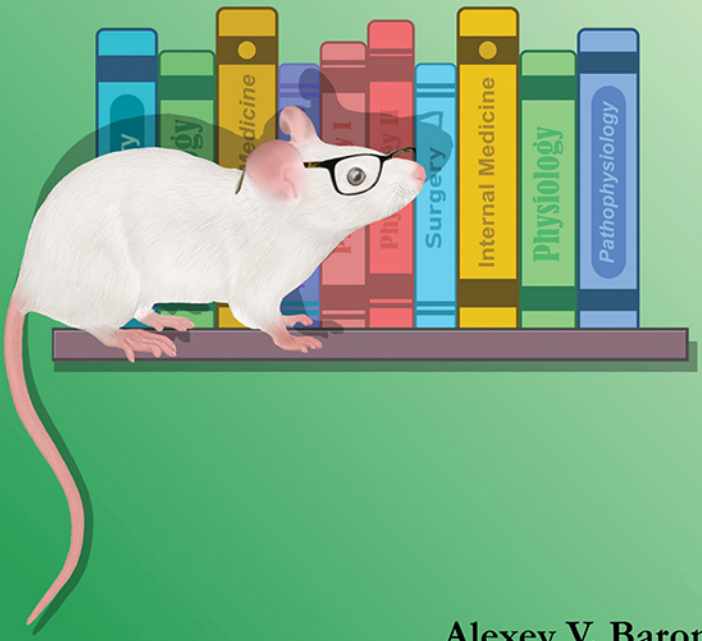
Easy Medicine for Biologists



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INTRODUCTION

People have mastered atomic energy, learned to fly, descended to the bottom of the oceans, and are able to study cosmic objects that are billions of lightyears from the Sun. However, we are subject to numerous diseases and the biological limit of a human's lifetime remains the same as in the Stone Age. Such a strange contradiction is not connected indifferently to our own existence. On the contrary, since ancient times people have been keenly interested in the causes of old age, diseases, and death. Interest in these issues is genetically programmed, since it is a meaningful manifestation of the self-preservation instinct; however, the answers require the accumulation of an extremely large amount of information about both man and wildlife. This accumulation of knowledge has been accomplished slowly, with stops and periods of degradation along the way. Therefore, it took almost five thousand years for medicine to approach its current state.

The centuries-long development of medical knowledge has evolved from the most common ideas about the nature of diseases to understanding their essence. Such a vector of development is absolutely natural, since only a detailed knowledge of a specific disease makes it possible to recognize and effectively treat it in a timely manner. The number of already known human diseases is extremely large, so while it is good to understand them all, this is an impossible task for any doctor. However, a doctor of any speciality should have a sufficient idea of what the disease is in general, its essence, the laws of its pathology development, and the principal differences in illness and health.

This knowledge is not only necessary for medical workers. Man emerged due to the evolution of organic matter over the course of billions of years. From his fossil ancestors, he inherited the principles of organizing the genome, an anatomical structure, a chain of metabolic processes, and a way to regulate physiological functions. Since these principles, chains, and methods are largely universal, one can learn a lot about the biology of other living beings that inhabit our planet when studying human medicine.

At the same time, people, as well as any living being, are born, live, and die in continuous interaction with a changing external environment. The unfavorable influence of the external environment can lead to the

development of a variety of diseases. This occurs so often that disease must be considered as an optional, but practically unavoidable variant for not only human existence but also for all other species of animals, plants, fungi, myxomycetes, or microorganisms. It follows that a biologist needs a certain amount of medical knowledge. Meanwhile, under standard education programs, students of biological specialties are devoted to studying the laws of life processes in detail, mostly within the limits of the norm. For a biologist, everything that is outside the norm can seem to be a kind of chaos that goes beyond the laws of life and rational explanation; this is completely untrue. Yes, medicine is not an exact science, but it is surprisingly logical.

Where should we begin if we want to understand medicine?

It is best to start on the sea shore. The ocean has been filled with medicine throughout the history of mankind. In order to describe it, we have used a system of special terms and concepts. Without getting acquainted with the basics of this system, medicine cannot be understood. First of all, it is necessary to have an understanding of health and disease.

1

General Concepts

Health and Disease

Unfortunately, there are no precise criteria that make it possible to clearly separate the notions of "health" and "illness" and, for several thousand years, medicine has used approximate definitions. In particular, according to the definition by the World Health Organization (WHO), health should be understood as ***"a state of complete physical, spiritual and social well-being, and not only the absence of disease or physical defects"***.

The essence of such a definition is quite understandable, but reliable units to fully measure well-being have yet to be invented. Therefore, every time a person is recognized as either healthy or sick, it is not a question of the presence of one of these conditions but, instead, the degree of their probability. In order to assess the state of the body, a set of qualitative and quantitative data are compared with the standard values for body temperature, heart rate, cholesterol concentration in the blood, and many other indicators. This approach greatly simplifies the diagnosis of diseases; however, it does not eliminate all problems.

The first of such problems is the impossibility of establishing uniform norms for all people, due to the fact that they differ in terms of genotype, age, environmental conditions, way of life, and previous diseases. Ideally, we would be able to provide a definition of individual norms for each living human, for each period of their existence, and their response to every sharp change in environmental conditions. In practice, this cannot be done; therefore, averaged norms are used for separate, yet relatively homogeneous, populations: men, women, children, old people, inhabitants of different climatic zones, representatives of different professions, nationalities, followers of various diets, and so on.

Another age-old problem relates to determining the number of criteria needed to assess the likelihood of a disease or health issue in each particular case. The more such criteria are used, the more reliable the answer to the question will be; however, this will also increase the cost of

determining the diagnosis. In practical medicine, when a disease is suspected it is necessary to establish a minimum acceptable list of indicators to be studied. It is clear that under such restrictions there can be no complete confidence in the results, although the additional factor of time helps: if the disease cannot be detected immediately, then after a certain period its signs may become more pronounced.

So, what is health? In addition to the World Health Organization's definition, health can be understood as *a* ***condition in which the body is able to maintain the optimal composition of its internal environment, to support the morphology given by the genome, and to have the sufficient reserve capacity of systems, organs, tissues, and cells.***

Therefore, disease[1] should be understood as the state of the organism in which at least one of these conditions is not fully met.

The quantitative characteristics of these conditions are variable, but the limits of the allowed values can be determined for them. Namely, these boundaries are used in practice to solve the "healthy/sick" dilemma. However, in addition to complying with classical anatomical features, we have to remember such boundaries are relatively arbitrary. For example, a person who has undergone a tooth extraction, or who has scars on their skin, should not be formally recognized as healthy, but also it would be wrong to treat them as sick. For this borderline category in medicine, the term "*practically healthy person*" has been adopted. This definition is used when a person has certain deviations from ideal health, but these deviations do not significantly affect his performance or his quality of life in general. In prosperous countries, the majority of the population conforms to the category of practically healthy people. However, this means that almost every person, excluding those defined as sick, has a health issue, even if it is small.

This situation is quite natural, if only because the number of already known human diseases is extremely high. The current International Classification of Diseases contains about 20,000 names and the number of options reaches 68,000, but these figures are not final because, according to some, estimates of the number of human diseases may stand at more than 100,000. Not surprisingly, with this number of diseases, the average probability of being sick is very high.

[1] In medical literature, the term "*pathology*" is often used as a synonym for *"disease*".

There are so many diseases that it is impossible to compile a full list of them within the framework of a single classification. Relative clarity in this issue can only be achieved by using several basic criteria in parallel. Currently, the main classifications of human diseases are as follows:

Etiological classification: Depending on the etiology, all diseases are divided into infectious (bacterial, viral, fungal) and non-infectious (inflammatory, traumatic, toxic, allergic, professional, etc.).

Topographic-anatomical classification: Diseases are grouped according to the most affected organ: the heart, blood vessels, lungs, brain, liver, joints, teeth, and so on.

Classification by age and sex: Diseases of the prenatal period, newborns, children, adults, and seniors; diseases of men and women.

Classification by generality of pathogenesis: This is the main mechanism of the development of the disease and includes allergic diseases, oncological, inflammatory, hereditary, metabolic diseases, and adaptation.

Disease Periods

The disease is a complex biological phenomenon, which consists of numerous specific and relatively universal changes that occur in the affected organism. However, despite the huge variety of diseases, in most cases they develop according to the following pattern:

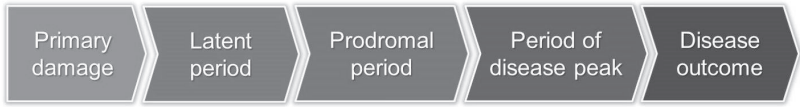

Fig. 1.1. General scheme of the disease.

Primary damage occurs due to the influence of an unfavorable factor from the external environment, the strength of which exceeds the resistance of tissues and which, at first, cannot be compensated for by the adaptive reactions of the organism.

The latent period begins from the moment of primary damage and continues until the appearance of the first external manifestations of the disease. The duration of this period is very variable. It can only be a fraction of a second for a mechanical trauma but, for some infectious diseases (e.g., leprosy, HIV infection, amebiasis) it can stretch for many years. The absence of external manifestations does not mean that the disease cannot be detected in the latent period, but this requires the use of instrumental or laboratory methods of patient examination. It should be noted that the term "latency period" is not synonymous for the term "incubation period", which refers to the time that passes between the moment of infection by a pathogenic microorganism and the moment at which the sick person becomes contagious.

Prodromal period (prodrome): This is the so-called "period of harbingers" (*Greek: προδρομος—harbinger*), albeit not entirely accurately, as the disease is already taking place. "Prodrome" means the interval of time between the appearance of the first manifestations of ill-health to their maximum extent. During this time, at first, nonspecific symptoms common to many diseases—such as fever, general weakness, sleep disorders, or loss of appetite—are found. However, at the end of the period, specific signs or specific combinations of symptoms are present: such as icteric sclera, skin and mucous membranes in acute hepatitis; a characteristic fruity odor in diabetes; tinnitus and so-called "flies before the eyes" in hypertensive disease.

The duration of the prodromal period is also variable, but not as much as the duration of the latent period. For infectious diseases, the time of the prodrome rarely exceeds three days, but it can last for several weeks at its worst. With severe radiation sickness, poisoning, and in especially dangerous infections, the prodromal period can be reduced to several hours; however, sometimes it is completely absent. Immediately after the latent phase, the height of the disease occurs, with the maximum severity of symptoms. This usually happens in the case of very serious diseases.

Period of pronounced manifestations, or height of illness: In the usual course of the disease, at this stage, the clinical picture becomes complete, and there are all, or most of, the inherent pathology signs. That said, in this period, the protective-adaptive capabilities of the body are also used to the fullest degree. In the acute course of the disease, the stress depletes the resources of cells, tissues, and organs. This means that the duration of the period of pronounced manifestations cannot be large, and it rarely exceeds two to three days, after which the outcome occurs.

However, in chronic diseases, the intensity of the process is significantly lower, and the duration of the period of pronounced manifestations can be stretched for weeks, or even months.

Outcome of disease: Recovering is the most favorable outcome of any disease and the most unfavorable outcome is death. Between these extremes, there are transitional options: incomplete recovery, chronic flow, recurrence, and the terminal states.

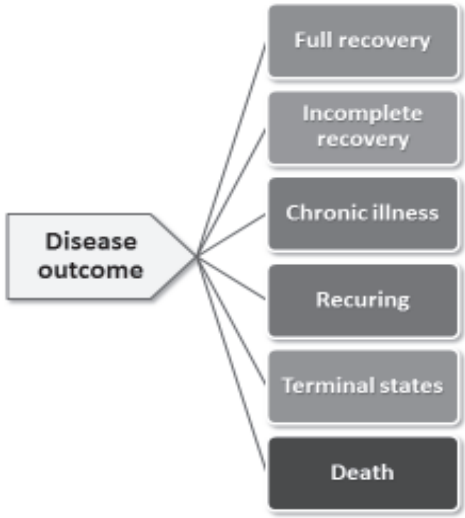

Fig. 1.2. Disease outcome

Recovering is the process of restoring damaged structures and disturbed functions. With complete recovery all the manifestations of the disease disappear and, although a return to the initial healthy state is observed, the formerly ill organism is never the same as it was before the disease. An incomplete recovery that is non-critical for the body can lead to violations of organ functions, anatomical defects in the form of scars, changes in the mass and shape of the organs, narrowing or widening of the blood vessels, and various physiological holes. Sometimes, as a result of additional treatment, an incomplete recovery can be turned into a complete one but, more often, recovery is still incomplete, and a person is recognized as “practically healthy”.

The process of recovery is provided by urgent and long-term mechanisms:

The urgent (emergency) recovery mechanism includes protective unconditioned and conditioned reflexes: withdrawal of limbs from hot or too cold objects, sneezing, lacrimation, coughing, vomiting, sweating, and the narrowing of the pupils in bright light. These urgent mechanisms also belong to the defensive reactions of the regulatory systems that aim to preserve the body's homeostasis: internal temperature, optimal hemodynamics, osmotic pressure and pH of biological fluids, blood glucose concentration, and so on.

The long-term mechanisms of recovery are provided by energy and plastic cell reserves, and the possibility of activating the functions of tissues and organs. They are also due to the mutual assistance of adjacent systems of organs (for example, the respiratory and cardiovascular system). A very important part of long-term recovery is based on the ability of most human cells to divide. Cellular proliferation allows the dead cells to be replaced and the number of the immune system’s protective cells to increase both in the right place and at the right time. The mechanisms of long-term recovery include the migration of phagocytic cells to the foci of pathology, phagocytosis and humoral immunity; increased blood supply to damaged tissues; poison detoxification processes; and connective tissue reactions (cicatricial wound healing, for example).

The coordination of various mechanisms of recovery is carried out by the nervous and endocrine systems, as well as by numerous protein factors of intercellular interaction.

Transition to chronic form, remission and recurring: There are situations when the amount of pathological change is counterbalanced by the protective and adaptive capabilities of the organism. In such cases, when the course of the disease continues for a long time, the disease becomes chronic.

Recurring is the term for the new manifestation of the disease (exacerbation) after remission (a period of relative well-being). A recurrent disease flow develops when the cause of the disease has not been completely eliminated. Under this condition, the accidental weakening of the body’s defenses, by additional adverse environmental effects or premature cessation of treatment, causes the exacerbation of the dormant pathology. An important common feature of chronic and relapsing diseases is that both of these outcomes are not final. Sooner or later, they are replaced by either recovery or death.

Terminal states:

Pre-agony develops after a serious illness or massive trauma. At this stage, the central nervous system is upset due to the loss of consciousness. Violations in the regulation of the tone of the smooth muscles of the arteries lead to a sharp drop in blood pressure (systolic pressure can drop to 60mm Hg and below). The deterioration of the blood supply is manifested in cyanotic or pale skin; in addition, hypoxia causes a reflex increase in heart rate and dyspnea. Pre-agony can last from several hours to several days, after which it passes either into a state of terminal pause, or directly into agony.

Fig. 1.3. Terminal states

Terminal pause has clear distinctive features. In this state, breathing stops for a few minutes. There are no diagnostically important corneal reflexes and a temporary cardiac arrest is possible. The duration of the terminal pause varies from a few seconds to several minutes, after which the agony begins.

Agony *(Greek: αγωνία—struggle)* can last up to several days. At the beginning of the period, in the absence of consciousness and when there is an inhibitory effect in the brain cortex, the activation of the brain's subcortical centers often occurs, which is manifested in uncoordinated motor excitement, resulting in convulsions. It might also involve the involuntary emptying of the bladder and intestines, as well as a short-term increase in blood pressure due to spasms in the blood vessels. Breathing will gradually become superficial and irregular. Arterial blood pressure will drop sharply and the pulse will only be detected on the carotid arteries. Pain sensitivity disappears. Skin covers are pale or cyanotic, as

well as cold and wet. The agony ends with either another terminal pause, or clinical death.

Death (i.e., the final cessation of the life of the organism) happens for three reasons. Death can be considered to be natural when it happens as a result of aging but it can also occur as a result of an accident, murder, and suicide; in addition, when it is due to illness, it can be pathological. Except in cases of massive, life-incompatible injuries, death does not occur as a one-time phenomenon, but as a process of several successive phases called terminal states. Terminal states include pre-agony, terminal pause, agony, as well as clinical and biological death.

Clinical death is confirmed by the cessation of the activity of the main life-supporting systems (cardiovascular and respiratory), as well as the extinction of the most important diagnostic reflexes, such as the pupils' reaction to light. However, even with clinical death, there are still chances of reanimation. This is because at a cellular level, minimal metabolic processes remain for a while due to the accumulated stocks of proteins, carbohydrates, lipids, and the possibility of ATP synthesis in anaerobic glycolysis process. The lifetime of different cell types suffering from a deadly combination of anoxia, acidosis, and uncontrolled proteolysis is not the same. The most highly resistant cells are the least resistant. The viability of neurons in the cerebral cortex stops on average 5 to 7 minutes after the onset of clinical death. However, this interval can be increased to about two hours with significant cooling of the organism, which prevents the decay processes.

Biological death is an irreversible stage of dying, in which not only disorders and injuries occur, but also the death of critical cells in the cerebral cortex; this means the death of the human's personality. Subsequently, the disorganization and decay of other parts of the nervous system, internal secretion glands, internal organs, and integumentary tissues takes place. Biological death is distinguished by distinct external manifestations. In particular, the signs of biological death are rigor mortis, due to the accumulation of lactic acid in the muscles; the appearance of cadaveric spots, due to the accumulation of blood in the lower parts of the body; the opacity and drying of the eyes' corneas; and a decrease in body temperature to an ambient level.

The Disease's Atypical Flow

In conclusion, it should be noted that not every disease passes through all the stages listed above. Many things depend on the force of the harmful

influence or the resistance of the effected organism, as well as whether the correct treatment has been received. Therefore, the combination of different factors determines the disease dynamics in each specific case. Due to the overall activity of the process, several variants of the flow (course) are possible for the same disease.

When the harmful influence is extremely dominant, an ***acute flow of pathology*** may develop, in which the outcome may occur immediately after a prodromal or even after a latent period and, here, the outcome can be unfavorable.

The ***chronic flow*** is characterized by a prolonged period of pronounced clinical manifestations, and this period repeatedly ends and resumes through the variant of the ***recurrent flow***.

When it is infected with viable, but not very active pathogens (tubercle bacillus, hepatitis viruses, some rickettsia), the ***latent flow*** of the disease is possible; although it is inhibited, in the same period, when there is a background of minimal symptomatology.

With proper treatment, or if there is a sharp activation of the body's protective-adaptive capabilities, any diseases can be stopped at an early stage and result in recovery. This is another version of the flow, which is called ***abortive*** (Latin: *abort* means "short"). Usually the abortive flow ends in a latent or in a prodromal period.

Etiology of Diseases

The study of the causes of diseases is devoted to a special section of medicine called **etiology** (*Greek: αἰτία—reason*). The cause is understood to be the primary impact that is the triggering event for the onset of the disease. For several centuries, the causes of diseases have traditionally been divided into external and internal ones. However, after clarifying the nature of hereditary diseases, it became clear that, in this case, the disease begins under the influence of mutagens and thus it is also the result of an external influence. Therefore, in order for the potential threat to have an effect, it must itself be strong enough, or the body has to be sufficiently weakened. If this happens, then the triggering effect that actually caused the disease is called the etiological factor.

The primary defect is the inevitable consequence—and thus indispensable evidence—of a realized ***etiological factor***. This is some kind of damage or violation, from which all other changes that are characteristic of a particular disease develop.

Environmental properties that are potentially dangerous to human health but have not yet caused the disease are considered to be ***pathogenic factors***.

Adverse effects that do not cause the disease itself but increase its possibility are ***risk factors***.

It should be borne in mind that the same adverse effects in different diseases may perform the role of any of these factors. For example, a low ambient temperature is considered to be a pathogenic factor, as it can cause harm to health; in addition, it can be a risk factor for pneumonia and, in the case of frostbite, a low temperature is already an etiological factor.

Historically, there were two opposing points of view on the causes of diseases. Proponents of the ***monocausal*** hypothesis believed that the reason is always singular; for example, infection by specific pathogenic microorganisms, or the impact of a solid thing. In contrast, the proponents of the ***conditionalism*** hypothesis adhered to the point of view that facilitating conditions are necessary—such as the action of risk factors, the weakening of the protective capabilities of the organism, or even both—in addition to the etiological factor.

The situation was clarified by Ivan Pavlov's (1849 – 1936) suggestion that unfavorable environmental factors were ranked according to the strength of their impact. It became clear that the impact of a very strong or especially harmful factor leads to violations or damages that are sufficient for disease to occur without any additional conditions. However, the influence of these extremely strong factors is rare. In reality, a person is much more likely to encounter either moderate or weak adverse effects, and the disease only occurs against a background of additional adverse effects.

It is also necessary to add that, at its onset, the duration, as well as the strength, of the etiological factor is important because with greater contact time, the likelihood of disease naturally increases. It is essential to take into account the peculiarities of the human genotype, since we all have sets of genes that differ in their degree of adaptation to the existing conditions of life. In a less adequate set, the higher the risk of disease, even with mild adverse effects on the body. Due to this, there are people with low resistance to infections and increased bone fragility, as well as a predisposition to obesity, allergies, malignant tumors, diabetes, atherosclerosis, and many other diseases.

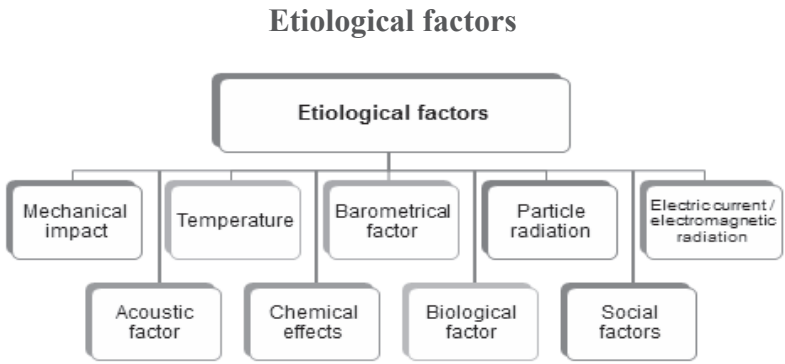

Fig. 1.4. Etiological factors

Mechanical effects: Falls from a height and impacts from solid or sharp bodies, as well as powerful jets of liquid or gas that exceed the limits of the elasticity and strength of human tissues, will cause various forms of injury, such as contusions, crush, bruises, wounds, sprains, or fractured bones. Pathological consequences can also be derived from prolonged contact with solid, vibrating surfaces. This can adversely affect the state of the sensory and motor nerve fiber tips and can lead to vibration disease.

Temperature: The human body is homoeothermic: i.e., able to maintain its internal temperature for a long time under adverse environmental conditions. However, this ability is not absolute and may not be sufficient. A relatively narrow range of ambient temperatures (approximately between +18°C and +26°C) is relatively comfortable for us. Prolonged exposure to low temperatures leads to the development of general overcooling or ***hypothermia***. Local exposure to low temperatures causes frostbite. At the other end of the spectrum, high environmental temperatures cause the body to overheat **(*hyperthermia*)**, which can develop into a state of thermal shock. This can lead to the brain overheating, thereby creating a substantial threat to life. Tissues that are severely overheated or that come into direct contact with fire will develop burns.

Barometric factor: Even minor changes in atmospheric pressure (within a few dozen mm of mercury) often exacerbate chronic diseases in the cardiovascular and respiratory systems of meteorically dependent people. Prolonged exposure to a reduced atmospheric pressure can trigger the onset of altitude sickness, which is also characterized by impaired

activity in the circulatory and respiratory organs. This is associated with the impaired function of the nervous system. It is very dangerous to rapidly reduce external pressure when a diver rises from deep water (*decompression sickness*). This is because the nitrogen dissolved in the blood can form numerous bubbles that impede the movement of blood through the vessels, which can cause the blood circulation to stop completely. Finally, sharp and very significant fluctuations in atmospheric pressure arising from explosions cause contusions and barotrauma, such as a rupture in the eardrum or the lungs. Barotrauma may also be caused by depressurization in an aircraft at high altitude.

Radiation: When it has sufficient strength, any kind of radiation can cause disease. The degree of biological threat correlates with the penetrating ability of the radiation, which is determined by the energy and mass of the emitted particles. Radiation from the visible part of the spectrum, with a wavelength of 380–780nm, has a flux of low-energy quanta and does not have a significant penetrating power. Infrared rays with wavelengths from 740nm to 2000μm exert a predominantly surface thermal effect. However, ultraviolet radiation (λ = 10 – 400nm) penetrates inside the cover tissues and can damage nucleic acid molecules, and in particular can cause malignant tumors.

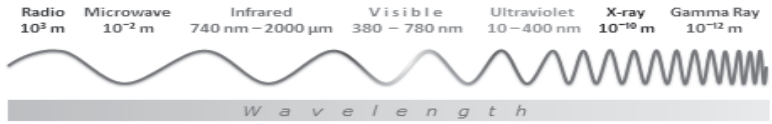

Fig. 1.5. The main types of the electromagnetic radiation

The danger of electromagnetic radiation is determined by its power, frequency, and the duration of exposure. Nervous, endocrine, and immune systems are the most sensitive to radiation and the disturbances in their functions form the basis of radio wave sickness. Strong radiation exacerbates chronic diseases in the nervous, cardiovascular, and endocrine systems, as well as oncological diseases. The same consequences can also occur with prolonged exposure to weak electromagnetic fields.

Sources of electromagnetic radiation are industrial power plants, electric motors, radars, high-voltage transmission lines, and some household electrical appliances. Solar flares also have a negative effect on the health of meteosensitive people. These result in showers of charged

particles reaching the earth, causing sharp fluctuations in the intensity of the geomagnetic field.

The three classic types of ionizing radiation—α, β, and γ—have different degrees of penetrating power: the maximum is γ-quanta. High-velocity fluxes in heavy elementary particles, especially neutrons, also have a large penetrating power. Due to their substantial mass, they are more dangerous to health. Damage caused by various types of radiation breaks covalent bonds, which directly damages the biomolecules and also leads to the formation of a large number of free radicals causing damage to nucleic acids and proteins. As a result, ***radiation sickness*** can develop. When this occurs, the radiosensitive cells of the bone marrow and various kinds of epithelium are the most easily damaged but, when significant amounts of radiation are absorbed, even more resistant cells, including nervous ones, can be affected. Radiation sickness occurs in varying severity from mild to extreme, such as in the case of receiving radiation from lightning, in which a person dies in a few minutes, depending on the dose. In less dramatic cases and even when radiation sickness does not occur, the effect of ionizing radiation can have long-term consequences in the form of oncological or hereditary diseases.

Electric currents: The powerful flow of electrons disrupts the processes of depolarization and repolarization of cell membranes. It is able to disorganize the synapses and cause spasmodic contractions in the muscles and so it is especially dangerous for nerve cells and muscle tissues. The inhibition or cessation of the transmission of nerve impulses can lead to a loss of consciousness, cardiac arrest, or breathing difficulties.

When a current is struck by a living organism, there is always a place for the entrance and exit of the electron flow; these are the places where significant damage to tissues can occur and they can become charred. The path between these points is called a “loop current”. It will be deadly if it passes through the brain or heart. This threat is represented by a current of only 0.35A and a voltage of 36V.

Chemical exposure: Any substances entering the human body from the outside, or synthesized endogenously, even when useful and necessary, can pose a threat to health. Some of these substances are harmful due to the peculiarities of the structure of their molecules, while others are dangerous in excessive quantities. Complex biomolecules that perform informational, regulatory, and catalytic functions are most vulnerable to chemical damage. Poisons with a denaturing action—such as water-soluble salts of arsenic and other heavy metals—can damage protein

molecules. Enzymatic proteins are sensitive to poisons and toxins that can cause irreversible inhibition of the catalytic center (e.g., hydrocyanic acid and its salts or neurotoxins synthesized by poisonous animals). Some end-products of normal metabolism, such as bilirubin or ammonia, have toxic properties; therefore, they are quickly eliminated from a healthy body. Many substances act as chemical mutagens, meaning that they damage nucleic acids. A number of substances possess ***teratogenic*** (*Greek: τέρας—monster*) properties—i.e., the ability to disrupt the interaction of cells in the fetal development of embryos—as a result of which various deformities develop. Finally, ***prions*** cause severe diseases in the nervous system.

Chemical factors are not always pathogenic because of their ability to damage other molecules or supramolecular structures. The excessive concentration of completely normal and necessary molecules can be harmful to the body. In particular, high blood glucose levels upset the osmotic balance between cells and the extracellular environment; extreme dietary lipid consumption increases the risk of disease in the blood vessels; and excessive synthesis of hormones underpins a number of endocrine diseases. In addition, many substances of industrial, plant, and animal origin can cause allergic reactions.

All medicinal substances, without exception, deserve special mention, and not only because they all have side effects. More importantly, the therapeutic effect itself can be toxic to the patient's body, in cases of an increased individual sensitivity to or an overdose of the drug; therefore, medications must be applied professionally and used for the minimum amount of time needed to heal.

Biological factors: The number of creatures that can harm a human is striking. The smallest of them are the viruses and pathogens of a number of diseases. A large number of diseases, including dangerous infections, are caused by bacteria. The simplest unicellular organisms (e.g., giardia and amoeba) and many fungi (ascomycetes, basidiomycetes, etc.) also have pathogenic importance. There is a group of infectious diseases caused by parasitism in the human body due to flatworms or roundworms. Different types of arthropods can be dangerous both in themselves (wasps, bees, scorpions) and due to their ability to carry the pathogens of serious infectious diseases (mosquitoes, cockroaches, fleas, lice, bugs). Small mammals, such as mice, rats, and ground squirrels, are also carriers of dangerous infections. Some infections can be easily transmitted from indoor pets—e.g., cats, dogs, birds, turtles, and even aquarium fishes. Poisons from snakes, as well as some amphibians and fishes, and

mechanical injuries from large predatory animals pose an absolute threat to human health and life.

Generally, a significant number of the species that inhabit our planet are very unfriendly to humans; however, there are exceptions. Some bacteria that harmlessly live in the human intestine supply us with certain vitamins. Others can prevent the reproduction of dangerous microorganisms. Therefore, a balanced composition of intestinal microflora is one of the conditions for human health. The death of beneficial symbionts (e.g., as a result of oral antibiotics) is one of the causes of serious disorders in the digestive system.

Social factors: People live in constant communication with each other. A person's lifestyle, the nature of their professional and interpersonal relationships, and the accumulation of everyday problems all have a significant impact on the psyche. Since the nervous system regulates the activity of important organs, its state is naturally reflected in the organism as a whole. Additionally, the human nervous system is very sensitive to psychological overload. Strong emotions can cause real hormonal storms, leading to spasms in the blood vessels of smooth muscles and hollow organs. It can also have numerous effects at the molecular level, which interfere with the activity of regulated enzymes.

Imbalances in the metabolism contribute to the exacerbation of chronic diseases and the emergence of new ones. The endocrine, cardiovascular, digestive, reproductive, and nervous systems are very vulnerable to neurogenic factors. Therefore, social distress is a major risk factor for mental disorders, coronary heart disease, diseases of the stomach, intestines, biliary tract, pancreas, male and female infertility, and a number of hormonal pathologies. In addition, stress disrupts the work of the immune system, which leads to an increase in the likelihood of infectious and oncological diseases. Finally, strong negative feelings can provoke a state of passion in which individuals cannot control themselves, as they are in the grip of instincts, reflexes, and emotions. In extreme cases, this can lead them to commit murder or suicide.

2

LEVELS AND TYPES OF VIOLATIONS AND DAMAGE

Depending on the type, strength, and location of the etiological factor, the nature, size, and localization of pathological changes can be very different. ***Violations*** or ***disorders*** usually imply forced changes in functions, but distinct structural changes are called ***damages***. Depending on their severity and depth, pathological changes can be both reversible and irreversible. In addition, these changes are divided into local and general. Both of these involve the entire body; all local disorders and damages cause general body reactions. The difference lies in the intensity of the reactions.

The individual combination of disorders and injuries determines the nature and degree of activity in the developing disease. At the same time, pathological changes in ions, molecules, cells, tissues, organs, and organ systems have their own characteristics. The damage and disorders which dominate the organization of living matter depend largely on the specificity of the individual's medical history.

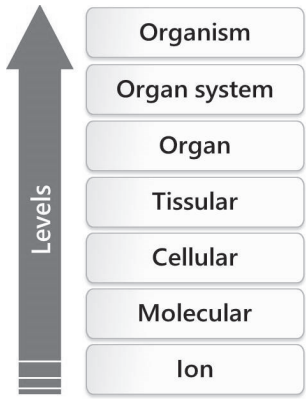

Fig. 2.1. Levels of disorders and damage

The Ions Level

The most important ions for humans are H^+, Na^+, K^+, Ca^{2+}, Cl^-, and HO^-; however, iron, magnesium, manganese, iodine, cobalt, zinc, selenium, and lithium also have biological significance. The number and ratio of different ions can have a great impact on the state of cellular structures and the whole human body. The most important indicators of the homeostasis of the human body, such as osmotic pressure and acid-base balance, depend on the content of various ions in biological fluids; without an optimal ratio of ions, bone mineralization is hampered, and the normal functioning of excitable tissues and implementation of the regulatory effects of some hormones are impossible. Finally, some ions act as coenzymes.

Ions can cause damage when there is a violation of their balance or their content in cells and biological fluids. These disorders are often secondary because they are generated by disorders in the endocrine, excretory, and digestive systems, or poor nutrition.

Ions not only enter the body but also leave it. The main organs performing the excretion of ions, in the absence of violations, are the kidneys, but most of the H^+, Na^+, Ca^{2+}, Cl^- and HO^- ions are reabsorbed and returned to the blood. However, when there is kidney disease, the efficiency of reabsorption may decrease, leading to a deficiency in different ions. Such deficiencies can also occur in cases of severe vomiting, excessive sweating, or prolonged diarrhea.

It is not only an abnormal number of ions but also their specific properties that can be harmful to health. Many metal ions are toxic, especially beryllium and arsenic, but almost all metals have toxic properties, including the ions in iodine, cobalt, selenium, zinc, and iron, despite the unconditional biological necessity of these elements.

Molecule Level

Due to the peculiarities of the chemical composition and structure of molecules, a huge number of substances represent a threat to human health and life. Strong inorganic acids and alkalis are capable of causing the denaturation of proteins, hydrolysis of peptide bonds, and extremely drastic changes in the pH of the medium with the subsequent development of either acidosis or alkalosis. The etiological factors of numerous allergic diseases are protein molecules, a variety of which can provoke abnormal reactions in the immune system. Substances that have a mutagenic, carcinogenic, or teratogenic effect constantly enter the human body via

water, food, and air. Poisons of an organic nature, such as tubocurarine or tetrodotoxin, are very dangerous as they block the functions of the nerve synapses. Additionally, infectious prion proteins can transform normal human proteins into inoperable isomers.

Of course, molecular threats also include the nucleic acids of human-infectious viruses. In addition, some pathogenic microorganisms have a kind of "molecular weapon". An example of this is the hyaluronidase enzyme used by microbes to destroy the non-cellular substance of the connective tissue in order to penetrate the human body. Neuraminidase is another substance that targets the cell membrane, breaking down its heteropolysaccharides, which facilitates its progress into the target cells. A number of pathogenic microorganisms—for example, penicillinase—are able to produce enzymes that destroy antibiotics. Many pathogenic microbes produce dangerous toxins (only one molecule of diphtheria toxin can kill a human cell).

Anti-enzymes are another molecular weapon produced by microbes, and it is because of these that intestinal parasites are not digested by human gastrointestinal tract enzymes. Anti-ferments of tissue and blood parasites block the actions of our phagocytic lytic enzymes. Leeches suck our blood with the help of anticoagulants such as hirudin and tabanin.

