(hyperthyreosis, feochromocytoma). The heart impairment in these diseases is caused in consequence of long-term increased ineffective performance which results in depletion of macroergic phosphates and sometimes even in the development of numerous necroses.

3.10 General adaptation syndrome – stress

The theory of stress belongs unambiquously to the greatest achievements in medecine of the 20 th century. However, this problem is not analyzed with adequate attention in textbook literature. The general adaptation syndrome – stress is a specific disease entity and terefore it seeks its place in internal medicine with difficulties. The textbooks of pathologic physiology traditionally included stress into their general parts. It coincided with the fact that not a single, but several systems participate in the stress reaction and consequently the entire organism is altered.

Without the need of appologizing it is necessary to admit that the adaptation syndrome has appeared at the brink of attention of both pedagogues and students. One of the most complex theories of modern medecine represented for a long time an untraced site in the system of medical education and postgradual study and therefore it has not become such a diagnostical and therapeutical instrument in the daily medical practise as it could have become due to its significance and impact.

Especially the facts mentioned above lead us to including the theory of stress into the tuition of cardiovascular system. The cardiovascular system has a crucial role in adaptation response of organism to stressor. Despite the central, i.e. regulatory and coordinatory function of nerves and hormones, the major effective organ is the cardiovascular system. The heart and vessels deliver the blood which is rich in oxygen and substrates in adequate amount to organs which perform the greatest activity during stress.

When presenting the stress reaction it is not our aim to specificate it. The reactions of the cardiovascular system to physical or psychical overload, heat, pressure, or gravitation differ according to the evoking factor. The development of all subsequent reactions is however very similar. Therefore these situations are not individually presented. We pay increased attention to the general term of adaptation as well as to possible negative consequences of an extensively or frequently repeated reaction to overload.

3.10.1 Adaptation

Man, being a psychosomatic entity is in comprehension of modern biology an **open system**. In contrary to the entirety per se which represents merely a conglomerate of entities there exist dynamic and at the same time constant hierarchically arranged relations of super and subordination between the components of the system. Organism is comprehended as an open system as its borders are sufficiently firm not to be diffused into the surrounding space, but at the same time partially permeabile, thus allowing the substances, energy and information pass in both directions. An organic system accepts substances rich in energy and excludes products with lower amount of energy. This energy gradient is utilized for internal performance of an organism. **Entropy, i.e. measure of derangement** decreases during the process of growth and maturation, afterwards its constant level is maintained and at the old age the entropy increases. An organism achieves the maximal degree of disorganization after death. At that time, however, the hierarchical manner of arrangement of its subsystems, as well as active exchange of substance and energy with the surrounding space cease to be functional.

One of the basic characteristics of organisms which secure a relative constancy and independence from changes of environment is the capability of autoregulation. The term regulation refers to minimalization of the difference between the actual values and the required value of the regulated variable, namely on the basis of investigation of the above mentioned gradient. Phylogenetically lower animals yield chemical regulation. Higher organisms yield humoral regulation which is allied to chemical regulation, and the phylogenetically youngest nervous regulation which supervises all levels of regulation. Both humoral and nervous regulation are basically of chemical character (hormones, mediators).

While the number of impulses from the exter-

nal and internal environment which may irritate the organism is infinite, the variation of instantaneous responses of organism is relatively very small. Pathogenic stimuli evoke two possible reactions of organism: direct protection (localization of the pathogenic agent, respectively its extinguishment) or **adaptation** to changed conditions.

From the phylogenetic point of view adaptation is comprehended as acquirement of new properties under new conditions, namely those which are as far as life and survival of each biologic species concerned more advantageous in comparison to the previous properties. The basic question which still cannot be unambiquously answered is as to whether what mechanism is responsible for acquirement of these altered properties.

All genes have a biochemical basis. Genes represent codes under influence of which a particular enzyme (or protein) is formed and the existence of which together with other enzymes (or proteins) are responsible for morphologic and functional signs and manifestetions of organism.

It is assumed that the offer of new possibilities for the development of new properties is realized accidentally, by means of genetic mutations. It is a spontaneous accidental change in the genome which is promoted under the influence of various factors. However, mutations are rare and only 1 % of mutations are favourable and preserved. In this way during history only a minute proportion of mutations could have been profitable and the development would have taken place in a much slower pace than it actually did in reality.

