomal dominant inheritance, which has been confirmed with the discovery of the causative mutations. Others have reported the presence of various chromosomal abnormalities, such as an inverted insertion in the long arm of chromosome 1 and an interstitial deletion of chromosome 1q23 (11), as possible contributing factors to the disease.

Affected children typically look normal at birth and in early infancy, but then grow more slowly than other children and do not gain weight at the expected rate (failure to thrive). Main first symptoms were failure to thrive (55 %), hair loss (40 %), skin problems (28 %), and lipodystrophy (20 %). Typical facial features include micrognathia (small jaw), craniofacial disproportion, alopecia (loss of hair), and prominent eyes and scalp veins. Growth in weight was more disturbed than growth in height, and growth delay started already prenatally. Lipodystrophy is generalized, only intra-abdominal fat depositions remain present. Pathologic findings in coronaries and aorta resemble sometimes the findings in elderly persons, but can also be much more limited. Loss of smooth muscle cells seems the most important finding.

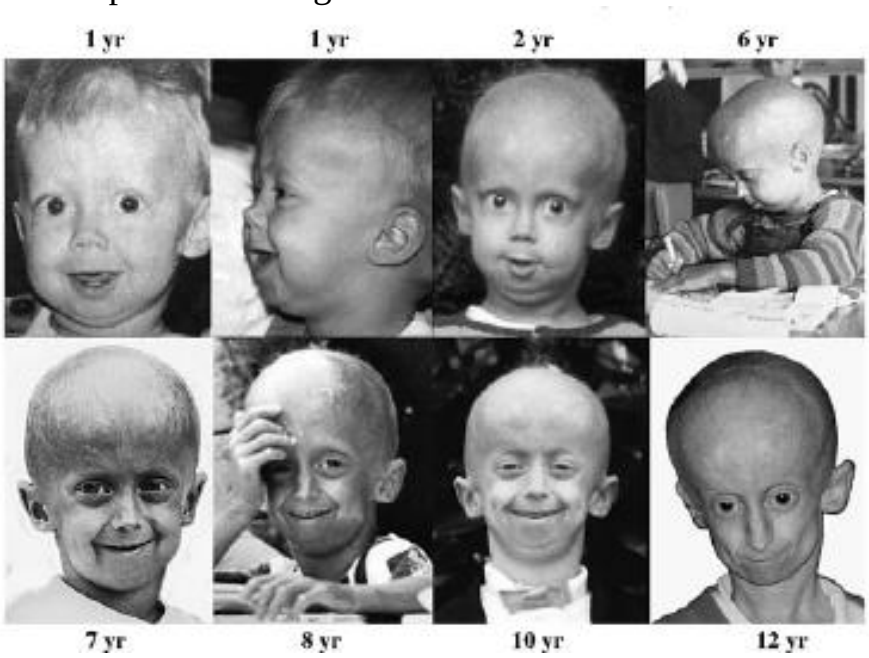

Figure 10 — Dutch Patient with progeria at the age of 1, 2, 6, 7, 8, 10 and 12 years (Hennekam R.C.M., 2006)

Lifespan not exceed 7–27 years (average — 13 years). Patients die of starvation, myocardial infarction, intercurrent diseases.

Progeria adults or Werner syndrome (WS)

WS is an autosomal recessive disease with features that are reminiscent of premature ageing. It manifested the disease in 20–30 years, more frequently in men. Clinical features of the syndrome: sharp-pointed «bird nose», prominent chin, a narrow mouth; high, hoarse voice, pale skin, thinning of the subcutaneous tissue and muscle atrophy of limbs, often — the appearance of venous ulcers, malignant tumors; stunting, early graying and balding, progressive cataracts, premature atherosclerosis, a violation of the cardiovascular system; generalized osteoporosis, hypogonadism; decrease of intelligence. Changes are progressive

and are not the consequence of another systemic disease process or the result of a primary endocrine deficiency or dysfunction

Patients die at about 40 years age from disease of the cardiovascular system, development of tumors intercurrent diseases.

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