At the molecular level, there are disorders as well as damage. The reason for a number of diseases is the lack or violation of the composition and structure of the body's own enzymes. Many diseases are caused by substances that are completely natural and necessary for normal life, when they accumulate in excessive amounts or appear in an inappropriate place. Violations of the content and/or ratios of organic molecules arise due to changes in their rate of synthesis and decomposition in the body, as well as the inadequate exchange between the body and the external environment. For each of these options, the discoordination of metabolic processes is inevitable. Under unfavorable conditions, it can develop into a disease.

Cell Level

Every second a huge number of chemical reactions take place in the cell, and many of these are in opposition to each other. They do not interfere with each other due to ***compartmentalization***: i.e., the spatial separation of incompatible reactions and their convergence.

The provision of the compartmentalization principle is a function of all intracellular structures, especially membranes, and a violation of this principle will occur in any injury. Since the initial cause of damage to both the organism as a whole and its individual cells is due to the action of

external factors, the cell surface will be the first area to make contact with them. Disruption to the membrane transport functions causes further swelling in the cell. Numerous outgrowths appear and disappear on their surface and the cytoplasmic globules can separate from the cell membrane and remerge with it. Within the cell, pathological vacuoles are formed from swollen mitochondria and the cisterns of the endoplasmic reticulum; following this, a violation of compartmentalization and a decrease in the efficiency of metabolism occur. With an unfavorable outcome, edema leads to a special state of hydropic degeneration and then cell death.

Predominantly, damage to the plasma membrane is caused by the action of either physical or chemical pathogenic factors, while biological factors may act differently. In particular, viruses damage the membrane less, due to the fact that they cheat. Harmful particles and molecules get into the cell through the completely normal process of endocytosis; therefore, primary damage can occur in areas other than the plasma membrane. Often this happens when a cell suffers from a lack of oxygen, water, or nutrients, which immediately affects its energy metabolism. Lack of energy or amino acids inhibits the synthesis of critical proteins, including membrane proteins. Erosion of the membranes prevents the maintenance of a normal concentration gradient between the cell and the external environment, which creates a threat of secondary cell edema and the risk of releasing hydrolytic enzymes from lysosomes. These enzymes are able to digest their own cells from the inside. Additionally, lysosomes can be damaged by particles of coal, metals, asbestos, silica, quartz crystals, uric acid, and a number of other substances, which may be randomly absorbed by the cell.

Another sign of cellular distress is the excessive formation of various deposits. Although some cytoplasmic deposits of reserve lipids and carbohydrates are inherent in all healthy cells to a certain extent, disturbances in metabolic regulation can lead to the excessive accumulation of such inclusions, which leads to the degeneration of organelles and even cytolysis. Deposits can be of protein, lipid, carbohydrate, pigment, inorganic, or mixed.

A frequent variant of protein deposits is amyloid infiltration, or ***amyloidosis***. Amyloid is the three-dimensional fibrillar structure of glycoproteins that accumulates in both the extracellular space and the cytoplasm of cells after prolonged intoxication or depletion.

Hyaline has a similar structure but with a slightly different composition and the accumulation of this leads to the development of ***hyalinosis***, or the infiltration of hyaline into the cells and the extracellular medium.

Hyalinosis is not only a consequence of disease but it can also develop as a result of the natural aging of tissues.

Protein-carbohydrate deposits are accompanied by ***mucoid degeneration***, which is where mucus-like contents accumulate in the cells. Pure carbohydrate cytoplasmic deposits, such as glycogen deposits, are also possible.

Lipoproteins, phospholipids, triglycerides, and cholesterol and its esters can also accumulate in cells. Among pigment deposits, the excessive accumulation of melanin, hemosiderin, and colored products of fatty acid oxidation are frequent occurrences. The most common type of mineral deposit is calcification: i.e., the deposition of calcium salts in soft tissue cells. Deposits of iron salts and other metals are also possible.

A violation of metabolic processes that is of sufficient severity or duration can result in damage to intracellular structures. At first, vacuoles and various "garbage" inclusions appear in the nucleus, and, later, chromatin turns into a homogeneous mass (*karyopycnosis*). Then the volume of nucleoplasm is clearly reduced (*karyorrhexis*), after which the nucleus can decay (*karyolysis*). Similar processes (*plasmorexis* and *plasmolysis*) are possible in cytoplasm.

The destruction of the nucleus means the termination of the transcription process and the end of protein synthesis. In the course of progressive degradation, polysome complexes disintegrate; the number of ribosomes decrease; the Golgi apparatus disappears; and microtubule proteins and microfilaments are depolymerized. The number of mitochondria also decrease, while the surviving organoids swell and stretch. This leads to the disappearance of cristae, the spatial separation of the respiratory chain enzymes and the inhibition of the oxidative phosphorylation process. For some time, the cell can survive through the synthesis of ATP in anaerobic glycolysis, but damaged lysosomes quickly release proteases, which are able to catalyze the hydrolysis of peptide bonds in proteins, including glycolysis enzymes. As a result, cytolysis occurs: i.e., the final disintegration of the membranes and the dissolution of cell residues.

The Tissue Level

Biological tissue is a collection of cells of the same type that perform the same function. In humans and animals, there are four types of tissue: epithelial, connective, muscular, and nervous. With certain reservations, this list can also include a special liquid tissue: blood.

Biological tissue is more complex than single cells. This complication opens up both new functionality and new vulnerabilities to adverse factors. Additional opportunities are realized when combining the potential of related cells to meet the needs of the body. However, firstly, the provision of such needs can lead to the depletion of cellular resources and, secondly, synergism is provided by intercellular interactions where malfunctions are possible. For these reasons, integrated cell masses are subject to the additional risks of similar and simultaneous disorders. These disorders are manifested in changes in the state and/or number of cells.

The most frequent pathological change in the state of cells, tissues, and organs is an imbalance in the metabolic processes. Adverse factors rarely lead to increased anabolism, since any synthesis requires a source of energy and this is released during catabolism. Of course, this energy can be used to move cells around the body in order to perform phagocytosis, secretion, muscle contractions, and for the generation of nerve impulses. However, the long-term activation of catabolism means the expenditure of cellular resources, and it is difficult to complete this in a sick organism. As a result, cells, tissues, and organs are all threatened with exhaustion, involution, and the prospect of death.

Degradation may be a consequence of a prolonged decrease in the activity of healthy tissues or organs. This is because low functional activity involves a decrease in the blood supply, which inevitably impairs nutrition. In addition, each of the above reasons can lead to a state of dystrophy and atrophy.

Dystrophy (*Greek δισ—disorder, loss; τροφια—nutrition*): In a narrow sense, dystrophies are deposits of ballast or harmful substances in the cytoplasm of cells and in the extracellular space. In a broader sense, dystrophies imply metabolic disorders in tissues (e.g., muscle) and organs (e.g., kidney dystrophy) or they refer to the overall result of an imbalance in the metabolism between the human body and the environment.

Dystrophies result from:

- ***infiltration***: i.e., excessive income from the blood into the tissues of various substances (cholesterol, fatty acids, glucose)
- ***abnormal synthesis*** of substances that are unusual for healthy tissue (amyloid, hyaline)
- ***transformation*** of molecules of one type into metabolites of others (e.g., amino acids are converted into fatty acids or carbohydrates)

- ***decomposition*** of supramolecular cellular structures into simpler fragments (e.g., the destruction of membranes leads to a local excess of proteins and lipids)

All four mechanisms of dystrophies are triggered following a previous pathological phenomenon, such as excessive food intake, damage to cytoplasmic receptors, inflammation, severe intoxication, circulatory disorders, or allergic reactions. The size of dystrophy foci is determined, on the one hand, by the nature and severity of the primary damage and, on the other, by the protective and adaptive capabilities of the affected organism. With an unfavorable ratio of these opposites, the dystrophy can spread to organs, tissues, and even the body as a whole. When the individual recovers, the signs of pathology disappear in reverse order but the initial state is almost never fully restored. In the case of an unfavorable outcome, dystrophy can turn into atrophy.

Atrophy (*Greek: ατροφια—I do not eat*) This is caused by progressive weight loss, structural involution, extinction of the functions of biological formation due to malnutrition, direct exposure to pathogenic factors, or a forced decrease in functional activity. In terms of prevalence, atrophy may be common and involve the entire body as a result of prolonged fasting, for example, or local, such as brain atrophy due to the excessive accumulation of fluid in the cranial cavity. The loss of mass and activity, as well as the simplification of biological structures, is a less pronounced form, which is known as **hypotrophy**. There is no clear boundary between these two states, and the difference is determined by experts on the basis of the number of signs.

Both atrophy and all types of dystrophies can lead to ***necrosis*** (*Greek: νεκρός—dead*): i.e., the death of a significant number of cells, tissue sections, and even entire organs. In addition to cell death, this process is also accompanied by significant changes in the intercellular substance, where the disintegration of composed substances dominates via the accumulation of non-physiological decomposition products. This complex phenomenon in the pathological anatomy, which includes cellular necrosis and destructive intercellular changes, is called ***necrobiosis***.

The most important condition for the normal functioning of any tissue and organ is the presence of an optimal number of healthy cells; there should be enough of them to perform functions, and it is possible to have a small surplus to form a reserve, but there should be no more than this. The regulation of the number of cells is carried out primarily by the cells themselves. The desire for reproduction is genetically incorporated in

them, so one problem of any multicellular organism is the need to limit spontaneous proliferation. It helps that the cells are able to sense each other through the physical contact of their membranes. Normally, this contact causes the cessation of cell movement, and blocks reproduction. Contact regulation allows the optimal cell size and spatial organization of the tissue to be maintained; however, tumor cells lose their ability to restrict themselves, which is one of the main problems in oncology.

The Organ Level

An organ is a separate anatomical formation of complex biological tissues that performs individual life support functions for a multicellular organism. Any organ can only work effectively with the optimal ratio of different types of cells and tissues. These normal proportions are formed in the period of prenatal development of the organism, when different types of embryonic cells have similar abilities to proliferate. Then, in the course of differentiation, the cells increasingly differ in their rate of reproduction. For instance, in adults, the Betz cells, which are the giant neurons in the cerebral cortex, completely lack this ability. Therefore, the restoration of damaged organs often leads to an imbalance in favor of less specialized cells, which are more resistant to nutritional deficiencies and oxygen; they also possess greater proliferative activity. This happens, for example, after myocardial damage, when a scar takes the place of dead muscle cells. However, the scar connective tissue, where the main cells are fibroblasts and fibrocytes, cannot provide the contractile function in the heart.

The diffuse replacement of specialized cells with connective tissue is called cirrhosis.

Meanwhile, the performance of the specific functions of an organ is ensured by specialized cells: in the heart, these are cardiomyocytes; in the liver, hepatocytes; in the brain, neurons; and in the eye, they are the cones and rods of the retina. At the same time, regardless of the nature of the damaging factor, the most specialized cells are also the most vulnerable in all organs.

As well as individual tissues, organs may be underdeveloped due to genetic causes, insufficient physiological load, or as a result of the in vivo influence of pathogenic factors. These violations are manifested in either a relatively uniform reduction in the size of all cell types, which is characteristic of hypotrophy, or in an insufficient number of cells, which is known as ***hypoplasia*** (at their most severe, these phenomena are called

atrophy and ***aplasia***, respectively). The reduction in the number of different cell types can often be disproportionate, and this is known as organ ***dysplasia***. There are possible deviations of an opposite nature, which is when the organ size and mass exceed the average statistical norm. In the case of hypertrophy, this occurs due to an increase in the size of the cells that make up the organ. If the organ is enlarged as a result of cell reproduction, ***hyperplasia*** takes place.

The Organ Systems Level

Systems are understood to be organs that are united by common functions and, in some cases, by common embryonic origin. It should be mentioned that since the same organ can perform several biological functions, it can also be part of several systems.

A system may include the main organ (or paired organs) where basic functions are implemented, as well as subsidiary organs providing the transportation of substances, or the distribution of biological effects. So, the lungs are the main organs of the respiratory system. However, without the trachea, through which atmospheric air enters, the lungs' activity becomes impossible and, without the transportation of oxygen and carbon dioxide through the circulatory system, this activity is useless. It is clear that serious damage to any part of this complex may become critical for the whole body. However, if the trachea is blocked by a foreign body then an operation is possible to allow the air to enter the lungs through an incision below the tracheal overlap area. A deficiency in the blood circulation can be partially compensated for by reducing physical activity or by intensively working the lungs. However, any pronounced pathology of the lungs—e.g., the accumulation of fluid in the alveoli (known as *pulmonary edema*)—makes breathing insufficient to sustain life, regardless of the state of the trachea or the circulatory system.

Therefore, violations of the main organs of the system are the most dangerous.

Traditionally, the human organ systems are designated as follows:

Table. 2.9. Basic systems of the human body

System	Organs	Main Functions
Musculoskeletal	Skeleton, muscles, fascia, tendons, ligaments	*Supporting; mechanical protection; moving in space; mitigation of shocks and vibrations; formation of the blood cells; exchange of calcium, iron, copper, and phosphorus; thermogenesis*
Respiratory	Respiratory tract, lungs, pleura, respiratory muscles, blood vessels, skin	*Gas exchange with the atmosphere, the elimination of water and volatile substances, thermoregulation*
Digestive	Oral cavity, esophagus, stomach, intestines, digestive glands	*Digestion and absorption of food, neutralization of hazardous substances and microorganisms, excretion of waste products*
Cardiovascular	Heart, blood vessels	*Transporting cells, gases, water, nutrients; end products of metabolism; protective and regulatory molecules*
Lymphatic	Lymphatic vessels, lymph nodes	*Transporting water, substances, white blood cells; protective functions*
Excretory	Kidneys, ureters, bladder, urethra, skin	*Excretion of water and metabolic end products; thermoregulation*
Nervous	Brain, spinal cord, nerves, nerve plexus	*Regulating the functions of organs and systems; ensuring the reactivity of the body; regulating metabolism*
Endocrine	Endocrine glands, mixed secretion glands, the local hormone synthesizing cells	*Regulating organs and metabolism functions; ensuring the reactivity of the body*
Immune	Bone marrow, thymus gland, lymph nodes, spleen, tonsils, appendix, skin	*Neutralization of cancer cells, dangerous microorganisms and molecules; elimination of degradation products; alien tissue rejection*
Reproductive	***Men:*** testicles, epididymis, prostate gland ***Women:*** ovaries, fallopian tubes, uterus, mammary glands	*Childbearing*

This is a consistent pattern. It is also important to take into account that any organ from any system does not constitute a morphological monolith or something homogeneous. Each organ has critical parts, and damage to these areas leads to the most adverse consequences. For example, the main organ of the central nervous system is the brain, and the most serious consequences arise when its stem section is damaged, as this is where the centers for regulating heart and lung activity are located.

Of course, damage to the main organ of the system is not the only thing that is dangerous. All parts of the system work to perform common functions.

Therefore, another pattern is that ***damage or dysregulation in any organ leads to an increase in the load on other organs in the system***.

Therefore, a decrease in the patency of the arteries in atherosclerosis causes the heart to contract increasingly frequently, and damage to one kidney causes the second one to work harder. But intensive work also requires the expenditure of reserve resources, thereby making the affected organs more vulnerable to additional pathogenic effects; it also contributes to new manifestations of previously compensated disorders.

This is also a pattern, which is valid not only within the system in which it originates, as it extends to both the interactions in the conjugated systems (cardiovascular and respiratory, nervous and endocrine, etc.) and the interactions in similar cells within a tissue or organ. At the same time, a moderate increase in load leads to hypertrophy and increased functionality, but an excessive load is undoubtedly a damaging factor.

The Whole Organism Level

The organ systems, with the exception of reproduction, must perform the basic task of ensuring the viability of the whole organism. This is only possible with the coordinated work and harmonious interactions of all the systems. These interactions occur within the whole organism and can also be broken.

The most common and most dangerous of all is discoordination in a system, which occurs due to primary nervous disorders or the endocrine regulation of metabolic processes. In addition, a serious primary pathology in any of the systems reduces its ability to respond to changing conditions and effectively interact with adjacent systems. It is also important to note that damage in one system will lead to the overloading of other systems.

For example, lung disease can lead to general body hypoxia. When these conditions occur, the cardiovascular system is forced to work more intensively. Conversely, heart disease leads to slower blood flow and the same hypoxia, which requires the activation of the respiratory system. At the same time, long-term intensive work depletes the organs and makes them more vulnerable to the effects of additional pathogenic factors. As a result, the “domino principle” can occur, which is when disease in one system leads to a disruption in the activity of or damage to other systems.

A human has social behaviors that can dominate the biological needs of the body. In such cases, the organ systems function for a long time in non-optimal conditions when they have increased loads and with insufficient nutrition or aeration. Intellectual work is accompanied by an overload of the nervous and endocrine systems, as well as hypotrophy of the musculoskeletal, cardiovascular, and respiratory systems. Additionally, intensive sports are associated with overloads in almost all systems. A number of professions are characterized by the dominant hypertrophy of individual muscle groups to the detriment of other organs and systems. Pathological dependencies on nicotine, alcohol, and drugs, as well as the irregular or unlimited consumption of food, cause enormous harm. Disorders that affect the natural rhythms of changing sleep and wakefulness, as well as work and rest, are extremely unfavorable for health.

Together and separately, all of these factors contribute to the formation of imbalances in the interactions between the systems and individual organs, and this increases the likelihood of disease. From a medical point of view, such factors should also include a passionate propensity for any type of activity, even if the subject is science, painting, music, or literature.

***Omne nimium nocet*:** all unnecessary harm (lat.).

3

PROTECTIVE AND ADAPTIVE OPPORTUNITIES IN THE ORGANISM

The long evolution of protective and adaptive mechanisms occurs at all levels in the structure of multicellular organisms, but it starts with ions and individual molecules. Finding opportunities to prevent the disease and eliminate both its causes and pathological consequences is a protective factor. The body's adaptive capabilities aim to compensate for the violations and injuries caused by the disease. Often these opportunities are realized in parallel: reinforcing and complementing each other. Depending on the type of etiological factor, severity, and level of the injury or disorder, the body can use different combinations of protective and adaptive capabilities, which also increase the chance of recovery.

Ion Level

One of the most important constants of the human body is the ratio of H^+ and OH^- ions in all cells and biological fluids. The normal pH level of the medium is in the range of weak alkaline values that are optimal for the functioning majority of enzyme systems, including intracellular and extracellular enzymes in the immune system. As a result of coevolution, many microorganisms that are pathogenic for humans have adapted to live in a neutral or slightly alkaline environment. However, an effective ionic barrier in the form of gastric juice has been created by nature in order to protect against these microbes. Hydrochloric acid in a healthy stomach provides a pH level between 1.5 to 3 units. Such an environment is destructive for many bacteria and protozoa. Lysosomes are also very acidic, which helps these organelles to digest multiple proteins and nucleic acids, including viral DNA and RNA.

The role of ions is indispensable with regard to facilitating the activity of a number of enzymatic and transport proteins; the generation and transmission of nerve impulses; muscle contractions; bone mineralization; the synthesis of hormones; and the realization of their biological effects. Each of the usual biological functions can acquire a protective/adaptive

value with corresponding damage or impairment. Due to the biological importance of ions, their content and ratio must be strictly controlled. Individual control over the content of particularly important calcium and sodium ions are exercised by the nerve and endocrine systems.

Molecule Level

The molecules that perform protective functions are primarily proteins. Receptor proteins help to recognize pathogens and harmful molecules. Structural proteins in plasma membranes prevent the penetration of harmful molecules into the cell. The most important protective role is played by immunoglobulins of various classes, which bind and promote the elimination of harmful substances, as well as the molecular fragments of dead cells in their own organism.

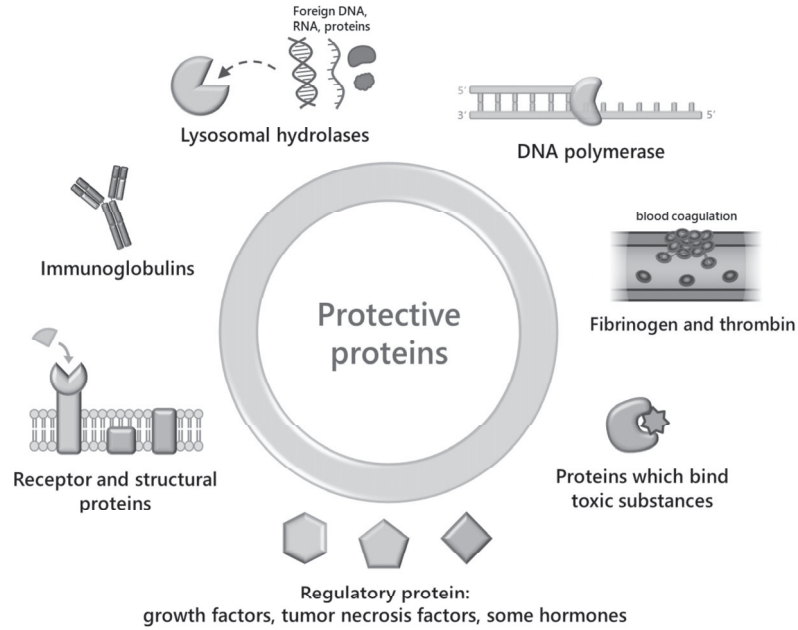

Fig. 3.1. Protective proteins

Protective tasks are also performed by enzymatic proteins, such as lysosomal hydrolases that break down foreign DNA, RNA, and proteins.

For example, the enzymatic restoration of the damaged nucleic acid molecules in the body, and the repair of damaged DNA sites using DNA polymerase I complex, has adaptive importance. Without enzymes, reparative protein synthesis, as well as the regeneration of organs and tissues in general, is not possible. In addition, a number of enzymes are involved in the process of blood coagulation. Enzymes are needed to neutralize toxic substances. The reserve capacity of enzyme systems is essential for the timely performance of all these functions. In a healthy body, most enzymes work a long way below their possible limits; however, in the event of an emergency, key enzymes in the metabolic chains can be activated, which allows cells to quickly synthesize molecules (for example, immunoglobulins, growth factors, and structural proteins) or use more energy.

A number of regulatory proteins (growth factors, tumor necrosis factors, some hormones) provide the body with the ability to quickly respond to any damage and disorders that may occur.

In addition to proteins, many low-molecular-weight organic molecules perform protective functions. Cardiolipin phospholipid ensures the impermeability of the mitochondrial inner membrane for most undesirable small molecules. Another example of this kind is a group of non-protein reducing agents: glutathione, ascorbic acid, and L-cysteine. These substances bind the active forms of oxygen that arise during the metabolism process and protect the surrounding biomolecules from oxidative damage.

The action of ionizing radiation in irradiated cells dramatically increases the content of free radicals in general, and reactive oxygen species in particular, which results in chemical damage to the nearest biomolecules. When this happens, reducing substances play the role of natural radio protectors; glutathione and L-cysteine, which have the sulfhydryl group SH in their composition, are crucial for this process as they provide an excellent trap for free radicals and ions. Substance-reducing agents are also capable of binding many poisons and toxins. As a result, these agents are also natural antidotes.

Cell Level

Any cell has a certain resistance to adverse effects. First, it is stabilized by the barrier functions of the cell membrane system: cytoplasmic, nuclear, lysosomal, and mitochondrial. Secondly, the reparative potential of cells—their ability to synthesize new molecules to replace lost or damaged ones—is of paramount importance. Thirdly, ***apoptosis*** (the

genetically programmed self-destruction of damaged, infected, and transformed cells that pose a threat to the body) reduces the risk of spreading a number of infections.

It is essential that a healthy cell always has ***trophic reserves***, which allow it to activate protective and adaptive capabilities when they are needed. Another important cellular resource is the ***ability to reproduce***. This is vital in order to replace aging cells, since some cells in our body only live for a few days. The rate of cell-death naturally increases in the presence of a disease, and thus the frequency of divisions in the surviving cells may grow significantly as a result. When tissue is restored after injury or necrosis, the power of cells to reproduce is especially important.

In addition to self-defense, specialized types of cells are endowed with the ability to attack. The body's greatest protective capabilities are found in the ***immune system cells***, which are destined to perform the phagocytosis of microorganisms and tumor cells, as well as any foreign cells.

A special role is played by ***dendritic cells***. They are present in various tissues, but are primarily found in the skin and mucous membranes. Dendritic cells absorb foreign particles, including microbes, and destroy them through fragmentation; some of these particles can be found on the surface of the phagocyte as foreign antigens. Next, dendritic cells move into the spleen or lymph nodes, where the immune system is "alerted" by the interaction of dendritic cells with B-lymphocytes, which produce antibodies, and with T-lymphocytes, which kill microbes and infected cells. Macrophages can synthesize the ***tumor necrosis factor***. Cytotoxic T-lymphocytes secrete ***granzymes***, which are a mixture of proteolytic enzymes that destroy target cells. In addition, T-killers and NK-lymphocytes have the ability to firmly connect with target cells (including tumor cells) and secrete special proteins called ***perforins***. These proteins form holes in the membranes of the attacked cells. With a sufficient amount of damage, maintaining the necessary difference in the concentration of substances and ions between the cell and the external environment becomes impossible and, as a result, the cell dies. Furthermore, leukocytes can secrete ***hydrogen peroxide***, which burns through the cell walls of bacteria, the membranes of tumor cells, and the alien antigen cells. In addition, immune cells are able to synthesize the broad-spectrum ***peptide antibiotics***, which are effective against many bacteria, viruses, and fungi.

We only become ill when any these forms of protection are insufficient.

Tissue Level

At the tissue level, the protective and adaptive capabilities of individual cells are consolidated. The upper levels of these capabilities are usually redundant and represent a tissue "power reserve". Minor disorders or damage are compensated for by these functional reserves. Thanks to the tissue regulatory systems, if a significant part of the tissue is damaged or perishes, the functional activity of all the surviving cells increases. Additionally, long-term pathological processes stimulate hypertrophic and hyperplastic changes in intact parts of tissues.

Hypertrophy appears in cell size and mass enlargement, which leads to similar changes in tissues and organs. However, serious injuries can only temporarily and partially be compensated for by hypertrophy in the surviving cells. Full recovery always requires the replenishment of cell deficiency by the process of tissue hyperplasia.

Hyperplasia refers to an increase in the number of cells, which occurs by way of mitotic division. With a favorable outcome, the result of this process will be tissue reparative regeneration. It usually means not only the restoration of tissues and organs, but also some cellular excess, which underlies hyperplasia.

During ***reparative regeneration***, some types of highly specialized cells have the capacity for partial dedifferentiation and so temporarily return to mitotic division. This greatly increases the regenerative potential for tissues. As the wound heals, the specialized cells should differentiate again.

The ***recombinant transformations*** of structures also help the body to counter pathogenic factors. At the subcellular level, such transformations can lead to the grouping of organelles (mitochondria, ribosomes), which increase their overall biological productivity in the places that they are most needed. At the tissue level, recombinant transformations can occur via interstitial movement and the concentration of motile cells in the lesions of the pathology. This often happens with cells from the immune system, such as phagocytes.

Organ Level

The presence of paired organs (cerebral hemispheres, lungs, kidneys, adrenal glands) acts as an insurance against damage to one of them. In these cases, the surviving organs take on an additional burden through the process of hypertrophy. Hypertrophy can also develop in unpaired organs with a prolonged increase in functional activity. Most human organs are

more or less able to regenerate after damage. This ability is particularly strong in the lungs, liver, stomach, intestines, and skin. It is less pronounced in the kidneys, bones, and skeletal muscles. The nerves struggle to regenerate and the brain and spinal cord cannot be restored sufficiently. However, all organs have a certain capacity for physiological hyperplasia.

Work efficiency may increase as a result of optimizing the ratios of different types of cells in organs and due to the hyperplasia of differentiated cells that perform specialized functions. In addition, all healthy organs have functional reserves; therefore, if it is necessary, they can work more actively. This happens, among other things, when part of an organ is damaged: the area that has survived works harder.

Level of Organ Systems

The adaptive capacity of an organ system is determined by its functional reserve. For example, the heart rate is normally 60–80 beats per minute but, if needed, it can more than double. In crisis situations, the blood pressure may increase and the blood supply to damaged organs, and organs whose functions are key to the survival of the body, will increase. The sum of such changes significantly increases the ability of the cardiovascular system to counteract pathogenic factors. All organ systems have the ability to pool reserves.

One of the advantages of the system is the functional reserves of individual organs complement each other.

In addition, the integration of individual organs that perform similar functions into a single system allows these organs to perform the same biological task in different ways. For example, the main organs in the excretory system are the kidneys, but some harmful substances can also be removed through the intestines, skin, and by exhaling. The importance of alternative excretion pathways increases with significant stress or kidney disease and, in severe cases, life may depend on these alternative pathways.

Furthermore, the integration of organs into systems allows their biological effects to be distributed throughout the entire body. One of the most important conditions for the existence of multicellular organisms is ***genostasis***: the genetic constancy of somatic cells. However, the cells' nucleic acids are exposed to chemical, physical, and biological factors that can change their composition. Most cells that undergo such changes are

destroyed by the immune system through the use of both humoral and cellular defense mechanisms within a single system. The same can be said about other functions of immunity, most of which can only be implemented in a single system.

The Whole Organism Level

The integration and coordination of all protective and adaptive capabilities is carried out at the organism level. All systems of the human body are functionally interrelated, so there is coordination between them. For this reason, the damage of one inevitably affects the condition of the others. However, organ systems can help each other by partially compensating for the decrease in the effectiveness of the affected link. This is manifested especially clearly in the interaction of the organs in the cardiovascular and respiratory systems but, in principle, all systems are involved in the correction of pathological changes, albeit it to varying degrees. In this regard, it is necessary to emphasize that for the coordination of the general vital activity of the whole organism, the regulatory systems—nervous and endocrine—are particularly important.

Finally, it is equally important to note that at the organism level, the most effective of all possibilities for self-preservation is conscious protective behavior due to intelligence.

The presence of intelligence allows us to:

- ***study diseases and develop ways to combat them***
- ***anticipate various threats to health and avoid contact with them***
- ***increase the body's resistance to adverse factors through vaccination, training, strengthening, optimizing lifestyle and nutrition***
- ***apply individual means of protection against pathogenic factors***
- ***use all the capabilities of modern medicine for the timely diagnosis and treatment of emerging diseases***

Conscious behavior and its protective forms especially, is a unique evolutionary advantage in the biological species *Homo sapiens*, which has allowed us to dominate the planet. This advantage should be used by each of us to the maximum extent possible.

4

PATHOGENESIS OF DISEASES

Pathogenesis (*Greek: παθος—illness, suffering*) means the disease mechanism, which includes all the phenomena caused, their sequence and their mutual influence throughout the entire period from the beginning of the pathological process to its outcome. Pathological changes are very diverse; they manifest themselves as a change in the concentration of various ions and molecules, and in violation of the normal anatomical structure of organs and tissues. The overall deviation from the norm in a sick organism is denoted by the term ***alteration*** (*Latin: alteratio—change*).

In a large variety of these changes there are patterns. There must be some kind of primary damage or disorder caused by the action of the etiological factor and the triggering event of the disease. There are the so-called entrance gates of pathology: molecules, groups of cells, or tissues or organs that have been subjected to a primary damaging effect. The primary damage causes a wave of subsequent violations and damage. Among the various changes, it is possible to find the damage or violation that caused all the rest. For example, in the case of influenza, headache and inflammation of the mucous membranes are caused by the presence of viruses in the human body; bleeding may be due to mechanical injury; and manifestations of hemophilia are due to a primary violation of the DNA structure.

Damage or disturbance that triggers or maintains a chain of subsequent pathological changes is called the ***central link of pathogenesis***. The most important practical significance of this central link is that its elimination leads to the cessation of other manifestations of the disease. Therefore, the correct determination of the central link of pathogenesis is fundamentally important in any disease: without the elimination of this "root of evil", full recovery is impossible. In the case of the abovementioned flu, the clinical manifestations of the disease are due to the pathogenic effects of the viral bodies; the presence of viruses is the central link of pathogenesis. Therefore, without freeing the body from viruses, it is only possible to temporarily suppress nasal discharge or headache, but these symptoms will

return again and again after the cessation of therapeutic effects. Treatment aimed at eliminating the central link of pathogenesis is called a ***pathogenic treatment***, and this is the most effective healing. Unfortunately, despite all the successes of modern medicine, it is not always possible. In such cases, in order to alleviate the patient's condition, doctors have to limit themselves to relieving the particular manifestations of the disease with the help of ***symptomatic therapy***, an example of which is the administration of narcotic drugs to patients with incurable cancer.

The body fights for its existence in any situation. This is manifested in the fact that besides the alteration, another mandatory side of pathogenesis is ***sanogenesis*** (*Latin: sanus—healthy*). This term denotes numerous protective and adaptive capabilities aimed at preventing diseases or returning the body to its original state, i.e. health recovery. Sanogenesis is provided by two basic abilities of the body.

First, all of the cells, tissues, organs have mechanical strength, heat and electrical insulating properties, and are distinguished by a certain resistance to chemical influences and the penetration of pathogenic microorganisms.

The sum of all these various capabilities is called ***resistance***, i.e. a genetically and environmentally determined overall stability of the organism and its parts against adverse effects. A second important component of sanogenesis is the body's reactivity.

Reactivity in medicine refers to the ability of both the organism as a whole and its systems, organs, tissues and cells to undertake adaptive and protective changes in response to the actions of harmful factors. Such changes can occur in the form of the use of reserve resources; changes in the activity of enzymes; restoration of damaged tissues; the production of specific antibodies; the directed migration of cells; the combination, activation and coordination of the work of organ systems; and the development of protective reflexes and conscious protective forms of human behaviour.

The dialectic confrontation of violations and protective-adaptive reactions is the basis of pathogenesis and determines the outcome of any disease. If one of these opposing forces prevails, the disease proceeds progressively, and it ends either in death or in recovery. This dynamic variant of pathogenesis is called the ***pathological process***. This option is observed in acute forms of diseases, relapses and exacerbations of chronic diseases.

However, there is not always a predominance of damage or restoration; sometimes these opposing phenomena can balance each other over a very

long period of time. In this case, there is a ***pathological condition***, very characteristic of chronic diseases.

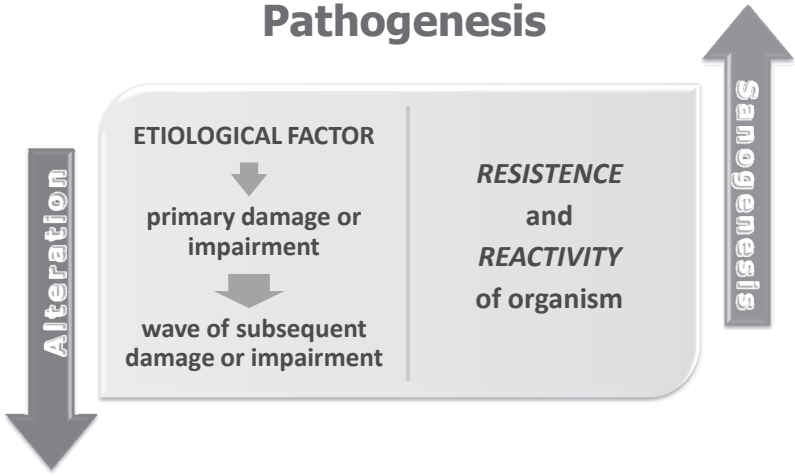

Fig. 4.1. Basics of pathogenesis

It is important to understand that the pathological process and the pathological state are intertwined. For example, pulmonary tuberculosis may have an active course, when the foci of infection and damage to these organs increase and merge. This is a typical pathological process. However, as a result of treatment or the natural activation of immunity, the infection can recede, remaining only in separate delimited loci, called "Ghon centers," each of which represents a typical version of the pathological condition. The tubercle bacilli, which survive in such pockets, become able to multiply again and begin to spread if the body's defenses are weakened or the treatment is stopped prematurely, at which point the pathological process resumes.

Pathological reaction is another frequently used notion. This term is understood as an inadequate or inappropriate response of the body's systems to various stimuli. Examples of such reactions can manifest as pathological reflexes by the nervous system or the excessive activity of the immune system. A common feature of pathological reactions is that they are secondary; they develop as a result of disorders or injuries that have happened before.