Aside from mutation also **combinatory variance** has its impact. It is realized on one hand by independent distribution of chromosomes in meiosis and their accidental connection at fertilization and on the other hand by crossing over and recombinations. This type of variance represents but a new combination of unchanged genes, while mutation means formation of new genes. Symbolically this type of accepting new properties is compared to a pack of playcards, the structure of which changes according to changed order caused by their shuffling, while individual cards stay unchanged.

Often the formation of new properties takes place surprisingly fast, already during a single generation, where the above mentioned mechanisms cannot have the possibility of their exertion. This situation can be explained by the possibility of adaptation on the basis of enormous **redundant genetic information**. One property can be coded by a whole series of genes, but only a minimmal amount of them is manifested. Other genes are blocked by repressor genes. The external impulses may activate some of the blocked genes and the manifested genes can be on the contrary partially or completely inhibited. This results in modification of the involved phenotypic manifestation - formation of new characteristics.

It is probable that in the historical development the organisms reacted to any stimuli by a larger number of reactions, or by a transitory acceptance of a much larger number of variations of a certain characteristic than it is normal currently. The acceptance of a particular property or manner of reaction was determined by maximmal appropriateness regarding the momentary conditions. However, those possibilities which had taken place and did not guarantee the possibility of existence under conditions differing from those under which the characteristics had been formed, i.e. those which represented too specific adaptations and coincided regarding the appropriateness with a quite narrow constellation of conditions, remained a reality from the developmental point of view merely for a very short period. It was caused by the fact that already a small change in conditions implied that the characteristic which had been under the previous conditions favourable for the organism (or even optimal) became useless or even harmful and caused death or extinguishment of the individual. On the other hand such manner of reaction which under particular conditions had been favourable and at the same time of a sufficiently general character in order to be positively exerted also under different conditions it became a permanent characteristic and at the same time a characteristic feature of the species. Hence, from an enormous variability of possible genetic combinations only those groups of genes are permanently fixed, the realization of which in form of phenotype secures survival and the possibility of the individual's existence in a relatively wide range of conditions.

3.10.2 Stress

Regarding the degree of diversity of situations under which a reaction is manifested as being favourable for an organism, the following reactions can be distinguished:

- highly specific (e.g. production of specific antibodies)
- general (fever, cough, inflammation...)
- general adaptation syndrome – stress is the most general reaction

The term stress was introduced in 1927 by a Canadian pathophysiologist Hans Selye whose predecessors came from Komárno. Stress in the original conception does not mean overload exerted upon organism (as it is often interpreted), but a response of organism to this overload. Salye introduced the term stressor which referred to overload which is responsible for stress development. Both terms are often confused and stress is often used in sense of overload.

Despite the intensive research in the field of stress there does not exist any unified definition as none of the suggested characteristics depicts all aspects of the stress reaction. Even the Sealye's original definition - *stress is a nonspecific, stereotypic response to any demands exerted upon organism* - does not suit the current conceptions. Selye himself admits, "We all know that there is stress, but nobody knows what stress is." We can agree without any doubts with the fact that **stress is a state of organism affected by stressor. A system of protective and reparatory processes is mobilized with the aim of survival**. As an organism is an open system **stress can be in general explained as a state of organism which is acquired if the organism accepts or gives out a too large or too small amount of matter, energy or information, or when the interior environment of organism is affected by such factors which compell variables to overstep the borders of the allowed variability**.

Any factor can represent a stressor:

- physical factors (cold, heat, radiation, vibrations...)
- chemical factors (toxic substances, mediators of inflammation, products of metabolism...)
- pain
- intensive psychical activity
- informative deprivation or over-supply

Owing to the second signal system which is based on the principle of existence of symbols, any of the symbols may play the role of an intensive stressor despite its nonbiological character (spoken or written word).

In spite of the fact that the terms stress and homeostasis on first sight differ in sense, in fact they are allied to a great extent. Homeostasis is a set of regulatory stabilizing principles of live matter owing to which organisms have the ability to self-attain a certain level of internal organization. The system of regulatory devices maintains variables (pressure, temperature, volume of fluids, ion composition of internal environment, level of metabolites, etc...) in the frame of a certain narrow interval, thus enabling its bearer a relative independence from the external environment.

