Сеченовский Университет

Федеральное государственное автономное образовательное учреждение высшего образования Первый Московский государственный медицинский университет имени И.М. Сеченова Министерства здравоохранения Российской Федерации (Сеченовский Университет)

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CLINICAL PATHOPHYSIOLOGY

CONCISE LECTURES, TESTS, CASES

STUDENT MANUAL

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СЕЧЕНОВСКИЙ УНИВЕРСИТЕТ

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CONTENTS

1. THE SUBJECT MATTER OF PATHOPHYSIOLOGY. GENERAL NOSOLOGY

The human being is the common object of studies of all medical disciplines. Some of them (for instance, anatomy and physiology) study and describe human activity in normal conditions or develop «normology» of a human being. Most of the medical disciplines study the nature and mechanisms of a patient's vital activity or a human being's pathology. Pathophysiology is among them.

Pathophysiology is the part of medicine and biology which investigates and describes actual causes, mechanisms and regularities of onset, development and outcomes of pathological process and disease; formulates principles and methods of their diagnostics, treatment and prophylaxis; develops the doctrine of a disease and an ailing body; formulates theoretical guidelines in medicine and biology.

The above is presupposed by the etymology of the term «pathophysiology»: from Greek *pathos* — suffering, illness; *physis* — nature, essence; *logos* — doctrine, science. In other words, pathophysiology is the doctrine of the nature of a pathological process and disease.

COMPONENTS OF THE SUBJECT MATTER OF PATHOPHYSIOLOGY

The object of pathophysiology studying and teaching covers the following three components (fig. 1):

1) disease;
2) typical (stereotypical) pathological processes (e.g. inflammation, fever, hypoxia, extreme conditions, etc.);
3) typical forms of organ and tissue pathology (e.g. anemia, abnormal heart rhythms, respiratory insufficiency, etc.)

Pathophysiology consists of three parts.

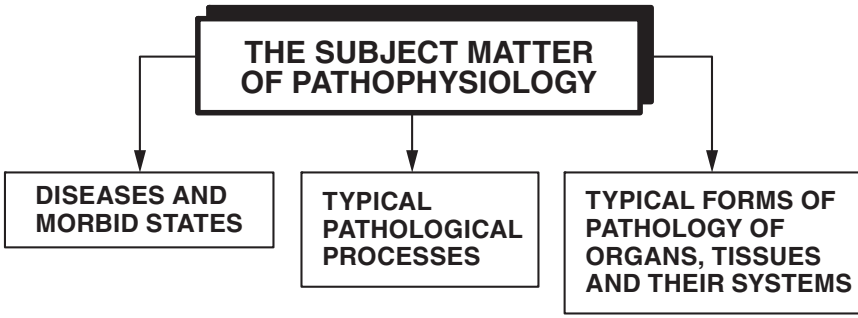

Fig. 1. The subject matter of pathophysiology

I. Nosology.

II. Studies of typical pathological processes. Typical are pathological processes that contribute to the pathogenesis of many diseases and syndromes, and serve as their significant and inseparable part.

III. Studies of typical forms of pathology of specific organs and organ systems. Similar to typical pathological processes typical forms of pathology of specific organs and organ systems are also components of various diseases.

Nosology is a science dealing with the description and classification of diseases.

Nosology comprises three divisions:

1. Study of disease which includes:
   a) general concepts and categories of pathology;
   b) classification and nomenclature of diseases;
   c) special aspects of pathology.
2. General etiology which includes:
   a) general features of pathogenic agents;
   b) main groups of pathogenic factors;
   c) the role of conditions and reactivity of the body in the initiation of disease;
   d) principles of etiotropic prevention and treatment.
3. General pathogenesis which includes:
   a) mechanisms of the body resistance to the effects of pathogenic factors;
   b) general mechanisms of diseases;
   c) mechanisms of convalescence;
   d) pathogenesis of dying;
   e) general principles of disease prevention and treatment.

NOSOLOGY

The notion of disease

A disease is a dynamic state of the body characterized by a loss of the well-being which essentially implies a decrease of the biological and social potentials of the individual.

Basic concepts of nosology

Pathological process

Pathological process is a natural progression of changes caused in the body by the action of pathogenic factors. These events include damage with the ensuing dysfunction, accompanied by adaptive reactions. A unique combination of these two processes determines the form of disease and its course.

«Pathological process» is a more general category than «disease». One and the same pathological process, such as thrombosis, hemolysis, or edema, may contribute to the pathogenesis of various diseases.