The terms "pathological process", "pathological condition" and "pathological reaction" are not identical to the concept of "disease".

Disease refers to the whole complex of pathological and protective-adaptive changes that encompass the body, including the reactions of tissues, organs and systems that have not undergone primary pathological effects.

For instance, a single furuncle (purulent inflammation of the skin hair follicle) is considered a pathological process. However, if boils occur regularly or are located in multiple places simultaneously, this is categorized as a furunculosis—that is, a disease. A significant feature of a disease is that it may include more than one pathological process, reaction or condition. In addition, during the development of a disease, one pathological process can generate other pathological processes or conditions, the severity and ratios of which are highly variable.

In this regard, a very important point is that one pathological process is capable of generating another pathological process, and this other process can support the first one. In such cases, ***circulus vitiosus*** *(Lat.)* is formed—a vicious circle of pathological changes, in which the chain of disorders acquires the ability of self-reproduction. For example, severe pain can cause a sharp drop in blood pressure followed by tissue hypoxia. Oxygen starvation of the brain vasomotor centre prevents the normalization of the blood pressure, hypoxia persists, and thus the vicious circle of pathological changes closes.

The rupture of a vicious circle of pathological changes (if it is present), as well as the elimination of the main link of pathogenesis, are indispensable conditions for the complete cure of any disease.

Cessante causa cessat effectus*—elimination of the cause eliminates the consequences (Lat.).*

5

TYPICAL PATHOLOGICAL PROCESSES

The number of potential threats to human health is huge, so our bodies do not have the ability to defend against each of them using a special biological technology. Instead, evolution has gone through the creation of a limited amount of relatively universal complexes of protective and adaptive reactions that can counteract a significant number of heterogeneous pathogenic factors. These standard reaction complexes are the basis of ***typical pathological processes***, which, with some nuances, manifest themselves in many very different diseases. For example, a typical pathological process of hypoxia may occur due to a lack of oxygen in the air, as a result of diseases of the lungs, heart or blood, after mechanical injuries, due to the action of certain poisons and under considerable physiological loads.

Another characteristic feature of each typical pathological process is that very diverse factors are able to trigger chains of surprisingly similar or even almost identical damage and disorders, since the targets of the damaging effects are ultimately the same cellular structures—enzymes, receptors, structural proteins, plasmatic, nuclear, lysosomal or mitochondrial membranes. Therefore, typical pathological processes are to some extent universal: the same basic process, with some variations, can occur in very different diseases. The difference in the pace of its development and in the intensity of the pathological manifestations depends on the extent of the damage, which structures are damaged the most, and on which organs these lesions are mainly localized.

The concept of typical pathological processes in medicine was formed a long time ago. But, oddly enough, there is still no single final list of such processes. The generally accepted typical pathological processes are hypoxia, inflammation, fever, and stress. The authors of this textbook support the point of view that such processes as tumour growth, aging, eating disorders, and some others can also be included in this list. At the same time, we consider various types of shock and coma to belong to a separate group of extreme states.

Pain

Pain is an unpleasant, sometimes unbearable feeling that occurs after mechanical, thermal or chemical irritations of the sensitive nerve endings in organs and tissues. The cause of pain can be an inflammatory process in which histamine and other substances that can cause pain are released from damaged cells. In addition, prostaglandin inflammatory mediators increase the sensitivity of nociceptors to chemical and thermal stimulation.

Pain receptor irritations occur with a huge number of diseases. This is due to the fact that the main biological function of pain is as a signal, allowing the body to mobilize for the elimination of the cause or consequences of the pathological effects regardless of where these effects occur. Such a function is vital, so pain receptors are omnipresent, and even minimal tissue damage leads to the activation some of them. Pathologies that occur without pain are still possible, but they are very rare. As a rule, such forms are caused by the primary pathology of the pain signal system itself.

This system is quite complicated. A typical nerve contains sensitive, somatic and autonomic motor fibres. Depending on the thickness, the presence or absence of the myelin sheath and the speed of propagation of the pulse, they are divided into groups A, B and C. Sensitive fibres of type A come in four subspecies—Aα, Aβ, Aγ and Aδ. Pain sensitivity is provided by thin myelin fibres of type Aδ, and also thin non-myelinic fibres of type C; these fibres terminate in the skin, internal organs and tissues receptors. Such receptors are called “nociceptors” (*Latin: noceo—damage*).

Pain impulses spread through the nerve fibres and enter the posterior horns of the spinal cord, from where excitement spreads:

- along the ascending afferent tracts to the brain to the reticular formation, thalamus, hypothalamus, to the basal ganglia and the limbic system, after which the pain is perceived and evaluated in the cerebral cortex and followed by conscious behavioural and unconscious vegetative reactions
- on the motor neurons of the spinal cord, which triggers protective motor reflexes, such as the involuntary withdrawing of a hand from a hot object
- on the neurons of the lateral horns of the spinal cord, as a result of which the adrenergic system is activated, which regulates, in particular, the tone of the arterial smooth muscle

From the above information, it is clear that pain is not only a signal of ill-being, but that it also has a protective-adaptive value, because it makes possible a change in behaviour and activates a number of useful reflexes—the involuntary pulling away of a hand from a hot object, for example. However, severe or prolonged pain causes disturbances in the nervous and endocrine systems, which can lead to an exacerbation of chronic diseases or the emergence of new ones. The pain provokes the development of stress reactions; very severe pain can provoke a state of pain shock, which represents an immediate threat to life. Therefore, nature provides physiological possibilities for reducing the intensity of pain.

The endogenous regulatory peptides enkephalins and endorphins (i.e., "internal morphines") have this ability. It is known that the same structures—the opiate receptors—are the site of action for both endogenous and exogenous narcotic drugs. Morphine and its analogues, as well as endorphins, can inhibit the release of neurotransmitters from the endings of nerve C-fibres, which leads to an increase in the pain threshold. Extreme stress, hypnotic trance and some mental disorders can lead to a significant increase in this threshold, up to a temporary loss of the ability to feel pain.

However, in some cases, the sensitivity to pain may increase, since the neurons of the medulla oblongata, which control the painful neurons of the spinal cord, can both inhibit and facilitate the conduction of a nerve impulse and even provoke pain. In the latter case, the feeling of pain does not arise because of some damage to the peripheral tissues: it will be false, or "imaginary". Therefore, the feeling of pain is largely subjective, and each person experiences it in his own way. The perception of pain depends not only on the location and strength of the injury, but also on the psychological state of the person, and on the characteristics of his personality.

Hypoxia *(Greek: ὑπό—below and Latin: oxigenium—oxygen)*

In most of the cells of the human body, the majority of the chemical energy obtained from food is digested and stored via processes that require a constant flow of oxygen. The path of oxygen delivery is intricate; the satisfaction of the oxygen demand of cells is influenced by many factors. The first of these is the oxygen content in the surrounding atmosphere. The adequate performance of the respiratory and cardiovascular systems, whose activity is regulated by the nervous and endocrine systems, is very important. Further satisfaction of the oxygen needs of the body is impossible without the presence of sufficient erythrocytes—a high number

of which must contain a sufficient level of normal haemoglobin—in the blood. Finally, the ability of consumer cells to absorb oxygen is not constant, and also depends on the influence of a lot of other factors. All of this creates numerous vulnerabilities to disruption in either the transport or the absorption of oxygen; therefore, some degree of hypoxia is inevitable in almost any disease.

Hypoxia is both the cause and the most significant constituent of metabolic disorders that lead to cell death. Hypoxia is omnipresent: it can occur in any part of the body, even in a healthy body, with prolonged or intense muscle exertion. This pathological process may be generalised, encompassing the entire body, or local, manifesting in individual tissues and organs. Acute and chronic hypoxia can be distinguished by duration. Depending on the activity of the mechanism that gave rise to the hypoxia, it can manifest itself both as a pathological process and as a pathological condition. Hypoxia is divided into the following main forms:

Hypoxic hypoxia occurs due to reduced oxygen content in the atmosphere. This happens in enclosed, poorly ventilated premises, in the unsealed cockpits of aircraft at altitudes above 10,000 feet, as well as during mountain climbing. A decrease in the partial pressure of atmospheric oxygen below 12.7 kPa (105 mmHg) leads to ***hypoxemia***, an insufficient amount of oxygen in the blood. As a result of reflexively-increased respiration, this is followed by an accelerated elimination of carbon dioxide from the body. Such an elimination leads to a state of ***hypocapnia***, a low CO_2 content in the blood. Hypocapnia is a very significant moment of pathogenesis. It is carbon dioxide that stimulates the activity of the respiratory centre of the brainstem. The lack of CO_2 contributes to the inhibition of this centre, and breathing slows down. As a result, hypocapnia strengthens the general oxygen deficiency. For this reason, it is detrimental to breathe pure oxygen for a long time. Instead of this, a gas mixture known as carbogen (95% oxygen and 5% carbon dioxide) is used for therapeutic purposes.

Respiratory hypoxia occurs when the respiratory system is operating inefficiently. This may be caused by various diseases of the respiratory tract; diseases of the alveoli, bronchi, intercostal muscles, diaphragm, or pleura; and primary disorders of the functions of the respiratory centre. Respiratory hypoxia is characterized by a combination of hypoxemia with hypercapnia. In an aquatic environment, carbon dioxide forms carbonic acid, the excess of which leads to a state of acidosis. The pH shift to the acidic side can inhibit the work of many extracellular and intracellular

enzymes, which, combined with a lack of oxygen, has a very adverse effect on the metabolism as a whole.

Cardiovascular hypoxia develops due to primary damage to the heart and blood vessels. The resulting decrease in blood circulation leads to a slowdown in the delivery of oxygen to the tissues, and to a slower transport of carbon dioxide to the lungs in the opposite direction. The result of such pathological changes can also be a combination of hypoxemia with hypercapnia.

Hemic (anaemic) hypoxia is a consequence of the deterioration of the blood's ability to transport gases. The transport potential of the blood may decrease due to a lack of red blood cells after bleeding or bone marrow diseases, accompanied by a slowdown in the formation of new red blood cells. This also occurs after massive intravascular red blood cell death as a result of the action of some poisons, or after an incompatible blood transfusion. The pathological forms of haemoglobin, which are contained in red blood cells in the presence of certain hereditary diseases, are another cause of hemic hypoxia.

Metabolic hypoxia occurs with increased oxygen consumption by actively functioning tissues, which happens during intensive work, both physical and mental.

Tissue hypoxia may be of a primary or secondary type.

Primary (cytotoxic) tissue hypoxia develops as a result of a deterioration in the ability of cells to absorb oxygen. Most of the molecules of this gas are used by the mitochondria in the processes of oxidative phosphorylation and free oxidation. A deficiency in vitamin B2 (riboflavin), PP (nicotinic acid) or Q (ubiquinone) will slow down the synthesis of enzymes and cytochromes, or cause a lack of the cofactors necessary for the respiratory chain, which inhibits oxygen consumption. As a result, a paradoxical situation may occur, with signs of hypoxia displayed against a background of normal or even elevated O_2 in the blood and cells within. Much more dramatic is the variant of tissue hypoxia which develops as a result of poisoning by prussic acid (HCN) and its salts, since cyanides irreversibly inhibit cytochrome oxidase—a key enzyme of the respiratory chain—which can lead a person to death in a few minutes. Another dangerous cytochrome oxidase inhibitor is carbon

monoxide (CO). The mitochondrial stage of biological oxidation can also be inhibited by alcohols, including ethanol, and certain drugs.

Secondary tissue hypoxia occurs as a result of reduced oxygen delivery to the cells, or accelerated oxygen use. The reasons for this may be a decrease in the partial pressure of O_2 in the atmosphere, or diseases of the respiratory system, cardiovascular system or blood, i.e., one of the forms of hypoxia listed above. These variants can exist in combination, resulting in a **mixed form of hypoxia**, which is the most common occurrence.

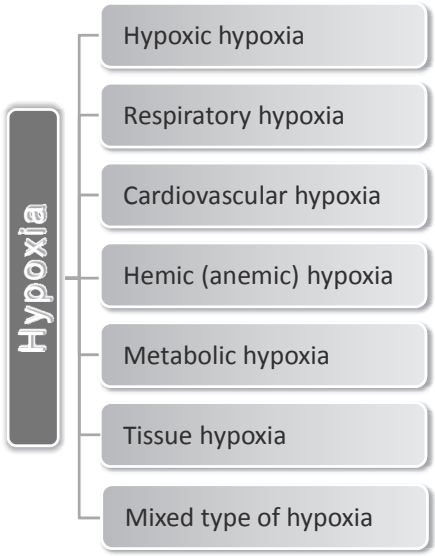

Fig. 5.1. Forms of hypoxia

Common to all of these variants of hypoxia in cells is that the synthesis of ATP and other macroergs decreases. The deficiency of these naturally leads to the inhibition of energy-dependent processes (the synthesis of biomolecules, transmission of nerve impulses, reduction of muscle fibres, and transmembrane transport of substances). The compensatory activation of glycolysis in combination with a slowing down of the Krebs cycle leads to the accumulation of lactic acid and further intracellular acidosis. The combined adverse metabolic effects of hypoxia cause damage to the membrane structures, followed by cell disintegration.

Of all the organs, the brain is the most sensitive to oxygen deficiency, especially the brain cortex. The death of its highly differentiated neurons begins when there is a complete cessation of oxygen access to the brain for 4–6 minutes. Hypoxia for the same duration (for example, in case of acute blockage of the coronary arteries of the heart) is enough for the development of myocardial infarction, and about thirty minutes of acute oxygen starvation is enough for severe necrotic changes in the kidneys. All other organs also suffer damage from a lack of oxygen, although irreversible changes in them develop after a longer time spent without oxygen.

Acute hypoxia is initially manifested by a general excitation of the nervous system, with some discoordination of movements, an uncritical attitude to the environment, and mild euphoria, which resembles the symptoms of alcohol intoxication. Following this, there are colour changes in the skin and mucous membranes, which can manifest as paleness, cyanosis, or reddening of the skin. Dyspnoea, headache, an increase in heart rate and an increase in blood pressure are also characteristic. As oxygen starvation increases, impairment of skin sensitivity to various stimuli are possible, there is deterioration in vision and hearing, arterial pressure begins to decrease, disorientation occurs in time and space, and this is followed by a loss of consciousness and the prospect of death. Less severe but prolonged hypoxia is characterized by decreased labour efficiency, emotional apathy, slower reactions, chronic headaches, loss of appetite, and a tendency to depression.

For any of its forms, the most effective way to combat hypoxia is to eliminate its causes. If this is not possible, a complex of standard protective-adaptive reactions is activated in the body, which includes more intensive work of the heart and respiratory system, as well as a sharp decrease in physical and mental activity. With severe hypoxia, since oxygen enters the tissues through the blood, the adaptive phenomenon of the “centralization of blood circulation” can develop. In this case, the blood supply to the organs that are relatively less important for survival (skin, muscles, genitals, intestines, and omentum) is reduced to maintain the maximum possible blood flow to the brain, heart, lungs, kidneys, and liver. In chronic hypoxia, long-term adaptation mechanisms—which include an increase in the number of red blood cells circulating in the blood, an increase in the haemoglobin saturation of erythrocytes, the activation of myoglobin synthesis in muscles, and the induction of the synthesis of the enzymes used in the anaerobic energy process of glycolysis in all tissues—have time to work. The basis of medical care during hypoxia is oxygen therapy, in the form of inhaled carbogen.

Ischemia

A very common disorder that occurs in a variety of diseases and pathological processes is the violation of local blood circulation. These local disorders, in combination with a complex of primary disorders caused by hypoxia and nutritional deficiencies, are called ischemia *(Greek ισχω—delaying; αἷμα—blood)*. It must be emphasized that ischemia and hypoxia are not the same thing. Ischemia is understood to mean the combination of hypoxia, nutritional deficiencies and initial metabolic disorders that develop as a result of a decrease in the efficiency of the blood supply to the tissues.

Causes of circulatory disorders can be:

- ***a general decrease in blood pressure*** due to heart disease, hypotension of arterial smooth muscle, or as a result of blood loss
- ***violation of local blood flow*** as a result of external compression, spasm of the vessel, or its blockage by atherosclerotic plaque, thrombus or embolus

Any serious illness disrupts the activity of the circulatory system in some way. Therefore, any serious disease that is sufficiently developed will be complicated by ischemic manifestations. Pathological changes in tissues that occur during ischemia belong to the category of disturbance or disorders. Usually, such changes are reversible over a period of time. The duration of this period depends on the severity of blood flow disorders, the sensitivity of tissues to hypoxia, and the level of the general reactivity of the organism. If ischemia is not eliminated in time, the beginning of necrotic processes in the tissues is fatal for these tissues and cells. The cerebral cortex and the nervous system as a whole, the myocardium, adrenal glands, and kidneys are most sensitive to ischemia. Statistically, the most frequent manifestation of chronic ischemia is coronary heart disease, and the most dangerous manifestations of acute ischemia are heart attacks and strokes.

Thermoregulation Disorders

For nucleic acids, most enzymes, structural proteins and lipids of the human body, the optimum temperature is approximately between +35° C and +37° C. The human organism is of the homoeothermic type, i.e., it is capable of maintaining a constant temperature, regardless of changes in the ambient temperature, if these changes are not too significant and

lasting. The necessary internal temperature of the body is maintained due to the thermoregulation system developed during evolution. Thermoregulation is carried out by physical and chemical mechanisms.

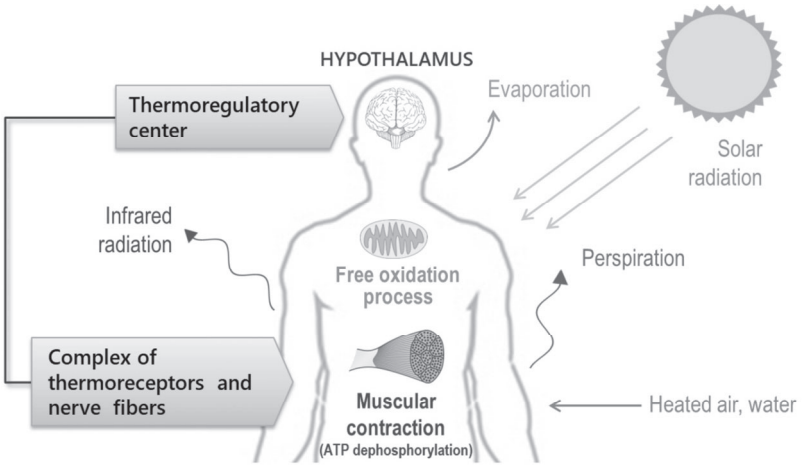

Fig.5.2. A heat transfer scheme of the human body and the environment

Physical mechanisms include the infrared radiation of the human body, the evaporation of water from the surface of the skin and mucous membranes of the respiratory organs, the release of heated faeces, as well as the heating of the environment on contact, if it has a temperature lower than the body temperature. Physical mechanisms are responsible for heat transfer, which is usually the elimination of excess thermal energy from the body. However, they can work in the opposite direction when the ambient temperature exceeds the temperature of the human body.

Chemical mechanisms are responsible for heat production, or thermogenesis. The body generates most of its heat during the process of free oxidation, which occurs in the mitochondria of cells. Partial heat production is also provided by muscle contractions, accompanied by local endogenous hyperthermia. Heat can also come from outside the body, when it is exposed to direct sunlight, heated air or water, and various hot objects.

The balance between the processes of heat production and heat transfer is provided by the thermoregulation system. This system consists of a thermoregulation centre located in the hypothalamus of the brain; a complex of thermoreceptors distributed throughout the body; and the

conductive impulses of nerve fibres. Under normal conditions, the thermoregulation system is very effective, but when exposed to strong pathogenic factors, its capabilities may not be enough. Factors that can disrupt the temperature balance of the body include the actions of substances that can separate the processes of oxidative phosphorylation and free oxidation in mitochondria, as well as prolonged external exposure to low or high temperatures. The violation of thermoregulation leads to either hypothermia (chill) or hyperthermia (overheating) of the body.

Hypothermia (a decrease in body temperature) may be exogenous or endogenous. Exogenous hypothermia occurs during prolonged contact with a cold external environment. The causes of endogenous hypothermia may be insufficient motor activity, or diseases of the thyroid gland and adrenal cortex, which are accompanied by a decrease in the incretion of iodothyronine and glucocorticosteroid hormones, respectively. Another hypothermia variant can be triggered by the use of drugs that reduce the activity of the pituitary and adrenal glands.

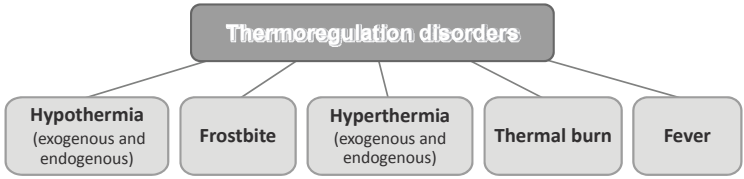

Fig. 5.3. Forms of the thermoregulation disorders

Exogenous hypothermia goes through three stages of development in its typical course. At the first stage, the internal body temperature remains normal due to a reflexive decrease in heat transfer and an increase in heat production. As the organism's cooling continues, thermoregulation disorders begin in the cover tissues. These are manifested in the expansion of the small blood vessels of the skin, which leads to an increase in heat transfer, but, in parallel, the heat production increases. Over time, the skin temperature decreases, and the lower and upper extremities cool down, but the temperature of the internal organs persists almost unchanged. However, the gradual cooling of the internal organs occurs at the third stage of hypothermia due to the impaired metabolic regulation processes. This is followed by the inhibition of the physiological functions of the organs. Critically, the central nervous system's activity decelerates. This leads to a loss of the sense of danger, to an uncritical attitude towards the

situation, and the desire to fall asleep. By this time, the person is no longer disturbed by unpleasant sensations, since the pain receptors in frozen skin have ceased to work. As hypothermia progresses, the external respiration is weakened, the work of the heart is slowed down, and the arterial pressure decreases; hypoxia of a mixed type develops. Very often the person falls asleep. The lack of oxygen reduces the efficiency of oxidative processes in the mitochondria, heat production falls below a critical level, and ATP synthesis stops, which subsequently leads to cardiac arrest and the cessation of respiration.

Frostbite is local tissue damage under the influence of low temperatures. Frostbite is possible not only in severe frosts, but also at temperatures close to 0° C in conditions of high atmospheric humidity and low muscle activity. Most often, the fingers and toes, nose, cheeks and auricles are frozen. The central link in the pathogenesis of frostbite is persistent spasms of vascular smooth muscle, which is a defensive response to the cold that reduces heat transfer. However, the same reaction limits the nutrition of tissues and contributes to the development of hypoxia.

Depending on the degree of damage, frostbite can be categorized as:

I degree: the changes are minimal; after warming up there is a slight pain or burning sensation; oedema develops in the affected area; the skin becomes purple or bluish; after a day or two these symptoms disappear; but peeling of the damaged epidermis is possible

II degree*:* in addition to signs of the first degree, vesicles (bubbles) with a clear liquid appear on the damaged skin

III degree*:* all layers of the skin are damaged, as well as local blood and lymphatic vessels; therefore, the vesicles formed in the skin contain bloody fluid

IV degree*:* not only the skin is affected, but also the fasciae under it: muscles, ligaments, nerves, large vessels and even bones. With good body reactivity, dead tissue is further rejected. In any case, bleedings and infectious complications are quite frequent. The healing process can stretch for months. As a rule, in the place of severe frostbite, coarse connective tissue scars are formed, which is not the worst outcome. In a weakened body, severe frostbite can lead to the development of gangrene, massive tissue necrosis and even necrosis of the limbs

Hyperthermia may also be exogenous or endogenous.

Exogenous hyperthermia occurs as a result of the external overheating of the body, when the incoming heat flux exceeds the capabilities of the heat-disposal systems. Such situations are possible in hot climates, when working in the hot workshops of the metallurgical industry or in overheated living conditions, such as when subjected to heat emission by infrared radiation, or when there is no opportunity to transmit heat away from the body by contact with the external environment. High atmospheric humidity and thick, poorly ventilated clothing, which prevent the evaporation of water from the surface of the body, also contribute to the development of hyperthermia. Sharp exogenous overheating in the form of "heat stroke" is an immediate threat to life, since it can lead to the irreversible damage of cells in the nervous system. A problem common to the various forms of exogenous hyperthermia is the lack of heat emission.

Endogenous hyperthermia, on the contrary, arises due to an excessive increase in heat production inside the organism. Excessive heat production occurs during heavy physical work as a result of numerous muscle contractions, as well as during prolonged emotional stress, which causes the uncoupling of the oxidative phosphorylation and free oxidation processes, due to the influence of the stress hormones on the mitochondria. This dissociation causes a reduction in ATP synthesis, and instead, heat production is enhanced. Iodothyronines have the same uncoupling action; therefore, endogenous hyperthermia is also observed in thyroid gland diseases associated with the overproduction of these hormones. Many exogenous toxic substances have an uncoupling influence. Moreover, toxins secreted by numerous pathogenic microorganisms have such an effect.

Thermal burns are defined as localized tissue damage caused by high temperatures. Just like frostbite, burns are divided into four degrees, depending on the severity of the damage.

I degree is manifested in redness and swelling of the skin

II degree: blisters with a clear liquid appearance on the reddened and oedematous skin

III degree is characterized by the necrosis of the affected skin area, which is subsequently rejected

IV degree: the death and charring of not only all layers of the skin, but also the muscles, ligaments, vessels and nerves underneath, occurs

In severe burns, necrotic tissue is rejected after several weeks, disfiguring scars are formed in their place, and muscle contractures (persistent muscle contractility) are possible.

Just as in the case of frostbite, the danger of burns is determined not only by their degree: the total area of thermal damage is no less important. In either case, the probability of recovery is inversely proportional to the total area of the damaged skin. The breakdown of the damaged tissues leads to the release of toxic molecules into the extracellular fluid, lymph and blood. Such concentrations of toxic molecules cause fever, disrupt the activity of the nervous, endocrine and immune systems, and can damage the kidneys and other internal organs. The quantity of such toxins depends on the degree of the burns and their prevalence. Burns covering more than 30% of the surface of the body are a severe threat to life, even with burns of I degree. Extensive II–IV-degree burns cause a long and dangerous burn-related disease. In this pathology, acute intoxication with tissue decomposition products occurs. In the absence of an effective treatment, the suppuration of burn surfaces may develop, with an intoxication of bacterial origin. At this stage there is often sharp slowdown in the burn healing process. With extensive or deep burns, a deadly burn shock can develop, in which the extent of the unfavourable changes exceeds the protective and adaptive capabilities of the body. Finally, just like after frostbite, gangrene of the damaged tissues can be a complication of burns.

Fever *(Latin: febris)* is understood to mean an increase in body temperature, which has arisen not because of external overheating, but as a result of a decrease in heat output or an increase in heat production in the cells of the organism itself. Fever is a typical pathological process, which is based on the protective and adaptive response of the body, caused by the action of a number of pathogenic factors, called pyrogens.

Pyrogens may be of external or internal origin. Exogenous pyrogens include the toxins produced by many pathogenic microorganisms, snake venom, the excretions of some insects, a number of harmful industrial chemicals, the most well-known of which is 2,4-dinitrophenol. The proteins of transfused blood, therapeutic sera and vaccines can have pyrogenic properties. As a rule, exogenous pyrogens act indirectly through endogenous pyrogens, which induce a displacement of the hypothalamic thermoregulation centre set point. Endogenous pyrogens include some hormones (catechol amines and iodothyronines), non-esterified serum fatty acids, and cellular debris. Immune complexes circulating in the blood can also have pyrogenic properties.

An increase in body temperature in febrile conditions is mainly due to either the direct or indirect effects of pyrogens on the work of the respiratory chain in the mitochondria. As a result of such exposure, there is an increase in the degree of separation of the processes of oxidative phosphorylation and free oxidation, which is accompanied by increased heat generation.

The biological meaning of the fever is that the increase in temperature can create unfavourable conditions for life, and that pathogenic microorganisms have penetrated the internal environment of the human body. This is due to the fact that the optimum temperature for many dangerous microorganisms' enzyme activity is close to the normal temperature of the human body. If this temperature rises, the enzymes begin to work more slowly, which adversely affects the rate of reproduction of the microbes. In turn, the slowed reproduction of the pathogenic microflora allows the body more time for the migration of phagocytic cells to the foci of infection, the synthesis of specific antibodies, the proliferation of immune cell clones, and the mobilization of other protective capabilities of the organism.

On the other hand, an increase in body temperature can slow down the work of the human body's own enzymatic systems and thereby reduce its resistance to pathogenic influences. For this reason, doctors usually prefer to suppress a fever with antipyretic drugs, and treat infections with antibiotics.

Inflammation *(Latin: inflammatio)*

This process is one of the body's general protective and adaptive responses to the action of a large number of physical, chemical and biological pathogenic factors. Regardless of the nature of these factors, inflammation in animals and humans occurs for the purposes of localization and reduction of the damaging effect, the separation of the source of damage from healthy tissues, the removal of decomposition products, the restoration of damaged tissues and the activation of immunity occur.

The pace of the development of these changes, the scale of the violations, and several other characteristics of the process can all vary. In each case, the features of inflammation are determined by the etiological factor that triggered the process; by the sum of the protective and adaptive capabilities of the affected organism; by the anatomical location of the inflammatory foci; and by the presence or absence of adequate treatment.

The aetiology of inflammation is extremely diverse. This process can be triggered by many physical factors—mechanical injuries, frostbite, burns, and various types of radiation. Inflammation also occurs after exposure to caustic chemicals and in response to penetration by numerous pathogenic bacteria, viruses, unicellular and multicellular parasites into the body. A special variant is immune inflammation caused by antigen, antibody and complement complexes. This type, in particular, accompanies various allergic diseases.

The pathogenesis of inflammation in any aetiology and localization usually consists of three phases that are consecutive in the usual course of the process—alteration, exudation and proliferation. However, with only a slight etiological effect, or in a strong and healthy body, inflammation may result in only an exudation or alteration stage.

Alteration *(Latin: alteration—change).* Inflammation begins with primary tissue damage. At first, the defect may be insignificant, but the primary changes entail a chain reaction of subsequent changes, both pathological and protective-adaptive. The lysosomes of the first dead cells release hydrolytic enzymes, which are capable of destroying protein molecules, lipids, carbohydrates and nucleic acids. The uncontrolled catalysis of biomolecules leads to morphological changes in the surrounding tissues and disrupts the balance of the metabolic processes inside the damaged cells. There, in particular, the activity of the Krebs cycle can decrease, which leads to a local increase in the concentration of unclaimed organic acids—lactic, pyruvic, citric, α-ketoglutaric, succinic, malic, and oxaloacetic. A natural consequence of this accumulation is the development of metabolic acidosis, both in the individual cells and in the entire area of the pathological changes.

In the pathogenesis of inflammation, this acidosis plays a dual role. On the one hand, a strong decrease in pH (up to 6.5–6.0 units instead of the usual level of about 7.4) inhibits activity, and may even cause the death of some of the organism's own nearby cells. However, exactly the same inconvenience is experienced by any pathogenic microbes which gave rise to inflammation or otherwise penetrated into the centre later, through damaged tissues. The second circumstance is more important, since the cells of the macro organism can multiply outside the source of inflammation, but bacteria, viruses and pathogenic fungi are forced to reproduce only within this source, at least at the beginning of the process. Therefore, this local acidosis is the first counterattack—the first defensive reaction of a diseased organism during inflammation. The biological grace

of this reaction lies in the fact that it is automatically triggered by the damage event itself, and activated quickly.

In addition, whatever the cause and wherever the inflammation starts, it inevitably spreads to the omnipresent connective tissue. Some of the special mast cells scattered in the connective tissue—labrocytes—are inevitably damaged, which leads to the next stage of the inflammation process: exudation.

Exudation *(Latin: exsudo—go out, stand out)*. A histamine—an inflammatory mediator—is released from damaged mastocytes in the focus of the inflammation, which can irritate pain receptors and increase the permeability of the walls of the small blood vessels. So begins the early phase of exudation, which refers to the release of the liquid part of the blood from the vessels into the inflamed tissue. Other inflammatory mediators—serotonin, kinins, the complement system—also contribute to this process.

The early phase of exudation begins 10 to 15 minutes after the beginning of the process of inflammation, and after a few hours this gives way to the late phase, which can last up to several days under the influence of another group of inflammatory mediators, which, in particular, includes prostanoids. The combined effect of all these biologically active substances causes an increase in the permeability of the vascular walls. As well as this, the blood vessels expand, which increases the filtration area. In local arterioles, venules and capillaries, the oncotic pressure decreases due to protein loss, which also contributes to exudation. However, colloid osmotic pressure rises in the surrounding tissues. Furthermore, oedema is formed, squeezing the blood vessels and leading to an increase the hydrostatic pressure inside. This increase in hydrostatic pressure, combined with an increase in the permeability of the walls of blood vessels, also accelerates the release of fluid and blood cells into the focus of the inflammation.

The changes arising during exudation have a double effect on the general state of the body. First of all, a low blood supply leads to the development of local hypoxia and impairs the nutrition of tissues. Widespread oedema interferes with the normal physiological activity of the organs and can lead, for example, to impaired gas exchange in the lungs, stagnation of bile in the liver, or impaired urine in the kidneys. Even more dangerous is the swelling of the meninges, which causes increased intracranial pressure and dysfunction of the brain.

However, exudation plays a clear protective and adaptive role. Due to this phenomenon, immunoglobulins, plasma enzymes, and phagocytic cells get into the focus of inflammation from the blood vessels more

easily. In addition, exudation enhances hypoxia and acidosis, both of which create unfavourable conditions for the life and reproduction of pathogenic microorganisms. Finally, the compression of regional vessels reduces the rate of propagation of microbes and harmful substances throughout the body.

Proliferation *(Latin: proles—scion, offspring and Latin: fero—carry*). During exudation, various types of white blood cells accumulate in the inflammatory focus. After several acts of phagocytosis, most of them die; it is leukocyte cells at different stages of decay that give the characteristic look to pus. However, during the cytolysis of leukocytes, regulatory proteins that stimulate the proliferation of predominantly connective tissue cells are released. If the general reactivity of the organism is sufficient, the proliferated fibroblasts form a dense granulation tissue surrounding the inflammatory focus. This is known as a *demarcation shaft*, and prevents the spread of infection, but a scar is subsequently formed from it. With a favourable outcome, everything that is inside the delimited hearth ultimately dies, and is also replaced by some type of scar.

Symptoms of inflammation. Local, so-called "Hippocratic" signs of inflammation have been known since antiquity.

There are five of them:

- ***redness***
- ***swelling***
- ***temperature rise***
- ***pain***
- ***impaired function*** of inflammatory tissues or organs

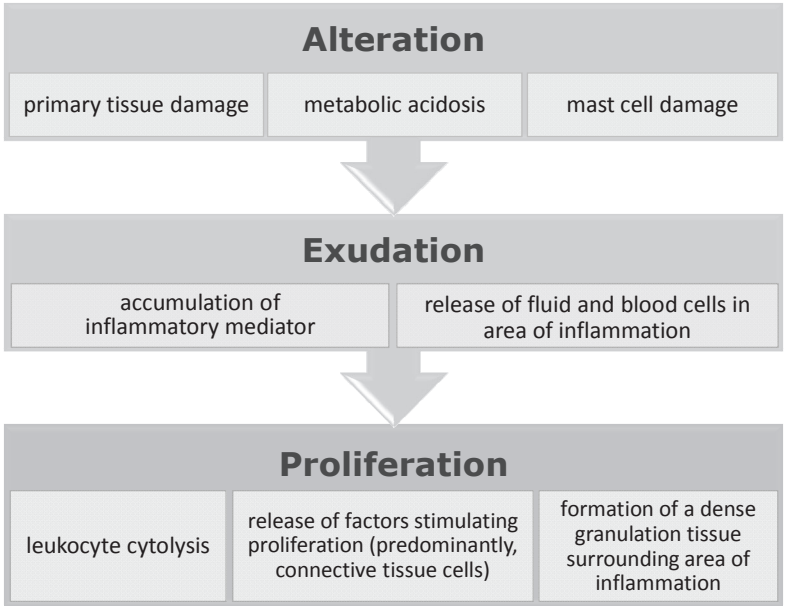

Fig. 5.4. Development of inflammation

In the event that the infection goes beyond the primary focus of inflammation, general body reactions develop, manifested in fever, a worsening of general well-being, and a loss of appetite and ability to work. Modern means of the laboratory diagnosis of diseases allow us to add to this list such signs as an increase in the number of leukocytes in the blood, an increase in the erythrocyte sedimentation rate, and an increase in the concentration of C-reactive protein, sialic acids and fibrinogen in the blood serum. A number of other indicators change, too—some characteristic signs of the inflammatory process are detected by radiology, ultrasound investigations, as well as by computed tomography.