Both homeostasis and stress involve hence a reaction of organism to its relatively changed relation to environment. Consequently those mechanisms are activated, the task of which is to secure adequate function of individual systems. The two reactions differ by the fact that while the homeostatic mechanisms secure integrity of the organism and a relative balance of functions under usual rest conditions, the stress mechanisms are activated when the integrity and life of organism are endangered. However, both homeostatic and stress mechanisms are basically equal (regulation of blood pressure, cardiac frequency, volume of somatic fluids). Stress, though, sets the function of important organs on a higher level. Stress, that is to say, was formed during the phylogenetic development as a reaction of fight or flight, which naturally required an increased performance of striated muscles. **All changes coinciding with stress are aimed at the development of a balanced state in which the organism is able to perform enormous physical and psychical performance**. Uneconomical amounts of energy, matter and information are exerted merely in order to secure survival under the condition of stressogenic situation. The presented facts imply that the difference between homeostasis and stress results from quantitative differences between both reactions.

The **mechanism of alarm reaction** is quite complex (viz. fig. 3.13 on page 142). Information from the external world is conveyed into CNS by means of sensory organs, while the stress information from the internal environment is intermediated via interoreceptors. Aside from specific sensory effectors, nonspecific mechanisms are activated from the reticu-

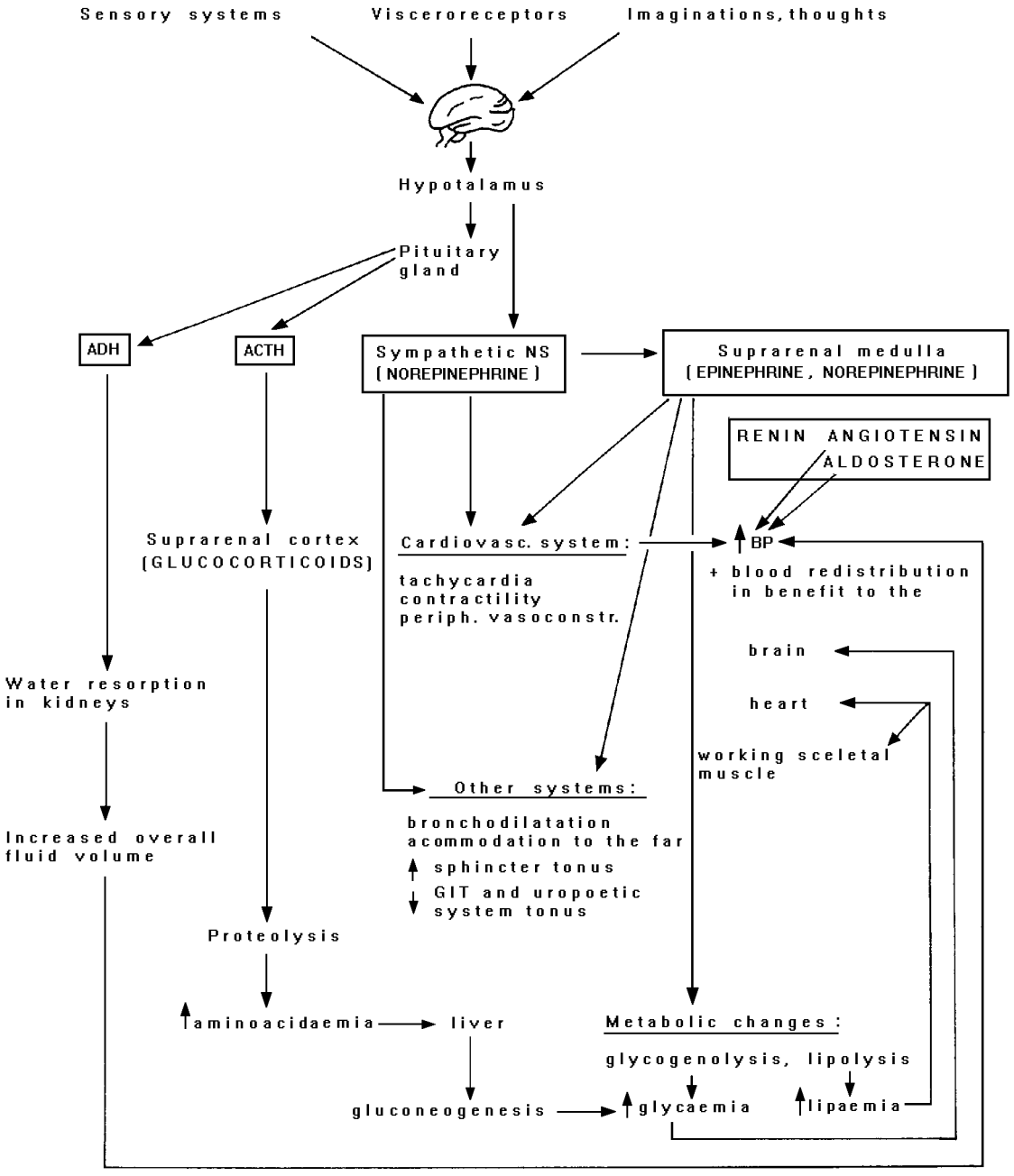

Figure 3.13: The most important endocrinological, metabolic and organic changes in stress

lar formation. On the one hand cerebral cortex is activated, on the other hand and striated muscles (somatomotor component), tonus and movement of smooth muscles (visceromotor component) and endocrine organs (humoral component) by means of the stressor. The original purpose of activation of all three presented systems was to prepare organism to intensive muscular performance. To meet this demand it is necessary for working muscles to receive an adequate amount of energy. The most effective energy producing reaction in phylogenetically higher animals is the process of oxidative phosphorylation where the substrate is oxidized in presence of oxygen producing thus CO_2 and H_2O. The produced energy accumulates in biologically utilizable form as adenosine triphosphate (ATP). With a little bit of simplification we can state that the reason why the stress reaction is to be performed is an increased ATP requirement of striated muscles. A sufficient amount of oxygen delivered to muscles during overload is