Some of the complex pathological processes contributing to the pathogenesis of many diseases are called typical. Typical pathological processes are inflammation, allergy, hypoxia, tumor growth, fever, and infection.

Pathological state

Pathological state is a relatively persistent and stable abnormality of the body limiting its adaptive potential.

Pathological reaction

Pathological reaction is an inadequate and harmful reaction of the body or some of its systems to the ordinary (e.g. some foods) or extraordinary (pathogenic) stimuli. Pathological reaction is inadequate in quantitative or qualitative sense and outruns the limits of the individual norm. The examples of pathological reactions are an anaphylactic reaction (a form of allergy), pathological reflexes, inadequate behavioral reactions, etc.

Remission

Remission is a temporary subsidence of symptoms of a disease or improvement of state.

Recurrence

Recurrence means reappearance or exacerbation of symptoms of a disease. In chronic illnesses the recurrence follows the period of remission, and also represents the natural stage in the course of a disease.

Complication

Complication is a pathological process accompanying a disease. It is in fact not obligatory for this disease, but it is caused by the same pathogenic factors, or arises from alterations developed in a primary disease. The examples of complications include nephrotic syndrome in chronic glomerulonephritis, infections after surgical interventions, myocardial infarction in patients with diabetes mellitus, arrhythmia due to coronary insufficiency. Pathological processes that are casually associated with the primary disease or the remote consequences of the disease are usually not viewed as complications.

CLASSIFICATION AND NOMENCLATURE OF DISEASES

Nomenclature is a structured catalogue of diseases and other nosological forms. Classification of diseases is a system of grouping diseases and pathological processes into nosological units. The grouping criteria are different and use various approaches:

- etiology of diseases. For example, infectious diseases, traumas, intoxication, etc.;
- anatomical/topographic features. For example, diseases of the heart, diseases of the respiratory tract, diseases of the gastrointestinal tract, etc.;
- sex and age. For example, diseases of children or adults; diseases of women;
- natural course — acute, subacute, and chronic diseases;
- pathogenic mechanisms. For example, allergies, tumors, malformations, etc.;
- social characteristics. For example, occupational diseases.

ETIOLOGY

Etiology is a science that studies causes and conditions of diseases. There are two major classes of etiological factors: intrinsic or genetic, and acquired

(e.g. infectious, nutritional, chemical, physical). A deficit of specific essential substances (such as vitamins or amino acids) or normal conditions of living may also be pathogenic.

Reactivity

Reactivity of the body is defined as a constellation of features that determine the quantitative and qualitative pattern of reaction to a specific stimulus. One and the same stimulus causes a broad range of reactions from severe damage to only minimal changes depending on the age, gender, race/ethnicity, and constitution of the individual.

Stages of disease

There are four stages in the course of diseases: the latent stage, the prodromal stage, the peak stage, and the outcome. This division is more attributable to infectious diseases. The course of chronic diseases, such as cardiovascular or endocrine disorders, or tumors may be divided into three stages: the onset, the stage of overt manifestations, and the outcome.

Pathogenesis

The term «pathogenesis» describes the study of mechanisms of a disease onset, development, and outcome. It refers to the sequence of events in response of the cells or tissues to an etiologic agent, from the initial signs of disorder to the ultimate expression of the disease.

«Vicious cycles» in pathogenesis of a disease

In this case the initial disorder becomes an etiologic factor of the subsequent disorder which in turn maintains and enhances the original defect forming a positive feedback loop.

Methods of pathophysiology

The main and specific method of pathophysiology (both as medico-biology science and as an academic discipline) is the method of modeling of pathological process and disease, as well as modeling of patient as a whole. It's important to stress that pathophysiologists were the ones who developed and implemented pathological process modeling in medicine.

The very emergence of pathophysiology was necessitated by the need to describe the essence of what was concealed from a doctor, namely mechanisms of onset, development and outcome of a disease. And it was necessary to simulate those mechanisms with the help of «artificial copies» — of their models — and describe them in pathophysiological terms.

1. Modeling of diseases, pathological states, various forms of pathological processes, and pathological reactions:
   a) physical modeling (in laboratory animals, isolated organs or cells);
   b) nonphysical modeling (logic simulation of diseases, pathological processes, or the patient).
2. Methods of clinical investigation.
3. Analysis of results, elaboration of concepts and theories.

General approaches used in pathophysiology to modeling pathology (fig. 2).