Depending on the individual characteristics of the organism and the nature of the etiological factor, the severity of the three sub processes of inflammation may be different. Depending on which of them dominates in a particular case, inflammation is subdivided into alterative, exudative and proliferative forms. The process is also divided by its activity into an acute, sub-acute, and chronic course. In addition, the diagnosis mentions the preferential localization of the pathology—inflammation of the lungs, liver, muscles, membranes of the brain, etc.

Disorders of Blood Circulation and Lymph Circulation

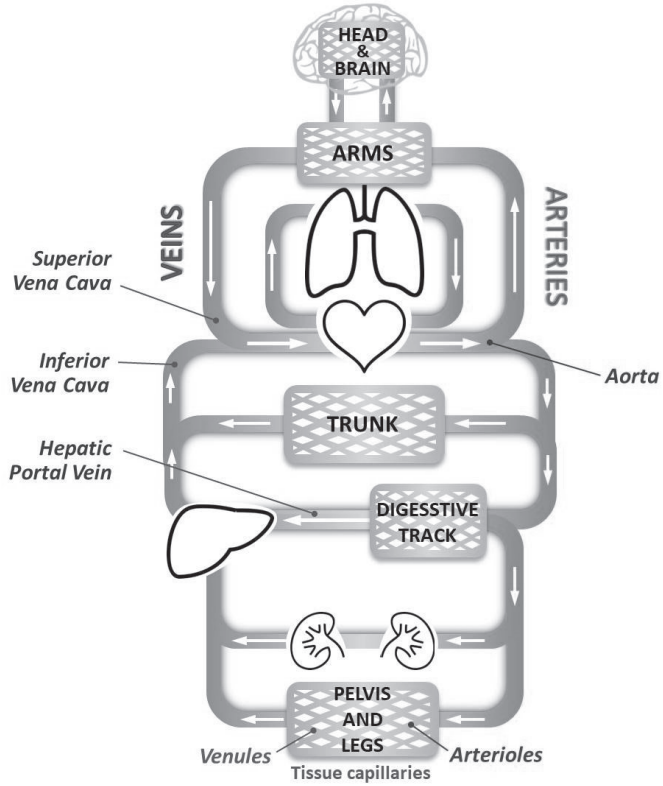

Figure 5.5. Blood circulation pattern

In practical medicine, the circulatory system is divided into three parts—central, peripheral and microcirculatory blood circulation.

Central blood circulation means the movement of blood in the heart and in several main vessels—the aorta, both of hollow veins, and the portal vein of the liver. The system of peripheral circulation includes all the other arteries and veins, thanks to which the organs are supplied with blood. Blood circulation in the smallest vessels—arterioles, precapillaries, capillaries, postcapillaries, venules, and arteriole/venular shunts is considered microcirculatory.

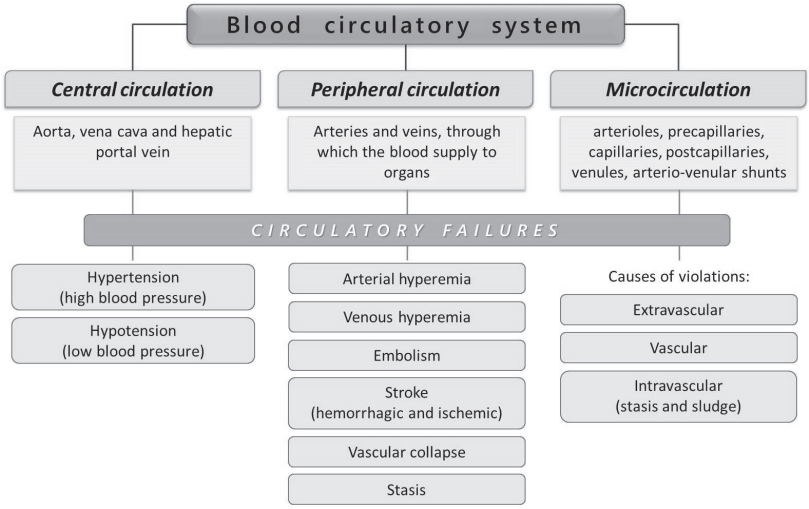

Fig. 5.6. The main types of blood circulation disorders

The pathology of each of these links in a single circulatory system has its own specifics. However, there are several common etiological factors that can disrupt the work of all parts of the system.

The first of these factors is ***heart disease***, leading to a general slowdown of the blood flow in the vessels. At the same time, most often, heart diseases develop as a result of blood flow disturbances in the vessels feeding the heart.

The second factor is a decrease in the circulating blood volume as a result of ***blood loss or uncompensated fluid loss*** through the kidneys, intestines and skin. The reverse is also possible: the volume of circulating blood increases as a result of impaired renal activity, or excessive consumption of water and salt.

The third factor is the presence of a ***disease of the blood*** itself, leading to impaired blood clotting and an abnormal number of circulating cells.

All these changes decrease the effectiveness of the central, peripheral and microcirculatory blood circulation systems in one way or another. However, there are additional etiological factors which selectively damage various parts of the system, each predominantly acting on either the arteries or the veins.

Violations of the central circulation are most often caused by heart disease, diseases of the circulatory system, or by disorders of the neuro-endocrine regulation of the cardiovascular system. A common consequence of such disorders is either an increase or a decrease in hydrodynamic pressure in the vessels, which is most pronounced in the arteries.

Hypertension, or an increase in blood pressure, can occur in the vessels of both the central and peripheral links. Hypertension develops during intensive work by the heart, or as a result of spasms of the smooth muscles of the arteries, leading to their narrowing. In such cases, an increase in blood pressure is temporary. However, another reason for the increase in pressure is the occurrence of pathological changes in the blood vessels. Such changes occur in the inflammation and lipid infiltration of angina. Inflammation and lipid infiltration are the pathogenetic basis of vascular atherosclerosis and lead to the development of hypertension, accompanied by a persistent increase in blood pressure.

Hypotension, or a reduction in blood pressure, can also occur in the vessels of both the central and peripheral circulation. Physiological hypotension occurs during sleep, after eating, with reduced muscle activity, and after warm baths. The pathological form of hypotension occurs as a result of blood loss, endocrine diseases, and in particular with a deficiency of iodothyronines and catechol amines, as well as a result of various forms of shock.

Violations of the peripheral blood circulation

Arterial hyperaemia (arterial plethora)—increased blood flow to the tissues and organs in the arteries. If hypertension is characterized by an increase in the kinetic energy of moving blood, then hyperaemia is an increase in the mass of blood in the vessels of a certain part of the body. Usually this occurs when the vessels expand, so the pressure in them may not increase significantly. Arterial plethora may be physiological or pathological. The physiological variant occurs when the tissue or organ is activated, and is caused by an increased need for oxygen and nutrients. Pathological arterial hyperaemia occurs due to inflammation, the actions of irritating chemicals, injuries, ultraviolet radiation, hypo-or hyperthermia, or endocrine or neurogenic dysregulation of the smooth muscle tone of the arteries. At the same time, some of these factors can

damage the walls of blood vessels. Subsequently, this can lead to arterial wall ruptures and haemorrhages.

Venous hyperaemia (venous plethora)—blood retention due to difficulty in the outflow of blood through the veins, as a result of external compression, veins clogged with blood clots, or impaired venous valves. Since the movement of blood through the veins is provided by the suction effect of the heart and the respiratory movements of the chest, primary diseases of the heart, diaphragm, intercostal muscles, pleura and lungs also lead to the development of venous hyperaemia. Stagnation in the veins ("venous stasis") may be associated with damage to or insufficient activity of the skeletal muscles, the contraction of which normally helps the movement of blood through the veins. With venous stasis, the hydrostatic pressure increases, the vessels stretch, and the permeability of the venous walls increases. Therefore, the venous plethora is often accompanied by local oedema and a decrease in local temperature. The stagnation of blood increases the risk of thrombosis. Another consequence of venous stasis is hypoxia of the surrounding tissues.

Embolism *(Greek: εμβολη—invasion)***—**mechanical blockage of the blood vessels. Most often, this blockage occurs due to the formation of blood clots (thromboembolism, thrombosis). However, gas embolism is also possible—when the lumen of the vessel is blocked by gas bubbles—as well as fat embolism, and embolism by fragments of damaged tissues, or parasite larvae. Lighter and more frequently-occurring thrombi and emboli are formed in the venous system, where the rate of blood flow is lower than in the arteries. When a vessel embolus causes nutrition to deteriorate, this leads to hyperaemia and hypoxia in the surrounding tissues. Beyond this, the course of the pathology depends on the specific balance between the etiological factor and the adaptive capabilities of the organism. A favourable combination of these may lead to the resorption of a blood clot. In the worst cases, the embolism can spread throughout the vascular system, causing multiple hemodynamic disturbances, up to a complete stop of the blood's circulation. Single emboli pose a threat to life if they overlap the lumens of vital vessels, such as the pulmonary artery or coronary arteries of the heart. It is important to note that with venous thrombosis at almost any site, there is always the potential threat of a subsequent pulmonary embolism. This threat is determined by the features of the anatomy of the venous system: peripheral veins have a smaller diameter than the central ones. If, for example, a thrombus from a vein in a lower extremity is dislodged, it can move through the blood stream into a

vein of a larger calibre, where the probability of getting stuck decreases. Then, from the inferior vena cava, the thrombus enters the even wider right atrium and the right ventricle of the heart, after which the relatively narrower pulmonary artery or even narrower branches of this artery can be blocked. Pulmonary thromboembolism is a very dangerous complication, due to the risk of a serious violation of pulmonary gas exchange, which can lead to suffocation and death.

Stroke *(Latin: insultus—attack, strike)*. A stroke is an acute localized violation of the cerebral or spinal cord blood flow. In a typical case, such a violation is accompanied by a sudden state of stupor, disorientation, a loss of ability to articulate speech, or even a loss of consciousness, all of which resembles the consequences of a strong mechanical blow to the head.

There are two main forms of stroke—haemorrhagic and ischemic. Haemorrhagic strokes occur due to the rupture of the walls of the arteries, which leads to haemorrhages, i.e., haemorrhages into the surrounding tissues. Ischemic strokes are caused by the impaired patency of the arteries that feed the brain, due to spasms, emboli, thrombosis, or atherosclerotic changes. However, in any case, the consequence of a stroke is ischemia, i.e., a complex of metabolic disorders developing due to oxygen deficiency. In severe cases, these disorders can lead to the formation of necrotic foci in the brain.

Vascular collapse *(Latin: collapsus—fallen)* is one of the forms of acute general circulatory disorders, the main pathogenetic link of which is a sharp relaxation of the arterial smooth muscles. As a result, these vessels expand, and their total volume increases significantly. Since the blood volume does not significantly change therein, a rapid decrease in the arterial and then venous pressure—sometimes even down to zero—is possible. There are many possible causes of the pronounced and simultaneous relaxation of the smooth muscles of the arteries. Vascular collapse can develop as a result of massive blood loss; severe pain; a blood transfusion from an incompatible donor; with extensive burns; with severe violations of the contractile function of the myocardium; as a result of the action of toxic substances; or due to an abnormal reaction to the introduction of certain drugs.

Stasis *(Greek: στάσις—standing)*—the movement of blood stopping in the vessels. Causes of blood stasis can be an external mechanical pressure on the tissues, a local temperature change (either an increase or decrease), local exposure to aggressive chemicals (for example, on contact with the

skin, lungs, or the digestive system), the effect of biological toxins, circulating immune complexes, or disruption of the blood coagulation system. While in the arteries all of these causes are insufficient to stop the blood flow, due to the rapid movement of blood, they can cause stasis in the veins and vessels of the microvasculature; however, the multiplicity of causes of microcirculation disorders makes blood stasis very likely in almost any serious illness. Meanwhile, it is through the capillaries that gas exchange occurs, as well as the exchange of nutrients and waste products between tissues and blood. Stopping the blood flow inevitably leads to hypoxia, the energy starvation of tissues, and to damage and cell death.

Violations of the blood microcirculation

The microcirculation system includes the smallest of the blood vessels—arterioles, venules, capillaries and arterial/venular shunts. Despite the fact that the diameter of the capillaries is comparable to the size of an erythrocyte, the total volume of the vessels of the microvasculature is huge: there are up to 2,000 capillaries per square millimetre of muscle tissue section. This is necessary for effective gas exchange and supply of nutrients to the tissues, but it also makes damage to the blood vessels of the microvasculature almost inevitable in any serious illness.

Microcirculation disorders have extra-vascular, vascular and intravascular causes. Extra-vascular causes include any pathological changes in the surrounding tissues. Most often, such changes are inflammatory, and therefore they are accompanied by oedema, which squeezes the micro vessels and hinders the diffusion of gases and nutrients. The same consequences lead to dystrophic processes, the development of tumors, and scars. The vessels themselves may be damaged as a result of autoimmune reactions, infections, and toxic effects. The intravascular dysfunction of the microvasculature is particularly notable as it develops rapidly and can have a significant distribution. Such violations may manifest as stasis and sludge.

Sludge. In medicine, this English word means a particular disorder of the microcirculation. For the normal functioning of the entire microvasculature, the physical/chemical state of the blood is extremely important: it must maintain a stable viscosity, pH, total protein concentration, gas saturation, and temperature. When one of these parameters exceeds the limits of normal values, the forces keeping the blood cells in suspension in their aquatic environment, as well as the

forces preventing their adhesion, decrease. As a result, an intravascular aggregation of erythrocytes occurs: they are assembled into complexes resembling columns of coins, which is the most characteristic sign of sludge. Clustered red blood cells fill the capillaries, disrupting their permeability, and thus the sludge is often accompanied by capillary stasis. Sludge may be due to inflammation; it also occurs when there is damage to the capillaries, and when there are primary pathological changes in the membranes of the red blood cells themselves. The adhesion of red blood cells dramatically reduces the efficiency of gas exchange, and is one of the causes of hypoxia and all its ensuing consequences. To localize such effects and prevent the spread of the phenomena of stasis and sludge, there are micro vessels that directly bind arterioles and venules, which are known as shunts. In healthy humans, shunts are blocked, but in pathological situations they open up and provide blood flow by bypassing the part of the capillary network in which sludge or other circulatory disorders have developed.

Violations of lymph circulation

The blood plasma is constantly filtered into tissues through the walls of the blood vessels—especially the vessels of the microcirculatory bed—and turned into tissue fluid. Phylogenetically, the most ancient task of the lymphatic system was to return this fluid to the bloodstream. Later in the course of evolution, other functions were added: in particular, protective functions, since the lymphatic vessels are convenient ways to move the mobile cells of the immune system, and the lymph nodes are able to prevent the spread of infections. With the implementation of the protective functions of the lymphatic system, pathological changes occur. These often take place in the form of inflammation of the lymphatic vessels and lymph nodes.

Lymphangitis—or the inflammation of the lymphatic vessels—occurs near tissue containing infectious and inflammatory foci due to hypoxia; due to changes in the pH of the medium; or due to exposure to pathogenic microorganisms and toxic molecules. Usually, lymphangitis is manifested in the spread of hyperaemia, local hyperthermia and a painful swelling along the lymphatic vessel. Lymphangitis may be accompanied by general body reactions—a deterioration of health, insomnia, fever, and allergies. In addition, inflammation of the lymphatic vessel often leads to the development of lymphadenitis.

Lymphadenitis, or inflammation of the lymph node, is a consequence of its barrier role. Pathogenic cells linger in the lymph nodes, where they undergo phagocytosis and attack by antibodies. The resulting mixture of cellular decay products, immune complexes and intermediate metabolites causes swelling, and accelerates the maturation of lymphocytes, which increase in size. As a result, the lymph node is stretched and becomes painful. In acute cases its destruction and purulent fusion are possible. Depending on the type of pathogenic microorganisms caught in the node, the nature, sequence and rate of violations may have different features. Specific signs of lymphadenitis are acquired with tuberculosis, syphilis, actinomycosis, and some other infections. In addition to pathogenic microorganisms, lymph nodes also prevent the spread of cancer cells, and because of this, lymph nodes are the site of the proliferation of primary metastases of various malignant tumours.

Blood clotting disorders

The ability to perform thrombosis is one of the most important adaptive mechanisms that protect against blood loss. However, if blood clots form at an unsuitable time for this, in insufficient or excessive amounts, or in an inappropriate part of the circulatory system, these clots turn into an independent pathogenetic factor, which can lead to secondary consequences of varying severity—from malnutrition to the necrosis of the surrounding tissues. The problems that arise with slow or insufficient thrombosis are no less serious, as this leads to haemorrhages and bleeding.

There are two main causes of blood clotting disorders: a primary violation of the functions of the blood vessels and platelets, or a disorder in the regulation of this system.

Pathology of platelets. Platelets are formed in the bone marrow during the fragmentation of megakaryocytes and live in the blood of an adult for about 10 days. The normal platelet count is 180,000 per 380,000 μl^{-1} blood. Within these limits, their level is variable; it depends on the effectiveness of nutrition, the stage of the menstrual cycle in women, and some other factors. Only a minority of platelets take part in thrombosis during their short lifespans; the majority age and are destroyed by the cells of the spleen, liver and phagocytes. A pathological decrease in the level of blood platelets (“thrombocytopenia”) is possible for three main reasons: slowing of their formation in the bone marrow, increased deposition in the spleen, or accelerated destruction.

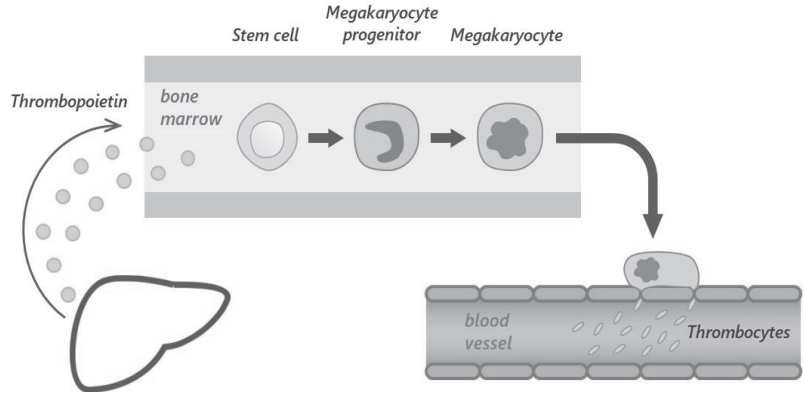

Fig. 5.7. Platelet life cycle

Slow platelet formation may be due to the death bone marrow stem cells, or their insufficiently active reproduction. This occurs as a result of toxic damage; with hereditary bone marrow inferiority; with a pathological proliferation of connective tissue in the bone marrow; with malignant bone marrow tumors; and with a number of other diseases.

Depositing (sequestration) of platelets in the spleen. One of the physiological functions of the spleen is to store excess platelets. In some diseases, the spleen volume can increase significantly, which leads to the excessive deposition of platelets. The most common causes of splenomegaly—a significant expansion of the spleen—are the deterioration of the blood flow through the veins, the growth of tumors in the organ itself, and the pathological accumulation of macrophages in it.

The shortening of platelet life is possible as a result of a high frequency of thrombosis with frequent bleeding and haemorrhage; with violations of the regulation of haemostasis; inflammation of the veins and arteries; or using poor quality materials for prosthetic heart valves or blood vessels. Another cause of thrombocytopenia is due to the fact that in infectious diseases, various toxins, antibodies and immune complexes are often adsorbed on the surface of platelets. Such “loaded” platelets are rapidly absorbed by the macrophages of the spleen and other tissues.

Drug thrombocytopenia may occur as a result of the use of cytostatics, some diuretic drugs, heparin, or drugs containing gold. The oppression of haematopoiesis with thrombocytopenia can be caused by the ingestion of a large dose of alcohol.

Idiopathic thrombocytopenic purpura. Diseases with an unknown aetiology are called ***idiopathic***. "Purpura", in medicine, refers to small-spotted or band-shaped haemorrhages in or under the skin or in the mucous membranes. Idiopathic thrombocytopenic purpura is a form in which a decrease in platelet count in the blood is accompanied by a haemorrhagic syndrome, i.e., frequent bleeding and haemorrhage. In most cases, the destruction of platelets in idiopathic thrombocytopenic purpura is due to an autoimmune process triggered by an infectious agent or medication. In children, this disease often occurs in an acute form, but in about 90% of cases it ends in a spontaneous recovery. In adults, the disease predominantly affects women, who often develop a chronic form that lasts a long time, but the percentage of self-healing is also high. Temporary immune thrombocytopenia can occur in a number of infectious diseases, including viral hepatitis and HIV. In these cases, the outcome of thrombocytopenia depends on the effectiveness of the treatment of the underlying disease.

Vascular pathology

Haemorrhages and bleeding may also be caused by various injuries and dysfunctions of the blood vessels. The bleeding in such diseases—which are called non-thrombocytopenic purpura—is usually limited to the skin or mucous membranes, but there are some diseases with an unidentified aetiology that can cause severe blood loss and dysfunction of the internal organs.

Thrombotic thrombocytopenic purpura develops very quickly and often leads to death. The central link in the pathogenesis of this disease is a large number of substances that cause platelet aggregation—and subsequent severe circulatory disorders—being released from the damaged endothelium of the blood vessels. Such a sequence of events can occur during pregnancy, the metastasis of tumours, or the use of large doses of anticancer drugs.

Haemorrhagic vasculitis (inflammation of the blood vessels) also manifests as purpura on the extensor surfaces of the limbs and buttocks, which is a consequence of impaired haemostasis. The disease usually begins after an infection, or is triggered by allergies. The resulting immune complexes can be deposited in the capillaries and small arterioles, which provoke the development of local foci of inflammation. Some pathogens are able to penetrate directly into endotheliocytes and damage them. The

resulting inflammation, in turn, increases the permeability or even damages the vessels from which blood enters the surrounding tissues.

Coagulopathy *(Latin: coagulum—coagulation, clotting)*

There are some relatively rare diseases that occur due to dysregulation of the balance of the coagulation and anticoagulation systems of the blood.

Hereditary coagulopathy is characterized by a deficiency of certain coagulation factors. The most common variants are haemophilia types A (a deficiency of the VIII blood clotting factor) and B (a deficiency of factor IX), due to a defect in the X chromosome. In women, this defect can be compensated for by the presence of a second healthy X chromosome, but in men, the Y chromosome cannot compensate for this defect; therefore, haemophilia in the vast majority of cases is clinically manifested in men. Its main characteristic is persistent and dangerous bleeding from minor injuries to the blood vessels. In addition, all hereditary coagulopathies are characterized by post-traumatic haemorrhages in the joints, body cavities or skeletal muscles, which are delayed for several hours or even days after the injury. It possible for the blood cells to appear in the urine.

Acquired coagulopathies are much more common than the hereditary types. Such coagulopathies are due to the deficiency of one or more of the various coagulation factors normally found in the blood. In addition, the cause of acquired coagulopathy may be an imbalance of coagulation and anticoagulation factors.

The most dangerous example of this form of coagulopathy is disseminated (i.e., widespread) intravascular coagulation syndrome, which can develop with severe injuries or tissue necrosis, as a result of surgical operations, or with multiple metastases of malignant tumours and sepsis. The triggers for pathological blood coagulation in all these cases may be different. For example, massive tissue damage is accompanied by the release of large amounts of tissue thromboplastin into the blood, but in sepsis, the toxins of bacteria stimulate the blood coagulation directly. Nevertheless, the consequences are similar: blood coagulation is sharply activated, there are multiple blood clots in small blood vessels, and this can lead to a complete stop of blood circulation.

Since the synthesis of fibrinogen and a number of coagulation factors occurs in the liver, diseases of this organ can be the cause of acquired coagulopathy. In addition, coagulopathies are caused by the pathologically accelerated disintegration of fibrin in the case of α2-antiplasmin or plasminogen anti-activator 1 deficiency. In both cases, blood clots in the

damaged parts of vessels dissolve prematurely, and this leads to a recurrence of bleeding.

Another group of coagulopathies is called inhibitory. Such pathologies are due to the excessive activity of coagulation inhibitors, most of which are class G immunoglobulins.

Thrombophilia. A characteristic feature of this group of diseases is periodic thrombosis due to hereditary disorders of the blood. For example, a point mutation makes factor V resistant to the regulatory action of protein C. A deficiency of ant thrombin III, protein C, or protein S can be hereditary.

Violations of Water and Mineral Balance

Although our ancestors left the ancient ocean long ago, each of us continues to carry a substantial amount of water. This reserve is not a random error of evolution. Water is an environment in which many chemical reactions that a living organism needs take place, and water itself participates in hydration and dehydration reactions. Moreover, in a living organism, the functions of water are not limited only to its own properties. Together with the substances dissolved and suspended in it, water forms a complex and dynamic system with a certain viscosity, thermal conductivity, osmotic pressure and pH. Water is necessary for the transport of nutrients, for the excretion of waste products from the body, for maintaining a normal body temperature and for the formation of the main structures of many complex molecules, cells, tissues and organs. It is therefore not surprising that more than 60% of the body weight of an adult is water; due to the large biological value of this liquid substance, water imbalances are very dangerous for health.

Water balance is supported by the opposite processes of consumption and excretion. Water enters the body mainly with food and drinks, but since we get most of our energy through the simplest chemical reaction $2H + O \rightarrow H_2O$, this leads to the fact that every day about 60–80 ml of water in an adult's body is synthesized endogenously as an associated product. However, a person's minimum water requirement for this time period is at least 800 ml, so consuming external water is vital, and usually the body can only go without it for less than three days. Water is mainly excreted from the body through the kidneys, but some of it evaporates from the surface of the skin, leaves with faeces, and in the exhaled air.

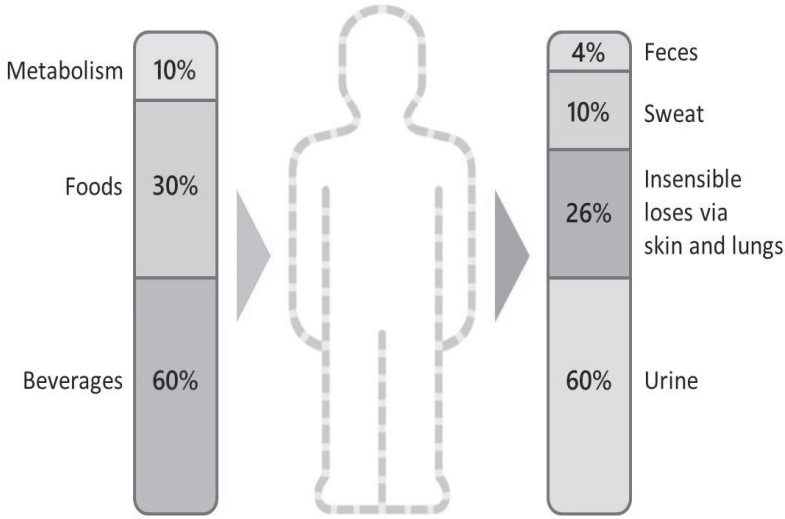

Fig. 5.8. Human water balance

Regulation of water and mineral metabolism

Together with water, dissolved mineral salts enter the body in large quantities. The combination of mineral salts and water is in many ways a single object of biological regulation. The importance of the water and mineral balance means that it is very strictly controlled. This control is carried out in the following ways.

Firstly, an increase in the osmotic pressure of the intercellular fluid by only 2% compared with its normal level activates the osmotic receptors, which leads to an increase in the incretion of antidiuretic hormone from the pituitary posterior lobe into the bloodstream. Under the influence of this hormone, the kidneys' reabsorption of water from the primary urine into the blood is enhanced; however, the amount of Na^+ ions transitioning from the blood into the urine increases, which leads to the normalization of blood osmotic pressure. In addition, the irritation of the osmosis receptors causes a feeling of thirst, which a person reflexively seeks to eliminate by taking in an additional amount of water. This additional water reduces the relative concentration of solutes and reduces the osmolarity of biological fluids. On the other hand, a decrease in the osmotic pressure of water inhibits the synthesis and release of new molecules of antidiuretic hormone, with all the ensuing consequences.

Secondly, the renin-angiotensin-aldosterone system, the initial link of which is located in the kidneys, plays a very important role in the regulation of water-mineral metabolism. This link is part of each nephron, since each arteriole-bearing area of a renal glomerulus is surrounded by special cells that form a structure known as the *juxtaglomerular apparatus (Latin: juxta—about)*. In the cells of the juxtaglomerular apparatus, the synthesis of the enzyme renin is activated when the blood pressure decreases. The synthesis and release into the blood of this enzyme can also be stimulated by increasing the concentration of sodium in the urine of the distal tubule of the nephron, as well as under the influence of the sympathetic division of the autonomic nervous system. It is now known that renin can be synthesized not only in the kidneys, but also in the endothelium of many blood vessels. However, in both cases it performs the same functions. Once in the bloodstream, renin catalyses the formation of decapeptide angiotensin I, which is further converted into octapeptide angiotensin II. One of the functions of angiotensin II is to stimulate the glomerular zone of the adrenal glands, where, in particular, aldosterone, the most active hormone from the mineralocorticoid group, is synthesized. Aldosterone enhances the reabsorption of sodium cations and chlorine anions from urine to the blood, which increases the body's general ability to retain water.

Another contour of the water-mineral metabolism regulation is provided by the baroreceptors located in the heart, the aorta and in the large blood vessels. Thanks to these receptors, which react to mechanical stretching and contraction, small reductions in the circulating blood volume or blood pressure also cause thirst and increase the release of antidiuretic hormones. Additionally, the baroreceptors of the aorta and the carotid arteries stimulate the vasomotor centre of the medulla oblongata and activate the sympathoadrenal system. As a result, cardiac contractions and the arteries' smooth muscle tone increases, which leads to an increase in hydrodynamic blood pressure. When the blood pressure becomes high, or the volume of circulating blood increases, the release of antidiuretic hormone into the blood is inhibited.

In addition, atriopeptin, a sodium-uretic peptide, is synthesized in the atria, and decreases the renal tubules' reabsorption of Na^+ but increases the overall rate of renal filtration. The same peptide is able to inhibit the synthesis of renin, aldosterone and antidiuretic hormone. The excretion of sodium from the blood into the urine is also stimulated by certain types of

prostaglandins. Following sodium excretion, in any case, the excretion of water naturally increases for osmotic reasons.

In general, a human body has significant biological capabilities that enable it to maintain its water and mineral homeostasis. However, under various severe conditions, these abilities are not enough, leading to either dehydration or hyper hydration (water retention) occurring in the affected organism.

Dehydration

This condition occurs when there is an insufficient water supply to the body (lack of drinking water, unconsciousness, obstruction of the oesophagus), or with significant water loss (heavy sweating, diarrhoea, vomiting, excessive urine output). Dehydration reduces the mass of the circulating blood, which reduces the efficiency of oxygen delivery to the tissues. Hypoxia, regardless of the reason for which it occurs, has its greatest and clearest effect on the state of the central nervous system. In particular, hypoxia that occurs during dehydration may be accompanied by apathy, disorientation, and disorders of consciousness. In cases of severe dehydration, there is a risk of a loss of consciousness, the inhibition of the most important respiration regulation centres, and cardiac activity oppression. Due to the loss of water, a decrease in blood pressure can significantly slow down the kidneys' filtration processes, making the excretion of waste products in the urine insufficient. In addition, the kidneys are very sensitive to hypoxia, the onset of which is inevitable with a significant decrease in blood pressure. Of course, both decreased blood pressure and dehydration will adversely affect the condition of all other organs in general, although to varying degrees.

Hyper hydration (hyperhidrosis)

Hyper hydration occurs either due to insufficient removal of water from the body, or due to excessive fluid intake. Hyper hydration may be general, or local, with a predominant accumulation of fluid in individual tissues or organs. The most common causes of general over hydration are diseases of the cardiovascular system, kidney, or endocrine system. Local fluid retention is a consequence of local primary disorders, such as inflammatory processes or the occurrence of barriers to the outflow of blood and lymph (damage, spasms, pressure on vessels, or embolism). The accumulation of water in the intercellular spaces is called edema; the

excess fluid in the vascular system is called hypervolemia; the water retention inside the cells is swelling; and the water retention in the cavities is called dropsy.

The main types of water retention in different cavities have their own names:

- ***Ascites***—abdominal dropsy
- ***Hydrothorax***—dropsy of the pleural cavity
- ***Hydro pericardium***—pericardial edema
- ***Hydrocele***—dropsy of the testicle
- ***Hydro arthrosis***—dropsy of the joint
- ***Hydro ophthalmus***—dropsy of the eye
- ***Hydro nephrosis***—dropsy of the kidney
- ***Hydro salpinx***—fallopian tube dropsy
- ***Hydrocephalus***—dropsy of the ventricles of the brain

When choosing a hyperhidrosis treatment, it is very important to identify the origin of the fluid forming the oedema or dropsy. The fluid accumulating as a result of inflammation has a special name: “exudate”. Non-inflammatory fluid is called “transudate”.

Exudate *(Latin: ex—out)* is a fluid released into the extracellular space or in the body cavity from small vessels during inflammation. This occurs as a result of an increase in the permeability of the vascular walls under the influence of inflammatory mediators, the effect of which may be enhanced by bacterial toxins in the case of infectious inflammation. Exudation is also promoted by an increase in the hydrodynamic pressure of the blood due to hypertension, hyperaemia or an increase in osmotic pressure during inflammation, resulting from the appearance in the intercellular fluid of a large number of ions and molecules from dead cells.

Transudate *(Latin: trans—through, and Latin: sudatum—to sweat)* accumulates in the body cavities due to increased permeability of the walls of blood or lymphatic vessels; the formation of transudate can also occur as a result of disorders of water-salt metabolism. Transudate is not always a sign of pathology. A small amount of this fluid is always contained in the pleural cavities, in the pericardium, and in the abdominal cavity.

Violations of Acid-Base Balance

Every second, a huge number of chemical reactions occur in the body, as a result of which hydrogen ions and hydroxyl groups are formed.

Spontaneous interaction with these ions by various molecules and subcellular structures is inevitable. Therefore, one of the most important constants of the human body is the optimal ratio of H^+ and OH^- ions in all biological fluids. Usually, the pH level of the medium is within the range of the weakly alkaline values that are optimal for the functioning of enzymatic systems, including the intracellular and extracellular enzymes of the immune system. Meanwhile, both in the course of normal vital activity and during pathological effects, numerous acidic and basic compounds are formed—either exogenously or endogenously. This is why the work of buffer systems ensuring the stability of the acid-base equilibrium has a protective significance. Several such systems work in the biological fluids of the human body. The most important of these are bicarbonate, phosphate, protein and haemoglobin.

In addition to the chemical systems, there is also a physiological regulation of the acid-base balance, which is performed by the lungs and kidneys. This is possible because the capacity of the bicarbonate blood buffer system depends on the amount of carbon dioxide dissolved in it. An excess of CO_2 is released through the lungs, but when its content in the blood decreases, respiration becomes less active; this is one of the mechanisms that body may use for the regulation of the blood pH. Alternatively, the kidneys can preferentially secrete either acidic or basic molecules, depending on which of them are in excess.

In humans, most enzymes work most efficiently in the pH range of 7.37–7.44. Within this range, the nucleic acids have an optimal conformation and numerous structural proteins that ensure the stability of the cell membranes, including the lysosomal ones. A deviation of only a few tenths of a unit from the optimum pH can be life threatening. However, this sometimes happens: under the action of strong pathogenic factors, the total capacity of the buffer systems—i.e., the excretory abilities of the lungs and kidneys—may not be enough, and as a result, either acidosis or alkalosis develops.