secured by increased perfusion of muscular capillaries and a sufficient level of substrate is secured by increased level of fatty acids and glucose. Aside from that also the heart's output must be increased securing thus a sufficient blood perfusion of working organs and the cerebral activity, the regulatory and coordinatory functions of which are significantly increased in a stressed organism. Practically all endocrine and neurogenic reactions and subsequent circulatory and metabolic changes take place with the aim to enable the performance of increased physical and psychical outputs necessary in order to survive the stress situation.

Activation of endocrine organs preserves a particular historical sequence. Sympathetic centre in hypothalamus, being phylogenetically the oldest, is activated as the first, stimulating thus the sympathetic nerveous system, and by means of the latter also suprarenal glands are activated. The nervous endings of the sympathetic nerve release noradrenaline, the pulp of suprarenal glands release adrenaline and noradrenaline. By means of their impact on beta-receptors the contractility of the heart increases resulting in the increase in frequency and minute volume. Vasoconstriction is achieved by means of alpha-receptors in vessels of peripheral tissues (periphery refers to the digestive organs and skin) resulting thus in redistribution of the blood to those organs where vasoconstriction is not present (resp. where vasodilatation takes place), namely in working muscles, heart and brain.

Adrenaline mobilizes glucose from the liver being the initial energetic contribution by means of the b phosphorylase activation with subsequent breakdown of glycogen. At the same time adrenaline activates lipase which splits neutral lipids to glycerol and fatty acids in adipose tissue. Glucose is inevitable for the activity of CNS, while the myocardium and striated muscles are able to utilize also fatty acids, lactate, pyruvate, aminoacids and ketone bodies. Preference of fatty acids to glucose which takes place in the heart and muscles is secured by the inhibitory effect of adrenaline on insulin on one hand, and by direct inhibition of glycolytic enzymes by fatty acids on the other, saving thus glucose for the brain.

The second phylogenetically oldest neuroendocrine system which is activated in the initial phase of stress is the antidiuretic hormone (ADH). It is synthetized in nucleus supraopticus and n. paraventricularis in hypothalamus, and stored in neurohypophysis from where it is released into the blood. Subsequently after entering the circulation it supports the reverse reabsorption of water in distal and collecting channels of the kidneys and aside from that it bears huge pressoric effects (vasopressin). ADH thus increases blood pressure on the basis of both volume and resistance principles.