Formalized or nonmaterial modeling is the form of intellectual modeling and realized as a logic, mathematical, computer, etc. modeling.

The intellectual modeling is widely used in the process of teaching students to solve situational, laboratory and other tasks. One of the forms of intellectual modeling is analysis of clinical situation. Students master the skill of clinical analysis by training in pathophysiological analysis of

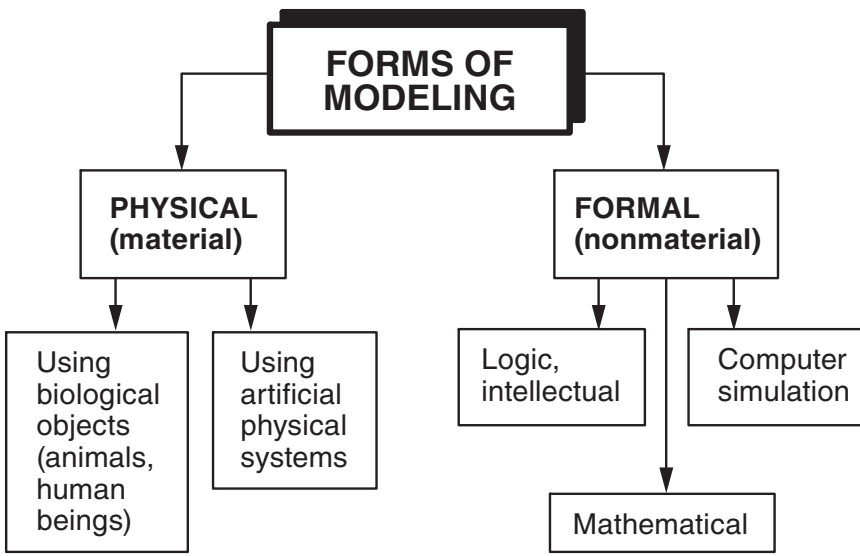

Fig. 2. Modeling of pathological processes and diseases

experimental and clinical data when they solve case problems during their class work. In the process of pathophysiological analysis students simulate doctor's behavior. It is well known that after the evaluation of all relevant information about a patient, that is parameters of physical, laboratory or special instrumental investigation, a doctor creates a disease model of a particular patient. Taking into account all the data concerning the patient's disease a doctor designs a scheme of diagnostic research and selects methods of therapy and prophylactic strategy.

2. CELL INJURY AND CELL DEATH

Cell injury implies such changes in cell structure, metabolism, physico-chemical properties or function, that seriously compromise cellular viability or the ability to adapt to noxious stimuli.

Common causes of cell injury

1. Chemical agents and drugs.
2. Physical agents (e.g. mechanical trauma, extremes of temperature (burns and deep cold), radiation, electric shock, sudden changes in barometric pressure).
3. Biological agents (infectious agents including viruses, rickettsiae, bacteria, fungi, and higher forms of parasites; genetic derangements: nutritional imbalance).

Mechanisms of cell injury

I. Derangements in the energy supply and utilization.
   1. Decrease in the rate or efficiency of ATP production.
   2. Decreased transport of ATP to the sites of utilization.
   3. Impaired ATP utilization in metabolic processes.

II. Loss of the integrity of cell membranes.
   1. An imbalance between production and utilization of free radicals causing lipid peroxidation.
   2. Activation of intracellular hydrolases.
   3. Defects in membrane permeability.
   4. Detergent effect of amphyphyllic compounds.
   5. Impaired resynthesis of the damaged membrane constituents.
   6. Overextension and the following rupture of membranes in the swelled cells or cellular organelles.

III. Ionic and water imbalance.
   1. Imbalance of the particular ions.
   2. Abnormal redistribution of ions in intracellular compartments.
   3. Overhydration of a cell.
   4. Dehydration of a cell.

IV. Changes in the genome and/or its abnormal realization.
  A. Changes in the genome.
    1. Changes in the gene structure.
    2. Derepression of pathogenic genes.
    3. Repression of the «vital» genes.
    4. Insertion of the alien DNA fragment with pathological information.
  B. Disorders of the gene realization program.
    1. Abnormalities of mitosis and meiosis:
      a) damage of chromosomes;
      b) damage of the structures, participating in cell division;
      c) abnormal division.
V. Disorders of intracellular regulatory mechanisms.
  1. Abnormal reception of a signal.
  2. Disorders in the secondary messengers.
  3. Impaired phosphorylation of protein kinases.