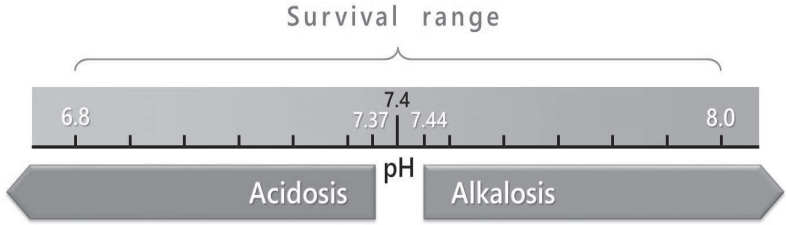

Fig. 5.9. Survival range of pH

Gas acidosis is a consequence of a decrease in the efficiency of the respiratory system, or it develops when someone is forced to stay in an atmosphere with a high carbon dioxide content (e.g., submarines, mines, or poorly ventilated rooms containing a large number of people or animals). Hypercapnia, i.e., an excessive accumulation of CO_2 in the blood, increases the likelihood of the formation of carbonic acid in the aquatic environment and contributes to a change in pH to the acid side.

Non-gas acidosis occurs for three main reasons:

- due to the accumulation of organic acids in the tissues ("metabolic acidosis")
- due to the insufficient excretion of organic acids by the kidneys, or excessive release of organic bases through the gastrointestinal tract ("excretory acidosis")
- when a large amount of acids or other substances enter the body, including drugs from which acids are synthesized in metabolic processes ("exogenous acidosis")

A very frequent type is the **mixed acidosis** that occurs when a combination of different forms of this pathology are present.

Gas alkalosis occurs when breathing is too active, leading to hypocapnia—a significant decrease in the CO_2 content in the blood. Hypocapnia can develop due to the action of certain toxic substances on the respiratory centre; with the artificial ventilation of the lungs; as a result of the development of certain brain tumours; with hyperthermia; after bleeding; or with repeated vomiting, which leads to a significant loss of hydrochloric acid from the stomach.

Non-gas alkalosis occurs:

- after repeated vomiting, as a result of a significant loss of gastric hydrochloric acid, which leads to a relative insufficiency of bases in the body
- when the excretion of sodium is impaired, such as when taking diuretic drugs or due to kidney disease, which is accompanied by excessive urine and other associated endocrine pathologies ("excretory alkalosis")
- with the introduction of alkaline solutions into the body—for example, sodium bicarbonate—or with the prolonged consumption

of food and mineral waters with alkaline pH values ("exogenous alkalosis")
- as a result of the haemolysis of erythrocytes, with hereditary electrolyte metabolism disorders, with rickets and some endocrine diseases ("metabolic alkalosis")

Mixed alkalosis may include combinations of gas- and various types of non-gas-alkalosis. The specific combination is determined by the etiological factors and the individual characteristics of the sick person.

Stress (General Adaptation Syndrome)

In modern-day medicine, being "under stress" refers to the mechanism which activates an organism's complex of nonspecific adaptive reactions, which arose in the course of evolution in response to a wide variety of dangers, disturbances and damage. The biological meaning of this mechanism lies in the urgent mobilization of all possible resources to counteract both the actual and the perceived threat to life. This is possible because stress reactions are triggered not only by injuries and impairments—stress can also arise under the threat of such effects.

Depending on its cause and characteristic manifestations, stress can result from adverse psycho-emotional, temperature, light, acoustic, or working conditions; stress can also develop due to hunger, etc. As can be understood from the above list, the nervous system certainly takes part in the implementation of each variant, but it is not the only factor involved.

Stress is a complex of many fairly universal reactions, among which Hans Selye (1907-1982) identified three main changes:
- ***mobilization of adaptive capabilities***
- ***increased resistance***
- ***exhaustion***

How does this happen?

The system of receptors allows a person to anticipate, feel and evaluate the actions of environmental factors. External touches, temperature, pain, vision, and olfactory, auditory and unconscious internal sensations can all trigger stressful processes that allow the body and its individual parts to better adapt to the changed conditions. Information from the receptors is analysed in the cortex and subcortical centres of the brain (both consciously and subconsciously), and, if it is regarded as a threat, two

systems of the executive organs are activated—the hypothalamic-pituitary-adrenal and sympathetic-adrenal.

The hypothalamic-pituitary-adrenal system (HPA) activation leads to a sharp enhancement (up to 10 times the normal amount) of the incretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. As a result of the stimulating effect of ACTH on the adrenal cortex, an even more significant amount of glucocorticosteroid hormones (GCSs) are released.

GCSs cause a number of strong biological effects. Corticosteroids can stimulate lipolysis in adipose tissue cells, resulting in free fatty acids, the subsequent oxidation of which provides a lot of energy to other types of cells. They can slow down glucose utilization, which saves carbohydrates. These two processes are the most important parts of the stress reaction. In addition, in a stressful situation, the ability of corticosteroids to inhibit protein synthesis in many cells may be useful, as it reduces energy expenditure. In a stressful situation, energy is necessary for more urgent processes, such as muscle work, increased secretion processes, or the generation of nerve impulses.

The sympathetic-adrenal-medullary system (SAM) includes the sympathetic part of the autonomic nervous system—in the synapses of which dopamine and noradrenaline are synthesized—and the adrenal medulla, where adrenaline and noradrenaline are formed. Dopamine works in the brain, and noradrenaline and adrenaline enter the blood from the sympathetic nerve endings and from the chromaphin cells of the adrenal medulla, respectively. With a stress reaction that takes place over a very short time, the concentration of adrenaline in the blood increases 200–300 times. This hormone enhances myocardial contractions and increases the frequency of such contractions. Noradrenaline stimulates contractions of the smooth muscles of the subcutaneous and internal arteries, which leads to an increase in blood pressure. In healthy people, under the influence of both of these hormones, the breakdown of glycogen in the liver is accelerated, the blood supply to the brain, heart, and skeletal muscles improves, and the bronchi expand, which contributes to the intensification of pulmonary gas exchange.

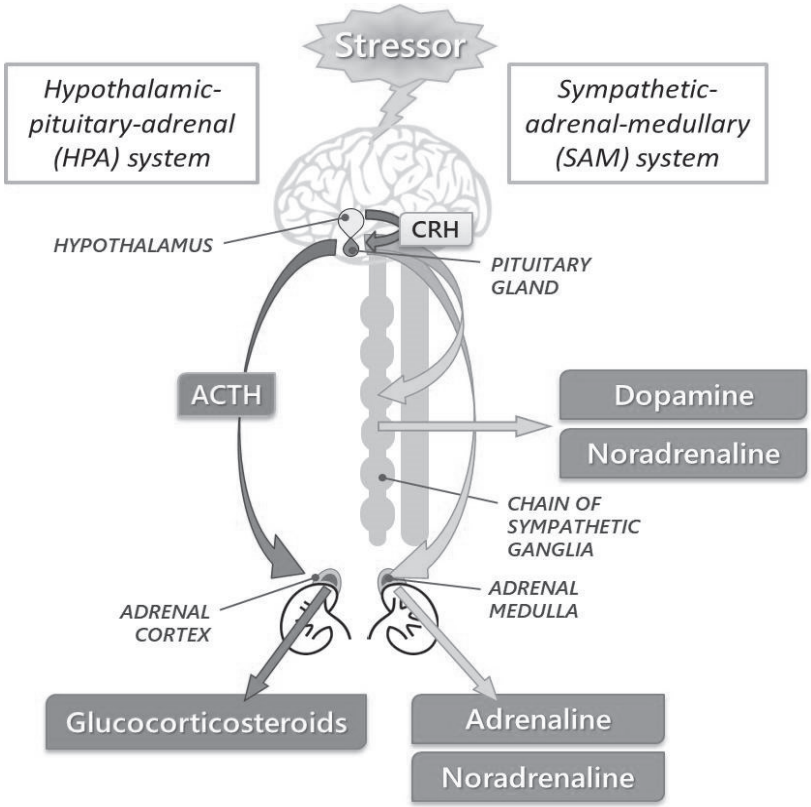

Fig. 5.10. Stress response scheme

Catechol amines, which can partially separate the processes of oxidative phosphorylation and free oxidation in the mitochondria, are known to have a calorigenic effect. The resulting moderate hyperthermia may interfere with the reproduction of pathogenic microorganisms.

In general, due to the effects of the HPA and SAM systems, the body mobilizes very quickly to counter various threats, both emerging and expected, and both real and imaginary. As a result, for some time it becomes possible to maximize the realization of the mental and physical potential of the organism. Under stress, sensitivity to pain is reduced, and the work of the brain is enhanced, which is reflected in fast analysis of the situation and quick decision-making, and in the increased ability to

concentrate and remember. Reflex reactions to the actions of various irritants become faster. In addition, under stress, a person is capable of considerable physical effort that exceeds his usual capabilities.

Harmful effects of stress

However, there is another side to the coin. Under stress, a large amount of energy is expended, and this cannot be sustained for a long time. A classic stress episode consists of two parts—the phase of excitation and the phase of inhibition. During the first stage, the mental and physical capabilities of the body are activated, and then, in the second stage, the body pays for it. The price is considerable. In the tissues, especially in the muscle tissue, lactic acid and other oxidized products of metabolism accumulate, which causes the pH to shift towards increased acidity. Under the conditions of acidosis, many enzymes work less efficiently, metabolic processes slow down, a person feels fatigued, and the preconditions for a depressive state are created. The effects of a number of undesirable tissue effects of the stress hormones are superimposed on this state.

In particular, GCSs inhibit the synthesis of proteins, including antibodies, in the cells of the lymphoid tissue. All classes of immunoglobulins do not live long, and thus their number should be constantly replenished. Two to four days after severe stress, there may, therefore, be a shortage of such protective proteins. Both humoral and cellular immunity are weakened, so the body finds itself in a kind of "immunological pit", as a result of which the risk of all kinds of infectious diseases increases substantially. Chronic stress can also lead to more serious consequences—the frequent suppression of antibody synthesis increases the likelihood of developing cancer cell clones that have not been destroyed in a timely manner by the immune system. Therefore, stress is also a risk factor for the development of cancer. GCSs also inhibit the synthesis of proteins in the cells of the stomach, which produce a mucous secretion to protect the walls of this organ from self-digestion. Therefore, gastritis and gastric ulcers can develop as a result of repeated stress.

The release of catechol amines into the blood during stress is no less a threat to health. Prolonged or frequent spasms of the smooth muscles of the arteries that occur under the influence of CA create conditions for lipid infiltration of the vascular walls, which is the initial stage of atherosclerosis, and a sharp increase in blood pressure can lead to a stroke. The strengthening of the contractile activity of the heart, which occurs under the action of catechol amines, may be a risk factor for myocardial

infarction or arrhythmias under certain conditions. During the first stage of stress, in the phase of excitation, an excess of dopamine in the brain disrupts the balance of activity between the sympathetic and parasympathetic parts of the vegetative nervous system. During the second stage, in the phase of inhibition, a shift in the opposite direction occurs, and the parasympathetic division dominates. A sharp imbalance of neurotransmitters leads to a deterioration in the coordination of movements, which under certain circumstances reduces the chance of survival. In addition, an excess of catechol amines often provokes the emergence or exacerbation of mental illness.

In general, the overall homeostatic disturbances resulting from the activation of the HPA and SAM systems, as well as a long list of the possible consequences of such disturbances, leads to the idea that stress should be eliminated from life. This cannot be fully achieved, and it is not necessary—otherwise life would become too dull—but it is possible to reduce stressful health risks. However, it is important to remember that in a crisis situation, stress can save lives; and all stresses are usually divided into two groups: "eustress" and "distress".

Eustress *(Greek: εὖ—good)*. This concept refers either to stress caused by positive emotions, or to moderate stress that arises in response to a real threat. However, the severity and duration of reactions to such stress do not result in a lasting pathogenic effect. This is the kind of stress that a person cannot do without: it is justified, as it can minimize frustration and damage, and sometimes even saves lives.

However, in some cases, stress arises because of suspiciousness or because of trivial interpersonal conflicts, when there is practically no threat to health or life, or when the magnitude and probability of such a threat is exaggerated. These are classic examples of **distress** *(Greek: δυσ—loss)*: unjustified stress that is not beneficial, but delivers many negative consequences. It is difficult to avoid it unilaterally in cases of conflict; it requires efforts from two sides, which is possible only with a sufficient understanding of everyday culture. From this it follows that culture has a very real medical value, and not only in matters of personal hygiene.

Atherosclerosis *(Greek: αθηρο—gruel and σκλήρωση—hardening)*

Aetiology. Atherosclerosis is a complex of consecutively developing metabolic disorders and morphological changes in the walls of blood vessels, representing the pathogenetic basis of a group of extremely

common diseases of the cardiovascular system. The first signs of such diseases may manifest as early as 16–18 years of age, and beyond this their probability increases progressively.

Atherosclerosis is a polyaetiologic pathology, the most frequent trigger events of which are:

- primary accumulation of lipoproteins in the vascular walls of arteries
- accidental damage to the endothelium, for example, by pathogenic microorganisms such as *Chlamydia*, or viruses
- dysregulation of the function of leukocytes, with the result that these cells are retained in the walls of the arteries
- the occurrence of a pathological clone of the smooth muscle cells in the artery walls
- dysregulation of the antioxidant system
- hereditary defect of the vascular wall
- age-related increase in gonadotropic and adrenocorticotropic hormones

The risk factors are adulthood, being male, a hereditary predisposition, and a non-optimal lifestyle, including dietary factors.

Pathogenesis. All these disorders lead to the formation of the main link of pathogenesis—lipid and protein deposits in the endothelium and in the muscle layer of large arteries, including the aorta. As a result, atherosclerotic plaques are formed, which can completely block the lumen of the vessel. The risk of such deposits is due to the very physiology of lipid transport. Lipids from food are digested, absorbed, and delivered by chylomicrons to the liver, where they become a component of lipoproteins and are distributed throughout the body via the circulatory system. Furthermore, in order to get to the consumer cells, these lipoproteins must pass through the vessel wall. This happens most easily in the capillaries, but transit is also possible in the arteries.

The walls of the arteries consist of an inner layer of endothelial cells, a middle layer of elastic tissue with smooth muscle fibres and an outer layer of connective tissue. Some of the lipoproteins pass through the gaps between the cells of the vascular wall, but their main path is an energy-dependent active transportation method consisting of three stages. In the first of these, the lipoprotein is absorbed by the cell; then it is subjected to intracellular digestion and recomposition; and after this, most of the lipid molecules are excreted from the opposite side of the cell.

In a healthy body, the passive and active transport mechanisms of lipids work in parallel, and complement each other. Unfortunately, a number of pathogenic factors can interfere with these processes. For example, during stress, the smooth muscle fibres of the arteries contract under the influence of catechol amines. The diameter of the vessels decreases; the intercellular spaces may disappear completely; and any lipoproteins that are in these gaps will become stuck.

Another important circumstance is that the absorption of a lipoprotein particle by the endothelium cell leads to the invagination and disintegration of part of the cell plasma membrane, together with a number of specific receptors. The synthesis of new receptor proteins takes time. In addition, the synthesis of receptors for low-density lipoproteins slows down with an increase in the intracellular cholesterol concentration. An insufficient number of such receptors inhibits the endocytosis of subsequent lipoprotein particles, and this increases the overall probability of lipid infiltration of the artery walls. Therefore, high blood cholesterol is considered to be a serious risk factor for atherosclerosis.

The likelihood of arterial lipid impregnation also depends on the total concentration of various classes of lipoproteins in the blood. With the frequent and abundant consumption of foods rich in fats, this concentration increases. The risk of the blood vessels developing atherosclerotic damage is especially increased by the consumption of food high in cholesterol, and fatty acids with saturated radicals, since the synthesis of endogenous cholesterol is possible from such acids.

Low and very low-density lipoproteins have atherogenic properties. They accumulate in the walls of the arteries, mainly due to binding to the components of the intercellular substance—proteoglycans. Furthermore, as a result of lipid oxidation, hydro peroxides, lysophospholipids, hydroxysterols and fatty acid aldehydes are formed. The hydrolysis of proteins leads to the linking of the side chains of amino acids with the products of the breakdown of fatty acids. The whole molecular ballast formed impedes the exchange of substances and gases between the blood and tissues.

In contrast, high-density lipoproteins exhibit anti-atherogenic activity. In the blood, these particles interact with other lipoproteins and with cells, capturing cholesterol and acquiring a spherical shape on maturity. Cholesterol on the surface of high-density lipoproteins is esterified by the enzyme lecithin-cholesterol-acyltransferase, after which the resulting ester is immersed in the hydrophobic core of the particle, making space available on the lipoprotein's surface and removing the cholesterol's ability to inhibit the synthesis of receptor proteins in endothelial cells.

Another risk factor is a sedentary lifestyle. Typically, 90% of the fatty acids in the body are used as “fuel” for energy-releasing processes, about 8% are needed for de novo resynthesis of fats, and only 1.5–2% of these acids are used for the synthesis of ketone acids and cholesterol. This means that reducing energy waste by only a few percent can dramatically increase the synthesis of endogenous cholesterol. Since physical inactivity does not require the additional consumption of cholesterol to enhance the synthesis of steroid hormones, bile acids, or to create new cell membranes, some of the excess cholesterol can be absorbed by endothelial cells and promote lipid infiltration of the blood vessels. At the same time, lipoproteins of various densities float in the blood of sedentary people in excessive concentrations, which further increases the risk of atherosclerosis.

However, lipid infiltration is only the initial stage of the disease. Next, leukocytes that absorb lipoprotein particles penetrate the vessel wall, which can be considered a method of partial correction of lipid metabolism disorders. As a result of lipoprotein absorption, monocytes are transformed into what is known as *foamy cells*, due to their characteristic appearance under the microscope. “Eating” lipids does not suit them, and they do not live long. With the death of foamy cells and as a result of some other processes, many biologically active substances are released that induce local inflammation of the artery. This inflammation is accompanied by enema and leads to hardening—the proliferation of connective tissue in the vascular wall. Sclerotic vessels lose their elasticity, which is a common cause of high blood pressure. In addition, the permeability of such vessels to oxygen and nutrients decreases and this adversely affects the state of the surrounding tissues, in which an ischemic state develops over time.

Adherent lipoproteins, oedema and hardening all change the configuration of the inner surface of the arteries. The resulting roughness significantly increases the risk of local thrombosis. Blood clots, in turn, contribute to the formation of atherosclerotic plaques. Expanding and accumulating insoluble calcium salts (plaques) can completely block the lumen of the artery and thus lead to a state of severe ischemia—that is, to malnutrition and gas exchange attenuation in the surrounding tissues. Such violations are the pathogenetic basis of strokes and heart attacks, which represent an immediate threat to life.

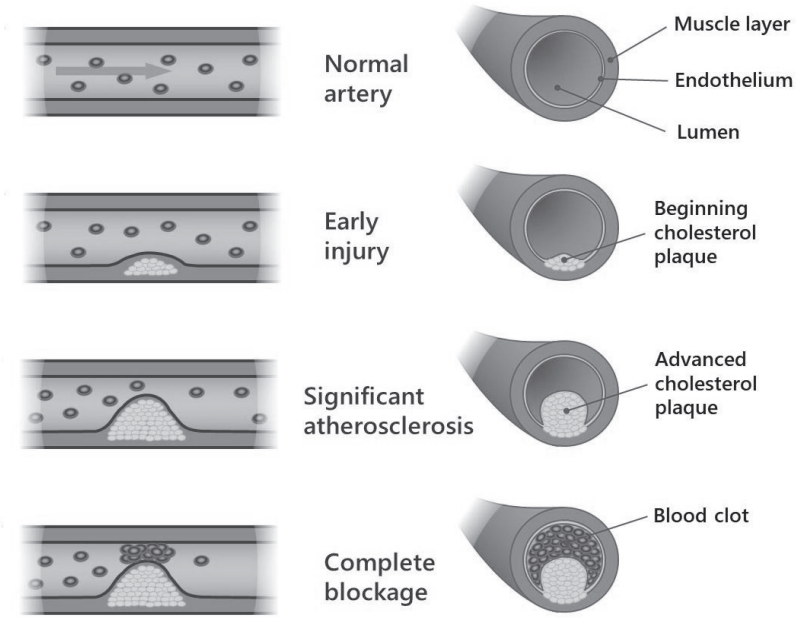

Fig. 5.11. Atherosclerotic plaque developmental stages

Symptoms. The clinical manifestations of atherosclerosis are very diverse; their nature is largely determined by which arterial vessels are predominantly damaged.

Coronary artery disease leads to coronary heart disease, the classic manifestations of which are various forms of angina pectoris, myocardial infarction and cardio sclerosis; acute coronary insufficiency may result in sudden cardiac arrest. The most common symptom of coronary heart disease is severe chest pain, accompanied by pain in the left shoulder or in the left scapula region. Electrocardiography is necessarily used for a final diagnosis. Laboratory studies of the activity of the cardiac isozymes—creatine phosphokinase and lactate dehydrogenase—are also used, as well as the determination of some proteins specifically used by myocardial cells, particularly troponins.

Atherosclerosis of the cerebral arteries is manifested by a slowly progressive weakening of the memory and cognitive abilities of the brain. This is followed by a reduction in the acuity of hearing and vision, deterioration of sleep, tinnitus, a tendency to depression, and a number of other signs of a decrease in the effectiveness of the central nervous system.

With the development of strokes, the accession of focal symptoms is possible (paresis, paralysis, loss of ability to articulate speech, etc.). Damage to the lower limb arteries is the cause of intermittent claudication and dry gangrene. Atherosclerosis of the abdominal cavity arteries leads to ischemia and intestinal infarction. It may also cause damage to the renal arteries, with subsequent renal dysfunction.

Diagnosis. The diagnosis of diseases associated with atherosclerosis necessarily includes the identification of clinical symptoms, electrocardiography, and an analysis of the blood lipid spectrum. Electroencephalography, examination of the chest by x-ray, ultrasound of the heart and abdominal organs, computer tomography and Doppler blood vessel investigations are also used if necessary.

Treatment. The treatment of atherosclerosis necessarily includes measures aimed at correcting lipid metabolism. An increase in motor activity, a decrease in total body weight, smoking cessation and an anti-sclerotic diet are necessary for this. An example of an anti-sclerotic diet is the “Mediterranean” diet, which is rich in polyunsaturated fatty acids, vegetables and fruits. Alcoholic beverages are allowed in the form of up to 150 ml per day of table wine, but it is better to completely give up alcohol, because its use increases the risk of strokes. Unfortunately, these measures are not enough.

Drug therapy for atherosclerosis involves the use of drugs that:

- inhibit the absorption of cholesterol from the intestine
- inhibit the synthesis of cholesterol and triglycerides in the liver
- or accelerate the breakdown and excretion of various lipids

The use of all of these drugs significantly slows down the development of atherosclerosis. Sometimes, with their help, it is even possible to temporarily improve the condition of the circulatory system. The use of anti-inflammatory drugs is often helpful. However, drugs that completely cure atherosclerosis do not yet exist, so in due course it becomes necessary to treat the complications of this pathology. The most frequent complications are coronary heart disease, degenerative changes in the brain, and hypertension.

Eating Disorders

Disorders of food absorption. Every living creature receives energy from the environment and is composed of environmental substances. At the same time, it is important to recognize the difference between heterotrophic and autotrophic organisms. Autotrophs feed on simple molecules (e.g., H_2O, CO_2, inorganic salts) that can be consumed immediately and directly, and their energy can be obtained directly from sunlight or from exoenergetic chemical reactions. The life of heterotrophs is more complicated. Their menu is a mixture of organic molecules, most of which can't be used by their bodies without specific changes, and in order to obtain energy they must break very strong σ-chemical bonds. Performing such tasks requires a phased catabolism—the disintegration of complex molecules into ever more simple ones. However, wherever there is a process, there is the possibility of failure. One of the main causes of human nutritional disorders is diseases of the digestive system, and the other is disorders of the intracellular catabolism of proteins, lipids, carbohydrates and nucleic acids.

The extracellular digestion of food occurs in the organs of the digestive system, under the influence of a complex of hydrolytic enzymes. Most of these enzymes are synthesized in the salivary glands, the mucous membrane of the stomach, and in the pancreas. Ideally, the polymer molecules break up into a mixture of monomers—amino acids, glycerol, fatty acids, monosaccharides, and nucleotides. Furthermore, for the successful absorption of hydrophobic molecules, bile—which is produced by the liver—is required. Absorption takes place in the intestine. Accordingly, the disease of any listed organ leads to a decrease in the effectiveness of the entire digestive system, and to starvation of varying severity.

Disturbances in the digestive system as a cause of starvation are a characteristic of economically prosperous countries. In poor countries, it is more often a simple case of food shortages. It is impossible to accurately calculate its total extent, but hunger is the most widespread pathology on Earth.

Full starvation is called absolute (dry) if there is no opportunity to receive not only food, but also water. Depending on the environmental conditions, primarily on the temperature, such starvation can last for no more than three days, after which a person dies of thirst. In the case of a non-absolute fasting—when there is an opportunity to get water, but not

food—life expectancy increases significantly, as the body manages to use endogenous nutrient reserves: carbohydrates, lipids and proteins.

The first to be consumed are the reserves of glycogen in the muscles and liver. Glucose-6-phosphate, formed during glycogenolysis, is used in glycolysis, in which each molecule of this metabolite produces two molecules of ATP and two molecules of pyruvic acid. Furthermore, these molecules are converted to acetyl-CoA, which undergoes oxidation in the Krebs cycle to produce the reduced coenzyme of $NADH^{+}$. In turn, the oxidation of these coenzymes allows the synthesis of additional ATP molecules in the respiratory chain of mitochondria.

However, the supply of carbohydrates is small. When a person is performing mental or physical work of an average intensity, they usually last for several hours. After that, the use of accumulated lipids begins. Lipids maybe deposited in the subcutaneous fatty tissue, in the omentum and inside the capsules surrounding the liver and kidneys, and are stored mainly in the form of neutral fats. During lipolysis, a mixture of glycerol and fatty acid molecules is formed from fats. Both can produce energy; a particularly large amount is released and stored in the form of ATP during theβ-oxidation of fatty acids. The total stock of lipids is very different in fat and thin people, and usually differs by several kilograms. Depending on the initial fatness and on the intensity of the total energy consumption during fasting, the lipid supply comes to an end within a period of 3–14 days.

After that, serious problems arise because the body has to waste its last resource, proteins, to meet its energy needs and to ensure the synthesis of vital substances. These last for about two weeks. By itself, the breakdown of protein provides almost no energy, but the process of proteolysis produces free amino acids. Through the process of deamination, these amino acids are converted into keto acids, which can be metabolized in the Krebs cycle and produce the reduced coenzyme $NADH^{+}$; the subsequent oxidation of this coenzyme allows energy to be stored in the form of macroergic ATP bonds. However, amino acids are very valuable raw materials which are necessary for the synthesis of new vital proteins, such as haemoglobin. Therefore, the use of amino acids to produce energy is biological waste, indicating the critical state of the body. To reduce the overall negative effects of this recycling, the first proteins to be used are those that are less important for the survival of the body—those found in the muscles and reproductive organs. However, the mass of the brain, even in cases of the most severe starvation, does not decrease by more than 5%, while the total body weight may decrease by 2–3 times.

The lifespan of a starving organism depends on several variable factors: the reserves accumulated in the body, their rate of expenditure, and the external conditions. On average, the duration of full starvation is 30–35 days. With a favourable set of circumstances, it can be doubled, but more often it is significantly reduced due to the resulting complications. The most frequent of such complications are infectious diseases, which contribute to the overall reduction of the protective and adaptive abilities of the body, weakening the immune system in particular. In addition, fasting exacerbates the course of chronic diseases and contributes to the emergence of new ones.

Incomplete starvation (malnutrition) is a consequence of nutrition which does not fully satisfy the body's need for energy or substance. In itself, such starvation does not lead to death, but can be the cause of numerous complications. First of all, malnutrition, as well as irregular nutrition, violates the regulation of secretory activity by the stomach, liver, pancreas and intestinal glands, which increases the risk of diseases of the digestive system. As well as this, chronic malnutrition negatively affects the state of all the organs and weakens the overall protective and adaptive potential of the body, making it more vulnerable to infections, and increasing the risk of cancer and metabolic diseases. In some cases, conscious starvation or the rejection of certain types of food is the result of either commonplace ignorance or mental disorders. Of particularly note is the fact that chronic malnutrition adversely affects the state of the nervous system; nutritional deficiencies can change patterns of behaviour, and may further contribute to the formation of mental abnormalities.

High-quality fasting develops when there is unbalanced nutrition. In this variant, the energy needs of the body are met, but there is a shortage of some of the substances necessary for life. These can be essential amino acids, essential fatty acids, vitamins or mineral salts.

Protein-energy deficiency (*"kwashiorkor", PED*) is one of the classic examples of this type of fasting. PED occurs either because of a chronic lack of proteins in the diet, or because of diseases in which the digestion of proteins in the stomach and intestines is disturbed. As a result of the lack of essential amino acids, the synthesis of many endogenous proteins is inhibited, and the overall condition of the body worsens. For a patient with BEN, there is a lack of subcutaneous and internal fat deposits, muscle wasting, hair loss, weakness, apathy, and a decrease in cognitive abilities. Due to the insufficient synthesis of digestive enzymes, diarrhoea often

occurs. Immunity is weakened, and wound healing is very slow. In cases of severe pancreatic diabetes due to protein deficiency, the oncotic pressure of the blood drops, and peripheral oedema develops. In addition, there is a loss of libido; in women, amenorrhea begins, and in men there are violations of spermatogenesis.

Protein-energy deficiency is characteristic of poor countries; however, another type of high-quality starvation has a much greater geographic prevalence. This is vitamin deficiency. It arises not only when there is a low content of vitamins in food, but also as a result of the high consumption of these obligate components of nutrition, due to the fast pace of life in often quite prosperous modern cities.

Hypovitaminosis C. Water-soluble vitamin C *(ascorbic acid, Latin: ascorbutus—antiscorbutic)* is a powerful natural reducing agent. Its active form, dehydroascorbic acid, performs a number of important biological functions. As cofactor enzymes prolylhydroxylase and lysylhydroxylase, this acid is involved in the conversion of procollagen to collagen, the main protein of the non-cellular substance of the connective tissue. Without the participation of vitamin C, it is impossible to synthesize the catecholamine stress hormones. This vitamin is necessary for the formation of the active form of another vitamin, folic acid. Vitamin C is an important component of the xenobiotic detoxification system and the antioxidant system. In addition, it protects high-density anti-atherogenic lipoproteins from oxidation, and is also involved in some other biological processes.

Since vitamin C is not synthesized in the human body, it must be fully supplied by food; the daily requirement of this vitamin is 50–75 mg. The main source of vitamin C is fresh vegetables and fruits, and it is found in smaller quantities in animal products, particularly in raw meat and fish. Vitamin C is thermo labile, so the heat treatment of food leads to its damage.

In adults with a vitamin C deficiency, scurvy develops, and in children, Moeller-Barlow disease. The early signs of these diseases include the effects of the inhibition of catecholamine synthesis—a decrease in interest in life and the outside world, lethargy, apathy, drowsiness, and light endogenous hypothermia. Later, there are signs of a lack of mature collagen—bleeding gums, frequent nasal and prolonged menstrual bleeding, haemorrhagic rashes on the skin, the loosening and loss of teeth, and the slow healing of wounds. If the causes of hypovitaminosis are not eliminated, patients die from adhering infections, or from haemorrhages in the internal organs.

Hypovitaminosis B1. Vitamin B1 (thiamine, aneurin) is a water-soluble vitamin. It is rapidly destroyed during the heat treatment of food or in an alkaline environment. The active form of B1is thiamine pyrophosphate; it is a cofactor for the enzymes of decarboxylation of α-keto acids, as well as for the enzymes responsible for the exchange of α-keto sugars. In all such reactions, the C–C bond breaks adjacent to the keto group of the substrate.

At the general body level, thiamine pyrophosphate improves blood circulation, participates in haematopoiesis, and is able to catalyse some reactions without the participation of enzymes. Vitamin B1 supports the cognitive activity of the brain, and has a positive effect on muscle tone; it has the properties of a natural antioxidant.

A lack of vitamin B1 in the body leads to the development of the illness *beriberi*. In the classic version of this pathology, disorders of the nervous, cardiovascular systems, stomach and intestines occur; its characteristic feature is the appearance of oedema in the face and joints of the hand. B1 hypovitaminosis is characterized by increased irritability, poor sleep, distraction, forgetfulness, pain in the abdomen, a tendency to vomiting, and a weakening of the tone of the smooth muscles of the stomach and intestines. The tongue becomes dry and dark red in colour, with less pronounced papillae. In children, the changes in the nervous system are distinct: they are capricious, quickly tired, and complain of unexplained pains along the nerves. In young children, the hypersensitivity of skin receptors, tearfulness, poor sleep, and a weakening of reflexes are often observed.

Hypovitaminosis B2. Vitamin B2 (riboflavin) is part of the cofactors flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), which are very important for a number of enzymes. In particular, these cofactors are necessary for the operation of dehydrogenases involved in the oxidation of fatty, succinic, and other acids. The flavin-dependent dehydrogenases deactivate toxic aldehydes, and break down foreign D-isomers of amino acids, which are formed as a result of the metabolic activity of bacteria. These enzymes are also involved in the work of the mitochondrial respiratory chain, participating in the synthesis of the active forms of vitamin B6 and folacin. In such reactions, FMN and FAD are used as carriers for electrons and protons. Vitamin B2, together with retinol, ensures the sharpness of colour perception, helps the organs of vision to adapt in the dark, and protects the retina from ultraviolet exposure. B2 also helps to reduce eye fatigue.

A significant percentage of the elderly population suffers from hypovitaminosis B2. Vitamin B2 deficiency is manifested in impaired colour perception, a decrease in the quality of twilight vision, the appearance of painful skin cracks at the corners of the mouth, inflammations of the mucous membranes of the mouth and tongue, inflammation of the conjunctiva and cornea of the eyes, tearing, photophobia, and dermatitis. In severe B2 hypovitaminosis, disturbances in the sensitivity of skin receptors and impaired coordination of movements are also present. A lack of B2 during pregnancy can lead to the development of fetal skeletal anomalies. A lack of B2 provokes the degradation of brain tissue and contributes to the emergence of nervous and mental disorders, as well as the development of persistent depression. A lack of this vitamin leads to poor iron absorption, which increases the patient's risk of developing hypochromic anaemia, and possible violations of the thyroid gland.

Vitamin B2 is the most scarce of all the B vitamins, so it is very important to consume foods with a high riboflavin content. These products include liver, kidney and heart, eggs, and fish. A sufficient amount of this vitamin is also found in foods of plant origin—in cereals, whole grain bread, legumes, tomatoes, mushrooms, fresh leafy vegetables, peanuts, and apricots.

Hypovitaminosis B3. Vitamin B3 is also called nicotinic acid, vitamin PP, or niacin. The active form of the vitamin is nicotinic acid amide or nicotinamide. As a result of nicotinamide in compound with adenine, nicotinamide adenine dinucleotide (NAD) is formed—one of the most common coenzymes in living organisms. NAD and its phosphorylated version, NADP, have the valuable ability to easily bind and release protons, so they are necessary for the work of a huge number of enzymes that catalyse redox reactions in the metabolism of lipids, amino acids, and nitrogenous bases. The NAD-dependent dehydrogenases also include key enzymes of the tricarboxylic acid cycle. It is probable that NAD participates in intercellular communication. It is assumed to be one of the neurotransmitters that can regulate the activity of cells in smooth muscle organs.