At the beginnig of the stress situation peripheral vasoconstriction causes hypoperfusion of the kidneys. Decreased number of impulses for the wall of vas afferens activates the system renin-angiotensinogen-angiotensin I, II-aldosterone. Aldosterone increases the volume of somatic fluids by a reabsorption of sodium and subsequently of water in the distal portions of nephrone. Angiotensin II is one of the central hormonal substances of stress reaction. It directly stimulates constriction of arterioles, enhances the synthesis and elimination of noradrenaline on the nerve endings and blocks its reuptake, it stimulates the release of aldosterone from the cortex and adrenaline from the pulp of suprarenal glands as well as of vasopressin from neurohypophysis, it increases the sensitivity of vessels to vasocstrictory effects. To a certain extent it hence plays the role of a coordinator of stress reaction.

Simultaneously to stimulation of the sympathetic nerve and suprarenal pulp the second defence line is activated. It is the system of hormones of the an-

terior lobe of the pituitary gland which are released and the most important of them in coincidence with stress is the adrenocorticotropic hormone (ACTH). Its effect supervenes as late as after tens of minutes from the beginning of irritation, but the effect is in comparison with catecholamines of a longer-term character. It causes a release of glucocorticoids from the pulp of suprarenal glands (the most important is cortisol). In spite of the fact that its effect manifests itself by a whole series of external reactions, basically all of them reside in the ability to synthetize glucose de novo from nonsugar sources – glucoplastic aminoacids (which are mostly gained by splitting of lymphatic and muscular tissue), from lactate (which is produced at a relative depletion of oxygen in working muscles) and from glycerol (which gets into the blood due to the splitting of neutral fats). The meaning of cortisole resides hence in the fact that after a fast depletion of hepatic glycogen under the influence of the sympathetic nervous system the permanent supply with glucose to the brain is secured from nonsugar sources. Catecholamines force organs to high performance under very uneconomical conditions and can have a utterly toxic effect on tissues. Under a common intensity of stress reaction the toxic effect is manifested only in individuals with decreased release of cortisol. This implies that glucocorticoids secure a somewhat protective effect on tissues against toxic effects of noradrenaline and adrenaline. An especially intensive stress can be sometimes managed by massive doses of glucocorticoids. Catecholamines and glucocorticoids increase blood clotting which can have in case of injury of tissues due to fight or flight reaction often a protective effect against exsanguination.

Parallel to ACTH also the so-called beta lipotropic hormone is relaeased. Lipotropic hormones give origin to endorphines and enkephalines. The reason of parallel production of ACTH and beta lipotropic hormone is the same precursor molecule – propiomelanocortin. Endorphines and enkephalines belong among the so-called endogenic opiates which bind on receptors of the morphine type. The main role of these neurohormones is the modulation of affective and reactive components of stress. Endorphines have an analgetic, euphorizing and hypotensive effects. They play probably also the role of modulator of elimination of the rest of stressogenic hormones.

The final nature of alarm reaction depends also on the somatotropic hormone, tri- and tetraiodothyronine, insulin, glucagon and lactotropic hormone (prolactine).

3.10.3 Civilization diseases

Experience has repeatedly convinced us that stress can evoke or deteriorate a number of diseases. As many as in 50 % of subjective difficulties of patients their case histories yield certain forms of chronic stress. The most frequent so-called civilization diseases which are to a smaller or greater extent determined by insufficient adaptation to various forms of stressors include atherosclerosis, ischemic heart disease (and infarction of myocardium being its most serious form), duodenal ulcer, hypertension, disturbances of cardiac rhythm, colitis ulcerosa ... Aside from these organic diseases civilization diseases include a much larger number of disturbances being of functional character, where patients despite of a series of subjective symptoms have only minimal or no morphological or biochemical disturbances. All these diseases are treated by an advise to be aware of stress, change of job, appropriate life style. In fact the problem is more complex.

First of all it is inevitable to adopt an attitude to the question as to why is the stress reaction which had been during the phylogenetic development million times proved as being positive for organism, is in a nowaday man a frequent cause of health disturbances.