Cell adaptation to injury

Mechanisms of the cell adaptation to injury.
1. Compensation for derangements in the energy supply:
  a) activation of anaerobic glycolitic ATP synthesis or aerobic respiration in the intact mitochondria;
  b) stimulation of the energy transport from the sites of production to the sites of utilization.
2. Protection of the membranes and cellular enzymes:
  a) activation of the antioxidative systems;
  b) increased synthesis of the microsomal cytochrome P-450 or other enzymes involved in detoxification;
  c) increased resynthesis of the damaged molecules.
3. Recovery of water and ionic balance:
  a) activation of ionic pumps;
  b) repair of membrane and removal of the «high-conductance channels».
4. Repair of damage to the cellular genetic program:
  a) removal of breaks in the DNA strands;
  b) excision of the altered sites in the DNA molecule;
  c) restoration of the native DNA fragment in the site of the damaged one.
5. Compensation for disturbance of the intracellular regulatory processes:

a) «up-» or «down-regulation» of the receptors;
b) changes in the activity of adenylate cyclase, guanylate cyclases, phospholipase C, proteinkinases or other factors involved in signal transduction.

6. Decrease of the cell functioning.
7. Regeneration.
8. Hypertrophy.
9. Hyperplasia.
10. Hibernation.

Pathogenic factors may cause the following states of a cell:

a) adaptation;
b) reversible injury;
c) irreversible injury;
d) cell death.

Common manifestations of reversible injury include the following changes:

a) ATP depletion and accumulation of PP, ADP, AMP;
b) decreased activity of Na-, K-ATPases and Ca-, Mg-ATPases;
c) activation of glycolysis and glycogenolysis and accumulation of lactate;
d) depletion of protein synthesis resulting from dissociation of polysomes into monosomes and energy deficit;
e) accumulation of Na^+, Ca^{2+} and loss of K^+;
f) cell swelling and acidosis.

Persistent or excessive injury causes cells to pass the threshold into irreversible injury that is associated with extensive damage to all cellular membranes causing their nonselective hyperpermeability, swelling of lysosomes with a leakage of enzymes and vacuolization of mitochondria.

Forms of cell death include necrosis and apoptosis

Differences between necrosis and apoptosis:

Necrosis:	Apoptosis:
is the result of casual degradation	in a series of physiologic events it is not casual, but programmed
is accompanied by destruction of membranes	is not accompanied by destruction; the cell shrinks
is executed by lysosoma hydrolases	is executed by cytosolic caspases
is accompanied by inflammation	is not accompanied by inflammation
causes damage to adjacent cells by intracellular hydrolases and indirectly by attracting neutrophils	disappears without trace

Mechanisms of apoptosis

Apoptosis is the endpoint of an energy-dependent cascade of molecular events, initiated by certain stimuli, and consisting of four separable but overlapping components. Apoptosis includes:

1. Signaling pathways that initiate apoptosis.
2. Control and integration processes, in which intracellular positive and negative regulatory molecules inhibit, stimulate, or forestall apoptosis and thus determine the outcome.
3. A common execution phase including realization of the death program and accomplished largely by the caspase family of proteases (fig. 3).
4. Removal of dead cells by phagocytosis.