Vitamin B3 is also able to exert physiological effects at the tissue and organ level. This acid is able to significantly expand the arteries, which leads to a sharp decrease in blood pressure. Vitamin B3 and its derivatives have detoxification properties, and they also normalize the concentration of blood lipoproteins. In high doses, they reduce the concentrations of both total cholesterol and low-density lipoproteins, while increasing the content

of high-density lipoproteins with an anti-atherogenic effect. In addition, under the influence of vitamin B3, small blood vessels can expand, which improves microcirculation in organs, including the brain. Vitamin B3 is necessary for the normal functioning of the nervous system, endocrine glands, skin, intestines, and liver.

Often the development of hypovitaminosis of vitamin B3 is promoted by dysbacteriosis—the disruption of the normal species ratio of the intestinal microflora (for example, as a result of taking antibiotics), as well as any diseases of the digestive system that interfere with the process of absorption from the intestine. The risk of hypovitaminosis increases in old age. The signs of hypovitaminosis B3 are often mistakenly regarded as symptoms of senile dementia. The risk group also includes people suffering from alcoholism, diabetes mellitus and Hartnap disease (a hereditary disorder affecting the absorption of tryptophan and other neutral amino acids).

Hypovitaminosis B3 is the central component of the pathogenesis of a particular disease called *pellagra*. In the prodromal period, this hypovitaminosis makes itself known by nonspecific signs—general weakness, poor appetite, and moderate endogenous hyperthermia. The first and most characteristic symptom of pellagra may be an increase in the sensitivity of the skin to UV rays. Then, at the height of the pathology, there is a specific symptom complex of the "three Ds": diarrhoea, dermatitis and dementia. Diarrhoea develops due to dysregulation of intestinal activity. Dermatitis, i.e. the inflammation of the skin, is initially manifested as a result of increased sensitivity to ultraviolet rays. Subsequently it becomes permanent and habitual, leaving scars in the form of sinking dents on strongly flaky skin. The process can also affect the mucous membranes, such as the oral cavity. At the same time, ulcerative defects ("aphthae") appear on it, and inflammation of the epithelium of the pharynx, gums, and tongue is observed. A bright red, "strawberry" tongue is considered a specific symptom of pellagra. Dementia develops as a result of a complex of metabolic disorders in the neurons, and can reach the level of loss of control over certain physiological reflexes. In less severe cases, hypovitaminosis B3 is accompanied by apathy, a constantly tired state, the loss of emotionality, and impaired memory.

Hypovitaminosis B4. Choline (B4) is not considered a recognized vitamin because it is synthesized in the human body, is an intermediate metabolite in the synthesis of acetylcholine, and is part of the myelin sheaths of nerve fibres; all this is not typical for classic vitamins, which perform two basic biological functions—coenzyme and regulatory.

Therefore, many researchers classify choline as a vitamin-like substance. However, regardless of what it is called, under the influence of choline, the operational memory improves and the blood pressure decreases somewhat. Choline also accelerates the recovery of damaged parts of the liver, prevents the occurrence of gallstones, helps to normalize blood glucose and cholesterol levels, and helps the absorption of fat-soluble vitamins A, D, E, and K. In addition, choline is necessary for the normal functioning of the prostate gland.

With a lack of choline, fat intolerance may occur, blood pressure rises, and a person becomes irritable and does not sleep well. Other symptoms include headaches, tinnitus, and arrhythmia of the heart. Diarrhoea often occurs, or the reverse—constipation. Choline deficiency also increases the risk of developing age-related brain diseases.

Hypovitaminosis B5. Vitamin B5 (pantothenic acid, pantothenate) turns into pantethine in the body. This is part of *coenzyme A* (CoA), which is indispensable in the processes of oxidation and acetylation.

CoA is involved in the metabolism of proteins, lipids, and carbohydrates. Without it, the synthesis of such biologically important substances as fatty acids, cholesterol, histamine, acetylcholine, haemoglobin, and steroid hormones is impossible. In addition, CoA is called the "metabolic gatekeeper" of the Krebs cycle. The ability of vitamin B5 to reduce the concentration of low- and very low-density lipoproteins in the blood is of significant medical importance, since the lipoproteins of these classes contribute to the development of atherosclerosis of the arterial vessels.

A lack of B5 leads to dermatitis, skin depigmentation, hair loss, and impaired motor coordination. An increase in gastric secretion activity can occur, leading to hyper secretory gastritis, erosions of the mucosa, and gastric and duodenal ulcers. Due to the impaired function of the adrenal glands and the nervous system, B5 hypovitaminosis is also characterized by increased fatigue, a tendency towards depressive states, and sleep disorders. Burning night pains in the lower limbs, redness of the feet, and numbness of the toes are also possible. In children with a pantothenic acid deficiency, growth and intellectual development slows down. Due to the general decrease in the efficiency of metabolism, immunity is weakened, and the probability of infectious diseases occurring increases.

Hypovitaminosis B6. Vitamin B6 (adermin, pyridoxine) is phosphorylated in the body by the formation of pyridoxal-5-phosphate—a cofactor of enzymes that perform the deamination, transamination and

decarboxylation of amino acids. In particular, pyridoxal-5-phosphate is necessary for the synthesis of nicotinic acid from tryptophan, as well as for the synthesis of the inflammatory mediators histamine and serotonin.

Vitamin B6 deficiency is rare. Primary hypovitaminosis occurs only in infants who are bottle-fed with formulas containing insufficient pyridoxine. Secondary hypovitaminosis type is possible in both children and adults; it may occur due to the suppression of pyridoxine-synthesizing intestinal bacteria by antibiotics. Some drugs accelerate the release of pyridoxine through the kidneys, which can also cause B6 deficiency. Another reason is an increased need for the vitamin under significant loads—e.g., strenuous physical work, stress, pregnancy, or intoxication.

In the prodromal period, B6 hypovitaminosis manifests itself as general weakness, fatigue, irritability, and insomnia. Further symptoms include the deterioration of the scalp, and of the skin joining the face and neck. There may be inflammation of the mucous membranes of the mouth and tongue. In severe hypovitaminosis, disturbances in the sensitivity of the peripheral nerve receptors develop, and infants may develop convulsions. There is often moderate anemia and lymphopenia (decrease of the number of leukocytes in the peripheral blood), resulting from the slow maturation of erythrocyte and leukocyte progenitor cells in the bone marrow.

Hypovitaminosis B7. With the participation of B7 (biotin, coenzyme R, vitamin H) the activation and transfer reactions of CO_2 proceed. In this role, vitamin B7 is a cofactor of gluconeogenesis enzymes, fatty acid metabolism enzymes, and leucine amino acid. It is also involved in the synthesis of glucokinase—an important enzyme that ensures the entry of monosaccharides into cells—as well as in the synthesis of purine nucleotides. Vitamin B7 also participates in the synthesis of collagen, and thus is necessary in order to maintain the normal state of the blood and lymphatic vessels, skin, hair, and nails.

A deficiency of this vitamin is initially manifested in peeling skin, a loss of shine and elasticity of the hair, and brittleness and peeling of the nails. Later, drowsiness, depression, muscle soreness and weakness, and an increase in the concentration of cholesterol and glucose in the blood occur; subsequently anaemia is possible.

Hypovitaminosis B8. Vitamin B8 (inositol) can be synthesized in the human body from glucose. When it penetrates the spinal cord or brain, this vitamin accumulates in the cell membranes. Vitamin B8 stimulates mental activity, improves concentration and memory, and reduces the fatigue of

the brain. A large amount of B8 is consumed by the retina and lens of the eye, and a lack of B8 can cause a decrease in visual acuity. Vitamin B8 promotes cholesterol normalization in the blood, helps to maintain the elasticity of the artery walls and to thin the blood, and also stimulates the growth of muscle and bone tissue, which is especially important for the normal development of a child's body. Taking vitamin B8 for fractures helps to speed up bone healing.

Vitamin B8 is involved in the transport systems of the cell, and contributes to the rapid recovery of the body after prolonged physical exertion, as well as after diet and fasting. The activity of the reproductive organs of men and women also depends on the content of inositol in the body, and vitamin B8 deficiency can cause infertility. Vitamin B8 has soothing properties. At the same time, taking vitamin B8 supplements does not cause the appearance of side effects. In contrast, B8 hypovitaminosis can lead to insomnia, bouts of irritability, and panic. Other frequent symptoms of this type of hypovitaminosis are disorders of the digestive system, muscular dystrophy, reduced mental efficiency, and increase in blood cholesterol level, impaired vision, skin rash, hair loss, and, lastly, dysfunction of the genitals.

Hypovitaminosis B9. Vitamin B9 (folic acid, folacin) is converted into its active form—tetrahydrofolic acid (THFA)—with the help of enzymes and vitamin B12. The main function of THFA is to transfer one-carbon groups, such as methyl and formyl groups, from one organic molecule to another. Such reactions are necessary in the synthesis of nucleic acid precursors; therefore, without THFA, cell division and reparative DNA synthesis are impossible.

A lack of folic acid can cause megaloblastic anaemia, and in men hypovitaminosis B9 causes impaired spermatogenesis. Another undesirable consequence of a deficiency of folic acid and its derivatives is the accumulation of homocysteine in the body, contributing to atherosclerosis development. A shortage of THFA during pregnancy is especially dangerous; this can lead to fetal defects in the development of the brain and spinal cord. All dividing cells, including cancer cells, need THFA. Therefore, for the treatment of a number of malignant tumours, drugs are used to block the formation of THFA from folic acid. The best-known of these drugs is methotrexate.

Hypovitaminosis B10. Vitamin B10 *(para-aminobenzoic acid, PABA)* has antiallergic effect, and it also participates in the synthesis of folacin, purine and the pyrimidine nitrogenous bases of nucleotides and some

amino acids. In particular, it has been established that Vitamin B10 is necessary for the synthesis of an interferon antiviral protein, which strengthens the body's resistance to a number of viruses. Vitamin B10 is necessary in order to maintain the normal condition of the skin and hair. It is able to stimulate the synthesis of melanin pigment, and therefore is used in medical creams and sunscreen. The effect of Vitamin B10 on melanin synthesis is used to combat the disease of *vitiligo*, in which a spotted skin discoloration occurs.

Signs of hypovitaminosis B10 are pallor of the skin, loss, breakage and early greying of the hair, increased fatigue, irritability, headaches, insufficient milk production in nursing mothers, the occurrence of sunburn with minimal insolation, muscular dystrophy, anaemia, and the weakening of sexual desire.

Hypovitaminosis B11. The active form of vitamin B11 is L-carnitine. L-carnitine is very important in energy metabolism processes. Its role in these processes is to transfer fatty acid acyls inside the mitochondria. When hypovitaminosis B11 occurs, the transport of fatty acids in the mitochondria is inhibited, and the activity of their oxidation decreases, leading to a shortage of energy. In the opposite case, the natural intake or artificial introduction of L-carnitine into the body increases its endurance in relation to physical exertion. It should be noted that this effect is manifested both in relation to the skeletal muscles, and in relation to the muscle cells of the myocardium. Accelerated fatty acid oxidation also helps to get rid of excess fat deposits. L-carnitine also has useful antioxidant properties: it protects tissues from the toxic effects of free radicals.

Chronic fatigue, obesity, irritability, asthenia, cardiac abnormalities, and exercise intolerance can all serve as indicators of carnitine deficiency in the body.

Hypovitaminosis B12. All the names of vitamin B12 (cyanocobalamin, antianaemic vitamin, *extrinsic factor of Castle*) unite a group of substances containing cobalt atoms in their composition, all of which have a cyclic corrin moiety associated with them, and contain a ribose nucleotide ligand. Vitamin B12 is absorbed mainly in the small intestine. This is due to the way it binds to the internal factor of the mucoprotein (the *intrinsic factor of Castle*) or (when entering the body in excess doses) due to passive diffusion. When they enter the blood, cobalamins are in contact with transport proteins. In combination with them, they enter organs and tissues. The active coenzyme forms of vitamin

B12—methyl cobalamin and deoxy adenosine cobalamin—are necessary for the enzymes catalysing the transfer of methyl groups of CH_3 (trans methylation reactions). These reactions are necessary in the synthesis of deoxy ribonucleotides, the polymerization of which produces DNA. Participation in the synthesis of DNA precursors makes the presence of a sufficient amount of vitamin B12 a prerequisite for the successful preparation of cells for division.

Methyl cobalamin is involved in the synthesis of methionine as a carrier of the methyl group from methyl tetrahydrofolate to homocysteine. Tetrahydrofolic acid, formed as a result of this reaction, is involved as a coenzyme in the metabolism of proteins and nucleic acids. Its deficiency leads to a situation in which single-carbon residues, such as formate and methylene, cannot be involved in metabolic processes due to the absence of their acceptor, tetrahydrofolic acid. As a result, the synthesis of purines, for which formate is required, is slowed down, as is the synthesis of thymidine, for which methylene is required. The consequence of this is the disrupted synthesis of nucleic acids and protein in the cells.

Addison–Biermer's disease is a classic manifestation of vitamin B12 deficiency. As a rule, the cause of this deficiency is atrophic gastritis and a deficiency of the intrinsic factor of Castle, which prevents the absorption of vitamin from the intestine. The consequences of this may be megaloblastic anaemia and damage to the lateral horns of the spinal cord. External signs of vitamin B12-deficient anaemia are caused by hypoxia: weakness, dizziness, shortness of breath, palpitations, irritability, loss of appetite, and oedema. In addition, there is hypotrophy and a decrease in the secretory activity of the gastric mucosa, and hypotrophy of the papillae of the tongue. The development of degenerative processes in the spinal cord is accompanied by disturbances in receptor sensitivity, an unstable gait, a weakening of natural reflex reactions and the appearance of pathological reflexes. In severe hypovitaminosis, mental disorders are possible. Vitamin B12 deficiency of any genesis is characterized by the suppression of immune responses and non-specific resistance factors, which increases the risk of infectious complications.

Hypovitaminosis A. The name vitamin A refers to a group of substances which have similar biological effects, chemical structure and origin. This group includes retinoic acid, retinol (vitamin A1, axeroftol), dehydroretinol (vitamin A2), and retinal (retinene). The group is also called retinoids. The vitamin A provitamins are the carotenoids, and the most important among them is β-carotene. Retinoids are found in animal products, while carotenoids are found in plants. All of these substances are

soluble in organic solvents, but poorly soluble in water. Vitamin A is deposited in the liver, but can accumulate in other tissues. Vitamin A and its derivatives enter the target cell and interact with specific receptor proteins in the cell cytoplasm. Furthermore, the vitamin-receptor complex enters the cell nucleus and binds to DNA, regulating the synthesis of a number of proteins, including enzymatic ones.

As they stimulate the formation of de novo enzymes, in this way retinoids perform many biochemical functions in the human body. They are necessary for the synthesis of chondroitin sulfuric acid sulfoglycans and hyaluronic acid—the basic components of the non-cellular substance of connective tissue. Without vitamin A, it is not possible for the body to synthesize fibronectin, heparin, taurocholic bile acid, or A1, A2, B and C somatomedins. Retinoids stimulate the synthesis of sex hormones and some immunoglobulins, and the glycosylation of blood glycoproteins and the glycoproteins of cell membranes. Interconversions of cis- and trans-retinal provide photoreception in the reticular membrane of the eye. Vitamin A stimulates cell growth and differentiation in the form of retinoic acid. The main effects of retinoids are realized in synergism with vitamin E, which is another fat-soluble vitamin.

With vitamin A deficiency, ***night-blindness*** develops. This deficiency also affects the skin and intestinal mucous membranes (which can result in the formation of ulcers), bronchi (causing frequent bronchitis), and the urinary system, where it facilitates infection. This form of hypovitaminosis causes the content of lysozyme in the serum and other fluids to decrease, and it also leads to a reduction in the activity of leukocytes. Over a long period of vitamin A deficiency, the hypotrophy of the lacrimal canals can stop the cornea from wetting; the eye dries out and softens, with the full loss of visual function.

Hypovitaminosis D. Vitamin D is a group of biologically active substances synthesized from cholesterol. A three-stage synthesis of the most active form, vitamin D3 (*cholecalciferol*), consistently occurs in the skin (under the action of ultraviolet rays), and in the liver and kidneys. Vitamins D2, D4, D5 and D6 are significantly less active forms. Vitamins of the D group are deposited in the liver. Stocks accumulated by the body during the summer can gradually be used over the winter months.

In the intestine, D vitamins promote calcium absorption, and in the muscles and kidneys these vitamins stimulate the reabsorption of free calcium. Under their influence, the mineralization of the bones of the skeleton and teeth with calcium, magnesium and phosphorus increases. The increase in the blood calcium level due to D vitamins promotes the

absorption of calcium ions by the cells of the nervous system. As they enhance the process of the assimilation of magnesium and calcium, the vitamins of group D probably contribute to the restoration of the protective shells of nerve fibers, and therefore may be useful in the complex treatment of multiple sclerosis. D vitamins are involved in the regulation of cell growth and have some cancer static effects on tumors of the mammary glands, ovaries, prostate and brain. This may be due to the stimulation of the development of the immune system's cells.

Hypovitaminosis D plays a major role in the development of ***rickets*** in children. The early symptomatology of rickets is caused by disorders of the nervous system, which are manifested in rapid changes of mood, restless and shallow sleep, sweating and tearfulness; the child's mental development is lagging behind the norm. Somewhat later, a weakening of the skeleton and abdominal muscles is detected. After this, violations in the development of the bone tissue are detected. In infants, rickets leads to a delayed mineralization of the fontanelle—the connective tissue areas of the skull bones—and the late eruption of milk teeth. In cases of severe rickets, characteristic deformities of the occipital, parietal and frontal bones occur (flat nape; "Socrates forehead"). The sternum ("chicken breast") is often deformed, and the cartilaginous parts of the ribs are slow to mineralize. When a child with rickets begins to walk, the bones of the lower legs develop curvature, and the pelvic bones can be deformed.

In adults, a long-term deficiency of the vitamins of group D contributes to the development of osteoporosis of the skeletal bones and the inhibition of bone tissue repair processes. Hypovitaminosis D is one of the causes of caries, contributes to the development of disorders of the nervous system, weakens the immune system, and increases the risk of cancer and cardiovascular diseases.

Hypovitaminosis E. Vitamin E is a group of biologically active substances which are related in structure and function. These varieties (*vitamer*) are divided into two classes—tocopherols and tocotrienols. Both of these classes are absorbed from the intestine. They then enter the liver through the lymphatic and blood circulatory systems, as a component of chylomicrons. There, tocopherols and tocotrienols are partially excreted in the bile, and partially incorporated into the composition of lipoproteins, after which they re-enter the bloodstream and spread throughout the body. Tocopherols possess antioxidant abilities, and are involved in the biosynthesis of heme and proteins, in cell proliferation, and tissue respiration. They also prevent increased capillary permeability and fragility, and stop the occurrence of erythrocyte hemolysis. E vitamers

protect the plasma membrane of cells from oxidative damage. Vitamin E, together with ascorbic acid, provides the inclusion of selenium in the active center of glutathione peroxidase. It thereby activates the enzymatic antioxidant protection, with the help of this enzyme and the reduced form of glutathione. Moreover, tocopherols are not only antioxidants, but also antihypoxants, due to their ability to stabilize mitochondrial membranes and reduce oxygen consumption by cells. At the same time, the conjugacy of oxidative phosphorylation increases in the mitochondria, and the formation of ATP and creatine phosphate is accelerated. Finally, tocopherols are involved in the synthesis of ubiquinone, an essential component of the respiratory chain. The oxidized forms of E vitamers can react with ascorbic acid or with other hydrogen donors, and return to their reduced forms. It is widely believed that vitamin E is able to slow down the aging process due to its antioxidant capabilities, but there is no reliable evidence of this yet. Undoubtedly, the E vitamins have a positive effect on the maturation of male and female sexual gametes and increase mutual sexual desire.

Hypovitaminosis E is manifested in a variety of symptoms—muscular weakness and deterioration of potency in men; and early toxicosis of pregnancy, and high risk of miscarriage or spontaneous abortion in pregnant women. Another possible manifestation is hemolysis of the red blood cells, followed by anemia. E-deficiency nervous system disorders consist of a weakening of reflexes and impaired motor coordination; in severe cases, impaired speech articulation is possible. In addition, a lack of E increases the risk of hepatic necrosis, retinal dystrophy, and male and female infertility.

Hypovitaminosis K. Vitamin K is the name for a group of naphthoquinone derivatives, which are similar in structure and biological function. The most active is phylloquinone (vitamin K1), which is ingested with plant-based foods. Vitamin K2 (menaquinone, menatetrenone) is produced by bacteria in the intestine; its deficiency is rare, and is mainly caused by dysbacteriosis. K vitamers provide the carboxylation of glutamic acid in some proteins. As a result of this enzymatic process, glutamic acid residues are converted into gamma-carboxyl glutamic acid residues (Gla-radicals) involved in calcium binding. Gla-radicals provide the biological activity of all known Gla-proteins, which play a key role in blood coagulation (prothrombin, factors VII, IX, and X, protein C, protein S, protein Z) and in the regulation of bone mineralization (osteocalcin).

Hypovitaminosis K can develop due to a violation of the absorption of food in the intestine, due to the therapeutic use of vitamin K antagonists. Very rarely this condition occurs due to a deficiency of vitamin K in the diet. As a result of hypovitaminosis, Gla proteins do not fully perform their functions. As a result, abundant internal hemorrhages, pathological ossification of cartilage, serious deformation of the developing bones, or salt deposits on the walls of arterial vessels are possible.

Hypovitaminosis N. Vitamin N (lipoic acid, lipoate, lipamide, thioctic acid, berlithione, para-amino benzoic acid) was until recently considered a vitamin-like substance, but is now considered to be a true vitamin. Lipoic acid is present in every cell and is formed by the oxidative decarboxylation of alpha-keto acids. Lipoate has powerful antioxidant properties that can neutralize any type of free radical, and it is therefore classified as a hepatoprotector—i.e., a substance that protects against damage to the liver cells. Lipoic acid is an excellent detoxicant; it binds and removes toxins and heavy metals from the body. In addition, vitamin N has an insulin-like effect on carbohydrate metabolism, partially replacing insulin when it is deficient.

Specific symptoms of lipoic acid deficiency have not yet been identified, but with an insufficient use of lipoic acid, dizziness and headaches can occur, and the risk of fatty hepatosis (fatty degeneration of the liver) and biliary formation disorders increases. Spasms of the skeletal muscles and dystrophic changes in the myocardium are possible; vascular atherosclerosis is accelerated.

Coenzyme Q (ubidecarenone, ubiquinone, coenzyme Q_{10}, KoQ) is a group of coenzymes containing the quinoid group (hence the designation Q). In humans and animals, ubiquinones are synthesized from phenylalanine and tyrosine. Coenzyme Q participates in oxidative phosphorylation reactions and is a link in the chain of electron transfer in mitochondria, and thus participates in the synthesis of ATP. Coenzyme Q is also an antioxidant and, unlike other antioxidants, is regenerated by the body. In addition, coenzyme Q restores the antioxidant activity of vitamin E.

A lack of CoQ_{10} in humans can be caused by a slowdown in its biosynthesis and an increased consumption of cells. Q_{10} deficiency can also develop due to genetic defects. The assimilation of exogenous coenzyme begins in the small intestine with the obligatory pre-emulsification of bile and the formation of micelles, in which CoQ penetrates into the intestinal cells and then spreads through the body

through the blood and lymph. Signs of hypovitaminosis Q have not yet been described, but it is assumed that coenzyme Q is useful in the complex therapy of heart disease and arterial hypertension.

Hypovitaminosis F. The term "vitamin F" (from the word *fat*) is considered obsolete, but can still be found in specialized literature. This term refers to indispensable polyunsaturated fatty acids, especially linoleic and α-linolenic ones, which are not synthesized in the human body, but are precursors of vital substances. For example, arachidonic acid—a material for the synthesis of prostaglandins and thromboxanes—is formed from linoleic acid. Essential polyunsaturated fatty acids are components of biological membranes, exhibit high antioxidant activity, slow the development of atherosclerosis, and increase the functional reserves of tissues. The total number of these acids is not yet definitively determined. Depending on the position of the double bond most distant from the carboxyl group, these acids are further divided into ω-3 and ω-6 variants. In the human body, they fall in the composition of vegetable oils and animal fats. The deficiency of omega-fatty acids in food slows down the growth and development of children, inhibits the activity of the reproductive organs, causes dermatitis, and damages the work of the hemostatic system.

Excess nutrition

For millions of years, our monkey-like ancestors were adapted to plant foods. Then the hominids learned to hunt, and meat was included in their diet. Approximately 10,000 years ago, after the transition to a sedentary lifestyle, people acquired the ability to use meat and dairy products from domesticated animals; they learned how to bake bread, and get sugar. The nature of nutrition has changed dramatically: many lipids and proteins have appeared in the diet, and carbohydrate intake has increased; in general, the prerequisites for excess nutrition have been created.

Overeating, or over-feeding, leads to an increase in body weight, which is a pressing issue for all economically-developed countries. This is not due to any particular prevalence of genetic susceptibility to overeating and obesity. Nowadays, although it is not the only factor, virtually unlimited access to food is one of the most important reasons for the increasing prevalence of overweight syndrome among the populations of North America, Europe, Russia and China in the short term.

Another reason is the intense rhythm of modern life, which is fraught with frequent stress. For many people, the pleasure of eating is a calming

distraction. Over time, this pleasant way of returning to the state of psychological equilibrium becomes a habit and even turns into a typical Pavlov's conditioned reflex. Then this reflex extends and becomes linked to the experience of watching TV, or to participation in social networks, and the forgotten sedentary body begins to grow.

The third reason for people becoming overweight is found in the molecular characteristics of the central nervous system's nutrition features. In wealthy countries, a huge number of people are engaged in intellectual work, for which the brain must be well-fed. But the most valuable substances in terms of energy—fatty acids—do not penetrate the blood brain barrier. The brain's energy is supported mainly by glucose. Meanwhile, although the food consists of more than carbohydrates alone, it is the carbohydrates that are most quickly consumed by actively working nerve cells, and the brain needs to consume more, while unused lipids are deposited in fat depots. Only hunger or considerable physical activity can effectively extract them from there, both of which require a fair amount of willpower.

The fourth cause is endocrine disease. Diabetes and thyroid diseases, which are associated with a decrease in the synthesis and incretion of the iodothyronine hormones, lead to an increase in body weight, in particular. However, such diseases are incomparably less common than an increase in body weight due to overeating.

Excess nutrition is highly undesirable due to the formation of a psychological dependence on food, and weight gain, with an inevitable increase in the load on the skeleton. This, over time, provokes diseases of the joints of the lower extremities and contributes to degenerative changes in the intervertebral discs. However, these are only some of the undesirable consequences, and they are not the most dangerous. Excessive food intake leads to chronic hyperlipidemia—an increase in the concentration of cholesterol and other lipids in the blood. Various forms of chronic hyperlipidemia are considered to be one of the most significant risk factors for atherosclerosis of the arteries. Pathological changes in the walls of blood vessels arising from atherosclerosis are the main cause of cardiovascular diseases, and it is from these conditions that most adults in developed countries die.

The real threat to life is not only quantitative, but also qualitative overeating. There are many substances in food that are useful and necessary in moderate quantities, but harmful or dangerous with excessive consumption.

This may seem paradoxical, but such substances primarily include vitamins:

- An overdose of nicotinic acid (vitamin B3) leads to a dramatic expansion of the arteries, a drop in blood pressure, and can lead to vascular collapse and death
- an overdose of ascorbic acid (vitamin C) can lead to the formation of ascorbate kidney stones and toxic hepatitis
- D hypervitaminosis in childhood can result in mental retardation, bone growth arrest, or even joint fusion

The abuse of most other vitamins does not bode well either.

Tumor Process

A tumor is a pathological process that is based on the unregulated multiplication of cells. Tumor cell multiplication (as opposed to cell reproduction during inflammation, physiological and reparative regeneration) has no compensatory-adaptive value. Tumor growth is one of the most ancient pathological processes in all living things. Signs of tumors have been found in fossil plants and animals that existed in the Cenozoic era. It is possible that the phenomenon of the malignant transformation of cells has the same age as that of multicellular organisms—that is, about 2.1 billion years. Among modern people, this pathology is very common—millions of people die from it every year—and in the structure of mortality in developed countries, cancer is in second place after cardiovascular diseases. On average, men die from cancer twice as often as women, and mortality from various types of cancer increases significantly after the age of 40. In addition to age, the likelihood of oncological diseases is increased by genetic predisposition, and unfavorable environmental and lifestyle factors.

Carcinogenesis

Of all the theories of cancer, the most reasonable seems to be mutational. According to this theory, the primary event that triggers the process of normal cells malignant transformation is DNA damage (mutations, aberrations) by carcinogens, which activate proto-oncogenes, i.e., normal genes that:

- control the inclusion of a cell division program
- inhibit the activity of cell division suppressor genes

- deactivate the genes responsible for the functioning of the DNA repair system.

Carcinogens, i.e. substances or effects that can cause the above violations and damages may be of a physical, chemical or biological nature. Physical factors include various types of radiation that can damage DNA.

There are many known chemical carcinogens, and more will be identified in the future. As a rule, they have either high reactivity, which allows direct interaction with nucleic acids, or a special structure, due to which they can firmly bind with the enzymes of the nucleic acids, and exchange and disable them.

Biological factors include nucleic acids, regulatory proteins, and the enzymes of oncogenic viruses that can interfere with the control of transcription, or damage the DNA molecules of a macro organism.

Despite the diversity of carcinogens, they all have similarities in that their transforming effect has a number of identical and mandatory features, namely:

- Threshold of the effect's manifestation, which occurs only when a certain concentration of a substance or a certain radiation power is reached
- The effect's additivity (summability)—the combined effect of two or more carcinogens reduces the threshold dose for each of them
- The effect's irreversibility

After the carcinogen is triggered, a malignant tumor may not develop immediately, and it does not always happen. Usually, a tumor goes through four stages of preclinical development—initiation, promotion, reproduction of the altered cell, and the initial growth of the tumor itself. The total duration of the preclinical stage of tumor development may reach several years, although during this period the disease is still considered to be taking place; it just has a very prolonged latent period.

The essence of the **initiation stage** is in the primary changes of the genome under the influence of a carcinogenic factor. After that, the cell may well die from any of a variety of natural causes. If this does not happen, the promotion phase begins, during which the proto-oncogenes are transformed into fully-fledged oncogenes, and the cell phenotype changes and takes on the features characteristic of tumor cells. It is believed that—at least in some cases—the stages of initiation and

promotion are reversible, and the cell may become normal if it does not experience repeated carcinogenic effects. If such effects do occur, the third stage begins, during which the pathological genotype becomes fixed, and the cell divides and gives rise to a tumor clone. The cells of such a clone acquire the ability for uncontrolled reproduction. They are significantly different from normal cells in shape, and their localization is not limited to certain tissues or organs. Many cancer cells are incredibly active in the absorption of carbohydrates from the environment, and they require less oxygen, because their energy is increasingly provided by anaerobic glycolysis.

The appearance of a ***clone of transformed cells*** is the beginning of the growth of an autonomous tumor. The primary colony is usually small—its diameter does not exceed a few millimeters. However, it can be recognized and destroyed by the immune system. In addition, it can die as a result of a massive apoptosis response—a genetically determined program for the self-destruction of defective cells. However, it can survive, and continue to grow.

The pace of further tumor development is largely determined by the effectiveness of its nutrition. Transformed cells are able to secrete metalloproteinases—enzymes that destroy the intercellular substance and facilitate the local growth of blood and lymphatic vessels. The development of the vascular network not only improves the nutrition of the tumor, but also increases the risk of its spread—the formation of metastases.

Another factor that ensures the survival and development of a tumor is the ability of its cells to synthesize growth factors in parallel with the synthesis of receptors specific for these factors. That is, tumors are capable of ***self-stimulation***. Furthermore, the consequences of the completely Darwinian natural selection among the cells of a growing tumor become more pronounced. The least differentiated cells have the greatest chance of survival, and thus of producing offspring. Such cells take less time to prepare for mitosis, and they are less sensitive to external inhibitory effects. They are also more malignant. At this point, the preclinical stage of tumor development ends.

The structure of tumors

Tumors occur in all tissues and organs. They can be benign and malignant, between which there are transitional forms called borderline neoplasms. The appearance and size of tumors are both very diverse: they

can be nodes of different sizes, shapes and consistencies, and they can diffusely grow into healthy tissues and have no clear boundaries. Tumors can undergo secondary changes—in particular, they may develop necrosis; calcium salts can be deposited in them; and areas of hyalinosis can appear. In relation to the surrounding tissues, the tumor is aggressive; it can damage blood vessels, causing bleeding and hemorrhage. Typically, a tumor consists of a parenchyma—a community of transformed cells—and a stroma, including connective tissue, blood vessels, and nerve endings. In cases of parenchyma predominance, the tumor has a soft consistency, and if the stroma prevails, the tumor is dense. The tumor's cells and stroma are generally different from the normal structures of the tissue from which the tumor developed; these differences are called atypism.

Atypism occurs at both the tissue and cellular levels. For the tissue variant of atypism, the only characteristic is a violation of the ratio of cellular and non-cellular components of the original tissue. For example, papilloma, a benign tumor of the skin, is characterized by a violation of the ratio of the epidermis and dermis. Cellular atypism is associated with pathological changes in the tumor's parenchyma cells, in which the cells lose their genetically programmed differentiation abilities. The inhibition of maturation makes tumor cells look like embryonic ones. Such cell changes are referred to as anaplasia.

Anaplasia is a complex of changes. Such cells can have a different size and shape to the cells in which they originated; their nuclei increase in size, and those nuclei acquire an unusual shape; the amount of chromatin within them increases; the quantity and sizes of the nucleoli change, and the ratio of the nucleus and cytoplasm volumes is altered in favor of the nucleus. Atypical changes also occur in the in other organelles of tumor cells. The shapes of mitochondria become deformed; they may decrease or increase in size, and the number of cristae in them often decreases. The endoplasmic reticulum expands in areas; the number of ribosomes, lysosomes, and various inclusions in the cytosol increases.

As a result of biochemical anaplasia, the metabolism of tumor cells changes significantly. It is manifested in all forms of exchange. The most characteristic is a significant acceleration of glycolysis—10–30 times faster than normal—against the background of a weakening of the processes of aerobic energy. As a result of the sharp increase in glycolysis, tumor cells intensively absorb glucose, "robbing" healthy cells. Acidosis resulting from a tumor's activation of glycolysis adversely affects the state

of surrounding tissues. The synthesis of proteins and nucleic acids is also significantly stimulated in tumor cells. Therefore, tumor tissue actively absorbs amino acids, nucleotides and nucleosides, turning into a "nitrogen trap". Moreover, in transformed cells there is not only an increase in the number of proteins, but also a qualitative change in their composition. As a result of this, abnormal antigen proteins appear in the plasma membrane of tumor cells, by which such cells are recognized by the immune system as foreign. In tumor cells, the synthesis of lipids necessary for the biological construction of membrane structures is now significantly enhanced. Biochemical atypism turns a tumor into a metabolic hole that drains vital juices from the body. This allows the tumor to obtain the resources for continual growth.

Tumor growth

Tumors can grow either quickly and slowly, but their growth is always continual. As a result, a tumor squeezes the surrounding tissues, causing their atrophy. This type of growth is called ***expansive***. This is not the most dangerous form of the disease. Gradually, from the atrophied, often inflamed and partially necrotic tissues, a capsule surrounding the tumor can form. Such a capsule inhibits the development of the tumor—both mechanically, and by hindering the transport of nutrients. The tumor grows slowly, and its slow growth increases the chances of timely detection and radical removal of pathologically altered tissues by surgery.

If tumor cells penetrate the capsule and grow into the surrounding tissue, this growth is called ***infiltrating*** or ***invasive***. In this case, the boundaries of the tumor cease to be clear. The tumor cells destroy the vessels; they penetrate the blood and lymph, and are carried throughout the body. Such tumors pose a much greater threat to life, as they grow rapidly and produce multiple metastases.