Life had been formed billions of years ago. Practically sice their origin the organisms had to accomodate to changing external environment. Stress in modified forms occurs in all species of organisms and even in plants. The stress reaction has been forming since the beginning of life. Human civilization, however, began to form only several ten thousands years ago. It brought about enormous changes – advanced technique, abundance of information, system of standard behavour, (moral, ethics, law). First of all it brings about a distinctly different world in comparison to that in which man had developed. It is a world of symbols. Symbols, although not having any biological value, are worth while for a man to be capable of deeds of various values. The biologic basis started to being dominated by the II. signal system represented by word.

The problem resides in that while the biologic al-

terations were formed millions of years ago, the civilized world brings about changes in material and spiritual world often during one or several generations. Human biosystem cannot always manage to adapt to these facts. The alarm reaction represents in fact an unconditioned automatic reflex. It functions immediately unerroneously, stereotypically. However, it has a disadvantage in lacking plasticity and ability of modification, resulting thus in loosing its justification. The stressor evokes a reaction according to experience gained during millions of years. Today majority of stressors do not entail fight, but flight. The majority of stress reactions are not linked to muscular work. In spite of that human organism mobilizes catecholamines, glucocorticoids, and other stress hormones. The blood pressure elevates, glucose and fatty acids are mobilized, blood circulation is rebuilt, sodium is resorbed, potassium and magnesium decrease, blood clotting increases. What is mobilized is not subsequently utilized by muscular work.

These facts result in inadequately prolonged increased blood pressure, which gradually becomes permanent and primary hypertension develops. Hypertension and hyperlipemia may cause accumulation of lipids in vascular walls and development of atherosclerosis.

3.11 Congenital heart diseases

Congenital cardiovascular malformations **result from an abnormal embryonal development of the normal structures or its absence**. They develop due to genetic causes and the effect of the external environment, which is affecting the growing embryo between 3–7 week of justation. Those factors are (ionizing radiation, some chemical substances, pharmaceutics, viruses).

Cardiac and large vessels malformation have different clinical manifestations. Some disorders are well tolerated by the body. Yet during adulthood the haemodynamic situation may deteriorate. Some malformations are manifested late in the 4th or 5th decade of life. An example of this are shunts, in these cases problems appear only when the pulmonary hypertension is stabilized due to the structural changes in the lung field. Pulmonary hypertension accompanies more than one cardiovascular malformation. The state of pulmonary area or (the lungs) will decide the intensity of clinical manifestation of the disease, as well as the possibility of a surgical treatment. In the beginning the pressure in the pulmonary field depends on the pulmonary blood flow. Later it depends as well on the vascular resistance, finally there will be some structural changes in the lung field. That is why it is very important to measure the blood flow into the lungs as well as the pulmonary vascular resistance.

As an attempt to compensate for oxygen insufficiency and in chronic hypoxia here will be increment in the number of erythrocytes in the peripheral blood. That is why here will be an extreme increase in the haematocrit. As a result of this there will be a change in blood viscosity. Increase in the erythrocyte count (polyglobulia) is a cause of hypervolaemia. Polyglobulia, a high haematocrit, and hypervolaemia accompany congenital cyanotic heart diseases. On one hand by the effect of these changes it is easier for the blood to carry oxygen due to high blood capacity for oxygen transport, but on the other hand these changes give many side effect. There is the occurrence of thrombotic complications and hemorrhages. That is why drugs that potentiate vascular thrombosis are strictly contraindicated in patients with congenital cyanotic heart diseases. In cases of a very prominent polycythemia we have to reduce the erythrocyte number by replacement with plasma or albumin to decrease the blood viscosity, increasing blood flow through the tissues, and hence provide more oxygen supply. Yet repeated venepunctions are not indicated because by this the organism is loosing too much iron and to compensate the erythrocyte loss they are replaced by fast formation of small erythrocytes - microcytes. They have a lower deferability, and hence are not good for oxygen transport.

The inborn incorrected cardiac diseases are a risk factor in females in time of gravidity and during birth. During gravidity the condition deteriorates in case there is already presence of pulmonary hypertension. Mortality rate is increasing in the group of females, in whom gravidity is terminated by cesarean section. In mothers with corrected cardiac