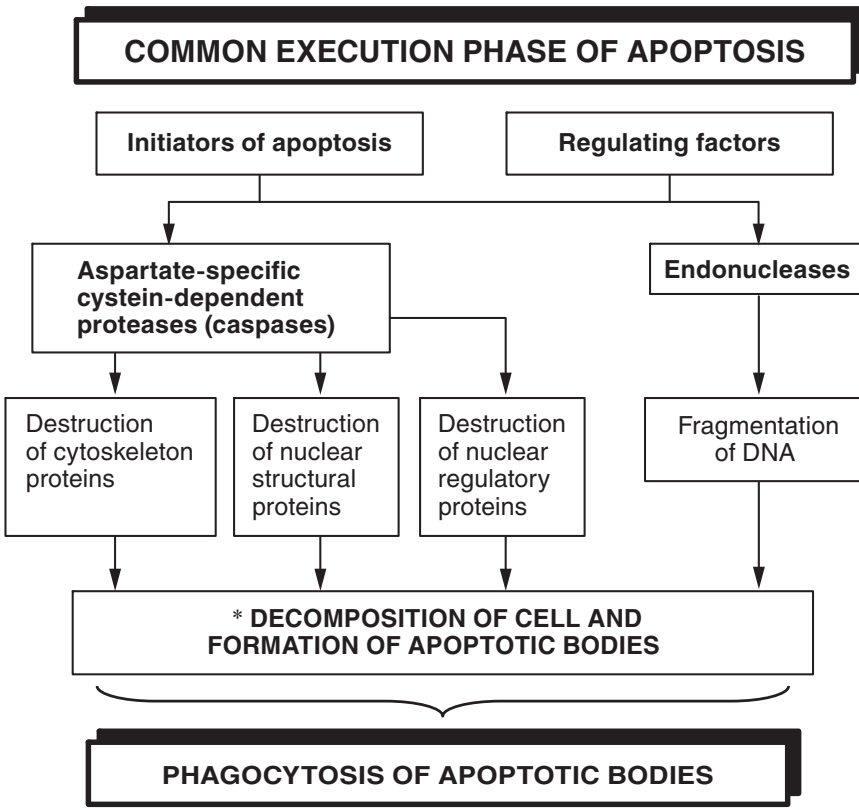

Fig. 3. The main events in common execution phase of apoptosis

3. HEREDITARY PATHOLOGY

Hereditary disorders, by definition, are derived from one's parents and are transmitted in the germ line through the generations. The term «congenital» simply implies «born with». Some congenital diseases are not genetic, as, for example, congenital syphilis. Not all genetic diseases are congenital; patients with Huntington's disease, for example, begin to manifest their condition only after the twenties or thirties.

Hereditary and some congenital diseases result from mutations.

MUTATIONS

Mutation is defined as a stable, heritable change in DNA. Mutations in somatic cells may be relevant to cancer or aging; mutations in germ cells have their impact on offspring of an individual. Types of mutations are the following (see fig. 3).

The concept that mutations are stable changes remains generally true, but the discovery of expanding triplet repeat mutations emphasizes that some mutations can be unstable either in somatic or in germ cells.

Mutations occur spontaneously during the process of DNA replication. Certain environmental influences, such as radiation, chemicals, and viruses, increase the rate of the so-called spontaneous mutations.

Classification of mutations

Based on the extent of genetic change, mutations may be classified into 3 categories.

I. Single-base or point mutations.
II. Chromosome mutations.
III. Genome mutations.

I. Single-base or point mutations

These involve only one or several base pairs in a gene.

Types of single-base mutations:

a) substitutions;
b) insertions;

c) deletions;
d) amplification of trinucleotide repeats.

II. Chromosome mutations

Chromosome mutations result from rearrangement of genetic material and give rise to structural changes in the chromosome. These involve millions of base pairs in the structure of a chromosome. Chromosome mutations include duplications, inversions, deletions, and translocations of a portion of one chromosome to another.

III. Genome mutations

Genome mutations involve loss or gain of whole chromosomes giving rise to monosomy, trisomy or polysomy.

CATEGORIES OF GENETIC DISORDERS

Genetic diseases generally fall into one of three categories.

1. Mendelian or monogenic disorders. They are determined primarily by a single mutant gene.
2. Complex disease traits. These disorders are caused by an interaction of multiple genes and multiple exogenous or environmental factors.
3. Chromosome disorders. Chromosome disorders involve the lack, excess, or abnormal arrangement of one or more chromosomes, producing large amounts of excessive or deficient genetic material and affecting many genes. If an entire chromosome is affected in an imbalance, the genome is said to be either trisomic or monosomic for the chromosome (e.g. trisomy 13, monosomy X). An abnormal dosage affecting less than an entire chromosome (the result of chromosome breakage and rearrangement) is often termed partial trisomy or partial monosomy, to indicate that segments rather than entire chromosomes are involved (e.g. partial trisomy 13 q, partial monosomy 4 p).

Monogenic (Mendelian disorders)

Single-gene disorders are those in which mutation in one gene plays a predominant role in determining disease.

Such disorders ordinarily exhibit one of three patterns of inheritance:
1) autosome-dominant;
2) autosome-recessive;
3) X-linked.

Autosome-dominant disorders

- Dominant diseases are manifested in the heterozygous state; by definition, the gene responsible for an autosome-dominant disorder must be located on one of the 22 autosomes.
- Each affected individual has an affected parent [unless the condition arose by a new mutation in the sperm or ovum that formed the individual or unless the mutant allele is present but without phenotypic effect in the affected parent (low penetrance or expressivity)].
- Since alleles segregate independently at meiosis, there is one in two chance (50% probability) that the offspring of an affected heterozygote will inherit the mutant allele.