If a tumor develops in the wall of a hollow organ (stomach, uterus, bronchus, gall bladder), its growth can be exophytic or endophytic. With exophytic growth, the tumor protrudes into the lumen of the organ, and protrusions appear outside it. With endophytic growth, the process develops in the wall itself. This is a more insidious option, since such a tumor is more difficult to detect. However, most often, there is a mixed type of growth, with the relative dominance of one form or the other.

Benign and malignant tumors

Benign tumors consist of relatively mature and relatively differentiated cells, and initially do not differ very much from the surrounding healthy tissues. In such tumors, there is usually no cellular atypism, but there is tissue atypism. Benign tumors do not develop metastases. They are characterized by slow, expansive growth, and although they compress the surrounding tissues, they do not have a noticeable negative effect on the patient's body condition for quite some time. However, a lot depends on the location of such a tumor. For example, a benign tumor of the dura mater can compress the brain and cause serious impairment of its functions. The main danger that is common to benign tumors is that—at a completely unpredictable moment—they can turn into malignant tumors.

Malignant tumors predominantly consist of immature, poorly differentiated cells and atypical stroma. The degree of deviation from the norm varies up to severe anaplasia, in which the tumor cells are almost no different from embryonic. The less differentiated they are, the more malignant the tumor is. However, for any malignant tumor, both tissue and cellular atypism is characteristic, which distinguishes them from benign tumors. In addition to atypism, malignant tumors are also characterized by invasive growth, metastasis and recurrence, as well as a significant negative effect on the general condition of the body. Metastasis is the process of the spread of individual tumor cells or their complexes (metastases) with the flow of lymph or blood to other organs, and the development of secondary tumor nodes there. It is possible for the metastases to spread in various anatomical cavities (abdominal, pleural, inside the uterus, urinary and biliary cavities), and in various canals (fallopian tubes, vas deferens, inguinal and tendon canals), as well as through the intercellular fissures.

A malignant tumor can destroy the walls of blood vessels, and squeeze vital organs, including large veins and even the aorta. A massive tumor intercepts the majority of the body's glucose and other nutrients, which leads to a sharp weakening and the emaciation of a sick person. Cancer cells secrete a large quantity of metabolic products into the bloodstream. In cases of the partial necrosis of malignant tumors, which happens quite often, the products of decay also enter the bloodstream.

Classification and nomenclature of tumors

Tumors are classified based on the principle of their belonging to a certain type of tissue. By this principle, seven groups of tumors are distinguished; in each group there are benign and malignant neoplasms.

The total number of tumors in these groups exceeds several hundred items:

- epithelial tumors without specific localization
- tumors of the exo- and endocrine glands and specific epithelial integument
- mesenchymal tumors
- tumors of melanin-forming tissue
- tumors of the nervous system and meninges
- tumors of the blood system
- teratomas (dysembryonic tumors)

The name of the tumor, as well as the classification, is built on the basis of the principle that the tumor belongs to a specific tissue or organ. The name of the tissue is the first part of the designation of a benign tumor, and the second part is the end of the "oma", derived from the Greek word for tumor (myoma is a tumor of muscle tissue, lipoma is a tumor of adipose tissue, chondroma is a tumor of cartilage). Names referring to the organ are also used (e.g., hepatoma—a tumor of the liver; nephroma—a tumor of the kidney). Malignant tumors from epithelial cells are called carcinomas or cancer (pancreatic carcinoma, lung cancer). Connective tissue malignancies are called sarcomas.

In practical terms, the classification of tumors according to the TNM system, taking into account the growth of primary tumor, regional and distant spread of metastases, is very important and necessary. It was developed by the French oncologist Pierre Denoix in 1950's and since 1987 it has become international. Based on this classification, treatment planning, prognosis, and evaluation of treatment outcomes are determined. It is possible to compare the results of the treatment of cancer patients in various clinics.

In this classification:

- T—the degree of the local spread of the primary tumor
- N—the absence or presence of regional metastases
- M—the absence or presence of distant metastases

Adding numbers to these three components refers to the prevalence of the process: for “T” it is 0–4; for “N” from 0 to 3; for “M” 0 or 1.

Before these indices, the abbreviated Latin or English name of the organ in which the primary tumor developed was written: OSS—bones, HEP—liver, BRA— brain, etc.

6

AGING

Thanks to the success of medicine, the average life expectancy of people is increasing from century to century. However, an increase in the average life expectancy is achieved by consistently reducing the risks of death from injuries and illnesses—that is, the risks of death from accidental causes. Sooner or later, this reserve of extension of existence will be exhausted, and then the problem of the species limit of a person's life expectancy will rise up to its full height. The problem is so complex that it is not yet clear whether it is solvable in principle. To answer this crucial question, first of all it is necessary to understand what aging is.

It has long been known that after reaching maturity, age-related changes in the human body are expressed in a gradual decrease in the activity and physiological capabilities of cells, tissues and organs. All of this happens to everyone. It always happens, even when a person is not ill. Aging is a rare example of a biological process with a one hundred percent effectiveness. From which the conclusion follows:

So far, none of the people has been able to avoid aging; this process is fatal; therefore, it has a fundamental biological basis.

Scientists have been trying to get to the bottom of this fundamental issue for centuries, and as yet have been unsuccessful, but progress has been made. There are about a hundred more or less well-founded hypotheses about the nature of aging.

Each of them can be reduced to one of two main theories.

- The theory of accidental damage (the "catastrophe of errors") suggests that aging is a necessary result of the stochastic process of accumulation of damage that the body fights with all its life, but sooner or later the number of metabolic errors exceeds a critical level, and death occurs.
- According to the evolutionary-genetic theory, aging is not an obligatory property of living organisms, but this property was fixed in the course of evolution, since aging and the subsequent death of

an individual ensures a generational change, and facilitates the survival of young individuals. The younger generation has new and more diverse combinations of genes, which increases the chance of the survival of the entire biological species.

Theory of accidental damage

This theory is based on two fundamental postulates:

1. Any complex system is unable to work endlessly without failures, especially when in a volatile environment.
2. The number of such failures is directly proportional to the time the system operates.

In living organisms, such failures should lead to disturbances in the activity of cells, organs and systems, to the appearance of damaged and "wrong" molecules, and changes in the quantitative ratios between different types of molecules.

Indeed, in an aging body, the brain, liver, heart, and other organs function increasingly poorly. There are two kinds of changes to molecules. In small organic molecules (glucose, cholesterol, amino acids), structural differences between those in an old and a young body have not yet been found, and most likely will not be found. These simple molecules can be damaged, but they do not age. However, the content of such molecules in various parts of the body changes with age. This is clearly manifested in a slow but steady increase in the average levels of glucose and cholesterol in the blood of aging people, with a parallel decrease in the concentration of a number of hormones, especially genital ones. Damage also occurs in the structures of complex biopolymers, notably protein and nucleic acid molecules. Numerous studies have shown that defective proteins (e.g., amyloid ones) accumulate in the tissues during aging. With increased age, the number of damaged intracellular proteins that partially retain their functionality also increases, and the number of different mutations in working chromosomes also increases. However, such molecules can already be considered conditionally aged. Thus, the minimum biological level of manifestations of age-related changes is large biopolymers.

The accumulation of molecular age-related changes has cellular consequences. Leonard Hayflick (born in 1928) discovered that human cells cannot multiply indefinitely, and that they die after about 52 divisions, with signs of aging appearing in them as they approach this boundary. For some types of cells, the Hayflick limit can extend to 70

divisions, but such a limit exists for all normal somatic cells. Subsequently, it was found that the loss of division ability by cells is associated with the gradual shortening of telomeres—end sections of chromosomes—by three to six nucleotides per cell cycle. When chromosomes lose 150–180 monomers, further fission becomes impossible. At first, these results were regarded as unconditional confirmation of the theory of accumulation of errors. However, later it was discovered to be more complex. There is a telomerase enzyme that can restore the lost telomeric parts of chromosomes. Thanks to this enzyme, germ cells are immortal, because with meiosis—in contrast to mitotic division—telomerase restores chromosomes, and the cellular "biological clock" is restarted. Unfortunately, the same thing happens in cancer cells; proliferatively, they are also immortal.

The discovery of telomerase made us take a fresh look at the theory of random damage. It turned out that simple statistical probability is not the only factor causing aging. Moreover, age-related changes are not always irreversible. There were other facts that went beyond the scope of this theory.

Evolutionary genetic theory of aging

According to this concept, aging is programmed genetically in order to facilitate the entry into life of new, more genetically diverse generations, representatives of which are more able to adapt to changing living conditions. In favor of the evolutionary genetic theory, several serious arguments were made. The absolute inevitability of aging itself can be ensured only if this phenomenon is genetically determined, and it is extremely strictly determined, since not a single case of immortality has been reliably described in the entire history of mankind. At the same time, searches for some "death genes" that regulate aging have not yet yielded results. It is more likely that aging is provided not by individual genes, but by a certain general pattern in which the shortening of telomeric regions of chromosomes is just a particular manifestation. Under the influence of external influences, the pace of age-related changes can be altered. In the direction of deceleration this may happen a little, and not for long. However, in the direction of acceleration, changes can be significant and, of course, irreversible.

The most impressive acceleration of age-related changes occurs with the rarest and incurable genetic disease, ***progeria*** (*Greek: προσ* — over and *γέρων*—an old man). Patients with this pathology may look like old people after 5 years. There are two forms of progeria—infant and adult.

The reason for children's progeria is a mutation of the LMNA gene, which encodes the synthesis of lamin A, an important protein that is part of the membrane of the cell nucleus. Usually, children's progeria manifests itself in the second or third year of life. The child's growth slows down or even stops, and dystrophic changes in the myocardium, genital hypoplasia, impaired fat metabolism, clouding of the lens, and atherosclerosis are observed. The muscles are hypotrophic, the skin becomes dry and thin, and the blood vessels shine through it. The protruding frontal tubercles above the underdeveloped pointed face give the child a characteristic bird-like appearance. The average life expectancy for patients who have childhood progeria is only thirteen years.

Adult progeria occurs as a result of a mutation in a gene encoding the synthesis of ATP-dependent helicase, which disrupts DNA repair processes. The disease usually manifests itself during puberty. Slow growth and the underdevelopment of the sex glands are noted. At the age of just over twenties years, the hair of such patients turns gray and falls out, and they have impaired vision, thinning of the skin, and hypotrophy of the muscles, as a result of which their arms and legs become thin. They have a characteristically motionless face, like a mask, with a thin nose and narrow mouth.

Both of these incurable and terrible diseases arise due to mutations; therefore, the secret of aging lies in the genome itself. However, the mutations that cause the two forms of progeria are different, which implies that age-related changes are controlled by more than one gene. Manifestations of the two forms of the disease partially coincide, but partially differ, from which it follows that these forms are the consequences of one more general and extensive phenomenon. The versatility of age-related changes at the post-translational level also testifies to this.

United concept

If the problem does not have an undeniable solution within the framework of one science, it is useful to look either from the side or from above. From the middle of the 19th century, the concept of ***entropy*** has been widely used in both the exact and natural sciences (*Greek: ἐντροπία*— conversion, transformation). In thermodynamics, this is a measure of irreversible energy dissipation; in statistical physics, entropy characterizes the probability of a certain macroscopic state of the system; in mathematical statistics, entropy characterizes the measure of the deviation of a real process from an ideal one. In general, according to the

laws of thermodynamics, all processes in a closed system lead to an increase in its entropy, i.e., less probable states are replaced by more probable states. This continues until the probability of the condition reaches the maximum. The most probable is the equilibrium state in which matter and energy in space are distributed evenly.

From a thermodynamic point of view, a living organism is a blatantly unlikely state of energy and matter. If, by a system, we mean a living organism, then the most probable state for it is death. Therefore, aging can be considered as a biological manifestation of entropy. Supporters of the evolutionary genetic theory are correct—age-related changes are controlled by the genome of multicellular organisms. However, the genome is not only the cause of aging; it is also a wall built across the path of entropy. This wall is not eternal—it is gradually corroded by the same entropy. The genome is protected from it by programs which eliminate accidental damage (for example, a DNA repair system); however, these programs are also subject to the influence of omnipotent entropy, and by the end of its life, they are no longer able to save an aging organism. Supporters of the theory of random damage are correct that the wall can be broken prematurely, and in many places, and that the result will be the acceleration of age-related changes. However, even in an ideal case—in the complete absence of optional damage—the finale is provided by the genetically determined limit of the species life span of multicellular organisms.

7

EXTREME STATES

The action of extremely strong etiological factors can lead to the development of special pathogenic conditions called extreme, since they are an immediate threat to life. Such extreme etiological factors are can be of any type—mechanical, chemical, biological or social—if at the time of exposure their strength significantly exceeds the sum of the protective and adaptive capabilities of the body. In such a situation, the body inevitably receives very strong primary damage, which quickly causes serious disruption to the activity of the main organ systems. Depending on which particular systems have suffered the most, one of the classic extreme conditions develops—shock, coma or collapse.

Shock *(French: choc—push, hit, collision)*

Shock is an acutely developing, deadly pathological process that occurs as a result of the action of an extreme etiological factor. The resulting very strong stress causes deep disturbances in the activity of the nervous and endocrine systems, from which violations of the regulation of the activity of organs and tissues radiate like circles in water. Shock can develop in the event of dangerous mechanical and psychological injuries, chemical and thermal burns, various intoxications, transfusion of incompatible blood, and as a result of allergic reactions.

Shock is characterized by a two-phase change in the activity of the central nervous system: the initial excitement (stage of adaptation, which is not always observed) is replaced by widespread depression of the cortex and subcortical centers of the brain (decompensation stage). Phase changes in the activity of the central nervous system are associated with excessive influences of various origins: severe irritation of receptors, damage to the nerve fibers, plexuses or the tissue of the brain itself. In shock, consciousness may be obscured, but until the stage of decompensation it is not completely lost.

In the **adaptation stage**, the activity of the sympathetic-adrenal and pituitary-adrenal systems increases, which, like when an organism is under stress, increase metabolism and stimulate the activity of the organs. As a rule, the cardiovascular system is stimulated—the heart rate increases, the blood pressure rises, and the volume of circulating blood in the kidneys, digestive tract, skin and muscles decreases; however, the blood circulation volume increases in the brain and heart. The respiratory rate increases. Red blood cell maturation is stimulated, and the number of these cells in the peripheral blood increases; its coagulability often increases. The adaptation stage is usually short-lived, since it requires large expenditures of energy and oxygen.

In the **stage of decompensation**, the activity of the sympathetic-adrenal system decreases, and the level of catecholamines and corticosteroids in the blood decreases. The blood pressure drops sharply; the heart rate may decrease; deposition and reduction in the volume of circulating blood in the central and peripheral parts of the circulatory system occur. Microcirculation disorders also occur. They are associated not only with a decrease in the blood's perfusion through the microvessels, but also with changes in its rheological properties and an increase in the permeability of the capillary walls. An increase in vascular permeability leads to the appearance of biologically-active substances (histamine, serotonin, kinins) and a mixture of proteins from dead cells in the blood. Microbes, their toxins and toxic metabolic products (ammonia, phenol, indole) can enter the bloodstream. All of this leads to inhibition of the activity of the nervous system. Furthermore, due to a disorder in the regulation of respiration and blood circulation, mixed-type hypoxia develops, which contributes to additional damage to the brain, heart and kidneys.

Shock is characterized by the emergence of what are known as vicious circles of pathological changes, in which individual disorders stimulate each other. In particular, disorders of the central nervous system lead to respiratory and circulatory disorders. The inhibition of these vital functions causes the development of hypoxia, which enhances disorders of the central nervous system. Thus, the circle of pathological reactions is closed. Without breaking this, recovery is impossible.

In shock, some organs are especially vulnerable, and their damage poses a threat to the patient's life. Such organs are called "shock organs". These include the lungs and kidneys. In the "shock lung", microcirculation is significantly impaired, which leads to multiple hemorrhages and atelectasis. At the same time, blood perfusion through the capillaries is

reduced, and the oxygen and carbon dioxide permeability of the alveolar-capillary membranes is disrupted. Acute pulmonary circulation disorders contribute to the development of pulmonary edema, and in general, all of these changes lead to an increase in hypoxia and increase the risk of depression of the nervous system.

In the kidneys, due to a redistribution of the blood during shock, a sharp decrease in the blood flow in the cortical layer occurs. This reaction triggers an adaptive mechanism: renin is released from the capillary glomeruli into the bloodstream during the ischemia of the kidney cortex, which stimulates the conversion of angiotensinogen to angiotensin. Angiotensin causes a reduction in the smooth muscles of the arterial vessels, and increases the blood pressure. As a result, the blood supply to the kidneys themselves, and to the brain and heart, is temporarily improved.

However, prolonged renal hypoxia causes significant dystrophic changes in the epithelium of the Bowman's capsule and convoluted tubules, up to and including cytolysis. The remnants of dead epithelial cells are knocked into the characteristic "hyaline cylinders" and close the lumens of the tubules, making the urination process impossible. What is known as cortical necrosis of the kidneys develops, in which the nephrons are irreversibly damaged and cease to fulfill their functions.

Types of shock

There is no generally accepted classification of shock, but the following variants are traditionally distinguished.

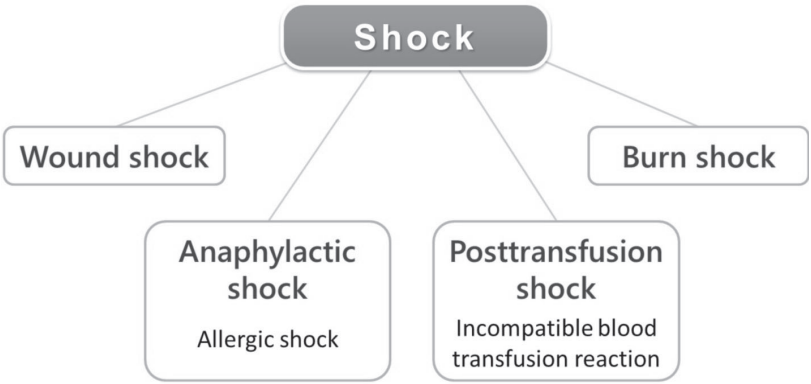

Fig. 7.1. Types of shock

Traumatic shock occurs with extensive injuries of the bones, muscles and internal organs. In this case, damage to the nerve endings, trunks and plexuses always occurs. The arising severe pain causes a short-term excitation of the central nervous system, which is replaced by a protective reflex—the inhibition of the activity of the cortex and subcortical centers of the brain, with a possible loss of consciousness. As a rule, traumatic shock is complicated by bleeding and the infection of wounds.

Burn shock develops with extensive thermal damage to the skin. The severity of the shock depends on many factors, but primarily on the area of the lesion of the body, and the degree of burn. Unlike other forms of shock, toxemia occurs very early after burns, so the stage of adaptation is quickly replaced by decompensation. An important mechanism for the development of burn shock is a violation of the barrier function of the skin, and infection of the burned surface with bacteria, fungi and viruses. Due to tissue necrosis, the products of decay and a large number of K + ions enter the bloodstream. Due to damage to the walls of the blood microvessels, plasma enters the burned surface, and the loss of fluid causes the blood to thicken, which can lead to heart overload. The loss of fluid, salts and proteins through the burn surface is accompanied by hemolysis of red blood cells. In the later stages of the burn process, due to the appearance of altered proteins, the development of autoallergy is possible, with damage to the blood microvasculature and cells of the parenchymal organs, which often leads to severe kidney disease. This entire complex of disorders represents the pathogenetic basis of the “burn disease”.

Anaphylactic shock is the most formidable and dangerous manifestation of immediate allergies in humans. It occurs with the introduction of therapeutic serums or vaccines, certain medications (antibiotics, anesthetics, vitamins), or from inhaling plant and household allergens dispersed in the air. This shock develops within a few minutes. The adaptation stage in this case is very short; it is characterized by a feeling of fear, anxiety, and motor excitement, which are joined by itching of the skin and pronounced sweating. Excitation of the central nervous system during anaphylactic shock is due to a strong irritation of the receptors of the vascular wall by an allergen with antibody complexes and inflammatory mediators. The inhibition of the central nervous system function also occurs quickly, and the development of seizures is possible. As a result of bronchospasm and other disorders, acute hypoxia develops, which can extend to suffocation. Allergy mediators cause a drop in blood

pressure and dramatically disrupt microcirculation. Stasis and sludge often develop in the vessels of the microvasculature, and disseminated intravascular coagulation occurs.

Blood transfusion shock develops as a result of a blood transfusion of a donor that is incompatible with the blood of the recipient by group factors (A, B, 0), Rh factor, or individual antigens. Shock can also develop if poor quality blood is used—e.g., if there is hemolysis of red blood cells, protein denaturation, or bacterial contamination. Blood transfusion shock develops extremely rapidly. After a very short adaptation phase, in which motor excitement, increased and labored breathing, and episodic pain in different parts of the body are usually noted, the inhibition of the nervous system occurs. Against the background of general weakness and motor passivity, the blood pressure significantly decreases. Due to changes in the properties of the blood proteins and the activation of the fibrinolytic system, blood coagulation often decreases, and multiple hemorrhages occur in the internal organs. An admixture of blood appears in the vomit, and there is hemorrhage at the injection site. These symptoms are characteristic of blood transfusion shock, and often determine its course into renal dysfunction. This is due to the entry into the tubules of the decay products of hemoglobin (hemoglobinuric nephrosis) and impaired renal circulation ("shock kidney"). Impaired renal function contributes to the deviation of the blood composition from normal, which is manifested in the accumulation of the products of nitrogen metabolism (azotemia, uremia). The balance of blood electrolytes is disturbed, and pH changes are possible.

Although they are not generally accepted types of diagnosis, nevertheless, in the medical literature such concepts as ***septic shock*** and ***psychogenic shock*** are often used. All types of shock, whatever they are called, are extremely dangerous because they can lead to death from multiple blood vessel thrombosis ("disseminated intravascular coagulation syndrome"), due to a transition to a coma or a state of vascular collapse, pulmonary edema, or cardiac arrest. In the event that the patient can be successfully treated for shock, there remains a risk of later complications, including irreversible damage to the kidneys. With a more unfavorable outcome, the most severe complications of shock are coma and blood vascular collapse.

Coma *(Greek: κῶμα—deep sleep)*

This name refers to a life-threatening condition between life and death, caused by a violation of the blood supply to the brain. It is characterized by a loss of consciousness, a sharp decrease in or lack of reaction to external stimuli, the fading of reflexes until they completely disappear, a decrease in the tone of the smooth muscles of the arterial walls, impaired heart rhythm, and a decrease in body temperature. Coma develops as a result of deep inhibition in the cerebral cortex, leading to the complete loss of consciousness. This inhibition of neuronal activity extends to the subcortical centers of the brain, which can lead to respiratory arrest, or cardiac arrest. There are disturbances in the acid-base balance in the nervous tissue, hypoxia, disturbances in ion exchange, and the energy starvation of nerve cells. A coma is often preceded by a precoma state, during which the development of these symptoms occurs.

Causes of coma. Coma arises for the same reasons as shock, but under the action of even more powerful damaging factors, or when the effects of shock per se are added to the action of these factors. Coma can also develop on its own, in the case of an increase in the force of a damaging factor; for example, hyperglycemic coma in diabetes is a consequence of a rapidly increasing concentration of glucose in the blood.

Coma that occurs under the influence of external damaging effects is called exogenous. It can be traumatic (brain damage), thermal (burns, heat stroke), toxic (poisoning with alcohol, mushrooms, carbon monoxide, drugs), nutritional (starvation), radiation, infectious-toxic, hypoxic, etc.

However, coma can also arise as a complication of a number of diseases. The causes of this type of coma (endogenous) are a variety of primary diseases and pathogenic conditions, including shock. In these cases, the etiology is also reflected in the name of the coma: apoplexy coma (in cases of cerebrovascular accident), anemic coma (oppression of hemopoiesis, erythrocyte hemolysis, bleeding and hemorrhage), uremic coma (severe kidney disease), etc.

The mechanisms of coma. Several common pathogenetic processes are involved in the development of coma.

The most dangerous of them is **intoxication**, due to the action of exogenous poisons or toxic metabolic products that are not removed from the body quickly enough. For example, carbon monoxide poisoning leads to hemic hypoxia followed by coma. Large doses of alcohol and a number

of drugs cause depression of the centers of regulation of respiration and vascular tone, which can also lead to a coma. Among the toxic metabolic products, the most dangerous is ammonia, which accumulates in the blood when the excretory function of the kidneys is impaired. In the case of insulin deficiency and the development of a diabetic coma, the accumulating keto acids (acetoacetic, β-ketobutyric and β-hydroxybutyric) have a toxic effect on the body.

The second general mechanism of coma is **oxygen and energy starvation of the brain**. Hypoxia and energy starvation occur as a result of the inhibition of tissue respiration under the influence of ammonia, deficiency of oxidation substrates (hypoglycemia), and oxygen deficiency.

The third general mechanism for the development of coma is a **violation of the acid-base, electrolyte and water balance** of the body. Such disorders can be expressed to varying degrees, but they are almost inevitable with any severe violation of the processes of tissue metabolism.

Coma almost always results in **circulatory disorders**—especially of the microcirculation—in the brain and parenchymal organs, particularly the kidneys. It also leads to the inhibition of the respiratory center, which in especially severe cases is manifested by **pathological forms of respiration** (Kussmaul, Chain-Stokes breathing). The appearance of such pathological forms usually indicates the transition of a coma to a terminal state, and the threat of death.

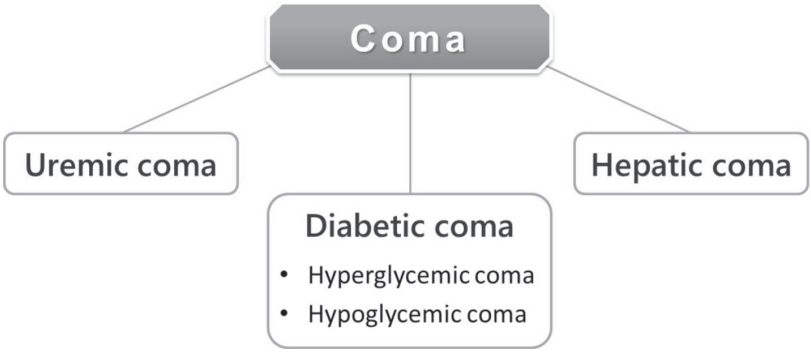

Fig. 7.2. The most common types of coma

Types of coma

The following types of coma are the most common.

Uremic coma. In acute or chronic insufficiency of the excretory function of the kidneys, nitrogen-containing metabolic products accumulate in the blood and cause the poisoning of the body. This condition is called uremia *(Latin: urina—urine; Greek: haima—blood)*. It develops with bilateral necrosis of the renal cortical layer. Such severe complications may result from shock, total inflammation, or acute toxic damage to the kidneys. Of all nitrogenous substances, urea accumulates in the blood the most. This alone is not very dangerous, but with an excess of urea, various glands begin to secrete, which leads to local inflammatory processes in the skin, pleura, lungs, stomach and intestines. Moreover, in the intestine, under the influence of microbial enzymes, urea decomposes, causing the release of toxic ammonia.

As a result of uremic intoxication, patients experience confusion, disorientation in time and space, apathy, sleep distortion (drowsiness during the day and wakefulness at night), and a complete lack of appetite. Periodically occurring diarrhea and bouts of vomiting lead to dehydration and the patient is constantly thirsty. As the condition worsens, consciousness is lost, there is a smell of urea from the mouth; and brain edema often develops, accompanied by motor excitement. Following this, there is a depression of the respiratory center, and a pathological breathing, indicating the approach of pre agony.

Hepatic coma is the most dangerous complication of diseases that cause damage to a significant quantity of hepatocytes. Such diseases include severe forms of viral and toxic hepatitis, and cirrhosis of the liver. The main negative consequence of hepatic coma is intoxication of the body with derivatives of ammonia and amino acids (phenol, indole), since the neutralization of these substances is one of the functions of the liver which is reduced by the action of these diseases.

Clinical signs of hepatic coma occur and increase gradually. Confusion and drowsiness are later replaced by verbal and motor excitement. Subsequently, jaundice builds up, and itching of the skin occurs. A peculiar hepatic smell spreads from the patient, and finally consciousness is lost. The course of hepatic coma can be complicated by toxic pneumonia and pulmonary edema.

A serious complication of diabetes mellitus can occur in two ways:

- hyperglycemic coma, due to a sharp increase in blood glucose, accumulation of keto acids, acidosis, electrolyte and water balance disturbances
- hypoglycemic coma, which occurs in connection with an overdose of insulin in the treatment of diabetes and is characterized by a sharp drop in the concentration of glucose in the blood

Hyperglycemic coma is characterized by a gradual development. In the beginning, general weakness, headache, severe thirst, and vomiting are possible. Later, a loss of consciousness, the absence of a number of reflexes, and a smell similar to acetone are possible. Dry skin and mucous membranes are usually observed; a significant increase in the volume of urine excreted occurs; a high blood level of glucose and ketone acids is determined; and the concentration of glucose in the urine—normally very small—increases.

Hypoglycemic coma develops quickly. It is characterized by symptoms of acute energy starvation of the brain, since glucose is the main source of energy in the cells of the nervous system. As a result, a general weakness develops, to which dizziness, tinnitus and strong feelings of hunger are added. Typically, trembling fingers, redness of the face, cold sweat, and dilated pupils occur. Consciousness is quickly lost, and convulsions of the skeletal muscles begin. During these seizures, the blood pressure increases, and after their cessation it sharply decreases. Other symptoms include a steadily increasing heart rate; and a low blood glucose level is detected in all cases.

In addition to those already mentioned above, medical literature also includes the names of other types of coma—traumatic, thermal, toxic, alimentary (resulting from starvation), radiation, infectious-toxic, hypoxic and any more. All of them have common features and similar pathogenesis, but differ in their details due to differences in etiology.

8

PREVENTION, DIAGNOSIS AND TREATMENT OF DISEASES

Prophylaxis of Diseases *(Greek: ρόφύλακτικός—safety)*

Despite all the successes of medicine, the ancient wisdom that the disease is easier to prevent than to cure has not lost its relevance in our time. Of course, not everything is within our power; there are situations in which it is impossible to prevent injury or infection. However, quite often you can anticipate this situation and try to avoid it, or try to make your body less susceptible to the influence of certain pathogenic factors. That is how disease prevention begins.

Primary prevention is aimed at preventing diseases by increasing the protective and adaptive capabilities of the body (vaccination, a rational regime of work and rest, optimal nutrition, physical activity, improving environmental conditions). However, a more effective measure is to avoid contact with hazardous exposures that can cause illness.

Secondary prevention aims to eliminate risk factors that, under additional adverse conditions (weakening of immunity, reaching a certain age, harmful working conditions), can lead to the onset, exacerbation or relapse of a disease. There is the possibility of introducing a tertiary prevention into medical practice, aimed at the rehabilitation of patients who have lost the possibility of full life.

The effectiveness of all social forms of prevention is never exhaustive; it depends on many factors, primarily financial. Therefore, personal responsibility for one's own health is very important.

Disease Recognition

The section of medicine devoted to the recognition of diseases is called **diagnostics** *(Greek: διαγνωστικος—capable of recognizing)*. Modern diagnostics is a complex multi-stage process, the purpose of which is to

answer the question of what kind of disease a particular patient has, as well as to determine the form of this disease, assess its severity, stage of development and anatomical prevalence, and to identify complications.

Answers to these questions allow us to formulate a ***diagnosis, i.e., the shortest possible conclusion about the type of disease in strictly standard terminology***.

The recognition of a disease occurs as a result of the detection and analysis of a complex of symptoms and syndromes characteristic of its pathology.

Symptoms are signs and manifestations of disorders or injuries caused by etiological factors. A symptom is an elementary diagnostic unit that reflects only one sign. It is necessary to distinguish between general and local, specific and nonspecific symptoms. General symptoms are signs of the disease, manifested at the level of the whole organism: weakness, sweating, hyperthermia. Local symptoms are determined locally in different parts of the body at the level of tissues or organs (scars, swelling, rash). Nonspecific symptoms are found in many diseases (nausea, fever, hyperglycemia, etc.), and specific symptoms are characteristic only for a certain disease ("night blindness" with hypovitaminosis A, logic defects in schizophrenia). In addition, all symptoms are divided into subjective and objective. Subjective symptoms are changes in the sensations of a sick person (pain, tinnitus, feeling of fear). Objective symptoms include those that a doctor can detect with their own senses, as well as the results of laboratory and instrumental studies that are officially approved for diagnostic use.

A **syndrome** is a complex of symptoms characteristic of a specific pathological process or for diseases of certain anatomical structures and systems (depressive, hemorrhagic, nephrotic syndromes). The detection of a syndrome gives an idea of the etiology and prevalence of pathology, and the degree of involvement of various systems and organs in the pathological process.

The identification of symptoms and syndromes is the basis of diagnostic work. The work of recognizing diseases is divided into clinical diagnosis and additional examination of the patient.

Clinical diagnostics

Clinical diagnostics consists of a survey, the collection of oral information about the patient and the disease, and an external examination, as well as an initial objective examination of the patient using the simplest tools—a stethoscope, thermometer, and tonometer. Specialists add some special tools and devices (gynecological mirrors, tables for measuring visual acuity, etc.) to this standard set.

Oral information can be obtained both from the patient himself, and from witnesses to the accident or manifestations of the disease. During the survey, the doctor must listen to and analyze the patient's complaints, as well as collect information about their life history and medical history.

Complaints. Most often, the patient gets an appointment with a medical professional at the prodromal stage of the disease or during the height of the clinical signs of pathology. "Complaints" refers to a description of the clinical symptoms by the patient or witnesses. The analysis of this information allows the doctor to create a primary idea of the nature and severity of the pathological processes.

The history of the disease (*Latin: anamnesis morbi—memory of the disease*).

This section of the diagnostic work is necessary in order to:

- establish the time of the onset of the disease
- identify and separate the symptoms of underlying and concomitant diseases, as well as the presence or absence of complications
- determine the list of violations and injuries, and evaluate the activity of the pathological processes

Since all people are individuals, any disease has features specific to the particular patient in each case. These features are important; they can determine both the nature of the flow and its outcome. In order to take into account individual specificity, the survey reveals facts related to the patient's life history.

The history of life *(Latin: anamnesis vitae—memory of life).* As part of this anamnesis, the nature of nutrition, the presence or absence of bad habits, the list of past illnesses and many other details that can affect the course of the underlying disease are clarified.

An objective examination begins with an examination, during which the condition and behavior of the patient are evaluated. Each of the many details characterizing their gait, posture, orientation in time and space, color of the skin, etc. can have diagnostic value. Sometimes pronounced and even specific signs of pathology (for example, jaundice) are immediately visible, allowing a doctor to make an instant diagnosis "from the threshold", but such a diagnosis will always be preliminary, requiring verification. To obtain more information, the examination is continued using methods of palpation, percussion (tapping), auscultation (listening); if necessary, thermometry and a determination of blood pressure are used.

Questioning and objective examination of the patient are necessary to identify the symptoms and syndromes; their combination determines the diagnosis. Very often, clinical diagnostic capabilities are not enough to establish a definitive diagnosis. In such cases, the patient is assigned an additional examination, which may include instrumental and laboratory diagnostics. The fundamental difference between these types of diagnostics lies in the fact that the patient himself is the subject of an instrumental examination, whereas for laboratory tests, tissue samples, excrement or biological fluids from the patient's body are used.

X-ray diagnostics arose thanks to Wilhelm Conrad Roentgen (1845–1923), who discovered X-rays, which in many countries are called Roentgen's rays. These two names now mean the part of the spectrum with wavelengths from about 10 to 10^{-3} nm. X-rays can penetrate through matter, and substances absorb them differently in proportion to their density. The rest of the radiation can be detected because X-rays can cause fluorescence in some substances. This effect is used for fluoroscopy (observing an image on a fluorescent screen) and X-ray photography. Medical photographic films are used in combination with reinforcing screens, which include phosphors that glow under the influence of X-ray radiation and illuminate the emulsion. The full-size image acquisition method is called radiography. With fluorography, the image is obtained on a reduced scale. A luminescent substance (scintillator) can be optically connected to an electronic detector of light radiation (photoelectron multiplier, photodiode, etc.), and the resulting device is called a scintillation detector. It makes it possible to register individual photons and measure their energy. In semiconductor detectors, X-rays create electron-hole pairs in the p-n junction of the diode, which is turned on in the blocking direction. In this case, a small current flows, the amplitude of which is proportional to the energy and intensity of the incidental X-ray radiation. In the pulsed mode, it is possible to register individual X-ray

photons and measure their energy. Individual X-ray photons can also be detected using ionizing radiation detectors. All of these possibilities are now used to create various types of X-ray detectors, which have made it possible to develop a computed tomography method.