Penetrance is the proportion of individuals with a given genotype who present with any phenotypic features of the disorder.

Expressivity, or variability in clinical expression, describes the range of phenotypic effects in individuals carrying a given mutation. This variability can include the type and severity of symptoms and the age of onset of symptoms.

Examples of autosome-dominant disorders: familial hypercholesterolemia, amyloidosis, osteogenesis imperfecta, the Marfan's syndrome, Huntington's chorea, polydactily.

Autosome-recessive disorders

Autosome-recessive conditions are clinically apparent only in the homozygous state. The following features are characteristic:

- the parents are clinically normal;
- only sibs are affected, and vertical transmission usually does not occur;
- consanguinity (единокровность) can be a contributing factor;
- if both parents are carriers for the same autosome-recessive gene, the probability for disease in offspring is 0.25, for a heterozygote (carrier) it is 0.50, and for a normal (noncarrier) offspring it is 0.25.

Examples of autosome-recessive disorders: phenylketonuria, alkaptonuria, lysosomal storage diseases, glycogenoses, hemochromatosis, hemoglobinopathies, galactosemia.

X-linked disorders

The genes responsible for X-linked disorders are located on the X chromosome, and the clinical risks are different for the two sexes. Since a female has two X chromosomes, she may be either heterozygous or homozygous for a mutant gene, and the mutant allele may demonstrate either recessive or dominant expression.

Examples of X-linked recessive disorders in humans include glucose-6-phosphate dehydrogenase deficiency, testicular feminization, color blindness, hemophylia A and B, Bruton's agammaglobulinemia.

COMPLEX DISEASE TRAITS

In complex disease traits, also known as multifactorial diseases, multiple genes and nongenetic factors interact to contribute to the presence or absence of disease in a single individual. One example of a complex disease trait is type I, or insulin-dependent, diabetes mellitus where familial clustering is believed to involve at least one gene, including the HLA region and the insulin gene. No one gene appears to contribute the major effect for type I diabetes.

CHROMOSOME DISORDERS

Trisomy of every chromosome except chromosome 1 has been observed in spontaneous abortions, trisomy 16 being the most frequent. The viable trisomies are those involving chromosome 21, 18, or 13 in order of decreasing frequency. Sex chromosome trisomies (XXY, XYY, and XXX) are compatible with intrauterine survival, whereas autosome-trisomies rarely permit survival to term.

The phenotype produced by the extra chromosome 21 is called the Down syndrome or trisomy 21 syndrome. It is characterized by a variety of moderate-to-severe mental retardation. Typical clinical features also include the flat facial profile, oblique palpebral fissures — mongolism.

The Kleinfelter's syndrome is caused by the addition of an extra X to the male complement (47, XXY). The extra X interferes with the survival of germ cells and causes atrophy of the spermatogenic tubules and azoospermia. Patients with the Kleinfelter's syndrome have small testes, infertility, gynecomastia, and a variable degree of under and rogenization, sometimes with mild mental deficiency. More extreme phenotypic effects and mental

deficiency result when more than one extra X chromosome is added to the normal male complement (48, XXXY or 49, XXXXY).

Monosomy: loss of the Y or of the second X has drastic effects on development causing the Turner's syndrome. This syndrome has the manifestation in the subsequent life: short stature, infantilism of the female external and internal genitalia, germ-cell-free gonads, and variable renal, cardiovascular, skeletal's and ectodermal anomalies.

4. DISORDERS OF REGIONAL CIRCULATION AND MICROCIRCULATION

Typical forms of disorders of regional circulation include disorders of circulation in the medium size vessels and in microvessels. Typical disorders or regional circulation are presented in fig. 4.

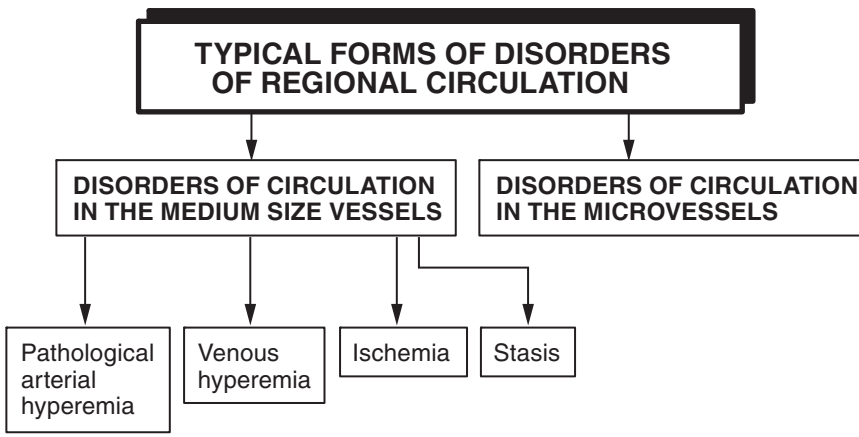

Fig. 4. Typical forms of disorders of regional circulation

Arterial hyperemia is characterized by a local deposition of the blood and an increased blood flow rate through the organ or tissue resulting from a dilation of arterial vessels. Pathological arterial hyperemia, compared physiological one, does not correspond to metabolic demands of the organ or tissue.

Mechanisms of arterial hyperemia:

- neurogenous mechanism — a decrease in the sympathetic drive tone;
- humoral mechanism — local accumulation of vasodilator substances: kinins, histamine, prostaglandins, leukotrienes, nitric oxide, adenosine, hydrogen and potassium ions, carbon dioxide;

- neuromyoparalytic — atrophy of sympathetic fibers and vessel smooth muscles following a prolonged compression of organs or tissues.

Manifestations and their mechanisms:

- redness — reduction of deoxygenated hemoglobin in the capillaries and venules;
- an increased temperature — an increased inflow of the warm blood from the body core;
- vessel pulsation;
- slight swelling — mild accumulation of fluid in the interstitial space resulted from an increase in filtration rate;
- an increased number of functioning capillaries — opening of precapillary sphincters;
- an increased lymphatic outflow — mild elevation of interstitial hydrostatic pressure.

The most common form of arterial hyperemia seen clinically is reactive hyperemia.

Reactive hyperemia is due to humoral and myoparalytic mechanisms. When the blood supply to tissue is blocked and then is unblocked, the flow through the tissue can increase to about five times normal. The duration of reactive hyperemia corresponds to the duration of the ischemic period. Reactive hyperemia may exert harmful effects that result from increased production of free oxygen radicals with the following membrane damage and an impairment of intracellular calcium exchange. Moreover accumulation of the blood during arterial hyperemia increases intracranial pressure that may cause a reduction of the cerebral blood flow and brain mass displacement.

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

Mechanisms of venous hyperemia:

- compression — tumor, swelling tissue, scar or tourniquet;
- obstruction thrombus or embolus;
- heart failure;
- a decrease in venous wall elasticity combined with vein extension and constriction;
- venous valves failure.

Manifestations and their mechanisms:

- cyanosis: accumulation of deoxygenated hemoglobin in the capillary bed;

- edema: elevation of hydrostatic pressure in veins and capillaries;
- decreased local temperature — a decrease in the rate of metabolic process and a reduced inflow of the warm arterial blood from the body core;
- distension of venous vessels;
- a decreased lymphatic outflow — high interstitial hydrostatic pressure that impairs the mechanisms of the lymph outflow.

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

Ischemia is an imbalance between the supply and demand of the organ or tissue for blood. Therefore ischemia may be classified as ischemia of supply, demand or both. Ischemia implies insufficient oxygen and nutrients delivery and inadequate removal of metabolites.

Mechanisms of ischemia:

- obstruction or compression of arterial vessels by tumor, scar, tourniquet, atherosclerotic plaque, thrombus and embolus;
- an increase in blood viscosity resulting from polycytemia;
- spasm of arterial vessels: increased sympathetic drive, excessive production of adrenaline, angiotensin II, thromboxane, some leukotrienes and endothelin;
- an increase in metabolic demand outpacing the blood supply;
- rapid lowering of the systemic blood pressure as in shock or collapse;
- the combination of the listed above.

Manifestations of ischemia and their mechanisms:

- a decrease in diameter and number of visible vessels;
- pallor: a reduction of hemoglobin in the capillary bed;
- a decrease or disappearance of arterial pulsation;
- a reduction of lymph output resulting from a decrease in interstitial pressure caused by a reduction of water filtration from capillaries into the interstitial space;
- a decrease in local temperature due to a reduced blood inflow and a decreased rate of oxygen-dependent metabolism;
- a reduction in functioning the capillary bed.