As they possess high energy, X-ray quanta easily penetrate through soft biological tissues, but, more significantly, they are absorbed by bone tissue. Thanks to this, it became possible to receive negative skeleton images and weak shadows of internal organs on photographic plates, and subsequently on photographic film and on computer screens. Over the past century, X-ray technology has become the ubiquitous, albeit not omnipotent, tool for instrumental diagnostics. Nowadays, it is used to diagnose skeletal diseases, detect soft tissue tumors, and confirm inflammatory changes in the lungs and other organs. However, X-rays are ionizing. They affect the tissues of living organisms and can be the cause of radiation sickness, radiation burns and malignant tumors. Modern X-ray diagnostic equipment gives very little radiation to the test object, but such radiation has not been completely eliminated.

Ultrasound diagnostics. The use of ultrasound has proven safer than X-ray studies in the recognition of soft tissue diseases. Ultrasound examinations are based on the principle of echolocation—that is, on the registration of sound signals reflected from the interface. Such studies (sonography) are cheap, harmless, simple, and informative. Ultrasound makes it possible to see kidney stones, the gall bladder, signs of inflammation, tumors and pathological cavities (cysts) in organs, as well as the fetus in the uterus. Using the Doppler effect it enables the determination of the speed and direction of the movement of fluids through the vessels in real time. However, ultrasound is ineffective in studies of the brain, lung and bone tissue.

Tomographic studies. Tomography *(Greek: τομή—section)* is the acquisition of a layered image of the internal structure of an object. To obtain such images in medicine, X-rays are used, as well as the phenomena of nuclear magnetic resonance, electron paramagnetic resonance and positron emission. Classic X-rays are a projection onto the plane of shadow images of internal organs. These can overlap each other, which makes their identification difficult; for the same reason, far from all the details that might have diagnostic value are visible on radiographs. In addition, to decipher complex radiographs, a qualified radiologist is required, the conclusions of whom can be quite subjective. However, there is also a much more advanced diagnostic tool available: X-ray computed

tomography (CT). The CT method is based on the measurement and complex computer processing of the difference in the attenuation of X-ray radiation by tissues of different densities. The basis of all variants of computed tomography is the ability to recreate the image of an object from a set of its projections. Such projections are obtained by X-raying the human body at various angles. Layered scanning makes it possible to obtain images of sections of internal organs with a very high resolution, which has dramatically improved the diagnosis of many diseases, including oncological ones. An even more perfect spiral CT consists of the simultaneous execution of two actions: the continuous rotation of the X-ray tube generating radiation around the patient's body, and the continuous translational movement of the table with the patient along the longitudinal axis of the scan. Spiral scanning technology has reduced research time and significantly reduced the patient's exposure to radiation. Multilayer computed tomography allows real-time observation of physiological processes occurring in living organs—for example, in the brain and in the heart.

Thanks to the new generation of CT technology, it has become possible to build 3D models of all the organs and systems of the body. A valuable feature of spiral tomography is the ability to scan an entire organ (heart, joints, brain, etc.) in one revolution of the X-ray tube around the patient's body, which significantly reduces the examination time. Using this technique, it is possible to scan organs even in patients who are in a very serious condition. Currently, CT in its various modifications is considered to be the basic method for studying the internal organs of a person using X-ray radiation. However, this can be done without X-ray radiation at all.

Magnetic resonance imaging (MRI*)* is a method that makes it possible to obtain volumetric images of internal organs due to the phenomenon of nuclear magnetic resonance. The essence of this method is to register the radiation of atomic nuclei, which occurs in response to resonant excitation by electromagnetic waves in a constant magnetic field of high intensity. The detection and analysis of resonant radiation after appropriate computer processing of signals makes it possible to create a three-dimensional image of the object. An important practical feature of this technology is that with MRI, X-ray radiation is not used to obtain images of organs and tissues, which eliminates the biological risk of irradiation. However, MRI has one significant limitation. This is that during the process, magnetic materials in a powerful alternating magnetic

field are significantly heated, so an MRI examination should not be performed on patients, for example, with metal implants or pacemakers.

Electron paramagnetic resonance imaging. Electron paramagnetic resonance is the absorption and subsequent resonant release of electromagnetic energy by substances or liquids containing paramagnetic particles. The impact of a strong magnetic field on such an object leads to a parallel and synchronous change in the orientation of the particles, causing the formation of the total magnetic moment. In other words, the particles temporarily become magnetic and acquire an ordered orientation in space. After the external field is turned off, such particles return to a chaotic arrangement, with the radiation of the previously absorbed energy. These emissions can be detected. The nature of the radiation allows the use of computer processing to obtain images of internal organs and tissues.

Positron emission tomography is based on the registration of a pair of gamma quanta arising from the annihilation of a positron by an electron. The source of the positrons is a radioactive drug that is injected into the body before the study. By using a large set of detectors located around the patient, or by moving a pair of detectors around him, you can perform a three-dimensional reconstruction of the distribution of the radionuclides in the scanned object. According to this distribution, volumetric images of organs are formed after computer processing of the received signals.

Endoscopic diagnostics is based on the examination of the hollow organs from the inside with the help of endoscopes—thin and flexible fiber optic fibers. For this type of examination, the trachea, bronchi, esophagus, stomach, intestines, bladder, ureters and uterus are available. These examinations can detect early tumors, ulcers, signs of inflammation, the presence of edema, damage, stones and anatomical defects in the structures of the hollow organs. Modern endoscopes do not only include image transmission systems: they are also equipped with devices for biopsy sampling, electrocoagulation, suction of liquids, the extraction of foreign bodies, and for the local administration of drugs. Therefore, the endoscopy procedure can be not only diagnostic, but also therapeutic. Even more importantly, the endoscopic technique allows complex surgeries to be performed through very small incisions, which is less traumatic than traditional surgery.

Electro diagnostic methods. In the life processes of the cells, changes in the ratios between ions and free radicals occur every second; the

number of positively and negatively charged functional groups in the molecules of nucleic acids, proteins, complex carbohydrates and lipids also changes. All of these changes are accompanied by fluctuations in the intensity and sign of electromagnetic fields, which can be detected using simple equipment. The information obtained is used to diagnose diseases of excitable tissues, primarily the muscles and nerves. Electrocardiography is extremely widely used, and has become indispensable in the diagnosis of heart muscle diseases, such as coronary heart disease, including myocardial infarction. The registration and analysis of changes in electromagnetic fields (electroencephalography) is also an important auxiliary way to diagnose brain diseases.

Laboratory diagnostics. According to the World Health Organization, laboratory research accounts for up to 80% of all types of medical research. The task of laboratory diagnostics is to obtain information of medical value by studying biological samples. The objects of research can be blood, cerebrospinal fluid, urine, feces, and tissue samples. These studies can detect deviations from normal values in the concentration of various ions and molecules, as well as in the cellular composition of tissues, which is necessary not only for the recognition of diseases, but also helps to monitor the patient's condition and the effectiveness of the treatment used. Laboratory diagnosis is indispensable in the detection and identification of pathogens of infectious diseases. Without analysis of the DNA structure, the diagnosis of hereditary diseases is very difficult. Finally, laboratory tests of water, food and air are necessary to identify the causes of poisoning and many infectious diseases.

In laboratory diagnostics, various types of microscopy, as well as microbiological, biochemical, immunochemical and physical methods are traditionally used. For several decades, numerous types and models of automated analyzers have been widely introduced into clinical laboratory practice, gradually displacing microscopes, photometers, flasks, and pipettes from everyday life. Modern automated systems have significantly reduced the time required for research, increased their accuracy, and significantly expanded the list of laboratory tests that can be performed. A large modern laboratory is able to perform such a variety of tests that in classic cases of an illness it is possible to make a diagnosis automatically, and in complicated cases it can at least determine the most probable diagnosis.

Special types of diagnostics. The professional use of all the clinical diagnosis possibilities, coupled with instrumental and laboratory

diagnostics, makes it possible to correctly recognize the disease in the overwhelming majority of cases.

Nevertheless, if these capabilities are not enough, there are three more means of final diagnosis:

1. ***Dynamic observation.*** Over a certain period of time, new symptoms may appear, allowing the clarification or verification of the preliminary diagnosis.
2. ***Trial, or diagnostic treatment.*** The patient is either prescribed medication against the most likely disease, or a diagnostic operation is performed. As a result of these activities, additional information appears, allowing us to come to the right conclusion.
3. ***Pathological autopsy*** of the body of a deceased patient. This is a very reliable, but the most extreme and most undesirable tool used in the most complicated clinical cases, or to check for the possibility of medical errors.

Disease Treatment

A complete cure for any disease is possible if two essential conditions are met—eliminating its cause and eliminating the central link of pathogenesis. ***Etiotropic*** or ***etiological*** *(Greek: αιτία—cause + Greek: ιρόπος—turn; change)* is a treatment aimed at eliminating the cause of the disease. An example of such a treatment is the use of antibiotics against pathogenic bacteria. However, after the elimination of the etiological factor in the body, injuries and disorders can remain, and these can turn into the central link of pathogenesis and cause secondary disorders. The elimination of the central link of pathogenesis is the goal of ***pathogenetic treatment***. An example of such a treatment is the use of anticoagulants for pathological thrombosis in blood vessels.

However, it is far from always possible to provide a combination of etiotropic and pathogenetic treatment; therefore, not every disease is treatable. Moreover, many treatable diseases are eliminated only when they are treated correctly and not neglected. However, in all these unfavorable cases, a reduction in the severity of the disease process, a minimization of complications, and the elimination of individual symptoms are all possible. This type of treatment is called ***symptomatic***.

Very often, pathogenetic treatment is accompanied by symptomatic treatment, in order to accelerate recovery and alleviate the patient's

condition. In this case, the main treatment is pathogenetic, and any symptomatic treatment is considered additional or auxiliary.

Each of the listed types of treatment can be performed in two main ways—therapeutic and surgical.

Therapeutic treatment

A therapeutic treatment *(Greek: θερᾰπεία—treatment)* is not accompanied by significant anatomical changes in the body. Infectious diseases and diseases of the cardiovascular, digestive, immune, nervous, reproductive, respiratory and excretory systems are all treated in a therapeutic way, as are diseases of the organs, blood diseases, and oncological, endocrine, dental, skin and eye diseases. Treatment is carried out either by creating a negative impact on the cause of the disease, or by activating the human body's own protective and adaptive capabilities.

Therapeutic effects can be carried out by:

- ***chemical drugs*** (pharmacotherapy)
- ***herbal medicines*** (herbal medicine)
- ***serums, vaccines, antibodies*** (immunotherapy)

Some types of radiation (infrared, ultraviolet, X-ray, proton, laser) have a therapeutic effect. In all cases, reflexology (acupuncture, special types of massage) is useful. The methods of purely auxiliary therapy include psychotherapy, general massage, physiotherapy exercises, the use of therapeutic baths and mud, the use of orthopedic shoes and furniture, etc.

There are very many medicines; no one knows their exact quantity. However, all medicines are produced in the following basic forms (some of which have been known since ancient times):

- solid dosage forms (tablets, dragees, powders)
- soft dosage forms (ointments, pastes, liniments, medicinal suppositories)
- liquid dosage forms (solutions, infusions, decoctions, mucus, emulsions, potions)

The speed of the therapeutic effect, its strength and the duration of its action depend on the dose used and the drug's route of administration. All the routes of drug administration are divided into enteric and parenteral

(bypassing the intestines). In practical medicine, the following methods of drug administration are most often used.

Enteric routes of drug administration *(Greek: ἔντερον—gut).* The most common option is ***oral*** *(Latin: per os—by mouth)*. This method is very simple, and most dosage forms can be used in this way. Usually the drugs are absorbed in the small intestine, although absorption is also possible in the stomach. Their effect becomes evident after 10–30 minutes. However, after absorption in the intestines, the drugs enter the liver, where their partial inactivation is possible. The oral route of administration of drugs is ineffective for diarrhea, and is not possible with frequent vomiting or with an unconscious patient.

Sublingual route of drug administration *(Latin: sub—under, lingua— tongue)*. Many medicinal substances are absorbed well through the mucous membrane of the hyoid area of the mouth. In this case, the medication enters the bloodstream fairly quickly (after a few minutes), bypassing the liver. This method is rarely used, since the suction surface of the hyoid area is small, so only small amounts of very active substances can be administered sublingually. For example, with angina attacks, nitroglycerin is administered in this way.

Not all medicines are effective when taken ***per os.*** Some of them are destroyed by the action of hydrochloric acid in the stomach, or by digestive enzymes, and others are poorly absorbed in the intestines. In addition, antibiotics can upset the natural balance of bacteria in the gut. Finally, the oral route of drug administration is not optimal in emergency situations when an immediate effect is needed. However, not all medicines must be swallowed.

Rectal route of drug administration. With the introduction of drugs through the rectum in the form of medicinal suppositories or enemas, the absorption of substances occurs somewhat faster than with prescriptions *per os*. By this method, drugs enter the bloodstream, bypassing the liver. Therefore, the rectal route is preferred when it is necessary to avoid exposure to the liver (for example, with its diseases), or if the drug is destroyed in the liver.

The **cutaneous method (application*)*** is used mainly for the treatment of skin diseases themselves. Various aqueous solutions, ointments, suspensions and solutions are used in this technique. However, some

substances have an increased ability to penetrate the skin; therefore, they can have a therapeutic effect on the subcutaneous tissue, and even have a noticeable general effect on the patient's body. The overall effect of topical drugs is greatly enhanced if they are applied to damaged skin (for example, burnt or frostbitten skin). To enhance the percutaneous penetrating ability of therapeutic ions and small molecules with a charge, a vector electromagnetic field can be used. This method of drug administration is called electrophoresis.

In general, the application method is very attractive because of its simplicity and inexpensiveness, and the absence of strong discomfort in the patient. However, drugs applied to the skin have a predominantly local effect.

The **subcutaneous administration** of drugs is carried out using a syringe or a jet injector. Following the introduction of drugs under the skin, their action usually begins to develop in five to 15 minutes. The solutions must be sterile and preferably aqueous, since the introduction of oil solutions or suspensions under the skin often leads to the development of local inflammatory phenomena; irritating substances and hypertonic solutions should not be injected sunder the skin.

Intramuscular route of drug administration. Only sterile solutions are used for this; these are injected into the muscles of the buttocks, shoulder or thigh using a syringe or injector, and less commonly, into the muscles of the abdomen. With this method of administration, medicinal substances begin to act somewhat faster and more efficiently than with subcutaneous injections. Intramuscularly, it is possible to inject not only aqueous, but also oily solutions, as well as suspensions of medicinal substances. In the case of suspensions, a kind of depot forms in the muscle, from which the medicine enters the blood over a long period of time.

The **intravenous route of drug administration** is used almost exclusively for aqueous solutions, which, of course, must be sterile. The intravenous administration of oily solutions or suspensions is very dangerous, due to the risk of blood vessel embolism. These injections are classified as small volume (up to 100 ml) and large volume, which are called as infusions. The classic site for injections and infusions is the ulnar vein, but medications can be injected into any large saphenous vein. Solutions are injected into a vein slowly, over several minutes, and by a drip administration, which may even take place over several hours. This is

done in order to avoid creating too high a concentration of the active substance in the blood, which can be dangerous for the heart, central nervous system, and for regulating the tone of the arteries. Even with a slow intravenous administration, the effect of the drugs begins in the first few minutes, which is extremely important when providing emergency medical care. Some substances with irritating properties (for example, calcium chloride) can be administered intravenously, since their concentration is quickly diluted by the mass of the circulating blood, and their undesirable effects are weak. For the same reason, hypertonic solutions (for example, 40% glucose solution) can also be injected into a vein. However, with intravenous administration, blood clots are possible. The accidental introduction of air into a vein is a great danger to life, as this can lead to air embolisms in important blood vessels. In addition, there is a risk of pathogenic microorganisms entering the circulatory system.

Subarachnoid route of drug administration *(Latin: sub—under; and Latin: arachnoidea—arachnoid membrane of the brain).* Once in the bloodstream, drugs are distributed throughout the body with the exception of the brain and spinal cord, as these organs are separated from the circulatory system by what is known as the blood-brain barrier. This barrier exists due to the tight contacts of endothelial cells in the brain capillaries. The absence of intercellular clefts protects the nervous tissue from toxins and other dangerous molecules circulating in the blood, but at the same time the blood-brain barrier also prevents the diffusion of many types of drugs, including some antibiotics. Therefore, the treatment of brain diseases often requires the introduction of drugs into the spinal canal. This is usually done through a puncture between the vertebrae in the lumbar region. Manipulation of this requires good professional training, as there is a risk of damage to the spinal cord. When injected correctly, the drug enters the cerebrospinal fluid, which is common to the spinal cord and the brain. Antibacterial drugs are administered this way, as are painkillers, which allow for spinal anesthesia in small operations. All solutions used in subarachnoid administration should be absolutely sterile.

The inhalation route is used to introduce gaseous, aerosol or vaporous medicinal substances into the body. Medicinal substances enter the bloodstream very quickly through the walls of the alveoli, and the therapeutic effect begins from the first few minutes of inhalation. Very often this method is used to provide gas anesthesia during complex surgical operations. Additionally, antibiotics, as well as substances that regulate the activity of the nervous system, the smooth muscles of the

bronchi and the blood vessels, and many other medicines, can be administered by inhalation. A significant drawback of the inhalation method is that it is difficult to control the concentration of the active substance in the blood, so there is a high risk of overdose.

The therapy treatment options are extremely varied; most human diseases are treated in this way. But, of course, not all are cured. The most significant drawback of the therapeutic method of treatment is its low selectivity. Due to this drawback, almost any therapeutic effect is accompanied by undesirable side effects. The presence of side effects limits the use of high doses of drugs or radiation, which reduces the effectiveness of treatment.

In recent times, scientists have been trying to solve the problem of low selectivity by developing “smart drugs” and using targeted therapy technology. The idea is to connect a drug molecule with a molecule (for example, a specific immunoglobulin) that recognizes the target of a therapeutic effect (for example, a cancer cell). There has been some success in this direction already. More achievements in this area may yet occur in the near future, but it is unlikely that the problem of selectivity of pharmacological drugs will be completely solved.

A very attractive medical application of ***genetic engineering*** is the correction of the genome. Technically, this is fairly easy to do with germ cells. Such “purified” sperm and eggs, ideally, will produce “clean” children, free from genetic pathology. In the longer term, genetic engineering may defeat cancer and improve the general gene pool of humanity. The fight against aging is also impossible without genetic engineering technologies.

The use of ***stem (embryonic) cells*** and genetic engineering may become a more revolutionary direction of XXI therapy. Stem cells can be extracted from the umbilical cord blood of newborns, frozen, and subsequently used for the individual treatment of an adult person as needed. The most important prospect is that theoretically, any highly differentiated cells can be obtained from the stem cells, in order to replace dead or aged cells. Moreover, stem cells are already used in experiments in growing organs for transplantation. This is a very difficult matter, but research and experiments in this direction are now taking place very intensively all over the world. Apparently, the first organ that people learn to grow in this way will be the heart.

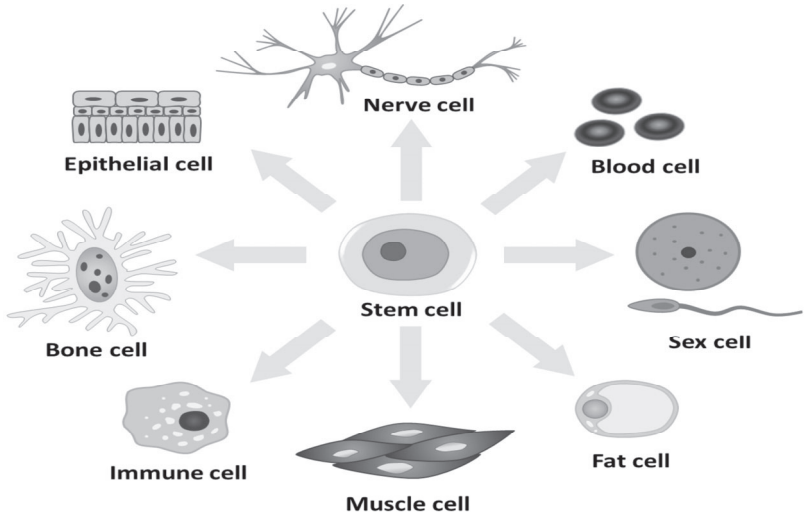

Fig. 8.1. Possible ways to differentiate stem cells

Surgery

Surgery *(Greek: χείρ—arm and ἔργον—action)* is a field of medicine that uses the cutting of a patient's tissue and suturing the wound that arises, in order to treat diseases. In general, therapy is preferable to surgery, since therapeutic treatment is less risky and does not involve the removal of human body parts. However, surgical treatment makes it possible to achieve a complete cure in cases where therapy is powerless (appendicitis, trauma, tumors, organ replacement).

Surgical treatment consists of several successive stages:

- preparing the patient for surgery
- pain relief
- actual operations
- postoperative rehabilitation of the patient

According to their nature and goals, operations are divided into diagnostic, radical and palliative. Diagnostic operations allow the surgeon to make a more accurate diagnosis; radical ones aim to completely eliminate the central link of pathogenesis; palliative operations temporarily

ease the general condition of the patient. Emergency, urgent and planned operations are distinguished according to the terms of execution. Emergency operations are necessary for severe injuries, vascular embolism, and massive bleeding, i.e., in situations in which there is an immediate threat to life. (This is why the postponement of surgical intervention is unacceptable.) Urgent interventions can be delayed until the diagnosis is clarified and the patient is minimally prepared. Scheduled operations are the most preferred, since they are performed after a full examination and sufficient preparation of the patient.

Historically formed types of surgical operations have the following Latin names:

- ***punctio***—puncturing (punctio fornicis posterions—rolling of the posterior vaginal fornix)
- ***incisio***—excision, cutting
- ***tomia***—dissection of an organ or opening of a cavity (dissection of a trachea—tracheotomia)
- ***stomia***—the formation of an external fistula of a hollow organ (for example, a stomach—gastrostomia) or an internal fistula between organs (for example, between a stomach and a small intestine—gastroenterostomia)
- ***resection***—partial organ removal (resectio ulcus ventriculi—gastric resection for peptic ulcer disease)
- ***amputation***—removal of the peripheral part of an organ
- ***ectomia***—complete removal of the organ (appendix—appendectomia)
- ***exarticulation***—removal of the peripheral limb at the joint level
- ***rrhaphia***—suturing (gastrorrhaphia—suturing on the wall of the stomach)
- ***trepanacio***—opening of bone cavities

In modern surgery, there is the addition of operations for the stitching of anatomical structures, the drainage of cavities in order to remove accumulated liquids, removing stones and foreign objects, restoring the patency of ducts and blood vessels, organ transplants, and cosmetic tissue changes. Modern surgery is increasingly becoming reconstructive surgery; it not only removes something, but also restores or replaces an organ. Surgery is also becoming less bloody, thanks to the improvement of operating equipment, the use of mini-accesses, and endoscopic technologies. Endoscopic surgery is usually performed through small

incisions with a diameter of about 5 mm, which makes the procedure less traumatic. And at the same time, thanks to special tools, such incisions are enough for serious intracavitary operations, including resections.

Another cutting-edge trend in surgery is the use of robotics. The famous ***Da Vinci*** surgical robot consists of two blocks—the first is a control system designed for a surgeon-operator, and the second block is a four-armed manipulator. One of the "arms" of the robot holds a video camera, which transmits an image of the operated area. The other two reproduce movements performed by the human surgeon, and the fourth "arm" acts as an assistant to the surgeon. As can be understood from the above description, strictly speaking, ***Da Vinci*** is not yet a robot, that is, an autonomous system. Rather, it is a device for remote operations. But this device certainly has a great future.

Conclusion

Suppose that due to the success of therapy, surgery, or a combination thereof, disease is left behind. But with the most favorable outcome, a person who has suffered a serious illness will no longer be the same as he/she was before the illness. An ill organism resembles a country that has survived a war. In both cases, reserves have been largely spent, there are significant imbalances, and there are insufficient defense opportunities. The number of accumulated problems encourages us to immediately address them. However, the most important thing in such a situation is the need to restore strength. Depending on the type of pathology that has been undergone, rehabilitation may have specific features, which the attending physician will best describe. However, there are several general rules that it is useful for any ill person to follow.

First, the usual level of physical and mental stress should be achieved gradually, according to the general condition of the body.

Secondly, proper nutrition should be provided. This should be sensible both in the composition of the food and in the regimen of its intake.

Thirdly, it is necessary to observe a gentle regime of sleep and wakefulness, work and rest. Be kind to yourself.

Fourth, if possible, avoid crowds of people, because these can be the source of further infections.

And finally, our body is our greatest wealth. It deserves care.

SOME BASIC MEDICAL TERMS

A

Acidosis: a situation in which there is a shift of the acid-base balance to the acidic side, in the biological fluids or tissues of the body

ACTH: adrenocorticotropic hormone

Agony *(Greek: αγωνία — struggle):* the terminal state prior to death

Alkalosis *(Arabic: al-qali — alkali):* the shift of the acid-base balance in tissues or body fluids to the alkaline side

Alteration (*Latin: alteratio — change):* the entire volume of deviations from the norm in a sick body

Amyloidosis: the accumulation of the amyloid three-dimensional fibrillar structure of glycoproteins both in the extracellular space and the cytoplasm of cells after prolonged intoxication or depletion

Apoptosis *(Greek: ἀπόπτωσις — leaf fall):* the mechanism of genetically programmed self-destruction of damaged, infected and transformed cells that pose a threat to the body

Ascites: fluid accumulation in the abdominal cavity

Atherosclerosis *(Greek: αθηρο—gruel and σκλήρωση—hardening):* a complex of sequentially developing metabolic disorders and morphological changes in the walls of the blood vessels, representing the pathogenetic basis of a group of extremely common diseases of the cardiovascular system

Atrophy *(Greek: ἀτροφία—lack of food, starvation):* reduction in the size of cells, tissues, and organs of animals and humans. This pathology is characterized by a violation or termination of the function of organs or tissues

Atypism: differences from the norm in cancerous cells and tissues

Auscultation *(Latin: auscultatio—listening):* a physical method of diagnosis, performed by listening to the sounds formed during the functioning of internal organs using a phonendoscope

C

CA: catecholamines

Carcinogenesis: a mechanism for the development of cancer

Carcinogens: substances or effects that may cause cancer

Central link of pathogenesis: damage or disorder that triggers or maintains a chain of subsequent pathological changes

Cirrhosis *(Greek: κίρρως —ginger)****:*** diffuse replacement of specialized cells with connective tissue

Coagulopathy *(Latin: coagulum—coagulation and Greek: πάθος—suffering):* a pathological condition of the body caused by widespread violations of the blood coagulability

Coma *(Greek: κῶμα—deep sleep):* a life-threatening condition between life and death, caused by a violation of the blood supply to the brain. Coma develops as a result of deep inhibition in the cerebral cortex, causing the complete loss of consciousness. This inhibition of neuronal activity extends to the subcortical centers of the brain, which can lead to respiratory arrest, or cardiac arrest

Compartmentalization: spatial separation of incompatible reactions and the convergence of conjugated reactions

CT: X-ray computed tomography

D

Damage: distinct structural changes caused by adverse factors

Dehydration: the body state that occurs when there is insufficient water intake (lack of drinking water, unconsciousness, esophageal obstruction), or when water is significantly lost (severe sweating, diarrhea, vomiting, excessive urine output)

Diagnosis *(Greek: διαγνωστικος—able to recognize)****:*** the shortest possible conclusion about the type and specific features of disease in strictly standard terminology

Diagnostics: the section of medicine dedicated to diseases recognition

Disorders: changes in the body's functions caused by the action of adverse factors

Dropsy: water retention in the body cavities

Dysplasia (*Greek: δισ—disorder; Greek: πλάσις—formation)*: reduction in the number of different cell types can often be disproportionate; this is known as organ dysplasia

Dystrophy (*Greek: δισ and Greek: τροφια—nutrition*): In a narrow sense, dystrophies are deposits of ballast substances in the cytoplasm of cells and in the extracellular space. In a broader sense, dystrophies imply metabolic disorders in tissues

E

Embolism *(Greek: εμβολη—intrusion)***:** a mechanical blockage of blood vessels

Etiology *(Greek: αίτία: reason)***:** a special section of medicine devoted to the study of the causes of disease

Etiotropic or etiological treatment *(Greek: αιτία—cause and Greek: τρόπος —turn; change):* a treatment aimed at eliminating the cause of the disease

Exudate *(Latin: exsudo—I go out, I stand out):* a fluid released from blood vessels into the intercellular space or the body cavity during inflammation

Exudation: the release of the liquid part of the blood into the tissue or body cavity

F

Fever**:** endogenous hyperthermia in which the separation of the processes of oxidative phosphorylation and free oxidation occurs as a result of the action of bacterial toxins and molecular decay products of cells

Frostbite: local tissue damage due to low temperatures

G

Gangrene *(Greek: γάγγραινα—corroding ulcer):* tissue necrosis of a living organism, which is black or very dark in color. This develops in the tissues of organs, directly or through anatomical channels associated with the external environment (skin, lungs, intestines, etc.)

GCSs: glucocorticosteroid hormones

H

HPA: the hypothalamic-pituitary-adrenal system

Hyalinosis: infiltration of the hyaline in the cells and the extracellular medium

Hydrocephalus *(Greek: ὕδωρ—water and κεφαλή—head)***:** dropsy of the brain

Hydrothorax *(Greek: ὕδωρ and θώραξ—chest)***:** accumulation of non-inflammatory fluid (*transudate*) in the pleural cavity

Hypercapnia *(Greek:ὑπερ—excessively; Greek:καπνός—smoke):* increased concentration of carbon dioxide in the blood

Hyperemia *(Greek: ὑπερ—super and αἷμα — blood):* the blood vessels overflow of the any organ or body area.

Hyperhydration (hyperhidrosis): the body state which occurs either due to insufficient removal of water from the body, or due to excessive fluid intake

Hyperplasia *(Greek: ὑπερ—super and πλάσις—formation)**:*** enlargement of the organ or tissue as a result of cell reproduction

Hypertension (*Greek: ὑπερ and Latin: tensio—tension)**:*** high blood pressure

Hypoplasia *(Greek: ὑπο—below and πλάσις—formation)*: an insufficient number of cells

Hypotension: a decrease in blood pressure

Hypotrophy *(Greek: ὑπο and τροφια—nutrition)**:*** a reduction in the size of all cell types; a reduction in the size of organs or tissues

Hypoxia *(Greek: ὑπό and Latin: oxigenium–oxygen):* an oxygen deficiency

I

Ischemia *(Greek: ἴσχω—I delay; αἷμα—blood):* violation of local blood circulation combined with a complex of tissue disorders caused by hypoxia and nutritional deficiency

K

Karyolysis *(Greek: κάρυον—nut, kernel and λύσις—decomposition)**:*** dissolution in the cytoplasm of a decayed cell nucleus

Karyopycnosis *(Greek: κάρυον—nut, kernel and πυκνός—dense)**:*** chromatin turning into a homogeneous mass

Karyorrhexis *(Greek: κάρυον—nut, kernel abd ρέξις—gap)**:*** the decay of the cell nucleus into fragmented parts

L

Lymphadenitis *(from lymph and other Greek: ἀδήν—gland)**:*** an inflammation of the lymph gland

Lymphangitis *(from lymph and other Greek: ἀγγεῖον—vessel)**:*** an inflammation of the lymph vessels

M

MRI: magnetic resonance imaging

Mucoid degeneration: the accumulation of mucus-like contents in the cells

N

Necrosis *(Greek: νεκρός—dead)**:*** the death of a significant number of cells, tissue sites and even whole organs

Necrobiosis: a complex of changes, including cell necrosis and destructive intercellular changes

P

Palpation *(Latin: palpatio—grope)**:*** a physical method of medical diagnosis, carried out by feeling

Pathogenesis *(Greek: πάθος—suffering and γένεσις—origin, occurrence)**:*** the mechanism of the origin and development of the disease and its individual manifestations

Pathogenetic therapy: a type of treatment aimed at eliminating a disorder or damage that induces secondary disorders

Percussion *(Latin: percussio, literally—striking, here—tapping)**:*** in medicine, this is a method of diagnosis, which consists of tapping individual parts of the body and analyzing the sound phenomena that arise

Proliferation *(Latin: proles—offspring, offspring and fero—I carry)**:*** cell reproduction

R

Reactivity of an organism: the ability of an organism to respond to adverse environmental effects with protective and adaptive changes in life activity

Resistance of an organism *(Latin: resisto—I resist, resist)**:*** the ability of an organism and its parts to resist the actions of physical, chemical and biological agents that cause a pathological condition

S

SAM: the sympathetic-adrenal-medullary system

Sanogenesis *(Latin: sanus—healthy and Greek: γενεσις—origin, occurrence)**:*** a set of protective and adaptive mechanisms aimed at restoring impaired self-regulation of the body

Shock *(French: choc—push, hit, collision):* an acutely developing, deadly pathological process that occurs as a result of the action of an extreme etiological factor which causes deep disturbances in the activity of the nervous and endocrine systems, from which violations of the regulation of the activity of organs and tissues spread

Sludge**:** in medicine, this term refers to a stop in the blood's movement through the microvessels, as a result of blood cells' adhesion

Stasis *(Greek: στάσις—standing):* a stop in the movement of the blood in the vessels

Stress: in medicine, this implies the mechanism which activates a complex of nonspecific adaptive reactions that arose during evolution in response to a wide variety of dangers, disorders and injuries

Stroke *(Latin: insultu**s—a**ttack, strike):* an acute local disturbance in the blood supply to the brain or spinal cord

Surgery *(Greek: χείρ—arm and ἔργον—action):* a field of medicine that uses the surgical method for treating diseases, including cutting the patient's tissue or suturing a wound that has arisen

Symptom *(Greek: σύμπτομα—case, coincidence, sign):* one elementary diagnostic sign or manifestation of disorder or injury caused by etiological factors

Symptomatic treatment: a type of treatment aimed at reducing the severity of the process, minimizing complications, or eliminating individual symptoms

Syndrome *(Greek: σύνδρομον, σύνδρομο—attendance; δρομο—road):* this is a complex of symptoms characteristic of a specific pathological process, or of diseases of certain anatomical structures and systems

T

Teratogenic (*Greek: τέρας—monster*)***:*** possessing the ability to disrupt the interaction of cells in the fetal development of embryos, as a result of which various deformities develop

Therapy *(Greek: θεράπεία—treatment):* a treatment which affects the body with medicine but not accompanied by significant anatomical changes

Thermal burns: local tissue damage caused by high temperature

Tomography *(Greek: τομή—section):* the acquisition of a layered image of the internal structure of an object

Transudate *(Latine: trans—through, and Latin: sudatum-—to sweat):* fluid that accumulates in the body cavities due to increased permeability of the walls of blood or lymph vessels; transudate formation can also occur as a result of disturbances in water-salt metabolism

U

Uremia *((Greek: οὖρον—urine and αἷμα—blood):* an auto-intoxication syndrome that develops with severe renal failure due to a delay in the body's nitrogenous metabolites and other toxic substances, or disorders of homeostasis. This is accompanied by secondary metabolic and hormonal disorders

V

Vascular collapse *(Latin collapsus—fallen):* one of the forms of acute general circulatory disturbance, in which the smooth muscles of the arteries relax and their total volume increases, resulting in a sharp drop in blood pressure

W

WHO: World Health Organization

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