The consequences of ischemia: necrosis, hypotrophy, atrophy and sclerosis. In moderate and prolonged ischemia apoptosis may also occur.

Stasis is a cessation of the blood flow in the microcirculatory bed.

Types of stasis: true stasis, ischemic stasis and venous-congestive stasis. True stasis begins with cell aggregation and cell adhesion to the vessel wall and is followed by hemodynamic changes.

Microcirculatory disorders

All disturbances of the microcirculation can be divided into intravascular, transmural and extravascular.

Intravascular disturbances of microcirculation

Causes of intravascular disturbances.

- Hemodynamic disturbances: ischemia, arterial and venous hyperemia, systemic hypotension.
- Alterations of blood fluidity: polycythemia, severe leukocytosis in leukemia, hyperproteinemia.
- Formation of microthrombi, aggregates of cells, sludging of blood.
- A decreased deformability of blood cells.

Forms of intravascular disorders of microcirculation:

- slowing of the blood flow;
- inadequate acceleration of the blood flow;
- non-laminar blood flow;
- excessive shunting of blood over arteriolar-venular anastomoses.

Transmural disturbances of microcirculation

They may be caused by increased or decreased permeability of blood vessels and take the form of:

1. An increased permeability of blood vessels.
2. A decreased permeability of blood vessels.

Mechanisms of an increased vascular permeability include: the formation of endothelial gaps, cytoskeletal reorganization, an increased transcytosis, the detachment of endothelial cells from the basement membrane and the distention of the capillary wall.

A decreased vascular permeability is caused by edema or accumulation of hyaline or amyloid.

Extravascular disturbances

Extravascular disturbances appear due to a decreased flow of the interstitial fluid. The rate of the interstitial fluid exchange depends on the rate of fluid filtration and lymphatic outflow. The rate of filtration depends on hydrostatic capillary pressure, the permeability of the capillary wall, and the density of the capillary bed. The lowering of lymph flow may result from an abnormal low or high interstitial hydrostatic pressure, and impairment contraction of endothelial cells forming lymphatic capillaries.

Sludge-phenomenon is defined as aggregation, adhesion and agglutination of blood cells, mainly erythrocytes, with further separation of blood into small and large cell aggregates and plasma. Mechanisms of the sludge-phenomenon are presented in fig. 5.

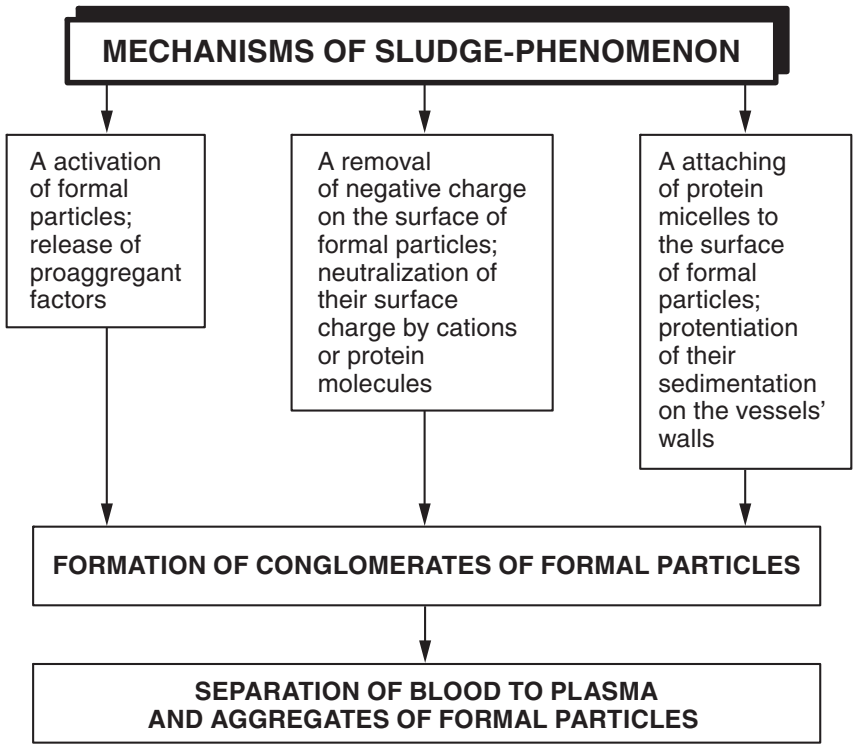

Fig. 5. Mechanisms of sludge-phenomenon